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Article

Compartmental Model to Study Calcium Distribution in Oocytes

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Abstract: Ca^{2+} plays an important role in the cellular processes. It is important to master the ability to develop model. Modelling of dynamic systems plays a very important role in applied sciences. Compartment models are among the most important tools used for analysing dynamical systems. Ca^{2+} is considered as second messenger in communication process. Ca^{2+} distribution in oocytes helps in oocyte maturation. Considering the importance of the Ca^{2+}, in the present paper an attempt has been made to develop a mathematical model to study the effect of various parameters on Ca^{2+} distribution in oocytes during the fertilization process. The main objective of the paper is to study the effect of buffers, Ca^{2+} channels and Ca^{2+} pumps on the intracellular Ca^{2+} concentration distribution in the oocyte cell.

Keywords: Ca^{2+} Distribution, Ca^{2+} Channels, Ca^{2+} Pumps, Buffers, MATLAB

Mathematic Subject Classification Code: 92BXX, 92CXX, 92C35, 92C50, 46N60

1. Introduction

Oocyte maturation in preparation for fertilization provides an exceptionally well-suited model to elucidate Ca^{2+} signaling regulation during cellular development. This was because a Ca^{2+} signal with specialized spatial and temporal dynamics is universally essential for egg activation at fertilization [1]. Furthermore, Ca^{2+} controls many cellular processes by relaying signals in form of their spatio-temporal distribution. Ca^{2+} triggered the secretion of neuroendocrine cells which is known to be a relatively slow

process with longer latencies when compared with the secretion of neurotransmitters in synapses [2, 3]. In chromaffin cells for instance it is known that secretion continues during tens of milliseconds after a short pulse [4]. In pancreatic b-cells latency between elevation of Ca^{2+} and exocytosis has recently been reported [5]. A plausible explanation for such slow mechanisms of secretion may be found in the existence of cytosolic buffers that delay the response by slowing down the free Ca^{2+} transient. The way in which Ca^{2+} exogenous chelators interfere with secretion, in both chromaffin and b-cells strongly support such a possibility [6]. Speaking in general terms, one can summarize the basic ingredients of Ca^{2+} signalling [7] in neuroendocrine cells as consisting of transient of Ca^{2+} ions through the cell membrane uptake and release of Ca^{2+} by internal stores, diffusion of Ca^{2+} and binding/unbinding by endogenous (or exogenous added) buffers. When secretion is studied the dynamics of the release granules responsible for secretion as well as their spatial distribution also have to be taken into account [7].

Researchers in their studies have considered the problem of buffered Ca^{2+} diffusion, Na^{+}/Ca^{2+} exchanger, SERCA pumps, RyR Ca^{2+} channels in both excitable as well as non-excitable cells. They have modelled the system by means of reaction-diffusion differential equations and solved the proposed models numerically using finite difference schemes [8, 9, 10], finite element scheme [11-18]. Other mathematical approaches simplify the models considered different kinds of approximations valid either for rapid buffers [19, 20] or in the linear regime [21]. Such previous studies have addressed the importance of buffered Ca^{2+} diffusion to gain insight into the secretory response [10] as well as to correctly interpret data from fluorescence experiments [9, 20]. They used exogenous buffers as indicators of Ca^{2+} intracellular activities. In this paper an attempt has been made to develop a compartmental model to study the buffered diffusion of Ca^{2+}. The motivation for adopting such a scheme was that the symmetry to reduce the number of spatial dimensions is not needed. Thus a three dimensional simulation of diffusion can be performed. Further the boundary conditions of the problem are more easily taken and one can vary such conditions with ease. For instance in the proposed model simulation, it is a simple task to model the entrance of ions through channel pores (not necessary regularly distributed) and to consider the possibility of clustered channels.

