International Journal of Modern Biology and Medicine, 2013, 4(3): 190-203

Modern Scientific Press

International Journal of Modern Biology and Medicine **ISSN: 2165-0136**

Journal homepage: www.ModernScientificPress.com/Journals/IJBioMed.aspx *Florida, USA*

Article

Finite Element Model to Study Effect of Buffers in Presence of Voltage Gated Ca^{2+} Channels on Calcium Distribution in Oocytes for One Dimensional Unsteady State Case

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Article history: Received 27 July 2013, Received in revised form 5 November 2013, Accepted 12 November 2013, Published 22 November 2013.

Abstract: Oocytes are responsible for reproduction. Calcium is a fundamental intracellular signal that mediates a variety of disparate physiological function often in the same cell. Calcium plays an important role during fertilization. In order to understand the mechanism of reproduction it is important to understand the calcium distribution in oocytes, as specific calcium distribution patterns are required for maturation of the egg. In this paper an attempt has been made to study the effect of buffers in presence of voltage gated calcium channels on calcium distribution in Oocytes for one dimensional unsteady state case. Finite Element Method is used to solve the proposed Mathematical Model. A program has been developed for entire problem using MATLAB 7.10.

Keywords: Finite element method; Buffers; MATLAB; Voltage gated calcium channels; Diffusion coefficient; Reaction diffusion equations.

1. Introduction

Ca^{2+} signalling is one of the most important intracellular signalling mechanisms, controlling e.g., the contraction of muscle cells, the release of neurotransmitter from neurons and astrocytes and metabolic processes in liver and pancreas. Calcium signalling is characterized by a hierarchy of

processes ranging from the spatially and temporally limited Ca^{2+} puffs over global oscillations(in small cells, such as astrocytes) to propagating waves in large cells like oocytes (Bootman et al., 1997; Merchant et al., 1999; Tovey et al., 2001).In both plants and animals, free calcium is used as a second messenger in cell signalling that mediates a wide variety of biological processes. Almost all cells respond to oscillations of the free cytosolic calcium concentration to a variety of physical and chemical stimuli. Calcium waves and oscillations arise due to influx of Ca^{2+} through the plasma membrane Voltage Gated Calcium channel, leak through ER membrane, influx through Inositol Triphosphate Receptor (IPR) channel on the ER membrane (M. S. Jafri et al., 1992; Machaty et al., 2002). Elementary calcium release events involving release through IPR channels in Xenopus oocytes. HeLa cells and analogous calcium sparks in cardiac, smooth and skeletal muscle are mediated through Ryanodine Receptor (RyR) channels. Most notably, the opening of L-type calcium channel is mediated by elevations of cytosolic calcium. This positive feedback underlies the process of calcium-induced calcium release (CICR) which accounts for the generation of propagating calcium waves (Lechleiter et al., 1992; X.P. Sun et al., 1998).

Oocyte maturation provides an exception model system to elucidate the mechanism regulating Ca^{2+} signalling differentiation during cellular development, because Ca^{2+}signalling differentiation during oocyte maturation is essential for the egg to acquire developmental competence at fertilization (Antoine et al., 2000; Stricker S. A., 2000; Ullah et al., 2007).In fact intracellular $Ca^{2+}$is the universal signal for egg activation in all sexually reproduction species (Antoine et al., 2000; Stricker S.A., 2000) and the fertilization induced specialized Ca^{2+}signal takes the form of a signal or multiple Ca^{2+}transients depending on the species (Stricker S. A.,2000; Ullah et al., 2007).Therefore Ca^{2+} signals differentiate in a dramatic fashion during oocyte maturation to endow the egg with the capacity to respond to sperm and initiate development. Some experimental studies of calcium dynamics in oocytes have been reported in the literature (Lopez et al., 2003; Neant et al., 1994; Tomkowiak et al., 1997) and have suggested that voltage gated calcium channels plays a significant role in oocyte activation. B.K Jha, N. Adlakha and M.N Mehta (B.K. Jha et al., 2013) studied the effect of voltage gated calcium channels in Astrocytes in steady state case and (Zeng et al., 2009) studied the Simulation of Spontaneous Ca^{2+} Oscillations in Astrocytes Mediated by Voltage-Gated Calcium Channels. Here an attempt has been made to study the effect of buffers in presence of voltage gated calcium channels on calcium distribution in oocytes for one dimensional unsteady state case. Finite Element Method is used to solve the proposed mathematical model (S. S. Rao, 2004)

2. Mathematical Modeling

Calcium kinetics in Oocytes is governed by a set of reaction-diffusion equations which can be framed assuming the following bimolecular reaction between Ca^{2+} and buffer species (Smith et al., 2000;

Smith G.D., 1996)

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

where $[Ca^{2+}]$, $[B_j]$ and $[CaB_j]$ represent the cytosolic Ca^{2+} concentration, free buffer concentration and calcium bound buffer concentration respectively and $'j'$ is an index over buffer species, k_j^+ and k_j^- are on and off rates for j^{th} buffer respectively. Using Fickian diffusion, the buffer reaction diffusion system in one dimension is expressed as (E. Neher, 1973; Smith G.D., 1996).

