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Modelling mechanism of calcium oscillations in pancreatic acinar cells

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Abstract We present a simple model for calcium oscillations in the pancreatic acinar cells. This model is based on the calcium release from two receptors, inositol trisphosphate receptors (IPR) and ryanodine receptors (RyR) through the process of calcium induced calcium release (CICR). In pancreatic acinar cells, when the Ca^{2+} concentration increases, the mitochondria uptake it very fast to restrict Ca^{2+} response in the cell. Afterwards, a much slower release of Ca^{2+} from the mitochondria serves as a calcium supply in the cytosol which causes calcium oscillations. In this paper we discuss a possible mechanism for calcium oscillations based on the interplay among the three calcium stores in the cell: the endoplasmic reticulum (ER), mitochondria and cytosol. Our model predicts that calcium shuttling between ER and mitochondria is a pacemaker role in the generation of Ca^{2+}oscillations. We also consider the calcium dependent production and degradation of (1,4,5) inositol-trisphosphate (IP_3), which is a key source of intracellular calcium oscillations in pancreatic acinar cells. In this study we are able to predict the different patterns of calcium oscillations in the cell from sinusoidal to raised-baseline, high frequency and low-frequency baseline spiking.

Keywords Pancreatic acinar cell · Calcium oscillations · CICR · Raised-baseline · MMOs

Introduction

The calcium plays a very vital role in many cell types. The oscillatory changes in the cytosolic calcium [Ca^{2+}] are called calcium oscillations. The frequency encoded in these signals regulates many cellular processes like exocytosis, saliva secretion, apoptosis, and necrosis (Berridge 1997; Petersen 2005; Dupont et al. 2007; Petersen and Tepikin 2008; Petersen 2009; Low et al. 2010; Parkash and Asotra 2010; Matveer et al. 2011). The exocrine cell of pancreas contains acinar cells which secrete digestive enzymes that enter into our duodenum for digestion of our daily food stuff (Leung 2010). Depending on the type of agonist such as neurotransmitter and hormone, as well as on its concentration (Petersen and Petersen 1991; Yule et al. 1991; Nathanson et al. 1992; Tepikin and Petersen 1992; Habara and Kanno 1993; Thorn 1993; Thorn et al. 1993; Tanimura 2009; Leite et al. 2010) the pancreatic acinar cells reveal different patterns of cytoplasmic calcium [Ca^{2+}]. When agonist binds to the cell membrane receptor it activates phospholipase C (PLC). PLC then catalyzes the production of IP_3. IP_3 as an intracellular messenger binds to IPR receptors on endoplasmic reticulum (ER), and thereby initiate the release of large amount of Ca^{2+} into the cytosol. As the Ca^{2+} concentration in the cytosol rises, it increases the probability of opening of both the IPR and the RyR receptors. Calcium release in the cytosol owns an autocatalytic nature, and calcium oscillations take place in the cell. The mechanism through which calcium activates its own release from the intracellular store is known as CICR. Ca^{2+} release is terminated by closure of the channels at high Ca^{2+} levels, after which Ca^{2+} is removed from the cytosol, or pumped back into ER, and the cycle can be repeated. This process leads to the formation of different patterns of calcium response in pancreatic acinar cell from baseline spike to sinusoidal oscillations, depending on changes in baseline (Straub et al. 2000; Giovannucci et al. 2002; Petersen and Tepikin 2008; Leite et al. 2010; Williams and Yule 2012).

Previously, the essential behaviors of oscillatory response in various cells have been modeled extensively. For instance: A molecular model was proposed by (Meyer and Stryer

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1988),which incorporated cooperativity and positive feedback between [Ca^{2+}] and IP_3, gave rise to repetitive Ca^{2+} transients. Based on hormone induced experimental data, (Somogyi and Stucki 1991) proposed a simple model for calcium oscillations in liver cells. A single pool model has been developed by (Keizer and De Young 1992; Young and Keizer 1992), which allows the random binding of Ca^{2+} and IP_3 molecule to each subunit. A spatial model has been proposed by (Atri et al. 1993), in which they used biphasic pattern of IPR where it is facilitated by moderate Ca^{2+} and inhibited at high level of cytosolic calcium. They investigated the phenomenon of spiral Ca^{2+} waves in the *Xenopus* laevis oocyte. With particular attention to pancreatic acinar cells, (LeBeau et al. 1999) have shown that agonist dependent phosphorylation of IPR is the elementary mechanism for agonist specific calcium oscillations. Then (Romeo and Jones 2003) focused on the stability of travelling pulses solutions of cytosolic calcium wave model given by (Sneyd et al. 2000) which was originally developed for pancreatic acinar cells. Again in the year (2003), based on the experimental work of Giovannucci et al. (2002); (Sneyd et al. 2003) constructed a mathematical model of calcium wave in the pancreatic and parotid acinar cell. Later, (Simpson et al. 2005) studied dynamics of the model developed by Sneyd et al. (2003) more intensely and explored various aspects of this model. All the models which have been developed for pancreatic acinar cells are work for certain fixed value of IP_3. Also, the mitochondrial uptake and release is not included in the study of calcium dynamics by previous research workers discussed above.

Mitochondria is not only responsible for energy production (Hajnoczky et al. 2002; Dedkova and Blatter 2008; McCoy and Cookson 2012; Szanda et al. 2012; Uchi et al. 2012; Lu et al. 2013) but also involves in a crucial cellular signaling processes. Number of theoretical studies are performed which explore the dynamic behavior of mitochondria in particular cells. For instance, (Marhl et al. 1997a) have shown that mitochondria is an important factor in the maintenance of constant amplitudes of intracellular calcium oscillations. (Marhl et al. 2000) also constructed a mathematical model which systematically explains the complex calcium oscillations in terms of bursting and chaos by introducing the role of mitochondria and cytosolic proteins. In year 2001 (Grubelnik et al. 2001) extended the work of Marhl et al. 2000. They used the simple plausible rate laws for Ca^{2+} fluxes across the inner mitochondrial membrane in the existing model and obtained the same effect on amplitude regulation. Some models have been developed which are focused on Ca^{2+} handling and its consequences by incorporating mitochondria only. With particular attention to β-cells a series of investigations (Magnus and Keizer 1997; 1998a; b), are reported which explored the role of mitochondria in calcium oscillations. (Fall and Keizer 2001) extended the work of Magnus and Keizer (1997; 1998a; b) to show Ca^{2+} stimulation of mitochondrial metabolism in ATP production and the interplay between mitochondrial and ER calcium signaling. Recently, Oster et al. (2011) extended the modular Magnus-Keizer computational model for respiration −driven Ca^{2+} handling to include a permeability transition based on a channel- like pore mechanism. They also determined both the excitability and Ca^{2+} wave propagation based on CICR mechanism. (Dyzma et al. 2012, 2013) constructed a mathematical model which is partially based on the model of Marhl et al. 2000, and introduced a new concept of physical connections between ER and mitochondria through membrane associated complexes.

