

A Model of Electrodiffusion and Osmotic Water Flow and its Energetic Structure

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Abstract

We introduce a system of partial differential equations that govern electrodiffusion and osmotic water flow through cells and tissues. The model satisfies a natural energy equality, in which the sum of the entropic, elastic and electrostatic free energies are dissipated through viscous, electrodiffusive and osmotic flows. We discuss limiting models when certain dimensionless parameters are small. Finally, we develop a numerical scheme for the one-dimensional case and present some simple applications of our model to cell volume control.

1. Introduction

Systems in with important electrodiffusion and osmotic water flow are found throughout life [1, 2, 3]. Such systems include brain ionic homeostasis [4, 5], fluid secretion by epithelial systems [6], electrolyte regulation in the kidney [7, 8], fluid circulation in ocular systems [9, 10], and water uptake by plants [11].

Mathematical models of electrodiffusion and/or osmosis have been proposed and used in many physiological contexts, and have formed a central topic in biology for a very long time [1, 12, 13]. Some are simple models using ordinary differential equations while others are more detailed in that they include partial differential equations (PDEs) describing the spatial variation of the concentration and flow fields [14, 15, 16, 17, 18, 19, 20]. In this paper, we propose a system of PDEs that describes ionic electrodiffusion and osmotic water flow at the cellular level. To the best of the authors' knowledge, this is the first model in which osmotic water flow and electrodiffusion have been treated within a unified framework including cells with deformable and capacitance-carrying membranes. A salient feature of our model is that it possesses a natural thermodynamic structure; it satisfies a free energy equality. As such, the present work may be viewed

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as a generalization of the classical treatment of osmosis and electrodiffusion in irreversible thermodynamics to spatially extended systems [21, 22, 23].

To introduce our approach, we first focus attention on uncharged systems. In Section 2, we treat the case in which the diffusing chemical species carry no electric charge. We write down equations that are satisfied by the water velocity field \mathbf{u} , the chemical concentrations $c_k, k = 1, \dots, N$ and the membrane position \mathbf{X} . The model is shown to satisfy a free energy equality in which the sum of the entropic free energy and the elastic energy of the membrane is dissipated through viscous water flow, bulk diffusion, transmembrane chemical fluxes and osmotic water flow. One interesting consequence of this analysis is that the classical van t'Hoff law of osmotic pressure arises naturally from the requirement that osmotic water flow be dissipative. We note that models with the similar purpose of describing diffusing non-electrolytes and their interaction with osmotic water flow across moving membranes, have been proposed in the literature [19, 24, 25] (in the Appendix Appendix A.2, we discuss the relationship of our model with that of [19, 24]).

In Section 3, we extend the model of Section 2 to treat the case of ionic electrodiffusion. We introduce the electrostatic potential ϕ which satisfies the Poisson equation. The membrane now carries capacitance, which can result in a jump in the electrostatic potential across the membrane. We shall see that this model also satisfies a free energy equality. The free energy now includes an electrostatic contribution. The verification of the free energy equality in this case is not as straightforward as in the non-electrolyte case, and requires a careful examination of surface terms.

In Section 4, we discuss simplifications of our model. We make the system dimensionless and assess the relative magnitudes of the terms in the equations. An important simplification is obtained when we take the electroneutral limit. In this case, the electrostatic potential becomes a Lagrange multiplier that helps to enforce the electroneutrality condition.

In Section 5, we develop a computational scheme to simulate the limiting system obtained in the electroneutral limit, when the geometry of the cell is assumed spherical. As an application, we treat animal cell volume control.

2. Diffusion of Non-electrolytes and Osmotic Water Flow

2.1. Model Formulation

Consider a bounded domain $\Omega \subset \mathbb{R}^3$ and a smooth closed surface $\Gamma \subset \Omega$. This closed surface divides Ω into two domains. Let $\Omega_i \subset \Omega$ be the region bounded by Γ , and let $\Omega_e = \Omega \setminus (\Omega_i \cup \Gamma)$. In the context of cell biology, Ω_i may be identified with the intracellular space and Ω_e the extracellular space. Although cell physiological systems of biological cells serve as our primary motivation for formulating the models of this paper, this identification is not necessary.

In this section we formulate a system of PDEs that governs the diffusion of *non*-electrolytes and osmotic flow of water in the presence of membranes. In Section 3, we shall build upon this model to treat the electrolyte case.

We consider N non-electrolyte chemical species whose concentrations we call $c_k, k = 1, \dots, N$. Let ω be the entropic part of the free energy per unit volume of this solution. The following expression for ω is the most standard choice:

$$\omega_0 = \sum_{k=1}^N k_B T c_k \ln c_k. \quad (2.1)$$

This expression is valid when the ionic solution is sufficiently dilute and lead to linear diffusion of solute. Our calculations, however, do not depend on this choice of ω . If the solution in question deviates significantly from ideality, other expressions for ω may be used in place of ω_0 .

Given ω , the chemical potential μ_k of the k -th chemical species is given as:

$$\mu_k = \sigma_k, \quad \sigma_k \equiv \frac{\partial \omega}{\partial c_k}. \quad (2.2)$$

We have introduced two symbols μ_k and σ_k in anticipation of the discussion of the electrolyte case, where μ_k and σ_k are different. For water, it is convenient to consider the water potential ψ_w , the free energy per unit volume, rather than the μ_w , the chemical potential (free energy per molecule). The water potential and water chemical potential are thus related by the relation $v_w \psi_w = \mu_w$ where v_w is the volume of water per molecule. We define:

$$\psi_w \equiv \pi_w + p, \quad \pi_w = \left(\omega - \sum_{k=1}^N c_k \sigma_k \right) = \left(\omega - \sum_{k=1}^N c_k \frac{\partial \omega}{\partial c_k} \right) \quad (2.3)$$

where p is the pressure. As we shall see, p will be determined in our model via the equations of fluid flow (Eq. (2.8)). The entropic part of ψ_w (or the *osmotic pressure*), π_w , is given as the *negative* multiple of the (semi)Legendre transform of ω with respect to all the ionic concentrations c_k . This expression for osmotic pressure can be found, for example, in [26]. As we shall see in the proof of Theorem 2.1, the above definition of π_w is forced upon us if we insist that our model satisfy a free energy dissipation principle.

We begin by writing down the equations of ionic concentration dynamics. At any point in Ω_i or Ω_e

$$\frac{\partial c_k}{\partial t} + \nabla \cdot (\mathbf{u} c_k) = \nabla \cdot \left(c_k \frac{D_k}{k_B T} \nabla \mu_k \right) \quad (2.4)$$

where D_k is the diffusion coefficient and \mathbf{u} is the fluid velocity field. Ions thus diffuse down the chemical potential gradient and are advected with the local fluid velocity. We have assumed here that cross-diffusion (concentration gradient of one species driving the diffusion of another species) is negligible.

We must supplement these equations with boundary conditions. Most formulations of non-equilibrium thermodynamic processes seem to be confined either to the bulk or to the interface between two bulk phases [21, 27, 23]. Here

we must couple the equations in the bulk and with boundary conditions at the interface, which as a whole give us a consistent thermodynamic treatment of diffusion and osmosis.

On the outer boundary $\Gamma_{\text{out}} = \partial\Omega$, for simplicity, we impose no-flux boundary conditions. Let us now consider the interfacial boundary conditions on the membrane Γ . Since we want to account for osmotic water flow, the membrane Γ will deform in time. Sometimes, we shall use the notation Γ_t to make this time dependence explicit. Let Γ_{ref} be the resting or reference configuration of Γ . The membrane will then be a smooth deformation of this reference surface. We may take some (local) coordinate system $\boldsymbol{\theta}$ on Γ_{ref} , which would serve as a material coordinate for Γ_t . The trajectory of a point that corresponds to $\boldsymbol{\theta} = \boldsymbol{\theta}_0$ is given by $\mathbf{X}(\boldsymbol{\theta}_0, t) \in \mathbb{R}^3$. For fixed t , $\mathbf{X}(\cdot, t)$ gives us the shape of the membrane Γ_t .

Consider a point $\mathbf{x} = \mathbf{X}(\boldsymbol{\theta}, t)$ on the membrane. Let \mathbf{n} be the outward unit normal on Γ at this point. The boundary conditions satisfied on the intracellular and extracellular faces of the membrane are given by:

$$c_k \left(\mathbf{u} - \frac{D_k}{k_B T} \nabla \mu_k \right) \cdot \mathbf{n} = c_k \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} + j_k + a_k \text{ on } \Gamma_i \text{ or } \Gamma_e. \quad (2.5)$$

The expression “on $\Gamma_{i,e}$ ” indicates that the quantities are to be evaluated on the intracellular and extracellular faces of Γ respectively. The term j_k is the passive chemical flux that passes through the membrane and a_k is the active flux. Fluxes going from Ω_i to Ω_e is taken to be positive. Equation (2.5) is just a statement of conservation of ions at the moving membrane. It is easy to check that (2.4) together with (2.5) implies conservation of each species.

The flux j_k is in general a function of concentrations of all chemical species on both sides of the membrane. The chemicals are usually carried by channels and transporters, and the functional form of j_k describe the kinetic features of these carriers. As we shall see in Section 2.3, j_k can also be a function of the difference in water chemical potential across the membrane.

The passive nature of the j_k is expressed by the following inequality:

$$[\mu_k] j_k \geq 0, \quad [\mu_k] = \mu_k|_{\Gamma_i} - \mu_k|_{\Gamma_e} \quad (2.6)$$

where $\cdot|_{\Gamma_{i,e}}$ expresses evaluation of quantities at the intracellular and extracellular faces of the membrane Γ respectively. We shall see that this condition is consistent with the free energy identity (2.20). For any quantity w , $[w] = w|_{\Gamma_i} - w|_{\Gamma_e}$ will henceforth always denote the difference between w evaluated on the intracellular and extracellular faces of Γ . A simple example of j_k occurs when j_k is a function only of $[\mu_k]$ and satisfies the following conditions:

$$j_k = j_k([\mu_k]), \quad j_k(0) = 0, \quad \frac{\partial j_k}{\partial [\mu_k]} \geq 0. \quad (2.7)$$

It is easily checked that j_k in this case satisfies (2.6). We shall see concrete examples in Section 3. Condition (2.6) is somewhat restrictive in the sense that it is possible to have a “passive” flux that does not satisfy (2.6) when multiple

species flow and interact. We shall discuss this briefly in Section 2.3. Condition (2.6) needs to be relaxed to describe systems in which different chemical species flow through one channel or (passive) transporter. Those systems usually couple fluxes of different chemical species. They often couple (unidirectional) influx and efflux of the same species (symporters and antiporters) [28, 12, 29, 2, 3]. The active flux a_k is typically due to ionic pump currents often driven by ATP [29, 2, 3].

We now discuss force balance. We shall treat the cytosol as a viscous fluid and the cell membrane as an elastic surface. The cell membrane itself is just a lipid bilayer, and cannot support a large mechanical load. The cell membrane is often mechanically reinforced by an underlying actin cortex and overlying system of connective tissue, and in the case of plant cells, by an overlying cell wall. If we view these structures as part of the membrane, our treatment of the membrane being elastic may be a useful simplification. We could employ a more complete model of cell mechanics incorporating, in particular, the mechanical properties of the cytoskeleton and extracellular lamina. However, our emphasis here is on demonstrating how osmosis can be seamlessly combined with mechanics, and we intentionally keep the mechanical model simple to clarify the underlying ideas.

Consider the equations of fluid flow. The flow field \mathbf{u} satisfies the Stokes equation at any point in Ω_i or Ω_e :

$$\nu\Delta\mathbf{u} - \nabla p = 0, \quad \nabla \cdot \mathbf{u} = 0 \quad (2.8)$$

where ν is the viscosity of the electrolyte solution. Note that the above equations can also be written as follows:

$$\nabla \cdot \Sigma_m(\mathbf{u}, p) = 0, \quad \nabla \cdot \mathbf{u} = 0, \quad \Sigma_m(\mathbf{u}, p) = \nu(\nabla\mathbf{u} + (\nabla\mathbf{u})^T) - pI \quad (2.9)$$

where I is the 3×3 identity matrix and $(\nabla\mathbf{u})^T$ is the transpose of $\nabla\mathbf{u}$. Here, Σ_m is the mechanical stress tensor. It is possible to carry out much of the calculations to follow even if we retain inertial terms and work with the Navier-Stokes equations or use other constitutive relations for the mechanical stress. In particular, such modifications will not destroy the free energy identity to be discussed below. We do note, however, that incompressibility is important for our computations.

We now turn to boundary conditions. We let $\mathbf{u} = 0$ on the outer boundary Γ_{out} for simplicity. On the cell membrane Γ , we have the following conditions. Take a point $\mathbf{x} = \mathbf{X}(\boldsymbol{\theta}, t)$ on the boundary Γ , and let \mathbf{n} be the unit outward normal on Γ at this point. First, by force balance, we have:

$$[\Sigma_m(\mathbf{u}, p)] = \mathbf{F}_{\text{elas}}. \quad (2.10)$$

Here, \mathbf{F}_{elas} is the elastic force per unit area of membrane.

We make some assumptions about the form of the elastic force. We assume that the membrane is a hyperelastic material in the sense that the elastic force can be derived from an elastic energy functional E_{elas} that is a function only of

the configuration \mathbf{X} :

$$E_{\text{elas}}(\mathbf{X}) = \int_{\Gamma_{\text{ref}}} \mathcal{E}(\mathbf{X}) dm_{\Gamma_{\text{ref}}} \quad (2.11)$$

where $m_{\Gamma_{\text{ref}}}$ is the surface measure of Γ_{ref} and \mathcal{E} is the elastic energy density measured with respect to this measure. It is possible that \mathcal{E} is a function of spatial derivatives of \mathbf{X} . The elastic force $\mathbf{F}_{\text{elas}}(\mathbf{x})$ satisfies the relation:

$$\left. \frac{d}{ds} \right|_{s=0} \int_{\Gamma_{\text{ref}}} \mathcal{E}(\mathbf{X}(\boldsymbol{\theta}) + s\mathbf{Y}(\boldsymbol{\theta})) dm_{\Gamma_{\text{ref}}} = - \int_{\Gamma} \mathbf{F}_{\text{elas}}(\mathbf{x}) \cdot \mathbf{Y}(\mathbf{X}^{-1}(\mathbf{x})) dm_{\Gamma} \quad (2.12)$$

where \mathbf{Y} is an arbitrary vector field defined on Γ_{ref} and m_{Γ} is the natural measure on the surface Γ and is related to $m_{\Gamma_{\text{ref}}}$ by $dm_{\Gamma} = Q dm_{\Gamma_{\text{ref}}}$ where Q is the Jacobian determinant relating Γ_t to the reference configuration Γ_{ref} . The expression $\mathbf{X}^{-1}(\mathbf{x})$ is the inverse of the map $\mathbf{x} = \mathbf{X}(\boldsymbol{\theta})$. Thus, \mathbf{F}_{elas} is given as the variational derivative of the elastic energy up to the Jacobian factor Q . Consequently, we have the following relation:

$$\frac{d}{dt} E_{\text{elas}}(\mathbf{X}) = - \int_{\Gamma} \mathbf{F}_{\text{elas}} \cdot \frac{\partial \mathbf{X}}{\partial t} dm_{\Gamma}. \quad (2.13)$$

In the above, $\frac{\partial \mathbf{X}}{\partial t}$ should be thought of as a function of \mathbf{x} , i.e., $\frac{\partial \mathbf{X}}{\partial t} = \frac{\partial \mathbf{X}}{\partial t}(\mathbf{X}^{-1}(\mathbf{x}))$. We shall henceforth abuse notation and let $\frac{\partial \mathbf{X}}{\partial t}$ be a function of \mathbf{x} or $\boldsymbol{\theta}$ depending on the context of the expression.

