A one-dimensional finite element model to study the effect of advection on calcium dynamic in Cardiac Myocyte Cell

Payal Desai [A1], Kunal Pathak [B]

ABSTRACT - Cardiac myocytes cells are the cell which are responsible for the expansion and contraction of heart. Specific calcium dynamics requires for these expansion and contraction mechanism. which is still not understood clearly. Hence, a one-dimensional finite element model is proposed in this paper to examine the effect of advection on calcium dynamics. In this model, different processes such as buffering, the reaction of calcium ions with excess buffers, diffusion of calcium ions, advection and source influx are considered to study individual and coordinated effects of advection on calcium dynamics. Significant initial and boundary conditions based on the biophysical properties of the region have been proposed. A program in MATLAB has been developed for the whole problem and simulated to figure out the numerical results. The individual and coordinated effects of source influx, advection, buffering, diffusion on calcium ions in cardiac myocytes cells are studied and presented here.

Key Words: Reaction diffusion equation, finite element method, Advection, cardiac myocytes, source influx, excess buffers.

I. INTRODUCTION

Heart is the main organ which is responsible for circulating the blood to different parts of the body. The smooth blood circulation is very much necessary for balancing the structure and functions of the different body parts. Calcium dynamics plays a critical part in contraction expansion of Heart, which leads to proper circulation of blood in the body.

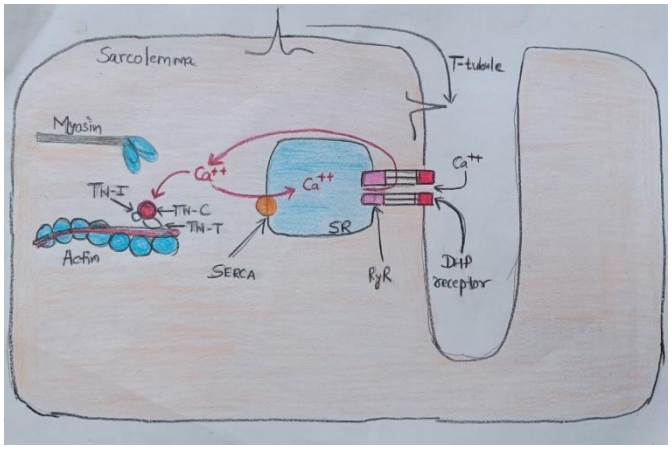

Figure 1: Mechanism of contraction process in the Cardiac myocyte cell

The contraction of the cardiac myocytes takes place when the intracellular binding proteins (Troponin C) that are present in the cell gets bind with the calcium ion as shown in Figure 1. The expansion of the cardiac myocytes takes place when the bonded protein gets separated with the calcium ion. Smith G.D et al1. The regulation of calcium gets maintained by different processes like source influx, diffusion, excess buffer, advection etc. There are two possibilities for the advection of the calcium ions inside the cells, may be one of them is due to the mechanical contraction which happens on the surface of the cell or another one is due to the appropriate transportation of the material through cytosolic fluid. In the cytoplasm of the cell, a cross flow of the calcium takes place due to the advection process. Panday S. et al2, Jha B. K. et al3. The specific mechanism that takes place in the regulation of calcium dynamics is not yet understood clearly. Although there are many attempts carried out to examine the amount of calcium distribution in the different cells like neuron cells, fibroblast cells, astrocyte cells, acinar cells, Oocyte cells etc. are reported in the literature survey, Jha A et al4, Jha B. K. et al5,6, Kotwani M. et al7,8, Manhasn N. et al9,10,11, Naik P. et al12,13, Pandey S. et al14, Tewari S. et al15,16. However, in order to study and examine the regulation of calcium ions in the myocyte cells, very less attempts are mentioned and reported in the literature survey, Backx P H. et al17, Luo C H. et al18, Michailova A. et al19. Amongst the very few reported studies on the regulation of calcium ions in the myocyte cells, most of them are experimental studies. Michailova A. et al19, Shannon T R. et al20. Researchers have carried out some attempts of research works in order to study and understand the effect of advection and diffusion in Oocytes and astrocytes, Jha B. K. et al21, Pandey S. et al2. While none or very less attempts are mentioned and reported in literature to study the effect of advection on calcium regulation in the myocyte cells. No or very few attempts have been studied or reported in the past to examine and study the regulation of calcium dynamics in the individual or coordinated effect of advection, buffer, diffusion and source influx. So, in this paper, to study the coordinated and individual effect of source influx, buffer, advection, diffusion on calcium dynamics in cardiac myocyte cells a model is proposed for a one-dimensional unsteady state case. Numerical simulation has been carried out using the finite element approach.

