Two Dimensional Coaxial Circular Elements in FEM to Study Calcium Diffusion in Neuron Cells

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Abstract

Calcium is the second messenger which plays an important role in communication process in neuron cells. The region in neuron cells where the flow of electric current cannot take place in the main region of activity for chemical signaling. The chemical signaling process is achieved by the diffusion of calcium. In view of above a mathematical model of calcium diffusion in neuron cell has been developed for a two dimensional steady state. The important parameters like rate of diffusion, buffers, potential activity and influx has been incorporated in the model. Appropriate boundary conditions have been framed. The finite element method has been applied to obtain the solution and the concentration profiles.

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Keywords: potential activity, association rate, influx, EBA, diffusion constant, FEM

1 Introduction

CALCIUM plays an important role in regulating the great variety of neuronal processes. In other types of cells, neurons use both extracellular and intracellular sources of calcium. The mechanism responsible of regulating the external influx of calcium voltage operated channels is used to trigger the release of neurotransmitter at synaptic junctions and they contribute the dendritic action potential. Neurotransmitter can induce an influx of calcium using receptor-operated channels [1, 12]. Calcium is very important second messenger of intracellular communication between neurons. There are two types of synapse
for communication in neuron. One is electrical synapse and other is chemical synapse. Electrical synapse is fast while the signaling through chemical synapse is slow. The signaling through chemical synapses is more significant than electrical synapses as it comes into play when the distance between the neurons is more than 4-5 nm. When the distance in between neurons is more, then signalling in between neurons cannot be done through electrical synapses. In this case, electrical signal is converted into chemical signal so that chemical signal can be transmitted through chemical synapse. This process conversion electrical signal into chemical signal is called the signal transduction [19, 21].

Mathematical and computational simulation of $Ca^{2+}$ kinetics provides an important alternative to study the effect of several parameters over $Ca^{2+}$ profile [15, 16]. In this paper, the $Ca^{2+}$ dynamics is studied by developing a finite element model in two dimension for Calcium diffusion in neuron cell. A computer program has been developed in MATLAB 7.5 for the whole approach and simulated on Core(TM) i3 CPU M 330 @ 2.13 GHz processing speed and 3 GB memory. The numerical results are used give the $Ca^{2+}$ profile in r and $\theta$ directions [7].

2 Mathematical Formulation

Calcium kinetics in neuron is governed by a set of reaction-diffusion equation given by [6, 11, 21]:

$$\left[ Ca^{2+} \right] + [B_j]^k \xrightarrow{k^+} [CaB_j]$$  \hspace{1cm} (1)

where $B_j$ and $CaB_j$ are free buffer and bound buffer, and $j$ is an index over buffer species. So the Calcium dynamics can be in the form of following equations [5, 13, 15, 16]:

$$\frac{\partial \left[ Ca^{2+} \right]}{\partial t} = D_{Ca} \left( \frac{\partial^2 \left[ Ca^{2+} \right]}{\partial r^2} + \frac{1}{r} \frac{\partial \left[ Ca^{2+} \right]}{\partial r} + \frac{\partial^2 \left[ Ca^{2+} \right]}{\partial \theta^2} \right) + \Sigma_j R_j$$  \hspace{1cm} (2)

$$\frac{\partial [B_j]}{\partial t} = D_{B_j} \left( \frac{\partial^2 [B_j]}{\partial r^2} + \frac{1}{r} \frac{\partial [B_j]}{\partial r} + \frac{\partial^2 [B_j]}{\partial \theta^2} \right) + R_j$$  \hspace{1cm} (3)

$$\frac{\partial [CaB_j]}{\partial t} = D_{CaB_j} \left( \frac{\partial^2 [CaB_j]}{\partial r^2} + \frac{1}{r} \frac{\partial [CaB_j]}{\partial r} + \frac{\partial^2 [CaB_j]}{\partial \theta^2} \right) - R_j$$  \hspace{1cm} (4)

