Advances in Computational Sciences and Technology
ISSN 0973-6107 Volume 10, Number 1 (2017) pp. 11-23

http://www.ripublication.com

Finite Element Simulation of Advection Diffusion of Calcium in Myocyes Involving Influx and Excess Buffer

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Abstract

Expansion and contraction of myocyte cells present in heart is responsible for pumping of blood in order to achieve circulation of blood to different parts of the body. The regulation of calcium concentration at different levels in the myocyte cells is required for expansion and contraction of myocytes. The mechanism of calcium regulation in myocytes is still not well understood. In this paper a finite element model is proposed to study the calcium regulation in circular shaped myocytes for a one dimensional steady state case. The processes like advection, diffusion, excess buffer and source influx are incorporated in the model. Appropriate boundary conditions have been proposed based on biophysical properties of region. Numerical simulation have been preformed to study the individual as well as coordinated effects of buffers, source influx, advection and diffusion on calcium distribution in myocytes.

Keywords: Cardiac myocytes, advection, reaction diffusion equation, excess buffer, finite element method

INTRODUCTION

Heart is responsible for blood circulation in the human body. This blood circulation is essential for maintaining structure and function of different organs of the body. Expansion and contraction of myocyte cells present in the heart is responsible for pumping of blood in the body through blood circulation system. The specific calcium regulation is required for expansion and contraction of myocytes, which is still not well understood. The intracellular binding proteins which are already present in the cell bind with calcium ion which results into the contraction of cardiac myocytes. The separation

of bonded protein from calcium ion results into the expansion of cardiac myocytes. Smith G. D. *et al* [1] Calcium regulation is maintained by various processes like source influx, buffer, diffusion and advection etc. In cells, the advection of calcium ions may occur due to mechanical contraction of the cell surface or due to significant transport of material through cytosolic fluid. Due to advection, there is a cross flow of calcium ion which occurs in the cytoplasm of cell. Panday S. *et al* [2] ,J ha B. K. *et al* [3] . Attempts are reported in the literature for the study the study of calcium distribution in neuron cell, astrocytes cell, fibroblast cell, Oocytes cell, acinar cell etc. Jha A *et al* [4], Jha B K *et al* [5,6], Kotwani M *et al* [7,8], Manhasn N *et al* [9,10,11], Naik P *et al* [12,13], Panday S *et al* [14], Tewari S *et al* [15,16] . But very few attempts are reported in the literature for the study of calcium regulation in myocytes. Backx P H *et al* [17], Luo C H *et al* [18], Michailova A *et al* [19]. Most of the studies reported on calcium regulation in myocytes are experimental. Michailova A *et al* [19], Shannon T R *et al* [20]. Some attempts have been made by research works to study the effect of advection and diffusion in astrocytes and Oocytes. Jha B K *et al* [21], Panday S *et al* [2]. But no attempts are reported in the literature for study the effect of advection on calcium regulation in cardiac myocytes. Also no attempt has been made so far in the past to study individual and coordinated effect of advection, diffusion, buffers and source influx on calcium concentration regulation in myocytes. In the present paper a model is proposed to study the effect of individual and coordinated effect of source influx, buffer, diffusion and advection on calcium regulation in myocytes for a one dimensional steady state case. The finite element approach has been employed to perform numerical simulation.

MATHEMATICAL FORMULATION

onsider reaction of calcium with buffer as

$$Ca^{2+} + B_i \underset{k^-}{\overset{k^+}{\Leftrightarrow}} CaB_i \tag{1}$$

where B_i and CaB_i are free and bound buffers respectively, and i is an index over buffer species. Smith G D *et al* [1], Panday S *et al* [2]. k_i^+ and k_i^- are association and dissociation rate constants for i respectively. Using mass action kinetic law and Flicks' law, the advection diffusion equation of calcium concentration for reaction given by equation (1) in polar cylindrical coordinates for one dimensional steady state case in presence of excess buffer can be stated as Smith G D *et al* [1], Panday S *et al* [2].

