Two Dimensional Coaxial Circular Elements in Finite Element Method to Study Calcium Diffusion in Cardiac Myocytes

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Abstract: ***The calcium signaling plays an important role in expansion and contraction of Myocytes. This calcium signaling is achieved by diffusion of calcium and buffering mechanisms in cardiac myocytes. In this paper an attempt has been made to develop model calcium signaling in myocytes incorporating diffusion of calcium and excess buffers. The model has been developed for a two dimensional steady state case. Appropriate boundary conditions 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 on calcium distribution in Myocytes.***

Index terms: cardiac myocytes, reaction diffusion equation, excess buffer, finite element method

I INTRODUCTION

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. In order to understand the function of heart it is of crucial interest to understand the processes involved in cardiac myocytes. The specific calcium signaling is required to achieve the above function of cardiac myocytes. But this calcium signaling in cardiac myocytes is still not well understood.

Chemical reaction and diffusion are central to quantitative computational biology. As Ca^{2+} ions diffuse away from the mouth of voltage gated plasma membrane through Ca^{2+} channels into the Cytosolic domain of elevated intracellular Ca^{2+} ion activate proteins associated with neurotransmitter release [1] .These Ca^{2+} domain are formed on the presence of ubiquitous Ca^{2+} binding proteins (Troponin-C) of the pre-synaptic terminal. 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 influence the time course of their effect and facilitate clearance of Ca^{2+} [1]. Concentration coupling, Ca^{2+} sparks activated by Ca^{2+} in flux through sarcoleminal Ca^{2+} channels is the "building blocks" of global Ca^{2+} responses that cause contraction. In the present study a mathematical model, for two dimensional steady state calcium diffusion in cardiac myocytes is developed under excess buffer approximation to understand the calcium diffusion in cardiac myocytes. The important parameters like buffers, diffusion coefficients and influx etc has been incorporated in the model.

II MATHEMATICAL FORMULATION

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

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

In equation (1), B represents free buffer, 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, it can be written the following system of ODEs for the change in concentration of each species is given by [1, 2, 3].

$$\frac{d\left[Ca^{2+}\right]}{dt} = R + J \tag{2}$$

$$\frac{d\left[B\right]}{dt} = R \tag{3}$$

$$\frac{d\left[CaB\right]}{dt} = -R \tag{4}$$

where the common reaction term R, is given by

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

and J represents Ca^{2+} influx. Both R and J have units of concentration per unit time. Equations (2) to (5)

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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 is written as [1],

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

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

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

where the reaction terms, R_i is given by

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

where, i is an index over Ca^{2+} buffers. D_{Ca} , D_{B_i} , 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 to 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 .[11, 12] Substituting this in equation (7) & (8) and on summation it gives

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

And

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

where

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

Thus, $[B_i]_T$, profiles are initially uniform and there are no source or sinks for Ca^{2+} buffer, $[B_i]_T$ remains uniform for all times.[11, 12] Thus, the following equations are written for the diffusion of Ca^{2+},

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

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

$$where$$

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

Here both R_i & J have units of concentration per unit time. Considering simplification of equations (6) to (8) that come about when buffer parameters are in select regimes: the so called "excess buffer" approximation.

In the excess buffer approximation (EBA), equations (6) to (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. [11, 12]

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.

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

This dissociation constant of the buffer has units of μM and is the concentration of Ca^{2+} is necessary to cause 50% of the buffer to be in Ca^{2+} bound form. To show this consider the steady state of equations (6) to (8) in the absence of influx (J=0). Setting the left hand sides of equation (7) and (8) to zero gives,[11, 12]

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

and

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

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 these 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,

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

To complete a reaction – diffusion formulation for the buffered diffusion of Ca^{2+}, a particular geometry of simulation must be specified and equation (19) must supplement with boundary conditions. If Ca^{2+} is released from intracellular Ca^{2+}stores deep within a large cell (so that the plasma membrane is far away and doesn't influence the time course of the event), and the intracellular milieu is homogenous and isotropic, then it has cylindrical symmetry [6]. In this case the evolving profiles of Ca^{2+} and buffer will be a function of r and θ only. For a two dimensional steady state case the equation (19) in polar in absence of influx (J = 0) is given by

$$\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial\left[Ca^{2+}\right]}{\partial r}\right) + \frac{1}{r^2}\frac{\partial^2\left[Ca^{2+}\right]}{\partial\theta^2} - \frac{k^+[B]_\infty}{D_{Ca}}\left(\left[Ca^{2+}\right] - \left[Ca^{2+}\right]_\infty\right) = 0 \quad (20)$$