II. MATHEMATICAL BACKGROUND

The reaction equation of calcium containing buffer is considered as

$$Ca^{2+} + B_i \underset{k^-}{\overset{k^+}{\rightleftarrows}} Ca\,B_i \qquad (1)$$

Where CaB_i and B_i are bound and free buffers respectively, 'i' is an index over the species of buffer. Smith G.D et al1, Pandey S. et al2. k_i^- and k_i^+ are dissociation and association rate constants respectively for 'i'. The advection diffusion equation considering mass action kinetic law and Flicks' law of calcium concentration for reaction given by equation (1) in the polar cylindrical coordinates for one

First A1. Author is with the Institute of Technology, Nirma University, Ahmedabad, India. (e-mail: 21ftphde58@nirmauni.ac.in).
Second B. Author is with the Institute of Technology, Nirma University, Ahmedabad, India. (e-mail: kunal.pathak@nirmauni.ac.in).

dimensional unsteady state in presence of excess buffer can be stated as Smith G.D et al1, Pandey S. et al2.

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

where -

$$[B_i]_{\infty}=\frac{K_i[B_i]_T}{K_i+[Ca^{2+}]_{\infty}} \quad (3)$$

and

$$[CaB_i]_{\infty}=\frac{[Ca^{2+}]_{\infty}[B_i]_T}{K_i+[Ca^{2+}]_{\infty}} \quad (4)$$

where $[Ca^{2+}]_{\infty}$ is the free background Ca^{2+} concentration. $[B_i]_{\infty}$ and $[CaB_i]_{\infty}$ are used for denoting the equilibrium concentrations of free and bound buffer to cause around 50% of buffer in calcium bound form with respect to index 'i'. $[B_i]_T$ is the total buffer concentration in the cell. Jha A et al4. K_i is the dissociation constant. V denotes the velocity of cytosolic calcium ion due to advection. Smith G.D et al1. D_{Ca} is the coefficient of diffusion. $[Ca^{2+}]$ represents the calcium concentration. Due to L-type calcium gated channel, the value at point source is assumed to be $r=0.01\mu m$ at the first node. Hence, the suitable boundary condition can be taken as Shannon T R. et al20

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

Here an influx of free Ca^{2+} is taken at the rate σ_{Ca} by Faraday's law Jha A et al21, Luo C H. et al22, $\sigma_{Ca}=\frac{I_{Ca}}{zF}$, where I_{Ca}, z and F are amplitude of Ca^{2+}release, valence of calcium ion and Faraday's constant respectively. Considering the background concentration of Ca^{2+}as $0.1\mu M$ on the boundary of the cell $r=7.8\mu m$ Luo C H. et al18, Jha A et al21.

$$\lim_{r\to 7.8}[Ca^{2+}]=[Ca^{2+}]_{\infty}=0.1\ \mu M \quad (6)$$

Now applying the method of finite element approach to solve the equation (2) with the given boundary conditions equations (5) and (6). Initially the calcium concentration is considered as 0.1μM at t = 0 second.

Consider the discretization of finite element in one-dimension which is given below by the figure 1,

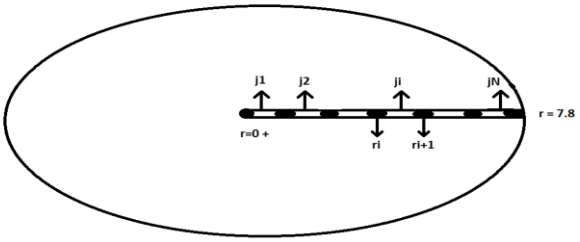

Figure 2: Discretization of finite elements in one dimension

Here j_i is the i^{th} element and r_i and r_{i+1} denotes the initial and final nodes of i^{th} element.