2. Model Formulation and Solution

The model is given as below. The cell is considered as a single compartment with the Ca^{2+} influx and Ca^{2+} efflux shown by arrows

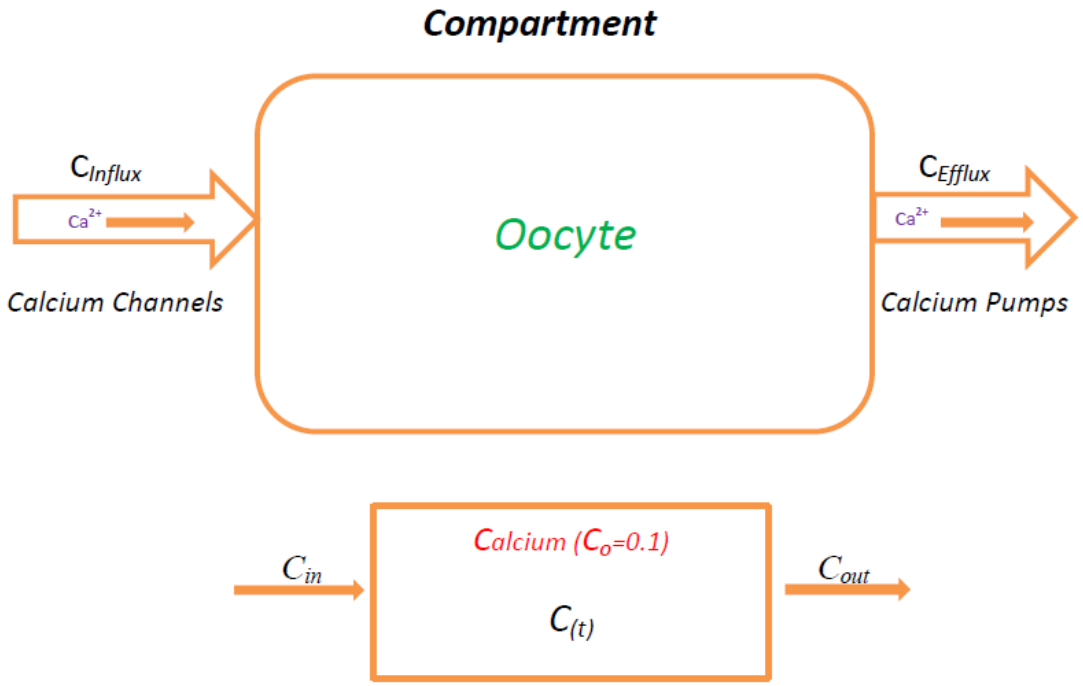


Fig. 1: Compartment illustrating influx and efflux of calcium

Let $C(t)$ be the amount of Ca^{2+} in the compartment which is the function of time 't'. The focus is to study how much Ca^{2+} has entered and left from the cell. The aim is to calculate the value of function $C(t)$ as a function of 't'. Here the aim is to develop an equation that describes how the volume changes during a small period of time from $(t \text{ to } t+\Delta t)$. The change in volume during the time increment Δt is given by

$$C(t+\Delta t)-C(t) \qquad (1)$$

By conservation of mass which states that the changes in volume equals the difference between what flows in and what flows out from the compartment. Consider that Ca^{2+} enter the compartment at a velocity of $0.5\,\mu M/\sec$. This Ca^{2+} contains $0.006\,\mu M$ of buffer per μM of Ca^{2+}. Also the efflux from the compartment at the same velocity is $0.5\,\mu M/\sec$ i.e., the volume of Ca^{2+} in the compartment does not change. Here the goal is to calculate the amount of Ca^{2+} per unit of time i.e., $C_{\inf lux}$ and $C_{\text{eff } lux}$. The first step towards determining C(t) is to derive an equation for mass conservation during a period of time from $(t \text{ to } t+\Delta t)$. During this period of time the amount of Ca^{2+} flowing into the compartment can be computed as

$$C_{\inf lux} = 0.5\mu M/\sec \times \Delta t.\sec \times 0.006 \qquad (2)$$

$$C_{\inf lux} = 0.003\mu M/\sec \times \Delta t.\sec \qquad (3)$$

At time 't', the Ca^{2+} flowing out has a concentration of $\frac{C(t)}{C_o(t)}$, where $C_o(t)$ is the initial Ca^{2+} concentration in the compartment. Hence the amount of Ca^{2+} efflux is given by

$$C_{\text{eff } lux} = 0.5\mu M / \sec \times \Delta t.\sec \times \frac{C(t)}{C_o(t)} \mu M \tag{4}$$

