RESEARCH ARTICLE

Journal of Medical Imaging and Health Informatics
Vol. 5, 1–6, 2015

Finite Element Model to Study Calcium Signalling in Cardiac Myocytes Involving Pump, Leak and Excess Buffer

Kunal B. Pathak[1] and Nerru Adlakha[2]

[1]*Nirma University, Ahmedabad and* [2]*SVNIT, Surat*

The calcium signaling plays an important role in expansion and contraction of myocytes. This calcium signaling is achieved by diffusion of calcium, out flux of calcium through pumps, in flow of calcium through leak and buffering mechanisms in cardiac myocytes. In this paper an attempt has been made to develop a model of calcium signaling in myocytes incorporating diffusion of calcium, pump, leak and excess buffers. The model has been developed for a one 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, pump and leak on calcium signaling in myocytes.

Keywords: Reaction Diffusion Equation, SERCA Pump, Leak, Finite Element Method.

1. 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.[15] 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.

The concentration dependent binding of calcium to buffers serves as an indicator of the concentration of free calcium in intracellular measurements. The active elements of the exchange process are channels, serca pump and leaks in the membrane. The intracellular binding proteins bind with calcium ion which results into the contraction of cardiac myocytes. SERCA pumps transport the calcium against its electro chemical gradient. Leak receives the calcium that comes from pump and is stored in the sarcoplasmic reticulum (SR).Within the SR calcium maintains the high capacity and low efficiency of calcium binding proteins. They maintain the balance of calcium ions through active and passive process.[16] Attempts are reported in the literature for the study of calcium regulation in neuron cell, astrocyte cell, fibroblast cell, oocyte cell, acinar cell etc.[3,4,7,9] But very few attempts are reported in the literature for the study of calcium signaling in myocytes.[1,5,6,8,12] Most of the studies reported on calcium signaling in myocytes are experimental.[8,11] Some attempts are reported for the study of individual effect of pump, leak and influx on calcium distribution in myocytes.[5,16] But no attempt is reported to study the combined effect of source in-flux, buffer, leak and pump altogether on calcium signaling in myocytes. In the present paper an attempt has been made in this direction to propose a model for calcium signaling in myocytes in the presence of influx, buffers, leak and pump for a one dimensional steady state case. The finite element method has been employed to obtain the solution. The effect of the parameters like source influx, pump, leak and buffers on the calcium signaling in myocytes have been studied with the help of numerical results.

2. MATHEMATICAL FORMULATION

The calcium kinetics in myocytes is governed by a set of following reaction diffusion equations[12]

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

where B_i and CaB_i are free and bound buffers respectively, and i is an index over buffer species. k_i^+ and k_i^- are association and dissociation rate constants for i respectively. Using mass action kinetic law and Fick's law, the diffusion equations can be stated as:[12]

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

$$\frac{\partial[B_i]}{\partial t} = D_{B_i}\nabla^2[B_i] + R_i \tag{3}$$

*Author to whom correspondence should be addressed.

$$\frac{\partial[CaB_i]}{\partial t} = D_{CaB_i}\nabla^2[CaB_i] - R_i \tag{4}$$

Here the reaction terms $R_i's$ are given by

$$R_i = -k_i^+[Ca^{2+}][B_i] + k_i^-[CaB_i] \tag{5}$$

Where D_{Ca}, D_{Bi}, D_{CaBi} are diffusion coefficients of free calcium, free buffer and Ca^{2+} bound buffer respectively. And J represents flux which is either influx or outflx.[12]