Mainly there are two basic mechanisms which are responsible for calcium oscillations. In the first mechanism, Ca^{2+} binds to the IPR, and opens IPR receptors; Ca^{2+} also binds to another binding site, and decreases the probability of opening of IPR. Thus calcium activates and deactivates IPR receptors. In second mechanism the Ca^{2+} dependent IP_3 metabolism is responsible for calcium oscillations. Ca^{2+} exerts positive and negative feedback on the production and degradation of IP_3. In positive feedback Ca^{2+} activates PLC, and thus the rate of production is an increasing function of [Ca^{2+}]. In negative feedback through the activity of the 3-kinase, IP_3 degrades to IP_4, and it is also an increasing function of [Ca^{2+}]. Recently (Sneyd et al. 2006) found that in pancreatic acinar cell, Ca^{2+} dependent IP_3 metabolism is the important phenomenon to derive the calcium oscillations. Till date no model is proposed which explores the dynamic behavior of IP_3 which determines Ca^{2+}oscillations in pancreatic acinar cell. In view of above the main aim of the present study is to develop model that can help us to understand the variety of Ca^{2+} oscillations in pancreatic acinar cell, by taking into account the Ca^{2+} stimulated production and degradation of IP_3 along with mitochondrial uptake and release in presence of IPR, RyR and various inward or/outward fluxes.

Calcium model description

Taking into the account the modulation of IP_3 production and degradation by calcium, we have constructed a simple calcium oscillation model in pancreatic acinar cell. For simplicity, we have considered that cytoplasmic calcium which has three main sources: one from internal store located in the ER; the other from extracellular calcium flux, and the mitochondria. There is sharp gradient across the plasma membrane. Generally the cells maintain over 10,000 fold ratio between cytosol (0.1–1) μM and extracellular (2 mM) calcium concentrations. The calcium level also differs significantly between specific organelles. Under these circumstances we

assume a small leak (J_{IN}) from extracellular pool to intracellular medium. The calcium oscillations are totally abolished without this leak. The IPR, RyR are continuously distributed through the interior of the ER membrane. Thus we includes two Ca^{2+} fluxes from the IPR (J_{IPR}) and RyR (J_{RyR}) receptors. Next we include the action of plasma membrane pump (J_{PM}) and SERCA pump (J_{SERCA}) which brings the [Ca^{2+}] in resting state. We also include calcium uptake ($J_{m,in}$), and calcium release ($J_{m,out}$) from mitochondria in the model. The systematic representations of all fluxes are shown in Fig. 1. The proposed model is well-mixed type, (for review see Keener and Sneyd 2008). We assume the concentration of each species as homogeneous throughout. We don't include the space coordinate, and the well- mixed solutions only vary with time. Our model is to show complex calcium oscillations, and incorporate following steps.

a) We have used latest simplified IPR model which incorporates steady state data instead of taking time dependent data (Gin et al. 2009).
b) We have used the detail of the RyR model developed by (Keizer and Levine 1996).
c) We have used variable IP_3 which is Ca^{2+} dependent through its production/or degradation which has not been used by earlier researcher in their models to study calcium dynamics in pancreatic acinar cells.
d) We have used mitochondria uptake and release mechanism which has not been used by earlier researcher in their model to study calcium dynamics in pancreatic acinar cells.
e) How these models are combined into a well-mixed model.

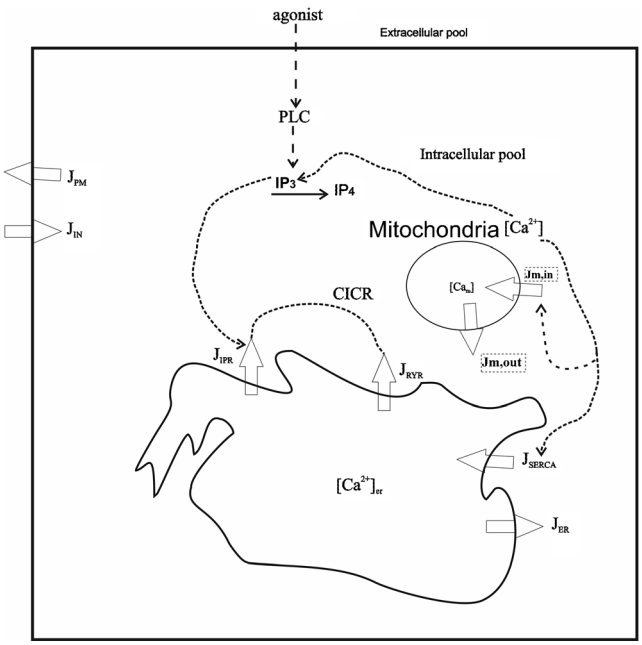

Fig. 1 Schematic presentation of the model system

Combining all the fluxes, the fundamental kinetic equations for Ca^{2+}oscillations are described as follows.

$$\frac{d[Ca^{2+}]}{dt} = \left(J_{IPR} + J_{RyR} + J_{ER}\right) - J_{SERCA} + \delta(J_{IN} - J_{PM}) + J_{m,out} - J_{m,in}, \quad (1)$$

$$\frac{d[Ca^{2+}]_{er}}{dt} = \gamma\left(-\left(J_{IPR} + J_{RyR} + J_{ER}\right) + J_{SERCA}\right), \quad (2)$$

$$\frac{d[IP_3]}{dt} = J_{IP_3prod} - J_{IP_3\deg}, \quad (3)$$

$$\frac{d[Ca^{2+}]_m}{dt} = \tau\left(J_{m,in} - J_{m,out}\right), \quad (4)$$

Here Eqs. (1–4) are the dynamic simulations for the [Ca^{2+}], ER calcium, cytoplasmic [IP_3] concentration and the mitochondria calcium $[Ca^{2+}]_m$ concentration, respectively. γ is the ratio of the cytoplasmic volume to the ER volume, and the δ is a parameter which controls the magnitude of the trans-membrane fluxes relative to the trans-ER fluxes, without changing the resting calcium concentration. The parameter τ is the ratio of cytoplasmic volume to the mitochondria volume. All parameter values are shown in Tables 1 and 2.

The IPR model

Our study is based on the model developed by (Gin et al. 2009; Palk et al. 2010) for single channel of type I IPR. They assumed that the most complex time dependent model can be unambiguously determined from the steady state data. The single channel can exists in four states, three closed states (C_1, C_2, C_3) and one open state (O_4) as shown in Fig. 2. Here the single channel data from the type 1 IPR is used to determine rate constants, and the transitions between channel states are dependent on both Ca^{2+} and IP_3. Thus the steady state open probability is given by.

$$P_{IPR} = \frac{q_{12}q_{32}q_{24}}{q_{12}q_{32}q_{24} + q_{42}q_{23}q_{12} + q_{42}q_{32}q_{12} + q_{42}q_{32}q_{21}}, \quad (5)$$

The dependency on both [Ca^{2+}] and [IP_3] and the transitions between the closed and open states may be expressed as

$$q_{12} = 0.74ms^{-1}, q_{24} = 7.84ms^{-1}, q_{42} = 3.6ms^{-1},$$

$$q_{21} = \phi_{21}([IP_3])ms^{-1}, \quad (6)$$

$$q_{23} = \alpha_{23}\psi_{23}\left(\left[Ca^{2+}\right]\right)\phi_{23}([IP_3])ms^{-1}, \quad (7)$$

$$q_{32} = \alpha_{32}\psi_{32}\left(\left[Ca^{2+}\right]\right)\phi_{32}([IP_3])ms^{-1}, \quad (8)$$

Table 1 Standard parameters: All parameters are taken from Gin et al. (2009), and Palk et al. (2010).