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

$$\frac{\partial[B_j]}{\partial t} = D_{B_j}\nabla^2[B_j] + \sum R_j \tag{3}$$

$$\frac{\partial[CaB_j]}{\partial t} = D_{CaB_j}\nabla^2[CaB_j] - \sum R_j \tag{4}$$

Where reaction term R_j is given by

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

$D_{Ca}, D_{B_j}, D_{CaB_j}$ are diffusion coefficients of free calcium, free buffer and Ca^{2+} bound buffer respectively and σ_{Ca} is net influx of Ca^{2+} from the voltage gated calcium channel. Let $[B_j]_T = ([B_j] + [CaB_j])$ be the total buffer concentration of j^{th} buffer and the diffusion coefficient of buffer is not affected by the binding of calcium i.e., $D_{B_j} = D_{CaB_j}$ .Then equation (5) can be written as (S. Tiwari, 2009)

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

By assuming buffer concentration is present in excess inside the cytosol so that the concentration of free buffer is constant in space and time, i.e., $[B_j] \cong [B_j]_\infty$. Under this assumption equation (6) is approximated by (Smith et al., 2000)

$$k_j^+[Ca^{2+}][B_j] = k_j^-([B_j]_T - [B_j]_\infty) \tag{7}$$

where $[B_j]_\infty = \frac{k_j^-[B_j]_T}{(k_j^- + k_j^+[Ca^{2+}]_\infty)}$ is the background buffer concentration. Thus for single mobile buffer species equation (2) can be written as (Smith et al., 2000; S. Tiwari, 2009)

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\nabla^2[Ca^{2+}] - k_j^+[B_j]_\infty([Ca^{2+}] - [Ca^{2+}]_\infty) + \sigma_{Ca} + \delta\sigma(x) \tag{8}$$

where D_{Ca} is the diffusion coefficient of free calcium, σ_{Ca} is the flux of calcium through voltage gated calcium channel. $\delta\sigma(x)$ is the source amplitude due to the calcium channel. This has been modelled using the Goldman-Hodgkin-Kartz (GHK) current equation (E. Neher, 1973; Keener J. and Sneyd J., 1998) and $[Ca^{2+}]$ is background calcium concentration. We assume a single point source of Ca^{2+}, $\sigma(x)$ at x=0,there are no sources for buffers and buffer concentration is in equilibrium with Ca^{2+} far from the source and ∇ is the Laplacian operator i.e.,

$$\nabla^2 = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2}$$

and GHK equation as

$$I_{Ca} = P_{Ca} z^2_{Ca} \frac{F^2 V_m}{RT} \frac{[Ca^{2+}]_i - [Ca^{2+}]_o \exp(-z_{Ca} \frac{FV_m}{RT})}{1 - \exp(-z_{Ca} \frac{FV_m}{RT})} \tag{9}$$

where $[Ca^{2+}]_i$ and $[Ca^{2+}]_o$ are the intracellular and extracellular calcium concentration respectively. P_{Ca} is the permeability of calcium ion, z_{Ca} is the valency of calcium ion. F is the Faradays constant. V_m is the membrane potential. R is gas constant and T is absolute temperature. Equation (9) is converted into molar/second by using the following equation

$$\sigma_{Ca} = \frac{-I_{Ca}}{z_{Ca} F V_{Oocyte}} \tag{10}$$

The negative sign in equation (10) is taken since by convection the inward current is taken to be negative. GHK current equation gives the current density as a function of voltage. The GHK equation is derived from the constant field which assumes that the electric field in the membrane is constant and thus ions move in the membrane as in free solution. Combining equations (8), (9) and (10) we get proposed mathematical model as given below

$$\frac{\partial [Ca^{2+}]}{\partial t} = D_{Ca} \nabla^2 [Ca^{2+}] - k_j^+ [B_j]_\infty ([Ca^{2+}] - [Ca^{2+}]_\infty) \tag{11}$$

$$+ P_{Ca} z^2_{Ca} \frac{F^2 V_m}{RT} \frac{[Ca^{2+}]_i - [Ca^{2+}]_o \exp(-z_{Ca} \frac{FV_m}{RT})}{1 - \exp(-z_{Ca} \frac{FV_m}{RT})} - P_{out} [Ca^{2+}] + \delta \sigma(x)$$

