

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

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Abstract—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. Calcium waves propagate inside cells due to a regenerative mechanism known as calcium-induced calcium release. Buffer-mediated calcium diffusion in the cytosol plays a crucial role in the process. A mathematical model has been developed for calcium waves by assuming the buffers are in equilibrium with calcium i.e., the rapid buffering approximation 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 $[\text{Ca}^{2+}]$ and buffer concentration time course regardless of the calcium influx. The comparative studies of the effect of the rapid buffered diffusion and kinetic parameters of the model on the concentration time course have been performed.

Keywords—Calcium Profile, Rapid Buffering Approximation, Influx, Dissociation rate constant.

I. INTRODUCTION

Calcium is one of the most important second messenger molecules, with a diverse array of effectors. Calcium directly moderates electrical activity, on a relatively fast time scale, through its control of calcium dependent potassium channels [10], [11], [15]. Long-term effects are mediated by various kinases and phosphatases. Calcium is one of the activators of protein kinase C, which plays a role in synaptic plasticity. One aspect of Ca^{2+} signaling that affects Ca^{2+} microdomains is the association of Ca^{2+} with cytosolic Ca^{2+} -binding proteins. Cellular Ca^{2+} buffers, whether stationary or mobile, reduce the basal free Ca^{2+} concentration and localize Ca^{2+} signals by reducing the effective diffusion coefficient for Ca^{2+} . 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+} clearance after channel inactivation. Ca^{2+} indicator dyes are themselves mobile Ca^{2+} buffers. 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. We can formulate the model for the equilibrium Ca^{2+} profile near an open channel [20]. These

formulas relate the Ca^{2+} concentration to the distance from the channel, and differ primarily in the treatment of Ca^{2+} buffers. G. D. Smith has developed a simplified mathematical description of Ca^{2+} diffusion that is valid in the presence of rapid buffering approximation [10]. Experimental buffers in the cytoplasm give equilibrium time on the order of few milliseconds. The validity of the rapid buffering approximation requires that the equilibrium time be much smaller than the time required for Ca^{2+} to diffuse across a region of the size of a typical gradient.

In a complex with calmodulin, calcium is an activator or regulator of several enzymes, including calcium-calmodulin dependent protein kinase, which plays a role in synaptic plasticity, and adenylate cyclase, which produces cAMP, another important second messenger [7], [18]. Neurons have numerous sources and sinks of calcium in order to tightly control this very active molecule. Sources include voltage dependent calcium channels (which allow electrical activity to moderate calcium concentration) and intracellular stores; sinks include buffers and membrane pumps.

Experimental attempts were made by many research workers to study the role of calcium in neuronal signaling [1], [2], [9], [10], [17]. They experimentally studied and explained the elementary and global aspects of calcium signaling, effects of mobile buffers on facilitation of calcium diffusion, the phenomenon of buffered diffusion of calcium in the cells and concentration profiles of intracellular Ca^{2+} in the presence of diffusible chelator.

Also theoretically attempts were made to study calcium diffusion problem in neuron cells [3], [8], [10], [13], [14], [19]. They derived an analytical steady state solution for the Ca^{2+} profile near an open Ca^{2+} channel based on a transport equation which described the buffered diffusion of Ca^{2+} in the presence of rapid stationary and mobile Ca^{2+} buffers. They also used the steady state rapid buffering approximation to estimate the source amplitude of local Ca^{2+} elevations that occur in the presence of several mobile Ca^{2+} buffers. Further their work also highlights all the effect of rapid mobile buffer and bulk cytosolic Ca^{2+} and $[\text{Ca}^{2+}]_d$ (domain concentration). Near source estimate of the effect of rapid mobile buffer on $[\text{Ca}^{2+}]_d$ the steady state rapid buffering approximation near an open Ca^{2+} channel is a novel analytical result that complements the excess buffer approximation, when the conditions for the validity of the rapid buffering approximation near a point source for Ca^{2+} ions are met, the steady state rapid buffering approximation provides an upper

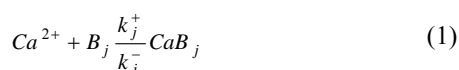
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limit on the Ca^{2+} profile during a local Ca^{2+} elevation [7]. It can also be used to relate source amplitude of a local Ca^{2+} elevation to an observed Ca^{2+} bound dye profile.

From the literature it is evident that most of the attempts have been made to study calcium diffusion problems in neuron cells for steady state case and almost no attention has been paid to unsteady state problems. In view of above an attempt has been made to study unsteady state calcium diffusion in neuron cells involving rapid buffers.

