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Chapter 1

Introduction

1.1 Ion Channels

Ion channels are cylindrical, hollow proteins that regulate the movement of ions (mainly Na^+, K^+, Ca^{++}, and Cl^-) across nearly all biological membranes. Since these membranes are otherwise impermeable to charged particles, the only way ions can cross the membrane is through the pore that runs down the long axis of a channel. (The structure of the KcsA channel from a recent x-ray crystallography study [15] is shown in Figure 1-1.) This property has been exploited by evolution to produce many varied phenomena necessary for life: channels are responsible for the initiation and continuation of the electrical signals in the nervous system; in the kidneys, lungs, and intestines, channels coordinate changes in ionic concentration gradients that result in the absorption or release of water; in muscle cells, a group of channels is responsible for the timely delivery of the Ca^{++} ions that initiate a contraction. Clinically, malfunctioning channels cause cystic fibrosis, cholera, and many other diseases and have recently been implicated in schizophrenia and bipolar disorders. Furthermore, a large number of drugs (including valium and PCP) act directly or indirectly on channels.

To produce such varied and complicated phenomena, channels act in groups, opening and closing at the same time and letting only specific ion types through

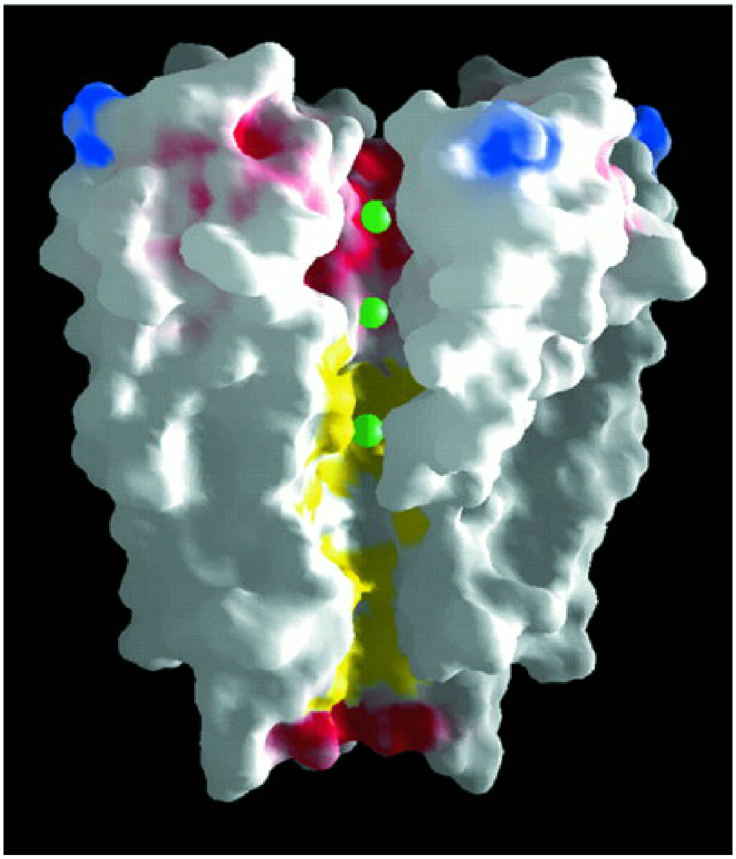

Figure 1-1: Molecular surface of the KcsA channel with a cut-away to expose part of the pore where three ions are shown. The pore runs up and down in the picture connecting the inside of the cell (bottom) to the outside (top). The cell membrane is not shown, but runs horizontally. The overall length of the pore is 45Å. Reprinted with permission from Doyle, D.A., Cabral, J.M., Pfuetzner, R.A., Kuo, A., Gulbis, J.M., Cohen, S.L., Chait, B.T., MacKinnon, R., The Structure of the Potassium Channel: Molecular Basis of K^+ Conduction and Selectivity, *Science* 280 (3 April 1998), 69-77. Copyright 1998 American Association for the Advancement of Science.

the membrane (for example, selectively passing far more Na^+ ions than K^+ ions). Despite such complex final results, individual channels only do two things: they open and close (called gating) and, when open, they conduct ions. It is possible to remove a single channel from the biological system and study it as an isolated physical system. (This is rarely possible to do with other objects in biology and still have interesting results, but for channels this is done everyday by thousands of scientists.) To do this the individual channel is placed in a phospholipid membrane that seperates two baths of known ionic concentration. In the baths there may be only one salt (NaCl, for example) or multiple salts (NaCl and KCl, for example). A voltage is applied to the system by electrodes in the baths that are far away from the channel and the amount of current passed by the channel (in the form of ions) is measured. It is these current/voltage relations that must be recreated by any theory of ion movement through channels. Our interest in this thesis is the conduction of current through an individual, open channel; we do not consider gating.

1.2 Theories of an Open Channel

The underlying assumption of charge transport through open channels is that the process is governed by the same physical principles for all channel types; that is, although the end results of many channels working in concert to produce an action potential in a nerve or the contraction of the heart are quite different, the principles by which ions cross a membrane through a single channel is the same for all channels.

There are several ways to study the permeation of ions through a channel. The most “realistic” is molecular dynamics (MD) where individual molecules are subjected to Newton’s laws and followed over time. This microscopic approach takes large amounts of computer time to “observe” the ions for even a few nanoseconds of real time (see, for example, [52]). Since an ion usually takes on the order of one microsecond to move through the channel, the exact detail gained by this first-principles approach is at the cost of being able to recover experimental data.

To overcome such difficulties, Brownian dynamics treats each ion as if it were a particle undergoing Brownian motion in a predetermined electric field. With this simplification, Chung, et al. [12], used more than 18 hours of CPU time for 1 microsecond of real time. Although this is a significant gain over MD, the computational output of the model is still below the millisecond time-scale on which experimental measurements are made.

On the other hand, macroscopic theories such as rate-constant theory and PNP (which can be derived from Brownian dynamics under assumptions of the presence of high barriers for rate-constant models [13] and high friction for PNP [17]) are not nearly as detailed in their descriptions of permeation. However, they do not suffer from these real-time-observed limitations, since they only consider the channel on larger time scales and after steady state has been achieved. (Recently a model that is intermediate to the microscopic and macroscopic models has been proposed [2], but has not yet been adapted to channels.)

The most successful macroscopic theory of charge transport through open channels is the Poisson-Nernst-Planck (PNP) theory developed by R.S. Eisenberg, D.P. Chen, and V. Barcilon (reviewed in [16]) and extended by W. Nonner [36]. With a small number of adjustable parameters (just one for the calcium release channel in muscle and one diffusion coefficient for each ion species [10]), PNP has fit the current/voltage data of approximately half a dozen channels over a large range of bath concentrations (e.g., 50mM to 2M) and applied voltages (-150mV to 150mV) ([9] and [10]). PNP can also explain the qualitative properties of a large class of channels [36] as well as other measurable properties of channels such as the anomolous mole fraction effect (AMFE) [37].

PNP assumes that on the biological times scale ($> 10^{-4}$ sec) ions move through an open channel by diffusion and electrostatic interactions with other ions and the protein residues that line the inside of the channel. Mathematically, if J_j is the flux density of ion species j, then

$$-J_j = D_j\left(x\right)\left[\frac{dc_j}{dx} + \frac{ez_j}{kT}c_j\frac{d\phi}{dx}\right] \tag{1.1}$$

where $c_j\left(x\right)$ is the concentration of species j at location x in the channel, ϕ is the electrostatic potential, z_j is the valence of species j, $D_j\left(x\right)$ is the diffusion coefficient of species j, e is the proton charge, k is the Boltzmann constant, and T is the absolute temperature. In biology this is called the Nernst-Planck equation. (In semiconductor research it is called the drift-diffusion equation [32].) The Nernst-Planck equations (one for each ion species) are then coupled with the Poisson equation to compute the electrostatic potential (a.k.a. Gauss's Law or Maxwell's First Law):

$$-\frac{d}{dx}\left(\epsilon\left(x\right)\frac{d\phi}{dx}\right) = e\sum_j z_j c_j\left(x\right) + eq\left(x\right) \tag{1.2}$$

where $\epsilon\left(x\right)$ is the dieletric at location x and $q\left(x\right)$ is the "permanent" charge due to the protein that makes up the channel. (The permanent charge is the key to the PNP theory: PNP distinguishes different channel *types* by requiring each channel type to have a different permanent charge; individual channels within a channel type have the same permanent charge since they are the same protein. The permanent charge is created by the inherent fixed charge of the amino acids that form the protein. Because the amino acids are coded for by DNA, these charges are a fundamental, unchanging aspect of the channel.)

In this thesis we do a mathematical analysis of the PNP system with the goal of deriving formulas for experimentally measurable quantities.

1.3 Outline of Thesis

In the next chapter we will derive a slightly different version of these equations. By starting with the three dimensional PNP equations, we average and get a set of one-dimensional equations that do not require constant cross-sectional area. This will allow us to consider the bath/channel interface in a new and hopefully more accurate way.

The following three chapters are all mathematics. Chapter 3 uses a detailed example to illustrate the mathematical procedure we will use in Chapters 4 and 5. In those chapters we will use the singular perturbation techniques discussed in Chapter 3 to derive some expressions for the reversal potential and conductances at the reversal potential for the case when there is only one salt in the baths (Chapter 4) and when there are several (Chapter 5). These chapters can be skipped for those interested only in the end results, which are reviewed in Chapter 7. Chapter 6 concerns the implications of a function that in the mathematical analysis is assumed to be given, but in reality is unknown. Finally, Chapter 8 relates the results of this thesis to previous work.

Chapter 2

The PNP Model

In this chapter we set up the equations used to describe ion transport through an open channel. In the following sections we discuss the placement of boundary conditions, derive the equations, remove their physical units, and then state some of their general mathematical properties.

2.1 Big Bath, Small Channel

In this thesis, the pore of a channel protein is represented by a generalization of the usual one-dimensional Poisson-Drift-Diffusion equations of semiconductor physics (see, for example, [27], [32], [34]). The conduction pathway in semiconductor theories (but not simulations) is usually given a constant cross-sectional area. While this is reasonable for an idealized semiconductor, it is problematic even for idealized channel proteins; their pores (through which ions move) are small "cylinders" (say 10Å in diameter) embedded in a lipid bilayer and attached to a bath on both ends that in experiments has a volume on the order of 1mm^3. It would be incorrect to represent the part of the bath near the channel as a cylinder with cross sectional area equal to that of the channel's pore. The bath disperses ions into a large volume and has little resistance to current flow; those crucial features must be retained in any model of the bath.

So how does one attach a small channel to a big bath? Mathematically, this is equivalent to asking what kind of boundary conditions to use and where to apply them. At first glance, one way to deal with this problem is to ignore the bath and apply suitable boundary conditions at the mouths of the channel. If the baths are assumed to be charge neutral everywhere and have an electrical potential independent of location, then the bulk bath concentrations and the applied voltage become boundary conditions at the ends of the channel. The problem with that argument is that the bath is not charge neutral at either channel entrance. The channel protein has a charge distribution which is not zero everywhere on the protein and rarely adds up to zero. The entire channel protein has a net charge and ions of opposite charge are attracted to (and ions of like charge are repelled from) the region of the bath near a channel entrance. This results in a local region of space charge; that is, the region is not charge neutral. This, in turn, creates a large local electrostatic potential. Therefore it is not physically reasonable to apply the bulk boundary conditions that apply far away from the channel in the regions near the channel.

Other boundary conditions can be used at the channel mouth to represent these local changes in concentrations and potential. One such approach is via the so-called built-in boundary conditions used widely in semiconductor physics (for semiconductors see [50], [47], and [34] under the heading Ohmic contacts; for use of built-in boundary conditions for channels see [9]). These boundary conditions are derived with two assumptions (as stated in [8]): (1) the baths are in thermal equilibrium (that is, there is no flux from any ion species) and (2) the area just inside the channel at the mouths is charge neutral if both permanent and mobile charges are counted. As discussed above, the second assumption is not physically plausible because the capacitance of the channel cannot be neglected. The first condition, upon initial consideration, seems not to be valid since the idea of studying current from a channel means to study the channel and the bath away from equilibrium. However, because the ions go from an essentially one-dimensional setting inside the channel to a three-dimensional setting in the bath, there is a sudden, large drop in resistance to the ions' movement. Therefore there is a large gradient in both the concentrations and the potential and the right-hand side of the Nernst-Planck equation will be much larger than the left-hand side which is flux. Thus, near the channel entrances, it is valid to use a zero-flux approximation.

In general, these boundary conditions have been very successful; data from several channels was fit very well using these boundary conditions (for example [9], [10], and [11]). These issues (especially the impact of the charge neutrality assumption) will be discussed further in Section 4.5.3. Also, in Section 4.5.2, we will show that the boundary conditions derived from the PNP model considered here are quantitatively similar to the built-in boundary conditions.

Given these two attempts, perhaps it is safer to apply bulk boundary conditions in the baths, away from the channel; far enough from the channel, it is reasonable to apply bulk boundary conditions. A model for how to do this for channels with a uniform fixed charge and cylindrical symmetry was proposed by Wolfgang Nonner in [36]. The basic idea behind the model (called Funnel-PNP) is that because of the geometric constraints imposed by the channel and because ions have small diffusion coefficients, the ions, in general, do not leave the channel moving parallel to the lipid bilayer. That is, the ions move, on average, along the axis of the channel much like water coming out of a garden hose. This is modeled by placing a "funnel" on each end of the channel. Each funnel has a monotonically increasing radius, and, since they represent the baths, do not have an inherent (a.k.a. permanent or fixed) charge like the protein. This is illustrated in Figure 2-1 where the radius function is denoted $R(x)$. It is important to note that this funnel is not part of the channel, but merely a way of representing the part of the bath close enough to the channel to matter (given the rapid diminution of the current/flux density as one moves from one dimensional flow in a channel to three dimensional flow in the bath). In the next section we will

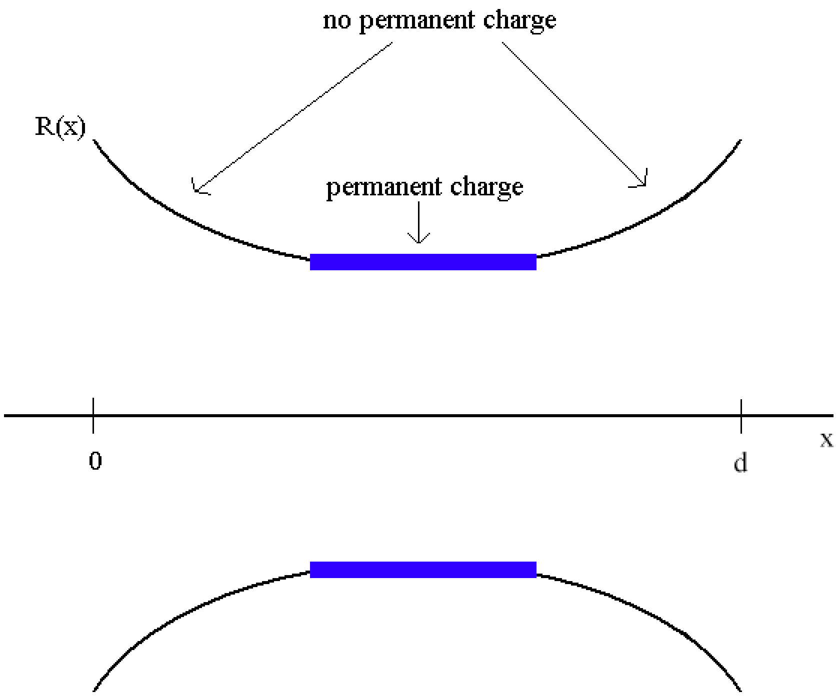

Figure 2-1: Representation of the funnel model described in the main text.

derive (almost) the same equations by considering a much more general case: we assume nothing about the fixed charge of the protein or how the ions enter the baths, nor do we assume there is any symmetry.

2.2 Derivation of the Equations

In this section we derive a set of one-dimensional Poisson-Nernst-Planck (PNP) equations from the full three-dimensional drift-diffusion equations that will become our transport model. (We defer until Sections 8.1 and 8.2 the discussion of whether PNP is or is not a good model of permeation.) We start by stating the three-dimensional drift-diffusion equations (see, for example, [27]):

$$-\nabla \cdot \left(\epsilon\left(\mathbf{x}\right) \nabla \Phi\left(\mathbf{x}\right)\right) = \sum_j z_j C_j\left(\mathbf{x}\right) + Q\left(\mathbf{x}\right) \qquad \text{(Poisson equation)} \tag{2.1}$$

$$-\mathbf{J}_j\left(\mathbf{x}\right) = D_j\left(\mathbf{x}\right)\Big(\nabla C_j\left(\mathbf{x}\right) + \frac{z_j e}{kT} C_j\left(\mathbf{x}\right) \nabla \Phi\left(\mathbf{x}\right)\Big) \qquad \text{(Nernst-Planck equation)} \tag{2.2}$$

$$\nabla \cdot \mathbf{J}_j\left(\mathbf{x}\right) = 0 \qquad \text{(continuity equation)} \tag{2.3}$$

where e is the proton charge, k is the Boltzmann constant, T is the absolute temperature,

$$\mathbf{x} = (x, y, z) \tag{2.4}$$

is the spatial coordinate, ϵ is the dielectric coefficient, Q is the permanent charge of the channel protein, Φ is the electrostatic potential, and, for ion species j, D_j is the diffusion coefficient, z_j is the valence, C_j is the concentration, and $\mathbf{J}_j$ is the flux density. Throughout we assume the Einstein relation between diffusion coefficient and mobility (see, for example, [18]).

Each equation has a physical meaning. The Poisson equation is a differential form of Maxwell's First Law which states that the flux of the electric field across any closed surface equals the total amount of charge enclosed inside the surface. The Nernst-Planck (a.k.a. drift-diffusion) equations state that the flux of species j has two components: simple diffusion and drift along the electric field. Finally, the continuity equations state that there are no sinks or sources for the flux of each species. Now consider the equipotential and equiconcentration surfaces of this system; that is, those

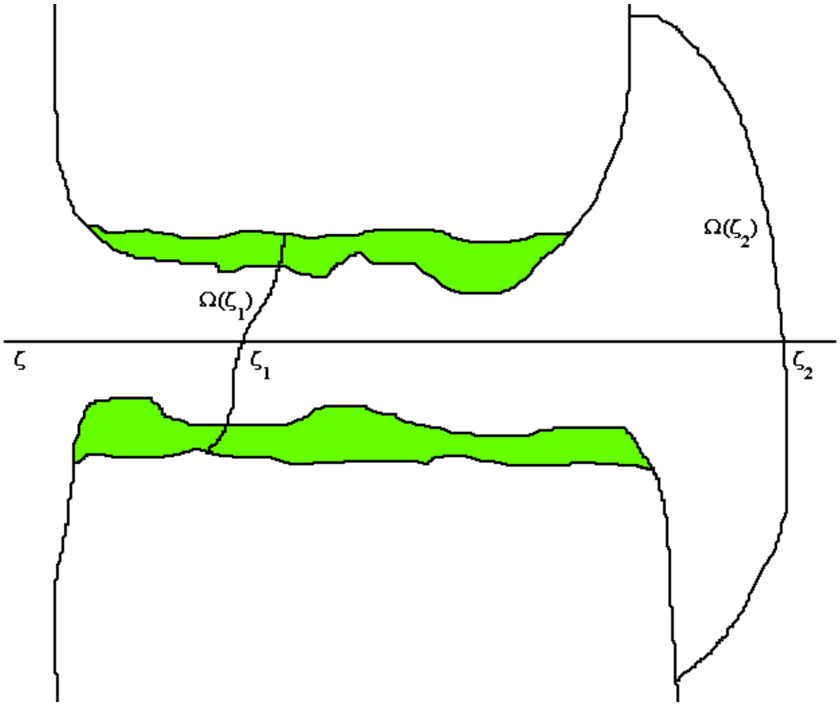

Figure 2-2: A two-dimensional view of the channel and its immediate neighborhood. The shaded area represents the permanent charge of the channel protein exposed to the conduction pathway. Also shown are two possible equipotential or equiconcentration curves $\Omega\left(\zeta_1\right)$ and $\Omega\left(\zeta_2\right)$ that intersect the ζ-axis at ζ_1 and ζ_2, respectively. (The subscript on the Ω's is omitted and depends on whether the curves represent equipotential or equiconcentration curves.)

surfaces Ω_Φ and Ω_j such that

$$\Phi\left(\Omega_\Phi\right) = \text{constant} \tag{2.5}$$

and

$$C_j\left(\Omega_j\right) = \text{constant.} \tag{2.6}$$

The only assumptions we make in the following are that all of these surfaces start and end on the lipid bilayers and that there is no particle or potential flux across the bilayers. If we also assume that the lipid bilayer we are using has no surface charges, then these are reasonable assumptions to make for channels. The inclusion of lipid surface charges is not in the realm of this work since they would result in unequal charge distributions in the baths which we do not take into account. (Because of the low relative permittivity of lipid bilayers, we can also exclude the possibility of induced charges in the lipid.)

We index these surfaces by drawing an imaginary number line along the center of the conduction pathway (referred to as the ζ-axis) and calling $\Omega_\Phi\left(\zeta_1\right)$ that equipotential surface that crosses this ζ-axis at ζ_1 (if it intersects more than once, take the smallest such ζ) and similarly for $\Omega_j\left(\zeta_1\right)$. This is illustrated in Figure 2-2. If we consider a small neighborhood of the channel, let $\zeta = 0$ be the smallest ζ of the surfaces inside the neighborhood and define d to be largest. Then d is the length of the new system we are considering. The surfaces $\Omega_\Phi\left(\zeta\right)$ and $\Omega_j\left(\zeta\right)$ are two-dimensional level surfaces and thus can be parametrized by two variables which we call s and t:

$$\Omega_\Phi\left(\zeta\right) = \left\{\boldsymbol{\omega}_\Phi\left(\zeta; s, t\right) = \left(\omega_\Phi^x\left(\zeta; s, t\right), \omega_\Phi^y\left(\zeta; s, t\right), \omega_\Phi^z\left(\zeta; s, t\right)\right) \mid 0 \leq s, t \leq 1\right\} \tag{2.7}$$

$$\Omega_j\left(\zeta\right) = \left\{\boldsymbol{\omega}_j\left(\zeta; s, t\right) = \left(\omega_j^x\left(\zeta; s, t\right), \omega_j^y\left(\zeta; s, t\right), \omega_j^z\left(\zeta; s, t\right)\right) \mid 0 \leq s, t \leq 1\right\}. \tag{2.8}$$

These are chosen so that all functions are continuous (and we furthermore assume their first derivatives are continuous). In other words,

$$\Phi\left(\boldsymbol{\omega}_{\Phi}\left(\zeta;s,t\right)\right)=\Phi\left(\omega_{\Phi}^{x}\left(\zeta;s,t\right),\omega_{\Phi}^{y}\left(\zeta;s,t\right),\omega_{\Phi}^{z}\left(\zeta;s,t\right)\right)=\text{constant} \tag{2.9}$$

and

$$C_{j}\left(\boldsymbol{\omega}_{j}\left(\zeta;s,t\right)\right)=C_{j}\left(\omega_{j}^{x}\left(\zeta;s,t\right),\omega_{j}^{y}\left(\zeta;s,t\right),\omega_{j}^{z}\left(\zeta;s,t\right)\right)=\text{constant} \tag{2.10}$$

whenever $0\leq s\leq 1$ and $0\leq t\leq 1$. As with any parameterization of a surface, there is an associated Jacobian, which we denote

$$\mathrm{Jac}_{\Phi}\left(\zeta;s,t\right) \tag{2.11}$$

for $\Omega_{\Phi}\left(\zeta\right)$ and

$$\mathrm{Jac}_{j}\left(\zeta;s,t\right) \tag{2.12}$$

for $\Omega_{j}\left(\zeta\right)$. We define $A_{\Phi}\left(\zeta\right)$ and $A_{j}\left(\zeta\right)$ to be the areas of $\Omega_{\Phi}\left(\zeta\right)$ and $\Omega_{j}\left(\zeta\right)$, respectively; that is,

$$A_{\Phi}\left(\zeta\right)=\iint\mathrm{Jac}_{\Phi}\left(\zeta;s,t\right)dsdt \tag{2.13}$$

and

$$A_{j}\left(\zeta\right)=\iint\mathrm{Jac}_{j}\left(\zeta;s,t\right)dsdt. \tag{2.14}$$

(Here and in the following, we suppress the range of integration over s and t since it is always from 0 to 1.) Next we define

$$\phi(\zeta) = \Phi(\Omega_\Phi(\zeta)) \tag{2.15}$$

and

$$c_j(\zeta) = C_j(\Omega_j(\zeta)). \tag{2.16}$$

By the indexing scheme, these functions are continuous in ζ and we will further assume they are in $C^1[0,d]$ (that is, they have a continuous first derivative on the interval $(0,d)$).

Before continuing, we need a lemma.

Lemma 2.1 *Let*

$$h(\zeta) = \frac{1}{A(\zeta)} \int_{\Omega(\zeta)} f \tag{2.17}$$

for some function $f(x,y,z)$ where $A(\zeta)$ is the surface area of the surface

$$\Omega(\zeta) = \{\boldsymbol{\omega}(\zeta;s,t) = (\omega^x(\zeta;s,t), \omega^y(\zeta;s,t), \omega^z(\zeta;s,t)) \mid 0 \le s,t \le 1\}. \tag{2.18}$$

Then

$$\begin{aligned} h'(\zeta) &= \frac{1}{A(\zeta)} \iint \nabla f \cdot \frac{\partial \boldsymbol{\omega}}{\partial \zeta}(\zeta;s,t)\,\mathrm{Jac}(\zeta;s,t)\,dsdt \\ &\quad + \frac{1}{A(\zeta)} \iint f(\boldsymbol{\omega}(\zeta;s,t)) \frac{\partial\,\mathrm{Jac}}{\partial \zeta}(\zeta;s,t)\,dsdt \\ &\quad - \frac{A'(\zeta)}{A(\zeta)^2} \iint f(\boldsymbol{\omega}(\zeta;s,t))\,\mathrm{Jac}(\zeta;s,t)\,dsdt \end{aligned} \tag{2.19}$$

where $\mathrm{Jac}\left(\zeta; s, t\right)$ *is the Jacobian of the parameterization of* $\Omega\left(\zeta\right)$*,*

$$\nabla f = \left(\frac{\partial f}{\partial x}, \frac{\partial f}{\partial y}, \frac{\partial f}{\partial z}\right), \tag{2.20}$$

and

$$\frac{\partial \boldsymbol{\omega}}{\partial \zeta}\left(\zeta; s, t\right) = \left(\frac{\partial \omega^x}{\partial \zeta}\left(\zeta; s, t\right), \frac{\partial \omega^y}{\partial \zeta}\left(\zeta; s, t\right), \frac{\partial \omega^z}{\partial \zeta}\left(\zeta; s, t\right)\right). \tag{2.21}$$

Furthermore, if

$$f\left(\Omega\left(\zeta\right)\right) = \mathit{constant} \tag{2.22}$$

for all $0 \leq \zeta \leq d$*, then*

$$h'\left(\zeta\right) = \frac{1}{A\left(\zeta\right)} \iint \nabla f \cdot \frac{\partial \boldsymbol{\omega}}{\partial \zeta}\left(\zeta; s, t\right) \mathrm{Jac}\left(\zeta; s, t\right) dsdt. \tag{2.23}$$

Proof. By the differentiating under the integral sign,

$$\begin{aligned} h'\left(\zeta\right) &= \frac{1}{A\left(\zeta\right)} \iint \frac{\partial}{\partial \zeta}\left[f\left(\boldsymbol{\omega}\left(\zeta; s, t\right)\right) \mathrm{Jac}\left(\zeta; s, t\right)\right] dsdt \\ &\quad - \frac{A'\left(\zeta\right)}{A\left(\zeta\right)} \iint f\left(\boldsymbol{\omega}\left(\zeta; s, t\right)\right) \mathrm{Jac}\left(\zeta; s, t\right) dsdt. \end{aligned} \tag{2.24}$$

Then

$$\begin{aligned} &\frac{\partial}{\partial \zeta}\left[f\left(\boldsymbol{\omega}\left(\zeta; s, t\right)\right) \mathrm{Jac}\left(\zeta; s, t\right)\right] \\ = {}& \nabla f \cdot \frac{\partial \boldsymbol{\omega}}{\partial \zeta}\left(\zeta; s, t\right) \mathrm{Jac}\left(\zeta; s, t\right) + f\left(\boldsymbol{\omega}\left(\zeta; s, t\right)\right) \frac{\partial \, \mathrm{Jac}}{\partial \zeta}\left(\zeta; s, t\right) \end{aligned} \tag{2.25}$$

and the first formula follows. If

$$f\left(\Omega\left(\zeta\right)\right) = \text{constant}, \tag{2.26}$$

then

$$\begin{aligned}&\iint f\left(\boldsymbol{\omega}\left(\zeta;s,t\right)\right)\frac{\partial\,\mathrm{Jac}}{\partial\zeta}\left(\zeta;s,t\right)dsdt-\frac{A'\left(\zeta\right)}{A\left(\zeta\right)}\iint f\left(\boldsymbol{\omega}\left(\zeta;s,t\right)\right)\mathrm{Jac}\left(\zeta;s,t\right)dsdt\\ =\;& f\left(\Omega\left(\zeta\right)\right)\left[\iint\frac{\partial\,\mathrm{Jac}}{\partial\zeta}\left(\zeta;s,t\right)dsdt-\frac{A'\left(\zeta\right)}{A\left(\zeta\right)}\iint\mathrm{Jac}\left(\zeta;s,t\right)dsdt\right]. \qquad (2.27)\end{aligned}$$

Since

$$A\left(\zeta\right)=\iint\mathrm{Jac}\left(\zeta;s,t\right)dsdt \qquad (2.28)$$

and thus

$$A'\left(\zeta\right)=\iint\frac{\partial\,\mathrm{Jac}}{\partial\zeta}\left(\zeta;s,t\right)dsdt, \qquad (2.29)$$

the two integrals are equal and the lemma follows. ■

We can now start averaging the three-dimensional equations to arrive at one-dimensional ones.

2.2.1 Reducing the Nernst-Planck Equations

To reduce the Nernst-Planck equations from three to one dimensions, we will average each Nernst-Planck equation over $\Omega_j\left(\zeta\right)$. We start by taking the dot product of both sides with the vector $\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta}$:

$$-\mathbf{J}_j\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta}=D_j\left(\nabla C_j\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta}+\frac{z_je}{kT}C_j\nabla\Phi\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta}\right) \qquad (2.30)$$

Next define

$$\bar{D}_j\left(\zeta\right)=\frac{1}{A_j\left(\zeta\right)}\int_{\Omega_j(\zeta)}D_j \qquad (2.31)$$

$$E_{D_j}\left(\boldsymbol{\omega}_j\left(\zeta;s,t\right)\right) = D_j\left(\boldsymbol{\omega}_j\left(\zeta;s,t\right)\right) - \bar{D}_j\left(\zeta\right) \tag{2.32}$$

$$E_{\Phi}\left(\zeta\right) = \phi\left(\zeta\right) - \frac{1}{A_j\left(\zeta\right)}\int_{\Omega_j(\zeta)}\Phi. \tag{2.33}$$

Then, by Lemma 2.1,

$$\begin{aligned}
\phi'\left(\zeta\right) - E'_{\Phi}\left(\zeta\right) &= \frac{d}{d\zeta}\frac{1}{A_j\left(\zeta\right)}\int_{\Omega_j(\zeta)}\Phi && (2.34)\\
&= \frac{1}{A_j\left(\zeta\right)}\iint \nabla\Phi\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta}\left(\zeta;s,t\right)\mathrm{Jac}_j\left(\zeta;s,t\right)dsdt + F_{\Phi}\left(\zeta\right) && (2.35)\\
&= \frac{1}{A_j\left(\zeta\right)}\int_{\Omega_j(\zeta)}\nabla\Phi\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta} + F_{\Phi}\left(\zeta\right) && (2.36)
\end{aligned}$$

where

$$\begin{aligned}
F_{\Phi}\left(\zeta\right) &= \frac{1}{A_j\left(\zeta\right)}\iint \Phi\left(\boldsymbol{\omega}\left(\zeta;s,t\right)\right)\frac{\partial\,\mathrm{Jac}_j}{\partial\zeta}\left(\zeta;s,t\right)dsdt && (2.37)\\
&\quad -\frac{A'_j\left(\zeta\right)}{A_j\left(\zeta\right)^2}\iint \Phi\left(\boldsymbol{\omega}\left(\zeta;s,t\right)\right)\mathrm{Jac}_j\left(\zeta;s,t\right)dsdt.
\end{aligned}$$

Taking the surface integral over $\Omega_j\left(\zeta\right)$ in (2.30), we get

$$\begin{aligned}
-\int_{\Omega_j(\zeta)}\mathbf{J}_j\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta} &= \bar{D}_j\left(\zeta\right)\left(\int_{\Omega_j(\zeta)}\nabla C_j\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta} + \frac{z_je}{kT}c_j\left(\zeta\right)\int_{\Omega_j(\zeta)}\nabla\Phi\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta}\right) && (2.38)\\
&\quad + \int_{\Omega_j(\zeta)}E_{D_j}\left(\boldsymbol{\omega}_j\left(\zeta;s,t\right)\right)\left(\nabla C_j\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta} + \frac{z_je}{kT}C_j\nabla\Phi\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta}\right)\\
&= \bar{D}_j\left(\zeta\right)A_j\left(\zeta\right)\left(c'_j\left(\zeta\right) + \frac{z_je}{kT}c_j\left(\zeta\right)\phi'\left(\zeta\right)\right) + E_j\left(\zeta\right) && (2.39)
\end{aligned}$$

where

$$\begin{aligned}
E_j\left(\zeta\right) &= \int_{\Omega_j(\zeta)}E_{D_j}\left(\boldsymbol{\omega}_j\left(\zeta;s,t\right)\right)\left(\nabla C_j\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta} + \frac{z_je}{kT}C_j\nabla\Phi\cdot\frac{\partial\boldsymbol{\omega}_j}{\partial\zeta}\right) && (2.40)\\
&\quad -\frac{z_je}{kT}\bar{D}_j\left(\zeta\right)A_j\left(\zeta\right)c_j\left(\zeta\right)\left[E'_{\Phi}\left(\zeta\right) + F_{\Phi}\left(\zeta\right)\right].
\end{aligned}$$

For the left-hand side of the Nernst-Planck equation, let

$$J_j = \int_{\Omega_j(\zeta)} \mathbf{J}_j \cdot \mathbf{n} \tag{2.41}$$

where $\mathbf{n}$ is the unit vector normal to $\Omega_j(\zeta)$ oriented in the positive ζ direction. This integral is the net flux of species j across $\Omega_j(\zeta)$ (with a positive sign if there is a net flux to the right, out of the channel) and since $\nabla \cdot \mathbf{J}_j = 0$ this flux is independent of ζ. Letting

$$E_{J_j}(\zeta) = J_j - \int_{\Omega_j(\zeta)} \mathbf{J}_j \cdot \frac{\partial \boldsymbol{\omega}_j}{\partial \zeta}, \tag{2.42}$$

we get the reduced Nernst-Planck equation

$$-J_j = D_j^*(\zeta)\, A_\Phi(\zeta) \left(c_j'(\zeta) + \frac{z_j e}{kT} c_j(\zeta)\, \phi'(\zeta) \right) + E_j(\zeta) - E_{J_j}(\zeta) \tag{2.43}$$

where

$$D_j^*(\zeta) = \bar{D}_j(\zeta)\, \frac{A_j(\zeta)}{A_\Phi(\zeta)}. \tag{2.44}$$

(The reason for this new definition of the diffusion coefficient is so that in the end we will only have one area function, namely $A_\Phi(\zeta)$.)

2.2.2 Reducing the Poisson Equation

Instead of averaging the Poisson equation, we rederive it starting with Maxwell's First Law: the flux of the electric field through any closed surface is equal to the total amount of charge inside the surface. For the surface we choose $\Omega_\Phi(\zeta + \Delta\zeta)$, $\Omega_\Phi(\zeta)$, and the segments on the lipid bilayer connecting them. Let $\mathbf{n}$ be the unit vector normal to this surface. On each $\Omega_\Phi(\xi)$ segment, let $\mathbf{n}(\Omega_\Phi(\xi))$ be the unit vector normal to $\Omega_\Phi(\xi)$ oriented outward of the closed surface. If we define

$$\bar{\epsilon}(\zeta) = \frac{1}{A_\Phi(\zeta)} \int_{\Omega_\Phi(\zeta)} \epsilon \tag{2.45}$$

and

$$E_\epsilon(\boldsymbol{\omega}_\Phi(\zeta; s, t)) = \epsilon(\boldsymbol{\omega}_\Phi(\zeta; s, t)) - \bar{\epsilon}(\zeta), \tag{2.46}$$

then

$$\begin{aligned}
\oint \epsilon \nabla\Phi \cdot \mathbf{n} &= \int_{\Omega_\Phi(\zeta+\Delta\zeta)} \epsilon \nabla\Phi \cdot \mathbf{n}(\Omega_\Phi(\zeta+\Delta\zeta)) + \int_{\Omega_\Phi(\zeta)} \epsilon \nabla\Phi \cdot \mathbf{n}(\Omega_\Phi(\zeta)) && (2.47)\\
&= \bar{\epsilon}(\zeta+\Delta\zeta) \int_{\Omega_\Phi(\zeta+\Delta\zeta)} \nabla\Phi \cdot \mathbf{n}(\Omega_\Phi(\zeta+\Delta\zeta)) && (2.48)\\
&\quad + \bar{\epsilon}(\zeta) \int_{\Omega_\phi(\zeta)} \nabla\Phi \cdot \mathbf{n}(\Omega_\Phi(\zeta))\\
&\quad + \int_{\Omega_\Phi(\zeta+\Delta\zeta)} E_\epsilon \nabla\Phi \cdot \mathbf{n}(\Omega_\Phi(\zeta+\Delta\zeta)) + \int_{\Omega_\Phi(\zeta)} E_\epsilon \nabla\Phi \cdot \mathbf{n}(\Omega_\Phi(\zeta)).
\end{aligned}$$

Let

$$G_\Phi(\zeta) = \begin{cases} \int_{\Omega_\Phi(\zeta)} \nabla\Phi \cdot \left[\frac{\partial\boldsymbol{\omega}_\Phi}{\partial\zeta} - \mathbf{n}(\Omega_\Phi(\zeta))\right] & \text{if } \mathbf{n}(\Omega_\Phi(\zeta)) \cdot \frac{\partial\boldsymbol{\omega}_\Phi}{\partial\zeta} > 0 \\ \int_{\Omega_\Phi(\zeta)} \nabla\Phi \cdot \left[\frac{\partial\boldsymbol{\omega}_\Phi}{\partial\zeta} + \mathbf{n}(\Omega_\Phi(\zeta))\right] & \text{otherwise} \end{cases} \tag{2.49}$$

Then

$$\begin{aligned}
\oint \epsilon \nabla\Phi \cdot \mathbf{n} &= \bar{\epsilon}(\zeta+\Delta\zeta) \int_{\Omega_\Phi(\zeta+\Delta\zeta)} \nabla\Phi \cdot \frac{\partial\boldsymbol{\omega}_\Phi}{\partial\zeta} - \bar{\epsilon}(\zeta) \int_{\Omega_\Phi(\zeta)} \nabla\Phi \cdot \frac{\partial\boldsymbol{\omega}_\Phi}{\partial\zeta} && (2.50)\\
&\quad + H_\Phi(\zeta+\Delta\zeta) - H_\Phi(\zeta)\\
&= \bar{\epsilon}(\zeta+\Delta\zeta) A_\Phi(\zeta+\Delta\zeta) \phi'(\zeta+\Delta\zeta) - \bar{\epsilon}(\zeta) A_\Phi(\zeta) \phi'(\zeta) && (2.51)\\
&\quad + H_\Phi(\zeta+\Delta\zeta) - H_\Phi(\zeta)
\end{aligned}$$

where

$$H_\Phi(\zeta) = \int_{\Omega_\Phi(\zeta)} E_\epsilon \nabla\Phi \cdot \mathbf{n}\left(\Omega_\Phi(\zeta)\right) \pm \bar{\epsilon}(\zeta)\, G_\Phi(\zeta). \tag{2.52}$$

(The choice of sign is determined by (2.49) and will soon become irrelevant.) As for the total charge inside the surface, it is

$$\sum_j z_j \int_\zeta^{\zeta+\Delta\zeta} \int_{\Omega_\Phi(\xi)} C_j d\xi + \int_\zeta^{\zeta+\Delta\zeta} \int_{\Omega_\Phi(\xi)} Q d\xi. \tag{2.53}$$

Letting

$$F_j(\zeta) = \frac{1}{A_\Phi(\zeta)} \int_{\Omega_\Phi(\zeta)} C_j - c_j(\zeta) \tag{2.54}$$

and

$$q(\zeta) = \frac{1}{A_\Phi(\zeta)} \int_{\Omega_\Phi(\zeta)} Q, \tag{2.55}$$

we have the total charge

$$\begin{aligned} &\sum_j z_j \int_\zeta^{\zeta+\Delta\zeta} A_\Phi(\xi)\, c_j(\xi)\, d\xi + \int_\zeta^{\zeta+\Delta\zeta} A_\Phi(\xi)\, q(\xi)\, d\xi \\ &+\sum_j z_j \int_\zeta^{\zeta+\Delta\zeta} A_\Phi(\xi)\, F_j(\xi)\, d\xi. \end{aligned} \tag{2.56}$$

Therefore we have

$$\begin{aligned} & \bar{\epsilon}(\zeta+\Delta\zeta)\, A_\Phi(\zeta+\Delta\zeta)\, \phi'(\zeta+\Delta\zeta) - \bar{\epsilon}(\zeta)\, A_\Phi(\zeta)\, \phi'(\zeta) \\ = & -\left[\sum_j z_j \int_\zeta^{\zeta+\Delta\zeta} A_\Phi(\xi)\, c_j(\xi)\, d\xi + \int_\zeta^{\zeta+\Delta\zeta} A_\Phi(\xi)\, q(\xi)\, d\xi\right] \\ & -\sum_j z_j \int_\zeta^{\zeta+\Delta\zeta} A_\Phi(\xi)\, F_j(\xi)\, d\xi - \left(H_\Phi(\zeta+\Delta\zeta) - H_\Phi(\zeta)\right). \end{aligned} \tag{2.57}$$

Expressing the left-hand side as

$$\begin{aligned}
&\overline{\epsilon}\left(\zeta+\Delta\zeta\right)A_{\Phi}\left(\zeta+\Delta\zeta\right)\phi'\left(\zeta+\Delta\zeta\right)-\overline{\epsilon}\left(\zeta\right)A_{\Phi}\left(\zeta+\Delta\zeta\right)\phi'\left(\zeta+\Delta\zeta\right)\\
&+\overline{\epsilon}\left(\zeta\right)A_{\Phi}\left(\zeta+\Delta\zeta\right)\phi'\left(\zeta+\Delta\zeta\right)-\overline{\epsilon}\left(\zeta\right)A_{\Phi}\left(\zeta+\Delta\zeta\right)\phi'\left(\zeta\right)\\
&+\overline{\epsilon}\left(\zeta\right)A_{\Phi}\left(\zeta+\Delta\zeta\right)\phi'\left(\zeta\right)-\overline{\epsilon}\left(\zeta\right)A_{\Phi}\left(\zeta\right)\phi'\left(\zeta\right),
\end{aligned} \tag{2.58}$$

dividing each side by $\Delta\zeta$, letting $\Delta\zeta\to 0$, and dividing by $A_{\Phi}\left(\zeta\right)$, we get the reduced Poisson equation

$$-\left(\overline{\epsilon}\left(\zeta\right)\phi'\left(\zeta\right)\right)'-\overline{\epsilon}\left(\zeta\right)\frac{A'_{\Phi}\left(\zeta\right)}{A_{\Phi}\left(\zeta\right)}\phi'\left(\zeta\right)=\sum_{j}z_jc_j\left(\zeta\right)+q\left(\zeta\right)+\sum_{j}z_jF_j\left(\zeta\right)-\frac{H'_{\Phi}\left(\zeta\right)}{A_{\Phi}\left(\zeta\right)}. \tag{2.59}$$

2.2.3 Summary

Above we derived the following reduced (one-dimensional) PNP equations for $0\leq x\leq d$:

$$\begin{aligned}
&-\left(\overline{\epsilon}\left(x\right)\phi'\left(x\right)\right)'-\overline{\epsilon}\left(x\right)\frac{A'_{\Phi}\left(x\right)}{A_{\Phi}\left(x\right)}\phi'\left(x\right)\\
=\;&\sum_{j}z_jc_j\left(x\right)+q\left(x\right)+\sum_{j}z_jF_j\left(x\right)-\frac{H'_{\Phi}\left(x\right)}{A_{\Phi}\left(x\right)}
\end{aligned} \tag{2.60}$$

$$-J_j=D^*_j\left(x\right)A_{\Phi}\left(x\right)\Big(c'_j\left(x\right)+\frac{z_je}{kT}c_j\left(x\right)\phi'\left(x\right)\Big)+E_j\left(x\right)-E_{J_j}\left(x\right) \tag{2.61}$$

$$\frac{dJ_j}{dx}=0 \tag{2.62}$$

where we have changed from using ζ to the more familiar x.

