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A Numerical Model to Study Excess Buffering Approximation near an Open Ca^{2+} Channel for an Unsteady State Case

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ABSTRACT

The elevation of the cytoplasmic calcium concentration is a central step in many intracellular signal transduction pathways. It is also observed in various systems that calcium signals can also mediate intracellular communication by eliciting and coordinating calcium signals in surrounding cells, for example, in the liver and the astrocytes network of the central nervous system. In view of above mathematical model of calcium signaling process in the presence of excess buffer has been developed for a one dimensional unsteady state case. This model incorporates important physical and physiological parameters like dissociation rate, diffusion rate, total buffer concentration and influx. The finite difference method has been employed to predict $[Ca^{2+}]$ and buffer concentration time course regardless of the calcium influx. The comparative study of the effect of the excess buffered diffusion and kinetic parameters of the model on the concentration time course have been performed.

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Introduction

Chemical reaction and diffusion are important phenomena in quantitative neurobiology and biophysics. The knowledge of 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 [1, 2, 3]. About 99% of our body's calcium is deposited in the bones and teeth. The remaining 1% is present in body fluids, approximately equally divided between diffusible calcium and non-diffusible calcium. The diffusible calcium is bound to blood proteins, chiefly to albumin, although a small amount is bound by the globulins in the blood. We need and use more calcium than any other mineral in the body. In fact there are 179 different known uses for calcium in the human body. It controls muscle contraction and relaxation, is responsible for nerve impulse transmission and the transfer of information between our brain cells. It controls osmosis and diffusion through the cell membranes, and also the passing of information within the cell. It controls the rhythm of the heart, the formation of enzymes and hormones, and also the DNA formation in chromosomes. It is used in blood clotting, urine filtration, and it's also used in the formation and maintenance of the bones and teeth.

Calcium indicates many hormonal responses. It is important inscription of hormones and neurotransmitters, in muscles contraction, and in regulation of gene expression because Ca^{2+} is a ubiquitous signaling agent and is toxic in high concentration. It is highly buffered by Ca^{2+} binding proteins, so that less then 1 % of the Ca^{2+} in cells exists in a free ionic form. The target that binds Ca^{2+} include secretory vesicles, Ca^{2+} activated K^{+} channels, and the channels that themselves conduct Ca^{2+}, through membrane. These targets are located very near the source of Ca^{2+}, often within tens of nanometers [4, 5, 7]. These Ca^{2+} domains are formed in the presence of ubiquitous Ca^{2+} binding protein of the presynaptic terminal. By binding and releasing free Ca^{2+} endogenous, Ca^{2+} binding proteins and other Ca2+ buffers determine the range of action of Ca^{2+} ions influence the time course of their effect and facilitate clearance of Ca^{2+}.

There have been numerous mathematical studies of the Ca^{2+} distribution near an open Ca^{2+} channel or within a presynaptic terminal [3, 5, 6, 15]. These studies show that the Ca^{2+} microdomain at the mouth of a channel forms quickly upon opening of the channel and dissipates quickly upon channel closure, reaching equilibrium within microseconds. These formulas relate the Ca^{2+} concentration to the distance from the channel, and differ primarily in the treatment of Ca^{2+} buffers. In present investigation, it is assumed that the buffers are unsaturable i.e., excess buffers. Neher [7] made the critical observation that if buffer is present in excess, then the free mobile buffer profile is not perturbed by the presence of source. In the present investigation a model has been developed to study the diffusion of Ca^{2+} in neuron cells. For a one dimensional unsteady state.

Mathematical Model

Reaction diffusion equations are often used to simulate the buffered diffusion of intracellular Ca^{2+} an important process to include in biophysically realistic neuronal models. The buffered diffusion of Ca^{2+} near isolated point sources can be described mathematically by a system of reaction- diffusion equations with spherical symmetry. It is standard to assume homogeneity, isotropy, and Fickian diffusion as well as bimolecular association reaction between Ca^{2+} and buffer of the form.

$$Ca^{2+} + B_j \frac{k_j^+}{k_j^-} CaB_j \qquad (1)$$

Where Bj and CaBj are free and bound buffer, respectively and j is an index over the buffer species.