In addition to the force balance condition (2.10), we need a continuity condition on the interface Γ . Since we are allowing for osmotic water flow, we have a slip between the movement of the membrane and the flow field. At a point $\mathbf{x} = \mathbf{X}(\boldsymbol{\theta}, t)$ on the boundary Γ we have:

$$\mathbf{u} - \frac{\partial \mathbf{X}}{\partial t} = j_w \mathbf{n} \quad (2.14)$$

where j_w is water flux through the membrane. We are thus assuming that water flow is always normal to the membrane and that there is no slip between the fluid and the membrane in the direction tangent to the membrane. Given that \mathbf{n} is the outward normal, j_w is positive when water is flowing out of the cell. Like j_k in (2.5), we let j_w be a passive flux in the following sense. We let:

$$j_w = j_w([\widehat{\psi}_w]), \quad \widehat{\psi}_w \Big|_{\Gamma_{i,e}} = \pi_w|_{\Gamma_{i,e}} - ((\Sigma_m(\mathbf{u}, p)) \cdot \mathbf{n})|_{\Gamma_{i,e}} \quad (2.15)$$

where π_w was the entropic contribution to the water potential defined in (2.3). In general, j_w can be a function of other variables (see Section 2.3). The function j_w satisfies the condition, analogous to (2.6):

$$[\widehat{\psi}_w] j_w \geq 0. \quad (2.16)$$

This condition is clearly satisfied if:

$$j_w = j_w([\widehat{\psi}_w]), \quad j_w(0) = 0, \quad \frac{\partial j_w}{\partial [\widehat{\psi}_w]} > 0. \quad (2.17)$$

Water flow across the membrane is thus driven by the difference in the entropic contribution to the chemical potential as well as the jump in the mechanical force across the cell membrane. When the flow field \mathbf{u} is equal to 0, the above expression for $\widehat{\psi}_w$ reduces to:

$$\widehat{\psi}_w \Big|_{\Gamma_{i,e}} = \pi_w|_{\Gamma_{i,e}} + p|_{\Gamma_{i,e}} = \psi_w|_{\Gamma_{i,e}}. \quad (2.18)$$

We may thus view $\widehat{\psi}_w$ as a modification of ψ_w to take into account dynamic flow effects. Let $\omega = \omega_0$ given in (2.1) in the definition (2.3) of π_w . Then, we have, under zero flow conditions,

$$[\widehat{\psi}_w] = \left[p - k_B T \sum_{k=1}^N c_k \right]. \quad (2.19)$$

We thus reproduce the standard statement that water flow across the membrane is driven by the difference in osmotic and mechanical pressure, where the osmotic pressure, π_w , is given by the van t'Hoff law.

2.2. Free Energy Identity

We now show that the system described above satisfies the following free energy identity.

Theorem 2.1. *Suppose c_k, \mathbf{u}, p be smooth functions that satisfy (2.4), (2.8), and in Ω_i and Ω_e and satisfy boundary conditions (2.5), (2.10), (2.14) on the membrane Γ . Suppose further that c_k and satisfy no-flux boundary conditions and $\mathbf{u} = 0$ on the outer boundary Γ_{out} . Then, c_k, \mathbf{u}, p and ϕ satisfy the following free energy identity.*

$$\begin{aligned} \frac{d}{dt}(G_S + E_{elas}) &= -I_p - J_p - J_a \\ G_S &= \int_{\Omega_i \cup \Omega_e} \omega d\mathbf{x} \\ I_p &= \int_{\Omega_i \cup \Omega_e} \left(\nu |\nabla \mathbf{u}|^2 + \sum_{k=1}^N c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 \right) d\mathbf{x} \\ J_p &= \int_{\Gamma} \left([\widehat{\psi}_w] j_w + \sum_{k=1}^N [\mu_k] j_k \right) dm_{\Gamma} \\ J_a &= \int_{\Gamma} \left(\sum_{k=1}^N [\mu_k] a_k \right) dm_{\Gamma}. \end{aligned} \quad (2.20)$$

Here, E_{elas} was given in (2.11) and $|\nabla \mathbf{u}|$ is the Frobenius norm of the 3×3 rate of deformation matrix $\nabla \mathbf{u}$.

If $a_k \equiv 0$, then the free energy is monotone decreasing.

The free energy is given as a sum of the entropic contribution G_S and the membrane elasticity term E_{elas} . This free energy is dissipated through bulk currents I_p and membrane currents J_p . Dissipation in the bulk comes from ionic electrodiffusion and viscous dissipation. Dissipation at the membrane comes from ionic channel currents and transmembrane water flow. If active membrane currents are present, they may contribute to an increase in the free energy through the term J_a . It is sometimes useful to rewrite $J_p + I_p$ as:

$$\begin{aligned} J_p + I_p &= F_w + F_c, \\ F_w &= \int_{\Omega_i \cup \Omega_e} \nu |\nabla \mathbf{u}|^2 d\mathbf{x} + \int_{\Gamma} [\widehat{\psi}_w] j_w dm_{\Gamma}, \\ F_c &= \int_{\Omega_i \cup \Omega_e} \sum_{k=1}^N c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 d\mathbf{x} + \int_{\Gamma} \sum_{k=1}^N [\mu_k] j_k dm_{\Gamma}, \end{aligned} \quad (2.21)$$

where F_w and F_c are the dissipations due to water flow and solute diffusion respectively. In the statement of the Theorem, it is important that (2.6) and (2.16) are used only to conclude that J_p be positive. Identity (2.20) should be seen as giving us the definition of what a passive current should be.

We now prove Theorem 3.1. An interesting point about the calculation to follow is how dissipation through transmembrane water flow comes from two different sources, equations for ionic concentration dynamics and the fluid equations. The former contributes the osmotic term π_w term, and the latter contributes the mechanical term p , which together add up to the water potential ψ_w .

Proof of Theorem 2.1. First, multiply (2.4) with μ_k in (3.1) and integrate over Ω_i and sum in k :

$$\sum_{k=1}^N \int_{\Omega_i} \mu_k \left(\frac{\partial c_k}{\partial t} + \nabla \cdot (\mathbf{u} c_k) \right) d\mathbf{x} = \sum_{k=1}^N \int_{\Omega_i} \mu_k \nabla \cdot \left(c_k \frac{D_k}{k_B T} \nabla \mu_k \right) d\mathbf{x}. \quad (2.22)$$

The summand in the right hand side becomes:

$$\begin{aligned} \int_{\Omega_i} \mu_k \nabla \cdot \left(c_k \frac{D_k}{k_B T} \nabla \mu_k \right) d\mathbf{x} &= \int_{\Gamma_i} \left(\mu_k c_k \frac{D_k}{k_B T} \nabla \mu_k \cdot \mathbf{n} \right) dm_{\Gamma} \\ &\quad - \int_{\Omega_i} \left(c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 \right) d\mathbf{x} \end{aligned} \quad (2.23)$$

where \mathbf{n} is the outward normal on Γ . Consider the left hand side of (2.22).

$$\sum_{k=1}^N \mu_k \left(\frac{\partial c_k}{\partial t} + \nabla \cdot (\mathbf{u} c_k) \right) = \sum_{k=1}^N \frac{\partial \omega}{\partial c_k} \left(\frac{\partial c_k}{\partial t} + \mathbf{u} \cdot \nabla c_k \right) = \frac{\partial \omega}{\partial t} + \nabla \cdot (\mathbf{u} \omega), \quad (2.24)$$

where we used (2.2) and the incompressibility condition in (2.8). Integrating the above over Ω_i , we have:

$$\begin{aligned} \int_{\Omega_i} \left(\frac{\partial \omega}{\partial t} + \nabla \cdot (\mathbf{u} \omega) \right) d\mathbf{x} &= \int_{\Omega_i} \frac{\partial \omega}{\partial t} d\mathbf{x} + \int_{\Gamma_i} \omega \mathbf{u} \cdot \mathbf{n} dm_\Gamma \\ &= \frac{d}{dt} \int_{\Omega_i} \omega d\mathbf{x} + \int_{\Gamma_i} \omega \left(\mathbf{u} - \frac{\partial \mathbf{X}}{\partial t} \right) \cdot \mathbf{n} dm_\Gamma \end{aligned} \quad (2.25)$$

where we used the fact that \mathbf{u} is divergence free in the first equality. The term involving $\frac{\partial \mathbf{X}}{\partial t}$ comes from the fact that the membrane Γ is moving in time. Performing similar calculations on Ω_e , and adding this to the above, we find:

$$\begin{aligned} &\frac{d}{dt} \int_{\Omega_i \cup \Omega_e} \omega d\mathbf{x} + \int_{\Gamma} [\omega] j_w dm_\Gamma \\ &= \sum_{k=1}^N \int_{\Gamma} \left[\mu_k c_k \frac{D_k}{k_B T} \nabla \mu_k \cdot \mathbf{n} \right] dm_\Gamma - \sum_{k=1}^N \int_{\Omega_i \cup \Omega_e} \left(c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 \right) d\mathbf{x}. \end{aligned} \quad (2.26)$$

where we used (2.14). Using (2.5) and (2.14), we may rewrite the second boundary integral as follows:

$$\int_{\Gamma} \left[\mu_k c_k \frac{D_k}{k_B T} \nabla \mu_k \cdot \mathbf{n} \right] dm_\Gamma = \int_{\Gamma} ([\mu_k c_k] j_w - [\mu_k] (j_k + a_k)) dm_\Gamma. \quad (2.27)$$

We now turn to equation (2.8). Multiply this by \mathbf{u} and integrate over Ω_i :

$$\int_{\Omega_i} \mathbf{u} \cdot (\nu \Delta \mathbf{u} - \nabla p) d\mathbf{x} = \int_{\Gamma_i} (\Sigma_m(\mathbf{u}, p) \mathbf{n}) \cdot \mathbf{u} dm_\Gamma - \int_{\Omega_i} \nu |\nabla \mathbf{u}|^2 d\mathbf{x} = 0 \quad (2.28)$$

Performing a similar calculation on Ω_e and adding this to the above, we have:

$$\int_{\Gamma} [(\Sigma_m(\mathbf{u}, p) \mathbf{n})] \cdot \mathbf{u} dm_\Gamma - \int_{\Omega_i \cup \Omega_e} \nu |\nabla \mathbf{u}|^2 d\mathbf{x} = 0 \quad (2.29)$$

We may use (2.10), (2.13) and (2.14) to find

$$\frac{d}{dt} E_{\text{elas}}(\mathbf{X}) = \int_{\Gamma} [(\Sigma_m(\mathbf{u}, p) \mathbf{n}) \cdot \mathbf{n}] j_w dm_\Gamma - \int_{\Omega_i \cup \Omega_e} \nu |\nabla \mathbf{u}|^2 d\mathbf{x} \quad (2.30)$$

Combining (2.26), (2.27) and (2.30), we have:

$$\begin{aligned}
& \frac{d}{dt} \left(\int_{\Omega_i \cup \Omega_e} \omega d\mathbf{x} + E_{\text{elas}}(\mathbf{X}) \right) \\
&= - \sum_{k=1}^N \int_{\Omega_i \cup \Omega_e} \left(c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 \right) d\mathbf{x} - \int_{\Omega_i \cup \Omega_e} \nu |\nabla \mathbf{u}|^2 d\mathbf{x} \\
& \quad - \int_{\Gamma} [\mu_k] (j_k + a_k) dm_{\Gamma} - \int_{\Gamma} [\omega - c_k \sigma_k - (\Sigma_m(\mathbf{u}, p) \mathbf{n}) \cdot \mathbf{n}] j_w dm_{\Gamma}
\end{aligned} \tag{2.31}$$

Recalling the definition of $\widehat{\psi}_w$ in (2.15), we obtain the desired equality. In the absence of active currents a_k , is decreasing given that j_k and j_w satisfy conditions (2.6) and (2.16) respectively. \square

In the last line of the above proof, note that the expression for $\widehat{\psi}_w$ arises naturally as a result of integrating by parts. In this sense, we may say that osmotic water flow arises as a natural consequence of requiring that the free energy be decreasing in time.

2.3. Cross Coefficients and Solvent Drag

As can be seen from (2.20) or (3.15) the only condition we need to impose for the free energy to decrease with time in the absence of active currents is the following:

$$[\widehat{\psi}_w] j_w + \sum_{k=1}^N [\mu_k] j_k \geq 0. \tag{2.32}$$

This condition is weaker than conditions (2.6) and (2.16) being satisfied separately by j_k and j_w . We now discuss an important case in which j_k and j_w may not individually satisfy (2.6) and (2.16) but (2.32) is satisfied nevertheless. This arises whenever fluxes are coupled as is usually the case for fluxes through transporters or (single filing) channels [28, 12, 29, 2, 3]. We note that such cross-diffusion can be relevant even in bulk solution [30, 31, 32, 33, 34].

If $[\mu_k]$ and $[\widehat{\psi}_w]$ remain small, the dissipation J_p in (2.20) may be approximated by a quadratic form in the jumps:

$$\begin{aligned}
J_p &= \int_{\Gamma} [\boldsymbol{\mu}] \cdot \mathbf{j} dm_{\Gamma} = \int_{\Gamma} [\boldsymbol{\mu}] \cdot (\mathcal{L} [\boldsymbol{\mu}]) dm_{\Gamma}, \\
\boldsymbol{\mu} &= (\mu_1, \dots, \mu_N, \widehat{\psi}_w)^T, \mathbf{j} = (j_1, \dots, j_N, j_w)^T,
\end{aligned} \tag{2.33}$$

where \mathcal{L} is a symmetric $(N+1) \times (N+1)$ matrix. Requiring that the free energy be decreasing implies that \mathcal{L} must be positive definite. The *maximum dissipation principle* requires that \mathbf{j} be given as variational derivatives of $J_p/2$ with respect to $[\boldsymbol{\mu}]$:

$$\mathbf{j} = \mathcal{L} [\boldsymbol{\mu}]. \tag{2.34}$$

Note that, without the maximum dissipation principle, (2.33) only implies $\mathbf{j} = (\mathcal{L} + \tilde{\mathcal{L}}) [\boldsymbol{\mu}]$ where $\tilde{\mathcal{L}}$ is an arbitrary skew symmetric matrix. The symmetry of the coefficient matrix \mathcal{L} relating $[\boldsymbol{\mu}]$ and \mathbf{j} is an instance of the Onsager reciprocity relation [27, 21, 23].

A lipid bilayer membrane is impermeable to many solutes, but only approximately so. In this case, a water flux may induce a solute flux, and this may be expressed as $\mathcal{L}_{kw} \neq 0$ where \mathcal{L}_{kw} is the $(k, N + 1)$ entry of the matrix \mathcal{L} . This is known as solvent drag. Given the presence of such cross coefficients, (2.6) and (2.16) are not necessary true, whereas condition (2.32) is true by construction.

3. Electrodiffusion of Ions and Osmotic Water Flow

3.1. Model Formulation

Let us now consider the case in which the chemical species are electrically charged. As in the previous section, we let $c_k, k = 1, \dots, N$ be the concentrations of the ionic species. Given ω , the entropic part of the free energy per unit volume, the chemical potential μ_k of the k -th species of ion is given as:

$$\mu_k = \frac{\partial \omega}{\partial c_k} + qz_k \phi = \sigma_k + qz_k \phi. \quad (3.1)$$

The chemical potential is thus a sum of the entropic term σ_k and the electrostatic term. In the electrostatic term, q is the elementary charge, z_k is the valence of the k -th species of ion, and ϕ is the electrostatic potential. The definition of the water potential, ψ_w and $\widehat{\psi}_w$, remain the same. The ionic concentrations c_k satisfy (2.4) and (2.5) except that we now use (3.1) as our expression for the chemical potential. Ions are thus subject to drift by the electric field in addition to diffusion and advection by the local flow field.

If the electrolyte solution is sufficiently dilute, the chemical potential μ_k is given by (3.1) with ω equal to (2.1). However, deviations from ideality can be significant in electrolyte solutions, especially in higher concentrations [35, 36, 37, 38, 39]. Cross-diffusion (or flux coupling) in the bulk can also be significant in electrolyte solutions [30, 31, 32, 33, 34]. These effects are clearly important in describing the *molecular* physiology of ion channel pores and enzyme active sites at which ionic concentrations can reach tens of molar [39, 40]. The question of whether these effects are significant in formulating phenomenological models in *cellular* physiology, where the typical ionic concentrations are two orders of magnitude lower, is largely unexplored. This exploration is beyond the scope of the present paper, but we point out that our formalism allows the incorporation of such effects [41].

The transmembrane flux j_k is now a function of the membrane potential $[\phi]$ in addition to the dependencies discussed in the previous section. We require that j_k satisfy condition (2.6).