Where

$$R_j = -k^+_j [B_j] \left[ Ca^{2+} \right] + k^-_j [CaB_j]$$

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). $D_{Ca}, D_{Bj}, D_{CaBj}$ 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. $[Ca^{2+}]_\infty$ is background calcium concentration. For stationary immobile buffers or fixed buffers . Further equation (1-5) can be written as [3, 4, 9, 19]

$$\left(\frac{\partial^2 [Ca^{2+}]}{\partial r^2} + \frac{1}{r} \frac{\partial [Ca^{2+}]}{\partial r} + \frac{\partial^2 [Ca^{2+}]}{\partial \theta^2}\right)$$

$$- \frac{k^+[B]_\infty}{D_{Ca}} ([Ca^{2+}] - [Ca^{2+}]_\infty) - \frac{P_{max}V}{zF D_{Ca}} \frac{[Ca^{2+}]_\infty - [Ca^{2+}]_e}{1 - e^\epsilon V} = 0 \quad (5)$$

$$\frac{1}{D_{Ca}} \left( k^+[B]_\infty - \frac{P_{max}V}{zF} \right) ([Ca^{2+}] - [Ca^{2+}]_\infty) = 0 \quad (6)$$

$$a = \frac{1}{D_{Ca}} \left( k^+[B]_\infty - \frac{P_{max}V}{zF} \right) u = [Ca^{2+}]$$

where $\epsilon = 0.07788 \text{ mV}^{-1}$ and $P_{max}$ (Potential Activity) = $8.2650 \times 10^{-5}$

Assuming that point source of calcium concentration is at $(r=-5, \theta = \pi)$. The boundary condition can be taken as [2]:

$$\lim_{r \to -5, \theta \to \pi} \left( \frac{\partial [Ca^{2+}]}{\partial r} \right) = \sigma_{Ca} \quad (7)$$

On the other hand the background concentration of $Ca^{2+}$ is 0.1 µM and as it goes far away from the source. That is,

$$\lim_{r \to 5, \theta \to 0} [Ca^{2+}] = [Ca^{2+}]_\infty \quad (8)$$

Assuming that the neuron of circular shape and it is divided into coaxial circular elements [8, 10], given in figure 1:

Here the circle represents the number of elements and without circle represents the nodal points.

$$I(e) = \frac{1}{2} \int \int_A \left[ \left( r \frac{du(e)}{dr} \right)^2 + \left( \frac{du(e)}{d\theta} \right)^2 + a \left( u(e)^2 - 2u(e)u_\infty \right) r \right] dA - \mu(e) \int_{\theta_i}^{\theta_j} \left( \frac{\sigma u(e)}{2\pi r D_{Ca}} \right) d\theta \quad (9)$$

Here, we have used $u$ in lieu of $Ca^{2+}$ for our convenience, $e=1, 2...8$. Also the second term $\mu(e) = 1$ for $e=4, 5$ and $\mu(e) = 0$ for rest of the elements. The
Figure 1: finite element discretization of circular cell, where element 4 and 5 represents point source of calcium

Table 1: element information the discretized variational form of equations (6-10) is given by [17, 20]:

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following bilinear shape function for the calcium concentration within each element has been taken as [14, 15, 19]:

\[ u^{(e)} = c_1^{(e)} + c_2^{(e)} r + c_3^{(e)} \theta + c_4^{(e)} r\theta \]  \hspace{1cm} (10)

\[ u^{(e)} = p^T c^{(e)} \]  \hspace{1cm} (11)

where

\[ p^T = \begin{bmatrix} 1 & r & \theta & r\theta \end{bmatrix} \]  \hspace{1cm} (12)

and

\[ \left( c^{(e)} \right)^T = \begin{bmatrix} c_1^{(e)} & c_2^{(e)} & c_3^{(e)} & c_4^{(e)} \end{bmatrix} \]  \hspace{1cm} (13)
Two dimensional coaxial circular elements in FEM  459

from equation (11) - (13) we get,

\[ u^{(e)} = p^{(e)} c^{(e)} \]  \hspace{1cm} (14)

where

\[
\begin{bmatrix}
    u_i \\
    u_j \\
    u_k \\
    u_l
\end{bmatrix}
\text{and}

\[
\begin{bmatrix}
    1 & r_i & \theta_i & r_i \theta_i \\
    1 & r_j & \theta_j & r_j \theta_j \\
    1 & r_k & \theta_k & r_k \theta_k \\
    1 & r_l & \theta_l & r_l \theta_l
\end{bmatrix}
\]  \hspace{1cm} (15)

From equation (14) we have,

\[ c^{(e)} = R^{(e)} \bar{u}^{(e)} \]  \hspace{1cm} (16)

where

\[ R^{(e)} = \left( p^{(e)} \right)^{-1} \]  \hspace{1cm} (17)

Substituting \( c \) from equation (16) in equation (14) we get,

\[ u^{(e)} = p^T R^{(e)} \bar{u}^{(e)} \]  \hspace{1cm} (18)