IP3 Receptor parameters					
bp_{21}	$0.11ms^{-1}$	bp_{23}	$0.001ms^{-1}$	bp_{32}	0
kp_{21}	$5\times10^{-10}nM^{-3}$	kp_{23}	$5\times10^{-9}nM^{-3}$	kp_{32}	$1.5\times10^{-10}nM^{-3}$
Vp_{21}	$0.0949nM^3ms^{-1}$	Vp_{23}	$0.162nM^3ms^{-1}$	Vp_{32}	$3\times10^{-12}nM^3ms^{-1}$
a_{21}	$1/1.023ms^{-1}$	α_{23}	1000	α_{32}	50
V_{23}	$1.08\times10^6nM^2ms^{-1}$	k_{23}	$2000nM$	b_{23}	$2.2ms^{-1}$
Vm_{23}	0.3545	km_{23}	$72nM$	bm_{23}	0.042
V_{32}	$7\times10^6nM^3ms^{-1}$	k_{32}	$520nM$	b_{32}	$0.005ms^{-1}$
Vm_{32}	1.06	km_{32}	$150nM$	bm_{32}	0.03

where

$$\phi_{21}([IP_3]) = \frac{VP_{21}}{1 + kp_{21}[IP_3]^3} + bp_{21}, \tag{9}$$

$$\psi_{23}([Ca^{2+}]) = a_{23} - \left(\frac{V_{23}}{k_{23}^2 + [Ca^{2+}]^2} + b_{23}\right)\left(\frac{Vm_{23}[Ca^{2+}]^5}{km_{23}^5 + [Ca^{2+}]^5} + bm_{23}\right), \tag{10}$$

$$\phi_{23}([IP_3]) = \frac{VP_{23}}{1 + kp_{23}[IP_3]^3} + bp_{21}, \tag{11}$$

$$\psi_{32}([Ca^{2+}]) = \left(\frac{V_{32}}{k_{32}^3 + [Ca^{2+}]^3} + b_{32}\right)\left(\frac{Vm_{32}[Ca^{2+}]^7}{km_{32}^7 + [Ca^{2+}]^7} + bm_{32}\right), \tag{12}$$

$$\phi_{32}([IP_3]) = \frac{VP_{32}[IP_3]^3}{1 + kp_{32}[IP_3]^3} + bp_{32}, \tag{13}$$

Table 2 Standard parameters: All parameters values for RyR are taken from Keizer and Levine (1996), IP3 parameters values are taken from Chen et al. (2009), mitochondrial parameters are taken from Marhl et al. (2000), and all other calcium transport parameters are taken from Sneyd et al. (2003).

RyR receptors parameters					
k_a^+	$1500s^{-1}(\mu M)^4$	k_b^+	$1500s^{-1}(\mu M)^3$	k_c^+	$1.75s^{-1}$
k_a^-	$28.8s^{-1}$	k_b^-	$385.9s^{-1}$	k_c^-	$0.1s^{-1}$
IP3 Parameters values					
K_{PLC}	$0.12\mu M$	$k_{\deg}$	$0.5s^{-1}$	$K_{\deg}$	$0.1\mu M$
Mitochondrial parameters					
k_{in}	$300\mu Ms^{-1}$	K_2	$1.6\mu M$	K_{out}	$125s^{-1}$
K_1	$5\mu M$	K_m	$0.1s^{-1}$		
Calcium parameters					
k_{IPR}	$0.71s^{-1}$	k_{RyR}	$0.08s^{-1}$	J_{ER}	$0.002s^{-1}$
δ	0.1	γ	5.405	τ	1.65
V_{SERCA}	$120(\mu M)^{-2}s^{-1}$	K_{SERCA}	$0.18\mu M$	V_{PM}	$28\mu Ms^{-1}$
K_{PM}	$0.425\mu M$	α_1	$0.4(\mu M)s^{-1}$	α_2	$0.05s^{-1}$

The rate constants q_{23} and q_{32} are the function of Ca^{2+} and IP_3, and other transition rates are taken as constants. All parameter values are shown in Table 1. Then the flux from the IPR receptor is given by

$$J_{IPR} = k_{IPR}P_{IPR}\left(\left[Ca^{2+}\right]_{er} - \left[Ca^{2+}\right]\right), \tag{14}$$

Here k_{IPR} is the density of IPR receptors, $[Ca^{2+}]$ and $[Ca^{2+}]_{er}$ are the calcium concentrations in cytosol and ER, respectively.

The RyR model

In the pancreatic acinar cell the RyR receptors are distributed throughout the cell (Leite et al. 1999; Ashby et al. 2002; Ashby and Tepikin 2002; Ashby et al. 2003). Thus it is important to incorporate RyR receptors in our model. Therefore, in this study we use a model for RyR which was previously developed by (Keizer and Levine 1996). This model represents the dynamic behavior of type II RyR receptor, which is originally established for heart cells. The RyR receptor can exist in four states two closed (C_1, C_2) states and two open (O_1, O_2) states as shown in Fig. 3. It is assumed that the transitions from O_1 to C_1 and O_1 to O_2 are fast, then the open probability can be expressed as.

$$P_{RyR} = \frac{w\left(1 + \left([Ca^{2+}]/Kb\right)^3\right)}{\left(1 + ([Ca^{2+}])^4 + \left([Ca^{2+}]/K_b\right)^3\right)}, \tag{15}$$

Where w is the fraction of RyR not in state C_2 and $K_a = \sqrt[4]{k_a^-/k_a^+}, K_b = \sqrt[3]{k_b^-/k_b^+}, K_c = k_c^-/k_c^+,$

Furthermore, w is governed by the differential equation

$$\frac{dw}{dt} = \frac{k_c^-(w^\infty[Ca^{2+}] - w)}{w^\infty[Ca^{2+}]}, \tag{16}$$

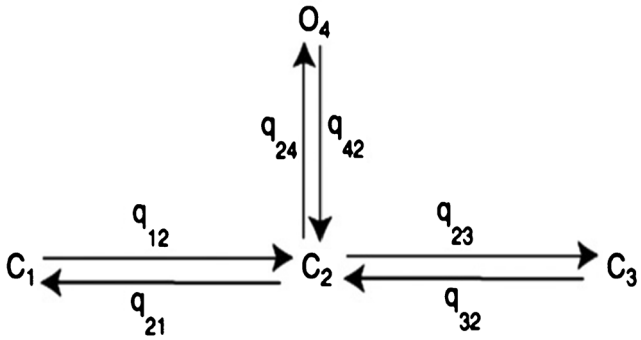

Fig. 2 Four state model of IPR receptor taken from Gin et al. (2009)

