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Two dimensional Finite Element Estimation of Calcium ions in presence of NCX and Buffers in Astrocytes

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ABSTRACT: Sodium calcium exchanger (NCX) plays effective role in signal transduction in most of the nerve cells like neuron and astrocytes. Sodium ion affects the cytosolic calcium concentration level in Astrocytes via various channels. This 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 simulated in Matlab to estimate the effect of various parameter like flux, diffusion coefficient, buffer concentration, etc.

Key Words: Calcium ion, Buffers,NCX,FEM.

Contents

1. Introduction

Computational neuroscience is now a day's attracted to the researchers and scientists to study the role of calcium ions in numerous physiological process and cellular functions, like membrane excitability, synaptic activity etc. Astrocytes plays leading role in synaptic transmission and calcium signalling process. Recent evidence suggests that the role of astrocytes is more significant in the functioning of various physiological processes like mammalian nervous system. Astrocytes response to various neurotransmitters and neuromodulater process and plays leading role in complex intracellular and intercellular signalling. The free cytosolic calcium ions concentration also known as second messenger, plays significant role in various astrocytic physiological processes. The high cytosolic calcium concentration is toxic for the cell. Various internal and external parameters affect the cytosolic calcium concentration level in astrocytes. Some of them are buffers, sodium calcium

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exchanger etc [1,2,4,8,14,16,20].
In present study calcium buffering and NCX is taken into consideration to study the effect of them on free Ca^{2+} concentration. There are numerous type of buffers which (one kind of protein) exists inside the plasma membrane. It varies in amount and affinity with calcium ions. EGTA and BAPTA are exogenous buffer. EGTA has low affinity than the BAPTA buffers. Buffers lead to the bidirectional reaction with free calcium ions and makes calcium bound buffers. NCX play important role in regulation of cytosolic calcium concentration level in astrocytes and thus control the astrocytic response to neurotransmitters. It regulates the bidirectional Ca^{2+} transport across the plasma membrane [16,20,21].
To integrate the role of cytosolic calcium concentration in computational model, we established in previous work [7] 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 techniques. Smith et al. [11] have studied the effect of rapid buffer on cytosolic calcium concentration in neuron. They obtained analytic steady state solution of the mathematical model. Tiwari et al. [16] 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. [6,7] 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. Jha et al. [8] have studied the effect of NCX on cytosolic calcium concentration in astrocytes. In this work authors have concentrated on geometry of astrocytes rather than the effect of other parameter like diffusion coefficient, affinity of buffers etc. Kotwani et al. [15] used finite difference method to study calcium diffusion in Fibroblast. Only the effect of buffer was 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. Finite element method is employed to simulate the result using triangular element.

2. Mathematical Formulation

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

2.1. Calcium Buffering

Calcium buffering is most common but effective process found in almost every kind of nerve cells. Previous researcher have studied the effect of rapid and excess buffers on cytosolic calcium concentration in nerve cells like neuron, astrocytes, fibrocytes etc [3,4,5,9,10,12,15,17,19,21]. 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 [11,12]:

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

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 is for equation (1) using Fickian diffusion can be stated as [11,12].

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\left(\frac{\partial^2[Ca^{2+}]}{\partial x^2} + \frac{\partial^2[Ca^{2+}]}{\partial y^2}\right) + \sum_j R_j + \sigma_{Ca} \tag{2}$$

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

$$\frac{\partial[CaB_j]}{\partial t} = D_{CaB_j}\left(\frac{\partial^2[CaB_j]}{\partial x^2} + \frac{\partial^2[B_j]}{\partial y^2}\right) - R_j \tag{4}$$

where

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

D_{Ca} ,D_B, D_{CaB} 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.

2.2. Sodium Calcium 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 : [1,8,13,16]

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

$$J_{NCX} = Ca_0[\frac{Na_i}{Na_0}]^3 exp(\frac{2FV_m}{RT}) \tag{7}$$

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

$$\frac{\partial u}{\partial t} = D_{Ca}\left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2}\right) - k_j^+[B]_\infty(C - C_\infty) - J_{NCX} \tag{8}$$

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

$$[Ca^{2+}] = 0.1\mu M \ 0 < x \leq 5\mu M, \ 0 < y \leq 5\mu M \tag{9}$$

$$- D_{Ca}\frac{\partial[Ca^{2+}]}{\partial n} = \sigma_{Ca} \tag{10}$$

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,

$$[Ca^{2+}]_{\infty} = 0.1\mu M \; x = y = 5\mu M \tag{11}$$

2.3. Discretization of The Region

The solution region is divided into 50 triangular elements as shown in figure 1. The numbers inside the circles denote the element number. The numbers without circles denote the node numbers. The element information is taken from jha et al. [6,7,18]

