

A THREE-DIMENSIONAL MODEL OF CELLULAR ELECTRICAL ACTIVITY

BY

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Abstract

The detailed three dimensional architecture of biological tissue and electrodiffusion effects of ions have been largely neglected in modeling studies of cellular electrical activity. Here, we develop a model of cellular electrical activity that takes into account both of these effects. We derive the system of partial differential equations that govern cellular electrical activity and discuss its biological significance. This is followed by a brief discussion of numerical simulations and a mathematical analysis of the system of equations.

1. Introduction

Electrophysiology, because of its importance in many physiological processes and its quantitative nature, has been a favorite subject in mathematical physiology. Traditional models of cellular electrical activity are based on the famous work of Hodgkin and Huxley [5], and may be collectively termed cable models [8, 9]. These models are based upon an ohmic current continuity relation on a branched one dimensional electrical cable. There are three major assumptions that go into the derivation of cable models [9]:

- The geometry of a cell is well-captured by a one dimensional tree representation. Geometrical details that are lost in making this simplified description have negligible effect on electrophysiology.

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- Ionic concentrations are effectively constant in space and time within each cell separately and in the extracellular space.
- The extracellular space can be reduced to a single isopotential electrical compartment.

Such assumptions are justified in many instances, for example in the isolated neuronal axon, where the cable model has been extremely successful in explaining the physiology and in making quantitative predictions – a triumph counted among the greatest successes of mathematics in biology. But there are many cases in which any or all of the above assumptions are probably violated. Neuroscience textbooks [7] will show pictures of cells of complex shape packed together embedded in a tortuous extracellular space. Such pictures are indicative of the important functional role geometry, ionic concentration profiles and extra-neuronal space (extracellular space and glia) may play in the workings of the nervous system. In this paper, we formulate a mathematical model that incorporates such effects.

We will begin by a detailed derivation of the model equations and a discussion of their biological significance. This will be followed by a brief discussion of the numerical method currently used and simulation results. The final section presents a mathematical analysis of the model.

We mention a recent effort that shares with our model some of the above objectives [6]. In comparison to our model, it takes a closer look at what happens near the membrane but takes a simpler approach with regard to neuroanatomy.

For a comprehensive exposition of our modeling methodology, we refer the reader to [11].

2. Drift-Diffusion and Electroneutrality

We begin with equations that hold away from the cell membranes, i.e., in the cell interior and in the interior of the extracellular space. We assume that the unknowns and the parameters change continuously within each of these regions, but we allow for jumps in these quantities as cell membranes are crossed.

Let there be N ion species, where the subscript i denotes each species. Let $c_i(\mathbf{x}, t)$ and $\phi(\mathbf{x}, t)$ denote the ion concentrations and the electrostatic

potential respectively. These quantities are related by the drift-diffusion equations:

$$\frac{\partial c_i}{\partial t} = -\nabla \cdot \mathbf{f}_i \quad (\text{ion conservation}) \quad (1)$$

$$\mathbf{f}_i = -D_i \left(\nabla c_i + \frac{qz_i c_i}{k_B T} \nabla \phi \right) \quad (\text{drift-diffusion flux}) \quad (2)$$

Here, \mathbf{f}_i denotes the flux of the i -th ion. \mathbf{f}_i is expressed as a sum of two terms, the diffusion term and the drift term. D_i is the diffusion coefficient of the i -th ion, qz_i is the amount of charge on the i -th ion, where q is the elementary charge, i.e., the charge on a proton. $qD_i/(k_B T)$ is the mobility of the ion species (Einstein relation) where k_B is the Boltzmann constant, and T the absolute temperature.

Moreover, the electrostatic potential satisfies the Poisson equation:

$$\Delta \phi = -\frac{1}{\epsilon} \left(\rho_0 + \sum_{i=1}^N qz_i c_i \right) \quad (\text{Poisson equation}) \quad (3)$$

where ρ_0 is the fixed background charge density (if any), and ϵ is the dielectric constant of the electrolyte solution. Note that we are applying these equations only in the electrolyte solution, not within the membrane itself. We shall discuss the treatment of the membrane in the following section. It is interesting to note that these equations are also used in semiconductor physics, where they are known as the van Roosbroeck equations [13].

Let L_0 be a typical length scale, and let c_0 be a typical concentration. By writing the equations in non-dimensional variables, we are led to consider the dimensionless parameter $\frac{\epsilon k_B T}{q^2 c_0 L_0^2} = \frac{r_d^2}{L_0^2}$, where r_d is the Debye length $r_d \equiv \sqrt{\frac{\epsilon k_B T}{q^2 c_0}}$. When this parameter is small, we have the limit of electroneutrality, which holds away from the cell membranes. This is indeed the case in physiological systems, where $r_d \approx 1\text{nm}$ and L_0 is typically on the order of microns or more. This limit can be obtained formally by letting $\epsilon \rightarrow 0$ in the Poisson equation. This implies

$$\rho_0 + \sum_{i=1}^N qz_i c_i = 0. \quad (4)$$

It should be noted that this does *not* imply $\Delta \phi = 0$, since (3) reduces to $\Delta \phi = 0/0$ in the limit considered, and thus we have to look to the other equa-

tions to find the limiting behavior of the electrostatic potential. Therefore, the equations to be satisfied away from the membrane are the drift-diffusion equations (1), (2) and the electroneutrality condition (4).

We may obtain the relation satisfied by ϕ by considering current continuity. Let $\mathbf{j}(\mathbf{x}, t)$ be the total electrical current density (current per unit area) at the position \mathbf{x} at time t . Multiply the flux densities \mathbf{f}_i by qz_i to obtain the current density for each ion, and add to obtain the total current density.

$$\mathbf{j}(\mathbf{x}, t) = -(a(\mathbf{x}, t)\nabla\phi + \nabla b(\mathbf{x}, t)) \quad (5)$$

$$a(\mathbf{x}, t) = \sum_{i=1}^N \frac{(qz_i)^2 D_i}{k_B T} c_i(\mathbf{x}, t) \quad (6)$$

$$b(\mathbf{x}, t) = \sum_{i=1}^N qz_i D_i c_i(\mathbf{x}, t) \quad (7)$$

By current continuity, $\nabla \cdot \mathbf{j} = 0$, we have the following elliptic equation for ϕ .

$$\nabla \cdot (a(\mathbf{x})\nabla\phi + \nabla b(\mathbf{x}, t)) = 0 \quad (8)$$

Thus, ϕ satisfies an elliptic constraint (since $a(\mathbf{x}, t) > 0$) instead of the Poisson equation in the limit $r_d/L \rightarrow 0$.