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

$$I^{(j)}=\frac{1}{2}\int_{r_i}^{r_{i+1}}\left[J_1^{(j)}-J_2^{(j)}+J_3^{(j)}-J_4^{(j)}\right]dr-\left[\frac{\sigma_{Ca}}{2\pi D_{Ca}}y^{(j)}\right]_{r_i}^{r_{i+1}} \quad (7)$$

where

$$J_1^{(j)}=r\left(\frac{\partial y^{(j)}}{\partial r}\right)^2-\frac{V}{D_{Ca}}\left[2ry^{(j)}\left(\frac{\partial y^{(j)}}{\partial r}\right)\right]+\frac{V}{D_{Ca}}\left(y^{(j)}\right)^2$$

$$J_2^{(j)}=\frac{k^{+}[B]_{\infty}}{D_{Ca}}\,r\left(y^{(j)}\right)^2$$

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

$$J_4^{(j)}=r\left(\frac{\partial y^{(j)}}{\partial t}\right)^2$$

Here 'y' is used in place of $[Ca^{2+}]$ for the convenience in the calculation, $j=1,2,3,\dots,N$ (number of elements).

Since each and every element is of very small thickness, $y^{(j)}$ is assigned linear variation with respect to the position which is given by the following equation:

$$y^{(j)}={c_1}^{(j)}+{c_2}^{(j)}r \quad (8)$$

Rewriting equation (8) in the matrix form, we have

$$y^{(j)}=P^{T}c^{(j)} \quad (9)$$

where

$$P^{T}=[1\quad r] \text{ and } c^{(j)}=\begin{bmatrix}{c_1}^{(j)}\\{c_2}^{(j)}\end{bmatrix}$$

At the nodal points r_i and r_{i+1} of the j^{th} element,

$$y^{(j)}(r_i)=y_i={c_1}^{(j)}+{c_2}^{(j)}r_i \quad (10)$$

$$y^{(j)}(r_{i+1})=y_{i+1}={c_1}^{(j)}+{c_2}^{(j)}r_{i+1} \quad (11)$$

From equations (9), (10) and (11) we have

$$\bar{y}^{(j)}=P^{(j)}c^{(j)} \quad (12)$$

where

$$P^{(j)}=\begin{bmatrix}1 & r_i\\1 & r_{i+1}\end{bmatrix} \text{ and } \bar{y}^{(j)}=\begin{bmatrix}{y_i}^{(j)}\\{y_{i+1}}^{(j)}\end{bmatrix}$$

From equations (8) and (12) we have

$$y^{(j)}=P^{T}R^{(j)}\bar{y}^{(j)} \quad (13)$$

where

$$R^{(j)}=\left(P^{(j)}\right)^{-1}=\frac{1}{r_{i+1}-r_i}\begin{bmatrix}r_{i+1} & r_i\\1 & 1\end{bmatrix}.$$

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

$$I^{(j)}=\frac{1}{2}\int_{r_i}^{r_{i+1}}\left[I_1^{(j)}-I_2^{(j)}+I_3^{(j)}-I_4^{(j)}\right]dr-\left[\frac{\sigma_{Ca}}{2\pi D_{Ca}}\bar{y}^{(j)}\right] \quad (14)$$

where

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

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

$$I_3^{(j)} = \frac{2k^+[B]_\infty}{D_{Ca}}\, r\, y_\infty\left(P^T R^{(j)} \bar{y}^{(j)}\right),$$

$$I_4^{(j)} = r\frac{\partial}{\partial t}\left(P^T R^{(j)} \bar{y}^{(j)}\right)^2.$$

Now, minimising $I^{(j)}$ with respect to $\bar{y}^{(j)}$, that is

$$\frac{dI^{(j)}}{d\bar{y}^{(j)}} = 0 \qquad (15)$$

where

$$\bar{y}^{(j)} = [y_i \quad y_{i+1}]^T, \text{ for } j = 1,2,3,\dots,N$$

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

where

$$\bar{M}^{(j)} = \begin{bmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 1 \\ \cdot & \cdot \\ \cdot & \cdot \\ 0 & 0 \end{bmatrix}_{((N+1)+2)}$$

Hence the above system of equations can be converted in the following system of linear equations:

$$[K]_{((N+1)\times(N+1))}\left[\frac{\partial \bar{y}}{\partial t}\right]_{((N+1)\times 1)} + [L]_{((N+1)\times(N+1))}[\bar{y}]_{((N+1)\times 1)} = [F]_{((N+1)\times 1)} \qquad (16)$$

where $\bar{y} = [y_1 \quad y_2 \quad . \quad . \quad . \quad y_{N+1}]^T$, K and L are the characteristic matrices and F is the characteristic vector. In order to solve and simplify the system of equations (16), method of Gauss elimination is carried out. For the solution and simulation of the entire problem, a MATLAB program in computer has been developed in the MATLAB R2021b on core i3 processor with 1.20GHz processing speed with 64-bit machine and 237 GB memory.