Also then $w^{\infty}[Ca^{2+}]$ takes the form

$$w^{\infty}[Ca^{2+}] = \frac{\left(1+\left(K_a/[Ca^{2+}]\right)^4+\left([Ca^{2+}]/K_b\right)^3\right)}{\left(1+\left(1/K_c\right)+\left(K_a/[Ca^{2+}]\right)^4+\left([Ca^{2+}]/K_b\right)^3\right)}, \tag{17}$$

Here k_{RyR} is the density of RyR receptors and values of all parameters are shown in Table 1. The flux through the RyR receptor is given by

$$J_{RyR} = k_{RyR}P_{RyR}\left([ca^{2+}]_{er} - [ca^{2+}]\right), \tag{18}$$

SERCA and plasma membrane pumps

The SERCA and Plasma membrane pumps (PMCA) are found in the ER membrane and in the plasma membrane, respectively. Once calcium is increased in the cytosol the SERCA pump transports calcium into the ER, and the PMCA transfers calcium

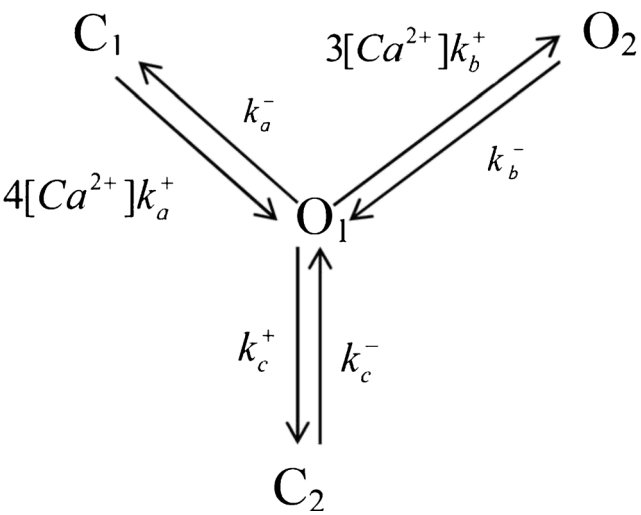

Fig. 3 Schematic Diagram of RyR model taken from Keizer and Levine (1996)

from the cytosol to the extracellular medium. Then the calcium returns to its resting state.

Firstly the mathematical description of SERCA pump on ER calcium concentration is given by (Favre et al. 1996). Based on the measurement with cell homogenates, Favre et al. (1996) reported a supralinear feedback inhibition of Ca^{2+} uptake by the Ca^{2+} load of intracellular stores. These complications are simplified by Sneyd et al. (2003) by modeling SERCA pump by quasi Hill form, whose activity is inversely proportional to ER calcium, and it ensures that the rate of SERCA pump increases as $[Ca^{2+}]$er decreases. The SERCA pump flux is given by

$$J_{SERCA} = V_{SERCA}\frac{[Ca^{2+}]}{K_{SERCA}+[Ca^{2+}]} \times \frac{1}{[Ca^{2+}]_{er}}, \tag{19}$$

Here V_{SERCA} is the maximum pump current and this model is only valid when $[Ca^{2+}]$er is bound away from zero.

The plasma membrane pump is modeled by Hill equation (Borghans et al. 1997; Gin et al. 2007; Palk et al. 2010) with hill coefficient of 2. Thus the flux from cytosol to extracellular medium is given as

$$J_{PM} = V_{PM}\frac{[Ca^{2+}]^2}{K_{PM}^2+[Ca^{2+}]^2}, \tag{20}$$

Calcium leaks

Calcium enters into the cytosol, and it modifies the intracellular calcium. The Ca^{2+} influx J_{IN} from extracellular medium to intracellular medium is assumed to be an increasing function of the maximum rate of IP_3 production. Thus J_{IN} is modeled as increasing function of agonist concentration by (Gin et al. 2007; Palk et al. 2010)with constant leak α_1,and agonist dependent influx $\alpha_2 v_{PLC}$.

$$J_{IN} = \alpha_1 + \alpha_2 v_{PLC}, \tag{21}$$

We also include a passive leak of Ca^{2+} from ER to cytoplasm J_{ER}, which is proportional to the difference in calcium concentrations.

Mitochondrial uptake and release

When calcium increases in the cytosol due to CICR, it will activate the special channel in the mitochondrial membrane, known as calcium uniporters. It leads to calcium uptake into mitochondrial matrix. Thus we assume mitochondria sequester calcium very fast by specific uniporter through the mechanism of rapid mode (RaM) of Ca^{2+} uptake. Therefore the mitochondrial Ca^{2+} uptake by uniporter ($J_{m,in}$)

is expressed as (Marhl et al. 2000; Grubelnik et al. 2001; Perc and Marhl 2004).

$$J_{m,in} = k_{in}\frac{[Ca^{2+}]^8}{K_2^8 + [Ca^{2+}]^8}, \tag{22}$$

Where k_{in}, represents the maximum permeability of the uniporter in the mitochondrial membrane and K_2 is the half-saturation rate constant for calcium. It is also known that under normal physiological conditions calcium $[Ca^{2+}]_m$ release from mitochondria is quite slow. It exits from mitochondria through the Na+/Ca^{2+} or H+/Ca^{2+} exchanger. Thus the calcium efflux ($J_{m,out}$) from mitochondria into cytosol may be expressed as (Mazel et al. 2009; Dyzma et al. 2012, 2013).

$$J_{m,out} = \left(K_{out}\frac{[Ca^{2+}]^2}{K_1^2 + [Ca^{2+}]^2} + K_m\right)\left[Ca_m^{2+}\right]^2, \tag{23}$$

Here K_{out} stands for the maximal rate of calcium flow through Na+/Ca^{2+} or H+/Ca^{2+} exchangers and K_1 is the half activation constant. The rate constant K_m represents the non-specific leak flux.

IP_3 dynamics

Calcium exerts positive and negative feedback on the production and degradation of IP_3. On positive time scale the IP_3 is produced by phospholipase C (PLC),(Blank et al. 1991; Harootunian et al. 1991; Politi et al. 2006) and its activity depends upon both the agonist concentration and the cytosolic calcium (Jacob 1989; Tsunoda 1991; Berridge 1993; Domijan et al. 2006). Thus the rate of production of IP_3 is given by (Politi et al. 2006; Chen et al. 2009).

$$J_{IP_3prod} = V_{PLC}\frac{[Ca^{2+}]^2}{K_{PLC}^2 + [Ca^{2+}]^2}, \tag{24}$$

Where, V_{PLC} is the maximal production rate of PLC isoforms (PLC_β), and depends on the agonist dose. Whereas K_{PLC} is the sensitivity of PLC on calcium.