With these assumptions the system of reaction – diffusion equations for the concentrations of Ca^{2+}, free buffer Bj and bound buffer CaBj respectively are as below,

$$\frac{\partial [Ca^{2+}]}{\partial t} = D_{Ca} \nabla^2 [Ca^{2+}] + \sum R_j \qquad (2)$$

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

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

Where reaction term Rj is given by

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

In this equation D_{Ca}, D_{Bj} and D_{CaBj} are diffusion coefficients for free Ca^{2+} free buffer and bound buffer respectively. k_j^+ and k_j^- are dissociation rate constants for buffer j respectively

Because Ca^{2+} has a molecular weight that is small in comparison to most Ca^{2+} binding species, The diffusion constant of each mobile buffer is not affected by the binding of Ca^{2+} that is $D_{Bj} = D_{CaBj} = D_j$. Using this assumption in equations (3) & (4), we get

$$\frac{\partial[B_j]_T}{\partial t} = \frac{\partial[B_j]}{\partial t} + \frac{\partial[CaB_j]}{\partial t} = D_j\nabla^2[B_j]_T$$

Where $$[B_j]_T = [CaB_j] + [B_j] \quad (6)$$

Providing that the $[B_j]_T$ profile is initially uniform and there is no source or sink for Ca^{2+} buffer , the $[B_j]_T$ will remain uniform for all time . Thus we write the following equation for the buffered diffusion of Ca^{2+}

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\ \nabla^2[Ca^{2+}] + \sum R_j \quad (7)$$

$$\frac{\partial[B_j]}{\partial t} = D_{Bj}\ \nabla^2[B_j] + R_j \quad (8)$$

Where $$R_j = -k_j^+[Ca^{2+}][B_j] + k_j^-([B_j]_T - [B_j]) \quad (9)$$

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 buffer is assumed to be in equilibrium with Ca^{2+} far from the source

A reasonable initial condition for their simulation is a uniform background Ca^{2+} profile of $[Ca^{2+}] = 0.1\ \mu M$

We further assume that all buffers are initially in equilibrium with Ca_{2+} and boundary conditions [6] are given by

$$\lim_{r\to\infty}[Ca^{2+}] = [Ca^{2+}]_\infty = C_\infty$$

and

$$\lim_{r\to\infty}[B_j] = [B_j]_\infty = \frac{K[B_j]}{K_j^+[Ca^{2+}]_\infty} \quad (10)$$

Near the source we enforce the boundary conditions

$$\lim_{r\to 0} 4\pi D_c\, r^2 \frac{\partial[Ca^{2+}]}{\partial t} = \sigma$$

and

$$\lim_{r\to 0} 4\pi D_c\, r^2 \frac{\partial[B_j]}{\partial t} = 0 \quad (11)$$

implying an influx of free Ca^{2+} at the rate σ, By Faraday's law, σ = ICa /zF

For notational simplicity we have written Dc and Db 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+}.

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

These full equations for the buffered diffusion of Ca^{2+} have been used to analyze the ability of endogenous buffers (fast BAPTA and slow EGTA) and exogenous Ca^{2+} buffers in the vicinity of a channel pore.

The Excess Buffeing Approximation

We know that the association and dissociation rate constants for the bimolecular association reaction between ca2+ and buffer j can be combined to obtain a dissociation constant, Kj

$$K_j = \frac{k_j^-}{k_j^+} \quad (12)$$

As r tends to ∞, the system achieves equilibrium and hence from (7) & (8) we get $R_j = 0$, 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:

$$[B]_\infty = \frac{K[B]_T}{K[Ca^{2+}]_\infty} \quad (13)$$

and

$$[CaB]_\infty = \frac{[Ca^{2+}]_\infty[B]_T}{K + [Ca^{2+}]_\infty} \quad (14)$$

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.

In this case, if we assume J=0 then the equations for the buffered diffusion of Ca^{2+} become.