III. NUMERICAL RESULTS

For the numerical simulation, the values which are used for the biophysical parameters are mentioned as follows: Michailova A. et al19.

Z represents the Valence of Ca^{2+}ion, its value 2. F is Faraday's constant, its value is 96500 C/mol. I_{Ca} is used for Amplitude of elemental Ca^{2+}release, which is 1pA. D_{Ca} is used for Diffusion coefficient of free Ca^{2+}in cytosol for Troponin C, its value is 780 $\frac{\mu m^2}{s}$. R is the Radius of the cell, whose value is 7.8μm. k^+ and k^- are Association and Dissociation rate constant for Ca^{2+}binding of Troponin C whose values are 39 $\mu M^{-1}S^{-1}$ and 20 S^{-1} respectively. K is Dissociation constant of Troponin C = k_i^-/k_i^+, its value is 0.51 μM. $[Ca]_\infty$ is the intracellular free Ca^{2+}concentration at rest, which is 0.1 μM. $[B_1]_T$ is Total concentration for each Ca^{2+}buffer of Troponin C, which is 70 μM.

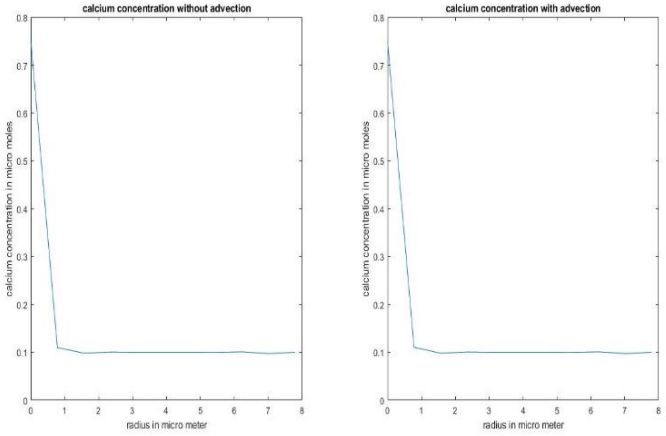

Figure 3: Calcium concentration without and with advection at time t=0.01 sec.

In Figure 3, the results are computed by considering 10 elements in finite element method. It has been observed that the concentration of calcium with advection increases than that of without advection at individual nodes. Initially, at $r = 0.01\mu m$, the calcium concentration is $0.74867\mu M$ and $0.74866\mu M$ in the absence and presence of advection respectively. When we move little away from the source, a sharp fall is observed in the concentration. At $r = 0.78\mu m$, the concentration is $0.1097\mu M$and $0.1104\mu M$ and little away from the source, the calcium concentration is $0.09990\mu M$ and $0.09994\mu M$ in the absence and presence of advection respectively at $r = 3.12\mu m$. When we further move away from the source the background concentration $0.1\mu M$ is achieved at $r = 7.566\mu m$. Hence it is observed due to advection the calcium concentration increases.

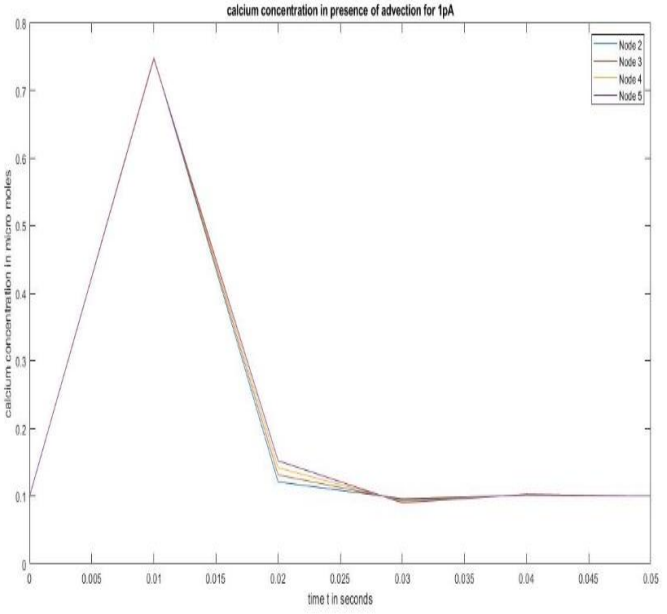

Figure – 4(a): Calcium concentration with advection at different time for source influx 1pA at different nodes.