On negative feedback mechanism [Ca^{2+}] activates the enzyme that degrades IP_3 to IP_4 (enzyme called 3-kinase) (Woodring and Garrison 1997; Nalaskowski and Mayr 2004; Leite et al. 2010; Williams and Yule 2012). Thus the kinetic equation for IP_3 degradation through phosphorylation by IP_3 kinase is expressed as.

$$J_{IP_3\deg} = k_{\deg}\frac{[Ca^{2+}]^2}{K_{\deg}^2 + [Ca^{2+}]^2}[IP_3], \tag{25}$$

Where, $k_{\deg}$ is the phosphorylation rate constant and $K_{\deg}$ is the half-saturation constant of IP_3 kinase. Then the rate of change of IP_3 concentration is given according to (Politi et al. 2006; Chen et al. 2009)

$$\frac{d[IP_3]}{dt} = J_{IP_3prd} - J_{IP_3\deg}, \tag{26}$$

It is also important to note that when K_{PLC} is equal to zero i.e. (K_{PLC}=0,$K_{\deg}\neq$0), then we obtain a negative feedback of [Ca^{2+}] on IP_3 metabolism. When $K_{\deg}$ equals to zero i.e. ($K_{PLC}\neq$0,$K_{\deg}$=0), it represents the positive feedback, and IP_3 degradation is independent of [Ca^{2+}] fluctuation. In this paper, our interest is to study the mixed feedback of [Ca^{2+}] on IP_3 metabolism. Thus we consider the IP_3 dynamics in such a way that K_{PLC} and $K_{\deg}$ are not equal to zero i.e. ($K_{PLC}\neq$0,$K_{\deg}\neq$0).

Calcium buffering

Calcium buffering is included implicitly in this model by treating all calcium fluxes as explicit fluxes. Thus we assume all the calcium buffers are fast, immobile and unsaturated (Sneyd 1994; Wagner and Keizer 1994; Keener and Sneyd 2008).

Analysis of the model

To study the transition from simple to complex calcium oscillations in the cell, the model Eqs (A1–A5) are solved numerically using the Matlab code ode15s and *Xppaut* (Ermentrout 2002). On stimulating with different agonist concentration and by changing the maximal rate of PLC i.e. V_{PLC}, we are able to predict the different patterns in calcium oscillations. On stimulation with V_{PLC}=75nMs^{-1}, we observe the sinusoidal behavior in all the three [Ca^{2+}],[IP_3] and [Ca^{2+}]m concentrations. The oscillations occur with smaller frequency and amplitude as shown in Fig. 4 panel A. As the calcium concentration in the cytosol increases, there is increase in the mitochondrial calcium concentration [Ca^{2+}]m, and it also shows sinusoidal oscillations as shown in Fig. 4 panel E. We also found that the turning point of cytosolic calcium is between 0.16 to 0.2 μM and the ER calcium is between 118.6 to 119.9 μM as shown in Fig. 4 panel C. It signifies that the calcium oscillates in the cell with smaller amplitude. When the calcium oscillates between 0.16 to 0.2 μM, the mitochondrial uniporter opens and calcium gets inside the cell. Then the calcium is removed from the mitochondria slowly and this cycle goes on repeatedly. In this mechanism [Ca^{2+}]m oscillates with quite small amplitude ranging between 7.3×10−4 to 7.95×10−4 μM as shown in Fig. 4 panel F. As a result, sinusoidal change in [Ca^{2+}]m followed in phase with the subsequent Ca^{2+} oscillations. Such type of behavior is reported previously by (Filippin et al. 2003; Ishii et al. 2006) and our results are consistent with these results.

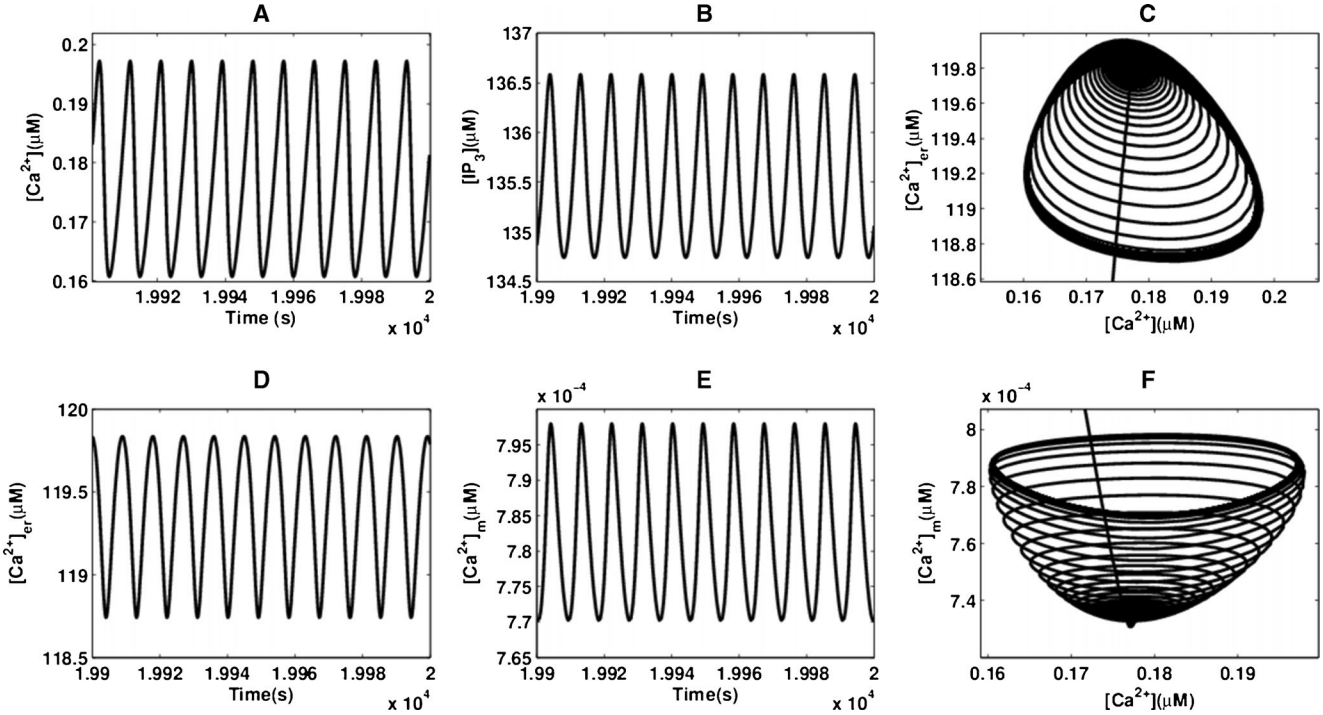

Fig. 4 Numerical integration of calcium oscillation model, when Eqs (A1–A5) in Appendix A are stimulated with VPLC=75 nMs−1. Panels A & B shows the Ca2+ and IP3 response in the cytosol. Panel D represents [Ca2+]er oscillations. Panel E shows the calcium oscillation in mitochondria. Panel C and Panel F, shows the projection of trajectories in phase –plane [Ca2+] vs. [Ca2+]er,and [Ca2+] vs. [Ca2+]m respectively. All the three ions concentrations [Ca2+], [IP3] and [Ca2+]m oscillate in the same phase, and their behavior is sinusoidal as shown in panels A,B & E

