Physica D, in the press

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

Yoichiro Mori[a,*], Chun Liu[b], Robert S. Eisenberg[c]

[a] *School of Mathematics, University of Minnesota, Minneapolis, MN 55414, U.S.A.*
[b] *Department of Mathematics, Pennsylvania State University, University Park, PA 16802, U.S.A.*
[c] *Department of Molecular Biophysics and Physiology, Rush University Medical Center, Chicago, IL 60612, U.S.A.*

Abstract

We introduce a model for ionic electrodiffusion and osmotic water flow through cells and tissues. The model consists of a system of partial differential equations for ionic concentration and fluid flow with interface conditions at deforming membrane boundaries. 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 which electrodiffusion and osmotic water flow are important can be 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

---

[*] Corresponding Author

Email addresses: `ymori@math.umn.edu` (Yoichiro Mori), `liu@math.psu.edu` (Chun Liu), `beisenbe@rush.edu` (Robert S. Eisenberg)

Preprint submitted to Elsevier *May 13, 2011*

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

katzir1965nonequilibrium,kedem1958thermodynamic,kjel

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 $c_k, k = 1, \cdots, N$ 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].

lee2008immersed,atzberger2009microfluidic,la

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.

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

diffosm

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 $\Omega_e = \Omega \backslash (\Omega_i \cup \Gamma)$. In the context of cell biology, Ω_i may be identified with the intracellular space and Ω_e the extracellular space (Fig. 1). 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.

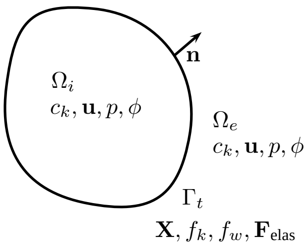

Figure 1: Ω_i and Ω_e are the extracellular and intracellular spaces respectively. Γ_t is the membrane, which may move with time. In the ionic concentrations c_k fluid velocity $\mathbf{u}$, and pressure p are defined in both Ω_i and Ω_e. The position of the time-dependent membrane location is given by $\mathbf{X}$. Defined on the membrane are the solute flux f_k, water flux f_w and the elastic force $\mathbf{F}_{\text{mem}}$. In the electrolyte case, we also have the electrostatic potential ϕ defined in Ω_i and Ω_e. $\mathbf{n}$ is the outward normal on Γ_t. `cellfig`

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

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

`ent`

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:

$$\mu_k = \sigma_k, \ \sigma_k \equiv \frac{\partial \omega}{\partial c_k}. \tag{2.2}$$

`mukc`

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.

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

$$\frac{\partial c_k}{\partial t} + \nabla \cdot (\mathbf{u} c_k) = \nabla \cdot \left(c_k \frac{D_k}{k_B T} \nabla \mu_k \right) \tag{2.3}$$

`ckeq`

where D_k is the diffusion coefficient and $\mathbf{u}$ is the fluid velocity field. Using (2.2) and (2.1), we see that c_k simply satisfies the advection-diffusion equation. 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.

katzir1965nonequilibrium,degroot1962non,kjelstrup2

On the outer boundary $\Gamma_{\rm out} = \partial\Omega$, 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 $\Gamma_{\rm ref}$ 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 $\Gamma_{\rm ref}$, 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:

$$c_k\left(\mathbf{u} - \frac{D_k}{k_BT}\nabla\mu_k\right)\cdot\mathbf{n} = c_k\frac{\partial\mathbf{X}}{\partial t}\cdot\mathbf{n} + f_k \text{ on } \Gamma_i \text{ or } \Gamma_e. \tag{2.4}$$

ckbc

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 f_k is the chemical flux that passes through the membrane, where the flux going from Ω_i to Ω_e is taken to be positive. Equation (2.4) is just a statement of conservation of ions at the moving membrane. It is easy to check that (2.3) together with (2.4) implies conservation of each species. To close the system of equations, we need constitutive relations for f_k. The flux f_k is often given as a function of the solute concentrations on both sides of the membrane, and will be discussed further in relation to the free energy identity (2.17) discussed in the next section.

We now discuss force balance. We shall treat the cytosol as a viscous stokes fluid and the cell membrane as a two-dimensional surface whose forces can be derived from a suitable energy functional. This encompasses two-dimensional elasticity as well as surface tension and bending forces (Helfrich forces). 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. The cytosol contains a cytoskeletal network and may other structures that may render the stokesian description of the cytosolic fluid inadequate. We could, in principle, employ a more complete model of cell mechanics incorporating such complexities. 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. Even when the mechanical model is more complex, the incorporation of osmosis should proceed along the same lines.

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

$$\nu\Delta\mathbf{u} - \nabla p = 0, \ \nabla\cdot\mathbf{u} = 0 \tag{2.5}$$

`stokes`

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

$$\nabla\cdot\Sigma_m(\mathbf{u},p) = 0, \ \nabla\cdot\mathbf{u} = 0, \ \Sigma_m(\mathbf{u},p) = \nu(\nabla\mathbf{u} + (\nabla\mathbf{u})^T) - pI \tag{2.6}$$

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:

$$[\Sigma_m(\mathbf{u},p)\mathbf{n}] = \mathbf{F}_{\text{mem}}, \tag{2.7}$$

`forcebalance`

where $[\Sigma_m(\mathbf{u},p)\mathbf{n}]$ is the jump in the mechanical stress across the membrane. For any quantity w we shall hence forth let:

$$[w] = w|_{\Gamma_i} - w|_{\Gamma_e} \tag{2.8}$$

where $\cdot|_{\Gamma_{i,e}}$ expresses evaluation of quantities at the intracellular and extracellular faces of the membrane Γ respectively. In (2.7), $\mathbf{F}_{\text{mem}}$ is the elastic force per unit area of membrane.

We make some assumptions about the form of the membrane mechanical force. We assume that the membrane mechanical force can be derived from an energy functional. In the case of two-dimensional elasticity, the energy functional E_{mem} is most conveniently written in terms of integration against a reference coordinate system:

$$E_{\text{mem}}(\mathbf{X}) = \int_{\Gamma_{\text{ref}}} \mathcal{E}(\mathbf{X})\,dm_{\Gamma_{\text{ref}}} \tag{2.9}$$

`elas`

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 $\mathbf{F}_{\mathrm{mem}}(\mathbf{x})$ satisfies the relation:

$$\left.\frac{d}{ds}\right|_{s=0}\int_{\Gamma_{\mathrm{ref}}}\mathcal{E}(\mathbf{X}(\boldsymbol{\theta})+s\mathbf{Y}(\boldsymbol{\theta}))dm_{\Gamma_{\mathrm{ref}}} = -\int_{\Gamma}\mathbf{F}_{\mathrm{mem}}(\mathbf{x})\cdot\mathbf{Y}(\mathbf{X}^{-1}(\mathbf{x}))dm_{\Gamma} \tag{2.10}$$

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 $m_{\Gamma_{\mathrm{ref}}}$ by $dm_\Gamma = Q dm_{\Gamma_{\mathrm{ref}}}$ 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, $\mathbf{F}_{\mathrm{mem}}$ is given as the variational derivative of the elastic energy up to the Jacobian factor Q. Consequently, we have the following relation:

$$\frac{d}{dt}E_{\mathrm{mem}}(\mathbf{X}) = -\int_{\Gamma}\mathbf{F}_{\mathrm{mem}}\cdot\frac{\partial\mathbf{X}}{\partial t}dm_{\Gamma}. \tag{2.11}$$ `dtelas`

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.

We point out that surface tension and bending forces (Helfrich forces), which are usually not considered "elastic", can also be derived as a variational derivative of a suitable energy functional, and thus falls within our framework. We shall not treat this case explicitly here, since the computations are more or less identical.

An variant of (2.7) is the following. Suppose the membrane is incompressible in the sense that $Q \equiv 1$ for all time. This is the condition that the membrane is a two-dimensional incompressibile material. When $Q \equiv 1$ for all time, we let:

$$[(\Sigma_m(\mathbf{u}, p)\mathbf{n}] = \mathbf{F}_{\mathrm{mem}} + \mathbf{F}_{\mathrm{p}} \tag{2.12}$$ `forcebalanceinc`

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

$$\mathbf{F}_{\mathrm{p}} = \lambda\kappa_\Gamma\mathbf{n} - \nabla_\Gamma\lambda. \tag{2.13}$$ `Fp`

The above is a surface pressure and λ is determined so that $Q \equiv 1$.

In addition to the force balance condition (2.7), 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:

$$\mathbf{u} - \frac{\partial\mathbf{X}}{\partial t} = f_w\mathbf{n} \tag{2.14}$$ `cont`

where f_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, f_w is positive when water is flowing out of the cell. To close the system of equations, we need constitutive relations for f_w. We will discuss this in relation to the free energy identity (2.17), to which we now turn.

2.2. Free Energy Identity

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

$$\psi_w^0 \equiv \pi_w + p,\ \pi_w = \left(\omega - \sum_{k=1}^{N} c_k\sigma_k\right) = \left(\omega - \sum_{k=1}^{N} c_k \frac{\partial \omega}{\partial c_k}\right) \tag{2.15}$$

`muw`

where p is the pressure that appeared in (2.5). We also define:

$$\begin{aligned} [\psi_w] &= \psi_w|_{\Gamma_i} - \psi_w|_{\Gamma_e} \\ \psi_w|_{\Gamma_{i,e}} &= \pi_w|_{\Gamma_{i,e}} - ((\Sigma_m(\mathbf{u},p)\mathbf{n})\cdot\mathbf{n})|_{\Gamma_{i,e}} \end{aligned} \tag{2.16}$$

`psiwexp`

where π_w was defined in (2.15). Note that $[\psi_w]$ reduces to $\left[\psi_w^0\right]$ when the fluid velocity $\mathbf{u} = \mathbf{0}$. We shall see shortly that ψ_w^0 has the physical interpretation as the water potential. We may now state the free energy identity.

`mainc` **Theorem 2.1.** *Suppose* $c_k, \mathbf{u}, p$ *be smooth functions that satisfy* (2.3), (2.5), *and in* Ω_i *and* Ω_e *and satisfy boundary conditions* (2.4), (2.7), (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.*

$$\begin{aligned} \frac{d}{dt}(G_S + E_{mem}) &= -I_p - J \\ G_S &= \int_{\Omega_i\cup\Omega_e} \omega d\mathbf{x} \\ I_p &= \int_{\Omega_i\cup\Omega_e} \left(\nu\left|\nabla\mathbf{u}\right|^2 + \sum_{k=1}^{N} c_k \frac{D_k}{k_BT}\left|\nabla\mu_k\right|^2\right) d\mathbf{x} \\ J &= \int_{\Gamma}\left([\psi_w]f_w + \sum_{k=1}^{N}[\mu_k]f_k\right) dm_\Gamma \end{aligned} \tag{2.17}$$

`FE`

Here, E_{mem} *was given in* (2.9), $|\nabla\mathbf{u}|$ *is the Frobenius norm of the* 3×3 *rate of deformation matrix* $\nabla\mathbf{u}$ *and* $[\psi_w]$ *was defined in* (2.16). *Identity* (2.17) *also holds if* (2.12) *is used in place of* (2.7).

An interesting point about the calculation to follow is that the quantity ψ_w arises naturally as a result of integrating by parts.