We point out that (8) may also be derived by differentiating the electroneutrality condition (4) with respect to t and using (1) and (2). We may understand (8) as imposing an elliptic constraint on ϕ so that electroneutrality is maintained. This procedure of obtaining an equation for ϕ from an algebraic relation is employed in index reduction for differential algebraic systems [12].

3. Electrical Boundary Condition

We shall treat the transmembrane currents and their associated quantities (as defined in Section 6) to be continuous quantities with respect to the spatial coordinate within the membrane. In our model, we are not resolving the individual membrane protein molecules such as ion channels that give rise to transmembrane currents. All relations that refer to membrane variables should thus be understood as the result of homogenization with respect to the membrane coordinate.

Near the membrane, there is an accumulation of electric charge, whose thickness is on the order of the Debye length r_d . In deriving the electroneutrality condition, we let $r_d/L \rightarrow 0$. In agreement with this limit, we consider this electric charge to form a layer of zero thickness concentrated on both sides of the membrane surface.

Let us consider a point \mathbf{x} on the membrane. The membrane separates two regions of space which we call $\Omega^{(k)}$ and $\Omega^{(l)}$. We label quantities in $\Omega^{(k)}$ and $\Omega^{(l)}$ by the superscripts k and l respectively.

Electric current \mathbf{j} that hits the membrane will contribute to the change in surface charge σ or will pass through the membrane as transmembrane current j . This statement of charge conservation on the $\Omega^{(k)}$ face of the membrane can be expressed as:

$$\frac{\partial \sigma^{(k)}}{\partial t}(\mathbf{x}, t) + j^{(kl)}(\mathbf{x}, t) = \mathbf{j}^{(k)}(\mathbf{x}, t) \cdot \mathbf{n}^{(kl)}(\mathbf{x}) \quad (9)$$

Here, $\sigma^{(k)}$ is the surface charge per unit area on face k of the membrane, $j^{(kl)}$ is the transmembrane current per unit area from $\Omega^{(k)}$ to $\Omega^{(l)}$, and $j^{(lk)} = -j^{(kl)}$. The functional form of this quantity will be discussed in Section 6. $\mathbf{n}^{(kl)}$ is the unit normal pointing from $\Omega^{(k)}$ to $\Omega^{(l)}$, and thus $\mathbf{n}^{(lk)} = -\mathbf{n}^{(kl)}$. The same relation holds with k and l interchanged on the side of the membrane facing $\Omega^{(l)}$:

$$\frac{\partial \sigma^{(l)}}{\partial t}(\mathbf{x}, t) + j^{(lk)}(\mathbf{x}, t) = \mathbf{j}^{(l)}(\mathbf{x}, t) \cdot \mathbf{n}^{(lk)}(\mathbf{x}) \quad (10)$$

We make two assumptions about the surface charge σ .

- Each patch of the membrane is electroneutral, i.e., $\sigma^{(k)}(\mathbf{x}, t) + \sigma^{(l)}(\mathbf{x}, t) = 0$. This means that any charge accumulation on one side of the membrane is instantaneously counterbalanced by charge on the other side.
- The membrane and its surface charge layers together behave like a capacitor. That is to say, the surface charge is linearly proportional to the transmembrane potential difference.

We may combine the above two assumptions to deduce:

$$\sigma^{(k)}(\mathbf{x}, t) = -\sigma^{(l)}(\mathbf{x}, t) = C_m \phi^{(kl)}(\mathbf{x}, t), \quad \phi^{(kl)}(\mathbf{x}, t) \equiv \phi^{(k)}(\mathbf{x}, t) - \phi^{(l)}(\mathbf{x}, t)$$

where C_m is the capacitance per unit area of the membrane. Thus we arrive at the electrical boundary conditions

$$C_m \frac{\partial \phi^{(kl)}}{\partial t}(\mathbf{x}, t) + j^{(kl)}(\mathbf{x}, t) = \mathbf{j}^{(k)}(\mathbf{x}, t) \cdot \mathbf{n}^{(kl)}(\mathbf{x}). \tag{11}$$

The same boundary condition but with k and l interchanged holds on the $\Omega^{(l)}$ face of the membrane.

We may add (9) and (10) and use the first assumption to obtain a relation satisfied by \mathbf{j} .

$$\mathbf{j}^{(k)}(\mathbf{x}, t) \cdot \mathbf{n}^{(kl)}(\mathbf{x}) + \mathbf{j}^{(l)}(\mathbf{x}, t) \cdot \mathbf{n}^{(lk)}(\mathbf{x}) = 0$$

This says that any current that comes onto the membrane from one side is exactly counterbalanced by current coming off the membrane from the other side, i.e., that there is no charge accumulation at the membrane.

4. Boundary Conditions for Each Ionic Species

Let us consider the flux of the i -th ion \mathbf{f}_i at the membrane. The i -th ion contributes a current per unit area of $qz_i \mathbf{f}_i \cdot \mathbf{n}$. Let $\sigma_i^{(k)}(\mathbf{x}, t)$ be the contribution of the i -th species of ion to the surface charge per unit area on the side of the membrane facing $\Omega^{(k)}$, and let $j_i^{(kl)}(\mathbf{x}, t)$ be the contribution of the i -th species of ion to the transmembrane current per unit area flowing from $\Omega^{(k)}$ into $\Omega^{(l)}$. By considering ion conservation at the membrane we find:

$$\frac{\partial \sigma_i^{(k)}}{\partial t}(\mathbf{x}, t) + j_i^{(kl)}(\mathbf{x}, t) = qz_i \mathbf{f}_i^{(k)}(\mathbf{x}, t) \cdot \mathbf{n}^{(kl)}(\mathbf{x}) \tag{12}$$

Note that,

$$\sum_{i=1}^N \sigma_i^{(k)}(\mathbf{x}, t) = \sigma^{(k)}(\mathbf{x}, t) = C_m \phi^{(kl)}(\mathbf{x}, t)$$

$$\sum_{i=1}^N j_i^{(kl)}(\mathbf{x}, t) = j^{(kl)}(\mathbf{x}, t)$$

and we may sum (12) over i to obtain (9).

To make (12) useful, we need an expression for $\sigma_i^{(k)}$ in terms of the ionic concentrations and the electrostatic potential. Through an approxi-

mate analysis of the space charge layer, it can be shown that

$$\sigma_i^{(k)}(\mathbf{x}, t) = \lambda_i^{(k)}(\mathbf{x}, t) \sigma^{(k)}(\mathbf{x}, t) \quad (13)$$

where,

$$\lambda_i^{(k)}(\mathbf{x}, t) = \frac{z_i^2 c_i^{(k)}(\mathbf{x}, t)}{\sum_{i'=1}^N z_{i'}^2 c_{i'}^{(k)}(\mathbf{x}, t)} \quad (14)$$

We now turn to the derivation of the above expression.