The reasonable boundary condition for this simulation is uniform background Ca^{2+} profile of $[Ca^{2+}]_\infty$ = 0.1 μM. It is required that buffer far from the source to remain in equilibrium with Ca^{2+} at all times. Thus the boundary condition on the boundary away from the source is given by [11, 12]

$$\lim_{r\to\infty,\theta\to 0}\left[Ca^{2+}\right] = \left[Ca^{2+}\right]_\infty \quad (21)$$

At the source, it is assumed that influx takes place and therefore the boundary condition is expressed as [11, 12]

$$\lim_{r\to\infty,\theta\to\pi}\left(-2\pi D_{Ca} r\frac{\partial\left[Ca^{2+}\right]}{\partial r}\right) = \sigma_{Ca} \quad (22)$$

We define an influx of free Ca^{2+} at the rate σ_{Ca} by Faraday's law, $\sigma_{Ca} = \frac{I_{Ca}}{zF}$ [11, 12]. Hence, the problem reduces to find the solution of equation (20) with respect to the boundary conditions (21) and (22).

Here, $\left[Ca^{2+}\right]_\infty$ is the background calcium concentration, $[B]_\infty$ is the total buffer concentration, σ_{Ca} represents the flux. $\left[Ca^{2+}\right]$ tends to the background concentration 0.1 μM as r tends to ∞ and θ tends to π. But the domain taken here is not infinite but finite one. Here, the distance is taken required for $\left[Ca^{2+}\right]$ to attain background concentration 7.8 μm for the Cardiac Myocytes (i.e. radius of the Cardiac Myocytes) [5]. Now the finite element method is employed to solve Equation (20) with boundary conditions (21) and (22). [6, 7, 8]

Assuming that the cardiac myocytes of circular shape and it is divided into coaxial circular elements [11, 12], given in figure 1.

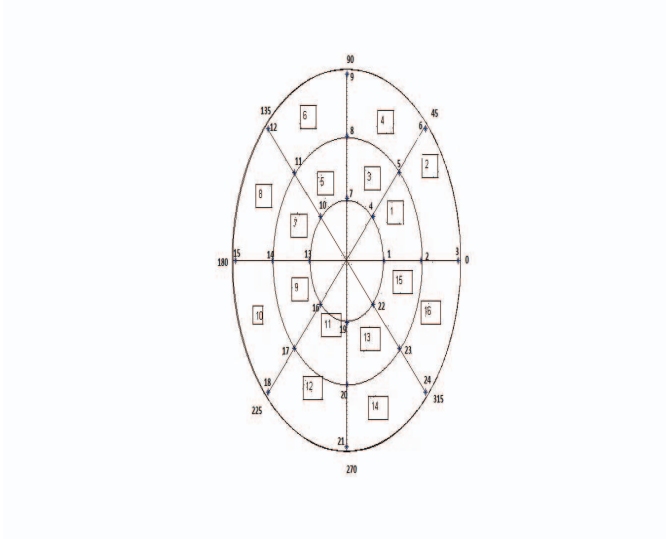

Figure 1: Finite element Discretization of circular cell

Here the square represents the number of elements and without square represents the nodal points where the nodal point 15 represents point source of calcium. The following table represents the element information.

Table 1: Element information

e	i	j	k	l
1	1	2	4	5
2	2	3	5	6
3	4	5	7	8
4	5	6	8	9
5	7	8	10	11
6	8	9	11	12
7	10	11	13	14
8	11	12	14	15
9	13	14	16	17
10	14	15	17	18
11	16	17	19	20
12	17	18	20	21
13	19	20	22	23
14	20	21	23	24
15	22	23	1	2
16	23	24	2	3

The discretize variational form of Equation (20) is given by

$$I^{(e)} = \frac{1}{2}\int_{r_i}^{r_j}\int_{\theta_i}^{\theta_l}\left[\left(\left(r\frac{\partial u^{(e)}}{\partial r}\right)^2 + \left(\frac{\partial u^{(e)}}{\partial \theta}\right)^2\right)\right]drd\theta$$
$$+\frac{1}{2}\int_{r_i}^{r_j}\int_{\theta_i}^{\theta_j}\left[\frac{k^+[B]_\infty}{D_{Ca}}r^2u^{(e)2} - \frac{2k^+[B]_\infty}{D_{Ca}}u_\infty u^{(e)}r^2\right]drd\theta$$
$$-\int_{\theta_i}^{\theta_j}\left[\frac{\sigma_{Ca}}{2\pi D_{Ca}}u^{(e)}\right]d\theta \qquad (23)$$

Here, 'u' is used in lieu of $\left[Ca^{2+}\right]$ for our convenience, e = 1, 2,…16.