Proof of Theorem 2.1. First, multiply (2.3) with μ_k in (3.1) and integrate over Ω_i and sum in k:

$$\sum_{k=1}^{N}\int_{\Omega_i} \mu_k\left(\frac{\partial c_k}{\partial t} + \nabla\cdot(\mathbf{u}c_k)\right) d\mathbf{x} = \sum_{k=1}^{N}\int_{\Omega_i} \mu_k \nabla\cdot\left(c_k\frac{D_k}{k_BT}\nabla\mu_k\right) d\mathbf{x}. \tag{2.18}$$

`mkck`

The summand in the right hand side becomes:

$$\begin{aligned}\int_{\Omega_i} \mu_k \nabla \cdot \left(c_k \frac{D_k}{k_B T} \nabla \mu_k \right) d\mathbf{x} = &\int_{\Gamma_i} \left(\mu_k c_k \frac{D_k}{k_B T} \nabla \mu_k \cdot \mathbf{n} \right) dm_\Gamma \\ &- \int_{\Omega_i} \left(c_k \frac{D_k}{k_B T} \left| \nabla \mu_k \right|^2 \right) d\mathbf{x}\end{aligned} \tag{2.19}$$

where $\mathbf{n}$ is the outward normal on Γ. Consider the left hand side of (2.18).

$$\sum_{k=1}^{N} \mu_k \left(\frac{\partial c_k}{\partial t} + \nabla \cdot (\mathbf{u} c_k) \right) = \sum_{k=1}^{N} \frac{\partial \omega}{\partial c_k} \left(\frac{\partial c_k}{\partial t} + \mathbf{u} \cdot \nabla c_k \right) = \frac{\partial \omega}{\partial t} + \nabla \cdot (\mathbf{u} \omega), \tag{2.20}$$

`mkcksum`

where we used (2.2) and the incompressibility condition in (2.5). Integrating the above over Ω_i, we have:

$$\begin{aligned}\int_{\Omega_i} \left(\frac{\partial \omega}{\partial t} + \nabla \cdot (\mathbf{u} \omega) \right) d\mathbf{x} &= \int_{\Omega_i} \frac{\partial \omega}{\partial t} d\mathbf{x} + \int_{\Gamma_i} \omega \mathbf{u} \cdot \mathbf{n} dm_\Gamma \\ &= \frac{d}{dt} \int_{\Omega_i} \omega d\mathbf{x} + \int_{\Gamma_i} \omega \left(\mathbf{u} - \frac{\partial \mathbf{X}}{\partial t} \right) \cdot \mathbf{n} dm_\Gamma\end{aligned} \tag{2.21}$$

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:

$$\begin{aligned}&\frac{d}{dt} \int_{\Omega_i \cup \Omega_e} \omega d\mathbf{x} + \int_\Gamma [\omega] f_w dm_\Gamma \\ =&\sum_{k=1}^{N} \int_\Gamma \left[\mu_k c_k \frac{D_k}{k_B T} \nabla \mu_k \cdot \mathbf{n} \right] dm_\Gamma - \sum_{k=1}^{N} \int_{\Omega_i \cup \Omega_e} \left(c_k \frac{D_k}{k_B T} \left| \nabla \mu_k \right|^2 \right) d\mathbf{x}.\end{aligned} \tag{2.22}$$

`domega`

where we used (2.14). Using (2.4) and (2.14), we may rewrite the second boundary integral as follows:

$$\int_\Gamma \left[\mu_k c_k \frac{D_k}{k_B T} \nabla \mu_k \cdot \mathbf{n} \right] dm_\Gamma = \int_\Gamma \left([\mu_k c_k] f_w - [\mu_k](f_k) \right) dm_\Gamma. \tag{2.23}$$

`concbndry`

We now turn to equation (2.5). Multiply this by $\mathbf{u}$ and integrate over Ω_i:

$$\int_{\Omega_i} \mathbf{u} \cdot (\nu \Delta \mathbf{u} - \nabla p) d\mathbf{x} = \int_{\Gamma_i} (\Sigma_m(\mathbf{u}, p)\mathbf{n}) \cdot \mathbf{u} dm_\Gamma - \int_{\Omega_i} \nu \left| \nabla \mathbf{u} \right|^2 d\mathbf{x} = 0 \tag{2.24}$$

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

$$\int_\Gamma [(\Sigma_m(\mathbf{u}, p)\mathbf{n})] \cdot \mathbf{u} dm_\Gamma - \int_{\Omega_i \cup \Omega_e} \nu \left| \nabla \mathbf{u} \right|^2 d\mathbf{x} = 0 \tag{2.25}$$

We may use (2.7), (2.11) and (2.14) to find

$$\frac{d}{dt}E_{\mathrm{mem}}(\mathbf{X}) = \int_\Gamma \left[(\Sigma_m(\mathbf{u},p)\mathbf{n})\cdot\mathbf{n}\right] j_w dm_\Gamma - \int_{\Omega_i\cup\Omega_e} \nu\left|\nabla\mathbf{u}\right|^2 d\mathbf{x} \tag{2.26}$$

elasen

Combining (2.22), (2.23) and (2.26), we have:

$$\begin{aligned}
&\frac{d}{dt}\left(\int_{\Omega_i\cup\Omega_e}\omega d\mathbf{x} + E_{\mathrm{mem}}(\mathbf{X})\right)\\
&= -\sum_{k=1}^N \int_{\Omega_i\cup\Omega_e}\left(c_k\frac{D_k}{k_BT}\left|\nabla\mu_k\right|^2\right)d\mathbf{x} - \int_{\Omega_i\cup\Omega_e}\nu\left|\nabla\mathbf{u}\right|^2 d\mathbf{x} \qquad (2.27)\\
&\quad - \int_\Gamma [\mu_k](f_k)dm_\Gamma - \int_\Gamma\left[\omega - c_k\sigma_k - (\Sigma_m(\mathbf{u},p)\mathbf{n})\cdot\mathbf{n}\right] f_w dm_\Gamma
\end{aligned}$$

Recalling the definition of ψ_w in (2.16), we obtain the desired equality. A similar calculation shows that the free energy identity holds under the boundary condition (2.12). □

Identity (2.17) should be viewed as expressing free energy balance. The free energy consists of the entropic contribution G_S and the membrane elasticity term E_{mem}. The change in free energy is through bulk fluxes (the term I_p) and through membrane fluxes (the term J). The term I_p is clearly positive and thus represents a dissipation of free energy. It consists of viscous dissipation due to fluid motion and dissipation due to solute diffusion. The term J is written as a sum of $[\mu_k]\,f_k$, the free energy contribution from ions and $[\psi_w]\,f_w$, the free energy contribution from transmembrane waterflow. Expression ψ_w may thus be interepreted as the change in free energy as a unit volume of water traverses the membrane. Thus, $[\psi_w]$ can be seen as the *water potential* (the free energy per unit volume of water) difference across the membrane. Under conditions of no flow ($\mathbf{u}=0$), $[\psi_w]$ reduces to:

$$[\psi_w] = \left[\psi_w^0\right] = [p] - [\pi_w]\,, \quad [\pi_w] = \sum_{k=1}^N [c_k]\,k_BT. \tag{2.28}$$

where we have used (2.16), (2.15) and (2.1) for the expression for ω. This is indeed the familiar expression for the water potential; it is given as the sum of the mechanical pressure difference $[p]$ and the *osmotic pressure* difference $-[\pi_w]$, where the osmotic pressure is given by the van't Hoff formula. In this sense, we may say that we have derived the van't Hoff expression for osmotic pressure as a natural consequence of the free energy identity. The quantity $[\psi_w]$ can be seen as the appropriate modification to the water potential jump under non-zero flow conditions.

The term J does not in general have a definite sign. Let us divide f_k and f_w as follows:

$$f_k = j_k + a_k, \quad f_w = j_w + a_w, \tag{2.29}$$

and assume that j_k and j_w together satisfy:

$$J_p \equiv [\psi_w]\, j_w + \sum_{k=1}^{N} [\mu_k]\, j_k \geq 0. \tag{2.30}$$

`Jppassive`

We also introduce the quantity:

$$J_a \equiv [\psi_w]\, a_w + \sum_{k=1}^{N} [\mu_k]\, a_k \tag{2.31}$$

`Ja`

so that $J_p + J_a = J$. Given its positivity, J_p represents dissipation of the free energy through solute fluxes and water flow across the membrane. Thus, j_k and j_w are the *passive* solute and water fluxes respectively. The fluxes a_k and a_w are the *active* fluxes and J_a does not have a definite sign. The term J_a represents external free energy input due to these active fluxes.

It is sometimes useful to rewrite $J_p + I_p$ as:

$$\begin{aligned} J_p + I_p &= F_w + F_c, \\ F_w &= \int_{\Omega_i \cup \Omega_e} \nu \left|\nabla \mathbf{u}\right|^2 d\mathbf{x} + \int_\Gamma [\psi_w] j_w dm_\Gamma, \\ F_c &= \int_{\Omega_i \cup \Omega_e} \sum_{k=1}^{N} c_k \frac{D_k}{k_B T} \left|\nabla \mu_k\right|^2 d\mathbf{x} + \int_\Gamma \sum_{k=1}^{N} [\mu_k] j_k dm_\Gamma, \end{aligned} \tag{2.32}$$

`Fwc`

where F_w and F_c are the dissipations due to water flow and solute diffusion respectively.

We now discuss the constitutive relations for j_k and j_w, which specify the functional dependence of j_k and j_w with respect to c_k, $\mathbf{u}$ and p evaluated on both sides of the membrane.. 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. The water flux j_w may represent passive water flow through the lipid bilayer or through water channels (aquaporins). If the constitutive relations for j_k and j_w satisfy the following inequalities, (2.30) is trivially satisfied:

$$[\mu_k] j_k \geq 0, \text{ for all } k, \tag{2.33}$$

`jkcond`

$$[\psi_w]\, j_w \geq 0. \tag{2.34}$$

`jwcond`

The flux functions j_k and j_w satisfy the above if:

$$\begin{aligned} j_k = j_k([\mu_k]),\ j_k([\mu_k] = 0) = 0,\ \frac{dj_k}{d[\mu_k]} > 0 \\ j_w = j_w([\psi_w]),\ j_w([\psi_w] = 0) = 0,\ \frac{dj_w}{d[\psi_w]} > 0. \end{aligned} \tag{2.35}$$

`monotone`

The condition on j_k says that the transmembrane flux of solute k is driven by $[\mu_k]$, the difference in chemical potential. Concrete examples of such a constitutive relation will be given in Section 3. The condition for j_w says that the transmembrane water flux is driven by the difference in water potential $[\psi_w]$, which is in turn given by the sum of mechanical pressure and osmotic pressure. We thus recover the familiar statement that water flows across the membrane according to mechanical and osmotic pressure differences.

There are important instances of passive currents j_k and j_w that satisfy (2.30) but do not satisfy (2.33) and (2.34). This is the case for 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) hille1982transport,Hille,tosteson1989membrane,boron2008medical,davson1970textbook [28, 12, 29, 2, 3]. Thus, the chemical potential gradient of one solute species can influence the flux of a different solute species. We note that such cross-diffusion can be relevant even in bulk solution tyrrell1971diffusion,justice1983conductance,hoheisel19 [30, 31, 32, 33, 34].

If $[\mu_k]$ and $[\psi_w]$ remain small, the dissipation J_p in (2.17) may be approximated by a quadratic form in the jumps:

$$\begin{aligned} J_p &= \int_\Gamma [\boldsymbol{\mu}]\cdot\mathbf{j}\,dm_\Gamma = \int_\Gamma [\boldsymbol{\mu}]\cdot(\mathcal{L}\,[\boldsymbol{\mu}])\,dm_\Gamma, \\ \boldsymbol{\mu} &= (\mu_1,\cdots,\mu_N,\psi_w)^T, \mathbf{j} = (j_1,\cdots,j_N,j_w)^T, \end{aligned} \tag{2.36}$$

quad

where $\mathcal{L}$ is a symmetric $(N+1)\times(N+1)$ matrix. Requiring that J_p be positive whenever $\boldsymbol{\mu}$ is not zero 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 $[\boldsymbol{\mu}]$:

$$\mathbf{j} = \mathcal{L}\,[\boldsymbol{\mu}]\,. \tag{2.37}$$

Note that, without the maximum dissipation principle, (2.36) 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 degroot1962non,katzir1965nonequilibrium,kjelstrup2008non [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, (2.33) and (2.34) are not necessarily true, whereas condition (2.30) is true by construction.

