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RESEARCH ARTICLE

Finite Element Model to Study Radial Calcium Distribution in Oocytes: A One Dimensional Steady State Case Study

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Abstract

Oocytes are responsible for reproduction. 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 view of above a finite element model has been developed to study calcium distribution in Oocytes for a one dimensional steady state case. The oocyte is assumed to be circular in shape. The important parameters like buffer and diffusion coefficient have been incorporated in the model. Appropriate boundary conditions have been taken. The results obtained have been used to study relationship among various parameters.

Introduction

Calcium is an important intracellular signalling molecule with rapid effect on the kinetics of many processes. The Ca^{2+} signalling affects several cellular functions such as gene expression, secretion, muscle contraction, synaptic plasticity, reproduction etc. Localised elevations of intracellular free Ca^{2+} due to release from intracellular Ca^{2+} stores and Ca^{2+} influx across the plasma membrane are observed in various cell types using confocal microscopy[1].Almost all cells response to oscillations of the free cytosolic calcium concentration to a variety of physical and chemical stimuli. Calcium wave 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) channels on the ER membrane [2,3]. The calcium waves and oscillations also arise due to reuptake of Ca^{2+} from the cytosol into the ER by Serco Endoplasmic Reticulum Ca^{2+} ATPase (SERCA) pump, into the extracellular space by Plasma Membrane Ca^{2+} ATPase (PMCA) pump and with the help of buffering by endogenous calcium buffers. The development of calcium imaging has allowed the spatiotemporal study of the global and elementary calcium release in cellular compartments of muscle cells, endothelial cells and egg cells [4,5]. 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 propagation calcium waves [6,7]. Oocyte maturation provides an exceptional model system to elucidate the mechanisms 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 [8,9,10].In fact intracellular Ca^{2+} is the universal signal for egg activation in all sexually reproducing species [8,11] and the fertilisation induced specialization Ca^{2+} signal takes the form of a single or multiple Ca^{2+} transients depending on the species [8,9].

In view of the above, here a one-dimensional finite element model for radial calcium distribution in an oocyte in presence of buffers has been developed. The model uses the partial differential equations with appropriate initial and boundary conditions, to describe the radial distribution process with buffers in oocytes. 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.

Mathematical Modelling

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 [8]

$$[Ca^{2+}]+[B_j] \underset{k_j^-}{\overset{k_j^+}{\rightleftharpoons}} [CaB_j] \quad (1)$$

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 [8,9].

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

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

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

Where reaction term R_j is given by

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

$D_{Ca}, D_{B_j}, D_{CaB_j}$ 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 source. 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 [12]

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

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 [13]

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

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 [12,13]

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

Here $[Ca^{2+}]$ is background calcium concentration. We assume a single point source of Ca^{2+}, σ_{Ca} at $r = 0$ 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.,

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

The point source of calcium is assumed at r =0 and as we move away from the source, the calcium concentration achieves its background value i.e.,0.1 μM ,Thus the initial and boundary conditions for the above problem are [1]

Initial Condition:

$$[Ca^{2+}]_{t=0} = 0.1\mu M \quad (9)$$

Boundary Conditions:

$$\lim_{r\to 0}(4\pi D_{Ca} r^2 \frac{d[Ca^{2+}]}{dr}) = \sigma_{Ca} \quad (10)$$

$$\lim_{r\to \infty}[Ca^{2+}] = 0.1\mu M \quad (11)$$

Our problem is to solve equation (8) coupled with equations (9-11).For our convenience we are writing $'y'$ in lieu of [Ca^{2+}]. Applying finite element method on equation (8) we can get variational form as:

$$I^{(e)} = \int_{r_i}^{r_j} r^2 \frac{y^{(e)'^2}}{2} + \frac{k_j^+}{D_{Ca}}[B]_\infty r^2(\frac{y^{(e)^2}}{2} - y^{(e)} y_\infty)dr + \mu^{(e)} \frac{\sigma_{Ca}}{4\pi D_{Ca}} y^{(e)}|_{r=0} \quad (12)$$

$$I^{(e)} = \int_{r_i}^{r_j} r^2 \frac{y^{(e)'^2}}{2} + \alpha\, r^2(\frac{y^{(e)^2}}{2} - y^{(e)} y_\infty)dr + \mu^{(e)} \frac{\sigma_{Ca}}{4\pi D_{Ca}} y^{(e)}|_{r=0} \quad (13)$$

