Abstract—Calcium is very important for communication among
the neurons. It is vital in a number of cell processes such as secretion,
cell movement, cell differentiation. To reduce the system of reaction-
diffusion equations of \([Ca^{2+}]\) into a single equation, two theories
have been proposed one is excess buffer approximation (EBA) other
is rapid buffer approximation (RBA). The RBA is more realistic than
the EBA as it considers both the mobile and stationary endogenous
buffers. It is valid near the mouth of the channel. In this work we have
studied the effects of different types of buffers on calcium diffusion
under RBA. The novel thing studied is the effect of sodium ions on
calcium diffusion. The model has been made realistic by considering
factors such as variable \([Ca^{2+}]\), \([Na^{+}]\) sources, sodium-calcium
exchange protein(NCX), Sarcolemmal Calcium ATPase pump. The
proposed mathematical leads to a system of partial differential equa-
tions which has been solved numerically to study the relationships
between different parameters such as buffer concentration, buffer
dissociation rate, calcium permeability. We have used Forward
Time CENTRED Space (FTCS) approach to solve the system of partial
differential equations.

Keywords—rapid buffer approximation, sodium-calcium exchange
protein, Sarcolemmal Calcium ATPase pump, buffer dissociation
rate, forward time centred space.

I. INTRODUCTION

CALCIUM \([Ca^{2+}]\) plays an important role in a number of
processes like cell movement , muscle contraction, gene
expression, synaptic plasticity, etc.
It helps in the mechanism of exocytosis by combining
with synaptotagmin to release neurotransmitters. It is used in
signal transduction where an electrical signal is converted
into chemical signal. Local \([Ca^{2+}]\) elevations participate in
the calcium signaling by regulating calcium-gated plasma
membrane ion channels [9]. \([Ca^{2+}]\) enters a cell via ion
channels and redistributes itself throughout the cell via dif-
fusion. Experiments have shown that a number of parameters
like buffer concentration, Sarcolemmal Calcium ATPase pump,
\(Na^+\cdotCa^{2+}\) exchange (NCX) protein, Endoplasmic Reticulum
(ER) stores, \(Na^+\cdotK^+\) ATPase pump affect the behaviour of
\([Ca^{2+}]\). So in order to have a complete model for cytosolic
\([Ca^{2+}]\) behaviour we should incorporate all the possible
necessary parameters. \([Ca^{2+}]\) is strongly buffered in living
cells. A number of experiments conducted in various cell types
suggest that only 1 – 5% of calcium ions in the cytoplasm are
free, i.e., not bound to buffers [9] [12]. RBA is valid near the
mouth of calcium channel [12]. The high affinity buffers affect
calcium signaling mechanisms, granule exocytosis, excitation
contraction coupling and a variety of other mechanisms in
which changes in calcium concentrations are important [10].
Cellular calcium buffers, whether stationary or mobile, reduce
the free calcium concentration and localize calcium signals
by reducing the effective diffusion coefficient for calcium [1].
RBA assumes that the buffering time scales are rapid, reaching
equilibrium at each point in space before appreciable diffusion
occurs, [12]. Both i.e., EBA and RBA assume hemispherical
symmetry and a point source for calcium ions. These two
approximations are complimentary in the sense that they are
valid in different parameter regimes, but it is important to note
that in some cases neither approximation can be applied.[9].
Another factor which might have significant effect on
\([Ca^{2+}]\) diffusion and which has not been given much im-
portance till date is the sodium ion concentration. Calcium
extrusion in heart muscles is caused by the electrochemical
sodium gradient across the plasma membrane. The dependence
of \(Na^+ – Ca^{2+}\) electrochemical gradient has been studied by
Sheu and Fozzard for sheep ventricular muscle and Purkinje
strands. It has been observed that the sodium gradient across
the plasma membrane influences the intracellular calcium
concentration via a counter-transport of sodium for calcium
ion. Fujioka et al. [4] also found that NCX is the major
mechanism by which cytoplasmic calcium is extruded from
cardiac myocytes. Thus, there is enough evidence that \(Na^+\)
is an important parameter to be considered when modelling
cytosolic \([Ca^{2+}]\) concentration. Thus, in our model, we have
considered NCX with an exchange ratio of 4:1 [4] with respect
to sodium and calcium ion respectively, to study the effect of
sodium influx over cytoplasmic calcium profile. Other novel
features incorporated in the model are a variable calcium and
sodium source instead of a constant source to study the effects
of calcium and sodium permeabilities on calcium and sodium
ions respectively. The proposed model has a Sarcolemmal
Calcium ATPase pump (SL \(Ca^{2+}\) ATPase pump) which is
expressed in Hill’s equation form with a Hill’s coefficient
of 1.6 [8]. For simulation of the model we have used Finite
Difference Method (Forward Time Centered Space) approach.
A MATLAB program has been developed for the above
process and simulated on a Pentium IV Dual Core, 1.00 GB
RAM, 1.73GHz processor to obtain the numerical result. The
time taken per simulation is 240 seconds for time, \(t = 10\)
milliseconds.