The active flux a_k and a_w is typically due to ionic pump currents often driven by chemical energy expenditure (most commonly, the hydrolysis of ATP) tosteson1989membrane,boron2008medical,davson1970textbook [29, 2, 3].

3. Electrodiffusion of Ions and Osmotic Water Flow

elecdiff

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 $c_k, k = 1,\cdots,N$ 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:

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

`muk`

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^0 and ψ_w, remain the same. The ionic concentrations c_k satisfy (2.3) and (2.4) 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. The transmembrane flux f_k is now a function also of the membrane potential $[\phi]$ in addition to the dependencies discussed in the previous section. We shall discuss the constitutive relations for f_k in relation to the free energy identity to be presented in Theorem (3.1).

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 `fawcett2004liquids,lee2008molecular,kunz`[35, 36, 37, 38, 39]. Cross-diffusion (or flux coupling) in the bulk can also be significant in electrolyte solutions `tyrrell1971diffusion,justice1983conductance,hoheisel1993theoretical, taylor1993multicompor`[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 molars `eisenberg2010crowded,zhang2010molecular`[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 `eisenberg2010energy`[41].

The electrostatic potential ϕ satisfies the Poisson equation:

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

`poisson`

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:

$$-\epsilon \left.\frac{\partial \phi}{\partial \mathbf{n}}\right|_{\Gamma_i} = -\epsilon \left.\frac{\partial \phi}{\partial \mathbf{n}}\right|_{\Gamma_e} = C_m[\phi]. \tag{3.3}$$

`cap`

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 $\mathbf{x} = \mathbf{X}(\boldsymbol{\theta}, t)$,

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

$\boxed{\texttt{CmQ}}$

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:

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

$\boxed{\texttt{Cm0}}$

As another example, we may set:

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

$\boxed{\texttt{Cmscaling}}$

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:

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

$\boxed{\texttt{stokesE}}$

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

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

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:

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

$\boxed{\texttt{forcebalanceE}}$

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

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

FcapCmQ

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 Appendix A, we give a physical interpretation of expression (3.10).

In the same way as discussed in the previous section, we may impose the membrane incompressiblity constraint $Q \equiv 1$. In this case, the boundary condition (3.9) is modified as follows:

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

forcebalancep

where the expression for $\mathbf{F}_p$ is the same as in (2.13). In (3.11) we do not need a capacitive force since it can be absorbed into the surface pressure term. 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.

The continuity condition (2.14) remains the same. We shall discuss the constitutive relation for f_w in relation to Theorem 3.1.

We remark that the model we just proposed *in the bulk* is nothing other than the Poisson-Nernst-Planck-Stokes system if we let $\omega = \omega_0$ given in (2.1) [42]. Indeed, the Poisson Nernst-Planck system has received much attention in the field of semiconductors [43, 44, 45], ionic channels [46], ion exchange membranes and desalination [42] as well as physical chemistry [47]. The novelty here is in the interface conditions at the membrane, (2.4), (3.3), (3.9) and (2.14). Most non-equilibrium thermodynamic field theories have focused on the bulk equations, and boundary conditions are usually very simple (Neumann or Dirichlet) if not an afterthought. On the other hand, non-equilibrium thermodynamic theories of membranes that deal with osmosis and/or electrodiffusion are usually ODE models that neglect any kind of spatial variation. Our model is the first in which bulk and membrane biophysical processes are seamlessly linked to produce a consistent thermodynamic field theory of electrodiffusion and osmosis. Indeed, the free energy indentity, to which we now turn, consists of both membrane and bulk terms.

3.2. Free Energy Identity

We now show that the system described in the previous section possesses a natural free energy. The proof of this result is somwhat technical and is relegated to Appendix Appendix B.

main **Theorem 3.1.** *Suppose* $c_k, \mathbf{u}, p$ *and* ϕ *are smooth functions that satisfy* (2.3), (3.7), *and* (3.2) *in* Ω_i *and* Ω_e *and satisfy boundary conditions* (2.4), (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.*

$$\begin{aligned}\frac{d}{dt}(G_S + E_{mem} + E_{elec}) &= -I_p - J \\ E_{elec} &= \int_{\Omega_e \cup \Omega_e} \frac{1}{2}\epsilon \left|\nabla\phi\right|^2 d\mathbf{x} + \int_\Gamma \frac{1}{2} C_m [\phi]^2 dm_\Gamma\end{aligned} \tag{3.12}$$ FEE

Here, G_S, E_{mem}, I_p, J *are the same as in* (2.17). *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 (3.12), in addition to the terms present in (2.17), we now have an electrostatic term in the energy.

Similarly to the non-electrolyte case, we let $f_k = j_k + a_k$ and $f_w = j_w + a_w$ so that j_k and j_w express passive fluxes. The property that j_k and j_w are passive is expressed by condition (2.30). In contrast to the non-electrolyte case, however, the chemical potential jump $[\mu_k]$ now depend on the membrane potential $[\phi]$, and thus, j_k (and j_w) may strongly depend on the membrane potential.

Let us briefly discuss the constitutive relations for j_k. The passive ionic flux is typically carried through ionic channels and transporters. Some of popular choices j_k include KS,Hille,HH [14, 12, 48]:

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

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

where g_k and P_k are positive and depend on the gating variables in certain modeling contexts Hille, HH [12, 48]. It is easily seen that both j_k^{HH} and j_k^{GHK} satisfy (2.33), which, together with (2.34), constitutes a sufficient condition for (2.30) to hold. We shall use expression (3.14) in our numerical computations in Section 5.

4. Limiting Systems

simple

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.

$$\mathbf{x} = L\mathbf{x}',\ \mathbf{X} = L\mathbf{X}',\ t = T_D t',\ T_D = \frac{L^2}{D_0},\ D_k = D_0 D_k', \tag{4.1}$$

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:

$$c_k = c_0 c_k',\ \phi = \frac{k_B T}{q}\phi'. \tag{4.2}$$

For pressure and the membrane elastic force, we let:

$$p = c_0 k_B T p',\ \mathbf{F}_{\text{mem}} = c_0 k_B T \mathbf{F}'_{\text{mem}}. \tag{4.3}$$

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:

$$\zeta = \left.\frac{\partial j_w}{\partial[\psi_w]}\right|_{[\psi_w]=0}. \tag{4.4}$$

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

$$\mathbf{u} = \zeta c_0 k_B T \mathbf{u}'. \tag{4.5}$$

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:

$$\mu_k' = z_k \phi' + \ln c_k'. \tag{4.6}$$

dlessfull

In Ω_i and Ω_e, we have:

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

dlessck

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

dlesspoisson

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

dlessstokes

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

$$\mathrm{Pe} = \frac{\zeta c_0 k_B T}{D/L},\ \beta = \frac{r_d}{L},\ r_d = \sqrt{\frac{\epsilon k_B T}{q^2 c_0}},\ \gamma = \frac{\nu\zeta}{L}. \tag{4.7d} \qquad \boxed{\texttt{Pebeta}}$$

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:

$$\left.\left(\left(c_k'\left(\mathrm{Pe}\mathbf{u}' - \frac{\partial \mathbf{X}'}{\partial t'}\right) + \mathbf{f}_k'\right)\cdot\mathbf{n}\right)\right|_{\Gamma_{i,e}} = \alpha(j_k' + a_k'), \tag{4.7e} \qquad \boxed{\texttt{dlessckbc}}$$

$$-\left.(\beta\nabla'\phi'\cdot\mathbf{n})\right|_{\Gamma_{i,e}} = \theta C_m' \left[\phi'\right], \tag{4.7f} \qquad \boxed{\texttt{dlessbcpoisson}}$$

$$\mathbf{u}' - \frac{1}{\mathrm{Pe}}\frac{\partial \mathbf{X}'}{\partial t'} = j_w' + a_w'\mathbf{n}, \tag{4.7g} \qquad \boxed{\texttt{dlesscont}}$$

$$\left[\left(\Sigma_m'(\mathbf{u}', p') + \beta^2\Sigma_e'(\phi')\right)\mathbf{n}\right] = \mathbf{F}_{\mathrm{mem}}' + \beta\theta\mathbf{F}_{\mathrm{cap}}'. \tag{4.7h} \qquad \boxed{\texttt{dlessforce}}$$

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:

$$\alpha = \frac{p_m}{D/L},\ p_m = \sum_{k=1}^{N} \frac{k_B T}{c_0} \left.\frac{\partial j_k}{\partial\left[\mu_k\right]}\right|_{[\mu_k]=0}. \tag{4.8} \qquad \boxed{\texttt{alphapm}}$$

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):

$$C_m = C_m^0 C_m',\ \theta = \frac{C_m^0 k_B T/q}{q c_0 r_d}, \tag{4.9}$$

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), $j_w = \zeta c_0 k_B T j_w'$ and similarly for a_w and a_w'. The variables in (4.7h), are defined by:

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

$$\Sigma_e'(\phi') = \nabla'\phi' \otimes \nabla\phi' - \frac{1}{2}\left|\nabla'\phi'\right|^2 I, \tag{4.11}$$

$$\mathbf{F}_{\mathrm{cap}} = \tau_{\mathrm{cap}}'\kappa_\Gamma'\mathbf{n} - \nabla_\Gamma'\tau_{\mathrm{cap}}',\ \tau_{\mathrm{cap}}' = \frac{1}{2}\left(C_m' + Q\frac{\partial C_m'}{\partial Q}\right)\left[\phi'\right]^2 \tag{4.12}$$

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 $\mathrm{Pe} \ll 1$. Assuming all primed quantities are $\mathcal{O}(1)$ with respect to Pe, we see, from (4.7g) that

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

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:

`Pe0`

$$\begin{aligned}
\frac{\partial c_k}{\partial t} &= -\nabla \cdot \mathbf{f}_k \text{ in } \Omega_{i,e} && (4.14\text{a})\\
-\nabla \cdot (\beta^2 \nabla \phi) &= \sum_{k=1}^{N} z_k c_k \text{ in } \Omega_{i,e} && (4.14\text{b})\\
(\mathbf{f}_k \cdot \mathbf{n})|_{\Gamma_{i,e}} &= \alpha(j_k + a_k), && (4.14\text{c})\\
-\left.(\beta \nabla \phi \cdot \mathbf{n})\right|_{\Gamma_{i,e}} &= \theta C_m [\phi], && (4.14\text{d})
\end{aligned}$$

where the membrane Γ is fixed in time. This model was introduced in [49] (see also [50, 51] for related models).

`leonetti_biomembrane_1998` `schaff1997general,choi1999electrodiffusion`

For single cell systems, the Péclet number is about $\mathrm{Pe} \approx 10^{-1}$ 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:*

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

`PeFE`

In the above, G_S, E_{elec}, F_c and J_a are dimensionless versions of the corresponding quantities in (2.17), (2.32) *and* (3.12).

