Electrochemical Neuromodulation Using Electrodes Modified with Ion-Selective Materials, Based on the Physical Process of Ion-Concentration Polarization

by

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Abstract

Developing precise and effective means of modulating the human nervous system is an aspiration of the fields of neuroscience and neurotechnology. Our research group is approaching this challenge by constructing a prosthetic device that can perform focal chemical modulation of selected ions in the interstitial space of neural tissue. Its principle of operation is based on ion-concentration polarization (ICP) generated by polarization of electrodes covered with ion-selective membranes (ISMs). In order to optimize this modality in terms of clinical effect and safety, we require a more fundamental understanding of the physical processes that give rise to ICP of the selected ion. Broadly, the goal of this thesis is to: (1) present and validate mathematical models for the description and prediction of polarized ISM systems, and (2) characterize transport phenomena that are uniquely captured using these models. To start, we used a semi-empirical equilibrium model to compare the integral transference of several common membrane formulations in a physiological electrolyte. Then, we introduced a 1-D model of Nernst-Planck-Poisson (NPP) with kinetic ion-ionophore reaction that could be solved using the finite element method (FEM). Our analysis of this model focused on four key features: the interfacial transition regions at the contact planes between the aqueous and membrane phases, the intra-membrane reaction boundary layer (RBL), ICP arising in the aqueous phase, and ICP arising in the membrane phase. Lastly, we presented several multidimensional models of ion transport in the aqueous phase. This was used to examine processes that limit the length-scale of aqueous ICP, such as forced convection and non-planar diffusion. Once fully realized, an ISM-based device could be used to manipulate extracellular ions in neural tissue to produce therapeutic effects. In the peripheral nervous system, this operation could potentially be used to lower the stimulus energy required to elicit muscle activation (via Ca$^{2+}$ depletion), or block aberrantly firing nerves that characterize neuropathic pain disorders (via either $K^+$ depletion or enhancement). Eventually, ISM-based stimulation could be applied to the central nervous system to address neurological and psychiatric disorders.

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List of symbols

Symbols

\(a_k\)  molar activity of solute \(k\)
\(c_k\)  molar concentration of solute \(k\)
\(c_k^0\)  initial and bulk concentrations of each solute \(k\) in the aqueous phase
\(c_L^0\)  total molar concentration of ionophore added to the membrane
\(c_p^{ip}\)  ingress point of the membrane, defined as the aqueous concentration of the primary ion at which the membrane has an integral transference of 50%
\(c_R^0\)  total molar concentration of mobile lipophilic counter-ion added to the membrane
\(d\)  thickness of the membrane
\(D\)  electric displacement flux density
\(D_k\)  diffusion coefficient for solute \(k\)
\(E\)  electromotive force measured across ion-selective membrane (ISM)
\(E^0\)  standard reference potential
\(F\)  Faraday constant
\(f_k\)  molar activity coefficient of solute \(k\)
\(f^0\)  frequency applied in electrochemical impedance spectroscopy (EIS) simulation
\(J\)  total electric current density
\(\bar{k}_i, \bar{k}_i\)  forward and backward first-order reaction rate constants for solute \(i\)
\(k_i^{ex}\)  backwards rate constant for ion-exchange interfacial adsorption process with ion \(i\)
\(K_i^{ex}\)  equilibrium constant for ion-exchange interfacial adsorption process with ion \(i\)
\(K_k^{part}\)  partition coefficient of solute \(k\) for the interface between membrane and aqueous phases
\(K_{Pj}^{in}\)  intrinsic selectivity coefficient for primary ion \(P\) and interfering ion \(j\)
\(K_{Pj}^{pot}\)  Nikolsky potentiometric selectivity coefficient for primary ion \(P\) and interfering ion \(j\)
\(l_{Debye}\)  characteristic length of the interfacial space-charge region
\(l_{FC}\)  characteristic length of a diffusion boundary layer that is size-limited by forced convection
\( l_{NP} \) characteristic length of a diffusion boundary layer that is size-limited by non-planar diffusion

\( l_{RBL} \) characteristic length of the reaction boundary layer inside the membrane

\( l_{SC} \) characteristic length of a diffusion boundary layer that is size-limited by spontaneous convection

\( n \) number of ionophore molecules that bind to a single ion in a particular complex

\( N_k \) molar flux density of solute \( k \)

\( p \) pressure

\( p(\phi) \) phase-fraction function

\( R \) universal gas constant

\( R_k \) net volume rate of formation of solute \( k \) by chemical reaction

\( R_{RBL} \) effective resistance that arises from the reaction boundary layer

\( s \) Laplace parameter

\( T \) absolute temperature

\( t_i \) transference number of ion \( i \)

\( T_i \) integral transference of membrane for ion \( i \)

\( T_P^{sp} \) integral transference number of the membrane for the primary ion adjacent to a standard physiological aqueous electrolyte

\( U_0 \) solvent velocity averaged across a channel

\( v \) molar-averaged solvent velocity

\( V_P \) phase-boundary potential at an interface between membrane and aqueous phases

\( z_i \) charge number of ion \( i \)

\( \beta_i^n \) stability constant for complex comprised of the neutral lipophilic ionophore bound to the ion \( i \) in a \( 1: n \) stoichiometric ratio

\( \delta_N \) length of the Nernst steady diffusion layer

\( \delta_{\gamma} \) length of the phase-field transition region

\( \Delta C \) characteristic concentration difference across a region specified by an index

\( \Delta N \) characteristic flux density difference across a region specified by an index

\( \epsilon_r \) relative permittivity

\( \epsilon_0 \) permittivity of free space

\( \nu \) kinematic viscosity
\( \rho \) solvent density
\( \sigma \) Ohmic electrical conductivity
\( \tau_{\text{aq}} \) characteristic time-scale of aqueous DBL formation
\( \tau_{\text{org}} \) characteristic time-scale of membrane DBL formation
\( \tau_r \) characteristic time-scale of charge relaxation
\( \phi \) phase-field state variable
\( \psi \) electric potential

Superscripts and subscripts
\( \text{app} \) externally applied quantities
\( \text{(aq)} \) properties and variables characteristic of the aqueous phase
\( \text{(org)} \) properties and variables characteristic of the membrane phase
\( b \) bulk region of either membrane or aqueous phases outside of interfacial zones characterized by space-charge or non-equilibrium reactions**
\( i \) index of any ion present in the system
\( j \) index within a subset of ions designated as interfering
\( k \) index of any solute present in the system
\( L \) ionophore
\( P \) primary ion for a particular ionophore-based system
\( R \) mobile lipophilic counter-ion
\( \gamma \) phase-field transition region at the interface between aqueous and membrane phases**
\( \rho \) interfacial space-charge region**

* The superscript is omitted for situations where we assume there is only one characteristic stoichiometric ratio.

** This designates properties intrinsic to the specified region, or variables that are located on the boundaries of it.
1 Introduction and background

1.1 Neural prostheses: successes, challenges, and new approaches

Traditional intervention strategies such as pharmaceutical treatment have always had limited success when applied to the neurological diseases. Recently, another promising Alzheimer’s treatment, the BACE inhibitor Verubecestat, failed its Phase III drug trial on the grounds of efficacy [1]. In the last few decades, enabled by advances in micro-technology, new therapies have emerged based on implantable neural prosthetic devices. These devices have made rapid progress, and therapies such as Deep Brain Stimulation (DBS), Vagus Nerve Stimulation (VNS), and Electric Acoustic Stimulation (EAS) for cochlear implants are finally being realized on the clinical level [2-4]. Last year, GlaxoSmithKline spun off its bioelectronics division with Alphabet’s Verily as a co-owner [5]. This new company, called Galvani, is betting on a technology for neuromodulation in the peripheral nervous system (PNS), hoping to treat a range of conditions such as cardiovascular, metabolic, respiratory, inflammatory, and autoimmune [6]. Although still nascent, technologies such as these could someday be used to overcome the intractable problems in neurology and psychiatry.

However, modalities based on electrical stimulation suffer from several constraints that might fundamentally limit precision and functionality. The current density around a disk-shaped electrode falls off roughly as $1/r^2$ which permits the effects of stimulation to spread non-specifically across neural tissue. The electrode size of the most commonly used DBS system, the Medtronic 3387, is 1.3 mm in diameter [7]. Meanwhile, it has been estimated that the volume of excited tissue in a typical Parkinson’s patient with this device extends out
hundreds of cubic millimeters [8]. Indiscriminate effects such as these have been thought to contribute to side effects such as mood swings and depression [4].

In addition, electrical stimulation modalities are limited by the finite charge injection capacity of the electrode material. If too much current is applied in a unipolar pulse, irreversible redox processes begin to occur, damaging both the electrode and surrounding tissue [9]. Thus, techniques based on direct-current (DC) pulses such as nerve blocking are considered infeasible for human interventions [10]. This also constrains the minimum dimensions of the electrode, since smaller electrodes require larger current densities to effectively excite tissue.

In order to address these issues and expand the capabilities of artificial neuromodulation, there has been a drive to develop new technologies for interfacing with the nervous system. In a broad sense, the field is searching for a chronically-implantable, minimally-invasive platform that could modulate neurons on a multiplexed, cell-by-cell basis. Additionally, it would be desirable to mimic the neuron’s natural mode of operation as much as possible. Various approaches have succeeded in partial measure with some aspects of this vision. However, most still have severe technical obstacles in terms delivery, toxicity, or efficacy [11-13]. One example is optogenetic neuromodulation, which has made rapid advances over the last decade. Its operation involves genetically modifying a group of neurons to make them artificially sensitive to light. Although this technique is currently an accepted method for pursuing scientific questions in in vitro and in vivo models, its use in humans faces considerable immune system compatibility issues [14]. Thus, while modalities such as optogenetics are promising, they have a long way to go before they can be applied as intervention strategies.
1.2 Electrochemical neuromodulation

One of the simplest methods of modulating the nervous system is through systemic administration of pharmaceutical agents. However, the effects of this type of chemical manipulation cannot be controlled spatially or temporally with any precision. Additionally, this approach has to deal with systemic barriers and buffers [15]. Local administration through injection solves some of these problems, but this is not feasible outside of the clinic [16]. Previous devices have attempted localized chemical modulation using microelectromechanical systems (MEMS) reservoirs that inject ions by iontophoresis, but they are prohibitively bulky and have finite supplies of ions [17]. Our research group has pioneered a strategy of electrochemical modulation which can be performed by polarizing an electrode modified with an ion-selective membrane (ISM). This operation results in ion-concentration polarization (ICP) in a spatially confined region adjacent to the electrode. In this region, the concentration of selected ions is either enhanced or depleted depending on the polarity. A successful implementation of this technology could allow spatially and temporally precise modulation of nervous tissue through chemical manipulation.

In a previous work of ours, we reported the use of a planar solid-contact Ca$^{2+}$-selective electrode that was able to lower the threshold for electrical excitation in an ex vivo frog sciatic nerve preparation. This change was affected by depletion of interstitial Ca$^{2+}$. In a fully realized clinical device, this type of modulation could be used to reduce the stimulus energy necessary for muscle activation. Additionally, using a K$^+$-selective material embedded in a glass micropipette, we were able to block action potential propagation along a particular segment of the nerve fiber. This could be achieved by either enhancing or depleting interstitial K$^+$. We could use this in a clinical device to block aberrantly firing nerves that
characterize neuropathic pain disorders [18]. In future work, we intend to target areas in the central nervous system (CNS), possibly modulating synaptic activity by manipulating extracellular Ca\textsuperscript{2+} and Mg\textsuperscript{2+} concentrations [19-21].

1.3 Evolution of the ion-selective membrane electrode

The ion-selective electrode arose early in the 20\textsuperscript{th} century, when it was discovered that the potential across a doped glass membrane varied directly with the difference in pH on both sides [22]. By changing the doping of the membrane, it could be made sensitive to other types of ions such as Na\textsuperscript{+} and Ag\textsuperscript{+} [23]. Larger ions however, such as Ca\textsuperscript{2+} and Mg\textsuperscript{2+}, were relatively immobile in this type of material and would not yield a potential response. This prompted the development of a new type of electrode, based on the liquid membrane [24].

The liquid membrane is composed of a nonpolar organic solvent within which ions can move freely. In most formulations, a polymer such as polyvinyl chloride (PVC) is added to increase the viscosity, making it stable enough to be mounted on electrode bodies. This composition, referred to as the plasticized PVC matrix, is the most common media used for the so-called liquid membrane electrode.

Materials such as glass and liquid membrane electrodes with ion-selective potential responses rely on some internal property that makes the selected ion dominant within the material. In the case of the glass electrode, this property arises from dopants such as aluminum and boron oxides that have an affinity for H\textsuperscript{+} and Na\textsuperscript{+}. Meanwhile, for the liquid membrane, selectivity is achieved by incorporation of a molecule called the ionophore. The role of the ionophore is to reversibly bind a particular ion species with a high affinity relative
to other co-ions which are designated as interfering. Ionophores generally must also be lipophilic to prevent leaching into adjacent aqueous domains.

Since the first proof-of-concepts for the liquid membrane electrode were reported, there has been a consistent stream of innovations. One of the early focuses of research and development has been the pursuit of new ionophores, both natural and synthetic. As a result, many key ionophores for species relevant to applications such as biological and environmental monitoring have been discovered, including some polyions [25]. Today, the Na⁺ ISM electrode has replaced atomic emission spectroscopy (AES) in laboratories for many use cases [26, 27]. Clinical assays for ions such as Na⁺, Ca²⁺ and K⁺ using ISM electrodes are carried out regularly, with more than 200 million performed for K⁺ every year [25]. Researchers continue to make improvements on ISM-based sensors in terms of selectivity, detection limit, response time, stability, and fabrication.

Thus, we can leverage decades of progress for the development of ISM-based neuromodulation devices. With multiple ionophores available for key monatomic ions such as Na⁺, K⁺, Ca²⁺, and Mg²⁺, transport parameters of the membrane can be finely tuned to suit our application. Also, since biological sensing is one of the primary applications of the ISM electrode, biocompatibility has been characterized extensively for many membrane formulations [28, 29]. These factors will facilitate rapid development and testing of devices.

1.4 Dynamic electrochemistry using ion-selective membrane electrodes

Recently, a new generation of ISM-based sensing modalities has emerged, deemed by some as “dynamic electrochemistry.” Instead of simply measuring the potential across the ISM in a zero-current mode, the membrane is electrically polarized. This operation results in
ICP of selected ions in both the aqueous and membrane phases, and this can be taken advantage of for more advanced sensing techniques.

Amperometric modalities such as cyclic voltammetry and stripping voltammetry treat the ISM interface similar to an electrode interface, where peaks that occur at a particular potential are associated with a specific ion-transfer process. With multiple ionophores added to the membrane, this technique can be used to assay multiple species simultaneously by analyzing independent peaks, analogous to a spectroscopic method. Furthermore, it has been shown that less calibration is necessary for the accurate determination of ion concentration [30-33]. This type of operation has been used for the implementation of liquid-membrane scanning electrochemical microscopy (SECM) probes. This type of probe can be used to detect concentrations of chemicals as well as reaction processes occurring on a surface. Similar to atomic force microscopy (AFM), the SECM probe is scanned across a surface creating a raster image [34-36].

In addition, some work has been done to realize ISM-based coulometry. This offers a calibration-free modality for assaying ions and could be particularly useful for testing outside of the laboratory. For this type of sensor, the concentration of a particular species is exhaustively depleted from the volume on one side of the membrane by applying a static potential. Then, by measuring the total amount of charge transferred, the amount of this ion species can be determined. Since this value is measured in absolute terms, this assay could potentially forego the requirement of calibration entirely, or at least recalibration [37-39].

