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Finite Element Model to Study Effect of Na^+/K^+ Pump and $\text{Na}^+/\text{Ca}^{2+}$ Exchanger on Calcium Distribution in Oocytes in Presence of Buffers

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ABSTRACT

Calcium, a second messenger for signal transduction in cells plays an important role in almost every cell of our human body. In oocytes calcium plays a significant role in oocyte maturation. In the process of reproduction calcium concentration is regulated at high levels in oocytes through various mechanisms so as to meet the requirements of oocytes maturation. Thus modelling of calcium distribution in oocytes can help us in understanding this mechanism in a better way. Here an attempt has been made to develop a finite element model to study calcium distribution in oocytes. The model incorporates the parameters like diffusion coefficient, Na^+/K^+ pump, $\text{Na}^+/\text{Ca}^{2+}$ exchanger and buffers like BAPTA and EGTA. The proposed model is solved numerically using appropriate initial and boundary conditions. The program has been developed in MATLAB 7.10 for the entire problem and simulated on a 64 bit machine to compute the numerical results.

Key words: Finite element method, buffers, Na^+/K^+ pump, $\text{Na}^+/\text{Ca}^{2+}$ exchanger, MATLAB, reaction, diffusion equations

INTRODUCTION

Panday and Pardasani (2013a) studied the effect of buffers, leak, advection and Ca^{2+} exchanger on calcium distribution in oocytes. Jha *et al.* (2013) studied the effect of voltage gated calcium channels in astrocytes. Tewari and Pardasani (2008) studied the effects of Na^+ influx on cytosolic Ca^{2+} diffusion in neurons. Here an attempt has been made to study the spatio-temporal behaviour of Na^+/K^+ pump and $\text{Na}^+/\text{Ca}^{2+}$ exchanger on calcium distribution in oocytes in presence of buffers. The model is formed by a set of partial differential equations with appropriate initial and boundary conditions. Finite element method is used to solve the proposed mathematical model (Rao, 2004). The model incorporates the parameters like diffusion coefficient, Na^+/K^+ Pump, $\text{Na}^+/\text{Ca}^{2+}$ exchanger and buffers like BAPTA and EGTA. The effect of Na^+/K^+ pump and $\text{Na}^+/\text{Ca}^{2+}$ exchanger on calcium distribution in oocytes is studied with the help of numerical results. The main aim of this study is to study the changes in intracellular calcium concentration in oocyte during the process of fertilization in presence and absence of these parameters as calcium acts as a switch for oocyte maturation.

MATHEMATICAL FORMULATION

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 (Eq. 1) (Smith, 1996; Sherman *et al.*, 2001):



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 (Eq. 2-4) Neher (1973) and Smith (1996):

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

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

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

where, reaction term R_j is given by Eq. 5:

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

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, Eq. 5 can be written as (Eq. 6) (Tewari, 2009):

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

We assume that buffer concentration is present in excess inside the cytosol so that the concentration of free buffer is constant in space and time, i.e., $[B_j] \approx [B_j]_\infty$. Under this assumption Eq. 6 is approximated by (Eq. 7) (Sherman *et al.*, 2001):

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

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 Eq. 2 can be written as (Eq. 8) (Tewari, 2009; Sherman *et al.*, 2001):

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

Here, $[Ca^{2+}]$ is background calcium concentration and $\delta(r)$ is the Dirac Delta function that is placed at source position. 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. From GHK current equation (Neher, 1973; Keener and Sneyd, 1998), we have (Eq. 9):

$$I_{Ca} = P_{Ca} z_{Ca}^2 \frac{FV_m}{RT} \left[\frac{Ca_i - Ca_o \exp(-z_{Ca} \frac{FV_m}{RT})}{1 - \exp(-z_{Ca} \frac{FV_m}{RT})} \right] \quad (9)$$

where, I_{Ca} is the current due to calcium gradient, P_{Ca} is the calcium permeability, z_{Ca} is the valency of calcium ion (i.e., +2), V_m is the membrane potential, F is the Faraday's constant, R is the gas constant, T is the absolute temperature, Ca_i and Ca_o are the intracellular and extracellular calcium concentration, respectively. The net influx, σ_{Ca} of Ca^{2+} ions flowing (Eq. 10) per second at the origin is Jha *et al.* (2011):

