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Galerkin Approximation for the Problem of Calcium Diffusion in Neuron Cell Involving Pump Leak and Excess Buffering Approximation

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Abstract

The electrical and chemical signaling processes are major processes involved in neuron communication system. Calcium is known as second messenger which plays an important role in chemical signaling process in neuron cell. The diffusion of calcium and reaction involving absorption and generation of calcium play an important role in achieving this communication process. A mathematical model has been developed incorporating the diffusion reaction and a excess buffer. The model has been developed for a one dimensional steady state case. The boundary conditions have been modeled using biophysical condition. Galerkin Method has been employed to obtain the solution. The relationships among various parameters have been studied with the help of solution obtained using Matlab.

Keywords: Calcium Diffusion , Galerkin Approximation, Chemical Signaling

1. Introduction

Calcium (Ca^{2+}) plays a pivotal role in the physiology and biochemistry of organisms and the cell. It plays an important role in signal transduction pathways, where it acts as a second messenger, in neurotransmitter release from neurons, contraction of all muscle cell types, and fertilization. Many enzymes require calcium ions as a cofactor, those of the blood-clotting cascade being notable examples. Extracellular calcium is also important for maintaining the potential difference across excitable cell membranes, as well as proper bone formation [2,6]. Calcium is an important intracellular signaling molecule with rapid effect on the kinetics of many processes. When the wave of Action Potentials reaches the end of the axon the electrical signal is converted into a chemical signal. This chemical neurotransmitter crosses the space between adjacent neurons and initiates an Action Potential on another neuron. The action potential activates a calcium channel and Ca^{2+} diffuses into the neuron. This Ca^{2+} causes vesicles to fuse with the cell membrane. Through exocytosis, neurotransmitters are released into the synapse. These neurotransmitters diffuse across the synapse and bind to receptors on another neuron. This causes special Na+ channels to open and an action potential is initiated in the next neuron [3]. Once the message has been passed on to the next neuron, the neurotransmitter is reabsorbed into the axon, diffuses away or it is destroyed by an enzyme [5,6].

The calcium ion is one of the most functionally important messengers known in the brain, mediating functions from neurotransmission to cytoarchitectonics. Neuronal calcium acts as a charge carrier during information processing and as a ubiquitous intracellular messenger. Calcium signals are fundamental to numerous aspects of neuronal development and plasticity. Specific and independent regulation of these vital cellular processes is achieved by a rich bouquet of different calcium signaling mechanisms within the neuron, which either can operate independently or may act in concert. This study demonstrates the existence of a novel calcium signaling mechanism by simultaneous patch clamping and calcium imaging from acutely isolated central neurons. These neurons possess a membrane voltage sensor that, independent of calcium influx, causes G-protein activation, which subsequently leads to calcium release from intracellular stores via phospholipase C and inositol 1,4,5-trisphosphate receptor activation. This allows neurons to monitor activity by intracellular calcium release without relying on calcium as the input signal and opens up new insights into intracellular signaling, developmental regulation, and information processing in neuronal compartments lacking calcium channels.[4,6,8]

Mobile Ca^{2+} buffers have an additional “sink” effect on free Ca^{2+} in proportion to the local Ca^{2+} gradient that both restricts Ca^{2+} elevations and facilitates .Ca^{2+} indicator dyes

are themselves mobile Ca^{2+} buffers. The Ca^{2+} micro domain at the mouth of a channel forms quickly upon opening of the channel and dissipates quickly upon channel closure reaching equilibrium with in micro seconds. We can formulate the model for the equilibrium Ca^{2+} profile near an open channel. These formulas relate the Ca^{2+} concentration to the distance from the channel and differ primarily in the treatment of calcium diffusion. G.D. Smith [8] has developed a simplified mathematical description of calcium diffusion that is valid in the presence of excess buffering approximation. Experimental buffers in the cytoplasm give equilibrium time on the order of few millisecond .The validity of the rapid buffering approximation requires that the equilibrium time be much smaller than the time required for calcium to diffuse across a region of the size of a typical gradient[6,7,9].