When the model is stimulated with $V_{PLC}=85nMs^{-1}$, calcium plays a dual action on the production and degradation of IP_3. As a result, the complex calcium oscillation is seen in the cell. Due to release of calcium from both the IPR and RyR receptors through the process of CICR, the $[Ca^{2+}]$ oscillates with small and large amplitudes as shown in Fig. 5 panel A. These $[Ca^{2+}]$ oscillations are accompanied by oscillations in the concentration of IP_3, and it oscillates between $\approx[151,164]\mu M$ as shown in Fig. 5 panel B. $[Ca^{2+}]$er shows the different calcium profiles with respect to $[Ca^{2+}]$ as shown in Fig. 5 panel D. Generally ER flux consists of four main parts, three outward fluxes that contains a leak, a flux from IPR channel, a flux from RyR channel, and inward flux from SERCA Pump. At maximum $[Ca^{2+}]$ ($\approx 0.63\mu M$), the SERCA pump allows a rapid uptake of cytoplasmic calcium and sends it back to ER. The plasma membrane calcium pump J_{PM} accelerates the clearance of cytosolic Ca^{2+} and results in the fast refilling of ER in combination with SERCA pump. In Fig. 5 panel C, we observe that turning point of cytosolic Ca^{2+} is $\approx 0.63\mu M$ at which the ER starts refilling with calcium, maximum up to $\approx 117\mu M$. After that, the cycle of refilling and release is repeated and $[Ca^{2+}]$ shows oscillations between $\approx[0.1,0.63]\mu M$. When the $[Ca^{2+}]$ increases, the mitochondria takes up calcium and gets filled with calcium, and then it releases calcium very slowly. This process leads to $[Ca^{2+}]$m oscillations with constant amplitudes as shown in Fig. 5 panel E. In Fig. 5 panel F, we observe that when $[Ca^{2+}]$ reaches between $\approx[0.55,0.63]\mu M$ the mitochondria take calcium. As $[Ca^{2+}]$m reaches between $\approx[0.09,0.1]\mu M$, mitochondria starts releasing calcium slowly, and this mechanism is repeated due to which $[Ca^{2+}]$m oscillates.

At ($V_{PLC}=90nMs^{-1}$), (Fig. 6) the time series for calcium is periodic with repeated section containing two different peaks (Panel A). Such types of oscillations are assist by oscillations in the concentration of IP_3 (Panel B). On comparing Fig. 5 (Panels A and E) with Fig. 6 (Panels A & D) respectively, it is noted that as V_{PLC} flux increases, the amplitude of oscillations for both $[Ca^{2+}]$ and $[Ca^{2+}]$m decreases. When the calcium in the cytosol reaches maximum up to $\approx 0.55\mu M$, the ER starts getting refilled and then the ER cycle of calcium uptake and release is repeated, and $[Ca^{2+}]$er oscillates between $\approx[104,114]\mu M$ as shown in panel C. The turning point of cytosolic calcium for mitochondrial Ca^{2+} uptake is $\approx 0.5\mu M$, as $[Ca^{2+}]$m reaches between $\approx[0.29,0.42]$, the mitochondria starts releasing calcium. Due to this mechanism the calcium starts oscillating in mitochondrial matrix.

In this model the calcium oscillations can be described approximately as a slow calcium flux from mitochondria and the fast exchange of calcium between cytosol and ER. Therefore one period of calcium oscillation is present in Fig. 7. For better explanation the cycle can be divided into three phases. In phase I, when the level of IP_3 in the cytosol increases, the calcium release from ER is the dominating process. This leads to the rapid increase of cytoplasmic calcium and it continues until the calcium in mitochondria reaches

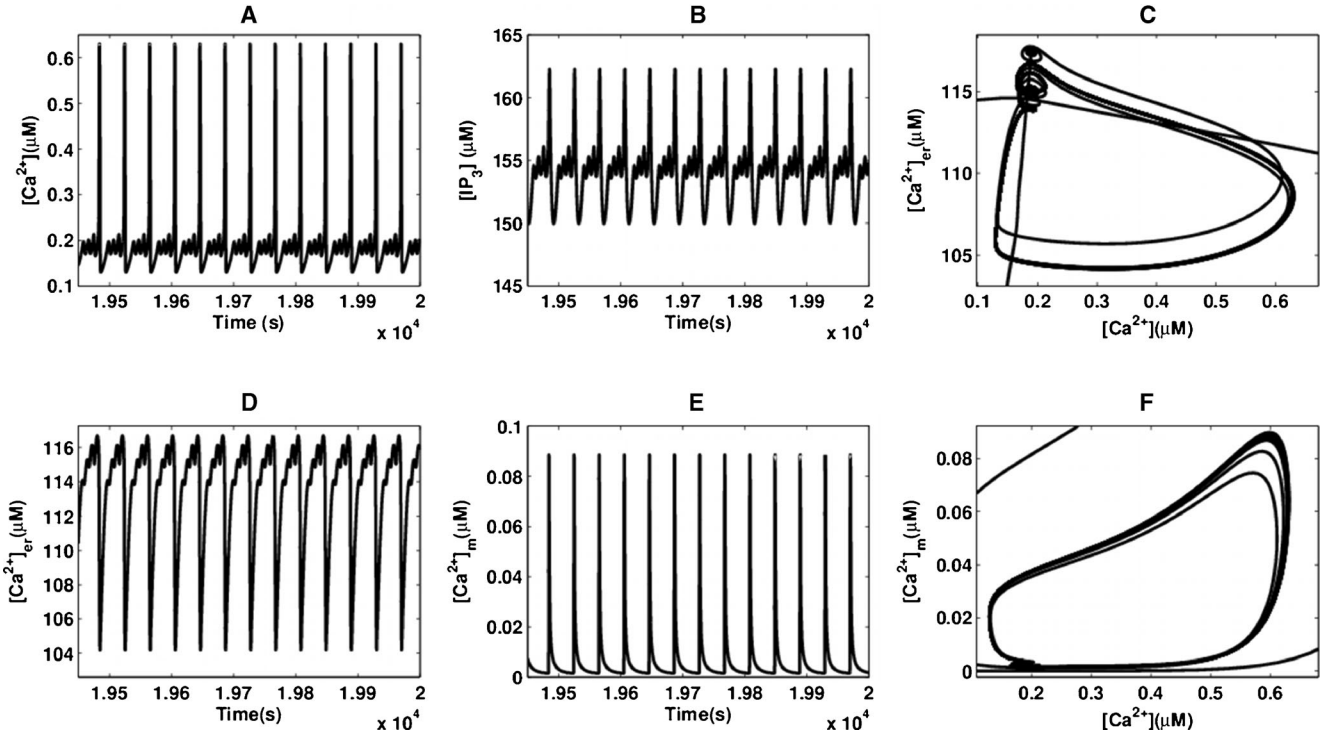

Fig. 5 Dynamic integration of model, and typical oscillation, when model is stimulated with VPLC=85nMs−1. Panel A and Panel B shows the time series of cytosolic calcium and cytosolic IP3 respectively. Both are in same phase. Panel E shows the time series of [Ca2+]m, which is periodic. Panel D represents ER oscillations. The phase - plane relationship,and projection of trajectories between [Ca2+] vs.[Ca2+]er is shown in Panel C, Panel F displays phase- plane portrait of [Ca2+] vs. [Ca2+]m

to its maximum level. In this phase the leading processes are: the increase of cytosolic IP_3, the release of Ca^{2+} ions from ER, the rapid increase of cytosolic calcium and uptake of calcium ions by mitochondria.