The electrostatic potential ϕ satisfies the Poisson equation:

$$-\nabla \cdot (\epsilon \nabla \phi) = \sum_{k=1}^N qz_k c_k \quad (3.2)$$

where ϵ is the dielectric constant. We shall assume that ϵ is constant in space and time. This restriction may be lifted, at the expense of introducing a relation that describes the evolution of ϵ . We also assume that there is no fixed background charge. It is easy to generalize the calculations below to the case when the immobile charges, if present, always stay away from the moving membrane. Otherwise, one would need to introduce ‘‘collision rules’’ to determine what happens when the membrane hits the immobile charges. We impose Neumann boundary conditions for (3.2) on the outer boundary Γ_{out} for simplicity. On the membrane Γ , we impose the following boundary condition:

$$-\epsilon \frac{\partial \phi}{\partial \mathbf{n}} \Big|_{\Gamma_i} = -\epsilon \frac{\partial \phi}{\partial \mathbf{n}} \Big|_{\Gamma_e} = C_m[\phi]. \quad (3.3)$$

where C_m is the capacitance per unit area of membrane. The above is simply a statement about the continuity of the electric flux density. Since the membrane is moving, the capacitance C_m is itself an evolving quantity. We assume the following family of constitutive laws for C_m . At $\mathbf{x} = \mathbf{X}(\boldsymbol{\theta}, t)$,

$$C_m(\mathbf{x}) = C_m(Q(\mathbf{X})) \quad (3.4)$$

where $Q(\mathbf{X})$ is the Jacobian or metric determinant of the configuration Γ_t at time t with respect to the reference configuration Γ_{ref} . This factor describes the extent to which the membrane is stretched from the rest configuration. A simple example of (3.4) would be:

$$C_m(\mathbf{x}) = C_m^0 = \text{const.} \quad (3.5)$$

As another example, we may set:

$$C_m(\mathbf{x}) = C_m^0 Q(\mathbf{X}) \quad (3.6)$$

where $C_m^0 = \text{const}$ is the capacitance per unit area measured in the reference configuration. Relation (3.6) is the natural scaling if we assume that the membrane is made of an incompressible material. For suppose the membrane is made of a material whose dielectric constant is ϵ_m . If the thickness of the membrane at the point $\mathbf{x} = \mathbf{X}(\boldsymbol{\theta}, t)$ is $d(\mathbf{x})$, the membrane capacitance there is given by $\epsilon_m/d(\mathbf{x})$. The incompressibility of the material implies that the local membrane volume remains constant in time: $d(\mathbf{x})Q(\mathbf{X}) = \text{const}$. Thus, $C_m(\mathbf{x})$ must be proportional to $Q(\mathbf{X})$.

Force balance must be modified to take into account electrostatic forces. The flow field \mathbf{u} satisfies the Stokes equation in Ω_i or Ω_e with an electrostatic force

term:

$$\nu \Delta \mathbf{u} - \nabla p - \left(\sum_{k=1}^N qz_k c_k \right) \nabla \phi = 0, \quad \nabla \cdot \mathbf{u} = 0 \quad (3.7)$$

Note that the above equations can also be written as follows:

$$\begin{aligned} \nabla \cdot (\Sigma_m(\mathbf{u}, p) + \Sigma_e(\phi)) &= 0, \quad \nabla \cdot \mathbf{u} = 0, \\ \Sigma_m(\mathbf{u}, p) &= \nu(\nabla u + (\nabla u)^T) - pI, \\ \Sigma_e(\phi) &= \epsilon \left(\nabla \phi \otimes \nabla \phi - \frac{1}{2} |\nabla \phi|^2 I \right). \end{aligned} \quad (3.8)$$

Here, Σ_e is the Maxwell stress tensor generated by the electric field. Note that we have used (3.2) to rewrite the electrostatic force in (3.7) in terms of Σ_e .

We now turn to boundary conditions. We continue to let $\mathbf{u} = 0$ on the outer boundary Γ_{out} . On the cell membrane Γ , we have the following conditions. First, by force balance, we have:

$$[(\Sigma_m(\mathbf{u}, p) + \Sigma_e(\phi))\mathbf{n}] = \mathbf{F}_{\text{elas}} + \mathbf{F}_{\text{cap}} \quad (3.9)$$

In addition to \mathbf{F}_{elas} , we have an additional term \mathbf{F}_{cap} which arises because the membrane carries capacitive energy. We shall call this the capacitive force, which is given as:

$$\mathbf{F}_{\text{cap}} = \tau_{\text{cap}} \kappa_{\Gamma} \mathbf{n} - \nabla_{\Gamma} \tau_{\text{cap}}, \quad \tau_{\text{cap}} = \frac{1}{2} \left(C_m + Q \frac{\partial C_m}{\partial Q} \right) [\phi]^2 \quad (3.10)$$

where κ_{Γ} is the sum of the principal curvatures of the membrane Γ and $\nabla_{\Gamma} = \nabla - \mathbf{n}(\mathbf{n} \cdot \nabla)$ is the surface gradient on Γ . The above expression shows that the capacitive force can be seen as a surface tension of strength $-\tau_{\text{cap}}$. The above capacitive force is chosen so that Theorem 3.1 holds, and in this sense, the proof of Theorem 3.1 provides a variational interpretation of this force. In Appendix A.1, we give a physical interpretation of expression (3.10).

An interesting variant of (3.9) is the following. Suppose the membrane is incompressible in the sense that $Q \equiv 1$ for all time. We note that this condition of two-dimensional incompressibility is *not* the same as assuming that the membrane is made of a (three-dimensional) incompressible material. In the case of three-dimensional incompressibility, the membrane may stretch, but this would lead to a thinning of the membrane, leading to the constitutive law (3.6) as we saw earlier. When $Q \equiv 1$ for all time, we let:

$$[(\Sigma_m(\mathbf{u}, p) + \Sigma_e(\phi))\mathbf{n}] = \mathbf{F}_{\text{elas}} + \mathbf{F}_{\text{p}} \quad (3.11)$$

where \mathbf{F}_{p} is given as:

$$\mathbf{F}_{\text{p}} = \lambda \kappa_{\Gamma} \mathbf{n} - \nabla_{\Gamma} \lambda. \quad (3.12)$$

The above is a surface pressure and λ is determined so that $Q \equiv 1$. Note that in (3.11) we do not need a capacitive force since it can be absorbed into the

surface pressure term.

The continuity condition (2.14) remains the same. We continue to require that the passive flux j_k satisfy (2.6). An important difference, however, is that j_k now depends strongly on the membrane potential $[\phi]$, given that μ_k depends on ϕ . Ions usually flow through ionic channels, which often have open and closed states. The passive flux j_k may also depend on such states, which are described by gating variables. This flux is the subject of the large experimental and theoretical work on ion channels [12]. For the present work, it is appropriate to use the classical phenomenological treatments of flux, although their molecular underpinnings are not clear [42, 43, 44]. Some of popular choices j_k include [14, 12, 45]:

$$j_k^{\text{HH}} = g_k[\mu_k] = g_k \left(z_k[\phi] + \ln \left(\frac{c_k|_{\Gamma_i}}{c_k|_{\Gamma_e}} \right) \right), \quad (3.13)$$

$$j_k^{\text{GHK}} = P_k z_k \phi' \left(\frac{c_k|_{\Gamma_i} \exp(z_k \phi') - c_k|_{\Gamma_e}}{\exp(z_k \phi') - 1} \right), \quad \phi' = \frac{q[\phi]}{k_B T}, \quad (3.14)$$

where g_k and P_k are positive and depend on the gating variables in certain modeling contexts. It is easily seen that both j_k^{HH} and j_k^{GHK} satisfy (2.6). We shall use expression (3.14) in our numerical computations in Section 5.

We remark that the model we just proposed is nothing other than the Poisson-Nernst-Planck-Stokes system if we let $\omega = \omega_0$ given in (2.1) [46]. The novelty here is in the interface conditions at the membrane, (2.5), (3.3), (3.9) and (2.14). The Poisson Nernst-Planck system has received much attention in the field of semiconductors [47, 48, 49], ionic channels [50], ion exchange membranes and desalination [46] as well as physical chemistry [51].

3.2. Free Energy Identity

We now show that the system described in the previous section possesses a natural free energy.

Theorem 3.1. *Suppose c_k, \mathbf{u}, p and ϕ are smooth functions that satisfy (2.4), (3.7), and (3.2) in Ω_i and Ω_e and satisfy boundary conditions (2.5), (3.9), (2.14) and (3.3) on the membrane Γ . Suppose further that c_k and ϕ satisfy no-flux boundary conditions and $\mathbf{u} = 0$ on the outer boundary Γ_{out} . Then, c_k, \mathbf{u}, p and ϕ satisfy the following free energy identity.*

$$\begin{aligned} \frac{d}{dt}(G_S + E_{elas} + E_{elec}) &= -I_p - J_p - J_a \\ E_{elec} &= \int_{\Omega_e \cup \Omega_e} \frac{1}{2} \epsilon |\nabla \phi|^2 d\mathbf{x} + \int_{\Gamma} \frac{1}{2} C_m [\phi]^2 dm_{\Gamma} \end{aligned} \quad (3.15)$$

Here, $G_S, E_{elas}, I_p, J_p, I_a$ are the same as in (2.20). The same identity holds if we require $Q \equiv 1$ and adopt (3.11) instead of (3.9).

If $a_k \equiv 0$, the free energy is monotone decreasing.

In addition to the terms present in (3.15), we now have an electrostatic term in the energy.

Before proving Theorem 3.1, we collect some calculus results. We first introduce some notation. Take a point $\mathbf{x} = \mathbf{x}_0 \in \Gamma$ at $t = t_0$. Let $\mathbf{X}^{\mathbf{n}}(t; \mathbf{x}_0, t_0)$ be the space-time curve that goes through $\mathbf{x} = \mathbf{x}_0$ at time $t = t_0$ and is orthogonal to Γ at each time instant. Equivalently, $\mathbf{X}^{\mathbf{n}}(t; \mathbf{x}_0, t_0)$ is the solution to the following ordinary differential equation:

$$\frac{d}{dt} \mathbf{X}^{\mathbf{n}}(t; \mathbf{x}_0, t_0) = v_{\Gamma}(\mathbf{X}^{\mathbf{n}}, t) \mathbf{n}(\mathbf{X}^{\mathbf{n}}, t), \quad \mathbf{X}^{\mathbf{n}}(t_0; \mathbf{x}_0, t_0) = \mathbf{x}_0. \quad (3.16)$$

Here, $\mathbf{n}(\mathbf{x}, t)$ is the unit normal at the point \mathbf{x} at time t pointing from Ω_i into Ω_e , and $v_{\Gamma}(\mathbf{x}, t) \mathbf{n}(\mathbf{x}, t)$ is the normal velocity of Γ at that point. Consider a quantity $w(\mathbf{x}, t)$ defined on the evolving surface Γ . Define:

$$(D_t^{\mathbf{n}} w)(\mathbf{x}_0, t_0) = \left. \frac{d}{dt} w(\mathbf{X}^{\mathbf{n}}(t; \mathbf{x}_0, t_0), t) \right|_{\mathbf{x}=\mathbf{x}_0, t=t_0}. \quad (3.17)$$

The above expression is an analogue of the convective derivative on the surface Γ . We shall make use of the following well-known identity:

$$\frac{d}{dt} \int_{\Gamma} w dm_{\Gamma} = \int_{\Gamma} (D_t^{\mathbf{n}} w + \kappa_{\Gamma} w v_{\Gamma}) dm_{\Gamma} \quad (3.18)$$

where κ_{Γ} is the sum of the principal curvatures of Γ . We now state two calculus identities that we shall find useful in the proof of Theorem 3.1.

Lemma 3.2. *Let $w(\mathbf{x}, t)$ be a smooth function on Γ_t . We have:*

$$\int_{\Gamma} \left(w Q^{-1} \frac{\partial Q}{\partial t} \right) dm_{\Gamma} = \int_{\Gamma} (\kappa_{\Gamma} w \mathbf{n} - (\nabla_{\Gamma} w)) \cdot \frac{\partial \mathbf{X}}{\partial t} dm_{\Gamma}. \quad (3.19)$$

where Q is the Jacobian determinant of Γ_t with respect to the reference configuration Γ_{ref} .

Proof. Note that

$$\frac{\partial w}{\partial t} = D_t^{\mathbf{n}} w + (\nabla_{\Gamma} w) \cdot \frac{\partial \mathbf{X}}{\partial t} \quad (3.20)$$

where the partial derivatives in t is along material trajectories (constant $\boldsymbol{\theta}$). The validity of the above identity should be clear by considering the geometric relation between the orthogonal trajectory $\mathbf{X}^{\mathbf{n}}$ and the material trajectory \mathbf{X} . We also have the following relation for the time derivative of the integral of w over Γ .

$$\begin{aligned} \frac{d}{dt} \int_{\Gamma} w dm_{\Gamma} &= \frac{d}{dt} \int_{\Gamma_{ref}} w Q dm_{\Gamma_{ref}} = \int_{\Gamma_{ref}} \left(\frac{\partial w}{\partial t} Q + w \frac{\partial Q}{\partial t} \right) dm_{\Gamma_{ref}} \\ &= \int_{\Gamma} \left(\frac{\partial w}{\partial t} + w Q^{-1} \frac{\partial Q}{\partial t} \right) dm_{\Gamma} \end{aligned} \quad (3.21)$$

Comparing this with (3.18) (with $v_\Gamma = \frac{\partial \mathbf{x}}{\partial t} \cdot \mathbf{n}$) and using the identity (3.20), we obtain the desired result. \square

Lemma 3.3. *Suppose $w(\mathbf{x}, t), \mathbf{x} \in (\Omega_i \cup \Gamma)$ is a smooth function defined in Ω_i whose derivatives are continuous up to the boundary Γ . Then, we have the following identity:*

$$\begin{aligned} & \int_{\Gamma_i} \left(w \frac{\partial}{\partial \mathbf{n}} \left(\frac{\partial w}{\partial t} \right) + (w \Delta w) v_\Gamma \right) dm_\Gamma \\ &= \int_{\Gamma_i} \left(w D_t^\mathbf{n} \left(\frac{\partial w}{\partial \mathbf{n}} \right) + \left(\kappa_\Gamma w \frac{\partial w}{\partial \mathbf{n}} - |\nabla_\Gamma w|^2 \right) v_\Gamma \right) dm_\Gamma \end{aligned} \quad (3.22)$$

where \int_{Γ_i} denotes integration over the Ω_i face of Γ . A similar identity holds for functions defined in $\Omega_e \cup \Gamma$.

As we shall see, we only need w to be defined in the vicinity of Γ for the above to be true.

Proof. We only treat the Γ_i case. The proof for Γ_e is exactly the same. We decompose the integrand in the left hand side of (3.22) into tangential and normal contributions. It is well-known that the Laplacian can be written as:

$$\Delta w = \frac{\partial^2 w}{\partial \mathbf{n}^2} + \kappa_\Gamma \frac{\partial w}{\partial \mathbf{n}} + \Delta_\Gamma w \quad (3.23)$$

where Δ_Γ is the Laplace-Beltrami operator of the surface Γ .

We now rewrite $\frac{\partial}{\partial t} \left(\frac{\partial w}{\partial \mathbf{n}} \right)$ in (3.22) in an analogous fashion. For this, we first introduce the signed distance function $\psi(\mathbf{x}, t)$ in a neighborhood of Γ :

$$\psi(\mathbf{x}, t) = \begin{cases} \text{dist}(\mathbf{x}, \Gamma_t) & \text{if } \mathbf{x} \in \Omega_e, \\ 0 & \text{if } \mathbf{x} \in \Gamma_t, \\ -\text{dist}(\mathbf{x}, \Gamma_t) & \text{if } \mathbf{x} \in \Omega_i, \end{cases} \quad (3.24)$$

where $\text{dist}(\mathbf{x}, \Gamma_t)$ is the distance between \mathbf{x} and Γ_t . Clearly, $\nabla \psi$ evaluated at any point on Γ gives the outward unit normal vector \mathbf{n} . Introduce the following vector field \mathbf{v} defined in a neighborhood of Γ where ψ is smooth:

$$\mathbf{v} = v_\Gamma \mathbf{n} \text{ on } \Gamma, \quad (\nabla \mathbf{v}) \nabla \psi = 0. \quad (3.25)$$

The second condition above just says that \mathbf{v} is constant along lines perpendicular to the level sets. It is well known that the signed distance function satisfies the following transport equation in a neighborhood of Γ :

$$D_v \psi \equiv \frac{\partial \psi}{\partial t} + \mathbf{v} \cdot \nabla \psi = 0. \quad (3.26)$$

Note that the above convective derivative evaluated on Γ is equal to $D_t^\mathbf{n}$ defined in (3.17).