Novel techniques such as pulsed-current chronopotentiometry and flash chronopotentiometry also offer various improvements, such as lower detection limits and the ability to measure total concentration. These sensors operate under galvantostatic
control, measuring potential during and after the pulse is applied. The flux of the selected ion results in ICP in the aqueous phase. When aqueous cations are depleted by application of a cathodic current (anodic for anions), the potentiometric response becomes more exaggerated, resulting in a steeper calibration curve. This is referred to as a super-Nernstian response, which is desirable for improving sensitivity and lowering detection limits. Furthermore, this type of procedure is thought to reveal information about the total concentration (that is, including free and bound forms) of ions rather than exclusively the free concentration [40-44].

Although not sensing, a related application is chemical extraction and purification. In some situations, it is desirable to remove a single component of a solution. This can be achieved by applying either an electric current or solvent flux across a membrane with an embedded ionophore. In order to decrease resistance, this is typically done in an organic solvent without PVC for stabilization. Instead, the membrane is supported by an inert polymer matrix such as porous polycarbonate [45-48].

With electrical polarization and ICP as central components of these techniques, their mode of operation is very similar to that applied in ISM-based electrochemical neuromodulation. Their results provide strong evidence that the ISM is capable of creating ICP, and that the ICP is specific to the selected ion. These earlier works in different applications have helped inform the fabrication and operation of our device. Likewise, we expect that our own contributions will be relevant to ISM-based sensing and chemical processing applications.
1.5 Functional role of membrane components

Our current understanding of ISM systems builds on decades of research on the interface between two immiscible electrolyte solutions (ITIES) [49-54]. As mentioned previously, the ISM media is composed of a nonpolar organic solvent, typically 2-nitrophenyl octyl ether (NPOE) or bis(2-ethylhexyl) sebacate (DOS). Being nonpolar, most hydrophilic ions such as Ca$^{2+}$, Na$^+$, and K$^+$ are relatively insoluble in the organic phase and are partitioned thermodynamically such that their concentrations are much smaller than in the aqueous phase. This property allows transport characteristics to be finely tuned by additions and modification to the membrane. Furthermore, it prevents lipophilic membrane components from leaching out into the aqueous solution.

Although free hydrophilic ions have low affinity for the membrane and are partitioned to have a low concentration, ion-ionophore complexes have a high affinity for the membrane and exist in relatively high concentration. Thus, the addition of the ionophore maintains the total concentration of the selected ion at a high level compared to interfering ions. This makes the potential response sensitive only to changes in the selected ion. Intuitively, we would assume that this also makes it so that electric current across the membrane is carried only by the selected ion. This notion is addressed in Chapter 2. The selected ion is conventionally referred to as the primary ion, while all other ions are designated as interfering ions.

In addition to the ionophore, the membrane must contain charge sites of opposite polarity as the primary ion. Otherwise, aqueous counter-ions such as Cl$^-$ will enter the membrane in order to maintain electroneutrality. This ingress will disrupt selectivity. The property of the membrane that excludes the ingress of counter-ions is called permselectivity.
These charge sites can either be provided by the ionophore itself, by fixed anionic sites in the PVC matrix, or by addition of a mobile lipophilic counter-ion. Lipophilic counter-ions that are commonly used for cation-selective membranes are tetraphenylborate (TPB⁻) and its synthetic derivative, tetrakis(4-chlorophenyl)borate (TpClPB⁻).

The membrane formulations used for electrochemical neuromodulation will rely on the same principles discussed here. As we develop a more complete framework for modeling and testing our operating principles, we will be able to optimize the membrane composition towards our application.

1.6 Potentiometric response towards selected ion

As discussed above, ions are maintained at different concentrations between the membrane phase of the ISM and the adjacent aqueous phase. This gives rise to a process referred to as Donnan equilibrium which is characterized by the formation of an electric potential across a nanometer-scale space-charge region at that interface between the two phases. By convention of previous literature in the ISM field, this potential is designated as the "phase-boundary potential." The magnitude of this potential is dependent on the concentration of ions in the aqueous phase. As long as the ionophore and mobile lipophilic counter ion are able to exclude interfering species, the membrane is dominated by the primary ion. Thus, the ISM has a selective potentiometric response to changes in the aqueous concentration of the primary ion.

The first modeling framework for the ISM was adapted from Nernst formulation for the standard hydrogen potential in early glass membrane pH electrodes [22]. Later, B. Nikolsky developed a model based on ion-exchange processes that allowed the contribution of
interfering ions to be taken into account [55]. This was expanded upon by G. Eisenman who incorporated empirical relationships [23]. Today, this formulation is still widely used, referred to as the Nikolsky-Eisenman equation:

\[
E = E^0 + \frac{RT}{z_P F} \ln \left[ a_P^{b(aq)} + \sum_j K_{Pj}^{\text{pot}} \left( a_j^{b(aq)} \right)^{z_P/z_j} \right],
\]

(1.1)

where \( R, T, F, \) and \( z \) have their usual meanings; \( K_{Pj}^{\text{pot}} \) is the Nikolsky potentiometric selectivity coefficient; \( E^0 \) is the standard reference potential; \( a_{i}^{b(aq)} \) is the bulk thermodynamic activity of an ion in the aqueous phase; and subscripts \( P \) and \( j \) denote primary and interfering ions respectively. For the case of electrolytes of mixed-valences, some improvements on the traditional Nikolsky-Eisenman formulation have been suggested [56]. The standard reference potential, \( E^0 \), conflates a number of constant factors such as the junction potential of the internal electrolyte solution. The Nikolsky potentiometric selectivity, \( K_{Pj}^{\text{pot}} \), coefficient is an empirically determined factor that reflects sensor selectivity for the primary ion over a particular interfering ion. A large value for this coefficient corresponds to a low selectivity. The activity, \( a_i \), of a particular ion is a dimensionless measure of “effective concentration” that is typically normalized to some standard state. Differences between the activity and concentration theoretically arise due to phenomena such as ion relaxation, solvent effects, and ion size effects. Activity can be substituted with molar concentration, \( c_i \), in cases where is appropriate to assume a dilute solution. The exact relationship between activity and concentration is discussed in Section 3.2.1.
This model is very effective because the equilibrium potentiometric response is evaluated in terms of empirical parameters. However, this does not help us if we want to determine other membrane response characteristics relevant to electrochemical neuromodulation such as integral transference. For this, we need to infer the values of internal state variables such as the total concentrations of primary and interfering ions. In Section 2.2, an equilibrium model was used to estimate these variables in terms of the empirical parameters.

1.7 Integral transference as a measure of transfer selectivity

In addition to the potential measured as a function of concentration and interfering ions, we are interested in how ions are transported when an electric field is applied. Transfer selectivity can be quantified by the transference number, $t_i$, of the membrane for the primary ion. This factor arises from the Nernst-Planck equation, as discussed in Section 5.1.2. In the scenario where there are no concentration gradients (i.e. diffusion-based flux) inside the membrane, the transference perfectly describes the relative amounts of ions that are transported across the membrane when an electric field is applied. Generally, gradients will form if there is any net flux of ions, so the transference does not entirely represent the full contribution of an ion to the electric current. However, it is useful to describe the transfer selectivity of the membrane using a single variable. Thus, we introduce the integral transference number, $T_i$, which is defined as the transference number under conditions where the contribution of intra-membrane gradients can be ignored. These conditions are met for short time-scales and small current densities. Keeping the limitations of this approach in mind, the flux of each ion $i$ can be described according to:
\[ \hat{n} \cdot N_i = \frac{T_i J}{z_i F} \]  \hspace{1cm} (1.2)

\[ T_i = \frac{z_i^2 D_i c_i}{\sum z_i^2 D_i c_i} \]  \hspace{1cm} (1.3)

where \( \hat{n} \) is the unit vector normal to the surface of the membrane pointing towards the aqueous phase, \( N_i \) is the molar flux density, \( T_i \) is the integral transference, \( J \) is the electrical current density, \( c_i \) is the molar concentration, and \( D_i \) is the diffusion coefficient \([57-60]\). The denominator of Equation 1.3 is the sum of contributions of all ionic species in the system. As we would intuitively expect, the sum of all integral transference numbers is unity. Put another way, the integral transference of the membrane is the ratio between a single ion’s contribution to Ohmic conductivity and the total Ohmic conductivity.

Accurate characterization of transference will be useful for any modality that involves electrical polarization of the ISM. This includes both electrochemical neuromodulation and dynamic electrochemical sensors. Typically, is assumed that transference of the selected ion in an ideal system is unity. However, as we discuss in Chapters 2 and 5, there are relevant conditions under which the flux of interfering ions is no longer negligible.

### 1.8 Ion-concentration polarization in the aqueous phase

As previously discussed, ICP is crucial to the operation of both dynamic electrochemical sensors and electrochemical neuromodulation devices. According to IUPAC Recommendations, “concentration polarization” is the formation of concentration gradients at the boundary between two immiscible phases due to an external driving force \([61]\). While this can refer to convection-based processes, in this thesis, we only consider ICP arising from electrical force \([62]\). This process will occur in both the membrane and aqueous phases. The
boundary region within which ICP occurs can also be referred to as the diffusion boundary layer (DBL).

In the aqueous phase, some of the most extensive theoretical work has been done by investigators in the field of desalination. The operation of a typical electro-desalination system involves application of a current across hydrophilic cation and anion permselective membranes. The flux of ions results in extraction from the target solution across the membranes and also ICP of the selected cations or anions. For sufficiently large driving current, there is an asymptotic relationship between voltage and current. This is referred to as "limiting behavior." This is important to consider because it decreases the desalination efficiency and increases the cost of operation [63]. Models for ion conduction in this regime should take into account several complex mechanisms such as electro-osmotic micro-vortex formation [64-68], gravitational convection [69-72], and water-splitting [73, 74]. However, as long as the limiting current is not exceeded, aqueous ICP can be modeled with Nernst-Plank and Poisson (NPP) mass transport equations. We assume that this is the case for the work presented in this thesis.

As we will discuss in greater detail in Chapter 5, ICP arises when there is a difference in transference between two phases. For 1-D galvanostatic polarization (i.e. current-controlled conditions) of magnitude $j^\text{app}_x$, the following relationship holds in the aqueous phase:

$$
\Delta C_i^{b(aq)} \propto \frac{j^\text{app}_x \delta_N}{D_i^{(aq)}},
$$

where $\Delta C_i^{b(aq)}$ is the characteristic difference in concentration between the membrane and the edge of the DBL at length $\delta_N$, $j^\text{app}_x$ is the applied electric current density, and the
superscript (aq) denotes properties and variables characteristic of the aqueous phase. It can also be determined that the time-scale of DBL formation is:

$$\tau_{ad} \sim \frac{\delta_N^2}{\pi^2 D_i^{(aq)}}. \quad (1.5)$$

These expressions give us important directional and scale information on some key variables involved in ICP.

The DBL length, $\delta_N$, is the distance from the membrane where the concentration of ions is effectively at bulk level. There are several physical processes that contribute to the size of this region: spontaneous convection, forced convection, non-planar diffusion, and bulk reactions. For 1-D models, the Nernst steady-layer approximation is commonly made which establishes a fixed point at length $\delta_N$ where the concentration is at bulk. In such models, the DBL length is typically assumed to be $\sim 300 \mu m$. This will be discussed further in Chapter 6.

The concentration profile throughout the DBL has been characterized using a variety of methods. Spectroelectrochemical techniques have been used to characterize a number of systems, determining concentration from light absorption [75-78]. In the desalination field, convective processes in the DBL have been investigated using dyes in a microfluidic device [79, 80]. Recently, the DBL adjacent to a $Pb^{2+}$-ISM under electrical polarization was measured using a SECM probe, giving direct evidence for ICP in polarized ISM systems [81].

Although the underlying principles of ICP in the aqueous phase are relatively well understood, the actual behavior depends on how ions are transported through the membrane. As discussed above, we can get a general idea using equilibrium models. However, it will be critical to establish a sophisticated model that incorporates both the aqueous and membrane phases to implement model-based optimization of ISM-ICP.
Our models for combined aqueous and membrane transport are discussed in Chapters 3-5, and we examine ICP specifically in Chapter 5.

1.9 Ion-concentration polarization in the membrane phase

As mentioned previously, the membrane itself is an electrolyte solution. The plasticized PVC matrix is essentially a viscous organic solvent that membrane additives are dissolved in. Thus, we must also consider ICP inside the membrane. This phenomenon has an effect on potentiometric response, and it is thought to be an important consideration for designing sensors. In polarized membranes, ICP will be more significant, and we expect it to have a major impact on transference.

As was the case in the aqueous phase, ICP in the membrane is a consequence of a difference in ion mobilities between the two phases. For 1-D galvanostatic polarization, the following relationship holds:

$$
\Delta C_i^{b(\text{org})} \propto \frac{J_x^{\text{app}} d}{D_i^{(\text{org})}}
$$

(1.6)

where $\Delta C_i^{b(\text{org})}$ is the characteristic difference in concentration across the membrane which has width $d$, and the superscript (org) denotes properties and variables characteristic of the membrane phase. It can also be determined that the time-scale of DBL formation is:

$$
\tau_{\text{org}} \sim \frac{d^2}{4\pi^2 D_i^{(\text{org})}}
$$

(1.7)

These expressions give us important directional and scale information on some key variables involved in membrane ICP. For more details, see Chapter 5.
Inside of the membrane, the profile of ICP has been measured in primarily two ways. The earliest way this was done was using slice techniques. A stack of membrane slices would be subject to polarization, and then each slice would be analyzed individually to determine concentration [82]. More recently, a new technique has emerged where the focus of an imaging system is scanned through a membrane containing a chromoionophore additive. The chromoionophore, which is co-selective with the primary ion, relays concentration information through optical absorbance measurements. This is combined with potentiometry, giving a more accurate “spectropotentiometric” measurement of concentration [83]. Altogether, these results give direct evidence for ICP in the membrane phase.

Understanding ICP in the membrane will be necessary for determining how transport properties vary over time. ICP affects the composition of ions in the membrane, and therefore the transference. Since transport in the membrane and aqueous phases are co-dependent, accurate modeling requires incorporation of both. Our models for combined aqueous and membrane transport are discussed in Chapters 3-5, and we examine ICP specifically in Chapter 5.

1.10 Full modeling of membrane systems

In order to capture key behavior of ISM transport, fully-detailed models that incorporate both aqueous and membrane transport must be used. Although electrolyte transport problems have been studied for centuries, analytical models have been the only tool for obtaining solutions during most of this time. For the highly nonlinear partial differential equations of NPP, investigators had no other option but to make approximations, save
implementing numerical methods with pen and paper. Today, ubiquitous access to incredible computational power allows investigators to model extraordinarily complex multidimensional systems such as NPP-Fermi [84] and NPP with Navier-Stokes [80]. Only a decade ago, models such as these were deemed too challenging for numerical solving. In addition, commercial software packages such as COMSOL Multiphysics, MathCAD, and ANSYS have come a long way over the last decade, and many complex models can be solved without the user having to deal with any of the underlying numerical methods [85].

As the power of computational tools has expanded, more and more investigators have been applying them to the modeling of ISM systems. The simplest models consider only a mobile lipophilic anion with a single primary ion-ionophore complex of equal net charge [86-88]. However, one of the most important aspects of ISM operation is the influence of interfering ions, especially at the limit of ISM performance. This cannot be accounted for without additional mechanisms. In order to consider this component, some investigators have incorporated ion-exchange surface adsorption processes at the interfaces between the membrane and the solution, usually in the form of first-order kinetics [89-93] or Butler-Volmer [94]. Thinking of an ISM model in terms of an “ion exchange reaction” is likely motivated by experimental results that suggest the ISM interface is similar to a metal/electrolyte interface with a mixed redox system. However, as we discuss in Section 3.3.1, ion-exchange adsorption models are only fully consistent with first-principles treatments under equilibrium conditions. In order to account for more complicated phenomena related to membrane polarization, we need more sophisticated models of ion-exchange. The first model taking into account non-equilibrium reaction was reported in Reference 95, and this lays the groundwork for some of the work reported here.
In this thesis, we present a first-principles model of ISM transport. The system is comprised of membrane and aqueous phases containing several lipophilic and hydrophilic chemical species. We incorporated separate reaction and partitioning processes which together account for the membrane’s ion-exchange characteristics. We examined model behavior using numerical and analytical tools, and we discussed several important features including ICP. Insights gained from this work will enable more sophisticated design and operation of ISM-based devices in the future.