Since Ca^{2+} has molecular weight that is small in comparison to most of Ca^{2+} binding species, the diffusion constant of each mobile buffer is not affected by the binding of Ca^{2+} that is $D_{Bi} = D_{CaBi} = D_i$. Hence Eqs. (3) and (4) gives[12]

$$\frac{\partial[B_i]_T}{\partial t} = D_i\nabla^2[B_i]_T \tag{6}$$

and

$$R_i = -k_i^+[Ca^{2+}][B_i] + k_i^-([B_i]_T - [B_i]) \tag{7}$$

where

$$[B_i]_T = [CaB_i] + [B_i] \tag{8}$$

In excess buffer approximation, Eqs. (2)–(5) are simplified by assuming that the concentration of free Ca^{2+} buffer is high enough such that its loss is negligible. There is no sink and source for proteins. 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,[12]

$$K_i = k_i^-/k_i^+ \tag{9}$$

The dissociation constant of the buffer has units of μM and the concentration of Ca^{2+} is necessary to cause 50% of the buffer to be in the Ca^{2+} bound form. Considering the steady state of Eqs. (2)–(4) in the absence of influx gives[15]

$$[B_i]_\infty = \frac{K_i[B_i]_T}{K_i + [Ca^{2+}]_\infty} \tag{10}$$

and

$$[CaB_i]_\infty = \frac{[Ca^{2+}]_\infty[B_i]_T}{K}_i + [Ca^{2+}]_\infty \tag{11}$$

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. The equation of calcium diffusion becomes[15]

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\nabla^2[Ca^{2+}] - \sum_i k_i^+[B_i]_\infty([Ca^{2+}] - [Ca^{2+}]_\infty) + J \tag{12}$$

Incorporating out flux due to serca pump J_{pump} and in flux due to leak J_{leak} in Eq. (12) for a one dimensional steady state case in polar coordinates is given by[16]

$$\frac{1}{r}\frac{d}{dr}\left(r\frac{d[Ca^{2+}]}{dr}\right) - \frac{k^+[B]_\infty}{D_{Ca}}([Ca^{2+}] - [Ca^{2+}]_\infty) + \frac{1}{D_{Ca}}(J_{\text{leak}} - J_{\text{pump}}) = 0 \tag{13}$$

Where

$$J_{\text{leak}} = V_{\text{leak}}([Ca^{2+}]_{SR} - [Ca^{2+}])$$

and

$$J_{\text{pump}} = V_{\text{pump}} \cdot \frac{[Ca^{2+}]^2}{K_{\text{pump}}^2 + [Ca^{2+}]^2}$$

Here V_{leak}, V_{pump} and K_{pump} are respectively the leak rate, serca pump rate and dissociation rate of serca pump. The point source of calcium is assumed at $r = 0$ μm. Thus the appropriate boundary condition can be taken as[13]

$$\lim_{r\to 0}\left(-2\pi D_{Ca} r\frac{\partial[Ca^{2+}]}{\partial r}\right) = \sigma_{Ca} \tag{14}$$

Here an influx of free Ca^{2+} is taken at the rate σ_{Ca} by Faraday's law, $\sigma_{Ca} = I_{Ca}/zF$.[13] It is assumed that background concentration of Ca^{2+} is 0.1 μM and as it goes far away from the source. The radial distance is considered as finite one i.e., radius of the cell.[13]

$$\lim_{r\to 7.8}[Ca^{2+}] = [Ca^{2+}]_\infty = 0.1\ \mu\text{M} \tag{15}$$

The one dimensional finite element discretization is given by Figure 1.

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

The study is performed for two cases as given below:

Case I: When $K_{\text{pump}} >> [Ca^{2+}]$ then we have[2]

$$\frac{[Ca^{2+}]^2}{K_{\text{pump}}^2 + [Ca^{2+}]^2} \le \frac{[Ca^{2+}]^2}{K_{\text{pump}}^2} \le \frac{[Ca^{2+}]}{K_{\text{pump}}} \tag{a}$$

In view of above Eq. (12) is taken as:

$$\frac{1}{r}\frac{d}{dr}\left(r\frac{d[Ca^{2+}]}{dr}\right) - \frac{k^+[B]_\infty}{D_{Ca}}([Ca^{2+}] - [Ca^{2+}]_\infty) + \frac{V_{\text{leak}}}{D_{Ca}}([Ca^{2+}]_{SR} - [Ca^{2+}]) - \frac{V_{\text{pump}}}{D_{Ca}} \cdot \frac{[Ca^{2+}]}{K_{\text{pump}}} = 0 \tag{16}$$