5. Space Charge Layer

The purpose of this section is to take a closer look at the surface charge layer. The physical reality is that these “surface charge layers” are not confined to the membrane surface, but are spread out over a thin layer near the membrane. Thus, they are better called “space charge layers” and that is the terminology we shall use in this section. We note that the space charge layers considered here are located near the membrane surface within the intracellular or extracellular spaces and do not straddle the cell membrane.

5.1. Derivation of expression for σ_i

We make three approximations in our analysis of the space charge layer.

- The space charge layer may be treated as one dimensional, and thus all quantities are only a function of the distance from the membrane.
- Within the space charge layer all quantities are nearly in thermodynamic equilibrium, despite any fluxes that may occur through the space charge layer.
- Within the space charge layer, the deviations of ion concentrations and electrostatic potential from their bulk values are small.

The first approximation can be taken because of our homogenization of the membrane quantities. Homogenization with respect to the spatial coordinate within the membrane coordinate smears out the steep gradients (parallel to the membrane) in concentration and electrostatic potential that may exist near the mouth of transmembrane current sources such as ion channels. Once we accept this first approximation, the second approximation is justified by the fact that the space charge layer is thin. The validity of the third approximation will be discussed later.

Let x denote the distance coordinate normal to the membrane surface. Then, according to the first two approximations we have just stated, (2) and (3) become:

$$0 = -D_i \left(\frac{\partial c_i}{\partial x} + \frac{qz_i c_i}{k_B T} \frac{\partial \phi}{\partial x} \right) \quad (15)$$

$$-\frac{\partial^2 \phi}{\partial x^2} = \frac{1}{\epsilon} \left(\rho_0 + \sum_{i=1}^N qz_i c_i \right) \quad (16)$$

which hold on $0 < x < \infty$ with $c_i(\infty)$ and $\phi(\infty)$ given. Here, $x = 0$ is the intracellular or extracellular face of the membrane, and $x = \infty$ corresponds to the bulk solution where c_i and ϕ values in the space charge layer are to be matched with the bulk values. Since we assume that the background fixed charge density ρ_0 varies on the scale of the cellular size L , its variation within the thickness of the space charge layer is negligible, of order $\mathcal{O}(r_d/L)$. Thus, we will treat ρ_0 as being constant within the space charge layer. It is important to note that these values at $x = \infty$ satisfy electroneutrality, i.e.,

$$\rho_0 + \sum_{i=1}^N qz_i c_i(\infty) = 0 \quad (17)$$

If the boundary conditions are functions of time, the above equations hold at each time t and since time plays no dynamical role in them, we drop the argument t for now.

Equation (15) can be integrated easily to obtain,

$$c_i(x) = c_i(\infty) \exp \left(-\frac{qz_i}{k_B T} (\phi(x) - \phi(\infty)) \right).$$

This equation can be substituted into (16) to yield,

$$-\frac{\partial^2 \phi}{\partial x^2} = \frac{1}{\epsilon} \left(\rho_0 + \sum_{i=1}^N qz_i c_i(\infty) \exp \left(-\frac{qz_i}{k_B T} (\phi(x) - \phi(\infty)) \right) \right). \quad (18)$$

Here we use our third approximation to linearize the above Poisson-Boltzmann equation. We suppose

$$\left| \frac{qz_i}{k_B T} (\phi(x) - \phi(\infty)) \right| \ll 1. \quad (19)$$

Then, taking into account the electroneutrality condition at $x = \infty$ (we have electroneutrality in the bulk),

$$c_i(x) = c_i(\infty) \left(1 - \frac{qz_i}{k_B T} (\phi(x) - \phi(\infty)) \right) \quad (20)$$

$$\frac{\partial^2}{\partial x^2} (\phi(x) - \phi(\infty)) = \gamma^2 (\phi(x) - \phi(\infty))$$

where,

$$\gamma^2 = \sum_{i=1}^N \frac{(qz_i)^2 c_i(\infty)}{\epsilon k_B T}. \quad (21)$$

Letting γ be the positive square root of γ^2 , we find the unique bounded solution,

$$\phi(x) - \phi(\infty) = (\phi(0) - \phi(\infty)) \exp(-\gamma x)$$

and hence according to (20),

$$c_i(x) - c_i(\infty) = -c_i(\infty) \frac{qz_i}{k_B T} (\phi(0) - \phi(\infty)) \exp(-\gamma x).$$

Using this equation, we may compute σ_i as

$$\sigma_i = \int_0^\infty qz_i (c_i(x) - c_i(\infty)) dx = -c_i(\infty) \frac{(qz_i)^2}{k_B T \gamma} (\phi(0) - \phi(\infty)).$$

Using the above and noting that $\sum_{i=1}^N \sigma_i = \sigma$, we immediately obtain:

$$\sigma_i = \frac{z_i^2 c_i(\infty)}{\sum_{i'=1}^N z_{i'}^2 c_{i'}(\infty)} \sigma$$

which is exactly expression (14), what we set out to find.

In summary, we have shown that the i -th species of ion makes a contribution to the membrane surface charge in proportion to its nearby bulk concentration weighted by the square of the ionic charge. Note that ions of either sign contribute charge with the same sign as that of the total surface charge, even though the sign may be opposite to that of their own charge! This is because the surface charge layer may involve a deficit rather than an excess of any particular ion, and a deficit of negative charge, for example makes a positive contribution to the surface charge.

