Finite Element Estimation of Calcium Ions in Presence of NCX and Buffer in Astrocytes

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***Abstract*—Sodium calcium exchanger (NCX) plays an effective role in signal transduction in most of the nerve cells like neuron, astrocytes etc. Sodium ion affects the cytosolic calcium concentration level in Astrocytes via various channels, which affects the movement of the nerve impulse from one cell to other cell. In this paper two dimensional model is developed in the form of diffusion equation to study the effect of NCX in presence and absence of buffer in Astrocytes. Finite element method is employed to solve the problem and results are simulated in Matlab to estimate the affect of various parameters like flux, diffusion coefficient, buffer concentration, etc. It is observed that the effect of NCX and buffer are significant. NCX is helpful to reduce the Ca^{2+} level in cytosol. High level of buffer concentration overlaps the effect of NCX on cytosolic calcium concentration in astrocytes.**

***Index Terms*—Calcium ion, buffer, NCX, FEM**

I. Introduction

The word glia also known as glue is derived from the greek word gliok which also means slime. Astrocytes, one of these glia cells, which are highly fibrous cells having great structural complexity, plays important role in signal transduction in our nervous system [1]-[3]. During the last two decades, astrocytes have been considered as one of the supportive cells of neurons, which provide structural and metabolic support to neurons [2], [4], [5]. Due to modern imaging technology such as fluorescence imaging the concept about the role of star shaped astrocytes is changed. Astrocytes interact with neurons and make interconnected network with other astrocytes that signal to each other through calcium excitability. Since interaction among astrocytes can monitor maximum of the cortical tissue volume, it interacts effectively with other neurons. Under normal conditions, Astrocytes provides glucose and metabolic substracts to neuron. It has tight control over pH homeostasis and local ions. Astrocytes processed bidirectional communication with blood-brain barrier as well as participate in synaptic transmission. Single cortical or hippocampus astrocytes are in contact with approximately 600 dendrites and more than 100,000 synapses [6]-[10]. Thus astrocytes work as multifunctional housekeeping cells in nervous system [4], [8], [9], [11]. Astrocytes express numerous types of neurotransmitter receptors. Release of these receptors initiate electrically silent activation of astrocytes by increasing intracellular calcium ion $[Ca^{2+}]_i$ levels. These receptors are coupled to G-protein and activate a wide range of intracellular second messenger pathways including production and release of IP_3 into the cytosol. Astrocytes express a wide variety of neurotransmitter receptors like $GABA_B$ receptors, acetylcholine muscarinie receptors, α – adrenergic receptors etc. [4], [8]. Ca^{2+} - mediated events required a effective raise in the cytosolic calcium concentration $[Ca^{2+}]_i$ even though major increases in $[Ca^{2+}]_i$ can be lethal to cell's death [11]. A numerous types of physical and physiological parameters have effect on intracellular calcium concentration level like, calcium buffering, voltage gated calcium channel, continuous shuttling of Ca^{2+} between mitrocondia and endoplasmic reticulum, sodium calcium exchanger (NCX) etc. To integrate the role of cytosolic calcium concentration in computational model, we established in previous work [12] a mathematical model that allows the modeling of the impact of other important parameter on $[Ca^{2+}]$ level. In view of above we have studied the effect of NCX along with buffer on Cytosolic calcium concentration distribution in astrocytes. Finite element method is employed to find the solution and the results are simulated in Matlab. In literature many authors have studied the effect of various physiological parameters on cytosolic calcium distribution in nerve cells using different analytic and numerical technique. Smith *et al*. [5], [13] have studied the effect of rapid