Now the finite element method is employed to solve Eq. (16) with boundary conditions (14) and (15). The discretized variational form of Eq. (16) is given by

$$I^{(e)} = \frac{1}{2}\int_{r_i}^{r_j}[J_1^{(e)} + J_2^{(e)} - J_3^{(e)} + J_4^{(e)} + J_5^{(e)}]dr - \left[\frac{\sigma_{Ca}}{2\pi D_{Ca}}u^{(e)}\right]_{r_i}^{r_j} \tag{17}$$

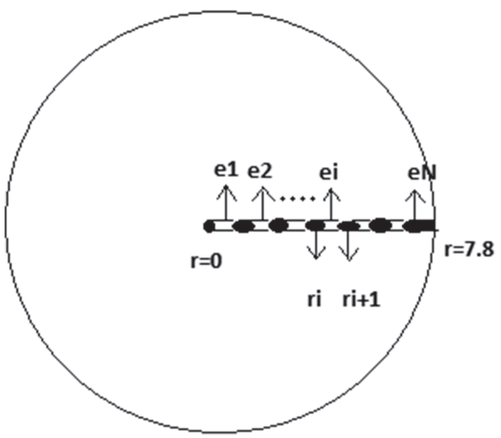

Fig. 1. One dimensional discretization.

where

$$J_1^{(e)} = r\left(\frac{du^{(e)}}{dr}\right)^2$$

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

$$J_3^{(e)} = \frac{2k^+[B]_\infty}{D_{Ca}} u_\infty u^{(e)} r$$

$$J_4^{(e)} = -\frac{V_{leak}}{D_{Ca}} r\left(u^{(e)} u_{SR} - \frac{u^{(e)2}}{2}\right)$$

$$J_5^{(e)} = -\frac{V_{pump} r}{D_{Ca} K_{pump}} \cdot \frac{u^{(e)2}}{2}$$

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

Case II: When $K_{\text{pump}} << [Ca^{2+}]$ then we assume $K_{\text{pump}} = \alpha[Ca^{2+}]$ for $0 \le \alpha \le 1$,[2]

$$\frac{[Ca^{2+}]^2}{K_{\text{pump}}^2 + [Ca^{2+}]^2} = \frac{1}{\alpha^2 + 1} \tag{b}$$

In view of above Eq. (12) is taken as:

$$\frac{1}{r}\frac{d}{dr}\left(r\frac{d[Ca^{2+}]}{dr}\right) - \frac{k^+[B]_\infty}{D_{Ca}}([Ca^{2+}] - [Ca^{2+}]_\infty) + \frac{V_{\text{leak}}}{D_{Ca}}([Ca^{2+}]_{SR} - [Ca^{2+}]) - \frac{V_{\text{pump}}}{D_{Ca}}\frac{1}{\alpha^2+1} = 0 \tag{18}$$

Now the finite element method is employed to solve Eq. (18) with boundary conditions (14) and (15). The discretized variational form of Eq. (26) is given by

$$I^{(e)} = \frac{1}{2}\int_{r_i}^{r_j} [J_1^{(e)} + J_2^{(e)} - J_3^{(e)} + J_4^{(e)} + J_5^{(e)}]dr - \left[\frac{\sigma_{Ca}}{2\pi D_{Ca}} u^{(e)}\right]_{r_i}^{r_j} \tag{19}$$

where

$$J_1^{(e)} = r\left(\frac{du^{(e)}}{dr}\right)^2$$

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

$$J_3^{(e)} = \frac{2k^+[B]_\infty}{D_{Ca}} u_\infty u^{(e)} r$$

$$J_4^{(e)} = -\frac{V_{\text{leak}}}{D_{Ca}} r\left(u^{(e)} u_{SR} - \frac{u^{(e)2}}{2}\right)$$

$$J_5^{(e)} = \frac{V_{\text{pump}} r}{D_{Ca} K_{\text{pump}}} \frac{2}{1+\alpha^2} \frac{u^{(e)2}}{2}$$