The point source of calcium is assumed at x=0 and as we move away from the source, the calcium concentration achieves its background value i.e., $0.1\ \mu M$, thus the initial and boundary conditions for the above problem are (Smith G. D., 1996)

Initial Condition:

$$[Ca^{2+}]_{t=0} = 0.1\mu M \qquad (12)$$

Boundary Conditions:

$$\lim_{x\to 0}(-D_{Ca}\frac{\partial[Ca^{2+}]}{\partial x}) = \sigma \qquad (13)$$

$$\lim_{x\to\infty}[Ca^{2+}] = 0.1\mu M \qquad (14)$$

Here $[Ca^{2+}]$ is the background calcium concentration, $P_{Ca}[Ca^{2+}]$ represents the rate of calcium efflux from the cytosol into extracellular space. σ_{Ca} represents the flux due to $[Ca^{2+}]$ and incorporated on the boundary tends to the background concentration of $0.1\,\mu M$ as $x\longrightarrow\infty$ but the domain taken by us is not infinite one. Here we are taking the distance requires for $[Ca^{2+}]$ to attain background concentration i.e. $5\mu m$ for Oocyte. Our problem is to solve equation (11) coupled with equations (12-14).For our convenience we are writing $'y'$ in lieu of [Ca^{2+}]. Applying finite element method on equation (11) we can get variational form as:

$$I = \frac{1}{2}\int_{x_i}^{x_j}\left[\left(\frac{\partial y}{\partial x}\right)^2 + ay^2 + 2by + \frac{1}{D_{Ca}}\left(\frac{\partial (y^2)}{\partial t}\right)\right]dx - \mu^{(e)}\left(\frac{\sigma}{2D_{Ca}}y\Big|_{x=0}\right) \qquad (15)$$

Where

$$a = \frac{1}{D_{Ca}}\left[P_{out} - k_j^+[B_j]_\infty + P_{Ca}z_{Ca}\frac{\frac{FV_m}{RT}}{1-\exp(-z_{Ca}\frac{FV_m}{RT})}\right]$$

and

$$b = \frac{1}{D_{Ca}}\left[k_j^+[B_j]_\infty y_\infty - \frac{P_{Ca}z_{ca}\frac{FV_m}{RT}\exp(-z_{Ca}\frac{FV_m}{RT})}{1-\exp(-z_{Ca}\frac{FV_m}{RT})}y_o\right] \qquad (16)$$

Here we have used 'y' in lieu of [Ca^{2+}] for our convenience and e=1, 2, 3……50.Also $\mu^{(e)}=1$ for e=1 and $\mu^{(e)}=0$ for rest of elements. The following linear shape function for calcium concentration within each element has been taken as

$$y^{(e)} = c_1^{(e)} + c_2 x^{(e)} \qquad (17)$$

$$y^{(e)} = p^T c^{(e)} \qquad (18)$$

where

$$p^T = [\ 1\ x\ ] \qquad (19)$$

and

$$c^{(e)T} = [c_1^{(e)}\ c_2^{(e)}] \qquad (20)$$

Substituting nodal conditions in equation (18), we get

$$\bar{y}^{(e)} = P^{(e)} * c^{(e)} \qquad (21)$$

where

$$\bar{y}^{(e)} = \begin{bmatrix} y_i \\ y_j \end{bmatrix}$$

and

$$P^{(e)} = \begin{bmatrix} 1 & x_i \\ 1 & x_j \end{bmatrix} \qquad (22)$$

From the equation (21), we have

$$c^{(e)} = R^{(e)} * \bar{y}^{(e)} \qquad (23)$$

Where

$$R^{(e)} = P^{e(-1)} \qquad (24)$$

Substituting $c^{(e)}$ from equation (23) in (18), we get

$$y^{(e)} = p^T R^{(e)} \bar{y}^{(e)} \qquad (25)$$

We get

$$I^{(e)} = I_l^{(e)} + I_m^{(e)} - I_n^{(e)} - I_k^{(e)} + I_p^{(e)} \qquad (26)$$

where

$$I_l^{(e)} = \frac{1}{2}\int_{x_i}^{x_j} y^{(e)'2} dx \tag{27}$$

$$I_m^{(e)} = \frac{1}{2}\int_{x_i}^{x_j} y^{(e)2} dx \tag{28}$$

$$I_n^{(e)} = \int_{x_i}^{x_j} y^{(e)}\, y_\infty dx \tag{29}$$

$$I_k^{(e)} = \mu^{(e)} \frac{\sigma}{2D_{Ca}} y^{(e)}\,|_{x=0} \tag{30}$$

$$I_p^{(e)} = \frac{1}{2D_{Ca}} \frac{d}{dt} \int_{x_i}^{x_j} (y^{(e)})^2 dx \tag{31}$$

