International Journal of Engineering, Mathematical and Physical Sciences
ISSN: 2517-9934
Vol:5, No:3, 2011

Finite Volume Model to Study the Effect of Buffer on Cytosolic Ca^{2+} Advection Diffusion

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***Abstract*—** Calcium [Ca^{2+}] is an important second messenger which plays an important role in signal transduction. There are several parameters that affect its concentration profile like buffer source etc. The effect of stationary immobile buffer on Ca^{2+} concentration has been incorporated which is a very important parameter needed to be taken into account in order to make the model more realistic. Interdependence of all the important parameters like diffusion coefficient and influx over [Ca^{2+}] profile has been studied. Model is developed in the form of advection diffusion equation together with buffer concentration. A program has been developed using finite volume method for the entire problem and simulated on an AMD-Turion 32-bit machine to compute the numerical results.

Keywords— Ca^{2+} profile, buffer, Astrocytes, Advection diffusion, FVM

I. Introduction

CALCIUM [Ca^{2+}] is an important second messenger, found in almost all types of cell. The dynamics of calcium Ca^{2+} is very important in cellular physiology because Ca^{2+} binds to many proteins and regulates their activity and interactions. For reference see [1-8] and the reference therein. Waves of elevated cytosolic calcium that travel both within individual astrocytes as well as between then constitute a newly discovered form of non-synaptic long-range signalling in the brain. Astrocytes are found to modulate and be modulated by neuronal and axonal activity. Consequently, these finding transformed the classical view of astrocytes from that of passive, structural, and supportive cells to one in which these cells may actively participate in information processing and hence in brain functioning.

The precise mechanism governing the initiation and propagation of astrocytic Ca^{2+} waves are not completely understood. Experimental studies have shown that intercellular wave propagation is critically dependent on the coupling of adjoining astrocytes by functional gap junction [7]. Ca^{2+} waves are dependent on the diffusion of Ca^{2+} ions both within and possibly between the cells; modulating Ca^{2+} ion diffusion may predictably alter the spatial and temporal character of the Ca^{2+} wave [7]. In cultured astrocytes monolayers calcium waves exposed to a range of cell-permeant, selective calcium-buffering agents having a variety of Ca^{2+} affinities, binding kinetics and structures. The astrocytic Ca^{2+} signalling depend of Ca^{2+} buffering.

This effect is a function of both the Ca^{2+} affinity and the quantity of the exogenous buffer. Experimentally Wang et al (1997) first reported and illustrate directly that cytoplasmic calcium buffering constitutes an important and powerful mechanism for modulating astrocytic Ca^{2+} waves. Most of this work has been done on neuron cell [2-5]. From literature survey it is observed that no investigation has been found using FVM to study calcium diffusion in Astrocytes. In review of above an attempt has been made to study the effect of buffer on cytosolic calcium diffusion for a one dimensional case.

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II. Mathematical Formulation

Calcium kinetics in astrocytes is governed by a set of reaction-diffusion equations which can be framed by assuming the following bimolecular reaction between Ca^{2+} and buffer species:

$$\left[Ca^{2+}\right]+\left[B_j\right]\underset{k_j^-}{\overset{k_j^+}{\Leftrightarrow}}\left[CaB_j\right] \tag{1}$$

where $[B_j]$ and $[CaB_j]$ are free and bound buffer respectively , and 'j' is an index over buffer species. The resulting partial differential equations for equation (1) using Fickian diffusion can be stated as (Smith, 1996).

$$\frac{\partial\left[Ca^{2+}\right]}{\partial t}=D_{Ca}\nabla^2\left[Ca^{2+}\right]+\sum_j R_j \tag{2}$$

$$\frac{\partial\left[B_j\right]}{\partial t}=D_{B_j}\nabla^2\left[B_j\right]+R_j \tag{3}$$

$$\frac{\partial\left[CaB_j\right]}{\partial t}=D_{CaB_j}\nabla^2\left[CaB_j\right]-R_j \tag{4}$$