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

$$u^{(e)} = C_1 + C_2 r \tag{20}$$

In matrix form the Eq. (20) can be written as

$$u^{(e)} = P^T C^{(e)} \tag{21}$$

where

$$P^T = [\,1 \quad r\,] \quad \text{and} \quad C^{(e)} = \begin{bmatrix} C_1 \\ C_2 \end{bmatrix}$$

Also

$$u^{(e)}(r_i) = u_i = C_1 + C_2 r_i \tag{22}$$

$$u^{(e)}(r_j) = u_j = C_1 + C_2 r_j \tag{23}$$

Using Eqs. (21)–(23) we get

$$\bar{u}^{(e)} = P^{(e)} C^{(e)} \tag{24}$$

Where

$$P^{(e)} = \begin{bmatrix} 1 & r_i \\ 1 & r_j \end{bmatrix} \quad \text{and} \quad \bar{u}^{(e)} = \begin{bmatrix} u_i \\ u_j \end{bmatrix}$$

From Eqs. (21) and (24) we get

$$u^{(e)} = P^T R^{(e)} \bar{u}^{(e)} \tag{25}$$

Where

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

and r_i and r_j are the boundaries of eth element. Now the integral given in Eq. (17) for case I and Eq. (19) for case II can also be written as,

$$I^{(e)} = \frac{1}{2}\int_{r_i}^{r_j} r[I_1^{(e)} + I_2^{(e)} + I_3^{(e)}]dr - \frac{1}{2}\int_{r_i}^{r_j} r[I_4^{(e)} + I_5^{(e)}]dr - \left[\frac{\sigma_{Ca}}{2\pi D_{Ca}} \bar{u}^{(e)}\right]_{e=1} \tag{26}$$

where

$$I_1^{(e)} = (P_r^T R^{(e)} \bar{u}^{(e)})^2$$

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

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

$$I_4^{(e)} = \frac{V_{leak}}{D_{Ca}} (2u_{SR}((P^T R^{(e)} \bar{u}^{(e)}) - (P^T R^{(e)} \bar{u}^{(e)})^2)$$

$$I_5^{(e)} = \frac{-V_{\text{pump}}}{D_{Ca} K_{\text{pump}}} (P^T R^{(e)} \bar{u}^{(e)})^2$$

and

$$I^{(e)} = \frac{1}{2}\int_{r_i}^{r_j} r[I_1^{(e)} + I_2^{(e)} + I_3^{(e)}]dr - \frac{1}{2}\int_{r_i}^{r_j} r[I_4^{(e)} + I_5^{(e)}]dr - \left[\frac{\sigma_{Ca}}{2\pi D_{Ca}} \bar{u}^{(e)}\right]_{e=1} \tag{27}$$

where

$$I_1^{(e)} = (P_r^T R^{(e)} \bar{u}^{(e)})^2$$

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

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

$$I_4^{(e)} = \frac{V_{leak}}{D_{Ca}} (2u_{SR}((P^T R^{(e)} \bar{u}^{(e)}) - (P^T R^{(e)} \bar{u}^{(e)})^2)$$

$$I_5^{(e)} = \frac{2V_{pump}}{D_{Ca} K_{pump}} \cdot \frac{1}{\alpha^2 + 1} (P^T R^{(e)} \bar{u}^{(e)})$$

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

$$\frac{dI^{(e)}}{d\bar{u}^{(e)}} = 0$$

Where

$$\bar{u}^{(e)} = [\, u_i \quad u_j \,]^T, \quad e = (1, 2, \ldots, N)$$

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

$$\bar{M}^{(e)} = \begin{bmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 1 \\ \bullet & \bullet \\ 0 & 0 \end{bmatrix}_{(16\times 2)} \quad \begin{array}{l} (i\text{throw}) \ ((i+1)\text{throw} \\ \text{and } I = \sum_{e=1}^{15} I^{(e)}) \end{array}$$