In Phase II due to degradation of IP_3 in the cytosol, its level decreases and it brings the calcium concentration down in the cytosol. In this phase, the slow flux of calcium from mitochondria to cytosol takes place. It agrees with some experimental observations that calcium release from mitochondria is much slower than its uptake (Park et al. 2001; Gunter et al. 2004; Ishii et al. 2006). Another process during this phase is the fast exchange of calcium between cytosol and ER. It results in small, fast calcium oscillations in these compartments.

In phase III, due to the production of IP_3, the concentration of IP_3 in the cytosol increases, while the calcium level in cytosol increases to reach its maximum value. The mitochondria and ER is again loaded with calcium, and it ends with phase III. In Fig. 7, a rapid $[Ca^{2+}]$ increase corresponding to ER calcium decrease has been seen reaching a peak after a few seconds. The peak of $[Ca^{2+}]$ precedes the peak of $[Ca^{2+}]$m and the minimum of $[Ca^{2+}]$er concentration. The shape and behavior of $[Ca^{2+}]$, $[Ca^{2+}]$er, and $[Ca^{2+}]$m in our model are similar to experimental observations (Filippin et al. 2003; Ishii et al. 2006).

In pancreatic acinar cells it was found experimentally (Straub et al. 2000; Ashby et al. 2002; Ashby and Tepikin 2002; Giovannucci et al. 2002; Ashby et al. 2003; Williams and Yule 2012) that calcium oscillations occur in the cell due to the activation of RyR receptors. To check whether the RyR receptors are responsible for CICR, we blocked RyR receptors in the cell. We found that oscillations are totally abolished in the absence of RyR, hence the calcium oscillations depends upon the functional RyR receptors in the cell. In the absence of IPR, an increase in agonist concentration or increase in calcium influx causes Ca^{2+} oscillations. These oscillations also depend on the calcium release through RyR, and are driven by the increase in calcium influx. Here, it is an important question to answer why oscillations arise as agonist value is increased even when there are no IPR in the cell i.e. $k_{IPR}=0$. In our model the calcium influx from outside the cell is modeled by a linear function that contains two fluxes: one constant calcium influx α_1, and another agonist dependent flux $\alpha_2 v_{PLC}$. This extracellular flux influences two processes in the cell: firstly, when constant Ca^{2+} influx α_1, enters into the cell, Ca^{2+} binds to the RyR receptor, and opens them. It boosts the calcium concentration in the cell and opens more RyR. Then the loss of calcium in the cytosol is seen because some of the calcium is sequestered by mitochondria or pumped out of the cell. When, $k_{IPR}=0$, the balance between ER emptying through RyR, its refilling through SERCA pump and the slow release of calcium from mitochondria mediate the appearance of calcium oscillations in the cell. Secondly, due to the entrance of agonist dependent flux $\alpha_2 v_{PLC}$ in the cell increases the concentration of PLC. Moreover, intracellular calcium enhances its production. The calcium release through RyR modulates IP_3 production and degradation, thus IP_3 oscillations are also seen

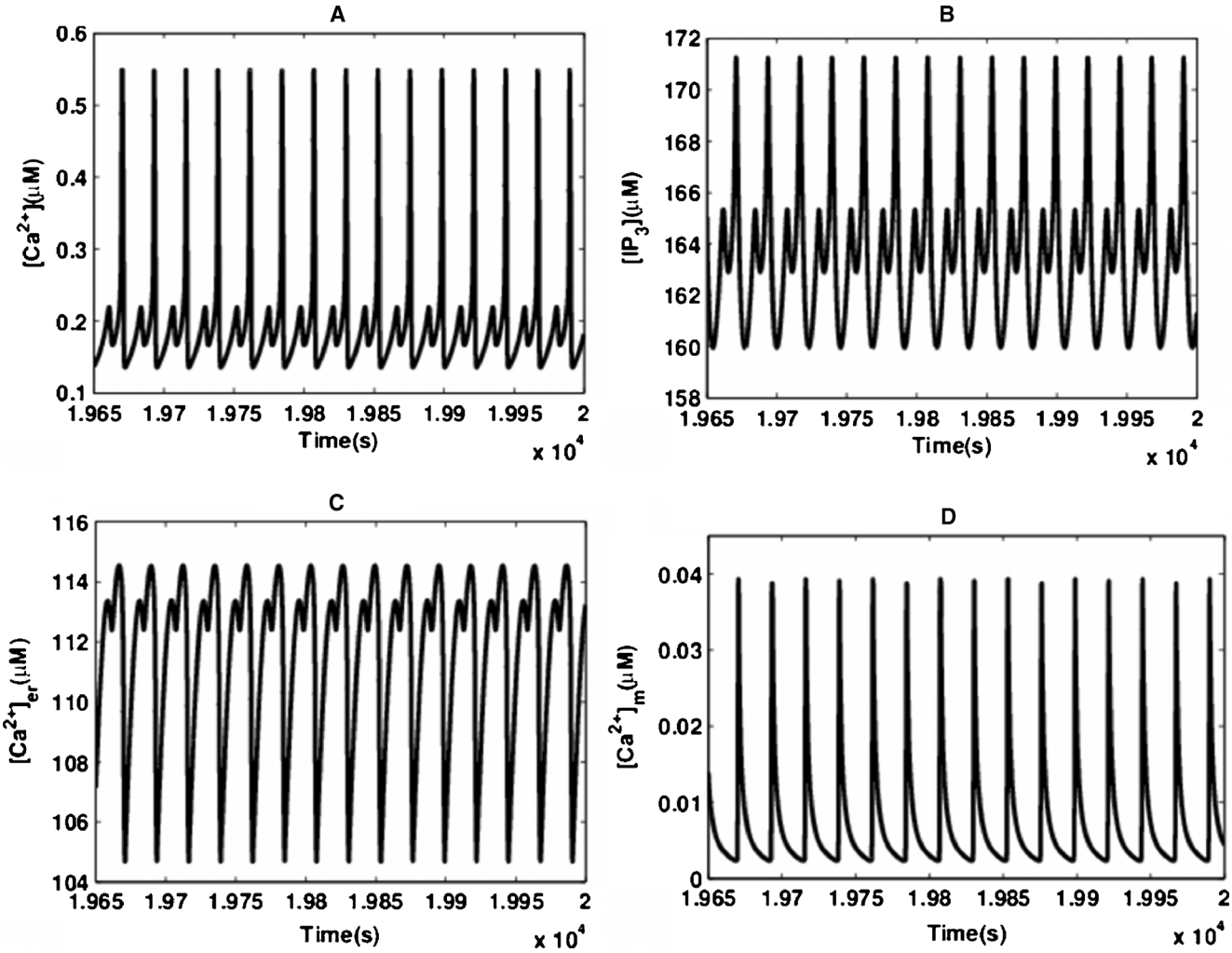

Fig. 6 Complex Oscillations, obtained by numerical integration of model for VPLC=90nMs−1. Panel A displays the periodic time series containing two different peaks. In panel B, [IP3] also oscillates with two different peaks but in phase with [Ca2+] as compared with panel A. Panel C shows the Ca2+ profile in ER. Panel D describes Ca2+ oscillations in the mitochondria