1.11 Statement of work

Broadly, the goal of this thesis is to: (1) present and validate mathematical models that can be used for description and prediction of polarized ISM systems, and (2) characterize transport phenomena that are uniquely captured using these models. Conditions and operations relevant to electrochemical neuromodulation will be emphasized here. However, results will be applicable to dynamic electrochemical modalities as well as the ISM field in general.

In Chapter 2, an equilibrium membrane model is presented which was used to solve for the total concentrations of primary and interfering ions inside the membrane in terms of empirical parameters. This was used to estimate integral transference for several common membrane formulations. In addition, we used these results to estimate stability constants for the numerical transport models.

Chapter 3 introduces a full phase-field ISM transport model based on NPP and non-equilibrium reactions. We compare our approach to that used in previous models that approximate ion-exchange adsorption processes. Additionally, scaling analysis and
numerical solving was used to examine the contribution of the phase-field interface to ion transport. This allowed us to identify conditions under which certain simplifications used in previous works were appropriate.

After discussing ion partitioning in Chapter 4, we look at the other component of ion-exchange: ion-ionophore reaction. When non-equilibrium reactions are implemented, a phenomenon can be observed which we refer to as the reaction boundary layer (RBL). We found that the RBL could have important contributions to current-voltage (I-V) characteristics of the membrane.

In Chapter 5, we used our full transport model to analyze ICP in the aqueous and membrane phases. Limiting behavior is observed in each phase, and we assess how this affects membrane transference. As with the reaction boundary layer, these phenomena cannot be modeled without using the non-equilibrium reaction approach.

Finally, multidimensional ICP in the aqueous phase is explored in Chapter 6. Two separate scenarios are considered: (1) polarization of an ISM embedded in a micropipette tip, and (2) polarization across an ISM in a microfluidic channel with tangential flow. These models are used to demonstrate the DBL-limiting effects of non-planar diffusion and forced convection respectively.
2 Investigating transference using equilibrium model

2.1 Introduction

The most common tool for modeling the potentiometric response of an ion-selective membrane (ISM) electrode is the Nikolsky-Eisenman (NE) equation. Although rooted in thermodynamic formalism, this equation relies on empirically determined parameters called potentiometric selectivity coefficients. For most electrolyte systems, these constants do not correspond directly to membrane parameters such as the total ionophore concentration or the complexation constant. As a result, membrane state variables such as the concentrations of bound ions cannot be easily determined from experimental potentiometric data.

The concentrations of bound ions are important to know for the purpose of characterizing a membrane system under electrical polarization. The relative amounts of primary and interfering ions inside the membrane dictate how much flux is carried by the selected primary ion. Although it has been assumed that potentiometric selectivity directly translates into flux selectivity, this has not been explored mathematically for many relevant scenarios. Previously, the following expression has been determined for the case of primary and interfering ions with equal valances and stoichiometric ratios [39, 96]:

\[ T_p = \frac{a_p^{b(aq)}}{a_p^{b(aq)} + K_{pot}^{b(aq)} a_j^{b(aq)'}} \]

(2.1)

Although useful, this does not allow us to consider systems with mixed-valence electrolytes.

In this chapter, transcendental equations for ISM equilibrium are established in terms of a parameters we refer to as the intrinsic selectivity coefficients. These parameters will be solved for in terms of the potentiometric selectivity coefficients as well as other formulation-
specific variables such as the total ionophore concentration. This will allow us to approximate integral transference values of primary and interfering ions for several common membrane formulations. In addition, it will provide us with more realistic parameters that we can use in the full numerical Nernst-Planck and Poisson (NPP) model introduced in Section 3.2.

2.2 Membrane equilibrium model

The equilibrium conditions of the membrane can be determined by solving a system of equations. The first of these, is the expression for the partitioning of the ions:

\[ K_{i}^{\text{part}} = \frac{a_{i}^{\gamma(\text{aq})}}{a_{i}^{\gamma(\text{org})}} \]  

(2.2)

where \( K_{i}^{\text{part}} \) is the ion partition coefficient, and the superscript \( \gamma \) specifies variables that are immediately adjacent to the interface between the two phases. The origin and role of this expression will be examined thoroughly in Section 3.3.2. Equation 2.2 can be combined with the expression for Donnan equilibrium, to yield:

\[ e^{-FV_{\phi}/RT} = \left( K_{i}^{\text{part}} \frac{a_{i}^{\text{b(og)}}}{a_{i}^{\text{b(aq)}}} \right)^{1/z_{i}} \]

(2.3)

where \( V_{\phi} \) is the phase boundary potential of the interface. Next, we incorporate the expression for equilibrium binding between a neutral ionophore and ion:

\[ \beta_{i}^{n} = \frac{a_{L_{n}i}}{(a_{L})^{n}a_{i}^{\prime}} \]  

(2.4)

that has various stoichiometric ratios of 1: \( n \) with the ionophore \( L \), where \( \beta_{i}^{n} \) is the complex stability coefficient. In addition, we assume electroneutrality, which has the form:
for each ion \( i \) in both the aqueous and lipophilic phases. This also assumes that that no ion-pair (ion-association) reactions are occurring. Finally, we assume that no ionophore is leaching out into the aqueous solution, and that the total concentration of ionophore within the membrane stays the same:

\[
 c_L^0 = c_L^{b(\text{org})} + \sum_i \sum_l n_i c_{L_n i}^{b(\text{org})},
\]

where \( c_L^0 \) is the total molar concentration of the ionophore added to the membrane and \( l \) is the index of one of the stoichiometric ratios that the ionophore forms with ion \( i \). Combining these equations, we can solve for the concentrations of bound ions and the phase boundary potential. Besides for the simplest case where the ionophore exclusively forms 1:1 stoichiometries and each ion is univalent, this system must be solved transcendentally.

For each interfering ion, we can write Equations 2.3 and 2.4 in terms of the primary ion. Assuming each ion forms only one stoichiometric ratio with the ionophore, we get:

\[
 K_{Pj}^{\text{in}} = \left( \frac{a_{L_{n j}}^{b(\text{org})}}{a_L^{b(\text{org})}} \right)^{z_p/z_j} \frac{a_{P}^{b(\text{aq})}}{a_{j}^{b(\text{aq})}} \left( \frac{a_L^{b(\text{org})}}{a_{L_{n j}}^{b(\text{org})}} \right)^{n_p-n_j z_p/z_j},
\]

\[
 K_{Pj}^{\text{in}} = \left( \frac{\beta_j}{\beta_P} \right)^{z_p/z_j} \frac{K_P^{\text{part}}}{K_j^{\text{part}}} \left( \frac{z_p/z_j}{z_p/z_j'} \right),
\]

for each interfering ion \( j \) where \( K_{Pj}^{\text{in}} \) is the intrinsic selectivity coefficient. We refer to this quantity as such because it exclusively reflects intrinsic membrane solvent and ionophore characteristics, the partition and binding stability coefficients. In contrast, the potentiometric selectivity depends on controllable variables such as total ionophore
concentration and mobile lipophilic counter-ion concentration. However, it should be acknowledged that realistically, the partition and stability coefficients will have some dependence on the presence of solutes in the membrane. Note that the term 
\[ K_p^{\text{part}} \left( K_f^{\text{part}} \right)^{z_p/z_j} \]

is equivalent to the “equilibrium constant for ion-exchange” used in some literature [25, 97]. Assuming the free interfering and primary ions in the membrane contribute negligibly to charge density due to fast binding and significant exclusion of free ions from the membrane, we can rewrite Equations 2.5 and 2.6 as:

\[ z_p c_{L_{n_p}}^{b(\text{org})} + \sum_j z_j c_{L_{n_j}}^{b(\text{org})} + z_R c_R^0 = 0, \]  
\[ (2.9) \]

\[ c_L^0 = c_L^{b(\text{org})} + n_p c_{L_{n_p}}^{b(\text{org})} + \sum_j n_j c_{L_{n_j}}^{b(\text{org})}, \]  
\[ (2.10) \]

where \( c_R^0 \) is the total concentration of added mobile lipophilic counter-ion. Again, this assumes each ion forms only one stoichiometric ratio with the ionophore. The variables \( a_p^{b(\text{aq})} \) and \( a_j^{b(\text{aq})} \) are independent variables of the system used as inputs. The variables \( a_{L_{n_p}}^{b(\text{org})} \), \( a_{L_{n_j}}^{b(\text{org})} \), and \( a_L^{b(\text{org})} \) are state variables that will be solved for each combination of inputs. Using the explicit values of the state variables, the membrane potential can be determined according to:

\[ V^p = -\frac{RT}{z_p F} \ln \left( \frac{a_{L_{n_p}}^{b(\text{org})}}{a_L^{b(\text{org})} a_p^{b(\text{aq})}} \right), \]  
\[ (2.11) \]

\[ E_T = E_T^0 + V^p, \]  
\[ (2.12) \]
where $E_T$ is the electromotive force applied by the entire membrane, calculated according to the system of equations we described. The corresponding standard potential, $E_0^p$, conflates explicit values for the stability constant $\beta_p$ and partition coefficient $K_p^{\text{part}}$.

In order to solve for the concentration of the ion-ionophore complexes in terms of the concentration of aqueous ions, we needed to calculate the intrinsic selectivity coefficients. This can be accomplished by evaluating the previously established expression [97]:

$$K_{pj}^{ln} = K_{pj}^{\text{pot}} \frac{z_p (c_L^0 - n_p c_R^0 / z_p)^{n_p}}{c_R^0} \left[ \frac{c_R^0}{z_j (c_L^0 - n_j c_R^0 / z_j)^{n_j}} \right]^{z_p / z_j}.$$  \hspace{1cm} (2.13)

Thus, using the empirical selectivity coefficients, we can estimate intrinsic properties of the ion complexation process.

The validity of this approach was tested by calculating the potentiometric response for a particular membrane formulation using Equation 2.11, and then comparing this to results with NE and modified-NE equations [56]. For one interfering ion and one primary ion where $z_p = 1$ and $z_j = 2$, the following was used:

$$E_{NE} = E_{NE}^0 - \frac{RT}{F} \ln \left( \frac{\alpha_p^{b(aq)}}{2} + \frac{1}{2} \sqrt{ \left( \alpha_p^{b(aq)} \right) ^2 + 4 \alpha_j^{b(aq)} \left( K_{pj}^{\text{pot}} \right) ^2} \right).$$  \hspace{1cm} (2.14)

where $E_{NE}$ is the electromotive force applied by the entire membrane, calculated according to NE formulation, and $E_{NE}^0$ is the corresponding standard reference potential. For one interfering ion and one primary ion where $z_p = 2$ and $z_j = 1$, the following was used:

$$E_{NE} = E_{NE}^0 - \frac{RT}{F} \ln \left( \sqrt{ \frac{\alpha_p^{b(aq)}}{2} + \frac{1}{4} K_{pj}^{\text{pot}} \left( \alpha_j^{b(aq)} \right) ^2 } + \frac{1}{4} K_{pj}^{\text{pot}} \left( \alpha_j^{b(aq)} \right) ^2 \right).$$  \hspace{1cm} (2.15)

Lastly, for the case of matched valences or multiple interfering species, the traditional form of the NE equation was used:
\[ E_{\text{NE}} = E_{\text{NE}}^0 + \frac{RT}{z_F F} \ln \left[ a_p^{b(aq)} + \sum_j K_{p_j}^{\text{pot}} (a_j^{b(aq)})^{z_p/z_j} \right]. \]  

(2.16)

Response curves were generated for each interfering ion spanning the range tested by the author of the corresponding selectivity coefficient data.

With explicit values for internal state variables, the integral transference for various membrane formulations could be determined using Equation 1.3. Since we are assuming free ions do not contribute significantly to charge density, this expression can be rewritten as:

\[ T_i = \frac{z_i^2 D_{L_i} c_{b(\text{org})}}{\sum_I z_I^2 D_{L_I} c_{b(\text{org})}}, \]

(2.17)

This expression assumes there are no concentration gradients inside the membrane. While not realistic in most scenarios, this gives us a useful first-order approximation.

This technique was used to estimate membrane transport properties for several membrane formulations in a physiological electrolyte system. Unless otherwise specified, the composition of the aqueous electrolyte was \( c_{\text{Na}}^{b(aq)} = 137 \text{ mM} \), \( c_{K}^{b(aq)} = 2.7 \text{ mM} \), \( c_{\text{Ca}}^{b(aq)} = 0.9 \text{ mM} \), and \( c_{\text{Mg}}^{b(aq)} = 0.493 \text{ mM} \). This was based on a common recipe for phosphate buffered saline (PBS) with added CaCl\(_2\) and MgCl\(_2\). As long as there is not a strong concentration-dependence, linear activity coefficients can be conflated into the semi-empirical parameter \( K_{p_j}^{\text{in}} \) in Equation 2.7. We can then effectively replace each activity term in the above equations with the respective molar concentration. The membrane formulations considered here were chosen on the basis of three criteria: (1) being commonly used, (2) having ionophores with well characterized selectivity and complexation properties, and (3) having a higher concentration of lipophilic electrolyte, making them more suitable.
for polarization. The selected formulations are shown in Table 2.1 along with potentiometric selectivity coefficients, assumed stoichiometries, and total concentrations of lipophilic species. For complex stoichiometries that could not be found in the literature, a 1:1 ratio was assumed. The total ionophore and mobile lipophilic anion concentrations were calculated from their respective weight percentages for each published formulation, approximating the solvent density as 1 g/mL. Finally, in order to calculated the integral transference, it was approximated in each case that the diffusivities of ions in the membrane were equal.

Table 2.1: Membrane properties for several common Ca\(^{2+}\), K\(^+\), Na\(^+\), and Mg\(^{2+}\) formulations.

<table>
<thead>
<tr>
<th>Membrane/ionophore</th>
<th>(c_0^R) (mM)</th>
<th>(c_0^M) (mM)</th>
<th>(\log K^\text{pot}<em>{P,\text{Na}}) (1: (n</em>{\text{Na}}))</th>
<th>(\log K^\text{pot}<em>{P,\text{K}}) (1: (n</em>{\text{K}}))</th>
<th>(\log K^\text{pot}<em>{P,\text{Ca}}) (1: (n</em>{\text{Ca}}))</th>
<th>(\log K^\text{pot}<em>{P,\text{Mg}}) (1: (n</em>{\text{Mg}}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca(^{2+}) formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[98] ETH 129</td>
<td>27.6</td>
<td>102</td>
<td>-5.6 (1:1)</td>
<td>-7.2 (1:1)</td>
<td>— (1:3)*</td>
<td>-6.7 (1:2)*</td>
</tr>
<tr>
<td>[99] ETH 5234</td>
<td>5.72</td>
<td>12.6</td>
<td>-5.9 (1:1)</td>
<td>-7.5 (1:1)</td>
<td>— (1:3)*</td>
<td>-4.4 (1:2)*</td>
</tr>
<tr>
<td>K(^+) formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[100] Valinomycin</td>
<td>10.3</td>
<td>18.5</td>
<td>-3.56 (1:1)</td>
<td>— (1:1)*</td>
<td>-4.3 (1:2)</td>
<td>—</td>
</tr>
<tr>
<td>[101] BME-44</td>
<td>4.07</td>
<td>20.9</td>
<td>-3.2 (1:1)</td>
<td>— (1:1)*</td>
<td>-4 (1:1)</td>
<td>-3.9 (1:1)</td>
</tr>
<tr>
<td>Na(^+) formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[102] ETH 157</td>
<td>2.04</td>
<td>18.2</td>
<td>— (1:2)*</td>
<td>-0.4 (1:1)</td>
<td>-2.6 (1:1)</td>
<td>-4 (1:1)</td>
</tr>
<tr>
<td>[103] Ionophore X</td>
<td>4.07</td>
<td>7.11</td>
<td>— (1:1)*</td>
<td>-1.9 (1:1)</td>
<td>-2.5 (1:1)</td>
<td>—</td>
</tr>
<tr>
<td>Mg(^{2+}) formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[104] ETH 1117</td>
<td>20.7</td>
<td>42.1</td>
<td>-2.1 (1:1)</td>
<td>-1.1 (1:1)</td>
<td>-1.3 (1:1)</td>
<td>— (1:3)*</td>
</tr>
<tr>
<td>[105] ETH 4030</td>
<td>13.1</td>
<td>18.7</td>
<td>-3.8 (1:1)</td>
<td>-3.7 (1:1)</td>
<td>0 (1:1)</td>
<td>— (1:2)*</td>
</tr>
</tbody>
</table>

* Stoichiometry taken from Reference 106

2.3 Integral transference for common membrane formulations

Using the system of equations and parameters described above, the integral transferences of the membrane formulations listed in Table 2.1 were evaluated for Na\(^+\), K\(^+\), Ca\(^{2+}\), and Mg\(^{2+}\). The theoretical potentiometric response of the transcendental system, \(E_T\), was compared to that predicted by the NE and modified-NE equations, \(E_{NE}\). Both showed excellent agreement, matching up perfectly in many cases. As shown by Table 2.2, the
integral transference of each membrane for the primary ion adjacent to the standard physiological aqueous electrolyte, $T_{p}^{sp}$, was close to 100%. The only formulation that had less than 90% transference was the one with the ETH 4030 ionophore for Mg$^{2+}$.