This leads to following system of linear algebraic equations

$$[K]_{(N+1\times N+1)}[\bar{u}]_{(N+1\times 1)} = [F]_{(N+1\times 1)} \tag{28}$$

Here, $\bar{u} = [\, u_1 \quad u_2 \quad \bullet \quad \bullet \quad \bullet \quad u_{N+1} \quad]^T$, K is characteristic matrix and F is characteristic vector. Gaussian Elimination method is employed to solve the system (28). 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.

3. NUMERICAL RESULTS AND DISCUSSION

The biophysical parameters used in computation of numerical results are given in Table I.

Table I. Numerical values of biophysical parameters.[8]

R	Radius of the cell	7.8 μm
I_{Ca}	Amplitude of elemental Ca^{2+} release	1 pA
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 $C = k_1^-/k_1^+$	0.51 μM
$[Ca]_\infty$	Intracellular free Ca^{2+} concentration at rest	0.1 μM
V_{pump}	Serca pump rate	400 μMS^{-1}
V_{leak}	Leak rate	0.02 μMS^{-1}
K_{pump}	Dissociation rate of Serca pump	0.2 μM

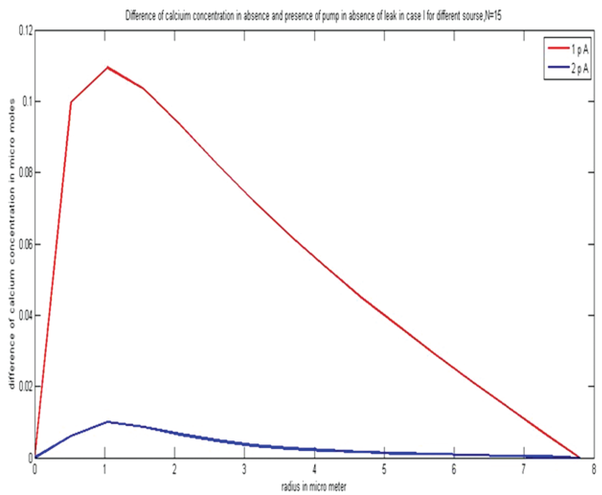

Fig. 2. Difference of calcium concentration in absence and presence of pump for case I for different values of source influx.

In Figure 2 the difference in calcium concentration in absence and presence of pump increases along radius r, from 0 to 1 μm and then gradually decreases along r between 1 and 3 μm and thereafter converges to zero rapidly. The difference in calcium concentration in absence and presence of pump is maximum at $r = 1$ μm in myocytes. The maximum difference in the calcium concentration in absence and presence of pump is higher for source influx of 1 p A as compared to that for 2 p A. This indicates that pump has more significant effect on calcium signaling in myocytes at lower values of source influx. This is because higher values of source influx are able to balance the effect of out flux from pump.

In Figure 3 the difference in calcium concentration in absence and presence of pump for $\sigma = 1$ p A and $\sigma = 2$ p A increases along radius r, from 0 to 2.6 μm and then gradually decreases along r between 2.6 μm and 5.2 μm and thereafter converges to zero. The difference in calcium concentration in absence and presence of pump is maximum i.e., 1 μM for $\sigma = 1$ p A and 0.3 μM for $\sigma = 2$ p A at $r = 2.6$ μm in myocytes. The maximum

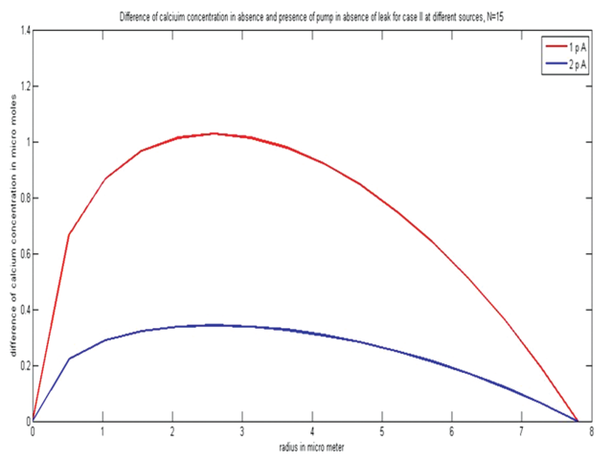

Fig. 3. Difference of calcium concentration in absence and presence of pump for case II for different values of source influx.