Where

$$R_j=-k_j^+[B_j][Ca^{2+}]+k_j^-[CaB_j] \tag{5}$$

$D_{Ca}, D_{B_j}, D_{CaB_j}$ are diffusion coefficients of free calcium, free buffer and Ca^{2+} bound buffer respectively. k_j^+ and k_j^- are

association and dissociation rate constants for buffer 'j' respectively. $\left[Ca^{2+}\right]_{\infty}$ is background calcium concentration. For stationary immobile buffers or fixed buffers $D_{B_j} = D_{CaB_j} = 0$. Further equation (2-5) can be written as

$$\frac{\partial\left[Ca^{2+}\right]}{\partial t} = D_{Ca}\nabla^2\left[Ca^{2+}\right] - k_j^{+}\left[B\right]_{\infty}\left(\left[Ca^{2+}\right] - \left[Ca^{2+}\right]_{\infty}\right) + \sigma_{Ca} \tag{6}$$

Here main objective is to study the calcium distribution in form of advection diffusion equation. Most of the authors studied the buffered calcium concentration in form of reaction diffusion equation [2-4]. Few attempts are reported which shows that advection diffusion of calcium occurs in the presence of mobile buffer [10]. The advection and diffusion are independent process because diffusion is to be random process due to calcium molecular motion. Due to the diffusion each calcium molecule will move one step to the right in given time and due to advection each calcium molecules also move $v\delta t$ in the cross flow direction. This process is clearly additive and independent. The presence of cross flow does not bias the probability that the molecule will take a diffusion step to the right. It just adds something to the step. The next movement to calcium molecules will be $v\delta t + \delta x$. Thus total flux in x-direction J_x including the advective transport and a Fickian diffusion term will be

$$J_x = vCa + q_x = vCa + D_{Ca}\frac{\partial Ca}{\partial x} \tag{7}$$

Therefore calcium profile has been taken in the form of incompressible fluid flow with advection diffusion of calcium as given below;

$$\frac{\partial\left[Ca^{2+}\right]}{\partial t} = D_{Ca}\nabla^2\left[Ca^{2+}\right] - v\frac{\partial\left[Ca^{2+}\right]}{\partial x} - k_j^{+}\left[B\right]_{\infty}\left(\left[Ca^{2+}\right] - \left[Ca^{2+}\right]_{\infty}\right) \tag{8}$$

Where v is velocity of calcium flux, for a steady state case the equation (8) is reduced in the form :

$$D_{Ca}\nabla^2\left[Ca^{2+}\right] - v\frac{\partial\left[Ca^{2+}\right]}{\partial x} - k_j^{+}\left[B\right]_{\infty}\left(\left[Ca^{2+}\right] - \left[Ca^{2+}\right]_{\infty}\right) = 0 \tag{9}$$

Along with the boundary conditions as:

$$\lim_{x\to 0}\left(-D_{Ca}\frac{d\left[Ca^{2+}\right]}{dx}\right) = \sigma_{Ca} \tag{10}$$

$$\lim_{x\to\infty}\left[Ca^{2+}\right] = 0.1\mu M \tag{11}$$

The finite volume scheme is employed to solve equation (9) together with (10) and (11). In order to apply the finite volume method the domain is divided into discrete control volumes (Figure 1). taking 30 nodal points in the space between A and B. Each node is surrounded by a control volume or cell. A general nodal point is identified by P and its neighbours in a one-dimensional geometry, the nodes to the

TABLE I
VALUES OF BIOPHYSICAL PARAMETERA USED

Symbol	Parameter	Values
D_{Ca}	diffusion coefficient	200-300 $\mu m^2/s$
k_j^{+} (EGTA)	buffer association rate	$1.5\mu M^{-1}s^{-1}$
k_j^{+} (BAPTA)	buffer association rate	$600\mu M^{-1}s^{-1}$
v	velocity of calcium flux	10-20μm/s
$[B_{\infty}]$	total buffer concentration	30-200μM