$$\sigma_{Ca} = \frac{-I_{Ca}}{(z_{Ca} F V_{cyt})} \quad (10)$$

where, V_{cyt} is the volume of the cytosol in oocytes. In Eq. 10 there is a negative sign before I_{Ca} because inward current is taken to be negative. The expression for the Na^+/K^+ pump is given by (Eq. 11) (Tewari, 2012):

$$J_{Pump} = \frac{I_{Pump}}{\tau_{Pump}} \left(k_f + \frac{k_b}{1 + \left(\frac{k_{0.5}(0) \exp(\lambda \frac{FV_m}{RT})}{[Na^+]_o} \right)^{H_{NaK}}} \right) \quad (11)$$

Here, I_{pump} is the scaling factor of Na^+/K^+ current (in $\mu A \text{ cm}^{-2}$), k_f (in ms) is the forward (deocclusion) rate constant, k_b (in ms) is the backward (deocclusion) rate constant, $k_{0.5}(0)$ is half activation (Na^+)_o concentration at 0 mV, H_{NaK} is the Hill's coefficient for half activation Na^+/K^+ current, λ is the fraction of electrical field dropped along the access channel and τ (in ms) is some constant.

NCLX is an essential component of mitochondrial Na^+/Ca^{2+} exchange (Palty *et al.*, 2010). It helps in the extrusion of cytosolic calcium in oocytes and hence regulates the process of fertilization. In our model we have taken an exchange ratio of 3:1 with respect to sodium and calcium ions respectively. The net transport of Ca^{2+} ions through Na^+/Ca^{2+} exchanger is given by (Eq. 12, 13) (Tewari, 2009; Panday and Pardasani, 2013b):

$$\Delta Ca^{2+} = 3\Delta Na^+ \quad (12)$$

$$J_{NCX} = Ca_o \left(\frac{Na_i}{Na_o} \right)^3 \exp\left(\frac{2FV_m}{RT}\right) \quad (13)$$

where, C_{ai} and C_{ao} are the intracellular and extracellular Ca^{2+} concentration, N_{ai} and N_{ao} are the intracellular and extracellular Na^+ concentration. We have incorporated a deactivation function in the Na^+/Ca^{2+} exchanger protein equation which deactivates the Na^+/Ca^{2+} exchanger protein once the (Ca^{2+}) reaches some value (15130 μM) concentration. Therefore, the (Ca^{2+}) increases and increase in (Na^+) decreases. Since, the change in cytosolic $(Na^+)_i$ given by the Eq. 14:

$$[Na^+]_i = Na_o \left(\frac{Ca_i}{Ca_o} \right)^{\frac{1}{3}} \exp\left(-\frac{FV_m}{2RT}\right) \quad (14)$$

Also diminishes. Thus, as $(Ca^{2+})_i$ increases rate of change in $(Na^+)_i$ decreases. Now summing all the above equation we get the final model as Eq. 15:

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca} \nabla^2 [Ca^{2+}] - k_j [B_j]_{\infty} ([Ca^{2+}] - [Ca^{2+}]_{\infty}) + J_{Pump} - J_{NCX} + \sigma_{Ca} \delta(r) \quad (15)$$

Along with the initial and boundary conditions (Tewari and Pardasani, 2008). Initial condition (Eq. 16):

$$[Ca^{2+}]_{t=0} = 0.1 \mu M \quad (16)$$

Boundary conditions (Eq.17, 18):

$$\lim_{r \rightarrow 0} (-2\pi D_{Ca} r^2 \frac{\partial[Ca^{2+}]}{\partial r}) = \sigma_{Ca} \quad (17)$$

$$\lim_{r \rightarrow \infty} [Ca^{2+}] = 0.1 \mu M \quad (18)$$

Our aim is to solve the Eq. 15 along with (16-18). We solve this model in one dimensional unsteady state by finite element method assuming the oocyte to be of circular in shape. The radius of the cell is taken as $r = 5 \mu m$ and the number of elements taken for simulation are $e = 1, 2, 3, \dots, 50$. In this model, we first take the effect of Na^+/Ca^{2+} exchanger which removes the cytosolic calcium by influx of Na^+ causes the decrease in intracellular calcium after that we consider the effect of Na^+/K^+ pump which blocks the influx of Na^+ causes the balance in cytosolic calcium. The numerical values of biophysical parameters used in the model are stated in the Table 1 (Jha *et al.*, 2013; Panday and Pardasani, 2013a; Naik and Pardasani, 2013; Tewari, 2012).