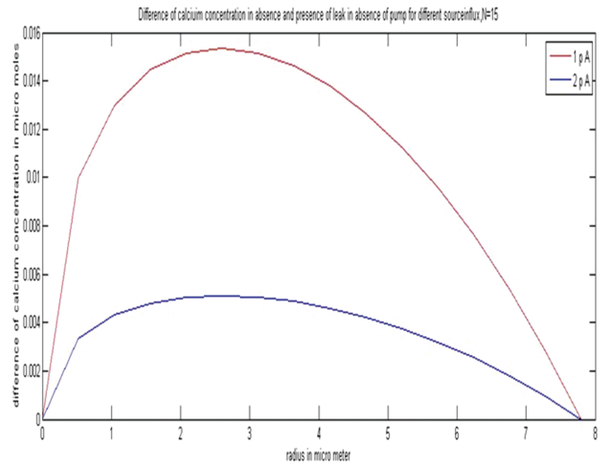

Fig. 4. Difference of calcium concentration in absence and presence of leak for case I for different values of source influx.

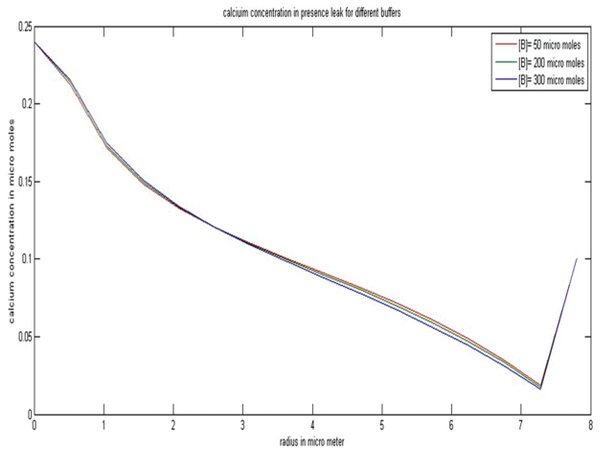

Fig. 6. Calcium concentration in presence of leak without pump for different buffer concentration.

difference for $\sigma = 2$ p A is less as compared to $\sigma = 1$ p A. This is because the calcium flushed out by the pump is made up by influx in case of higher rates of influx. Here the effect of pump out flux on calcium signaling in myocytes is quite significant for case II as compared to that in Case I. This is because the out flux is lower in case I as compared to that in case II.

In Figure 4 the difference in calcium concentration in the cell without pump in absence and presence of leak increases along radius r, from 0 to 2.6 μm and then rapidly converges to zero for both $\sigma = 1$ p A and $\sigma = 2$ p A. The maximum difference in calcium concentration in absence and presence of leak are 0.015 μM for $\sigma = 1$ p A and 0.005 μM for $\sigma = 2$ p A. The difference in calcium concentration in absence and presence of leak is higher at lower source influx. But when the source influx is higher, it dominates over the influx calcium due to leak. This implies that leak plays an important role in raising the calcium concentration in the cell when the source influx is low or zero.

Figure 5 shows the calcium distribution in myocytes without leak and pump for different values of buffer. It is observed from the result that gap between the curves increases between $r = 2.08$ μm to $r = 6.76$ μm which indicates that buffer concentration have significant effect in lowering calcium concentration in the cell.