Now we extremize the integral $I^{(e)}$ w.r.t. each nodal calcium concentration y_i as given below

$$\frac{dI^{(e)}}{d\bar{y}^{(e)}} = \frac{dI_l^{(e)}}{d\bar{y}^{(e)}} + \frac{dI_m^{(e)}}{d\bar{y}^{(e)}} - \frac{dI_n^{(e)}}{d\bar{y}^{(e)}} - \frac{dI_k^{(e)}}{d\bar{y}^{(e)}} + \frac{dI_p^{(e)}}{d\bar{y}^{(e)}} = 0 \tag{32}$$

$$\frac{dI}{d\bar{y}} = \sum_{e=1}^{50} \bar{M}^{(e)} \frac{dI^{(e)}}{d\bar{y}^{(e)}} \bar{M}^{(e)^T} = 0 \tag{33}$$

Where

$$\bar{M}^{(e)} = \begin{bmatrix} 0 & 0 \\ . & . \\ 1 & 0 \\ 0 & 1 \\ . & . \\ 0 & 0 \end{bmatrix} \quad and \quad \bar{y} = \begin{bmatrix} y_1 \\ y_2 \\ . \\ . \\ . \\ y_{51} \end{bmatrix} \tag{34}$$

and

$$I = \sum_{e=1}^{50} I^{(e)} \tag{35}$$

This leads to a following system of linear differential equation

$$[A]_{51\times 51}\left[\frac{\partial \bar{y}}{\partial t}\right]_{51\times 1} + [B]_{51\times 51}[\bar{y}]_{51\times 1} = [C]_{51\times 1} \tag{36}$$

Here $[\bar{y}] = [y_1\ y_2\ y_3 \ldots\ldots\ldots\ldots\ldots y_{51}]$, A and B are the system matrices and C is the system vector. The Crank-Nicolson method is used to solve the system of differential equations (36). A computer program has been developed in MATLAB 7.10 for the whole problem and executed on Intel(R) Core™ i3 CPU, 4.00 GB RAM, 2.40 GHz processor. The numerical values of biophysical parameters used in the model are stated in the Table 1. [B. K. Jha et al., 2013; Panday S. and Pardasani K. R., 2013).

Table 1. Values of Biophysical Parameters

Symbol	Parameter	Value
D_{Ca}	Diffusion Coefficient	$250\,\mu m/\sec^2$
k_j^+	On rate for EGTA	$3/\mu M$ sec
k_j^-	Off rate for EGTA	$1/\sec$
k_j^+	On rate for BAPTA	$100/\mu M$ sec
k_j^-	Off rate for BAPTA	$10/\sec$
$[B]_\infty$	Total Buffer Concentration	$50\mu M$
σ	Source Amplitude	$1pA$
$[Ca^{2+}]_o$	Extracellular Calcium Concentration	$300\ \mu M$
P_{Ca}	Calcium Permeability	$4.3\times10^{-8}\,m/\sec$
V_m	Membrane Potential	0.05 *Volts*
z_{Ca}	Valency of Calcium	2
V_{Oocyte}	Volume of Oocyte cytosol	5.48×10^{-11} *litre*
F	Faraday's Constant	96487 *Coulombs / Mole*
R	Gas Constant	8.314 *Joule / Kelvin Mole*
T	Absolute Temperature	37^oC
P_{out}	Rate of Calcium Efflux	$0.5M/\sec$

m=Meter, M=Mole, s=Second

3. Results and Discussion

The numerical results for calcium profile against different biophysical parameters have been obtained using numerical values of parameters given in table-1unless stated along with figures. We have shown the variation in Ca^{2+} along the x-axis for buffers in the presence of VGCC. In Fig. 1 the calcium concentration falls quickly from 0 μm to 1.5 μm and then fall gradually and achieves background concentration 0.1 μM at x=5 μm. Fig. 2 shows the calcium concentration distribution along x-axis in oocytes for different values of buffer concentration in the presence of VGCC. We observe that the effect of VGCC is more clearly visible at lower buffer concentration i.e., the calcium concentration is higher

