Nonlinear Dynamic Modeling of 2-Dimensional Interdependent Calcium and Inositol 1,4,5-Trisphosphate in Cardiac Myocyte

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Abstract. Calcium (Ca$^{2+}$) and inositol 1,4,5-trisphosphate (IP$_3$) is critically important parameters for a vast array of cellular functions. One of the main functions is communication in all parts of the body which is achieved through cell signaling. Abnormalities in Ca$^{2+}$ signaling have been implicated in clinically important conditions such as heart failure and cardiac arrhythmias. We propose a mathematical model which systematically investigates complex Ca$^{2+}$ and IP$_3$ dynamics in cardiac myocyte. This two dimensional model is based on calcium-induced calcium release via inositol 1,4,5-trisphosphate receptors and includes calcium modulation of IP$_3$ levels through feedback regulation of degradation and production. Forward-Time Center-Space method has been used to solve the coupled equations. We were able to reproduce the observed oscillatory patterns in Ca$^{2+}$ as well as IP$_3$ signals. The model predicts that calcium-dependent production and degradation of IP$_3$ is a key mechanism for complex calcium oscillations in cardiac myocyte. The impact and sensitivity of source, leak, diffusion coefficients on both Ca$^{2+}$ and IP$_3$ dynamics have been investigated. The results show that the relationship between Ca$^{2+}$ and IP$_3$ dynamics is nonlinear.

Key words: calcium and inositol 1,4,5-trisphosphate signaling; cardiac myocyte; finite difference method; nonlinear coupled dynamics.

2. INTRODUCTION

In living systems, one of the universal and most versatile signaling mechanism is governed by intracellular calcium (Ca$^{2+}$) [1]. To fulfill its vital role for cellular processes, Ca$^{2+}$ behaves as an intracellular messenger giving information within cells [2]. Examples include contraction of the heart, information processing in the brain, synaptic plasticity and the release of digestive enzymes by the liver [3]. The growth phase of an organism, cell differentiation and proliferation are controlled by Ca$^{2+}$ signaling in the cell. Further the calcium is vital in the sustenance of life but increased cytosolic calcium concentration ([Ca$^{2+}$]$_C$) for longer duration spell death [4]. To coordinate all these cellular activities Ca$^{2+}$ signals need to be flexible, yet precisely regulated [2]. To be able to participate in the variety of cellular functions, Ca$^{2+}$ signals within cells exhibit diverse and complex spatio-temporal organization. Information is encoded in Ca$^{2+}$ signals through variations in frequency, amplitude, duration and spatial profile of [Ca$^{2+}$]$_C$.

A cell has access to two sources of Ca$^{2+}$: external and internal. Channels on the plasma
membrane pass extracellular $\text{Ca}^{2+}$ from the outside into the cell cytosol. Calcium can also be released into the cytosol through channels on the membranes of internal $\text{Ca}^{2+}$ rich sources like the endoplasmic reticulum (ER) and the mitochondria. Calcium release from internal stores is mediated by inositol 1,4,5-trisphosphate receptors (IP$_3$Rs) present on the membrane of the ER. The IP$_3$R is a ligand operated channel. Closing and opening of these channels controls $\text{Ca}^{2+}$ release into the cytosol. By the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP$_2$) by phospholipase C (PLC), two distinct second messengers, diacylglycerol and IP$_3$ are produced that binds with the IP$_3$Rs to allow $\text{Ca}^{2+}$ flow in cytosol from ER [5].

![Fig. 1. Ca$^{2+}$ and IP$_3$ dynamics in the cytosol of cardiac myocyte including inositol 1,4,5-trisphosphate receptor (IP$_3$R) channel, sarco/endoplasmic reticulum $\text{Ca}^{2+}$-ATPase (SERCA) pump and leak.](image)

The extracellular calcium concentration ($[\text{Ca}^{2+}]$) is on the order of 1 mM while cytosolic calcium concentrations ($[\text{Ca}^{2+}]_c$) are on the order of 0.1 $\mu$M. Internal stores within the cell, like the endoplasmic reticulum (ER), have calcium concentrations ($[\text{Ca}^{2+}]_E$) of the order of 500 $\mu$M. Since, the $[\text{Ca}^{2+}]_c$ are low, a steep gradient exists from the outside to the inside of a cell [6]. Similarly, a steep gradient exists across the ER membrane-cytosol interface. These steep gradients ensure a quick flow of $\text{Ca}^{2+}$ to the cytosol once a channel opens. Sustained high $[\text{Ca}^{2+}]_c$ spell death for the cell [7]. Therefore, the cell expends energy to pump out excess $[\text{Ca}^{2+}]_c$ and reloads the ER, in order to maintain low $[\text{Ca}^{2+}]_c$. Thus, a finely tuned mechanism operates to control the influx and removal of $[\text{Ca}^{2+}]_c$. Despite a great deal of experimental data, the exact mechanism underlying $\text{Ca}^{2+}$ dynamics in a cardiac myocyte remains unclear, as do the interactions between the IP$_3$ and $\text{Ca}^{2+}$ in coupled dynamics.