$$\frac{d}{dr}\left(r\frac{d[Ca^{2+}]}{dr}\right) - \frac{V}{D_{Ca}}\left(r\frac{d[Ca^{2+}]}{dr}\right) - \sum_i k_i^+ [B_i]_\infty \left(\left[Ca^{2+}\right] - \left[Ca^{2+}\right]_\infty\right) = 0 \tag{2}$$

where

$$[B_i]_\infty = \frac{K_i [B_i]_T}{K_i + \left[Ca^{2+}\right]_\infty} \tag{3}$$

and

$$\left[CaB_i\right]_\infty = \frac{\left[Ca^{2+}\right]_\infty \left[B_i\right]_T}{K_i + \left[Ca^{2+}\right]_\infty} \tag{4}$$

Here $[Ca^{2+}]_\infty$ is the background free Ca^{2+} concentration. $[B_i]_\infty$ and $[CaB_i]_\infty$ are the equilibrium concentrations of free and bound buffer to cause 50% of buffer will be in calcium bound form with respect to index i. $[B_i]_T$ is total buffer concentration in the cell. Jha A *et al* [4]. K_i is dissociation constant. V represents the velocity of cytosolic calcium ion due to advection. Smith G D *et al* [1]. D_{Ca} is diffusion coefficient. $[Ca^{2+}]$ denotes the concentration of calcium. The point source due to L-type calcium channel of calcium is assumed at first node r = 0.01 µm. Thus the appropriate boundary condition can be taken as Shannon T R *et al* [20]

$$\lim_{r\to 0^+}\left(-2\pi D_{Ca} r \frac{\partial\left[Ca^{2+}\right]}{\partial r}\right) = \sigma_{Ca} \tag{5}$$

Here an influx of free Ca^{2+} is taken at the rate σ_{Ca} by Faraday's law Jha A *et al* [21], Luo C H *et al* [22], $\sigma_{Ca} = \frac{I_{Ca}}{zF}$, where I_{Ca}, z and F are amplitude of Ca^{2+} release, valence of calcium ion and Faraday's constant respectively. Let the background concentration of Ca^{2+} is 0.1 µM on the boundary of the cell at r = 7.8 µm Luo C H *et al* [18], Jha A *et al*[21]

$$\lim_{r\to 7.8}\left[Ca^{2+}\right] = \left[Ca^{2+}\right]_\infty = 0.1\mu M \tag{6}$$

Now the finite element method is employed to solve equation (2) with boundary conditions (5) and (6). The one dimensional finite element discretization is given by figure1,

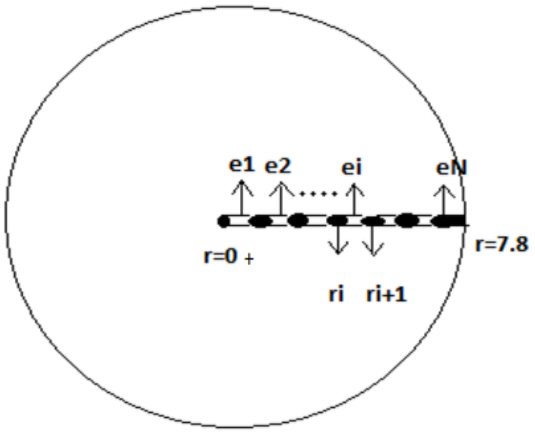

Figure 1: One dimensional finite element discretization

Here e_i denotes the i^{th} element. And r_i and r_{i+1} denotes initial and terminal nodes of i^{th} element.