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_C\nabla^2[Ca^{2+}] - k^+[B]_\infty\ \left([Ca^{2+}] - [Ca^{2+}]_\infty\right) \quad (15)$$

Employing finite differences technique, we get

$$U_i^{j+1} = U_i^j + \frac{kD_C}{2r_i^2h^2}[(r_{i+1/2})^2(U_{i+1}^j - U_i^j) - (r_{i-1/2})^2(U_i^j - U_{i-1}^j)] - k\left(k^+([B]_\infty\left(U_i^j - [Ca^{2+}]_\infty\right)\right)$$

for $r_i \neq 0$ (16)

Where U_i^j is an approximation to the function $u(r_i, t_j)$, and u represents the concentration of Ca^{2+}. h and k are the step sizes for the r and t,

$$r_{i+1/2} = r_i + h/2 \text{ and } r_{i-1/2} = r_i - h/2$$

At the origin (r_i=0,i=0) a finite difference approximation to equation (15) gives

$$U_0^{j+1} = U_0^j + \frac{6kD_C}{h^2}(U_1^j - U_0^j) - -k\left(k^+([B]_\infty\left(U_0^j - [Ca^{2+}]_\infty\right)\right) \quad (17)$$

A computer program has been developed and executed of P-IV computer to obtain numerical results.

Numerical Results & Discussion

The following numerical values [15]for various parameters have been used to compute the numerical results

Table-1, Numerical values of various calcium buffers

A) Endogenous

Ca2+ buffer	k+ μM-1s-1	k- s-1	K μM	[B]T μM
Troponin-C	90-100	7-300	0.05-3 0	50(varied)
Calmodulin D28K	100-500	37-470	0.2-2.0	32
Triponin C	39	20	0.51	70
Parvalbumin	6	1	0.00037	36

B) Exogenous

Ca2+ buffer	k+ μM-1s-1	k- s-1	K μM	[B]T μM
EGTA	1.5	0.3	0.2	113
BAPTA	600	100	0.1-0.7	95

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. [3] 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∞ (EBA), buffer unsaturated

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.

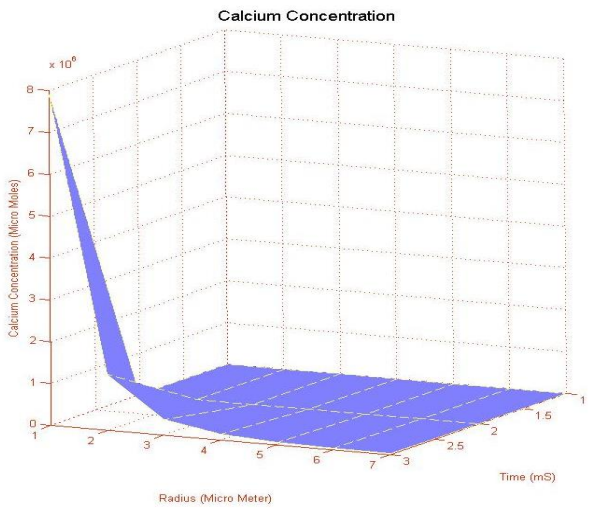

Figure-1: Calcium concentration profile with respect to position and time, for, Dc =250 μμm2/s, $[B]_T$=50μM, k^+= 5 $\mu M^{-1}s^{-1}$,σ =1 pA,

The concentration at time t = 0 ms is taken to be 0.1 μM. The calcium concentration increases with time and reaches steady state with in 100 ms. The increase in $[Ca^{2+}]$ takes place because when the gates open the free Ca^{2+} ions enter the cells. As soon as calcium concentration reaches to the peak values the neurotransmitters leave the cell and thus the gates close and system reaches the steady state within 100 ms.

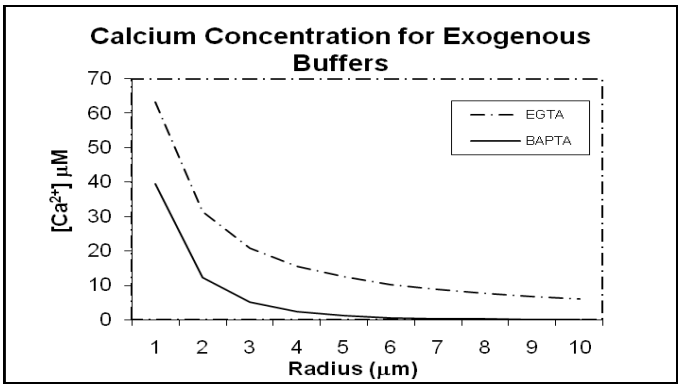

Figure-2: Calcium concentration profile with respect to position for fixed time t=1 ms, for, Dc =250 μμm^2/s, σ =1 pA, for EGTA: $[B]_T$=50μM, k^+= 1.5 $\mu M^{-1}s^{-1}$, for BAPTA: $[B]_T$=50μM, k^+= 600 $\mu M^{-1}s^{-1}$