II. 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.



where B_j and CaB_j 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 B_j and bound buffer CaB_j respectively are as below,

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

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

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

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} , D_{B_j} and D_{CaB_j} 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. 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

$$K_j = \frac{k_j^-}{k_j^+}$$

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 $D_{B_j} = D_{CaB_j} = D_j$ and substitute it in (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+}

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

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

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 are given by

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

and

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

Near the source we enforce the boundary conditions

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

and

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

implying an influx of free Ca^{2+} at the rate σ , By Faraday's law, $\sigma = I_{Ca} / zF$ [6].

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+} [5].

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

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.

A. The Rapid Buffering Approximation

In case of rapid buffering approximation, buffer concentration is variable [4], [13], [14], [16]. We can make a quasi-steady-state approximation and assume that changes in buffer concentration occur in such a manner that Ca^{2+} and buffer are essentially always in equilibrium (i.e. $R_j = 0$). Thus we have the following equilibrium expressions for single rapid buffer.

$$[CaB_j] = \frac{[Ca^{2+}][B]_T}{K + [Ca^{2+}]} \quad (12)$$

and

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

From above the total concentration of Ca^{2+} (free and bound) is a simple function of $[Ca^{2+}]$ and can be expressed as given below

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

Now with the help of (12), (13) & (14) we define the "buffer capacity" i.e. the rate of change of bound $[Ca^{2+}]$ with respect to free $[Ca^{2+}]$

$$\begin{aligned} \kappa &= \frac{d}{d[Ca^{2+}]} \{[CaB]\} = \frac{d[CaB]}{d[Ca^{2+}]} \\ \kappa &= \frac{K[B]_T}{(K + [Ca^{2+}])^2} \end{aligned} \quad (15)$$

and the "buffering factor" as the differential of free $[Ca^{2+}]$ with respect to total $[Ca^{2+}]$ that is

$$\beta = \frac{d[Ca^{2+}]}{d[Ca^{2+}]_T} = \frac{1}{1 + k} \quad (16)$$

where β is always some number between zero and one ($\beta = 1/100$ is not unreasonable, but the exact value depends on $[Ca^{2+}]$ and buffer parameters). Using these buffered diffusion equations of Ca^{2+} for one buffer becomes

$$\frac{\partial[Ca^{2+}]}{\partial t} = \beta \left[(D_c + D_b \kappa) \nabla^2 [Ca^{2+}] - \frac{2D_b \kappa}{K + [Ca^{2+}]} (\nabla[Ca^{2+}])^2 \right] \quad (17)$$

It allows us to quantify the effect of rapid buffers on Ca^{2+} diffusion. The pre-factor of the laplacian term in (17) can be identified as an effective diffusion coefficient, D_{eff} , given by

$$D_{eff} = \beta(D_c + D_b \kappa) \quad (18)$$

Case-I: When the $[Ca^{2+}] \gg K$,

Although β and κ are general function of $[Ca^{2+}]$ but in

certain circumstances this dependence can be weak, eg, when the $[Ca^{2+}] \gg K$, κ approaches 0 and β approaches one, reflecting the fact that nearly saturated buffers will have little effect on $[Ca^{2+}]$.

Then (17) becomes

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_c \nabla^2 [Ca^{2+}] \quad (19)$$

By applying finite differences technique, we get for $r_i \neq 0$

$$U_i^{j+1} = U_i^j + A \frac{kD_c}{2r_i^2 h^2} [(r_{i+1/2})^2 (U_{i+1}^j - U_i^j) - (r_{i-1/2})^2 (U_i^j - U_{i-1}^j)] \quad (20)$$

for $r_i \neq 0$

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 step sizes for the r and t , $r_{i+1/2} = r_i + h/2$ and $r_{i-1/2} = r_i - h/2$.

At the origin ($r_i=0, i=0$) a finite difference approximation to (19) gives

$$U_0^{j+1} = U_0^j + \frac{6kD_c}{h^2} (U_1^j - U_0^j) \quad (21)$$

Case-II: When the $[Ca^{2+}] \ll K$,

Then the value of κ and β are given by

$$\kappa = \frac{[B]_T}{K} \quad \text{and} \quad \beta = \frac{K}{K + [B]_T}$$

Then (17) becomes

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{eff} \nabla^2 [Ca^{2+}] - B \frac{1}{K + [Ca^{2+}]} (\nabla[Ca^{2+}])^2 \quad (22)$$

where

$$D_{eff} = \left(\frac{K}{K + [B]_T} \right) \left(D_c + \frac{[B]_T}{K} D_b \right) \quad \text{and} \quad B = \frac{2D_b[B]_T}{K + [B]_T}$$