The difference equation obtained by computing the difference between $C_{\text{inf } lux}$ (what flows in) and $C_{\text{eff } lux}$ (what flows out) divided by Δt is given by

$$\frac{C(t+\Delta t)-C(t)}{\Delta t} = 0.003\,\mu M / \sec - \frac{0.5\times C(t)}{C_o(t)} \mu M / \sec \tag{5}$$

$$\frac{C(t+\Delta t)-C(t)}{\Delta t} = 0.003\,\mu M / \sec - \frac{C(t)}{5} \mu M / \sec \tag{6}$$

Letting $\Delta t \to \infty$, to get $C'(t)$ as

$$C'(t) = 0.003\,\mu M / \sec - \frac{C(t)}{5} \mu M / \sec \tag{7}$$

Eq. (7) is a linear differential equation, where $C'(t)$ is a function of $C(t)$. A function $C(t)$ that fulfils above equation is the solution of the given differential equation. This equation can be solved using separation of variables. The solution is given by

$$C(t) = 1.08\,\mu M + \beta\,\mu M\, e^{-\frac{t}{5}} \tag{8}$$

To determine β, let $C_o = 0.1\mu M$ at $t = 0$, then

$$C(0) = 0.1 = 1.08 + \beta\, e^{0} \tag{9}$$

$$\beta = 0.1 - 1.08 \tag{10}$$

Hence

$$C(t) = (1.08 - .98\, e^{-\frac{t}{5}})\,\mu \text{M} \tag{11}$$

On differentiation, the Eq. (11) gives

$$C'(t) = (-.98\, e^{-\frac{t}{5}})\,\mu \text{M}\ (-\frac{1}{5}) \tag{12}$$

$$C'(t) = \frac{.98}{5}\, e^{-\frac{t}{5}}\,\mu \text{M/ sec} \tag{13}$$

Substituting value of $C'(t)$ in Eq. (7), to get

$$C'(t) = 0.003\,\mu M / \sec - \frac{1.08}{5} e^{-\frac{t}{5}} \mu M / \sec \tag{14}$$

$$= \frac{e^{-\frac{t}{5}}}{5} \mu M / \sec$$

Letting $t \to \infty$, to get

$$\lim_{t\to\infty} e^{-\frac{t}{5}} = 0 \tag{15}$$

3. Results and Discussion

In this section, the numerical results for Ca^{2+} profile against different biophysical parameters and for different concentrations of buffer had shown.

The Ca^{2+} concentration distribution when the channels are open and pumps were closed as shown in Fig. 2. From the Fig. 2 it is clear that the Ca^{2+} concentration is higher when the channels are open and pumps are closed, this is because the channels release more Ca^{2+} in the cytosol, thus making the concentration higher. The concentration is higher from $t = 0$ *to* 20 seconds after then the concentration reaches the equilibrium state. At time $t = 20\,\sec$ the Ca^{2+} concentration is higher approximately upto $1.1\,\mu M$ after then the concentration becomes steady this is because of the presence of buffer in the cytosol. The buffer binds more Ca^{2+} thereby reducing the free Ca^{2+} in the cell.