In fig-2 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 $[Ca^{2+}]$ for slow buffer becomes almost constant at a position far away (100 μs) from the source as compared to that in case of fast buffer where the concentration of calcium becomes constant at small distance (20 μm) 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.

For the standard values given by Klingauf and Neher [5], the endogenous buffer time course closely follows the behavior of the $[Ca^{2+}]$ time course. 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.

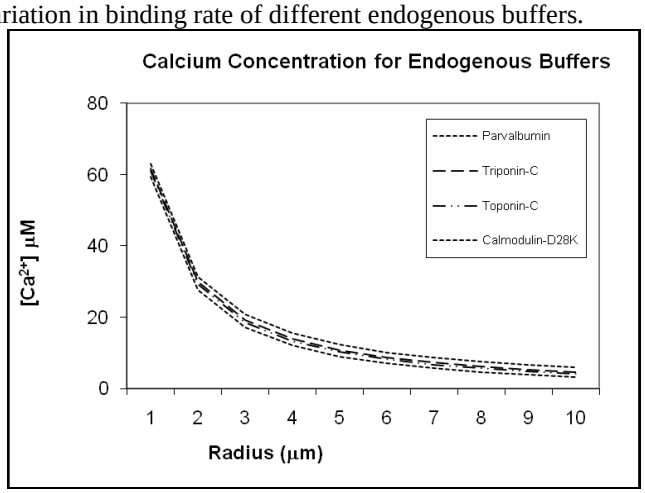

Figure-3: Calcium concentration profile with respect to position for fixed time t=1 ms, for, Dc =250 μμm2/s,σ =1 pA, for parvalbumin: [B]T=50μM, k+= 6 μM-1s-1, for Tripomin-C: [B]T=50μM, k+= 39 μM-1s-1, Troponin: [B]T=50μM, k+= 90μM-1s-1, Calmodulin D28K: [B]T=50μM, k+= 120μM-1s-1

We observe from figure-4 that fall in calcium concentration is very sharp initially for low source amplitude in comparison to the cases of higher source amplitude. The sharpness of the fall in

$[Ca^{2+}]$ profile decreases with the increase in source amplitude. This is because as source amplitude increases the movement of free calcium ions from extracellular space to intracellular space also increases. In all figures the response of free $[Ca^{2+}]$ profile is highly nonlinear near the source

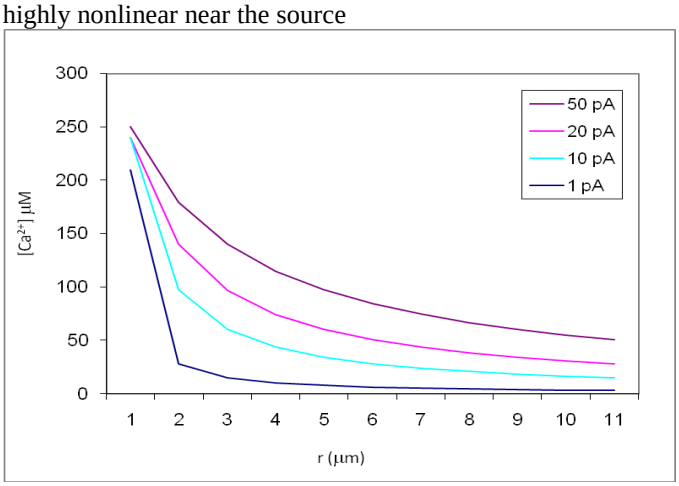

Figure-4: Calcium concentration profile with respect to position and time t=1 ms, for, Dc =250 µµm2/s, [B]T=50µM, k+= 5 µM-1s-1

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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