For the better understanding and insight of cytosolic $\text{Ca}^{2+}$ dynamics a number of theoretical models have been developed earlier. A model proposed by Dupont et al. [8] predicts that 5-phosphatase primarily controls the levels of IP$_3$ and, thereby, the occurrence and frequency of $\text{Ca}^{2+}$ dynamics. Dawson et al. [9] have discussed the importance of IP$_3$ in $\text{Ca}^{2+}$ signaling. They have discussed various experimental works in support of role of IP$_3$ [10]. Dupont et al. [11] have shown that sustained dynamics can still occur in a one-pool model, provided that the same $\text{Ca}^{2+}$

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channels are sensitive to both Ca\(^{2+}\) and IP\(_3\) behaving as co-agonists. Sneyd et al. [12] have reported that muscarinic receptor-mediated, long-period Ca\(^{2+}\) dynamics in pancreatic acinar cells depend on IP\(_3\) dynamics, whereas short-period Ca\(^{2+}\) dynamics in airway smooth muscle do not. Politi et al. [13] have proposed mathematical models of the interaction of both second messengers. These models incorporates both positive and negative feedbacks of Ca\(^{2+}\) on IP\(_3\) metabolism mediated by calcium activation of PLC and IP\(_3\) 3-kinase, respectively. Hund et al. [14] have reported the importance and role of “the other” calcium-release channel i.e., IP\(_3\) in cardiac myocyte. Wagner et al. [15] have worked on a wave of IP\(_3\) production accompanies the fertilization Ca\(^{2+}\) wave in the egg of the frog, Xenopus laevis. Their work is experimental as well as theoretical. Also, their are few studies [16, 17] on this coupled dynamics but none is on cardiac myocyte. Pathak et al. [18] have developed a two dimensional mathematical model to understand Ca\(^{2+}\) signaling process in cardiac myocyte but they have not considered the impact of IP\(_3\) dynamics in their model. There are other studies of different cells in literature like hepatocytes [19], neurons [20, 21], astrocytes [22, 23], fibroblasts [24, 25], pancreatic acinar [26, 27] and oocytes [28]. But in the existing literature, many mathematical work on Ca\(^{2+}\) signaling in cardiac myocyte have not paid attention on the role of IP\(_3\) signaling in their mathematical model [29] while those works which state about the impact of IP\(_3\) signaling on Ca\(^{2+}\) signaling are experimental [30, 31, 32].

These models are Class 1 models, as they assume that Ca\(^{2+}\) dynamics are caused by sequential positive and negative feedback of Ca\(^{2+}\) on the IP\(_3\)R; and that Ca\(^{2+}\) dynamics occur at a constant value of IP\(_3\) concentration ([IP\(_3\)])]. Class 2 models assume instead that Ca\(^{2+}\) modulations of IP\(_3\) levels, through feedback regulation of production and/or degradation, is the cause of calcium dynamics [26]. Ca\(^{2+}\) modulation of IP\(_3\) production and degradation occurs in two principal ways: (i) the activity of PLC, and thus the rate of production, is an increasing function of cytoplasmic calcium; (ii) the activity of the 3-kinase that degrades IP\(_3\) to IP\(_4\) is an increasing function of Ca\(^{2+}\) [26]. Many experimental works [8, 9, 10] have proposed that in cardiac myocyte, Ca\(^{2+}\)-dependent IP\(_3\) metabolism is the underlying mechanism driving the calcium dynamics, and thus the calcium dynamics in cardiac myocyte are of Class 2. However, yet there has been no detailed analysis of a Class 2 model for calcium dynamics in cardiac myocyte. In view of the above, the main aim of the present study is to develop and analyse a model that can help, to understand the Ca\(^{2+}\) dynamics in cardiac myocyte by taking into account Ca\(^{2+}\) stimulated production and degradation of IP\(_3\) and also give a better insight to the relationship between these two signaling processes.