The discretized variational integral of equation (2) is given by

$$I^{(e)} = \frac{1}{2}\int_{r_i}^{r_j}\left[J_1^{(e)} + J_2^{(e)} - J_3^{(e)}\right]dr - \left[\frac{\sigma_{Ca}}{2\pi D_{Ca}} y^{(e)}\right]_{r_i}^{r_j} \tag{7}$$

where

$$J_1^{(e)} = r\left(\frac{dy^{(e)}}{dr}\right)^2 + \frac{V}{D_{Ca}} 2ry^{(e)}\left(\frac{dy^{(e)}}{dr}\right) - \frac{V}{D_{Ca}} y^{(e)^2}$$

$$J_2^{(e)} = \frac{k^+\left[B\right]_\infty}{D_{Ca}} ry^{(e)2}$$

$$J_3^{(e)} = \frac{2k^+\left[B\right]_\infty}{D_{Ca}} y_\infty y^{(e)} r$$

Here, 'y' is used in lieu of $\left[Ca^{2+}\right]$ for our convenience, e = 1, 2, …, N (number of elements).

The thickness of each element is very small, therefore $y^{(e)}$ is assigned linear variation with respect to position as given by

$$y^{(e)} = A_1 + A_2 r \tag{8}$$

In matrix form the equation (8) can be written as

$$y^{(e)} = P^T A^{(e)} \tag{9}$$

where

$$P^T = \begin{bmatrix}1 & r\end{bmatrix} \text{ and } A^{(e)} = \begin{bmatrix}A_1 \\ A_2\end{bmatrix}$$

Also at nodal points r_i and r_j of the e^{th} element,

$$y^{(e)}(r_i) = y_i = A_1 + A_2 r_i \tag{10}$$

$$y^{(e)}(r_j) = y_j = A_1 + A_2 r_j \tag{11}$$

Using Equations (9)-(11) we get

$$\bar{y}^{(e)} = P^{(e)} A^{(e)} \tag{12}$$

where

$$P^{(e)} = \begin{bmatrix}1 & r_i \\ 1 & r_j\end{bmatrix} \text{ and } \bar{y}^{(e)} = \begin{bmatrix}y_i^{(e)} \\ y_j^{(e)}\end{bmatrix}$$

From Equations (8) and (12) we get

$$y^{(e)} = P^T R^{(e)} \bar{y}^{(e)} \tag{13}$$

where

$$R^{(e)} = P^{(e)-1} = \frac{1}{r_j - r_i}\begin{bmatrix} r_j & r_i \\ 1 & 1 \end{bmatrix}$$

Now the integral given in equation (7) can also be written in terms of nodal values as,

$$I^{(e)} = \frac{1}{2}\int_{r_i}^{r_j}\left[I_1^{(e)} + I_2^{(e)} + I_3^{(e)}\right]dr - \left[\frac{\sigma_{Ca}}{2\pi D_{Ca}}\bar{y}^{(e)}\right]_{e=1} \tag{14}$$

where

$$I_1^{(e)} = r(\mathrm{P_r}^T R^{(e)}\bar{y}^{(e)})^2 + \frac{2Vr}{D_{Ca}}\left(\mathrm{P}^T R^{(e)}\bar{y}^{(e)}\right)\left(\mathrm{P_r}^T R^{(e)}\bar{y}^{(e)}\right) - \frac{V}{D_{Ca}}\left(\mathrm{P}^T R^{(e)}\bar{y}^{(e)}\right)^2,$$

$$I_2^{(e)} = \frac{k^+[B]_\infty}{D_{Ca}}\, r(\mathrm{P}^T R^{(e)}\bar{y}^{(e)})^2,$$

$$I_3^{(e)} = \frac{-2k^+[B]_\infty}{D_{Ca}}\, u_\infty\, r(\mathrm{P}^T R^{(e)}\bar{y}^{(e)})$$

Now $I^{(e)}$ is minimized with respect to $\bar{y}^{(e)}$

$$\frac{dI^{(e)}}{d\bar{y}^{(e)}} = 0 \tag{15}$$

where

$$\bar{y}^{(e)} = \begin{bmatrix} y_i & y_j \end{bmatrix}^T, e = (1, 2, \ldots N)$$

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

$$\bar{M}^{(e)} = \begin{bmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 1 \\ \bullet & \bullet \\ 0 & 0 \end{bmatrix}_{((N+1)\times 2)} \qquad \begin{matrix} (i^{th}\ row) \\ ((i+1)^{th}\ row) \end{matrix} \quad and\ I = \sum_{e=1}^{N} I^{(e)}$$