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buffer on cytosolic calcium concentration in neuron. He obtained analytic steady state solution of the mathematical model. Tiwari *et al*. have studied the effect of Na^+ influx on cytosolic Ca^{2+} diffusion in neuron cell using finite difference method. Tripathi *et al*. [2], [3] studied the effect of buffers on Ca^{2+} in neuron cell using finite element method. Circular shape of the neuron is considered by taking the polar form of the mathematical model. Triangular ring element and coaxial circular elements are used to discretize the region. Jha *et al*. [12], [14] have studied the effect of buffer and VGCC on $[Ca^{2+}]$ in astrocytes. Finite element method employed to solve the model using triangular element with rectangular region. Kotwani *et al*. [15] used finite difference method to study calcium diffusion in Fibroblast. Only the effect of buffer studied in one dimensional unsteady state case. Jha *et al*. [1] have studied the effect of Na^+- Ca^{2+} exchangers on Ca^{2+} in neuron cell using finite element method. Coaxial circular sector element has been used to discretize the circular region. In present work an attempt has been made to study the effect of Na^+- Ca^{2+} exchangers on Ca^{2+} in astrocytes. To fit actual shape of astrocytes region a star shaped figure is plotted in MATLAB using pde tool. Finite element method is employed to simulate the result using triangular element.

II. Mathematical Formulation

The proposed model includes two different factors that affect the cytosolic calcium concentration in astrocytes. The detail mathematical expression is given below:

A. Calcium Buffering

Calcium buffering is most common but effective process found in almost every kind of nerve cells. Previous researchers have studied the effect of rapid and excess buffers on Cytosolic calcium concentration in nerve cells like neuron, astrocytes, fibrocytes etc [2], [3], [5], [13], [15]-[20]. Calcium kinetics in nerve cells is governed by a set of reaction-diffusion equations which can be framed assuming the following bimolecular reaction between Ca^{2+} and buffer species [5], [13], [18]:

$$[Ca^{2+}]+[B_j] \Leftrightarrow [CaB_j] \tag{1}$$

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 [5], [13], [18].

$$\frac{\partial [Ca^{2+}]}{\partial t} = D_{Ca}\frac{\partial^2 [Ca^{2+}]}{\partial x^2} + \sum_j R_j - P_{out}[Ca^{2+}] \tag{2}$$

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

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

where

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

D_{Ca}, D_B, $D_{Ca\mathbf{B}}$ are diffusion coefficients of free calcium, free buffer and Ca^{2+} bound buffer respectively whereas k^+ and k^- are association and dissociation rate constants for buffer respectively.

B. Na^+ / Ca^{2+} Exchanger

NCX is an essential component of calcium extrusion of cytosolic calcium in astrocytes. In our model we have taken an exchange ratio of 3:1 with respect to sodium and calcium ions respectively. The net transport of Ca^{2+} ions through Na^+/ Ca^{2+} exchanger is given by: [5], [13], [21]

$$\Delta Ca^{2+} = 3\Delta Na^+ \tag{6}$$

$$J_{NCX} = Ca_o\left(\frac{Na_i}{Na_o}\right)^3 \exp\left(\frac{2FV_m}{RT}\right) \tag{7}$$

Now from equation (1) - (7), we get the final model

$$D_{Ca}\left(\frac{d^2C}{dx^2}\right)+\left(\frac{d^2C}{dy^2}\right)-k_j^+[B]_\infty(C-C_\infty)-J_{NCX}+\sigma_{Ca}=0 \tag{8}$$

Considering the point source of calcium at x=0 the boundary condition can be given as

$$-D_{Ca}\frac{\partial [Ca^{2+}]}{\partial n} = \sigma_{Ca}, x = y = 0 \tag{9}$$

Also, the background concentration of $[Ca^{2+}]$ is 0.1 μM. As we move far away from the source, the calcium concentration tends to background concentration and thus boundary condition is expressed as,

$$[Ca^{2+}] = 0.1\mu M, x = y = 5\mu M \tag{10}$$

III. Discretization of the Region

As shown in Fig. 1 the solution region of given problem is divided into 62 triangular elements. The element information is drawn in matlab 10b. It is considered that the free calcium ions Ca^{2+} enters from node 10 and hence the first boundary condition is considered at node 10. For rest of the boundary second boundary condition is considered. It is assumed that initially calcium ions maintain it background concentration throughout the region.