Here $\alpha = \frac{k_j^+}{D_{Ca}}[B]_\infty$ and $\mu^{(e)} = 1$ for e=1 and $\mu^{(e)} = 0$ for rest of the elements where e=1,2,3……50 and the radius of the cell is taken as 5 μm. The shape function of concentration variation within each element is defined as:

$$u^{(e)} = c_1^{(e)} + c_2^{(e)} r \quad (14)$$

$$u^{(e)} = p^T c^{(e)} \quad (15)$$

where

$$p^T = [1 \quad r] \quad (16)$$

and

$$c^{(e)T} = [c_1^{(e)} \qquad c_2^{(e)}] \quad (17)$$

Substituting nodal conditions in equation (15), we get

$$\bar{y}^{(e)} = P^{(e)} * c^{(e)} \quad (18)$$

where

$$\bar{y}^{(e)} = \begin{bmatrix} y_i \\ y_j \end{bmatrix} \text{ and } P^{(e)} = \begin{bmatrix} 1 & r_i \\ 1 & r_j \end{bmatrix} \quad (19)$$

From the equation (18),we have

$$c^{(e)} = R^{(e)} * \bar{y}^{(e)} \quad (20)$$

where

$$R^{(e)} = P^{(e)^{-1}} \quad (21)$$

Substituting $c^{(e)}$ from equation (20) in (15),we get

$$y^{(e)} = p^T R^{(e)} \bar{y}^{(e)} \quad (22)$$

We get

$$I^{(e)} = I_l^{(e)} + I_m^{(e)} - I_n^{(e)} + I_k^{(e)} \quad (23)$$

Where

$$I_l^{(e)} = \frac{1}{2}\int_{r_i}^{r_j} r^2 y^{(e)'^2} dr \quad (24)$$

$$I_m^{(e)} = \frac{1}{2}\int_{r_i}^{r_j} r^2 y^{(e)^2} dr \quad (25)$$

$$I_n^{(e)} = \int_{r_i}^{r_j} r^2 y^{(e)} y_\infty dr \quad (26)$$

$$I_k^{(e)} = \mu^{(e)} \frac{\sigma_{Ca}}{4\pi D_{Ca}} y^{(e)} |_{r=0} \quad (27)$$

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

$$\frac{dI^{(e)}}{d\,\bar{y}^{(e)}} = \frac{dI_l^{(e)}}{d\,\bar{y}^{(e)}} + \frac{dI_m^{(e)}}{d\,\bar{y}^{(e)}} - \frac{dI_n^{(e)}}{d\,\bar{y}^{(e)}} + \frac{dI_k^{(e)}}{d\,\bar{y}^{(e)}} \quad (28)$$

$$\frac{dI}{d\,\bar{y}} = \sum_{e=1}^{50} \overline{M}^{(e)} \frac{dI^{(e)}}{d\,\bar{y}^{(e)}} \overline{M}^{(e)^T} = 0 \quad (29)$$

where

$$\overline{M}^{(e)} = \begin{bmatrix} 0 & 0 \\ . & . \\ 1 & 0 \\ 0 & 1 \\ . & . \\ 0 & 0 \end{bmatrix}, \qquad \bar{y} = \begin{bmatrix} y_1 \\ y_2 \\ . \\ . \\ . \\ y_{51} \end{bmatrix}, \qquad I = \sum_{e=1}^{50} I^{(e)} \quad (30)$$

This leads to a following system of linear differential equations.

$$[A]_{51\times 51}\left[\bar{y}\right]_{51\times 1} = [B]_{51\times 1} \quad (31)$$