Table 2.2: Calculations for each membrane formulation listed in Table 2.1.

<table>
<thead>
<tr>
<th>Membrane/ionophore</th>
<th>$\log K_{P,Na}^{in}$</th>
<th>$\log K_{P,K}^{in}$</th>
<th>$\log K_{P,Ca}^{in}$</th>
<th>$\log K_{P,Mg}^{in}$</th>
<th>$c_p^{ip}$ (M)</th>
<th>$T_{p}^{sp}$</th>
<th>dom. int.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca$^{2+}$ formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETH 129</td>
<td>-2.63</td>
<td>-3.43</td>
<td>-5.10</td>
<td>$10^{-10}$</td>
<td>&gt;99.9%</td>
<td>Mg$^{2+}$</td>
<td></td>
</tr>
<tr>
<td>ETH 5234</td>
<td>-3.85</td>
<td>-4.65</td>
<td>-4.26</td>
<td>$10^{-8.3}$</td>
<td>&gt;99.9%</td>
<td>Mg$^{2+}$</td>
<td></td>
</tr>
<tr>
<td>K$^+$ formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valinomycin</td>
<td>-3.56</td>
<td>-6.21</td>
<td>-5.10</td>
<td>$10^{-4.4}$</td>
<td>98.6%</td>
<td>Na$^+$</td>
<td></td>
</tr>
<tr>
<td>BME-44</td>
<td>-3.20</td>
<td>-4.73</td>
<td>-4.53</td>
<td>$10^{-4.0}$</td>
<td>96.9%</td>
<td>Na$^+$</td>
<td></td>
</tr>
<tr>
<td>Na$^+$ formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETH 157</td>
<td>-0.4</td>
<td>-3.43</td>
<td>-0.628</td>
<td>$10^{-2.3}$</td>
<td>99.0%</td>
<td>Ca$^{2+}$</td>
<td></td>
</tr>
<tr>
<td>Ionophore X</td>
<td>-1.90</td>
<td>-2.65</td>
<td>-</td>
<td>$10^{-3.7}$</td>
<td>&gt;99.9%</td>
<td>Ca$^{2+}$</td>
<td></td>
</tr>
<tr>
<td>Mg$^{2+}$ formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETH 1117</td>
<td>-1.51</td>
<td>-1.01</td>
<td>0.328</td>
<td>$10^{-5.4}$</td>
<td>97.2%</td>
<td>Ca$^{2+}$</td>
<td></td>
</tr>
<tr>
<td>ETH 4030</td>
<td>-2.69</td>
<td>-2.64</td>
<td>0.412</td>
<td>$10^{-3.6}$</td>
<td>63.0%</td>
<td>Ca$^{2+}$</td>
<td></td>
</tr>
</tbody>
</table>

As the aqueous concentration of the primary ion is reduced, however, interfering ions are transported as a higher percentage of the total charge flux (shown by Figure 2.1). For each primary ion in its respective membrane system, there is a point, designated as $c_p^{ip}$, where ingress of interfering ions begins to dominate (i.e. $T_p = 50\%$). The calculated values for the ingress point are shown in Table 2.2, and we can see that the Na$^+$ membranes are most susceptible to ingress while the Ca$^{2+}$ membranes are most resistant. For each membrane, the ingress was dominated by one particular interfering ion, listed in the last column in Table 2.2. This ion was typically the one with the largest intrinsic selectivity, $K_{P,j}^{in}$, associated with it. However, in the case of the Na$^+$-selective membranes, Ca$^{2+}$ dominated instead of K$^+$. 
Figure 2.1: Integral transference of Na⁺, K⁺, Ca²⁺, and Mg²⁺ versus aqueous primary ion concentration for each membrane formulation listed in Table 2.1. A ETH 129 (Ca²⁺). B ETH 5234 (Ca²⁺). C Valinomycin (K⁺). D BME-44 (K⁺). E ETH 157 (Na⁺). F Na⁺ ionophore X (Na⁺). G ETH 1117 (Mg²⁺). H ETH 4030 (Mg²⁺).

2.4 Comparing membrane formulations

In many important Na⁺ sensing applications, the analyte concentration is relatively large compared with other ions. In a typical biological sample, for example, the Na⁺ concentration ranges from ~10⁻² M (intracellular) to ~10⁻¹ M (extracellular). Thus, the membranes used
for Na⁺ sensing do not require the same order of selectivity to achieve a functional detection limit. In line with this, the Na⁺ formulations considered here had larger values for $K_{Pj}^{\text{pot}}$ and correspondingly $K_{Pj}^{\text{in}}$ compared with the other membranes. As a result, we can see from Table 2.2 and Figure 2.1 that these had the poorest ingress limits. Regardless, the calculated transference is nearly 100% under normal physiological conditions since the concentration of Na⁺ is so high. Although K⁺ had the largest $K_{Pj}^{\text{pot}}$ and largest concentration among the interfering ions, Ca²⁺ dominated for both of these Na⁺-selective formulations. This emphasizes how valence is a key factor in the competitive ionophore binding process.

While Na⁺ has a high extracellular concentration and lower intracellular concentration, K⁺ is the opposite. In a typical biological sample, the K⁺ concentration ranges from $\sim 10^{-3}$ M (extracellular) to $\sim 10^{-1}$ M (intracellular). Thus, detection limits less than $10^{-3}$ M are necessary for K⁺-selective membranes to be used as extracellular sensors. Accordingly, the K⁺-selective membranes analyzed above have higher selectivity than the Na⁺-selective membranes did. As a result, the ingress limits were lower by an order of magnitude. Due to its high concentration and the low selectivity of the membrane against it, Na⁺ was the dominant interfering ion in this case.

In human cells, Ca²⁺ plays a ubiquitous role as a chemical messenger. For this reason, sensing intracellular Ca²⁺ has been of major scientific interest. The challenge here, is that intracellular Ca²⁺ exists in nanomolar concentrations, far below the detection limits of conventional liquid membrane sensors for other biologically-relevant ions. To solve this, high-selectivity ionophores have been developed, and membranes with sub-nanomolar detection limits are now possible [98]. Analyzing these membranes in terms of integral transference, we see that the ingress limits are much lower than what can be achieved with
the other membranes discussed here. Similar to the case of the Na\textsuperscript{+}-selective membranes, a
divalent cation, Mg\textsuperscript{2+}, dominated the interfering transference despite not having the largest
selectivity coefficient.

Another critical intracellular messenger is Mg\textsuperscript{2+}, which exists in free concentration of
\(~10^{-3}\) M in both the intracellular and extracellular space. Although the ingress limits we
determined were good compare with the K\textsuperscript{+} and Na\textsuperscript{+}-selective membranes, the integral
transference under physiological conditions was relatively low. This occurs because the
physiological concentration of Mg\textsuperscript{2+} is low compared to the other ions. The main challenge
with Mg\textsuperscript{2+}-selective membranes has been developing ionophores that are selective against
Ca\textsuperscript{2+}. As we can see by Table 2.2, the selectivity of both ETH 1117 and ETH 4030 against Ca\textsuperscript{2+}
are relatively poor. Thus, as expected, Ca\textsuperscript{2+} is the dominant interfering ion determined for
this system. New Mg\textsuperscript{2+} ionophores have been developed that are much more selective than
ETH 1117 and ETH 4030, however, we chose these because they are better characterized.

2.5 Conclusions

As shown by Table 2.2 and Figure 2.1, each membrane in the physiological electrolyte
transports the primary ion almost exclusively. This supports the general intuition that
transference selectivity correlates with potentiometric selectivity. Likewise, the
potentiometric detection limit correlates with the transference ingress limit. In other words,
both potentiometric and transference selectivity fails once the concentration of the primary
ion in the aqueous phase is reduced below a certain limit. As we discuss ion-concentration
polarization (ICP) in the aqueous phase in following chapters, this will be an important
consideration. Using these estimations for integral transference, we can get an idea for the
lower limit of ion depletion for each membrane formulation. For the design of devices for electrochemical neuromodulation, this information can help us to predict how much current will be necessary to elicit a therapeutic effect.
3 First-principles examination of interfacial charge transfer

3.1 Introduction

As discussed previously, the membrane phase can be considered an organic lipophilic solvent, within which an electrolyte is subject to migration and diffusion. Relative to the aqueous phase, hydrophilic ions such as Na\(^+\), K\(^+\), Ca\(^{2+}\), and Mg\(^{2+}\) are insoluble inside the nonpolar membrane. This quality, together with ionophore binding, permits transport to be tailored to a particular ion. While the low solubility will impede free ions within the membrane, the selected ion will be bound to the lipophilic ionophore which can move freely. These processes are referred to here as partitioning and reaction respectively. Together, these are responsible for the membrane feature commonly known as ion-exchange. As this is fundamental to the operation of the ion-selective membrane (ISM), it is analyzed in detail in this and following chapters.

In Section 3.2, a full membrane transport model is introduced that has two novel features: (1) it applies separate mechanisms for partitioning and reaction, and (2) it uses a phase-field approach to simulate the continuous transition of intrinsic transport properties across the adjacent phases. In the discussion relating to this model, we focus mainly on partitioning in this chapter and reactions in Chapter 4. In Section 3.3.1, we compare the ion-exchange approach of our model to the simplified interfacial-adsorption approach used in some previously reported models. Then, in Section 3.3.2, we characterize partitioning across the phase-field transition region using scaling analysis and numerical simulation.
3.2 Model description

3.2.1 Equations governing transport of chemical species

The time-varying behavior of the system is dictated by continuity, which is given in this case as:

\[
\frac{\partial c_k}{\partial t} + \nabla \cdot N_k = R_k, \tag{3.1}
\]

where \( N_k, c_k, \) and \( R_k \) are the molar flux density, molar concentration, and net volume formation rate of chemical reaction of solute \( k \) respectively. The molar concentration relates to molar activity as:

\[
a_k = f_k c_k, \tag{3.2}
\]

where \( f_k \) is the activity coefficient. Here, the activity coefficient is used to describe contributions to the chemical energy gradient from solubility differences between membrane and aqueous phases. Chemical flux from diffusion, migration, and convection is given by the Nernst-Planck equations for dilute solutions:

\[
N_k = -D_k \left( \nabla c_k + \frac{z_k F}{RT} c_k \nabla \psi + c_k \nabla \ln f_k + c_k \nabla v \right), \tag{3.3}
\]

where \( \nabla, \psi, D_k, \) and \( z_k \) are the molar-averaged solvent velocity, electric potential, diffusivity, and charge number of solute \( k \) respectively. For all uncharged solutes, the charge number is zero and migration has no contribution. In every case discussed here aside from those in Sections 6.2.2 and 6.3.1, convective flux is ignored and the rightmost term in Equation 3.3 is zero. The electric potential is coupled to the space charge density through the Poisson equation:

\[
\nabla D = -\varepsilon_0 \varepsilon_r \nabla^2 \psi = F \sum_i z_i c_i, \tag{3.4}
\]
where $D$ is the electric displacement flux density, $\varepsilon_0$ is the permittivity of free space, and $\varepsilon_r$ is the relative permittivity. The electric current density is given as:

$$J = F \sum_i z_i N_i + \frac{\partial D}{\partial t},$$  

which is comprised of the sum of faradaic and displacement currents.

In the membrane phase, ionophore binding can be described by the following reversible reactions:

$$nL + P^{z^+} \rightleftharpoons L_n P^{z^+},$$  

$$nL + J^{z^+} \rightleftharpoons L_n J^{z^+}.$$  

where $L$ is the ionophore, $P^{z^+}$ is the primary ion, $J^{z^+}$ is an interfering ion, and $n$ is the complex stoichiometry. These reactions are modeled according to first-order kinetics:

$$R_{LnP} = \bar{k}_p(c_L)^n c_P + \bar{k}_p c_{LnP},$$  

$$R_{Lnj} = \bar{k}_j(c_L)^n c_j + \bar{k}_j c_{Lnj},$$  

$$R_P = -R_{LnP},$$  

$$R_j = -R_{Lnj},$$  

$$R_L = R_P + \sum_j R_j,$$

where $\bar{k}_i$ and $\bar{k}_i$ are the forwards and backwards rate constants respectively for the primary and interfering ions. Generally, there can be multiple interfering ions present. However, in this thesis, we generally consider the case where there is only one interfering ion.

From our assumption of dilute chemical species, we ignore any concentration-dependence of the activity coefficients, and we take the diffusion coefficients to be constant.
for each ion. We ignore the potential contributions of ionic size effects [107, 108], non-electrostatic ion-ion interaction [109], and solvent effects [110]. We assume there is negligible ion-pair formation, although it has been shown that this is not accurate in some cases [111]. In addition, we assume the intrinsic fixed charges in the membrane are negligible compared to the added mobile lipophilic anion [112-114]. Finally, the dielectric permittivity is assumed to be homogeneous in each region of the model, which is not necessarily the case if uneven water distributions are taken into account [115-117].

3.2.2 1-D phase-field model of transport in aqueous and membrane phases

The formulation described by Equations 3.1-3.12 was applied to a 1-D geometry making the appropriate transform. The system, as shown in Figure 3.1, is composed of a membrane of width \(d\) placed between two equidistant ideal electrodes at a distance of \(\delta_N\) from the membrane. As per the Nernst steady diffusion layer approximation, the concentrations of aqueous ions are fixed at their bulk levels at the site of each electrode. In each case described in this thesis, the bulk concentrations on each side of the membrane are the identical. This gives us the following Dirichlet boundary condition:

\[
c_k \left( x = -\frac{d}{2} - \delta_N \right) = c_k \left( x = \frac{d}{2} + \delta_N \right) = c_k^0,
\]

for each solute \(k\) in the aqueous phase. The initial conditions in the aqueous phase are given by:

\[
c_k \left( -\frac{d}{2} - \delta_N \leq x \leq -\frac{d}{2} \right) = c_k \left( \frac{d}{2} \leq x \leq \frac{d}{2} + \delta_N \right) = c_k^0.
\]

Meanwhile, initial values in the membrane phase are given by estimations for the equilibrium conditions using Equations 2.2-2.6.
In order to model galvanostatic polarization across the electrodes, we implement an electric displacement field boundary condition at the electrode in location \( x = -d/2 - \delta_N \). This is formulated by rearranging Equations 3.3 and 3.5:

\[
D_x(x = -d/2 - \delta_N) = D_x^{\text{app}},
\]

\[
\frac{\partial D_x^{\text{app}}}{\partial t} + \frac{\sigma(x = -d/2 - \delta_N)}{\varepsilon_0 \varepsilon_r} D_x^{\text{app}} + J_x^{\text{diff}}(x = -d/2 - \delta_N) - J_x^{\text{app}} = 0,
\]

\[
\sigma = \frac{F^2}{RT} \sum_i z_i^2 D_i c_i,
\]

\[
J_x^{\text{diff}} = -F \sum_i z_i D_i \frac{\partial c_i}{\partial x},
\]

where \( D_x^{\text{app}} \) is the displacement flux density applied at the boundary, \( J_x^{\text{app}} \) is the target electric current density, \( \sigma \) is electrical conductivity, and \( J_x^{\text{diff}} \) is the faradaic current arising from diffusion of charged species. For a particular current density, \( J_x^{\text{app}} \), this first-order ordinary differential equation is solved over time for the applied electric displacement field, \( D_x^{\text{app}} \).