3. MATHEMATICAL FORMULATION

The Ca\(^{2+}\) and IP\(_3\) dynamics in a cardiac myocyte for a two dimensional unsteady state case in polar cylindrical coordinates is given by [15],

\[
\frac{\partial [\text{Ca}^{2+}]_C}{\partial t} = D_C \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial [\text{Ca}^{2+}]_C}{\partial r} \right) + \frac{1}{r} \frac{\partial}{\partial \theta} \left( \frac{1}{r} \frac{\partial [\text{Ca}^{2+}]_C}{\partial \theta} \right) \right) + \frac{J_{IR} - J_S + J_L}{F_C}, \tag{1}
\]

\[
\frac{\partial [\text{IP}_3]}{\partial t} = D_I \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial [\text{IP}_3]}{\partial r} \right) + \frac{1}{r} \frac{\partial}{\partial \theta} \left( \frac{1}{r} \frac{\partial [\text{IP}_3]}{\partial \theta} \right) \right) + \frac{J_{Pr} - \lambda(J_K + J_{ps})}{F_C}, \tag{2}
\]

where diffusion coefficients of Ca\(^{2+}\) and IP\(_3\) are represented by D\(_C\) and D\(_I\) respectively, r is the radial position variable, \(\theta\) is the angle and \(t\) is the time variable. In this formulation, F\(_C\) is the fractions of the volume of cytosol to the total volume of cell, \(\lambda\) is the rate scaling factor of IP\(_3\) production and the various flux terms involved are as follows [15].

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\[ J_{IR} = V_{IR} a b^3 ([\text{Ca}^{2+}]_E - [\text{Ca}^{2+}]_C), \]

\[ J_L = V_L ([\text{Ca}^{2+}]_E - [\text{Ca}^{2+}]_C), \]

\[ J_S = V_S \frac{[\text{Ca}^{2+}]_C^2}{K_S^2 + [\text{Ca}^{2+}]_C^2}, \]

\[ J_{Pr} = V_{Pr} \frac{[\text{Ca}^{2+}]_C^2}{[\text{Ca}^{2+}]_C^2 + K_{Pr}^2}, \]

\[ J_K = (1 - \theta')V_K \frac{[\text{IP}_3]}{[\text{IP}_3] + 2.5} + \theta'V_K \frac{[\text{IP}_3]}{[\text{IP}_3] + 0.5}, \]

\[ J_{Ps} = V_{Ps} \frac{[\text{IP}_3]}{[\text{IP}_3] + 30}, \]

where \(J_{IR}, J_L, J_S, J_{Pr}, J_K\) and \(J_{Ps}\) are fluxes of IP\(_3\) receptor, leak, SERCA pump, production, kinase and phosphatase respectively. \(V_{IR}\) and \(V_L\) are flux rate constants of IP\(_3\)R and leak respectively. \(V_S\) and \(V_{Ps}\) are maximum rate of SERCA pump and IP\(_3\) production. \(V_{K1}, V_{K2}\) and \(V_{Ps}\) are maximum rate constant at low \(\text{Ca}^{2+}\) (3-kinase), at high \(\text{Ca}^{2+}\) (3-kinase) and phosphatase respectively.

Here, the equilibrium equation is given by [15],

\[ a = \frac{[\text{IP}_3]}{[\text{IP}_3] + K_I [\text{Ca}^{2+}]_C + K_{Ac}}, \]

where \(K_S\) and \(K_{Pr}\) are Michaelis constant for SERCA pump and \(\text{Ca}^{2+}\) activation respectively. \(K_I\) and \(K_{Ac}\) are dissociation constant of binding site of activating IP\(_3\) and activating \(\text{Ca}^{2+}\) respectively.

The variable \(b\) is the fraction of subunits not yet inactivated by \(\text{Ca}^{2+}\). It is defined as follows [15],

\[ \frac{db}{dt} = b_{\infty} - b \frac{w}{w}, \]

where \(w\) is the inactivation time scale (2 s) and equilibrium value, i.e., \(b_{\infty}\) is defined as follows [15],

\[ b_{\infty} = \frac{K_{Ih}}{K_{Ih} + [\text{Ca}^{2+}]_C}. \]

Here, \(K_{Ih}\) is dissociation constant of inhibiting \(\text{Ca}^{2+}\) and Hill function is given by [15],

\[ \theta' = \frac{[\text{Ca}^{2+}]}{[\text{Ca}^{2+}] + 0.39}. \]

The analysis of the complete model is not possible using basic phase plane techniques. However, in a whole-cell model (i.e. where the diffusion terms are eliminated), the \([\text{Ca}^{2+}]_E\) equation can be eliminated using the conservation relation for the total cellular \(\text{Ca}^{2+}\) concentration, \([\text{Ca}^{2+}] = F_C[\text{Ca}^{2+}]_C + F_E[\text{Ca}^{2+}]_E\).