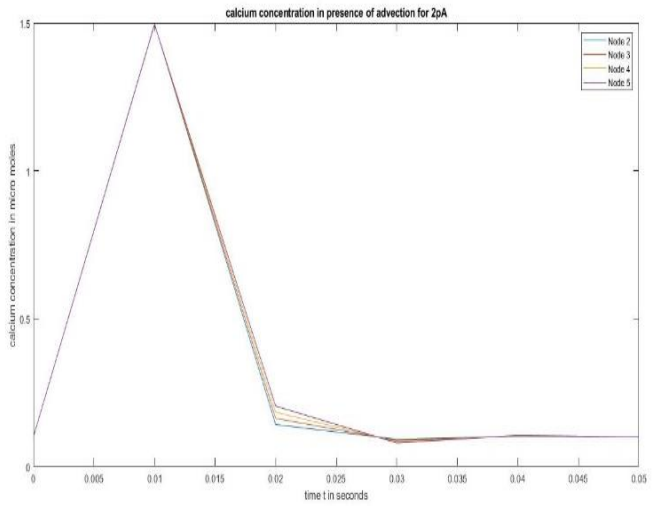

Figure – 4(b): Calcium concentration with advection at different time for source influx 2pA at different nodes.

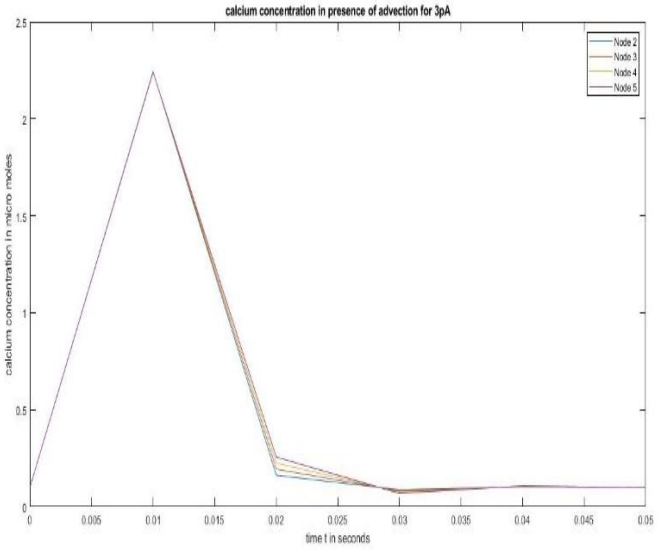

Figure – 4(c): Calcium concentration with advection at different time for source influx 3pA at different nodes.

In figures 4(a), 4(b) and 4(c), the calcium concentration by considering different time and source influx 1pA, 2pA and 3pA are shown in the presence of advection. Initially at time t=0 seconds, 0.1 μM calcium concentration is observed due to the initial boundary condition, then at time 0.01 seconds the concentration obtains the peak value 0.7487 μM due to source influx. Then the sharp fall is observed in the concentrations at time 0.02 seconds at the nodes 2,3,4 and 5 which are $0.1104\mu M$, $0.098\mu M$, $0.1005\mu M$ and $0.0999\mu M$ respectively for source influx 1pA. The concentrations observed at time 0.02 seconds at the nodes 2,3,4 and 5 are $0.1208\mu M$, $0.0959\mu M$, $0.101\mu M$ and $0.0998\mu M$ respectively for source influx 2pA. And for source influx 3pA, the concentrations observed at time 0.02 seconds at the nodes 2,3,4 and 5 are $0.1312\mu M$, $0.0938\mu M$, $0.1015\mu M$ and $0.0997\mu M$ respectively. Similarly, the concentrations observed at time 0.03 seconds are $0.1209\mu M$, $0.0961\mu M$, $0.1011\mu M$ and $0.0999\mu M$ for source influx 1pA, the concentrations observed for source influx 2pA are $0.1417\mu M$, $0.0919\mu M$, $0.102\mu M$ and $0.0997\mu M$ and the concentrations observed for source influx 3pA are $0.1624\mu M$, $0.0877\mu M$, $0.1029\mu M$ and $0.0995\mu M$. It has been observed that the concentration of calcium increases in ratio with source influxes. As time increases from 0 to 0.05 seconds, oscillations are seen in the calcium concentrations near to the source. It is further observed that as we further move away from the source from node 2 to node 4 these oscillations also increase in ratio with source influxes. If we move further away from the source these oscillations vanish as background concentration 0.01 μM achieved.