Here $\left[\bar{y}\right] = [y_1\ y_2\ y_3 \ldots\ldots\ldots\ldots\ldots y_{51}]$, A is the system matrix and B is the system vector. 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 [3, 9, 12]

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_{Ca}	Source Amplitude	$1pA$

Results & 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 radial directionfor $\sigma = 1\,pA, r = 5\,\mu m$ and for $\sigma = 1\,pA, r = 10\,\mu m$ respectively. In Fig. 1 the calcium concentration falls quickly between 0 μm to 1.5 μm and then fall gradually and achieves background concentration 0.1 μM at r=5 μm .Fig. 2 shows the calcium concentration distribution along radius in oocytes for the source amplitude $\sigma = 1\,pA$ and $r = 10\,\mu m$. In Fig. 2 the calcium concentration falls quickly between 0 μm to 1 μm and then fall gradually and achieves background concentration 0.1 μM at $r = 10\,\mu m$ .We observe that the effect of radius is more clearin the figures i.e., the calcium concentration is higher for small radius means as radius of the cell increases the calcium concentration decreases as the concentration is higher near the source and decreases with increase in radius. Fig. 3 shows the calcium concentration for different concentrations of BAPTA buffer. It is clear from the Fig.3 that as buffer concentration increases the cytosolic calcium concentration near the source decreases, as the increase in calcium concentration is almost inversely proportional to the buffer concentration. The fall in calcium concentration is sharp from $r = 0\,\mu m$ to $r = 2\,\mu m$ and thereafter this fall becomes gradual and it reaches background concentration at $r = 5\mu m$. Fig. 4 shows the calcium concentration for different concentrations of BAPTA buffer for the radius $r = 10\,\mu m$. Graph is plotted for different values of buffer for the radius $r = 10\,\mu m$. It is observed that calcium concentration is higher for lower concentration of buffer throughout $r = 0\,\mu m$ to $r = 1\,\mu m$ and there after converges to 0.1 μM .It is clear from Fig.3 and Fig.4 that calcium concentration is higher for lower concentrations of buffer and for the small radius of the cell.Fig. 5 shows the calcium concentration for different concentrations of EGTA buffer. The effect of changing buffer concentration is more clear in the figure. From Fig. 5calcium concentration is higher for lower concentration of buffer throughout $r = 0\,\mu m$ to $r = 2\mu m$ and there after converges to 0.1 μM &in Fig. 6 it is observed that the peak value of Ca^{2+} concentration is higher for lower concentration of buffers. 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. 7 and Fig. 8show the calcium concentration for different source amplitudes along the radial direction. It is clear from the figures that the calcium concentration is higher for higher source amplitude but for small radius of the cell and the calcium concentration decreases as the radius of the cell increases.