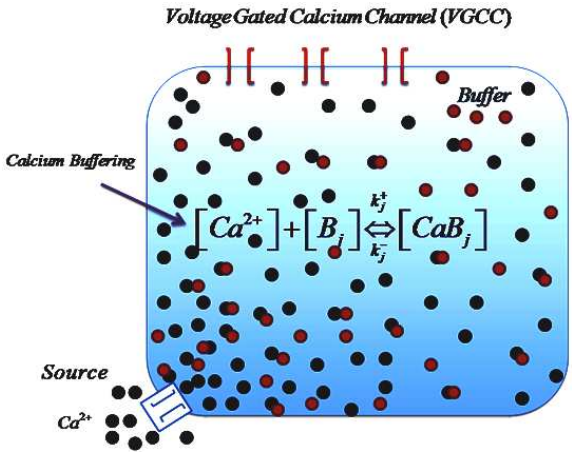

Figure 1: Discretization of the solution region [6,7,18]

Here, we have used $'u'$ in lieu of $[Ca^{2+}]$ for our convenience, e = 1, 2 .....50. In the term outside the integral, $\mu^e = 1$ for $e = 1$ and $\mu^e = 0$ for rest of the elements. The shape function of concentration variation within each element is defined by [7,18]

For the convenience the equation (8) can be written as

$$\frac{\partial u}{\partial t} = D_{Ca}\left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2}\right) - au + b \tag{12}$$

The discretized variational form of equations (12) can be written as:

$$\begin{aligned} I^e \;=\; & \frac{1}{2}\int\int_A \{\left(\frac{\partial u^{(e)}}{\partial x}\right)^2 + \left(\frac{\partial u^{(e)}}{\partial y}\right)^2 + au^{(e)^2} - 2bu^{(e)} \\ & + \frac{1}{D_{Ca}}u^{(e)}\frac{\partial u^{(e)}}{\partial t}\}dA - \mu^{(e)}\left(\frac{\sigma}{D_{Ca}}u^{(e)}|x = 5\right)dy \end{aligned} \tag{13}$$

The shape function of concentration variation within each element is defined by [7,18]

$$u^{(e)} = c_1^{(e)} + c_2^{(e)}x + c_3^{(e)}y \tag{14}$$

$$u^{(e)} = P^T c^{(e)} \tag{15}$$

where

$$P^T = [1 \quad x \quad y] \quad and \quad {c^{(e)}}^T = [c_1^{(e)} \quad c_2^{(e)} \quad c_3^{(e)}] \tag{16}$$

From equation (14) and (15) we get

$$\overline{u^{(e)}} = P^{(e)}c^{(e)} \tag{17}$$

where $\overline{u^{(e)}} = \begin{bmatrix} u_i \\ u_j \\ u_k \end{bmatrix}$ and $P^e = \begin{bmatrix} 1 & x_i & y_i \\ 1 & x_j & y_j \\ 1 & x_k & y_k \end{bmatrix}$ from the equation (17) we have

$$c^{(e)} = R^{(e)}\overline{u^{(e)}} \tag{18}$$

$$Where \quad R^{(e)} = {P^{(e)}}^{-1} \tag{19}$$

Substituting c(e) from equation (17), (18)and (19) we get

$$u^{(e)} = P^T R^{(e)}\overline{u^{(e)}} \tag{20}$$

Now the integral $I^{(e)}$ can be written in the form

$$I^{(e)} = I_k^{(e)} + I_m^{(e)} - I_s^{(e)} - I_z^{(e)} \tag{21}$$

where

$$I_k^{(e)} = \frac{1}{2}\int\int_A \{\left(\frac{\partial u^{(e)}}{\partial x}\right)^2 + \left(\frac{\partial u^{(e)}}{\partial y}\right)^2\} dA \tag{22}$$

$$I_m^{(e)} = \frac{1}{2}\int\int_A \frac{{u^{(e)}}^2}{\lambda^2} dA \tag{23}$$

$$I_s^{(e)} = \frac{1}{2}\int\int_A \{\frac{2u^{(e)}u_\infty}{\lambda^2}\} dA \tag{24}$$

$$I_z^{(e)} = \frac{1}{2}\mu^{(e)}\left(\frac{\sigma}{D_{Ca}}\mu^{(e)}|_{x=5}\right) dy \tag{25}$$