2. Mathematical Model

Calcium kinetics in neurons is governed by a set of reaction-diffusion equations which can be framed assuming the following bimolecular reaction between Ca^{2+} and buffer Species. The buffered diffusion of calcium near isolated point sources can be described mathematically by a system of reaction diffusion equation with spherical symmetry.
It is standard to assume homogeneity, isotropy and Fickian diffusion as well as bimolecular association reaction between calcium and buffer of the form.[8]

$$Ca^{2+} + B_j \underset{k_j^-}{\overset{k_j^+}{\rightleftharpoons}} CaB_j$$

Where Bj and CaBj are free and bound buffer and j is an index over the buffer species. Based on these assumption the concentration of free, Ca^{2+} free buffer ([Bj]) and bound buffer ([CaBj]) is written in this equation form.[8,9]

$$\partial[Ca^{2+}] / \partial t = D_{Ca} \nabla^2 [Ca^{2+}] + \sum Rj \quad (2)$$

$$\partial[B_j] / \partial t = D_{Bj} \nabla^2 [B_j] + R_j \quad (3)$$

$$\partial[CaB_j] / \partial t = D_{CaBj} \nabla^2 [CaB_j] - R_j \quad (4)$$

Where reaction term R_j is given by

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

In this equation $D_{Ca,}B_j$ and D_{CaBj} are diffusion coefficients for free , free buffer and bound buffer, respectively $k^+{}_j$,$k^-{}_j$ are the association and dissociation constant for buffer j, respectively. Buffers that do not diffuse are referred to as stationary , immobile or fixed and are accounted for by setting DBj = DCaBj=0.

We know that the association and dissociation rate constant for the bimolecular association reaction between Ca^{2+} and buffer j can be combined to obtain dissociation constant K_j

$$K_j = k^-{}_j \Big/ k^+{}_j$$

Ca^{2+} has a molecular weight that is small in comparison to most Ca^{2+} binding species. If we further assume that the diffusion constant of each mobile buffer is not affected by the binding of Ca^{2+} and also assume that $[B_j]_T$ is initially uniform then $[B_j]_T$ will remain uniform for all time. Thus we can omit (3) and rewrite (2) and (4) as

$$R_j = -k_j[B_j][Ca^{2+}] + k_j([B_j]_T - [B_j]) \tag{6}$$

For fixed buffers $D_{Bj} = D_{CaBj} = 0$

If all the buffers are fixed then the steady state Ca^{2+} distribution is the unbuffered steady state solution. For mobile buffers on the other hand the reaction term is not zero at general.At steady state case; net production of buffer at a point in space can be balanced by diffusion of free buffer away from that point if there is standing gradient.

For boundary condition we assume a point source Ca^{2+} at the origin and a fixed background Ca^{2+} concentration. There is no source for buffer and the buffers are assumed to be equilibrium with Ca^{2+} for from the source. A reasonable initial condition for their simulation is a uniform background $(4\pi D_c r^2 \partial[Ca^{2+}] \Big/ \partial t) = \sigma$ profile of $[Ca^{2+}]$=.01 μ m. We further assume that all buffers are initially in equilibrium with Ca^{2+} and boundary conditions are given by

$$\lim_{r \longrightarrow \infty} [Ca^{2+}] = [Ca^{2+}]_\infty \tag{7}$$

And

$$\lim [B_j] = [B_j]_\infty = K [B_j]_T \Big/ K_j + [Ca^{2+}]_\infty \tag{8}$$

Near the source we enforce the boundary condition.

$$\text{Lim } r \to \infty \ (4\pi D_c r^2 \partial[Ca^{2+}] \Big/ \partial t) = \sigma \tag{9}$$

$$(4\pi D_c r^2 \partial[B_j]/\partial t) = 0 \tag{10}$$

Implying an influx of free Ca^{2+} at the rate σ, by Faraday's Law $\sigma = iCa/zF$.

For notational simplicity we have written D_c and D_b for the diffusion coefficient of free Ca^{2+} and free buffer, respectively and ∇^2 as an abbreviation for equations for the buffered diffusion of Ca^{2+}.[8,12,14]

$$\nabla^2 = \frac{\partial^2}{\partial r^2} + \frac{2}{r}\frac{\partial}{\partial r}$$

2.1 THE EXCESS BUFFERING APPROXIMATION

EBAis appropriate when the saturability of mobile buffer is negligible. For example, this is the case for millimolar concentrations of Calbindin-D28K in the saccular hair cell. RBA appropriate when there is significant saturability of mobile buffer and when buffer kinetics are fast relative to Ca2+ diffusion. This is often the case near Ca2+ channels in synapses, and near IP3 or ryanodine receptors in the ER/SR. Smith et al. (2001) did an asymptotic analysis of buffered Ca2+ diffusion near a point source, and determined mathematical conditions for when RBA or EBA are appropriate.[8,9]