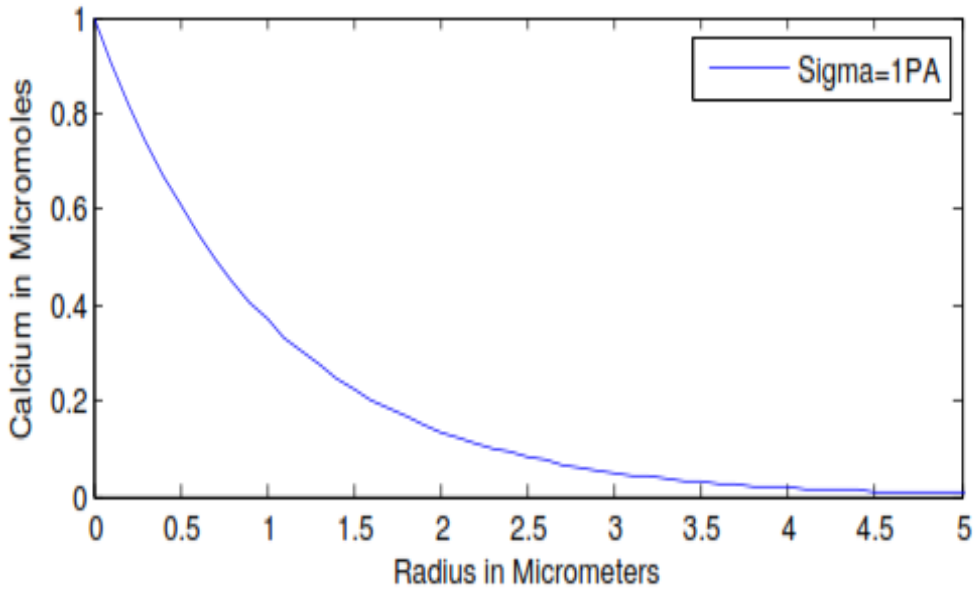

Figure.1: Radial variation of Calcium concentration for $\sigma = 1pA$ and $r = 5\,\mu m$

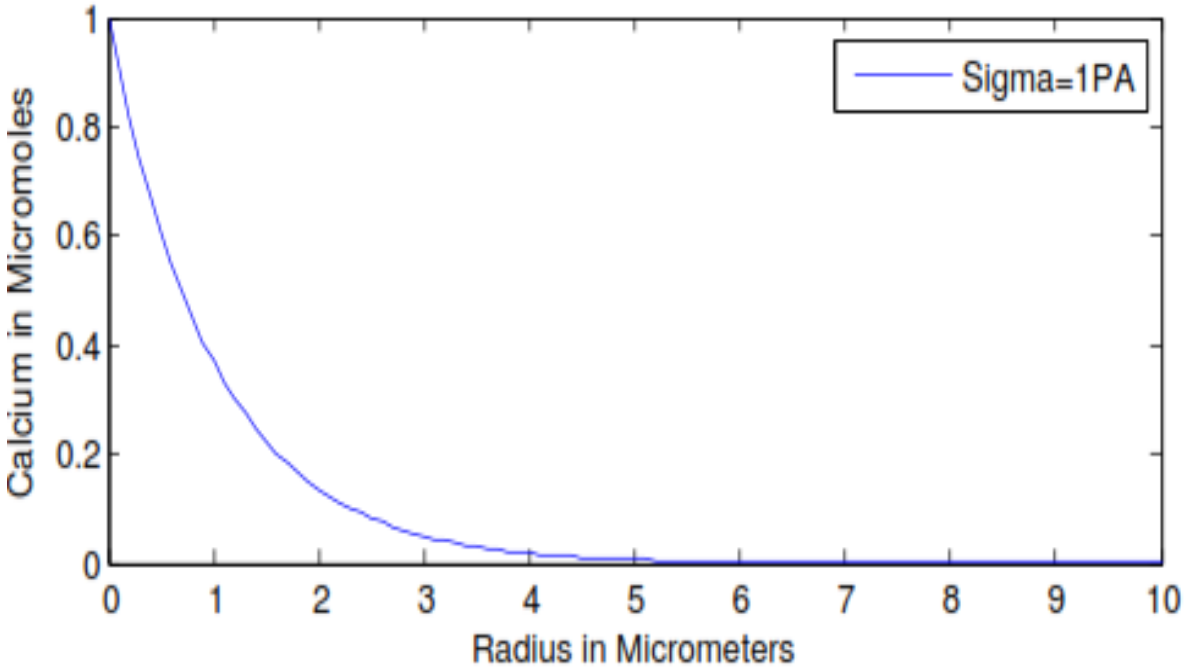

Figure.2: Radial variation of Calcium concentration for $\sigma = 1pA$ and $r = 10\ \mu m$

