An Electrodiffusive Formalism for Ion Concentration Dynamics in Excitable Cells and the Extracellular Space Surrounding Them

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Abstract In processes where ionic concentrations vary significantly, the standard cable equation fails to accurately predict the transmembrane potential. Such processes call for a mathematical description able to account for the spatiotemporal variations in ion concentrations as well as the subsequent effects of these variations on the membrane potential. We here derive a general electrodiffusive formalism for consistently modeling the dynamics of ion concentration and the transmembrane potential in a one-dimensional geometry, including both the intra- and extracellular domains. Unlike standard cable theory, the electrodiffusive formalism accounts for diffusive currents and concentration-dependent variation of the longitudinal resistivities.

Keywords Ion concentrations • Spatiotemporal variations • Membrane potential • Electrodiffusive formalism • Two-domain model

1 Introduction

In standard cable theory, the effect of ionic diffusion on the net electrical currents is neglected. Longitudinal resistivities, which in reality depend on ion concentrations, are assumed to be constant [6,9,12]. These are typically good approximations when modelling short-term electrical neural activity, as ion concentration typically vary little at the relevant time scale (<100 ms). However, in small intracellular volumes, such as dendritic spines, the local ion concentration can change quite dramatically

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within a few milliseconds [11], and in slower, macroscopic transport processes, concentration gradients may build up over time [2, 7]. For processes involving significant ion concentration gradients, the cable model will fail to give accurate predictions.

Qian and Sejnowski [11] have previously developed a consistent, electrodiffusive scheme for modelling the dynamics on v_M and ion concentrations [11]. Like the standard cable model, the electrodiffusive model assumes that transport phenomena are essentially one-dimensional. Unlike the standard cable model, the electrodiffusive model derived v_M from the ion concentration dynamics, accounting for all ionic movements (membrane fluxes, longitudinal diffusion, and longitudinal electrical migration), as well as for the concentration-dependent variation of the intracellular resistivities. An important limitation with this model [11] is that it only includes the dynamics in the intracellular space (ICS), whereas the extracellular space (ECS) was assumed to be isopotential and with constant ion concentrations.

Here expand the electrodiffusive formalim [11] to explicitly include both the ICS and the ECS. The result is a general mathematical framework for consistently modelling the dynamics of the membrane potential and ion concentrations in the intra- and extracellular domain. We believe that this framework will be of general value for the field of neuroscience. In the discussion, we give a few examples of processes that the formalism can be applied to.

2 Electrodiffusive Formalism

We seek a general mathematical framework for consistently modelling the dynamics of the membrane potential (v_M) and the concentrations in the ICS ($[k]_I$) and ECS ($[k]_E$) of a set (k) of ionic species in a geometry as that depicted in Fig. 1.

2.1 Particle Conservation

We consider the continuity equations for an ion species k with valence z_k in domains I and E:

$$\frac{\partial j_{kI}(x,t)}{\partial x} + \frac{O_M}{a_I} j_{kM}(x,t) + \frac{O_M}{a_I} j_{kI}^{in}(x,t) + \frac{\partial [k]_I(x,t)}{\partial t} = 0 \tag{1}$$

$$\frac{\partial j_{kE}(x,t)}{\partial x} - \frac{O_M}{a_E} j_{kM}(x,t) + \frac{O_M}{a_E} j_{kE}^{in}(x,t) + \frac{\partial [k]_E(x,t)}{\partial t} = 0, \tag{2}$$

with the sealed-end boundary conditions ($n = I$ or E):

$$j_{kn}(0,t) = j_{kn}(l,t) = 0. \tag{3}$$

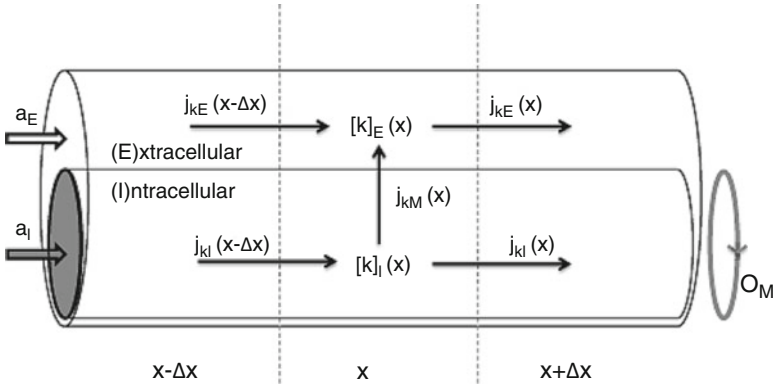

Fig. 1 A two domain-model for ion concentration dynamics in the intra- and extracellular space. The ICS is represented as a cylindrical cable (I), coated by ECS (E). The geometry is specified by three parameters, where a_I is the cross section area of the cable, a_E is the cross section area of the ECS and O_M is the circumference of the cable. The concentration of ion species k is denoted $[k]_n$ where n represents domain I or E. Ionic movement is described by the transmembrane flux density (j_{kM}) and the longitudinal flux densities due to electrical migration (j^f_{kn}) and diffusion (j^d_{kn})