This leads to following system of linear algebraic equations

$$[K]_{(N+1\times N+1)}[\bar{y}]_{(N+1\times 1)} = [F]_{(N+1\times 1)} \tag{16}$$

Here, $\bar{y} = [y_1 \quad y_2 \quad \bullet \quad \bullet \quad \bullet \quad y_{N+1}]^T$, K is characteristic matrix and F is characteristic vector. Gauss Elimination method is employed to solve the system (16). A computer program has been developed in MATLAB 7.10 for the entire problem and simulated on Core i5 processor with 2.40 GHz processing speed, 64-bit machine with 320 GB memory.

NUMERICAL RESULTS AND DISCUSSION

The values of biophysical parameters used for numerical simulation are given in Table 1. Michailova A *et al* [19]. The results were computed by taking 100, 200 and 400 elements for the same region of the cell. The difference in calcium concentration at a node r = 0.01 is 0.0778 for results between 100 and 200 elements and 0.044 for 200 and 400 elements, which amount to relative error of 8% and 4% respectively. But at the node r = 0.08 relative error for 100 and 200 elements is 1% and for 200 and 400 elements is 0.2%. The relative errors for the nodal points r = 0.08 to r = 7.8 for both cases are found to be less than 1%. Thus the error is not significant and grid with 100 elements gives very good results and the results are fairly independent of the grid. In view of above in this section the results obtained by taking grid size of 100 elements have been presented.

Table 1: Numerical values of biophysical parameters Michailova A *et al* [19]

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 for Troponin C	780 $\mu m^2 / s$
$[B_1]_T$	Total concentration for each Ca^{2+} buffer of Troponin C	70 μM
k^+	Association rate constant for Ca^{2+} binding of Troponin C	39 $\mu M^{-1} S^{-1}$
k^-	Dissociation rate constant for Ca^{2+} binding of Troponin C	20 S^{-1}
K	Dissociation constant of Troponin C $= k_i^- / k_i^+$,	0.51 μM
$[Ca]_\infty$	Intracellular free Ca^{2+} concentration at rest	0.1 μM