II. MATHEMATICAL MODEL

Our mathematical model assumes the following reaction-
diffusion kinetics [9] [12].
\[ [Ca^{2+}] + [B_j] \stackrel{k_+}{\rightleftharpoons} [CaB_j] \quad (1) \]

where, \([B_j]\) and \([CaB_j]\) are free and bound buffers respectively, and ‘\(j\)’ is an index over buffer species. Using Fick’s law of diffusion and law of mass action we have the following partial differential equation [9],

\[
\frac{\partial [Ca^{2+}]}{\partial t} = \beta (D_{Ca} + \gamma_m D_{CaBm}) \nabla^2 [Ca^{2+}] - \frac{2\sigma_{NCX} D_{CaBm}}{K_{m} + [Ca^{2+}]} \nabla [Ca^{2+}] \cdot \nabla [Ca^{2+}] 
\]

where,

\[
\beta = (1 + \gamma_s + \gamma_m)^{-1} \quad and \\
\gamma_m = \frac{K_m [B_m]}{(K_m + [Ca^{2+}])^2} \quad (2)
\]

where, \(D_{Ca}, D_{Bm}\) and \(D_{CaBm}\) are the diffusion coefficients of free calcium, free buffer and calcium bound buffer respectively and \(K_m\) is dissociation rate constant. For stationary buffers \(D_{Bm}, D_{CaBm} = 0\).

The proposed mathematical model also contains the following parameters, to study the effect of rapid buffer and \(Na^+\) ions over \(Ca^{2+}\) diffusion.

**A. Ion channels**

The \(Ca^{2+}\) and \(Na^+\) channels have been modelled using the Goldman-Hodgkin-Katz(GHK) current equation [5],

\[
I_s = P_s z_s^2 F^2 V_m (S_i - S_o) \exp \left( \frac{-z_s F V_m}{RT} \right) \frac{1}{1 - \exp \left( \frac{-z_s F V_m}{RT} \right)} 
\]

Where \([S_i],[S_o]\) are the intracellular and extracellular ion concentration (Molar),respectively. \(P_s\) is the permeability (m/s) of \(S\) ion, \(z_s\) is valence of \(S\) ion. \(F\) is Faraday’s constant (C/moles). \(V_m\) is membrane potential (Volts). \(R\) is Real gas constant (J/K moles) and \(T\) is Absolute temperature (Kelvin).

Equation (3) is converted into molar/second by using the following equation

\[
\sigma_s = \frac{-I_s}{z_s F V_{cyt}} \quad (4)
\]

The negative sign in equation (4) is taken because by convention inward current is taken to be negative. The GHK equation is derived from the constant field approximation which assumes that the electric field in the membrane is constant, and thus decoupled from the effects of charges moving through the membrane.