For any point on Γ :

$$\frac{\partial}{\partial \mathbf{n}} \left(\frac{\partial w}{\partial t} \right) = \nabla \psi \cdot \nabla w_t \quad (3.27)$$

where the subscript t indicates the partial derivative with respect to t . We now rewrite this expression as follows:

$$\begin{aligned} \nabla \psi \cdot \nabla w_t &= D_v(\nabla \psi \cdot \nabla w) - \nabla \psi_t \cdot \nabla w - \mathbf{v} \cdot \nabla(\nabla \psi \cdot \nabla w) \\ &= D_v(\nabla \psi \cdot \nabla w) + \nabla(\mathbf{v} \cdot \nabla \psi) \cdot \nabla w - \mathbf{v} \cdot \nabla(\nabla \psi \cdot \nabla w) \end{aligned} \quad (3.28)$$

where we used (3.26) in the last equality. Now, consider the second term in the last line:

$$\begin{aligned} \nabla(\mathbf{v} \cdot \nabla \psi) \cdot \nabla w &= \nabla_\Gamma(\mathbf{v} \cdot \nabla \psi) \cdot \nabla_\Gamma w + (\nabla \psi \cdot \nabla(\mathbf{v} \cdot \nabla \psi))(\nabla \psi \cdot \nabla w) \\ &= \nabla_\Gamma(\mathbf{v} \cdot \nabla \psi) \cdot \nabla_\Gamma w + (\nabla \psi \cdot ((\nabla \mathbf{v}) \nabla \psi))(\nabla \psi \cdot \nabla w) \\ &\quad + (\mathbf{v} \cdot ((\nabla^2 \psi) \nabla \psi))(\nabla \psi \cdot \nabla w) \end{aligned} \quad (3.29)$$

where ∇_Γ is the surface gradient on Γ . Note that $\nabla^2 \psi$ is *not* the Laplacian but the matrix of second derivatives of ψ . The second to last term in (3.29) is 0 by (3.25). The last term is also 0, since:

$$(\nabla^2 \psi) \nabla \psi = \frac{1}{2} \nabla(|\nabla \psi|^2) = 0 \quad (3.30)$$

where we used $|\nabla \psi|^2 = 1$. Thus (3.29) reduces to

$$\nabla(\mathbf{v} \cdot \nabla \psi) \cdot \nabla w = \nabla_\Gamma(\mathbf{v} \cdot \nabla \psi) \cdot \nabla_\Gamma w. \quad (3.31)$$

Let us look at the final term in (3.28).

$$\mathbf{v} \cdot \nabla(\nabla \psi \cdot \nabla w) = (\mathbf{v} \cdot \nabla \psi)(\nabla \psi \cdot (\nabla \psi \cdot \nabla w)) = (\mathbf{v} \cdot \nabla \psi)(\nabla \psi \cdot ((\nabla^2 w) \nabla \psi)) \quad (3.32)$$

where we used (3.30) in the last equality. Combining (3.31), (3.32) and (3.28), we have:

$$\nabla \psi \cdot \nabla w_t = D_v(\nabla \psi \cdot \nabla w) + \nabla_\Gamma(\mathbf{v} \cdot \nabla \psi) \cdot \nabla_\Gamma w - (\mathbf{v} \cdot \nabla \psi)(\nabla \psi \cdot ((\nabla^2 w) \nabla \psi)) \quad (3.33)$$

or equivalently:

$$\frac{\partial}{\partial \mathbf{n}} \left(\frac{\partial w}{\partial t} \right) = D_t^{\mathbf{n}} \left(\frac{\partial w}{\partial \mathbf{n}} \right) + \nabla_\Gamma v_\Gamma \cdot \nabla_\Gamma w - v_\Gamma \left(\frac{\partial^2 w}{\partial \mathbf{n}^2} \right) \quad (3.34)$$

where we used (3.25), $\mathbf{n} = \nabla \psi$ on Γ and the equality of $D_t^{\mathbf{n}}$ and D_v on Γ .

Now, consider the integral:

$$\begin{aligned}
& \int_{\Gamma_i} \left(w \frac{\partial}{\partial \mathbf{n}} \left(\frac{\partial w}{\partial t} \right) + (w \Delta w) v_\Gamma \right) dm_\Gamma \\
&= \int_{\Gamma_i} \left(w D_t^n \left(\frac{\partial w}{\partial \mathbf{n}} \right) + w \nabla_\Gamma v_\Gamma \cdot \nabla_\Gamma w + w \left(\Delta_\Gamma w + \kappa_\Gamma \frac{\partial w}{\partial \mathbf{n}} \right) v_\Gamma \right) dm_\Gamma \quad (3.35) \\
&= \int_{\Gamma_i} \left(w D_t^n \left(\frac{\partial w}{\partial \mathbf{n}} \right) + \left(\kappa_\Gamma w \frac{\partial w}{\partial \mathbf{n}} - |\nabla_\Gamma w|^2 \right) v_\Gamma \right) dm_\Gamma
\end{aligned}$$

where we used (3.23) and (3.34) in the first equality and integrated by parts along Γ in the second equality. Note that there are no boundary terms since Γ is a closed compact surface. This proves (3.22). \square

We are now ready to prove Theorem 3.1.

Proof of Theorem 3.1. First, multiply (2.4) with μ_k in (3.1) and integrate over Ω_i and sum in k :

$$\sum_{k=1}^N \int_{\Omega_i} \mu_k \left(\frac{\partial c_k}{\partial t} + \nabla \cdot (\mathbf{u} c_k) \right) d\mathbf{x} = \sum_{k=1}^N \int_{\Omega_i} \mu_k \nabla \cdot \left(c_k \frac{D_k}{k_B T} \nabla \mu_k \right) d\mathbf{x}. \quad (3.36)$$

The summand in the right hand side becomes:

$$\begin{aligned}
\int_{\Omega_i} \mu_k \nabla \cdot \left(c_k \frac{D_k}{k_B T} \nabla \mu_k \right) d\mathbf{x} &= \int_{\Gamma_i} \left(\mu_k c_k \frac{D_k}{k_B T} \nabla \mu_k \cdot \mathbf{n} \right) dm_\Gamma \\
&\quad - \int_{\Omega_i} \left(c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 \right) d\mathbf{x}
\end{aligned} \quad (3.37)$$

where \mathbf{n} is the outward normal on Γ . Consider the left hand side of (3.36).

$$\begin{aligned}
& \sum_{k=1}^N \mu_k \frac{\partial c_k}{\partial t} = \sum_{k=1}^N \left(\sigma_k \frac{\partial c_k}{\partial t} + q z_k \phi \frac{\partial c_k}{\partial t} \right) \\
&= \sum_{k=1}^N \frac{\partial \omega}{\partial c_k} \frac{\partial c_k}{\partial t} + \phi \frac{\partial}{\partial t} \left(\sum_{k=1}^N q z_k c_k \right) = \frac{\partial \omega}{\partial t} - \phi \frac{\partial}{\partial t} (\nabla \cdot (\epsilon \nabla \phi))
\end{aligned} \quad (3.38)$$

We used (3.1) in the first equality and (3.2) in the last equality. Integrate final expression in (3.38) over Ω_i .

$$\begin{aligned}
& \int_{\Omega_i} \left(\frac{\partial \omega}{\partial t} - \phi \nabla \cdot \left(\epsilon \nabla \left(\frac{\partial \phi}{\partial t} \right) \right) \right) d\mathbf{x} \\
&= \int_{\Gamma_i} \left(-\phi \frac{\partial}{\partial \mathbf{n}} \left(\epsilon \frac{\partial \phi}{\partial t} \right) \right) dm_\Gamma + \int_{\Omega_i} \frac{\partial}{\partial t} \left(\omega + \frac{\epsilon}{2} |\nabla \phi|^2 \right) d\mathbf{x}.
\end{aligned} \quad (3.39)$$

For the second term in the left hand side of (3.36), we have, similarly to (3.38):

$$\sum_{k=1}^N \mu_k \mathbf{u} \cdot \nabla c_k = \nabla \cdot (\mathbf{u}\omega) + \phi \cdot \nabla \left(\mathbf{u} \sum_{k=1}^N qz_k c_k \right). \quad (3.40)$$

Integrate the above expression over Ω_i :

$$\begin{aligned} & \int_{\Omega_i} \left(\nabla \cdot (\mathbf{u}\omega) + \phi \cdot \nabla \left(\mathbf{u} \sum_{k=1}^N qz_k c_k \right) \right) d\mathbf{x} \\ &= \int_{\Gamma_i} \left(\omega + \phi \sum_{k=1}^N qz_k c_k \right) \mathbf{u} \cdot \mathbf{n} dm_\Gamma - \int_{\Omega_i} \left(\sum_{k=1}^N qz_k c_k \right) \mathbf{u} \cdot \nabla \phi d\mathbf{x} \end{aligned} \quad (3.41)$$

Collecting the above calculations, we have rewritten identity (3.36) as:

$$\begin{aligned} & \int_{\Omega_i} \frac{\partial}{\partial t} \left(\omega + \frac{\epsilon}{2} |\nabla \phi|^2 \right) d\mathbf{x} + \int_{\Gamma_i} \left(-\phi \frac{\partial}{\partial \mathbf{n}} \left(\epsilon \frac{\partial \phi}{\partial t} \right) \right) dm_\Gamma \\ &= - \int_{\Gamma_i} \left(\left(\omega - \sum_{k=1}^N c_k \sigma_k \right) \mathbf{u} \cdot \mathbf{n} + \sum_{k=1}^N \mu_k \left(c_k \left(\mathbf{u} - \frac{D_k}{k_B T} \nabla \mu_k \right) \cdot \mathbf{n} \right) \right) dm_\Gamma \\ &+ \int_{\Omega_i} \left(- \sum_{k=1}^N c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 + \left(\sum_{k=1}^N qz_k c_k \right) \mathbf{u} \cdot \nabla \phi \right) d\mathbf{x} \end{aligned} \quad (3.42)$$

where we used $qz_k \phi = \mu_k - \sigma_k$ (Eq. (3.1)) in the boundary integral after the equality. Performing a similar calculation on Ω_e , and adding this to the above, we find:

$$\begin{aligned} & \frac{d}{dt} \int_{\Omega_i \cup \Omega_e} \left(\omega + \frac{\epsilon}{2} |\nabla \phi|^2 \right) d\mathbf{x} - \int_{\Gamma} \left[\phi \frac{\partial}{\partial \mathbf{n}} \left(\epsilon \frac{\partial \phi}{\partial t} \right) \right] dm_\Gamma \\ & - \int_{\Gamma} \left(\left[\omega + \frac{\epsilon}{2} |\nabla \phi|^2 \right] \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} \right) dm_\Gamma \\ &= - \int_{\Gamma} \left([\pi_w] \mathbf{u} \cdot \mathbf{n} + \sum_{k=1}^N \left([\mu_k] (j_k + a_k) + [c_k \mu_k] \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} \right) \right) dm_\Gamma \\ &+ \int_{\Omega_i} \left(- \sum_{k=1}^N c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 + \left(\sum_{k=1}^N qz_k c_k \right) \mathbf{u} \cdot \nabla \phi \right) d\mathbf{x} \end{aligned} \quad (3.43)$$

where we used (2.3) and (2.5) to rewrite the boundary integral after the equality. Note that the second boundary integral before the equality comes from the fact

that the boundary Γ is moving. Rearranging terms and using (2.14), we have:

$$\begin{aligned}
& \frac{d}{dt} \int_{\Omega_i \cup \Omega_e} \left(\omega + \frac{\epsilon}{2} |\nabla \phi|^2 \right) d\mathbf{x} \\
&= \int_{\Gamma} \left(\left[\phi \frac{\partial}{\partial \mathbf{n}} \left(\epsilon \frac{\partial \phi}{\partial t} \right) \right] + \left[\frac{\epsilon}{2} |\nabla \phi|^2 + \phi \nabla \cdot (\epsilon \nabla \phi) \right] \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} \right) dm_{\Gamma} \\
&- \int_{\Gamma} \left([\pi_w] j_w + \sum_{k=1}^N [\mu_k] (j_k + a_k) \right) dm_{\Gamma} \\
&+ \int_{\Omega_i \cup \Omega_e} \left(- \sum_{k=1}^N c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 + \left(\sum_{k=1}^N q z_k c_k \right) \mathbf{u} \cdot \nabla \phi \right) d\mathbf{x}.
\end{aligned} \tag{3.44}$$

We used $\mu_k - \sigma_k = q z_k \phi$ and used (3.2) to rewrite the first boundary integral after the equality. Note that:

$$\begin{aligned}
& \int_{\Gamma} \left[\phi \frac{\partial}{\partial \mathbf{n}} \left(\epsilon \frac{\partial \phi}{\partial t} \right) + \phi \nabla \cdot (\epsilon \nabla \phi) \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} \right] dm_{\Gamma} \\
&= \int_{\Gamma} \left[\phi D_t^{\mathbf{n}} \left(\epsilon \frac{\partial \phi}{\partial \mathbf{n}} \right) + \left(\kappa_{\Gamma} \phi \epsilon \frac{\partial \phi}{\partial \mathbf{n}} - \epsilon |\nabla_{\Gamma} \phi|^2 \right) \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} \right] dm_{\Gamma}
\end{aligned} \tag{3.45}$$

where we used Lemma 3.3 with $w = \phi$ and $v_{\Gamma} = \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n}$ in (3.22). Using this and the definition of ∇_{Γ} , we may rewrite the first boundary integral in (3.44) as:

$$\begin{aligned}
& \int_{\Gamma} \left(\left[\phi \frac{\partial}{\partial \mathbf{n}} \left(\epsilon \frac{\partial \phi}{\partial t} \right) \right] + \left[\frac{\epsilon}{2} |\nabla \phi|^2 + \phi \nabla \cdot (\epsilon \nabla \phi) \right] \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} \right) dm_{\Gamma} \\
&= - \int_{\Gamma} [\phi] D_t^{\mathbf{n}} (C_m[\phi]) dm_{\Gamma} \\
&+ \int_{\Gamma} \left(-\kappa_{\Gamma} C_m[\phi]^2 + \left[\frac{\epsilon}{2} \left(\left| \frac{\partial \phi}{\partial \mathbf{n}} \right|^2 - |\nabla_{\Gamma} \phi|^2 \right) \right] \right) \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} dm_{\Gamma}
\end{aligned} \tag{3.46}$$

where we used (3.3).

We now turn to equation (3.7). Multiply this by \mathbf{u} and integrate over Ω_i :

$$\begin{aligned}
& \int_{\Omega_i} \mathbf{u} \cdot (\nu \Delta \mathbf{u} - \nabla p) d\mathbf{x} - \int_{\Omega_i} \left(\sum_{k=1}^N q z_k c_k \right) \mathbf{u} \cdot \nabla \phi d\mathbf{x} \\
&= \int_{\Gamma_i} (\Sigma(\mathbf{u}, p) \mathbf{n}) \cdot \mathbf{u} dm_{\Gamma} - \int_{\Omega_i} \nu |\nabla \mathbf{u}|^2 d\mathbf{x} \\
&- \int_{\Omega_i} \left(\sum_{k=1}^N q z_k c_k \right) \mathbf{u} \cdot \nabla \phi d\mathbf{x} = 0
\end{aligned} \tag{3.47}$$

Performing a similar calculation on Ω_e and by summation, we have:

$$\int_{\Gamma} [(\Sigma(\mathbf{u}, p)\mathbf{n}) \cdot \mathbf{u}] dm_{\Gamma} - \int_{\Omega_i \cup \Omega_e} \nu |\nabla \mathbf{u}|^2 d\mathbf{x} = \int_{\Omega_i \cup \Omega_e} \left(\sum_{k=1}^N qz_k c_k \right) \mathbf{u} \cdot \nabla \phi d\mathbf{x} \quad (3.48)$$

Let us first assume (3.9) holds. First write $\Sigma_e(\phi)\mathbf{n}$ in the following form:

$$\begin{aligned} \Sigma_e(\phi)\mathbf{n} &= \epsilon \left(\frac{\partial \phi}{\partial \mathbf{n}} \nabla \phi - \frac{1}{2} |\nabla \phi|^2 \mathbf{n} \right) \\ &= \epsilon \left(\frac{1}{2} \left(\left| \frac{\partial \phi}{\partial \mathbf{n}} \right|^2 - |\nabla_{\Gamma} \phi|^2 \right) \mathbf{n} + \frac{\partial \phi}{\partial \mathbf{n}} \nabla_{\Gamma} \phi \right) \end{aligned} \quad (3.49)$$

We may now write (3.9) as:

$$[\Sigma_m(\mathbf{u}, p)\mathbf{n}] = \mathbf{F}_{\text{elas}} + \mathbf{F}_{\text{cap}} - \left[\frac{\epsilon}{2} \left(\left| \frac{\partial \phi}{\partial \mathbf{n}} \right|^2 - |\nabla_{\Gamma} \phi|^2 \right) \right] \mathbf{n} + C_m[\phi] \nabla_{\Gamma}[\phi] \quad (3.50)$$

where we used (3.3) in the last term.