This allows the model to be reduced to the three variables \([\text{Ca}^{2+}]_C\), \([\text{IP}_3]\), and \(b\) [15]. Here, it is assumed that all the calcium buffers are fast, immobile and unsaturated [33, 34]. Thus, the
calcium buffering is included implicitly in this model by treating all calcium fluxes as explicit fluxes. The initial and boundary conditions governing the Ca$^{2+}$ and IP$_3$ diffusion process are given by [35, 36, 37],

(i) Initial condition,

\[ [\text{Ca}^{2+}]_{C,t=0} = 0.1 \, \mu\text{M}, \]  
\[ [\text{IP}_3]_{t=0} = 0.16 \, \mu\text{M}. \]  

(ii) Boundary condition,

\[
\lim_{r \to 4, \theta \to \pi} \left( -2\pi r D_c \frac{\partial [\text{Ca}^{2+}]_C}{\partial r} \right) = \sigma, \\
\frac{\partial [\text{Ca}^{2+}]_C}{\partial r} \bigg|_{r=4, \theta \neq \pi} = 0, \\
\frac{\partial [\text{Ca}^{2+}]_C}{\partial r} \bigg|_{r=0, 0 \leq \theta \leq 2\pi} = 0, \\
\lim_{r \to 4, \theta \to \pi} [\text{Ca}^{2+}]_C = 0.1 \, \mu\text{M}. 
\]

Brown et al. [35] experimentally derived 3-D geometry displayed time-dependent behavior of the IP$_3$, therefore following boundary condition used was the polynomial fit,

\[
\lim_{r \to 4, \theta \to 0} [\text{IP}_3] = 0.1882(t)^6 + 1.3121(t)^5 + 3.5391(t)^4 + 4.5312(t)^3 + \\
+ 2.5893(t)^2 + 0.3648(t) + 0.1691 \leq 3, \\
\frac{\partial [\text{IP}_3]}{\partial r} \bigg|_{r=4, \theta \neq 0} = 0, \\
\frac{\partial [\text{IP}_3]}{\partial r} \bigg|_{r=0, 0 \leq \theta \leq 2\pi} = 0, \\
\lim_{r \to 4, \theta \to \pi} [\text{IP}_3] = 3 \, \mu\text{M},
\]

where $t > 0$ denotes time.

4. SOLUTION

The model equations (1)–(22) are solved numerically using Forward-Time Centered-Space method (FTCS).

Using FTCS approach, the equations (1) and (2) takes the following form,

\[
\frac{u_{i,j}^{n+1} - u_{i,j}^n}{k} = D_C \left\{ \frac{u_{i+1,j}^n - 2u_{i,j}^n + u_{i-1,j}^n}{h^2} + \frac{u_{i+1,j}^n - u_{i-1,j}^n}{2h} + u_{i,j+1}^n - u_{i,j-1}^n - 2u_{i,j}^n + u_{i,j+1}^n \right\} + \\
+ \frac{1}{F_C} \left\{ V_{IR} \left( \frac{p_{i,j}^n}{p_{i,j}^n + K_I} \right)^3 \left( \frac{u_{i,j}^n}{u_{i,j}^n + K_{Ac}} \right)^3 \left( \frac{K_{Ih}}{K_{Ih} + u_{i,j}^n} \right)^3 (u_E - u_{i,j}) - V_S \frac{u_{i,j}^n}{K_S + u_{i,j}^2} + V_L (u_E - u_{i,j}) \right\}
\]

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Fig. 2. Discretization of the cytosol of cell, where the bigger dark black and red shade on the left hand side and right hand side denotes the point source of Ca^{2+} and IP_{3}, respectively.

\[
\frac{p_{i,j}^{n+1} - p_{i,j}^{n}}{k} = \frac{D_I}{2} \left\{ \frac{p_{i+1,j}^{n} - 2p_{i,j}^{n} + p_{i-1,j}^{n}}{h^2} + \frac{p_{i,j+1}^{n} - p_{i,j-1}^{n}}{2r h} + \frac{p_{i,j-1}^{n} - 2p_{i,j}^{n} + p_{i,j+1}^{n}}{(r l)^2} \right\} + \\
+ \frac{1}{F_C} \left\{ \frac{u_{i,j}^{n+2}}{u_{i,j}^{n+2} + K_{Pr}} \right\} - \\
- \lambda \left\{ \frac{V_{Ps}}{p_{i,j}^{n}} \left( \frac{p_{i,j}^{n}}{p_{i,j}^{n} + \lambda} \right) + \left( 1 - \frac{u_{i,j}^{n}}{u_{i,j}^{n} + 0.39} \right) V_{K1} \frac{p_{i,j}^{n}}{p_{i,j}^{n} + 2.5} + \frac{u_{i,j}^{n}}{u_{i,j}^{n} + 0.39} V_{K2} \frac{p_{i,j}^{n}}{p_{i,j}^{n} + 0.5} \right\},
\]

where \( u \) denotes the [Ca^{2+}]_{c} and \( p \) denotes the [IP_{3}], both are a function of \((r, \theta, t)\). Also, \( u_{E} \) denotes [Ca^{2+}]_{E}. Here, \( h \) denotes the radial step, whereas \( l \) represents angular step. The time step is denoted by \( k \). Also, \( i \) and \( j \) represents the index of space and \( n \) represents the index of time.