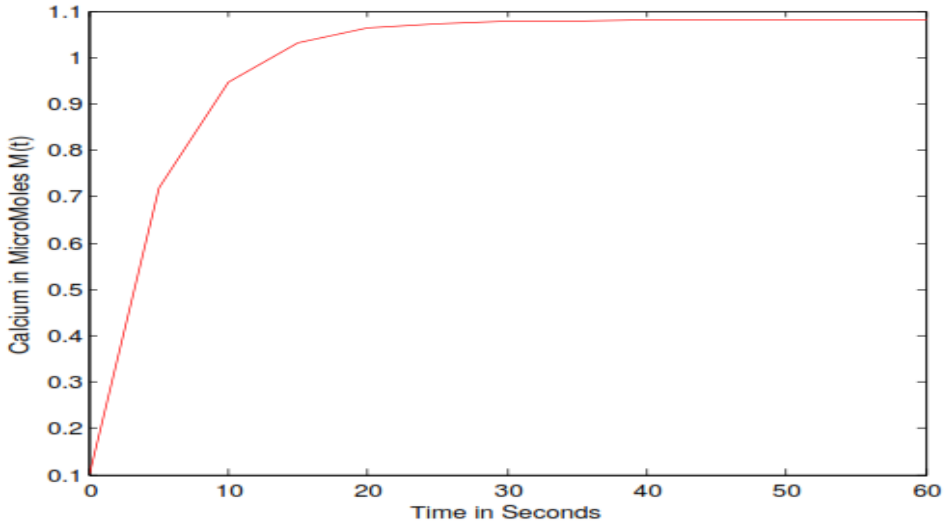


Fig. 2: Intracellular Ca^{2+} concentration distribution when channels are open and pumps are closed.

The Ca^{2+} concentration distribution when the channels are closed and pumps are open as shown in Fig. 3. From the Fig. 3 it is clear that the Ca^{2+} concentration is initially high when the channels are

closed and pumps are open, this is because the Ca^{2+} concentration in the cytosol before pumps get active is very high as time increases the pumps becomes more active then start to remove the Ca^{2+} from the cell thus prevent the cell death. The high concentration of Ca^{2+} is toxic for longer time as the cell becomes dead due to high concentration. The concentration is higher from $t = 0$ *to* 15 seconds after then the concentration decreases gradually upto $t = 20$ and finally reaches to the steady state.

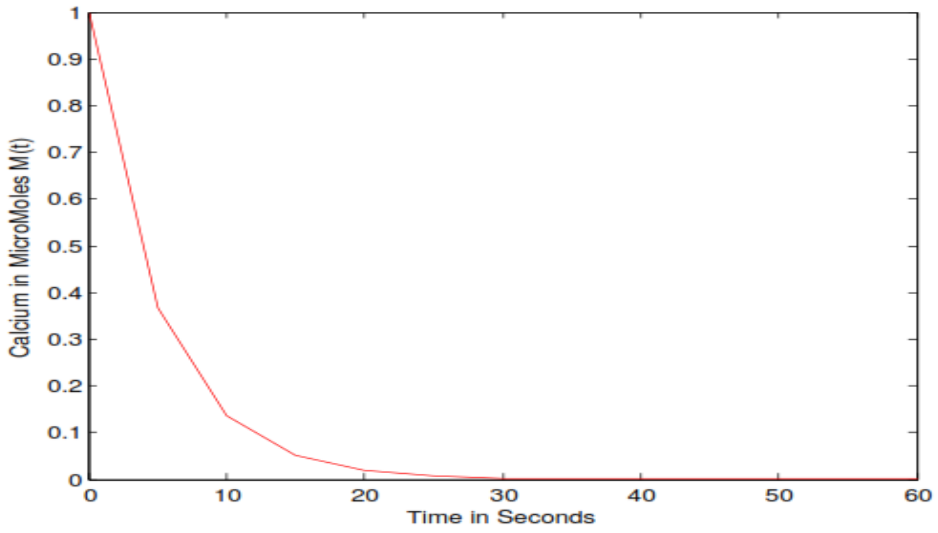
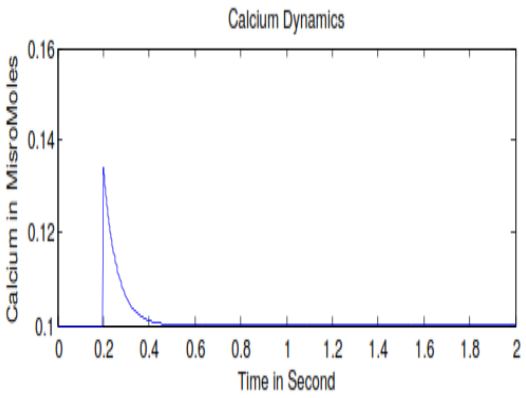


Fig. 3: Intracellular Ca^{2+} concentration distribution when channels are closed and pumps are open.