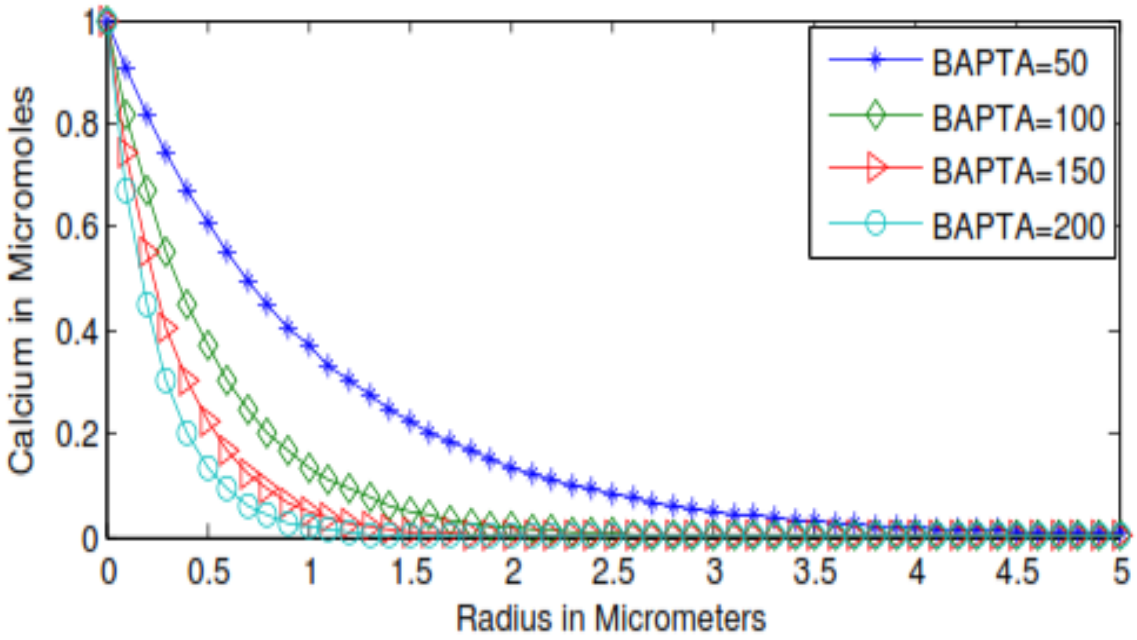

Figure.3: Radial variation of Calcium concentration for $\sigma = 1pA$ and $r = 5\ \mu m$ for different concentration of BAPTA buffer