We know that the association and dissociation rate constants for the bimolecular association reaction between ca^{2+} and buffer j can be combined to obtain a dissociation constant, K_j

$$K_j = k_j^-/k_j^+ \tag{11}$$

As r tends to ∞, the system achieves equilibrium and hence from (6) & (7) we get Rj = 0, i.e., reaction term is zero in equilibrium position. This implies that the system has achieved the level of concentration of $[Ca^{2+}]$, which is necessary to cause 50% of the buffer to be in bound form and 50% in free form. For equilibrium using equations (7)-(9), we get:

$$[B]_\infty = \frac{K[B]_T}{K[Ca^{2+}]_\infty} \tag{12}$$

and

$$[CaB]_\infty = \frac{[Ca^{2+}]_\infty [B]_T}{K + [Ca^{2+}]_\infty} \tag{13}$$

Where $[Ca^{2+}]_\infty$ is "background" or ambient free Ca^{2+} concentration, and $[B]_\infty$ and $[CaB]_\infty$ are the equilibrium concentrations of free and bound buffer. The higher values for K imply that the buffer has a lower affinity for Ca^{2+} and is less easily saturated.

When ions diffuse through pores, they begin to ruin the normal distribution of ions. This type of movement of the ions is called leaking. And the pores that allow leaking to occur are called leak pores. Because this leaking is not a good thing for the cell, there are very, very few of these leak pores. And, to counteract them, there has to be a way to return the ions back to their appropriate compartments. Returning a sodium ion to the extracellular fluid is moving it against its concentration gradient. Movement against the concentration gradient has to be accomplished by active transport, which requires protein pumps and ATP. There is one pump that simultaneously moves sodium ions back out and potassium ions back in. It is called the sodium-potassium pump.[8,9,14]

In this case, if we take $J=(J_{pump})+(J_{leak})$

Where

$$J_{Pump} = v_P \frac{[Ca^{2+}]^2}{k^2 + [Ca^{2+}]^2}$$

where K_{pump} is 184 nM, m is 3.98, and v_{pump}^{max} is 208 μMs^{-1}. The contribution of SL Na^+/Ca^{2+} exchanger is ignored because of its minor role in regulating cellular $[Ca^{2+}]$ transients in rat ventricular myocytes. Because we do not explicitly keep track of the concentration of Ca^{2+} in the SR, the model requires an SR leak to balance J_{pump} when Ca^{2+} is at the background concentration ($c_{\infty} = 0.1$ μM).

Therefore, as sodium and potassium ions leak (just a bit) through the few leak pores that exist for them, the sodium-potassium pump shoves them back into their appropriate compartments. This constant leaking and shoving back is what keeps the concentrations of these ions steady. This is what maintains the concentration gradients on both ions. [16,18,19]

And The magnitude of the SR leak is thus constant and given by

$$J_{Leak} = v_L\left([Ca^{2+}]_{ER} - [Ca^{2+}]\right)$$

where $[Ca^{2+}]_{ER}$ denotes the $[Ca^{2+}]$ in the ER.

The parameter values in the model are: $v_P = 0.5\ s^{-1}$, $v_L = 0.001$ μM/s, $[Ca^{2+}]_{ER} = 15.0$ μM, $k = 0.1$ μM.

then the equations for the buffered diffusion of Ca^{2+} become.

$$\frac{\partial [Ca^{2+}]}{\partial t} = D_c\ \nabla^2 [Ca^{2+}] - k^+ [B]_\infty ([Ca^{2+}] - [Ca^{2+}]_\infty) + v_P \frac{[Ca^{2+}]^2}{k^2 + [Ca^{2+}]^2} + v_L\left([Ca^{2+}]_{ER} - [Ca^{2+}]\right)$$

Or (15)

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_c \nabla^2 [Ca^{2+}] - k^+ [B]_\infty ([Ca^{2+}] - [Ca^{2+}]_\infty) + J_{pump} + J_{leak} \quad (16)$$

