HOMOGENIZATION OF THE CELL CYTOPLASM: THE CALCIUM BIDOMAIN EQUATIONS*

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Abstract. All previous models of the dynamics of intracellular calcium concentration have either made the ad hoc assumption that the cytoplasm and the endoplasmic reticulum (ER) coexist at every point in space or have explicitly separated the cytoplasm and the ER into different spatial domains. The former approach is unjustified, and the dependence on the diffusion coefficients on the geometry of the ER is unclear; the latter approach leads to extreme computational difficulties. To avoid the disadvantages of these approaches, we derive a bidomain model of calcium concentration inside the ER network, and outside it, in the cytosol. The homogenized macroscopic behavior is described in a two-concentration field model, a formula is derived for the effective diffusion coefficients of calcium in the ER and in the cytoplasm, and the effective diffusion coefficients are numerically computed for different ER geometries.

Key words. homogenization, formal asymptotic expansion

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1. Introduction. Calcium is one of the most important intracellular messengers, and thus the mechanisms that control the intracellular free calcium concentration are of fundamental physiological importance. At steady state, the concentration of free Ca\textsuperscript{2+} is determined by a number of factors. First, Ca\textsuperscript{2+} is actively pumped from the cytoplasm into the sarcoplasmic or endoplasmic reticulum (SR or ER) by calcium ATPase pumps. Thus the ER, which is physically separated from the rest of the cytoplasm by the ER membrane, has a much higher Ca\textsuperscript{2+} concentration than does the cytoplasm. Similarly, Ca\textsuperscript{2+} is pumped out of the cell by a variety of active mechanisms, including Ca\textsuperscript{2+} ATPase pumps, and Na\textsuperscript{+} – Ca\textsuperscript{2+} exchangers. Thus, at steady state, there are very large Ca\textsuperscript{2+} gradients across both the ER and cell membranes, and the cell must continually do work to maintain them. Calcium is also highly buffered, with approximately 99\% of cytoplasmic Ca\textsuperscript{2+} being bound to large buffering proteins.

In a wide variety of cell types, both excitable and nonexcitable, the binding of agonists such as hormones or neurotransmitters to cell-membrane receptors results, via G-protein activation, in the activation of phospholipase C and the resultant production of inositol 1,4,5-trisphosphate (IP\textsubscript{3}). IP\textsubscript{3} diffuses through the cell cytoplasm and binds to IP\textsubscript{3} receptors located on the ER membrane. These IP\textsubscript{3} receptors are also calcium channels, and their open probability is controlled by both IP\textsubscript{3} and Ca\textsuperscript{2+}; the binding of IP\textsubscript{3} causes an increase in the open probability, which in turn causes the release of Ca\textsuperscript{2+} from the ER. Calcium released from the ER is then pumped back into the ER by Ca\textsuperscript{2+} ATPases or pumped out of the cell. Modulation of the IP\textsubscript{3} receptor open

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probability by IP$_3$ and Ca$^{2+}$ can then lead to cycles of Ca$^{2+}$ release and reuptake into the ER, resulting in oscillations of the intracellular free calcium concentration and, in some cases, periodic waves [5].

In muscle cells calcium is controlled by similar, but not identical, mechanisms. In cardiac cells a small influx of calcium through voltage-gated channels in the cell membrane leads to the release of a much larger amount of calcium through the ryanodine receptors, which are located on the surface of the SR. This process is called calcium-induced calcium release (CICR). This released calcium diffuses through the cytoplasm of the cell and activates the contractile proteins, leading to muscle contraction. As the calcium is removed from the myoplasm by the calcium pumps, the muscle relaxes. In skeletal muscle the process is essentially identical, except that the opening of the voltage-gated channels causes a direct opening of the ryanodine receptors, instead of via the “calcium synapse” of the cardiac cell, which relies on CICR.

These oscillations and waves of calcium have been studied in detail by both experimentalists and theoreticians [5]. Most models to date, although differing in their treatment of many of the biochemical details, nevertheless all make the same approximation of ignoring the detailed structure of the ER. Thus, although it is well known that the ER forms a branching network (largely interconnected), with an interior that is distinct from the cell cytoplasm, this fact has largely been ignored, with most models making the a priori assumption that a Ca$^{2+}$ concentration for both the ER and the cytoplasm can be defined at each point in space. If we let $c$ and $e$ denote, respectively, the concentration of Ca$^{2+}$ in the cytoplasm and the ER (or SR), then this results in equations of the form

$$\frac{\partial c}{\partial t} = \text{div}(A \nabla c) + f(c,e),$$

$$\frac{\partial e}{\partial t} = \text{div}(B \nabla e) + g(c,e)$$

for some functions $f$ and $g$ that model the Ca$^{2+}$ fluxes in and out of the cytoplasm or ER. We call these the calcium bidomain equations. In general, these equations for $c$ and $e$ will be coupled with other equations that describe various receptor states, ATPase pump states, or other model variables. In this simple formulation, the diffusion coefficients $A$ and $B$ will be related to the geometry of the ER in some unknown way. Also note that the functions $f$ and $g$ that model Ca$^{2+}$ kinetics and fluxes may be defined only on the surface of the ER. For instance, a Ca$^{2+}$ ATPase pump that moves Ca$^{2+}$ from the cytoplasm to the ER should be modeled by a flux term that occurs only on the surface of the ER. The bidomain equations ignore this complication, as they assume that ER and cytoplasm coexist at all points.

Although this has been a useful approach, it suffers from two principal disadvantages. First, the effective diffusion coefficients must depend upon the detailed geometry of the ER, but this dependence is neither clear nor explicit in the bidomain equations. Second, the terms $f$ and $g$ denote volume fluxes (with units of concentration per time, i.e., moles per volume per time), but physically, many of the terms in them represent boundary fluxes (i.e., the flux of calcium across the ER membrane, with units of moles per area per time). Again, it is not clear how to derive the correct expression for the volume flux in terms of the underlying boundary flux.

Since the ER (and, in muscle cells, the SR) forms an interconnected network through the cytoplasm, it is natural to use homogenization techniques to derive the calcium bidomain equations and to answer the two questions above. In this approach...
the ER is assumed to form a periodic network on a scale much smaller than that of the entire cell. The bidomain equations then arise in the limit as the scale of the ER tends to zero. There are thus two crucial assumptions for the use of homogenization: first, that the ER forms a periodic network, and second, that the period of this network is much smaller than the length of a typical cell. As is the case in the application of all homogenization techniques, neither of these assumptions is exactly correct. The ER, although forming a network structure, is not periodic over an entire cell, although regions of local approximate periodicity may occur. In these regions the period can range from less than 0.1 μm up to 0.5 μm, while a typical cell has a diameter of around 30 μm. The smooth ER tends to have a tubular structure, while the rough ER tends to come in sheets. Nevertheless, it is believed that the ER is so extensive, and so highly reticulated, that no region of the cell is far from some portion of the ER. Thus, it is not unreasonable to approximate the ER as a periodic network with a period much smaller than the diameter of the cell, a network that extends throughout all regions of the cell.