Proof. This follows from a simple calculation. □

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 (3.12) 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 $\beta \to 0$ `beta0` in (4.7) we obtain the following system of equations:

$$\begin{aligned}
\frac{\partial c_k}{\partial t} + \mathrm{Pe}\mathbf{u}\cdot\nabla c_k &= -\nabla\cdot\mathbf{f}_k \text{ in } \Omega_{i,e} && \text{(4.16a)} \quad \boxed{\texttt{dlessckbeta0}}\\
\sum_{k=1}^{N} z_k c_k &= 0 \text{ in } \Omega_{i,e}, && \text{(4.16b)} \quad \boxed{\texttt{dlessEN}}\\
\gamma\Delta\mathbf{u} - \nabla p = 0, \quad \nabla\cdot\mathbf{u} &= 0 \text{ in } \Omega_{i,e}, && \text{(4.16c)} \quad \boxed{\texttt{beta0stokes}}\\
\alpha(j_k + a_k) &= \left(\left(c_k\left(\mathrm{Pe}\mathbf{u} - \frac{\partial \mathbf{X}}{\partial t}\right) + \mathbf{f}_k\right)\cdot\mathbf{n}\right)\Big|_{\Gamma_{i,e}}, && \text{(4.16d)} \quad \boxed{\texttt{dlessbeta0ckbc}}\\
\mathbf{u} - \frac{1}{\mathrm{Pe}}\frac{\partial \mathbf{X}}{\partial t} &= (j_w + a_w)\mathbf{n}, \quad [\Sigma_m(\mathbf{u},p)\mathbf{n}] = \mathbf{F}_{\mathrm{mem}} \text{ on } \Gamma. && \text{(4.16e)} \quad \boxed{\texttt{beta0stokesbc}}
\end{aligned}$$

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):

$$\begin{aligned}
0 &= \nabla\cdot(a\nabla\phi + \mathbf{b})\\
a &= \sum_{k=1}^{N} z_k^2 D_k c_k, \; \mathbf{b} = \sum_{k=1}^{N} z_k D_k \nabla c_k.
\end{aligned} \qquad \text{(4.17)} \quad \boxed{\texttt{phieqbeta0}}$$

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 $\beta \to 0$, $\Delta\phi$ 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):

$$-\left(a\nabla\phi + \tilde{\mathbf{b}}\right)\cdot\mathbf{n}\Big|_{\Gamma_{i,e}} = \sum_{k=1}^{N} \alpha z_k (j_k + a_k). \qquad \text{(4.18)} \quad \boxed{\texttt{phieqbeta0bc}}$$

Suppose

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

`currdownhill`

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 (2.35)). 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:

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

`phieq`

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

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

`phieqbc`

If we formally let $\beta\to 0$ 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 $\beta\to 0$. It is thus only when the evolution of ϕ and $[\phi]$ is sufficiently slow that we can reliably use system (4.16) as 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 HH,KS [48, 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 Sinica [52] and was applied in mori_ephaptic_2008 [53] 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 morithesis,mori2009tde [54, 55] 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* $c_k, \phi, \mathbf{u}$ *and* p *are smooth functions that satisy system* (4.16)*. Then, the following equality holds:*

$$\frac{d}{dt}\left(G_S + E_{mem}\right) = -I_p - J_p - J_a. \tag{4.22}$$ ENFE

In the above, G_S, E_{mem}, I_p, J_p *and* J_a *are dimensionless versions of corresponding quantities in* (2.17) *and* (3.12)*.*

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

Thus, system (4.16) may be seen as the system associated with the energy principle (4.22) in which the electrostatic energy in (3.12) is discarded.

5. Numerical Simulation of Animal Cell Volume Control

animal

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 $\Gamma_{\text{out}} = \partial\Omega$ 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

radial are functions only of the (dimensionless) radial coordinate r, we have:

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

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

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 a the radius of the outer boundary sphere Γ_{out}. The boundary conditions are:

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

$$-\frac{1}{\text{Pe}}\frac{\partial R}{\partial t} = j_w + a_w,\ [p] = F_{\text{mem}} \text{ at } r = R, \tag{5.1d}$$ radialflow

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_{mem} 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:

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

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:

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

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

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

The l-th segment is given by $r_{l-1} < r < r_l$. Of the $2N_v$ segments, segments $1 \le l \le N_v$ 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:

$$R^n = R^{n-1} - \mathrm{Pe}(j_w^{n-1} + a_w^{n-1})\Delta t. \tag{5.5}$$

In evaluating j_w, we need the osmotic pressure as well as the elastic force F_{mem}, 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:

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

`ckinr`

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 $c_{k,l}^n$:

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

`ckln`

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

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

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:

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

`ckmem`

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 $(R^n)^2 a_k^n$ and $(R^n)^2 j_k^n$ 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 in 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:

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

`discEN`

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:

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

In this case, we set:

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

`discbc`

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 6×10^{-14}mmol/ℓ for all simulation results shown below.

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

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

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 [56] 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, 57, 58, 59]. 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 $k = 1, \cdots, 4$ 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 $R_{\mathrm{out}} = 2R_0$. We assume that the membrane does not generate any mechanical force, so that $F_{\mathrm{mem}} = 0$. Passive water flow across the membrane is proportional to the water chemical potential. Given that $F_{\mathrm{mem}} = 0$, water flow across the cell membrane is driven osmotic pressure difference across the membrane:

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

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. We take the active water flux a_w to be equal to 0.

T (K)	$273.15 + 37$	K_k (mmol/ℓ)	0.75 [61]
ζ (cm/s/mPa)	5.2507×10^{-13} [60]	K_{Na} (mmol/ℓ)	3.5 [61]
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.

miscparams

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

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

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 [60, 61]. 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 [61] to use the following expression for the Na-K ATPase flux:

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

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 [61]. 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 $\Delta t =$ 500ms.

	z_k	D_k (cm^2/s)	P_k (cm/s)	$c_{k,\mathrm{int}}^{\mathrm{init}}$	$c_{k,\mathrm{ext}}^{\mathrm{init}}$
Na$^+$	$+1$	1.33×10^{-5} koch_biophysics_1999 [62]	1.0×10^{-7} fernandez_modeling_1998 [63]	10	145
K$^+$	$+1$	1.96×10^{-5} koch_biophysics_1999 [62]	-	140	5
Cl$^-$	-1	2.03×10^{-5} koch_biophysics_1999 [62]	1.0×10^{-7} fernandez_modeling_1998 [63]	-	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 $c_{k,\mathrm{int}}^{\mathrm{init}}$ and $c_{k,\mathrm{ext}}^{\mathrm{init}}$ 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.

ionparams

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 $t \geq 10$s:

$$c_{1,e} = 100,\ c_{2,e} = 50,\ c_{3,e} = 150, \tag{5.17}$$

hKcb

where the units are in mmol/ℓ. The boundary concentrations are thus isotonic 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 2. 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 $R = R_{\mathrm{out}}$. 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:

$$c_{1,e} = 100,\ c_{2,e} = 5,\ c_{3,e} = 105, \tag{5.18}$$

hypcb

where the concentrations are in mmol/ℓ. A snapshot of the computational results are given in Figure 3. The cell expands due to the hypotonic shock but tends to a new stationary state with time.

6. Conclusion

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

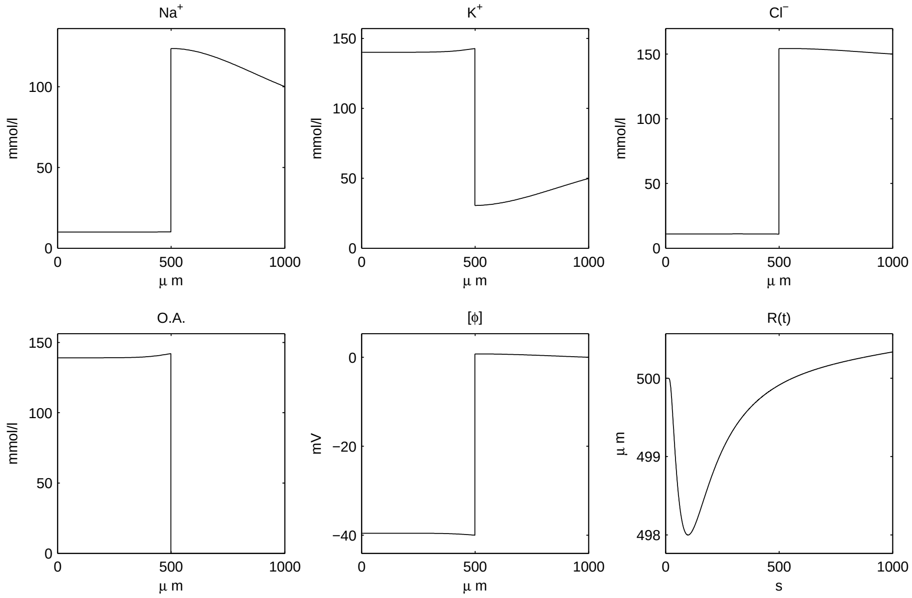

Figure 2: Computational results under a high K^+ stimulus (see (5.17)). The first five figures are the snapshots of the ionic concentrations and the electrostatic potential at $t = 50$s. The horizontal axis represents the radius r. The last figure plots the cell radius $R(t)$ as a function of time.

`highK`

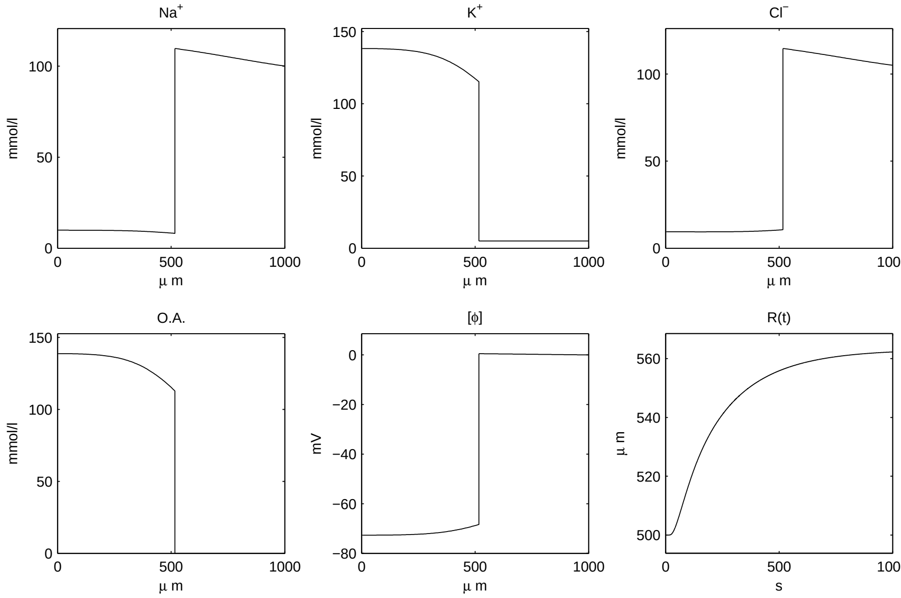

Figure 3: Computational results under hypotonic stimulus (see (5.18)). The first five figures are the snapshots of the ionic concentrations and the electrostatic potential at $t = 100$s. The horizontal axis represents the radius r. The last figure plots the cell radius $R(t)$ as a function of time.

`hypotonic`

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 (2.17), 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 `finkelstein1987water` [64].

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. The relationship between diffuse and sharp interface approaches have been clarified in `jamet2008thermodynamically,jamet2008toward,jamet2007towards,du2004phase, du2006simulating` [65, 66, 67, 68, 69, 70]. It should likewise 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 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 `onsager1931reciprocal` [71]. This procedure has been used successfully in deriving dynamic equations for soft matter systems `doi1988theory,doi2009gel` [72, 73]. In `eisenberg2010energy,hyon2010energetic` [41, 74], a model for non-ideal electrolyte solutions is derived by combining, in the spirit of Rayleigh (see `goldstein1980classical` [75]), the principle of least action with the above variational principle for dissipative system.

Biological systems are not purely dissipative, and are maintained through external free energy input (in the models presented here, this is provided by the active membrane fluxes a_k and a_w). Free energy equalities do not necessarily imply a decay in the free energy of the system. In particular, the free energy does not serve as a Lyapunov function. It is then natural to question the utility of such free energy equalities.

We believe these equalities are nonetheless important for at least two reasons. First, any mathematical model of a biophysical system should, ideally, satisfy a free energy decay inequality if external free energy input is set to zero. This places important restrictions on the equations one writes down. Indeed, this was our guiding principle in writing down the equations in Section 2 and Section 3. The second reason is that the free energy equality may be useful in obtaining dynamical insight into the solution to the system even in the presence of external free energy input. Recently the first author succeeded in showing that homeostatic steady states of a large class of pump-leak models are stable `mori2011cvctrl` [26]. Pump-leak models, used widely in the study of epithelial systems, may be seen as an ordinary differential equation reduction of the models presented in this paper. The stability proof was accomplished by constructing a Lyapunov function by suitably modifying the free energy. Even in the case of the full PDE system described in this paper, it is conceivable that some modifications of the energy identities introduced here may be used to discuss stability of steady states `biler2000long,ryham2009existence` [76, 77].