Using (3.46), (3.48) and (3.50) in (3.44) we have:

$$\begin{aligned} & \frac{d}{dt} \int_{\Omega_i \cup \Omega_e} \left(\omega + \frac{\epsilon}{2} |\nabla \phi|^2 \right) d\mathbf{x} \\ &= \int_{\Gamma} \left(-[\phi] D_t^{\mathbf{n}}(C_m[\phi]) + (-\kappa_{\Gamma} C_m[\phi]^2 \mathbf{n} + C_m[\phi] \nabla_{\Gamma}[\phi] + \mathbf{F}_{\text{cap}}) \cdot \frac{\partial \mathbf{X}}{\partial t} \right) dm_{\Gamma} \\ &+ \int_{\Gamma} \mathbf{F}_{\text{elas}} \cdot \frac{\partial \mathbf{X}}{\partial t} dm_{\Gamma} - \int_{\Gamma} \left([\widehat{\psi}_w] j_w + \sum_{k=1}^N [\mu_k] (j_k + a_k) \right) dm_{\Gamma} \\ &- \int_{\Omega_i \cup \Omega_e} \left(\sum_{k=1}^N c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 + \nu |\nabla \mathbf{u}|^2 \right) d\mathbf{x}. \end{aligned} \quad (3.51)$$

Comparing (3.51), (3.15) and using (2.13), we see that the proof of (3.15) rests on the evaluation of the first boundary integral after the equality in (3.51).

$$\begin{aligned} & \int_{\Gamma} [\phi] D_t^{\mathbf{n}}(C_m[\phi]) dm_{\Gamma} = \int_{\Gamma} \left(D_t^{\mathbf{n}} \left(\frac{1}{2} C_m[\phi]^2 \right) + \frac{1}{2} (D_t^{\mathbf{n}} C_m)[\phi]^2 \right) dm_{\Gamma} \\ &= \frac{d}{dt} \int_{\Gamma} \frac{1}{2} C_m[\phi]^2 dm_{\Gamma} - \int_{\Gamma} \left(\left(\frac{1}{2} C_m[\phi]^2 \right) \kappa_{\Gamma} \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} - \frac{1}{2} (D_t^{\mathbf{n}} C_m)[\phi]^2 \right) dm_{\Gamma} \end{aligned} \quad (3.52)$$

where we used (3.18) with $w = [\phi]$, $v_{\Gamma} = \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n}$ in the second equality. We also

have:

$$\int_{\Gamma} (C_m[\phi] \nabla_{\Gamma}[\phi]) dm_{\Gamma} = \int_{\Gamma} \left(\nabla_{\Gamma} \left(\frac{1}{2} C_m[\phi]^2 \right) - \frac{1}{2} (\nabla_{\Gamma} C_m)[\phi]^2 \right) dm_{\Gamma} \quad (3.53)$$

Using (3.52) and (3.53), we have:

$$\begin{aligned} & \int_{\Gamma} \left(-[\phi] D_t^{\mathbf{n}}(C_m[\phi]) + (-\kappa_{\Gamma} C_m[\phi]^2 \mathbf{n} + C_m[\phi] \nabla_{\Gamma}[\phi]) \cdot \frac{\partial \mathbf{X}}{\partial t} \right) dm_{\Gamma} \\ &= -\frac{d}{dt} \int_{\Gamma} \frac{1}{2} C_m[\phi]^2 dm_{\Gamma} - \int_{\Gamma} \frac{1}{2} \left(D_t^{\mathbf{n}} C_m + (\nabla_{\Gamma} C_m) \cdot \frac{\partial \mathbf{X}}{\partial t} \right) [\phi]^2 dm_{\Gamma} \quad (3.54) \\ &+ \int_{\Gamma} \left(-\left(\frac{1}{2} C_m[\phi]^2 \right) \kappa_{\Gamma} \mathbf{n} + \nabla_{\Gamma} \left(\frac{1}{2} C_m[\phi]^2 \right) \right) \cdot \frac{\partial \mathbf{X}}{\partial t} dm_{\Gamma} \end{aligned}$$

Consider the second boundary integral after the equality.

$$\begin{aligned} & \int_{\Gamma} \frac{1}{2} \left(D_t^{\mathbf{n}} C_m + (\nabla_{\Gamma} C_m) \cdot \frac{\partial \mathbf{X}}{\partial t} \right) [\phi]^2 dm_{\Gamma} \\ &= \int_{\Gamma} \left(\frac{1}{2} \frac{\partial C_m}{\partial t} [\phi]^2 \right) dm_{\Gamma} = \int_{\Gamma} \left(\frac{1}{2} \frac{\partial C_m}{\partial Q} \frac{\partial Q}{\partial t} [\phi]^2 \right) dm_{\Gamma} \quad (3.55) \\ &= \int_{\Gamma} \left(\frac{1}{2} Q \frac{\partial C_m}{\partial Q} [\phi]^2 \kappa_{\Gamma} \mathbf{n} - \nabla_{\Gamma} \left(\frac{1}{2} Q \frac{\partial C_m}{\partial Q} [\phi]^2 \right) \right) \cdot \frac{\partial \mathbf{X}}{\partial t} dm_{\Gamma} \end{aligned}$$

where we used (3.20) with $w = C_m$ in the first equality, and (3.19) with $w = \frac{1}{2} Q \frac{\partial C_m}{\partial Q} [\phi]^2$ in the last equality. From (3.55), (3.54), (3.51) and expression (3.10) of \mathbf{F}_{cap} , we obtain the desired result.

If $Q \equiv 1$ and (3.11) holds, we may argue as follows. Equation (3.51) remains valid with \mathbf{F}_{cap} replaced by \mathbf{F}_p . Verification of (3.15) rests on the evaluation of the first boundary integral in (3.51). Proceeding as in the above, we have:

$$\begin{aligned} & \int_{\Gamma} \left(-[\phi] D_t^{\mathbf{n}}(C_m[\phi]) + (-\kappa_{\Gamma} C_m[\phi]^2 \mathbf{n} + C_m[\phi] \nabla_{\Gamma}[\phi] + \mathbf{F}_p) \cdot \frac{\partial \mathbf{X}}{\partial t} \right) dm_{\Gamma} \\ &= -\frac{d}{dt} \int_{\Gamma} \frac{1}{2} C_m[\phi]^2 dm_{\Gamma} - \int_{\Gamma} \left(\frac{1}{2} \frac{\partial C_m}{\partial Q} \frac{\partial Q}{\partial t} [\phi]^2 \right) dm_{\Gamma} \\ &+ \int_{\Gamma} \left(\left(\lambda - \frac{1}{2} C_m[\phi]^2 \right) \kappa_{\Gamma} \mathbf{n} - \nabla_{\Gamma} \left(\lambda - \frac{1}{2} C_m[\phi]^2 \right) \right) \cdot \frac{\partial \mathbf{X}}{\partial t} dm_{\Gamma} \quad (3.56) \end{aligned}$$

where we used the (3.12). Since $\frac{\partial Q}{\partial t} = 0$, the second boundary integral after the equality is 0. Using (3.19) with $w = \lambda - \frac{1}{2} C_m[\phi]^2$ and $\frac{\partial Q}{\partial t} = 0$, we see that the last boundary integral is also 0.

In the absence of active currents a_k , the free energy is decreasing since j_k and j_w satisfying conditions (2.6) and (2.16) respectively. \square

4. Limiting Systems

We now discuss some limiting cases of the model we introduced in the previous section. For this purpose, we shall first make the equations dimensionless. In what follows, the primed symbols denote dimensionless variables. We introduce the following non-dimensionalization of space and time.

$$\mathbf{x} = L\mathbf{x}', \mathbf{X} = L\mathbf{X}', t = T_D t', T_D = \frac{L^2}{D_0}, D_k = D_0 D'_k, \quad (4.1)$$

where L is the characteristic length scale (for example the size of the domain Ω_i) and D_0 is the characteristic diffusion coefficients of ions. We thus measure time with respect to the diffusive time scale of ions. For concentrations and the electrostatic potential, we let:

$$c_k = c_0 c'_k, \phi = \frac{k_B T}{q} \phi'. \quad (4.2)$$

For pressure and the membrane elastic force, we let:

$$p = c_0 k_B T p', \mathbf{F}_{\text{elas}} = c_0 k_B T \mathbf{F}'_{\text{elas}}. \quad (4.3)$$

For the characteristic fluid and membrane velocity, we turn to relation (2.14). Let ζ be the characteristic hydraulic permeability of the membrane, which we may take as follows:

$$\zeta = \frac{\partial j_w}{\partial [\widehat{\psi}_w]} \Big|_{[\widehat{\psi}_w]=0}. \quad (4.4)$$

Then, $\zeta c_0 k_B T$ is the characteristic velocity generated by an osmotic gradient across the membrane. We thus let:

$$\mathbf{u} = \zeta c_0 k_B T \mathbf{u}'. \quad (4.5)$$

With the above dimensionless variables, we may rewrite our system as follows. For simplicity, we shall adopt expression (2.1) as our definition of the entropic part of the free energy ω , so that:

$$\mu'_k = z_k \phi' + \ln c'_k. \quad (4.6)$$

In Ω_i and Ω_e , we have:

$$\frac{\partial c'_k}{\partial t'} + \text{Pe} \nabla' \cdot (\mathbf{u}' c'_k) = -\nabla' \cdot \mathbf{f}'_k, \quad \mathbf{f}'_k = -D'_k (\nabla' c'_k + z_k c'_k \nabla' \phi'), \quad (4.7a)$$

$$-\nabla' \cdot (\beta^2 \nabla' \phi') = \sum_{k=1}^N z_k c'_k, \quad (4.7b)$$

$$\gamma \Delta' \mathbf{u}' = \nabla' p' + \left(\sum_{k=1}^N z_k c'_k \right) \nabla' \phi', \quad \nabla' \cdot \mathbf{u}' = 0, \quad (4.7c)$$

where ∇' , $\nabla' \cdot$ and Δ' are the gradient, divergence and Laplace operators in the \mathbf{x}' coordinate and the dimensionless constants are:

$$\text{Pe} = \frac{\zeta c_0 k_B T}{D/L}, \quad \beta = \frac{r_d}{L}, \quad r_d = \sqrt{\frac{\epsilon k_B T}{q^2 c_0}}, \quad \gamma = \frac{\nu \zeta}{L}. \quad (4.7d)$$

In the above, Pe is the Péclet number which, in this case, measures the ratio between the fluid velocity induced by osmotic gradients and the characteristic diffusive velocity. The constant β measures the ratio between r_d , the Debye length and L . The constant γ is the ratio between the viscosity of water and the hydraulic resistance of the membrane. The boundary conditions at the membrane interface Γ become:

$$\left(\left(c'_k \left(\text{Pe} \mathbf{u}' - \frac{\partial \mathbf{X}'}{\partial t'} \right) + \mathbf{f}'_k \right) \cdot \mathbf{n} \right) \Big|_{\Gamma_{i,e}} = \alpha (j'_k + a'_k), \quad (4.7e)$$

$$-(\beta \nabla' \phi' \cdot \mathbf{n}) \Big|_{\Gamma_{i,e}} = \theta C'_m [\phi'], \quad (4.7f)$$

$$\mathbf{u}' - \frac{1}{\text{Pe}} \frac{\partial \mathbf{X}'}{\partial t'} = j'_w \mathbf{n}, \quad (4.7g)$$

$$[(\Sigma'_m(\mathbf{u}', p') + \beta^2 \Sigma'_e(\phi')) \cdot \mathbf{n}] = \mathbf{F}'_{\text{elas}} + \beta \theta \mathbf{F}'_{\text{cap}}. \quad (4.7h)$$

In equation (4.7e), α is a dimensionless constant given by the ratio of the characteristic membrane permeability p_m and diffusion in the bulk:

$$\alpha = \frac{p_m}{D/L}, \quad p_m = \sum_{k=1}^N \frac{k_B T}{c_0} \frac{\partial j_k}{\partial [\mu_k]} \Big|_{[\mu_k]=0}. \quad (4.8)$$

The currents j_k and a_k are scaled so that $j_k = p_m c_0 j'_k$ and $a_k = p_m c_0 a'_k$. In (4.7f):

$$C_m = C_m^0 C'_m, \quad \theta = \frac{C_m^0 k_B T / q}{q c_0 r_d}, \quad (4.9)$$

where C_m^0 is the characteristic magnitude of the membrane capacitance per unit area (see (3.5) or (3.6)). The dimensionless constant θ is the ratio between the membrane charge and the total amount of charge in a layer of thickness on the order of the Debye length. In (4.7g), $j_w = \zeta c_0 k_B T j'_w$. The variables in (4.7h),

are defined by:

$$\Sigma'_m(\mathbf{u}', p') = \gamma(\nabla' \mathbf{u}' + (\nabla' \mathbf{u}')^T) - p' I, \quad (4.10)$$

$$\Sigma'_e(\phi') = \nabla' \phi' \otimes \nabla \phi' - \frac{1}{2} |\nabla' \phi'|^2 I, \quad (4.11)$$

$$\mathbf{F}_{\text{cap}} = \tau'_{\text{cap}} \kappa'_\Gamma \mathbf{n} - \nabla'_\Gamma \tau'_{\text{cap}}, \quad \tau'_{\text{cap}} = \frac{1}{2} \left(C'_m + Q \frac{\partial C'_m}{\partial Q} \right) [\phi']^2 \quad (4.12)$$

where $\kappa'_\Gamma (= \kappa_\Gamma L)$ is the sum of the two principal curvatures of Γ measured in the \mathbf{x}' spatial variable and ∇'_Γ is the surface gradient operator with respect to \mathbf{x}' . Equations (4.7a)-(4.7c) and the boundary conditions (4.7e)-(4.7h) constitute our dimensionless system. In the rest of this section we shall drop the $'$ in the variables with the understanding that all variables, unless otherwise stated, are dimensionless.

The dimensionless system above possesses five dimensionless constants $\alpha, \beta, \gamma, \theta$ and Pe . We consider two limiting cases of the above system. First of all, consider the case when $\text{Pe} \ll 1$. Assuming all primed quantities are $\mathcal{O}(1)$ with respect to Pe , we see, from (4.7g) that

$$\frac{\partial \mathbf{X}}{\partial t} = \mathcal{O}(\text{Pe}). \quad (4.13)$$

Therefore, the membrane does not move to leading order. If we collect all leading order terms, we see that the equations (4.7a) and (4.7b) decouple from (4.7c). We thus obtain the following Poisson-Nernst-Planck system with interface boundary conditions:

$$\frac{\partial c_k}{\partial t} = -\nabla \cdot \mathbf{f}_k \text{ in } \Omega_{i,e} \quad (4.14a)$$

$$-\nabla \cdot (\beta^2 \nabla \phi) = \sum_{k=1}^N z_k c_k \text{ in } \Omega_{i,e} \quad (4.14b)$$

$$(\mathbf{f}_k \cdot \mathbf{n})|_{\Gamma_{i,e}} = \alpha(j_k + a_k), \quad (4.14c)$$

$$-(\beta \nabla \phi \cdot \mathbf{n})|_{\Gamma_{i,e}} = \theta C_m[\phi], \quad (4.14d)$$

where the membrane Γ is fixed in time. This model was introduced in [52] (see also [53, 54] for related models).

For single cell systems, the Péclet number is about $\text{Pe} \approx 10^{-1}$ to 10^{-4} . The above may thus be a good approximation to the full system in the T_D time scale. In the context of multicellular systems, however, L may be large and Pe can reach unity, as can be seen from expression (4.7d) of Pe . It should be pointed out that there are situations in which the representative fluid velocity is not dictated by the osmotic pressure, in which case one should adopt a different definition for the Péclet number. For example, if we are interested in blood cells in a flow environment, the ambient hemodynamic flow velocity should be taken as the representative velocity.

We note that (4.14) also satisfies a free energy equality.

Proposition 4.1. *Suppose c_k and ϕ are smooth functions that satisfy (4.14). Then, the following equality holds:*

$$\frac{d}{dt}(G_S + E_{elec}) = -F_c - J_a. \quad (4.15)$$

In the above, G_S, E_{elec}, F_c and J_a are dimensionless versions of the corresponding quantities in (2.20), (2.21) and (3.15).

Proof. This follows from a simple calculation. \square

In this sense, system (4.14) may be seen as the system associated with the energy law (4.15) where the mechanical energy and dissipation in (3.15) is discarded.