M = meter, s = second, M = molar,

west and east, are identified by W and E respectively. The west sides face of

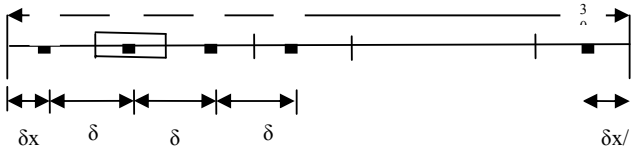

Fig. 1 discretized the domain into number of nodes

the control volume is referred by w and the east side control volume face by e. The distances between the nodes W and P, and between nodes P and E, are identified by δx. Similarly the distance between face w and point P and between P and face e are denoted by $\delta x/2$. Nodal values to the east and west are available at nodal values 2, 3, 4.....29. Now equation (9) can be written in one dimensional case.

$$\frac{d^2\left[Ca^{2+}\right]}{dx^2} - p\frac{\partial\left[Ca^{2+}\right]}{\partial x} - q\left(\left[Ca^{2+}\right] - \left[Ca^{2+}\right]_{\infty}\right) = 0 \tag{12}$$

Where $p = \frac{v}{D_{Ca}}$ *and* $q = \frac{k_j^{+}\left[B\right]_{\infty}}{D_{Ca}}$

Integration of equation (12) over control volume gives:

$$\int_{\Delta V}\frac{d^2C}{dx^2}dV - \int_{\Delta V} p\frac{dC}{dx}dV - \int_{\Delta V} q\left(\left[Ca^{2+}\right] - \left[Ca^{2+}\right]_{\infty}\right)dV = 0 \tag{13}$$

$$\left[\left(A\frac{d\left[Ca^{2+}\right]}{dx}\right)_e - \left(A\frac{d\left[Ca^{2+}\right]}{dx}\right)_w\right] - \left[pA\left[Ca^{2+}\right]_e - pA\left[Ca^{2+}\right]_w\right] - \left[q\left(\left[Ca^{2+}\right]_p - q\left[Ca^{2+}\right]_{\infty}\right)A\delta x\right] = 0 \tag{14}$$

Where A is a cross section area. Subsequent division by cross sectional area A and the calcium concentration $\left[Ca^{2+}\right]$ is replaced by u for convenience. Equation (14) becomes

$$\left(\frac{u_E-u_P}{\delta x}\right)-\left(\frac{u_P-u_W}{\delta x}\right)-p\left[\left(\frac{u_E+u_P}{2}\right)-\left(\frac{u_P+u_W}{2}\right)\right]-q\left(u_p-u_\infty\right)\delta x=0 \tag{15}$$

This can be rearranged as

$$\left[\left(\frac{1}{\delta x}+\frac{p}{2}\right)+\left(\frac{1}{\delta x}-\frac{p}{2}\right)+q\delta x\right]u_P=\left(\frac{1}{\delta x}+\frac{p}{2}\right)u_W+\left(\frac{1}{\delta x}-\frac{p}{2}\right)u_E+q\delta x u_\infty \tag{16}$$

The general form for the interior nodal point 2, 3, 4.....29 is given by:

$$a_P u_P = a_W u_W + a_E u_E + S_u \tag{17}$$

Where

$$a_W=\left(\frac{1}{\delta x}+\frac{p}{2}\right),\quad a_E=\left(\frac{1}{\delta x}-\frac{p}{2}\right),$$
$$a_P=a_W+a_E-S_P,\quad S_P=-q\delta x,$$
$$and\quad S_u=q\delta x u_\infty \tag{18}$$

We apply the boundary conditions at node points 1and 30. At node 1 west control volume boundary is kept at specified concentration

$$a_W=0,\quad a_E=\left(\frac{1}{\delta x}-\frac{p}{2}\right),\ a_P=a_W+a_E-S_P,$$
$$S_P=-\left(\frac{2}{\delta x}+p+q\delta x\right),$$
$$and\ \ S_u=\left(\frac{2}{\delta x}+p\right)u_A+q\delta x u_\infty \tag{19}$$