RESULT AND DISCUSSION

The numerical results for calcium profile against different biophysical parameters have been obtained using numerical values of parameters given in Table 1 unless stated along with figures. Figure 1 shows that the calcium concentration near the source is higher and as we move away from the source the calcium concentration decreases slowly and finally tend to its initial value of 0.1 μM . The calcium concentration is higher from 0 to 1 μm and then decrease gradually upto 1.5 μm and finally reaches the initial value of 0.1 μm .

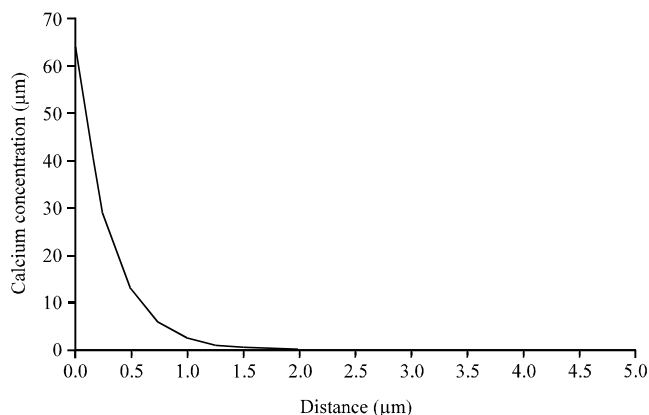


Fig. 1: Spatial variation of calcium concentration for the source amplitude $\sigma = 1$ pA

Table 1: Values of biophysical parameters

Symbol	Parameter	Value
D_{Ca}	Diffusion coefficient ($\mu\text{m sec}^{-2}$)	250
k_j^+	On rate for EGTA ($\mu\text{M sec}^{-1}$)	3
k_j^-	Off rate for EGTA (sec)	1
k_j^+	On rate for BAPTA ($\mu\text{M sec}^{-1}$)	100
k_j^-	Off rate for BAPTA (sec)	10
$[B]^\infty$	Total buffer concentration (μM)	50
σ	Source amplitude (pA)	1
Ca_o	Extracellular calcium concentration (μM)	300
P_{Ca}	Calcium permeability (m sec^{-1})	4.3×10^{-8}
V_m	Membrane potential (V)	0.05
z_{Ca}	Valency of calcium	2
V_{Oocyte}	Volume of oocyte cytosol (L)	5.48×10^{-11}
F	Faraday's constant (C mol^{-1})	96487
R	Gas constant ($\text{J K}^{-1} \text{mol}^{-1}$)	8.314
T	Absolute temperature ($^\circ\text{C}$)	37
P_{out}	Rate of calcium efflux (M sec^{-1})	0.5
Na_i	Intracellular Na^+ concentration (μM)	20
Na_o	Extracellular Na^+ concentration (μM)	140
I_{Pump}	Scaling factor of the pump ($\mu\text{A cm}^{-2}$)	1.5
k_f	Pump de-occlusion rate (m sec)	0.097
k_b	Pump occlusion rate (m sec)	1.444
$K_{(0.5)}(0)$	$[\text{Na}^+]_o$ when I_{Pump} is halved (mM)	6.95×10^{-3}
λ	Electric field dropped along pump	0.71
K_{NaK}	Hill's coefficient of pump	1.17
τ_{Pump}	Constant for pump (m sec)	0.2824

M: Mole, Sec: Second

Figure 2 shows the calcium concentration for different concentrations of EGTA buffer. It is clear from the figure that the calcium concentration is higher for lower concentration of buffer. The calcium concentration is higher from 0 to 0.5 μm after then decreases slowly and finally tends to the initial value of 0.1 μM . The reason for lower calcium concentration in response of higher value of buffer is that the higher concentration of buffer binds more calcium in oocytes thus lowers the calcium concentration.