Figure 6 shows calcium distribution in myocytes without pump, in presence of leak and different values of buffer concentration. The gap between the curves here are less than as those in Figure 5. This implies that the calcium influx due to leak raises the $[Ca^{2+}]$ to balance the effect of buffer concentration and vice versa.

Figure 7 shows the calcium distribution in presence of pump and in absence of leak for case I and different values of buffer concentration. The fall in $[Ca^{2+}]$ in cell is more for higher values buffer. The gap between the curves indicates that the effect of buffer concentration on has significant effect on calcium distribution in myocytes is very small in presence of pump.

Figure 8 shows the calcium distribution in presence of pump for case II and different values of buffer. The fall in $[Ca^{2+}]$ in the cell is more for higher values of buffer. The gap between

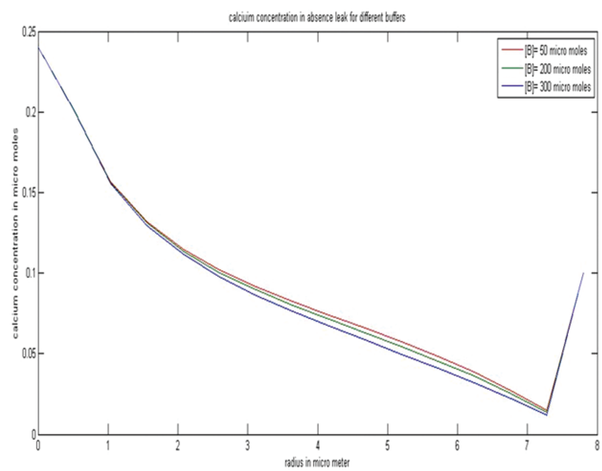

Fig. 5. Calcium concentration in absence of leak and pump for different buffer concentration.

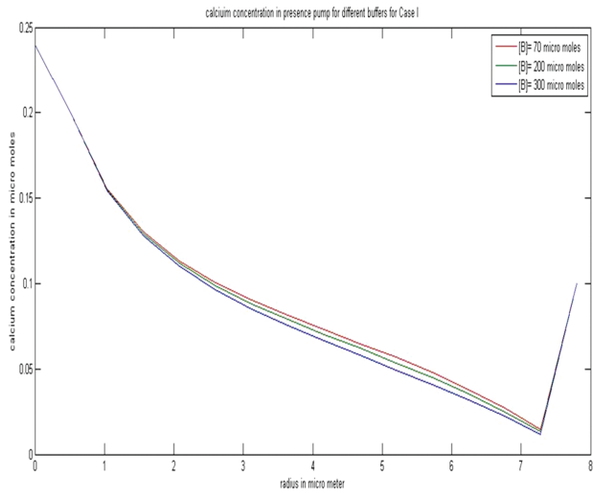

Fig. 7. Calcium concentration in presence of pump without leak in case I for different buffer concentration.

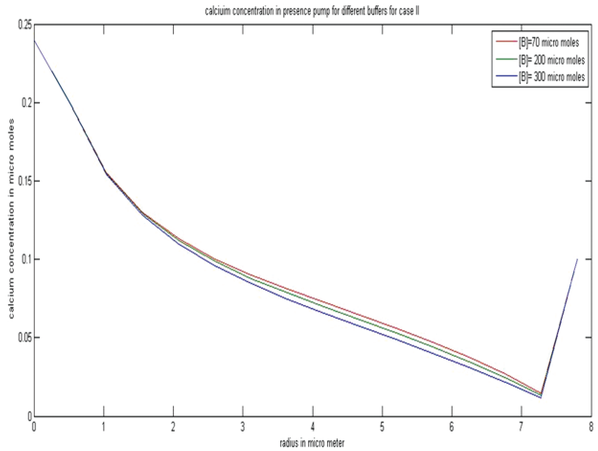

Fig. 8. Calcium concentration in presence of pump without leak in case II for different buffers.

the curves indicates the buffer has a very small effect on Ca^{2+} distribution in myocytes in presence of pump. The gaps between the curves here are more as compared to case I in Figure 7. This implies that the effect of buffer for case II as compared to that for case I is more significant. This is due to the fact that the rate constant of the pump is higher in case II leading to fall in $[Ca^{2+}]$. The combined effect of pump and buffers is quite significant in lowering down $[Ca^{2+}]$ in the cell. Further the out flux due to pump dominates over the effect of buffers on calcium signaling in myocytes.