We next consider the limit when $\beta \ll 1$. This limit is motivated by the fact that the Debye length r_d is approximately 1nm in typical physiological systems, far smaller than the typical length scale of interest. By formally letting $\beta \rightarrow 0$ in (4.7) we obtain the following system of equations:

$$\frac{\partial c_k}{\partial t} + \text{Pe} \mathbf{u} \cdot \nabla c_k = -\nabla \cdot \mathbf{f}_k \text{ in } \Omega_{i,e} \quad (4.16a)$$

$$\sum_{k=1}^N z_k c_k = 0 \text{ in } \Omega_{i,e}, \quad (4.16b)$$

$$\gamma \Delta \mathbf{u} - \nabla p = 0, \quad \nabla \cdot \mathbf{u} = 0 \text{ in } \Omega_{i,e}, \quad (4.16c)$$

$$\alpha(j_k + a_k) = \left(\left(c_k \left(\text{Pe} \mathbf{u} - \frac{\partial \mathbf{X}}{\partial t} \right) + \mathbf{f}_k \right) \cdot \mathbf{n} \right) \Big|_{\Gamma_{i,e}}, \quad (4.16d)$$

$$\mathbf{u} - \frac{1}{\text{Pe}} \frac{\partial \mathbf{X}}{\partial t} = j_w \mathbf{n}, \quad [\Sigma_m(\mathbf{u}, p) \mathbf{n}] = \mathbf{F}_{elas} \text{ on } \Gamma. \quad (4.16e)$$

We have discarded all terms in (4.7) that involve β and have eliminated the boundary condition (4.7f). The most important feature of the above system is that we have, in place of the Poisson equation (4.7b), the electroneutrality condition (4.16b). The electrostatic potential ϕ thus evolves so that the electroneutrality constraint (4.16b) is satisfied at each time instant. Although ϕ is thus determined only implicitly through the electroneutrality condition, it is possible to obtain a PDE satisfied by ϕ by taking the derivative of (4.16b) with respect to t and using (4.16a):

$$\begin{aligned} 0 &= \nabla \cdot (a \nabla \phi + \mathbf{b}) \\ a &= \sum_{k=1}^N z_k^2 D_k c_k, \quad \mathbf{b} = \sum_{k=1}^N z_k D_k \nabla c_k. \end{aligned} \quad (4.17)$$

We point out that the electroneutrality condition does *not* imply that $\Delta \phi = 0$ as may be erroneously inferred from (4.7b). In fact, as $\beta \rightarrow 0$, $\Delta \phi$ may remain

order 1 with respect to β while the right hand side of (4.7b) will go to 0 like β^2 . This is a common fallacy in applications of the electroneutral limit. The boundary condition for this elliptic equation can be obtained by taking the sum in k in boundary condition (4.16d):

$$- \left(a \nabla \phi + \tilde{\mathbf{b}} \right) \cdot \mathbf{n} \Big|_{\Gamma_{i,e}} = \sum_{k=1}^N \alpha z_k (j_k + a_k). \quad (4.18)$$

Suppose

$$\frac{\partial}{\partial [\phi]} \sum_{k=1}^N z_k j_k > 0. \quad (4.19)$$

The above inequality states that current flowing out of the cell should increase if $[\phi]$ increases, and is thus satisfied by biophysically reasonable expressions for j_k . This inequality is clearly satisfied if j_k are of the form (3.13) or (3.14) (see also (2.7)). Condition (4.19) is necessary for the boundary value problem (4.17) and (4.18) to be uniquely solvable (up to an arbitrary constant), assuming a_k is a given function of \mathbf{x} (and t).

In connection to (4.17) and (4.18), we perform the following calculation to illuminate the nature of system (4.16) as it relates to (4.7). Suppose ϕ satisfies (4.7). By taking the time derivative of (4.7b) with respect to t , we obtain:

$$\begin{aligned} \nabla \cdot \mathbf{0} &= \left(\beta^2 \nabla \frac{\partial \phi}{\partial t} + a \nabla \phi + \tilde{\mathbf{b}} \right), \\ a &= \sum_{k=1}^N z_k^2 D_k c_k, \quad \tilde{\mathbf{b}} = \sum_{k=1}^N (-\text{Pe} z_k c_k \mathbf{u} + z_k D_k \nabla c_k), \end{aligned} \quad (4.20)$$

We used (4.7a) in deriving the above. At the boundary, we may use (4.7f) and (4.7e) to find that:

$$\begin{aligned} &- \left(\beta^2 \nabla \frac{\partial \phi}{\partial t} + a \nabla \phi + \tilde{\mathbf{b}} \right) \cdot \mathbf{n} \Big|_{\Gamma_{i,e}} \\ &= \beta \theta \frac{\partial}{\partial t} (C_m [\phi]) + \sum_{k=1}^N \left(z_k c_k \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} + \alpha z_k (j_k + a_k) \right). \end{aligned} \quad (4.21)$$

If we formally let $\beta \rightarrow 0$ in (4.20) and (4.21), we obtain (4.17) and (4.18) respectively. For the above limit to be justified, we must require that $\frac{\partial \phi}{\partial t}$ and $\frac{\partial [\phi]}{\partial t}$ remain order 1 with respect to β as $\beta \rightarrow 0$. It is thus only when the evolution of ϕ and $[\phi]$ is sufficiently slow that we can reliably use system (4.16) as an approximation to (4.7).

We see from (4.20) and (4.21) that there are two other time scales in the system besides the diffusive time scale T_D . The first is the Debye time scale, $\beta^2 T_D$. This is the relaxation time scale of deviations from electroneutrality. This Debye time scale is too small to be of physiological interest, and we may

safely ignore the $\beta^2 \frac{\partial \phi}{\partial t}$ terms except for the very short initial layer that may exist depending on initial conditions. The other time scale, $\beta \theta T_D$, which we shall call the cable time scale, is the time scale over which the membrane potential $[\phi]$ can change. In excitable tissue, the ionic currents j_k can change on a time scale comparable to $\beta \theta T_D$. The interaction of rapid changes in j_k and the capacitive current $\beta \theta \frac{\partial}{\partial t}(C_m[\phi])$ term lead to cable effects, including the propagation of action potentials, which is essential in describing a wide range of electrophysiological behavior. Such phenomena are usually described by the cable model, in which the intracellular and extracellular media are treated as ohmic resistive media [45, 14].

Setting $\beta \theta \frac{\partial}{\partial t}(C_m[\phi])$ term to 0 could thus be problematic for certain applications. It is thus of interest to develop a model in which the term $\beta^2 \frac{\partial \phi}{\partial t}$ is ignored but $\beta \theta \frac{\partial}{\partial t}(C_m[\phi])$ is not, while retaining electrodiffusive and osmotic effects contained in the full model. Such a model (without osmotic effects) is proposed in [55] and was applied in [56] to a problem in cardiology. A key ingredient in the derivation of such a model is an analysis of a boundary layer that forms at the membrane interface Γ . This boundary layer, in physical terms, correspond to charge accumulation on both sides of the membrane. We refer the reader to [57, 58] for this model and its relationship to conventional cable models.

An important feature of system (4.16) is that it satisfies the following energy equality.

Proposition 4.2. *Suppose c_k, ϕ, \mathbf{u} and p are smooth functions that satisfy system (4.16). Then, the following equality holds:*

$$\frac{d}{dt}(G_S + E_{elas}) = -I_p - J_p - J_a. \quad (4.22)$$

In the above, G_S, E_{elas}, I_p, J_p and J_a are dimensionless versions of corresponding quantities in (2.20) and (3.15).

Proof. The proof follows from a calculation similar to the proof of Theorem 2.1. \square

Thus, system (4.16) may be seen as the system associated with the energy principle (4.22) in which the electrostatic energy in (3.15) is discarded.

5. Numerical Simulation of Animal Cell Volume Control

In this section, we take the problem of cell volume control to illustrate some aspects of the model we introduced above. Cells contain a large number of organic molecules that do not leak out through membrane. This results in excess intracellular osmotic pressure, which may cause the cell to burst. Cells have developed countermeasures to prevent this from happening.

We shall use the electroneutral system (4.16) to study cell volume control. We continue to work with the dimensionless equations. To simplify matters, we suppose that the cell membrane Γ and the outer boundary $\Gamma_{out} = \partial\Omega$ are

concentric spheres for all time and that the velocity field \mathbf{u} only has a radial component. Assuming the boundary condition $\mathbf{u} = \mathbf{0}$ on Γ_{out} we immediately see that $\mathbf{u} = \mathbf{0}$ throughout $\Omega_i \cup \Omega_e$. We can thus drop equation (4.16c) and set $\mathbf{u} = \mathbf{0}$ wherever \mathbf{u} appears in system (4.16). Assuming further that c_k and ϕ are functions only of the (dimensionless) radial coordinate r , we have:

$$\frac{\partial c_k}{\partial t} = -\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 f_k), \quad f_k = -\left(D_k \frac{\partial c_k}{\partial r} + z_k c_k \frac{\partial \phi}{\partial r} \right), \quad (5.1a)$$

$$\sum_{k=1}^N z_k c_k = 0, \quad (5.1b)$$

for $0 < r < R$ and $R < r < R_{\text{out}}$ where $R(t)$ is the radius of the membrane sphere Γ and $R_{\text{out}} = \text{const.}$ is the radius of the outer boundary sphere Γ_{out} . The boundary conditions are:

$$f_k = \begin{cases} 0 & \text{at } r = 0, \\ c_k \frac{\partial R}{\partial t} + \alpha(j_k + a_k) & \text{at } r = R_{\pm}, \end{cases} \quad (5.1c)$$

$$-\frac{1}{\text{Pe}} \frac{\partial R}{\partial t} = j_w, \quad [p] = F_{\text{elas}} \text{ at } r = R, \quad (5.1d)$$

where $r = R_{\pm}$ denote limiting values as r approaches R from above or below. Boundary conditions at $R = R_{\text{out}}$, will be specified later. The elastic force F_{elas} can now be viewed as a scalar quantity since the force is only in the radial direction.

We now develop a numerical algorithm to simulate system (5.1) and apply this to animal cell volume control as a demonstrative example.

We first discuss the numerical algorithm used to simulate system (5.1). Consider (5.1) in the region $a < r < b$. First, suppose $b < R$ or $a > R$. Then, we have:

$$\frac{d}{dt} \int_a^b r^2 c_k dr = a^2 f_k(a) - b^2 f_k(b). \quad (5.2)$$

If we let $b = R(t)$ in the above, we must account for the fact that $R(t)$ is changing in time. Using (5.1a) and (5.1c), we have:

$$\frac{d}{dt} \int_a^{R(t)} r^2 c_k dr = a^2 f_k(a) - R^2(t) \alpha(j_k + a_k). \quad (5.3)$$

A similar expression is true when $a = R(t)$. The above conservation relations will be the basis for our discretization.

Let Δt be the time step, and let R^n be the position of the membrane at $t = n\Delta t$. We divide $0 < r < R^n$ and $R^n < r < R_{\text{out}}$ into N_v equal segments. Let

$$r_l^n = \begin{cases} \frac{kR^n}{N_v}, & \text{if } 0 \leq l \leq N_v \\ R^n + \frac{R_{\text{out}} - R^n}{N_v}, & \text{if } N_v + 1 \leq l \leq 2N_v. \end{cases} \quad (5.4)$$

The l -th segment is given by $r_{l-1} < r < r_l$. Of the $2N_v$ segments, segments $1 \leq l \leq N_v$ are in the interior of the cell, whereas the the rest are in the exterior of the cell. In each segment, we have the concentrations $c_{k,l}^n$ and the electrostatic potential ϕ_l^n .

Suppose we are to advance from time $(n-1)\Delta t$ to $n\Delta t$. We use a splitting scheme. Each time step is divided into two substeps. In the first substep, we advance membrane position:

$$R^n = R^{n-1} - \text{Pe}j_w^{n-1}\Delta t. \quad (5.5)$$

In evaluating j_w , we need the osmotic pressure as well as the elastic force F_{elas} , both of which are evaluated using at time $(n-1)\Delta t$. For concentrations of ions at the intracellular and extracellular sides of the membrane, we use c_{k,N_v}^{n-1} and c_{k,N_v+1}^{n-1} respectively.

In the second substep, we update the concentrations and compute the electrostatic potential. We use one step of a backward Euler discretization. We first describe our discretization for the intracellular region. Define:

$$c_{k,i}^n(r) = \begin{cases} c_{k,l}^n & \text{if } r_{l-1}^n \leq r < r_l^n, \\ 0 & \text{if } r \geq r_{N_v}^n = R^n. \end{cases} \quad (5.6)$$

Suppose first that $R^n \leq R^{n-1}$. For $1 \leq l \leq N_v - 1$, we discretize (5.2) to obtain an equation for $c_{k,l}^n$:

$$\begin{aligned} \frac{4\pi}{3}((r_l^n)^3 - (r_{l-1}^n)^3)c_{k,l}^n &= \int_{r_{l-1}^n}^{r_l^n} 4\pi r^2 c_{k,i}^{n-1}(r) dr \\ &+ 4\pi((r_{l-1}^n)^2 f_{k,l-1}^n - (r_l^n)^2 f_{k,l}^n) \Delta t. \end{aligned} \quad (5.7)$$

where $f_{k,l}^n$ is set to 0 for $l = 0$ and

$$f_{k,l}^n = -D_k \left(\frac{c_{k,l}^n - c_{k,l-1}^n}{\Delta x_i} + \frac{c_{k,l}^n + c_{k,l}^n}{2} \frac{\phi_{k,l}^n - \phi_{k,l-1}^n}{\Delta x_i} \right), \text{ for } 1 \leq l \leq N_v - 1, \quad (5.8)$$

where $\Delta x_i = R^n/N_v$. Note that the integral in (5.7) can be evaluated exactly given expression (5.6). As for segment $l = N_v$, we view the endpoint $r_{N_v}^n = R^n$ as having evolved from R^{n-1} , and thus discretize (5.3). We have:

$$\begin{aligned} \frac{4\pi}{3}((r_{N_v-1}^n)^3 - (R^n)^3)c_{k,N_v}^n &= \int_{r_{N_v-1}^n}^{R^{n-1}} 4\pi r^2 c_{k,i}^{n-1}(r) dr \\ &+ 4\pi((r_{N_v-1}^n)^2 f_{k,N_v-1}^n - (R^n)^2 \alpha(a_k^n + j_k^n)) \Delta t. \end{aligned} \quad (5.9)$$

The important point here is that the upper end point of the above integral is R^{n-1} and not R^n . The total membrane fluxes $(R^{n-1})^2 a_k^n$ and $(R^{n-1})^2 j_k^n$ are

evaluated at time $n\Delta t$, and are thus functions of $c_{k,N_v}^n, c_{k,N_v+1}^n$ and $[\phi]^n = \phi_{N_v}^n - \phi_{N_v+1}^n$.

If $R^n > R^{n-1}$, the discretized equations are the same as (5.7) and (5.9) except that in (5.9) the upper endpoint of the integral is R^n instead of R^{n-1} . The fact that the endpoint of the integral is time-dependent in (5.3) is taken into account by the 0 extension of $c_{k,i}^{n-1}(r)$ when $r \geq R^{n-1}$ (see (5.6)).

The final equation we impose is that electroneutrality be satisfied in each segment:

$$\sum_{k=1}^N z_k c_{k,l}^n = 0 \text{ for all } l. \quad (5.10)$$

For the extracellular segments $N_v + 1 \leq l \leq 2N_v$, we essentially use the same discretization as in the intracellular segments. The only difference is in treating boundary conditions at the $l = 2N_v$ segment. We impose either no-flux or Dirichlet boundary conditions. For no-flux boundary conditions, we simply let $f_{k,N_v}^n = 0$ in (5.7) for $l = 2N_v$. Suppose the Dirichlet boundary conditions are given by:

$$c_k(R_{\text{out}}, t) = c_{k,e}. \quad (5.11)$$

In this case, we set:

$$c_{k,e}^n = c_{k,e}, \quad c_{k,e}^n = \frac{3}{2}c_{k,2N_v}^n - \frac{1}{2}c_{k,2N_v-1}^n. \quad (5.12)$$

For either boundary condition, the electrostatic potential is determined only up to an additive constant, and we thus set $\phi_e^n = 3\phi_{2N_v}^n/2 - \phi_{2N_v-1}^n/2 = 0$.

For the second substep, we thus have equations (5.7), (5.9) and (5.10) with suitable boundary conditions at $r_{2N_v}^n = R_{\text{out}}$, which we must solve for $c_{k,l}^n$ and ϕ_l^n . This system of nonlinear algebraic equations is solved using a Newton iteration where the Jacobian matrix is computed analytically. In all simulations reported here, we obtained convergence to within a relative tolerance of 10^{-12} within less than 4 iterations. In particular, the electroneutrality condition at each time step was satisfied at each point to within $6 \times 10^{-14} \text{mmol}/\ell$ for all simulation results shown below.

Note that the discretization is conservative. For example, we have:

$$\sum_{l=1}^{2N_v} \frac{4\pi}{3} ((r_l^n)^3 - (r_{l-1}^n)^3) c_{k,l}^n = \text{const} \quad (5.13)$$

so long as we impose the no-flux boundary condition at $r = R^{\text{out}}$. We have checked this property numerically, we achieve conservation of ions to 14 to 15 digits. This property is very important in studying long time behavior.