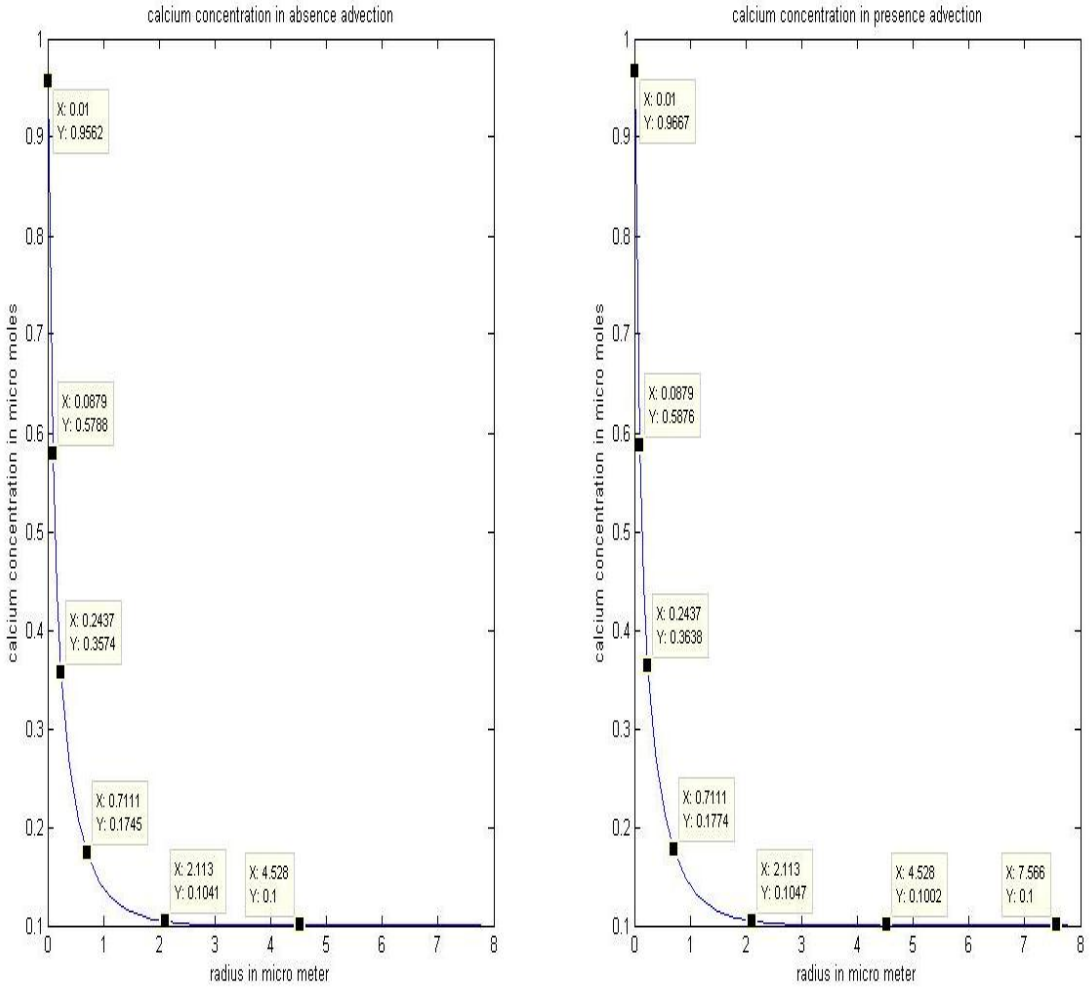

Figure 2: Calcium distribution along radial direction without and with advection

Figure 2 shows the calcium distribution along radial direction in absence and presence of advection. The maximum calcium concentrations observed are 0.9562 μM in absence of advection and 0.9667 μM in presence of advection at source i.e. at r = 0.01 μm. As we move away from the source the calcium concentration decreases sharply from r = 0.01 μm to r = 0.7111 μm and reaches 0.1745 μM and 0.1774 in absence and presence of advection respectively. As we move further away from the source from r = 0.7111 μm to r = 3.113 μm the concentration of calcium decreases to 0.1041 μM and 0.1047 in absence and presence of advection and thereafter it achieves its background concentration 0.1 μM.