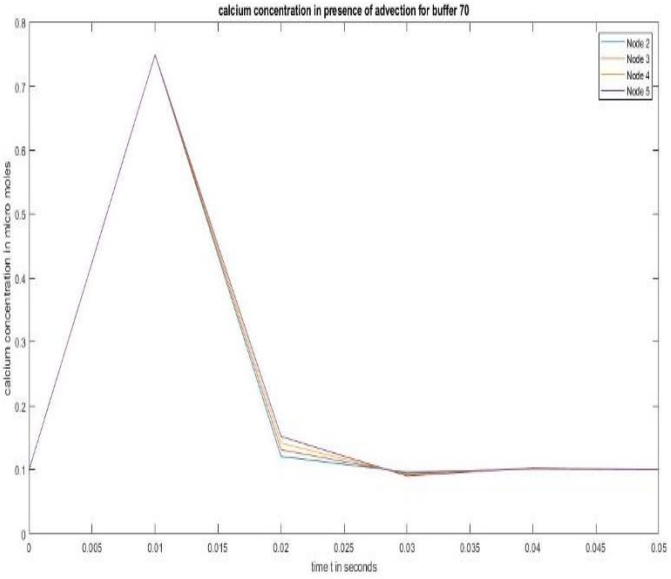

Figure – 5(a): Calcium concentration with advection at different time for excess buffer 70 μM

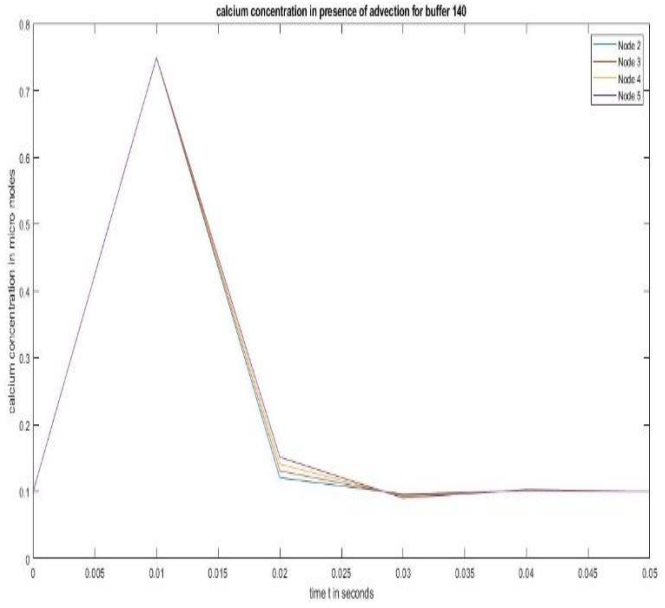

Figure – 5(b) : Calcium concentration with advection at different time for excess buffer 140 μM

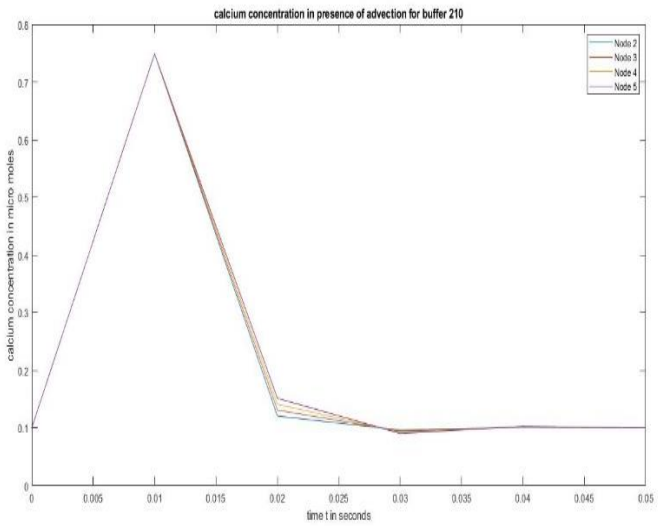

Figure – 5(c) : Calcium concentration with advection at different time for excess buffer 210 μM