for lower concentration of buffers in presence of VGCC. Fig. 3 shows the calcium concentration for different source amplitudes. It is clear from the Fig.3 that as source amplitude increases the cytosolic calcium concentration near the source, as the increase in calcium concentration is almost proportionally. The fall in calcium concentration is sharp from x=0 μm to x=3 μm and thereafter this fall becomes gradual and it reaches background concentration at x=5 μm . Fig. 4 shows the variation of calcium with the time. Graph is plotted for different values of membrane potential $V_m = -85\,mV$ and $V_m = -65\,mV$. It is observed that calcium concentration is higher for lower membrane potential throughout $t = 0.2\,\text{sec}$ to $t = 0.3\text{sec}$ and there after converges to 0.1 μM as the time for calculation is taken as $t = 2\,\text{sec}$. Fig. 5 shows the temporal variation of calcium distribution in presence of VGCC for four different concentration of buffer. The effect of changing buffer concentration is clearer in the figure. From Fig. 5 &Fig. 6 it is observed that the peak value of Ca^{2+} concentration is higher for lower concentration of buffers. The effect of changing buffer concentration is observed within 5 μm & $t = 2\,\text{sec}$ and 5 μm & $t = 5\text{sec}$ respectively for the calcium channel. It is also observed that the steady state is achieved early for higher buffer concentration. The higher the concentration of buffers the lower is the concentration of calcium the reason for this is that the higher concentration of buffers binds more calcium and then forcing the system to reach the steady state early.

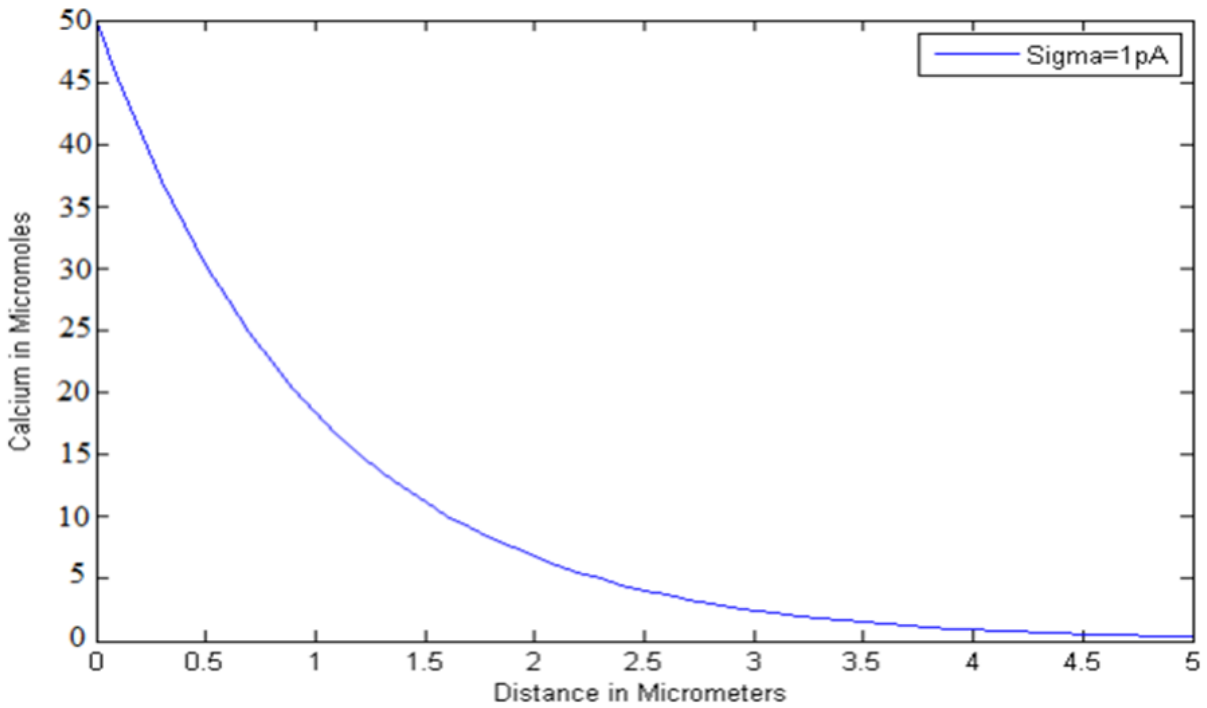

Fig. 1: Spatial variation of Calcium concentration in oocytes for the source amplitude $\sigma = 1pA$

