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Finite element model to study two dimensional unsteady state calcium distribution in cardiac myocytes

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Abstract The calcium signaling plays a crucial role in expansion and contraction of cardiac myocytes. This calcium signaling is achieved by calcium diffusion, buffering mechanisms and influx in cardiac myocytes. The various calcium distribution patterns required for achieving calcium signaling in myocytes are still not well understood. In this paper an attempt has been made to develop a model of calcium distribution in myocytes incorporating diffusion of calcium, point source and excess buffer approximation. The model has been developed for a two dimensional unsteady state case. Appropriate boundary conditions and initial condition have been framed. The finite element method has been employed to obtain the solution. The numerical results have been used to study the effect of buffers and source amplitude on calcium distribution in myocytes.

1. Introduction

Heart is responsible for circulation of blood which is essential for life and functioning of different organs in human body. The functioning of heart is achieved through expansion and contraction of cardiac myocytes. This expansion and contraction of myocytes is responsible for pumping of blood from heart to arteries.[1,2] In order to understand the function of heart it is of crucial interest to understand the processes involved in cardiac myocytes. The various processes involved in spatiotemporal calcium dynamics required for the initiation, termination and sustenance of the activity of the cell are not well understood. Thus there is a need to study the calcium dynamics in cardiac myocytes along with its constituent processes.

Chemical reaction and diffusion are central to quantitative computational biology. Ca^{2+} ions diffuse away from the mouth of voltage gated plasma membrane through Ca^{2+} channels into the cytosolic domain.[1] This domain contains Ca^{2+} binding proteins (Troponin-C). By binding and releasing free Ca^{2+}, endogenous Ca^{2+} binding proteins and other "Ca^{2+} buffers" determine the range of action of Ca^{2+} ions that influence the time course of their effect and facilitate clearance of Ca^{2+}.[1,2] The intracellular binding proteins bind with calcium ion which results in the contraction of cardiac myocytes. The separation of bonded proteins from calcium ion

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results in the expansion of cardiac myocytes. The balance of calcium ion is maintained by diffusion of calcium, source influx and buffering mechanism.[1,2]

Attempts are reported in the literature for the study of calcium regulation in neuron cell, astrocyte cell, fibroblast cell, oocyte cell, acinar, etc.[3–19] But very few attempts are reported in the literature for the study of calcium dynamics in myocytes.[1,2,20,21] Most of the studies reported on calcium diffusion in myocytes are experimental.[22–24] In the present paper an attempt has been made to propose a model for calcium dynamics in cardiac myocytes in the presence of excess buffers for a two dimensional unsteady state case. The finite element method has been employed to obtain the solution. The effects of the parameters such as source influx and buffers on the calcium distribution in myocytes have been studied with the help of numerical results.

2. Mathematical formulations

By assuming a bimolecular association reaction between Ca^{2+} and buffer, we have[1]

$$Ca^{2+} + B \underset{k^-}{\overset{k^+}{\Longleftrightarrow}} CaB \tag{1}$$

In Eq. (1), B represents free buffer, and CaB represents Ca^{2+} bound buffer. k^+ and k^- are association and dissociation rate constants, respectively. If it is further assumed that the reaction of Ca^{2+} with buffer follows mass action kinetics, then the system of ODEs for the change in concentration of each species is given by[1,2]

$$\frac{\partial[Ca^{2+}]}{\partial t} = R + J \tag{2}$$

$$\frac{\partial[B]}{\partial t} = R \tag{3}$$

$$\frac{\partial[CaB]}{\partial t} = -R \tag{4}$$

where the common reaction term R, is given by

$$R = -k^+[Ca^{2+}][B] + k^-[CaB] \tag{5}$$

and J represents Ca^{2+} influx. Both R and J have units of concentration per unit time. Eqs. (2)–(5) are extended to include multiple buffers and the diffusive movement of free Ca^{2+}, Ca^{2+} bound buffer and Ca^{2+} free buffer. Assuming, Fick's diffusion in a homogeneous, isotropic medium, the system of reaction diffusion equations can be written as[1,2]

