Physica D 308 (2015) 94–108

Contents lists available at ScienceDirect

Physica D

journal homepage: www.elsevier.com/locate/physd

A multidomain model for ionic electrodiffusion and osmosis with an application to cortical spreading depression

Yoichiro Mori

School of Mathematics, University of Minnesota, MN 55455, USA

HIGHLIGHTS

- We develop a PDE model for ionic electrodiffusion and osmosis in biological tissue.
- An important feature of the model is the presence of a free energy identity.
- Relations to other electrophysiology models including the cardiac bidomain and cable models are discussed.
- The model is applied to the study of cortical spreading depression (SD).
- The model allows for successful computation of the extracellular DC shift in SD.

ARTICLE INFO

Article history:
Received 28 August 2014
Received in revised form
9 March 2015
Accepted 22 June 2015
Available online 29 June 2015
Communicated by K. Josic

Keywords:
Ionic electrodiffusion
Osmosis
Tissue physiology
Free energy identity
Cortical spreading depression

ABSTRACT

Ionic electrodiffusion and osmotic water flow are central processes in many physiological systems. We formulate a system of partial differential equations that governs ion movement and water flow in biological tissue. A salient feature of this model is that it satisfies a free energy identity, ensuring the thermodynamic consistency of the model. A numerical scheme is developed for the model in one spatial dimension and is applied to a model of cortical spreading depression, a propagating breakdown of ionic and cell volume homeostasis in the brain.

1. Introduction

In this paper, we formulate a system of partial differential equations (PDE) that governs ionic electrodiffusion and osmotic water flow, to study tissue-level physiological phenomena. To demonstrate the use of the model, we apply this to the study of cortical spreading depression, a pathological phenomenon of the brain that is linked to migraine aura and other diseases.

We now describe our modeling approach. Biological tissue can often be seen as composed of multiple interpenetrating compartments. Cardiac tissue, for example, can be seen as composed of two interpenetrating compartments, the space that consists of interconnected cardiomyocytes and the extracellular space. The number of compartments may not be restricted to two. In the central nervous system, one may consider the neuronal, glial and extracellular compartments. In studying physiological phenomena at the tissue level, it is often impractical to use models with exquisite cellular detail. If the spatial variations in the biophysical variables of interest are slow compared to the cellular spatial scale, we may model the system instead as a homogenized continuum. The first such model, the *bidomain model*, was introduced in [1–3], and its application to cardiac electrophysiology [4–6] is probably the most important and successful example of this coarse-grained approach in physiology. Let us use the cardiac bidomain model to further to illustrate this approach. The main variables of interest in cardiac electrophysiology are the intracellular and extracellular potentials, $\phi_i(\mathbf{x})$ and $\phi_e(\mathbf{x})$ where $\mathbf{x}$ is the spatial coordinate. From a microscopic standpoint, these values should only be defined within their respective compartments. At the coarse-grained level, however, we take the view that it is impossible to distinguish whether a given spatial point is inside the cell or outside the cell. The intracellular and extracellular potentials are now defined everywhere and cardiac tissue is thus seen as an biphasic continuum. In this paper, we shall call such models *multidomain models* to emphasize the fact that the formalism is not restricted to just two interpenetrating phases. We note that such coarse-grained models are also

E-mail address: ymori@umn.edu.

http://dx.doi.org/10.1016/j.physd.2015.06.008
0167-2789/

widely used in the material sciences to describe, for example, multiphase flow [7].

Our goal is to formulate a multidomain model that describes ionic electrodiffusion and osmosis. This can be seen as a generalization of the cardiac bidomain model, which only treats electrical current flow. Ionic electrodiffusion and osmosis have been modeled to varying degrees of detail in different physiological systems. These include the kidney [8], gastric mucosa [9], cerebral edema and hydrocephalus [10], cartilage [11,12], and the lens [13] and cornea [14] of the eye. Here, we develop a time-dependent PDE model that fully incorporates both ionic electrodiffusion and osmotic water flow in multiphasic tissue. Ion balance is governed by the Nernst–Planck electrodiffusion equations with source terms describing transmembrane ion flux. For water balance, we have the usual continuity equations with source terms describing transmembrane water flow. An important feature that distinguishes our model from previous models is that it satisfies a free energy identity, which ensures that electrodiffusive and osmotic effects are treated in a thermodynamically consistent fashion. The use of free energy identities as a guiding principle in formulating equations originates in the work of Onsager [15], and this approach has been widely adopted in soft condensed matter physics [16–19]. The present work is closely related to our recent work in [20–23], wherein the free energy identity played an essential role in ionic electrodiffusion problems arising in physiology and the material sciences. One practical benefit of the physically consistent formulation of our model is that it treats fast cable (or electrotonic/electrical current) effects and the much slower effects mediated by ion concentration gradients in a single unified framework. This is significant especially in the context of ion homeostasis in the brain, in which these fast and slow effects are both important and tightly coupled.