Not only do we wish to gain a better understanding of the mathematical basis of the calcium bidomain equations, and of the connection between the geometry of the ER and the effective diffusion coefficients, but we also wish to derive a method by which a homogenized domain may be coupled with a nonhomogenized domain. Such coupled problems are becoming more important, particularly in detailed spatial studies of cardiac cells. In these cells the release of Ca\(^{2+}\) occurs in a very narrow region, around 12 nm across (called the diadic cleft); the junctional SR, positioned very close to L-type calcium channels, is connected to a sparse, reticular network SR in the bulk of the myocyte (for a recent discussion of SR microanatomy, see, for example, Brochet et al. [3]). The ryanodine receptors open to this (cleft) region, as do the voltage-sensitive Ca\(^{2+}\) channels, and thus the principal control of calcium release occurs there. However, experimental techniques do not yet allow the direct measurement of Ca\(^{2+}\) in the diadic cleft; Ca\(^{2+}\) can be measured only once it has left the diadic cleft and entered the myoplasm of the cardiac cell. Thus, in order to study both the control of calcium release at the level of the diadic cleft, as well as the calcium transient on the level of the entire sarcomere, it is necessary to construct multiscale models in which one part of the domain (the myoplasm) is homogenized, while another part of the domain (the diadic cleft) has separated SR and myoplasm regions.

Here we use the technique of homogenization (Bensoussan, Lions, and Papanicolaou [2] and Jikov et al. [4]) to study these questions. There is a large body of work on similar problems. The bidomain model for cardiac tissue [7, 6, 5] is based on essentially the same assumptions as those underlying calcium models, and Neu and Krassowska (see [7, 6]) have used homogenization to show how the bidomain model may be derived from the underlying equations. However, that work is in a completely different physiological context, being applied to the electrical activity of a syncytium of cardiac cells, and thus the resulting homogenized equations do not apply to calcium dynamics. The techniques of homogenization are also well known in the theory of porous media [2, 4]. Although the approach we use here is not new, its application to the construction of calcium dynamics models is. In particular, our construction of a model with both homogenized and nonhomogenized regions is unique in the field of calcium dynamics, as is our derivation and calculation of the effective diffusion coefficients.
2. Formal homogenization.

2.1. Formulation of the problem. We consider a region $\Omega$ of $\mathbb{R}^3$ in which calcium is present both in the cytosol and the ER. We visualize the ER as forming a periodic network that occupies a fraction of $\Omega$, as shown in Figure 1. Taking the period of a unit cell to be $\varepsilon$, the ER calcium occupies a connected domain $\Omega^\varepsilon_c$, and cytosolic calcium occupies the connected domain $\Omega^\varepsilon_e = \Omega \setminus \Omega^\varepsilon_c$. We denote these concentrations as $c^\varepsilon$ and $e^\varepsilon$, respectively. A superscript $\varepsilon$ indicates that the quantity depends on the period $\varepsilon$ used to define the geometry. We thus obtain a family of problems parameterized by $\varepsilon$, and we shall seek solutions in the limit $\varepsilon \to 0$.

The concentrations $c^\varepsilon$ and $e^\varepsilon$ obey the diffusion equation in their respective domains:

\begin{align}
(2.1a) \quad \frac{\partial c^\varepsilon}{\partial t} &= \text{div} (A^\varepsilon \nabla c^\varepsilon), \quad x \in \Omega^\varepsilon_c, \\
(2.1b) \quad \frac{\partial e^\varepsilon}{\partial t} &= \text{div} (B^\varepsilon \nabla e^\varepsilon), \quad x \in \Omega^\varepsilon_e,
\end{align}

where $A^\varepsilon = a_{ij}(x)$ and $B^\varepsilon = b_{ij}(x)$ are the diffusion coefficients corresponding to calcium in the cytosol and the ER, respectively. The boundary condition on the membrane $\Gamma^\varepsilon$, which separates $\Omega^\varepsilon_c$ from $\Omega^\varepsilon_e$, is a flux due to the Serca pumps:

\begin{align}
(2.2a) \quad A^\varepsilon \nabla c^\varepsilon \cdot n^\varepsilon_c &= \varepsilon \lambda f(c^\varepsilon, e^\varepsilon) \quad \text{on } \Gamma^\varepsilon, \\
(2.2b) \quad -B^\varepsilon \nabla e^\varepsilon \cdot n^\varepsilon_e &= \varepsilon \lambda f(c^\varepsilon, e^\varepsilon) \quad \text{on } \Gamma^\varepsilon,
\end{align}

where $n^\varepsilon_c$, $n^\varepsilon_e$ denote the unit exterior normals to the boundary of $\Omega^\varepsilon_c$ and $\Omega^\varepsilon_e$, respectively, satisfying $n^\varepsilon_c = -n^\varepsilon_e$ on $\Gamma^\varepsilon$. In the appendix we explain the appearance of the small parameter $\varepsilon$ in (2.2); $\lambda$ and $f$ are related to the physical properties of the

Fig. 1. The periodic geometry of the ER network.
Serca pumps. The parameter $\lambda$ can depend on $x$, but for simplicity we take it to be a constant.

### 2.2. The asymptotic expansion.

In addition to the macroscopic variable $x$, we introduce a “periodic” unit cube with microscopic variable $y$ ($y = (y_1, y_2, y_3)$, $0 \leq y_i \leq 1$) and denote by $\Omega$, the set of points $y = \frac{x}{\varepsilon}$ in the unit cube for which $x \in \Omega_c$; similarly we denote by $\Omega_c$ the set of points $y = \frac{x}{\varepsilon}$ in the unit cube for which $x \in \Omega_e$. We assume that both concentrations $c^\varepsilon$ and $c^{\varepsilon^2}$ are functions of $x$ and $y$, $x \in \Omega$, $y \in \Omega_c$ for $c^\varepsilon$, and $x \in \Omega$, $y \in \Omega_e$ for $c^{\varepsilon^2}$:

\[ c^\varepsilon = c(x, y, t), \quad c^{\varepsilon^2} = e(x, y, t) \]

with $y = x/\varepsilon$. The formal asymptotic expansions for $c^\varepsilon$ and $c^{\varepsilon^2}$ are of the form

\[ c^\varepsilon = c^0(x, y, t) + \varepsilon c^1(x, y, t) + \varepsilon^2 c^2(x, y, t) + \cdots, \]

\[ c^{\varepsilon^2} = c^0(x, y, t) + \varepsilon c^1(x, y, t) + \varepsilon^2 c^{2}(x, y, t) + \cdots, \]

where

$c^k(\cdot, y)$ and $c^k(\cdot, y)$ are 1-periodic in $y$.