4. CONCLUSION

A finite element model of calcium signaling in myocytes involving leak, pump and excess buffer have been proposed for a one dimensional steady state case. The model gives us interesting relationship of calcium concentration in myocytes with the parameters like source influx, buffers, leak and pump. The results indicate that the pump and buffer have significant role in lowering the $[Ca^{2+}]$ in myocytes cell while leak play an important role in raising the $[Ca^{2+}]$ levels in myocytes cell. 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, leak, buffer and pump 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.

Acknowledgment: The authors are grateful to DST New Delhi for providing bioinformatics infrastructure facility at SVNIT, Surat to carry out this work.

References and Notes

1. P. H. Backx, P. P. De Tonb, H. K. Jurjen, V. Deen, J. M. Barbara, Mulder, and D. J. Henke, A Model of Propagating Calcium-induced Calcium Release Mediated by Calcium diffusion. *The Journal of General Physiology* 93, 963 **(1989)**.
2. N. Bhargava and K. R. Pardasani, Galerkin approximation for the problem of calcium diffusion in neuron cell involving pump, leak and excess buffering approximation. *Applied Mathematical Science* 5, 2707 **(2011)**.
3. A. Jha and N. Adlakha, Finite Element Model to study the effect of excess buffers on calcium dynamics in dendritic spines. *International Journal of Modeling, Simulation and Scientific Computing* 5 **(2013)**.
4. B. K. Jha, N. Adlakha, and M. N. Mehta, Two dimensional finite element model to study calcium distribution in Astrocytes in presence of excess buffers. *International Journal of Biomathematics* 7 **(2014)**.
5. Luo and Rudy, A dynamic model of the cardiac ventricular action potential. I simulations of ionic currents and concentration changes. *Circular Research* 74, 1071 **(1994)**.
6. Luo and Rudy, A dynamic model of the cardiac ventricular action potential. II After depolarization, triggered activity, and potentiation. *Circular Research* 74, 1097 **(1994)**.
7. N. Manhas, J. Sneyd, and K. R. Pardasani, Modelling the transition from simple to complex calcium oscillation in acinar cell. *Journal of Bioscience* 1 **(2014)**.
8. A. Michailova, F. Del, M. Egger, and E. Niggli, Spatiotemporal features of Ca^{2+} buffering and diffusion in atrail cardiac myocytes with inhibited sarcoplasmic reticulum. *Biophys. J.* 83, 3134 **(2002)**.
9. S. Panday and K. R. Pardasani, Finite element model to study the mechanics of calcium regulations in Oocyte. *Journal of Mechanics in Medicine and Biology* 14 **(2014)**.
10. J. Post and G. Langer, Sarcolemma Ca^{2+} binding sites in Heart: I. Molecular origin in gas dissected. *J. Membr. Biol.* 129 **(1992)**.
11. T. R. Shannon, F. Wang, J. Puglisi, C. Weber, and D. M. Bers, A mathematical treatment of integrated ca dynamics within the ventricular myocytes. *Biophys. J.* 87, 3351 **(2004)**.
12. G. D. Smith, J. E. Keizer, M. D. Stern, W. J. Lederer and H. Cheng, A simple numerical model of calcium spark formation and detection in cardiac myocytes. *Biophys. J.* 75, 15 **(1998)**.
13. A. Tripathi and N. Adalkha, Finite volume model to study calcium diffusion in neuron involving JRYR, JSERCA and JLEAK. *Journal of computing* 13, ISS 2151 **(2011)**.

Received: 6 June 2014. Revised/Accepted: 22 August 2014.