We hope that our model has wide-ranging applications in cellular physiology. In principle, our model is applicable to most problems of classical physiology `davson1970textbook,boron2008medical,pappenheimer1987silver` [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 `leonetti_biomembrane_1998,leonetti_pattern_2004,mori_ephaptic_2008` [49, 78, 53]. 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 `CAMCoS, brera2010conservative` [56, 79] 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 `layton2006modeling,ibmethod,li_immersed_2006` [25, 80, 81].

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 `KS,eisenberg_three-dimensional_1970,eisenberg1979electrical, mathias1979electrical,neu1993hst` [14, 82, 83, 84, 85]. We shall report on a such a multidomain model in a future publication.

Appendix A. Physical Interpretation of the Capacitive Force

`capforce`

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 $d \to 0$.

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 total stress inside the membrane, which we call Σ^{mem}, is given by:

$$\Sigma^{\mathrm{mem}} = \Sigma_e^{\mathrm{mem}} - p^{\mathrm{mem}} I \tag{A.1}$$

sigmamem

where Σ_e^{mem} is the Maxwell stress, $p^{\mathrm{mem}} I$ 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:

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

sigmaemem

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:

$$\Sigma^{\mathrm{mem}}\mathbf{n} = \Sigma^{\Omega_e}\mathbf{n} \tag{A.3}$$

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

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

sigmamemexp

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

$$p^{\mathrm{mem}} = C_m \frac{[\phi]^2}{2d} \tag{A.5}$$

to leading order in d.

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

$$\Sigma^{\mathrm{mem}}\mathbf{t} = -\frac{1}{d} C_m [\phi]^2 \mathbf{t}, \tag{A.6}$$

to leading order in d. Multiplying the above by the thickness d of the membrane, and taking the limit as $d \to 0$, 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 B. Proof of Theorem 3.1

proof_of_thm_main

We first collect some calculus results. Let us introduce some notation. Take a point $\mathbf{x} = \mathbf{x}_0 \in \Gamma$ at $t = t_0$. Let $\mathbf{X}^{\mathbf{n}}(t; x_0, t_0)$ 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:

$$\frac{d}{dt}\mathbf{X}^{\mathbf{n}}(t; \mathbf{x}_0, t_0) = v_\Gamma(\mathbf{X}^{\mathbf{n}}, t)\mathbf{n}(\mathbf{X}^{\mathbf{n}}, t),\ \mathbf{X}^{\mathbf{n}}(t_0; , \mathbf{x}_0, t_0) = \mathbf{x}_0. \tag{B.1}$$

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:

$$(D_t^{\mathbf{n}} w)(\mathbf{x}_0, t_0) = \left.\frac{d}{dt} w(\mathbf{X}^{\mathbf{n}}(t; \mathbf{x}_0, t_0), t)\right|_{\mathbf{x}=\mathbf{x}_0, t=t_0}. \tag{B.2}$$ Dnt

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

$$\frac{d}{dt}\int_\Gamma w dm_\Gamma = \int_\Gamma (D_t^{\mathbf{n}} w + \kappa_\Gamma w v_\Gamma)\, dm_\Gamma \tag{B.3}$$ Dtw

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.

divongamma **Lemma Appendix B.1.** *Let $w(\mathbf{x}, t)$ be a smooth function on Γ_t. We have:*

$$\int_\Gamma \left(wQ^{-1}\frac{\partial Q}{\partial t}\right) dm_\Gamma = \int_\Gamma (\kappa_\Gamma w \mathbf{n} - (\nabla_\Gamma w)) \cdot \frac{\partial \mathbf{X}}{\partial t} dm_\Gamma. \tag{B.4}$$ Qt

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

Proof. Note that

$$\frac{\partial w}{\partial t} = D_t^{\mathbf{n}} w + (\nabla_\Gamma w) \cdot \frac{\partial \mathbf{X}}{\partial t} \tag{B.5}$$ wt

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.

$$\begin{aligned}\frac{d}{dt}\int_\Gamma w dm_\Gamma = \frac{d}{dt}\int_{\Gamma_{\text{ref}}} wQ dm_{\Gamma_{\text{ref}}} = \int_{\Gamma_{\text{ref}}}\left(\frac{\partial w}{\partial t}Q + w\frac{\partial Q}{\partial t}\right)dm_{\Gamma_{\text{ref}}}\\ = \int_\Gamma\left(\frac{\partial w}{\partial t} + wQ^{-1}\frac{\partial Q}{\partial t}\right)dm_\Gamma\end{aligned} \tag{B.6}$$

Comparing this with (B.3) (with $v_\Gamma = \frac{\partial \mathbf{x}}{\partial t}\cdot\mathbf{n}$) and using the identity (B.5), we obtain the desired result. $\square$

calcidentity **Lemma Appendix B.2.** *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:*

$$\begin{aligned}\int_{\Gamma_i}\left(w\frac{\partial}{\partial \mathbf{n}}\left(\frac{\partial w}{\partial t}\right) + (w\Delta w)v_\Gamma\right)dm_\Gamma\\ = \int_{\Gamma_i}\left(wD_t^{\mathbf{n}}\left(\frac{\partial w}{\partial \mathbf{n}}\right) + \left(\kappa_\Gamma w\frac{\partial w}{\partial \mathbf{n}} - |\nabla_\Gamma w|^2\right)v_\Gamma\right)dm_\Gamma\end{aligned} \tag{B.7}$$

identity

where $\int_{\Gamma_i}$ 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 (B.7) into tangential and normal contributions. It is well-known that the Laplacian can be written as:

$$\Delta w = \frac{\partial^2 w}{\partial \mathbf{n}^2} + \kappa_\Gamma\frac{\partial w}{\partial \mathbf{n}} + \Delta_\Gamma w \tag{B.8}$$

lapphi

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 (B.7) in an analogous fashion. For this, we first introduce the signed distance function $\psi(\mathbf{x}, t)$ in a neighborhood of Γ:

$$\psi(\mathbf{x}, t) = \begin{cases}\operatorname{dist}(\mathbf{x}, \Gamma_t) & \text{if } \mathbf{x} \in \Omega_e,\\ 0 & \text{if } \mathbf{x} \in \Gamma_t,\\ -\operatorname{dist}(\mathbf{x}, \Gamma_t) & \text{if } \mathbf{x} \in \Omega_i,\end{cases} \tag{B.9}$$

where $\operatorname{dist}(\mathbf{x}, \Gamma_t)$ 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:

$$\mathbf{v} = v_\Gamma\mathbf{n} \text{ on } \Gamma,\ (\nabla\mathbf{v})\nabla\psi = 0. \tag{B.10}$$

defv

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:

$$D_v\psi \equiv \frac{\partial \psi}{\partial t} + \mathbf{v}\cdot\nabla\psi = 0. \qquad \text{(B.11)} \qquad \boxed{\texttt{vtransport}}$$

Note that the above convective derivative evaluated on Γ is equal to $D_t^{\mathbf{n}}$ defined in (B.2).

For any point on Γ:

$$\frac{\partial}{\partial \mathbf{n}}\left(\frac{\partial w}{\partial t}\right) = \nabla\psi\cdot\nabla w_t \qquad \text{(B.12)}$$

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

$$\begin{aligned}\nabla\psi\cdot\nabla w_t &= D_v(\nabla\psi\cdot\nabla w) - \nabla\psi_t\cdot\nabla w - \mathbf{v}\cdot\nabla(\nabla\psi\cdot\nabla w)\\ &= D_v(\nabla\psi\cdot\nabla w) + \nabla(\mathbf{v}\cdot\nabla\psi)\cdot\nabla w - \mathbf{v}\cdot\nabla(\nabla\psi\cdot\nabla w)\end{aligned} \qquad \text{(B.13)} \qquad \boxed{\texttt{psiphit}}$$

where we used (B.11) in the last equality. Now, consider the second term in the last line:

$$\begin{aligned}\nabla(\mathbf{v}\cdot\nabla\psi)\cdot\nabla w =& \nabla_\Gamma(\mathbf{v}\cdot\nabla\psi)\cdot\nabla_\Gamma w + (\nabla\psi\cdot\nabla(\mathbf{v}\cdot\nabla\psi))(\nabla\psi\cdot\nabla w)\\ =& \nabla_\Gamma(\mathbf{v}\cdot\nabla\psi)\cdot\nabla_\Gamma w + (\nabla\psi\cdot((\nabla\mathbf{v})\nabla\psi))(\nabla\psi\cdot\nabla w)\\ &+ (\mathbf{v}\cdot((\nabla^2\psi)\nabla\psi))(\nabla\psi\cdot\nabla w)\end{aligned} \qquad \text{(B.14)} \qquad \boxed{\texttt{vpsiphi1}}$$

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 (B.14) is 0 by (B.10). The last term is also 0, since:

$$(\nabla^2\psi)\nabla\psi = \frac{1}{2}\nabla(|\nabla\psi|^2) = 0 \qquad \text{(B.15)} \qquad \boxed{\texttt{d2psi0}}$$

where we used $|\nabla\psi|^2 = 1$. Thus (B.14) reduces to

$$\nabla(\mathbf{v}\cdot\nabla\psi)\cdot\nabla w = \nabla_\Gamma(\mathbf{v}\cdot\nabla\psi)\cdot\nabla_\Gamma w. \qquad \text{(B.16)} \qquad \boxed{\texttt{vpsiphi11}}$$

Let us look at the final term in (B.13).

$$\mathbf{v}\cdot\nabla(\nabla\psi\cdot\nabla w) = (\mathbf{v}\cdot\nabla\psi)(\nabla\psi\cdot\nabla(\nabla\psi\cdot\nabla w)) = (\mathbf{v}\cdot\nabla\psi)(\nabla\psi\cdot((\nabla^2 w)\nabla\psi)) \quad \text{(B.17)} \qquad \boxed{\texttt{vpsiphi2}}$$

where we used (B.15) in the last equality. Combining (B.16), (B.17) and (B.13), we have:

$$\nabla\psi\cdot\nabla w_t = D_v(\nabla\psi\cdot\nabla w) + \nabla_\Gamma(\mathbf{v}\cdot\nabla\psi)\cdot\nabla_\Gamma w - (\mathbf{v}\cdot\nabla\psi)(\nabla\psi\cdot((\nabla^2 w)\nabla\psi)) \quad \text{(B.18)}$$

or equivalently:

$$\frac{\partial}{\partial \mathbf{n}}\left(\frac{\partial w}{\partial t}\right) = D_t^{\mathbf{n}}\left(\frac{\partial w}{\partial \mathbf{n}}\right) + \nabla_\Gamma v_\Gamma\cdot\nabla_\Gamma w - v_\Gamma\left(\frac{\partial^2 w}{\partial \mathbf{n}^2}\right) \qquad \text{(B.19)} \qquad \boxed{\texttt{dtdphidn}}$$

where we used (B.10), $\mathbf{n} = \nabla\psi$ on Γ and the equality of $D_t^{\mathbf{n}}$ and D_v on Γ.

Now, consider the integral:

$$\begin{aligned}
&\int_{\Gamma_i} \left(w\frac{\partial}{\partial \mathbf{n}}\left(\frac{\partial w}{\partial t}\right) + (w\Delta w)v_\Gamma \right) dm_\Gamma \\
=&\int_{\Gamma_i} \left(wD_t^{\mathbf{n}}\left(\frac{\partial w}{\partial \mathbf{n}}\right) + w\nabla_\Gamma v_\Gamma \cdot \nabla_\Gamma w + w\left(\Delta_\Gamma w + \kappa_\Gamma \frac{\partial w}{\partial \mathbf{n}}\right) v_\Gamma \right) dm_\Gamma \\
=&\int_{\Gamma_i} \left(wD_t^{\mathbf{n}}\left(\frac{\partial w}{\partial \mathbf{n}}\right) + \left(\kappa_\Gamma w\frac{\partial w}{\partial \mathbf{n}} - |\nabla_\Gamma w|^2\right) v_\Gamma \right) dm_\Gamma
\end{aligned} \tag{B.20}$$

where we used (B.8) and (B.19) 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 (B.7). □

We are now ready to prove Theorem 3.1.