As they stand, this system is only true if the full three-dimensional problem has been solved. If the goal is to use these equations *instead* of solving the full three-dimensional problem, then we will need some further simplifying assumptions. Although we will not prove it, we claim that when the functions $\overline{\epsilon}\,(x)$, $D_j^*\,(x)$, $q\,(x)$, $A_\Phi\,(x)$, $H_\Phi\,(x)$, $E_j\,(x)$, $F_j\,(x)$, and $E_{J_j}\,(x)$ are given, then the system has at least one solution $(\phi\,(x)\,, c_j\,(x)\,, J_j)$ for a given set of bulk boundary conditions applied in the baths along the surfaces $\Omega_\Phi\,(0)$, $\Omega_\Phi\,(d)$, $\Omega_j\,(0)$, and $\Omega_j\,(d)$. (We claim this because we have a numerical solver for this case that seems always to give a solution.) These functions, however, depend on the equipotential and equiconcentration surfaces and thus are difficult to estimate. One way to get around this is to assume that the shapes of the equipotential and equiconcentration surfaces do not change much under different bath concentrations and applied voltages. Then, in the Poisson equation, the terms $q\,(x)+\sum_j z_j F_j\,(x)-\frac{H'_\Phi(x)}{A_\Phi(x)}$ can be combined into a new effective permanent charge term which may be recovered for individual channel types by data fitting current/voltage curves. If, further, the shapes of the equipotential and equiconcentration surfaces are assumed to be roughly the same and the diffusion coefficients to be roughly constant on them, then the terms $E_j\,(x)$ and $E_{J_j}\,(x)$ may be neglected. Although we will use these assumptions in this thesis, we do not assert they are numerically valid. It is important that they be verified by averaging the numerical solutions of the full three dimensional system. We do not do so here because it is not feasible at the present time. Since, however, the usual PNP equations are recovered for the case when A is constant, this analysis does include one case of interest.

With these assumptions, we get the final reduced PNP system for $0 \le x \le d$ (cast in slightly different variables) that we will use in this thesis to model the transport of ions through open channels:

$$-\left(\epsilon\,(x)\,\phi'\,(x)\right)' - \epsilon\,(x)\,\frac{A'\,(x)}{A\,(x)}\phi'\,(x) = \sum_j z_j c_j\,(x) + q\,(x) \tag{2.63}$$

$$-J_j = D_j\,(x)\,A\,(x)\left(c'_j\,(x) + \frac{z_j e}{kT} c_j\,(x)\,\phi'\,(x)\right) \tag{2.64}$$

$$\frac{dJ_j}{dx} = 0 \tag{2.65}$$

where we assume $\epsilon(x)$, $D_j(x)$, $q(x)$, and $A(x)$ are given. For the boundaries, we define

$$c_L = \sum_{z_j=+1} c_j(0) = \sum_{z_j=-1} c_j(0) \qquad c_R = \sum_{z_j=+1} c_j(d) = \sum_{z_j=-1} c_j(d) \tag{2.66}$$

$$V = \phi(0) - \phi(d). \tag{2.67}$$

In this form, these equations are the same as for the funnel model used in [36].

2.3 Scaling the System

As described in Section 3.2.2, the first step in singular perturbation theory is to nondimensionalize (or scale) the system being considered. As in that section, we will use tildes to denote variables with units of measurement:

$$-\left(\tilde{\epsilon}(\tilde{x})\,\tilde{\phi}'(\tilde{x})\right)' - \frac{\tilde{A}'(\tilde{x})}{\tilde{A}(\tilde{x})}\tilde{\phi}'(\tilde{x}) = \sum_j z_j\tilde{c}_j(\tilde{x}) + \tilde{q}(\tilde{x}) \tag{2.68}$$

$$-\tilde{J}_j = \tilde{D}_j(\tilde{x})\,\tilde{A}(\tilde{x})\left(\tilde{c}_j'(\tilde{x}) + \frac{z_j e}{kT}\tilde{c}_j(\tilde{x})\,\tilde{\phi}'(\tilde{x})\right) \tag{2.69}$$

$$\frac{d\tilde{J}_j}{d\tilde{x}} = 0 \tag{2.70}$$

$$\tilde{c}_L = \sum_{z_j=+1} \tilde{c}_j(0) = \sum_{z_j=-1} \tilde{c}_j(0) \qquad c_R = \sum_{z_j=+1} \tilde{c}_j\left(\tilde{d}\right) = \sum_{z_j=-1} \tilde{c}_j\left(\tilde{d}\right) \tag{2.71}$$

$$\tilde{V} = \tilde{\phi}(0) - \tilde{\phi}\left(\tilde{d}\right). \tag{2.72}$$

We scale as follows:

$$\tilde{x} = x \cdot \tilde{d} \qquad \tilde{\phi} = \phi \cdot \frac{kT}{e} \qquad \tilde{c}_j = c_j \cdot \tilde{C} \tag{2.73}$$

$$\tilde{\epsilon} = \epsilon \cdot \tilde{\epsilon}_0 \epsilon_{\max} \qquad \tilde{D}_j = D_j \cdot \tilde{D}_{\max} \qquad \tilde{A} = A \cdot \tilde{d}^2 \qquad \tilde{J}_j = J_j \cdot \tilde{d}\tilde{C}\tilde{D}_{\max} \tag{2.74}$$

where $\tilde{\epsilon}_0$ is the permittivity of vacuum and

$$\epsilon_{\max} = \sup_{\tilde{x}} \left\{ \frac{\tilde{\epsilon}(\tilde{x})}{\tilde{\epsilon}_0} \right\} \qquad \tilde{D}_{\max} = \max_j \left\{ \sup_{\tilde{x}} \tilde{D}_j(\tilde{x}) \right\} \tag{2.75}$$

$$\tilde{C} = \max \left\{ \sup_{\tilde{x}} |\tilde{q}(\tilde{x})|, \tilde{c}_L, \tilde{c}_R \right\}. \tag{2.76}$$

The system then becomes

$$-\varepsilon^2 \left[(\epsilon(x)\phi'(x))' + \frac{A'(x)}{A(x)}\phi'(x) \right] = \sum_j z_j c_j(x) + q(x) \tag{2.77}$$

$$-J_j = D_j(x) A(x) \left(c_j'(x) + z_j c_j(x) \phi'(x) \right) \tag{2.78}$$

$$c_L = \sum_{z_j=+1} c_j(0) = \sum_{z_j=-1} c_j(0) \qquad c_R = \sum_{z_j=+1} c_j(d) = \sum_{z_j=-1} c_j(d) \tag{2.79}$$

$$V = \phi(0) - \phi(d). \tag{2.80}$$

where $0 \leq x \leq 1$ and

$$\varepsilon = \sqrt{\frac{\epsilon_{\max}\tilde{\epsilon}_0 kT}{e^2\tilde{d}^2\tilde{C}}}. \tag{2.81}$$

For the remainder of this thesis we will assume $\varepsilon \ll 1$.

As always, the scaling chosen here is not unique. For example, one can scale the potential with the applied potential V instead of $\frac{kT}{e}$. This becomes important when $|V| \gg \frac{kT}{e} \approx 25\text{mV}$. This change in the potential scaling factor, however, does not change any of the results we will derive since $V \sim \frac{kT}{e}$ for channels. Furthermore, we are not aware of any other scalings that would change the results or extend their range of validity. Here we consider the small voltages usually used in experiments.

As for the choice of using ε as the perturbation parameter, it is a natural one to make for channels since it tends to be small for channels. It is also the parameter that is used when similar equations for semiconductors are expanded (see, for example, [42] and [53]). There are also other approaches possible. In [49] Syganow and von Kitzing, for example, use a completely different parameter. Although they do not explicitly state so, they use the perturbation parameter

$$\delta = \max_{x,j}\left\{\left|\frac{c_j'(x)}{c_j(x)\,\phi'(x)}\right|\right\} \tag{2.82}$$

to reach the drift limit of the PNP equations (that is, when contributions from diffusion are small). In this case, which is applicable when V is large enough, they derive some approximate current/voltage relations.

2.4 Mathematical Assumptions

Before getting to the actual pertubation approximation of this system, we list the mathematical assumptions we will use throughout this thesis in order to have reasonably simple results. First, however, we must understand what the averaging process has done to the smoothness of the functions we will be using. In (2.31) (along with (2.44)), (2.45), and (2.55) we defined new, one-dimensional versions of the diffusion coefficients, dielectric coefficient, and permanent charge, respectively. These were defined as averages over the equipotential surfaces. Because of that averaging they are always at least continuous functions, even if the original, three-dimensional function they are approximating are discontinuous; taking the integral guarantees that. Furthermore, the smoothness of these functions (that is, how many derivatives they have with respect to ζ, to use the variable with which they were originally defined) is determined solely by the smoothness of the geometry of the channel and, again, not by the original, three-dimensional function. This is especially important for the dielectric coefficient since, in three dimensions, it is usually approximated as discontinuous with different values in the baths, protein, channel pore, and lipid and such discontinuities have large impacts on the electric field. However, in its new, one-dimensional version, this function is at the very least continuous. (Below we will insist that it must have a continuous first derivative.)

We now come to the mathematical assumptions we use throughout this thesis:

- $D_j\left(x\right)$ is piecewise constant for all species j
- $q\left(x\right)$ is piecewise constant
- $\epsilon\left(x\right)$ is in $C^1\left[0,1\right]$; that is, it has a continuous first derivative (with appropriate one-sided derivatives at the points 0 and 1)
- $A\left(x\right)$ is in $C^1\left[0,1\right]$

Note that these assumptions are only applied to functions that are given before the problem is solved; they are not assumptions about the actual solutions. These assumptions are made so we can approximate a reasonably general channel by a composite of step functions as shown in Figure 4-3 on page 68. These assumptions do not describe the most general possible case; nonetheless they include a great deal more than the case of constant fixed charge, and they certainly allow a wide range of behavior, including all that semiconductor diodes can have.

The first two assumptions go against what we just discussed about the smoothness of these functions. These assumptions are, however, necessary for the mathematics to be tractable and the results to come out in any sort of nice way. That having been said, these approximations are probably not too bad since these functions ($D_j(x)$ and $q(x)$) are required to go from bath values to channel values quickly if the orginal, three-dimensional functions were also piecewise constant.

These assumptions will be used throughout this thesis. When other assumptions are required for a specific section or chapter they will be stated there.

2.5 Regularity of the Solutions

In this section we briefly consider the regularity (smoothness) of the solution functions ϕ, n, and p. Throughout this thesis we assume that q, D_n, and D_p are piecewise constant and that ϵ is C^1.

Theorem 2.2 *Assume q and the D_j are piecewise continuous functions and ϵ and A are C^1 functions on $[0,1]$. Then ϕ is C^1 in $[0,1]$ with ϕ'' having jump discontinuities where q does. Furthermore, each c_j is continuous in $[0,1]$ and is C^1 everywhere except where D_j and q are discontinuous.*

Proof. We start by noting that the worst discontinuity any of the functions ϕ'', ϕ', c_j', and c_j can have is a jump discontinuity since all the other functions have, at worst, a jump discontinuity. It immediately follows that ϕ' and the c_j are continuous on $[0,1]$. Furthermore, since ϵ' and A' are continuous on $[0,1]$, it follows that ϕ'' must have a jump discontinuity where q does and is continuous otherwise. Also, at any point x that is not a point of discontinuity of D_j or q, there is a neighborhood in which we can differentiate the Nernst-Planck equation for species j and therefore c_j'' exists at x and the c_j' are continuous as x. ■

Chapter 3

A Primer on Singular Perturbation Theory

The work in this thesis uses a mathematical theory called Singular Perturbation (SP). The purpose of this chapter is to introduce the reader to the basics of SP by means of an example.

3.1 Introduction

SP is a well-used and proven approximation technique, dating to the turn of the century when it was first applied to fluid dynamics. Later, SP was applied to quantum mechanics [4] and semiconductor modeling ([42], [53]) and is still used to study a wide range of problems. References [4], [28], and [39] are textbooks on SP with many examples of applications. A history of SP is given in [38]. Some current papers using SP can be found at the Society for Industrial and Applied Mathematics web site [46]. The idea behind SP is that a problem (usually a differential equation and its boundary conditions) with a small parameter (call it ε) is just a "perturbation" of the same problem without the parameter (that is, the problem with $\varepsilon = 0$) plus successive "correction" terms. These correction terms result from breaking the problem up into a hierarchy of subproblems, which in many cases have physical interpretations (for an example see [41]). What is especially important to the average scientist is that this hierarchy of subproblems comes from a systematic method. Since there is then little intuition (a.k.a. guessing) involved, there are no accidentally dropped terms and answers are complete.

One of the strengths of SP is that few terms (usually) need to be calculated. The first correction term is usually ε times an "order 1" function (a function that never gets very large), the second correction term usually ε^2 times another order 1 function, and so on. Since ε is small, each successive power of ε is smaller than the previous and thus successive correction terms make smaller and smaller contributions. An excellent approximation can be reached very quickly, many times even without any correction terms; that is, the solution to the unperturbed problem by itself can be an adequate approximation.

The perturbation series produced by SP is a generalization of the familiar Taylor series. The difference between the two comes from the choice of the expansion parameter: in a Taylor series the expansion variable is a location or time, while in a perturbation series it is often a parameter of the problem. For example, if we expand an appropriately smooth function $f(x)$ in a Taylor series around the point x_0, the resulting series has the form

$$f(x) = \sum_{k=0}^{\infty} a_k (x - x_0)^k \tag{3.1}$$

where the coefficients a_k are constants. On the other hand, the perturbation expansion with parameter ε is

$$f(x) = \sum_{k=0}^{\infty} a_k(x)\, \varepsilon^k \tag{3.2}$$

where the coefficients a_k are now functions of x. A major difference (although not necessarily a drawback) is that perturbation series are rarely convergent. Instead they are asymptotic to the function $f(x)$. To explain the difference, consider the error after $N+1$ terms in the series:

$$R_N(x) = f(x) - \sum_{k=0}^{N} a_k(x)\,\varepsilon^k. \tag{3.3}$$

In order for the series to converge it is necessary (although not sufficient) for $R_N(x) \to 0$ as $N \to \infty$ for each x. On the other hand, if the series if asymptotic to $f(x)$ as $\varepsilon \to 0$, written

$$f(x) \sim \sum_{k=0}^{\infty} a_k(x)\,\varepsilon^k \qquad (\varepsilon \to 0)\,, \tag{3.4}$$

then, by definition, for each N the remainder $R_N(x)$ goes to 0 faster than ε^N as $\varepsilon \to 0$; that is,

$$\lim_{\varepsilon \to 0} \frac{R_N(x)}{\varepsilon^N} = 0 \qquad (N \text{ fixed})\,. \tag{3.5}$$

Then the remainder $R_N(x)$ is much smaller than the last retained term as $\varepsilon \to 0$, but it is not necessary for $R_N(x)$ to go to 0 as N goes to ∞. (Another way to say it is that for a fixed x the addition of more terms gives a better and better approximation (smaller error) for a convergent series, while for an asymptotic series, the better approximation comes from taking smaller and smaller ε.) This subtle difference has important implications, however. To illustrate that, consider the function

$$f(x) = \frac{1}{1-x}\operatorname{erf}\left(\frac{1}{\varepsilon}\right) \tag{3.6}$$

where

$$\operatorname{erf}(y) = 1 - \frac{2}{\sqrt{\pi}}\int_y^{\infty} \exp\left(-t^2\right) dt \tag{3.7}$$

is the Error function (see, for example, [56]). Then the Taylor expansion of $f(x)$ is

$$f(x) = \operatorname{erf}\left(\frac{1}{\varepsilon}\right)\sum_{k=0}^{\infty} x^k \tag{3.8}$$

which converges for when $|x| < 1$ and is useless when $|x| \geq 1$. The perturbation expansion of $f(x)$ is

$$f(x) \sim \frac{1}{1-x}\left(1 - \frac{\exp\left(-\varepsilon^{-2}\right)}{\sqrt{\pi}}\sum_{k=1}^{\infty}(-1)^{k-1}\frac{1\cdot 3\cdot 5\cdots(2k-3)}{2^{k-1}}\varepsilon^{2k-1}\right) \qquad (\varepsilon \to 0) \tag{3.9}$$

which is divergent (apply the ratio test to check) but is asymptotic to $f(x)$ for all x. (A derivation of this series expansion for erf may be found in [28].) The power of the expansion in ε is now obvious: (3.8) is only valid when x is small, while (3.9) is valid for all x. In other words, the Taylor series is a local approximation (near $x = 0$), while the perturbation series is a global approximation (valid for all x). Furthermore, these properties are true generally for these types of series and therefore the perturbation expansion can have great advantages over the more traditional method of Taylor expansions.

One might worry about using a divergent series to approximate anything. The answer is that typically the terms of an asymptotic series get smaller for a while and eventually, because the series diverges, become larger and larger. Just like the first few terms in a convergent series are a good approximation, those terms that are still getting smaller are a good approximation to the function. Unlike a convergent series, however, there is a limit to the accuracy of the approximation (for a given ε) since after a while adding more terms in the asymptotic series makes the error worse. (An algorithm for optimal truncation of asymptotic series is discussed in [4].)

Next, we turn to an example to discuss some of the finer details of implementing an SP expansion.

3.2 Enzyme Kinetics as an Example

3.2.1 Setting Up the Problem

We use the Michaelis-Menton theory of enzyme kinetics to illustrate the basic methods of SP. (The following mathematical discussion is a modified version of what appears in [39]. A detailed exposition of Michaelis-Menton theory from the chemistry point of view may be found in [48].) We consider a chemical reaction initiated at time zero that converts substrate S into product P with a single enzyme E:

$$S + E \underset{\tilde{k}_{-1}}{\overset{\tilde{k}_1}{\rightleftarrows}} SE \overset{\tilde{k}_2}{\rightarrow} P + E \tag{3.10}$$

where SE is an intermediate substrate/enzyme complex and where the rate constants $\tilde{k}_i$ are independent of reactant concentration. Let $\tilde{s}, \tilde{e}, \tilde{c}$, and $\tilde{p}$ be the concentrations of S, E, SE, and P, respectively. (The tildes ($\tilde{\ }$) indicate that these quantities are dimensional; that is, they have units, such as moles per liter for the concentrations. They will soon be gone.) We adopt the customary *ad hoc* constraint that almost none of P reverts to the initial substrate S. This assumption holds at the initial stages of the reaction before the concentration of P becomes appreciable. An in-depth mathematical analysis of this reaction requires derivation of this constraint instead of assuming it.

The equations governing this reaction are

$$\frac{d\tilde{s}}{d\tilde{t}} = -\tilde{k}_1\tilde{s}\tilde{e} + \tilde{k}_{-1}\tilde{c} \tag{3.11}$$

$$\frac{d\tilde{e}}{d\tilde{t}} = -\tilde{k}_1\tilde{s}\tilde{e} + \left(\tilde{k}_{-1} + \tilde{k}_2\right)\tilde{c} \tag{3.12}$$

$$\frac{d\tilde{c}}{d\tilde{t}} = \tilde{k}_1\tilde{s}\tilde{e} - \left(\tilde{k}_{-1} + \tilde{k}_2\right)\tilde{c} \tag{3.13}$$

$$\frac{d\tilde{p}}{d\tilde{t}} = \tilde{k}_2\tilde{c}. \tag{3.14}$$

These are derived by considering the formation and destruction of each species. For example, the rate of formation of SE is $\tilde{k}_1\tilde{s}\tilde{e}$ while the rate of breakdown of SE is $\left(\tilde{k}_{-1} + \tilde{k}_2\right)\tilde{c}$. The initial conditions, which represent the source of energy and matter for the equations, are

$$\tilde{s}(0) = \tilde{s}_0 > 0 \qquad \tilde{e}(0) = \tilde{e}_0 > 0 \tag{3.15}$$

($\tilde{s}_0$ and $\tilde{e}_0$ are the known initial concentrations)

$$\tilde{c}(0) = \tilde{p}(0) = 0 \tag{3.16}$$

(i.e., before the reaction there is no product or complex).

The system can be simplified by noting that

$$\frac{d\tilde{e}}{d\tilde{t}} + \frac{d\tilde{c}}{d\tilde{t}} = 0 \tag{3.17}$$

and

$$\frac{d\tilde{s}}{d\tilde{t}} + \frac{d\tilde{c}}{d\tilde{t}} + \frac{d\tilde{p}}{d\tilde{t}} = 0. \tag{3.18}$$

These, respectively, imply that

$$\tilde{e}\left(\tilde{t}\right) = \tilde{e}_0 - \tilde{c}\left(\tilde{t}\right) \tag{3.19}$$

and

$$\tilde{p}\left(\tilde{t}\right) = \tilde{s}_0 - \tilde{s}\left(\tilde{t}\right) - \tilde{c}\left(\tilde{t}\right). \tag{3.20}$$

Using these expressions for $\tilde{e}$ and $\tilde{p}$, we get the final (nonlinear) system

$$\frac{d\tilde{s}}{d\tilde{t}} = -\tilde{k}_1\tilde{e}_0\tilde{s} + \left(\tilde{k}_1\tilde{s} + \tilde{k}_{-1}\right)\tilde{c} \tag{3.21}$$

$$\frac{d\tilde{c}}{d\tilde{t}} = \tilde{k}_1\tilde{e}_0\tilde{s} - \left(\tilde{k}_1\tilde{s} + \tilde{k}_{-1} + \tilde{k}_2\right)\tilde{c} \tag{3.22}$$

with boundary conditions

$$\tilde{s}\left(0\right) = \tilde{s}_0 \qquad \tilde{c}\left(0\right) = 0. \tag{3.23}$$

It is these equations we will attempt to solve.

3.2.2 Scaling the System

The first step in SP is to nondimensionalize (or scale) the system by dividing each quantity by an appropriate scaling factor. This removes any dependence on which units of measurement are used. Only when this is done, is it possible to determine which quantities or parameters are small compared to others. There is more than one way to nondimensionalize any system, and one of the tricks in SP is to find a scaling that makes one parameter small as compared to everything else and that will remain small for the largest possible set of boundary conditions.

Here we scale by setting

$$t = \tilde{k}_1 \tilde{e}_0 \tilde{t} \qquad s(t) = \frac{1}{\tilde{s}_0} \tilde{s}\left(\frac{t}{\tilde{k}_1 \tilde{e}_0}\right) \qquad c(t) = \frac{1}{\tilde{e}_0} \tilde{c}\left(\frac{t}{\tilde{k}_1 \tilde{e}_0}\right). \tag{3.24}$$

The variables t, s, and c (without tildes) are now nondimensional (that is, independent of units of measurement). To see why this scaling is used, consider the two natural concentration sizes: the concentration of the substrate S and the concentration of the enzyme E. Since there cannot be more complex than enzyme, it therefore makes sense to scale the complex concentration by the known beginning enzyme concentration. Similarly, it is natural to scale the substrate concentration by its starting value. That leaves the question of how to scale the time variable. If we use the following intermediate scaling

$$t = t_{\text{scale}} \tilde{t} \qquad s(t) = \frac{1}{\tilde{s}_0} \tilde{s}\left(\frac{t}{t_{\text{scale}}}\right) \qquad c(t) = \frac{1}{\tilde{e}_0} \tilde{c}\left(\frac{t}{t_{\text{scale}}}\right), \tag{3.25}$$

we get

$$\tilde{s}_0 t_{\text{scale}} \frac{ds}{dt} = -\tilde{k}_1 \tilde{e}_0 \tilde{s}_0 s + \tilde{k}_1 \tilde{e}_0 \tilde{s}_0 \left(s + \frac{\tilde{k}_{-1}}{\tilde{k}_1 \tilde{s}_0}\right) c \tag{3.26}$$

$$\tilde{e}_0 t_{\text{scale}} \frac{d\tilde{c}}{d\tilde{t}} = \tilde{k}_1 \tilde{e}_0 \tilde{s}_0 s - \tilde{k}_1 \tilde{e}_0 \tilde{s}_0 \left(s + \frac{\tilde{k}_{-1} + \tilde{k}_2}{\tilde{k}_1 \tilde{s}_0}\right) c. \tag{3.27}$$

Therefore, defining

$$t_{\text{scale}} = \tilde{k}_1 \tilde{e}_0 \tag{3.28}$$

cleans up the equations nicely. (It should be noted that other scalings are possible. In [45], Segel and Slemrod introduce a scaling which results in the small parameter

$$\mu = \frac{\tilde{e}_0}{\tilde{s}_0 (1 + \kappa)} = \frac{\varepsilon}{1 + \kappa} \tag{3.29}$$

which has the advantage of being small when ε is small and when κ is large will therefore be valid for a larger range of parameters than the scaling we use here.) In order that our new scaled system of equations looks as simple as possible, we group several variable into nondimentional parameters:

$$\varepsilon = \frac{\tilde{e}_0}{\tilde{s}_0} \qquad \lambda = \frac{\tilde{k}_2}{\tilde{k}_1 \tilde{s}_0} \qquad \kappa = \frac{\tilde{k}_{-1} + \tilde{k}_2}{\tilde{k}_1 \tilde{s}_0} = \frac{K_M}{\tilde{s}_0} \tag{3.30}$$

where K_M is the Michaelis constant. The system of equations then becomes

$$\frac{ds}{dt} = -s + (s + \kappa - \lambda)\, c \tag{3.31}$$

$$\varepsilon \frac{dc}{dt} = s - (s + \kappa)\, c \tag{3.32}$$

with boundary conditions

$$s\,(0) = 1 \qquad c\,(0) = 0. \tag{3.33}$$

In most enzyme reactions the initial enzyme concentration is much less than the initial substrate concentration, or, mathematically, that $\varepsilon \ll 1$. This will be our small parameter.

3.2.3 Outer and Inner Solutions

The next step in SP is to state the form of the answer that is expected. It usually consists of two parts: an "outer" solution that describes the solution when t is far enough from 0 and an "inner" solution whose only contribution is very near $t = 0$ and is assumed to go to 0 very quickly. (The reason for the inner solution is a technical one: the outer solutions may not be able to reach the boundary values they need to, so the inner solutions are introduced to make up the difference. We will come back to this towards the end of the example.) For this problem we write,

$$s(t) = s_{\text{out}}(t) + S_{\text{in}}(\tau) \tag{3.34}$$

$$c(t) = c_{\text{out}}(t) + C_{\text{in}}(\tau) \tag{3.35}$$

where $\tau = \frac{t}{\varepsilon}$. ($\tau$ is called a stretched variable. Because ε is small, τ becomes large very quickly as t increases from 0 and thus it is a good variable to examine what happens when t is close to 0.) Substituting these into (3.31) and (3.32) we get

$$\begin{aligned} & \frac{ds_{\text{out}}}{dt} + \frac{1}{\varepsilon}\frac{dS_{\text{in}}}{d\tau} \\ = \; & -s_{\text{out}}(t) - S_{\text{in}}(\tau) + \left(s_{\text{out}}(t) + S_{\text{in}}(\tau)\right)\left(c_{\text{out}}(t) + C_{\text{in}}(\tau)\right) && (3.36) \\ & + (\kappa - \lambda)\left(c_{\text{out}}(t) + C_{\text{in}}(\tau)\right) \\ = \; & -s_{\text{out}}(t) - S_{\text{in}}(\tau) + s_{\text{out}}(t)\, c_{\text{out}}(t) + S_{\text{in}}(\tau)\, c_{\text{out}}(t) + s_{\text{out}}(t)\, C_{\text{in}}(\tau) && (3.37) \\ & + S_{\text{in}}(\tau)\, C_{\text{in}}(\tau) + (\kappa - \lambda)\, c_{\text{out}}(t) + (\kappa - \lambda)\, C_{\text{in}}(\tau) \end{aligned}$$

$$\begin{aligned} & \varepsilon\frac{dc_{\text{out}}}{dt} + \frac{dC_{\text{in}}}{d\tau} \\ = \; & s_{\text{out}}(t) + S_{\text{in}}(\tau) - \kappa\left(c_{\text{out}}(t) + C_{\text{in}}(\tau)\right) && (3.38) \\ & - \left(s_{\text{out}}(t) + S_{\text{in}}(\tau)\right)\left(c_{\text{out}}(t) + C_{\text{in}}(\tau)\right) \\ = \; & s_{\text{out}}(t) + S_{\text{in}}(\tau) - \kappa c_{\text{out}}(t) + \kappa C_{\text{in}}(\tau) - s_{\text{out}}(t)\, c_{\text{out}}(t) && (3.39) \\ & - S_{\text{in}}(\tau)\, c_{\text{out}}(t) - s_{\text{out}}(t)\, C_{\text{in}}(\tau) - S_{\text{in}}(\tau)\, C_{\text{in}}(\tau). \end{aligned}$$

Because the outer solutions are the solutions to the system when t is away from 0, they must satisfy the original system of equations; that is,

$$\frac{ds_{\text{out}}}{dt} = -s_{\text{out}} + \left(s_{\text{out}} + \kappa - \lambda\right) c_{\text{out}} \tag{3.40}$$

$$\varepsilon\frac{dc_{\text{out}}}{dt} = s_{\text{out}} - \left(s_{\text{out}} + \kappa\right) c_{\text{out}}. \tag{3.41}$$

The inner solutions are set to satisfy the rest:

$$\begin{aligned}\frac{1}{\varepsilon}\frac{dS_{\text{in}}(\tau)}{d\tau} &= -S_{\text{in}}(\tau) + c(\varepsilon\tau)\,S_{\text{in}}(\tau) + (s_{\text{out}}(\varepsilon\tau) + \kappa - \lambda)\,C_{\text{in}}(\tau) \\ &\quad + S_{\text{in}}(\tau)\,C_{\text{in}}(\tau)\end{aligned} \tag{3.42}$$

$$\frac{dC_{\text{in}}(\tau)}{d\tau} = S_{\text{in}}(\tau) - c(\varepsilon\tau)\,S_{\text{in}}(\tau) - (s_{\text{out}}(\varepsilon\tau) + \kappa)\,C_{\text{in}}(\tau) - S_{\text{in}}(\tau)\,C_{\text{in}}(\tau)\,. \tag{3.43}$$

The next step is to start approximating both the outer and inner solutions. This is usually done by expanding all the functions in powers of ε:

$$s_{\text{out}}(t) = s^{(0)}(t) + \varepsilon s^{(1)}(t) + \varepsilon^2 s^{(2)}(t) + \cdots \tag{3.44}$$

$$c_{\text{out}}(t) = c^{(0)}(t) + \varepsilon c^{(1)}(t) + \varepsilon^2 c^{(2)}(t) + \cdots \tag{3.45}$$

$$S_{\text{in}}(\tau) = S^{(0)}(\tau) + \varepsilon S^{(1)}(\tau) + \varepsilon^2 S^{(2)}(\tau) + \cdots \tag{3.46}$$

$$C_{\text{in}}(\tau) = C^{(0)}(\tau) + \varepsilon C^{(1)}(\tau) + \varepsilon^2 C^{(2)}(\tau) + \cdots\,. \tag{3.47}$$

This expresses the functions as the solution to the unperturbed problem (those terms with superscript (0)) plus correction terms. Substituting these into (3.40) – (3.43), multiplying the series, and equating all terms multiplied by the same power of ε, we get a hierarchy of systems:

first level

$$\frac{ds^{(0)}}{dt} = -s^{(0)} + \left(s^{(0)} + \kappa - \lambda\right) c^{(0)} \tag{3.48}$$

$$0 = s^{(0)} - \left(s^{(0)} + \kappa\right) c^{(0)} \tag{3.49}$$

$$\frac{dS^{(0)}}{d\tau} = 0 \tag{3.50}$$

$$\frac{dC^{(0)}}{d\tau} = S^{(0)} - c^{(0)}(0)\,S^{(0)} - \left(s^{(0)}(0) + \kappa\right) C^{(0)} - S^{(0)}C^{(0)} \tag{3.51}$$

second level

$$
\begin{aligned}
\frac{ds^{(1)}}{dt} &= -s^{(1)}+c^{(0)}s^{(1)}+\left(s^{(0)}+\kappa-\lambda\right)c^{(1)} && (3.52)\\
\frac{dc^{(0)}}{dt} &= s^{(1)}-c^{(0)}s^{(1)}-\left(s^{(1)}+\kappa\right)c^{(1)} && (3.53)\\
\frac{dS^{(1)}}{d\tau} &= -S^{(0)}+c^{(0)}\left(0\right)S^{(0)}+\left(s^{(0)}\left(0\right)+\kappa-\lambda\right)C^{(0)}+S^{(0)}C^{(0)} && (3.54)\\
\frac{dC^{(1)}}{d\tau} &= S^{(1)}-c^{(0)}\left(0\right)S^{(1)}-\left(\frac{dc^{(0)}}{dt}\left(0\right)\tau+c^{(1)}\left(0\right)\right)S^{(0)} && (3.55)\\
&\quad -\left(s^{(0)}\left(0\right)+\kappa\right)C^{(1)}-\left(\frac{ds^{(0)}}{dt}\left(0\right)\tau+s^{(1)}\left(0\right)+\kappa\right)C^{(0)}\\
&\quad -S^{(0)}C^{(1)}-S^{(1)}C^{(0)}
\end{aligned}
$$

and so on. For the boundary conditions we require that

$$s\left(0\right)=s^{(0)}\left(0\right)+S^{(0)}\left(0\right)\qquad c\left(0\right)=c^{(0)}\left(0\right)+C^{(0)}\left(0\right) \tag{3.56}$$

$$0=s^{(k)}\left(0\right)+S^{(k)}\left(0\right)\qquad 0=c^{(k)}\left(0\right)+C^{(k)}\left(0\right)\qquad \left(k\geq 1\right). \tag{3.57}$$

These may seem daunting at first, but they will reduce considerably. From the first two equations, we get

$$
\begin{aligned}
c^{(0)} &= \frac{s^{(0)}}{s^{(0)}+\kappa} && (3.58)\\
\frac{ds^{(0)}}{dt} &= -\frac{\lambda s^{(0)}}{s^{(0)}+\kappa}. && (3.59)
\end{aligned}
$$

The last one can be solved implicitly:

$$s^{(0)}\left(t\right)+\kappa\ln\left(s^{(0)}\left(t\right)\right)=s^{(0)}\left(0\right)+\kappa\ln\left(s^{(0)}\left(0\right)\right)-\lambda t. \tag{3.60}$$

Also, $\frac{dS^{(0)}}{d\tau} = 0$ along with the fact that inner solutions must go to 0 as $\tau \to \infty$ gives

$$S^{(0)} \equiv 0. \tag{3.61}$$

The boundary condition for s requires that

$$s^{(0)}(0) + S^{(0)}(0) = s(0) \tag{3.62}$$

Thus

$$s^{(0)}(0) = 1 \tag{3.63}$$

and we have

$$s^{(0)}(t) + \kappa \ln\left(s^{(0)}(t)\right) = 1 - \lambda t. \tag{3.64}$$

Also, now

$$\frac{dC^{(0)}}{d\tau} = -(1+\kappa)\, C^{(0)} \tag{3.65}$$

and thus

$$C^{(0)}(\tau) = \alpha \exp\left[-(1+\kappa)\,\tau\right] \tag{3.66}$$

where α is a constant of integration to be determined by the boundary condition

$$0 = c(0) = c^{(0)}(0) + C^{(0)}(0) = \frac{1}{1+\kappa} + \alpha. \tag{3.67}$$

Thus

$$C^{(0)}(\tau) = -\frac{1}{1+\kappa}\exp\left[-(1+\kappa)\tau\right]. \tag{3.68}$$

Notice that $C^{(0)}$ goes to 0 very fast so that any contribution of $C^{(0)}$ to the solution $C(t)$ is near $t = 0$. The equations also show that during the initial stages of the reaction, the complex concentration increases exponentially, while the substrate concentration varies much less quickly (since its inner solution $S^{(0)}$ turned out to be identically 0.) Having assumed that there was much more substrate than enzyme, this makes sense. We have now solved for all the unknown terms in the first level of the hierarchy. The next step is to take the first-level solutions, substitute them into the second-level equations, solve for the second-level solutions, and continue to the third level. We do not show this here since this is straight-forward and would not offer any more insight into the ideas behind SP.

Before continuing with the example, we give a short discussion of the inner solutions (also called boundary layers). At the beginning of the section we said that the inner solutions are there because the outer solutions cannot meet the boundary conditions of the problem. The reason for that is when ε is set to 0 in the first level of the hierarchy of equations, the term $\frac{dc_{\text{out}}}{dt}$ disappears (compare equations (3.41) and (3.49)). This loss of a derivative is the reason c_{out} cannot meet the boundary condition of c: for all differential equations, the order of the highest derivative sets the number of unknowns which are found by having the solution satisfy the boundary conditions. In this example, the order of the highest derivative for c_{out} was 1 (see equation (3.41)) and so there was one unknown. But after setting $\varepsilon = 0$, there were no derivatives of $c^{(0)}$ (see equation (3.49)) and therefore there are no unknowns. In other words, when we solved for $c^{(0)}(t)$ (equation (3.58)), $c^{(0)}(0)$ was already determined and unless we were very lucky, $c^{(0)}(0)$ would not equal the boundary condition of the original function c (equation (3.33)) as it must. Therefore, we needed an inner solution to make up the difference. By comparison, all the derivatives of the s terms

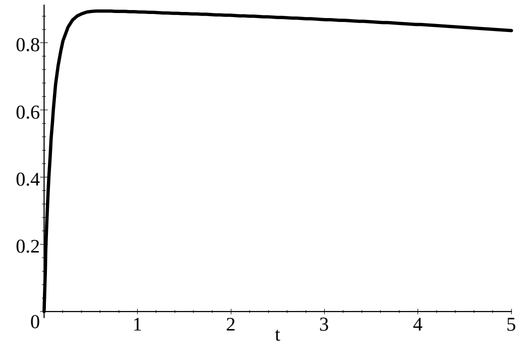

Figure 3-1: Concentration of complex vs. time for $\tilde{s}_0 = 10^{-2}M$ and $\tilde{e}_0 = 10^{-3}M$ with $\tilde{k}_1 = 10^6 M^{-1}s^{-1}$, $\tilde{k}_{-1} = 10^2 s^{-1}$, and $\tilde{k}_2 = 10^2 s^{-1}$. Because the rate constant $\tilde{k}_2$ is an order of magnitude smaller than in Figure 3-2, the complex dissociates much more slowly. In this case the heuristic approximation $\frac{dc}{dt} = 0$ is valid.

survived when $\varepsilon = 0$ and so $s^{(0)}$ could meet the s boundary condition. There was then no need for an inner solution, as was verified when we found that $S^{(0)} \equiv 0$.

3.2.4 The Results

To give a little flavor of the validity of these results, consider the Figures 3-1 and 3-2. They show the graphs of complex concentration (which is directly proportional to the rate of product production) as a function of time for

$$\tilde{s}_0 = 10^{-2}M \qquad \tilde{e}_0 = 10^{-3}M \tag{3.69}$$

$$\tilde{k}_1 = 10^6 M^{-1}s^{-1} \qquad \tilde{k}_{-1} = 10^2 s^{-1} \qquad \tilde{k}_2 = \begin{cases} 10^2 s^{-1} & \text{Figure 3-1} \\ 10^3 s^{-1} & \text{Figure 3-2.} \end{cases} \tag{3.70}$$

The graphs then show the expected qualitative features: in Figure 3-1, where the SE complex dissociates more slowly than in Figure 3-2, c quickly reaches a large maximum and very slowly returns to 0 (not shown on the time scale of the figure);

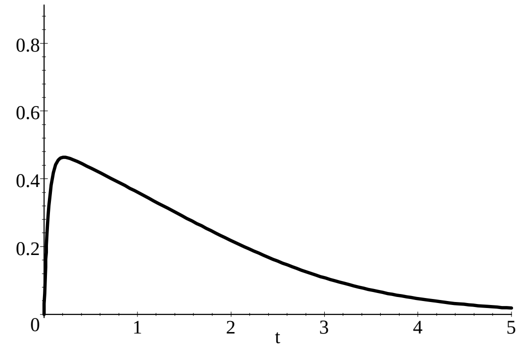

Figure 3-2: Concentration of complex vs. time for $\tilde{s}_0 = 10^{-2}M$ and $\tilde{e}_0 = 10^{-3}M$ with $\tilde{k}_1 = 10^6 M^{-1}s^{-1}$, $\tilde{k}_{-1} = 10^2 s^{-1}$, and $\tilde{k}_2 = 10^3 s^{-1}$. Now the reaction with rate constant $\tilde{k}_2$ is no longer rate-limiting and the heuristic approximation $\frac{dc}{dt} = 0$ is no longer valid.

there is a bottleneck in the process. When the complex dissociates more quickly there is less of a bottleneck and c still quickly reaches a maximum, but it is not as large, and it returns to 0 much more quickly. The graphs also nicely show the inner and outer solutions at work. The inner solution (a.k.a., layer function or boundary layer) is the sharp increases from 0 to the maximum near $t = 0$ and the outer solution is the part of the graph to the right of the maximum.

To conclude this example, we briefly discuss the biochemistry approach this problem. As argued in [48], biochemists assume a steady state exists such that the concentrations of intermediates stay the same while the concentrations of the starting materials change; that is, they assume

$$\frac{dc}{dt} = 0. \tag{3.71}$$

One might argue that that is essentially how we achieved (3.49) and so this is equivalent to considering the outer solutions and is valid if t is large. This, however, is not quite true, as illustrated in Figure 3-2. There is an implicit assumption that the reaction described by rate constant $\tilde{k}_2$ is the rate-limiting step in the process. When it is not, it is possible for c to never achieve a steady state and the heuristic argument breaks down (compare Figures 3-1 and 3-2).

The advantages of a systematic mathematical analysis over any heuristic argument, no matter how wise, should be clear. This is not to say that heuristic arguments are not of importance. They motivate the SP analysis and indicate what variables and conditions are important. Furthermore, they show what results the analysis is expected to give and are important for communicating with previous contributors to the field, particularly experimental biologists.

3.3 Concluding Thoughts on SP

This discussion was meant to illustrate the power of SP: because SP solves a problem very close to the original, at even the first level of the approximation the important features are already present. Furthermore, their formulations are relatively simple. It is important to note that these are properties of SP, and do not result from the choice of example. The equations in this example are nontrivial; they are nonlinear and there are no neat formulations for the functions s and c. In these respects they are very much like the PNP equations studied in this thesis.

SP, although a powerful method, comes with some caveats. The first of the three most important is that while SP gives excellent approximations to functions (such as c above), it sometimes does not give accurate approximations to the *derivative* of the function; in some problems the approximation to the function intersects the actual function many times and thus the derivatives at most points may not be close to those of the actual function. Therefore, when derivatives are the objects of interest, more analysis is necessary to ensure that information about them is accurate.

Secondly, many times it is difficult to know the size of error terms in an expansion. Thus it difficult to know how many terms in the perturbation series (as in equations (3.44) – (3.47)) constitute a "good" approximation. For example, as illustrated in Figure 7.7 of [4], increasing the number of terms (in that particular case from two to four) can increase the range of validity of the expansion an order of magnitude. This is one reason why one must always compare the SP approximation to the numerically calculated solution of the problem.

Lastly, for many problems it is difficult to know for what range of parameters the approximation is valid. For example, in the work in this thesis, we will find that when the bath concentrations become too small, the SP approximation is no longer close to the numerical solution. The parameter range for which an approximation is valid is a function both of the problem being studied and the choice of nondimensionalization and must be evaluated on a case-by-case basis, usually by comparing the approximation with the numerical solution of the problem.

In general, the direct checking of the validity of the approximation to numerical solutions serves another purpose: one can concentrate one's energy on the physical meaning of the problem and its approximations, which is after all what SP is good for. Therefore the exponential growth in computing power should produce a congruent growth in the utility and use of SP. It has done the former, but as far as we know unfortunately not the latter.

Chapter 4

Single Salt Case

In this chapter and the next we describe the singular perturbation expansion of the model derived in Chapter 2. We consider the cases of single and multiple salts in the baths seperately because the latter case is more difficult and yields less precise results.