Now we extremize I w.r.t. each nodal calcium concentration ui as given below

$$\frac{dI}{d\overline{u}} = \sum_{e=1}^{N} \overline{M}^{(e)} \frac{dI^{(e)}}{d\overline{u}^{(e)}} \overline{M}^{(e)T} = 0 \tag{26}$$

where

$$\overline{M}^{(e)} = \begin{bmatrix} 0 & 0 & 0 \\ . & . & . \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ . & . & . \\ 0 & 0 & 0 \end{bmatrix}, \quad I = \sum_{e=1}^{36} I^{(e)} \quad and \quad \overline{u} = \begin{bmatrix} u_1 \\ u_2 \\ . \\ . \\ . \\ . \\ u_{36} \end{bmatrix} \tag{27}$$

$$\frac{dI^{(e)}}{d\overline{u}^{(e)}} = \frac{dI_k^{(e)}}{d\overline{u}^{(e)}} + \frac{dI_m^{(e)}}{d\overline{u}^{(e)}} - \frac{dI_s^{(e)}}{d\overline{u}^{(e)}} - \frac{dI_p^{(e)}}{d\overline{u}^{(e)}} \tag{28}$$

This leads to a following system of linear algebraic equations.

$$[K]_{36\times 36}\,[\overline{u}]_{36\times 1} = [F]_{36\times 1} \tag{29}$$

Here,$\bar{u} = u_1, u_2, ...u_{36}$, K is the system matrices, and F is system vector. The Gaussian elimination method is employed to solve the system (29). A computer program in MATLAB is developed to find numerical solution to the entire problem.

3. Results and Discussion

The numerical values of physical and physiological parameters used for computation of numerical results are given in Table I:

Symbol	Parameter	Values
D_{Ca}	Diffusion Coefficient	200-300 $\mu m^2/second$
σ	Source Amplitude	1 pA
k^+EGTA	Buffer Association Rate	$1.5\mu M^{-1}s^{-1}$
k^+BAPTA	Buffer Association Rate	$600\mu M^{-1}s^{-1}$
$[B]_\infty$	Buffer Concentration	$50\mu M - 150\mu M$
$[Ca^{2+}]_\infty$	Background $[Ca^{2+}]$ Concentration	$0.1\mu M$
V_{AST}	Volume of Cytosol	$5.233 * 10^{13} l$

Table 1: List of Physiological parameters

In figure 2 (a) and (b) the effect of NCX is shown in presence of buffer. It is found that Ca^{2+} concentration goes high with time Span but it decreases gradually in spatial direction in absence of NCX. While in presence of NCX the Ca^{2+} level goes high in time spam but the pick value is lesser than the previous one (in absence of NCX). It happens due to the behaviour of NCX. Ca^{2+} excursion happens due to NCX. Thus the effect of NCX is found significant in the present study.

In figure 3 (a), (b), (c) and (d) the spatial and temporal Ca^{2+} distribution is shown in absence of NCX to study the effect of various type of buffers (in amount and affinity). In figure 3(a) low amount of buffer having low affinity for Ca^{2+} is studied. It is found that the Ca^{2+} is same as discussed in figure 1 (a). But it

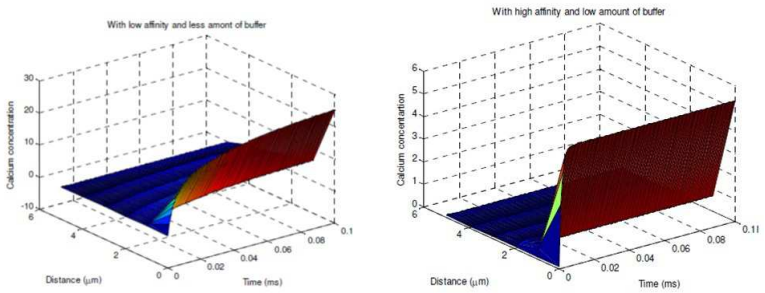

Figure 2: Spatial and temporal Ca^{2+} distribution with variation in buffer concentration and affinity of buffer in absence of NCX