The initial and boundary conditions governing the Ca^{2+} and IP_{3} diffusion process are given by equations (13)–(22), which are rewritten as given below:

(i) Initial condition,

\[
\begin{align*}
\frac{u_{i,j}^{0}}{h} &= 0.1 \, \mu M, \\
\frac{p_{i,j}^{0}}{h} &= 0.16 \, \mu M.
\end{align*}
\]

(ii) Boundary condition.

Since, the above equations are not valid at origin \((r = 0 \, \mu m, \theta = 0)\), near the Ca^{2+} source \((r = 4 \, \mu m, \theta = \pi)\) and far away from the Ca^{2+} source \((r = 4 \, \mu m, \theta = 0)\), therefore the approximation at these nodes is given by,

\[
\frac{u_{i+1,j}^{n} - u_{i-1,j}^{n}}{2h} = \frac{-\sigma}{2\pi r Dc}, \text{ at } r = 4 \, \mu m, \theta = \pi;
\]

\[
\frac{u_{i+1,j}^{n} - u_{i-1,j}^{n}}{2h} = 0, \text{ at } r = 0 \, \mu m, 0 \leq \theta \leq 2\pi;
\]

\[
\frac{u_{i+1,j}^{n} - u_{i-1,j}^{n}}{2h}, \text{ at } r = 4 \, \mu m, 0 \leq \theta < \pi;
\]

\[
\frac{u_{i+1,j}^{n} - u_{i-1,j}^{n}}{2h}, \text{ at } r = 4 \, \mu m, \theta = \pi;
\]

\[
\frac{u_{i+1,j}^{n} - u_{i-1,j}^{n}}{2h}, \text{ at } r = 4 \, \mu m, 0 < \theta \leq 2\pi;
\]

\[
\frac{u_{i+1,j}^{n} - u_{i-1,j}^{n}}{2h}, \text{ at } r = 4 \, \mu m, \theta = 2\pi.
\]
\[
\frac{u^n_{i+1,j} - u^n_{i-1,j}}{2h} = 0, \text{ at } r = 4 \ \mu m, \theta \neq \pi;
\]
(29)

\[
u^n_{4,0} = 0.1 \ \mu M;
\]
(30)

\[
p^n_{4,0} = 0.1882(kn)^6 + 1.3121(kn)^5 + 3.5391(kn)^4 + 4.5312(kn)^3 + 2.5893(kn)^2 + 0.3648(kn) + 0.1691 \leq 3;
\]
(31)

\[
\frac{p^n_{i+1,j} - p^n_{i-1,j}}{2h} = 0, \text{ at } r = 0 \ \mu m, 0 \leq \theta \leq 2\pi;
\]
(32)

\[
\frac{p^n_{i+1,j} - p^n_{i-1,j}}{2h} = 0, \text{ at } r = 4 \ \mu m, \theta \neq 0;
\]
(33)

\[
p^n_{4,\pi} = 3 \ \mu M; \quad n > 0.
\]
(34)

The resulting system (23)–(34) provides simultaneous algebraic equations in the terms of \(u^n_{i,j}\) and \(p^n_{i,j}\). The resulting equations are solved using Gaussian elimination method to obtain the nodal concentrations.

### 5. RESULTS AND DISCUSSION

In this investigations, we have used some important parameters for cardiac myocyte in our mathematical model as presented in Table 1 [15]. The variation of \([\text{Ca}^{2+}]_C\) at different radius \(r\) and \(\theta\) with respect to time is shown in Fig. 3. Initially, the variation of \([\text{Ca}^{2+}]_C\) increases linearly. From Fig. 3 it is observed that \([\text{Ca}^{2+}]_C\) increases rapidly with increasing time but it reaches constant concentration states beyond 0.2 s at different radius and angle. Also, it is confirm that, the \([\text{Ca}^{2+}]_C\) will decrease as we move from the source of IP_3 (which is located at \(r = 4 \ \mu m\) and \(\theta = 0\)) to source of \(\text{Ca}^{2+}\) (which is located at \(r = 4 \ \mu m\) and \(\theta = \pi\)), which is shown in Fig. 3. Initially, \([\text{Ca}^{2+}]_C\) across the cell will be steady concentration (0.1 \(\mu M\)). As source channel opens and starts releasing \(\text{Ca}^{2+}\), \([\text{Ca}^{2+}]_C\) increases very fast and then it approaches steady state as SERCA pump comes into picture. SERCA pump starts to pump out excess \(\text{Ca}^{2+}\) from cytosol to ER to maintain the concentration of \(\text{Ca}^{2+}\) in cytosol. And this whole cycle of processes takes place again and again.