**B. \(Na^+ / Ca^{2+}\) Exchange(NCX) Protein**

The NCX protein is essential for excitation-contraction coupling in cardiac myocytes [4]. It helps in the extrusion of cytosolic calcium in neurons and hence regulates neurotransmitter release. In our model we have taken an exchange ratio of 4:1 with respect to sodium and calcium ions respectively[4]. The amount of energy required to extrude an ion against its concentration gradient is given by:

\[
\Delta_s = z_s F V_m + RT \log \left( \frac{S_i}{S_o} \right) \quad (5)
\]

So using \(\Delta [Ca^{2+}] = 4[Na^+]\) we have,

\[
\sigma_{NCX} = \frac{Na_o}{Ca_o} \left( \frac{Na_o}{Ca_o} \right)^{4/3} \exp \left( \frac{2 F V_m}{RT} \right) \quad (6)
\]

\[
\sigma_{NCX} = \frac{Na_o}{Ca_o} \left( \frac{Na_o}{Ca_o} \right)^{1/3} \exp \left( - \frac{F V_m}{RT} \right) \quad (7)
\]

**C. Sarcolemmal Calcium ATPase pump (SL CaATPase pump)**

It is a P-type ATPase which is also known as Plasma Membrane Calcium ATPase pump (PMCA). Energy obtained from ATP is used to extrude calcium ions out of the cytosol. The kinetics of the pump follows Michaelis - Menten kinetics [7][2]. So the net efflux of calcium ions out of the cytosol is given by:

\[
\sigma_{SLPump} = \frac{V_{SLPump}}{1 + \left( \frac{K_{SLPump}}{Ca_o} \right)^{H}} \quad (8)
\]

where, \(V_{SLPump}\) is the maximum pump capacity, \(K_{SLPump}\) is half of the maximum pump capacity at steady state and \(H\) is the Hill’s coefficient.

Combining equations (1-8) we get the proposed mathematical model as given below,

\[
\frac{\partial [Ca^{2+}]}{\partial t} = \beta \left( \frac{D_{Ca} + \gamma_m D_{CaBm}}{K_m + [Ca^{2+}]} \nabla [Ca^{2+}] \cdot \nabla [Ca^{2+}] \right) - \sigma_{NCX} - \sigma_{SLPump} \quad (9)
\]

\[
\frac{\partial [Na^+]}{\partial t} = \beta_{sod} (-[Na^+] + \sigma_{NCX}) \quad (10)
\]

Along with the initial-boundary conditions,

**Initial condition:**

\[
[Ca^{2+}]_{r=0} = 0.1 \mu M \quad (11)
\]

\[
[Na^+]_{r=0} = 12 \mu M \quad (12)
\]

**Boundary conditions:**

\[
\lim_{r \rightarrow 0} \left( -2\pi r^2 \beta (D_{Ca} + \gamma_m D_{CaBm}) \frac{d[Ca^{2+}]}{dr} \right) = \beta \sigma_{Ca} \quad (13)
\]

\[
\lim_{r \rightarrow \infty} [Ca^{2+}] = 0.1 \mu M \quad (14)
\]

Our problem is to solve equation (9) and (10) coupled with equations (11 - 13). For our convenience we are writing ‘u’ in lieu of \([Ca^{2+}]\) and ‘v’ in lieu of \([Na^+]\). Applying finite difference method (Forward Time Centered Space) on
where, \( \varepsilon = \frac{FV_m}{RT} \) is a dimensionless quantity, 'h' represents spatial step and 'k' represents time step, 'i' and 'j' represents the index of space and time respectively. Since, the above expression is not valid at the mouth of the channel; therefore the approximation at the mouth of the channel is given by

\[
\frac{u_i^{j+1} - u_i^j}{k} = \beta_i^j \left( \frac{(D_{eff})^{(1/4)}}{h^2} \right)^4 e^{\varepsilon/2} - u_{out} \left( \frac{v_i^{j+1}}{v_{out}} \right) + u_i^j
\]