Now, the integral \( I^e \) can be in the form

\[ I^e = I_k^{(e)} + I_m^{(e)} - I_s^{(e)} - I_z^{(e)} \]  \hspace{1cm} (19)

where

\[
I_k^{(e)} = \frac{1}{2} \int_{\theta_i}^{\theta_j} \int_{r_i}^{r_j} \left[ \frac{du^{(e)}}{dr} \right]^2 + \left( \frac{du^{(e)}}{d\theta} \right)^2 dr d\theta
\]  \hspace{1cm} (20)

\[
I_m^{(e)} = \frac{1}{2} \int_{\theta_i}^{\theta_j} \int_{r_i}^{r_j} [a u^{(e)}]^2 r dr d\theta
\]  \hspace{1cm} (21)

\[
I_s^{(e)} = \frac{1}{2} \int_{\theta_i}^{\theta_j} \int_{r_i}^{r_j} [2 u^{(e)} u^{(e)} \sigma u^{(e)} ar] dr d\theta
\]  \hspace{1cm} (22)

\[
I_z^{(e)} = \mu^{(e)} \int_{\theta_i}^{\theta_j} \left( \frac{\sigma u^{(e)}}{2 \pi D_{Ca}} \right) d\theta
\]  \hspace{1cm} (23)

Now from equation (19) we have following the equation:

\[
\frac{dI^{(e)}}{du^{(e)}} = \frac{dI_k^{(e)}}{du^{(e)}} + \frac{dI_m^{(e)}}{du^{(e)}} - \frac{dI_s^{(e)}}{du^{(e)}} - \frac{dI_z^{(e)}}{du^{(e)}}
\]  \hspace{1cm} (24)

On substituting values of equations, we get,

\[
\frac{dI}{d\bar{u}} = \sum_{e=1}^{N} \bar{M}^{(e)} \frac{dI^{(e)}}{du^{(e)}} \bar{M}^{(e)}^T
\]  \hspace{1cm} (25)
Symbol | Parameter | Values
--- | --- | ---
$D_{Ca}$ | diffusion coefficient | $250 \mu m^2/s$
$k^+_{EGTA}$ | buffer association rate | $1.5 \mu M^{-1}s^{-1}$
$k^-_{BAPTA}$ | buffer association rate | $600 \mu M^{-1}s^{-1}$
$[B]_\infty$ | total buffer concentration | $50 \mu M$
$[Ca]_\infty$ | background $Ca^{2+}$ concentration | $0.1 \mu M$
$\sigma$ | source amplitude | $1pA$
$F$ | Faraday Constant | $96487 coulM$
$V$ | Resting Potential | $-0.07 volt$
$z$ | valency of $Ca^{2+}$ concentration | $2$

$m=$meter, $s=$ second, $M=$ Mole

Table 2: List of Physiological Parameters Used for Numerical Results

where

$$M^{(e)} = \begin{bmatrix}
0 & 0 & 0 & 0 \\
\ldots & \ldots & \ldots & \ldots \\
0 & 0 & 0 & 0 \\
1 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1 \\
\ldots & \ldots & \ldots & \ldots \\
0 & 0 & 0 & 0 \\
\end{bmatrix}$$

and

$$I = \sum_{e=1}^{8} I^{(e)}$$

$$[\bar{x}]_{16\times16} [\bar{u}]_{16\times1} = [\bar{y}]_{16\times1}$$

The integral $I$ is extremized with respect to each nodal calcium concentration $u_i$ ($i=1, 2.....16$). This is given in the form of differential equation for steady state in terms of calcium concentration. The gauss elimination method has been used to obtain the solution [10, 19, 20].

3 Results and Discussion

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

BAPTA $k^+_{BAPTA}$: In this case BAPTA Buffer association rate is taken as $600 \mu M$. In figure 2, it is observed that the background calcium concentration is $0.1 \mu M$ at $r=5 \mu m$, Initially calcium concentration $0.05 \mu M$ at $r=-5 \mu m$ i.e. the
source and it increases along the radius as we move away from the source and it becomes maximum at other end of the boundary at \( r=5 \mu m \). Initially from \( r=-5 \mu m \) to \( r=-3 \mu m \) the rise in calcium concentration is very-very slow but the calcium concentration rises quickly between \( r=-3 \mu m \) to \( r=3 \mu m \). Further the rise in calcium concentration is gradually slow beyond \( r=3 \mu m \) up to \( r=5 \mu m \). The main reason of quick rise in calcium concentration between \( r=-3 \mu m \) to \( r=3 \mu m \) is that action potential activates the calcium channel.