When calculating for electric potential, the electrode at \( x = d/2 + \delta_N \) is used as the ground reference point.
Figure 3.1: Schematic for geometry of 1-D ISM transport model. An electrolyte system composed of Ca\(^{2+}\), Na\(^{+}\), and Cl\(^{-}\) are shown here as an example. Within the membrane, there is a lipophilic electrolyte, R\(^{-}\), and a neutral carrier, L. The neutral carrier can bind the primary ion (Ca\(^{2+}\)) with high affinity and the interfering ion (Na\(^{+}\)) with relatively low affinity. Region a is the transition region with dimensions \(\delta_y = 0.1\) nm. Region b is the interfacial space charge region with dimensions \(l_{\text{Debye}} \approx 1\) nm. Region c is the reaction boundary layer (RBL) with dimensions \(l_{\text{RBL}} \approx 10\) nm.

A phase-field approach was used to model the transition in properties between the two phases [118]. We define a state variable, \(\phi\), that varies continuously in the range \([0,1]\), with a value of 0 in the bulk aqueous phase and a value of 1 in the bulk membrane phase. The phase-field equation has previously been solved [119, 120], giving the expression:

\[
\phi(x) = \frac{1}{2} \left[ 1 - \tanh \left( \frac{-|x| + d/2}{2\delta_y} \right) \right], \tag{3.19}
\]

where \(\delta_y\) is the width of the interfacial transition region. We define a phase-fraction function, \(p(\phi)\), that describes the volume fraction of each phase across the interface in terms of the state variable. Our choice for this function, taken from a previously reported model [118], is:

\[
p(\phi) = \phi^3(6\phi^2 - 15\phi + 10). \tag{3.20}
\]
There are three transport properties that vary continuously across the geometry according to the phase-fraction: diffusivity, solubility, and relative permittivity. Their values are linearly interpolated according to:

\[ D_i(x) = D_i^{(\text{org})} p(\phi) + D_i^{(\text{aq})} [1 - p(\phi)], \]  

\[ f_i(x) = f_i^{(\text{org})} p(\phi) + f_i^{(\text{aq})} [1 - p(\phi)], \]  

\[ \varepsilon_r(x) = \varepsilon_r^{(\text{org})} p(\phi) + \varepsilon_r^{(\text{aq})} [1 - p(\phi)]. \]

The coefficients \( f_i^{(\text{aq})} \) and \( f_i^{(\text{org})} \) are chosen such that \( f_i^{(\text{org})} / f_i^{(\text{aq})} = K_i^{\text{part}} \) where \( K_i^{\text{part}} \) is the partition coefficient of the aqueous phase over the lipophilic phase.

The parameters used in these simulations, shown in Table 3.1, were compiled from various sources for room temperature, \( T = 298.15 \text{ K} \). The primary, interfering, and counter ions with their corresponding bulk/initial concentrations were chosen here to be relevant with a physiological electrolyte. These ions are denoted as \( P, J, \) and \( N \) respectively. The aqueous diffusivity of these ions are given by their commonly published values \([121-123]\). Meanwhile, membrane diffusivity of the ionophore, ion-ionophore complex, and mobile lipophilic counter-ion were estimated based on published values for the nearest plasticizer/PVC composition \([124]\). We approximated diffusivity values for each ion in their respective insoluble phases such that the aqueous phase was 100× larger \([95]\). The partition coefficients were adjusted to the point where ion transport across the membrane was negligibly small without ionophore carriers. The dielectric permittivity of the aqueous and membrane phases are \( \varepsilon^{(\text{aq})} = 80\varepsilon_0 \) and \( \varepsilon^{(\text{org})} = 14\varepsilon_0 \) respectively, taken from published values \([112]\). The diffusion boundary layer (DBL) thickness, \( \delta_N \), was estimated from
reported measurements under non-forced hydrodynamic conditions [125]. Finally, the membrane has a thickness of \( d = 50 \, \mu m \).

Binding stability coefficients have been published for a number of ionophores [106]. However, their values are so large, that the concentration of free ions inside the membrane become too close to machine precision, creating numerical issues. Therefore, we chose values that were small enough that the simulation would converge but large enough that the free ions still made up a negligibly small fraction of the transference. In future work, true binding property values could be used if the model was solved in terms of logarithmic transforms.

Table 3.1: Default model parameters used for each ion in the 1-D ISM transport model.

<table>
<thead>
<tr>
<th>( i )</th>
<th>( z_i )</th>
<th>( D_i^{(aq)} ) ( (\times 10^{-9} \text{ m}^2/\text{s}) )</th>
<th>( D_i^{(h)} ) ( (\times 10^{-11} \text{ m}^2/\text{s}) )</th>
<th>( c_i^0 ) ( (\text{mol}/\text{m}^3) )</th>
<th>( \beta_i ) ( (\text{m}^3/\text{mol}) )</th>
<th>( k_i ) ( (1/\text{s}) )</th>
<th>( K_i^{\text{part}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P = \text{Ca}^{2+} )</td>
<td>+2</td>
<td>0.789 ( (\times 10^{-9}) )</td>
<td>0.789 ( (\times 10^{-11}) )</td>
<td>2</td>
<td>( 10^4 )</td>
<td>( 10^4 )</td>
<td>( 10^4 )</td>
</tr>
<tr>
<td>( N = \text{Cl}^- )</td>
<td>-1</td>
<td>2.01</td>
<td>2.01</td>
<td>104</td>
<td>—</td>
<td>—</td>
<td>( 10^4 )</td>
</tr>
<tr>
<td>( J = \text{Na}^+ )</td>
<td>+1</td>
<td>1.35</td>
<td>1.35</td>
<td>100</td>
<td>10</td>
<td>10</td>
<td>( 10^4 )</td>
</tr>
<tr>
<td>( R = \text{TFPB}^- )</td>
<td>-1</td>
<td>0.1</td>
<td>0.1</td>
<td>5*</td>
<td>—</td>
<td>—</td>
<td>( 10^{-4} )</td>
</tr>
<tr>
<td>( L )</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
<td>( 10^* )</td>
<td>—</td>
<td>—</td>
<td>( 10^{-4} )</td>
</tr>
<tr>
<td>( \text{LCa}^{2+} )</td>
<td>+2</td>
<td>0.1</td>
<td>0.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>( 10^{-4} )</td>
</tr>
<tr>
<td>( \text{LNa}^+ )</td>
<td>+1</td>
<td>0.1</td>
<td>0.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>( 10^{-4} )</td>
</tr>
</tbody>
</table>

* These values constitute the total initial concentrations of lipophilic ions added to the membrane.

The combined transport and continuity equations from Equations 3.1-3.3 and 3.8-3.12 were converted to weak form and implemented in COMSOL Multiphysics using the Partial Differential Equation physics module. The Electrostatics module was used for Equation 3.4 and the Ordinary Differential Equation module was used for Equations 3.16-3.18. Elements of size \( \delta = 0.005 \, \text{nm} \) were used at the contact planes between the membrane and aqueous layers and size \( \delta = 0.24 \, \mu m \) throughout the rest of the geometry. This system was solved numerically in two phases carried out to steady-state: (1) zero-current equilibration
\( t_{eq} = 1000 \text{ s} \), and (2) galvanostatic polarization \( t_p = 1000 \text{ s} \). Finally, the results were processed using Matlab.

### 3.3 Results and discussion

#### 3.3.1 Limitations of ion-exchange interfacial adsorption approach

In order to avoid technical challenges with implementing non-equilibrium reactions inside the membrane, some previous models have taken a simplified approach using an interfacial adsorption process \[89-94\]. Our model presented in Section 3.2, differs from this previous method mainly in two aspects: (1) replacing the continuous phase-field transition regions at the two aqueous/membrane interfaces with pointwise interior boundaries, and (2) removing the contribution of reaction from the continuity equation. The interior boundaries are given the following Neumann conditions for flux:

\[
N_{i,x}(x = \pm d/2) = \pm \overline{k_i^{ex}} \cdot \left( K_i^{ex} c_i^{b(aq)} - c_i^{b(org)} \right)_{x=\pm d/2}, \tag{3.24}
\]

where \( \overline{k_i^{ex}} \) and \( K_i^{ex} \) are the backwards rate constant and equilibrium constant for the adsorption process respectively.

In order to test the validity of this approach, we can try to evaluate this model under equilibrium conditions. In Equation 3.24, for a sufficiently fast backwards rate constant satisfying \( N_{i,x}/k_i^{ex} \rightarrow 0 \), we can see that:

\[
K_i^{ex} = \frac{c_i^{b(org)}}{c_i^{b(aq)}}, \tag{3.25}
\]

Combining this with the expression for Donnan equilibrium, we get:
\[ e^{-\frac{FV^p}{RT} + 1} \left( \frac{c_i^{b(aq)}}{c_i^{b(\text{org})}} \right)^{-1/z_i} \] (3.26)

Now, we look at the equilibrium solution for the full model which considers reaction and partitioning separately. Combining Equations 2.3 and 2.4, we get the following:

\[ e^{-\frac{FV^p}{RT}} = \left( \frac{\beta_i c_L^n c_i^{b(aq)}}{K_i^{\text{part}} c_i^{b(\text{org})}} \right)^{-1/z_i} \] (3.27)

Comparing Equations 3.26 and 3.27, we see that the ion-exchange equilibrium constant is effectively a combination of multiple parameters:

\[ K_i^{\text{ex}} = \frac{\beta_i c_L^n}{K_i^{\text{part}}} \] (3.28)

Thus, if we approximate that unbound ionophore concentration is equal across the membrane, the adsorption model gives identical results to the full model under equilibrium conditions. However, the ion-exchange rate constants themselves have no direct physical basis in terms of reaction and partitioning.

In addition to limitations caused by these approximations, the adsorption model is unable to simulate more complicated phenomena that we can with our full numerical model. Since non-equilibrium reactions are ignored, we cannot consider the reaction boundary layer (RBL). Since free ions inside the membrane are not accounted for, membrane failure and the ingress of interfering and counter ions cannot be modeled. We address both of these in Chapters 4 and 5 respectively using our full model.
3.3.2 Analyzing charge transfer and partitioning

We model the interfacial transition region between the two insoluble phases by specifying a space-dependent thermodynamic activity coefficient, \( f_i \), that has a larger value for each ion in the phase it is less soluble in. The transition region is thus characterized by a sharp gradient in the activity coefficient that results in the partitioning of ions. This can be analyzed by putting Equation 3.3 into integral form:

\[
N_{x,i}(x,t) = -z_i^2 z^2 D_i \left( c_i(x,t) f_i(x) e^{\frac{z_i F \psi(x,t)}{RT}} - c_i^{(org)}(x) f_i^{(org)}(x) \right) \int_0^x f_i(y) e^{\frac{z_i F \psi(y,t)}{RT}} \, dy
\]

(3.29)

where \( \gamma \) denotes the interfacial transition regions of widths \( \delta_y \) that exist at \( x = \pm d/2 \).

Focusing on the left aqueous/membrane contact plane, the concentrations on each side of the transition region for ion \( i \) are \( c_i^{(aq)} = c_i(x = -d/2 - \delta_y/2) \) and \( c_i^{(org)} = c_i(x = -d/2 + \delta_y/2) \) on each side of the transition region. Respectively, the activity coefficients are \( f_i^{(aq)} = f_i(x = -d/2 - \delta_y/2) \) and \( f_i^{(org)} = f_i(x = -d/2 + \delta_y/2) \). The potential throughout the transition region with respect to a reference point at \( x = -d/2 - \delta_y/2 \) is denoted by \( \psi^\gamma \).

In other words: \( \psi^\gamma(x,t) = \psi(x,t) - \psi(x = -d/2 - \delta_y/2, t) \).

We can start to simplify this by applying scale analysis to the continuity equation in Equation 3.1:

\[
\frac{\partial c_i}{\partial t} \sim \frac{\Delta C^\gamma}{\tau},
\]

(3.30)

\[
\frac{\partial N_{i,x}}{\partial x} \sim \frac{\Delta N^\gamma}{\delta_y}.
\]

(3.31)

where \( \tau \) is an arbitrary time-constant. The change in flux over the transition region will therefore scale as:
For each hydrophilic ion, the characteristic concentration difference will be \( \Delta C_i^{(aq)} = c_i^{(aq)} \).

Meanwhile, for a lipophilic ion, the characteristic concentration difference will be \( \Delta C_i^{(org)} = c_i^{(org)} \). The time-scales to consider in this region are charge relaxation (\( \tau_r \)), and ion-concentration (ICP) (\( \tau_{aq} \) and \( \tau_{org} \) for each phase respectively). Since charge relaxation (\( \tau_r \sim 1 \mu s \)) is very fast compared to ICP (discussed in Section 5.1), we can say that the characteristic time scale is either \( \tau \sim \tau_{aq} \) or \( \tau \sim \tau_{org} \) depending on the particular system. By an order-of-magnitude approximation, \( \Delta C_i \sim 1 \text{mM} \) and \( \tau \sim 1 \text{s} \). Thus, for a sufficiently small transition region (\( \delta_{\gamma} \rightarrow 0 \)), we can say that \( \Delta N_i \approx 0 \). With no significant gradient in flux over the transition region, we can re-write Equation 3.29 as:

\[
N_{x,i}(x, t) \approx N_{x,i}(t) = \left( z_i^{(aq)}(t) \right)_a \left( -z_i^{(org)}(t) \right)_o \frac{F V(t)}{RT} 
\]

where \( V(t) \) is the total potential drop across the transition region (\( V(t) = \psi(x = -d/2 + \delta_{\gamma}/2, t) - \psi(x = -d/2 - \delta_{\gamma}/2, t) \)). Looking again to scale analysis, the denominator in Equation 3.33 goes to zero for a sufficiently small transition region, allowing us to simplify further:

\[
N_{x,i}(t) = M \cdot \left( z_i^{(aq)}(t) \right)_a \left( -z_i^{(org)}(t) \right)_o 
\]

where \( M \) is an arbitrary constant that approaches infinity for \( \delta_{\gamma} \rightarrow 0 \). At this limit, the concentration gradient across the transition region is no longer dependent on flux, but it is still dependent on the potential drop.

Next, we apply scale analysis to Poisson's equation:
\[
\frac{\partial^2 \psi}{\partial x^2} \approx \frac{V^\gamma}{\delta^2_\gamma},
\]
from which we see that the potential drop scales as:

\[
V^\gamma \sim -\rho_0 \delta^2_\gamma,
\]
where \(\rho_0\) is the space charge that is equal to the right-hand side of Equation 3.4. Thus, the potential drop will also go to zero for a sufficiently small transition length, and Equation 3.34 becomes:

\[
N^\gamma_{x,i}(t) = M \cdot \left( c_i^{\gamma(aq)}(t) f_i^{(aq)}(t) - c_i^{\gamma(\text{org})}(t) f_i^{(\text{org})}(t) \right).
\]

For \(M \to \infty\), we end up with this simple result:

\[
\frac{c_i^{\gamma(aq)}}{c_i^{\gamma(\text{org})}} = K_i^{\text{part}},
\]

\[
K_i^{\text{part}} = \frac{f_i^{(\text{org})}}{f_i^{(aq)}},
\]

In other words, if an infinitely thin transition region is assumed, the contribution of the gradient in activity coefficient can be effectively replaced by applying an interior boundary condition of Equations 3.38 and 3.39.