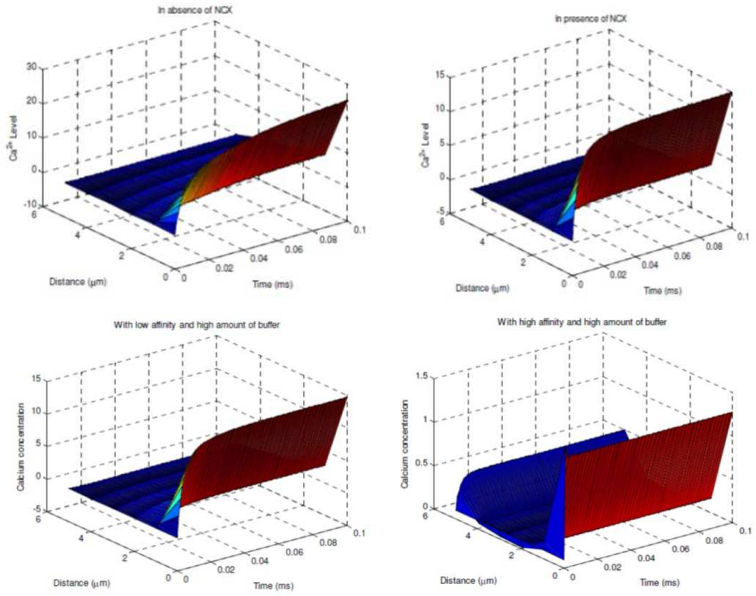

Figure 3: Spatial and temporal Ca^{2+} distribution with variation in buffer concentration and affinity of buffer in absence of NCX

varies when the high affinity of buffer is used with same amount of buffer. It is found that Ca^{2+} increase in time span but is unable reach upto level shown in figure 3(a). Ca^{2+} level increased when high amount of buffer having low affinity is used shown in figure 3(c). It remains at lower level when high amount of buffer having high affinity to calcium ion is used is shown in figure 3(d). Thus the effect of affinity and amount of buffer on cytosolic calcium concentration is found significant.

In figure 4 (a), (b), (c) and (d) the spatial and temporal Ca^{2+} distribution is

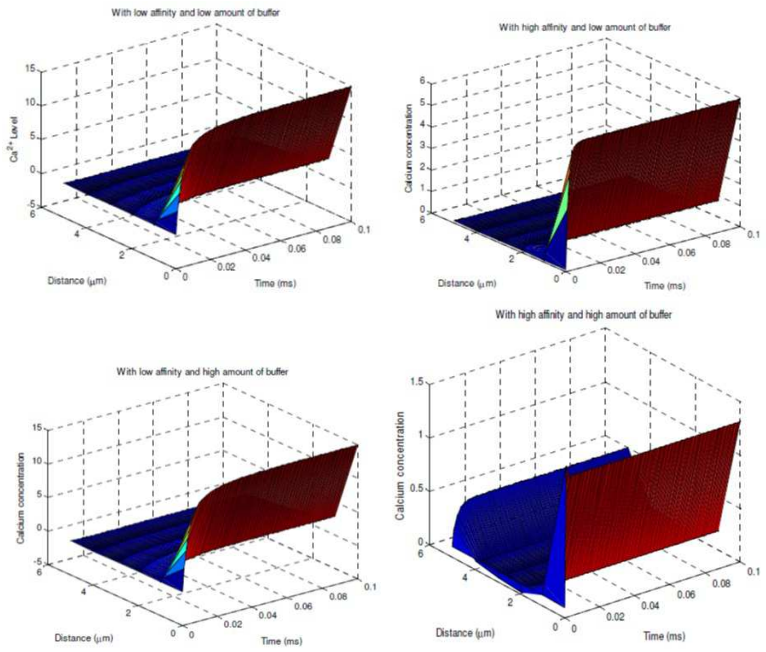

Figure 4: Spatial and temporal Ca^{2+} distribution with variation in buffer concentration and affinity of buffer in presence of NCX

shown in presence of NCX to study the effect of various type of buffers (in amount and affinity). In figure 4(a) low amount of buffer having low affinity for Ca^{2+} is studied. It is found that the Ca^{2+} profile is same as discussed in figure 1 (b). But it varies when the high affinity of buffer is used with same amount of buffer. It is found that Ca^{2+} increase time span but it does not reache to the level shown in figure 3(b). Ca^{2+} level increased when high amount of buffer having low affinity is used as shown in figure 4(c). It remains at lower level when high amount of buffer having high affinity to calcium ion is as used shown in figure 4(d). When we compare figure 4 with figure 3 it is found that the effect of NCX is visible at low affinity and less amount of buffer. Thus the effect of NCX on cytosolic calcium concentration is found significant in the absence of buffer or presence of less amount of buffer.

4. Conclusion

It is observed that the effect of buffer and NCX is more significant at the source or mouth of the calcium ion channel in comparison to the rest of the channel i.e. when more away from source. The effect of NCX is found significant in less amount of buffer. The triangular elements used here give us better approximations. 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 in this situation and reduces the amount of computation.

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