Here, we have used 'u' in lieu of $[Ca^{2+}]$ for our convenience, $e = 1, 2, 3, \ldots . 62$ λ is the characteristic length and is equal to $\sqrt{\frac{D_{Ca}}{k^+[\mathbf{B}]_\infty}}$. In the term outside the integral $\mu^{(e)} = 1$ for $e = 10$ and $\mu^{(e)} = 0$ for rest of the elements. For the convenience the equation (8) can be written as

$$\left(\frac{\partial^2 u}{\partial x^2}\right)+\left(\frac{\partial^2 u}{\partial y^2}\right)-au+b=0 \quad (11)$$

To match with actual shape of astrocytes a star shaped region is drawn in Matlab. Equation (11) is solved using finite element solver in Matlab with boundary conditions (9) and (10).

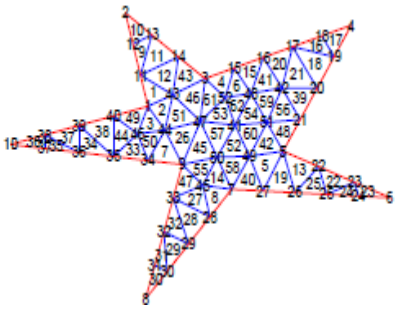

Figure 1. Discretization of the region.

IV. Result and Discussions

Two types of buffers studied in literature first endogenous and other is exogenous. Calamudin, Katamine etc are endogenous buffer and EGTA and BAPTA are exogenous buffers. There are number of endogenous buffers exist inside the cells. The amount and affinity of these buffers play different but effective role to control the cytosolic calcium concentration in cell and hence the flow of transmitter from one cell to another cell. In present study we have considered a common buffer term having some amount and affinity due to its common behavior. The numerical values of physical and physiological parameters used for computation of numerical results are given in Table I.

TABLE I. List of Parameters Used for Numerical Results

Symbol	Parameter	Value
DCa	Diffusion Coefficient	250-400 m^2/s
k^+ (EGTA)	Buffer association rate (Exogenous buffer)	1.5 $M^{-1} s^{-1}$
$[B_m]$	Buffer Concentration	50-200 M
$[Ca^{2+}]_\infty$	Background Ca^{2+} Concentration	0.1 M
Σ	Source amplitude	1-5 pA
Vast	Volume of Cytosol	5.233 x 10^{-13} l
F	Faraday's Constant	96,485 C/mol
R	Real Gas Constant	8.31 J / (mol K)
T	Temperature	300 K
Pout	Rate of calcium efflux from cytosol	0.5 s^{-1}
ZCa	Valance of calcium ion	2
Na_i	Cytosolic sodium concentration	5-10 µM
Na_o	Extracellular sodium concentration	10-150 µM

In Fig. 2 the spatial distribution of Ca^{2+} ion is shown in two dimensional spaces in absence of buffer and NCX. In absence of buffer and NCX the equation (11) becomes two dimensional Laplace equations. The behavior of analytic solution of Laplace equation is same as shown in Fig. 2. Due to calcium influx Ca^{2+} ion concentration is higher than the rest of the region. Ca^{2+} ion concentration level decrease rapidly as it moves far away from the source and finally obtains its background concentration level.

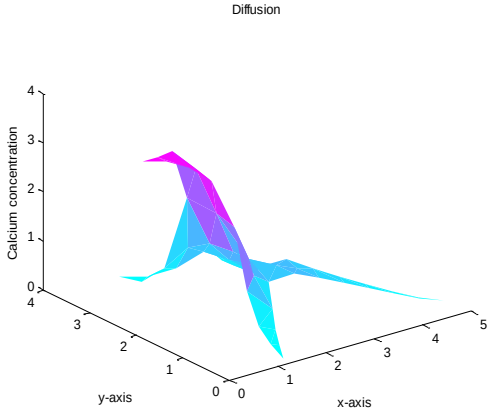

Figure 2. Spatial distribution of Ca^{2+} ion in absence of buffer and NCX.