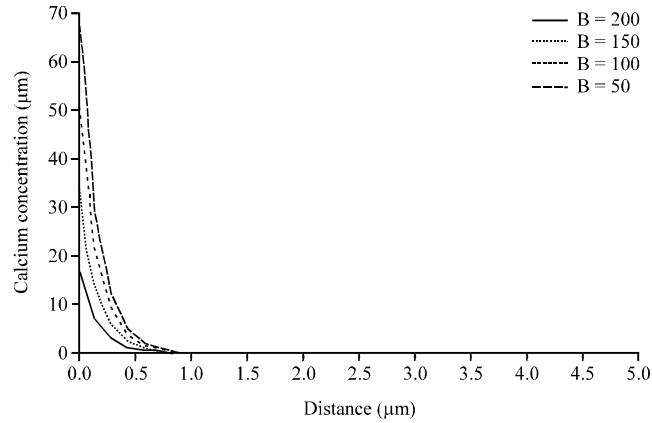


Fig. 2: Spatial variation of calcium concentration for different concentration of buffer

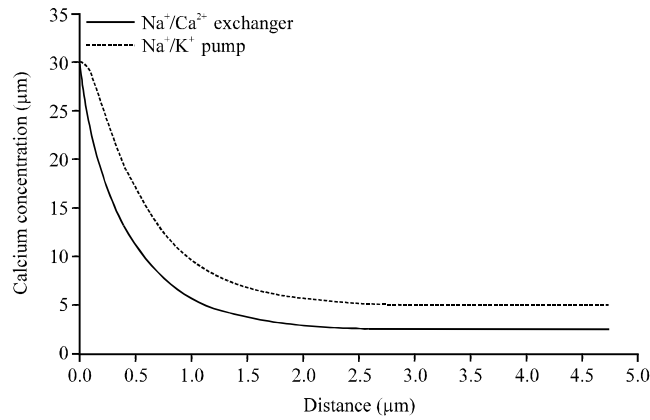


Fig. 3: Spatial variation of calcium concentration for the effect of $\text{Na}^+/\text{Ca}^{2+}$ exchanger and Na^+/K^+ pump. $\text{Na}_0 = 100 \text{ mM}$ and $\text{Na}_i = 60 \text{ mM}$

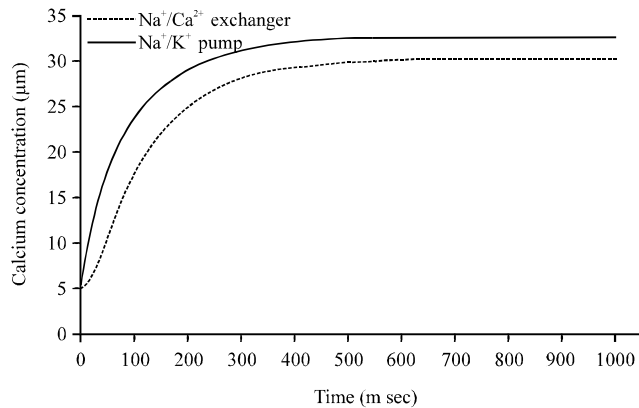


Fig. 4: Temporal variation of calcium concentration for the effect of $\text{Na}^+/\text{Ca}^{2+}$ exchanger and Na^+/K^+ pump. $\text{Na}_0 = 100 \text{ mM}$ and $\text{Na}_i = 60 \text{ mM}$

Figure 3 and 4 gives the spatial and temporal variation of calcium concentration in presence and absence of $\text{Na}^+/\text{Ca}^{2+}$ exchanger and Na^+/K^+ pump, respectively. The effect of these parameters