Here a_I and a_E are the cross sections of the ICS and ECS, respectively, and O_M is the circumference of the membrane. The longitudinal flux densities are given by the generalized Nernst-Planck equation (to keep notation short, we skip the functional arguments (x, t) from here on):

$$j_{kn} = -\frac{D_k}{\lambda_n^2}\frac{\partial [k]_n}{\partial x} - \frac{D_k z_k}{\lambda_n^2 \psi}[k]_n \frac{\partial v_n}{\partial x}, \tag{4}$$

where the first term on the right represents the diffusive flux density (j^d_{kn}) and the last term is the flux density due to ionic migration in the electrical field (j^f_{kn}). The effective diffusion constant $D^*_k = D_k/\lambda_n^2$ is composed of the diffusion constant D_k in dilute solutions and the tortuosity factor λ_n, which summarizes the hindrance imposed by the cellular structures [2, 10]. We use $\psi = RT/F$, where R is the gas constant, T the absolute temperature, and F is Faraday's constant. The formalism we derive is general to the transmembrane flux density (j_{kM}), as long as j_{kM} is a local function of v_M, ionic concentrations in I and E, and possibly some additional local state variables. The formalism can be combined with any external input (j^{in}_{kn}) which fulfills the constraint:

$$\sum_k z_k j^{in}_{kE} = -\sum_k z_k j^{in}_{kI}, \tag{5}$$

as we shall explain later.

With N ion species, Eqs. 1 and 2 (with j_{kn}, j_{kM} and j_{kn}^{in} as described above) represent a system of $2N+3$ variables which are functions of x and t. These are the $2N$ concentration variables ($[k]_n$ for $k = 1, 2, \ldots N$ and $n = E, I$), and the three additional variables (v_M, $\partial v_I/\partial x$ and $\partial v_E/\partial x$) occurring in the expressions for the flux densities. We now seek to express v_M, $\partial v_I/\partial x$ and $\partial v_E/\partial x$ as functions of ionic concentrations, so that Eqs. 1 and 2 constitute a fully specified (and numerically solvable) system of equations.

2.2 Voltage Expressions

To reduce the number of independent variables to the $2N$ state variables ($[k]_n$) we use three additional constraints:

$$v_M = \frac{a_I}{C_M O_M}\rho_I \tag{6}$$

$$\frac{a_I}{C_M O_M}\rho_I = -\frac{a_E}{C_M O_M}\rho_E. \tag{7}$$

$$v_M = v_I - v_E \Rightarrow \frac{\partial v_M}{\partial x} = \frac{\partial v_I}{\partial x} - \frac{\partial v_E}{\partial x} \tag{8}$$

Equation 6 is the assumption that the membrane is a parallel plate capacitor. Then v_M is determined by the density of charge on the inside of the membrane, which in turn is determined by the ionic concentrations:

$$\rho_n = F\sum_k z_k[k]_n + \rho_{sn}. \tag{9}$$

For practical purposes, we have included a density of static charges (ρ_{sn}) in Eqs. 6 and 7, representing contributions from ions that are not considered in the conservation equations. If the set $[k]_n$ include all present species of ions, then $\rho_{sn} = 0$.

As a capacitor separates a charge Q from a charge $-Q$ (equal in magnitude, opposite in sign), the ECS charge density must be also consistent with v_M. This is the second constraint (Eq. 7). To our knowledge, we are the first to make use of it in an electrodiffusive model. When using Eqs. 6 and 7, we implicitly assume that all local net charge in the system is stuck on the capacitive membrane (in the Debye-layers), and that the bulk solutions in the ICS and ECS are electroneutral [4, 8]. In order not to violate Eq. 7, the external input to the system must also be locally electroneutral (cf. Eq. 5).

We shall now use Eq. 7 together with the general definition of the transmembrane potential (Eq. 8) to derive our expressions for $\partial v_I/\partial x$ and $\partial v_E/\partial x$. We start by summing the particle conservation laws (Eqs. 1 and 2) to obtain:

$$\frac{\partial j_{kI}}{\partial x} + \frac{\partial j_{kE}}{\partial x} + \frac{O_M}{a_I} j_{kI}^{in} + \frac{O_M}{a_E} j_{kE}^{in} + \frac{\partial [k]_I}{\partial t} + \frac{\partial [k]_E}{\partial t} = 0 \tag{10}$$

If we multiply this by Fz_k and take the sum over all ion species, k, the terms involving j_{kn}^{in} disappear due to Eq. 5 and the terms involving $[k]_n$ disappear due to Eqs. 7 and 9. We are left with:

$$a_I F \sum_k z_k \frac{\partial j_{kI}}{\partial x} = -a_E F \sum_k z_k \frac{\partial j_{kE}}{\partial x} \rightarrow a_I F \sum_k z_k j_{kI} = -a_E F \sum_k z_k j_{kE}. \tag{11}$$

The last implication follows from the sealed-end condition (Eq. 3). If the charge symmetry condition is satisfied at a given time $t = 0$, Eq. 11 is the condition that it remains satisfied at all times t.