Similarly at node 30 east control volume boundary is at specified concentration.

$$a_W=\left(\frac{1}{\delta x}+\frac{p}{2}\right),\quad a_E=0,\quad a_P=a_W+a_E-S_P,$$
$$S_P=-\left(\frac{2}{\delta x}-p+q\delta x\right),\ \ and\ \ S_u=\left(\frac{2}{\delta x}-p\right)u_B+q\delta x u_\infty \tag{20}$$

Substituting the values from equation (18-20) in equation (17), obtained a system of algebraic equation as below where u_A and u_B be the specified boundary conditions in terms of calcium concentration.

$$AU=B \tag{21}$$

Here, $U=u_1,u_2.....u_{30}$ represents the calcium concentration, A is system matrices and B is the system vector.

III Results And Discussion

In this section we have shown the numerical results for calcium profile against different biophysical parameters. The biophysical parameters used in the model are as stated in the table below unless stated along with figures. A program has been developed using finite volume method for the entire problem and simulated on an AMD-Turion 32-bit machine to compute the numerical results. Figure 2 shows the variation of calcium with the space. To see the effect of buffer with different affinity the different values of dissociation constant is taken. Dissociation constant is the ratio of disassociation to association rate

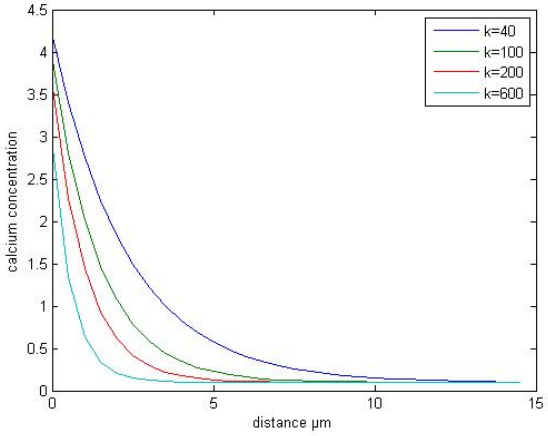

Fig. 2 Effect of buffer with different values of Kd

We observe that calcium concentration falls down quickly up to $x=0$ to $x=6$ and then gradually converges to $0.1\mu M$. This fall in concentration decrease with increase in the value of k_j^+. Thus if k_j^+ is increases than the calcium concentration is decreases.

Figure 3 shows the variation of calcium concentration with different values of diffusion constants. We have considered three different values of D_{Ca}, $D_{Ca}=200$, $D_{Ca}=250$ and $D_{Ca}=300$. Hence as the diffusion coefficient increases more numbers of calcium ions get free as lesser number of calcium ions bind, hence the calcium concentration increases. Calcium concentration approaches to $0.1\mu M$ as we move away from the source.

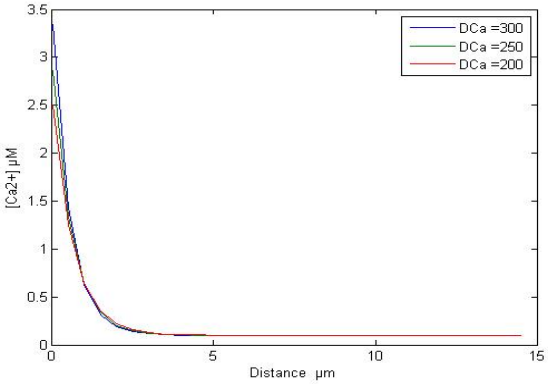

Fig. 3 Effect of different diffusion coefficient on calcium profile. Buffer concentration is taken 30 μM

In Figure 4 we have shown the variation of calcium concentration with amount of buffer. The amount of buffer has a profound effect on the calcium concentration as is evident in