Setting

\[ \nabla \equiv \frac{d}{dx_i} = \frac{\partial}{\partial x_i} + \varepsilon^{-1} \frac{\partial}{\partial y_i}, \]

it follows that $\text{div}(A_\varepsilon \nabla)$ acts on a function of $(x, y)$ with $y = \frac{x}{\varepsilon}$ as follows:

\[ \text{div}(A_\varepsilon \nabla) = \left( \frac{\partial}{\partial x_i} + \varepsilon^{-1} \frac{\partial}{\partial y_i} \right) a_{ij}(y) \left( \frac{\partial}{\partial x_i} + \varepsilon^{-1} \frac{\partial}{\partial y_j} \right) 
\]

\[ = \varepsilon^{-2} A_0 + \varepsilon^{-1} A_1 + A_2, \]

where

\[ A_0 = \frac{\partial}{\partial y_i} \left( a_{ij}(y) \frac{\partial}{\partial y_j} \right), \]

\[ A_1 = \frac{\partial}{\partial y_i} \left( a_{ij}(y) \frac{\partial}{\partial x_j} \right) + \frac{\partial}{\partial x_i} \left( a_{ij}(y) \frac{\partial}{\partial y_j} \right), \]

\[ A_2 = a_{ij}(y) \frac{\partial^2}{\partial x_i \partial x_j}. \]

### 2.3. The microdescription.

Applying (2.5) to the function (2.3), the equations (2.1) become

\[ \frac{\partial c^\varepsilon}{\partial t} = (\varepsilon^{-2} A_0 + \varepsilon^{-1} A_1 + A_2) c^\varepsilon \quad \text{for } x \in \Omega, y \in \Omega_c, \]

\[ \frac{\partial c^{\varepsilon^2}}{\partial t} = (\varepsilon^{-2} A_0 + \varepsilon^{-1} A_1 + A_2) c^{\varepsilon^2} \quad \text{for } x \in \Omega, y \in \Omega_e, \]

and the boundary conditions (2.2) become

\[ a_{ij}^\varepsilon \left( \frac{\partial c^\varepsilon}{\partial x_j} + \varepsilon^{-1} \frac{\partial c^{\varepsilon^2}}{\partial y_j} \right) n_{ei} = \varepsilon \lambda f(c^\varepsilon, c^{\varepsilon^2}) \quad \text{for } x \in \Omega, y \in \Gamma, \]

\[ b_{ij}^{\varepsilon^2} \left( \frac{\partial c^{\varepsilon^2}}{\partial x_j} + \varepsilon^{-1} \frac{\partial c^\varepsilon}{\partial y_j} \right) n_{ei} = \varepsilon \lambda f(c^\varepsilon, c^{\varepsilon^2}) \quad \text{for } x \in \Omega, y \in \Gamma, \]

where the $n_i$ are now unit normals on $\Gamma$.

We proceed to equate to zero the coefficients $\varepsilon^{-2+i}$ of (2.7) and $\varepsilon^{-1+i}$ of (2.8).
2.4. The problem at lowest order. The equations (2.7) at order $\varepsilon^{-2}$ are
\begin{align}
\frac{\partial}{\partial y_i} \left( a_{ij}(y) \frac{\partial c^0}{\partial y_j} \right) &= 0, \quad y \in \Omega_c, \\
\frac{\partial}{\partial y_i} \left( b_{ij}(y) \frac{\partial e^0}{\partial y_j} \right) &= 0, \quad y \in \Omega_e,
\end{align}
and the boundary conditions at order $\varepsilon^{-1}$ are
\begin{align}
a_{ij}(y) \frac{\partial c^0}{\partial y_j} n_i &= 0 = b_{ij}(y) \frac{\partial e^0}{\partial y_j} n_i, \quad y \in \Gamma,
\end{align}
with $c^0$ and $e^0$ 1-periodic in $y$. For fixed $x$, the only periodic solution to the above equations is $c^0 = \text{constant}$ and $e^0 = \text{constant}$ as functions of $y$, so that
\begin{align}
c^0 &= c^0(x,t), \quad e^0 = e^0(x,t).
\end{align}

2.5. The problem at first order. The equations at order $\varepsilon^{-1}$ are
\begin{align}
\frac{\partial}{\partial y_i} \left[ a_{ij}(y) \left( \frac{\partial c^0}{\partial x_j} + \frac{\partial c^1}{\partial y_j} \right) \right] &= 0, \quad y \in \Omega_c, \\
\frac{\partial}{\partial y_i} \left[ b_{ij}(y) \left( \frac{\partial e^0}{\partial x_j} + \frac{\partial e^1}{\partial y_j} \right) \right] &= 0, \quad y \in \Omega_e,
\end{align}
and boundary conditions of order 1 are
\begin{align}
a_{ij}(y) \left( \frac{\partial c^0}{\partial x_j} + \frac{\partial c^1}{\partial y_j} \right) n_i &= 0 = b_{ij}(y) \left( \frac{\partial e^0}{\partial x_j} + \frac{\partial e^1}{\partial y_j} \right) n_i, \quad y \in \Gamma.
\end{align}

We introduce the solutions $\chi^c(y)$ and $\chi^e(y)$ of the following system (the “cell problems”):
\begin{align}
\frac{\partial}{\partial y_i} \left[ a_{ij}(y) \left( \frac{\partial \chi^c_k}{\partial y_j} + \delta_{jk} \right) \right] &= 0, \quad y \in \Omega_c, \\
\frac{\partial}{\partial y_i} \left[ b_{ij}(y) \left( \frac{\partial \chi^e_k}{\partial y_j} + \delta_{jk} \right) \right] &= 0, \quad y \in \Omega_e,
\end{align}
\begin{align}
a_{ij}(y) \left( \frac{\partial \chi^c_k}{\partial y_j} + \delta_{jk} \right) n_i &= 0 \quad \text{for } y \in \Gamma, \\
b_{ij}(y) \left( \frac{\partial \chi^e_k}{\partial y_j} + \delta_{jk} \right) n_i &= 0 \quad \text{for } y \in \Gamma,
\end{align}
where $\chi^c_k$ and $\chi^e_k$ are 1-periodic in $y$. Then we can write
\begin{align}
c^1 &= \chi^c_i \frac{\partial c^0}{\partial x_i} + \bar{c}^1, \\
e^1 &= \chi^e_i \frac{\partial e^0}{\partial x_i} + \bar{e}^1,
\end{align}
where $\bar{c}^1, \bar{e}^1$ satisfy a homogeneous system in $y$ whose solution is a constant independent of $y$. Hence $\bar{c}^1 = \bar{c}^1(x,t)$ and $\bar{e}^1 = \bar{e}^1(x,t)$. Note that $\chi^c_k$ and $\chi^e_k$ are unique up to a constant, but this constant can be chosen in an arbitrary manner, since this will cause only a change in $c^1(x,t)$ and $e^1(x,t)$. 
2.6. The problem at second order. The equations at order $\varepsilon^0$ are

$$
\frac{\partial}{\partial x_i} \left[ a_{ij}(y) \left( \frac{\partial c^0}{\partial x_j} + \frac{\partial c^1}{\partial y_j} \right) \right] + \frac{\partial}{\partial y_i} \left[ a_{ij}(y) \left( \frac{\partial c^1}{\partial x_j} + \frac{\partial c^2}{\partial y_j} \right) \right] = \frac{\partial c^0}{\partial t}, \quad y \in \Omega_c,
$$

(2.18)

$$
\frac{\partial}{\partial x_i} \left[ a_{ij}(y) \left( \frac{\partial c^0}{\partial x_j} + \frac{\partial c^1}{\partial y_j} \right) \right] + \frac{\partial}{\partial y_i} \left[ a_{ij}(y) \left( \frac{\partial c^1}{\partial x_j} + \frac{\partial c^2}{\partial y_j} \right) \right] = \frac{\partial c^0}{\partial t}, \quad y \in \Omega_c,
$$

(2.19)

and the boundary conditions of order $\varepsilon$ give

$$
a_{ij}(y) \left( \frac{\partial c^1}{\partial x_j} + \frac{\partial c^2}{\partial y_j} \right) n_{ei} = \lambda f(c^0, e^0), \quad y \in \Gamma,
$$