\[
u_i^{j+1} = k \cdot \frac{\beta_i^j}{\varepsilon} \left( \frac{u_i^{j+1} - 2u_i^j + u_i^{j-1}}{\varepsilon} \right) + \frac{\left( \frac{1}{(1-e^{\varepsilon})} \right)}{1+u_i^j}
\]

\[
u_i^{j+1} = k \cdot \frac{\beta_i^j}{\varepsilon} \left( \frac{u_i^{j+1} - 2u_i^j + u_i^{j-1}}{\varepsilon} \right) + \frac{\left( \frac{1}{(1-e^{\varepsilon})} \right)}{1+u_i^j}
\]

\[
u_i^{j+1} = k \cdot \frac{\beta_i^j}{\varepsilon} \left( \frac{u_i^{j+1} - 2u_i^j + u_i^{j-1}}{\varepsilon} \right) + \frac{\left( \frac{1}{(1-e^{\varepsilon})} \right)}{1+u_i^j}
\]

The numerical results are computed using a program developed in MATLAB on a Pentium IV Dual Core,1.00 GB RAM,1.73GHz processor.

### III. RESULTS AND DISCUSSION

In this section we have shown the results for calcium profile against different biophysical parameters. The biophysical parameters used in the proposed model are as stated in the table below unless stated along with figures. Figures [1-6] show variation for mobile buffers. Figures [1-3] show variation of \([Ca^{2+}]\) with respect to space. Figures [4-6] show variation of \([Ca^{2+}]\) with respect to time where the time limit is taken to be 10 milliseconds. Figures [7,8] show variation of \([Ca^{2+}]\) with time for stationary buffers.

#### Mobile buffers (Simulation time =240s)

Figure1 shows the variation of calcium concentration with buffer concentration and space. Mobile buffers influence both the spatial and temporal calcium profiles. Since in RBA the buffer binding kinetics is faster than calcium diffusion the variation of calcium with space is very rapid. To see the effects of buffer more clearly the log scale of space has been taken. The figure is in agreement with the biophysical facts. As the buffer concentration increases there are more number

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
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<tr>
<td>F</td>
<td>Faraday's Constant</td>
<td>96485 Coulombs/Mole</td>
<td>Known fact</td>
</tr>
<tr>
<td>R</td>
<td>Gas Constant</td>
<td>8.314 Joule / Kelvin Mole</td>
<td>Known fact</td>
</tr>
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<td>T</td>
<td>Absolute Temperature</td>
<td>310 K</td>
<td>In this paper</td>
</tr>
<tr>
<td>(P_{Ca})</td>
<td>Calcium Permeability ([Ca^{2+}])</td>
<td>5.41x10^{-10} metre s^{-1}</td>
<td>In this paper</td>
</tr>
<tr>
<td>(P_{Na})</td>
<td>Sodium Permeability ([Na^+])</td>
<td>6.07x10^{-10} metre s^{-1}</td>
<td>[11]</td>
</tr>
<tr>
<td>(z_{Ca})</td>
<td>Calcium valence</td>
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<td>Known fact</td>
</tr>
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<td>(z_{Na})</td>
<td>Sodium valence</td>
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<td>Known fact</td>
</tr>
<tr>
<td>(V_m)</td>
<td>Resting membrane potential</td>
<td>-0.07 Volts</td>
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</tr>
<tr>
<td>([Na^+])</td>
<td>Cytosolic ([Na^+])</td>
<td>12 mM</td>
<td>[8]</td>
</tr>
<tr>
<td>([Ca^{2+}])</td>
<td>Extracellular ([Na^+])</td>
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<td>[8]</td>
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<td>Extracellular ([Ca^{2+}])</td>
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<td>[8]</td>
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<td>(D_{Ca})</td>
<td>Diffusion coefficient</td>
<td>250 (\mu)m^2 s^{-1}</td>
<td>[11]</td>
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<td>(D_m)</td>
<td>Mobile buffer diffusion coefficient</td>
<td>32 (\mu)m^2 s^{-1}</td>
<td>[10]</td>
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<tr>
<td>(K_m)</td>
<td>Mobile buffer dissociation rate</td>
<td>2 (\mu)M</td>
<td>[10]</td>
</tr>
<tr>
<td>(K_{Na,diss})</td>
<td>Sodium mobile buffer dissociation rate</td>
<td>10 (\mu)M</td>
<td>[8]</td>
</tr>
<tr>
<td>(B_m)</td>
<td>Mobile buffer concentration</td>
<td>24 (\mu)M</td>
<td>[8]</td>
</tr>
<tr>
<td>(B_s)</td>
<td>stationary buffer concentration</td>
<td>70 (\mu)M</td>
<td>[8]</td>
</tr>
<tr>
<td>(B_{Na,diss})</td>
<td>Sodium mobile buffer concentration</td>
<td>5.35 (\mu)M</td>
<td>[8]</td>
</tr>
<tr>
<td>(V_{SLPump})</td>
<td>Maximum pump capacity of PMCA</td>
<td>45 (\mu)M s^{-1}</td>
<td>[13]</td>
</tr>
<tr>
<td>(K_{SLPump})</td>
<td>Half maximal pump capacity</td>
<td>0.1 (\mu)M</td>
<td>[13]</td>
</tr>
<tr>
<td>H</td>
<td>Hill's coefficient</td>
<td>1.6</td>
<td>[8]</td>
</tr>
</tbody>
</table>
of sites available for calcium binding and thus the calcium concentration decreases. The calcium concentration eventually achieves steady state as we move away from the source.