TABLE I
NUMERICAL VALUES OF VARIOUS CALCIUM BUFFERS
A) ENDOGENOUS BUFFERS

Ca ²⁺ buffer	k ⁺ μM ⁻¹ s ⁻¹	k ⁻ s ⁻¹	K μM	[B] _T μM
Troponin-C	90-100	7-300	0.05-3.0	50(varied)
Calmodulin D _{28K}	100-500	37-470	0.2-2.0	32
Triponin C	39	20	0.51	70
Parvalbumin	6	1	0.00037	36

TABLE II
NUMERICAL VALUES OF VARIOUS CALCIUM BUFFERS
B) EXOGENOUS BUFFERS

Ca ²⁺ buffer	k ⁺ μM ⁻¹ s ⁻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

Applying finite differences technique, we get

$$U_i^{j+1} = U_i^j + \frac{kD_{\text{eff}}}{2r_i^2 h^2} [(r_{i+1/2})^2 (U_{i+1}^j - U_i^j) - (r_{i-1/2})^2 (U_i^j - U_{i-1}^j)] - \left(\frac{B}{K + U_i^j} \right) \left(\frac{U_{i+1}^j - U_i^j}{h} \right)^2 \quad (23)$$

for $r_i \neq 0$

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 step sizes for the r and t , $r_{i+1/2} = r_i + h/2$ and $r_{i-1/2} = r_i - h/2$

At the origin ($r_i=0, i=0$) a finite difference approximation to (21) gives

$$U_0^{j+1} = U_0^j + \frac{6kD_c}{h^2} (U_1^j - U_0^j) - \left(\frac{B}{K + U_0^j} \right) \left(\frac{U_1^j - U_0^j}{h} \right)^2 \quad (24)$$

A computer program has been developed and executed of P-IV computer to obtain numerical results and using MATLAB we construct the graphs.

III. NUMERICAL RESULTS & DISCUSSION

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

RBA is appropriate when there is significant saturability of mobile buffer and when buffer kinetics is fast relative to Ca^{2+} diffusion. This is often the case near Ca^{2+} channels in synapses. Smith et al. did an asymptotic analysis of buffered Ca^{2+} diffusion near a point source, and determined following mathematical condition for the case where RBA is appropriate [3], [12]. $B = 0$ (RBA), buffer saturates. Here buffer and the source parameters are chosen such that RBA is valid.

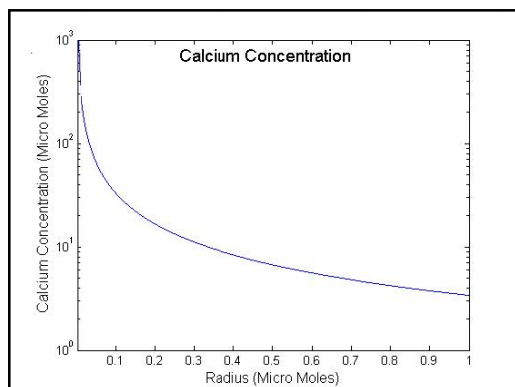


Fig. 1 Calcium concentration profile with respect to position, for, $D_c = 250 \mu\text{m}^2/\text{s}$, $[B]_T = 50 \mu\text{M}$, $K = 1 \mu\text{M}$, $\sigma = 1 \text{ pA}$, $D_b = 75 \mu\text{m}^2/\text{s}$

In Fig. 1 we observe that calcium concentration falls very sharply for r between 0-0.3 μm and then gradually decreases for r between 0.3-0.6 μm and thereafter converges to 0.1 μM and becomes uniform throughout. This is because near the source buffers are more saturable. So there is a highly nonlinear response of free $[\text{Ca}^{2+}]$ at buffer saturation levels; the response becomes more linear as the buffers are farther from saturation.

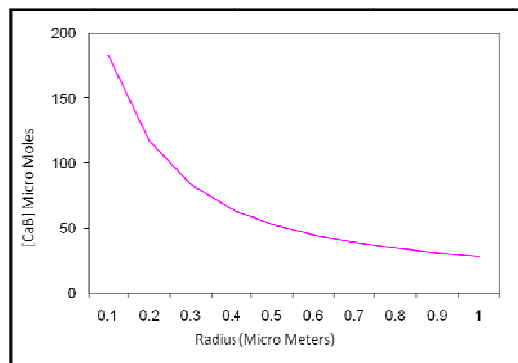


Fig. 2 Bound calcium concentration profile with respect to position, for, $D_c = 250 \mu\text{m}^2/\text{s}$, $[B]_T = 50 \mu\text{M}$, $K = 1 \mu\text{M}$, $\sigma = 1 \text{ pA}$, $D_b = 75 \mu\text{m}^2/\text{s}$

In Fig. 2 we observe that bound calcium concentration falls sharply for r between 0-0.3 μm and then gradually decreases for r between 0.3-0.8 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.