(2.20)

$$
b_{ij}(y) \left( \frac{\partial e^1}{\partial x_j} + \frac{\partial e^2}{\partial y_j} \right) n_{ei} = -\lambda f(c^0, e^0), \quad y \in \Gamma.
$$

(2.21)

Integrating (2.18) on $\Omega_c$ we get

$$
\int_{\Omega_c} \frac{\partial}{\partial x_i} \left[ a_{ij}(y) \left( \frac{\partial c^0}{\partial x_j} + \frac{\partial c^1}{\partial y_j} \right) \right] dy + \int_{\Omega_c} \frac{\partial}{\partial y_i} \left[ a_{ij}(y) \left( \frac{\partial c^1}{\partial x_j} + \frac{\partial c^2}{\partial y_j} \right) \right] dy = \int_{\Omega_c} \frac{\partial c^0}{\partial t} dy
$$

(2.22)

and

$$
\int_{\Omega_c} \frac{\partial c^0}{\partial t} dy = \gamma_c \frac{\partial c^0}{\partial t},
$$

(2.23)

where $\gamma_c = \int_{\Omega_c} dy$ is the volume fraction of the unit cell occupied by the cytosol. Using (2.16) we then have

$$
\int_{\Omega_c} \frac{\partial}{\partial x_i} \left[ a_{ij}(y) \left( \frac{\partial c^0}{\partial x_j} + \frac{\partial c^1}{\partial y_j} \right) \right] dy = \int_{\Omega_c} \frac{\partial}{\partial x_i} \left[ a_{ij}(y) \left( \frac{\partial c^0}{\partial x_j} + \frac{\partial c^1}{\partial y_j} \right) \left( \chi_k \frac{\partial c^0}{\partial x_k} \right) \right] dy
$$

$$
= \int_{\Omega_c} \frac{\partial}{\partial x_i} \left[ a_{ij}(y) \left( \delta_{jk} + \frac{\partial \chi_k^c}{\partial y_j} \right) \frac{\partial c^0}{\partial x_k} \right] dy
$$

$$
= \frac{\partial}{\partial x_i} \left( \tilde{a}_{ik} \frac{\partial c^0}{\partial x_k} \right),
$$

(2.24)

where the $\tilde{a}_{ik}$ are defined by

$$
\tilde{a}_{ik} = \int_{\Omega_c} a_{ij}(y) \left( \delta_{jk} + \frac{\partial \chi_k^c}{\partial y_j} \right) dy.
$$

(2.25)
Applying the divergence theorem to the second term on the left-hand side of (2.22) gives

\[
\int_{\Omega} \frac{\partial}{\partial x_i} \left[ a_{ij}(y) \left( \frac{\partial c_1}{\partial x_j} + \frac{\partial c_2}{\partial y_j} \right) \right] dy = \int_{\Gamma} a_{ij}(y) \left( \frac{\partial c_1}{\partial x_j} + \frac{\partial c_2}{\partial y_j} \right) n_{ci} d\Gamma(y) = \int_{\Gamma} \lambda_f(c_0, e_0) d\Gamma(y) \quad \text{by (2.20)}
\]

(2.26)

where \( \tilde{\lambda} = \lambda \int_{\Gamma} d\Gamma \).

From (2.23), (2.24), (2.25), and (2.26) we obtain the macroscopic equation for \( c_0 \):

\[
\gamma_c \frac{\partial c_0}{\partial t} = \frac{\partial}{\partial x_i} \left( \tilde{a}_{ik} \frac{\partial c_0}{\partial x_k} \right) + \tilde{\lambda} f(c_0, e_0).
\]

(2.27)

The coefficients \( \tilde{a}_{ik} \) are called the \textit{homogenized diffusion coefficients} of \( A_\varepsilon \). The coefficients \( \tilde{a}_{ik}/\gamma_c \) are called the \textit{effective diffusion coefficients (EDCs)} of the homogenized (macroscopic) description of the problem.

By a similar reasoning, the macroscopic equation for \( e_0 \) is

\[
\gamma_c \frac{\partial e_0}{\partial t} = \frac{\partial}{\partial x_i} \left( \tilde{b}_{ik} \frac{\partial e_0}{\partial x_k} \right) - \tilde{\lambda} f(c_0, e_0),
\]

(2.28)

where the \( \tilde{b}_{ik} \) are the homogenized diffusion coefficients of \( B_\varepsilon \), given by a formula similar to (2.25). Observe that the cell problems for the operators \( A_\varepsilon \) and \( B_\varepsilon \) are decoupled.

\[ \text{2.7. Numerical calculation of } \chi_i. \]

The preceding formulas for the homogenized problem are valid for any geometry of the ER. Below we shall consider the special case when the ER consists of three pipes, orthogonal at the center of the unit cube as shown in Figure 2. The dimensions of the pipes are taken to be 0.1 units along the short edge, and we take \( a_{ij} = a \delta_{ij}, b_{ij} = b \delta_{ij} \) with \( a = b = 0.25 \ \mu m^2/ms \).

The functions \( \chi_i(y) \) can be evaluated numerically as we now demonstrate. Let \( \chi^e \) denote the vector field with components \( \chi^e_i \). The \( \chi^e_i(y) \) are determined by solving the boundary value problem on the unit cell given by

(2.29a) \quad \text{div } [B(\nabla \chi^e + I)] = 0 \quad \text{on } \Omega^e,

(2.29b) \quad [B(\nabla \chi^e + I)] \cdot n = 0 \quad \text{on } \Gamma

with \( \chi^e \) periodic across opposite boundaries on the unit cube. We fix the arbitrary constant in \( \chi^e_i \) by taking \( \chi^e_i = 0 \) at the center of the cube \((0.5, 0.5, 0.5)\).

The values of each of the \( \chi^e_i \) are shown in Figure 3, and the vector field \( \chi^e = (\chi^e_1, \chi^e_2, \chi^e_3) \) is plotted in Figure 4.

We compute that \( \int_{\Omega^e} (\partial \chi^e_1 / \partial y_1 + 1) dy = 0.01047 \). Since \( b = 0.25 \), (2.25) gives the homogenized diffusion coefficient \( \tilde{b}_{ij} = 2.6175 \times 10^{-3} \delta_{ij} \). The computation shows that the integrals \( \int_{\Omega^e} \chi^e_i dy \) are zero. Furthermore, \( \int_{\Omega^e} \partial \chi^e_i / \partial y_j dy \) vanish also if \( i \neq j \), implying that the effective diffusion is again isotropic.