Using the full model introduced in Section 3.2, we wish to evaluate the conditions under which the thin transition region assumption is appropriate. As we can see from Figure 3.2, even for a transition length on the molecular scale, there is a measurable departure from Equation 3.38. This difference mainly arises due to the non-equilibrium reaction process which creates a large gradient in flux across the transition region. This suggests that the structure of the interface could play an important role in how ions distribute themselves in complex systems such as the one considered here.
3.4 Conclusions and future directions

In this chapter, we introduced a full model of aqueous and membrane transport that makes very few approximations and assumptions. As we will discuss more in following chapters, this model is able to capture phenomena that previously reported models cannot such as RBL formation and membrane failure in terms of selectivity. In this chapter, we looked closely at the phase-field transition region which has never before been implemented in an ISM model. Using scaling analysis, we determined that for a sufficiently thin transition region, the interface essentially maintains a fixed ratio of ions on each side equal to the partition coefficient. In the full simulation, this relationship did not strictly hold true. However, the thin transition region assumption is useful because it reduces model complexity significantly. In Section 4.2.1, we introduce a model that makes use of this assumption, and we use this for analysis in Chapters 4 and 5.
This model can be enhanced by making the following adjustments: (1) solving in terms of logarithmic concentrations, (2) incorporating granular features of the phase transition region, and (3) using more complete data on membrane transport properties. As mentioned in Section 3.3.2, using a logarithmic transform [118] would allow us to apply more realistic complexation coefficients [106, 126], giving us a more accurate simulation. In addition, we could improve the model by considering features such as water uptake [116, 127] and the microstructure of the plasticized PVC matrix [128]. This could provide us with a more fundamental basis for the properties of the phase transition region. Lastly, ISM simulation can be improved if we had more complete experimental characterization of membrane transport properties such as partition coefficients and reaction rate constants. However, we could potentially fill in the blanks by solving the inverse problem.

In this chapter, we characterized ion-exchange processes within the ISM using a full transport model solved with numerical methods. As a key component of membrane transport, this will help facilitate accurate simulation of ISM operation. Thus, this work is relevant to the implementation of traditional potentiometric sensing modalities as well as our goal of constructing devices for electrochemical neuromodulation.
4 Impact of non-equilibrium reaction processes

4.1 Introduction

As discussed in Chapter 3, ion-exchange is an effect of partitioning and reaction processes working together. Partitioning restricts free ions, and reaction selectively allows primary ions into the membrane. While the partitioning component was the focus in Chapter 3, here we focus on reaction.

In the full transport model introduced in Section 3.2, reaction is implemented as a non-equilibrium process. Solving it, we observe a feature that we refer to as the reaction boundary layer (RBL). Since the concentration of free ions inside the membrane is extremely small, we hypothesized that any perturbation caused by such a boundary layer phenomenon could impact the phase boundary potential significantly. Possibly, this could result in a small-signal charge-transfer type impedance.

A small-signal resistance along these lines has previously been observed in experimental electrochemical impedance spectroscopy (EIS) results [129-131]. This has led investigators to phenomenologically model charge transfer at the ion-selective (ISM) interface as an electrode-like Butler-Volmer process [94]. We would like to determine if the RBL could be the underlying source of this observed impedance.

In Section 4.3.1, we take both numeric and symbolic approaches to characterize the RBL and its impact on current-voltage (I-V) relationships. In order to reduce complexity, we make use of the thin transition region assumption discussed in Section 4.2.1.
4.2 Model description

4.2.1 Full transport model using thin transition region

A slightly reduced version of the model presented in Section 3.2 was used for the simulations discussed in this chapter and in Chapter 5. It is identical in all aspects except that the partitioning of ions between the two phases is achieved with a pointwise interior boundary condition instead of a gradient in the activity coefficient. In other words, the term corresponding to the activity coefficient in Equation 3.3 is removed, and we apply the following boundary condition:

\[ K_i^{\text{part}} = \left. \frac{c_i^{\text{aq}}}{c_i^{\text{org}}} \right|_{x = \pm d/2}, \quad (4.1) \]

for \( i \in \{J, P, N\} \) where \( c_i^{\text{aq}} \) and \( c_i^{\text{org}} \) are the concentrations of ions immediately adjacent to the two interfaces between the phases. In COMSOL, this is implemented as a boundary condition of the stiff spring type:

\[ N_{i,x}(x = \pm d) = \pm M \cdot \left( c_i^{\text{aq}} - K_i^{\text{part}} c_i^{\text{org}} \right) \bigg|_{x = \pm d/2}, \quad (4.2) \]

where \( M \) is an arbitrary constant of sufficient magnitude that \( c_i^{\text{aq}} - K_i^{\text{part}} c_i^{\text{org}} \bigg|_{x = \pm d/2} \approx 0. \)

Instead of using the Partial Differential Equations module for Equations 3.1-3.3 and 3.8-3.12, the Transport of Diluted Species module was used. Meanwhile, the Equation 3.4 was implemented in the same way as the full model. Elements of size \( \delta = 0.005 \) nm were used at the contact planes between the membrane and aqueous layers and size \( \delta = 0.24 \) \( \mu \)m throughout the rest of the geometry.
4.2.2 Electrochemical impedance spectroscopy simulation

In order to assess our model in terms of reported experimental EIS results, we simulated EIS numerically using COMSOL Multiphysics. Here, we made use of the thin transition region assumption discussed above in Section 4.2.1. The potential-controlled method was used with the two electrodes at \( x = \pm (d/2 + \delta_N) \) corresponding to the two sense leads in a 4-wire electrode configuration. This gives us the following Dirichlet boundary condition:

\[
\psi(x = -d/2 - \delta_N, t) = V_{\text{rms}}^{\text{app}} \sqrt{2} \sin(2\pi f^0 t), \quad (4.3)
\]

where \( V_{\text{rms}}^{\text{app}} \) is the root-mean-squared magnitude of the applied potential and \( f^0 \) is the frequency of the sinusoidal waveform. This replaces the electric displacement field boundary condition described in Equations 3.15-3.18. Based on standard experimental conditions, the applied magnitude was \( V_{\text{rms}}^{\text{app}} = 10 \text{ mV} \) and frequency ranged from \( 1 \text{ mHz} - 1 \text{ MHz} \).

The current density, calculated using Equation 3.5, was recorded for each frequency. The phase and magnitude were then determined by analyzing the Fourier spectrum of the simulated current density waveform. Finally, the corresponding real and imaginary components of this waveform were plotted in a Nyquist chart.

4.3 Results and discussion

4.3.1 Symbolic and numerical analysis of non-equilibrium reactions

Since the reaction process inside the membrane is typically thought to be fast compared with the diffusion of species, we can say that for the bulk region of the membrane, the concentration of reactive species satisfies:

\[
\beta_i = \frac{k_i'}{k_i} = \frac{c_{Li}}{(c_L)^{n_i} c_i^2}, \quad (4.4)
\]
for $i \in \{J, P\}$. However, when there is significant flux across the membrane, our models show that a non-equilibrium process can develop in a boundary layer adjacent to the interface between the two phases. Under certain conditions, this boundary layer can significantly affect the concentrations of free ions in the membrane, which in turn changes the phase boundary potential.

We can analyze this boundary layer by starting with the 1-D form of Equations 3.1-3.12 as used in the 1-D ISM transport models. We are considering a region outside of the transition region, so the contribution of the gradient in activity coefficient can be ignored in Equation 3.3. In addition, for the sake of developing an analytical solution, we approximate that diffusion dominates over migration, allowing us to ignore migration. This approximation can be made under the condition of excess supporting electrolyte, which is met for free ions which are minority carriers in the membrane [57]. This is discussed further in Section 5.1.3. We can therefore start with the following equation:

$$\frac{\partial c_p}{\partial t} - D_p^{(\text{org})} \frac{\partial^2 c_p}{\partial x^2} = -(\bar{k}_p (c_L)^n c_p + \bar{k}_p c_{L_P}) \cdot (4.5)$$

Since the bulk concentrations of $c_{L_P}$ and $c_L$ are much larger than $c_p$, their departures from their equilibrium will be much less significant over their gradient throughout the RBL. Therefore, we can approximate Equation 4.5 by substituting $c_L \rightarrow c_L^{\rho(\text{org})}$ and $c_{L_P} \rightarrow c_{L_P}^{\rho(\text{org})}$. These superscripts denote values at the edge of the interfacial double layer in the membrane phase.

Now, we are dealing with a single partial differential equation. This can be solved by first applying a Laplace transform:

$$s \bar{c}_p - \frac{c_L^{\rho}}{\beta_p c_L^{\rho}} - D_p^{(\text{org})} \frac{\partial^2 \bar{c}_p}{\partial x^2} = -(\bar{k}_p \left(c_L^{\rho(\text{org})}\right)^n \bar{c}_p + \bar{k}_p c_{L_P}^{\rho(\text{org})} / s), \quad (4.6)$$

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where \( s \) is the Laplace parameter and the accent marks the transformed variables. The general solution to this is:

\[
\tilde{c}_p = \frac{c_{Ln}^{\rho(\text{org})}}{s \beta_p c_L^{\rho(\text{org})}} + A \cdot \exp \left( \sqrt{\frac{k_p c_L^{\rho(\text{org})}}{D_p^{(\text{org})}}} x \right) + B \cdot \exp \left( -\sqrt{\frac{k_p c_L^{\rho(\text{org})}}{D_p^{(\text{org})}}} x \right),
\]

(4.7)

where \( A \) and \( B \) are undetermined coefficients. We can solve for these using the following boundary conditions:

\[
\tilde{N}_{p,x}(x = 0) = \frac{f_x}{z_p F},
\]

(4.8)

\[
\tilde{c}_p(x \to \infty) = \frac{c_{Ln}^{\rho(\text{org})}}{s \beta_p c_L^{\rho(\text{org})}}.
\]

(4.9)

We arrive at Equation 4.8 because the primary ions are carrying all of the flux across the interface. Over the length of the RBL, the free ion flux is converted to bound ion flux and the concentration reaches equilibrium level. Thus, in the bulk region at an effectively an infinite distance from the interface, we can apply Equation 4.9. The origin of the coordinate system used in this section lies at the interface between the membrane and aqueous phases, and the positive direction extends into the membrane.

Evaluating Equations 4.7-4.9, we arrive at the following solutions:

\[
\tilde{c}_p = \frac{c_{Ln}^{\rho(\text{org})}}{s \beta_p c_L^{\rho(\text{org})}} + \frac{f_x^{\text{app}}}{z_p F \sqrt{D_p^{(\text{org})} (k_p c_L^{\rho(\text{org})} + s)}} \exp \left( -\sqrt{\frac{k_p c_L^{\rho(\text{org})}}{D_p^{(\text{org})}}} x \right),
\]

(4.10)

It also follows that:

\[
c_p(x, t \to \infty) = \frac{c_{Ln}^{\rho(\text{org})}}{\beta_p c_L^{\rho(\text{org})}} + \frac{f_x^{\text{app}}}{z_p F \sqrt{D_p^{(\text{org})} k_p c_L^{\rho(\text{org})}}} \exp \left( -\sqrt{\frac{k_p c_L^{\rho(\text{org})}}{D_p^{(\text{org})}}} x \right).
\]

(4.11)
\[ c_p(x = 0, t) = \frac{\rho^{\text{org}}}{\beta_p c_L^p} + \frac{j_x^{\text{app}}}{z_p F \sqrt{D_p^{\text{org}} k_p c_L^0}} \text{erf} \left( \sqrt{\frac{k_p c_L^0}{k_p c_L^0}} \right), \]  

(4.12)

where \( j_x^{\text{app}} \) is an applied galvanostatic current density that starts at \( t = 0 \) s. From these expressions, we get a characteristic time and length of the RBL:

\[ \tau_{\text{RBL}} \sim \frac{1}{k_p c_L^0}, \]  

(4.13)

\[ l_{\text{RBL}} \sim \frac{D_p^{\text{org}}}{\sqrt{k_p c_L^0}}, \]  

(4.14)

which, as we can see, get faster and smaller for a larger reaction rate.

As validation of Equations 4.10-4.12, we compared results to solutions of the full numerical model. In Figure 4.1, both analytical and numerical solutions are plotted for several rate constants. As we can see, there is excellent agreement between the two. Thus, we can say that Equations 4.10-4.12 give us some insight into the structure of the RBL.
Figure 4.1: The concentration of Ca²⁺ throughout the RBL as obtained from analytical and numerical solutions to the 1-D ISM transport model under galvanostatic polarization of $J_x^{app} = -1$ A/m².

4.3.2 Reaction boundary layer and current-voltage characteristics

As mentioned in Section 4.1, we predict that the RBL will have a significant effect on the I-V characteristics of the membrane. The established expression for the phase boundary potential is:

$$\frac{K_p^{\text{part}} c_p^{\rho (\text{org})}}{c_p^{\rho (\text{aq})}} = e^{-z_p F V/RT},$$  \hspace{1cm} (4.15)

This expression arises from integrating Nernst-Planck over the length of this region. Combining Equations 4.10 and 4.15, we get:

$$J_x^{app} = c_p^{\rho (\text{aq})} \left( \frac{z_p F \sqrt{k_p D_p^{\rho (\text{org})} c_L^{\rho (\text{org})}}}{K_p^{\text{part}}} \right) e^{\frac{z_p F V_p}{RT}} - c_{\text{ln} p}^{\rho (\text{org})} \left( \frac{k_p D_p^{\rho (\text{org})}}{\sqrt{\beta_p c_L^{\rho (\text{org})}}} \right).$$  \hspace{1cm} (4.16)
As we can see, this takes on the form of the Butler-Volmer equation. The corresponding small-signal impedance for this process across both interfaces of the membrane is:

\[
\tilde{Z}_{ss} = \left. \frac{\tilde{V}_p}{J_{app}} \right|_{J_{app}=0} = \frac{RT}{Z_p^2F^2} \left( \frac{\beta_p}{D_p^{(org)}} \right) \left( \frac{C_L^{L(\text{org})}}{c_{LnP}^{L(\text{org})}} \sqrt{k_p c_L^{R(\text{org})}} - \frac{c_{LnP}^{R(\text{org})}}{C_L^{R(\text{org})}} \sqrt{k_p c_L^{L(\text{org})}} \right),
\]

where \(\tilde{Z}_{ss}\) is the small-signal complex impedance that corresponds to the RBL process, and the superscripts \(L\) and \(R\) denote the values of variables immediately adjacent to the space charge region at the left and right boundaries of the membrane respectively. Assuming fast RBL formation, the effective resistance is:

\[
R_{RBL} = \frac{RT}{Z_p^2F^2} \left( \frac{\beta_p}{k_p D_p^{(org)}} \right) \left( \frac{C_L^{R(\text{org})}}{c_{LnP}^{R(\text{org})}} \sqrt{c_L^{L(\text{org})}} - \frac{c_{LnP}^{L(\text{org})}}{C_L^{L(\text{org})}} \sqrt{k_p c_L^{R(\text{org})}} \right).
\]

Thus, we would expect to see a charge-transfer type impedance arising from the RBL.