For One Dimensional steady State Case it will convert into this form

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_c \nabla^2 [Ca^{2+}] - k^+ [B]_\infty ([Ca^{2+}] - [Ca^{2+}]_\infty) + J_{pump} + J_{leak} \quad (17)$$

$$D_c \nabla^2 [Ca^{2+}] - k^+ [B]_\infty ([Ca^{2+}] - [Ca^{2+}]_\infty) + J_{pump} + J_{leak} = 0 \quad (18)$$

$$\frac{d^2[Ca^{2+}]}{dr^2} = \frac{2}{r}\frac{d[Ca^{2+}]}{dr} + \frac{[Ca^{2+}] - c_\infty}{\gamma^2} + v_p \frac{[Ca^{2+}]}{k^2 + [Ca^{2+}]} v_l([Ca^{2+}]_{ER} - [Ca^{2+}]) \quad (19)$$

$$\int_0^\infty \frac{d^2[Ca^{2+}]}{dr^2} + \frac{2}{r}\frac{d[Ca^{2+}]}{dr} - \frac{[Ca^{2+}] - c_\infty}{\gamma^2} + v_p \frac{[Ca^{2+}]}{k^2 + [Ca^{2+}]} + v_l([Ca^{2+}]_{ER} - [Ca^{2+}]) N_k(r)\, d = 0 \quad (20)$$

$$\sum_{e=1}^{E} [N^{(e)}]^T \left[\frac{d^2[Ca^{2+}]}{dr^2} + \frac{2}{r}\frac{d[Ca^{2+}]}{dr} - \frac{[Ca^{2+}] - c_\infty}{\gamma^2} + v_p \frac{[Ca^{2+}]}{k^2 + [Ca^{2+}]} + v_l([Ca^{2+}]_{ER} - [Ca^{2+}])\right] dr = 0 \quad (21)$$

$$\int_{r_i}^{r_j} [N^{(e)}]^T \frac{du}{dr} \Big]_{r_i} - \int_{r_i}^{r_j} \frac{d}{dr}[N^{(e)}]^T \frac{du^{(e)}}{dr} dr \left(\frac{2}{r}\right) \int_{r_i}^{r_j} \frac{du}{dr} [N^{(e)}]^T dr \int_{r_i}^{r_j} [N^{(e)}]^T \frac{u^{(e)}}{\gamma^2} dr$$
$$- \int_{r_i}^{r_j} [N^{(e)}]^T \frac{u_\infty}{\gamma^2} dr - \int_{r_i}^{r_j} [N^{(e)}]^T v_p \frac{[u]}{k^2 + [u]} - \int_{r_i}^{r_j} [N^{(e)}]^T v_l([u]_{ER} - [u]) dr = 0 \quad (22)$$

Applying Galarkin approximation We get this equation.Where u is the function of r, which represents Calcium Concentration.

Where E is the no. of elements and r_i, r_j are the values of r at the first and second nodes of element respectively and Where u is the function of r .which represents Calcium Concentration.

We shall assume a linear interpolation model for $\emptyset^{(e)}$ so that

$$\emptyset^{(e)}(r) = N_i(r)\emptyset_i^{(e)} + N_j(r)\emptyset_j^{(e)}$$

And hence

$$[N^{(e)}]=[N_i^{(e)}(r)\ N_j^{(e)}(r)]$$

Where

$$N_i(r) = \frac{r_j - r}{l^{(e)}} \quad \text{and} \quad N_j(r) = \frac{r - r_i}{l^{(e)}}$$

$$\sum_{e=1}^{E}[K^{(e)}]\,u^{(e)} = \sum_{e=1}^{E}\overline{\rho^{(e)}}$$

Where

$$\int_{r_i}^{r_j}[N^{(e)}]^T u^{(e)}\,dr = \frac{1}{l^{(e)}}\begin{bmatrix}2 & 1\\ 1 & 2\end{bmatrix}\begin{Bmatrix}u_i^{(e)}\\ u_j^{(e)}\end{Bmatrix}$$

$$\int_{r_i}^{r_j}[N^{(e)}]^T u\,dr = \frac{1}{6}\begin{Bmatrix}r_j^2 + r_i r_j + 2r_i^2\\ 2r_j^2 - r_i r_j + r_i^2\end{Bmatrix}$$

$$\frac{d}{du}[N^{(e)}]^T = \begin{Bmatrix}-1\\ 1\end{Bmatrix}$$

$$\int_{r_i}^{r_j}\frac{d}{dx}[N^{(e)}]^T\frac{du^{(e)}}{dr}dr = \frac{1}{l^{(e)}}\begin{bmatrix}1 & -1\\ -1 & 1\end{bmatrix}\begin{Bmatrix}u_i^{(e)}\\ u_j^{(e)}\end{Bmatrix} \tag{22}$$

RESULTS & DISCUSSION

EBA is appropriate when the saturability of mobile buffer is negligible. This is often the case near Ca^{2+} channels in synapses. Smith et al. [8] did an asymptotic analysis of buffered Ca^{2+} diffusion near a point source, and determined following mathematical conditions for the case where EBA is appropriate.