**Table 1.** The standard values of different biophysical parameters

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>(V_{IR})</td>
<td>8.5 s(^{-1})</td>
<td>(V_{K1})</td>
<td>0.001 (\mu M/s)</td>
</tr>
<tr>
<td>(V_L)</td>
<td>0.01 s(^{-1})</td>
<td>(V_{K2})</td>
<td>0.005 (\mu M/s)</td>
</tr>
<tr>
<td>(V_S)</td>
<td>0.65 (\mu M/s)</td>
<td>(V_{Pr})</td>
<td>0.02 (\mu M/s)</td>
</tr>
<tr>
<td>(K_I)</td>
<td>0.15 (\mu M)</td>
<td>(V_{Pr1})</td>
<td>0.075 (\mu M/s)</td>
</tr>
<tr>
<td>(K_{Pr})</td>
<td>0.4 (\mu M)</td>
<td>(F_C)</td>
<td>0.83</td>
</tr>
<tr>
<td>(K_{Ac})</td>
<td>0.8 (\mu M)</td>
<td>(\lambda)</td>
<td>30</td>
</tr>
<tr>
<td>(K_S)</td>
<td>0.4 (\mu M)</td>
<td>(D_C)</td>
<td>16 (\mu m^2/s)</td>
</tr>
<tr>
<td>(K_{Ih})</td>
<td>1.9 (\mu M)</td>
<td>(D_I)</td>
<td>283 (\mu m^2/s)</td>
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Variation of \([\text{Ca}^{2+}]_C\) profile in a cardiac myocyte with increase in time with respect to radial position (\(r\)) and angular position (\(\theta\)) can be observed from Fig. 4. Initially \([\text{Ca}^{2+}]_C\) is high at
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Fig. 3. [Ca\textsuperscript{2+}]\textsubscript{C} profile in a cardiac myocyte with respect to time at different radius \( r \) and angle \( \theta \) for \( \sigma = 10 \) pA and \( V_{Pr} = 0.075 \) \( \mu \)M/s.

Fig. 4. [Ca\textsuperscript{2+}]\textsubscript{C} profile in a cardiac myocyte at different points of time for \( \sigma = 10 \) pA: \( t = 0.01 \) s (a), \( t = 0.02 \) s (b), \( t = 0.03 \) s (c), \( t = 0.04 \) s (d).

The profile of [IP\textsubscript{3}] at different radial position \( r \) and angle \( \theta \) is investigated in Fig. 5. As time increases, [IP\textsubscript{3}] rises rapidly for few milliseconds and then attains constant concentration. As we move from the source of IP\textsubscript{3} (which is located at \( r = 4 \) \( \mu \)m and \( \theta = 0 \)) to source of Ca\textsuperscript{2+} (which is located at \( r = 4 \) \( \mu \)m and \( \theta = \pi \)), IP\textsubscript{3} steady state concentration increases. Initially, [IP\textsubscript{3}] across the cell will be steady concentration (0.16 \( \mu \)M). As source channel opens and starts releasing IP\textsubscript{3}, [IP\textsubscript{3}] in cytosol increases very fast and then it becomes steady after some time as it binds to IP\textsubscript{3}Rs and reaches the steady state concentration in cytosol. At \( r = 2 \) \( \mu \)m, \( \theta = 0 \) and \( r = 0 \) \( \mu \)m, \( \theta = 0 \), the [IP\textsubscript{3}] goes down slightly below the minimum value of [IP\textsubscript{3}] maintained in the cell. This may be due to the fact that the initially available IP\textsubscript{3} is moving out of the cell.
by pump till the IP$_3$ reaches from source to these locations by diffusion process.

The study of the changes in [IP$_3$] at different time intervals with respect to radial position ($r$) and angular position ($\theta$) is shown in Fig. 6. Here, the source of IP$_3$ is assumed to be situated at $r = 4 \mu m$ and $\theta = 0$. With the increase in time, [IP$_3$] near the source of IP$_3$ also increases. [IP$_3$] decreases as we go away from source of IP$_3$ ($r = 4 \mu m$, $\theta = 0$) then it increase to achieve its maximum peak concentration at ($r = 2 \mu m$, $\theta = 0$). Again at center i.e., ($r = 0 \mu m$, $\theta = 0$), [IP$_3$] decreases. Then as we move towards the source of Ca$^{2+}$ i.e., at ($r = 4 \mu m$, $\theta = \pi$), [IP$_3$] increases and attains its maximum peak at ($r = 2 \mu m$, $\theta = \pi$) and then it decreases gradually till 0.16 $\mu M$ as we reach source of Ca$^{2+}$. This gradual increase and decrease in [IP$_3$] verifies it wave nature as per the physiology of cardiac myocyte. Also, it validates similar findings proved by experimental works [15].