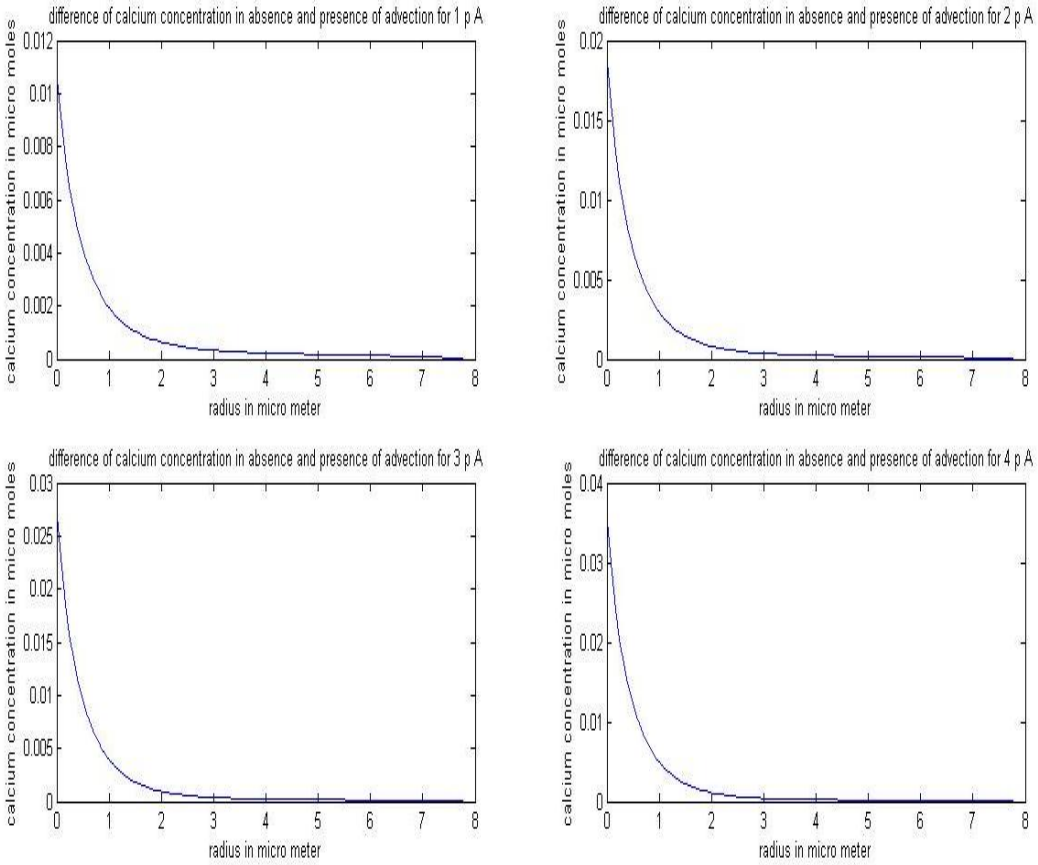

Figure 3: Difference of calcium concentration in absence and presence of advection for different values of source influx.

Figure 3 shows the difference of calcium concentration in absence and presence of advection at different source influx values 1 p A, 2 p A, 3 p A and 4 p A. The maximum differences at source r = 0.01 μm are 0.012 μM for source influx 1 p A, 0.018 μM for source influx 2 p A, 0.026 μM for 3 p A and 0.035 μM for 4 p A. The effect of source influx on advection observed more near the source. But as we move away from the source from r = 0.01 μm to r = 1 μm the differences in calcium concentration due to absence and presence of advection decreases sharply due to advection and buffering process. From r = 1 μm to r = 2 μm these differences in calcium concentration gradually decrease and thereafter become zero as calcium concentration achieves its background concentration 0.1 μM. It shows that the effect of advection increases in ratio of source influx.