5.2. Validity of the linear approximation to the Poisson-Boltzmann equation for the space charge layer

We now consider the validity of the third approximation. We take the Poisson-Boltzmann equation (18) as our starting point:

$$-\frac{\partial^2 \phi}{\partial x^2} = \frac{1}{\epsilon} \left(\rho_0 + \sum_{i=1}^N qz_i c_i(\infty) \exp \left(-\frac{qz_i}{k_B T} \phi(x) \right) \right). \quad (22)$$

We have taken $\phi(\infty) = 0$, since the electrostatic potential is only determined up to an arbitrary constant. We will also assume in the following that $\phi(0) > 0$. By the end of the discussion, it will be clear that the $\phi(0) < 0$ case can be handled in an identical way. We note that

$$\rho_0 + \sum_{i=1}^N qz_i c_i(\infty) = 0. \quad (23)$$

Our goal is to derive a condition that guarantees the relation

$$\left| \frac{qz_i}{k_B T} \phi(x) \right| \ll 1$$

to hold. We note that the above expression concerns the deviation of the electrostatic potential within the space charge layer, and not the potential jump across the cell membrane. Since z_i takes integer values not too different from 1 in absolute value, we shall be content to establish the condition:

$$\left| \frac{q}{k_B T} \phi(x) \right| \ll 1. \quad (24)$$

Consider the function $f(\phi)$,

$$f(\phi) = - \left(\rho_0 + \sum_{i=1}^N qz_i c_i(\infty) \exp \left(-\frac{qz_i}{k_B T} \phi \right) \right).$$

Note that (22) can be written as $\frac{\partial^2 \phi}{\partial x^2} = \frac{1}{\epsilon} f(\phi)$. We see that,

$$\frac{\partial f}{\partial \phi} = \left(\sum_{i=1}^N \frac{(qz_i)^2 c_i(\infty)}{k_B T} \exp \left(-\frac{qz_i}{k_B T} \phi \right) \right) > 0.$$

Therefore, $f(\phi)$ is monotone increasing in ϕ . From (23), we see that $f(0) = 0$. Therefore, $f(\phi) > 0$ if $\phi > 0$ and $f(\phi) < 0$ if $\phi < 0$.

Suppose that $\phi(x) > \phi(0)$ for some values of x . Since $\phi(\infty) = 0$, $\phi(x)$ must attain a positive local maximum at some interior point x_0 . Since $\phi(x_0) > 0$, $f(\phi(x_0)) > 0$. But this is impossible since $f(\phi(x_0)) > 0$ implies that $\frac{\partial^2 \phi}{\partial x^2}(x_0) > 0$. Next, suppose that $\phi(x)$ is negative for some values of x . Since $\phi(\infty) = 0$, $\phi(x)$ must attain a negative local minimum at some interior point x_1 . Since $\phi(x_1) < 0$, $f(\phi(x_1)) < 0$. This is again impossible since this implies $\frac{\partial^2 \phi}{\partial x^2}(x_1) < 0$. This argument may be considered a simple application of the maximum principle for elliptic partial differential equations.

From the above we conclude that $0 \leq \phi(x) < \phi(0)$. From $\phi \geq 0$, we see that $\frac{\partial^2 \phi}{\partial x^2} \geq 0$ for all x , and thus, $\frac{\partial \phi}{\partial x}$ is non-decreasing. Since $\phi(\infty) = 0$, this implies that $\frac{\partial \phi}{\partial x}(\infty) = 0$. The two conclusions we have reached so far are:

$$0 \leq \phi(x) < \phi(0) \quad (25)$$

$$\frac{\partial \phi}{\partial x}(\infty) = 0. \quad (26)$$

From (25) we see that (24) will be true for all x if

$$\left| \frac{q}{k_B T} \phi(0) \right| \ll 1. \quad (27)$$

We next integrate (22) from $x = 0$ to $x = \infty$.

$$-\frac{\partial \phi}{\partial x}(\infty) + \frac{\partial \phi}{\partial x}(0) = \frac{1}{\epsilon} \int_0^\infty \left(\rho_0 + \sum_{i=1}^N qz_i c_i(\infty) \exp\left(-\frac{qz_i}{k_B T} \phi\right) \right) dx.$$

Noting that the integral on the right hand side is the total charge in the space charge layer σ and using (26), we find,

$$\frac{\partial \phi}{\partial x}(0) = \frac{\sigma}{\epsilon}. \quad (28)$$

We may find another relation by multiplying (22) by $\frac{\partial \phi}{\partial x}$ and again integrating from $x = 0$ to $x = \infty$. Using (26) and (28) one finds,

$$\frac{1}{2} \sigma^2 = \epsilon \left(k_B T \sum_{i=1}^N c_i(\infty) \left(\exp\left(-\frac{qz_i \phi(0)}{k_B T}\right) - 1 \right) - \rho_0 \phi(0) \right) \equiv \epsilon F(\phi(0)). \quad (29)$$

We estimate $F(\phi)$ from below. We note first that

$$F(0) = 0, \quad \frac{\partial F}{\partial \phi}(0) = f(0) = 0. \quad (30)$$

We examine the second derivative of F with respect to ϕ . For $\phi > 0$,

$$\begin{aligned} \frac{\partial^2 F}{\partial \phi^2} &= \frac{\partial f}{\partial \phi} = \sum_{i=1}^N \frac{(qz_i)^2 c_i(\infty)}{k_B T} \exp\left(-\frac{qz_i}{k_B T} \phi\right) \\ &> \sum_{z_i < 0} \frac{(qz_i)^2 c_i(\infty)}{k_B T} \exp\left(-\frac{qz_i}{k_B T} \phi\right) > \sum_{z_i < 0} \frac{(qz_i)^2 c_i(\infty)}{k_B T}. \end{aligned}$$

Since z_i is at least equal to 1 in absolute value,

$$\frac{\partial^2 F}{\partial \phi^2} > \frac{q^2 C^-}{k_B T}, \quad C^- \equiv \sum_{z_i < 0} c_i(\infty).$$

Using (30) and the above, for $\phi(0) > 0$ we conclude that,

$$F(\phi(0)) > \frac{q^2 C^-}{2k_B T} \phi(0)^2.$$

Therefore, by (29), we find:

$$\sigma^2 > \epsilon \frac{q^2 C^-}{k_B T} \phi(0)^2.$$

We may take C^- , the total concentration of anions, to be the typical concentration. In this case, the Debye length $r_d = \sqrt{\frac{\epsilon k_B T}{q^2 C^-}}$. Therefore,

$$\left(\frac{\sigma}{qC^- r_d}\right)^2 > \left(\frac{q}{k_B T} \phi(0)\right)^2.$$

Taking the square root of the above, we see that

$$\frac{|\sigma|}{qC^- r_d} > \frac{q}{k_B T} |\phi(0)|.$$

Thus, condition (27) should hold if $\frac{|\sigma|}{qC^- r_d} \ll 1$. For $\phi(0) < 0$, an identical argument shows that

$$\frac{|\sigma|}{qC^+ r_d} > \frac{q}{k_B T} |\phi(0)|$$

where C^+ is the total concentration of cations at the bulk, and r_d is computed using C^+ as the typical concentration. Hence, we conclude $\frac{|\sigma|}{qC^+ r_d} \ll 1$ is sufficient for condition (27). Since C^- and C^+ are of the same order of magnitude, we finally conclude that the following condition is sufficient for

the validity of the linear approximation:

$$\frac{|\sigma|}{qc_0r_d} \ll 1 \quad (31)$$

where c_0 is the typical concentration in the bulk solution.