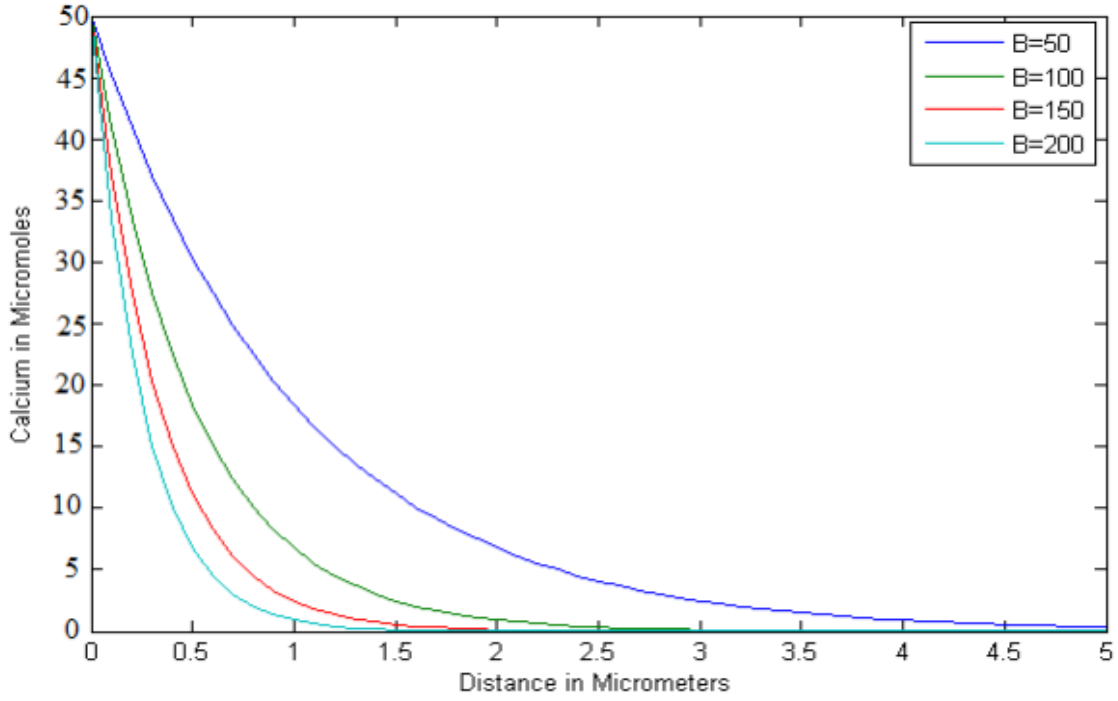

Fig. 2: Spatial variation of Calcium concentration in oocyte for different values of Buffer i.e., for B=50,100,150,200 and for $x = 5\ \mu m, \sigma = 1\ pA$.

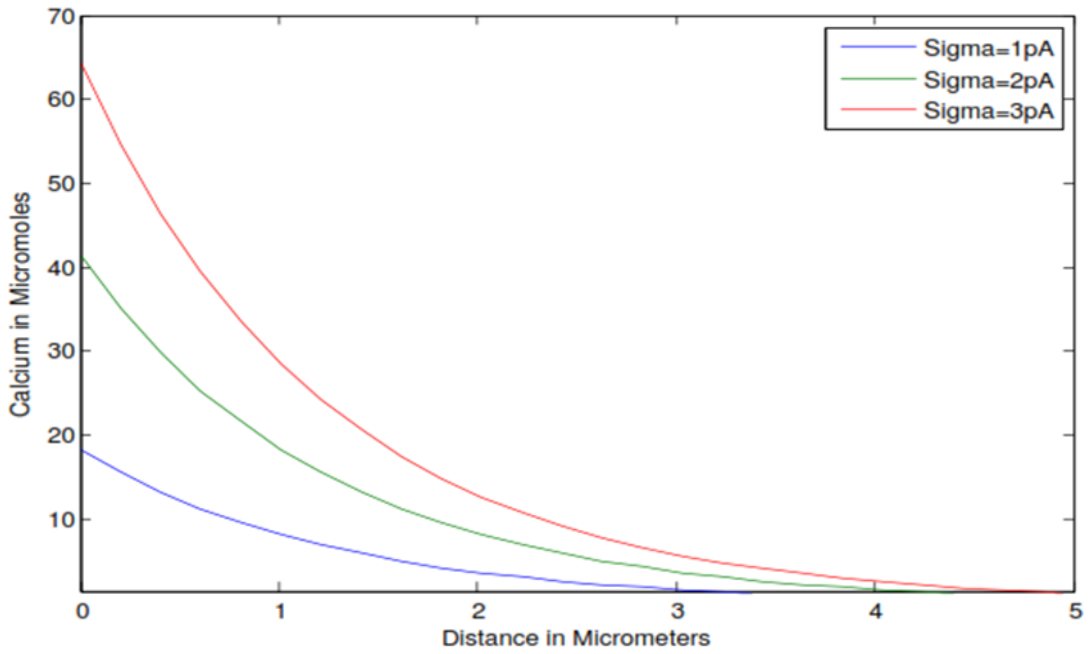

Fig. 3: Spatial variation of Calcium concentration in oocyte for different Source amplitudes i.e., for $\sigma = 1\ pA, \sigma = 2\ pA, \sigma = 3\ pA$ and $x = 5\ \mu m$