Proof of Theorem 3.1. First, multiply (2.3) with μ_k in (3.1) and integrate over Ω_i and sum in k:

$$\sum_{k=1}^{N} \int_{\Omega_i} \mu_k \left(\frac{\partial c_k}{\partial t} + \nabla\cdot(\mathbf{u}c_k) \right) d\mathbf{x} = \sum_{k=1}^{N} \int_{\Omega_i} \mu_k \nabla\cdot\left(c_k \frac{D_k}{k_BT}\nabla\mu_k \right) d\mathbf{x}. \tag{B.21}$$

mkcke

The summand in the right hand side becomes:

$$\begin{aligned}
\int_{\Omega_i} \mu_k \nabla\cdot\left(c_k \frac{D_k}{k_BT}\nabla\mu_k \right) d\mathbf{x} = &\int_{\Gamma_i} \left(\mu_k c_k \frac{D_k}{k_BT}\nabla\mu_k\cdot\mathbf{n} \right) dm_\Gamma \\
&- \int_{\Omega_i} \left(c_k \frac{D_k}{k_BT} |\nabla\mu_k|^2 \right) d\mathbf{x}
\end{aligned} \tag{B.22}$$

where $\mathbf{n}$ is the outward normal on Γ. Consider the left hand side of (B.21).

$$\begin{aligned}
&\sum_{k=1}^{N} \mu_k \frac{\partial c_k}{\partial t} = \sum_{k=1}^{N} \left(\sigma_k \frac{\partial c_k}{\partial t} + qz_k\phi\frac{\partial c_k}{\partial t} \right) \\
=&\sum_{k=1}^{N} \frac{\partial \omega}{\partial c_k}\frac{\partial c_k}{\partial t} + \phi\frac{\partial}{\partial t}\left(\sum_{k=1}^{N} qz_kc_k \right) = \frac{\partial\omega}{\partial t} - \phi\frac{\partial}{\partial t}\left(\nabla\cdot(\epsilon\nabla\phi)\right)
\end{aligned} \tag{B.23}$$

mkcksume

We used (3.1) in the first equality and (3.2) in the last equality. Integrate final expression in (B.23) over Ω_i.

$$\begin{aligned}
&\int_{\Omega_i} \left(\frac{\partial\omega}{\partial t} - \phi\nabla\cdot\left(\epsilon\nabla\left(\frac{\partial\phi}{\partial t}\right)\right) \right) d\mathbf{x} \\
=&\int_{\Gamma_i} \left(-\phi\frac{\partial}{\partial \mathbf{n}}\left(\epsilon\frac{\partial\phi}{\partial t}\right) \right) dm_\Gamma + \int_{\Omega_i} \frac{\partial}{\partial t}\left(\omega + \frac{\epsilon}{2}|\nabla\phi|^2 \right) d\mathbf{x}.
\end{aligned} \tag{B.24}$$

For the second term in the left hand side of (B.21), we have, similarly to (B.23):

$$\sum_{k=1}^{N} \mu_k \mathbf{u} \cdot \nabla c_k = \nabla \cdot (\mathbf{u}\omega) + \phi \cdot \nabla \left(\mathbf{u} \sum_{k=1}^{N} q z_k c_k \right). \tag{B.25}$$

Integrate the above expression over Ω_i:

$$\begin{aligned} &\int_{\Omega_i} \left(\nabla \cdot (\mathbf{u}\omega) + \phi \cdot \nabla \left(\mathbf{u} \sum_{k=1}^{N} q z_k c_k \right) \right) d\mathbf{x} \\ =&\int_{\Gamma_i} \left(\omega + \phi \sum_{k=1}^{N} q z_k c_k \right) \mathbf{u} \cdot \mathbf{n} dm_\Gamma - \int_{\Omega_i} \left(\sum_{k=1}^{N} q z_k c_k \right) \mathbf{u} \cdot \nabla \phi d\mathbf{x} \end{aligned} \tag{B.26}$$

Collecting the above calculations, we have rewritten identity (B.21) as:

$$\begin{aligned} &\int_{\Omega_i} \frac{\partial}{\partial t} \left(\omega + \frac{\epsilon}{2} |\nabla \phi|^2 \right) d\mathbf{x} + \int_{\Gamma_i} \left(-\phi \frac{\partial}{\partial \mathbf{n}} \left(\epsilon \frac{\partial \phi}{\partial t} \right) \right) dm_\Gamma \\ =& -\int_{\Gamma_i} \left(\left(\omega - \sum_{k=1}^{N} c_k \sigma_k \right) \mathbf{u} \cdot \mathbf{n} + \sum_{k=1}^{N} \mu_k \left(c_k \left(\mathbf{u} - \frac{D_k}{k_B T} \nabla \mu_k \right) \cdot \mathbf{n} \right) \right) dm_\Gamma \\ &+ \int_{\Omega_i} \left(-\sum_{k=1}^{N} c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 + \left(\sum_{k=1}^{N} q z_k c_k \right) \mathbf{u} \cdot \nabla \phi \right) d\mathbf{x} \end{aligned} \tag{B.27}$$

where we used $q z_k \phi = \mu_k - \sigma_k$ (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:

$$\begin{aligned} &\frac{d}{dt} \int_{\Omega_i \cup \Omega_e} \left(\omega + \frac{\epsilon}{2} |\nabla \phi|^2 \right) d\mathbf{x} - \int_{\Gamma} \left[\phi \frac{\partial}{\partial \mathbf{n}} \left(\epsilon \frac{\partial \phi}{\partial t} \right) \right] dm_\Gamma \\ &- \int_{\Gamma} \left(\left[\omega + \frac{\epsilon}{2} |\nabla \phi|^2 \right] \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} \right) dm_\Gamma \\ =& -\int_{\Gamma} \left([\pi_w] \mathbf{u} \cdot \mathbf{n} + \sum_{k=1}^{N} \left([\mu_k] f_k + [c_k \mu_k] \frac{\partial \mathbf{X}}{\partial t} \cdot \mathbf{n} \right) \right) dm_\Gamma \\ &+ \int_{\Omega_i} \left(-\sum_{k=1}^{N} c_k \frac{D_k}{k_B T} |\nabla \mu_k|^2 + \left(\sum_{k=1}^{N} q z_k c_k \right) \mathbf{u} \cdot \nabla \phi \right) d\mathbf{x} \end{aligned} \tag{B.28}$$

where we used (2.15) and (2.4) 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:

$$\begin{aligned}&\frac{d}{dt}\int_{\Omega_i\cup\Omega_e}\left(\omega+\frac{\epsilon}{2}\left|\nabla\phi\right|^2\right)d\mathbf{x}\\ =&\int_\Gamma\left(\left[\phi\frac{\partial}{\partial\mathbf{n}}\left(\epsilon\frac{\partial\phi}{\partial t}\right)\right]+\left[\frac{\epsilon}{2}\left|\nabla\phi\right|^2+\phi\nabla\cdot(\epsilon\nabla\phi)\right]\frac{\partial\mathbf{X}}{\partial t}\cdot\mathbf{n}\right)dm_\Gamma\\ -&\int_\Gamma\left([\pi_w]f_w+\sum_{k=1}^N[\mu_k]f_k\right)dm_\Gamma\\ +&\int_{\Omega_i\cup\Omega_e}\left(-\sum_{k=1}^N c_k\frac{D_k}{k_BT}\left|\nabla\mu_k\right|^2+\left(\sum_{k=1}^N qz_kc_k\right)\mathbf{u}\cdot\nabla\phi\right)d\mathbf{x}.\end{aligned}\tag{B.29}$$

`main1`

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

$$\begin{aligned}&\int_\Gamma\left[\phi\frac{\partial}{\partial\mathbf{n}}\left(\epsilon\frac{\partial\phi}{\partial t}\right)+\phi\nabla\cdot(\epsilon\nabla\phi)\frac{\partial\mathbf{X}}{\partial t}\cdot\mathbf{n}\right]dm_\Gamma\\ =&\int_\Gamma\left[\phi D_t^{\mathbf{n}}\left(\epsilon\frac{\partial\phi}{\partial\mathbf{n}}\right)+\left(\kappa_\Gamma\phi\epsilon\frac{\partial\phi}{\partial\mathbf{n}}-\epsilon\left|\nabla_\Gamma\phi\right|^2\right)\frac{\partial\mathbf{X}}{\partial t}\cdot\mathbf{n}\right]dm_\Gamma\end{aligned}\tag{B.30}$$

where we used Lemma Appendix B.2 with $w=\phi$ and $v_\Gamma=\frac{\partial\mathbf{X}}{\partial t}\cdot\mathbf{n}$ in (B.7). Using this and the definition of ∇_Γ, we may rewrite the first boundary integral in (B.29) as:

$$\begin{aligned}&\int_\Gamma\left(\left[\phi\frac{\partial}{\partial\mathbf{n}}\left(\epsilon\frac{\partial\phi}{\partial t}\right)\right]+\left[\frac{\epsilon}{2}\left|\nabla\phi\right|^2+\phi\nabla\cdot(\epsilon\nabla\phi)\right]\frac{\partial\mathbf{X}}{\partial t}\cdot\mathbf{n}\right)dm_\Gamma\\ =&-\int_\Gamma[\phi]D_t^{\mathbf{n}}(C_m[\phi])dm_\Gamma\\ &+\int_\Gamma\left(-\kappa_\Gamma C_m[\phi]^2+\left[\frac{\epsilon}{2}\left(\left|\frac{\partial\phi}{\partial\mathbf{n}}\right|^2-\left|\nabla_\Gamma\phi\right|^2\right)\right]\right)\frac{\partial\mathbf{X}}{\partial t}\cdot\mathbf{n}dm_\Gamma\end{aligned}\tag{B.31}$$

`phibterms`

where we used (3.3).

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

$$\begin{aligned}&\int_{\Omega_i}\mathbf{u}\cdot(\nu\Delta\mathbf{u}-\nabla p)d\mathbf{x}-\int_{\Omega_i}\left(\sum_{k=1}^N qz_kc_k\right)\mathbf{u}\cdot\nabla\phi d\mathbf{x}\\ =&\int_{\Gamma_i}(\Sigma(\mathbf{u},p)\mathbf{n})\cdot\mathbf{u}dm_\Gamma-\int_{\Omega_i}\nu\left|\nabla\mathbf{u}\right|^2d\mathbf{x}\\ &-\int_{\Omega_i}\left(\sum_{k=1}^N qz_kc_k\right)\mathbf{u}\cdot\nabla\phi d\mathbf{x}=0\end{aligned}\tag{B.32}$$

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

$$\int_\Gamma \left[(\Sigma(\mathbf{u},p)\mathbf{n})\cdot\mathbf{u}\right] dm_\Gamma - \int_{\Omega_i\cup\Omega_e} \nu\left|\nabla\mathbf{u}\right|^2 d\mathbf{x} = \int_{\Omega_i\cup\Omega_e}\left(\sum_{k=1}^{N} qz_k c_k\right)\mathbf{u}\cdot\nabla\phi d\mathbf{x} \tag{B.33}$$

`sigupgamma`

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

$$\begin{aligned}\Sigma_e(\phi)\mathbf{n} &= \epsilon\left(\frac{\partial\phi}{\partial\mathbf{n}}\nabla\phi - \frac{1}{2}\left|\nabla\phi\right|^2\mathbf{n}\right)\\ &= \epsilon\left(\frac{1}{2}\left(\left|\frac{\partial\phi}{\partial\mathbf{n}}\right|^2 - \left|\nabla_\Gamma\phi\right|^2\right)\mathbf{n} + \frac{\partial\phi}{\partial\mathbf{n}}\nabla_\Gamma\phi\right)\end{aligned} \tag{B.34}$$

We may now write (3.9) as:

$$\left[\Sigma_m(\mathbf{u},p)\mathbf{n}\right] = \mathbf{F}_{\text{mem}} + \mathbf{F}_{\text{cap}} - \left[\frac{\epsilon}{2}\left(\left|\frac{\partial\phi}{\partial\mathbf{n}}\right|^2 - \left|\nabla_\Gamma\phi\right|^2\right)\right]\mathbf{n} + C_m[\phi]\nabla_\Gamma[\phi] \tag{B.35}$$

`bup`

where we used (3.3) in the last term.