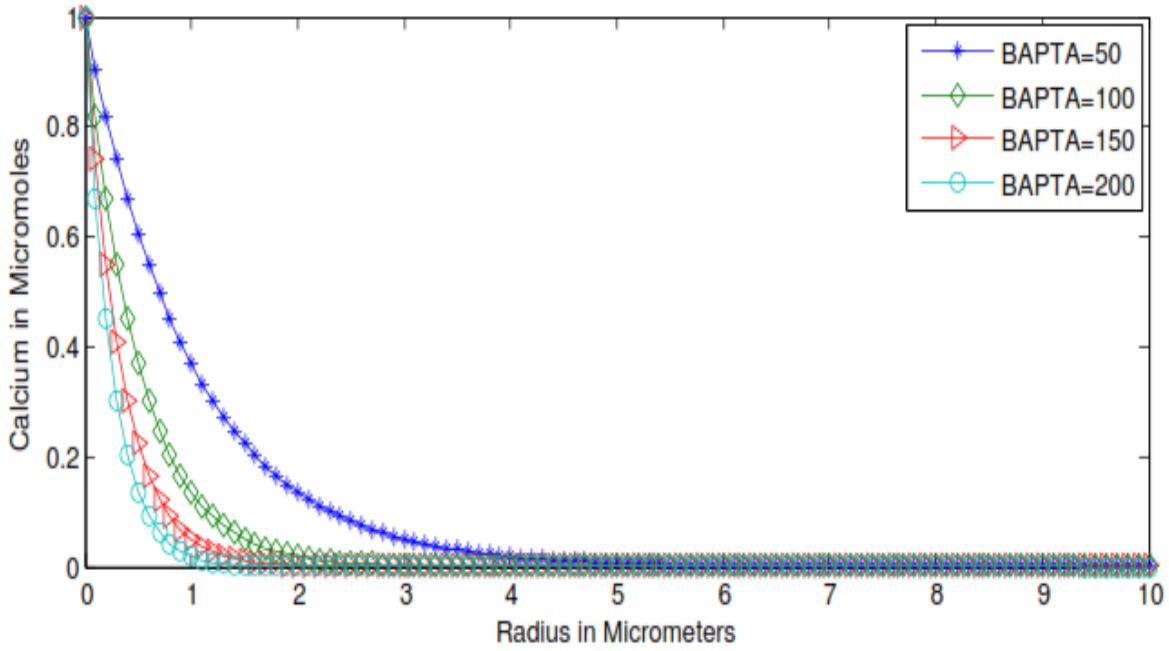

Figure.4: Radial variation of Calcium concentration for $\sigma = 1pA$ and $r = 10\mu m$ for different concentration of BAPTA buffer

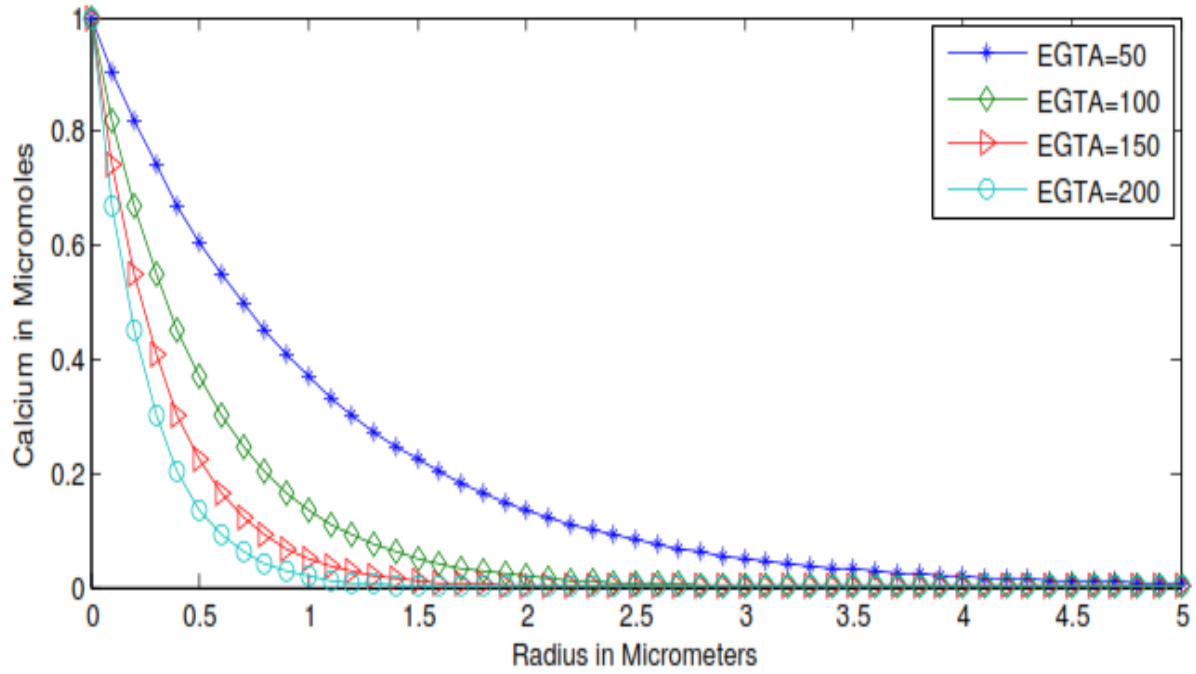

Figure.5: Radial variation of Calcium concentration for $\sigma = 1pA$ and $r = 5\mu m$ for different concentration of EGTA buffer