The expression in Equation 4.18 suggests that the impedance is largest when the concentration of ions in the membrane are different on both sides. Interestingly, this seems to be consistent with some previously published electrochemical impedance spectroscopy (EIS) results [129-131]. However, Equation 4.18 does not tell the full story. Significantly, a depletion current (positive flux exiting the membrane) will have a much greater effect than an enrichment current (positive flux entering the membrane). This occurs because the RBL gradient is linear with flux, while its contribution to phase boundary potential is exponential.
Using the numerical model, we can simulate how EIS would look for this membrane system. Looking at Figure 4.2, we can see there are both a high-frequency arc and a low frequency arc. In previous reports, this low-frequency arc has been associated with an interfacial ion-exchange process. Consistent with this conclusion as well as that of the analytical expression in Equation 4.18, the low frequency arc exhibited by our simulated results diminishes with faster reaction rates. Furthermore, this arc disappears for a sufficiently large reaction rate, at which point the model behaves more like an equilibrium-reaction model.

Figure 4.2: Nyquist plot showing numerical simulation of potential-controlled EIS for the ISM system described by our full 1-D transport model. A sinusoidal potential was applied in the range of $1 \text{ MHz} - 1 \text{ mHz}$ with magnitude $V_{\text{rms}}^{\text{app}} = 10 \text{ mV}$.

4.4 Conclusions

Using the full ISM transport model introduced in Chapter 4, we investigated the effects of non-equilibrium reactions. Looking at numerical solutions, we noticed that a RBL can form when the membrane is polarized and that this has a significant impact on the phase-
boundary potential. In order to understand what was going on at a more intuitive level, we applied several informed assumptions which allowed us to characterize this feature analytically. We derived an analytical expression for the concentration throughout the RBL and also the effective charge-transfer impedance of the RBL process. In addition, we simulated EIS to show that this charge-transfer impedance is observable as a low-frequency arc on a Nyquist plot. This feature has previously been seen in experimental results, but its basis is currently poorly understood. We think it is reasonable to propose that the RBL is the source of this observed charge-transfer impedance.

Thus, non-equilibrium reaction processes could have a significant impact on the I-V relationships of the membrane. For polarized membrane systems used for such applications as electrochemical neuromodulation, this is an important consideration. In order to provide more rigorous validation, we will need to have better characterization of kinetic properties (i.e. forward and backward rate constants) for the ionophore reaction processes.
5 Ion-concentration polarization and its effect on transference

5.1 Introduction

5.1.1 The significance of ion-concentration polarization

Ion-concentration polarization (ICP), which occurs in both aqueous and membrane phases, is an important feature to consider in any ion-selective membrane (ISM) system. This phenomenon arises when an electric current forces a particular ion to flow into a region faster than migration in the bulk can carry it away. Depending on the polarity, this excess flux results in ions either building up or depleting in that region. Put another way, the excess flux is eventually resolved by diffusion which forms concentration gradients. This has a significant effect on both the potentiometric response and transference. In order to understand ICP on a basic level, we start in Sections 5.1.2-5.1.4 by reviewing some analytical solutions.

5.1.2 Fundamentals of ion-concentration polarization

Insight into the behavior of ICP can be attained by examining the constitutive equations of ion transport. Manipulating Nernst-Planck, the flux of each ion can be written in terms of total current density and ion concentration gradients:

\[ N_{i,x} = -D_i(1-t_i) \frac{\partial c_i}{\partial x} + \frac{t_i}{z_i} \sum_{j \neq i} z_j D_j \frac{\partial c_j}{\partial x} + \frac{t_i J_x}{z_i F} \]  \hspace{1cm} (5.1)

\[ t_i = \frac{z_i^2 D_i c_i}{\sum_j z_j^2 D_j c_j^2} \]  \hspace{1cm} (5.2)
where $t_i$ is the transference number. The leftmost term in the above equation corresponds to flux arising from self-diffusion, the middle term to that from cross-diffusion, and the last term to that from migration.

The integral transference expressed in Equation 1.3 is simply an instance of Equation 5.2 where concentration gradients are assumed to have no contribution. In that case, Equation 5.1 becomes:

$$N_{i,x} \approx \frac{T_i J_x}{z_i F}. \quad (5.3)$$

This is useful for thinking of the membrane as a filter for the selected ion which passes through selected ions as some percentage of the total current.

### 5.1.3 Analytical solutions in the aqueous phase

ICP in the aqueous phase can be thought of as a phenomenon that arises when there is a difference in transference between the aqueous and membrane phases. We can state Equation 5.1 in the following way, assuming integral transference inside the membrane:

$$-D_i(1 - t_i) \frac{\partial c_i}{\partial x} + t_i \sum_{j \neq i} z_j D_j \frac{\partial c_j}{\partial x} = \frac{J_x}{z_i F} (T_i - t_i). \quad (5.4)$$

This expression indicates that concentration gradients in the aqueous phase exist when there is a difference between the aqueous transference ($t_i$) and the membrane integral transference ($T_i$).

It is feasible to determine an analytical expression for this situation if the following is satisfied:

$$t_i = \frac{z_i^2 D_i c_i}{\sum_j z_j^2 D_j c_j} \rightarrow 0, \quad (5.5)$$
for each minority ion $i$ that contribute negligibly to the total electric flux. This criterion is met in a system with “excess supporting electrolyte.” In a physiological electrolyte, for example, Na$^+$ is in excess with roughly 100$\times$ the concentration of ions such as Ca$^{2+}$ and K$^+$, and we can solve for these minority ion. Making this approximation, Equations 3.1 and 3.3 reduces to the standard diffusion equation:

$$\frac{\partial c_i}{\partial t} = D_i^{(aq)} \frac{\partial^2 c_i}{\partial x^2}, i \neq E$$

(5.6)

where $E$ is the index of an ion with an excess bulk concentration. This can be solved for each minority ion as:

$$c_i(x, t) = c_i^0 + \sum_{l=0}^{\infty} \frac{1}{\pi^2(l + 1/2)^2} \cos \left( \frac{\pi x}{2\delta_N} \right) \left[ 1 - \exp \left( \frac{-\pi^2 D_i^{(aq)} t (l + 1/2)^2}{\delta_N^2} \right) \right]$$

(5.7)

Examining the largest time constant in the series for this solution, we can see that the characteristic time-scale is:

$$\tau_{aq} \sim \frac{\delta_N^2}{\pi^2 D_i^{(aq)}}$$

(5.8)

Thus, we arrive at the relationships introduced in Section 1.8.

### 5.1.4 Analytical solutions in the membrane phase

If a binary electrolyte is considered, Poisson’s equation can be replaced with the electroneutrality expression, $\Sigma_i z_i c_i = 0$. In a previous work, this has been used to solve for the electrolyte composition of an ISM in one-dimension \cite{87}:
\[ c_{\text{L}, n, P}(x, t) = \frac{|Z_R|}{Z_P} c_0 \frac{f_x}{z_P F D_{L,n,P}^{(\text{org})}} \frac{d}{z_P F D_{L,n,P}^{(\text{org})}} \left( 1 - \frac{z_p}{Z_R} \right) \sum_{l=0}^{\infty} \frac{(-1)^l}{\pi^2 (l + 1/2)^2} \sin \left( \frac{(2l + 1) \pi x}{d} \right) \right] \left[ 1 - \exp \left( \frac{-4 \pi^2 D_s t (l + 1/2)^2}{d^2} \right) \right] \]  

\[ D_s = \frac{(z_p - z_R) D_{L,n,P}^{(\text{org})} D_{R}^{(\text{org})}}{z_P D_{L,n,P}^{(\text{org})} - z_R D_{R}^{(\text{org})}}, \]  

where \( D_s \) is the "salt diffusivity," a harmonic mean of diffusivity weighted by valence. The origin at \( x = 0 \) is the midpoint of the membrane which has width \( d \). This approach approximates that the ionophore is perfectly selective to the primary ion. From Equation 5.9, we get the characteristic time-scale of membrane ICP:

\[ \tau_{\text{ISM}} \sim \frac{d^2}{4 \pi^2 D_s} \]  

which comes from the largest time-constant of the series.

5.1.5 Gaining insight from the full numerical model

Although the analytical expressions discussed in Sections 5.1.2-5.1.4 are useful for helping us understand the basic operation of ICP, we need a way of characterizing more complicated phenomenon. Specifically, we wish to understand the factors that affect selective transference, as well as the circumstances that lead to its failure. Although we were able to perform some analysis on this using the equilibrium model discussed in Chapter 2, the relevance of these results are limited since the membrane is perturbed from equilibrium immediately upon electrical polarization. Thus, we turn to the full numerical model presented in Section 3.2, making use of the thin transition region assumption presented in Section 4.2.1. We have identified two critical processes: (1) limiting concentration gradients
in the aqueous phase, and (2) limiting concentration gradients in the membrane phase. These are discussed in Section 5.2.1 and 5.2.2 respectively.

5.2 Results and discussion

5.2.1 Limiting concentration gradients in the aqueous phase

When an electric current is applied that causes a depletion of the primary ion on one side of the membrane, it also reduces the concentration of free primary ions inside the membrane. For a sufficiently large depletion of the primary ion, any interfering ions that are present will take up a larger fraction of the ionophore binding sites. This will result in a higher concentration of interfering ions inside the membrane, and accordingly, a lower transference for the primary ion. This can be seen from the analytical expression shown in Equation 2.1 which suggests that the transference is inversely proportional to the concentration of free ions in the aqueous phase. Meanwhile, an enrichment current can be applied without any limiting behavior, as long as there is no depletion process occurring on the other side of the membrane.

Using numerical solutions to the 1-D ISM transport model, we can evaluate the transference of the membrane in greater detail. The relationship between total electrical current and the flux of the primary ion is shown in Figure 5.1 for several bulk aqueous concentrations of Ca\(^{2+}\). As predicted, the selective transference diminishes for a larger depletion current. This occurs for both negative currents and positive currents because the membrane is symmetric with an equivalent depletion on both sides for alternate polarities.
Figure 5.1: Flux of primary ion (Ca$^{2+}$) vs. current density at $t = \infty$ for several bulk ion concentrations. The lipophilic ion concentrations used here were $c_K^0 = 137 \text{ mol/m}^3$ and $c_L^0 = 517 \text{ mol/m}^3$.

By this mechanism, the primary ion in the aqueous phase reaches a limiting concentration that is dictated by the selectivity of the membrane. As a result, the primary ion will never be depleted enough that other over-limiting processes take over, such as electro-osmotic micro-vortex formation [64-68], gravitational convection [69-72], or interfacial water-splitting [73, 74].

5.2.2 Limiting concentration gradients in the membrane phase

As in the aqueous phase, ion species inside the membrane are subject to ICP. For a sufficiently large polarization, the concentration of ions will deplete to zero on one side of the membrane, initiating a limiting regime. While over-limiting conduction in an aqueous system typically occurs through convection-coupled processes in the aqueous phase, our model reveals a distinct mechanism for the ISM. In this system, over-limiting conduction occurs when the free energy barrier created by ion partitioning is overcome by a sufficiently
large electromotive force. This permits ingress of interfering and counter ions and leads to a breakdown in selective transference for the primary ion. In Figure 5.2, we see the distribution of counter and interfering ions that enter the membrane upon failure.

![Figure 5.2](image)

**Figure 5.2:** Counter (Cl⁻) and interfering (Na⁺) ion concentrations throughout the membrane at steady-state for different magnitudes of current density.

The process of transitioning to an over-limiting regime can be seen by the current-voltage (I-V) characteristics shown in Figure 5.3. The current varies approximately linearly with potential for smaller polarizations, and we call this the Ohmic regime. For larger
partition coefficients and corresponding free energy barriers, we see that the slope decreases and levels off once a certain current is reached. This is the point where ICP has depleted ions and the limiting regime begins. Finally, once the potential is increased enough to overcome the energy barrier, the over-limiting regime begins and the slope increases.

Figure 5.3: I-V characteristics of ISM system for several partition coefficients, where parameters are adjusted such that membrane ICP reaches a limiting regime before the aqueous ICP does.

The consequence of this, is that the membrane loses selective transference, and along with it, the ability to polarize concentration in the aqueous phase. As we can see by Figure 5.4A, the transference of the primary ion at steady-state is closer to that of an unselective membrane for over-limiting currents. However, Figure 5.4B shows that the magnitude of concentration change in the DBL still trends upward with larger current densities. It is also important to note that up to the point at $t \approx 50$ s where transference is maximal, the membrane still has significant transference. This maximum corresponds to the time at which the membrane is fully polarized, estimated as $\tau_{ISM} = d^2/4\pi^2 D_{Ca^{(org)}} \approx 44.9$ s. Thus, the membrane will operate effectively under two conditions: (1) the applied current is
less than the limiting current, or (2) the duration of polarization is less than the characteristic time-constant for the membrane.

![Graph A](image1.png)

**Figure 5.4:** Transfer selectivity of the membrane over time, as measured by integral transference (A) and magnitude of concentration change at the boundary of the membrane (B).

### 5.3 Conclusions

In this chapter, we were able to consider ICP arising in a full membrane transport model. We examined how transference varies over time, and we identified different types of
membrane failures that result in a loss of selective transference. One type of failure arises when the aqueous concentration of ions is depleted past a certain level, allowing ingress of interfering ions. As a result, there is a sigmoidal relationship between total current and current carried by the selected ion. The other type of failure occurs when ICP inside the membrane reaches a limiting regime beyond which counter ions are allowed into the membrane. In this situation, the transference reaches a maximum at approximately the time-constant of the membrane before diminishing as the ingress of counter ions occurs.

This type of analysis is critical for understanding the optimal procedures and also the limitations of polarized ISM systems. Applied to electrochemical neuromodulation, we can use this approach to predict, for example, how much current can be injected across the membrane before the selective properties are diminished.
6 Aqueous ion-concentration polarization, multidimensional

6.1 Introduction

While it is convenient to consider transport in 1-D, practical systems are multidimensional and we can obtain important insights by modeling them accordingly. 2-D and 3-D models of ion-concentration polarization (ICP) in the aqueous phase are characterized by unique and relevant phenomena. Therefore, we should use them to inform the design and operation of real-world ion-selective membrane (ISM) devices used for such applications as electrochemical neuromodulation.

Fundamentally, ICP is a region where ion concentration is perturbed as a result of a driving force such as electrical polarization. Accordingly, the profile of concentration perturbation is the key feature that we want to describe and predict using our models. So far in this thesis, the models that have been presented make use of the Nernst steady layer approximation which allow us to characterize many key time-dependent behaviors. They are unable, however, to factor in the processes that shape the effective dimensions of the ion concentration profile, such as forced convection and non-planar diffusion. In this chapter, we discuss the fundamental basis of the effective diffusion boundary layer (DBL) length, $\delta_N$, that we use in several of our models.

Forced convection tangential to the electrical current will push ions away from the electrode and effectively limit how far the DBL extends [71]. This was investigated using a simulation of a microfluidic channel with an embedded ISM. This is relevant to devices for electro-desalination prototyping [132-135] and pre-concentration of analytes [136-139] for
biological assays. Our model of ICP in the microfluidic channel is introduced in Section 6.2.2, and we discuss simulation results in Section 6.3.1.

Another process that will limit the effective dimensions of the DBL, is non-planar diffusion arising in 3-D systems [140]. As an example of this, we modeled ICP adjacent to an ISM embedded in a micropipette tip. This was based on the micropipette we used to manipulate K+ concentration in the interstitial electrolyte of an ex vivo frog sciatic nerve, reported in Reference 18. Our model of 3-D ICP adjacent to the micropipette tip is introduced in Section 6.2.1, and we discuss simulation results in Section 6.3.2.

Although it was not modeled in this thesis, the third process that must generally be considered is spontaneous convection. This is random turbulence that can arise from external sources such as thermal gradients or ambient vibrations. Its length scale is commonly taken to be $l_{SC} = 300 \, \mu m$ [125, 141]. In a system with more than one of these three limiting processes present, the one with the smallest length-scale most accurately determines the characteristic dimensions. Thus, spontaneous convection need only be considered when the characteristic length-scales of forced convection and non-planar diffusion are larger than $l_{SC}$. Since spontaneous convection is ubiquitously present in macroscale, non-low Reynolds number systems, its length scale is effectively the maximum dimension of the DBL. On the other hand, scenarios found in in vivo neuromodulation applications (as well as many microfluidic system) are characterized by low Reynolds number, rendering $l_{SC}$ less relevant.
6.2 Model description

6.2.1 Non-planar diffusion in 3-D micropipette model

In this model, processes within the membrane are ignored and we focus on the DBL that forms in the aqueous solution. Thus, we apply Equations 3.1 and 3.3 with the terms corresponding to reaction, convection, and activity removed.