Fig. 1. Variation of calcium with respect to space and mobile buffer concentration. Parameters: As stated in the Table I.

Steady state is achieved when the inflow of calcium ions via L-type calcium channels is balanced by an equal amount of calcium extrusion via NCX protein and Sarcolemmal pumps. It is observed that the calcium achieves steady state faster in rapid buffering approximation compared to excess buffering approximation.

The above figure shows variation of calcium concentration with buffer dissociation rate. We have considered two different endogenous mobile buffers, calbindin (Km=1μM) and calmodulin (Km=2μM). The dissociation rate is the ratio of dissociation to association rates. Hence as the dissociation rate increases, more number of calcium ions gets free and lesser number of calcium ions bind, hence the calcium concentration increases. The steady state value of 0.1 μM for calcium in the cytosol is rapidly achieved.

Fig. 2. Variation of calcium with space and Mobile buffer Disassociation constant. Parameters: As stated in the Table I.

In the above figure we have shown the spatial variation of calcium concentration with permeability of calcium. The permeability has a profound effect on the calcium concentration as is evident in the figure. As the permeability increases, more amount of calcium ions enter into the cytosol through the L-type calcium channel hence the calcium concentration increases. As the permeability is increased, the calcium ions inflow exceeds the outflow due to NCX protein and Sarcolemmal pump i.e.,

\[ [Ca^{2+}]_{inflow} > \sigma_{NCX} + \sigma_{SLPump} \]

And hence there is a net inflow of calcium ions and thus the calcium concentration increases.

Fig. 3. Variation of calcium with space and calcium permeability. Parameters: As stated in the Table I.

The above figure shows the temporal calcium profile. Log of time scale has been taken as the change was very rapid. The variations shown with respect to buffer concentration are in agreement with the biophysical facts. As the buffer concentration increases the calcium concentration decreases. The calcium concentration achieves steady state fast compared to EBA. For simulation of EBA we had taken minimum time of 100ms whereas in-case of RBA we have taken 10ms.
steady state is achieved when the inflow of calcium ions from the L-type calcium channels is balanced by the outflow due to NCX protein and Sarcolemmal pump. The maximum value achieved by calcium is about 0.2 μM which is very low compared to the extracellular concentration of 1.8 mM. It is so because we have not incorporated the calcium concentration changes due to the Endoplasmic Reticulum in this model.

\[ Ca^{2+}_{inflow} > σ_{NCX} + σ_{SLPump} \]

Eventually, the inflow of calcium ions is balanced by the outflow and the calcium attains steady state.