This means that the linear approximation is valid when the amount of surface charge is small in comparison to the absolute total charge concentration in a layer of width r_d . We may calculate this ratio in physiological systems since we can estimate σ with the values of the capacitance and the transmembrane potential, and qc_0r_d by using typical values of ionic concentrations and the Debye length. It turns out that this ratio is on the order of 10^{-2} and this justifies the linear approximation.

6. Transmembrane Ionic Currents

We have yet to specify j_i , the transmembrane currents. Biophysically, these are currents that flow through ion channels, transporters, or pumps that are located within the cell membrane [1, 4, 7]. We use the formalism of Hodgkin and Huxley for ion channel currents [5, 8, 9], generalized to allow for nonlinear instantaneous current-voltage relations and ion concentration effects.

$$j_i^{(kl)}(\mathbf{x}, t) = J_i^{(kl)}\left(\mathbf{x}, s^{(kl)}(\mathbf{x}, t), \phi^{(kl)}(\mathbf{x}, t), c^{(k)}(\mathbf{x}, t), c^{(l)}(\mathbf{x}, t)\right) \quad (32)$$

Here, $J_i^{(kl)}$ is a function characteristic of the channels (possibly of more than one type) that carry the i -th species of ion across the membrane separating $\Omega^{(k)}$ from $\Omega^{(l)}$. The explicit dependence of $J_i^{(kl)}$ on \mathbf{x} reflects the possible inhomogeneity of the membrane: the density of channels may vary from one location to another. The other arguments of $J_i^{(kl)}$ are as follows:

First, there is a vector of gating variables $s^{(kl)}(\mathbf{x}, t) = (s_1^{(kl)}, \dots, s_G^{(kl)})$ where G is the total number of gating variables in all of the channel types that arise in our system. (Only some of these influence the channels that conduct ions of species i .) The individual components $s_g^{(kl)}$ of $s^{(kl)}$ are dimensionless variables as introduced by Hodgkin and Huxley [5] that take values in the interval $[0, 1]$ and satisfy ordinary differential equations of the form,

$$\frac{\partial s_g^{(kl)}}{\partial t}(\mathbf{x}, t) = \alpha_g\left(\phi^{(kl)}(\mathbf{x}, t)\right)\left(1 - s_g^{(kl)}(\mathbf{x}, t)\right) - \beta_g\left(\phi^{(kl)}(\mathbf{x}, t)\right)s_g^{(kl)}(\mathbf{x}, t) \quad (33)$$

for $g = 1, \dots, G$ where α_g and β_g are positive, empirically defined functions of the transmembrane potential.

The next argument of $J_i^{(kl)}$ is again the transmembrane potential $\phi^{(kl)}$. Holding the other arguments fixed in $J_i^{(kl)}$, and letting only $\phi^{(kl)}$ vary, we get the instantaneous current-voltage relationship for current carried by the i -th ion from $\Omega^{(k)}$ to $\Omega^{(l)}$ at point \mathbf{x} at time t .

The last two arguments of $J_i^{(kl)}$ are the vectors of ion concentrations on the two sides of the membrane: $c^{(k)} = (c_1^{(k)}, \dots, c_N^{(k)})$ and similarly for $c^{(l)}$. By including the whole vector of ion concentrations, we allow for the possibility that the current carried by the i -th species of ion is influenced by the concentrations of other ionic species on the two sides of the membrane.

As an example of the foregoing, consider the Na^+ channel current in the Hodgkin Huxley model, which has the following form.

$$J_{\text{Na}} = g_{\text{Na}}(\mathbf{x})m(\mathbf{x}, t)^3h(\mathbf{x}, t) \times \left((\phi^{\text{int}}(\mathbf{x}, t) - \phi^{\text{ext}}(\mathbf{x}, t)) - \frac{k_B T}{q} \log \left(\frac{c_{\text{Na}}^{\text{ext}}(\mathbf{x}, t)}{c_{\text{Na}}^{\text{int}}(\mathbf{x}, t)} \right) \right) \quad (34)$$

In this equation, the regions k and l are identified as the intracellular and extracellular spaces, denoted by the superscript int and ext. m and h are the gating variables, and g_{Na} is the ion channel density. Keeping m , h , g_{Na} , $c_{\text{Na}}^{\text{int}}$, $c_{\text{Na}}^{\text{ext}}$ fixed, we happen to have a linear instantaneous current voltage relationship, but this may not be so in general. The gating variables m and h satisfy a first order ordinary differential equation of the form (33). Functions α and β are determined experimentally.

Note that the above formalism is more general than the words that we have used to describe them. The “ions” that we have described do not need to be charged (one can have $z_i = 0$ for some i) and they can include neurotransmitters (whether charged or not) that have been released at synapses. We may have ligand-gated channels, by introducing gating variables whose evolution is governed by the local concentration of chemical species. The only restriction is that the binding of ligands to these channels does not significantly alter the unbound concentrations of these chemicals. Other ion carrying mechanisms such as transporters and pumps may also be easily incorporated using the above formalism or a slight generalization thereof.

A subtle and important question that remains is precisely where to evaluate the electrostatic potential and the various ion concentrations on the two

sides of the membrane. As we have seen in the foregoing sections, there is a thin space charge layer near each face of the membrane in which the electrostatic potential and the ion concentrations may deviate somewhat from those in the bulk solution, away from the membranes. Several of the arguments of the functions $J_i^{(kl)}$ that define the transmembrane currents involve the boundary values of the electrostatic potential or the ion concentrations. Do these literally refer to the values right on the face of the membrane, or do they refer to the values in the bulk solution, near the membrane but outside the space charge layer?

From a mathematical standpoint, the answer is clear. We are trying to solve a set of partial differential equations (1), (2), and (4) that are satisfied away from the membrane under certain boundary conditions with expressions involving $c_i^{(k)}$, $c_i^{(l)}$ and $\phi^{(kl)}$. Thus, the boundary conditions will not be useful unless these quantities are evaluated away from the membrane, i.e., near the membrane but within the bulk solution.

When $J_i^{(kl)}$ is measured experimentally, the controlled values of voltage and ion concentrations are always those of the bulk solution. The space charge layers are, of course, present during these measurements, but they are experimentally inaccessible, on account of their thinness. This means that the experimentally determined functions $J_i^{(kl)}$ can be used directly in the equations without corrections.