The following bilinear shape function for the calcium concentration within in each element has been taken as [4, 11, 12].

$$u^{(e)} = C_1^{(e)} + C_2^{(e)}r + C_3^{(e)}\theta + C_4^{(e)}r\theta \quad (24)$$

The thickness of each element is very small, therefore $u^{(e)}$ is assigned bilinear variation with respect to position as given by Equation (24).

In matrix form the equation (24) can be written as

$$u^{(e)} = P^T C^{(e)} \qquad (25)$$

where

$$P^T = \begin{bmatrix}1 & r & \theta & r\theta\end{bmatrix} \text{ and } C^{(e)} = \begin{bmatrix}C_1^{(e)}\\ C_2^{(e)}\\ C_3^{(e)}\\ C_4^{(e)}\end{bmatrix}$$

Also

$$u_i^{(e)} = C_1^{(e)} + C_2^{(e)}r_i + C_3^{(e)}\theta_i + C_4^{(e)}r_i\theta_i \qquad (26)$$
$$u_j^{(e)} = C_1^{(e)} + C_2^{(e)}r_j + C_3^{(e)}\theta_j + C_4^{(e)}r_j\theta_j \qquad (27)$$
$$u_k^{(e)} = C_1^{(e)} + C_2^{(e)}r_k + C_3^{(e)}\theta_k + C_4^{(e)}r_k\theta_k \qquad (28)$$
$$u_l^{(e)} = C_1^{(e)} + C_2^{(e)}r_l + C_3^{(e)}\theta_l + C_4^{(e)}r_l\theta_l \qquad (29)$$

Using Equations (26)-(29) we get

$$\overline{u}^{(e)} = P^{(e)}C^{(e)} \qquad (30)$$

where

$$P^{(e)} = \begin{bmatrix}1 & r_i & \theta_i & r_i\theta_i\\ 1 & r_j & \theta_j & r_j\theta_j\\ 1 & r_k & \theta_k & r_k\theta_k\\ 1 & r_l & \theta_l & r_l\theta_l\end{bmatrix} \text{ and } \overline{u}^{(e)} = \begin{bmatrix}u_i^{(e)}\\ u_j^{(e)}\\ u_k^{(e)}\\ u_l^{(e)}\end{bmatrix}$$

From Equation (25) and (30) we get

$$u^{(e)} = P^T R^{(e)}\overline{u}^{(e)} \qquad (31)$$

where $R^{(e)} = P^{(e)-1}$

Now the integral given in Equation (23) can also be written as,

$$I^{(e)} = \frac{1}{2}\int_{r_i}^{r_j}\int_{\theta_i}^{\theta_k}\left[\left(r\,\mathrm{P_r}^T R^{(e)}\overline{u}^{(e)}\right)^2 + \left(P_\theta^T R^{(e)}\overline{u}^{(e)}\right)^2\right]drd\theta$$
$$+\frac{1}{2}\int_{r_i}^{r_j}\int_{\theta_i}^{\theta_k}\left[\frac{k^+[B]_\infty}{D_{Ca}}r\left(\mathrm{P}^T R^{(e)}\overline{u}^{(e)}\right)^2\right]drd\theta$$
$$-\frac{1}{2}\int_{r_i}^{r_j}\int_{\theta_i}^{\theta_k}\left[\frac{2k^+[B]_\infty}{D_{Ca}}u_\infty r\left(\mathrm{P}^T R^{(e)}\overline{u}^{(e)}\right)\right]drd\theta$$
$$-\int_{\theta_i}^{\theta_k}\left[\frac{\sigma_{Ca}}{2\pi D_{Ca}}\overline{u}^{(e)}\right]d\theta \qquad (32)$$

Now $I^{(e)}$ is minimized with respect to $\overline{u}^{(e)}$

$\frac{dI^{(e)}}{d\overline{u}^{(e)}} = 0$, where

$\overline{u}^{(e)} = \begin{bmatrix}u_i & u_j & u_k & u_l\end{bmatrix}^T, e = (1, 2, ...16)$

$$\frac{dI}{d\overline{u}^{(e)}} = \sum_{e=1}^{N}\overline{M}^{(e)}\frac{dI^{(e)}}{d\overline{u}^{(e)}}\overline{M}^{(e)T}$$

$$\overline{M}^{(e)} = \begin{bmatrix}0&0&0&0\\ 1&0&0&0\\ 0&1&0&0\\ 0&0&1&0\\ 0&0&0&1\\ \bullet&\bullet&\bullet&\bullet\\ 0&0&0&0\end{bmatrix}_{(24\times4)} \begin{matrix}\\ (i^{th}\ row)\\ (j^{th}\ row)\\ (k^{th}\ row)\\ (l^{th}\ row)\\ \\ \\ \end{matrix} \text{ and } I = \sum_{e=1}^{16} I^{(e)}$$

This leads to following system of linear algebraic equations

$$[K]_{(24\times24)}[\overline{u}]_{(24\times1)} = [F]_{(24\times1)} \qquad (33)$$

Here, $\overline{u} = \begin{bmatrix} u_1 & u_2 & \bullet & \bullet & \bullet & u_{24} \end{bmatrix}^T$, K is characteristic matrix and F is characteristic vector. Gaussian Elimination method is employed to solve the system (33).