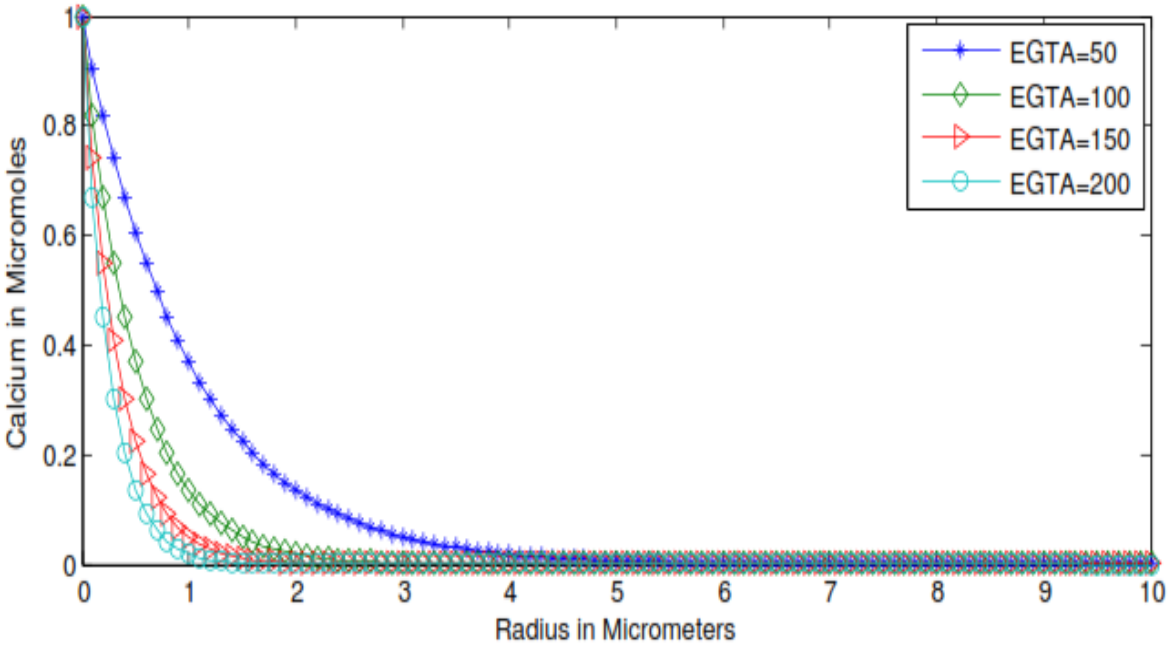

Figure.6: Radial variation of Calcium concentration for $\sigma = 1pA$ and $r = 10\,\mu m$ for different concentration of EGTA buffer