We would also like to comment on our use of the backward Euler scheme and the Newton iteration in the second substep of each time step. Rather than use a backward Euler step, we may split the second substep further into two substeps. In the first substep, one compute the updates of ϕ given values of c_k

at time $(n-1)\Delta t$ and in the second substep, we update c_k using the updated ϕ . A variant of this scheme is to use the above as one step of a fixed point iteration to solve the backward Euler problem. An advantage of these schemes is that the associated matrix problem is much simpler and smaller than that of a full Newton iteration we use in this paper. This was indeed the first algorithm we used in our attempt to simulate the system. This algorithm, however, turned out to have serious stability and convergence issues and led to large pile-up of charges close to the membrane. This difficulty was clearly caused by the moving membrane. Indeed, a similar algorithm was successfully used in [59] to simulate a similar but higher dimensional system, in which the membrane was stationary. We also found that if Δt or the membrane velocity is very small, the fixed-point algorithm does produce computational results in agreement with those obtained using a Newton iteration. We do point out that even the backward Euler, Newton scheme, that we use here was not unconditionally stable, though the time step restriction was never serious. A more stable algorithm may be possible by developing a scheme in which the membrane position and concentrations (and electrostatic potential) are computed simultaneously.

We now describe the model example we simulate. The cell membrane of animal cells is not mechanically strong enough to resist osmotic pressure due to the presence of organic solutes in the cell. Cell volume control is achieved by actively maintaining a concentration gradient of ions across the cell membrane. Many modeling studies have been performed to study cell volume control in animal cells. To the best of our knowledge, all such studies use ODE systems in which the cellular and extracellular concentrations are assumed to have no spatial variation [14, 15, 60, 61, 62]. The novelty here is that we use the PDE system (5.1), a field theory, to study cell volume control.

We consider a generic spherical animal cell whose sodium and potassium concentration differences across the membrane is maintained by the presence of the Na-K ATPase. Henceforth, we shall use variables with their original dimensions, since we will be dealing with a concrete biophysical setup. We consider four species of ion, Na^+ , K^+ , Cl^- and the organic anions, which we index as $k = 1, \dots, 4$ in this order. The diffusion coefficients of the four species is given in the Table 2. We make the simplification that the organic anions are a homogeneous species with a single diffusion coefficient. The diffusion coefficient for the organic anion is somewhat arbitrary, one order of magnitude smaller than the small inorganic ions.

We take the initial radius of the spherical cell to be R_0 . We let the outer edge of the simulation domain $R_{\text{out}} = 2R_0$. We assume that the membrane does not generate any mechanical force, so that $F_{\text{elas}} = 0$. Passive water flow across the membrane is proportional to the water chemical potential. Given that $F_{\text{elas}} = 0$, water flow across the cell membrane is driven osmotic pressure difference across the membrane:

$$j_w = \zeta N_A k_B T \sum_{k=1}^4 [c_k] \quad (5.14)$$

where N_A is the Avogadro constant (so that $N_A k_B$ is the ideal gas constant), T is the absolute temperature, c_k is measured in mmol/ ℓ and ζ is measured in velocity per pressure.

For the passive membrane flux j_k , we take expression (3.14):

$$j_k = \frac{R_0^2}{R(t)^2} P_k z_k \phi' \left(\frac{c_k|_{R-} \exp(z_k \phi') - c_k|_{R+}}{\exp(z_k \phi') - 1} \right), \quad \phi' = \frac{q[\phi]}{k_B T}. \quad (5.15)$$

where the subscript $R-$ and $R+$ denote evaluation at the inner and outer faces of the membrane. This choice is standard for cell volume studies [63, 64]. The number P_k is measured in cm/sec and is the permeability of a unit area of membrane for ionic species k when the radius of the cell is R_0 . Assuming that this permeability is determined by the presence of ionic channels and that the number of ionic channels remains constant, j_k must be made inversely proportional to the membrane area. For sodium, potassium and chloride, P_k is positive but we set the permeability for organic solutes to 0.

We follow [64] to use the following expression for the Na-K ATPase flux:

$$a_1 = A_p \left(\frac{c_1|_{R-}}{c_1|_{R-} + K_{Na}} \right)^3 \left(\frac{c_2|_{R+}}{c_2|_{R+} + K_K} \right)^2, \quad a_2 = -\frac{2}{3} a_1. \quad (5.16)$$

Recall here that a_1, c_1 are the active Na^+ flux and concentration respectively and a_2, c_2 are the active K^+ flux and concentration respectively. The exponents of 3, 2 and the factor of $-2/3$ reflects the 3 : 2 stoichiometry of the NaK ATPase in pumping Na^+ out and K^+ into the cell. The constants K_{Na} and K_K are given in Table 1.

All constants and initial conditions are given in Tables 1 and 2. Initial concentrations are assumed spatially uniform. The constants that are not listed in the tables are computed so that the initial state is a stationary state under no-flux boundary conditions at $R = R_{\text{out}}$. This is similar to what is done in [64]. This procedure determines the initial intracellular Cl^- concentration, Na-K ATPase maximal pump rate A_p , K^+ permeability p_2 , initial intracellular organic solute concentration, and the organic solute valence z_4 . We point out that $[\phi]^{\text{init}}$, the initial value of the membrane potential is only needed to compute the initial conditions. Once all the concentrations are known, the concentrations serve as the initial conditions and there is no need to know $[\phi]$ at the initial time to evolve the system forward.

In the simulations to follow, we took $N_v = 100$ and the time step $\Delta t = 500\text{ms}$.

We perform the following numerical experiments. Starting with the initial conditions specified above with no-flux boundary conditions, we set the following Dirichlet boundary conditions for $t \geq 10\text{s}$:

$$c_{1,e} = 100, \quad c_{2,e} = 50, \quad c_{3,e} = 150, \quad (5.17)$$

where the units are in mmol/ ℓ . The boundary concentrations are thus isotonic

T (K)	$273.15 + 37$	K_k (mmol/ ℓ)	0.75 [64]
ζ (cm/s/mPa)	5.2507×10^{-13} [63]	K_{Na} (mmol/ ℓ)	3.5 [64]
R_0 (mm)	0.5	A_p (cm/s)	-
R_{out} (mm)	1	$[\phi]^{\text{init}}$ (mV)	-70

Table 1: Constants used in the numerical simulation. $[\phi]^{\text{init}}$ is the initial membrane voltage. Symbols labeled with '-' are determined so that the initial condition is a stationary state (see main text). The ion related constants are listed in Table 2.

	z_k	D_k (cm ² /s)	P_k (cm/s)	$c_{k,\text{int}}^{\text{init}}$	$c_{k,\text{ext}}^{\text{init}}$
Na ⁺	+1	1.33×10^{-5} [65]	1.0×10^{-7} [66]	10	145
K ⁺	+1	1.96×10^{-5} [65]	-	140	5
Cl ⁻	-1	2.03×10^{-5} [65]	1.0×10^{-7} [66]	-	150
O.A.	-	1.0×10^{-6}	0	-	0

Table 2: Parameters related to ionic concentrations. O.A. stands for organic anions. The initial intracellular and extracellular concentrations are given by $c_{k,\text{int}}^{\text{init}}$ and $c_{k,\text{ext}}^{\text{init}}$ respectively (listed here in mmol/ ℓ). Symbols labeled with '-' are determined so that the initial condition is a stationary state (see main text). Other parameters are listed in Table 1.

with the initial concentrations, but the extracellular K⁺ concentration is now increased 10-fold. Such a stimulus should lead to immediate depolarization together with expansion of the cell.

The computational results are given in Figure 1. What is interesting here is that there is a transient drop in the cell radius, followed by an expected gradual increase. This transient drop is due to the following. After a sudden change in the boundary condition, Na⁺ ions diffuse out whereas K⁺ ions should diffuse in from $R = R_{\text{out}}$. Since K⁺ diffuses faster than Na⁺, there is a transient increase in total ionic concentration near the membrane, leading to excess osmotic pressure immediately outside the cell compared to the inside. This gives rise to a transient drop in the cell radius. However, as the ionic concentration becomes spatially uniform within the extracellular and intracellular domains, the cell starts to expand.

The next computational results describe a hypotonic shock. We set the boundary conditions to the following for $t \geq 10$ s:

$$c_{1,e} = 100, c_{2,e} = 5, c_{3,e} = 105, \quad (5.18)$$

where the concentrations are in mmol/ ℓ . A snapshot of the computational results are given in Figure 2. The cell expands due to the hypotonic shock but tends to a new stationary state with time.

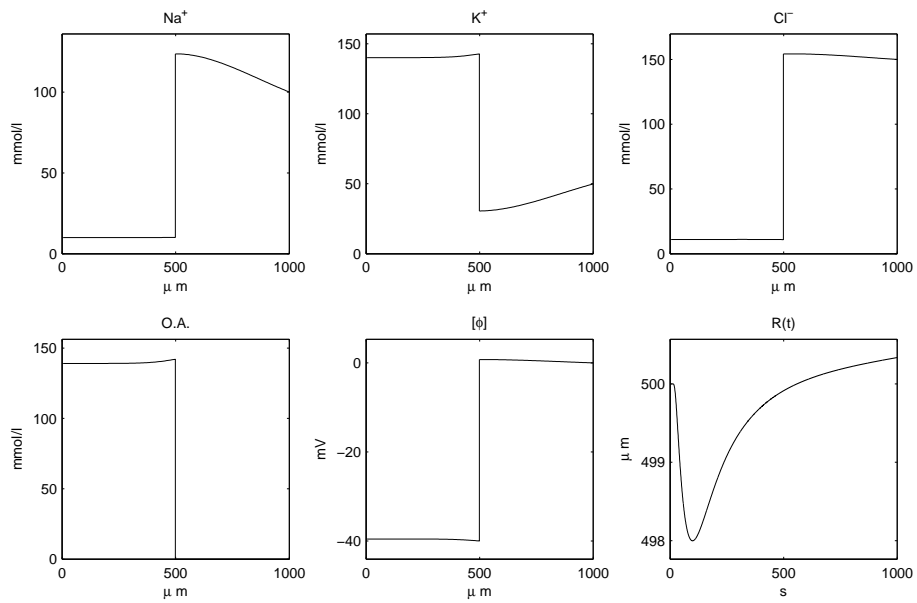


Figure 1: Computational results under a high K^+ stimulus (see (5.17)). The first five figures are the snapshots of the ionic concentrations and the electrostatic potential at $t = 50$ s. The horizontal axis represents the radius r . The last figure plots the cell radius $R(t)$ as a function of time.

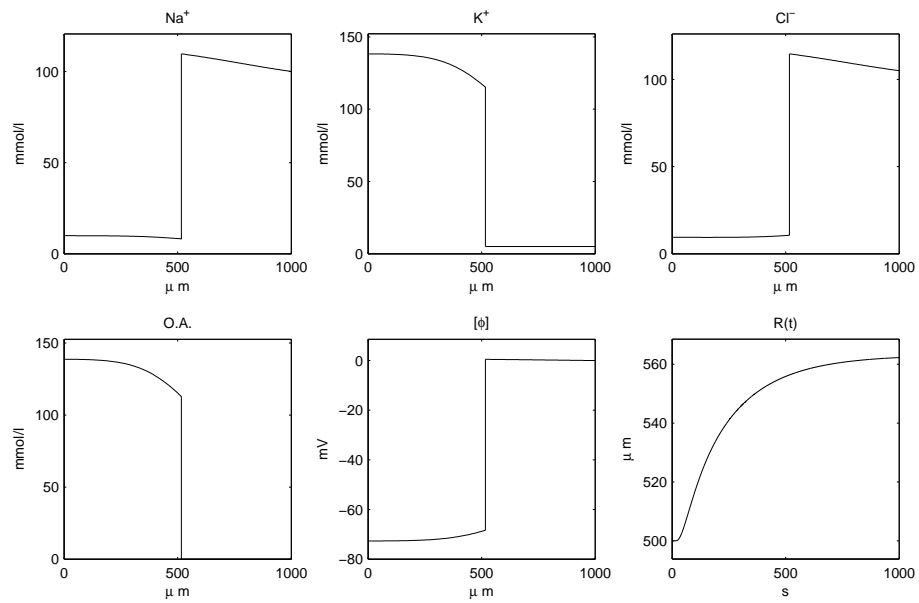


Figure 2: Computational results under hypotonic stimulus (see (5.18)). The first five figures are the snapshots of the ionic concentrations and the electrostatic potential at $t = 100$ s. The horizontal axis represents the radius r . The last figure plots the cell radius $R(t)$ as a function of time.

6. Conclusion

We introduced a PDE system of electrodiffusion and osmotic water flow in the presence of deformable capacitance-carrying membranes. The salient feature of the model is that it satisfies an energy equality, and thus possesses a natural thermodynamic structure. We discussed simplifications of the model and applied the electroneutral limit to the problem of cell volume control.

In the proof of Theorem 2.1, we showed that the van t'Hoff expression for osmotic pressure arises naturally, simply through an integration by parts argument. This observation seems to be new. It is interesting that, in expression (2.20), the mechanical pressure p and osmotic pressure π_w only appear in the combination $\psi_w = p + \pi_w$. This is consistent with experimental results indicating that the effect of osmotic pressure on transmembrane water flow is indistinguishable from that of mechanical pressure [67].

The models introduced here are *sharp interface* models in the sense that the membrane is treated as a surface without thickness and the physical quantities of interest are allowed to have discontinuities across Γ . This is in contrast to *diffuse interface* models in which the membrane has some small but finite thickness and the physical quantities transition rapidly but smoothly across the interface. It should be possible to obtain at least parts of the model by taking the thin interface limit of an appropriate diffuse interface (or finite thickness) model. This may lead to a simpler verification of the energy identity of Theorem 3.1. Establishing such a connection may also help in understanding the physical nature of the capacitive force (3.10). The calculations in Appendix Appendix A.1 may be seen as an initial step in establishing this relationship.

Given the natural thermodynamic structure of the problem, it is almost certainly the case that our model has a *variational* structure. A variational principle for dissipative systems dates back to [68]. This procedure has been used successfully in deriving dynamic equations for soft matter systems [69, 70]. In [41, 71], a model for non-ideal electrolyte solutions is derived by combining, in the spirit of Rayleigh (see [72]), the principle of least action with the above variational principle for dissipative system.

The energy identities introduced here provide a natural apriori estimate for our PDE system. For related systems, the corresponding free energy identity has been used successfully to prove stability of steady states [73, 74]. It would be interesting to see if similar analytical results can be obtained for the system proposed here.

We hope that our model has wide-ranging applications in cellular physiology. In principle, our model is applicable to most problems of classical physiology [3, 2, 1]. As we saw in Section 4, our model admits simplifications when certain dimensionless parameters are small. In the short time scale when water movement is not significant, the system is reduced to the Poisson-Nernst-Planck model with interface boundary conditions. This and related models have been successfully applied in [52, 75, 56]. If the physiological processes of interest are slow and happen over a long time scale, the electroneutral limit may be taken. This was applied to the problem of cell volume control in Section 5 of this paper.

Any serious application of our model will require the development of an efficient numerical algorithm. The electrodiffusive part of the problem with stationary membranes (without fluid flow) has been treated successfully in [59, 76] in a two-dimensional setting. In the model presented here, the membrane interface is dynamic. We must therefore solve an electrodiffusive problem in a domain with a moving interface across which physical quantities experience discontinuities. We have presented successful computations in one-dimension for the electroneutral limit in Section 5, but simulations are bound to be more challenging in higher dimension. If a regular mesh is to be used, immersed boundary or immersed interface schemes could be a major component of the algorithm [25, 77, 78].

Many physiological phenomena in which both electrodiffusion and osmosis play an important role take place over spatial scales of whole tissues or organs rather than the cellular spatial scale we focused on in this paper. Such systems include ocular fluid circulation, electrolyte regulation in the kidney or brain ionic homeostasis. For such systems, it is important to develop an appropriate homogenized model. In the context of cable models, this is known as the bidomain model, and has found great utility in many contexts, especially in cardiac electrophysiology [14, 79, 80, 81, 82]. We shall report on a such a multidomain model in a future publication.

Appendix A. Appendix

Appendix A.1. Physical Interpretation of the Capacitive Force

Let the membrane be made of an incompressible material. In this case, we argued that C_m should satisfy (3.6). We shall show that the incompressibility of the material implies $\tau_{\text{cap}} = -C_m[\phi]^2$, in agreement with (3.10). To this end, we take a membrane of finite thickness d and consider the limit as the thickness tends to 0. Let Γ be the midplane of this membrane of finite thickness. The membrane thus coincides with Γ as $d \rightarrow 0$.