Using (B.31), (B.33) and (B.35) in (B.29) we have:

$$\begin{aligned}&\frac{d}{dt}\int_{\Omega_i\cup\Omega_e}\left(\omega + \frac{\epsilon}{2}\left|\nabla\phi\right|^2\right)d\mathbf{x}\\ =&\int_\Gamma\left(-[\phi]D_t^{\mathbf{n}}(C_m[\phi]) + \left(-\kappa_\Gamma C_m[\phi]^2\mathbf{n} + C_m[\phi]\nabla_\Gamma[\phi] + \mathbf{F}_{\text{cap}}\right)\cdot\frac{\partial\mathbf{X}}{\partial t}\right)dm_\Gamma\\ +&\int_\Gamma \mathbf{F}_{\text{mem}}\cdot\frac{\partial\mathbf{X}}{\partial t}dm_\Gamma - \int_\Gamma\left([\psi_w]f_w + \sum_{k=1}^{N}[\mu_k]f_k\right)dm_\Gamma\\ -&\int_{\Omega_i\cup\Omega_e}\left(\sum_{k=1}^{N}c_k\frac{D_k}{k_BT}\left|\nabla\mu_k\right|^2 + \nu\left|\nabla\mathbf{u}\right|^2\right)d\mathbf{x}.\end{aligned} \tag{B.36}$$

`main2`

Comparing (B.36), (3.12) and using (2.11), we see that the proof of (3.12) rests on the evaluation of the first boundary integral after the equality in (B.36).

$$\begin{aligned}&\int_\Gamma[\phi]D_t^{\mathbf{n}}(C_m[\phi])dm_\Gamma = \int_\Gamma\left(D_t^{\mathbf{n}}\left(\frac{1}{2}C_m[\phi]^2\right) + \frac{1}{2}(D_t^{\mathbf{n}}C_m)[\phi]^2\right)dm_\Gamma\\ =&\frac{d}{dt}\int_\Gamma\frac{1}{2}C_m[\phi]^2dm_\Gamma - \int_\Gamma\left(\left(\frac{1}{2}C_m[\phi]^2\right)\kappa_\Gamma\frac{\partial\mathbf{X}}{\partial t}\cdot\mathbf{n} - \frac{1}{2}(D_t^{\mathbf{n}}C_m)[\phi]^2\right)dm_\Gamma\end{aligned} \tag{B.37}$$

`phiDtnphi`

where we used (B.3) with $w = [\phi]$, $v_\Gamma = \frac{\partial\mathbf{X}}{\partial t}\cdot\mathbf{n}$ in the second equality. We also have:

$$\int_\Gamma (C_m[\phi]\nabla_\Gamma[\phi])dm_\Gamma = \int_\Gamma \left(\nabla_\Gamma\left(\frac{1}{2}C_m[\phi]^2\right) - \frac{1}{2}(\nabla_\Gamma C_m)[\phi]^2\right)dm_\Gamma \tag{B.38}$$

phiCmphi

Using (B.37) and (B.38), we have:

$$\begin{aligned}
&\int_\Gamma \left(-[\phi]D_t^{\mathbf{n}}(C_m[\phi]) + \left(-\kappa_\Gamma C_m[\phi]^2\mathbf{n} + C_m[\phi]\nabla_\Gamma[\phi]\right)\cdot\frac{\partial \mathbf{X}}{\partial t}\right)dm_\Gamma \\
=& -\frac{d}{dt}\int_\Gamma \frac{1}{2}C_m[\phi]^2 dm_\Gamma - \int_\Gamma \frac{1}{2}\left(D_t^{\mathbf{n}}C_m + (\nabla_\Gamma C_m)\cdot\frac{\partial \mathbf{X}}{\partial t}\right)[\phi]^2 dm_\Gamma \\
&+\int_\Gamma \left(-\left(\frac{1}{2}C_m[\phi]^2\right)\kappa_\Gamma\mathbf{n} + \nabla_\Gamma\left(\frac{1}{2}C_m[\phi]^2\right)\right)\cdot\frac{\partial \mathbf{X}}{\partial t}dm_\Gamma
\end{aligned} \tag{B.39}$$

main3

Consider the second boundary integral after the equality.

$$\begin{aligned}
&\int_\Gamma \frac{1}{2}\left(D_t^{\mathbf{n}}C_m + (\nabla_\Gamma C_m)\cdot\frac{\partial \mathbf{X}}{\partial t}\right)[\phi]^2 dm_\Gamma \\
=&\int_\Gamma \left(\frac{1}{2}\frac{\partial C_m}{\partial t}[\phi]^2\right)dm_\Gamma = \int_\Gamma \left(\frac{1}{2}\frac{\partial C_m}{\partial Q}\frac{\partial Q}{\partial t}[\phi]^2\right)dm_\Gamma \\
=&\int_\Gamma \left(\frac{1}{2}Q\frac{\partial C_m}{\partial Q}[\phi]^2\kappa_\Gamma\mathbf{n} - \nabla_\Gamma\left(\frac{1}{2}Q\frac{\partial C_m}{\partial Q}[\phi]^2\right)\right)\cdot\frac{\partial \mathbf{X}}{\partial t}dm_\Gamma
\end{aligned} \tag{B.40}$$

Cmtterm

where we used (B.5) with $w = C_m$ in the first equality, and (B.4) with $w = \frac{1}{2}Q\frac{\partial C_m}{\partial Q}[\phi]^2$ in the last equality. From (B.40), (B.39), (B.36) and expression (3.10) of $\mathbf{F}_{\mathrm{cap}}$, we obtain the desired result.

If $Q \equiv 1$ and (3.11) holds, we may argue as follows. Equation (B.36) remains valid with $\mathbf{F}_{\mathrm{cap}}$ replaced by $\mathbf{F}_{\mathrm{p}}$. Verification of (3.12) rests on the evaluation of the first boundary integral in (B.36). Proceeding as in the above, we have:

$$\begin{aligned}
&\int_\Gamma \left(-[\phi]D_t^{\mathbf{n}}(C_m[\phi]) + \left(-\kappa_\Gamma C_m[\phi]^2\mathbf{n} + C_m[\phi]\nabla_\Gamma[\phi] + \mathbf{F}_p\right)\cdot\frac{\partial \mathbf{X}}{\partial t}\right)dm_\Gamma \\
=& -\frac{d}{dt}\int_\Gamma \frac{1}{2}C_m[\phi]^2 dm_\Gamma - \int_\Gamma \left(\frac{1}{2}\frac{\partial C_m}{\partial Q}\frac{\partial Q}{\partial t}[\phi]^2\right)dm_\Gamma \\
&+\int_\Gamma \left(\left(\lambda - \frac{1}{2}C_m[\phi]^2\right)\kappa_\Gamma\mathbf{n} - \nabla_\Gamma\left(\lambda - \frac{1}{2}C_m[\phi]^2\right)\right)\cdot\frac{\partial \mathbf{X}}{\partial t}dm_\Gamma
\end{aligned} \tag{B.41}$$

where we used the (2.13). Since $\frac{\partial Q}{\partial t} = 0$, the second boundary integral after the equality is 0. Using (B.4) 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. $\square$

Acknowledgments

The authors gratefully acknowledge support from the following sources: National Science Foundation (NSF) grant DMS-0914963, the Alfred P. Sloan Foundation and the McKnight Foundation (to YM), NSF grant DMS-0707594 (to CL), and National Institutes of Health grant GM076013 (to RSE). The authors are grateful to the Institute of Mathematics and its Application (IMA) at the University of Minnesota at which much of the discussion took place. YM thanks Charles S. Peskin for pointing to reference finkelstein1987water [64] and experimental observations on osmosis described therein.

References

pappenheimer1987silver [1] J. Pappenheimer, A silver spoon, Annual review of physiology 49 (1) (1987) 1–16.

boron2008medical [2] W. Boron, E. Boulpaep, Medical physiology, 2nd Edition, W.B. Saunders, 2008.

davson1970textbook [3] H. Davson, A Textbook of General Physiology, 4th Edition, Churchill, 1970.

somjen2004ions [4] G. Somjen, Ions in the Brain, Oxford University Press, 2004.

kahle2009molecular [5] K. Kahle, J. Simard, K. Staley, B. Nahed, P. Jones, D. Sun, Molecular mechanisms of ischemic cerebral edema: role of electroneutral ion transport, Physiology 24 (4) (2009) 257.

hill2008fluid [6] A. Hill, Fluid Transport: A Guide for the Perplexed, Journal of Membrane Biology 223 (1) (2008) 1–11.

koeppen2007renal [7] B. Koeppen, B. Stanton, Renal physiology, The Mosby physiology monograph series, Mosby Elsevier, 2007.

layton2009mammalian [8] A. Layton, H. Layton, W. Dantzler, T. Pannabecker, The mammalian urine concentrating mechanism: hypotheses and uncertainties, Physiology 24 (4) (2009) 250.

mathias2007lens [9] R. Mathias, J. Kistler, P. Donaldson, The lens circulation, Journal of Membrane Biology 216 (1) (2007) 1–16.

fischbarg2005mathematical [10] J. Fischbarg, F. Diecke, A mathematical model of electrolyte and fluid transport across corneal endothelium, Journal of Membrane Biology 203 (1) (2005) 41–56.

taiz2010plant [11] L. Taiz, E. Zeiger, Plant Physiology, Sinauer Associates, Incorporated, 2010.

Hille [12] B. Hille, Ion Channels of Excitable Membranes, 3rd Edition, Sinauer Associates, 2001.

aidley_physiology_1998 [13] D. Aidley, The Physiology of Excitable Cells, 4th Edition, Cambridge University Press, New York, 1998.