7. Summary of the Model

We can now write down the equations to be solved together with their boundary conditions. Let $\Gamma^{(kl)}$ denote the membrane separating $\Omega^{(k)}$ and $\Omega^{(l)}$. In $\Omega^{(k)}$ and $\Omega^{(l)}$,

$$0 = \frac{\partial c_i}{\partial t} + \nabla \cdot \mathbf{f}_i \quad (35)$$

$$\mathbf{f}_i = -D_i \left(\nabla c_i + \frac{qz_i c_i}{k_B T} \nabla \phi \right) \quad (36)$$

$$0 = \rho_0 + \sum_{i=1}^n qz_i c_i \quad (37)$$

The boundary conditions at the face of $\Gamma^{(kl)}$ facing $\Omega^{(k)}$ are,

$$\frac{\partial \sigma_i^{(k)}}{\partial t} = qz_i \mathbf{f}_i^{(k)} \cdot \mathbf{n}^{(kl)} - j_i^{(kl)} \quad (38)$$

$$\sum_{i=1}^N \sigma_i^{(k)} = \sigma^{(k)} = C_m \phi^{(kl)}, \quad \sigma_i^{(k)} = \frac{z_i^2 c_i^{(k)}}{\sum_{i'=1}^N z_{i'}^2 c_{i'}^{(k)}} \sigma^{(k)} \quad (39)$$

$$j_i^{(kl)} = J_i^{(kl)}(\mathbf{x}, s^{(kl)}, \phi^{(kl)}, c^{(k)}, c^{(l)}) \quad (40)$$

$$\frac{\partial s_g^{(kl)}}{\partial t} = \alpha_g(\phi^{(kl)})(1 - s_g^{(kl)}) - \beta_g(\phi^{(kl)})s_g^{(kl)} \quad (41)$$

The boundary conditions on the $\Omega^{(l)}$ face are the same as above with k and l interchanged.

One easy extension of the above model is to include chemical reactions (including the important example of the binding and unbinding of ions to buffers). We may add reaction terms on the left hand side of (35). Since no chemical reaction destroys or creates charge, reaction terms will always be consistent with the electroneutrality condition (37) as long as we keep track of all chemical species in the reaction. Addition of reaction terms may prove especially important with respect to calcium, a physiologically important ion that is heavily buffered in biological cells.

8. Numerical Simulation

We briefly discuss the numerical challenges and the numerical methods that we currently use to solve the above system of equations, followed by a brief account of our simulation results. Further details on the methods and results will be presented in a future publication.

8.1. Numerical method

Let us begin with the time marching scheme. We have encountered two major difficulties in developing an efficient algorithm for time evolution. The first of these is the electroneutrality condition. Small deviations from electroneutrality seem to make simple-minded numerical schemes unstable. The second is that the equations are ‘stiff’, i.e., that they involve at least two very different time scales. The reason for this stiffness of our model can be understood in the following way. Starting from our governing equations,

one can derive the cable model of Hodgkin and Huxley under simplifying assumptions. This cable model, which is in some sense contained within our model since it can be derived from it, involves a constant with the units of a diffusion coefficient associated with the spread of electrical potential. This electrical ‘diffusion’ constant is several orders of magnitude greater than any of the ionic diffusion constants of the model from which it is derived. Indeed, we find that the ratio of the electrical diffusion coefficient to the ionic diffusion coefficients is about $10^4 \sim 10^7$. To overcome the numerical difficulties associated with the stiffness of the model, we are led to the use of the backward Euler method. The resulting nonlinear equations are solved iteratively, by a method that is in part the subject of the mathematical analysis presented in the final section of this paper.

We perform spatial discretization with the finite volume method. The equations of the model can all be written in divergence form, which makes a finite volume discretization physically intuitive. The electroneutrality condition can be expressed easily as a condition that the electric current that flows into each computational voxel sums to zero.

8.2. Simulation results

We present two simulations based on the above numerical method. Each involves a different implementation, one for cylindrically symmetric membrane geometries, and the other for arbitrary two dimensional membrane geometries.

Using code for cylindrically symmetric geometries, we have shown the possibility of unusual modes of communication between neurons (and cardiomyocytes), distinct from the extensively studied chemical transmission with neurotransmitters or electrical transmission through gap junctions [1, 7]. When two neurons are closely apposed, with a high density of channels in the membranes facing the interneuronal cleft, two other kinds of communication are shown to be possible. One (the faster of the two) arises from the large electrical current (recall the high density of ionic channels facing the interneuronal cleft) that flows in the narrow and hence highly resistive gap between the cells. This results in a substantial voltage drop within the interneuronal cleft, which in turn has a substantial effect on the potential difference across the two membranes facing that cleft. The second (slower) kind of communication arises from ion accumulation within the interneuronal cleft, which may significantly change the equilibrium potentials for the

different ionic currents across the membranes facing the gap. These effects can launch action potentials that propagate away from the gap. In Figure 1, we show a case in which an action potential indeed travels across a narrow gap and gets reflected, primarily due to the second mechanism. Although these mechanisms have been previously discussed on a conceptual level and have even been modeled by systems of ordinary differential equations that lump the gap into a single compartment [10], they have never been demonstrated in the context of a spatially distributed model such as ours. The importance of the spatially distributed approach reveals itself, for example, in the nonuniform radial distribution of potential within the gap (see Figure 1), which has the effect of lowering the threshold for transmission to occur.