To demonstrate the use of the model (and to test our computational scheme), we have included a preliminary modeling study of cortical spreading depression (SD). SD is a pathological phenomenon of the central nervous system, first reported 70 years ago [24]. Neurons sustain a complete depolarization and loss of functions for seconds to minutes. A massive redistribution of ions takes place [25] resulting in extracellular potassium concentrations in excess of 50 mmol/l. Also seen is neuronal swelling and narrowing of the extracellular space. This breakdown in ionic and volume homeostasis spreads across gray matter at speeds of 2–7 mm/min. SD is the physiological substrate of migraine aura, and it is also related to other brain pathologies such as stroke, seizures and trauma [26]. Studying SD is important, not only because of its close relationship with important diseases but also because a good understanding of SD will lead to a better understanding of brain ionic homeostasis, and hence of the workings of the central nervous system. Despite intensive research efforts, basic questions about SD remain unanswered [27,28]. We refer the reader to [29–34] for reviews on SD.

There have been many modeling studies on SD propagation [35–47], most of which are of reaction–diffusion type. The large excursions in ionic concentration necessitates incorporation of ionic *electro*diffusion and osmotic effects, and our model is well-suited for this application. As a natural output of our model, we can compute the negative shift in the extracellular potential (negative DC shift), an important experimental signal of SD. To the best of our knowledge, this is the first successful computation of this quantity. We then examine the effect of gap junctional coupling and extracellular chloride concentration on SD propagation speed. In particular, we argue that gap junctional coupling is unlikely to play an important role in SD propagation [42].

The paper is organized as follows. In Section 2 we formulate the model. In Section 3, we discuss the free energy identity. This identity allows us to place thermodynamic restrictions on the constitutive laws for the transmembrane fluxes. In Section 4, we make the equations dimensionless and discuss model reduction when certain dimensionless quantities are taken to 0. In particular, we clarify the relationship between our multidomain electrodiffusion model with the cardiac bidomain model. In Section 5, we discuss the numerical discretization of our system. We devise a implicit numerical method that preserves ionic concentrations and satisfies a discrete free energy inequality. In Section 6, we perform simulations of SD. Appendix A describes some of the details of the SD model and simulation and Appendix B includes some remarks on the computation of the extracellular voltage.

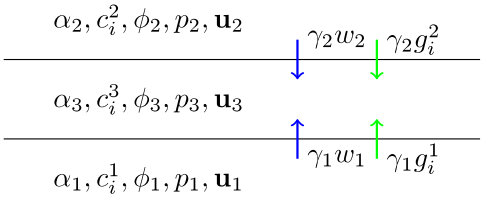

Fig. 1. Biophysical variables in the model when the number of compartments $N = 3$. Compartment 1 (bottom compartment) communicates with the extracellular compartment 3 (middle compartment) through membrane 1, and compartment 2 (top compartment) with compartment 3 through membrane 2. The biophysical variables of interest in each compartment are the volume fractions α_k, concentrations c_i^k, the voltages ϕ_k, the pressures p_k and the fluid velocities $\mathbf{u}_k$. The transmembrane water flux $\gamma_k w_k$ is given in blue arrows and the transmembrane ionic flux $\gamma_k g_i^k$ in green arrows. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. Model formulation

We suppose that the tissue of interest occupies a smooth bounded region $\Omega \in \mathbb{R}^3$. As discussed in Introduction, we view biological tissue as being a multiphasic continuum. Suppose the tissue is composed of N interpenetrating compartments which we label by k. We assume that $k = N$ corresponds to the extracellular space and that all other compartments communicate with the extracellular space only. When we only consider the intracellular and extracellular spaces, $N = 2$ and the 2nd compartment will be the extracellular space. In the central nervous system, we may consider neuronal, glial and extracellular spaces and the extracellular space corresponding to the 3rd compartment, and the other two compartments communicating with the extracellular compartment. A schematic diagram showing the biophysical variables in the model is given in Fig. 1.

To each point in space, we assign a volume fraction α_k for each compartment. By definition, we have:

$$\sum_{k=1}^{N} \alpha_k(\mathbf{x}, t) = 1. \tag{2.1}$$

Note that α_k is a function of space and time.

In the following we shall introduce several parameters that may be influenced by the microscopic geometric details of the tissue. Mechanical properties of cells and hydraulic conductivity are examples of such parameters. We shall make the assumption that these parameters depend on the underlying microscopic geometry only through its influence on α_k.

In order to describe the time evolution of α_k, we introduce the water flow velocity field $\mathbf{u}_k$ defined for each compartment. The volume fraction α_k satisfies the following equation:

$$\frac{\partial \alpha_k}{\partial t} + \nabla \cdot (\alpha_k \mathbf{u}_k) = -\gamma_k w_k, \quad k = 1, \ldots, N-1 \tag{2.2}$$

$$\frac{\partial \alpha_N}{\partial t} + \nabla \cdot (\alpha_N \mathbf{u}_N) = \sum_{k=1}^{N-1} \gamma_k w_k. \tag{2.3}$$