In figures 5(a), 5(b) and 5(c), the calcium concentration by considering different time and buffer concentrations $70\mu M$, $140\mu M$ and $210\mu M$ are shown in the presence of advection. Initially at time t=0 seconds, 0.1 μM calcium concentration is observed due to the initial boundary condition, then at time 0.01 seconds the concentration obtains the peak value 0.7487 μM. Then the sharp fall is observed in the concentrations at time 0.02 seconds at the nodes 2,3,4 and 5 which are $0.1104\mu M$, $0.098\mu M$, $0.1005\mu M$ and $0.0999\mu M$ respectively for buffer concentration $70\mu M$. The concentrations observed at time 0.02 seconds at the nodes 2,3,4 and 5 are $0.1104\mu M$, $0.098\mu M$, $0.1005\mu M$ and $0.0999\mu M$ respectively for buffer concentration $70\mu M$. The concentrations observed at time 0.02 seconds at the nodes 2,3,4 and 5 are $0.1104\mu M$, 0.098 μM, $0.1005\mu M$ and $0.0999\mu M$ respectively for buffer concentration $140\mu M$. And for buffer concentration $210\mu M$, the concentrations observed at time 0.02 seconds at the nodes 2,3,4 and 5 are $0.1103\mu M$, $0.098\mu M$, $0.1005\mu M$ and $0.0999\mu M$ respectively. Similarly, the concentrations observed at time 0.03 seconds are $0.1209\mu M$, $0.0961\mu M$, $0.1011\mu M$ and $0.0999\mu M$ for buffer concentration $70\mu M$, the concentrations observed are $0.1207\mu M$, $0.0961\mu M$, $0.101\mu M$ and $0.0999\mu M$ for buffer concentration $140\mu M$ and the concentrations observed are $0.1205\mu M$, $0.0961\mu M$, $0.101\mu M$ and $0.0999\mu M$ for buffer concentration $210\mu M$. It has been observed that the concentration of calcium decreases in small ratio with buffer concentrations. As time increases from 0 to 0.05 seconds, oscillations are seen in the calcium concentration. It is further observed that as we move little away from the source from node 2 to node 4 these oscillations also decrease in ratio with buffer concentrations. If we move further away from the source these oscillations vanish as background concentration $0.01\mu M$ achieved.

IV. CONCLUSION

The individual and coordinated effects of advection, source influx, buffering and diffusion on calcium ions in cardiac myocytes cells are studied using finite element model in calcium dynamics. From the study and results it is observed that, at the source the highest concentration of calcium is observed in absence and presence of advection. Then as we move away from the source the concentrations falls sharply in absence and presence of advection. This sharp fall is observed due to buffering process. If we move far away from the source the background concentration is achieved. It has been also observed due to advection the concentration of calcium increases. Further the oscillations are also observed in presence of advection as time increases. These oscillations are observed more near the source and when we move away from the source the oscillations decrease. These oscillations increase in ration of source influx as more free calcium ions are available. It is also observed that the oscillations decreases in the ration of buffer concentrations as less free calcium ions are available. From the study it is concluded that advection play a critical role for the higher values of source influx and play limited role for the higher values of buffer concentration for reducing calcium concentration.

V. DATA AVAILABLITY STATEMENT

In this study, authors have not created or analysed new data.

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Payal Desai is currently working as an assistant professor in the General Department at L. J. University, Ahmedabad. She has received degree of Bachelor of Science in Mathematics from C. U. Shah science college in year 2009 and degree of Master of Science in Mathematics from School of Sciences, Gujarat University in 2011. Currently she is research scholar at Institute of Technology, Nirma University, Ahmedabad.

Dr Kunal Pathak is working as Assistant Professor and I/C Head in the Department of Mathematics. He has experience of more than fifteen years in the field of teaching and research. He obtained his PhD degree from Sardar Vallabhbhai National Institute of Technology (SVNIT), Surat. His research work is on Computational Models to Study Calcium Dynamics in Cardiac Myocytes. Currently, he is working in the same field and upgrading the models by incorporating more realistic parameters like the coupling of cells, ununiformed distribution of buffer, source, and action potential. His research work has been published in Scopus and Web of Science indexed journals.