The single salt case is considered in this chapter. By single salt we mean that the baths only contain, for example, NaCl or KCl but not a mixture of the two. That is to say, the baths are "electroneutral" with the concentration of cations (for example, Na^+ in a NaCl solution) equal to the concentration of anion (for example, Cl^- in a NaCl solution) everywhere in the bath, but not in the channel itself. Furthermore, throughout this chapter (and the next) we only consider the case of monovalent ion species (for example, Na^+, K^+, and Cl^-, but not Ca^{2+}). In this case, the transport equations become

$$-\varepsilon^2\left[(\epsilon\phi_x)_x + \epsilon\frac{A_x}{A}\phi_x\right] = n - p - q \tag{4.1}$$

$$-\frac{J_n}{D_n A} = n_x - n\phi_x \tag{4.2}$$

$$-\frac{J_p}{D_p A} = p_x - p\phi_x. \tag{4.3}$$

(Here we use the notation

$$f_x = f' = \frac{df}{dx} \tag{4.4}$$

because later we will use superscripts to index the expansions and thus this notation is more convenient.) For the boundary conditions we have

$$c_L = n(0) = p(0) \qquad c_R = n(1) = p(1) \tag{4.5}$$

$$V = \phi(0) - \phi(1). \tag{4.6}$$

Again, the functions q, D_n, and D_p are assumed to be piecewise constant on $[0,1]$. This is illustrated for q in Figure 4-3 (page 68). We use these boundary conditions because they correspond to the setup usually used in experiments. Note that they are not trivial to enforce. In particular, the chemical boundary conditions (4.5) are only satisfied approximately, because of the relatively small amount of current that flows through a single channel. For some types of channels (most notably Ca channels) it cannot be satisfied at all because the concentration on one side of a calcium channel is typically $10^{-8}M$ while the currents through a calcium channel can be quite large (100 pA). The electrical boundary condition (4.6) is enforced by a complicated electronic circuit in experimental situations. In real life, it is sometimes enforced by the properties of other channels, and active transport systems, but in so called "excitable" cells, like nerve fibers and skeletal muscle, the potential is not controlled at all. Indeed, the main role of channels in these cells is to change the potential and thereby carry and manipulate information. The central task of traditional physiology, epitomized by the work of Hodgkin and Huxley [24], was to show that channels existed and that their properties, studied under voltage clamp conditions account for all the physiological properties of nerve fibers and skeletal muscle fibers under NONvoltage clamp conditions. While this is certainly a proven case for K and Na channels, one might argue that it has not been proven for calcium channels because of the problems just mentioned in controlling or knowing local concentrations. Whether this lapse in rigor has any practical significance, either physiological or biophysical (or mathematical) is not known.

4.1 SP Expansion on an Interval with Constant Permament Charge

We first consider the subproblem of an expansion on the interval $[a, b]$. The results will be the basic building blocks for later sections.

In this section we will assume that the permanent charge q and the diffusion coefficients D_n and D_p are identically constant. That is, we consider one of the interals of $[0, 1]$ on which q, D_n, and D_p are constant (for example, (x_1, x_2) in Figure 4-3 on page 68). Furthermore, we assign arbitrary boundary conditions to the functions ϕ, n, and p:

$$f\left(a\right) = \beta_{L,f} \qquad f\left(b\right) = \beta_{R,f} \qquad \left(f = \phi, n, p\right). \tag{4.7}$$

This notation is shorthand to mean

$$\phi\left(a\right) = \beta_{L,\phi} \qquad \phi\left(b\right) = \beta_{R,\phi} \tag{4.8}$$

$$p\left(a\right) = \beta_{L,p} \qquad p\left(b\right) = \beta_{R,p} \tag{4.9}$$

$$n(a) = \beta_{L,n} \qquad n(b) = \beta_{R,n}. \tag{4.10}$$

To start we will do a major change of variables. The reason for this is that, depending on the sign of the permanent charge q, which ions are the counter-ions and which are the co-ions changes. With this change of variables, we will only have to do the problem once. Otherwise, we would have to do our analysis twice, once for positive fixed charge and once for negative. If there is only one region of permanent charge, then this is equivalent to doing the problem once for cation channels (in which the fixed charge is expected to be predominantly negative, because the permeating ions are predominantly positive, and are of course the counter-ions), and once for anion channels (in which the fixed charge is expected to be predominantly positive, because the permeating ions are predominantly negative, and are the counter-ions). For this purpose we define

$$u(x) = \begin{cases} n(x) - |q| & \text{if } q > 0 \\ p(x) - |q| & \text{if } q \leq 0 \end{cases} \qquad z_u = \begin{cases} -1 & \text{if } q > 0 \\ 1 & \text{if } q \leq 0 \end{cases} \tag{4.11}$$

$$J_u = \begin{cases} J_n & \text{if } q > 0 \\ J_p & \text{if } q \leq 0 \end{cases} \qquad D_u = \begin{cases} D_n & \text{if } q > 0 \\ D_p & \text{if } q \leq 0 \end{cases} \tag{4.12}$$

$$\beta_{L/R,u} = \begin{cases} \beta_{L/R,n} & \text{if } q > 0 \\ \beta_{L/R,p} & \text{if } q \leq 0 \end{cases}. \tag{4.13}$$

$$w(x) = \begin{cases} p(x) & \text{if } q > 0 \\ n(x) & \text{if } q \leq 0 \end{cases} \qquad z_w = \begin{cases} 1 & \text{if } q > 0 \\ -1 & \text{if } q \leq 0 \end{cases} \tag{4.14}$$

$$J_w = \begin{cases} J_p & \text{if } q > 0 \\ J_n & \text{if } q \leq 0 \end{cases} \qquad D_w = \begin{cases} D_p & \text{if } q > 0 \\ D_n & \text{if } q \leq 0 \end{cases} \tag{4.15}$$

$$\beta_{L/R,w} = \begin{cases} \beta_{L/R,p} & \text{if } q > 0 \\ \beta_{L/R,n} & \text{if } q \leq 0. \end{cases} \tag{4.16}$$

Intuitively, w and the variables with that subscript refer to the co-ions (those with the same sign as q). The variables with the u subscript refer to the counter-ions, while the function u itself is the difference between the permanent charge concentration and the counter-ion concentration. We expect the co-ions to be present in much smaller concentration than the counter-ions. They will be the minority carriers (in the language of semiconductors) because most of the ions will have the opposite charge from the fixed charge of the channel wall. The fixed charge of the channel wall will be balanced approximately by the mobile charge; otherwise a very large electrical potential will develop. To put it another way, in the time dependent generalization of the problem we are considering, mobile ions will flow to dramatically reduce such a potential. Roughly speaking one can expect only a small deviation (a few percent) from electroneutrality (that is, equality of the sum of mobile and fixed charges) and only a slightly larger deviation between the concentration of counter ions and fixed charge in regions away from the boundaries. At the boundaries, it is quite a different story. Depletion layers develop there that control the properties of many devices.

Next we make an assumption about the size of the area function A. Because the area function is expected to be much smaller inside the channel than in the baths, we assume $A = O\left(\varepsilon\right)$, and we define

$$A^{(1)} = \frac{A}{\varepsilon}. \tag{4.17}$$

Further, we assume $A^{(1)}$ is $O\left(1\right)$ while $\frac{A_x^{(1)}}{A^{(1)}} \ll \frac{1}{\varepsilon^2}$. This means that $A^{(1)}$ never gets very large (which is the same as saying that we only include a small part of the baths in our analysis) and that $A^{(1)}$ does not increase or decrease too quickly. Examples of acceptable and not acceptable functions $A^{(1)}$ are shown in Figure 4-1.

With these definitions the system becomes

$$-\varepsilon^2\left[(\epsilon\phi_x)_x+\epsilon\frac{A_x^{(1)}}{A^{(1)}}\phi_x\right]=z_u u+z_w w \tag{4.18}$$

$$-\frac{1}{\varepsilon}\frac{J_u}{D_u A^{(1)}}=u_x-z_u q_x+z_u u\phi_x-q\phi_x \tag{4.19}$$

$$-\frac{1}{\varepsilon}\frac{J_w}{D_w A^{(1)}}=w_x+z_w w\phi_x, \tag{4.20}$$

Similar to what we did in Section 3.2.3, we assume expansions of the following form:

$$f\left(x\right)=f_{\text{out}}\left(x\right)+F_L\left(\frac{x-a}{\varepsilon}\right)+F_R\left(\frac{b-x}{\varepsilon}\right)\qquad\left(f=\phi,u,w;F=\Phi,U,W\right). \tag{4.21}$$

Substituting these into (4.18) – (4.20) and multiplying out all the sums, we set the outer solutions to satisfy the original differential operator (4.18) – (4.20) (but not the boundary conditions) and the inner solutions to satisfy the remaining terms of this multiplication. Together they will meet the boundary conditions. For the left side, the inner solution equations are

$$-\frac{d}{d\zeta}\left(\hat{\epsilon}_L\frac{d\Phi_L}{d\zeta}\right)+\hat{\epsilon}_L\frac{\hat{A}_\zeta}{\hat{A}}\frac{d\Phi_L}{d\zeta}=z_u U_L+z_w W_L \tag{4.22}$$

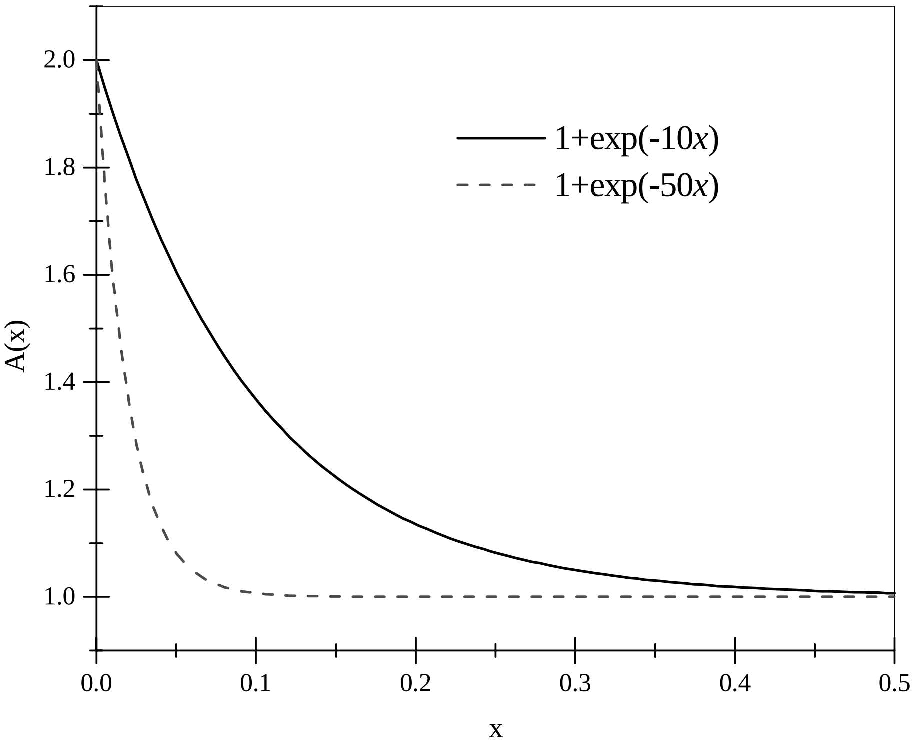

Figure 4-1: Examples of area functions $A^{(1)}$ that are and are not acceptable. The basic idea is that $A^{(1)}$ cannot suddenly become large, as one of the functions below. For this example, let $\varepsilon = 0.1$ and consider only the interval $[0, 0.5]$. The curve $A^{(1)}(x) = 1 + \exp(-10x)$ is acceptable because its derivative is at worst -10 and so $\left|\frac{A_x^{(1)}}{A^{(1)}}\right| \le 5 \ll \frac{1}{\varepsilon^2} = 100$. However, the curve $A^{(1)}(x) = 1 + \exp(-50x)$ is not acceptable because its derivative at $x = 0$ is -50 and so $\left|\frac{A_x^{(1)}(0)}{A^{(1)}(0)}\right| \le 25 \not\ll \frac{1}{\varepsilon^2} = 100$.

$$0 = \frac{dU_L}{d\zeta} + z_u U_L \frac{d\hat{\phi}_L}{d\zeta} + z_u \hat{u}_L \frac{d\Phi_L}{d\zeta} + z_u U_L \frac{d\Phi_L}{d\zeta} - q\frac{d\Phi_L}{d\zeta} \tag{4.23}$$

$$0 = \frac{dW_L}{d\zeta} + z_w W_L \frac{d\hat{\phi}_L}{d\zeta} + z_w \hat{w}_L \frac{d\Phi_L}{d\zeta} + z_w W_L \frac{d\Phi_L}{d\zeta} \tag{4.24}$$

where

$$\zeta = \frac{x-a}{\varepsilon} \tag{4.25}$$

and

$$\hat{f}_L(\zeta) = f(a+\varepsilon\zeta) \qquad (f = \epsilon, u, w)\,. \tag{4.26}$$

For the right side the equations are

$$-\frac{d}{dX}\left(\hat{\epsilon}_R \frac{d\Phi_R}{dX}\right) + \hat{\epsilon}_R \frac{\hat{A}_X}{\hat{A}} \frac{d\Phi_R}{dX} = z_u U_R + z_w W_R \tag{4.27}$$

$$0 = \frac{dU_R}{dX} + z_u U_R \frac{d\hat{\phi}_R}{dX} + z_u \hat{u}_R \frac{d\Phi_R}{dX} + z_u U_R \frac{d\Phi_R}{dX} - q\frac{d\Phi_R}{dX} \tag{4.28}$$

$$0 = \frac{dW_R}{dX} + z_w W_R \frac{d\hat{\phi}_R}{dX} + z_w \hat{w}_R \frac{d\Phi_R}{dX} + z_w W_R \frac{d\Phi_R}{dX} \tag{4.29}$$

where

$$X = \frac{b-x}{\varepsilon} \tag{4.30}$$

and

$$\hat{f}_R\left(X\right) = f\left(b - \varepsilon X\right) \qquad \left(f = \epsilon, u, w\right). \tag{4.31}$$

In writing seperate equations for the left and right sides of the interval $[a, b]$, we have assumed that the layers on each side are well seperated. This is a standard technique in SP since all functions describing layers are expected to go to zero very quickly. If they do not go to zero fast enough and the layers from each side do interact with one another, the situation is usually too complex to work out nicely. However, assuming that layers are independent and do not interact when they actually do can be a major source of error (both quantitative and qualitative). Later in this chapter (Section 4.6) we will show when boundary layers are likely to interact for the PNP equations. (If the boundary layers interact enough, the numerical solution of the full PNP equations must be used.)

Next, all of the functions are expanded in powers of ε:

$$f_{\text{out}}\left(x\right) = f^{(0)}\left(x\right) + \varepsilon f^{(1)}\left(x\right) + \cdots \qquad \left(f = \phi, u, w\right) \tag{4.32}$$

$$F_L\left(\zeta\right) = F_L^{(0)}\left(\zeta\right) + \varepsilon F_L^{(1)}\left(\zeta\right) + \cdots \qquad \left(F = \Phi, U, W\right) \tag{4.33}$$

$$F_R\left(X\right) = F_R^{(0)}\left(X\right) + \varepsilon F_R^{(1)}\left(X\right) + \cdots \qquad \left(F = \Phi, U, W\right) \tag{4.34}$$

$$J_f = \varepsilon J_f^{(1)} + \varepsilon^2 J_f^{(2)} + \cdots \qquad \left(f = u, w\right). \tag{4.35}$$

These functions will be solved to satisfy

$$\lim_{\zeta\to\infty} F_{L/R}^{(k)}(\zeta) = \lim_{\zeta\to\infty} \frac{dF_{L/R}^{(k)}}{d\zeta}(\zeta) = \lim_{\zeta\to\infty} \frac{d^2F_{L/R}^{(k)}}{d\zeta^2}(\zeta) = 0 \qquad (F = \Phi, U, W; k \geq 0) \tag{4.36}$$

and the boundary conditions

$$\begin{array}{ll}
\phi^{(0)}(a) + \Phi_L^{(0)}(0) = \beta_{L,\phi} & \phi^{(k)}(b) + \Phi_R^{(k)}(0) = \beta_{R,\phi} \\
\phi^{(k)}(a) + \Phi_L^{(k)}(0) = 0 \qquad (k \geq 1) & \phi^{(k)}(b) + \Phi_R^{(k)}(0) = 0 \qquad (k \geq 1) \\
u^{(0)}(a) + U_L^{(0)}(0) = \beta_{L,u} - |q| & u^{(0)}(b) + U_R^{(0)}(0) = \beta_{R,u} - |q| \\
u^{(k)}(a) + U_L^{(k)}(0) = 0 \qquad (k \geq 1) & u^{(k)}(b) + U_R^{(k)}(0) = 0 \qquad (k \geq 1) \\
w^{(0)}(a) + W_L^{(0)}(0) = \beta_{L,w} & w^{(0)}(b) + W_R^{(0)}(0) = \beta_{R,w} \\
w^{(k)}(a) + W_L^{(k)}(0) = 0 \qquad (k \geq 1) & w^{(k)}(b) + W_R^{(k)}(0) = 0 \qquad (k \geq 1) .
\end{array} \tag{4.37}$$

4.1.1 The Outer Solutions

If we substitute (4.32) into (4.18) – (4.20), multiply the series, and equate like powers of ε, we get a hierarchy of equations for the outer solutions. At leading order, these equations are

$$u^{(0)} = w^{(0)} \tag{4.38}$$

$$-\frac{J_u^{(1)}}{D_u A^{(1)}} = u_x^{(0)} - z_u q_x + z_u u^{(0)} \phi_x^{(0)} - q \phi_x^{(0)} \tag{4.39}$$

$$-\frac{J_w^{(1)}}{D_w A^{(1)}} = w_x^{(0)} + z_w w^{(0)} \phi_x^{(0)} \tag{4.40}$$

which reduce to

$$-\frac{J_u^{(1)}}{D_u A^{(1)}} = u_x^{(0)} - z_u q_x + z_u u^{(0)} \phi_x^{(0)} - q\phi_x^{(0)} \tag{4.41}$$

$$-\frac{J_w^{(1)}}{D_w A^{(1)}} = u_x^{(0)} - z_u u^{(0)} \phi_x^{(0)}. \tag{4.42}$$

Instead of working with this system directly, we will do one more change of variables; it will be more convenient to work with the following system which results from adding and subtracting the equations above:

$$-\frac{1}{2}\left(\frac{J_u^{(1)}}{D_u} + \frac{J_w^{(1)}}{D_w}\right)\frac{1}{A^{(1)}} = \left(u^{(0)} + \frac{|q|}{2}\right)_x - \frac{q}{2}\phi_x^{(0)} \tag{4.43}$$

$$-\frac{1}{2}\left(\frac{J_u^{(1)}}{D_u} - \frac{J_w^{(1)}}{D_w}\right)\frac{1}{A^{(1)}} = z_u\left(u^{(0)} + \frac{|q|}{2}\right)\phi_x^{(0)} \tag{4.44}$$

where we have used the identity

$$|q| = -z_u q. \tag{4.45}$$

Letting

$$J_{\pm}^{(1)} = \frac{1}{2}\left(\frac{J_n^{(1)}}{D_n} \pm \frac{J_p^{(1)}}{D_p}\right) \tag{4.46}$$

and

$$\mu = u^{(0)} + \frac{|q|}{2} \tag{4.47}$$

these equations become the final equations for the outer solutions

$$-\frac{J_+^{(1)}}{A^{(1)}} = \mu_x - \frac{q}{2}\phi_x^{(0)} \tag{4.48}$$

$$\frac{J_-^{(1)}}{A^{(1)}} = \mu\phi_x^{(0)}. \tag{4.49}$$

With this new notation, the boundary conditions become

$$\begin{array}{rr} \phi^{(0)}(a) + \Phi_L^{(0)}(0) = \beta_{L,\phi} & \phi^{(k)}(b) + \Phi_R^{(k)}(0) = \beta_{R,\phi} \\ \mu(a) + \frac{|q|}{2} + U_L^{(0)}(0) = \beta_{L,u} & \mu(b) + \frac{|q|}{2} + U_R^{(0)}(0) = \beta_{R,u} \\ \mu(a) - \frac{|q|}{2} + W_L^{(0)}(0) = \beta_{L,w} & \mu(b) - \frac{|q|}{2} + W_R^{(0)}(0) = \beta_{R,w}. \end{array} \tag{4.50}$$

(It is important to note that the "+" and "–" in the $J_\pm^{(1)}$ notation do not refer to the charge of any ion species, but only to the mathematical operations of addition and subtraction. Furthermore, this will always hold true; the symbols "+" and "–" will never be used to indicate charge, but will always refer to addition and subtraction. Charge is always referred to by p and n.) Intuitively, $\mu(x)$ can be thought of as the average mobile ion concentrations at x since

$$\mu = u^{(0)} + \frac{|q|}{2} = \frac{1}{2}\left(u^{(0)} + w^{(0)} + |q|\right) \sim \frac{1}{2}(n+p). \tag{4.51}$$

Unfortunately, we do not have an intuitive feeling for the $J_\pm^{(1)}$. These variables arise so naturally that one suspects they have a simple physical meaning, at the least in reduced problems.

Next we solve these outer solution equations.

Theorem 4.1 (Outer Solutions) *The outer solutions are given by*

$$\mu(x) - \mu(a) + \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}} \ln\left(\frac{\mu(x) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}{\mu(a) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}\right) + J_+^{(1)} \int_a^x \frac{ds}{A^{(1)}(s)} = 0 \tag{4.52}$$

$$\phi^{(0)} = \phi^{(0)}(a) - \frac{J_-^{(1)}}{J_+^{(1)}} \ln\left(\frac{\mu(x) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}{\mu(a) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}\right). \tag{4.53}$$

Therefore the outer solutions are completely determined if we know $\mu(a)$ and $\phi^{(0)}(a)$.

Proof. Eliminating $\phi_x^{(0)}$ from equations (4.48) and (4.49) gives

$$\mu\mu_x + \frac{J_+^{(1)}}{A^{(1)}}\mu = \frac{q}{2}\frac{J_-^{(1)}}{A^{(1)}} \tag{4.54}$$

$$\phi^{(0)} = \phi^{(0)}(a) + J_-^{(1)} \int_a^x \frac{ds}{\mu(s)A^{(1)}(s)}. \tag{4.55}$$

The first equation is a seperable differential equation (see, for example, [5]) and can be solved implicitly by

$$\mu(x) - \mu(a) + \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}} \ln\left(\frac{\mu(x) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}{\mu(a) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}\right) + J_+^{(1)} \int_a^x \frac{ds}{A^{(1)}(s)} = 0. \tag{4.56}$$

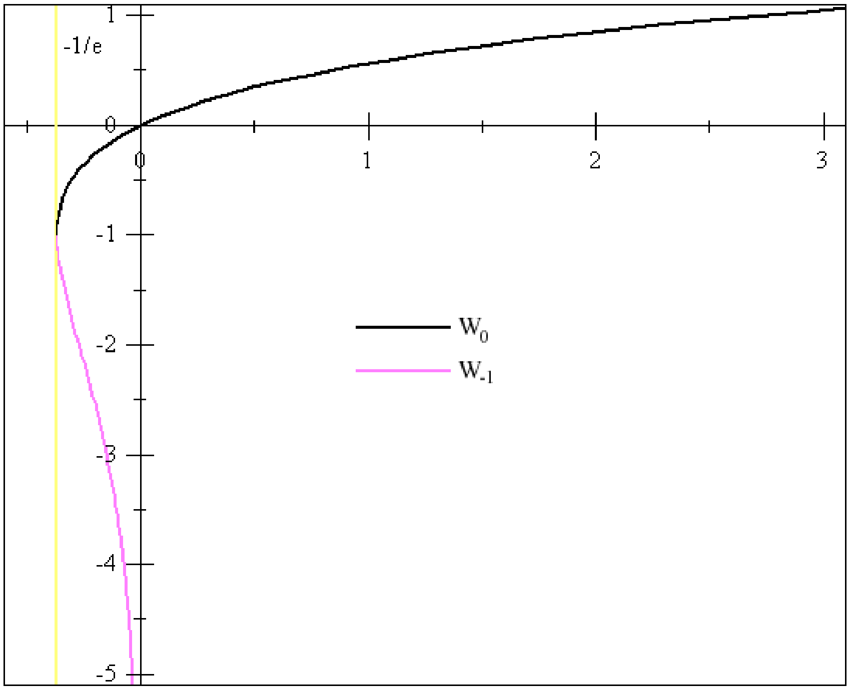

Figure 4-2: Graph of the two real branches (W_0 and W_{-1}) of the Lambert W function. A detailed review of the properties of this special function are given in [14].

Also from the first equation,

$$J_-^{(1)} \int_a^x \frac{ds}{\mu(s) A^{(1)}(s)} = \begin{cases} \frac{2}{q}\left[\mu(x) - \mu(a) + J_+^{(1)} \int_a^x \frac{ds}{A^{(1)}(s)}\right] & \text{if } q \neq 0 \\ -\frac{J_-^{(1)}}{J_+^{(1)}} \ln\left(\frac{\mu(x)}{\mu(a)}\right) & \text{if } q = 0 \end{cases} \tag{4.57}$$

$$= -\frac{J_-^{(1)}}{J_+^{(1)}} \ln\left(\frac{\mu(x) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}{\mu(a) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}\right) \tag{4.58}$$

and the theorem follows. ■

Before going on to the inner solutions, we make a brief digression into how to (numerically) compute $\mu(x)$ from (4.52). To start, we introduce the Lambert W

function as that function which solves the equation

$$W(x)\exp(W(x)) = x. \tag{4.59}$$

(Note: This function is not related to the layer functions $W_{L/R}$.) This special function is known to Maple (cf. [14] and [21]) and its properties are reviewed in [14]. As discussed in that article, the Lambert W function has two real branches, denoted W_0 and W_{-1} with $W_0 > -1$ and $W_{-1} < -1$. These are illustrated in Figure 4-2.

Lemma 4.2 *For $\mu(x)$ as in (4.52) and $qJ_-^{(1)} \neq 0$*

$$\mu(x) = \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}\left[1 + W_k(Z)\right] \tag{4.60}$$

where

$$Z = \frac{\mu(a) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}{\frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}\exp\left(\frac{\mu(a) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}} - J_+^{(1)}\int_a^x \frac{ds}{A^{(1)}(s)}}{\frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}\right) \tag{4.61}$$

$$k = \begin{cases} 0 & \textit{if } \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}} > 0 \\ -1 & \textit{if } \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}} < 0. \end{cases} \tag{4.62}$$

Proof. Let

$$y = \frac{\mu(x) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}{\mu(a) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}} \qquad A = \frac{\frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}{\mu(a) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}} \qquad B = \frac{J_+^{(1)}\int_a^x \frac{ds}{A^{(1)}(s)}}{\mu(a) - \frac{q}{2}\frac{J_-^{(1)}}{J_+^{(1)}}}. \tag{4.63}$$

Then

$$0 = y - 1 + A\ln(y) + B \tag{4.64}$$

which is solved by

$$y = AW_k\left(\frac{1}{A}\exp\left(\frac{1-B}{A}\right)\right). \tag{4.65}$$

The choice of k comes from the fact that $\mu(x) > 0$ and thus if $A > 0$ ($A < 0$) then $W > -1$ ($W < -1$) which occurs if and only if $k = 0$ ($k = -1$). ■

The reason for introducing this form of the solution for $\mu(x)$ is that [14] describes an efficient and easily implemented numerical technique (specifically Halley's method [1]) for computing W. In order to use some of the later results of this work, it will be necessary to numerically solve (4.52) many times and therefore an efficient algorithm becomes adventageous.

4.1.2 The Inner Solutions

For the inner solutions, we show the work on the left and suppress the L/R notation.

As with the outer solutions, we get a hierarchy of equations after substituting (4.33) into (4.22) – (4.24), multiplying the series, and equating like powers of ε. At leading order the equations are

$$\epsilon(a)\,\Phi^{(0)}_{\zeta\zeta} = -z_u\left(U^{(0)} - W^{(0)}\right) \tag{4.66}$$

$$0 = U^{(0)}_\zeta + z_u U^{(0)}\Phi^{(0)}_\zeta + z_u\left(\mu(a) + \frac{|q|}{2}\right)\Phi^{(0)}_\zeta \tag{4.67}$$

$$0 = W^{(0)}_\zeta - z_u W^{(0)}\Phi^{(0)}_\zeta - z_u\left(\mu(a) - \frac{|q|}{2}\right)\Phi^{(0)}_\zeta. \tag{4.68}$$

Theorem 4.3 (Inner Solutions) *The inner solutions are given by*

$$\frac{\epsilon\left(a\right)}{4}\left(\frac{d\Phi_{L}^{(0)}}{d\zeta}\right)^{2}=\mu\left(a\right)\cosh\left(\Phi_{L}^{(0)}\right)+\frac{q}{2}\sinh\left(\Phi_{L}^{(0)}\right)-\frac{q}{2}\Phi_{L}^{(0)}-\mu\left(a\right) \tag{4.69}$$

$$U_{L}^{(0)}=\left(\mu\left(a\right)+\frac{|q|}{2}\right)\left(\exp\left(-z_{u}\Phi_{L}^{(0)}\right)-1\right) \tag{4.70}$$

$$W_{L}^{(0)}=\left(\mu\left(a\right)-\frac{|q|}{2}\right)\left(\exp\left(z_{u}\Phi_{L}^{(0)}\right)-1\right) \tag{4.71}$$

$$\frac{\epsilon\left(b\right)}{4}\left(\frac{d\Phi_{R}^{(0)}}{dX}\right)^{2}=\mu\left(b\right)\cosh\left(\Phi_{R}^{(0)}\right)+\frac{q}{2}\sinh\left(\Phi_{R}^{(0)}\right)-\frac{q}{2}\Phi_{R}^{(0)}-\mu\left(b\right) \tag{4.72}$$

$$U_{R}^{(0)}=\left(\mu\left(b\right)+\frac{|q|}{2}\right)\left(\exp\left(-z_{u}\Phi_{R}^{(0)}\right)-1\right) \tag{4.73}$$

$$W_{R}^{(0)}=\left(\mu\left(b\right)-\frac{|q|}{2}\right)\left(\exp\left(z_{u}\Phi_{R}^{(0)}\right)-1\right). \tag{4.74}$$

These results still hold when $q=0$ *by taking* $z_u=-1$ *and* $u=n$ *and* $w=p$ *or by taking* $z_u=1$ *and* $u=p$ *and* $w=n$.

Theorem 4.4 *At the boundary we have the following relations:*

$$\beta_{L,u}=\left(\mu\left(a\right)+\frac{|q|}{2}\right)\exp\left(-z_{u}\left(\beta_{L,\phi}^{(0)}-\phi^{(0)}\left(a\right)\right)\right) \tag{4.75}$$

$$\beta_{L,w}=\left(\mu\left(a\right)-\frac{|q|}{2}\right)\exp\left(z_{u}\left(\beta_{L,\phi}^{(0)}-\phi^{(0)}\left(a\right)\right)\right) \tag{4.76}$$

$$\beta_{R,u} = \left(\mu\left(b\right) + \frac{|q|}{2}\right) \exp\left(-z_u\left(\beta_{R,\phi}^{(0)} - \phi^{(0)}\left(b\right)\right)\right) \tag{4.77}$$

$$\beta_{R,w} = \left(\mu\left(b\right) - \frac{|q|}{2}\right) \exp\left(z_u\left(\beta_{R,\phi}^{(0)} - \phi^{(0)}\left(b\right)\right)\right). \tag{4.78}$$

Proof. The second theorem follows from the first by evaluating $U_{L/R}^{(0)}$ and $W_{L/R}^{(0)}$ at 0 and the boundary conditions (4.50). ■

Proof of Theorem 4.3. We will work on the L side and leave out the L subscripts. The equations are solved to satisfy

$$\lim_{\zeta\to\infty} \Phi^{(0)}\left(\zeta\right) = \lim_{\zeta\to\infty} \Phi_{\zeta}^{(0)}\left(\zeta\right) = \lim_{\zeta\to\infty} \Phi_{\zeta\zeta}^{(0)}\left(\zeta\right) = 0 \tag{4.79}$$

$$\Phi^{(0)}\left(0\right) = \beta_{\phi}^{(0)} - \phi^{(0)}\left(a\right). \tag{4.80}$$

Adding and substracting (4.67) and (4.68), substituting (4.66), and integrating the equations with the dissipation conditions (4.79), gives

$$U^{(0)} + W^{(0)} = \frac{\epsilon\left(a\right)}{2}\left(\Phi_{\zeta}^{(0)}\right)^2 + q\Phi^{(0)} \tag{4.81}$$

$$0 = z_u\left(U^{(0)} - W^{(0)}\right)_{\zeta} + \left(U^{(0)} + W^{(0)}\right)\Phi_{\zeta}^{(0)} + 2\mu\left(a\right)\Phi_{\zeta}^{(0)}. \tag{4.82}$$

Substituting the first equation into the second and using (4.66) we get that $\Phi^{(0)}$ must satisfy

$$0 = \Phi_{\zeta\zeta\zeta}^{(0)} - \frac{1}{2}\left(\Phi_{\zeta}^{(0)}\right)^3 - \frac{q}{\epsilon\left(a\right)}\Phi^{(0)}\Phi_{\zeta}^{(0)} - \frac{2\mu\left(a\right)}{\epsilon\left(a\right)}\Phi_{\zeta}^{(0)}. \tag{4.83}$$

To make the notation less cumbersome, let

$$f(\zeta) = \Phi^{(0)}(\zeta). \tag{4.84}$$

Then

$$0 = f_{\zeta\zeta\zeta} - \frac{1}{2}(f_\zeta)^3 - \frac{q}{\epsilon(a)} f f_\zeta - \frac{2\mu(a)}{\epsilon(a)} f_\zeta. \tag{4.85}$$

The standard way to solve equations of this type (autonomous: where the independent variable ζ does not explicitly appear; see, for example, [4, page 24]) is to introduce a new function v:

$$v(f) = f_\zeta. \tag{4.86}$$

Then

$$\left(v^2\right)_{ff} - v^2 = \frac{2}{\epsilon(a)}\left(qf + 2\mu(a)\right). \tag{4.87}$$

Solving this for v and substituting back we get

$$\left(\Phi^{(0)}_\zeta\right)^2 = B_1 \exp\left(\Phi^{(0)}\right) + B_2 \exp\left(-\Phi^{(0)}\right) - \frac{2}{\epsilon(a)}\left(q\Phi^{(0)} + 2\mu(a)\right) \tag{4.88}$$

and, by differentiating this,

$$\Phi^{(0)}_{\zeta\zeta} = \frac{B_1}{2}\exp\left(\Phi^{(0)}\right) - \frac{B_2}{2}\exp\left(-\Phi^{(0)}\right) - \frac{q}{\epsilon(a)}. \tag{4.89}$$

Letting $\zeta \to \infty$ and using the dissipation conditions (4.79) gives

$$B_1 = \frac{2}{\epsilon(a)}\left(\mu(a) + \frac{q}{2}\right) \tag{4.90}$$

$$B_2 = \frac{2}{\epsilon(a)}\left(\mu(a) - \frac{q}{2}\right). \tag{4.91}$$

Therefore

$$\begin{aligned}\left(\Phi_\zeta^{(0)}\right)^2 &= \frac{2}{\epsilon(a)}\left(\mu(a) + \frac{q}{2}\right)\exp\left(\Phi^{(0)}\right) + \frac{2}{\epsilon(a)}\left(\mu(a) - \frac{q}{2}\right)\exp\left(-\Phi^{(0)}\right) \qquad (4.92)\\ &\quad - \frac{2}{\epsilon(a)}\left(q\Phi^{(0)} + 2\mu(a)\right)\\ &= \frac{4}{\epsilon(a)}\left(\mu(a)\cosh\left(\Phi^{(0)}\right) + \frac{q}{2}\sinh\left(\Phi^{(0)}\right) - \frac{q}{2}\Phi^{(0)} - \mu(a)\right) \qquad (4.93)\end{aligned}$$

and

$$\Phi_{\zeta\zeta}^{(0)} = \frac{2}{\epsilon(a)}\left(\mu(a)\sinh\left(\Phi^{(0)}\right) + \frac{q}{2}\cosh\left(\Phi^{(0)}\right) - \frac{q}{2}\right). \tag{4.94}$$

We do not continue to find a closed form solution for $\Phi^{(0)}$ since we are not aware of a formulation that would be useful for any later work. Furthermore, we do not need such a formulation since we are not interested in the functions ϕ, n, and p themselves, but only in the current/voltage relations.

To find $U^{(0)}$ and $W^{(0)}$, we start with (4.66):

$$\begin{aligned}U^{(0)} - W^{(0)} &= -z_u\epsilon(a)\,\Phi_{\zeta\zeta}^{(0)} && (4.95)\\ &= -2z_u\mu(a)\sinh\left(\Phi^{(0)}\right) + |q|\cosh\left(\Phi^{(0)}\right) - |q| && (4.96)\\ &= 2\mu(a)\sinh\left(-z_u\Phi^{(0)}\right) + |q|\cosh\left(-z_u\Phi^{(0)}\right) - |q| && (4.97)\end{aligned}$$

From (4.81) we have

$$\begin{aligned}U^{(0)} + W^{(0)} &= \frac{\epsilon(a)}{2}\left(\Phi_\zeta^{(0)}\right)^2 + q\Phi^{(0)} && (4.98)\\ &= 2\mu(a)\cosh\left(\Phi^{(0)}\right) + q\sinh\left(\Phi^{(0)}\right) - 2\mu(a) && (4.99)\\ &= 2\mu(a)\cosh\left(-z_u\Phi^{(0)}\right) + |q|\sinh\left(-z_u\Phi^{(0)}\right) - 2\mu(a) && (4.100)\end{aligned}$$

where we have used the identities

$$\sinh(-x) = -\sinh(x) \tag{4.101}$$

$$\cosh(-x) = \cosh(x)\,. \tag{4.102}$$

Thus

$$\begin{aligned}
U_L^{(0)} &= \left(\mu(a) + \frac{|q|}{2}\right)\left(\cosh\left(-z_u\Phi^{(0)}\right) + \sinh\left(-z_u\Phi^{(0)}\right)\right) && (4.103)\\
&\quad - \left(\mu(a) + \frac{|q|}{2}\right) \\
&= \left(\mu(a) + \frac{|q|}{2}\right)\left(\exp\left(-z_u\Phi^{(0)}\right) - 1\right) && (4.104)
\end{aligned}$$

$$\begin{aligned}
W_L^{(0)} &= \left(\mu(a) - \frac{|q|}{2}\right)\left(\cosh\left(-z_u\Phi^{(0)}\right) - \sinh\left(-z_u\Phi^{(0)}\right)\right) && (4.105)\\
&\quad - \left(\mu(a) - \frac{|q|}{2}\right) \\
&= \left(\mu(a) - \frac{|q|}{2}\right)\left(\exp\left(z_u\Phi_L^{(0)}\right) - 1\right). && (4.106)
\end{aligned}$$

The proofs for the R side and when $q = 0$ are similar. ■

4.2 Matching across a Junction of Two Intervals of Constant Permanent Charge

If we want an expansion of the PNP equations for a piecewise constant permanent charge and diffusion coefficients, we must match the solutions found in the previous section across any discontinuities. To start, let $M+1$ be the number of discontinuities

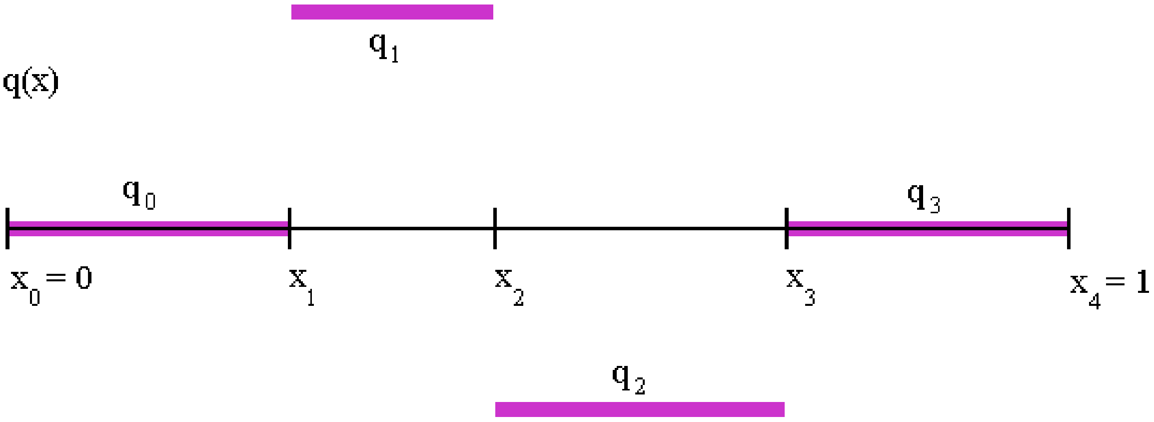

Figure 4-3: Dividing up the interval $[0,1]$. In this example we divide up the interval $[0,1]$ into 4 segments, which corresponds to $M = 2$. The baths (where $q = 0$) are the $M - 2$ intervals (x_0, x_1) and (x_3, x_4) and the channel (where $q \neq 0$) is represented by M intervals (x_1, x_2) and (x_2, x_3) where q takes on M different values, one one each interval.

of q, D_n, and D_p. Call the discontinuties $x_1, \ldots, x_{M+1}$ and order them such that

$$x_1 < x_2 < \cdots < x_{M+1}. \tag{4.107}$$

Lastly, define $x_0 = 0$ and $x_{M+2} = 1$. Then the baths are represented by the two intervals (x_0, x_1) and (x_{M+1}, x_{M+2}) (intervals 0 and $M+1$, respectively) and the channel by the M intervals (x_1, x_2), ..., (x_M, x_{M+1}). This is illustrated in Figure 4-3. Throughout we will assume that the baths are of equal length (that is, $x_1 - x_0 = x_{M+2} - x_{M+1}$) and that the diffusion coefficient of each species is the same in the two baths.

On each interval (x_i, x_{i+1}) the permanent charge and diffusion coefficients are identically constant, as in the previous section. For $x_i < x < x_{i+1}$, let $q(x) = q_i$, $D_n(x) = D_{i,n}$ and $D_p(x) = D_{i,p}$. Furthermore, since each interval (x_i, x_{i+1}) will be different, we rename the outer and inner solutions from the previous section as

$$u_i^{(0)}, \mu_i, \phi_i^{(0)}, U_{i,L/R}^{(0)}, W_{i,L/R}^{(0)}, \Phi_{i,L/R}^{(0)}. \tag{4.108}$$

Since, in the baths, there are no differences in diffusion coefficient, we have

$$D_{0,f} = D_{M+1,f} \qquad (f = n, p)\,. \tag{4.109}$$

(We will always use $D_{0,n}$ and $D_{0,p}$ for the bath diffusion coefficients.) To be technically complete, we also define

$$f_i\left(x_i\right) = \lim_{x \to x_i, x > x_i} f_i\left(x\right) \qquad f_i\left(x_{i+1}\right) = \lim_{x \to x_{i+1}, x < x_{i+1}} f_i\left(x\right) \qquad \left(f = \mu, \phi^{(0)}\right). \tag{4.110}$$

In the new notation, on the interval (x_i, x_{i+1}), (4.52) and (4.53) evaluated at the endpoint x_{i+1} become:

$$0 = \mu_i\left(x_{i+1}\right) - \mu_i\left(x_i\right) + \frac{q_i}{2} \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}} \ln\left(\frac{\mu_i\left(x_{i+1}\right) - \frac{q_i}{2} \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}}{\mu_i\left(x_i\right) - \frac{q_i}{2} \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}}\right) + S_i J_{i,+}^{(1)}. \tag{4.111}$$

$$\phi_i^{(0)}\left(x_{i+1}\right) = \phi_i^{(0)}\left(x_i\right) - \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}} \ln\left(\frac{\mu_i\left(x_{i+1}\right) - \frac{q_i}{2} \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}}{\mu_i\left(x_i\right) - \frac{q_i}{2} \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}}\right) \tag{4.112}$$

where, to simplify notation,

$$S_i = \int_{x_i}^{x_{i+1}} \frac{ds}{A^{(1)}\left(s\right)} \tag{4.113}$$

and

$$J_{i,\pm}^{(1)} = \frac{1}{2}\left(\frac{J_n^{(1)}}{D_{i,n}} \pm \frac{J_p^{(1)}}{D_{i,p}}\right). \tag{4.114}$$

Now consider the two intervals (x_i, x_{i+1}) (a.k.a. the i segment) and (x_{i+1}, x_{i+2}) (a.k.a. the $i+1$ segment). By Theorem 2.2, at the junction x_{i+1} we require that all the functions (ϕ, n, and p) are continuous:

$$\beta_{i,R,f} = \beta_{i+1,L,f} \equiv \beta_{i+1,f} \qquad (f = \phi, n, p)\,. \tag{4.115}$$

In order to use equations (4.111) and (4.112) for the outer solutions in (x_{i+1}, x_{i+2}), we must know the left-side boundary conditions $\phi_{i+1}^{(0)}(x_{i+1})$ and $\mu_{i+1}(x_{i+1})$. The next theorem expresses these in terms of the right-side boundary values $\phi_i^{(0)}(x_{i+1})$ and $\mu_i(x_{i+1})$ of the previous interval (x_i, x_{i+1}).