Fig. 7 shows the changes in [Ca$^{2+}$]$_c$ for various values of source influx. It is observed that the increase in source amplitude increases the peak [Ca$^{2+}$]$_c$. The relationship between them is approximately proportional. This indicates that the influx of Ca$^{2+}$ through calcium channel is the mechanism by which cell can achieve the required level of peak [Ca$^{2+}$]$_c$ by proportionally increasing the influx.

The impact of leak on the concentration of Ca$^{2+}$ in cytosol of a cardiac myocyte is studied in Fig. 8. As we can observe that in Fig. 8a and Fig. 8b [Ca$^{2+}$]$_c$ is not affected by presence of leak.

Fig. 5. [IP$_3$] profile in a cardiac myocyte with respect to time at different radius $r$ and angle $\theta$ at $\sigma = 10$ pA and $V_{Pr} = 0.075 \mu M/s$. 

Fig. 6. [IP$_3$] profile in a cardiac myocyte at different points of time for $\sigma = 10$ pA: $t = 0.01$ s (a), $t = 0.02$ s (b), $t = 0.03$ s (c), $t = 0.04$ s (d).
NONLINEAR DYNAMIC MODELING OF 2–D INTERDEPENDENT Ca$^{2+}$ AND IP$_{3}$

Fig. 7. $[\text{Ca}^{2+}]_{C}$ profile in a cardiac myocyte for different values of source influx: $\sigma = 5$ pA (a), $\sigma = 10$ pA (b), $\sigma = 15$ pA (c), $\sigma = 20$ pA (d).

Fig. 8. $[\text{Ca}^{2+}]_{C}$ profile in a cardiac myocyte: with leak (a) and without leak (b).

initially near the source i.e., $r = 4 \, \mu \text{m}$ and $\theta = \pi$, which is due to the fact that at source $[\text{Ca}^{2+}]_{C}$ is high due to source influx and the effect of presence of leak is negligible there but away from the source the impact of leak can be observed. $[\text{Ca}^{2+}]_{C}$ increases in the presence of leak.

The concentration of Ca$^{2+}$ and IP$_{3}$ decreases as their diffusion coefficient increases (see Fig. 9). This shows that the relation between $[\text{Ca}^{2+}]_{C}$ and $[\text{IP}_{3}]$ with their diffusion coefficient is inversely proportional. This is due to the fact that as diffusion increases the accumulated Ca$^{2+}$ or IP$_{3}$ in cytosol decreases as the released Ca$^{2+}$ and IP$_{3}$ from the source is diffused throughout the cell. This increases in diffusion decreases the amount of $[\text{Ca}^{2+}]_{C}$ or $[\text{IP}_{3}]$ accumulated in cytosol.

The interdependence of Ca$^{2+}$ and IP$_{3}$ dynamics can be observed from the Fig. 10. It shows the ratio of $[\text{Ca}^{2+}]_{C}$ to $[\text{IP}_{3}]$ with respect to time at different positions in the cytosol of a cardiac myocyte. After few milliseconds this ratio between $[\text{Ca}^{2+}]_{C}$ and $[\text{IP}_{3}]$ at different positions in cytosol of a cardiac myocyte, attains its equilibrium state which can be observed from Table 2. It is observed from Table 2 that as moving away from the source of Ca$^{2+}$ (moving towards source of IP$_{3}$), equilibrium ratio increases. This matches with the biological fact that IP$_{3}$ ions
accumulate near IP₃R which is near source of Ca²⁺, therefore the concentration of IP₃ near the source of Ca²⁺ is very high. This results in the decrease of ratio \((u/p)\) near the source of Ca²⁺. Similarly, moving towards the source of IP₃, the ratio \((u/p)\) increases as there is less amount of IP₃ ions available due to accumulating of IP₃ ions near IP₃R. Also, from Table 2 it is observed that the time taken to reach the equilibrium state by the Ca²⁺ and IP₃ dynamics is less near the sources of Ca²⁺ and IP₃ respectively as compared to the center of cytosol. This observation implies that at the center of the cytosol impact of both the signaling (Ca²⁺ and IP₃ signaling) is very prominent. The center of the cytosol experiences the force \([Ca²⁺]C\) and \([IP₃]\) from both the sources which are placed opposite to each other, which leads to more disturbance in this region of cytosol. Due to this disturbance, it takes more time to attain equilibrium state at the center of the cytosol of a cardiac myocyte.