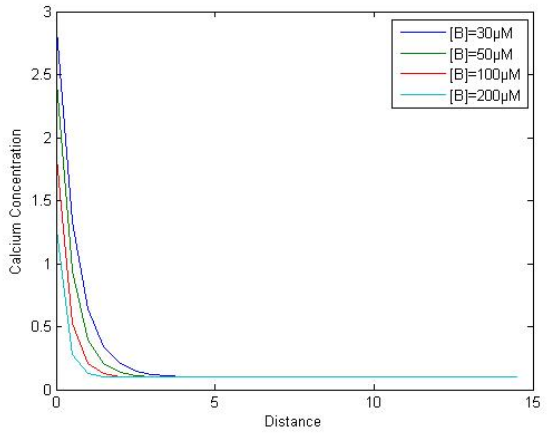

Fig. 4 Graph between Calcium Concentration and distance with different amount of buffer concentration

the figure. As buffer concentration increases as net flow of calcium decreases. Diffusion coefficient is taken constant as $D_{Ca} = 250$. Calcium profile decrease rapidly and achieves the steady state as shown in the figure.

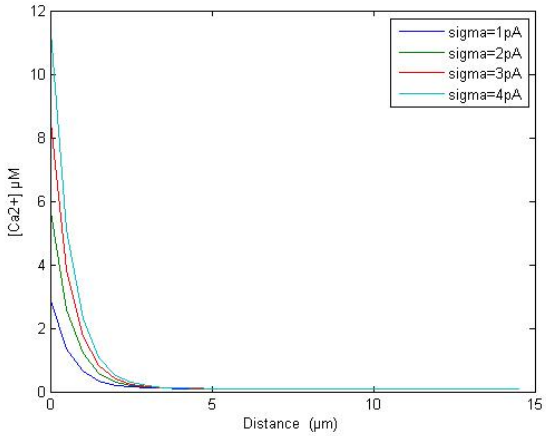

Fig. 5 graph between Calcium Concentration and distance with different value of sigma σ_{Ca}

In Figure 5 we have shown the variation of calcium concentration with amount of sigma σ_{Ca}. As amount of σ_{Ca} increases the net flow of calcium increases. Calcium concentration fall rapidly and achieves the steady state as moves far from the source.

REFERENCES

[1] Berridge M. J. ,Elementary and global aspects of calcium signalling, J physiol. 499, pp. 291-306,1997

[2] G.D. Smith, L. Dai, R. M. Miura, and A. Sherman, Asymptotic analysis of buffered calcium diffusion near a point source, SIAM J. Of Applied of Math, vol.61,pp.1816-1838.2000

[3] G.D. Smith, Analytical steady-state solution to the rapid buffering approximation near an open Ca^{2+} channel, Biophysical Journal, vol.71, pp.3064-3072,1996.

[4] J. Wagner and J Keizer, Effect of rapid buffers on ca^{2+} diffusion and Ca^{2+} oscillations, Biophysical Journal, vol.67, pp. 447-456,1994.

[5] Neher, E.,Concentration profiles of intracellular Ca^{2+} in the presence of diffusible chelator, Exp. Brain Res. 14 pp. 80-96,1986

[6] T. Hofer, A. Politi and R. Heinrich, Interecellular Ca^{2+} wave propagation through gap-junctional Ca^{2+} diffusion: a theoretical study, *Biophysical Journal*, vol. 80, pp.75-87,2001

[7] Z. Wang,M.Tymianski,O.T.Jones,M.Nedergaard, Impact of calcium buffering on the spatial and temporal characteristics of intercellular calcium signals in astrocytes, The Journal of Neuroscience, pp.7359-7371, 1997

[8] B.K. Jha, N. Adlakha, M.N. Mehta, Solution of advection diffusion equation arising in cytosolic calcium concentration distribution, International Journal of Applied Mathematics and Mechanics, accepted (2011)

[9] H. K. Versteeg, W. Malalasekera, An introduction to computational fluid dynamics the finite volume method, Longman Scientific & Technical, 1995

[10] L. A. Mironova and S. L. Mironov, Approximate Analytical Time dependent solutions to describe large amplitude local calcium transients in the presence of buffers, Biophysical Journal Vol. 94 pp. 349-358,2008