**Stationary buffers** (only affect temporal variations)

Figure 7 shows the variation of calcium with stationary buffer concentration. The RBA is more realistic compared to EBA as we consider both the mobile and stationary buffers. Stationary buffers only affect the temporal profile and not the spatial profile as the buffers are immobile. We have considered two very common buffers for this study, these are Troponin C and Troponin C Ca-Mg (Ca). As the buffer concentration increases the calcium concentration decreases as there is an increase in calcium binding sites due to increase in buffer concentration.

In the above figure we have shown the temporal variation of calcium concentration with permeability of calcium. The permeability has a profound effect on the calcium concentration as changing the permeability by a slight amount has a great effect on the calcium profile. The source amplitude (σ) is directly proportional to the permeability of calcium ions. So as the permeability increases, more amount of calcium ions enter into the cytosol through the L-type calcium channel hence the calcium concentration increases. This can be stated mathematically as follows,
the calcium concentration increases. The calcium achieves a steady state after some time.

Some of the results shown in this paper are in agreement with the results obtained by previous researchers (Neher, Smith, Wagner and Keizer). The new results shown are also in agreement with the physiological facts. The results obtained in this paper may be useful to biomedical scientists for development of new protocols for treatment and diagnosis of neurological diseases.

**APPENDIX**

Using Laplacian operator ‘∇’ in spherical symmetry, we have

\[ \nabla^2 = \frac{\partial^2}{\partial r^2} + \frac{2}{r} \frac{\partial}{\partial r} \]

(17)

Further, we have used Forward Time Centered Space (FTCS) technique to solve eqn. (9) i.e.

\[ \frac{\partial u}{\partial t} \approx \frac{u_{i+1}^j - u_{i-1}^j}{2h} \]
\[ \frac{du}{dr} \approx \frac{u_{i}^{j+1} - u_{i}^{j-1}}{2h} \]
\[ \frac{d^2 u}{dr^2} \approx \frac{u_{i+1}^j - 2u_{i}^j + u_{i-1}^j}{h^2} \]

(18)

Using equation(18) in equation(9) and solving we get equation(14) i.e.

\[ \frac{u_{i+1}^j - u_{i}^j}{k} = \beta_i \left( \left( \frac{(D_{ef})_{i}^j}{h^2} \frac{(u_{i+1}^{j-2}u_i^j + u_{i-1}^j)}{k^2} \right) + \frac{(u_{i}^{j+1} - u_{i}^{j-1})}{h} \right) \]

\[ = \frac{(D_{ef})_{i}^j}{h^2} \frac{(u_{i}^{j+1} - u_{i}^{j-1})}{2h} + \frac{u_{out}(u_{i}^{j-1} - u_{i}^{j+1})}{k^2} \]

But this approximation does not hold for i = 1, as it gives rise to an imaginary node \( u_0^j \). To eliminate this problem, we have used centered difference over equation (12) to yield,

\[ u_0^j \approx u_1^j - \frac{2P_{Ca}h}{(1-e^{2\varepsilon})} D_{ef} (u_0^e2\varepsilon - u_{out}) \]

Here, the scale used for distance was [0.0001, 1.0001] \( \mu \)m. Thus for i = 1, we have equation (15) i.e.

\[ \frac{u_{i+1}^{j+1} - u_{i}^{j+1}}{k} = \beta_i \left( [D_{ef}]_{1}^j \left( \frac{2u_{i}^{j-2} - u_{i}^{j-1} - u_{i+1}^{j-1}}{2h} \right) + \frac{u_{out}(u_{i}^{j-1} - u_{i}^{j+1})}{k^2} \right) \]

\[ = \frac{u_{1}^{j-1} - u_{1}^{j+1}}{2h} + \frac{u_{out}(u_{1}^{j+1} - u_{1}^{j-1})}{k^2} \]

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