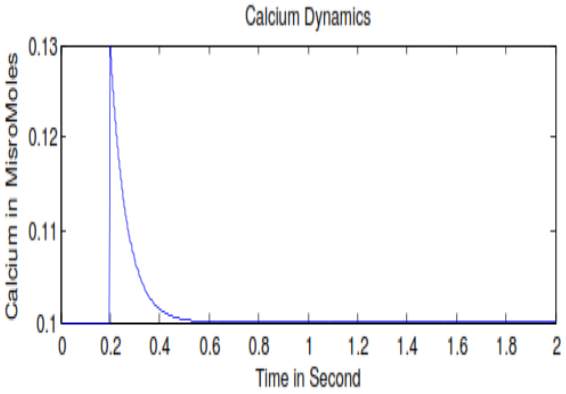
Ca^{2+} distribution in an oocyte cell for buffer concentrations $50\,\mu M, 100\,\mu M$ and $150\,\mu M$ respectively was shown in Fig. 4. It was observed in Fig. 4 that the Ca^{2+} concentration is highest at lowest concentration of buffer this was due to increase in the value of buffer concentration the quantity of free Ca^{2+} concentration reduces. The Ca^{2+} concentration converges to background concentration $0.1\,\mu M$ away from the source. It was observed that the Ca^{2+} concentration is maximum from $t = 0.2$ *to* 0.3 about $0.135\,\mu M$ for the buffer concentration $50\,\mu M$ and then it decreases sharply between $t = 0.3$ and $t = 0.4$, and finally achieves background cytosolic Ca^{2+} concentration. When buffer concentration is $150\,\mu M$, the maximum value of Ca^{2+} concentration is $0.125\,\mu M$ and then it decreases sharply between $t = 0.3$ and $t = 0.4$, and finally achieves background cytosolic Ca^{2+} concentration. It is also observed that the cytosolic Ca^{2+} concentration in oocyte decreases as the buffer concentration increases. The Ca^{2+} concentration for concentration of buffer $50\,\mu M, 100\,\mu M, 150\,\mu M$ is $0.135\,\mu M, 0.130\,\mu M$ and $0.125\,\mu M$ respectively. The reason for lower Ca^{2+} concentration with higher buffer concentration is that the higher concentration of buffer binds more Ca^{2+} to decrease the value of the Ca^{2+} concentration. The results obtained in this study were in a close agreement with the results

obtained by Panday *et al*. [13], Naik *et al*. [22, 23, 28], Tarray *et. al.* [26, 27] and the experimental studies [24, 25, 29, 30].



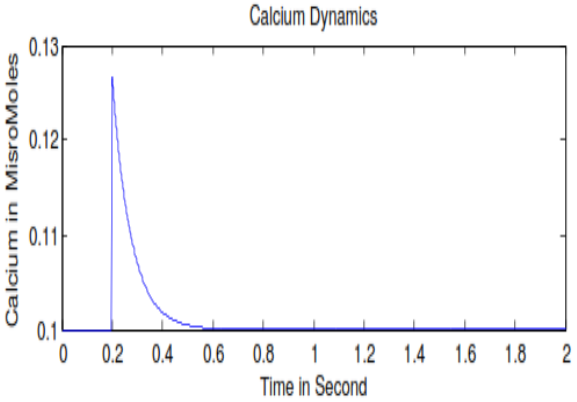
$Buffer = 50\ \mu M$

(a)



$Buffer = 100\ \mu M$

(b)



$Buffer = 150\ \mu M$

(c)

Fig. 4: Temporal variation of intracellular Ca^{2+} concentration distribution in Oocytes for source amplitude $\sigma_{Ca} = 1pA$ at different concentrations of EGTA buffer.

4. Conclusion

The compartmental model has been proposed and employed to study the effect of Ca^{2+} channels, Ca^{2+} pumps and buffers on Ca^{2+} concentration distribution in oocytes. The model gives us better insight for the Ca^{2+} distribution in oocytes. The results obtained clearly indicate that these parameters i.e., exogenous buffers, Ca^{2+} channels and Ca^{2+} pumps play an important role in regulation of Ca^{2+} dynamics in oocytes which in turn have impact on fertilization process. Such models can be further developed for

more realistic studies in higher dimension in near future to obtain information which can be of great use to biomedical scientists for developing protocols for diagnosis and treatment of reproductive diseases.

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