Theorem 4.5 *The boundary conditions at the $i+1$ segment (x_{i+1}, x_{i+2}), in terms of results from the previous segment (x_i, x_{i+1}), are given by the following:*

$$\mu_{i+1}(x_{i+1}) = \sqrt{\mu_i(x_{i+1})^2 + \frac{q_{i+1}^2}{4} - \frac{q_i^2}{4}} \tag{4.116}$$

$$\phi_{i+1}^{(0)}(x_{i+1}) = \phi_i^{(0)}(x_{i+1}) + \frac{1}{2}\ln\left(\frac{B_{i+1}(x_{i+1})}{B_i(x_{i+1})}\right) \tag{4.117}$$

where

$$B_k(y) = \frac{\mu_k(y) + \frac{q_k}{2}}{\mu_k(y) - \frac{q_k}{2}}. \tag{4.118}$$

Proof. Multiplying the results of Theorem 4.4 for the left and right sides, we get

$$\begin{aligned}
& \left(\mu_i\left(x_{i+1}\right)+\frac{\left|q_i\right|}{2}\right)\left(\mu_i\left(x_{i+1}\right)-\frac{\left|q_i\right|}{2}\right) \\
= \ & \beta_{i,R,u}\beta_{i,R,w}=\beta_{i+1,L,u}\beta_{i+1,L,w} && (4.119) \\
= \ & \left(\mu_{i+1}\left(x_{i+1}\right)+\frac{\left|q_{i+1}\right|}{2}\right)\left(\mu_{i+1}\left(x_{i+1}\right)-\frac{\left|q_{i+1}\right|}{2}\right). && (4.120)
\end{aligned}$$

Solving for $\mu_{i+1}\left(x_{i+1}\right)$ gives the first result. Similarly, dividing the results of Theorem 4.4 for the left and right sides, along with

$$\sigma_i \equiv \operatorname{sign}\left(q_i\right)=-z_{u_i}, \tag{4.121}$$

we get

$$\begin{aligned}
\frac{\beta_{i+1,n}}{\beta_{i+1,p}} &= \left(\frac{\mu_i\left(x_{i+1}\right)+\left|\frac{q_i}{2}\right|}{\mu_i\left(x_{i+1}\right)-\left|\frac{q_i}{2}\right|}\right)^{\sigma_i}\exp\left[2\left(\beta_{i+1,\phi}-\phi_i^{(0)}\left(x_{i+1}\right)\right)\right] && (4.122) \\
&= \left(\frac{\mu_{i+1}\left(x_{i+1}\right)+\left|\frac{q_{i+1}}{2}\right|}{\mu_{i+1}\left(x_{i+1}\right)-\left|\frac{q_{i+1}}{2}\right|}\right)^{\sigma_{i+1}}\exp\left[2\left(\beta_{i+1,\phi}-\phi_{i+1}^{(0)}\left(x_{i+1}\right)\right)\right]. && (4.123)
\end{aligned}$$

Since

$$\left(\frac{a+\sigma q}{a-\sigma q}\right)^{\sigma}=\frac{a+q}{a-q} \qquad (\sigma=\pm 1), \tag{4.124}$$

the second result follows. ■

We conclude this section by presenting a theorem that will be needed later.

Theorem 4.6 *If $\epsilon(x)$ is C^1 on $[0,1]$, then at the boundary between segments i and $i+1$ we have*

$$\left(\frac{q_i}{2}-\frac{q_{i+1}}{2}\right)\beta_{i+1,\phi}=\frac{q_i}{2}\phi_i^{(0)}\left(x_{i+1}\right)-\frac{q_{i+1}}{2}\phi_{i+1}^{(0)}\left(x_{i+1}\right)-\mu_i\left(x_{i+1}\right)+\mu_{i+1}\left(x_{i+1}\right). \tag{4.125}$$

If $q_i = q_{i+1}$, *then*

$$\beta_{i+1,\phi} = \phi_i^{(0)}\left(x_{i+1}\right) = \phi_{i+1}^{(0)}\left(x_{i+1}\right). \tag{4.126}$$

Proof. By Theorem 2.2 we require ϕ_x to be continuous. At leading order this becomes

$$\frac{d\Phi_{i,R}^{(0)}}{d\zeta}(0) = \frac{d\Phi_{i+1,L}^{(0)}}{d\zeta}(0). \tag{4.127}$$

By (4.93) and (4.80) and assuming that ϵ is C^1, this becomes

$$\begin{aligned} & \mu_i\left(x_{i+1}\right)\cosh\left(\beta_{i+1,\phi} - \phi_i^{(0)}\left(x_{i+1}\right)\right) - \frac{q_i}{2}\left(\beta_{i+1,\phi} - \phi_i^{(0)}\left(x_{i+1}\right)\right) \\ & +\frac{q_i}{2}\sinh\left(\beta_{i+1,\phi} - \phi_i^{(0)}\left(x_{i+1}\right)\right) - \mu_i\left(x_{i+1}\right) \\ = \; & \mu_{i+1}\left(x_{i+1}\right)\cosh\left(\beta_{i+1,\phi} - \phi_{i+1}^{(0)}\left(x_{i+1}\right)\right) - \frac{q_{i+1}}{2}\left(\beta_{i+1,\phi} - \phi_{i+1}^{(0)}\left(x_{i+1}\right)\right) \\ & +\frac{q_{i+1}}{2}\sinh\left(\beta_{i+1,\phi} - \phi_{i+1}^{(0)}\left(x_{i+1}\right)\right) - \mu_{i+1}\left(x_{i+1}\right) \end{aligned} \tag{4.128}$$

By (4.75) – (4.78) this reduces to

$$\begin{aligned} & \frac{q_i}{2}\left(\beta_{i+1,\phi} - \phi_i^{(0)}\left(x_{i+1}\right)\right) + \mu_i\left(x_{i+1}\right) \\ = \; & \frac{q_{i+1}}{2}\left(\beta_{i+1,\phi} - \phi_{i+1}^{(0)}\left(x_{i+1}\right)\right) + \mu_{i+1}\left(x_{i+1}\right). \end{aligned} \tag{4.129}$$

The result for $q_i = q_{i+1}$ follows from the previous theorem. ■

4.3 The Current/Voltage Relations

With the work done so far, there are two ways to determine how the applied voltage and the current through the channel are related. First, however, some definitions. At leading order the nondimensional current is $\varepsilon I^{(1)}$ where

$$I^{(1)} = J_p^{(1)} - J_n^{(1)} \tag{4.130}$$

and the applied voltage is

$$V^{(0)} = \phi_0^{(0)}(0) - \phi_{M+1}^{(0)}(1). \tag{4.131}$$

(Being potentials, $\phi_{M+1}^{(0)}(1)$ may be taken to be 0.) In the following we will drop the order notation for $I^{(1)}$ and $V^{(0)}$, writing them only as I and V, respectively.

The first way to find the current/voltage relations from the work done so far is to fix bath concentrations c_L and c_R and an applied potential V. To find $J_n^{(1)}$ and $J_p^{(1)}$ that make up the current, we start on the interval $(0, x_1)$. Using $\mu_0(x_0) = c_L$, solve (4.111) for $\mu_0(x_1)$ and (4.116) then gives $\mu_1(x_1)$. Solving (4.111) with this $\mu_1(x_1)$ and $i = 1$, then gives $\mu_1(x_2)$. Continue this process through $i = M + 1$. In the same way solve (4.112) repeatedly starting with $\phi_0^{(0)}(0) = V$. The solution $\left(J_n^{(1)}, J_p^{(1)}\right)$ is that ordered pair such that after this procedure, $\mu_{M+1}(x_{M+2}) = c_R$ and $\phi_{M+1}^{(0)}(x_{M+2}) = 0$.

Another way to find the current is via a $V(I)$ curve; that is, the applied voltage as a function of the output current. This may seem backwards since, in general, one wishes to consider how the output current I depends on the given applied voltage V. However, from semiconductor modeling (which uses the same type of equations) it is known that this function is not well-defined. Specifically, in a device called a thyristor, one voltage may correspond to two or more output currents (see, for example, [53]). Therefore, in order to have a well-defined function, it is necessary to consider the function $V(I)$. Once that is found, it is only necessary to reverse the axes of the graph to get $I(V)$. It is this $V(I)$ approach we will use.

We now come to the theorem from which everything in this chapter follows.

Theorem 4.7 (Current/Voltage Relation: General Case) *Let I be given. We define*

$$\Xi_i(I) = \mu_i(x_i) \tag{4.132}$$

the left-side boundary value of μ on the interval (x_i, x_{i+1})

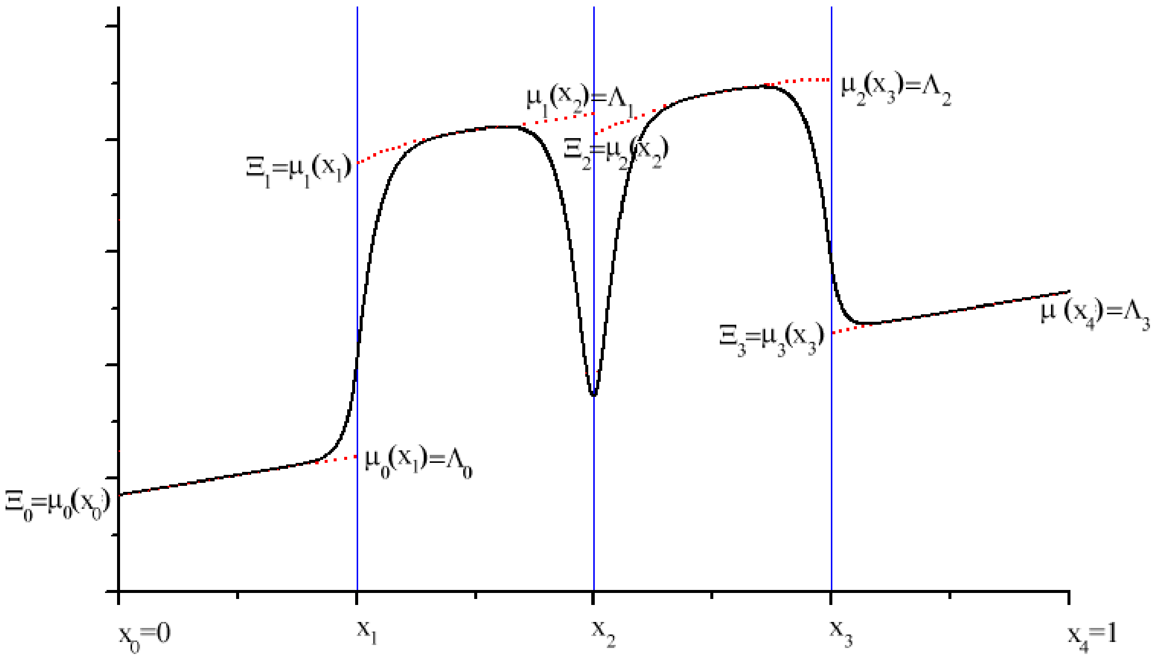

Figure 4-4: The figure illustrates the definitions of the Ξ_i and Λ_i for the case $M = 2$ (which was illustrated in Figure 4-3) from a graph of $\frac{1}{2}(n + p)$ for which μ_i is the outer solution in the interval (x_i, x_{i+1}). The functions μ_i, shown with the dotted line, are outer solutions and thus are only valid as solutions of the equations away from the points x_1, x_2, and x_3. By Theorem 4.5 is possible to calculate Ξ_{i+1} if Λ_i is known.

$$\Lambda_i\left(I\right)=\mu_i\left(x_{i+1}\right) \tag{4.133}$$

the right-side boundary value of μ *on the interval* $\left(x_i,x_{i+1}\right)$

to explicitly indicate the dependence of $\mu_i\left(x_i\right)$ *and* $\mu_i\left(x_{i+1}\right)$ *on* I*. (This is illustrated in Figure 4-4.) Then*

$$J_{i,\pm}^{(1)}\left(I\right)=\frac{\alpha_{i,\pm}}{S_0}\left(c_L-\Lambda_0\left(I\right)\right)+\beta_{i,\pm}I \tag{4.134}$$

where

$$\alpha_{i,\pm}=\frac{D_{0,n}D_{0,p}}{D_{i,n}D_{i,p}}\frac{D_{i,p}\pm D_{i,n}}{D_{0,p}+D_{0,n}} \tag{4.135}$$

$$\beta_{i,\pm}=-\frac{1}{2}\frac{1}{D_{i,n}D_{i,p}}\frac{D_{0,n}D_{i,p}\mp D_{0,p}D_{i,n}}{D_{0,p}+D_{0,n}}. \tag{4.136}$$

Let $\Lambda_0\left(I\right)$ *be that number which gives* $\Lambda_{M+1}\left(I\right)=c_R$ *after repeatedly solving* (4.111) *in conjunction with* (4.116) *as described before. Then*

$$\begin{aligned} V\left(I\right) &= \sum_{i=0}^{M+1}\frac{J_{i,-}^{(1)}\left(I\right)}{J_{i,+}^{(1)}\left(I\right)}\ln\left(\frac{\Lambda_i\left(I\right)-\frac{q_i}{2}\frac{J_{i,-}^{(1)}(I)}{J_{i,+}^{(1)}(I)}}{\Xi_i\left(I\right)-\frac{q_i}{2}\frac{J_{i,-}^{(1)}(I)}{J_{i,+}^{(1)}(I)}}\right) \\ &\quad +\frac{1}{2}\sum_{i=1}^{M}\ln\left(\frac{\left(\Xi_i\left(I\right)-\frac{q_i}{2}\right)\left(\Lambda_i\left(I\right)+\frac{q_i}{2}\right)}{\left(\Xi_i\left(I\right)+\frac{q_i}{2}\right)\left(\Lambda_i\left(I\right)-\frac{q_i}{2}\right)}\right). \end{aligned} \tag{4.137}$$

Proof. We start by writing

$$V=\phi_0^{(0)}\left(0\right)-\phi_{M+1}^{(0)}\left(1\right) \tag{4.138}$$

as the telescoping series

$$V=\sum_{i=0}^{M+1}\left(\phi_i^{(0)}\left(x_i\right)-\phi_i^{(0)}\left(x_{i+1}\right)\right)+\sum_{i=0}^{M}\left(\phi_i^{(0)}\left(x_{i+1}\right)-\phi_{i+1}^{(0)}\left(x_{i+1}\right)\right). \tag{4.139}$$

The $V(I)$ formula then follows from (4.112) and (4.117).

Next, note that

$$\begin{aligned} 2J_{i,\pm}^{(1)} &= \frac{J_n^{(1)}}{D_{i,n}}\pm\frac{J_p^{(1)}}{D_{i,p}}=\left(\frac{1}{D_{i,n}}\pm\frac{1}{D_{i,p}}\right)J_n^{(1)}\pm\frac{1}{D_{i,p}}I && (4.140)\\ &= \frac{D_{i,p}\pm D_{i,n}}{D_{i,n}D_{i,p}}J_n^{(1)}\pm\frac{1}{D_{i,p}}I && (4.141)\end{aligned}$$

and therefore, by (4.111) with $i=0$,

$$\frac{D_{0,p}+D_{0,n}}{D_{0,n}D_{0,p}}J_n^{(1)}+\frac{1}{D_{0,p}}I=2J_{0,+}^{(1)}=\frac{2\left(c_L-\mu_0\left(x_1\right)\right)}{S_0}. \tag{4.142}$$

Thus

$$J_n^{(1)}=2\frac{D_{0,n}D_{0,p}}{D_{0,p}+D_{0,n}}\frac{c_L-\mu_0\left(x_1\right)}{S_0}-\frac{D_{0,n}}{D_{0,p}+D_{0,n}}I \tag{4.143}$$

and

$$J_{i,\pm}^{(1)}=\frac{D_{0,n}D_{0,p}}{D_{i,n}D_{i,p}}\frac{D_{i,p}\pm D_{i,n}}{D_{0,p}+D_{0,n}}\frac{c_L-\mu_0\left(x_1\right)}{S_0}-\frac{1}{2}\frac{1}{D_{i,p}D_{i,n}}\frac{D_{0,n}D_{i,p}\mp D_{0,p}D_{i,n}}{D_{0,p}+D_{0,n}}I. \tag{4.144}$$

Letting

$$\alpha_{i,\pm}=\frac{D_{0,n}D_{0,p}}{D_{i,n}D_{i,p}}\frac{D_{i,p}\pm D_{i,n}}{D_{0,p}+D_{0,n}} \tag{4.145}$$

$$\beta_{i,\pm}=-\frac{1}{2}\frac{1}{D_{i,n}D_{i,p}}\frac{D_{0,n}D_{i,p}\mp D_{0,p}D_{i,n}}{D_{0,p}+D_{0,n}}, \tag{4.146}$$

it follows that

$$J_{i,\pm}^{(1)} = \frac{\alpha_{i,\pm}}{S_0}\left(c_L - \mu_0\left(x_1\right)\right) + \beta_{i,\pm} I \tag{4.147}$$

where $\mu_0\left(x_1\right)$ is the only unknown in the problem. It is found as described above. (Note that $\alpha_{0,+} = 1$ and $\beta_{0,+} = 0$. Also, since the baths are assumed to be identical (except for ion concentration), we have $S_0 = S_{M+1}$, $\alpha_{0,\pm} = \alpha_{M+1,\pm}$, and $\beta_{0,\pm} = \beta_{M+1,\pm}$.) ■

4.4 The Reversal Potential and Conductance at Reversal Potential

Next we concentrate on finding the reversal potential V_{rev} (the potential at which no net current is flowing) and the conductance $\frac{dI}{dV}$ at the reversal potential. Since by Theorem 4.7 we have a formula for $V\left(I\right)$, to find the conductance we will find $\frac{dV}{dI}$ and use the relation

$$\frac{dI}{dV} = \frac{1}{dV/dI}. \tag{4.148}$$

In our notation,

$$V_{\text{rev}} = V\left(0\right) \tag{4.149}$$

and the conductance at reversal potential is

$$\frac{dI}{dV}\left(V_{\text{rev}}\right) = \frac{1}{\frac{dV}{dI}\left(0\right)}. \tag{4.150}$$

We will use the same notation as in Theorem 4.7:

$$\Xi_i\left(I\right) = \mu_i\left(x_i\right) \qquad \Lambda_i\left(I\right) = \mu_i\left(x_{i+1}\right) \tag{4.151}$$

to explicitly indicate the dependence of $\mu_i\left(x_i\right)$ and $\mu_i\left(x_{i+1}\right)$ on I (see Figure 4-4 on page 74). We start by expanding these in Taylor series for small I, defining the Taylor coefficients with a notation similar to (4.32) – (4.35):

$$\Xi_i\left(I\right) = \xi_i^{[0]} + \xi_i^{[1]} I + \xi_i^{[2]} I^2 + \cdots \tag{4.152}$$

$$\Lambda_i\left(I\right) = \lambda_i^{[0]} + \lambda_i^{[1]} I + \lambda_i^{[2]} I^2 + \cdots . \tag{4.153}$$

Note that since the bath concentrations are held constant, we have

$$\xi_0^{[0]} = \Xi_0\left(0\right) = \Xi_0\left(I\right) = c_L \tag{4.154}$$

$$\xi_0^{[k]} = \frac{d^k \Xi_0}{dI^k}\left(0\right) = \frac{d^k \Xi_0}{dI^k}\left(I\right) = 0 \qquad \left(k \geq 1\right) \tag{4.155}$$

$$\lambda_{M+1}^{[0]} = \Lambda_{M+1}\left(0\right) = \Lambda_{M+1}\left(I\right) = c_R \tag{4.156}$$

$$\lambda_{M+1}^{[k]} = \frac{d^k \Lambda_{M+1}}{dI^k}\left(0\right) = \frac{d^k \Lambda_{M+1}}{dI^k}\left(I\right) = 0 \qquad \left(k \geq 1\right). \tag{4.157}$$

Substituting these series into (4.116) and expanding the result around $I = 0$, it follows that

$$\xi_i^{[0]} = \sqrt{\left(\lambda_{i-1}^{[0]}\right)^2 + \frac{q_i^2}{4} - \frac{q_{i-1}^2}{4}} \qquad \left(i \geq 1\right) \tag{4.158}$$

$$\xi_i^{[1]} = \frac{\lambda_{i-1}^{[0]}\lambda_{i-1}^{[1]}}{\xi_i^{[0]}} \qquad (i \geq 1)\,. \tag{4.159}$$

Similarly we have

$$J_{i,\pm}^{(1)} = \frac{\alpha_{i,\pm}}{S_0}\left(c_L - \lambda_0^{[0]}\right) + \left(\beta_{i,\pm} - \frac{\alpha_{i,\pm}}{S_0}\lambda_0^{[1]}\right) I + O\left(I^2\right) \tag{4.160}$$

Next, we rename two quantities we will encounter several times:

$$\alpha_i = \frac{\alpha_{i,-}}{\alpha_{i,+}} = \frac{D_{i,p} - D_{i,n}}{D_{i,p} + D_{i,n}} \tag{4.161}$$

and

$$\gamma_i = \beta_{i,-} - \frac{\alpha_{i,-}}{\alpha_{i,+}}\beta_{i,+} = -\frac{1}{D_{i,p} + D_{i,n}}. \tag{4.162}$$

Note that these are only functions of the diffusion coefficients in segment i.

Before starting on our next results, we need some quick lemmas.

4.4.1 Lemmas

Lemma 4.8

$$0 = \lambda_i^{[0]} - \xi_i^{[0]} + \frac{q_i}{2}\alpha_i \ln\left(\frac{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i}\right) + \frac{S_i}{S_0}\alpha_{i,+}\left(c_L - \lambda_0^{[0]}\right) \tag{4.163}$$

$$\begin{aligned} 0 \;=\; & \lambda_i^{[1]} - \xi_i^{[1]} + \frac{q_i}{2}\alpha_i\left(\frac{\lambda_i^{[1]}}{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i} - \frac{\xi_i^{[1]}}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i}\right) \\ & - \frac{S_i}{S_0}\alpha_{i,+}\lambda_0^{[1]} + S_i\beta_{i,+} + \frac{q_i}{2}K_i \end{aligned} \tag{4.164}$$

where

$$K_i = \frac{S_0 \gamma_i}{\alpha_{i,+}\left(c_L - \lambda_0^{[0]}\right)} \left[\ln\left(\frac{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i} \right) + \frac{q_i}{2}\alpha_i \frac{\lambda_i^{[0]} - \xi_i^{[0]}}{\left(\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i\right)\left(\xi_i^{[0]} - \frac{q_i}{2}\alpha_i\right)} \right]. \tag{4.165}$$

Equation (4.163) *is the* $I = 0$ *version of* (4.111)*.*

Proof. This result follows from expanding the right-hand side of (4.111) in powers of I and setting the first two powers of I equal to zero. ■

Lemma 4.9

$$\begin{aligned} & \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}} \ln\left(\frac{\Lambda_i - \frac{q_i}{2}\frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}}{\Xi_i - \frac{q_i}{2}\frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}} \right) \\ = \; & \alpha_i \ln\left(\frac{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i} \right) + \left[\alpha_i \left(\frac{\lambda_i^{[1]}}{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i} - \frac{\xi_i^{[1]}}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i} \right) + K_i \right] I \\ & + O\left(I^2\right) \end{aligned} \tag{4.166}$$

$$\begin{aligned} & \frac{1}{2}\ln\left(\frac{\left(\Xi_i - \frac{q_i}{2}\right)\left(\Lambda_i + \frac{q_i}{2}\right)}{\left(\Xi_i + \frac{q_i}{2}\right)\left(\Lambda_i - \frac{q_i}{2}\right)} \right) \\ = \; & \frac{1}{2}\ln\left(\frac{\left(\xi_i^{[0]} - \frac{q_i}{2}\right)\left(\lambda_i^{[0]} + \frac{q_i}{2}\right)}{\left(\xi_i^{[0]} + \frac{q_i}{2}\right)\left(\lambda_i^{[0]} - \frac{q_i}{2}\right)} \right) \\ & + \frac{1}{2}\left(\frac{\xi_i^{[1]}}{\xi_i^{[0]} - \frac{q_i}{2}} - \frac{\lambda_i^{[1]}}{\lambda_i^{[0]} - \frac{q_i}{2}} - \frac{\xi_i^{[1]}}{\xi_i^{[0]} + \frac{q_i}{2}} + \frac{\lambda_i^{[1]}}{\lambda_i^{[0]} + \frac{q_i}{2}} \right) I + O\left(I^2\right) \end{aligned} \tag{4.167}$$

where K_i *is given by* (4.165)*.*

Proof. These are Taylor expansions of the given functions for small I. ■

Lemma 4.10 *For* $1 \leq i \leq M$*,*

$$\lambda_i^{[0]}\lambda_i^{[1]} = \left(\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i\right)\left[\frac{\lambda_{i-1}^{[0]}\lambda_{i-1}^{[1]}}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i} + \frac{S_i}{S_0}\alpha_{i,+}\lambda_0^{[1]} - \left(S_i\beta_{i,+} + \frac{q_i}{2}K_i\right)\right] \tag{4.168}$$

where

$$\lambda_0^{[1]} = S_0\frac{\sum_{m=1}^{M}\omega_{m,M+1}\left(S_m\beta_{m,+} + \frac{q_m}{2}K_m\right)\left(\lambda_m^{[0]} - \frac{q_m}{2}\frac{\alpha_{m,-}}{\alpha_{m,+}}\right)}{\sum_{m=0}^{M+1}\omega_{m,M+1}S_m\alpha_{m,+}\left(\lambda_m^{[0]} - \frac{q_m}{2}\frac{\alpha_{m,-}}{\alpha_{m,+}}\right)} \tag{4.169}$$

and $\omega_{m,i}$ *is given by* (4.172) *and* K_i *is given by* (4.165)*. Therefore each* $\lambda_i^{[1]}$ *can be found in terms of* $\lambda_0^{[1]}$*.*

Proof. We start with (4.164). Using (4.159) this becomes

$$\begin{aligned} \lambda_i^{[0]}\lambda_i^{[1]} &= \frac{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i}\lambda_{i-1}^{[0]}\lambda_{i-1}^{[1]} + S_0\alpha_{i,+}\left(\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i\right)\lambda_0^{[1]} \\ &\quad - \left(S_i\beta_{i,+} + \frac{q_i}{2}K_i\right)\left(\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i\right). \end{aligned} \tag{4.170}$$

By induction, we get

$$\begin{aligned} \lambda_i^{[0]}\lambda_i^{[1]} &= \frac{1}{S_0}\left(\sum_{m=0}^{i}\omega_{m,i}S_m\alpha_{m,+}\left(\lambda_m^{[0]} - \frac{q_m}{2}\frac{\alpha_{m,-}}{\alpha_{m,+}}\right)\right)\lambda_0^{[1]} \\ &\quad - \sum_{m=0}^{i}\omega_{m,i}\left(S_m\beta_{m,+} + \frac{q_m}{2}K_m\right)\left(\lambda_m^{[0]} - \frac{q_m}{2}\frac{\alpha_{m,-}}{\alpha_{m,+}}\right) \end{aligned} \tag{4.171}$$

where

$$\omega_{m,i} = \begin{cases} \prod_{r=m+1}^{i}\frac{\lambda_r^{[0]} - \frac{q_r}{2}\frac{\alpha_{r,-}}{\alpha_{r,+}}}{\xi_r^{[0]} - \frac{q_r}{2}\frac{\alpha_{r,-}}{\alpha_{r,+}}} & \text{if } m < i \\ 1 & \text{if } m = i. \end{cases} \tag{4.172}$$

Therefore, in order to find $\lambda_i^{[1]}$ for $i \geq 1$ all we need to know is $\lambda_0^{[1]}$ and $\lambda_m^{[0]}$ for $0 \leq m \leq i$. By letting $i = M+1$ and using the fact that $\lambda_{M+1}^{[1]} = 0$ (from (4.157)), we can then solve for $\lambda_0^{[1]}$ and the lemma follows. ■

4.4.2 General Results

Theorem 4.11 (Reversal Potential: General Case) *Let* $\lambda_0^{[0]}$ *be such that if* (4.163) *is solved repeatedly for* $i = 0, 1, \ldots, M+1$ *in conjunction with* (4.158)*, then* $\lambda_{M+1,0} = c_R$*. Then*

$$V_{rev} = \sum_{i=0}^{M+1} \alpha_i \ln\left(\frac{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i}\right) + \frac{1}{2}\sum_{i=1}^{M} \ln\left(\frac{\left(\xi_i^{[0]} - \frac{q_i}{2}\right)\left(\lambda_i^{[0]} + \frac{q_i}{2}\right)}{\left(\xi_i^{[0]} + \frac{q_i}{2}\right)\left(\lambda_i^{[0]} - \frac{q_i}{2}\right)}\right). \tag{4.173}$$

Proof. Taylor-expanding $V(I)$ for small I gives

$$V(I) = V(0) + \frac{dV}{dI}(0)\, I + \frac{d^2V}{dI^2}(0)\, I^2 + \cdots . \tag{4.174}$$

Therefore V_{rev} is the first term of the two expansions in Lemma 4.9. ■

Theorem 4.12 (Conductance at Reversal Potential: General Case) *Let* $\lambda_0^{[0]}$ *be as in Theorem 4.11. Then*

$$\frac{dV}{dI}(0) = \sum_{i=0}^{M} \left(H_i - H_i'\right)\lambda_i^{[1]} + \sum_{i=0}^{M+1} K_i \tag{4.175}$$

where H_i*,* H_i'*, and* K_i *are given by* (4.178)*,* (4.180)*, and* (4.165) *respectively and the* $\lambda_i^{[1]}$ *are given by Lemma 4.10.*

Proof. By (4.166), (4.167), (4.174), and (4.159) we have

$$\begin{align}
\frac{dV}{dI}(0)-\sum_{i=0}^{M+1}K_i &= \sum_{i=0}^{M+1}\alpha_i\left(\frac{\lambda_i^{[1]}}{\lambda_i^{[0]}-\frac{q_i}{2}\alpha_i}-\frac{\xi_i^{[1]}}{\xi_i^{[0]}-\frac{q_i}{2}\alpha_i}\right) \tag{4.176}\\
&\quad +\frac{1}{2}\sum_{i=0}^{M+1}\left(\frac{\xi_i^{[1]}}{\xi_i^{[0]}-\frac{q_i}{2}}-\frac{\lambda_i^{[1]}}{\lambda_i^{[0]}-\frac{q_i}{2}}-\frac{\xi_i^{[1]}}{\xi_i^{[0]}+\frac{q_i}{2}}+\frac{\lambda_i^{[1]}}{\lambda_i^{[0]}+\frac{q_i}{2}}\right) \notag\\
&= \sum_{i=0}^{M}\lambda_i^{[1]}\left(\frac{\alpha_i}{\lambda_i^{[0]}-\frac{q_i}{2}\alpha_i}-\frac{\frac{q_i}{2}}{\left(\lambda_i^{[0]}\right)^2-\frac{q_i^2}{4}}\right) \tag{4.177}\\
&\quad -\sum_{i=1}^{M+1}\lambda_{i-1}^{[1]}\frac{\lambda_{i-1}^{[0]}}{\xi_i^{[0]}}\left(\frac{\alpha_i}{\xi_i^{[0]}-\frac{q_i}{2}\alpha_i}-\frac{\frac{q_i}{2}}{\left(\xi_i^{[0]}\right)^2-\frac{q_i^2}{4}}\right). \notag
\end{align}$$

where we also used $\xi_0^{[1]}=0$ and $\lambda_{M+1}^{[1]}=0$. Let

$$H_i=\frac{\alpha_i}{\lambda_i^{[0]}-\frac{q_i}{2}\alpha_i}-\frac{\frac{q_i}{2}}{\left(\lambda_i^{[0]}\right)^2-\frac{q_i^2}{4}} \qquad (i=0,1,\ldots,M) \tag{4.178}$$

$$\begin{align}
H_i' &= \frac{\lambda_i^{[0]}}{\xi_{i+1}^{[0]}}\left(\frac{\alpha_{i+1}}{\xi_{i+1}^{[0]}-\frac{q_{i+1}}{2}\alpha_{i+1}}-\frac{\frac{q_{i+1}}{2}}{\left(\xi_{i+1}^{[0]}\right)^2-\frac{q_{i+1}^2}{4}}\right) \qquad (i=0,1,\ldots,M) \tag{4.179}\\
&= \frac{\lambda_i^{[0]}}{\sqrt{\left(\lambda_i^{[0]}\right)^2-\frac{q_i^2}{4}+\frac{q_{i+1}^2}{4}}}\left(\frac{\alpha_{i+1}}{\sqrt{\left(\lambda_i^{[0]}\right)^2-\frac{q_i^2}{4}+\frac{q_{i+1}^2}{4}}-\frac{q_{i+1}}{2}\alpha_{i+1}}-\frac{\frac{q_{i+1}}{2}}{\left(\lambda_i^{[0]}\right)^2-\frac{q_i^2}{4}}\right). \tag{4.180}
\end{align}$$

Then

$$\begin{align}
\frac{dV}{dI}(0)-\sum_{i=0}^{M+1}K_i &= \sum_{i=0}^{M}\lambda_i^{[1]}H_i-\sum_{i=1}^{M+1}\lambda_{i-1}^{[1]}H_{i-1}' \tag{4.181}\\
&= \sum_{i=0}^{M}\lambda_i^{[1]}H_i-\sum_{i=0}^{M}\lambda_i^{[1]}H_i'=\sum_{i=0}^{M}\left(H_i-H_i'\right)\lambda_i^{[1]} \tag{4.182}
\end{align}$$

which proves the theorem. ■

At this point it seems in order to discuss Theorems 4.11 and 4.12 and Lemma 4.10. The important thing to note is that after $\lambda_0^{[0]}$ is found for a pair of bath concentrations as described in the hypothesis of Theorem 4.11, then *both* the reversal potential (Theorem 4.11) and the conductance at the reversal potential (Theorem 4.12) follow immediately: the reversal potential $V(0)$ only depends on $\xi_i^{[0]}$ and $\lambda_i^{[0]}$ which, through (4.163), only depend on $\lambda_0^{[0]}$; the conductance at reversal potential is a function of K_i, H_i, and H_i' (which depend on the $\xi_i^{[0]}$ and $\lambda_i^{[0]}$ and thus only on $\lambda_0^{[0]}$) and $\lambda_i^{[1]}$ (which are functions of $\lambda_0^{[0]}$ by Lemma 4.10).

4.4.3 Special Case: Equal Bath Concentrations

We now consider the special case of equal bath concentrations (when $c_L = c_R = c$), since in this case many of the formulas of the previous section simplify greatly and is of experimental interest.

Lemma 4.13 *When* $c_L = c_R = c$,

$$\lambda_0^{[0]} = c \tag{4.183}$$

and

$$\lambda_i^{[0]} = \xi_i^{[0]} = \sqrt{c^2 + \frac{q_i^2}{4}}. \tag{4.184}$$

Therefore, in this case, we have an exact expression for the unknown $\lambda_0^{[0]}$.

Proof. It is straight-forward to see that $\lambda_0^{[0]} = c$ is the solution as described in the hypothesis of Theorem 4.11. From (4.163) it immediately follows that $\lambda_i^{[0]} = \xi_i^{[0]}$ and the lemma follows from (4.158). ■

The next theorem is obvious by physical intuition, but we include it to show that we do get this result exactly; that is, in this case, after all the approximating, we get an exact result.

Theorem 4.14 (Reversal Potential: Equal Bath Concentrations) *When* $c_L = c_R = c$, $V_{rev} = 0$.

Proof. The result follows immediately from Lemma 4.13 and Theorem 4.11. ■

These two results have been straight-forward. To find the conductance, however, there is a technical problem: the function K_i is not defined when $\lambda_0^{[0]} = c$ and $\lambda_i^{[0]} = \xi_i^{[0]}$. Therefore we need the following lemma.

Lemma 4.15

$$\lim_{\lambda_0^{[0]} \to c} K_i = -\frac{S_i \gamma_i}{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i} \tag{4.185}$$

Proof. We start with a rearrangement of (4.163):

$$c - \lambda_0^{[0]} = -\frac{S_0}{S_i \alpha_{i,+}} \left[\lambda_i^{[0]} - \xi_i^{[0]} + \frac{q_i}{2}\alpha_i \ln\left(\frac{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i} \right) \right]. \tag{4.186}$$

Therefore

$$\begin{aligned} \lim_{\lambda_0^{[0]} \to c} \frac{c - \lambda_0^{[0]}}{\ln\left(\frac{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i} \right)} &= -\frac{S_0}{S_i \alpha_{i,+}} \lim_{\lambda_i^{[0]} \to \xi_i^{[0]}} \left[\frac{\lambda_i^{[0]} - \xi_i^{[0]}}{\ln\left(\frac{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}{\xi_i^{[0]} - \frac{q_i}{2}\alpha_i} \right)} + \frac{q_i}{2}\alpha_i \right] && (4.187) \\ &= -\frac{S_0 \xi_i^{[0]}}{S_i \alpha_{i,+}} && (4.188) \end{aligned}$$

and

$$\lim_{\lambda_0^{[0]}\to c} \frac{c-\lambda_0^{[0]}}{\frac{q_i}{2}\alpha_i \frac{\lambda_i^{[0]}-\xi_i^{[0]}}{\left(\lambda_i^{[0]}-\frac{q_i}{2}\alpha_i\right)\left(\xi_i^{[0]}-\frac{q_i}{2}\alpha_i\right)}} \tag{4.189}$$

$$= -\frac{S_0}{S_i\alpha_{i,+}} \frac{\left(\xi_i^{[0]}-\frac{q_i}{2}\alpha_i\right)^2}{\frac{q_i}{2}\alpha_i} \lim_{\lambda_i^{[0]}\to\xi_i^{[0]}} \left[1+\frac{q_i}{2}\alpha_i \frac{\ln\left(\frac{\lambda_i^{[0]}-\frac{q_i}{2}\alpha_i}{\xi_i^{[0]}-\frac{q_i}{2}\alpha_i}\right)}{\lambda_i^{[0]}-\xi_i^{[0]}}\right] \tag{4.190}$$

$$= -\frac{S_0\xi_i^{[0]}}{S_i\alpha_{i,+}} \frac{\xi_i^{[0]}-\frac{q_i}{2}\alpha_i}{\frac{q_i}{2}\alpha_i}. \tag{4.191}$$

The lemma follows from the definition of K_i in (4.165). ■

There is now enough information to prove a theorem on conductance in this special case.

Theorem 4.16 (Conductance at $V_{\mathbf{rev}}$: Equal Bath Concentrations) *When*

$$c_L = c_R = c, \tag{4.192}$$

$$\frac{dV}{dI}(0) = \frac{1}{c^2}\sum_{i=0}^{M+1} S_i \left[\left(\frac{\alpha_{i,-}}{S_0}\lambda_0^{[1]} - \beta_{i,-}\right)\sqrt{c^2+\frac{q_i^2}{4}} - \frac{q_i}{2}\left(\frac{\alpha_{i,+}}{S_0}\lambda_0^{[1]} - \beta_{i,+}\right)\right] \tag{4.193}$$

where

$$\lambda_0^{[1]} = S_0 \frac{\sum_{m=1}^{M} S_m \left(\beta_{m,+}\sqrt{c^2+\frac{q_m^2}{4}} - \frac{q_m}{2}\beta_{m,-}\right)}{\sum_{m=0}^{M+1} S_m \left(\alpha_{m,+}\sqrt{c^2+\frac{q_m^2}{4}} - \frac{q_m}{2}\alpha_{m,-}\right)}. \tag{4.194}$$

Note that this a closed-form formula; there are no unknowns $\lambda_0^{[0]}$ to find like in Theorems 4.7, 4.11, and 4.12.

Proof. Instead of starting with Theorem 4.11, in the light of Lemma 4.13 it is easier to derive the result from scratch. Rearranging (4.164) with Lemmas 4.13 and 4.15

gives

$$\frac{\lambda_i^{[0]}}{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}\left(\lambda_i^{[1]} - \xi_i^{[1]}\right) = \frac{S_i}{S_0}\alpha_{i,+}\lambda_0^{[1]} - S_i\beta_{i,+} + \frac{q_i}{2}\frac{S_i\gamma_i}{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}. \tag{4.195}$$

Using (4.166), (4.167), and Lemmas 4.13 and 4.15 we have

$$\begin{aligned}
\frac{dV}{dI}(0) &= \sum_{i=0}^{M+1}\left(\frac{\alpha_i}{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i} - \frac{\frac{q_i}{2}}{\left(\lambda_i^{[0]}\right)^2 - \frac{q_i^2}{4}}\right)\left(\lambda_i^{[1]} - \xi_i^{[1]}\right) && (4.196)\\
&\quad - \sum_{i=0}^{M+1}\frac{S_i\gamma_i}{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}\\
&= \frac{1}{c^2}\sum_{i=0}^{M+1}\left(\alpha_i\lambda_i^{[0]} - \frac{q_i}{2}\right)\frac{\lambda_i^{[0]}}{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}\left(\lambda_i^{[1]} - \xi_i^{[1]}\right) - \sum_{i=0}^{M+1}\frac{S_i\gamma_i}{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i} && (4.197)\\
&= \frac{1}{c^2}\sum_{i=0}^{M+1}\left(\alpha_i\lambda_i^{[0]} - \frac{q_i}{2}\right)S_i\left(\alpha_{i,+}\lambda_0^{[1]} - \beta_{i,+}\right) && (4.198)\\
&\quad + \frac{1}{c^2}\sum_{i=0}^{M+1}\left[\frac{q_i}{2}\left(\alpha_i\lambda_i^{[0]} - \frac{q_i}{2}\right) - c^2\right]\frac{S_i\gamma_i}{\lambda_i^{[0]} - \frac{q_i}{2}\alpha_i}\\
&= \frac{1}{c^2}\sum_{i=0}^{M+1}\left(\alpha_i\lambda_i^{[0]} - \frac{q_i}{2}\right)S_i\left(\alpha_{i,+}\lambda_0^{[1]} - \beta_{i,+}\right) - \frac{1}{c^2}\sum_{i=0}^{M+1}\lambda_i^{[0]}S_i\gamma_i. && (4.199)
\end{aligned}$$

The formula for $\lambda_0^{[1]}$ follows from Lemma 4.10 (noting that $\omega_{m,i} = 1$ for all m and i) and Lemma 4.15. ■

4.4.4 Special Case: $M = 1$ with Diffusion Coefficient Drops

In this section we consider a special case that will be the focus of study for multiple salts. In particular we consider the case of uniform permanent charge (which means that there is only one interval of permanent charge or, equivalently, $M = 1$) where there is also a significant drop in the size of the diffusion coefficients of all the mobile ions as they enter the channel. The latter condition is generally believed to be true for channels on physical principles and has always been a result of the data fitting

([9], [10], [11]). The former condition is an important case both mathematically and experimentally: mathematically, along with the diffusion coefficient drops, it is possible in this case to approximate the unknown $\lambda_0^{[0]}$ in Theorems 4.11 and 4.12; experimentally, this is how the data of the calcium release channel was fit ([10], [11]).

We start by stating the simplifying assumptions about the diffusion coefficients:

Condition 4.17 (Diffusion Coefficient Drop) *Mathematically, the diffusion coefficient drop (DCD) condition is stated as: $\tau \ll 1$, where τ is defined as*

$$\tau = \max_{1 \leq i \leq M} \{D_{i,n}, D_{i,p}\}; \tag{4.200}$$

that is, τ is the maximum of all the diffusion coefficients inside the channel and this number is assumed to be small. With the scaling we have chosen (see Section 2.3), requiring $\tau \ll 1$ is equivalent to having both $D_{i,n} \ll D_{0,n}$ and $D_{i,p} \ll D_{0,p}$ for $1 \leq i \leq M$.