III RESULTS AND DISCUSSION

A computer program in MATLAB 7.10.0.499 is developed to find numerical solution to the entire problem. The time taken for simulation is nearly 8.81 seconds on Core (TM) i 5-520M 330 @ 2.40 GHz processing speed and 4 GB memory. [6, 7, 8] To find the solution of equation (3.2.10) the biophysical parameters are taken from the literature as given in Table 2,

R	Radius of the cell	7.8 μm
I_{Ca}	Amplitude of elemental Ca^{2+} release	1 p A
F	Faraday's constant	96500 C/mol
Z	Valence of Ca^{2+} ion	2
D_{Ca}	Diffusion coefficient of free Ca^{2+} in cytosol	250 $\mu m^2 / s$
$[B_i]_T$	Total concentration for each Ca^{2+} buffer (Troponin C)	70 μM
k_i^+	Association rate constant for Ca^{2+} binding (Troponin C)	39 $\mu M^{-1} S^{-1}$
k_i^-	Dissociation rate constant for Ca^{2+} binding (Troponin C)	20 S^{-1}
K_i	Dissociation constant (Troponin C) $= \frac{k_i^-}{k_i^+}$,	0.51 μM
$[Ca]_\infty$	Intracellular free Ca^{2+} concentration at rest	0.1 μM

Table 2: Numerical values of biophysical parameters [5]

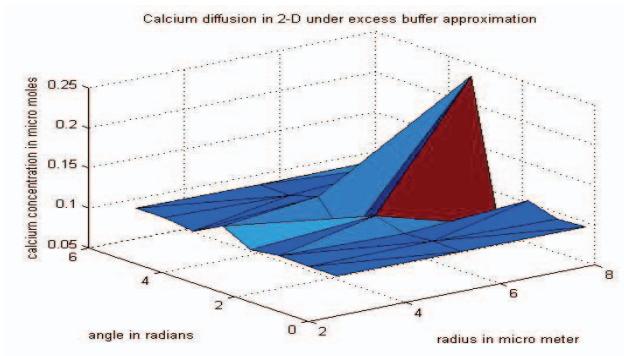

Figure 2: Two dimensional calcium diffusion under excess buffer approximation

Figure 2 represents the variation in Ca^{2+} concentration along angular and radial direction. We observe that maximum calcium concentration is 0.24 µM at a node (r=7.8, θ= π) i.e. source and it decreases along the angle as we move away from the source and it achieves its background concentration 0.1 µM at the other end i.e. at θ = 0. Initially from θ = π to θ = 3π/2 and θ = π to θ = π/2 the concentration falls rapidly due to buffering and slowly then after converges to its background concentration 0.1 µ M as θ approaches to 0 and 2π along the radial direction.

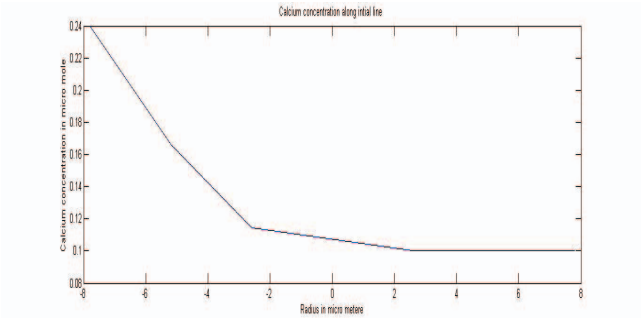

Figure 3: Calcium concentration along initial line

Figure 3 represents the variation in Ca^{2+} concentration along radial direction for initial line. We observe that maximum calcium concentration is 0.24 µM at r = -7.8 µm i.e. source and it decreases along the radius as we move away from the source and it achieves its background concentration 0.1 µM at the other end i.e. at r = 7.8 µm. Initially from r = -7.8 µm to r = -2.6 µm the concentration falls rapidly due to buffering and slowly then after converges to its background concentration 0.1 µ M as r approaches to -2.6 µm to 2.6 µm. Then it achieves its background concentration 0.1 µM and remains 0.1 µ M from r= 2.6 µm to 7.8 µm.

Conclusion: It is observe that due to excess buffer, the buffering activity has significant effect in calcium diffusion in cardiac myocytes give us better central regions little away from the source. The coaxial elements used here give us better approximations. The finite element method is quite flexible and powerful in dealing such problems and gives useful results in two dimensions.

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