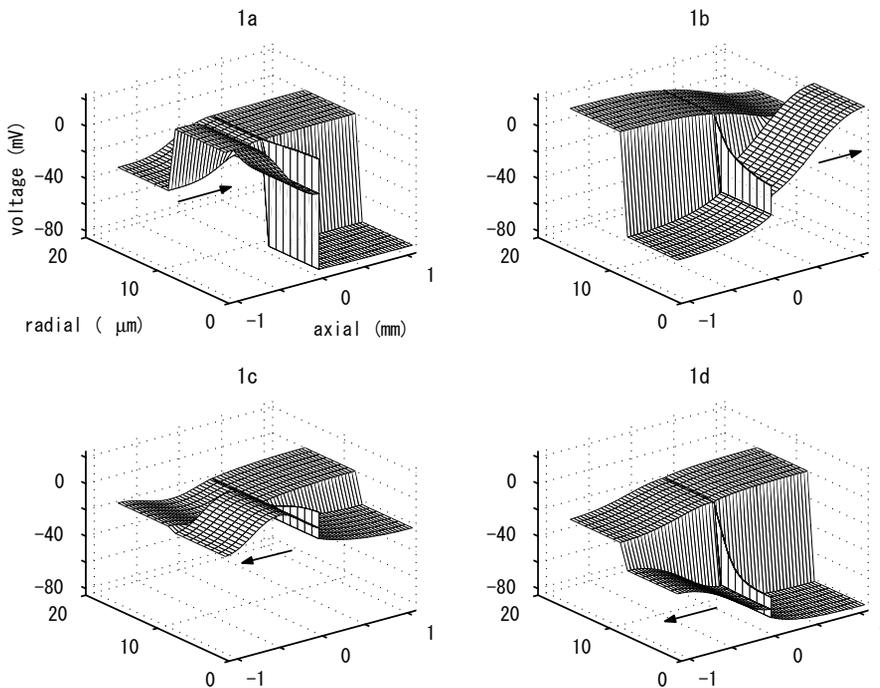


Figure 1. The above shows radial cross sections of two cylindrical cells separated by a narrow gap. Plotted in each figure is the electrostatic potential. The cell membrane is located half way in the radial direction and the region closer to the viewer is the intracellular side. A wave of excitation approaches the gap from the cell on the left(1a) and is transmitted across the narrow gap to the cell on the right(1b). This wave propagates back into the cell on the left(1c) and eventually leaves the simulation domain(1d). Note the radial gradient of the electrostatic potential in the narrow gap.

With the code for arbitrary two dimensional geometries, we have shown the theoretical possibility of a ‘surface wave’. Consider a large circular biological cell, and suppose there is some excitatory input at a location on the membrane. An action potential is initiated at this location, and propagates through the circular cell. As the action potential propagates, the change in electrostatic potential is seen to be much larger near the membrane than away from the membrane near the center of the cell. We see that the action potential propagates along the membrane as a ‘surface wave’. This situation could not have been modeled with a traditional approach using the one dimensional cable model. This simulation is shown in Figure 2

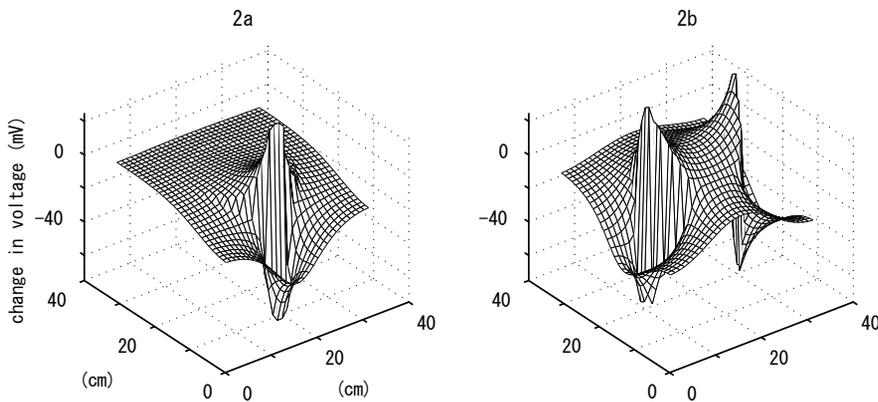


Figure 2. This figure shows a surface wave of excitation in a circular cell. An action potential was initiated at a location on the membrane (2a) and has propagated half way to the middle of the cell (2b). Note that this figure plots the *change* in electrostatic potential from the initial values.

9. Analysis of the Model

In this final section, we present a mathematical analysis of the model. We believe that the present and future mathematical analyses will not only yield valuable theoretical insight, but will also lead to a better understanding of our current numerical algorithm and guide us to more efficient and stable numerical methods, which should prove all the more important in the context of a fully three dimensional simulation of the model.

The system described above, with electroneutrality enforced by the elliptic equation for the potential, admits of an analysis defined by Rothe’s

method of horizontal lines. The first part of this program involves the well-posedness of the time semidiscretization, which involves operator composition of several steps; (i) determination of the potential, coupled across regions $\Omega^{(k)}$ and $\Omega^{(l)}$; (ii) determination of the boundary variables associated with flux representations; and (iii) determination of the concentrations in each region. Rothe's method has the advantage of organizing the problem effectively, while decoupling the principal subsystems as described.

9.1. Notation and initial/boundary conditions

Ω will denote the entire region of tissue which is subdivided. If the potential differences across cell membranes and all species' concentrations are known at any time, then the bulk membrane current can be determined on cell membranes, which permits the determination of the rate of change of transmembrane potential differences, if the transmembrane ionic current is known. The initial value problem assumes then that the potential differences $\phi^{(0,kl)}$ across cells, and the concentrations $c_i^{(0,k)}$ are given at time $t = 0$, together with the gating variables $s^{(0,kl)}$ defined on the membrane $\Gamma^{(kl)}$. It is required that the initial data satisfy

$$\sum_j z_j^2 D_j c_j^{(0,k)} \geq \alpha_k > 0, \text{ on } \Omega^{(k)},$$

so that the electrostatic problem is uniformly elliptic. This is preserved by the evolution. It is also assumed that appropriate boundary conditions are imposed on $\partial\Omega$.

9.2. Decoupled composition map

Suppose that the 'solution map' has been defined at time $t = t_{n-1}$. We discuss the first step of the composition map at the discrete time $t = t_n$ as follows. Thus, we consider the elliptic equation which preserves the electroneutrality as the system evolves.

- On $\Omega^{(k)}$ (similarly for $\Omega^{(l)}$, coupled across the common boundary), solve the Robin boundary value problem for $\phi^{(n,k)}$ with equation given by (8). The flux is coupled on each $\Gamma^{(kl)}$ to the adjacent region $\Omega^{(l)}$ and is defined by the semidiscretization of (11). We have:

$$-\sum_{i=1}^N qz_i D_i \left(\frac{\partial c_i^{(n-1,k)}}{\partial \mathbf{n}^{(kl)}} + \frac{qz_i}{k_B T} \frac{\partial \phi^{(n,k)}}{\partial \mathbf{n}^{(kl)}} c_i^{(n-1,k)} \right)$$

$$= C_m \frac{\phi^{(n,kl)} - \phi^{(n-1,kl)}}{\Delta t} + \sum_i j_i(\phi^{(n,kl)}, c_i^{(n-1,k)}, c_i^{(n-1,l)}, s_g^{(n-1,k)}).$$

Here, we have used the notation $\Delta t = t_n - t_{n-1}$ as well as

$$\phi^{(n,kl)} = \text{trace } \phi^{(n,k)} - \text{trace } \phi^{(n,l)},$$

where the trace is taken on each boundary surface element $\Gamma^{(kl)}$.