By this condition,

$$D_{i,f} = O(\tau) \qquad (1 \leq i \leq M;\ f = n, p), \tag{4.201}$$

and so we define

$$D'_{i,f} = \frac{D_{i,f}}{\tau} = O(1) \qquad (1 \leq i \leq M;\ f = n, p). \tag{4.202}$$

Substituting these into the definitions of the $\alpha_{i,\pm}$ and $\beta_{i,\pm}$ in (4.135) and (4.136), we find that

$$\alpha_{i,\pm} = O\left(\frac{1}{\tau}\right) \qquad (1 \leq i \leq M), \tag{4.203}$$

$$\beta_{i,\pm} = O\left(\frac{1}{\tau}\right) \qquad (1 \leq i \leq M)\,. \tag{4.204}$$

Then, by defining

$$\alpha'_{i,\pm} \equiv \frac{D_{0,n}D_{0,p}}{D'_{i,n}D'_{i,p}} \frac{D'_{i,p} \pm D'_{i,n}}{D_{0,p} + D_{0,n}} = O\left(1\right) \tag{4.205}$$

and

$$\beta'_{i,\pm} \equiv -\frac{1}{2} \frac{1}{D'_{i,n}D'_{i,p}} \frac{D_{0,n}D'_{i,p} \mp D_{0,p}D'_{i,n}}{D_{0,p} + D_{0,n}} = O\left(1\right), \tag{4.206}$$

we get

$$\alpha'_{i,\pm} = \tau\alpha_{i,\pm} \qquad \beta'_{i,\pm} = \tau\beta_{i,\pm} \qquad (i = 1, \ldots, M)\,. \tag{4.207}$$

Lastly we expand $\Lambda_i\left(I\right)$ and $\Xi_i\left(I\right)$ in powers of τ:

$$\Lambda_i\left(I\right) = \mu_i\left(x_{i+1}\right) = \Lambda_i^{\langle 0\rangle}\left(I\right) + \Lambda_i^{\langle 1\rangle}\left(I\right)\tau + \Lambda_i^{\langle 2\rangle}\left(I\right)\tau^2 + O\left(\tau^3\right) \tag{4.208}$$

$$\Xi_i\left(I\right) = \mu_i\left(x_i\right) = \Xi_i^{\langle 0\rangle}\left(I\right) + \Xi_i^{\langle 1\rangle}\left(I\right)\tau + \Xi_i^{\langle 2\rangle}\left(I\right)\tau^2 + O\left(\tau^3\right). \tag{4.209}$$

Theorem 4.18 *If Condition 4.17 is satisfied,* $M \geq 1$*, and* $I = O\left(\tau\right)$*, then*

$$\Lambda_0\left(I\right) = \mu_0\left(x_1\right) = c_L + O\left(\tau\right) \qquad \Xi_{M+1}\left(I\right) = \mu_{M+1}\left(x_{M+1}\right) = c_R + O\left(\tau\right). \tag{4.210}$$

Proof. From the above definitions, we have

$$S_i J_{i,\pm}^{(1)} = S_i\left(\frac{\alpha'_{i,\pm}}{S_0}\left(c_L - \Lambda_0\left(I\right)\right) + \beta'_{i,\pm} I\right)\frac{1}{\tau}. \tag{4.211}$$

Then, using the notation of (4.208),

$$S_i J_{i,\pm}^{(1)} = S_i \left(\frac{\alpha'_{i,\pm}}{S_0} \left(c_L - \Lambda_0^{\langle 0 \rangle}(I) \right) + \beta'_{i,\pm} I \right) \frac{1}{\tau} = O\left(\frac{1}{\tau}\right). \tag{4.212}$$

Rearranging (4.111) slightly, gives

$$\Lambda_i(I) - \Xi_i(I) + \frac{q_i}{2} \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}} \ln \left(\frac{\Lambda_i(I) - \frac{q_i}{2} \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}}{\Xi_i(I) - \frac{q_i}{2} \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}} \right) = -S_i J_{i,+}^{(1)}. \tag{4.213}$$

Since $\Lambda_i(I)$ and $\Xi_i(I)$ are $O(1)$ so is the left-hand side and from the above we have that the right-hand side is $O\left(\frac{1}{\tau}\right)$. Therefore we must have

$$\frac{\alpha'_{i,+}}{S_0} \left(c_L - \Lambda_0^{\langle 0 \rangle}(I) \right) + \beta'_{i,+} I = 0 \tag{4.214}$$

for all $1 \le i \le M$. In general this only makes sense if

$$I = o(\tau) \tag{4.215}$$

so that

$$\beta'_{i,+} I \ll \frac{\alpha'_{i,+}}{S_0} \left(c_L - \Lambda_0^{\langle 0 \rangle}(I) \right) \tag{4.216}$$

which we will assume since we are most interested in the case $I = 0$. (If $I = O(1)$, for example, then $\Lambda_0^{\langle 0 \rangle}(I)$ will depend on i, which is not possible. It does balance for all I only if $\frac{\beta'_{i,+}}{\alpha'_{i,+}}$ are equal for all i. However, this is not very useful, since resulting equations cannot be solved neatly unless $I = 0$.) In that case it follows that

$$\Lambda_0^{\langle 0 \rangle}(I) = c_L. \tag{4.217}$$

A similar argument for the $M + 1$ segment, proves the theorem. ■

Theorem 4.19 *Let $M = 1$. If Condition 4.17 is satisfied, then*

$$\Lambda_0(0) = \lambda_0^{[0]} = c_L + B_1 + B_2 + O\left(\tau^3\right) \tag{4.218}$$

$$\begin{aligned}\Xi_1(0) = \xi_1^{[0]} &= \sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{c_L}{\sqrt{c_L^2 + \frac{q_1^2}{4}}} B_1 \\ &\quad + \frac{c_L}{\sqrt{c_L^2 + \frac{q_1^2}{4}}} B_2 + \frac{1}{2\sqrt{c_L^2 + \frac{q_1^2}{4}}}\left(1 - \frac{c_L^2}{c_L^2 + \frac{q_1^2}{4}}\right) B_1^2 \\ &\quad + O\left(\tau^3\right)\end{aligned} \tag{4.219}$$

$$\begin{aligned}\Lambda_1(0) = \lambda_1^{[0]} &= \sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{c_R}{\sqrt{c_R^2 + \frac{q_1^2}{4}}} B_1 \\ &\quad - \frac{c_R}{\sqrt{c_R^2 + \frac{q_1^2}{4}}} B_2 + \frac{1}{2\sqrt{c_R^2 + \frac{q_1^2}{4}}}\left(1 - \frac{c_R^2}{c_R^2 + \frac{q_1^2}{4}}\right) B_1^2 + O\left(\tau^3\right)\end{aligned} \tag{4.220}$$

$$\Xi_2(0) = \xi_2^{[0]} = c_R - B_1 - B_2 + O\left(\tau^3\right) \tag{4.221}$$

where

$$\begin{aligned}B_1 &= \frac{1}{\alpha_{1,+}} \frac{S_0}{S_1}\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\alpha_1 \ln\left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1}\right)\right) \\ &= O(\tau)\end{aligned} \tag{4.222}$$

$$\begin{aligned}B_2 &= -B_1 \frac{1}{\alpha_{1,+}} \frac{S_0}{S_1} \frac{c_L\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1\right) + c_R\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1\right)}{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1\right)} \\ &= O\left(\tau^2\right).\end{aligned} \tag{4.223}$$

Proof. We start with some relations between the Ξ_i's and Λ_i's. From (4.111) with $i = 0$ and 2, (4.154), (4.156), and the assumption that the baths are identical (except ion concentration) we get

$$\Xi_2(I) = c_R - S_2 J_{2,+}^{(1)} = c_R - S_0 J_{0,+}^{(1)} = c_R + c_L - \Lambda_0(I). \tag{4.224}$$

Also, from (4.116) we have

$$\Xi_1(I) = \sqrt{\Lambda_0^2(I) + \frac{q_1^2}{4}} \tag{4.225}$$

and

$$\Xi_2(I) = \sqrt{\Lambda_1^2(I) - \frac{q_1^2}{4}}. \tag{4.226}$$

Therefore

$$\Lambda_1(I) = \sqrt{(c_R + c_L - \Lambda_0(I))^2 + \frac{q_1^2}{4}}. \tag{4.227}$$

Evaluating (4.111) at $i = 1$ with $I = 0$ gives

$$0 = \Lambda_1(0) - \Xi_1(0) + \frac{q_1}{2}\alpha_1 \ln\left(\frac{\Lambda_1(0) - \frac{q_1}{2}\alpha_1}{\Xi_1(0) - \frac{q_1}{2}\alpha_1}\right) + \frac{S_1}{S_0}\alpha_{1,+}(c_L - \Lambda_0(0)) \tag{4.228}$$

and therefore

$$\begin{aligned} 0 \;=\; & \sqrt{(c_R + c_L - \Lambda_0(0))^2 + \frac{q_1^2}{4}} - \sqrt{\Lambda_0^2(0) + \frac{q_1^2}{4}} \\ & + \frac{q_1}{2}\alpha_1 \ln\left(\frac{\sqrt{(c_R + c_L - \Lambda_0(0))^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1}{\sqrt{\Lambda_0^2(0) + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1}\right) + \frac{S_1}{S_0}\alpha_{1,+}(c_L - \Lambda_0(0)). \end{aligned} \tag{4.229}$$

From Theorem 4.18 we know that

$$\Lambda_0(0) = c_L + O(\tau). \tag{4.230}$$

With

$$\Lambda_0(0) = c_L + \Lambda_0^{\langle 1\rangle}(0)\,\tau + \Lambda_0^{\langle 2\rangle}(0)\,\tau^2 + O\left(\tau^3\right) \tag{4.231}$$

and expanding (4.229) in powers of τ (keeping in mind that $\alpha_{1,+} = O\left(\frac{1}{\tau}\right)$) and equating like powers of τ, we get

$$0 = \sqrt{c_R^2 + \frac{q_1^2}{4}} - \sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\alpha_1 \ln\left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1}\right) - \frac{\alpha_{1,+}' S_1}{S_0}\Lambda_0^{\langle 1\rangle}(0) \tag{4.232}$$

$$\begin{aligned} 0 \;&=\; \frac{q_1}{2}\alpha_1\left(-\frac{c_R}{\sqrt{c_R^2 + \frac{q_1^2}{4}}}\frac{\Lambda_0^{\langle 1\rangle}(0)}{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1} - \frac{c_L}{\sqrt{c_L^2 + \frac{q_1^2}{4}}}\frac{\Lambda_0^{\langle 1\rangle}(0)}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1}\right) \\ &\quad - \frac{c_L}{\sqrt{c_L^2 + \frac{q_1^2}{4}}}\Lambda_0^{\langle 1\rangle}(0) - \frac{c_R}{\sqrt{c_R^2 + \frac{q_1^2}{4}}}\Lambda_0^{\langle 1\rangle}(0) - \frac{\alpha_{1,+}' S_1}{S_0}\Lambda_0^{\langle 2\rangle}(0). \end{aligned} \tag{4.233}$$

Solving for $\Lambda_0^{\langle 1\rangle}(0)$ and $\Lambda_0^{\langle 1\rangle}(0)$ and letting $B_1 = \Lambda_0^{\langle 1\rangle}(0)\,\tau$ and $B_2 = \Lambda_0^{\langle 2\rangle}(0)\,\tau^2$ gives the formula for $\Lambda_0(0)$.

For the other formulas, start by expanding (4.227) in powers of τ:

$$\begin{aligned} \Lambda_1(0) \;&=\; \sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{c_R}{\sqrt{c_R^2 + \frac{q_1^2}{4}}}\Lambda_0^{\langle 1\rangle}(0)\,\tau \\ &\quad - \left(\frac{c_R}{\sqrt{c_R^2 + \frac{q_1^2}{4}}}\Lambda_0^{\langle 2\rangle}(0) - \frac{1}{2\sqrt{c_R^2 + \frac{q_1^2}{4}}}\left(1 - \frac{c_R^2}{c_R^2 + \frac{q_1^2}{4}}\right)\left(\Lambda_0^{\langle 1\rangle}(0)\right)^2\right)\tau^2 \\ &\quad + O\left(\tau^3\right) \end{aligned} \tag{4.234}$$

and then use the definitions of B_1 and B_2 given above. Similarly, expanding

$$\Xi_1\left(I\right) = \sqrt{\Lambda_0^2\left(I\right) + \frac{q_1^2}{4}} \tag{4.235}$$

in powers of τ, we get

$$\begin{aligned} \Xi_1\left(0\right) &= \sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{c_L}{\sqrt{c_L^2 + \frac{q_1^2}{4}}}\Lambda_0^{\langle 1\rangle}\left(0\right)\tau \\ &\quad + \left(\frac{c_L}{\sqrt{c_L^2 + \frac{q_1^2}{4}}}\Lambda_0^{\langle 2\rangle}\left(0\right) + \frac{1}{2\sqrt{c_L^2 + \frac{q_1^2}{4}}}\left(1 - \frac{c_L^2}{c_L^2 + \frac{q_1^2}{4}}\right)\left(\Lambda_0^{\langle 1\rangle}\left(0\right)\right)^2\right)\tau^2 \\ &\quad + O\left(\tau^3\right). \end{aligned} \tag{4.236}$$

Finally, using

$$\Xi_2\left(0\right) = c_R + c_L - \Lambda_0\left(0\right) \tag{4.237}$$

the theorem follows. ■

Since the only unknown for all the formulas derived in the previous sections was $\Lambda_0\left(0\right)$, for $M = 1$ we now have explicit, closed-form formulas for V_{rev} and $\frac{dV}{dI}\left(0\right)$ from Theorems 4.11 and 4.12:

Theorem 4.20 (Reversal Potential: $M = 1$ and Diffusion Coefficient Drop) *Let $M = 1$. If Condition 4.17 is satisfied, then*

$$\begin{aligned} V_{rev} &= \alpha_0 \ln\left(\frac{c_R\lambda_0^{[0]}}{c_L\xi_2^{[0]}}\right) + \alpha_1 \ln\left(\frac{\lambda_1^{[0]} - \frac{q_1}{2}\alpha_1}{\xi_1^{[0]} - \frac{q_1}{2}\alpha_1}\right) \\ &\quad + \frac{1}{2}\ln\left(\frac{\left(\xi_1^{[0]} - \frac{q_1}{2}\right)\left(\lambda_1^{[0]} + \frac{q_1}{2}\right)}{\left(\xi_1^{[0]} + \frac{q_1}{2}\right)\left(\lambda_1^{[0]} - \frac{q_1}{2}\right)}\right) \end{aligned} \tag{4.238}$$

where $\lambda_0^{[0]}$, $\xi_1^{[0]}$, $\lambda_1^{[0]}$, and $\xi_2^{[0]}$ are given in Theorem 4.19. As stated in Theorem 4.19, $B_1 = O\left(\tau\right)$ and $B_2 = O\left(\tau^2\right)$. If both B_1 and B_2 are used in the calculation of V_{rev}, *then the error terms are* $O\left(\tau^3\right)$. *If the* $O\left(\tau^2\right)$ *terms are not used, then the error terms are* $O\left(\tau^2\right)$. *If both* B_1 *and* B_2 *are set to zero, then the error terms are* $O\left(\tau\right)$. *In that case, we have*

$$\begin{aligned} V_{rev} &= \alpha_1 \ln\left(\frac{\sqrt{c_R^2+\frac{q_1^2}{4}}-\frac{q_1}{2}\alpha_1}{\sqrt{c_L^2+\frac{q_1^2}{4}}-\frac{q_1}{2}\alpha_1}\right) \\ &\quad +\frac{1}{2}\ln\left(\frac{\left(\sqrt{c_L^2+\frac{q_1^2}{4}}-\frac{q_1}{2}\right)\left(\sqrt{c_R^2+\frac{q_1^2}{4}}+\frac{q_1}{2}\right)}{\left(\sqrt{c_L^2+\frac{q_1^2}{4}}+\frac{q_1}{2}\right)\left(\sqrt{c_R^2+\frac{q_1^2}{4}}-\frac{q_1}{2}\right)}\right)+O\left(\tau\right). \end{aligned} \tag{4.239}$$

As before, we get $V_{rev}=0$ *when* $c_L=c_R$.

Theorem 4.21 (Conductance at $V_{\mathbf{rev}}$: $M=1$ and Diffusion Coeff. Drop) *Let* $M=1$. *If Condition 4.17 is satisfied, then*

$$\begin{aligned} \frac{dV}{dI}(0) &= \left(\frac{\alpha_0}{\lambda_0^{[0]}}-H_0'\right)\lambda_0^{[1]}+\left(H_1-\alpha_0\frac{\lambda_1^{[0]}}{\left(\xi_2^{[0]}\right)^2}\right)\lambda_1^{[1]}+K_1 \\ &\quad +\frac{S_0\gamma_0}{c_L-\lambda_0^{[0]}}\ln\left(\frac{c_R\lambda_0^{[0]}}{c_L\xi_2^{[0]}}\right) \end{aligned} \tag{4.240}$$

where

$$H_0'=\frac{\lambda_0^{[0]}}{\xi_1^{[0]}}\left(\frac{\alpha_1}{\xi_1^{[0]}-\frac{q_1}{2}\alpha_1}-\frac{\frac{q_1}{2}}{\left(\lambda_1^{[0]}\right)^2}\right) \tag{4.241}$$

$$H_1=\frac{\alpha_1}{\lambda_1^{[0]}-\frac{q_1}{2}\alpha_1}-\frac{\frac{q_1}{2}}{\left(\lambda_1^{[0]}\right)^2-\frac{q_1^2}{4}} \tag{4.242}$$

$$\lambda_0^{[1]} = \frac{S_1\beta_{1,+} + \frac{q_1}{2}K_1}{\alpha_{0,+}\left(\frac{\lambda_0^{[0]}}{\xi_1^{[0]} - \frac{q_1}{2}\alpha_1} + \frac{\xi_2^{[0]}}{\lambda_1^{[0]} - \frac{q_1}{2}\alpha_1}\right) + \frac{S_1}{S_0}\alpha_{1,+}} \tag{4.243}$$

$$\lambda_1^{[1]} = \frac{\lambda_1^{[0]} - \frac{q_1}{2}\alpha_1}{\lambda_1^{[0]}}\left[\left(\frac{\lambda_0^{[0]}}{\xi_1^{[0]} - \frac{q_1}{2}\alpha_1} + \frac{S_1}{S_0}\alpha_{1,+}\right)\lambda_0^{[1]} - \left(S_1\beta_{1,+} + \frac{q_1}{2}K_1\right)\right] \tag{4.244}$$

$$K_1 = \frac{S_0\gamma_1}{\alpha_{1,+}\left(c_L - \lambda_0^{[0]}\right)}\left[\ln\left(\frac{\lambda_1^{[0]} - \frac{q_1}{2}\alpha_1}{\xi_1^{[0]} - \frac{q_1}{2}\alpha_1}\right) + \frac{q_1}{2}\alpha_1\frac{\lambda_1^{[0]} - \xi_1^{[0]}}{\left(\lambda_1^{[0]} - \frac{q_1}{2}\alpha_1\right)\left(\xi_1^{[0]} - \frac{q_1}{2}\alpha_1\right)}\right] \tag{4.245}$$

and $\lambda_0^{[0]}$, $\xi_1^{[0]}$, $\lambda_1^{[0]}$, *and* $\xi_2^{[0]}$ *are given in Theorem 4.19. As stated in Theorem 4.19,* $B_1 = O(\tau)$ *and* $B_2 = O(\tau^2)$. *If both* B_1 *and* B_2 *are used in the calculation of* $\frac{dV}{dI}(0)$, *then the error terms are* $O(\tau^3)$. *If* B_2 *is set to zero, then the error terms are* $O(\tau^2)$. *However,* B_1 *and* B_2 *cannot both be set to zero, since then* K_1 *is not defined. (It is assumed the* $c_L \neq c_R$. *When this is the case, Theorem 4.16 should be used.)*

4.4.5 Special Case: $M = 2$ with Diffusion Coefficient Drops

In this section we consider how the case $M = 2$ (that is, two intervals of constant permanent charge) is simplified by the Diffusion Coefficient Drop Condition 4.17 and Theorem 4.18.

Theorem 4.22 *Let* $M = 2$. *If Condition 4.17 is satisfied, then*

$$\Lambda_0^{\langle 0\rangle}(0) = c_L \tag{4.246}$$

$$\Xi_1^{\langle 0\rangle}(0) = \sqrt{c_L^2 + \frac{q_1^2}{4}} \tag{4.247}$$

$$\Lambda_2^{\langle 0\rangle}(0) = \sqrt{c_R^2 + \frac{q_1^2}{4}} \tag{4.248}$$

$$\Xi_3^{\langle 0\rangle}(0) = c_R \tag{4.249}$$

$\Lambda_1^{\langle 0\rangle}(0)$ is the solution to

$$\begin{aligned} &\Lambda_1^{\langle 0\rangle}(0) + \frac{S_1}{S_2}\frac{\alpha_{1,+}}{\alpha_{2,+}}\sqrt{\left(\Lambda_1^{\langle 0\rangle}(0)\right)^2 - \frac{q_1^2}{4} + \frac{q_2^2}{4}} + \frac{q_1}{2}\alpha_1 \ln\left(\frac{\Lambda_1^{\langle 0\rangle}(0) - \frac{q_1}{2}\alpha_1}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1}\right) \\ &-\frac{q_2}{2}\alpha_2\frac{S_1}{S_2}\frac{\alpha_{1,+}}{\alpha_{2,+}}\ln\left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_2}{2}\alpha_2}{\sqrt{\left(\Lambda_1^{\langle 0\rangle}(0)\right)^2 - \frac{q_1^2}{4} + \frac{q_2^2}{4}} - \frac{q_2}{2}\alpha_2}\right) \\ = \;& \sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{S_1}{S_2}\frac{\alpha_{1,+}}{\alpha_{2,+}}\sqrt{c_R^2 + \frac{q_1^2}{4}} \end{aligned} \tag{4.250}$$

and

$$\Xi_2^{\langle 0\rangle}(0) = \sqrt{\left(\Lambda_1^{\langle 0\rangle}(0)\right)^2 - \frac{q_1^2}{4} + \frac{q_2^2}{4}}. \tag{4.251}$$

Proof. The first three equations are merely a restatement of Theorem 4.18. $\Lambda_1^{\langle 0\rangle}(0)$ is found by considering (4.111) with $I = 0$ for both $i = 1$ and $i = 2$:

$$0 = \Lambda_1(0) - \Xi_1(0) + \frac{q_1}{2}\alpha_1 \ln\left(\frac{\Lambda_1(0) - \frac{q_1}{2}\alpha_1}{\Xi_1(0) - \frac{q_1}{2}\alpha_1}\right) + S_1\alpha_{1,+}\left(c_L - \Lambda_0(0)\right) \tag{4.252}$$

$$0 = \Lambda_2(0) - \Xi_2(0) + \frac{q_2}{2}\alpha_1 \ln\left(\frac{\Lambda_2(0) - \frac{q_2}{2}\alpha_1}{\Xi_2(0) - \frac{q_2}{2}\alpha_1}\right) + S_2\alpha_{2,+}\left(c_L - \Lambda_0(0)\right). \tag{4.253}$$

Exanding these in τ using (4.208) and (4.209) gives

$$0 = \Lambda_1^{\langle 0\rangle}(0) - \Xi_1^{\langle 0\rangle}(0) + \frac{q_1}{2}\alpha_1 \ln\left(\frac{\Lambda_1^{\langle 0\rangle}(0) - \frac{q_1}{2}\alpha_1}{\Xi_1^{\langle 0\rangle}(0) - \frac{q_1}{2}\alpha_1}\right) - S_1\alpha_{1,+}\Lambda_0^{\langle 1\rangle}(0) \tag{4.254}$$

$$0 = \Lambda_2^{\langle 0\rangle}(0) - \Xi_2^{\langle 0\rangle}(0) + \frac{q_2}{2}\alpha_2 \ln\left(\frac{\Lambda_2^{\langle 0\rangle}(0) - \frac{q_2}{2}\alpha_2}{\Xi_2^{\langle 0\rangle}(0) - \frac{q_2}{2}\alpha_2}\right) - S_2\alpha_{2,+}\Lambda_0^{\langle 1\rangle}(0). \tag{4.255}$$

Eliminating $\Lambda_0^{\langle 1\rangle}(0)$ gives

$$\begin{aligned} & \Lambda_1^{\langle 0\rangle}(0) - \Xi_1^{\langle 0\rangle}(0) + \frac{q_1}{2}\alpha_1 \ln\left(\frac{\Lambda_1^{\langle 0\rangle}(0) - \frac{q_1}{2}\alpha_1}{\Xi_1^{\langle 0\rangle}(0) - \frac{q_1}{2}\alpha_1}\right) \\ = \; & \frac{S_1}{S_2}\frac{\alpha_{1,+}}{\alpha_{2,+}}\left[\Lambda_2^{\langle 0\rangle}(0) - \Xi_2^{\langle 0\rangle}(0) + \frac{q_2}{2}\alpha_2 \ln\left(\frac{\Lambda_2^{\langle 0\rangle}(0) - \frac{q_2}{2}\alpha_2}{\Xi_2^{\langle 0\rangle}(0) - \frac{q_2}{2}\alpha_2}\right)\right] \end{aligned} \tag{4.256}$$

and since

$$\Xi_2^{\langle 0\rangle}(0) = \sqrt{\left(\Lambda_1^{\langle 0\rangle}(0)\right)^2 - \frac{q_1^2}{4} + \frac{q_2^2}{4}} \tag{4.257}$$

the theorem follows. ■

Theorem 4.23 (Reversal Potential: $M = 2$ and Diffusion Coefficient Drop) *Let $M = 2$. If Condition 4.17 is satisfied, then*

$$\begin{aligned} V_{rev} = {} & \alpha_1 \ln \left(\frac{\Lambda_1^{\langle 0 \rangle}(0) - \frac{q_1}{2}\alpha_1}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1} \right) + \alpha_2 \ln \left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_2}{2}\alpha_2}{\sqrt{\left(\Lambda_1^{\langle 0 \rangle}(0)\right)^2 - \frac{q_1^2}{4} + \frac{q_2^2}{4}} - \frac{q_2}{2}\alpha_2} \right) \\ & + \frac{1}{2} \ln \left(\frac{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)\left(\Lambda_1^{\langle 0 \rangle}(0) + \frac{q_1}{2}\right)}{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)\left(\Lambda_1^{\langle 0 \rangle}(0) - \frac{q_1}{2}\right)} \right) \\ & + \frac{1}{2} \ln \left(\frac{\left(\sqrt{\left(\Lambda_1^{\langle 0 \rangle}(0)\right)^2 - \frac{q_1^2}{4} + \frac{q_2^2}{4}} - \frac{q_2}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} + \frac{q_2}{2}\right)}{\left(\sqrt{\left(\Lambda_1^{\langle 0 \rangle}(0)\right)^2 - \frac{q_1^2}{4} + \frac{q_2^2}{4}} + \frac{q_2}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_2}{2}\right)} \right) \\ & + O(\tau) \end{aligned} \tag{4.258}$$

where $\Lambda_1^{\langle 0 \rangle}(0)$ is given by (4.250).

Unfortunately it is not possible to apply the results of Theorem 4.22 to find the conductance at reversal potential since the functions K_i have $c_L - \Lambda_0(0)$ in the denominator and this approximated in Theorem 4.22 by 0. Thus the K_i are undefined without a better approximation of $c_L - \Lambda_0(0)$ which is not possible for $M = 2$ in a simple way.

4.5 Boundary Conditions at the Channel Entrances

In this section we derive boundary conditions for the function ϕ, n, and p at the channel entrances (so that the baths may be ignored) as discussed in Section 2.1. We then compare these results to the boundary conditions that have been used in the past to fit the data of several channels.

4.5.1 Derivation

Theorem 4.24 *For one salt, if Condition 4.17 is satisfied and when currents are small, the problem of considering the channel along with the baths may be reduced to the problem of considering only the channel with following boundary conditions:*

$$\beta_{L,\phi} = \phi_0^{(0)}(0) + \Psi_L + O(\varepsilon,\tau) \qquad \beta_{R,\phi} = \phi_{M+1}^{(0)}(x_{M+1}) + \Psi_R + O(\varepsilon,\tau) \tag{4.259}$$

$$\beta_{L,n} = c_L \exp(\Psi_L) + O(\varepsilon,\tau) \qquad \beta_{R,n} = c_R \exp(\Psi_R) + O(\varepsilon,\tau) \tag{4.260}$$

$$\beta_{L,p} = c_L \exp(-\Psi_L) + O(\varepsilon,\tau) \qquad \beta_{R,p} = c_R \exp(-\Psi_R) + O(\varepsilon,\tau) \tag{4.261}$$

where

$$\Psi_L = -\frac{2}{q_1}\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} - c_L\right) + \frac{1}{2}\ln\left(\frac{\sqrt{c_L^2+\frac{q_1^2}{4}}+\frac{q_1}{2}}{\sqrt{c_L^2+\frac{q_1^2}{4}}-\frac{q_1}{2}}\right) \tag{4.262}$$

$$\Psi_R = -\frac{2}{q_M}\left(\sqrt{c_R^2 + \frac{q_M^2}{4}} - c_R\right) + \frac{1}{2}\ln\left(\frac{\sqrt{c_R^2+\frac{q_M^2}{4}}+\frac{q_M}{2}}{\sqrt{c_R^2+\frac{q_M^2}{4}}-\frac{q_M}{2}}\right). \tag{4.263}$$

Proof. By Theorems 4.5 and 4.6 with $i = 0$ and $i = M$ we have

$$\begin{aligned}
\beta_{1,\phi}^{(0)} &= \frac{2}{q_1}\left(\mu_0(x_1) - \mu_1(x_1)\right) + \phi_1^{(0)}(x_1) && (4.264)\\
&= \phi_0^{(0)}(0) + \frac{2}{q_1}\left(c_L - \sqrt{c_L^2+\frac{q_1^2}{4}}\right) + \frac{1}{2}\ln\left(\frac{\sqrt{c_L^2+\frac{q_1^2}{4}}+\frac{q_1}{2}}{\sqrt{c_L^2+\frac{q_1^2}{4}}-\frac{q_1}{2}}\right) && (4.265)\\
&\quad + O(\tau)
\end{aligned}$$

$$\begin{aligned}\beta^{(0)}_{M+1,\phi} &= \frac{2}{q_M}\left(\mu_{M+1}\left(x_{M+1}\right)-\mu_M\left(x_{M+1}\right)\right)+\phi^{(0)}_M\left(x_{M+1}\right) &\quad (4.266)\\ &= \phi^{(0)}_{M+1}\left(x_{M+1}\right)+\frac{2}{q_M}\left(c_R-\sqrt{c_R^2+\frac{q_M^2}{4}}\right)+\frac{1}{2}\ln\left(\frac{\sqrt{c_R^2+\frac{q_M^2}{4}}+\frac{q_M}{2}}{\sqrt{c_R^2+\frac{q_M^2}{4}}-\frac{q_M}{2}}\right)\\ &\quad +O\left(\tau\right). &\quad (4.267)\end{aligned}$$

The concentration boundary conditions follow from the above and (4.75) – (4.78). ■

4.5.2 Comparison to Built-In Boundary Conditions

As discussed in Section 2.1, the so-called built-in boundary conditions have been used in the data fitting of several channels (for example, [9], [10], [11]). The resulting fits have been very good, leading to the hypothesis that perhaps these boundary conditions, while perhaps not completely physically plausible, are not too far off. Here we numerically compare the results of the previous theorem to the built-in boundary conditions and find that this is true (at least in the case of small currents and two monovalent ion species that experience a drop in diffusion coefficient upon entering the channel).

The built-in boundary conditions are as follows (for reference, see [8] and [9]) for a channel on the interval (x_1, x_{M+1}) (we use the notation of the previous sections):

$$\phi_{\mathrm{bi}}\left(x_1\right)=\ln\left(\frac{\sqrt{c_L^2+\frac{q_1^2}{4}}+\frac{q_1}{2}}{c_L}\right) \quad (4.268)$$

$$\phi_{\mathrm{bi}}\left(x_{M+1}\right)=\ln\left(\frac{\sqrt{c_R^2+\frac{q_{M+1}^2}{4}}+\frac{q_{M+1}}{2}}{c_R}\right) \quad (4.269)$$

$$\phi\left(x_1\right)=\phi\left(0\right)+\phi_{\mathrm{bi}}\left(x_1\right) \qquad \phi\left(x_{M+1}\right)=\phi\left(1\right)+\phi_{\mathrm{bi}}\left(x_{M+1}\right) \quad (4.270)$$

$$n\left(x_1\right)=c_L \exp\left(\phi_{\mathrm{bi}}\left(x_1\right)\right) \qquad n\left(x_{M+1}\right)=c_R \exp\left(\phi_{\mathrm{bi}}\left(x_{M+1}\right)\right) \tag{4.271}$$

$$p\left(x_1\right)=c_L \exp\left(-\phi_{\mathrm{bi}}\left(x_1\right)\right) \qquad p\left(x_{M+1}\right)=c_R \exp\left(-\phi_{\mathrm{bi}}\left(x_{M+1}\right)\right). \tag{4.272}$$

The (single) potentials $\phi_{\mathrm{bi}}\left(x_1\right)$ and $\phi_{\mathrm{bi}}\left(x_{M+1}\right)$ are also called Donnan potentials (see, for example, [22]).

To compare these boundary conditions with those of Theorem 4.5 we consider one side of a channel with permanent charge q. In Figure 4-5 we graph the Donnan potential and the SP-derived boundary condition as function of $\frac{c}{q}$ (c is the bath concentration on that side of the channel). In Figure 4-6 we graph $\frac{n}{q}$ (the concentration of the negative ion species compared to the permanent charge) from the built-in boundary conditions and the SP-derived boundary condition as functions of $\frac{c}{q}$. From these graphs it is easy to see why the built-in boundary conditions can work well; they and the SP-derived boundary conditions have the similar shapes and are numerically similar.

4.5.3 Why Doesn't SP Give Donnan Potentials?

Since Donnan potentials are a classical result of permeable membranes theory (see, for example, [22] and [44]), it seems in order to discuss why the singular perturbation approach does not give Donnan potentials, but rather potentials that are (in absolute value) smaller (see Figure 4-5).

In short, the problem does not lie with the SP approach or approximations, but rather with the way the Donnan potentials are classically derived. Whether the Donnan potential is derived by thermodynamic arguments ([22, Chapter 5], [44]) or from a Nernst-Planck equation ([8], [22, Chapter 8]) the argument is always made that the ionic solution and the system must be electrically neutral *everywhere*. This assumption is wrong. As mentioned in Section 2.1, there is a simple physical

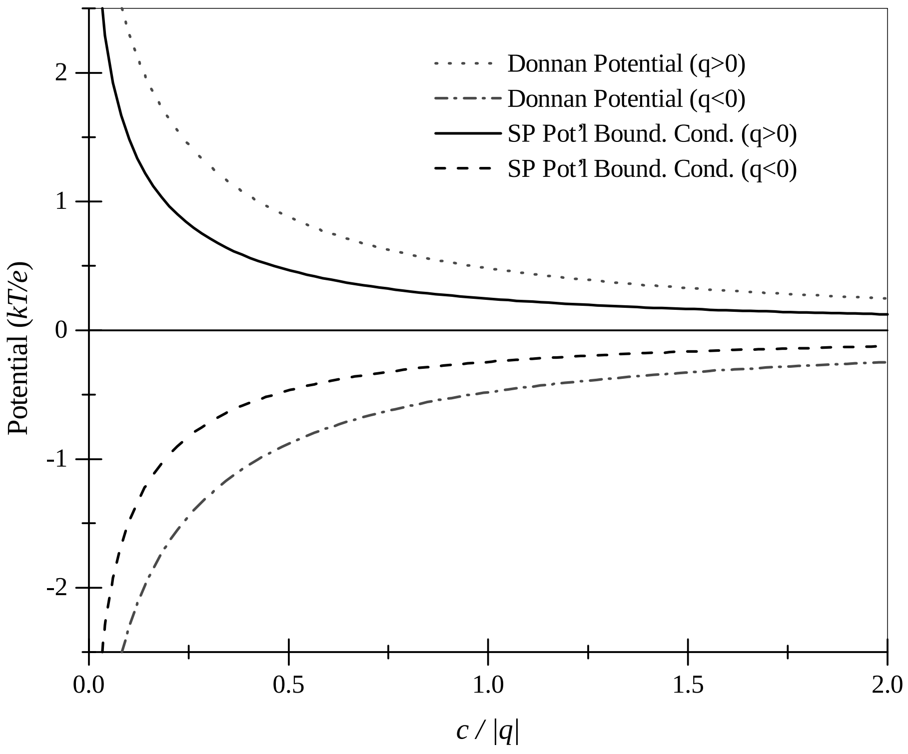

Figure 4-5: Comparision of the Donnan potential and SP-derived boundary condition from Theorem 4.5 at a channel entrance. c is the bath concentration on the side of the entrance and q is the permanent charge of the channel at the entrance.

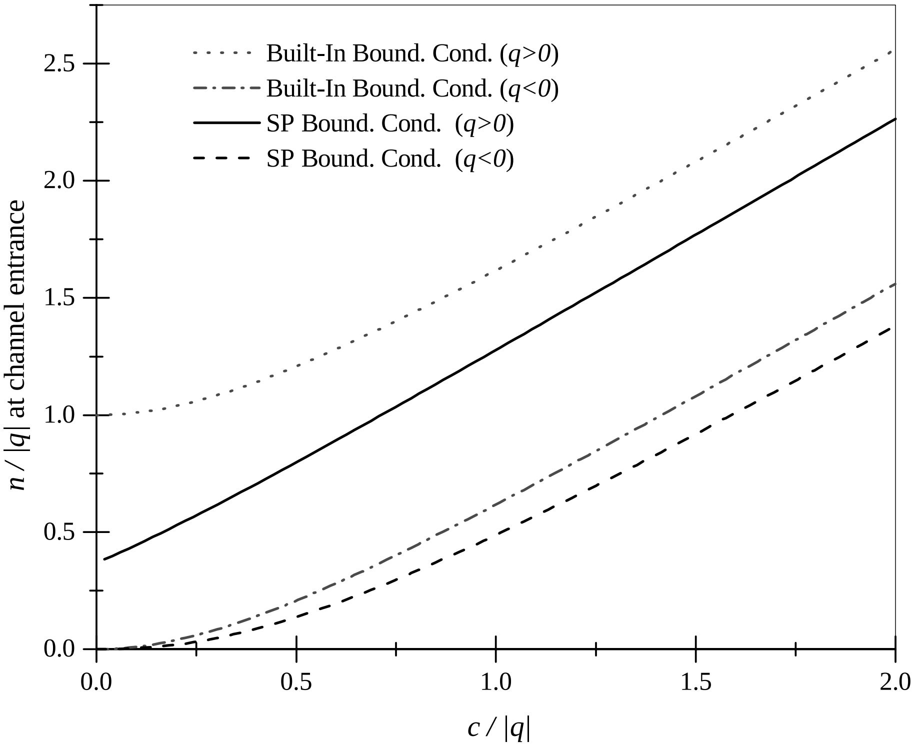

Figure 4-6: Comparision of the built-in boundary condition and SP-derived boundary condition from Theorem 4.5 at a channel entrance for n. c is the bath concentration on the side of the entrance and q is the permanent charge of the channel at the entrance.

argument why it is plausible to have a thin layer of space charge near the membrane. Perhaps the argument can be made that when considering membranes (which are huge compared to the thickness of these layers) that this layer can be neglected. This argument does not work for channels, however; the sizes of the channel opening and the bath considered in the analysis are roughly the same size as the layer of space charge and therefore cannot be ignored.

4.6 Comparing Formulas to Numerical Solutions

In this section we attempt to dissect how well the derived formulas work and what parameters are most important in determining the accuracy of the approximations.

The single largest source of error is break-down of the mathematical condition that the layer functions on each side of an interval (x_i, x_{i+1}) (on which q and the diffusion coefficients are constant) do not interact with one another (see the discussion on page 55). The breakdown of this condition is illustrated in Figures 4-7 and 4-8. There are several causes for the breakdown of this condition. Intuitively, it happens under conditions when it is difficult for the channel to achieve electroneutrality and therefore the outer solutions (which were derived under the condition of electroneutrality) do not have a chance to assert themselves. The conditions that bring this about include: the intervals (x_i, x_{i+1}) are too short; the bath concentrations are too low compared to the permanent charge; there is too much current flowing through the channel. Since we are mainly focusing on when there is no net current flowing, we will not discuss this last one.

The other two conditions, as stated, are a little vague. What is "too short" and what is "too low"? The short answer is that it depends on all the other parameters in the system. Specifically, take a channel with a uniform permanent charge distribution (that is, $M = 1$) and length d_1. Then, lowering one or both the bath concentrations will eventually lead to the breakdown of the condition that layers do not interact.

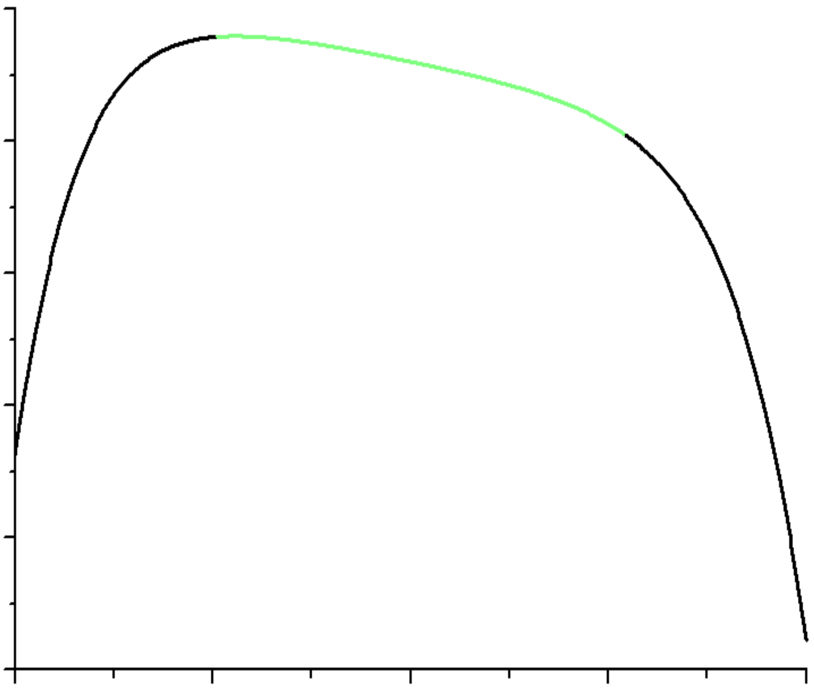

Figure 4-7: This figure is meant to illustrate how a function (for example, concentration as a function of position inside the channel) can be decomposed into an outer solution (light color) and layer functions (black). In this case the layers are seperated far enough so they are (very close to) zero well before reaching the other side. Thus they do not interact with one another and in the middle (light colored) section the outer solution dominants.

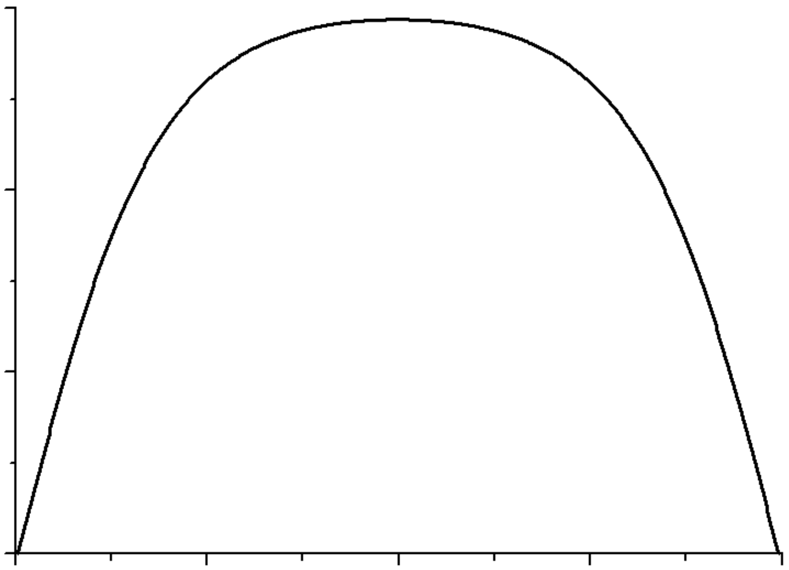

Figure 4-8: This figure illustrates what happens when the layer functions on each side of the interval do not go to zero fast enough and thus interact with one another (cf. Figure 4-7). In this case there is no (almost) linear section where the layers are small and the outer solution dominates.

This is always true. (This is how Figures 4-7 and 4-8 were created.) However, if we take another channel with the same permanent charge distribution but with length $d_2 > d_1$, then the breakdown of the condition is delayed; that is, it remains valid for lower bath concentration to permanent charge ratios. If we have $M \geq 2$, then this still holds, except instead of d_1 and d_2 being the channel length, they are the length of the permanent charge intervals.

Another way to look at this situation is the following: the results of the previous sections (specifically, Theorems 4.7, 4.11, 4.12, and 4.16) are always valid if the intervals (x_i, x_{i+1}) are long enough and the bath concentrations are high enough. However, when it comes to studying channels, changing the channel length is not possible. Experimentally, changing the bath concentrations is possible. Therefore, in general, **in order to use the formulas derived here, experiments should be done at the highest bath concentrations possible** (and then lowered until the formulas breakdown).

We illustrate these points in the next two sections by comparing the formulas to the numerical solutions of the full equations. We break the discussion into three parts: $M = 1$, $M = 2$, and $M \geq 3$.

