Alexandria Journal of Medicine (2016) **52**, 43–49

HOSTED BY

ELSEVIER

Alexandria University Faculty of Medicine

Alexandria Journal of Medicine

http://www.elsevier.com/locate/ajme

Finite element model to study calcium distribution in oocytes involving voltage gated Ca^{2+} channel, ryanodine receptor and buffers

Parvaiz Ahmad Naik *, **Kamal Raj Pardasani**

Department of Mathematics, Maulana Azad National Institute of Technology, Bhopal 462051, India

Received 17 November 2014; accepted 22 February 2015
Available online 20 March 2015

KEYWORDS

FEM;
VGCC;
Buffers;
RyR;
MATLAB;
Reaction diffusion equation

Abstract Calcium is one of the most important signalling ions in cell biology performing numerous functions with high specificity. A calcium wave triggers life at fertilization but also can cause cell death. The means by which this single ion can be both highly specific and universal is believed to lie in its spatiotemporal dynamics mediated by ion channels, pumps, receptors and calcium buffers. During oocyte maturation the calcium signalling machinery undergoes differentiation which results in distinctly different calcium release patterns on all organizational scales from puffs to waves. The calcium concentration patterns required during different stages of oocyte maturation are still not completely known. Also the mechanisms involved in calcium dynamics in oocyte cell are still not well understood. In view of above a two dimensional model has been proposed to study calcium dynamics in an oocyte cell. The parameters such as buffers, ryanodine receptor and voltage gated calcium channel are incorporated in the model. Based on the biophysical conditions the initial and boundary conditions have been framed. The model is transformed into variational form and Ritz finite element method has been employed to obtain the solution. A program has been developed in MATLAB 7.10 for the entire problem and executed to obtain numerical results. The numerical results have been used to study the effect of buffers, RyR and VGCC on calcium distribution in oocyte. The results indicate that buffers can significantly decrease the calcium concentration and RyR & VGCC can significantly raise the calcium concentration level in the oocyte cell in order to initiate, sustain and terminate specific activities in the cell. The information generated from the model can be useful to biomedical scientists for clinical and biomedical applications.

1. Introduction

Ca^{2+} is a second messenger that mediates a plethora of cellular function ranging from neurotransmitter release to fertilization. Specially Ca^{2+} signalling is encoded in the spatial, temporal and amplitude features of cytoplasmic Ca^{2+} dynamics.[1] That

* Corresponding author. Mobile: +91 8602981993.
E-mail address: naik.parvaiz@yahoo.com (P.A. Naik).
Peer review under responsibility of Alexandria University Faculty of Medicine.

http://dx.doi.org/10.1016/j.ajme.2015.02.002

is in the same cell Ca^{2+} signals of disparate duration, amplitude or frequency result in different cellular response. For example localized Ca^{2+} release through ryanodine receptor in vascular smooth muscle leads to vasodilation.[2] Whereas global sustained Ca^{2+} signals lead to vasoconstriction.[3] Ca^{2+} signals achieve this specificity by differentially activating Ca^{2+} dependent efforts based on their frequency, location, duration and amplitude. At fertilization, vertebrate eggs undergo a major transition from gametogenesis with dramatic cellular alteration referred to collectively as egg activation. Ca^{2+} is the universal signal for egg activation in all sexually reproducing species studied to date from plants to humans.[4,6] The fertilization induced Ca^{2+} signal has specific spatial and temporal dynamics which is essential to activate the egg and initiate embryonic development.[4,5] This specialized Ca^{2+} signal takes the form of a single or multiple Ca^{2+} transients depending on the species.[4] Changes in the concentration of cytosolic free calcium have been found to be responsible for the initiation and regulation of a variety of cellular functions including cellular proliferation, secretion, metabolic, adjustments and changes in gene expression.[7,8] The spatiotemporal patterns of $[Ca^{2+}]_c$ as a result of agonist stimulation are as diverse as the roles of Ca^{2+} play in different cells. The temporal pattern of $[Ca^{2+}]_c$ observed in a variety of cells includes oscillations or repetitive spiking.[7,9–11] Some cells, most notably Xenopus oocyte also exhibit interesting spatial patterns of $[Ca^{2+}]_c$ including propagating waves and target and spiral patterns.[12] Ca^{2+} waves have also been observed in myocytes, astrocytes[13] hepatocytes[10] and airways epithelial cells.[14] The dynamics of Ca^{2+} is very important in cellular physiology because Ca^{2+} regulates their activity and interactions.[15] Ca^{2+} waves are dependent on the diffusion of Ca^{2+} ions both within and possibly between the cells: modulating Ca^{2+} ion diffusion may predictably alter the spatial and temporal character of the Ca^{2+} wave. Zeng and co-workers[25] developed a mathematical model of simulation of spontaneous Ca^{2+} oscillations in astrocytes mediated by voltage gated calcium channels (VGCC). A good number of attempts have been made by scientists on study of calcium distribution in neurons cells, astrocyte cells, but very few attempts are reported in the literature on modelling of calcium distribution in oocytes. No attempt is reported in the literature for modelling calcium distribution in oocytes in the presence of VGCC. In view of above a mathematical model has been developed to study effect of buffers and ryanodine receptor over Ca^{2+} profile in oocytes in the presence of VGCC. The model has been developed for a two dimensional unsteady state case. The finite element method[17] is employed to solve the problem. 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.