A similar computation for \( \chi^e_1 \) gives \( \int_{\Omega^e} (\partial \chi^e_1 / \partial y_1 + 1) dy = 0.95 \).
3. The macroscopic equations in the presence of calcium buffers. Let us now assume that calcium reacts with buffering proteins that are present in the cytosol and the ER. If we denote the concentrations of the buffer with calcium bound by $b_c$ and $b_e$, respectively, in the cytosol and the ER, and $c$ and $e$ now denote the concentration of free calcium, then the corresponding equations for reaction-diffusion of the species can be taken to be (to avoid confusion we denote the diffusion coefficient $B$ by $M$ in this section)

\begin{align*}
\frac{\partial c^\varepsilon}{\partial t} &= \text{div} \left( A \nabla c^\varepsilon \right) + \kappa_{c-} b_c^\varepsilon - \kappa_{c+} c^\varepsilon (B_c^\varepsilon - b_c^\varepsilon), \quad x \in \Omega_c^\varepsilon, \\
\frac{\partial b_c^\varepsilon}{\partial t} &= \text{div} \left( D_c \nabla b_c^\varepsilon \right) - \kappa_{c-} b_c^\varepsilon + \kappa_{c+} c^\varepsilon (B_c^\varepsilon - b_c^\varepsilon), \quad x \in \Omega_c^\varepsilon, \\
\frac{\partial e^\varepsilon}{\partial t} &= \text{div} \left( M \nabla e^\varepsilon \right) + \kappa_{e-} b_e^\varepsilon - \kappa_{e+} e^\varepsilon (B_e^\varepsilon - b_e^\varepsilon), \quad x \in \Omega_e^\varepsilon, \\
\frac{\partial b_e^\varepsilon}{\partial t} &= \text{div} \left( D_e \nabla b_e^\varepsilon \right) - \kappa_{e-} b_e^\varepsilon + \kappa_{e+} e^\varepsilon (B_e^\varepsilon - b_e^\varepsilon), \quad x \in \Omega_e^\varepsilon,
\end{align*}

where $\kappa_{c-}$ is the association rate of calcium binding to the buffer, and $\kappa_{c+}$ is the rate of dissociation of buffered calcium. $D_c = d_{ij}^c(\xi)$ and $D_e = d_{ij}^e(\xi)$ are the diffusion coefficients of $b_c^\varepsilon$ and $b_e^\varepsilon$, respectively.

The boundary conditions on $\Gamma^\varepsilon$, (3.5a) and (3.6a), are supplemented by (3.5b) and (3.6b), assuming that the buffer proteins are confined to their respective domains:

\begin{align*}
(3.5a) & \quad A \nabla c^\varepsilon \cdot n_c^\varepsilon = \varepsilon \lambda f(c^\varepsilon, e^\varepsilon), \\
(3.5b) & \quad D_c \nabla b_c^\varepsilon \cdot n_c^\varepsilon = 0 \quad \text{on } \Gamma^\varepsilon \\
\text{and} & \\
(3.6a) & \quad -M \nabla e^\varepsilon \cdot n_e^\varepsilon = \varepsilon \lambda f(c^\varepsilon, e^\varepsilon), \\
(3.6b) & \quad D_e \nabla b_e^\varepsilon \cdot n_e^\varepsilon = 0 \quad \text{on } \Gamma^\varepsilon.
\end{align*}
If we assume that
\[ b_\varepsilon^c = b_0^c(x, y, t) + \varepsilon b_1^c(x, y, t) + \varepsilon^2 b_2^c(x, y, t) + \cdots, \]
\[ b_\varepsilon^e = b_0^e(x, y, t) + \varepsilon b_1^e(x, y, t) + \varepsilon^2 b_2^e(x, y, t) + \cdots, \]
we can then proceed as in the previous section. For example, instead of (2.7), we now have
\[ \frac{\partial c_\varepsilon}{\partial t} = (\varepsilon^{-2} A_0 + \varepsilon^{-1} A_1 + A_2) c^\varepsilon + k_{c-} b_\varepsilon^c - k_{c+} b_\varepsilon^e (B_c - b_\varepsilon^c) \quad \text{in } \Omega_c, \]
whereas the boundary condition (2.8) is unchanged:
\[ a_{ij}^c(y) \left( \frac{\partial c_\varepsilon}{\partial x_j} + \varepsilon^{-1} \frac{\partial c_\varepsilon}{\partial y_j} \right) n_{ci} = \varepsilon \lambda f(c^\varepsilon, e^\varepsilon) \quad \text{on } \Gamma. \]

The effect of the additional terms in (3.8) can be seen at the order \( \varepsilon^0 \) level of the differential equation
\[ \frac{\partial \varepsilon^0}{\partial t} = \frac{\partial}{\partial x_i} \left[ a_{ij}(y) \left( \frac{\partial c^0}{\partial x_j} + \frac{\partial c^1}{\partial y_j} \right) \right] + \frac{\partial}{\partial y_i} \left[ a_{ij}(y) \left( \frac{\partial c^1}{\partial x_j} + \frac{\partial c^2}{\partial y_j} \right) \right] \]
\[ = \frac{\partial c^0}{\partial t} - \left( k_{c-} b_0^c - k_{c+} c^0 (B_c - b_0^c) \right), \quad y \in \Omega_c, \]
while the boundary conditions are as before,
\[ a_{ij}(y) \left( \frac{\partial c^0}{\partial x_j} + \frac{\partial c^1}{\partial y_j} \right) n_{ci} = \lambda f(c^0, e^0), \quad y \in \Gamma. \]

Thus the macroscopic equation for \( c^0 \) is now
\[ \gamma_c \frac{\partial c^0}{\partial t} = \frac{\partial}{\partial x_i} \bar{a}_{ik} \frac{\partial c^0}{\partial x_k} + \gamma_c \left( k_{c-} b_0^c - k_{c+} c^0 (B_c - b_0^c) \right) + \lambda f(c^0, e^0). \]

Similarly, the macroscopic equation for \( e^0 \) is
\[ \gamma_e \frac{\partial e^0}{\partial t} = \frac{\partial}{\partial x_i} \bar{m}_{ik} \frac{\partial e^0}{\partial x_k} + \gamma_e \left( k_{c-} b_0^e - k_{c+} e^0 (B_e - b_0^e) \right) + \lambda f(c^0, e^0). \]
and the macroscopic equations for $b_0^c$ and $b_0^e$ are obtained as

$$
\gamma_c \frac{\partial b_0^c}{\partial t} = \frac{\partial}{\partial x_i} \tilde{d}_{cik} \frac{\partial b_0^c}{\partial x_k} - \gamma_c \left( k_c^- b_0^c - k_c^+ c^0 (B_c - b_0^c) \right),
$$

(3.14)

$$
\gamma_e \frac{\partial b_0^e}{\partial t} = \frac{\partial}{\partial x_i} \tilde{d}_{eik} \frac{\partial b_0^e}{\partial x_k} - \gamma_e \left( k_e^- b_0^e - k_e^+ e^0 (B_e - b_0^e) \right),
$$

(3.15)

where the $\tilde{d}_{cik}$ and $\tilde{d}_{eik}$ are obtained by solving the cell problems corresponding to $b_0^c$ and $b_0^e$. Note that in the special case, for example, $a_{ij} = \text{const} \times d_{ij}$, $c^0$ and $b_0^c$ share the same solution to the cell problem similar to (2.29).

In a similar way one may include the effects of multiple buffers.

4. Combining homogenized domains with nonhomogenized domains.

We next consider the case that the homogenized domain is a part of a larger domain. In Figure 5, for example, we indicate a region where cytosolic calcium is in contact with a region where the domain has been homogenized. For simplicity, we will consider the case with no buffers. The extension to the case of buffered calcium is straightforward.