Table 2. Equilibrium state in coupled dynamics

<table>
<thead>
<tr>
<th>Radius (r) (µm)</th>
<th>Angle (\theta) (radian)</th>
<th>Time (t) (s)</th>
<th>Equilibrium Ratio (u/p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>(\pi)</td>
<td>0.11</td>
<td>0.2016</td>
</tr>
<tr>
<td>2</td>
<td>(\pi)</td>
<td>0.21</td>
<td>0.2214</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0.71</td>
<td>0.2612</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.73</td>
<td>0.3238</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0.62</td>
<td>0.6250</td>
</tr>
</tbody>
</table>

These spatio-temporal model results are consistent with experimental studies \([15, 41]\) that suggest that on IP₃ fluctuation the cell can evoke Ca²⁺ dynamics and vice-versa. Calcium dynamics in a cardiac myocyte obtained is consistent qualitatively with mathematical modeling studies \([42, 37, 18]\). Also, it is observed from Fig. 10 that the ratio of \([Ca²⁺]C\) and \([IP₃]\) decreases and increases again and again. And then, it shows fluctuation before attaining equilibrium state.
NONLINEAR DYNAMIC MODELING OF 2–D INTERDEPENDENT $\text{Ca}^{2+}$ AND $\text{IP}_3$

Fig. 10. Ratio of $[\text{Ca}^{2+}]_C$ and $[\text{IP}_3]$ with respect to time at different positions i.e., radius ($r$) and angle ($\theta$) in a cardiac myocyte: $\theta = \pi$ and $r = 4 \mu m$ (a), $\theta = \pi$ and $r = 2 \mu m$ (b), $\theta = 0$ and $r = 0 \mu m$ (c), $\theta = 0$ and $r = 2 \mu m$ (d), $\theta = 0$ and $r = 4 \mu m$ (e).

This oscillatory pattern shows that these two signaling are non-linearly interdependent.

6. CONCLUSIONS

There has been increasing evidence in the literature that $\text{Ca}^{2+}$ signaling can be accompanied by dynamics of $\text{IP}_3$ [43, 44, 45]. The experimental results raise the questions of the underlying mechanisms of $\text{IP}_3$ dynamics and their potential functional role in $\text{Ca}^{2+}$ signaling. The theoretical analysis presented in the present study provide understanding of both questions. In the generation of $\text{IP}_3$ signals, various processes could be involved. Feedbacks of $\text{IP}_3$ and the second product of the PLC reaction, diacylglycerol, on PLC and upstream agonist receptor/G-protein could produce $\text{IP}_3$ dynamics without involvement of $\text{Ca}^{2+}$ [46, 47]. Alternatively, feedbacks on $\text{IP}_3$ metabolism may be mediated by $\text{Ca}^{2+}$, resulting in coupled $\text{IP}_3$-$\text{Ca}^{2+}$ dynamics [8, 31, 48, 49]. In this work, we have focused on the latter type of feedback oscillators because they can naturally account for the experimental observations of i), $\text{Ca}^{2+}$ signaling at clamped $[\text{IP}_3]$ and ii), coupled $\text{IP}_3$ and $\text{Ca}^{2+}$ dynamics. We considered prototypical positive and negative feedbacks of $\text{Ca}^{2+}$ ions on $\text{IP}_3$ metabolism: $\text{Ca}^{2+}$ activation of PLC and $\text{Ca}^{2+}$ activation of $\text{IP}_3$ 3-kinase, respectively. Also, we have systematically investigate the two dimensional coupled...
A mathematical model of interdependent Ca$^{2+}$ and IP$_3$ dynamics in cardiac myocyte using finite difference method. In which the reaction-diffusion equations for Ca$^{2+}$ and IP$_3$ were successfully coupled to obtain the inter-relationship of Ca$^{2+}$ and IP$_3$ signaling in cardiac myocyte. The investigated results shows that, ratio of [Ca$^{2+}]_C$ and [IP$_3$] has oscillatory patterns with respect to time. Therefore, these two signaling processes are non-linearly interdependent and exhibit a coordination in regulating [Ca$^{2+}]_C$ and [IP$_3$] levels in the cell required for maintaining the structure and function of the cardiac myocyte. Also, the source channels, leak and diffusion coefficients act as an important parameter in order to regulate the [Ca$^{2+}]_C$ and [IP$_3$] at appropriate level required for initiation, sustenance and termination of various activities of the cardiac myocyte. The Forward-Time Center-Space method has proved to be quite effective in obtaining the results in the present study. Such models can be developed further to generate the information of Ca$^{2+}$ and IP$_3$ dynamics in cardiac myocytes which can be useful to biomedical scientists for handling the general cause and developing protocols for diagnosis and treatment for heart diseases. During heart disease various physiological changes in the heart occurs such as increased chamber dimensions and thinning of ventricle walls, are accompanied by myocyte morphological changes, including an increase in length/size. These abnormalities often stem from changes in calcium dynamics caused by altered expression or function of calcium transporting. Also, this changes in concentration of the Ca$^{2+}$ is found to be affected by change in IP$_3$ signaling. Therefore, imbalance of this coupled dynamics are the major factors for heart diseases. Abnormalities in calcium signaling have been implicated in clinically important conditions such as heart failure and cardiac arrhythmias.

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