![Graph between radius and Calcium Concentration](image)

**Figure 2:** graph between radius and Calcium Concentration

The Voltage Gated Calcium Channel (VGCC) will be open, and firstly electrical signal is converted into chemical signal because ions are in chemical form. Calcium molecules fuse into the synaptic vesicles, due to the high concentration. Thus neurotransmitter releases into the synaptic cleft and interacts with buffer which comes from the post-synaptic membrane. Some molecules go to pre-synaptic membrane by re-uptake pump. So at the mouth of the channel the calcium concentration is 0.1 \( \mu M \). So due to the depolarization of action potential, calcium concentration falls very fast between \( r=3 \mu m \) to \( r=-3 \mu m \).

The figure 3 and figure 4 represent the variation in \( Ca^{2+} \) concentration along angular direction and radial direction. We observe that calcium concentration is 0.1 \( \mu M \) at \( \theta = 3\pi/2 \) i.e. the source, and it decreases along the angle as we move away from the source and it becomes minimum at other end of the boundary at \( \theta = \pi/2 \). Initially from \( \theta = 3\pi/2 \) to \( \theta = 2\pi \) the fall in concentration is very-very slow but the calcium concentration falls quickly between \( \theta = 2\pi \) to \( \theta = 3\pi/2 \). Further the fall in calcium concentration is gradually slow beyond \( \theta = \pi \) to \( \theta = \pi/2 \). The figure 3 and figure 4, also shows calcium concentration at different radial distances. The concentration is \( r=5\mu m \) at source. It decreases along the angle from \( \theta = 3\pi/2 \) to \( \theta = 2\pi \). The calcium concentration at \( r=-3 \mu m \) falls quickly between \( \theta = 3\pi/2 \) to \( \theta = \pi/2 \).
At the place of VGCC, at radius $r=1.5 \, \mu m$ away from the source the fall in concentration is very slow between $\theta = 2\pi$ to $\theta = 3\pi/2$, but rapidly falls between $\theta = 3\pi/2$ to $\theta = \pi$, and then it becomes gradually slow between $\theta = 3\pi/2$ to $\theta = \pi/2$. At $r=3.3 \, \mu m$, fall in calcium concentration between $\theta = \pi$ to $\theta = \pi/2$ is slow but it becomes more fast between $\theta = \pi/2$ to $\theta = 2\pi$. Then it again becomes slow between $\theta = 2\pi$ to $\theta = 3\pi/2$. These figures represent the cytosolic diffusion as shown in two directions, radius $r$ and angle $\theta$. Its background concentration $0.1 \, \mu M$ as it goes far away from the $Ca^{2+}$ calcium channel. Source amplitude is taken to be only $1pA$, therefore its highest $Ca^{2+}$ concentration $0.1124 \, \mu M$, as signal arrives into the synaptic cleft, upper part of the channel [19]. Results obtained in agreement with the biological facts.
EGTA $k_m^+$: In Figure 5, it is observed the variation in $Ca^{2+}$ along radial direction. The changes in calcium concentration are initially very slow but it quickly falls between $r=-3 \, \mu m$ to $r=3 \, \mu m$. Further it becomes slow between $r=-5 \, \mu m$ to $r=-3 \, \mu m$ and $r=3 \, \mu m$ and $r=5 \, \mu m$. This is as if we are studying calcium diffusion in only one dimension. $Ca^{2+}$ is highest at the source and it starts decaying along radial direction. The result of EGTA buffer is just reverse to the BAPTA buffer due to the difference of these values.

Figure 6 and figure 7, represent the cytosolic diffusion is shown in two dimensions, radius ($r$) and angle $\theta$. These results are also opposite to that of BAPTA buffer. Its background concentration 0.1 M as it goes far away from
the $Ca^{2+}$ calcium channel. It falls, source amplitude is taken to be only 1pA, and therefore its highest $Ca^{2+}$ concentration is 0.1294 µM. If signal arrives at mouth of the channel, so depolarization occur, then VGCCs can only increase the intracellular $Ca^{2+}$ concentration to extent of 0.1294 µM. At high cytosolic $Ca^{2+} \quad 10 \mu M$ and at low concentrations $Ca^{2+} \quad 1 \mu M$.

4 Conclusion

It is observed that potential activity has significant effect calcium concentration give us better central regions little away from the source. The coaxial 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.

References


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