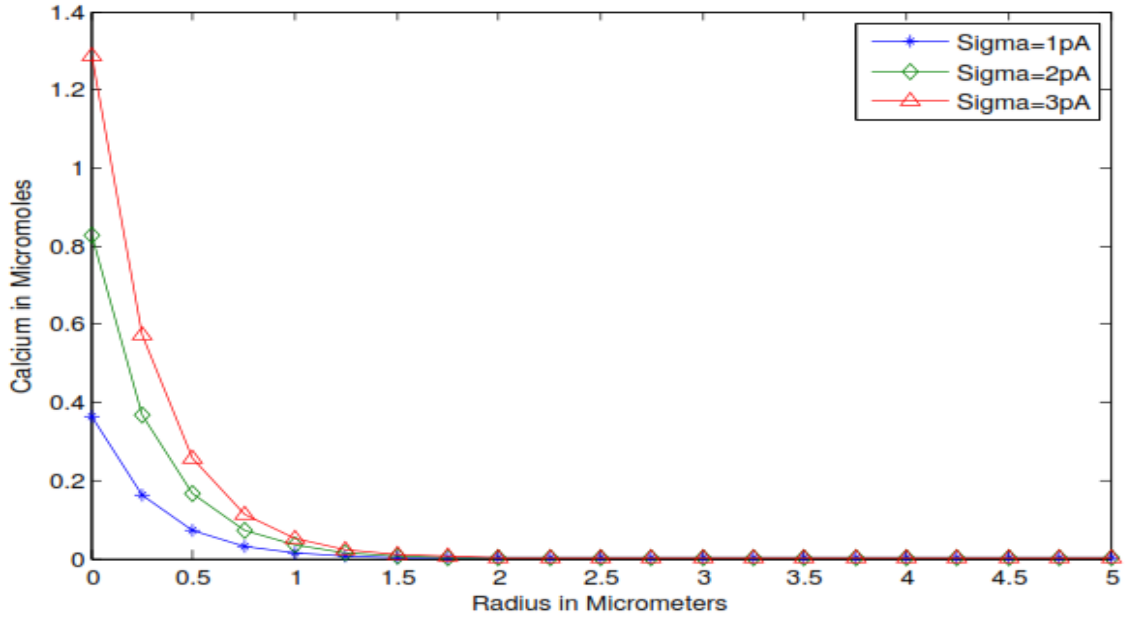

Figure.7: Radial variation of Calcium concentration for different source amplitudes i.e., $\sigma = 1pA,\ \sigma = 2\,pA,\ \sigma = 3\,pA,$ and $r = 5\,\mu m$.

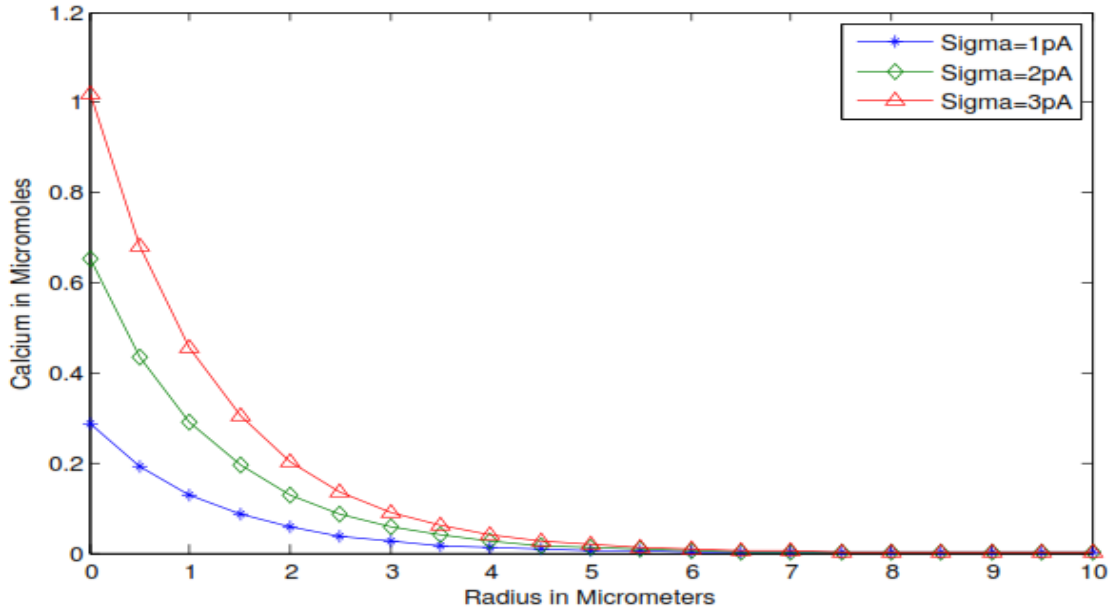

Figure.8: Radial variation of Calcium concentration for different source amplitudes i.e., $\sigma = 1pA,\ \sigma = 2pA,\ \sigma = 3pA,$ **and** $r = 10\mu m$.

Conclusion

With our studies we have seen that the buffers have significant effects on calcium concentration at the central regions near the source along the radial direction.It is concluded that the buffers have significant effect on calcium distribution in oocytes near the channel between $r = 0\,\mu m$ to $r = 2\ \mu m$. 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 upto a required distance from source within short period of time.It is observed that EGTA buffers being slow buffers allow to regulate little higher levels of calcium concentration than background calcium concentration upto wider distances from the source as compared to that in BAPTA buffers.The finite element method is quite flexible and powerful in dealing such problems. 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. [15] and the results obtained by Tripathi et al.[14], Zeller et al. [16].

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