2. Mathematical model and solution

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[18,19]

$$[Ca^{2+}] + [B_j] \underset{k_j^-}{\overset{k_j^+}{\longleftrightarrow}} [CaB_j] \tag{1}$$

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 jth buffer respectively. Using Fickian diffusion, the buffer reaction diffusion system in two dimensions is expressed as[20,30,32,33]

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\left(\frac{\partial^2[Ca^{2+}]}{\partial x^2} + \frac{\partial^2[Ca^{2+}]}{\partial y^2}\right) + \sum R_j + \sigma_{VGCC} + \sigma_{RyR} + \delta(x)\sigma_{Ca} \tag{2}$$

$$\frac{\partial[B_j]}{\partial t} = D_{B_j}\left(\frac{\partial^2[B_j]}{\partial x^2} + \frac{\partial^2[B_j]}{\partial y^2}\right) + \sum R_j \tag{3}$$

$$\frac{\partial[CaB_j]}{\partial t} = D_{CaB_j}\left(\frac{\partial^2[CaB_j]}{\partial x^2} + \frac{\partial^2[CaB_j]}{\partial y^2}\right) - \sum R_j \tag{4}$$

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. Where σ_{VGCC} is net influx of Ca^{2+} from the voltage gated calcium channel, σ_{RyR} is net influx of Ca^{2+} from the ryanodine receptor which is assumed to be within the cell i.e., at the centre ($x = 2.5\ \mu m\, y = 2.5\ \mu m$) and σ_{Ca} is net influx of Ca^{2+} from the source and $\delta(x)$ is the standard Dirac delta function placed at the Ca^{2+} source. Let $[B_j]_T = ([B_j] + [CaB_j])$ be the total buffer concentration of jth 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[21]

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

It is assumed that the buffer concentration is present in excess inside the cytosol so that the concentration of free buffer is constant in space and time, i.e. $[B_j] \doteq [B_j]_\infty$. Under this assumption Eq. (3) is approximated by[19]

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

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 Eq. (2) can be written as[18,19]

$$\frac{\partial[Ca^{2+}]}{\partial t} = D_{Ca}\left(\frac{\partial^2[Ca^{2+}]}{\partial x^2} + \frac{\partial^2[Ca^{2+}]}{\partial y^2}\right) - k_j^+[B_j]_\infty([Ca^{2+}] - [Ca^{2+}]_\infty) + \sigma_{VGCC} + \sigma_{RyR} + \delta(x)\sigma_{Ca} \tag{8}$$

where D_{Ca} is the diffusion coefficient of free calcium, $\delta(x)\sigma_{Ca}$ is the source amplitude due to the calcium channel. σ_{VGCC} is the flux due to VGCC and this has been modelled using the Goldman–Hodgkin–Kartz (GHK) current equation.[20,22] We assume a single point source of Ca^{2+}, σ_{Ca} at $x = 0$, $y = 0$, there are no sources for buffers and buffer concentration is in equilibrium with Ca^{2+} far from the source and GHK equation as

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