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\nabla^2[Ca^{2+}] + \sum_i R_i + J \tag{6}$$

$$\frac{\partial[B_i]}{\partial t} = D_{B_i}\nabla^2[B_i] + R_i \tag{7}$$

$$\frac{\partial[CaB_i]}{\partial t} = D_{CaB_i}\nabla^2[CaB_i] - R_i \tag{8}$$

where the reaction term, R_i is given by

$$R_i = -k_i^+[Ca^{2+}][B_i] + k_i^-[CaB_i] \tag{9}$$

Here i is an index over Ca^{2+} buffers. $D_{Ca}, D_{B_i}, and D_{CaB_i}$ are diffusion coefficients of free Ca^{2+}, bound calcium and free buffer respectively.

Since Ca^{2+} has a molecular weight that is small in comparison with most Ca^{2+} binding species, the diffusion constant of each mobile buffer is not affected by the binding of Ca^{2+} that is $D_{B_i} = D_{CAB_i} = D_i$.[1,2] Substituting this in Eqs. (7) and (8) and on summation it gives

$$\begin{aligned}\frac{\partial[B_i]_T}{\partial t} &= \frac{\partial[CaB_i]}{\partial t} + \frac{\partial[B_i]}{\partial t} \\ &= D_i\nabla^2[CaB_i] + D_i\nabla^2[B_i] \\ &= D_i\nabla^2[B_i]_T\end{aligned} \tag{10}$$

And

$$R_i = -k_i^+[Ca^{2+}][B_i] + k_i^-([B_i]_T - [B_i]) \tag{11}$$

where

$$[B_i]_T = [CaB_i] + [B_i] \tag{12}$$

Thus, $[B_i]_T$, profiles are initially uniform and there are no sources or sinks for Ca^{2+} buffer, and $[B_i]_T$ remains uniform for all times.[1,2] Thus, the following equations can be written for the diffusion of Ca^{2+}:

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\nabla^2[Ca^{2+}] + \sum_i R_i + J \tag{13}$$

$$\frac{\partial[B_i]}{\partial t} = D_i\nabla^2[B_i] + R_i \tag{14}$$

where

$$R_i = -k_i^+[Ca^{2+}][B_i] + k_i^-([B_i]_T - [B_i]) \tag{15}$$

In the excess buffer approximation (EBA), Eqs. (6)–(8) are simplified by assuming that the concentration of free Ca^{2+} buffer $[B_i]$, is high enough such that its loss is negligible. The EBA gets its name because this assumption of the unsaturability of Ca^{2+} buffer is likely to be valid when Ca^{2+} buffer is in excess.[7]

The association and dissociation rate constants for the bimolecular association reaction between Ca^{2+} and buffer can be combined to obtain a dissociation constant, K_i as follows:

$$K_i = k_i^-/k_i^+ \tag{16}$$

This dissociation constant of the buffer has units of μM and is the concentration of Ca^{2+} which is necessary to cause 50% of the buffer to be in Ca^{2+} bound form. To show this consider the steady state of Eqs. (6)–(8) in the absence of influx ($J = 0$). Setting the left hand sides of Eqs. (7) and (8) to zero gives[7]

$$[B_i]_\infty = \frac{K_i[B_i]_T}{K_i + [Ca^{2+}]_\infty} \tag{17}$$

and

$$[CaB_i]_\infty = \frac{[Ca^{2+}]_\infty[B_i]_T}{K_i + [Ca^{2+}]_\infty} \tag{18}$$

where $[Ca^{2+}]_\infty$ is the "background" or ambient free Ca^{2+} concentration. And $[B_i]_\infty$ and $[CaB_i]_\infty$ are the equilibrium concentrations of free and bound buffer with respect to index i. In this expression K_i is the dissociation rate constant of buffer i. Note that higher values for K_i imply that the buffer has a lower affinity for Ca^{2+} and is less easily saturated. In this case, the equation for the diffusion of Ca^{2+} becomes

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\nabla^2[Ca^{2+}] - \sum_i k_i^+[B_i]_\infty([Ca^{2+}] - [Ca^{2+}]_\infty) \tag{19}$$