The geometry used here, depicted schematically in Figure 6.1, is based on an ISM micropipette of the type used for cellular recordings. Being axial-symmetric, this geometry can be solved in two dimensions with cylindrical coordinates. The domain extends from the micropipette surface to a spherical boundary that encloses a region of aqueous electrolyte. At the surface of this sphere, a boundary condition similar to Equation 3.13 is used to establish bulk concentrations of ions:

\[ c_i |_{(r,z) \in S} = c_i(t = 0) = c_i^0, \]

where \( S \) is the set of coordinates that lie on the enclosing surface. Additionally, this surface is set to be isopotential at the ground reference. In each simulation, the dimensions of this domain is increased until it no longer any effect on the DBL which drops of exponentially from the tip of the pipette. In this way, the domain is approximated as being infinitely large.

At micropipette tip, ion flux across the ISM is approximated by making use of the integral transference number:

\[ \hat{n} \cdot N_i = \frac{T_i J^{\text{app}}_x}{z_i F}, \]

where \( T_i \) is the integral transference for ion \( i \), and \( \hat{n} \) is the unit vector normal to the ISM surface pointing into the aqueous phase. For these simulations, it is assumed that ionophore selectivity is perfect and integral transference is unity for the primary ion.
Figure 6.1: Geometry for the 3-D micropipette model. The label $r_1$ denotes the radius of the micropipette tip, and the label $r_0$ denotes the radius of the embedded ISM.

The composition of the aqueous domain used in this model was chosen to mimic that of phosphate buffered saline containing Ca$^{2+}$ and Mg$^{2+}$, with parameters given by Table 6.1. As with the previous model, the primary ion was chosen to be Ca$^{2+}$. The radius of the pipette was chosen as $r_1 = 1$ mm and the default ISM radius as $r_0 = 800$ μm.

Table 6.1: Default model parameters used in the 3-D micropipette transport model.

<table>
<thead>
<tr>
<th>$i$</th>
<th>$z_i$</th>
<th>$c_i^0$ (mol/$m^3$)</th>
<th>$D_i$ ($\times 10^{-9} m^2/s$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$^+$</td>
<td>+1</td>
<td>141.25</td>
<td>1.35</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>-1</td>
<td>147</td>
<td>2.01</td>
</tr>
<tr>
<td>Ca$^{2+}$</td>
<td>+2</td>
<td>2</td>
<td>0.789</td>
</tr>
<tr>
<td>K$^+$</td>
<td>+1</td>
<td>3</td>
<td>1.96</td>
</tr>
<tr>
<td>Mg$^{2+}$</td>
<td>+2</td>
<td>5</td>
<td>0.706</td>
</tr>
<tr>
<td>HCO$_3^-$</td>
<td>-1</td>
<td>1.25</td>
<td>1.18</td>
</tr>
<tr>
<td>H$_2$PO$_4^-$</td>
<td>-1</td>
<td>10</td>
<td>0.88</td>
</tr>
</tbody>
</table>

This model was setup using the Transport of Diluted Species and Electrostatics modules in COMSOL. The results were simulated using the stationary and time-dependent solvers.
6.2.2 Forced convection in 2-D microfluidic channel

In this model, processes within the membrane are ignored and we focus on the DBL that forms in the aqueous solution. As in the micropipette model, we ignore reaction and activity from Equations 3.1 and 3.3. However, in this model, we consider the scenario of solvent transport with convective transport of solutes. Thus, we must also use Navier-Stokes:

\[
\frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v} \cdot \nabla) \mathbf{v} = -\frac{1}{\rho} \nabla p + \nu \nabla^2 \mathbf{v},
\]

(6.3)

where \( \rho \) is the solvent density, \( \nu \) is the kinematic viscosity, and \( p \) is the pressure.

The geometry for this model, depicted schematically in Figure 6.2, is based on that of a microfluidic channel of dimensions 5x2x0.2 mm. A constant flow of electrolyte solution is applied through the length of the channel with composition given by Table 6.1. At the inlet and outlet, laminar outflow boundary conditions create virtual regions extending past the model geometry that simulates fully developed flow with no-slip walls. An internal ODE solver in COMSOL applies an exit pressure at the outlet of the extended virtual region such that an average velocity is established according to:

\[
\frac{1}{W_{\text{out}}} \int_{\partial \Omega} \mathbf{v} \cdot dS = U_0,
\]

(6.4)

where \( W_{\text{out}} \) is the width of the outlet, \( \partial \Omega \) is the geometric region associate with the outlet, and \( U_0 \) is the average fluid velocity throughout the channel. Meanwhile, the inlet is given a "suppress backflow" boundary condition which applies a pressure such that:

\[
\hat{n} \cdot \mathbf{v} \geq 0,
\]

(6.5)

where \( \hat{n} \) is the unit vector normal to the surface of the outlet in the plane of fluid flow. The remaining walls of the channel are given no-slip boundary conditions. An electric current is applied across the width of the channel between ISM and counter electrodes that conduct
ions according to Equation 6.2. In the case of the ISM, it is assumed that ionophore selectivity is perfect and integral transference for the primary ion (Ca\(^{2+}\)) is unity. Meanwhile, a perfect Cl\(^{-}\) redox system is assumed at the counter electrode with an integral transference of unity for that ion.

This model was solved in COMSOL using the Transport of Diluted Species module for Equations 3.1-3.3 and 3.8-3.12, the Electrostatics module for Equation 3.4, and the Laminar Flow module for Equation 6.3. A triangular mesh was used (element size \(\delta = 134 \, \mu m\)) in combination with a boundary layer mesh (smallest element of \(\delta = 100 \, \mu m\)). Finally, this was solved in two stages, both with the Stationary solver. In stage one, the velocity profile was solved using Navier-Stokes in the Laminar Flow module, independent from solute transport. In stage two, the remaining physics were solved using the results from stage one as the initial values.
6.3 Results and discussion

6.3.1 Analysis of ion-concentration polarization in 2-D microfluidic channel

Solvent flow moving perpendicular to the direction of electrical current flow will push the ions away from the electrode, preventing the DBL from building up indefinitely. As reported previously, we can approximate an analytical expression for the concentration profile throughout the DBL as:

\[
c_i(y, z, t) = c_i^0 + \frac{j_i^{\text{app}}}{Fz_i} \sqrt{\frac{\pi}{D_iU_0}} \frac{x}{D_iU_0} \text{erfc} \left( \frac{y}{2\sqrt{D_i x/U_0}} \right),
\]

for each minority ion \(i\), where \(U_0\) is the average solvent velocity, \(y\) is the position along to axis parallel to electric current, and \(x\) is the position along the axis parallel to solvent flow.

From this, we see the characteristic length scale is:

\[
l_{FC} \sim 2 \frac{D_i x}{U_0}.
\]
As shown in Figure 6.3, solutions to the full model agree with this suggested relationship. However, the analytical expression makes a number of simplifying approximations, and we can see from Figure 6.3B that the full numerical result can be significantly different.
Figure 6.3: Concentration change of Ca\(^{2+}\) in 2-D microfluidic system upon application of current density of \(J_y = -1\) A/m\(^2\). This membrane is assumed to be perfectly selective with Ca\(^{2+}\) integral transport number of unity. A 2-D heat-map of Ca\(^{2+}\) concentration throughout channel for \(Q = 5\) μL/min. B Concentration profile of Ca\(^{2+}\) for different flow rates (taken along dotted line drawn on heat-map in A). The solutions corresponding to the analytical expression are marked with squares.

### 6.3.2 Analysis of ion-concentration polarization in 3-D micropipette model

As discussed previously, another process that plays an important role in shaping the DBL is non-planar diffusion. Because the current density spreads by a factor of \(1/r^2\), the DBL approaches the bulk concentration level for \(r \rightarrow \infty\). Therefore, if the characteristic length-
scale is less than those of spontaneous and forced convection, non-planar diffusion will dictate the dimensions of the DBL. It has been established that the characteristic length-scale of this process is equivalent to the dimensions of the electrode. In the case of a disk-shaped electrode, this dimension would be the radius (i.e. $l_{np} \sim r_0$) [142]. Using the 3-D axial-symmetric Nernst-Planck and Poisson (NPP) model described in Section 6.2.1, we can generate numerical solutions for the DBL whose length is limited by nonplanar diffusion. The results are shown in Figure 6.4. As predicted, the effective length of the DBL increases with larger electrode dimensions.
Figure 6.4: Concentration profile of Ca$^{2+}$ following application of galvanostatic current of $J_z = -1 \text{ A/m}^2$ for several electrode diameters. This membrane is assumed to be perfectly selective with Ca$^{2+}$ integral transport number of unity. In the top row, we see 3-D heat-maps of Ca$^{2+}$ concentration in spherical volume radiating out from simulated micropipette tip for tip diameters: (A) $r_o = 200 \mu\text{m}$ and (B) $r_o = 800 \mu\text{m}$. C Concentration profile of Ca$^{2+}$ at $x = 0$ for several ISM diameters.

6.4 Summary and future directions

Using multidimensional models, we were able to simulate the behavior of ICP in two example systems: a microfluidic channel, and a micropipette. These results allowed us to analyze the dimension-limiting processes of forced convection and non-planar diffusion. These have a significant effect on the shape of the concentration profile, and are thus
important to consider for the accurate modeling of practical systems. The insights gained from these results will help us design and operate ISM devices for applications such as electrochemical neuromodulation.
7 Conclusions and future directions

In this thesis, we presented mathematical tools for describing and predicting the behavior of polarized ion-selective membrane (ISM) systems. We used these tools to characterize unique phenomena that could not be simulated using previously reported models. Starting with Chapter 2, we used an equilibrium model to estimate membrane transference for common membrane formulations. Then, in Chapter 3, we introduced a full transport model that could be solved numerically using the finite element method (FEM). This model was used to analyze the components of ion-exchange, ion partitioning and reaction in Chapters 3 and 4 respectively. Additionally, in Chapter 5, the model was used to characterize the effects of ion-concentration polarization (ICP) on selective membrane transport. Then, we moved onto multidimensional transport models in Chapter 6, using them to characterize processes that determine the size of the diffusion boundary layer (DBL).

Using the equilibrium model in Chapter 2, we analyzed the selectivity of integral transference for several common membrane formulations. The main question we addressed here was: does potentiometric selectivity translate directly into transfer selectivity? It has generally been assumed that this is the case. Both types of selectivity arise from exclusion of interfering ions, and intuitively, we would expect that metrics of potentiometric selectivity would reflect their common origin. However, we wanted to back this up by applying rigorous mathematical examination. For each of the membrane formulations we considered, the primary ion transference was near unity under typical physiological conditions. Furthermore, we found that better potentiometric selectivity correlated with better transfer selectivity. Thus, we conclude that selective transference can be roughly evaluated on the basis of the selectivity of the potentiometric response. In the context of electrochemical
neuromodulation, this type of analysis can be used to optimize ISM formulation for higher transference and predict the limits of transference for a particular formulation.

In Chapter 3, we introduced our full ISM transport model. Our analysis here was focused on investigating the significance of its added complexity relative to previously reported models. The main enhancement featured in this model was the implementation of separate partitioning and reaction processes. We presented several arguments for how ion-exchange can be more appropriately modeled as a collusion of these two processes rather than a simplified interfacial-adsorption process. Then, we analyzed the ion distribution throughout a phase-field transition region and assessed the thin transition region assumption. It was determined that the thin transition region assumption did not strictly hold true for the parameters we tested. However, results based on this assumption have a smaller computational burden and are still generalizable to the full phase-field model. With this in mind, we chose to apply the thin transition region assumption in following chapters. This analysis gives us insight into the underlying basis of ion-exchange and tells us how it can be effectively modeled. For the characterization of devices for electrochemical neuromodulation, this is crucial.

Continuing the analysis of our full transport model, we focused next in Chapter 4 on the other component of ion-exchange: reaction. We hypothesized that a boundary layer of non-equilibrium ion-ionophore reaction could form adjacent to aqueous/membrane interfaces upon polarization. Since free ions inside the membrane exist in extremely small concentrations, small perturbations could have a significant impact on the phase boundary potential. We investigated the reaction boundary layer (RBL) as a feature of our full transport model by considering analytical and numerical solutions. Making some
approximations, we were able to derive a closed-form expression for the concentration profile of ions throughout the RBL and show that there is a Butler-Volmer type relationship between phase-boundary potential and electric current. Numerical solutions confirmed the existence of the RBL and revealed corresponding current-voltage (I-V) characteristics that resemble a Butler-Volmer charge-transfer process. These characteristics have been observed previously in experimental electrochemical impedance spectroscopy (EIS) results, and we propose that the RBL is the underlying mechanism. Accordingly, we suggest that it is necessary to consider non-equilibrium reaction for complete assessment of ISM I-V characteristics. Such will allow us to: (1) make more accurate predictions of power requirements for electrical polarization, and (2) develop more effective calibration curves for dynamic potentiometric sensing. Both of these are relevant to our design of devices for electrochemical neuromodulation.

Following this, in Chapter 5 we used the full transport model to investigate important phenomena related to ICP. Specifically, we explored how transfer selectivity is affected when polarization causes excessive depletion in either the aqueous or membrane phase. We show that depletion of the primary ion in the aqueous phase driven be electrical current directed into the membrane results in the diminishing of membrane transference for that ion. This is consistent with the results of our equilibrium model discussed in Chapter 2. A point is reached for each membrane formulation where the primary ion flux levels off, no longer increasing as the applied current increases. Effectively, this creates a lower-limit on the concentration of the primary ion that can be affected by operation of an ISM device. We could take advantage of this characteristic, engineering membranes to have a particular
concentration limit. This type of device could be used to maintain a fixed concentration of
the selected ion in the interstitial space of neural tissue.

Later in Chapter 5, we discussed ICP in the membrane phase. One of our main goals was
to determine how integral transference is effected when any membrane ions reach a limiting
concentration. We hypothesized that over-limiting conduction would occur through
membrane failure characterized by the ingress of counter and interfering ions. Looking at
various features within numerical solutions to the full transport model, we found that once
the limiting concentration is reached, the phase-boundary potential increases until the
potential energy barrier associated with ion partitioning is overcome. At this point, free
counter and interfering ions are admitted into the membrane, and transfer selectivity is
reduced. Thus, transfer selectivity increases over a brief period while membrane ICP is still
developing, and then it diminishes once the limiting regime is initiated. These results tell us
how to avoid the loss of transfer selectivity during the operation of polarized ISM systems.

Finally, in Chapter 6, we shifted our focus to multidimensional models of ICP in the
aqueous phase. Our goal here was to outline a modeling framework for processes that
determine the size of the diffusion boundary layer (DBL). In addition, we sought to validate
previously formulated expressions for the characteristic dimensions of the DBL shaped by
these processes. We focused primarily on two different processes: forced convection and
non-planar diffusion. These were addressed using 2-D and 3-D models of ion transport
respectively. We showed that our numerical solutions had reasonable agreement with
previous expressions for the characteristic length scale of the DBL subject to these processes.
These expressions are useful for comparing the various size-limiting processes that could
exist in a practical system. The modeling principles described in Chapter 6 can be applied to
predict the effective area of chemical modulation affected by the operation of polarized ISM devices.

The mathematical tools discussed here can be directly applied to modeling of polarized ISM devices. Overall, this work sets the stage for the development of ISM-based devices that focally manipulate chemical concentration via the physical process of ICP.
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