Take a point $\mathbf{x} \in \Gamma$ and let \mathbf{n} be the unit normal and d the thickness of the membrane at \mathbf{x} . The stress inside the membrane is given by:

$$\Sigma^{\text{mem}} = \Sigma_e^{\text{mem}} - p^{\text{mem}}I \quad (\text{A.1})$$

where Σ_e^{mem} is the Maxwell stress, $\Sigma_{\text{elas}}^{\text{mem}}$ the elastic stress $p^{\text{mem}}I$ is the isotropic pressure term that enforces incompressibility of the material. We have made the simplification that the material can only generate isotropic stresses.

Let us now consider the limiting behavior of this stress when d is very small. To leading order in d , the Maxwell stress tensor inside the membrane is given by:

$$\Sigma_e^{\text{mem}} = \epsilon_m \frac{[\phi]^2}{d^2} \left(\mathbf{n} \otimes \mathbf{n} - \frac{1}{2}I \right) = C_m \frac{[\phi]^2}{d} \left(\mathbf{n} \otimes \mathbf{n} - \frac{1}{2}I \right) \quad (\text{A.2})$$

where ϵ_m is the dielectric constant of the membrane. We assumed that the electric field inside the membrane is given by $[\phi]\mathbf{n}/d$, given that the membrane is very thin. We used $\epsilon_m/d = C_m$ in the second equality.

Now, let us consider stress balance at $\mathbf{x} + \frac{d}{2}\mathbf{n}$, the point where the membrane touches Ω_e . Here, we have the following stress balance condition:

$$\Sigma^{\text{mem}}\mathbf{n} = \Sigma^{\Omega_e}\mathbf{n} \quad (\text{A.3})$$

where Σ^{Ω_e} is the stress in Ω_e . Using (A.1) and (A.2) $\Sigma^{\text{mem}}\mathbf{n}$, to leading order in d , can be written as:

$$\Sigma^{\text{mem}}\mathbf{n} = \left(C_m \frac{[\phi]^2}{2d} - p^{\text{mem}} \right) \mathbf{n}. \quad (\text{A.4})$$

As $d \rightarrow 0$, $\Sigma^{\Omega_e}\mathbf{n}$ must remain finite if there is a finite distinguished limit. Therefore, $\Sigma^{\text{mem}}\mathbf{n}$ must remain order 1 with respect to d . In (A.4), the term $C_m \frac{[\phi]^2}{2d}$ grows like $1/d$ as $d \rightarrow 0$. The elastic stress stays order 1 with respect to d . Therefore, $p^{\text{mem}}\mathbf{n}$, must satisfy:

$$p^{\text{mem}} = C_m \frac{[\phi]^2}{2d} \quad (\text{A.5})$$

to leading order in d .

Take any unit vector \mathbf{t} tangent to Γ at \mathbf{x} . We have:

$$\Sigma^{\text{mem}}\mathbf{t} = -\frac{1}{d}C_m[\phi]^2\mathbf{t}, \quad (\text{A.6})$$

to leading order in d . Multiplying the above by the thickness d of the membrane, and taking the limit as $d \rightarrow 0$, we conclude that a ‘‘surface tension’’ of magnitude $-C_m[\phi]^2$ is generated at the membrane.

The above derivation suggests the following physical interpretation of expression (3.10). The term $\frac{1}{2}C_m[\phi]^2$ comes directly from the Maxwell stress. More simply put, this tension comes from large coulomb forces squeezing the thin membrane. This force must be counter balanced to maintain the mechanical integrity of the membrane, which is given by an isotropic pressure in the case of incompressible materials. This contributes the term $\frac{1}{2}Q\frac{\partial C_m}{\partial Q}[\phi]^2$ to the capacitive force.

Appendix A.2. Relation to an Immersed Boundary Model of Osmosis

In this appendix, we explore a model of osmosis proposed in [19, 24] and compare this with the model presented in this paper.

Consider the system of equations introduced in Section 2. We shall take $\omega = \omega_0$ given in (2.1). Let there be only one solute species and suppose that it is impermeable to the membrane. Let c be the concentration of this solute. We have:

$$\frac{\partial c}{\partial t} + \nabla \cdot (\mathbf{u}c) = \nabla \cdot (D(\nabla c)), \quad (\text{A.7a})$$

$$\nu \Delta \mathbf{u} - \nabla p = 0, \quad (\text{A.7b})$$

and at the boundary, we have:

$$[\Sigma(\mathbf{u}, p)] = \mathbf{F}_{\text{elas}}, \quad \mathbf{u}c - D \frac{\partial c}{\partial \mathbf{n}} = c \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} \quad (\text{A.7c})$$

and (2.14). We impose no-flux and no-flow boundary conditions on $\partial\Omega$. We know from Theorem 2.1 that the solutions to (A.7) satisfy:

$$\begin{aligned} & \frac{d}{dt} \int_{\Omega} (k_B T c \ln c + E_{\text{elas}}) d\mathbf{x} \\ &= - \int_{\Omega} Dc |\nabla \ln c|^2 d\mathbf{x} + \int_{\Gamma} (\mathbf{F}_{\text{elas}} \cdot \mathbf{n} + k_B T [c]) j_w dm_{\Gamma}. \end{aligned} \quad (\text{A.8})$$

Dissipation in the free energy will be guaranteed if, for example, j_w is a linear function of $\mathbf{F}_{\text{elas}} \cdot \mathbf{n} + k_B T [c]$ of negative slope.

In [19, 24], the authors propose the following immersed boundary model of osmosis. We argue why this may be considered a regularization of the above model. The concentration c satisfies:

$$\frac{\partial c}{\partial t} + \nabla \cdot (\mathbf{u}c) = \nabla \cdot \left(D \left(\nabla c + \frac{c}{k_B T} \nabla \psi_{\eta} \right) \right). \quad (\text{A.9a})$$

Here, ψ_{η} is a ‘‘barrier’’ potential localized near the membrane:

$$\psi_{\eta}(\mathbf{x}) = \int_{\Gamma_{\text{ref}}} \varphi_{\eta}(\mathbf{x} - \mathbf{X}(\boldsymbol{\theta}, t)) dm_{\Gamma_{\text{ref}}} \quad (\text{A.9b})$$

$$\varphi_{\eta}(\mathbf{x}) = \eta^{-3} \varphi_1 \left(\frac{\mathbf{x}}{\eta} \right), \quad (\text{A.9c})$$

where $\varphi_1(\mathbf{x})$ is a positive function of compact support. For simplicity, we shall take $\varphi(\mathbf{x})$ to be radially symmetric and nonzero only if $\mathbf{x} \leq 1$. The parameter $\eta > 0$ is the width of the barrier potential. As $\eta \rightarrow 0$, one would expect the barrier to be so high that the solute will be effectively blocked from crossing the membrane.

The fluid velocity field satisfies the Stokes equation in $\Omega \setminus \Gamma$ with an external force term that comes from the presence of solutes interacting with the barrier:

$$\nu \Delta \mathbf{u} - \nabla p = c \nabla \psi_{\eta}. \quad (\text{A.9d})$$

At the boundary, we suppose that the velocity field is continuous and that the stress tensor $\Sigma_m(\mathbf{u}, p)$ satisfies the following jump condition:

$$[\Sigma_m(\mathbf{u}, p)\mathbf{n}] = \mathbf{F}_{\text{elas}} + \mathbf{F}_{\text{sol}}, \quad (\text{A.9e})$$

$$\mathbf{F}_{\text{sol}} \Big|_{\frac{\partial \mathbf{X}}{\partial \boldsymbol{\theta}}} = \int_{\Omega} c \nabla \varphi_{\eta}(\mathbf{x} - \mathbf{X}(\boldsymbol{\theta}, t)) d\mathbf{x}. \quad (\text{A.9f})$$

The force \mathbf{F}_{sol} should be seen as a reaction force to the $c \nabla \psi$ term in (A.9d).

The membrane velocity $\frac{\partial \mathbf{X}}{\partial t}$ and \mathbf{u} satisfy relation (2.14). The following energy identity is satisfied by this system:

$$\begin{aligned} & \frac{d}{dt} \int_{\Omega} (k_B T c \ln c + E_{\text{elas}} + c\psi_{\eta}) d\mathbf{x} \\ &= - \int_{\Omega} Dc \left| \nabla \left(\ln c + \frac{\psi_{\eta}}{k_B T} \right) \right|^2 d\mathbf{x} + \int_{\Gamma} (\mathbf{F}_{\text{elas}} + \mathbf{F}_{\text{sol}}) \cdot \mathbf{n} j_w dm_{\Gamma}. \end{aligned} \quad (\text{A.10})$$

We leave the verification of this identity to the reader. The above energy will be monotonically decreasing if j_w is a linear function of $\mathbf{F}_{\text{elas}} + \mathbf{F}_{\text{sol}}$ of negative slope.

Let us now consider the limit as $\eta \rightarrow 0$. First, consider the advection-diffusion equation satisfied by the solute. The $\eta \rightarrow 0$ limit corresponds to the barrier potential becoming infinitely thin and high, and thus, this limit should lead to (A.7a) in $\Omega \setminus \Gamma$ and the impermeable boundary condition (A.7c) for the solute.

To examine the limiting behavior of the Stokes equation rewrite (A.9d) and (A.9e) in the following *immersed boundary* fashion:

$$\nu \Delta \mathbf{u} - \nabla p = c \nabla \psi_{\eta} + \mathbf{f}_{\text{sol}} + \mathbf{f}_{\text{elas}}. \quad (\text{A.11})$$

Here $\mathbf{f} = \mathbf{f}_{\text{sol}}$ or \mathbf{f}_{elas} are surface measures supported on Γ whose action on a test function \mathbf{v} is given by:

$$\langle \mathbf{f}, \mathbf{v} \rangle = \int_{\Gamma} \mathbf{F}(\mathbf{X}) \cdot \mathbf{v}(\mathbf{X}) dm_{\Gamma} \quad (\text{A.12})$$

where $\mathbf{F} = \mathbf{F}_{\text{sol}}$ or \mathbf{F}_{elas} . Equation (A.11) is thus to be understood in the sense of distributions. The interface conditions (A.9e) are now expressed in terms of singular force fields. This reformulation of interface boundary conditions is a key ingredient in the immersed boundary method [77].

Given that $c \nabla \psi_{\eta}$ and \mathbf{f}_{sol} are forces of action and reaction, as $\eta \rightarrow 0$, one expects $c \nabla \psi + \mathbf{f}_{\text{sol}}$ to go to 0 in a distributional sense. The right hand side of (A.11) will thus be reduced to \mathbf{f}_{elas} . Equation (A.11) will then be equivalent imposing the boundary condition (A.7c) at Γ to the Stokes equation satisfied in $\Omega \setminus \Gamma$.

In view of (A.8), (A.10) and the discussion after these equations, we would like to show that \mathbf{F}_{sol} approaches $[c]k_B T$, the van t'Hoff expression of osmotic pressure, as $\eta \rightarrow 0$. If this is the case, we can view system (A.9) as giving a mechanical interpretation of osmotic pressure. In this view, osmotic pressure is generated by solute molecules hitting the impermeable membrane. We now sketch a boundary layer calculation that lends credence to this claim. Take a point on Γ and let this point be the origin without loss of generality. Assume Γ is locally flat. Let Γ coincide with the $x - y$ plane and let z be the direction normal to Γ the positive z axis to be pointing into Ω_e . Assume furthermore,

that $\left|\frac{\partial \mathbf{X}}{\partial \boldsymbol{\theta}}\right| = \text{const}$ over this flat region. Consider the solute flux for $z > 0$:

$$J_z = \frac{\partial c}{\partial z} + \frac{c}{k_B T} \frac{\partial \psi_\eta}{\partial z} \quad (\text{A.13})$$

Introduce the stretched boundary layer coordinate $\eta Z = z$:

$$\eta J_z = \frac{\partial c}{\partial Z} + \frac{c}{k_B T} \frac{\partial \psi_\eta}{\partial Z} \quad (\text{A.14})$$

We conclude, to leading order, that

$$c(Z) = c(Z=1) \exp(-\psi_\eta(Z)/k_B T) + o(1). \quad (\text{A.15})$$

In original coordinates, we have, for $0 < z < \eta$,

$$c(\mathbf{x}', z) = c(\mathbf{x}', \eta) \exp\left(-\frac{\psi_\eta(z)}{k_B T}\right) + o(1) \quad (\text{A.16})$$

where $\mathbf{x}' = (x, y)$ and $o(1)$ denotes terms that tend to 0 as $\eta \rightarrow 0$. Likewise, for $-\eta < z < 0$, we have:

$$c(\mathbf{x}', z) = c(\mathbf{x}', -\eta) \exp\left(-\frac{\psi_\eta(z)}{k_B T}\right) + o(1). \quad (\text{A.17})$$

Let us now compute \mathbf{F}_{sol} at $x = y = 0$.

$$\begin{aligned} \mathbf{F}_{\text{sol}} \left| \frac{\partial \mathbf{X}}{\partial \boldsymbol{\theta}} \right| &= \int_{|\mathbf{x}| \leq \eta} c \nabla \varphi_\eta(\mathbf{x}) d\mathbf{x} \\ &= \int_{|\mathbf{x}| \leq \eta, z \geq 0} c \nabla \varphi_\eta(\mathbf{x}) d\mathbf{x} + \int_{|\mathbf{x}| \leq \eta, z \leq 0} c \nabla \varphi_\eta(\mathbf{x}) d\mathbf{x} \\ &\equiv (\mathbf{F}_{\text{sol}}^+ + \mathbf{F}_{\text{sol}}^-) \left| \frac{\partial \mathbf{X}}{\partial \boldsymbol{\theta}} \right|. \end{aligned} \quad (\text{A.18})$$

where we used the fact that φ_η is supported in $|\mathbf{x}| \leq \eta$. Consider the first term:

$$\begin{aligned} \mathbf{F}_{\text{sol}}^+ \left| \frac{\partial \mathbf{X}}{\partial \boldsymbol{\theta}} \right| &= \int_{|\mathbf{x}| \leq \eta, z \geq 0} c \nabla \varphi_\eta(\mathbf{x}) d\mathbf{x} \\ &= \int_{|\mathbf{x}| \leq \eta, z \geq 0} \left(c(\mathbf{x}', \eta) \exp\left(-\frac{\psi_\eta(z)}{k_B T}\right) \nabla \varphi_\eta(\mathbf{x}) \right) d\mathbf{x} + o(1) \\ &= \int_{|\mathbf{x}| \leq \eta, z \geq 0} \left(c(\mathbf{x}', \eta) \exp\left(-\frac{\psi_\eta(z)}{k_B T}\right) \frac{\partial}{\partial z} \varphi_\eta(\mathbf{x}', z) \right) d\mathbf{x}' dz \mathbf{e}_z + o(1) \end{aligned} \quad (\text{A.19})$$

where \mathbf{e}_z is the unit coordinate vector in the z direction. Note that:

$$\psi_\eta = \left| \frac{\partial \mathbf{X}}{\partial \boldsymbol{\theta}} \right|^{-1} \int_{|\mathbf{y}'| \leq \eta} \varphi_\eta(\mathbf{y}', z) d\mathbf{y}' \quad (\text{A.20})$$

near the origin. Here, we used the fact that the membrane is flat and that $\left| \frac{\partial \mathbf{X}}{\partial \boldsymbol{\theta}} \right|$ is constant. Using this, we have:

$$\begin{aligned} \mathbf{F}_{\text{sol}}^+ &= \int_{z \geq 0} \left(c(0, \eta) \exp\left(-\frac{\psi_\eta(z)}{k_B T}\right) \frac{\partial}{\partial z} \psi_\eta(z) \right) dz \mathbf{e}_z + o(1) \\ &= \left(-c(0, \eta) k_B T + c(0, 0) k_B T \exp\left(-\frac{\psi_\eta(0)}{k_B T}\right) \right) \mathbf{e}_z + o(1). \end{aligned} \quad (\text{A.21})$$

Likewise, we have:

$$\mathbf{F}_{\text{sol}}^- = \left(c(0, -\eta) k_B T - c(0, 0) k_B T \exp\left(-\frac{\psi_\eta(0)}{k_B T}\right) \right) \mathbf{e}_z + o(1). \quad (\text{A.22})$$

Thus, as $\eta \rightarrow 0$, we have:

$$\mathbf{F}_{\text{sol}} = (c(0, 0-) - c(0, 0+)) k_B T \mathbf{e}_z \quad (\text{A.23})$$

as desired.

We emphasize that the above calculation is purely symbolic. We are not attempting to prove that the solutions to (A.9) approach the solutions to (A.7) in the $\eta \rightarrow 0$ limit.

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