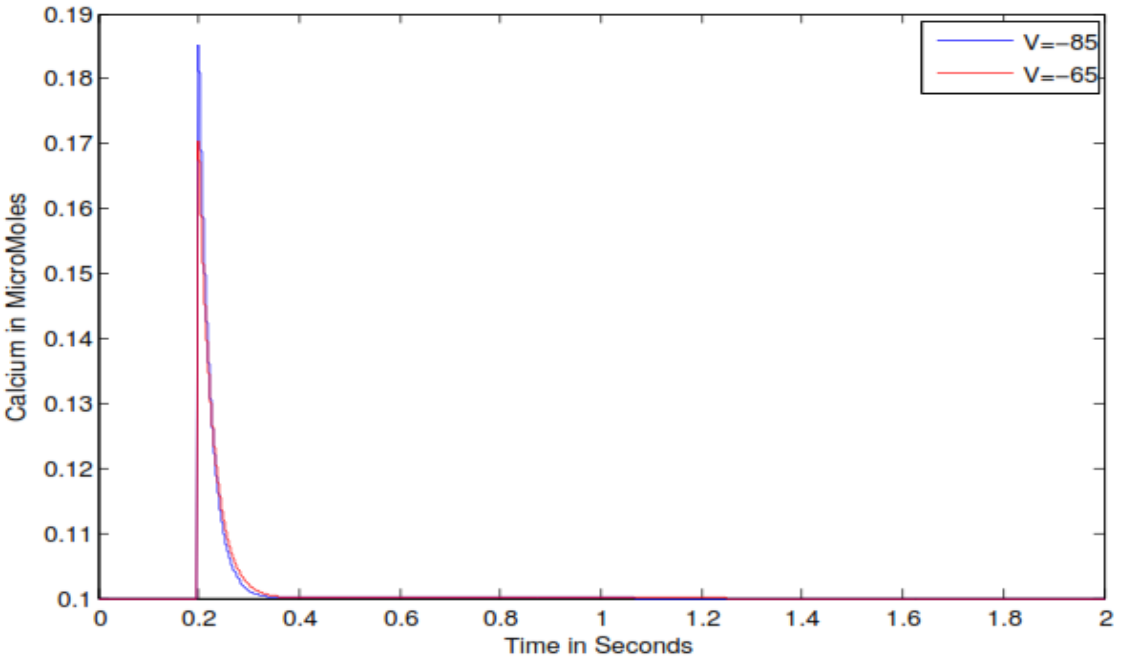

Fig. 4: Temporal variation of Calcium concentration for different values of Membrane Potential $V_m = -65, -85$ for $t = 2\,\text{sec}$.