Let us assume the homogenized domain $\Omega_+ (x_1, x_2, x_3)$ and the “nonhomogenized” domain $\Omega_- (x_1, x_2, x_3)$ are separated by the plane $x_1 = 0$. The boundary $\Gamma_0$ between $\Omega_+ \text{ and } \Omega_-$ has “holes” $\Gamma_{c,i}^\varepsilon$ ($i = 1, \ldots, m_c$) through which calcium can diffuse across $\Gamma_{c,i}^\varepsilon = \partial \Omega_+^\varepsilon, i \cap (x_1 = 0)$ from $x_1 < 0$ to $x_1 > 0$. Those parts of $\Gamma_0$ across which calcium is insulated between $\Omega_+$ and $\Omega_-$ are denoted as $\Gamma_{c,i}^\varepsilon = \partial \Omega_+^\varepsilon, i \cap (x_1 = 0)$ so
that $\Gamma_0 = \Gamma_{\varepsilon, i} \cup \Gamma_{\varepsilon, c, i}$. Let us denote the calcium concentration in the nonhomogenized cytosol to be $c_-$ and that in the bidomain to be $c_+^\varepsilon$. Then on $\Gamma_0$ we have the boundary conditions

(4.1a) \quad A_\varepsilon \nabla c_-^\varepsilon \cdot n_\varepsilon = 0,

(4.1b) \quad B_\varepsilon \nabla c_+^\varepsilon \cdot n_\varepsilon = 0 \quad \text{on} \quad \Gamma_\varepsilon \equiv \bigcup_i \Gamma_{\varepsilon, i},

and

(4.2) \quad c_-^\varepsilon = c_+^\varepsilon \quad \text{on} \quad \Gamma_\varepsilon \equiv \bigcup_i \Gamma_{\varepsilon, i}.

In the limit $\varepsilon \to 0$, we claim that the following continuity of concentration holds:

(4.3) \quad c_- = c^0 \quad \text{on} \quad \Gamma_0,

and flux continuity is given as

(4.4) \quad a_{ij} \frac{\partial c_-}{\partial x_j} n_i = \hat{a}_{ij} \frac{\partial c^0}{\partial x_j} n_i \quad \text{on} \quad \Gamma_0.

In homogenization problems considered in literature, the functions $c_+^\varepsilon, c_-^\varepsilon$ are often assumed to be continuous across the interface, and in this situation one derives the homogenized problem for both the Dirichlet problem and the Neuman problem (with homogenized conormal derivative) (see [2, p. 87]). There is no rigorous mathematical proof that covers our situation, however. Using asymptotic analysis with inner and
outer expansions, Krassowska and Neu gave a formal proof of the transmission conditions of the type (4.3) and (4.4) for a similar problem. Here we give intuitive proofs of the assertions (4.3) and (4.4).

Suppose first that \( c^+_{\varepsilon} \) is a constant, \( c^+ \), in \( \Omega^+_\varepsilon \in \Omega^+ \); see Figure 6. From any point \( Y \) on \( \Gamma_{e,i}^{\varepsilon} \) we draw a curve \( l_{Y,i}^\varepsilon \) in \( \Omega^- \) with length \( O(\varepsilon) \) and with end-point \( Z \) on either \( \Gamma_{c,i+2}^{\varepsilon} \) or \( \Gamma_{c,i-2}^{\varepsilon} \). Since \( c_-^\varepsilon = c^+_{\varepsilon} = c^+ \) at \( Z \), we can write

\[
(4.5) \quad c^-(Y) = c^+ + \int_{l_{Y,i}^\varepsilon} \frac{\partial c^-_\varepsilon}{\partial s} ds,
\]

where \( s \) is the length parameter. We can choose the curve \( l_{Y,i}^\varepsilon \) such that when \( Y \) varies along \( \Gamma_{e,i}^{\varepsilon} \), the curves \( l_{Y,i}^\varepsilon \) trace a region in \( \Omega^-_\varepsilon \) in \( x_1 < 0 \) with volume \( O(\varepsilon^3) \).

By the Cauchy–Schwarz inequality we then have

\[
(4.6) \quad |c^-(Y) - c^+|^2 \leq \left( \int_{l_{Y,i}^\varepsilon} |\nabla c^\varepsilon_-|^2 \right) O(\varepsilon).
\]

Integrating over \( Y \) in \( \Gamma_{e,i}^{\varepsilon} \), taking the sum over \( i \), we obtain (since \( c^\varepsilon_- = c^+ \) on the \( \Gamma_{c,i}^{\varepsilon} \))

\[
(4.7) \quad \int_{\Gamma_0} |c^-(Y) - c^+|^2 \leq \sum_i \left( \int_{\Omega_{0,i}} |\nabla c^\varepsilon_-|^2 \right) O(\varepsilon) = O(\varepsilon),
\]

where \( \Omega_{0,i} \) is a domain in \( x_1 < 0 \) lying within \( O(\varepsilon) \) distance from \( \Gamma_0 \). As \( \varepsilon \to 0 \), the right-hand side converges to zero, and thus we obtain

\[
(4.8) \quad \int_{\Gamma_0} |c^\varepsilon_- - c^+|^2 = 0.
\]
Hence \( c_- = c^* \) on \( \Gamma_0 \).

The above argument can be applied in any interval \( J \) of \( \Gamma_0 \) on which \( c_+ \) is a constant. Suppose that \( c_+ \) is not constant, but \( c^\varepsilon_+ \to c_+ \) uniformly on \( \Gamma_0 \) as \( \varepsilon \to 0 \), as well as \( c^\varepsilon_- \to c_- \) uniformly on \( \Gamma_0 \) as \( \varepsilon \to 0 \), where \( c_+ \) and \( c_- \) are continuous functions. Then for any interval \( J \) of small length \( \delta \), \( c_+ = c^* + \sigma(\delta) \), where \( \sigma(\delta) \to 0 \) as \( \delta \to 0 \).

As before,

\[
\int_{\Gamma^\varepsilon_{c,i}} |c^\varepsilon_-(Y) - c^*|^2 \leq \left( \int_{\Gamma^\varepsilon_{c,i}} |\nabla c^\varepsilon_-|^2 \right) O(\varepsilon) + |c^\varepsilon_-(Z) - c^*|^2, \quad Y \in \Gamma^\varepsilon_{c,i} \subset J,
\]

so that \( \int_{\Gamma^\varepsilon_{c,i}} |c^\varepsilon_-(Y) - c^*|^2 \leq \left( \int_{\Omega_{0,i}} |\nabla c^\varepsilon_-|^2 \right) O(\varepsilon) + (\sigma_1(\delta) + \sigma_1(\varepsilon)) \int_{\Omega_{0,i}} 1,
\]

where \( \sigma_1(\delta) \to 0 \) as \( \delta \to 0 \) and \( \sigma_1(\varepsilon) \to 0 \) as \( \varepsilon \to 0 \), since \( c_+ = c^* + \sigma(\delta) \) and \( c^\varepsilon_- = c^\varepsilon_+ \) on \( \Gamma^\varepsilon_{c,i+2} \). Summing over \( i \),

\[
\int_{J} |c^\varepsilon_-(Y) - c^*|^2 \leq \left( \int_{\Omega_0} |\nabla c^\varepsilon_-|^2 \right) O(\varepsilon) + (\sigma_1(\delta) + \sigma_1(\varepsilon)) |J|.
\]

Decomposing \( \Gamma_0 \) into such intervals \( J = J_k \), applying (4.10), and letting \( \varepsilon \to 0 \) and \( \delta \to 0 \), we get

\[
\int_{\Gamma_0} |c_- - c^*|^2 = 0,
\]

and the assertion (4.3) follows.