$\lim_{r\to 0} B = B_\infty$ (EBA), buffer unsaturated

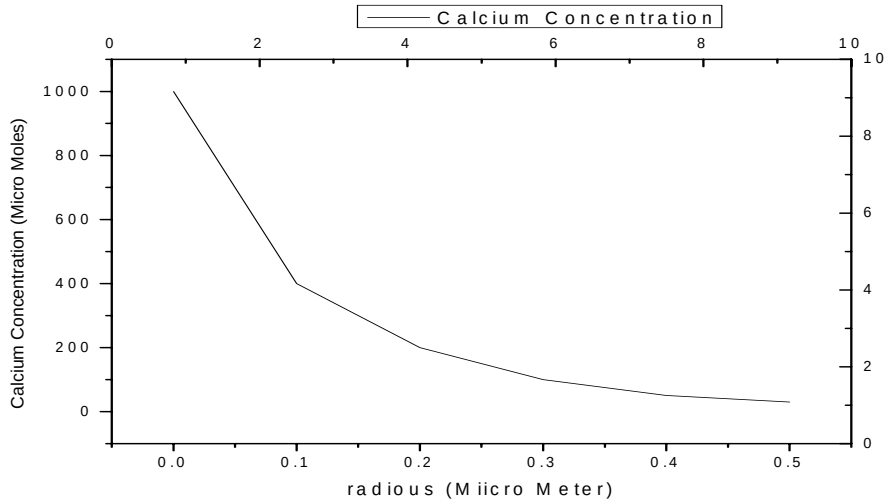

Figure-1: Calcium concentration profile with respect to position, for, Dc =250 $\mu\mu m^2/s$, $[B]_T$=50μM, k^+= 5 $\mu M^{-1}s^{-1}$,σ =1 pA,

In fig-1 we observe that calcium concentration falls very sharply for r between 0-.3μm and then gradually decreases for r between .3-.5 μm and thereafter converges to 0.1 μM and becomes uniform throughout. This is because near the source, the concentration of Ca^{2+} is high and it decreases as we move far away the source. The sharp fall in concentration of calcium near the source indicates that the binding activity of the buffers with Ca^{2+} is high which makes the concentration to fall at a faster rate initially and

thereafter the binding activity slows down gradually as we away the source with the decrease in calcium concentration.

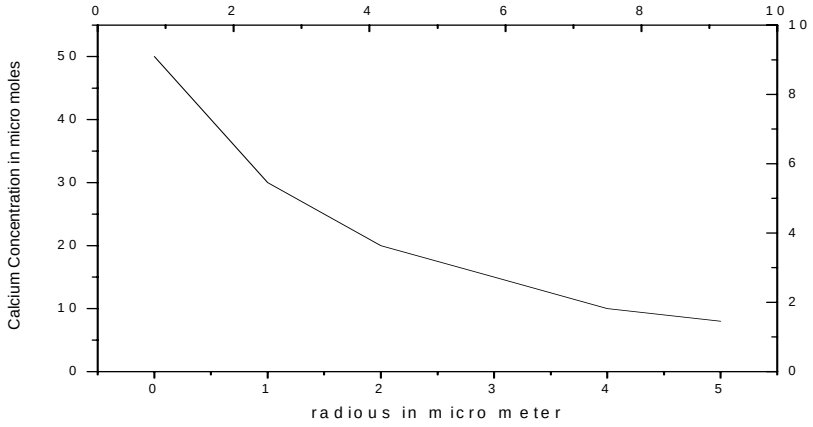

Figure-2: Bound calcium concentration profile with respect to position, for, Dc =250 $\mu m^2/s$, $[B]_T$=50μM, K= 1 μM,σ =1 pA, D_b=75 $\mu m^2/s$

In figure-2 we observe that bound calcium concentration falls sharply for r between 0-3μm and then gradually decreases for r between 3-5 μm and thereafter it becomes almost constant. This is because near the source more free calcium is available for binding with buffers. The response of bound calcium is nonlinear with respect to position.