Here in Fig. 3, we have attempted to analyze the effect of single mobile buffer on $[\text{Ca}^{2+}]$ by fixing r . We take $r = 0.03 \mu\text{m}$ to plot $[\text{Ca}^{2+}]$ as a function of source amplitude (σ) for various mobile buffer parameters. When the source amplitude (σ) greater than 10-3 pA and high dissociation constant ($K=100 \mu\text{M}$), the calcium concentration increases linearly with increase in source amplitude. But for intermediate and lower values of K ($K=10, 1, 0.1 \mu\text{M}$), this relationship is nonlinear between $\sigma = 10^{-3}$ to 10^{-1} pA and for $\sigma > 10^{-1}$ pA, the relationship becomes linear. Further the slope of curves for $K=0.1, 1, 10 \mu\text{M}$ changes at the points $\sigma = 10^{-3}$ to 10^{-2} pA significantly.

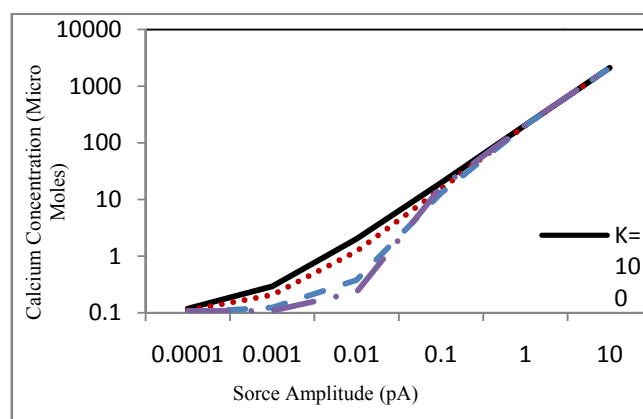


Fig. 3 Calcium concentration profile with respect to Source Amplitude, for $D_c = 250 \mu\text{m}^2/\text{s}$, $[B]_T = 50 \mu\text{M}$, $r = 0.03 \mu\text{m}$, $D_b = 75 \mu\text{m}^2/\text{s}$

This nonlinearity decreases as dissociation rate K increases and the $[\text{Ca}^{2+}]$ profile approaches the limiting case of calcium concentration in the absence of mobile buffer i.e., case-I when the buffering capacity $\kappa=0$ and buffering factor $\beta=1$. This is because with increase in dissociation constant K the buffer

saturability increases and reaches its limiting case of saturated buffer and therefore there is no binding with calcium ions. Thus the relation between calcium concentrations depend only source amplitude and relationship becomes linear.

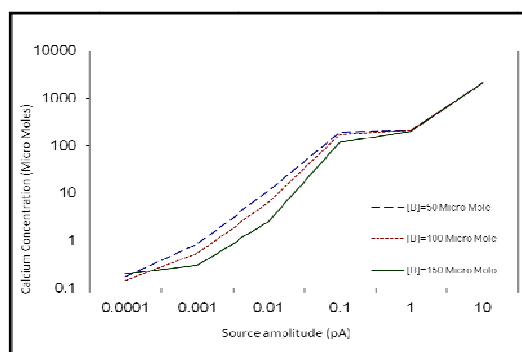


Fig. 4 Calcium concentration profile with respect to Source Amplitude, for $D_c = 250 \mu\text{m}^2/\text{s}$, $r = 0.03 \mu\text{m}$, $D_b = 75 \mu\text{m}^2/\text{s}$, $K = 10 \mu\text{M}$

In Fig. 4 we analyze the effect of single mobile buffer on $[\text{Ca}^{2+}]$ by fixing r . We take $r = 0.03 \mu\text{m}$ to plot $[\text{Ca}^{2+}]$ as a function of source amplitude (σ) for various mobile buffer concentration. Here we use $r = 0.03 \mu\text{m}$ to plot the graph between calcium concentration and the source amplitude. We plot the graphs for different buffer concentrations ($[B] = 50, 100, 150 \mu\text{M}$). From Fig. 4 we can see that as the curves are more nonlinear for high mobile buffer concentration. This is because as concentration of the buffer increases the binding capacity that is buffering factor also decreases for a fixed value $K = 10 \mu\text{M}$. So the binding rate of the buffer with calcium will slow down that causes the nonlinearity in curves for higher values of the buffer concentration. The limiting case of this is the buffer diffusion in absence of buffer i.e. buffer concentration is zero, when the buffering capacity $\kappa = 0$ and buffering factor $\beta = 1$.

The results obtained above are in agreement with those obtained by earlier research workers [3], [7], [8], [13], [14]. 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. The information obtained from these models can be of great use to biomedical scientist to understand the biological processes and for developing protocols for detection and treatment of abnormalities in the phenomena arising due to diseases and other abnormal physiological conditions.

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