KS [14] J. Keener, J. Sneyd, Mathematical Physiology, Springer-Verlag, New York, 1998.

hoppensteadt2002modeling [15] F. Hoppensteadt, C. Peskin, Modeling and simulation in medicine and the life sciences, Springer Verlag, 2002.

weinstein1994mathematical [16] A. Weinstein, Mathematical models of tubular transport, Annual review of physiology 56 (1) (1994) 691–709.

yi2003mathematical [17] C. Yi, A. Fogelson, J. Keener, C. Peskin, A mathematical study of volume shifts and ionic concentration changes during ischemia and hypoxia, Journal of Theoretical Biology 220 (1) (2003) 83–106.

shapiro2001osmotic [18] B. Shapiro, Osmotic forces and gap junctions in spreading depression: a computational model, Journal of Computational Neuroscience 10 (1) (2001) 99–120.

lee2008immersed [19] P. Lee, The immersed boundary method with advection-electrodiffusion, Ph.D. thesis, NEW YORK UNIVERSITY (2008).

mathias1985steady [20] R. Mathias, Steady-state voltages, ion fluxes, and volume regulation in syncytial tissues, Biophysical journal 48 (3) (1985) 435–448.

katzir1965nonequilibrium [21] A. Katzir-Katchalsky, P. Curran, Nonequilibrium thermodynamics in biophysics, Harvard University Press, 1965.

kedem1958thermodynamic [22] O. Kedem, A. Katchalsky, Thermodynamic analysis of the permeability of biological membranes to non-electrolytes, Biochimica et Biophysica Acta 27 (1958) 229–246.

kjelstrup2008non [23] S. Kjelstrup, D. Bedeaux, Non-equilibrium thermodynamics of heterogeneous systems, World Scientific Pub Co Inc, 2008.

atzberger2009microfluidic [24] P. Atzberger, S. Isaacson, C. Peskin, A microfluidic pumping mechanism driven by non-equilibrium osmotic effects, Physica D: Nonlinear Phenomena 238 (14) (2009) 1168–1179.

layton2006modeling [25] A. Layton, Modeling water transport across elastic boundaries using an explicit jump method, SIAM Journal on Scientific Computing 28 (2006) 2189.

mori2011cvctrl [26] Y. Mori, Mathematical Properties of Pump-Leak Models of Cell Volume Control and Electrolyte Balance, Arxiv preprint arXiv:1104.4097.

degroot1962non [27] S. De Groot, P. Mazur, Non-equilibrium thermodynamics, Vol. 17, Amsterdam North Holland, 1962.

hille1982transport [28] B. HILLE, Transport across cell membranes: carrier mechanisms, Excitable tissues and reflex control of muscle (1982) 47.

tosteson1989membrane [29] D. Tosteson (Ed.), Membrane transport: people and ideas, People and Ideas Series/American Physiological Society Book, American Physiological Society, 1989.

tyrrell1971diffusion [30] H. Tyrrell, K. Harris, Diffusion in liquids, in: Diffusion processes: proceedings of the Thomas Graham Memorial Symposium, University of Strathclyde, Gordon & Breach Publishing Group, 1971, p. 67.

justice1983conductance [31] J. Justice, Conductance of electrolyte solutions, Comprehensive Treatise of Electrochemistry 5.

hoheisel1993theoretical [32] C. Hoheisel, J. Winkelmann, Theoretical treatment of liquids and liquid mixtures, Elsevier, 1993.

taylor1993multicomponent [33] R. Taylor, R. Krishna, Multicomponent mass transfer, Wiley-Interscience, 1993.

accascina1959electrolytic [34] F. Accascina, R. Fuoss, Electrolytic Conductance, Interscience, New York, 1959.

fawcett2004liquids [35] W. Fawcett, Liquids, solutions, and interfaces: from classical macroscopic descriptions to modern microscopic details, Oxford University Press, USA, 2004.

lee2008molecular [36] L. Lee, Molecular Thermodynamics of Electrolyte Solutions, World Scientific Pub Co Inc, 2008.

kunz2010specific [37] W. Kunz, Specific Ion Effects, World Scientific, 2010.

fraenkel2010simplified [38] D. Fraenkel, Simplified electrostatic model for the thermodynamic excess potentials of binary strong electrolyte solutions with size-dissimilar ions, Molecular Physics 108 (11) (2010) 1435–1466.

eisenberg2010crowded [39] B. Eisenberg, Crowded charges in ion channels, Advances in Chemical PhysicsIn press.

zhang2010molecular [40] C. Zhang, S. Raugei, B. Eisenberg, P. Carloni, Molecular Dynamics in Physiological Solutions: Force Fields, Alkali Metal Ions, and Ionic Strength, Journal of Chemical Theory and Computation (2010) 2–4.

eisenberg2010energy [41] B. Eisenberg, Y. Hyon, C. Liu, Energy variational analysis of ions in water and channels: Field theory for primitive models of complex ionic fluids, The Journal of Chemical Physics 133 (2010) 104104.

Rubinstein [42] I. Rubinstein, Electro-Diffusion of Ions, SIAM, 1990.

roosbroeck_theory_1950 [43] W. V. Roosbroeck, Theory of flow of electrons and holes in germanium and other semiconductors, Bell System Tech. J. 29 (1950) 560–607.

Jerome_semiconductor [44] J. Jerome, Analysis of Charge Transport: A Mathematical Study of Semiconductor Devices, Springer-Verlag, 1995.

selberherr1984analysis [45] S. Selberherr, Analysis and simulation of semiconductor devices, Springer-Verlag, 1984.

eisenberg1996computing [46] R. Eisenberg, Computing the field in proteins and channels, Journal of Membrane Biology 150 (1) (1996) 1–25.

bazant2004diffuse [47] M. Bazant, K. Thornton, A. Ajdari, Diffuse-charge dynamics in electrochemical systems, Physical Review E 70 (2) (2004) 21506.

HH [48] A. Hodgkin, A. Huxley, A quantitative description of the membrane current and its application to conduction and excitation in nerve, Journal of Physiology 117 (1952) 500–544.

leonetti_biomembrane_1998 [49] M. Léonetti, On biomembrane electrodiffusive models, European Physical Journal B 2 (1998) 325–340.

schaff1997general [50] J. Schaff, C. Fink, B. Slepchenko, J. Carson, L. Loew, A general computational framework for modeling cellular structure and function, Biophysical journal 73 (3) (1997) 1135–1146.

choi1999electrodiffusion [51] Y. Choi, D. Resasco, J. Schaff, B. Slepchenko, Electrodiffusion of ions inside living cells, IMA Journal of Applied Mathematics 62 (3) (1999) 207.

Sinica [52] Y. Mori, J. Jerome, C. Peskin, A three-dimensional model of cellular electrical activity, Bulletin-Institute of Mathematics Academia Sinica 2 (2) (2007) 367–390.

mori_ephaptic_2008 [53] Y. Mori, G. I. Fishman, C. S. Peskin, Ephaptic conduction in a cardiac strand model with 3D electrodiffusion, Proceedings of the National Academy of Sciences 105 (17) (2008) 6463.

morithesis [54] Y. Mori, A three-dimensional model of cellular electrical activity, Ph.D. thesis, New York University (2006).

mori2009tde [55] Y. Mori, From Three-Dimensional Electrophysiology to the Cable Model: an Asymptotic Study, Arxiv preprint arXiv:0901.3914.

CAMCoS [56] Y. Mori, C. Peskin, A numerical method for cellular electrophysiology based on the electrodiffusion equations with internal boundary conditions at internal membranes, Communications in Applied Mathematics and Computational Science 4 (2009) 85–134.

tosteson1960regulation [57] D. Tosteson, J. Hoffman, Regulation of cell volume by active cation transport in high and low potassium sheep red cells, The Journal of general physiology 44 (1) (1960) 169.

tosteson1964regulation [58] D. Tosteson, Regulation of cell volume by sodium and potassium transport, The cellular functions of membrane transport (1964) 3–22.

jakobsson1980interactions [59] E. Jakobsson, Interactions of cell volume, membrane potential, and membrane transport parameters, American Journal of Physiology- Cell Physiology 238 (5) (1980) C196.

eter_volume-activated_1990 [60] J. Strieter, J. L. Stephenson, L. G. Palmer, A. M. Weinstein, Volume-activated chloride permeability can mediate cell volume regulation in a mathematical model of a tight epithelium., The Journal of General Physiology 96 (2) (1990) 319.

lew_behaviour_1979 [61] V. L. Lew, H. G. Ferreira, T. Moura, The behaviour of transporting epithelial cells. i. computer analysis of a basic model, Proceedings of the Royal Society of London. Series B, Biological Sciences 206 (1162) (1979) 53–83.

koch_biophysics_1999 [62] C. Koch, Biophysics of Computation, Oxford University Press, New York, 1999.

hernandez_modeling_1998 [63] J. A. Hernandez, E. Cristina, Modeling cell volume regulation in nonexcitable cells: the roles of the na+ pump and of cotransport systems, American Journal of Physiology- Cell Physiology 275 (4) (1998) C1067.

finkelstein1987water [64] A. Finkelstein, Water movement through lipid bilayers, pores, and plasma membranes: theory and reality, Distinguished lecture series of the Society of General Physiologists, Wiley, 1987.

amet2008thermodynamically [65] D. Jamet, C. Misbah, Thermodynamically consistent picture of the phase-field model of vesicles: Elimination of the surface tension, Physical Review E 78 (4) (2008) 041903.

jamet2008toward [66] D. Jamet, C. Misbah, Toward a thermodynamically consistent picture of the phase-field model of vesicles: Curvature energy, Physical Review E 78 (3) (2008) 031902.

jamet2007towards [67] D. Jamet, C. Misbah, Towards a thermodynamically consistent picture of the phase-field model of vesicles: local membrane incompressibility, Physical Review E 76 (5) (2007) 051907.

du2004phase [68] Q. Du, C. Liu, X. Wang, A phase field approach in the numerical study of the elastic bending energy for vesicle membranes* 1, Journal of Computational Physics 198 (2) (2004) 450–468.

du2006simulating [69] Q. Du, C. Liu, X. Wang, Simulating the deformation of vesicle membranes under elastic bending energy in three dimensions, Journal of Computational Physics 212 (2) (2006) 757–777.

du2005phase [70] Q. Du, C. Liu, R. Ryham, X. Wang, A phase field formulation of the willmore problem, Nonlinearity 18 (2005) 1249.

onsager1931reciprocal [71] L. Onsager, Reciprocal Relations in Irreversible Processes. II., Physical Review 38 (12) (1931) 2265–2279.

`doi1988theory` [72] M. Doi, S. Edwards, The theory of polymer dynamics, International series of monographs on physics, Clarendon Press, 1988.

`doi2009gel` [73] M. Doi, Gel dynamics, J. Phys. Soc. Jpn 78 (2009) 052001.

`hyon2010energetic` [74] Y. Hyon, D. Kwak, C. Liu, Energetic variational approach in complex fluids: Maximum dissipation principle, DCDS-A 26 (4) (2010) 1291–1304.

`goldstein1980classical` [75] H. Goldstein, Classical mechanics, Addison-Wesley series in physics, Addison-Wesley Pub. Co., 1980.

`biler2000long` [76] P. Biler, J. Dolbeault, Long time behavior of solutions to Nernst-Planck and Debye-H
”uckel drift-diffusion systems, Annales Henri Poincaré 1 (3) (2000) 461–472.

`ryham2009existence` [77] R. Ryham, Existence, Uniqueness, Regularity and Long-term Behavior for Dissipative Systems Modeling Electrohydrodynamics, Arxiv preprint arXiv:0910.4973.

`leonetti_pattern_2004` [78] M. Léonetti, E. Dubois-Violette, F. Homblé, Pattern formation of stationaly transcellular ionic currents in fucus, Proc. Natl. Acad. Sci. USA 101 (28) (2004) 10243–10248.

`brera2010conservative` [79] M. Brera, J. Jerome, Y. Mori, R. Sacco, A Conservative and monotone mixed-hybridized finite element approximation of transport problems in heterogeneous domains, Computer Methods in Applied Mechanics and Engineering 199 (2010) 2709–2720.

`ibmethod` [80] C. Peskin, The immersed boundary method, Acta Numerica 11 (2002) 479–517.

`li_immersed_2006` [81] Z. Li, K. Ito, The Immesed Interface Method: Numerical Solutions of PDEs Involving Interfaces and Irrgular Domains, SIAM, 2006.

`erg_three-dimensional_1970` [82] R. S. Eisenberg, E. A. Johnson, Three-dimensional electrical field problems in physiology, Prog. Biophys. Mol. Biol 20 (1).

`eisenberg1979electrical` [83] R. Eisenberg, V. Barcilon, R. Mathias, Electrical properties of spherical syncytia, Biophysical Journal 25 (1) (1979) 151–180.

`mathias1979electrical` [84] R. Mathias, J. Rae, R. Eisenberg, Electrical properties of structural components of the crystalline lens, Biophysical Journal 25 (1) (1979) 181–201.

`neu1993hst` [85] J. Neu, W. Krassowska, Homogenization of syncytial tissues, Critical reviews in biomedical engineering 21 (2) (1993) 137–199.