4.6.1 $M = 1$

In this section we present the comparison of the numerical solutions to the formulas for the case $M = 1$ for two different channel lenghts (10Å and 30Å). In both cases $q_1 = -5M$ and the baths were 90Å long, which was necessary to have the outer solutions of the ion concentrations be valid when the bath concentrations were low. The diffusion coefficients for the negative ion were 1.0×10^{-9} m^2/sec in the baths and 1.0×10^{-10} m^2/sec in the channel. The diffusion coefficients for the positive ion were 3.0×10^{-9} m^2/sec in the baths and 1.5×10^{-10} m^2/sec in the channel. In these calculations, for simplicity, the function A was kept constant at 38.48Å^2 (the area of a circle of radius 3.5Å).

c_L	c_R	actual	(4.173)	% error	(4.238)	% error	(4.239)	% error
2.0	2.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2.0	1.0	−12.6	−13.3	−5.6	−14.5	−15.1	−16.3	−29.4
2.0	0.5	−25.9	−27.1	−4.6	−29.5	−13.9	−33.7	−30.1
2.0	0.1	−53.6	−55.8	−4.1	−66.8	−24.6	−75.1	−40.1
0.5	0.2	−21.2	−21.7	−2.4	−21.8	−2.8	−23.5	−10.8
0.2	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.1	0.2	17.1	17.3	−1.2	17.3	−1.2	17.9	−4.7
0.05	0.2	34.4	34.5	−0.3	34.6	−0.6	35.8	−4.1
0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.05	0.1	17.6	17.6	0.0	17.6	0.0	17.9	−1.7

Table 4.1: Comparison of V_{rev} for the 10Å channel. All concentrations are given in molar and all potentials in mV. Entries in the “actual” column are calculated from numerical solutions of the full PNP equations. The other entries are calculated from the equations given in the column title. Equation (4.173) is the general solution from Theorem 4.11 without taking the diffusion coefficient drops into consideration. Equations (4.238) and (4.239) take the diffusion coefficient drops into consideration, with (4.239) being the crudest approximation.

c_L	c_R	actual	(4.173)	% error	(4.238)	% error	(4.239)	% error
2.0	2.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2.0	1.0	−14.7	−14.9	−1.4	−15.0	−2.0	−16.3	−10.9
2.0	0.5	−30.3	−30.6	−0.1	−31.1	−2.6	−33.7	−11.2
2.0	0.1	−64.0	−64.1	−0.2	−68.9	−7.7	−75.1	−17.3
0.5	0.2	−22.8	−22.8	0.0	−22.9	−0.4	−23.5	−3.1
0.2	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.1	0.2	17.7	17.7	0.0	17.7	0.0	17.9	−1.1
0.05	0.2	35.4	35.3	0.3	35.4	0.0	35.8	−1.2
0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.05	0.1	17.8	17.8	0.0	17.8	0.0	17.9	−0.6

Table 4.2: Comparison of V_{rev} for the 30Å channel. All concentrations are given in molar and all potentials in mV. Entries in the “actual” column are calculated from numerical solutions of the full PNP equations. The other entries are calculated from the equations given in the column title. Equation (4.173) is the general solution from Theorem 4.11 without taking the diffusion coefficient drops into consideration. Equations (4.238) and (4.239) take the diffusion coefficient drops into consideration, with (4.239) being the crudest approximation.

c_L	c_R	actual	(5.122)	% error
2.0	2.0	0.397	0.406	-2.3
0.2	0.2	0.0511	0.0469	8.2
0.1	0.1	0.0280	0.0234	16.4

Table 4.3: Comparison of conductance at V_{rev} for the 10Å channel at equal bath concentrations. All concentrations are given in molar and all conductances in pA/mV (or nS). Entries in the "actual" column are calculated from numerical solutions of the full PNP equations. The other entries are calculated from equation (5.122) from Theorem 4.16.

c_L	c_R	actual	(5.122)	% error
2.0	2.0	0.243	0.248	-2.1
0.2	0.2	0.0460	0.0426	7.4
0.1	0.1	0.0264	0.0225	14.8

Table 4.4: Comparison of conductance at V_{rev} for the 30Å channel at equal bath concentrations. All concentrations are given in molar and all conductances in pA/mV (or nS). Entries in the "actual" column are calculated from numerical solutions of the full PNP equations. The other entries are calculated from equation (5.122) from Theorem 4.16.

c_L	c_R	actual	(4.175)	% error	(4.240)	% error
2.0	1.0	0.292	0.297	-1.7	0.211	28.9
2.0	0.5	0.215	0.214	0.5	0.171	20.5
2.0	0.1	0.108	0.101	6.5	0.071	34.3
0.5	0.2	0.0738	0.0692	6.2	0.0681	7.7
0.1	0.2	0.0365	0.0319	12.6	0.0318	12.9
0.05	0.2	0.0248	0.0198	20.2	0.0197	20.6
0.05	0.1	0.0203	0.0159	21.7	0.0159	21.7

Table 4.5: Comparison of conductance at V_{rev} for the 10Å channel at unequal bath concentrations. All concentrations are given in molar and all conductances in pA/mV (or nS). Entries in the "actual" column are calculated from numerical solutions of the full PNP equations. The other entries are calculated from equation (4.175) which does not take the diffusion coefficient drops into consideration and (4.240) which does.

c_L	c_R	actual	(4.175)	% error	(4.240)	% error
2.0	1.0	0.190	0.194	−2.1	0.188	1.1
2.0	0.5	0.145	0.146	−0.7	0.161	−11.0
2.0	0.1	0.0683	0.0651	4.7	0.0583	14.6
0.5	0.2	0.0622	0.0592	4.8	0.0591	5.0
0.1	0.2	0.0336	0.0296	11.9	0.0296	11.9
0.05	0.2	0.0231	0.0185	19.9	0.0185	19.9
0.05	0.1	0.0194	0.0154	20.6	0.0154	20.6

Table 4.6: Comparison of conductance at V_{rev} for the 30Å channel at unequal bath concentrations. All concentrations are given in molar and all conductances in pA/mV (or nS). Entries in the "actual" column are calculated from numerical solutions of the full PNP equations. The other entries are calculated from equation (4.175) which does not take the diffusion coefficient drops into consideration and (4.240) which does.

In Tables 4.1 and 4.2 is presented the reversal potential data from the 10 and 30Å channels, respectively. The actual numerical solutions to the PNP equations are compared with the major equations for V_{rev} that were derived in this chapter: (4.173) is the general reversal potential formula for any M and any diffusion coefficients (it had an unknown $\lambda_0^{[0]}$ which had to be found numerically); (4.238) is (4.173) evaluated at the approximate $\lambda_0^{[0]}$, $\xi_1^{[0]}$, $\lambda_1^{[0]}$, and $\xi_2^{[0]}$ found for $M = 1$ with diffusion coefficient drops (Condition 4.17) in Theorem 4.19 (with all of the B_i as in that theorem); (4.239) is the crudest form of (4.238) obtained by ignoring all the B_i of Theorem 4.19.

These tables show several trends about the approximation formulas for V_{rev} when $M = 1$:

1. All the approximations become better when the channel is longer, even under very asymmetric conditions.
2. The general formula (4.173) is generally very good, but is better when the channel is longer.
3. The cruder approximations become worse when bath concentrations become more asymmetric.

4. All the approximations become *better* as both the bath concentrations are lowered. This is a complete surprise, and we do not understand why this is so. It is important to stress that this is only true when $M = 1$.

Next, Tables 4.3 and 4.4 show the conductances at reversal potential under symmetric conditions (that is, when bath concentrations are equal) from the 10 and 30Å channels. Interestingly, these conductances (as well as the ones from asymmetric conditions) are influenced much less by the length of the channel, than by the bath concentration to permanent charge ratio. Therefore, when conductances are the object of study, it is very important to have the bath concentrations as high as possible.

Lastly, Tables 4.5 and 4.6 show the conductances at reversal potential under asymmetric conditions (that is, when bath concentrations are not equal) from the 10 and 30Å channels. Lowering the bath concentrations on either side causes large errors in the approximations, especially in the cruder approximation (4.240). It is important to note, that the only improvement gained by making the channel longer is for the rougher approximation (4.240), which improves dramatically.

4.6.2 $M = 2$

In this section we consider the case $M = 2$. In this case $q_1 = 5M$ and $q_2 = -5M$. The channel was 30Å long (divided equally between the two intervals of permanent charge) and, as before, the baths were 90Å long. The diffusion coefficients for the negative ion were 1.0×10^{-9} m^2/sec in the baths and 1.0×10^{-10} m^2/sec in the channel. The diffusion coefficients for the positive ion were 3.0×10^{-9} m^2/sec in the baths and 1.5×10^{-10} m^2/sec in the channel. In these calculations, as before, the function A was kept constant at 38.48Å^2 (the area of a circle of radius 3.5Å).

As before, the general reversal potential formula (4.173) does very well, as shown in Table 4.7. (Despite the seemingly large percent errors at low bath concentrations, the absolute differences of about 0.3mV are barely measurable in experi-

c_L	c_R	actual	(4.173)	% error
2.0	3.0	2.26	2.10	7.1
2.0	2.0	0.0	0.0	0.0
2.0	1.0	-7.42	-7.61	-2.6
2.0	0.5	-19.1	-19.8	-3.6
2.0	0.1	-49.5	-50.9	-2.8
0.5	0.2	-12.4	-12.6	-1.6
0.2	0.2	0.0	0.0	0.0
0.1	0.2	-1.60	-1.94	-21.3
0.05	0.2	-12.3	-13.0	-5.7
0.1	0.1	0.0	0.0	0.0
0.05	0.1	-1.97	-2.20	-11.7

Table 4.7: Comparison of V_{rev} for the channel with $M = 2$ described in the text. All concentrations are given in molar and all potentials in mV. Entries in the "actual" column are calculated from numerical solutions of the full PNP equations. The other entries are calculated from equation (4.173), the general solution from Theorem 4.11.

ments.) Also, as shown in Table 4.8, the conductance approximation becomes very bad as the bath concentrations are lowered.

4.6.3 $M \geq 3$

In general, to have good results from the approximations (4.173) and (4.175) for any M it is necessary to have the lengths of the intervals (x_i, x_{i+1}) be at least 20Å (preferably 30Å or longer). If this is not true, then both the reversal potential and the conductance there have large errors. Even when the intervals are long, very high bath concentrations (beyond experimental limits) are many times needed in order to get good results. Therefore, if one is considering biological channels, it is not feasible to have $M \geq 3$.

c_L	c_R	actual	(4.175)	% error
2.0	3.0	0.167	0.157	6.0
2.0	2.0	0.243	0.248	−2.1
2.0	1.0	0.0941	0.0844	10.3
2.0	0.5	0.0766	0.0689	10.1
2.0	0.1	0.0516	0.0461	10.7
0.5	0.2	0.0106	0.00711	32.9
0.2	0.2	0.00287	0.00185	35.5
0.1	0.2	0.00162	0.00102	37.0
0.05	0.2	0.00126	0.000790	37.3
0.1	0.1	0.000792	0.000470	40.7
0.05	0.1	0.000446	0.000258	42.2

Table 4.8: Comparison of the conductance at V_{rev} for the channel with $M = 2$ described in the text. All conductances are given in pA/mV (nS). Entries in the "actual" column are calculated from numerical solutions of the full PNP equations. The other entries are calculated from equation (4.175), the general solution from Theorem 4.12.

Chapter 5

Multiple Salts Case

In the previous chapter we only had two monovalent ions (one salt) in the system. We now consider the case of multiple monovalent ions. This case is much more difficult to do rigorously than the single salt case. The main reason for this is that the general case of s salts reduces to a system of $2s-1$ equations that must be solved simultaneously. This is difficult to do numerically, let alone analytically or with closed-form formulas. (Even when $s=1$ as in the previous chapter, clean, closed-form formulas were hard to come by.) Our approach to overcoming this problem is to consider the simplified problem with the following assumptions:

1. The channel has uniform permanent charge (that is, $M=1$).
2. All the ions experience a significant drop in their diffusion coefficients as they enter the channel.
3. The area function A is constant inside the channel (but not the baths).
4. For some of the results we require that there be only one anion in the system; that is, all the salts have a common anion (which experimentally is usually Cl^-). It is possible to derive similar results when there is only one cation, but experimentally the one-anion condition is much more common.

Luckily this is still a very interesting and important case. The uniform permanent charge then excludes rectifying channels (as far as we are aware, uniform permanent charge only gives (almost) linear current/voltage relations), but at the very least it already includes the calcium release channel ([10] and [11]).

Before continuing, we make assumptions #1 and #2 mathematically rigorous.

Condition 5.1 (Diffusion Coefficient Drops) *Mathematically, the diffusion coefficient drop (DCD) condition is stated as:* $\tau \ll 1$*, where* τ *is defined as*

$$\tau = \max_{1 \le j \le s} \left\{ D_{1,n_j}, D_{1,p_j} \right\} \tag{5.1}$$

where s *is the number of salts in the baths; that is,* τ *is the maximum of all the diffusion coefficients inside the channel and this number is assumed to be small. With the scaling we have chosen (see Section 2.3), requiring* $\tau \ll 1$ *is equivalent to having both* $D_{1,n_j} \ll D_{0,n_j}$ *and* $D_{1,p_j} \ll D_{0,p_j}$ *for all salts* j*. (Keeping with the notation of the previous chapter, we have* $M = 1$ *and so* D_{1,n_j}*, for example, is the diffusion coefficient inside the channel and* $D_{0,n_j} = D_{2,n_j}$ *is the diffusion coefficient in the baths for the* j^{th} *negative ion species.)*

Condition 5.2 (A **is constant in the channel)** *In the interval* $[x_1, x_2]$ *the function* A *is identically constant:*

$$A(x) \equiv A_1 \qquad (x_1 \le x \le x_2). \tag{5.2}$$

In the baths A *is not required to be constant and it is still assumed that on the entire interval* $[0, 1]$ A *has a continuous first derivative.*

Next consider the original PNP equations for multiple monovalent ions (no approximations):

$$\varepsilon^2 \left[\left(\epsilon(x)\,\phi_x(x)\right)_x + \epsilon(x)\,\frac{A_x(x)}{A(x)}\phi_x(x) \right] = \sum_{z_j=-1} n_j - \sum_{z_j=1} p_j - q \tag{5.3}$$

$$-\frac{J_{n_j}}{D_{n_j}(x)\,A(x)} = \frac{dn_j}{dx}(x) - n_j(x)\,\frac{d\phi}{dx}(x) \tag{5.4}$$

$$-\frac{J_{p_j}}{D_{p_j}(x)\,A(x)} = \frac{dp_j}{dx}(x) + p_j(x)\,\frac{d\phi}{dx}(x) \tag{5.5}$$

$$c_L = \sum_{z_j=-1} n_j(0) = \sum_{z_j=1} p_j(0) \qquad c_R = \sum_{z_j=-1} n_j(1) = \sum_{z_j=1} p_j(1)\,. \tag{5.6}$$

To simplify the notation, we assume without loss that the concentrations n_j and p_j come from salt j. Since these salts are electrically neutral, we have

$$n_j(0) = p_j(0) \equiv c_j(0) \qquad n_j(1) = p_j(1) \equiv c_j(1)\,. \tag{5.7}$$

If the same anion (for example, Cl^-) is used in all salts, then we *formally* consider it as a different ion species with concentrations $n_1, n_2, \ldots$ and equal diffusion coefficients.

Letting

$$N = \sum_{z_j=-1} n_j \qquad P = \sum_{z_j=1} p_j \qquad J_N = \sum_{z_j=-1} \frac{J_{n_j}}{D_{n_j}} \qquad J_P = \sum_{z_j=1} \frac{J_{p_j}}{D_{p_j}} \tag{5.8}$$

it follows that

$$\varepsilon^2 \left[\left(\epsilon(x)\,\phi_x(x)\right)_x + \epsilon(x)\,\frac{A_x(x)}{A(x)}\phi_x(x) \right] = N - P - q \tag{5.9}$$

$$-\frac{J_N}{A(x)} = N_x(x) - N(x)\,\phi_x(x) \tag{5.10}$$

$$-\frac{J_P}{A(x)} = P_x(x) + P(x)\,\phi_x(x)\,. \tag{5.11}$$

Note that these equations are the same mathematical equations as (4.1) – (4.3) for the singe salt case. The only difference is that the variables now represent different things. Therefore, most of the mathematics done in the previous chapter is still valid for these variables. The most important difference mathematically is that now $J_P - J_N$ is no longer the current. However, since much of the mathematical results are still valid, in the following we will set up the multiple salts case to look like the single salt case and then exploit the already existing mathematics to derive new results.

In order to do that, we make the same definitions as before:

$$u_i(x) = \begin{cases} N(x) - |q_i| & \text{if } q_i > 0 \\ P(x) - |q_i| & \text{if } q_i \leq 0 \end{cases} \qquad z_{u_i} = \begin{cases} 1 & \text{if } q_i > 0 \\ -1 & \text{if } q_i \leq 0 \end{cases} \tag{5.12}$$

$$J_{i,u} = \begin{cases} J_N & \text{if } q_i > 0 \\ J_P & \text{if } q_i \leq 0 \end{cases} \qquad D_{i,u} = 1 \tag{5.13}$$

$$\beta_{i,L/R,u} = \begin{cases} \beta_{L/R,N} & \text{if } q_i > 0 \\ \beta_{L/R,P} & \text{if } q_i \leq 0 \end{cases} . \tag{5.14}$$

$$w_i(x) = \begin{cases} P(x) & \text{if } q_i > 0 \\ N(x) & \text{if } q_i \leq 0 \end{cases} \qquad z_{w_i} = \begin{cases} 1 & \text{if } q_i > 0 \\ -1 & \text{if } q_i \leq 0 \end{cases} \tag{5.15}$$

$$J_{i,w} = \begin{cases} J_P & \text{if } q_i > 0 \\ J_N & \text{if } q_i \leq 0 \end{cases} \qquad D_{i,w} = 1 \tag{5.16}$$

$$\beta_{i,L/R,w} = \begin{cases} \beta_{L/R,P} & \text{if } q_i > 0 \\ \beta_{L/R,N} & \text{if } q_i \leq 0 \end{cases} \tag{5.17}$$

for $i = 0, 1, 2$. We have set $D_{i,u} = D_{i,w} = 1$ since no diffusion coefficients appear in (5.9) – (5.11). Also, we have the same types of expansions on each interval (x_i, x_{i+1}) as before:

$$f(x) = f_{\text{out}}(x) + F_L\left(\frac{x-a}{\varepsilon}\right) + F_R\left(\frac{b-x}{\varepsilon}\right) \qquad (f = \phi, u, w; F = \Phi, U, W). \tag{5.18}$$

$$f_{\text{out}}(x) = f^{(0)}(x) + \varepsilon f^{(1)}(x) + \cdots \qquad (f = \phi, u, w) \tag{5.19}$$

$$F_L(\zeta) = F_L^{(0)}(\zeta) + \varepsilon F_L^{(1)}(\zeta) + \cdots \qquad (F = \Phi, U, W) \tag{5.20}$$

$$F_R(X) = F_R^{(0)}(X) + \varepsilon F_R^{(1)}(X) + \cdots \qquad (F = \Phi, U, W) \tag{5.21}$$

$$J_{f_j} = \varepsilon J_{f_j}^{(1)} + \varepsilon^2 J_{f_j}^{(2)} + \cdots \qquad (f = n, p) \tag{5.22}$$

$$J_f = \varepsilon J_f^{(1)} + \varepsilon^2 J_f^{(2)} + \cdots \qquad (f = u, w) \tag{5.23}$$

$$A^{(1)} = \frac{A}{\varepsilon}. \tag{5.24}$$

Next define

$$\mu_i(x) = u_i^{(0)}(x) + \frac{|q_i|}{2}, \tag{5.25}$$

$$I = \sum_{z_j=1} J_{p_j}^{(1)} - \sum_{z_j=-1} J_{n_j}^{(1)}, \tag{5.26}$$

$$\Xi_i(I) = \mu_i(x_i) \qquad \Lambda_i(I) = \mu_i(x_{i+1}), \tag{5.27}$$

and

$$J_{i,\pm}^{(1)} = \frac{1}{2}\left(\frac{J_N^{(1)}}{D_N} \pm \frac{J_P^{(1)}}{D_P}\right). \tag{5.28}$$

Theorem 5.3 *Here we quickly restate some the single salt results we will need.*

$$0 = \Lambda_i - \Xi_i + \frac{q_i}{2}\frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}} \ln\left(\frac{\Lambda_i - \frac{q_i}{2}\frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}}{\Xi_i - \frac{q_i}{2}\frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}}\right) + S_i J_{i,+}^{(1)} \tag{5.29}$$

$$\phi_i^{(0)}(x_{i+1}) = \phi_i^{(0)}(x_i) - \frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}} \ln\left(\frac{\Lambda_i - \frac{q_i}{2}\frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}}{\Xi_i - \frac{q_i}{2}\frac{J_{i,-}^{(1)}}{J_{i,+}^{(1)}}}\right) \tag{5.30}$$

$$\Xi_{i+1} = \sqrt{\Lambda_i^2 + \frac{q_{i+1}^2}{4} - \frac{q_i^2}{4}} \tag{5.31}$$

$$\phi_{i+1}^{(0)}(x_{i+1}) = \phi_i^{(0)}(x_{i+1}) + \frac{1}{2}\ln\left(\frac{\Xi_{i+1} + \frac{q_{i+1}}{2}}{\Xi_{i+1} - \frac{q_{i+1}}{2}}\right) - \frac{1}{2}\ln\left(\frac{\Lambda_i + \frac{q_i}{2}}{\Lambda_i - \frac{q_i}{2}}\right) \tag{5.32}$$

$$J_{i,\pm}^{(1)} = \frac{1}{2}\left(\sum_{z_j=-1} \frac{J_{n_j}^{(1)}}{D_{i,n_j}} \pm \sum_{z_j=1} \frac{J_{p_j}^{(1)}}{D_{i,p_j}}\right) \tag{5.33}$$

Soon we will define $\alpha_{i,\pm}$ and $\beta_{i,\pm}$ such that, for $I = O(\tau)$,

$$J_{i,\pm}^{(1)} = \frac{\alpha_{i,\pm}}{S_0}\left(c_L - \Lambda_0(I)\right) + \beta_{i,\pm} I \qquad (i = 0, 1, 2), \tag{5.34}$$

to complete the analogy to the single salt case.

5.1 Technical Lemmas

Lemma 5.4 *Let $M = 1$. If for some E_{n_j} and E_{p_j} we have*

$$J_{f_j} = \frac{D_{1,f_j}}{D_{1,f_1}} \frac{E_{f_j}}{E_{f_1}} J_{f_1} \qquad (f = n, p), \tag{5.35}$$

then

$$\alpha_{0,\pm} = \alpha_{2,\pm} = \frac{F_p G_n \pm F_n G_p}{F_p G_n + F_n G_p} \tag{5.36}$$

$$\beta_{0,\pm} = \beta_{2,\pm} = -\frac{1}{2} G_p \frac{G_n \mp G_n}{F_p G_n + F_n G_p} \tag{5.37}$$

$$\alpha_{1,\pm} = \frac{F_p E_n \pm F_n E_p}{F_p G_n + F_n G_p} \tag{5.38}$$

$$\beta_{1,\pm} = -\frac{1}{2} \frac{G_p E_n \mp G_n E_p}{F_p G_n + F_n G_p} \tag{5.39}$$

where

$$E_n = \sum_{z_j=-1} E_{n_j} \qquad E_p = \sum_{z_j=1} E_{p_j} \tag{5.40}$$

$$F_n = \sum_{z_j=-1} D_{1,n_j} E_{n_j} \qquad F_p = \sum_{z_j=1} D_{1,p_j} E_{p_j} \tag{5.41}$$

$$G_n = \sum_{z_j=-1} \frac{D_{1,n_j}}{D_{0,n_j}} E_{n_j} \qquad G_p = \sum_{z_j=1} \frac{D_{1,p_j}}{D_{0,p_j}} E_{p_j}. \tag{5.42}$$

Proof. From (5.35), (5.26), and (5.41) it follows that

$$I = \frac{F_p}{D_{1,p_1} E_{p_1}} J_{p_1}^{(1)} - \frac{F_n}{D_{1,n_1} E_{n_1}} J_{n_1}^{(1)} \tag{5.43}$$

and, from (5.28),

$$J_{1,\pm}^{(1)} = \frac{1}{2} \left(\sum_{z_j=-1} \frac{J_{n_j}^{(1)}}{D_{1,n_j}} \pm \sum_{z_j=1} \frac{J_{p_j}^{(1)}}{D_{1,p_j}} \right) = \frac{1}{2} \frac{E_n}{E_{n_1}} \frac{J_{n_1}^{(1)}}{D_{1,n_1}} \pm \frac{1}{2} \frac{E_p}{E_{p_1}} \frac{J_{p_1}^{(1)}}{D_{1,p_1}}. \tag{5.44}$$

Then

$$J_{1,\pm}^{(1)} = \frac{1}{2} \frac{1}{D_{1,n_1} E_{n_1}} \left(E_n \pm \frac{F_n}{F_p} E_p \right) J_{n_1}^{(1)} \pm \frac{1}{2} \frac{E_p}{F_p} I. \tag{5.45}$$

Similarly, when $i = 0$, then

$$\begin{aligned} J_{0,\pm}^{(1)} &= \frac{1}{2} \left(\sum_{z_j=-1} \frac{1}{D_{0,n_j}} \frac{D_{1,n_j}}{D_{1,n_1}} \frac{E_{n_j}}{E_{n_1}} J_{n_1}^{(1)} \pm \sum_{z_j=1} \frac{1}{D_{0,p_j}} \frac{D_{1,p_j}}{D_{1,p_1}} \frac{E_{p_j}}{E_{p_1}} J_{p_1}^{(1)} \right) && (5.46) \\ &= \frac{1}{2} \left(\frac{1}{D_{1,n_1}} \frac{G_n}{E_{n_1}} J_{n_1}^{(1)} \pm \frac{1}{D_{1,p_1}} \frac{G_p}{E_{p_1}} J_{p_1}^{(1)} \right). && (5.47) \end{aligned}$$

Then, by (5.43),

$$J_{0,\pm}^{(1)} = \frac{1}{2}\frac{1}{D_{1,n_1}E_{n_1}}\left(G_n \pm \frac{F_n}{F_p}G_p\right)J_{n_1}^{(1)} \pm \frac{1}{2}\frac{G_p}{F_p}I. \tag{5.48}$$

Since, by (5.29),

$$J_{0,+}^{(1)} = \frac{c_L - \Lambda_0(I)}{S_0} \tag{5.49}$$

we have

$$\frac{1}{2}\frac{1}{D_{1,n_1}E_{n_1}}J_{n_1}^{(1)} = \frac{1}{G_n + \frac{F_n}{F_p}G_p}\left(\frac{c_L - \Lambda_0(I)}{S_0} - \frac{1}{2}\frac{G_p}{F_p}I\right) \tag{5.50}$$

and thus

$$J_{1,\pm}^{(1)} = \frac{F_pE_n \pm F_nE_p}{F_pG_n + F_nG_p}\frac{c_L - \Lambda_0(I)}{S_0} - \frac{1}{2}\frac{G_pE_n \mp G_nE_p}{F_pG_n + F_nG_p}I \tag{5.51}$$

and

$$J_{0,\pm}^{(1)} = \frac{F_pG_n \pm F_nG_p}{F_pG_n + F_nG_p}\frac{c_L - \Lambda_0(I)}{S_0} - \frac{1}{2}G_p\frac{G_n \mp G_n}{F_pG_n + F_nG_p}I \tag{5.52}$$

and the lemma follows. ■

Lemma 5.5 *For multiple salts, if Condition 5.1 is satisfied, and $I = O(\tau)$, then*

$$\Lambda_0(I) = c_L + O(\tau) \qquad \Xi_{M+1}(I) = c_R + O(\tau). \tag{5.53}$$

Proof. From the previous lemma, it follows that if Condition 5.1 is satisfied, then $\alpha_{1,\pm} = O\left(\frac{1}{\tau}\right)$ and $\beta_{1,\pm} = O\left(\frac{1}{\tau}\right)$. The rest of the proof of this exactly the same as for the single salt case (Theorem 4.18). ■

Theorem 5.6 *Let $M = 1$. If Condition 5.1 is satisfied, then*

$$\Lambda_0(0) = c_L + B_1 + O\left(\tau^2\right) \tag{5.54}$$

$$\Xi_1(0) = \sqrt{c_L^2 + \frac{q_1^2}{4}} + O(\tau) \tag{5.55}$$

$$\Lambda_1(0) = \sqrt{c_R^2 + \frac{q_1^2}{4}} + O(\tau) \tag{5.56}$$

$$\Xi_2(0) = c_R - B_1 + O\left(\tau^2\right) \tag{5.57}$$

where

$$\begin{aligned} B_1 &= \frac{1}{\alpha_{1,+}} \frac{S_0}{S_1} \left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2} \frac{\alpha_{1,-}}{\alpha_{1,+}} \ln \left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2} \frac{\alpha_{1,-}}{\alpha_{1,+}}}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2} \frac{\alpha_{1,-}}{\alpha_{1,+}}} \right) \right) \\ &= O(\tau) \end{aligned} \tag{5.58}$$

and all the $\alpha_{1,\pm}$ are evaluated at $I = 0$.

Proof. With the previous lemma, the proof of this is the same as the proof of Theorem 4.19. ■

Lemma 5.7 *Let $M = 1$. If Conditions 5.1 and 5.2 are satisfied, then*

$$J_{f_j}^{(1)} = \frac{D_{1,f_j}}{D_{1,f_1}} \frac{E_{f_j}(V)}{E_{f_1}(V)} J_{f_1}^{(1)} + O(\tau) \qquad (f = n, p) \tag{5.59}$$

for all species j*, where*

$$E_{f_j}\left(V\right)=\frac{c_j\left(1\right)-c_j\left(0\right)\exp\left(z_{f_j}V\right)}{\frac{D_{1,f_j}}{D_{0,f_j}}+\frac{S_1}{S_0}\rho_L^{z_{f_j}/2}\frac{1}{z_{f_j}V-\frac{1}{2}z_{f_j}\ln\left(\frac{\rho_R}{\rho_L}\right)}\frac{\exp\left(z_{f_j}V\right)-\left(\frac{\rho_R}{\rho_L}\right)^{z_{f_j}/2}}{\exp\left(z_{f_j}V\right)+1}}\qquad\left(f=n,p\right)\tag{5.60}$$

and

$$\rho_L=\frac{\sqrt{c_L^2+\frac{q_1^2}{4}}+\frac{q_1}{2}}{\sqrt{c_L^2+\frac{q_1^2}{4}}-\frac{q_1}{2}}\qquad\rho_R=\frac{\sqrt{c_R^2+\frac{q_1^2}{4}}+\frac{q_1}{2}}{\sqrt{c_R^2+\frac{q_1^2}{4}}-\frac{q_1}{2}}.\tag{5.61}$$

In general, V *is small enough and* $\frac{\rho_R}{\rho_L}$ *is close enough to* 1 *so that* E_{f_j} *may be well approximated by*

$$E_{f_j}^{\#}\left(V\right)=\frac{c_j\left(1\right)}{\eta_{f_j}}-\frac{c_j\left(0\right)}{\eta_{f_j}}\exp\left(z_{f_j}V\right)\qquad\left(f=n,p\right)\tag{5.62}$$

where, if $c_L\neq c_R$*,*

$$\eta_{f_j}=\frac{D_{1,f_j}}{D_{0,f_j}}+\frac{1}{2}\frac{S_1}{S_0}\frac{\rho_R^{z_{f_j}/2}-\rho_L^{z_{f_j}/2}}{\ln\left[\left(\frac{\rho_R}{\rho_L}\right)^{z_{f_j}/2}\right]}\qquad\left(f=n,p\right).\tag{5.63}$$

When $c_L=c_R=c$*, then*

$$\eta_{f_j}=\frac{D_{1,f_j}}{D_{0,f_j}}+\frac{z_{f_j}}{2}\frac{S_1}{S_0}\rho^{z_{f_j}/2}\qquad\left(f=n,p\right)\tag{5.64}$$

where

$$\rho=\frac{\sqrt{c^2+\frac{q_1^2}{4}}+\frac{q_1}{2}}{\sqrt{c^2+\frac{q_1^2}{4}}-\frac{q_1}{2}}.\tag{5.65}$$

Then E_{f_j} *from* (5.60) *or* $E_{f_j}^{\#}$ *from* (5.62) *define* $\alpha_{0,\pm}$*,* $\alpha_{1,\pm}$*,* $\beta_{0,\pm}$*, and* $\beta_{1,\pm}$ *through Lemma 5.4.*

Corollary 5.8 *With these E_{f_j}, the $\alpha_{1,\pm}$ and $\beta_{1,\pm}$ given by Lemma 5.4 give*

$$J_{1,\pm}^{(1)}(V,I)=\frac{\alpha_{1,\pm}(V)}{S_0}\left(c_L-\Lambda_0(I)\right)+\beta_{1,\pm}(V)\,I+O(\tau). \tag{5.66}$$

It is the error term in these equations that limits the error terms in all the following theorems to $O(\tau)$.

Proof of Lemma 5.7. Integrating the orginal Nernst-Planck equations from 0 to 1 gives

$$-J_{n_j}^{(1)}\int_0^1\frac{\exp(-\phi(s))}{D_{n_j}(s)\,A^{(1)}(s)}ds=n_j(1)\exp(-\phi(1))-n_j(0)\exp(-\phi(0)) \tag{5.67}$$

$$-J_{p_j}^{(1)}\int_0^1\frac{\exp(\phi(s))}{D_{p_j}(s)\,A^{(1)}(s)}ds=p_j(1)\exp(\phi(1))-p_j(0)\exp(\phi(0)). \tag{5.68}$$

We start approximating the integrals in these equations by the integrals over their outer solutions:

$$\begin{aligned}&\int_0^1\frac{\exp(z\phi(s))\,ds}{D_{f_j}(s)\,A^{(1)}(s)}\\=\;&\frac{1}{D_{0,f_j}}\int_0^{x_1}\frac{\exp\left(z\phi_0^{(0)}(s)\right)ds}{A^{(1)}(s)}+\frac{1}{D_{0,f_j}}\int_{x_2}^1\frac{\exp\left(z\phi_2^{(0)}(s)\right)ds}{A^{(1)}(s)}\\&+\frac{1}{D_{1,f_j}}\int_{x_1}^{x_2}\frac{\exp\left(z\phi_1^{(0)}(s)\right)ds}{A^{(1)}(s)}+O(\varepsilon).\end{aligned} \tag{5.69}$$

This is justified because we interested in the *integral* of $\exp(z\phi)$, not the function $\exp(z\phi)$ itself. Furthermore, the layers at the edges become narrower since the function is the exponential of ϕ, reducing the error even more. By Lemma 5.5 and (5.30) we have

$$\int_0^{x_1} \frac{\exp\left(z\phi_0^{(0)}(s)\right) ds}{A^{(1)}(s)} = S_0 \exp\left(z\phi_0^{(0)}(0)\right) + O(\tau) \tag{5.70}$$

$$\int_{x_2}^{1} \frac{\exp\left(z\phi_2^{(0)}(s)\right) ds}{A^{(1)}(s)} = S_0 \exp\left(z\phi_2^{(0)}(1)\right) + O(\tau). \tag{5.71}$$

The last integral in (5.69) is approximated by

$$\begin{aligned} & \int_{x_1}^{x_2} \frac{\exp\left(z\phi_1^{(0)}(s)\right) ds}{A^{(1)}(s)} \\ \approx\ & \frac{1}{A_1^{(1)}} \int_{x_1}^{x_2} \exp\left(z\left(\phi_1^{(0)}(x_2) - \phi_1^{(0)}(x_1)\right)\frac{s-x_1}{x_2-x_1} + z\phi_1^{(0)}(x_1)\right) ds && (5.72) \\ =\ & zS_1 \frac{\exp\left(z\phi_1^{(0)}(x_2)\right) - \exp\left(z\phi_1^{(0)}(x_1)\right)}{\phi_1^{(0)}(x_2) - \phi_1^{(0)}(x_1)}. && (5.73) \end{aligned}$$

What is done here is to use a linear approximation of the outer solution to approximate the integral. This is justified because, when A is constant (and only then), this is not a bad approximation. Furthermore, all of these approximations have been validated by numerical calculations.

Since, by (5.32), (5.30), and Lemma 5.5,

$$\phi_1^{(0)}(x_1) = \phi_0^{(0)}(x_1) + \frac{1}{2}\ln\left(\frac{\Xi_1 + \frac{q_1}{2}}{\Xi_1 - \frac{q_1}{2}}\right) = \phi_0^{(0)}(0) + \frac{1}{2}\ln\left(\frac{\Xi_1 + \frac{q_1}{2}}{\Xi_1 - \frac{q_1}{2}}\right) + O(\tau) \tag{5.74}$$

$$\phi_1^{(0)}(x_2) = \phi_2^{(0)}(x_2) + \frac{1}{2}\ln\left(\frac{\Lambda_1 + \frac{q_1}{2}}{\Lambda_1 - \frac{q_1}{2}}\right) = \phi_2^{(0)}(1) + \frac{1}{2}\ln\left(\frac{\Lambda_1 + \frac{q_1}{2}}{\Lambda_1 - \frac{q_1}{2}}\right) + O(\tau) \tag{5.75}$$

it follows that

$$\int_{x_1}^{x_2} \frac{\exp\left(z\phi_1^{(0)}(s)\right) ds}{A^{(1)}(s)} = S_1 \frac{\left(\frac{\Lambda_1+\frac{q_1}{2}}{\Lambda_1-\frac{q_1}{2}}\right)^{\frac{z}{2}} \exp\left(z\phi_2^{(0)}(1)\right) - \left(\frac{L_1+\frac{q_1}{2}}{L_1-\frac{q_1}{2}}\right)^{\frac{z}{2}} \exp\left(z\phi_0^{(0)}(0)\right)}{z\left(-V + \frac{1}{2}\ln\left(\frac{\Lambda_1+\frac{q_1}{2}}{\Lambda_1-\frac{q_1}{2}}\right) - \frac{1}{2}\ln\left(\frac{L_1+\frac{q_1}{2}}{L_1-\frac{q_1}{2}}\right)\right)} + O(\tau). \tag{5.76}$$

Letting

$$\rho_L = \frac{\sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}} \qquad \rho_R = \frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}}{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}}, \tag{5.77}$$

then

$$\int_{x_1}^{x_2} \frac{\exp\left(z\phi_1^{(0)}(s)\right) ds}{A^{(1)}(s)} \approx S_1 \rho_L^{z/2} \exp\left(z\phi_2^{(0)}(1)\right) \frac{\exp(zV) - \left(\frac{\rho_R}{\rho_L}\right)^{z/2}}{zV - \frac{z}{2}\ln\left(\frac{\rho_R}{\rho_L}\right)} \tag{5.78}$$

and so

$$\frac{J_{f_j}^{(1)}}{J_{f_1}^{(1)}} \approx \frac{D_{1,f_j}}{D_{1,f_1}} \frac{E_{f_j}}{E_{f_1}} + O(\tau) \tag{5.79}$$

where

$$E_{f_j} = \frac{c_j(1) - c_j(0)\exp\left(z_{f_j}V\right)}{\frac{D_{1,f_j}}{D_{0,f_j}} + \frac{S_1}{S_0}\rho_L^{z_{f_j}/2} \frac{1}{z_{f_j}V - \frac{1}{2}z_{f_j}\ln\left(\frac{\rho_R}{\rho_L}\right)} \frac{\exp\left(z_{f_j}V\right) - \left(\frac{\rho_R}{\rho_L}\right)^{z_{f_j}/2}}{\exp\left(z_{f_j}V\right)+1}}. \tag{5.80}$$

The approximation $E_{f_j}^{\#}$ comes by using the first term of the expansion

$$\frac{1}{v - \ln(\gamma)} \frac{\exp(v) - \gamma}{\exp(v) + 1} = \frac{1}{2}\frac{\gamma - 1}{\ln\gamma} - \frac{1}{2\ln\gamma}\left(\frac{1-\gamma}{\ln\gamma} + \frac{1}{2}(1+\gamma)\right) v + O\left(v^2\right) \tag{5.81}$$

with $v = z_{f_j}V$ and $\gamma = \left(\frac{\rho_R}{\rho_L}\right)^{z_{f_j}/2}$. The result for $c_L = c_R = c$ follows from taking the limit $\rho_R \to \rho_L$. ■

Notes:

1. It is this lemma that does not carry over when $M > 1$ since a generalization would require *a priori* knowledge of Λ_i for $2 \leq i \leq M$ which are generally not known. It was because $M = 1$ that we were able to find approximations for Λ_0 and Λ_1 through Lemma 5.5.
2. If $E^{\#}_{f_j}$ is used, then the E's, F's, and G's will be denoted by $E^{\#}$, $F^{\#}$, and $G^{\#}$.

The problem is now set up analogous to the single salt case. There is one very important difference, however: the α's and β's are now functions of V by the definitions of E's, F's, and G's. The single salt results only carry through directly if these are independent of V.

5.2 General Results

5.2.1 Current/Voltage Relations

Theorem 5.9 *Let $M = 1$. For multiple salts, if Conditions 5.1 and 5.2 are satisfied, then $V(I)$ is found by simultaneously solving the following equations for $V(I)$ and $\Lambda_0(I)$:*

$$\begin{aligned} V(I) &= \frac{J^{(1)}_{1,-}(V,I)}{J^{(1)}_{1,+}(V,I)} \ln\left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\frac{J^{(1)}_{1,-}(V,I)}{J^{(1)}_{1,+}(V,I)}}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\frac{J^{(1)}_{1,-}(V,I)}{J^{(1)}_{1,+}(V,I)}} \right) \\ &\quad + \frac{1}{2}\ln\left(\frac{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)}{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)} \right) + O(\tau) \end{aligned} \tag{5.82}$$

$$\begin{aligned} 0 &= \sqrt{\left(c_R + c_L - \Lambda_0(I)\right)^2 + \frac{q_1^2}{4}} - \sqrt{\Lambda_0^2(I) + \frac{q_1^2}{4}} \\ &\quad + \frac{q_1}{2}\frac{J_{1,-}^{(1)}(V,I)}{J_{1,+}^{(1)}(V,I)} \ln\left(\frac{\sqrt{\left(c_R + c_L - \Lambda_0(I)\right)^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\frac{J_{1,-}^{(1)}(V,I)}{J_{1,+}^{(1)}(V,I)}}{\sqrt{\Lambda_0^2(I) + \frac{q_1^2}{4}} - \frac{q_1}{2}\frac{J_{1,-}^{(1)}(V,I)}{J_{1,+}^{(1)}(V,I)}}\right) + S_1 J_{1,+}^{(1)}(V,I). \end{aligned} \tag{5.83}$$

Proof. Copying the first part of the proof of Theorem 4.19 we have the formula for $\Lambda_0(I)$ and the rest follows from (4.137) with substitutions from Lemma 5.4 and Theorem 5.6. ■

5.2.2 Reversal Potential

Similar to before, we define

$$\alpha_i(V) = \frac{\alpha_{i,-}(V)}{\alpha_{i,+}(V)}. \tag{5.84}$$

Theorem 5.10 (Reversal Potential: General Case) *Let $M = 1$. For multiple salts, if Conditions 5.1 and 5.2 are satisfied, and $c_L \neq c_R$, then V_{rev} is the solution of the following equation:*

$$\begin{aligned} V_{rev} &= \alpha_1(V_{rev}) \ln\left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1(V_{rev})}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1(V_{rev})}\right) \\ &\quad + \frac{1}{2}\ln\left(\frac{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)}{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)}\right) + O(\tau). \end{aligned} \tag{5.85}$$

To emphasize it, note that this formulation is implicit since the α_1 depend on V_{rev}. Furthermore, this equation is one V_{rev} must necessarily satisfy but it is, in general not sufficient to give a unique value of V_{rev}; that is, there can be multiple solutions to this equation. In some cases, there are no solutions to this equation. This will be discussed later.