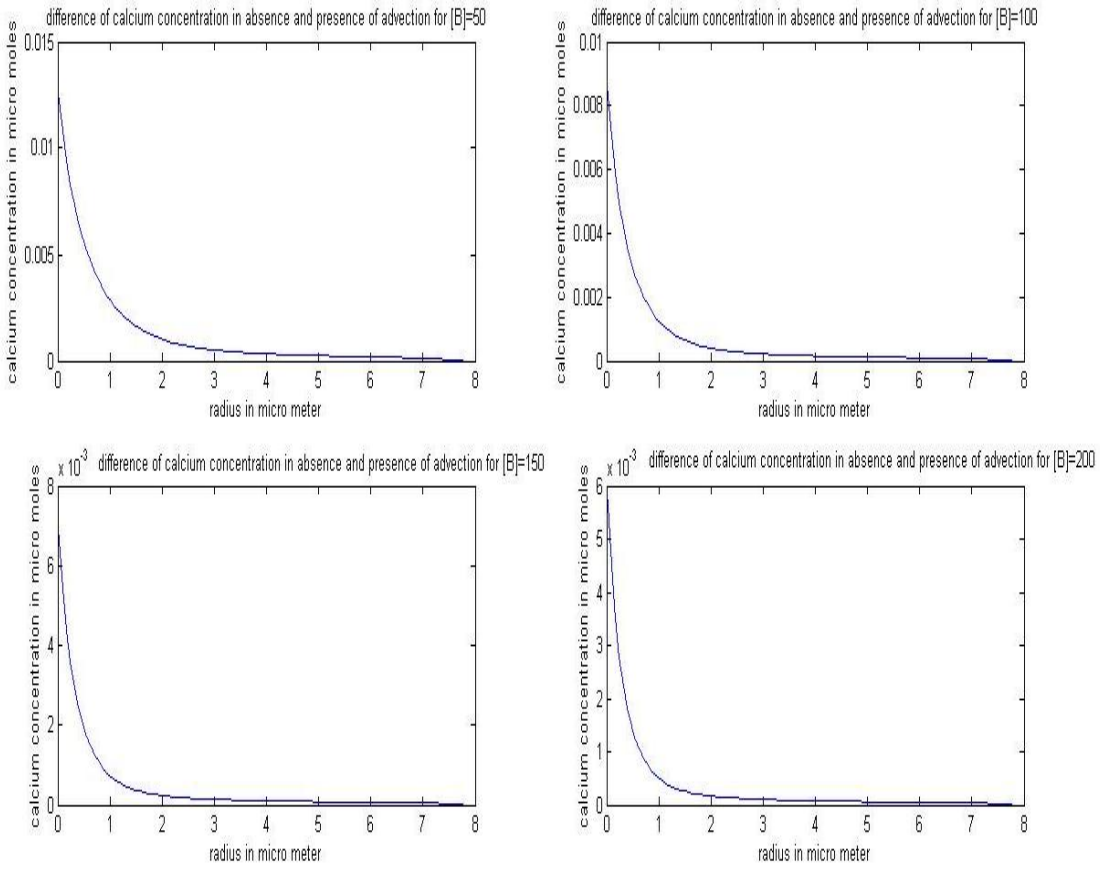

Figure 4: Difference of calcium concentration in absence and presence of advection for different values of buffer concentration.

Figure 4 shows the difference of calcium concentration in absence and presence of advection at different buffer concentration 50 μM, 100 μM, 150 μM and 200 μM. The maximum calcium concentration differences due to absence and presence of advection at source r = 0.01 μm are 0.013 μM for [B] = 50 μM, 0.008 μM for [B] = 100 μM, 0.0007 μM for [B] = 150 μM and 0.00058 μM for [B] = 200 μM. The effect of buffer concentration on advection observed more near the source. But as we move away from the source from r = 0.01 μm to r = 1 μm the differences in calcium concentration decreases sharply due to buffering process. From r = 1 μm to r = 2 μm these differences in calcium concentration gradually decreases and thereafter become zero as calcium concentration achieves its background concentration 0.1 μM. It is also observed that the effect of advection decreases in ratio of increase in buffer concentration.