9.3. Weak formulation of the electrostatic problem

The electrostatic problem has a nonstandard formulation involving coupling with respect to a common boundary. We give the weak formulation for $\phi^{(n,k)}$. For simplicity, we treat here the case of two regions and write the solution unknowns as

$$\phi^{(1)} = \phi^{(n,1)}, \quad \phi^{(2)} = \phi^{(n,2)},$$

and the Hilbert function spaces as $\mathcal{H}^{(k)} = W^{(1,2)}(\Omega^{(k)})$. The weak formulation is facilitated by the definitions,

$$a_k(\phi^{(k)}, v) := \int_{\Omega^{(k)}} a^{(n-1,k)} \nabla \phi^{(k)} \cdot \nabla v \, dx, \quad v \in \mathcal{H}^{(k)},$$

where $a^{(n-1,k)}$ is given by (6) with $c_i = c_i^{(n-1,k)}$, and $\phi^{(k)} \in \mathcal{H}^{(k)}$ is to be determined for $k = 1, 2$,

$$b_k(v) := \int_{\Omega^{(k)}} \nabla b^{(n-1,k)} \cdot \nabla v \, dx,$$

$$g_k(\phi^{(k)}, \phi^{(k')}, \gamma v) := \int_{\Gamma^{(kk')}} \left\{ C_m \frac{\phi^{(kk')} - \phi^{(n-1,kk')}}{\Delta t} + \sum_{i=1}^N j_i(\phi^{(kk')}, \dots) \right\} \gamma v \, d\sigma,$$

where $b^{(n-1,k)}$ is given by (7) with $c_i = c_i^{(n-1,k)}$, $k' = 2$ if $k = 1$ and $k' = 1$ if $k = 2$. Here, γ is the continuous trace operator. The weak form of the electrostatic system is:

$$a_k(\phi^{(k)}, v) + b_k(v) + g_k(\phi^{(k)}, \phi^{(k')}, \gamma v) = 0, \quad \forall v \in \mathcal{H}^{(k)}, \quad k = 1, 2. \tag{42}$$

9.3.1. Approach via trapping regions

This technique takes advantage of standard approaches to elliptic theory, which allows use of built-in computational tools. It makes use of the isotone

property of the ‘back and forth’ map V , to be developed presently, but requires the context of a trapping region. We formulate its existence here as a postulate. The advantage at the numerical level, such as piecewise linear finite elements, is that the discretizations are confined to the function space trapping region associated with, alternately, the cell and its exterior. An alternative viewpoint is also possible: the cell and its exterior are viewed as a single spatial domain, with the membrane serving as an ‘interior’ charge constraint surface, across which conservation of charge must hold. This will be explored in future work. We now posit the existence of the trapping region.

Assumption. There exists a trapping region for the system. Thus, there are functions $\underline{u}^{(k)} \leq \bar{u}^{(k)}$ in \mathcal{H}^k , such that, for

$$\mathcal{K}_{k'} := [\underline{u}^{(k')}, \bar{u}^{(k')}],$$

one has $\forall v \in \mathcal{H}^{(k)}, \gamma v \geq 0$,

$$\begin{aligned} a_k(\bar{u}^{(k)}, v) + b_k(v) + g_k(\bar{u}^{(k)}, w, \gamma v) &\geq 0, \quad \forall w \in \mathcal{K}_{k'}, \\ a_k(\underline{u}^{(k)}, v) + b_k(v) + g_k(\underline{u}^{(k)}, w, \gamma v) &\leq 0, \quad \forall w \in \mathcal{K}_{k'}. \end{aligned}$$

9.3.2. The isotone map

We shall introduce some notation. Set

$$\langle F_k(u, w), v \rangle := b_k(v) + g_k \circ \gamma(u, w, v).$$

The proof of the existence of a solution of the system (42) proceeds by defining a fixed point mapping V defined on the interval \mathcal{K}_1 with range in \mathcal{K}_1 .

1. Given $w \in \mathcal{K}_1$, an intermediate mapping, $T : \mathcal{K}_1 \mapsto \mathcal{K}_2$, $Tw = u$, is introduced, where $u \in \mathcal{K}_2$ is the solution of the equation and integration constraint,

$$a_2(u, v) + \langle F_2(u, w), v \rangle = 0, \quad \forall v \in \mathcal{H}^2, \quad \int_{\Omega^{(2)}} u \, dx = \int_{\Omega^{(1)}} w \, dx. \quad (43)$$

2. Vw is then defined as UTw , where $U : \mathcal{K}_2 \mapsto \mathcal{K}_1$, $Uu = u_1$, and where $u_1 \in \mathcal{K}_1$ is the solution of the equation and integration constraint,

$$a_1(u_1, v) + \langle F_1(u_1, u), v \rangle = 0, \quad \forall v \in \mathcal{H}^1, \quad \int_{\Omega^{(1)}} u_1 \, dx = \int_{\Omega^{(2)}} u \, dx. \quad (44)$$

Lemma 9.1. *Let $w \in \mathcal{K}_1$ be given. There is a unique solution $u = Tw$ of the equation (43) subject to the condition that the integrals of u, w are equal. In addition, T is isotone from \mathcal{K}_1 to \mathcal{K}_2 . Similarly, let $u \in \mathcal{K}_2$ be given. There is a unique solution $u_1 = Uu$ of the equation (44) subject to the condition that the integrals of u_1, u are equal. In addition, U is isotone from \mathcal{K}_2 to \mathcal{K}_1 .*

The mapping V is then isotone on \mathcal{K}_1 . We comment briefly on the validation of the lemma, which will be detailed in a future publication. The decoupling leads to gradient formulations, which are well understood. The integration constraint imposes uniqueness of solutions, and is compatible with the isotone properties of T and U ; these depend on the monotone structure of g_k . The functionals are increasing in the trace of the principal variable and decreasing in the trace of the coupled variable. If \mathcal{K}_1 were a complete lattice, then we would automatically conclude the existence of a fixed point of V by Tarski's theorem. Closed subintervals of Lebesgue spaces are complete, in this sense, but subintervals of Sobolev spaces are not. One needs a theory of ordered spaces, specifically [2, Proposition 1.1.1], which imposes a form of continuity on V . We will accept this, and obtain a fixed point: $Vu_1 = u_1$. One argues analogously to [3] to demonstrate these assertions.

Not only does V have a (unique) fixed point, but iterations starting with the lower bound are increasing, and iterations starting with the upper bound are decreasing. With proper continuity, these sequences converge to a fixed point. This may prove useful for computation.

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