Proof. This theorem follows by evaluating Theorem 5.9 at $I = 0$ and using Theorem 5.6. ■

Corollary 5.11 *Let $M = 1$. For multiple salts, if Conditions 5.1 and 5.2 are satisfied and α_1 is independent of V, then the right-hand side of* (5.85) *is independent of V_{rev} and gives V_{rev} directly (up to order τ).*

Theorem 5.12 (Reversal Potential: Equal Bath Concentrations) *Let $M = 1$. For multiple salts, if Conditions 5.1 and 5.2 are satisfied and $c_L = c_R = c$, then V_{rev} (up to order τ) is the solution to*

$$\alpha_1 \left(V_{rev}\right)\big|_{c_L=c_R} = \frac{2}{q_1}\sqrt{c^2 + \frac{q_1^2}{4}}. \tag{5.86}$$

Proof. If $c_R \to c_L$ in the previous theorem, then

$$V_{\text{rev}} = 0 + O\left(\tau\right) \tag{5.87}$$

unless, perhaps,

$$\alpha_{1,+}\big|_{I=0,c_L=c_R} = 0 \tag{5.88}$$

or

$$\lim_{c_L,c_R\to c} \frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\left.\frac{\alpha_{1,-}}{\alpha_{1,+}}\right|_{I=0}}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\left.\frac{\alpha_{1,-}}{\alpha_{1,+}}\right|_{I=0}} = \nu \tag{5.89}$$

where ν exists, is positive, finite, and not equal to 1. The first possibility ($V_{\text{rev}} = 0$) implies that V_{rev} is always the same and independent of q_1, which is not true just by examining the numerical solutions for the full PNP equations. Thus we reject that possibility. Next, taking the limit $\alpha_{1,+} \to 0$ in (5.9) gives $V_{\text{rev}} = 0$ which we have already dismissed and is in contradiction to the requirement that $\alpha_{1,+}\left(V_{\text{rev}}\right) =$

0. The sole remaining possibility necessarily requires that both the numerator and denominator go to 0 as $c_L, c_R \to c$. Therefore

$$\left.\frac{\alpha_{1,-}}{\alpha_{1,+}}\right|_{I=0,c_L=c_R} = \frac{2}{q_1}\sqrt{c^2 + \frac{q_1^2}{4}} \tag{5.90}$$

and the theorem follows. ■

5.3 Special Case: One Anion

The main reason for considering this special case is the simple formulations of the α's and β's, which are given in the next theorem.

Theorem 5.13 *Let $M = 1$. For multiple salts, if Conditions 5.1 and 5.2 are satisfied, the approximation* (5.62) *is used, and there is only one anion, then*

$$\alpha_{0,\pm}(V) = \frac{\bar{a}_\pm(R) - \bar{a}_\pm(L)\exp(V)}{\bar{a}_+(R) - \bar{a}_+(L)\exp(V)} \qquad \beta_{0,\pm}(V) = \frac{\bar{b}_\pm(R) - \bar{b}_\pm(L)\exp(V)}{\bar{a}_+(R) - \bar{a}_+(L)\exp(V)} \tag{5.91}$$

$$\alpha_{1,\pm}(V) = \frac{a_\pm(R) - a_\pm(L)\exp(V)}{\bar{a}_+(R) - \bar{a}_+(L)\exp(V)} \qquad \beta_{1,\pm}(V) = \frac{b_\pm(R) - b_\pm(L)\exp(V)}{\bar{a}_+(R) - \bar{a}_+(L)\exp(V)} \tag{5.92}$$

where

$$a_\pm(Y) = f_Y \pm D_{1,n_1} e_Y \qquad (Y = L, R) \tag{5.93}$$

$$b_\pm(Y) = -\frac{1}{2}\left(g_Y \mp \frac{D_{1,n_1}}{D_{0,n_1}} e_Y\right) \qquad (Y = L, R) \tag{5.94}$$

$$\bar{a}_\pm(Y) = \frac{D_{1,n_1}}{D_{0,n_1}} f_Y \pm D_{1,n_1} g_Y \qquad (Y = L, R) \tag{5.95}$$

$$\bar{b}_{\pm}(Y) = -\frac{1}{2}\frac{D_{1,n_1}}{D_{0,n_1}}(1 \mp 1)\, g_Y \qquad (Y = L, R) \tag{5.96}$$

$$e_L = \sum_{z_j=1} \frac{c_j(0)}{\eta_{p_j}} \qquad e_R = \sum_{z_j=1} \frac{c_j(1)}{\eta_{p_j}} \tag{5.97}$$

$$f_L = \sum_{z_j=1} D_{1,p_j}\frac{c_j(0)}{\eta_{p_j}} \qquad f_R = \sum_{z_j=1} D_{1,p_j}\frac{c_j(1)}{\eta_{p_j}} \tag{5.98}$$

$$g_L = \sum_{z_j=1} \frac{D_{1,p_j}}{D_{0,p_j}}\frac{c_j(0)}{\eta_{p_j}} \qquad g_R = \sum_{z_j=1} \frac{D_{1,p_j}}{D_{0,p_j}}\frac{c_j(1)}{\eta_{p_j}}. \tag{5.99}$$

In the notation of Lemma 5.4,

$$E_p^{\#} = e_R - e_L \exp(V) \qquad F_p^{\#} = f_R - f_L \exp(V) \tag{5.100}$$

$$G_p^{\#} = g_R - g_L \exp(V). \tag{5.101}$$

Note that $a_{\pm}(Y)$, $b_{\pm}(Y)$, $\bar{a}_{\pm}(Y)$, *and* $\bar{b}_{\pm}(Y)$ *are independent of the voltage* V *and the current* I.

Proof. This is a straight-forward substitution of the given definitions into (5.36), (5.38), (5.37), and (5.39). ■

5.3.1 Current/Voltage Relations

Theorem 5.14 *For multiple salts, if Conditions 5.1 and 5.2 are satisfied, the approximation* (5.62) *is used, there is only one anion, and*

$$\frac{c_j(0)}{c_L} = \frac{c_j(1)}{c_R} \quad \textit{for all } j, \tag{5.102}$$

then $\alpha_{0,\pm}$*,* $\alpha_{1,\pm}$*,* $\beta_{0,\pm}$*, and* $\beta_{1,\pm}$ *are independent of* V*. In this case, all the single salt results (specifically Equations 4.239 and 4.240) carry over with*

$$\alpha_{0,\pm} = \frac{f_L \pm D_{0,n_1} g_L}{f_L + D_{0,n_1} g_L} \qquad \alpha_{1,\pm} = \frac{f_L \pm D_{1,n_1} e_L}{\frac{D_{1,n_1}}{D_{0,n_1}} f_L + D_{1,n_1} g_L} \qquad \alpha_1 = \frac{f_L - D_{1,n_1} e_L}{f_L + D_{1,n_1} e_L} \tag{5.103}$$

$$\beta_{0,\pm} = -\frac{1}{2}\frac{(1 \mp 1)\, g_L}{f_L + D_{0,n_1} g_L} \qquad \beta_{1,\pm} = -\frac{1}{2}\frac{g_L \mp \frac{D_{1,n_1}}{D_{0,n_1}} e_L}{\frac{D_{1,n_1}}{D_{0,n_1}} f_L + D_{1,n_1} g_L}. \tag{5.104}$$

Proof. We start with the relations

$$\alpha_{1,\pm} = \frac{F_p^{\#} E_n^{\#} \pm F_n^{\#} E_p^{\#}}{F_p^{\#} G_n^{\#} + F_n^{\#} G_p^{\#}} = \frac{\frac{E_n^{\#}}{F_n^{\#}} \pm \frac{E_p^{\#}}{F_p^{\#}}}{\frac{G_n^{\#}}{F_n^{\#}} + \frac{G_p^{\#}}{F_p^{\#}}} \tag{5.105}$$

$$\beta_{1,\pm} = -\frac{1}{2}\frac{G_p^{\#} E_n^{\#} \mp G_n^{\#} E_p^{\#}}{F_p^{\#} G_n^{\#} + F_n^{\#} G_p^{\#}} = -\frac{1}{2}\frac{\frac{E_n^{\#}}{G_n^{\#}} \mp \frac{E_p^{\#}}{G_p^{\#}}}{\frac{F_n^{\#}}{G_n^{\#}} + \frac{F_p^{\#}}{G_p^{\#}}}. \tag{5.106}$$

If

$$c_j(1) = \rho c_j(0) \quad \text{for all } j \tag{5.107}$$

then

$$\frac{\sum_j d_j \frac{c_j(1)}{\eta_{f_j}} - \exp\left(z_{f_j} V\right) \sum_j d_j \frac{c_j(0)}{\eta_{f_j}}}{\sum_j d'_j \frac{c_j(1)}{\eta_{f_j}} - \exp\left(z_{f_j} V\right) \sum_j d'_j \frac{c_j(0)}{\eta_{f_j}}} = \frac{\sum_j d_j \frac{c_j(0)}{\eta_{f_j}}}{\sum_j d'_j \frac{c_j(0)}{\eta_{f_j}}}. \tag{5.108}$$

The result follows from the formulas for $\alpha_{1,\pm}$ and $\beta_{1,\pm}$ given above (and similar ones for $\alpha_{0,\pm}$ and $\beta_{0,\pm}$) and the fact that there is $F_n^{\#} = D_{1,n_1} E_n^{\#}$ and $G_n^{\#} = \frac{D_{1,n_1}}{D_{0,n_1}} E_n^{\#}$. ∎

5.3.2 Reversal Potential

Theorem 5.15 (Reversal Potential: One Anion, Equal Bath Concentrations) *Let* $M = 1$. *For multiple salts, if Conditions 5.1 and 5.2 are satisfied, the approximation* (5.62) *is used, there is only one anion, and* $c_L = c_R = c$ *but* $c_j(0) \neq c_j(1)$ *for some salt* j, *then*

$$V_{rev} = \ln\left(\frac{\frac{q_1}{2} a_-(R) - a_+(R)\sqrt{c^2 + \frac{q_1^2}{4}}}{\frac{q_1}{2} a_-(L) - a_+(L)\sqrt{c^2 + \frac{q_1^2}{4}}}\right) + O(\tau) \tag{5.109}$$

If $c_j(0) = c_j(1)$ *for all salts* j *(that is, the baths are identical), then*

$$V_{rev} = O(\tau). \tag{5.110}$$

Proof. By the previous theorem and Theorem 5.13 and we have

$$\frac{a_-(R) - a_-(L)\exp(V_{\text{rev}})}{a_+(R) - a_+(L)\exp(V_{\text{rev}})} = \frac{2}{q_1}\sqrt{c^2 + \frac{q_1^2}{4}}. \tag{5.111}$$

Solving for V_{rev} gives the result. When $c_j(0) = c_j(1)$ for all j, then by Theorem 5.14 the α_1 is independent of V and $V_{\text{rev}} = 0 + O(\tau)$. ∎

5.3.3 Conductance at Reversal Potential

Theorem 5.16 (Conductance at $V_{\mathbf{rev}}$: One Anion) *Let $M = 1$. For multiple salts, if Conditions 5.1 and 5.2 are satisfied, the approximation* (5.62) *is used, there is only one anion, and $c_L \neq c_R$, then*

$$\frac{dV}{dI}(0) = \frac{S_0}{B_1 \alpha_{1,+}(V_{rev})} \frac{K\left(\beta_{1,-}(V_{rev}) - \alpha_1(V_{rev})\,\beta_{1,+}(V_{rev})\right)}{K \exp(V_{rev}) \frac{a_+(L)a_-(R)-a_-(L)a_+(R)}{\left(a_+(R)-a_+(L)\exp(V_{rev})\right)^2} - 1} + O(\tau) \tag{5.112}$$

where B_1 is as defined in Theorem 5.6 and

$$\begin{aligned} K &= \ln\left(\frac{\sqrt{c_R^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1(V_{rev})}{\sqrt{c_L^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1(V_{rev})}\right) \\ &\quad + \frac{q_1}{2}\alpha_1(V_{rev}) \frac{\sqrt{c_R^2+\frac{q_1^2}{4}} - \sqrt{c_L^2+\frac{q_1^2}{4}}}{\left(\sqrt{c_R^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1(V_{rev})\right)\left(\sqrt{c_L^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1(V_{rev})\right)}. \end{aligned} \tag{5.113}$$

Proof. In general, by Theorem 4.7 we have

$$\begin{aligned} V(I) &= \frac{J_{1,-}^{(1)}(I)}{J_{1,+}^{(1)}(I)} \ln\left(\frac{\sqrt{c_R^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\frac{J_{1,-}^{(1)}(I)}{J_{1,+}^{(1)}(I)}}{\sqrt{c_L^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\frac{J_{1,-}^{(1)}(I)}{J_{1,+}^{(1)}(I)}}\right) \\ &\quad + \frac{1}{2}\ln\left(\frac{\left(\sqrt{c_L^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\right)\left(\sqrt{c_R^2+\frac{q_1^2}{4}} + \frac{q_1}{2}\right)}{\left(\sqrt{c_L^2+\frac{q_1^2}{4}} + \frac{q_1}{2}\right)\left(\sqrt{c_R^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\right)}\right) + O(\tau). \end{aligned} \tag{5.114}$$

Differentiating this with respect to I and evaluating at $I = 0$, we get

$$\frac{dV}{dI}(0) = K \frac{dJ_1}{dI}(0) \tag{5.115}$$

where K is as defined in the theorem and

$$J_1(I) = \frac{J_{1,-}^{(1)}(I)}{J_{1,+}^{(1)}(I)} = \frac{\alpha_{1,-}(V(I))(c_L - \Lambda_0(I)) + S_0\beta_{1,-}(V(I))\,I}{\alpha_{1,+}(V(I))(c_L - \Lambda_0(I)) + S_0\beta_{1,+}(V(I))\,I}. \tag{5.116}$$

Differentiating this last expression with respect to I and evaluating at $I = 0$, we get

$$\frac{dJ_1}{dI}(0) = \frac{\left(\frac{d\alpha_{1,-}}{dI} - \frac{\alpha_{1,-}}{\alpha_{1,+}}\frac{d\alpha_{1,+}}{dI}\right)\Big|_{I=0}}{\alpha_{1,+}|_{I=0}} - S_0\frac{\left(\beta_{1,-} - \frac{\alpha_{1,-}}{\alpha_{1,+}}\beta_{1,+}\right)\Big|_{I=0}}{B_1\;\alpha_{1,+}|_{I=0}} \tag{5.117}$$

where, as in Theorem 5.6,

$$B_1 = \Lambda_0(0) - c_L. \tag{5.118}$$

From Theorem 5.13, we have

$$\left.\frac{d\alpha_{1,\pm}}{dI}\right|_{I=0} = \frac{dV}{dI}(0)\exp(V_{\text{rev}})\frac{\bar{a}_+(L)\,a_\pm(R) - a_\pm(L)\,\bar{a}_+(R)}{(\bar{a}_+(R) - \bar{a}_+(L)\exp(V_{\text{rev}}))^2}. \tag{5.119}$$

Then

$$\frac{\left(\frac{d\alpha_{1,-}}{dI} - \frac{\alpha_{1,-}}{\alpha_{1,+}}\frac{d\alpha_{1,+}}{dI}\right)\Big|_{I=0}}{\alpha_{1,+}|_{I=0}} = \frac{a_+(L)\,a_-(R) - a_-(L)\,a_+(R)}{(a_+(R) - a_+(L)\exp(V_{\text{rev}}))^2} \tag{5.120}$$

and thus

$$\begin{aligned}\frac{dJ_1}{dI}(0) &= \frac{dV}{dI}(0)\exp(V_{\text{rev}})\frac{a_+(L)\,a_-(R) - a_-(L)\,a_+(R)}{(a_+(R) - a_+(L)\exp(V_{\text{rev}}))^2} \\ &\quad - S_0\frac{\left(\beta_{1,-} - \frac{\alpha_{1,-}}{\alpha_{1,+}}\beta_{1,+}\right)\Big|_{I=0}}{B_1\;\alpha_{1,+}|_{I=0}}.\end{aligned} \tag{5.121}$$

Substituting this into (5.115) and solving for $\frac{dV}{dI}(0)$ gives the theorem. ■

Theorem 5.17 (Conductance at V_{rev}: One Anion, Equal Bath Concentrations) *Let $M = 1$. For multiple salts, if Conditions 5.1 and 5.2 are satisfied, the approxi-*

mation (5.62) *is used, there is only one anion, and* $c_L = c_R = c$ *but* $c_j(0) \neq c_j(1)$ *for some* j*, then*

$$\begin{aligned}\tfrac{dV}{dI}(0) &= \frac{S_1\left(\beta_{1,-}(V_{rev}) - \frac{2}{q_1}\beta_{1,+}(V_{rev})\sqrt{c^2+\frac{q_1^2}{4}}\right)}{\frac{q_1}{2}V_{rev}} \\ &\quad\times\frac{\left(a_+(R) - a_+(L)\exp(V_{rev})\right)^2}{\exp(V_{rev})\left(a_+(L)a_-(R) - a_-(L)a_+(R)\right)} \\ &\quad+O(\tau).\end{aligned} \tag{5.122}$$

Proof. As in the proof of Theorem 5.12, let

$$\nu = \lim_{c_L,c_R\to c}\frac{\sqrt{c_R^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1(V_{\text{rev}})}{\sqrt{c_L^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1(V_{\text{rev}})} \tag{5.123}$$

which is assumed to be positive, finite, and not equal to 1. Then

$$\alpha_1(V_{\text{rev}}) = \frac{2}{q_1}\sqrt{c^2+\frac{q_1^2}{4}} \tag{5.124}$$

and

$$V_{\text{rev}} = \frac{2}{q_1}\sqrt{c^2+\frac{q_1^2}{4}}\ln(\nu). \tag{5.125}$$

Next, to make the next limits easier to see, let

$$x = \sqrt{c_R^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1(V_{\text{rev}}) \tag{5.126}$$

$$y = \sqrt{c_L^2+\frac{q_1^2}{4}} - \frac{q_1}{2}\alpha_1(V_{\text{rev}}). \tag{5.127}$$

Then

$$\alpha_{1,+}(V_{\text{rev}})B_1 = \frac{S_0}{S_1}\left(x - y + \frac{q_1}{2}\alpha_1(V_{\text{rev}})\ln\left(\frac{x}{y}\right)\right) \tag{5.128}$$

$$K = \ln\left(\frac{x}{y}\right) + \frac{q_1}{2}\alpha_1\left(V_{\text{rev}}\right)\frac{x-y}{xy} \tag{5.129}$$

and

$$\begin{aligned}
&\frac{dV}{dI}(0) = \\
&\frac{S_1\left(\beta_{1,-}\left(V_{\text{rev}}\right) - \alpha_1\left(V_{\text{rev}}\right)\beta_{1,+}\left(V_{\text{rev}}\right)\right)}{x - y + \frac{q_1}{2}\alpha_1\left(V_{\text{rev}}\right)\ln\left(\frac{x}{y}\right)} \\
&\times\frac{\ln\left(\frac{x}{y}\right) + \frac{q_1}{2}\alpha_1\left(V_{\text{rev}}\right)\frac{x-y}{xy}}{\exp\left(V_{\text{rev}}\right)\frac{a_+(L)a_-(R)-a_-(L)a_+(R)}{\left(a_+(R)-a_+(L)\exp\left(V_{\text{rev}}\right)\right)^2}\left(\ln\left(\frac{x}{y}\right) + \frac{q_1}{2}\alpha_1\left(V_{\text{rev}}\right)\frac{x-y}{xy}\right) - 1} \\
&+O\left(\tau\right).
\end{aligned} \tag{5.130}$$

Taking the limit $x, y \to 0$ gives the result since, by the above, $\frac{x}{y} \to \nu$. ■

Theorem 5.18 (Conductance at V_{rev}: One Anion, Identical Baths) *Let* $M = 1$. *For multiple salts, if Conditions 5.1 and 5.2 are satisfied, the approximation* (5.62) *is used, there is only one anion, and* $c_j(0) = c_j(1)$ *for all* j, *then* $\frac{dV}{dI}(0)$ *is given by Theorem 4.16 with* $\alpha_{0,\pm}$, $\alpha_{1,\pm}$, $\beta_{0,\pm}$, *and* $\beta_{1,\pm}$ *given by Theorem 5.14.*

Proof. By Theorem 5.14, $\alpha_{0,\pm}$, $\alpha_{1,\pm}$, $\beta_{0,\pm}$, and $\beta_{1,\pm}$ are independent of V_{rev} and thus the single salt results carry over directly. ■

5.4 The Anomalous Mole Fraction Effect

Consider the following experiment: identical mixtures of two electrolytes of equal valence (one with mole fraction $\rho = \frac{c_1}{c}$ and the other with mole fraction $\frac{c_2}{c} = 1 - \rho$) are placed on each side of a channel and the conductance at reversal potential (in this case $V_{\text{rev}} = 0$ since we have identical bath solutions) is measured as a function of ρ. (Total bath concentration is held constant at c.) For most channels, this function of conductance versus mole fraction has a minimum. Physically this means that the channel is conducting less current after a second electrolyte of the same charge is added than if the channel were bathed in pure solution of either electrolyte. Since one would intuitively expect this function to be linear, the occurance of such a minimum is called the anomalous mole fraction effect (AMFE). In this section we will examine this effect from the point of view of PNP theory.

With the addition of one extra parameter for each ion species, it is known that PNP theory can explain the AMFE [37]. This parameter is a constant added to the Nernst-Planck equation of each ion species and is called an excess chemical potential. Its purpose is to account for possible chemical interactions between the ions and the channel protein or to account for any errors from reducing the three dimensional equations to one. It is conjectured that PNP cannot explain the AMFE without this parameter. This is in essence what we find here.

From Theorem 5.18 it is straight-forward to derive a formula to describe the experiment:

Theorem 5.19 (Conductance vs. Mole Fraction) *Let $M = 1$. Let the baths have equal total concentrations c of two monovalent salts with one common anion at concentrations c_1 and c_2. Defining*

$$\rho = \frac{c_1}{c} \tag{5.131}$$

we have $\frac{c_2}{c} = 1 - \rho$. Then

$$\eta_{p_j} = \frac{D_{1,p_j}}{D_{0,p_j}} + \frac{1}{2}\frac{S_1}{S_0}\sqrt{\frac{\sqrt{c^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}}{\sqrt{c^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}}} \qquad (j = 1, 2) \tag{5.132}$$

$$e_L = \frac{1}{\eta_{p_2}} + \left(\frac{1}{\eta_{p_1}} - \frac{1}{\eta_{p_2}}\right)\rho \tag{5.133}$$

$$f_L = \frac{D_{1,p_2}}{\eta_{p_2}} + \left(\frac{D_{1,p_1}}{\eta_{p_1}} - \frac{D_{1,p_2}}{\eta_{p_2}}\right)\rho \tag{5.134}$$

$$g_L = \frac{D_{1,p_2}}{D_{0,p_2}}\frac{1}{\eta_{p_2}} + \left(\frac{D_{1,p_1}}{D_{0,p_1}}\frac{1}{\eta_{p_1}} - \frac{D_{1,p_2}}{D_{0,p_2}}\frac{1}{\eta_{p_2}}\right)\rho \tag{5.135}$$

$$\alpha_{0,\pm} = \frac{f_L \pm D_{0,n_1} g_L}{f_L + D_{0,n_1} g_L} \qquad \alpha_{1,\pm} = \frac{f_L \pm D_{1,n_1} e_L}{\frac{D_{1,n_1}}{D_{0,n_1}} f_L + D_{1,n_1} g_L} \tag{5.136}$$

$$\beta_{0,\pm} = -\frac{1}{2}\frac{(1 \mp 1)\, g_L}{f_L + D_{0,n_1} g_L} \qquad \beta_{1,\pm} = -\frac{1}{2}\frac{g_L \mp \frac{D_{1,n_1}}{D_{0,n_1}} e_L}{\frac{D_{1,n_1}}{D_{0,n_1}} f_L + D_{1,n_1} g_L} \tag{5.137}$$

and

$$\begin{aligned} &\frac{c^2}{S_1}\left(\frac{dV}{dI}(0)\right)(\rho) = \\ &\left(2\frac{S_0}{S_1}c\alpha_{0,-} + \sqrt{c^2 + \frac{q_1^2}{4}}\alpha_{1,-} - \frac{q_1}{2}\alpha_{1,+}\right) \frac{\sqrt{c^2 + \frac{q_1^2}{4}}\beta_{1,+} - \frac{q_1}{2}\beta_{1,-}}{2\frac{S_0}{S_1}c\alpha_{0,+} + \sqrt{c^2 + \frac{q_1^2}{4}}\alpha_{1,+} - \frac{q_1}{2}\alpha_{1,-}} \\ &-2\frac{S_0}{S_1}c\beta_{0,-} - \sqrt{c^2 + \frac{q_1^2}{4}}\beta_{1,-} + \frac{q_1}{2}\beta_{1,+}. \end{aligned} \tag{5.138}$$

The graph plotted in the AMFE experiment then is

$$\frac{1}{\left(\frac{dV}{dI}(0)\right)(\rho)}. \tag{5.139}$$

At first glance (5.138) is a very complicated formula, both as function of ρ and other parameters like S_0, S_1, c, q_1, and the diffusion coefficients. However, when this function is analyzed numerically, it is a linear function of ρ no matter what values the other parameters take. In numerical experiments (5.139) which used both very large and very small values for the parameters listed above, the results have always shown (5.139) to be a linear function of ρ to at least ten significant figures. Since this formula is such a complicated function of these parameters and because of the approximations made in its derivation, this is a complete surprise. Unfortunately, we have not been able to prove the linearity of (5.139) with mathematical certainty; the formula is just too large to work out by hand or with the help of Maple. This numerical evidence, however, does support the conjecture that the AMFE cannot be accounted for by the PNP model considered in this thesis.

5.5 Comparing Formulas to Numeric Solutions

In this section we compare the formulas to the numerical solutions of the full PNP equations. For all of the cases given below we use the following parameters:

- bath length: 90 Å unless otherwise indicated
- channel length: 30 Å
- the function A is constant with a value of 38.48 Å^2 or, equivalently, the area of a circle of radius 3.5 Å.
- permanent charge: -5 molar
- diffusion coefficients:
  - $D_{0,n_1} = 1.0 \times 10^{-9}$ m^2/sec, $D_{1,n_1} = 1.0 \times 10^{-10}$ m^2/sec. If there is a second anion, $D_{0,n_2} = 2.5 \times 10^{-9}$ m^2/sec, $D_{1,n_2} = 1.5 \times 10^{-10}$ m^2/sec.
  - $D_{0,p_1} = 2.0 \times 10^{-9}$ m^2/sec, $D_{1,p_1} = 2.0 \times 10^{-10}$ m^2/sec. $D_{0,p_2} = 3.0 \times 10^{-9}$ m^2/sec, $D_{1,p_2} = 1.5 \times 10^{-10}$ m^2/sec. If there are more than two salts, $D_{0,p_3} = 5.0 \times 10^{-9}$ m^2/sec, $D_{1,p_3} = 5.0 \times 10^{-10}$ m^2/sec.

In the following all concentrations are given in molar (M), all potentials in millivolts (mV), and all conductances in picoamps per millivolt (pA/mV).

$c_1(0)$	$c_2(0)$	$c_1(1)$	$c_2(1)$	actual	(5.60)	% error	(5.62)	% error
1.25	0.75	1.80	0.20	0.975	0.624	36.0	0.613	37.1
1.25	0.75	0.20	0.80	−15.9	−17.1	−7.5	−17.2	−8.2
1.25	0.75	0.80	0.20	−14.9	−15.4	3.4	−15.4	3.4
1.25	0.75	0.10	0.40	−32.3	NS	—	NS	—
1.25	0.75	0.40	0.10	−32.3	−32.9	−1.9	−32.9	−1.9
1.25	0.75	0.02	0.08	−67.8	−73.5	−8.4	−75.2	−10.9
0.02	0.03	0.10	0.10	35.0	34.6	1.1	34.6	1.1
0.04	0.01	0.08	0.02	17.9	17.9	0.0	17.9	0.0
0.04	0.01	0.02	0.08	23.5	23.8	1.3	23.8	1.3

Table 5.1: Reversal potentials from Theorems 5.10 and 5.12 using the values of E_{f_j} given by the formulas indicated in the column head. "NS" indicates that there was no solution to the equation for V_{rev}. When there were multiple solutions, the closest to the actual value was chosen. Since there are no formulas for conductance in this case, it was not possible to distinguish multiple solutions for the reversal potential in that way as was done in later sections.

5.5.1 Two Salts with Different Anions

For the case of multiple salts with multiple anions there are only formulas for reversal potentials via Theorems 5.10 and 5.12. For the case of two salts with two different anions, Table 5.1 shows the results of the comparison.

As in the single salt case with $M = 1$, the reversal potentials work well at low bath concentrations (again a surprise) and only give bad estimates for very asymmetric bath concentrations. (The 36% error in the first line may be large, but the absolute difference of 0.3 mV is quite small.)

5.5.2 Two Salts with a Common Anion

In this section we present the comparison in a different way. With 30Å baths we set $c_1(0) = 1.25M$, $c_2(0) = 0.75M$, and $c_1(1) = 0.2M$ and let the right-side bath concentration of salt #2 vary from 0.01 to $6M$. The graph of the reversal potential and the conductance at reversal potential for this set-up are shown Figures 5-1 and 5-2, respectively. In this case, if there were multiple solutions for V_{rev}, then the

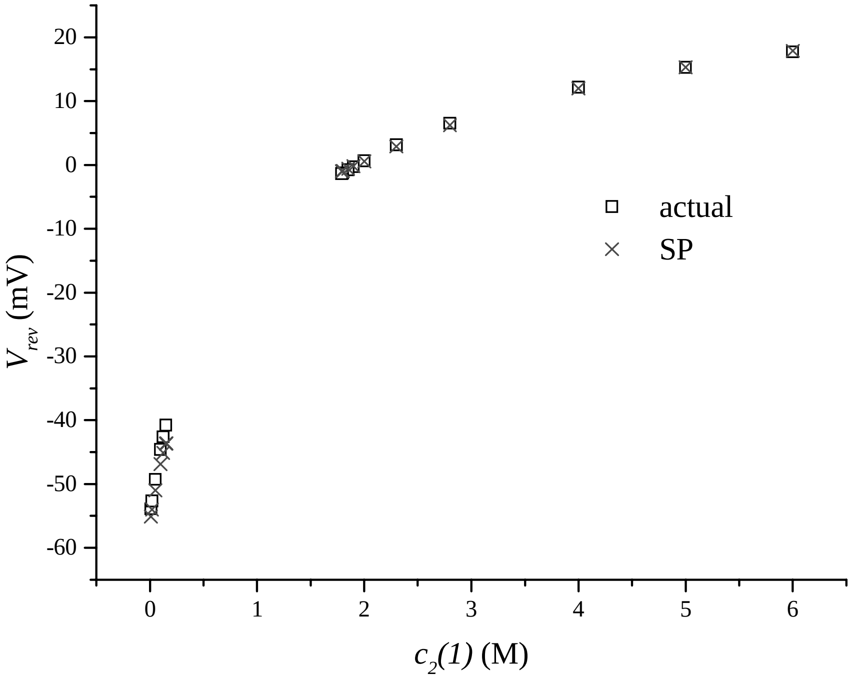

Figure 5-1: Graph of V_{rev} as a function of $c_2(1)$ as explained in the main text. The empty region $0.16 \lesssim c_2(1) \lesssim 1.8$ is where there is no solution to (5.85).

"correct" was determined to be the one that gave a positive conductance. Two things are immediate from these figures:

1. The reversal potential formula (5.85) works well (when it has a solution) and is more accurate at higher bath concentrations.
2. Equations (5.112) and (5.122) for the conductance at reversal potential do not seem to be good approximations, although they are somewhat reasonable at high bath concentrations.

While these results for the conductance formulas are not very impressive, one interesting result is that the formula for conductance at reversal potential for identical baths given in Theorem 5.18 is very good, as shown in Table 5.2. It is interesting

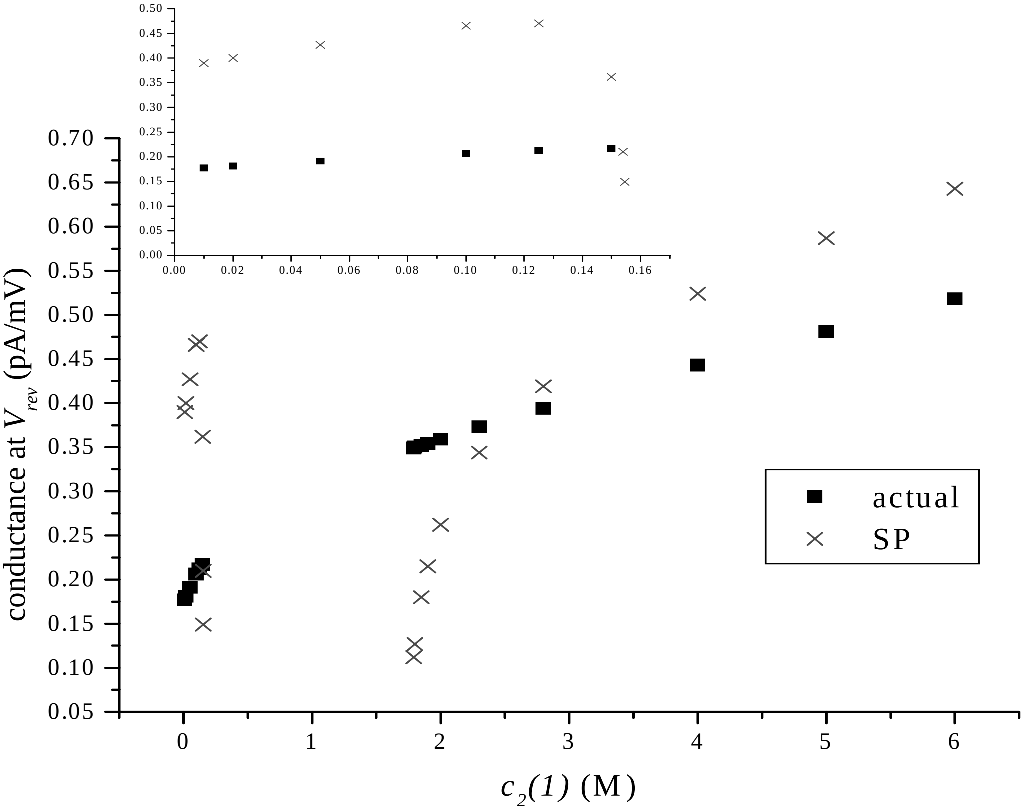

Figure 5-2: Graph of conductance at reversal potential as a function $c_2\,(1)$ as explained in the main text. The inset shows the region $[0, 0.16]$ in more detail. From this graph it is intuitively obvious why there sometimes there is no solution to (5.85): the conductance is not defined in certain regions defined by rapid changes near the edges.

$c_1(0) = c_1(1)$	$c_2(0) = c_2(1)$	actual	SP	% error
1.0	0.01	0.130	0.130	0.0
0.3	0.7	0.144	0.147	-2.1
0.03	0.07	0.0240	0.0204	15.0
0.1	0.07	0.0336	0.0304	9.5

Table 5.2: Conductance at reversal potential for identical baths as outlined in Theorem 5.18. The accuracy increases as the total concentration on each side increases.

$c_1(0)$	$c_2(0)$	$c_3(0)$	$c_1(1)$	$c_2(1)$	$c_3(1)$	actual	SP	% error
1.25	0.75	0.1	1.80	0.20	1.0	14.2	14.7	3.5
0.125	0.075	0.01	0.02	0.08	0.1	15.0	15.1	0.7

Table 5.3: Reversal potential for three salts with a common anion. The approximation which uses the coarse approximation (5.62) is good for both high and low bath concentrations, which is the same as for the one and two salt cases discussed earlier.

to note that the accuracy seems to be a function of *total* bath concentration (with accuracy diminishing as it is lowered), rather than concentration of one individual salt; that is, even if one salt has a concentration of $0.01M$, for example, the results are still very accurate as long as the other salt has a large concentration, say $1.0M$. Since this is the formula used in the AMFE calculation, this gives even more credence to the results from that section.

5.5.3 Three Salts with a Common Anion

The trends observed above (namely the good performance of the formulas for reversal potential and conductance for identical baths) are true for more than two salts. This is illustrated in Tables 5.3 and 5.4 where we have used only the crudest approximations (that is, using (5.62)). Since the general formulas for conductance at reversal potentials does not appear to work well, we do not show them here.

$c_1(0) = c_1(1)$	$c_2(0) = c_2(1)$	$c_3(0) = c_3(1)$	actual	SP	% error
0.3	0.7	0.1	0.171	0.173	1.2
0.03	0.07	0.01	0.0281	0.0242	13.9

Table 5.4: Conductance at reversal potential for identical baths as outlined in Theorem 5.18. As in the one and two salt cases, the accuracy increases as the total concentration on each side increases.

Chapter 6

Dealing with the Area Function

The only thing not addressed so far has been how to deal with the area function A. As was shown in Chapter 2, A is the area of the equipotential surfaces in the three dimensional problem. So far we have treated it as a given function and have found that it only comes into the final formulas we have derived in the form

$$S_i = \int_{x_i}^{x_{i+1}} \frac{ds}{A(s)}; \tag{6.1}$$

that is, all we have to know about A are two or three of its integrals, depending on the number of intervals of permanent charge. In this chapter we briefly consider what to do with these integrals.

The most correct (and thus the least useful) answer is that because A represents a property of the three dimensional equipotential surfaces which are sensitive functions of the bath concentrations and the applied potential, one has to solve the full three dimensional PNP equations given in Chapter 2 for at least some cases in order to emperically determine regimes where some approximations of these integrals can be made. This is unfortunately not possible at this point in time since the computations of the full three dimensional PNP equations are too time-consuming.

The next possibility is to try and eliminate these integrals from the final results by some argument. The one fact that we do know about A is that in the baths, the farther the equipotential is away from the channel, the larger its surface area and so A tends to be large away from the channel. Thus the only contribution to S_0 is near the channel. Furthermore, inside the channel, because the channel is narrow, A must be roughly the same size as the cross-sectional area of the channel πr^2 where r is the radius of the channel (if we model the channel as a right cylinder). Therefore, if A becomes large (relative to the cross-sectional area πr^2) quickly, then $\frac{S_1}{S_0}$ is large. We will try to use this fact to get some A-independent results.

First let us consider the formulas for the reversal potentials. In the coarsest approximation of the reversal potential in the single salt case (4.239), because of the diffusion coefficient drop, we were able to obtain a result independent of the S_i. All the multiple salts results, however, still have these integrals (in the form $\frac{S_1}{S_0}$). Specifically, they come in through the η_{p_j} (in the case of a common anion):

$$\eta_{p_j} = \frac{D_{1,p_j}}{D_{0,p_j}} + \frac{1}{2}\frac{S_1}{S_0}\frac{\rho_R - \rho_L}{\ln\left(\frac{\rho_R}{\rho_L}\right)} \qquad (c_L \neq c_R) \tag{6.2}$$

where

$$\rho_L = \sqrt{\frac{\sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}}} \qquad \rho_R = \sqrt{\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}}{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}}} \tag{6.3}$$

and

$$\eta_{p_j} = \frac{D_{1,p_j}}{D_{0,p_j}} + \frac{1}{2}\frac{S_1}{S_0}\sqrt{\frac{\sqrt{c^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}}{\sqrt{c^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}}} \qquad (c_L = c_R = c)\,. \tag{6.4}$$

With the way the formulas are written, if

$$\frac{\eta_{p_j}}{\eta_{p_1}} \approx 1 \tag{6.5}$$

for all salts j, then it is valid to drop out the η terms by setting them equal to 1. This happens when

$$\frac{D_{1,p_j}}{D_{0,p_j}} \ll \frac{1}{2}\frac{S_1}{S_0}\frac{\rho_R - \rho_L}{\ln\left(\frac{\rho_R}{\rho_L}\right)} \qquad (c_L \neq c_R) \tag{6.6}$$

or

$$\frac{D_{1,p_j}}{D_{0,p_j}} \ll \frac{1}{2}\frac{S_1}{S_0}\sqrt{\frac{\sqrt{c^2+\frac{q_1^2}{4}}+\frac{q_1}{2}}{\sqrt{c^2+\frac{q_1^2}{4}}-\frac{q_1}{2}}} \qquad (c_L = c_R = c)\,. \tag{6.7}$$

Since $\frac{S_1}{S_0}$ is large and $\frac{D_{1,p_j}}{D_{0,p_j}}$ is small, that condition is true if the quantities multiplying $\frac{S_1}{S_0}$ are not too small. However, for small bath concentration to permanent charge ratios ($\frac{c_L}{q_1}$ and $\frac{c_R}{q_1}$), the terms multiplying $\frac{S_1}{S_0}$ can be small enough to make

$$\frac{D_{1,p_j}}{D_{0,p_j}} \sim \frac{1}{2}\frac{S_1}{S_0}\frac{\rho_R - \rho_L}{\ln\left(\frac{\rho_R}{\rho_L}\right)} \qquad (c_L \neq c_R) \tag{6.8}$$

or

$$\frac{D_{1,p_j}}{D_{0,p_j}} \sim \frac{1}{2}\frac{S_1}{S_0}\sqrt{\frac{\sqrt{c^2+\frac{q_1^2}{4}}+\frac{q_1}{2}}{\sqrt{c^2+\frac{q_1^2}{4}}-\frac{q_1}{2}}} \qquad (c_L = c_R = c) \tag{6.9}$$

(depending what the size of $\frac{S_1}{S_0}$ is). This is especially true in the equal bath concentration case. What is always true is that

$$\frac{\eta_{p_j}}{\eta_{p_1}} \to 1 \tag{6.10}$$

as $\frac{S_1}{S_0} \to \infty$. Therefore, the graph of V_{rev} as a function of $\frac{S_1}{S_0}$ (for given bath concentrations and diffusion coefficients) will tend to a limiting value as $\frac{S_1}{S_0} \to \infty$, call it V^*_{rev}. (V^*_{rev} is the same as V_{rev} with the η's set to 1.) Consequently, if the graph of V_{rev}

as a function of $\frac{S_1}{S_0}$ is already close to its limiting value for small values of $\frac{S_1}{S_0}$ (say, for example, 5), then V^*_{rev} should be a good approximation of the true channel. (In the case of multiple solutions to the V_{rev} equation, each root changes continuously as a function of $\frac{S_1}{S_0}$ and in this case all solutions can be plotted and analyzed in the same way.) This illustrated in the following examples with

$$\frac{D_{1,p_1}}{D_{0,p_1}} = \frac{1}{20} \qquad \frac{D_{1,p_2}}{D_{0,p_2}} = \frac{1}{10} \tag{6.11}$$

$$q_1 = -5M. \tag{6.12}$$

These are illustrated in the Figures 6-1 and 6-2. In Figure 6-1 none of the multiple solutions to the reversal potential equation vary too much over the range of $\frac{S_1}{S_0}$ making V^*_{rev} a good approximation of the true channel in this case. In Figure 6-2 the reversal potential does vary a lot and so V^*_{rev} is probably not a good approximation of the true channel in this case. It is important to note that Figure 6-1 is the same experimental set-up as in Figure 6-2 except that 0.1M of salt #1 was added to the right bath. Therefore it is difficult to tell without the graphs when V^*_{rev} is a good approximation of the true channel. We are not sure exactly what the cause of this is. The only discernible difference between these two cases is that inside the channel the concentrations of the two cations are roughly equal for case shown in Figure 6-2 and are not equal for case shown in Figure 6-1. Also, this does not appear to be because $c_L = c_R$ for case shown in Figure 6-2.

As for the formulas for the conductances, they are functions of the absolute values of S_0 and S_1, not just their ratios. This is problematic because we do not know how to estimate these parameters, especially S_0. Therefore, at these points, these formulas are not practical for interpretation of data or for gaining intuitive insight and it is an open question if there is a better way to derive equations for these quantities that incorporates the baths in a more managable way.

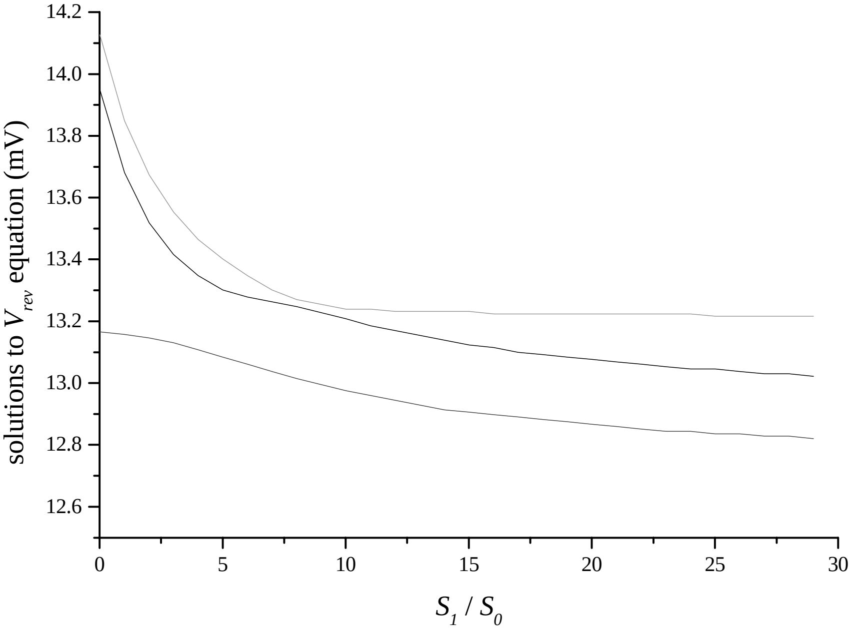

Figure 6-1: In this graph the bath concentrations were: $c_1(0) = 0.1M$, $c_2(0) = 0.05M$, $c_1(1) = 0.15M$, and $c_2(1) = 0.1M$.