We next provide an intuitive proof for the relation (4.4). For simplicity we consider the stationary two-dimensional case where the ER consists of isolated “cells” instead of a connected network, as in Figure 7. Let \( \Gamma_0 \) be the boundary that separates the homogenized domain, \( \Omega^+ \in \{x_1 > 0\} \), and the nonhomogenized domain, \( \Omega^- \in \{x_1 < 0\} \). In the ER, \( \Omega^\varepsilon_c \), we take \( \Delta c^\varepsilon_+ = 0 \) and in the cytosol we take \( \Delta c^\varepsilon = 0 \). Let \( \Gamma_{\pm\delta,\eta} = \{x_1 = \pm \delta, \ -\eta \leq x_2 \leq \eta\} \). Assume, first, that \( \Gamma_{+\delta,\eta} \) does not cut any of the cells \( \Omega^\varepsilon_c \cap \{x_1 = \delta\} \). Then

\[
a \int_{\Gamma_{-\delta,\eta}} \frac{\partial c^\varepsilon_-}{\partial x_1} = a \int_{\Gamma_0} \frac{\partial c^\varepsilon_-}{\partial x_1} + \sigma_1(\delta)
\]

\[
= a \int_{\Gamma_{+\delta,\eta}} \frac{\partial c^\varepsilon_-}{\partial x_1} + \sigma_1(\delta),
\]

where \( \Gamma_{\pm\delta,\eta} = (\bigcup \Gamma^\varepsilon_{c,i}) \cap \{-\eta \leq x_2 \leq \eta\} \), since \( \frac{\partial c^\varepsilon_+}{\partial x_1} = 0 \) on \( \Gamma_0 \setminus \Gamma^\varepsilon_{c,i} \). \( \sigma_1(\delta) \to 0 \) as \( \delta \to 0 \), since the integrals computed on the horizontal segments \( \Gamma_{\pm\delta,\eta} \) go to zero with \( \delta \).

Because of the transmission conditions (2.2), on every \( \Omega^\varepsilon_{c,i} \) between \( x_1 = 0 \) and \( x_1 \leq \delta \), \( \frac{\partial c^\varepsilon_+}{\partial x_1} = 0 \). By the divergence theorem and the conditions, \( a \frac{\partial c^\varepsilon_-}{\partial x_1} = a \frac{\partial c^\varepsilon_+}{\partial x_1} \)

\[
a \int_{\Gamma_{\pm\delta,\eta}} \frac{\partial c^\varepsilon_-}{\partial x_1} = a \int_{\Gamma_{\pm\delta,\eta}} \frac{\partial c^\varepsilon_+}{\partial x_1}
\]

\[
= a \int_{\Gamma_{+\delta,\eta}} \frac{\partial c^\varepsilon_+}{\partial x_1} + \sigma_2(\delta) \quad (\sigma_2(\delta) \to 0 \text{ as } \delta \to 0).
\]
CALCIUM BIDOMAIN EQUATIONS

\[ \Omega^- \quad \Gamma_0 \quad \Omega^+ \]

\[ \Gamma_{-\delta,\eta} \quad \Gamma_{+\delta,\eta} \]

\[ \Gamma_{\delta,-\eta} \quad \Gamma_{\delta,\eta} \]

\[ x_1 = 0 \]

**Fig. 7.** Flux is continuous across the boundary between the homogenized and nonhomogenized domains. Hence \( a_{ij} \frac{\partial c}{\partial x_j} n_i = \tilde{a}_{ij} \frac{\partial c}{\partial x_j} n_i \) on \( \Gamma_0 \).

Taking \( \varepsilon \to 0 \) and assuming that \( a \nabla c_+^{\varepsilon} \to \tilde{a} \nabla c_+ \) in a weak sense, we get

\[
(4.14) \quad a \int_{\Gamma_{-\delta,\eta}} \frac{\partial c_-}{\partial x_1} = \tilde{a} \int_{\Gamma_{+\delta,\eta}} \frac{\partial c_+}{\partial x_1} + (\sigma_1(\delta) + \sigma_2(\delta)).
\]

Taking \( \delta \to 0 \), we get

\[
(4.15) \quad a \int_{\Gamma_{0,\eta}} \frac{\partial c_-}{\partial x_1} = \tilde{a} \int_{\Gamma_{0,\eta}} \frac{\partial c_+}{\partial x_1}.
\]

Since \( \Gamma_{0,\eta} \) is arbitrary, (4.4) follows.

If \( \Gamma_{+\delta,\eta} \) does cut some cells \( \Omega_{c,k}^{\varepsilon} \), we need to replace the right-hand side in (4.13) by

\[
(4.16) \quad a \int_{\Gamma_{+\delta,\eta}} \frac{\partial c_-^{\varepsilon}}{\partial x_1} + a \int_{\partial \Omega_{c,k}^{\varepsilon}(x<\delta)} \frac{\partial c_+^{\varepsilon}}{\partial x_1} + \sigma_3(\delta) \to 0 \quad \text{as} \quad \delta \to 0.
\]

But as \( \varepsilon \to 0 \), the sum of the last integrals converges to \( a \int_{\Gamma_{+\delta,\eta}} \frac{\partial c_+}{\partial x_1} \) (assuming again that the derivative of \( c_+^{\varepsilon}(x, \frac{x}{\varepsilon}) \) converges to the derivative of \( c_+(x) \) in a weak sense).

5. Discussion.

5.1. Conservation of calcium. The homogenized equations are consistent with conservation of calcium. Consider a homogenized domain, \( \Omega^+ \), and a nonhomogenized domain, \( \Omega^- \), separated by a boundary \( \Gamma_0 \) as in Figure 5. We assume, for simplicity, that cytosolic calcium in \( \Omega^- \) obeys the diffusion equation (ignoring buffering for the moment)

\[
(5.1) \quad \frac{\partial c_-}{\partial t} = \frac{\partial}{\partial x_1} \left( a_{ij} \frac{\partial c_-}{\partial x_j} \right).
\]
and in \( \Omega^+ \) cytosolic calcium obeys the equation

\[(5.2)\quad \gamma_c \frac{\partial c_+}{\partial t} = \frac{\partial}{\partial x_i} \left( \tilde{a}_{ij} \frac{\partial c_+}{\partial x_j} \right) + \tilde{\lambda} f(c_+, e_+),\]

while ER calcium obeys

\[(5.3)\quad \gamma_e \frac{\partial e_+}{\partial t} = \frac{\partial}{\partial x_i} \left( \tilde{b}_{ij} \frac{\partial e_+}{\partial x_j} \right) - \tilde{\lambda} f(c_+, e_+).\]

Let us also assume that calcium flux across all other boundaries except \( \Gamma_0 \) is zero, that is, \( \Omega^- \) and \( \Omega^+ \) are isolated with respect to calcium. We wish to show that net calcium in the two domains is conserved. Between \( \Omega^- \) and \( \Omega^+ \), calcium is exchanged across the boundary \( \Gamma_0 \) while obeying the boundary condition (4.4)

\[(5.4)\quad a_{ij} \frac{\partial c_-}{\partial x_j} n_i = \tilde{a}_{ij} \frac{\partial c_+}{\partial x_j} n_i \quad \text{on} \quad \Gamma_0.\]

Integrating (5.1), (5.2), and (5.3) over their respective domains, and summing, it is easily obtained (using the divergence theorem and (5.4)) that

\[(5.5)\quad \int_{\Omega^-} \frac{\partial c_-}{\partial t} + \gamma_c \int_{\Omega^+} \frac{\partial c_+}{\partial t} + \gamma_e \int_{\Omega^+} \frac{\partial e_+}{\partial t} = 0.\]

Equation (5.5) shows that the total calcium \( (\int_{\Omega^-} c_- + \gamma_c \int_{\Omega^+} c_+ + \gamma_e \int_{\Omega^+} e_+) \) is invariant in time. We remark here that the \( c_+ \) can be thought of as “occupying” the fraction \( \gamma_c \) of \( \Omega^+ \); similarly \( e_+ \) can be thought of as being distributed over the fraction \( \gamma_e \) of \( \Omega^+ \). We note that adding buffering reactions to the equations also preserves calcium similarly.