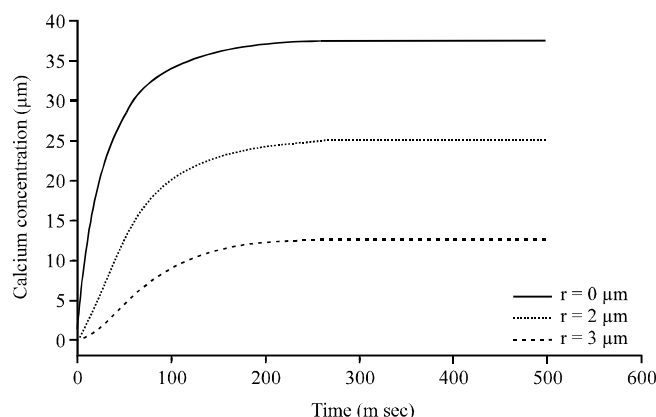


Fig. 5: Temporal variation of calcium concentration for different radial positions i.e., for $r = 0, 2$ and $3 \mu\text{m}$ and for Buffer = $50 \mu\text{M}$, $\sigma = 1 \text{ pA}$

is clearly shown in figures. The $\text{Na}^+/\text{Ca}^{2+}$ exchanger works as it removes one Ca^{2+} ions from the cell in response of entering three Na^+ ions into the cell causing the increase in Na^+ inside the cell i.e., in the ratio of $\text{Ca}^{2+}:3\text{Na}^+$ and Na^+/K^+ pump works by removing three ions of Na^+ from the cell by entering two ions of K^+ into the cell i.e., in the ratio of $3\text{Na}^+:2\text{K}^+$. Thus the mechanism of these two parameters is $\text{Ca}^{2+}:3\text{Na}^+:2\text{K}^+$. From figures we see that the calcium concentration is lower in presence of $\text{Na}^+/\text{Ca}^{2+}$ exchanger this is because the exchanger removes Ca^{2+} ions from the cytosol thus causing lower concentration of calcium in the cell. Also the figures shows that in presence of Na^+/K^+ pump the calcium concentration is higher than in presence of $\text{Na}^+/\text{Ca}^{2+}$ the reason for this is that the presence of Na^+/K^+ pump blocks the efflux of calcium by blocking the function of $\text{Na}^+/\text{Ca}^{2+}$ exchanger thus increases the calcium in the cytosol. Figure 3 shows that the calcium concentration is higher from $r = 0-1.5 \mu\text{m}$ after then tends to the steady state case while Fig. 4 shows that the calcium concentration is higher from $t = 0$ to $t = 200 \text{ ms}$ and then onwards remains in the steady state case. The presence of Na^+/K^+ pump thus controls the efflux of calcium from the cell by stopping the function of $\text{Na}^+/\text{Ca}^{2+}$ exchanger makes the balance of calcium in the cytosol as is clearly visible from the above Fig. 3 and 4.

Figure 5 gives the intracellular temporal Ca^{2+} distribution at different radical positions for the buffer with respect to time. As time increase the Ca^{2+} concentration rises sharply and after some time it achieves the steady state. With increase in distance from the source calcium concentration decreases and takes less time to reach steady state. In the figure the green curve corresponds to $r = 0 \mu\text{m}$, the red curve corresponds to $r = 2 \mu\text{m}$ and the blue curve corresponds to $r = 3 \mu\text{m}$. The Ca^{2+} concentration is higher from $t = 0-200 \text{ msec}$ and after then tends to the steady state. The concentration of buffer in the study is taken as $B = 50 \mu\text{M}$ for the oocyte.

CONCLUSION

The mathematical models developed give us interesting results regarding relationships among various parameters like calcium concentration, diffusion coefficient, radius, influx, buffers, $\text{Na}^+/\text{Ca}^{2+}$ exchanger and Na^+/K^+ Pump etc. The finite element method used is quite flexible to study relationship among these parameters and gives better relationship between them. Such models can be developed to generate information for better insights and understanding for the calcium signaling in Oocytes. The results obtained are very helpful for the Biomedical scientists in

understanding the mechanisms of oocyte cell growth, maturation of oocyte and reproduction. The results obtained in this study are in close agreement with the experimental studies (Clarke and Kane, 2007; Palty *et al.*, 2010; Lee *et al.*, 2002; Morris, 2011) and the results obtained by Panday and Pardasani (2013b) and Tewari and Pardasani (2008).

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