The flux densities j_{kn} are defined by Eq. 4. We note that Eq. 11 contains the sum of j_{kn} over all ionic species. These sums can be converted to current densities. For convenience, we distinguish between the current densities due to diffusion (i_n^d) and migration in the electrical field (i_n^f), defined as [6]:

$$i_n^d = -\sum_k \frac{FD_k z_k}{\lambda_n^2 \psi} \frac{\partial [k]_n}{\partial x}, \tag{12}$$

and

$$i_n^f = -\sum_k \frac{FD_k z_k^2}{\lambda_n^2 \psi} [k]_n \frac{\partial v_n}{\partial x} = -\frac{1}{r_n} \frac{\partial v_n}{\partial x}, \tag{13}$$

where r_n denotes the resistivity [6]. With Eqs. 4, 12 and 13, Eq. 11 can be rewritten as:

$$a_I \left(i_I^d + \frac{1}{r_I} \frac{\partial v_I}{\partial x} \right) = -a_E \left(i_E^d + \frac{1}{r_E} \frac{\partial v_E}{\partial x} \right), \tag{14}$$

By combining Eq. 8 with Eq. 14 we may finally derive our expressions for the voltage gradients:

$$\frac{\partial v_I}{\partial x} = \left(\frac{\partial v_M}{\partial x} + \frac{r_E a_I}{a_E} i_I^d + r_E i_E^d \right) \left(1 + \frac{r_E a_I}{r_I a_E} \right)^{-1} \tag{15}$$

$$\frac{\partial v_E}{\partial x} = \left(-\frac{\partial v_M}{\partial x} + r_I i_I^d + \frac{r_I a_E}{a_I} i_E^d \right) \left(1 + \frac{r_I a_E}{r_E a_I} \right)^{-1}. \tag{16}$$

Here, r_n is given by Eq. 13, i_n^d by Eq. 12, and v_M by Eqs. 6 and 9. All voltage terms are thereby expressed in terms of ionic concentrations, and the conservation equations (Eqs. 1 and 2) represent a fully specified system.

3 Discussion

We presented a one-dimensional, electrodiffusive framework for modeling the dynamics of the membrane potential (v_M) and the ion concentrations ($[k]_n$) of all included ion species (k) in an intra- and extracellular domain.

3.1 Implementation

A step-wise procedure of how to use this formalism is a follows:

1. Specify initial conditions for the membrane potential (v_{M0}) and k ion concentrations ($[k]_{n0}$) that is to be simulated. The main charge carriers are believed to be Na^+, K^+ and Cl^-, but other species can be included.
2. Specify the static charge density (ρ_{sn}) so that $[k]_{n0}$ and v_{M0} are consistent according to Eqs. 6 and 7.
3. Specify the membrane mechanisms (functions for j_{kM}) representing ion channels, ion pumps and other membrane mechanisms relevant for the cell type that is to be modelled.
4. Specify an external input function that fulfills Eq. 5.
5. Solve the $2N$ conservation equations (Eqs. 1 and 2), with the boundary condition in Eq. 3. This can be done numerically by using a spatial discretization method (e.g., the Matlab-solver *pdepe*). For each time step, v_M, $\partial V_I/\partial x$ and $\partial V_E/\partial x$ are defined algebraically by Eqs. 8, 15 and 16.

3.2 Applications

In the most direct interpretation, the ICS in Fig. 1 represents a single neurite coated with a thin sheath of ECS. For example, the ICS could represent an axon that has been removed from the ionic solution and placed in air or oil, so that only a thin layer of the ionic solution surrounds its membrane [12]. Alternatively, the ICS could represent an individual axon in e.g., the optical nerve, where axons are densely packed in bundles, and separated by constrained gaps of extracellular space [1]. However, cases where it is biologically meaningful to consider the ECS as a relatively thin coating faithfully following a single cell may be limited. For most single cell processes, the assumption that $a_I \ll a_E$, and that conditions in

the ECS are constant, may be more reasonable. In this limit the electrodiffusive formalism reduces to the one-domain (ICS) model presented previously by Qian and Sejnowski [11].

A geometrical simplification as that in Fig. 1 has also been justified for certain macroscopic transport processes through a chunk of neural tissue [2,3,5]. Typically, the ECS comprises about 20 % of the total neural tissue volume, while the remaining 80 % is the ICS of various cells [2]. Assuming that a large number of cells (e.g., all cells belonging to a specific species) participate in simultaneous ion exchange with the ECS, the impact on the ion concentrations in the ICS and ECS may be of the same order of magnitude. This calls for a two-domain formalism such as ours. When addressing a macroscopic transport process, the ICS in Fig. 1 does not refer to a single cell, but the total amount, within the chunk of tissue, of the participatory cell type. Similarly, ECS refers to the total extracellular volume in the chunk. For the geometrical parameters a_E, a_I and O_M, one could then use, respectively, the ECS volume per total tissue volume, the ICS volume per total tissue volume, and the membrane surface area per total tissue volume. Such a macroscopic interpretation of Fig. 1 allows for a broader range of applications.

We have previously presented the electrodiffusive formalism with the specific application to a model of spatial potassium buffering by astrocytes [5]. We refer to the previous work for a specific, illustrative implementation.

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