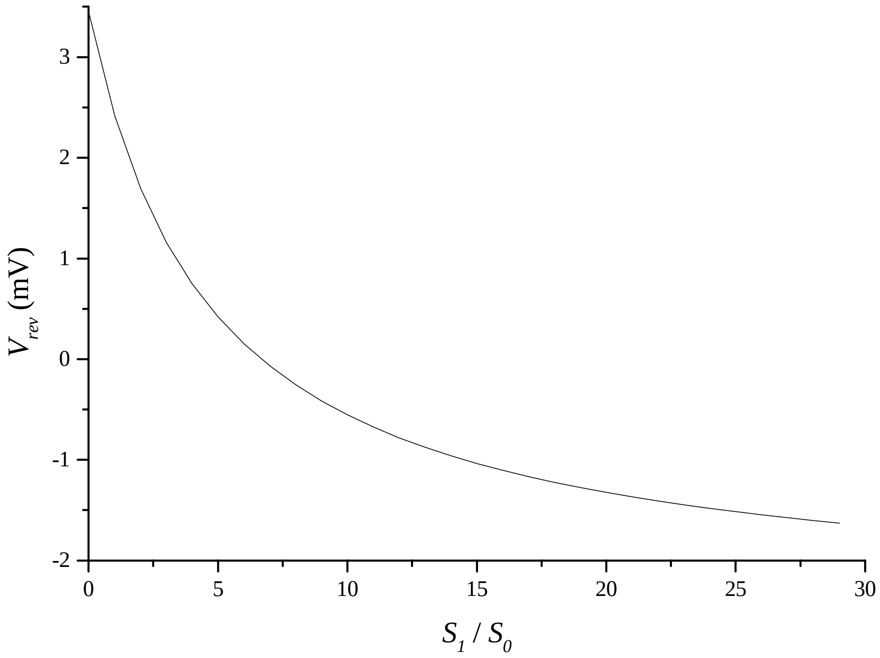

Figure 6-2: In this graph the bath concentrations were: $c_1(0) = 0.1M$, $c_2(0) = 0.05M$, $c_1(1) = 0.05M$, and $c_2(1) = 0.1M$.

Chapter 7

Summary of Results

In this chapter we distill the results of the last two chapters into formulas that are solely in terms of biological variables. Again we divide the results into single and multiple salts results.

7.1 Single Salt Results

As was discussed in Section 4.6, unless the channel under consideration is extremely long (> 50Å), the results in the single salt case are only useful when the permanent charge is modeled with one or two intervals on which it is constant; more than two requires a longer channel. Here we present only the uniform (one interval) permanent charge results because of the complexity of the other results. Furthermore, it is generally believed to be true that ions undergo a significant drop in the values of their diffusion coefficient. One of the results we derived (Theorem 4.18) was that when this occurs one can neglect the baths in the analysis. This result is independent of the area function A (Chapter 6).

In the following, the cation has diffusion coefficient D_p^* in the baths and D_p inside the channel and the anion has diffusion coefficient D_n^* in the baths and D_n inside the channel. The left and right baths have concentration c_L and c_R, respectively.

When the baths are taken into consideration, they must be taken long enough so that the mobile ion concentrations reach c_L and c_R well before the edge of the bath. For a 30Å channel this is usually satisfied with 90Å baths in the worst-case scenario of treating the baths as cylindrical extensions of the channel. Usually 30Å baths are more than sufficient.

In the single salt case the reversal potential is given by

$$\begin{aligned} \frac{e}{kT}V_{\text{rev}} &= \frac{D_p - D_n}{D_p + D_n}\ln\left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\frac{D_p - D_n}{D_p + D_n}}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\frac{D_p - D_n}{D_p + D_n}}\right) \\ &\quad + \frac{1}{2}\ln\left(\frac{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)}{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)}\right). \end{aligned} \tag{7.1}$$

This formula appears to work well when compared to the numerical solutions of the full PNP equations (Section 4.6), although it seems to break down with very asymmetric bath concentrations.

Other, more accurate formulas that involve the area function A (see Chapters 2 and 6) are given in Chapter 4, as are formulas for the conductance at reversal potential.

7.2 Multiple Salts Results

When there are more than two ion species (that is, more than one salt) in the system, results were much more difficult to obtain and the results we do have are not nearly as nice as those in the single salt case. In this summary we will only include the case of multiple salts with a common anion. Furthermore, it is important that the conditions set out in Chapter 6 are met. Only then can one ignore the contributions of the area function A and have the practical results stated below. Otherwise the full PNP equations should be solved numerically or a good model for A must be developed. In that case the general results are listed in Chapter 5.

In this section the salts are denoted by j and each salt j has bath concentration $c_j(L)$ and $c_j(R)$ in the left and right baths, respectively. Then the total bath concentrations are

$$c_L = \sum_j c_j(L) \qquad \text{and} \qquad c_R = \sum_j c_j(R). \tag{7.2}$$

When $c_L \neq c_R$ and

$$\frac{c_j(L)}{c_L} \neq \frac{c_j(R)}{c_R} \tag{7.3}$$

for some j, then V_{rev} is the solution to the following equation:

$$\begin{aligned} & V_{\text{rev}} - \frac{1}{2}\frac{kT}{e} \ln\left(\frac{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)}{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)} \right) \\ = \; & \frac{kT}{e} \frac{\sum_j \left(D_{p_j} - D_n\right)\left(c_j(R) - c_j(L)\exp\left(\frac{eV_{\text{rev}}}{kT}\right)\right)}{\sum_j \left(D_{p_j} + D_n\right)\left(c_j(R) - c_j(L)\exp\left(\frac{eV_{\text{rev}}}{kT}\right)\right)} \\ & \times \ln\left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\frac{\sum_j\left(D_{p_j} - D_n\right)\left(c_j(R) - c_j(L)\exp\left(\frac{eV_{\text{rev}}}{kT}\right)\right)}{\sum_j\left(D_{p_j} + D_n\right)\left(c_j(R) - c_j(L)\exp\left(\frac{eV_{\text{rev}}}{kT}\right)\right)}}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\frac{\sum_j\left(D_{p_j} - D_n\right)\left(c_j(R) - c_j(L)\exp\left(\frac{eV_{\text{rev}}}{kT}\right)\right)}{\sum_j\left(D_{p_j} + D_n\right)\left(c_j(R) - c_j(L)\exp\left(\frac{eV_{\text{rev}}}{kT}\right)\right)}} \right). \end{aligned} \tag{7.4}$$

This implicit equation is not as nice as one might hope; usually there are multiple (two or three) solutions for this equation and for some ranges of the parameters there may not be any solutions.

When $c_L \neq c_R$ and

$$\frac{c_j(L)}{c_L} = \frac{c_j(R)}{c_R} \tag{7.5}$$

for all salts j, then

$$\begin{aligned} \frac{e}{kT}V_{\text{rev}} &= \frac{\sum_j \left(D_{p_j} - D_n\right) c_j\left(L\right)}{\sum_j \left(D_{p_j} + D_n\right) c_j\left(L\right)} \ln\left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2} \frac{\sum_j \left(D_{p_j} - D_n\right) c_j(L)}{\sum_j \left(D_{p_j} + D_n\right) c_j(L)}}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2} \frac{\sum_j \left(D_{p_j} - D_n\right) c_j(L)}{\sum_j \left(D_{p_j} + D_n\right) c_j(L)}} \right) \\ &+ \frac{1}{2} \ln\left(\frac{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)}{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2}\right)\left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2}\right)} \right). \end{aligned} \tag{7.6}$$

Unlike the previous result, this is an explicit equation for V_{rev} (that is, V_{rev} does not appear on the right-hand side) and thus has exactly one solution.

In the usual cases we have that the function

$$\alpha\left(V\right) = \frac{\sum_j \left(D_{p_j} - D_n\right)\left(c_j\left(R\right) - c_j\left(L\right)\exp\left(\frac{eV}{kT}\right)\right)}{\sum_j \left(D_{p_j} + D_n\right)\left(c_j\left(R\right) - c_j\left(L\right)\exp\left(\frac{eV}{kT}\right)\right)} \tag{7.7}$$

is not constant. For some combinations of diffusion coefficients and bath concentrations, however, ω is constant. (The most common case is $\frac{c_j(L)}{c_L} = \frac{c_j(R)}{c_R}$ for all salts j with we have just deal explicitly because these are experimentally possible. Other instances include the theoretical limits $D_{p_j} = 0$ for all salts j and $D_n = 0$. These limits should in general be avoided because the function $\alpha\left(V\right)$ is a very nonlinear function that is linear if one of these limits is taken. Since diffusion coefficients are never exactly zero, there is always a V such that the denominator of $\alpha\left(V\right)$ is zero while the numerator is not. Furthermore, the analysis we did to get to these formulas requires that all the diffusion coefficients inside the channel are of the same order in size.) When $c_L = c_R = c$ and $\alpha\left(V\right)$ is not a constant function, then

$$V_{\text{rev}} = \frac{kT}{e} \ln\left(\frac{\sqrt{c^2 + \frac{q_1^2}{4}} \sum_j \left(D_{p_j} + D_n\right) c_j\left(R\right) - \frac{q_1}{2} \sum_j \left(D_{p_j} - D_n\right) c_j\left(R\right)}{\sqrt{c^2 + \frac{q_1^2}{4}} \sum_j \left(D_{p_j} + D_n\right) c_j\left(L\right) - \frac{q_1}{2} \sum_j \left(D_{p_j} - D_n\right) c_j\left(L\right)} \right). \tag{7.8}$$

(Again, in this case there is exactly one solution.) Specifically, when $c_j\left(L\right) = c_j\left(R\right)$

for all salts j (that is, all the individual salt concentrations are equal), then

$$V_{\text{rev}} = 0. \tag{7.9}$$

Chapter 8

Discussion

8.1 Why PNP?

In this thesis we have focused on the one-dimensional Poisson-Nernst-Planck (PNP) theory as a description of ion permeation through an open channel. Why would one want to use this theory? Ideally, of course, one would want to model permeation by molecular dynamics where all particles in the channel interact according to the laws of physics. However, these simulations only last up to nanoseconds of real time and so cannot reach the time scales of permeation. Therefore some reductions must be made. PNP is the reduced form of at least two models of transport. One of these is the modeling of ions as undergoing Brownian motion in an electric field generated by the applied potential and the channel protein. Then, in the limit of high friction and relatively low fluxes, the Nernst-Planck equation can be derived [17]. PNP can also be derived from the Boltzmann Transport Equation (BTE) [7] for gases which treats the collisions of particles in a different way than Brownian motion. By taking one integral moment of the BTE (which corresponds to the conservation of mass), one derives the Nernst-Planck equation [27]. Finally, the Nernst-Planck equation must be coupled to the Poisson equation for the electric field (which is a differential form of Maxwell's First Law). Physically this is necessary because the distribution of charges in the system changes the potential (Poisson equation), which, in turn, changes the distribution of charges (Nernst-Planck). Mathematically this is necessary so that the number of unknown functions is equal to the number of equations and the system is then consistent and solvable.

Furthermore, the PNP system of equations has had great success in the modeling of semiconductors for over 40 years. There the system is called Drift-Diffusion. (This model has been so successful and the engineers are so comfortable with it that new transistors are being designed to fit the PNP equations [54].) This is important because the basic problem of semiconductors is similar to channels: charged particles must move from region to another through a medium that contains permanent electrical charges under the influence of an applied potential. Furthermore, a recent analysis of the applicability of the Drift-Diffusion (PNP) system in semiconductors showed that this system is applicable in situations where it was once thought it could not be used [3]. Essentially it established that it is possible to formally model much smaller devices with the Drift-Diffusion (PNP) system than for which it had originally been designed. While this is not directly applicable to channels, it is further evidence that the PNP is a much broader theory than one might think. (Another example of this is the derivation of the PNP equations from the BTE which was originally designed to model gases.)

The biggest reason, however, for using the PNP theory is a much more practical one: PNP fits the data of several channels very well ([9], [10], [11], [36]) over a large range of bath concentrations and applied voltages with a minimum of fitting parameters. This alone is an indication that PNP is on the correct track for modeling permeation. Specific issues such as selectivity and chemical interactions between ions and the channel are not explicitly addressed in this electrostatic theory, and must be dealt with. However, the data fitting alone indicates that the PNP theory is a good place to start.

8.2 Why Not PNP?

PNP is, of course, not the be all and end all of ion permeation theories; it has many problems.

One such problem is that it is not possible to tell how the parameters (for example, the permanent charge q) from the one-dimensional theory relate to the reality of the three-dimensional structure of the channel. In this thesis we have outlined a possible way to relate these, but, because it is currently not possible to do the three dimensional numerical calulations, that cannot be verified. At a time when more and more channel structures are known at atomic scales, it is important to have atomic detail in any model of permeation. This problem can be alleviated by using the three dimensional PNP equations (see Chapter 2) which include permanent charge distributions based on known atomic structures [29].

Another problem with PNP (which cannot be fixed by using the three dimensional PNP equations) is that it treats ions as point particles; by ignoring the volume of the permeating ions, PNP can miss single-filing effects due to the small channel geometry. There are a couple of ways to try and deal with this issue. First, for uncharged particles it has been shown that single-filing, diffusing particles can be modeled by Fick's Law of Diffusion with an effective diffusion coefficient that is smaller than the normal bulk diffusion coefficient of the particle [35]. A drop in diffusion coefficient inside the channel is something that is already believed to be true for channel permeation (and we have used it in this thesis many times). Therefore PNP may in some way already have inadvertantly have addressed this issue – but only in part. There is now increasing evidence that the so-called "excluded volume" effects have a large impact on the electrostatics inside channels and that the inclusion of the Mean Spherical Approximation into the channel geometry may explain many aspects of selectivity [6]. This work is at an early stage and must be explored in more depth.

A similar fundamental problem is that the channel protein, the lipid bilayer, and the water molecules are modeled as a simple dielectric material. This is not appropriate since the channel is so small that all analysis must be done at atomic length scales; dielectrics are, by definition, the approximation to be used when the length scale of a system is large compared to atomic length scales such as for wires or capacitors. In the channel environment, the microscopic electric field is almost certainly not the same as the spatially-averaged electric field that is implied by a dielectric. (Griffiths [20] gives an excellent discussion of this point.) This problem may perhaps be addressed by invoking a different kind of averaging. PNP is a mean field theory and thus involves an average, not over spatial coordinates, but over time; averaging the permeation of many particles over a long time gives the concentrations (actually probabilities [17]) and potentials that are used in the equations and removes the results of atomic vibrations and other phenomena that occur on times scales that are much less than the microsecond time scale necessary for permeation. This kind of time averaging may also give something like a dielectric, at least for the channel protein and the lipid bilayer, on the biological times scale.

8.3 Analytic Treatments of PNP

Attempts to derive formulas for measurable quantities from the PNP equations in the past have largely come from work on liquid junctions in solutions (reviewed in [33]) and ion transport through membranes (reviewed in [51] and [22]). For liquid junctions, much of the analytical interest focused on the electrostatic potential at the junction, while for membrane transport, the goal was to describe the flux as we are attempting to do for channels.

In all of these attempts to derive formulas for measurable quantities, the authors have used assumptions which may be appropriate for the situation they were considering, but that are not necessarily justifiable for individual channels. The two most commonly used of these assumptions are setting the permanent charge of the membrane to zero or to assume electroneutrality everywhere in the system. An assumption that is always made is that the cross-sectional area of the system is constant. For the case of liquid junctions all of these assumptions are perfectly reasonable; when one is considering only ionic solutions there is no structure with a permanent charge and thus pointwise electroneutrality is true, as is constant cross-sectional area. When modeling a homogeneous membrane seperating two baths of ionic solutions, the zero permanent charge assumption depends on the specific substance used to construct the membrane. When the permanent charge is nonzero, then the pointwise electroneutrality condition is technically not true at the bath/membrane junctions because of the accumulation of counter-ions and repulsion of co-ions near the channel entrances. However, if the membrane is relatively thick, then the pointwise electroneutrality condition is a good approximation of reality and the concentration and electrostatic profiles can be treated as discontinuous functions with jump conditions provided by Donnan potential theory. The constant cross-sectional area condition is also valid, even when including part of the baths in the analysis, if the membrane is assumed to be homogeneous.

When considering individual channels, however, none of those three assumptions is generally valid. Because channels are such small structures, any amount of charge on the amino acid residues of the channel protein has an impact on ion permeation (see Section 8.4.1 below). Also, channels can be short enough that the regions of space charge near the channel entrances can be a significant fraction of the channel length. Therefore imposing pointwise electroneutrality is not *a priori* valid. Furthermore, because Donnan potential theory requires pointwise electroneutrality, the jump conditions offered by it are not necessarily the best to use (see Section 4.5.3). Lastly, because channels have small openings that are exposed to big baths, the constant cross-sectional area assumption cannot be valid; the ions disperse into the baths and diffuse in three dimensions, not just one as would be required by this assumption. In this way, the baths would act as resistors and any results regarding flux would be incorrect. (All of these points are also discussed in Section 2.1.)

In this thesis we tried to analytically solve the PNP equations with a minimum of assumptions, being especially mindful never to include the ones discussed above. These equations can be useful for intuitive thinking about what makes a reversal potential or conductance at reversal potential, but it is important to stress that these are only valid for channels that can be described by a uniform permanent charge. This then immediately excludes any rectifying channels and, from one of our other results, channels that have little or no anomalous mole fraction effect. Also, it is generally much better to use the full PNP system to describe a channel. That means that for any particular channel (and each of its mutants) a permanent charge profile and the diffusion coefficients should be derived from data fitting as has already been done for several channels. This is the way only to be sure that there are no errors from using the formulas on channels which do not satisfy the assumptions we made or from more subtle errors. This is something the computational semiconductor community took to heart long ago where these quantities are calculated numerically directly from models (most notably PNP). This eliminates any errors made from reducing a system of differential equations to formulas, while still allowing intuitive interpretation from graphical representations.

In the mathematics community, work similar to that done in this thesis has been presented in the context of semiconductors. The work of Ward, *et al.*, [53] is closest in form, but they consider a case which corresponds to an unrealistically long channel. Furthermore, they only consider the case of built-in boundary conditions with a very specific permanent charge and do not explicitly calculate the boundary layers as was done here. Ward, *et al.*, based their approach on that of Please [42] who seems to have done the first mathematical asymptotic expansion of the PNP system.

8.4 PNP and the Permeability Ratio

In this section we consider the concept of relative permeability (that is, which ion species a channel prefers to pass). We start with the classical approach and offer a new twist on this approach. Next we consider the subject without any assumptions and derive some results and then relate these to the classical approach.

8.4.1 The GHK Equation

To quote the book almost every paper on channels quotes at some point [23, p. 341]: "By far the most commonly used formalism for describing ionic permeability and selectivity of membranes has been the Goldman [19] and Hodgkin and Katz [25] constant-field theory." To add some weight to that statement, a quick search in the *Biophysical Journal* found several articles published in 1998 and 1999 alone that use the GHK equation in the case of monovalent ion species, the case we are considering here (for example, [30], [43], [55]). This is why we have included this section comparing our results for the reversal potential to that of what has historically been called the Goldman-Hodgkin-Katz (GHK) equation.

First, a quick review of the GHK equation. As succinctly described in [23, p. 341], the underlying assumptions of GHK are:

1. The membrane is considered a homogeneous slab of materical into which the permeant particles partition instantaneously from the bulk solution; no reference is made to pores.
2. Flux for each species is governed by a Nernst-Planck equation.
3. The ions cross the membrane independently (without interacting with each other).
4. The electric field in the membrane is constant; that is, the potential drops linearly across the membrane.

5. The ions do not interact with the membrane in any way, except perhaps by having their diffusion coefficients change. This is not stated in [23], but is necessary for the arguments that allow to the GHK equation to work.

Having been stated in this way, the limitations of the GHK equation should be immediately clear. The only *a priori* physically reasonable assumption is that the flux is described by the Nernst-Planck equation. Assumption #1 may be reasonable when considering whole-cell patch clamping experiments, but not for the single channel bilayer experiments we have in mind. Assumptions #3, #4, and #5 are used to remove the Poisson equation from the full PNP system that we have considered. Assumptions #3 and #5 are especially problematic assumptions: this would suppose that all the millions of charged particles per second that go through a channel do not interact with themselves or the channel protein despite the basic fact that Coulombic interactions go as $\frac{1}{R^2}$ and the channel is 30Å long channel and 4-10Å in diameter and lined with charged and polar amino acid residues. These assumptions are usually given without a reason as in [23], [19], and [25]. From this one can infer that they were used as mathematical simplifications more than anything else. (It is understandable that Goldman, Hodgkin, and Katz did this because they did not have the computation capabilities to solve the full PNP equations. Fifty years later, however, this approach is no longer appropriate.)

Having reduced the problem to the stage that the Nernst-Planck equations can be integrated by hand, the GHK equation can be derived:

$$V_{\text{rev}} = \frac{kT}{e} \ln \left(\frac{\sum_j D_{p_j} \beta_{p_j} c_j (R) + D_n \beta_n c_L}{\sum_j D_{p_j} \beta_{p_j} c_j (L) + D_n \beta_n c_R} \right) \tag{8.1}$$

where we have assumed a common anion. (In this form technically this is the Hodgkin/Katz (HK) equation since Goldman [19] did not include the β's. In the following we will refer to it as the HK equation.) The β's are the so-called partition coefficients, defined by

$$\beta_{p_j} = \frac{c^*_{p_j}(L)}{c_j(L)} = \frac{c^*_{p_j}(R)}{c_j(R)} \tag{8.2}$$

$$\beta_n = \frac{c^*_n(L)}{c_L} = \frac{c^*_n(R)}{c_R} \tag{8.3}$$

where $c^*_{p_j}(L/R)$ and $c^*_n(L/R)$ are the concentrations of the given ion species just inside the channel on the left and right sides. These partition coefficients are another peculiarity of the HK equation. If there is no permanent charge (that is, $q = 0$) as is assumed in #5, then all the partition coefficients must be 1; this is something we proved in this thesis (Theorem 4.5), but is also true from Donnan potential theory, and intuitively, without some charge from the membrane, and no source of energy there is no reason for the concentration of one species to increase in relation to another. If, however, there is a permanent charge associated with the membrane, then that negates Assumption #5. Thus, for the sake of consistency, in the following we set all the partition coefficients to 1:

$$V_{\text{rev}} = \frac{kT}{e} \ln \left(\frac{\sum_j D_{p_j} c_j(R) + D_n c_L}{\sum_j D_{p_j} c_j(L) + D_n c_R} \right). \tag{8.4}$$

To illustrate that the assumptions that were made in deriving the GHK/HK equations do have an impact on the final results we consider the following examples. First we consider the case of one salt in the system. In Figure 8-1 the reversal potential is plotted as a function of c_L (while c_R is kept fixed) as predicted from GHK and singular perturbation with and without permanent charge. GHK and SP with $q_1 = 0$ are surprisingly close. This is, however, the only time that happens; when some permanent charge is added the results are quite different. When two salts are present, Figure 8-2 shows the reversal potential as a function of $c_1(L)$ such that the total bath concentration is identical on both sides while in Figure 8-3 $c_2(L)$ is kept

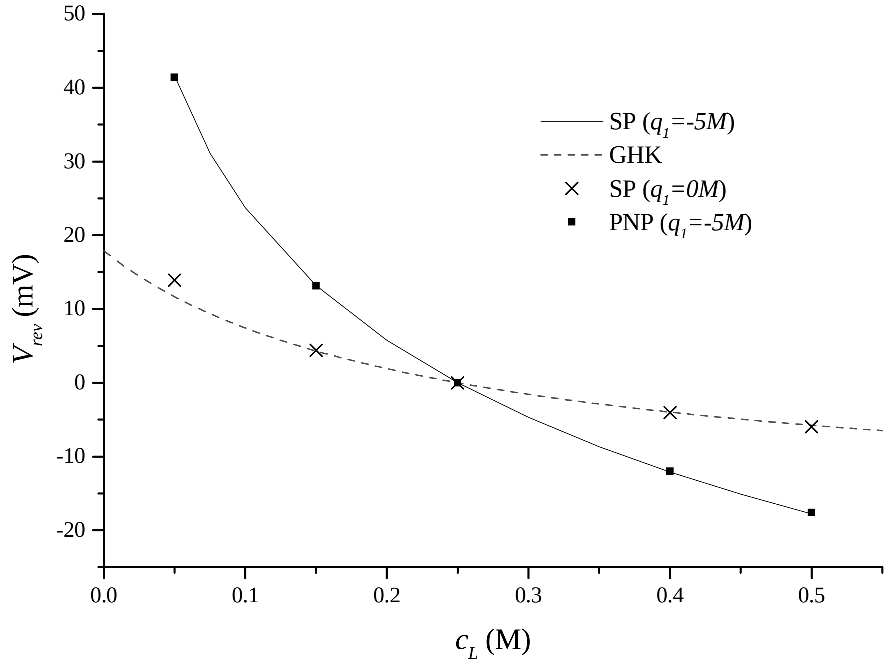

Figure 8-1: Comparison of the GHK equation for reversal potential and the singular perturbation (SP) approach for uniform permanent charge in the case of only one salt. Here $\frac{D_p}{D_n} = 2$, $c_R = 0.25$ M, and the channel has length 30 Å and radius 3.5 Å.

fixed while $c_1\,(L)$ is varied. In this case, again when $q_1 = 0$, the GHK is roughly the same as the singular perturbation approach for large concentrations, but not when permanent charge is added to the system.

Today the HK equation is mainly used to estimate permability ratios

$$\frac{P_p}{P_{Cl}} \equiv \frac{D_p\beta_p}{D_{Cl}\beta_{Cl}} \tag{8.5}$$

for various cations p through a channel where

$$P_p = \frac{D_p\beta_p}{d_{\text{ch}}} \qquad P_{Cl} = \frac{D_{Cl}\beta_{Cl}}{d_{\text{ch}}}. \tag{8.6}$$

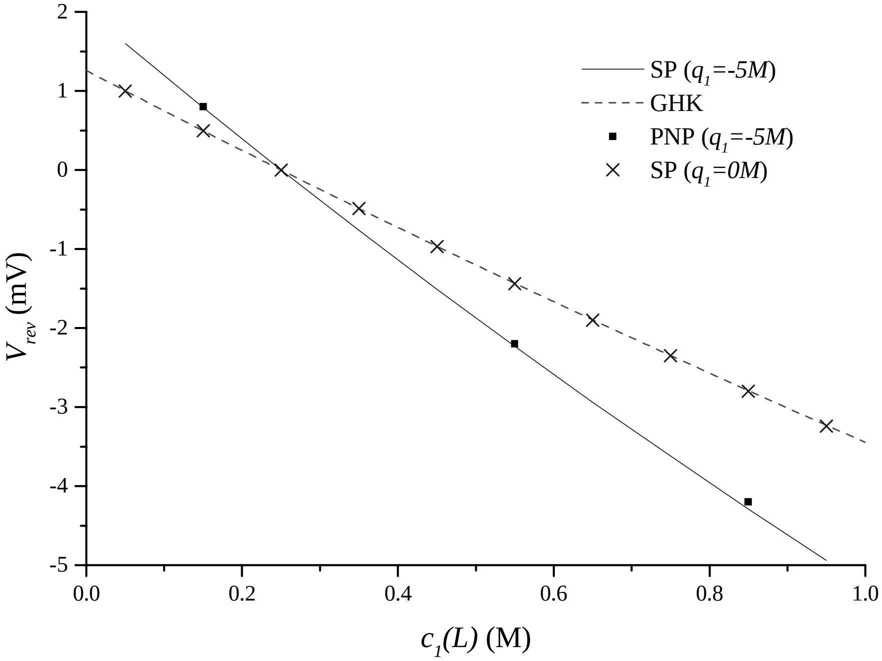

Figure 8-2: Comparison of the GHK equation for reversal potential and the singular perturbation (SP) approach for uniform permanent charge in the case of two salts. Here we have used the same channel dimensions as in Figure 8-1 with $\frac{D_{p1}}{D_n} = 2$, $\frac{D_{p2}}{D_n} = 1.5$, $c_1(R) = 0.25$ M, and $c_2(R) = 0.75$ M. The total bath concentration is maintained at 1 M on both sides.

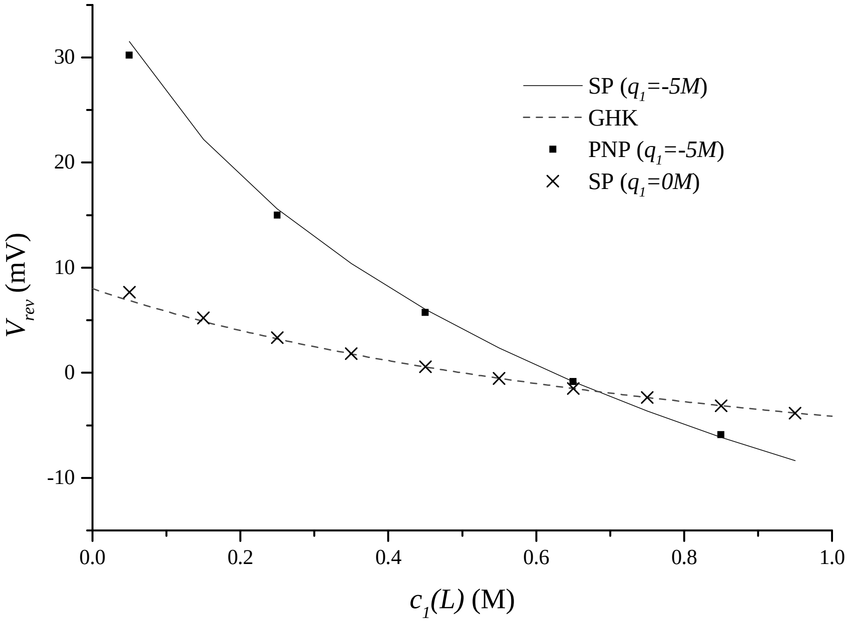

Figure 8-3: Comparison of the GHK equation for reversal potential and the singular perturbation (SP) approach for uniform permanent charge in the case of two salts. Here we have used the same channel dimensions as in Figure 8-1 with $\frac{D_{p_1}}{D_n} = 2$, $\frac{D_{p_2}}{D_n} = 1.5$, $c_2(L) = 0.25$ M, $c_1(R) = 0.25$ M, and $c_2(R) = 0.75$ M.

Since the partition coefficients are not necessarily well-defined (see above) in the HK formula, we now derive a formula for them from the result of our work in the case of one salt in the baths. If we take as the concentrations just inside the channel (defined as $c^*_{p_j}(L/R)$ and $c^*_n(L/R)$ above) the concentrations that would result if the channel were electroneutral there (this is not reality, but is a well-defined quantity that is easy to calculate), then we can define the left and right partition coefficients as

$$\beta_p^{L/R} = \frac{c^*_p(L/R)}{c_{L/R}} = \frac{\sqrt{c^2_{L/R} + \frac{q_1^2}{4}} - \frac{q_1}{2}}{c_{L/R}} \tag{8.7}$$

and

$$\beta_n^{L/R} = \frac{c^*_n(L/R)}{c_{L/R}} = \frac{\sqrt{c^2_{L/R} + \frac{q_1^2}{4}} + \frac{q_1}{2}}{c_{L/R}}. \tag{8.8}$$

These are true for all forms of permanent charge, even when it is not constant. Note that for different ion species of the same valence, the partition coefficients are equal; that is, for two cation species p_1 and p_2 we have $\beta^L_{p_1} = \beta^L_{p_2}$ and $\beta^R_{p_1} = \beta^R_{p_2}$. One can then define left and right "permeability ratios"

$$P_p^{L/R} = \frac{D_p \beta_p^{L/R}}{d_{\text{ch}}} \qquad P_n^{L/R} = \frac{D_n \beta_n^{L/R}}{d_{\text{ch}}} \tag{8.9}$$

When $c_L = c_R = c$, the left and right partition coefficients for each ion species are equal (call them β^*_p and β^*_n) and it is then possible to write a definition for the permeability of each ion species

$$P_p^L = P_p^R = \frac{D_p \beta^*_p}{d_{\text{ch}}} \equiv P^*_p \qquad P_n^L = P_n^R = \frac{D_n \beta^*_n}{d_{\text{ch}}} \equiv P^*_n \tag{8.10}$$

and the permeability ratios are then

$$\frac{P_p^*}{P_n^*} = \frac{D_p\beta_p^*}{D_n\beta_n^*} = \frac{D_p}{D_n}\frac{\sqrt{c^2+\frac{q_1^2}{4}}-\frac{q_1}{2}}{\sqrt{c^2+\frac{q_1^2}{4}}+\frac{q_1}{2}}. \tag{8.11}$$

In order to determine the permeability ratios, one then needs the value of the uniform permanent charge (assuming this is a valid description of the channel in the first place) and the ratio of the diffusion coefficients of the ions inside the channel.

However, knowing these quantities is not necessary when one is interested in the permeability ratios of two ion species of the same valence, $\frac{P_{p2}^*}{P_{p1}^*}$ for instance. If the two experiments are done with a common anion, then

$$\frac{P_{p2}^L}{P_{p1}^L} = \frac{P_{p2}^R}{P_{p1}^R} = \frac{P_{p2}^*}{P_{p1}^*} = \frac{D_{p2}}{D_{p1}}. \tag{8.12}$$

This is true not only when $c_L = c_R = c$ and the permanent charge is uniform, but under all circumstances since the left and right partition coefficients defined above are equal and thus cancel when we consider this particular ratio.

Whether this is a useful way to infer which ion species the channel prefers to pass is a question we consider next.

8.4.2 Taking a Fresh Look at Permeabilities

In this section we want to take a new look at the entire notion of the relative permeability of various ion species and then relate the results of the PNP approach to the classical HK a equation. In order to tie in with the results of this thesis, we consider only 1,1-monovalent electrolytes and permeability ratios of two ion species with the same valence will be done by two one-salt experiments, not one two-salts experiments as is sometimes done (see, for example, [23]).

First, we need a definition of what it means for one ion to be more permeable than another. The simplest such definition seems to be that under identical conditions (that is, same applied voltage and bath concentrations), the fluxes J_1 and J_2 measured in the two experiments are not equal and so the more permeable ion is that with the larger flux. Therefore, the permeability ratio can be defined to be

$$\frac{J_2}{J_1}. \tag{8.13}$$

In the notation of the previous chapters, these ratios can be

$$\frac{J_p}{J_n}, \frac{J_{p_2}}{J_{p_1}}, \text{ and } \frac{J_{n_2}}{J_{n_1}}. \tag{8.14}$$

Let us consider the permeability ratios of two ions with the same charge (that is, $\frac{J_{p_2}}{J_{p_1}}$ and $\frac{J_{n_2}}{J_{n_1}}$). For simplicity, we will only discuss the case of cation ratios since the anion ratios are derived similarly. Consider the Nernst-Planck equation for these ions:

$$-\frac{J_{p_1}}{D_{p_1}A} = p_1' + p_1\phi' \tag{8.15}$$

$$-\frac{J_{p_2}}{D_{p_2}A} = p_2' + p_2\phi'. \tag{8.16}$$

Integrating these over the channel region (x_1, x_2) gives

$$-\frac{J_{p_i}}{D_{p_i}} \int_{x_1}^{x_2} \frac{\exp(\phi)}{A(x)} dx = p_i(x_2)\exp(\phi(x_2)) - p_i(x_1)\exp(\phi(x_1)) \qquad (i = 1, 2). \tag{8.17}$$

The values on the right-hand side are not *a priori* the same for both ion species. However, if there is a large drop in all the diffusion coefficients between the bath and the channel, then one of the results derived in this thesis (Theorem 4.24) shows that they are (almost) equal. Thus, we have

$$\frac{J_{p2}}{J_{p_1}} \approx \frac{D_{p2}}{D_{p_1}}. \tag{8.18}$$

This formula is true for all forms of permanent charge, not just uniform. Note that then the new definition of permeability from the previous section is a useful indicator of the flux ratios we have used as our working definition of permeability ratios (cf. (8.12)).

Next we consider the case of uniform permanent charge to derive an approximate expression for $\frac{D_{p2}}{D_{p_1}}$. We start with the reversal potential formula (7.1):

$$\begin{aligned} \frac{e}{kT}V_i &= \frac{D_{p_i} - D_n}{D_{p_i} + D_n} \ln \left(\frac{\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2} \frac{D_{p_i} - D_n}{D_{p_i} + D_n}}{\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2} \frac{D_{p_i} - D_n}{D_{p_i} + D_n}} \right) \\ &\quad + \frac{1}{2} \ln \left(\frac{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} - \frac{q_1}{2} \right) \left(\sqrt{c_R^2 + \frac{q_1^2}{4}} + \frac{q_1}{2} \right)}{\left(\sqrt{c_L^2 + \frac{q_1^2}{4}} + \frac{q_1}{2} \right) \left(\sqrt{c_R^2 + \frac{q_1^2}{4}} - \frac{q_1}{2} \right)} \right) \end{aligned} \tag{8.19}$$

where $i = 1, 2$ and V_1 and V_2 are the reversal potentials of p_1 and p_2, respectively. (We assume a common anion in both experiments.) If both the bath concentrations c_L and c_R are small compared to the uniform permanent charge q_1 (which is usually the case in channel experiments), then

$$\frac{e}{kT}V_i = -\sigma \ln \left(\frac{c_R}{c_L} \right) + \sigma \left(c_R^2 - c_L^2 \right) \left(\frac{D_{p_i}}{D_n} \right)^{\sigma} \frac{1}{q_1^2} + O\left(\frac{c_R^4 - c_L^4}{q_1^4} \right) \tag{8.20}$$

where

$$\sigma = \operatorname{sign}(q_1). \tag{8.21}$$

Therefore

$$\frac{J_{p_2}}{J_{p_1}} \approx \frac{D_{p_2}}{D_{p_1}} \approx \left(\frac{\frac{e}{kT}V_2 + \sigma \ln\left(\frac{c_R}{c_L}\right)}{\frac{e}{kT}V_1 + \sigma \ln\left(\frac{c_R}{c_L}\right)} \right)^{\sigma}. \tag{8.22}$$

If we consider a cation channel where presumably $\sigma = -1$, then $\frac{e}{kT}V_i + \sigma \ln\left(\frac{c_R}{c_L}\right)$ is the difference between the measured reversal potential and the Nernst potential of cation species i and thus the permeability ratio $\frac{J_{p_2}}{J_{p_1}}$ is approximately the ratio of these differences.

8.4.3 Back to HK

Now that we have a working definition of relative permeabilities, how do the permeability ratios used in the HK equation relate to our definition? At least in the uniform permanent charge case we can give an answer.

If we solve the HK equation for one salt for the permeability ratio of the cation to the anion, we get

$$\frac{P_p}{P_n} = \frac{c_R \exp\left(V_{\text{rev}}\right) - c_L}{c_R - c_L \exp\left(V_{\text{rev}}\right)}. \tag{8.23}$$

Using (8.19) in this expression for species 1 and 2, we can then relate the GHK permeability ratios to the diffusion coefficient ratios (which approximate the flux ratios):

$$\frac{P_{p_2}}{P_{p_1}} = \frac{c_R \exp\left(V_2\right) - c_L}{c_R - c_L \exp\left(V_2\right)} \frac{c_R - c_L \exp\left(V_1\right)}{c_R \exp\left(V_1\right) - c_L}. \tag{8.24}$$

Through Figures 8-4 and 8-5 we consider several properties of this function. First we consider how the HK permeability ratios relate to the ratio of the diffusion coefficients. As is shown for one example in Figure 8-4, this relationship is almost linear, despite the fact that (8.24) is a very complicated-looking function. Further-

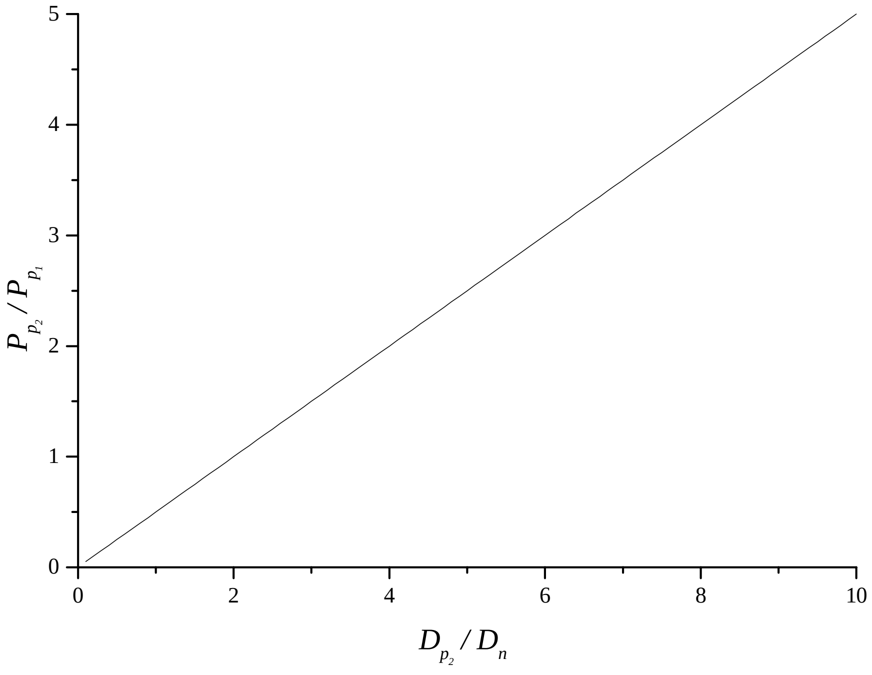

Figure 8-4: Graph of (8.24) for $c_L = 1.0M$, $c_R = 0.5M$, and $q_1 = -5M$. The ratio $\frac{D_{p1}}{D_n}$ was kept constant at 2 while $\frac{D_{p2}}{D_n}$ was varied. Varying the bath and permanent charge concentrations does not produce significantly different curves.

more, from (8.19) and (8.24) it is possible to prove that whenever $D_{p_1} = D_{p_2}$, we have $P_{p_1} = P_{p_2}$. Therefore, the GHK permeability ratios correctly predict when the permeability ratio as we have defined it is less than or greater than 1. From a mathematical point of view this a surprising result since the HK formula does not take into consideration permanent charge or ion-ion interactions.

Next we consider the result of changing the bath concentrations in (8.24). In Figure 8-5 are the graphs of (8.24) as a function of c_L with different permanent charges q_1 which show that the HK permeabilities become concentration dependent as the permanent charge gets lower. Because of the small structure of channels, one would expect that the charge concentration inside the channel is large and when that

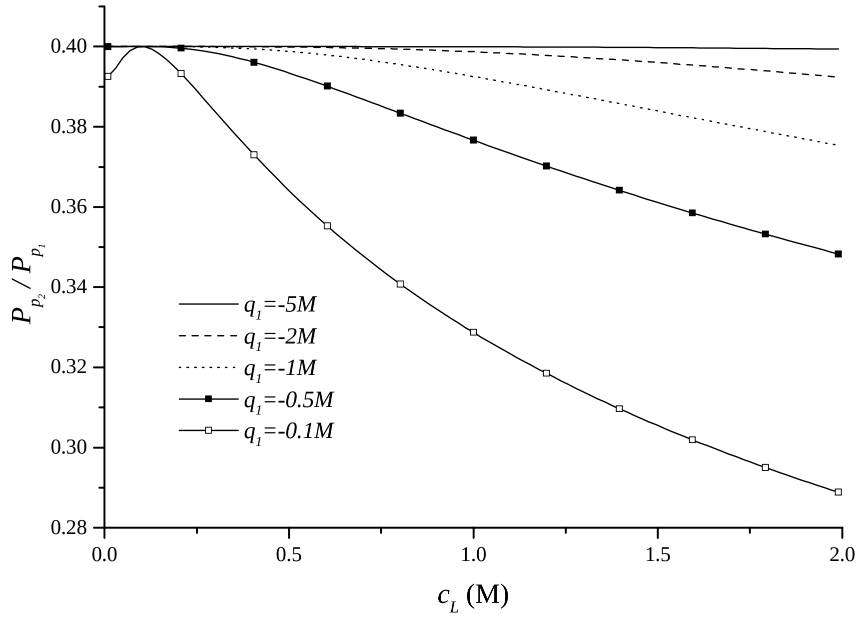

Figure 8-5: Graph of (8.24) as a function of c_L for the permanent charge values q_1 shown. The bath concentration c_R was kept constant at $0.1M$ with $\frac{D_{p1}}{D_n} = 2$ and $\frac{D_{p2}}{D_n} = 5$. A similar pattern of less concentration dependence with larger $|q_1|$ is exhibited for $q_1 > 0$.

is the case, $\frac{P_{p2}}{P_{p1}}$ is concentration independent which is observed in many, but not all, experiments [23]. In the cases when the HK permeability ratios are concentration dependent, this has been attributed to multiple ions occupying a channel at one time [23]. If the presence of multiple ions influences the diffusion coefficients of the ions inside the channel, then this may still have an effect on the flux ratios, but it is no longer necessary to explain the concentration dependence of the HK permeability ratios.

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