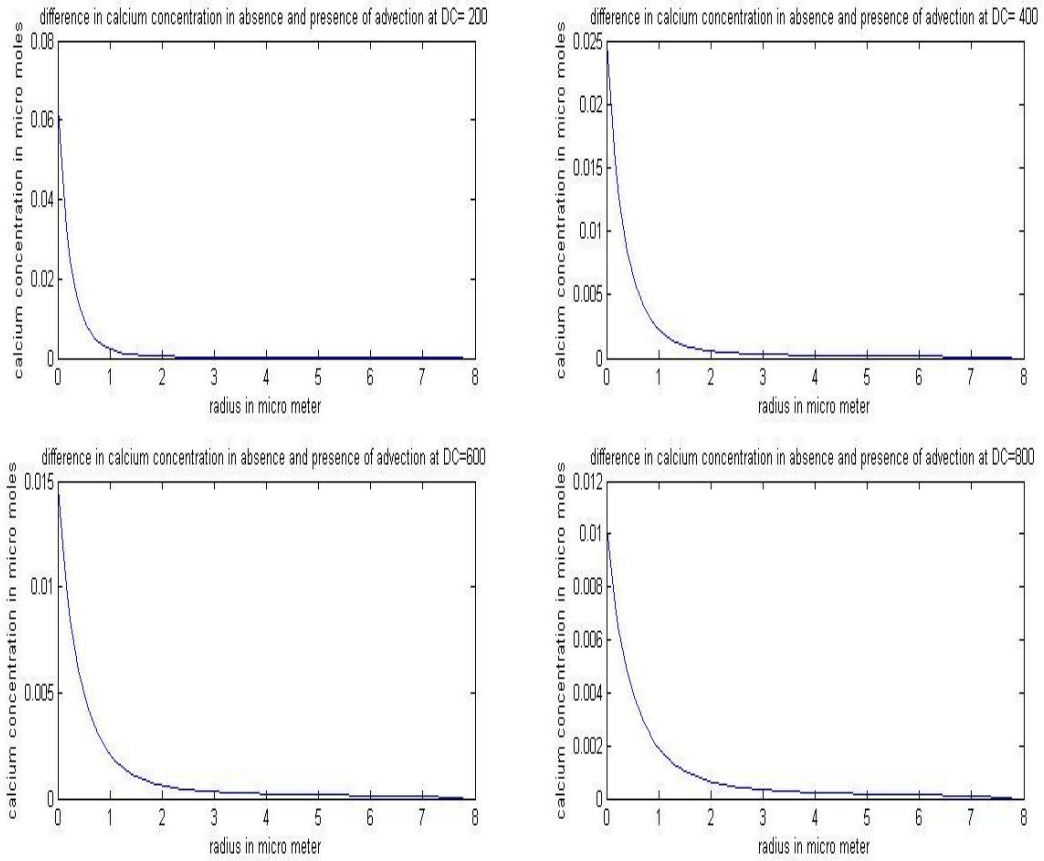

Figure 5: Difference of calcium concentration in absence and presence of advection for different values diffusion coefficient.

Figure 5 shows the difference of calcium concentration in absence and presence of advection for different values of diffusion coefficient i.e. 200 $\mu m^2 / s$, 400 $\mu m^2 / s$, 600 $\mu m^2 / s$ and 800 $\mu m^2 / s$. The maximum calcium concentration difference at source r = 0.01 µm are 0.06 µM for diffusion coefficient 200 $\mu m^2 / s$, 0.024 µM for diffusion coefficient 400 $\mu m^2 / s$, 0.014 µM for diffusion coefficient 600 $\mu m^2 / s$ and 0.01 µM for diffusion coefficient 800 $\mu m^2 / s$ observed. But as we move away from the source from r = 0.01 µm to r = 1 µm these differences in calcium concentration decrease sharply. From r = 1 µm to r = 2 µm the differences in calcium concentration gradually decrease and thereafter become zero as calcium concentration achieves its background concentration 0.1 µM. It is also observed that at higher value of diffusion coefficient the effect of advection is very less. That means the effect of advection decreases in ratio of diffusion coefficient and diffusion process dominates the advection process.

CONCLUSION

Finite element models are proposed and employed to study one dimensional calcium distribution in Cardiac Myocytes involving multi physical process like source influx, excess buffer, advection and diffusion for steady case. The model gives us interesting spatial calcium patterns in relation to these multi physical processes in cell. The results indicate that the effect of advection increases on calcium concentration increases in ratio of increase in influx. The results show that the effect of advection on calcium concentration decreases in ratio to buffer concentration. The effect of advection increases with decrease in the diffusion coefficient. Thus it can be concluded that at lower values of diffusion coefficient the advection comes into play for regulation of calcium concentration in myocytes. However for higher values of diffusion coefficient the diffusion process dominate over advection in calcium regulation in myocytes.

From the above results it can be concluded that the myocytes cell has a beautiful mechanism involving well-coordinated effect of parameters like source influx, buffer, advection and diffusion coefficient in regulating the $[Ca^{2+}]$ required for maintaining the structure and function of the cell. The finite element approach used here is quite versatile as it gives us flexibility to incorporate important parameters in the model. Such models can be developed further to generate information of calcium signaling in myocytes required for contraction and expansion of myocytes which is responsible for circulation of blood in the body. It can be of great use to biomedical scientist for developing protocols for diagnosis and treatment of diseases related to heart.

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