5.2. Variation of the diffusion properties with the geometry of the ER.

The effective diffusion coefficient varies with the geometry of the ER. Figure 8 shows a plot of the effective diffusion coefficient as a function of the short edge length, \( l \),
Fig. 9. An example of an alternate geometry of the ER.

for an ER composed of three orthogonal pipes of uniform, square cross-section (as in section 2.7), as well as the volume fraction, \(3l^2 - 2l^3\), of the ER. In absence of an ER (that is, when \(\gamma_e = 0\), we take the diffusion coefficient in the cytosol to be 250 \(\mu m^2/s\).

As the volume of the ER increases, the effective diffusion coefficient of ER calcium also increases, while the effective diffusion coefficient of cytosolic calcium decreases. Notice that, for this geometry, the symmetry between the ER and the cytosolic structures is reflected in the relation, \(EDC_{ER}(ER \text{ edge length } = l) = EDC_{Cytosol}(ER \text{ edge length } = 1 - l)\).

The effective diffusion coefficient also depends upon the geometry of the ER, with a more tortuous geometry resulting in a lower effective diffusion coefficient in the ER. In Figure 9 we consider another example of a periodic ER geometry. For this geometry, the ER occupies a volume fraction \(\gamma_e = \int_{\Omega_e} dy = 0.0285\). The solution to the cell problem for this geometry gives \(\int_{\Omega_e} \left(\frac{\partial X_i}{\partial y_i} + 1\right) dy = 6.7 \times 10^{-3}\), while \(\int_{\Omega_e} \left(\frac{\partial X_i}{\partial y_i} + 1\right) dy = 1.04 \times 10^{-2}\). The effective diffusion coefficient in this case is therefore anisotropic. \(\int_{\Gamma} d\Gamma\) for this geometry is close to 1.2.

By comparison, a “three-pipe” geometry (section 2.7) of similar ER volume (which implies that the short edge must be 0.10092) has \(\int_{\Gamma} d\Gamma\) of 1.09. That is, the more tortuous geometry of Figure 9 expresses the Serca flux over a slightly larger surface area. The factors \(\int_{\Omega_e} \left(\frac{\partial X_i}{\partial y_i} + 1\right) dy\) are \(1.07 \times 10^{-2}\) for each \(i = 1, 2, 3\). Thus, while the diffusion coefficients \(\tilde{a}_{33}\) are similar for either geometry, the components \(\tilde{a}_{11}, \tilde{a}_{22}\) are significantly smaller for the more circuitous ER.

Figure 9 suggests that as the path length of the ER increases (while the volume is kept fixed) the diffusion coefficients in the direction of the curved geometry \((\tilde{a}_{11}, \tilde{a}_{22})\) will decrease. It would be interesting to prove such a result rigorously.

5.3. Generalization to other expressions for the Serca flux \(f(c^\varepsilon, e^\varepsilon)\). In this paper we have assumed that the flux of calcium transported across the Serca pumps can be represented by an algebraic expression \(f(c^\varepsilon, e^\varepsilon)\). Such an expression arises, for example, under a suitable quasi-steady-state assumption used to reduce the reaction rate equations of the enzyme’s kinetics (see, for example, Keener and Sneyd [5]). To accommodate more general expressions of the flux, however, we can consider \(f\) to be of the form \(f(c^\varepsilon, e^\varepsilon, \frac{dc^\varepsilon}{dt}, \frac{de^\varepsilon}{dt}, X)\), with \(\frac{dX}{dt} = \Phi(c^\varepsilon, e^\varepsilon, X)\). That is,
the boundary conditions (2.2) may instead be written as

\[
A_\varepsilon \nabla c_\varepsilon \cdot n_\varepsilon = \varepsilon \lambda f_1 \left( c_\varepsilon, e_\varepsilon, \frac{\partial c_\varepsilon}{\partial t}, \frac{\partial e_\varepsilon}{\partial t}, X \right) \quad \text{on } \Gamma_\varepsilon,
\]

\[
-B_\varepsilon \nabla e_\varepsilon \cdot n_\varepsilon = \varepsilon \lambda f_2 \left( c_\varepsilon, e_\varepsilon, \frac{\partial c_\varepsilon}{\partial t}, \frac{\partial e_\varepsilon}{\partial t}, X \right) \quad \text{on } \Gamma_\varepsilon,
\]

\[
\frac{dX}{dt} = \Phi(c_\varepsilon, e_\varepsilon, X).
\]

In this case, the results obtained in the paper continue to hold by suitably replacing \( f(c^0, e^0) \rightarrow f(c_\varepsilon^0, e_\varepsilon^0, \frac{\partial c_\varepsilon^0}{\partial t}, \frac{\partial e_\varepsilon^0}{\partial t}, \int \Phi(c^0, e^0, X) \, dt) \).

6. Appendix. The boundary flux of the Serca pumps in (2.2) is related to the parameters of the problem as follows:

\[
A \nabla c_\varepsilon \cdot n_\varepsilon = \sigma f(c_\varepsilon, e_\varepsilon) \quad \text{on } \Gamma_\varepsilon,
\]

where \( f(c_\varepsilon, e_\varepsilon) \) is the flux per unit pump concentration, and \( \sigma \) is the surface density of the pump protein on \( \Gamma_\varepsilon \). Note that \( f(\cdot, \cdot) \) is independent of the parameter \( \varepsilon \) of the geometry. For a periodic cubic cell of length \( \varepsilon \), \( \sigma \) is equal to \( \rho_V \times \frac{\varepsilon^3}{\tilde{\sigma}^2} \), where \( \rho_V \) is the volume density of \( N \) pumps distributed in the domain \( \Omega \) of volume \( V \), and \( \tilde{\sigma} \) is a shape parameter associated with the surface area of \( \Gamma \). For example, for the geometry considered above in section 2.7, \( \tilde{\sigma} \varepsilon^2 = 3 \times 0.4 \varepsilon \times 0.9 \varepsilon \). Thus, taking \( \rho_V / \tilde{\sigma} = \lambda \) leads to (2.2).

In the general case, \( \lambda \) can be taken to vary with \( x \) to allow for a nonhomogeneous spatial distribution of the pump proteins. All of the results obtained in the paper continue to hold with \( \lambda = \lambda(x) \).

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