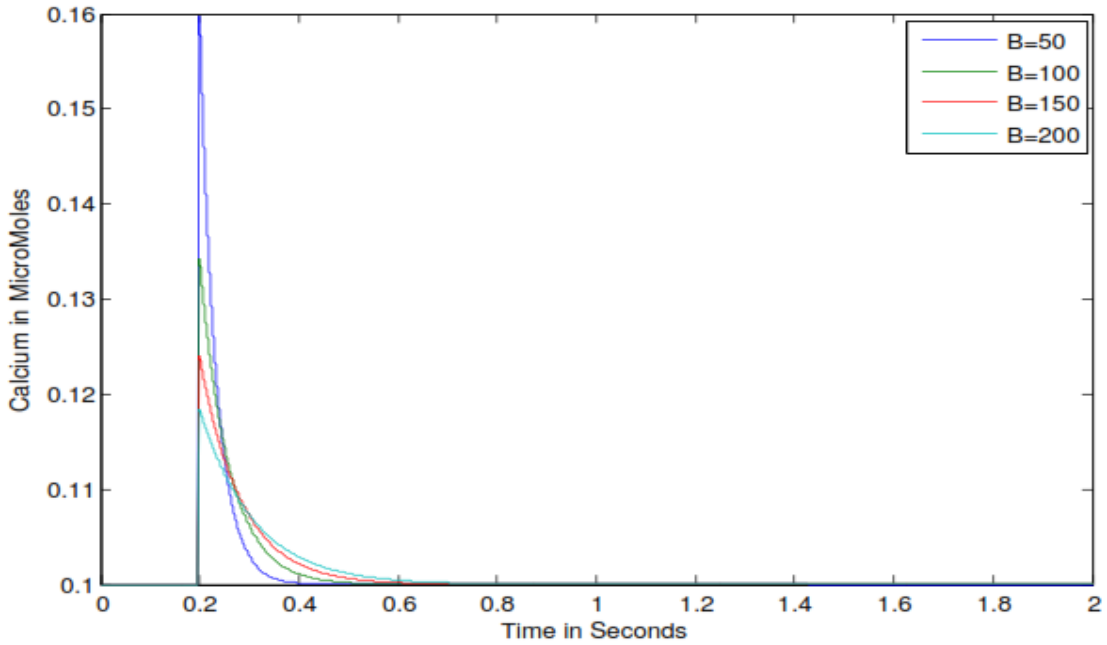

Fig. 5: Temporal variation of Calcium concentration in oocytes in presence of Buffers i.e., B=50,100,150,200 for $t = 2\,\text{sec}$.

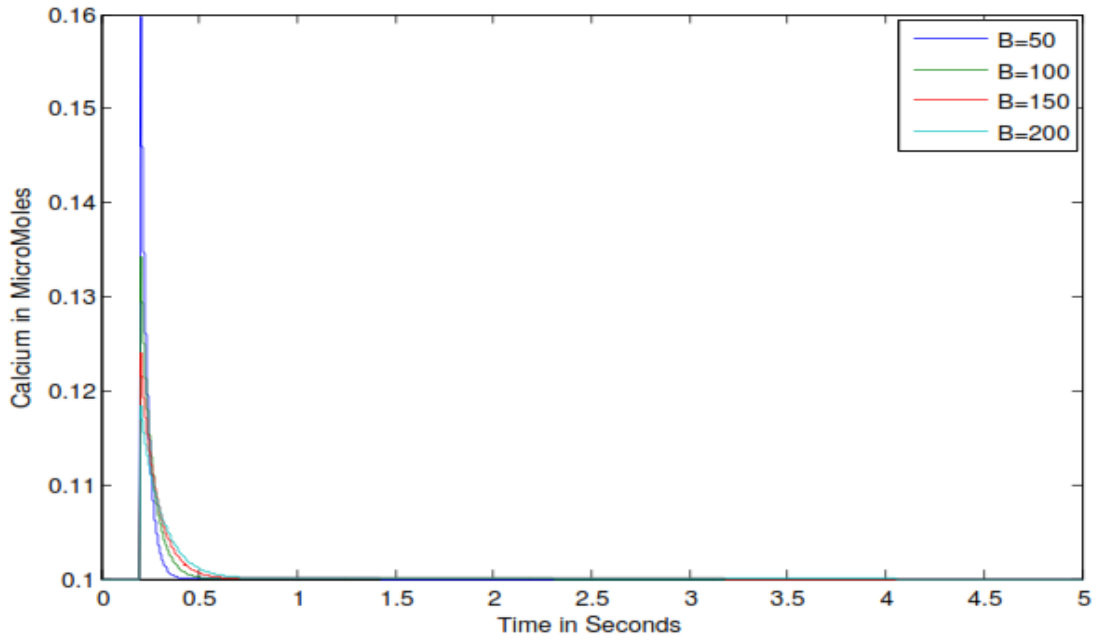

Fig. 6: Temporal Variation of Calcium concentration in oocytes in presence of Buffers i.e., B=50, 100, 150, 200 for $t = 5\,\text{sec}$

4. Conclusions

With our studies we have seen that the buffers and potential activity has significant effects on calcium concentration at the central regions near the source. It is concluded that the buffers have significant effect on calcium distribution in oocytes near the channel between x=0 to x=1 μm and during $t = 0\,\text{sec}$ to $t = 2\,\text{sec}$. The buffer plays an important role in quickly reducing the free calcium concentration inside the cytosol in order to regulate free ion concentration to desired level up to a required distance from source within short period of time. The FEM used gives us better relationship among various physical and physiological parameters. The results obtained by FEM gives us better insights and understanding for the calcium signalling in Oocytes which may be of great use to biomedical scientists in understanding the mechanisms of oocyte cell growth and maturation of oocyte and reproduction. The results obtained in this study are in a close agreement with the experimental studies obtained by Wassim et al. (2005), Francisco et al. (2009), Catherine et al. (2011) and the results obtained by Tripathi et al. (2011).

Acknowledgments

The authors are highly thankful to University Grants Commission (UGC), New Delhi, India for providing financial support to carry out this work.

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