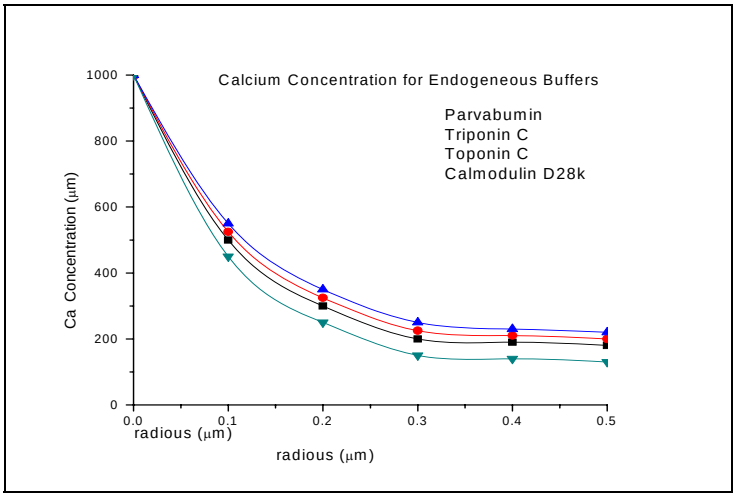

Figure-3: Calcium concentration profile with respect to position for, Dc =250 $\mu\mu m^2/s$,σ =1 pA, for parvalbumin: $[B]_T$=50μM, k^+= 6 $\mu M^{-1}s^{-1}$, for Tripomin-C: $[B]_T$=50μM, k^+= 39 $\mu M^{-1}s^{-1}$, Troponin: $[B]_T$=50μM, k^+= 90$\mu M^{-1}s^{-1}$, Calmodulin D_{28K}: $[B]_T$=50μM, k^+= 120$\mu M^{-1}s^{-1}$

In fig-3, we see that the difference between the curves is not much. This is because there is little variation in binding rate of different endogenous buffers.

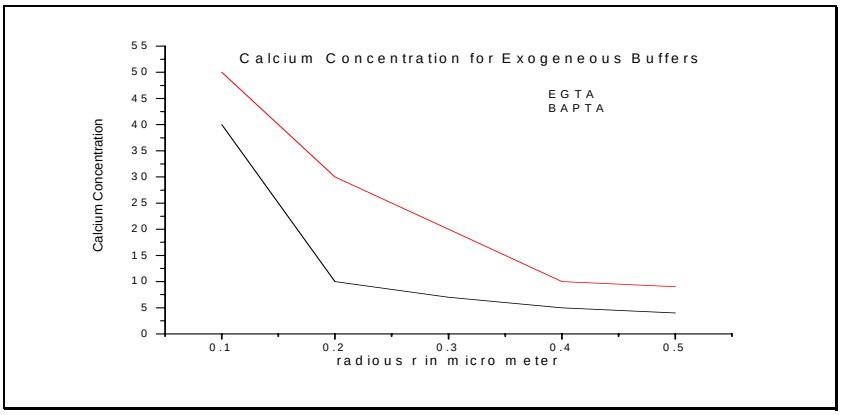

Figure-4: Calcium concentration profile with respect to position, for, Dc =250 $\mu\mu m^2/s$, $[B]_T$=50μM, k^+= 5 $\mu M^{-1}s^{-1}$,σ =1 pA,

In fig-4 we see that the fall in [Ca^{2+}] for slow buffer (EGTA) is less sharp and low as compared to that for fast buffer (BAPTA). Also the [Ca2+] for slow buffer becomes almost constant at a position far away from the source as compared to that in case of fast buffer where the concentration of calcium becomes constant at small distance from the source. This is because the binding rate of fast buffer is very high and causes the [Ca^{2+}] to fall more sharply as compared to that in the case of slow buffer.

The results obtained above are in agreement with those obtained by earlier research workers [6]. Further these results are also in agreement with the biological facts. The mathematical model developed above yields interesting results and gives us understanding of the phenomenon & relationships among various biophysical parameters. Such mathematical models can be developed for normal & abnormal cases to generate information, which may be of great useful to biomedical scientist for developing protocols for diagnosis and treatment of neuronal diseases.

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