In Fig. 3 the spatial distribution of Ca^{2+} ion is shown in two dimensional spaces in presence of buffer and NCX. Due to calcium influx Ca^{2+} ion concentration is higher than the rest of the region. Ca^{2+} ion concentration label decreases rapidly as it moves far away from the source and finally obtain its background concentration label. Ca^{2+} ion concentration level at the point source is lower than the Fig. 2. Due to presence of buffer, free Ca^{2+} ion react with buffers and makes calcium bound buffer. In presence of buffer, calcium ion level is minimum throughout the region and thus many gliotransmitters are blocked to move into the synapse.

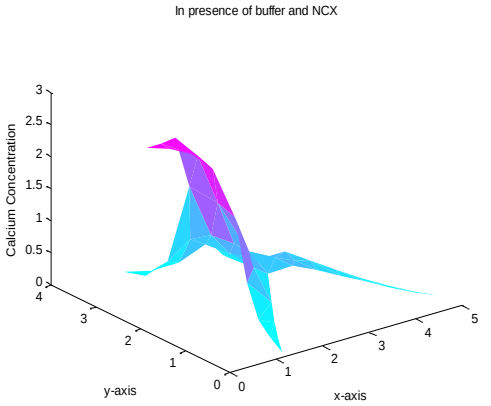

Figure 3. Spatial distribution of Ca2+ ion in presence of buffer and NCX

In Fig. 4 the spatial distribution of Ca^{2+} ion is shown in two dimensional space in presence of buffer only (absence of NCX). Due to calcium influx Ca^{2+} ion concentration is higher than the rest of the region. Ca^{2+} ion concentration level decrease rapidly as it moves far away from the source and finally obtains its background concentration level. As compare to Fig. 2 and 3 it is

observed that due to presence of buffer calcium concentration is lesser at point source, but it is higher than the Fig. 3 due to absence of NCX. Here it is observed that the NCX plays significant role to control the Ca^{2+} level in the region and thus control the flow of nerve impulse from one cell to another cell or in synapse. The difference in Ca^{2+} level may vary with different amount of buffer.

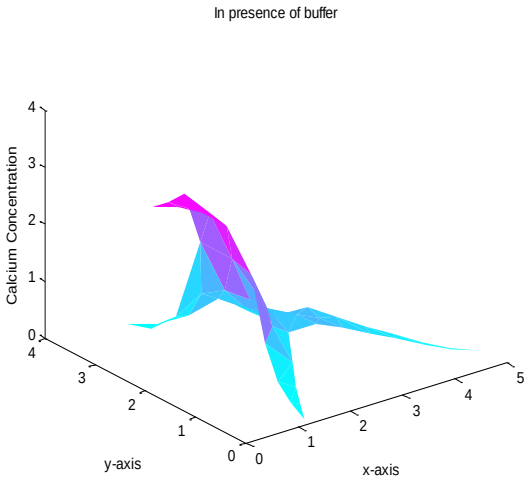

Figure 4. Spatial distribution of Ca2+ ion in presence of buffer

V. Conclusion

It is observed that the effect of buffer and NCX is more significant on the source or mouth of the calcium ion channel in comparison to little away from the source. The effect of NCX is found significant in less amount of buffer. The triangular elements used here give us better approximations. Role of NCX is found important to reduce the cytosolic calcium concentration level in astrocytes. It is helpful to block the movement of neuro transmitter from one cell to another cell or synapse. It also helps to determine the level of Ca^{2+} to be toxic. The finite element method is quite flexible and powerful in dealing such problems and gives useful results in two dimensions. The model developed here makes the use of a finite element method easier. The results obtained in present study might be useful for scientist and biomedical researcher to study biophysical and physiological disorders in nervous system. Furthermore the important parameters like voltage gated calcium channel (VGCC), endoplasmic reticulum (ER) etc needed to add in the mathematical model to understand the mechanism of biophysical and physiological process. .

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