in the cell. Such types of oscillations are seen in previous modeling work of Ventura and Sneyd (2006). To see whether calcium influx influences the intracellular calcium we set J_{IN}=0,. The temporal model does not show any oscillations while J_{IN}= 0,. As J_{IN} is set to zero, calcium is extracted from the cell through the leak J_{PM}, it decreases the calcium concentration in the cell and stops oscillations entirely. When J_{IN} is restored to its nonzero value calcium oscillations are seen again. This is consistent with some experimental results (Yule et al. 1991; Tepikin and Petersen 1992) that intracellular calcium does not show any oscillation in absence of extracellular calcium in pancreatic acinar cells. Moreover, in pancreatic acinar cells the mitochondrial Ca^{2+} import plays a great role in regulating the spread of calcium signals. It restricts the cytosolic calcium and modulates the amplitude and frequency of oscillations by varying the shape of oscillations (for review see Petersen 2005). It is clear in Fig. 8, when there is no mitochondria in the cell (Panel A) the amplitude and frequency of oscillation is high as compared with the diagram with mitochondria in panel B, and significant change is seen in the pattern of Ca^{2+} oscillations when mitochondria are present. One can see when mitochondria are included (panel B); the amplitude of oscillations remains almost same. This effect can also be seen in panels E and D of Figs. 5 and 6 respectively. In contrast, in the case without mitochondria, panel A of Fig. 8, the amplitude undergoes enormous changes, and [Ca^{2+}] oscillates with multiple amplitudes. This indicates that Ca^{2+} sequestration by mitochondria maintain the constant amplitudes of cytosolic Ca^{2+} oscillations. Our findings are consistent with the theoretical work of Marhl et al. 1997a, b. Thus, the mitochondria affect the propagation of calcium signals in the cell. It also indicates that on physiological agonist concentrations the Ca^{2+} signals are restricted in the cell. These signals can form complex patterns of [Ca^{2+}] oscillations and shows transients to baseline spikes. The restriction of Ca^{2+} signals by mitochondria in pancreatic acinar cells provide Ca^{2+} transients for Ca^{2+} dependent exocytosis and Ca^{2+} dependent fluid secretion.

The IPR and RyR receptors are the two main functional units for the regulated release of Ca^{2+} from ER. It is well

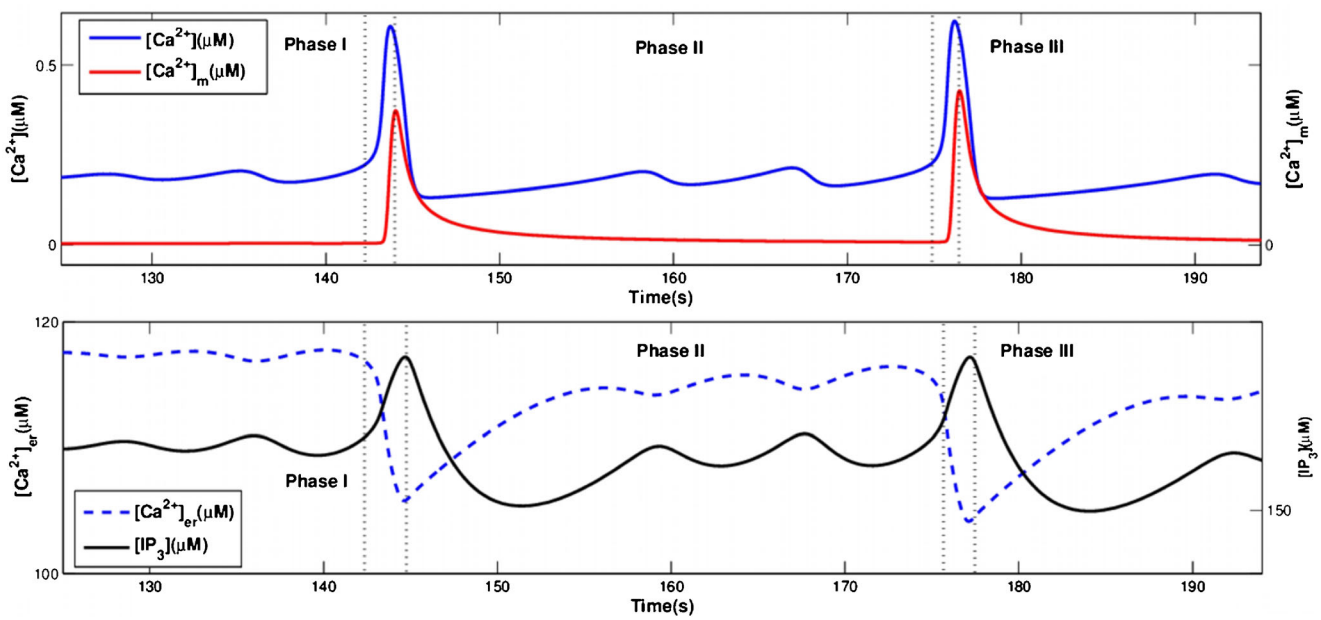

Fig. 7 One period of complex calcium oscillation: [Ca2+] thick blue line, [Ca2+]m thick red line,[Ca2+]er dashed blue line,[IP3] black thick line, when stimulated with VPLC=87nMs−1

known that IP_3 (Jouaville et al. 1995; Nassar and Simpson 2000; Spat et al. 2008; Iino 2010) induced calcium release from IPR receptors through CICR is very important mechanism for elevating the Ca^{2+} in mitochondria. Some studies (Nassar and Simpson 2000; Spat et al. 2008) also reveal that there is functional coupling between RyR receptors and mitochondria. Thus we want to see whether a similar relationship exists between the release of calcium from RyR receptors (through CICR) and the elevation of mitochondria calcium.

To recreate this experiment we varied the densities of both the receptors (IPR & RyR) and observed the changes in the frequencies and amplitudes of oscillations. Then we see the corresponding $[Ca^{2+}]$m frequency and amplitude. In this model the approximate values of IPR density (k_{IPR}=0.71) and RyR density (k_{RyR}=0.08) are in good agreement with the observed oscillatory response in pancreatic acinar cells. Thus, we investigate the model behavior by treating these values as initial values. For values of k_{RyR} between [0, 0.07], the model does not show any oscillation. Between these values of densities, the RyR receptors are unable to mediate CICR, so the model does not show oscillations. To see whether CICR from IPR is important mechanism to elevate the $[Ca^{2+}]$m, firstly we fix the RyR density (k_{RyR}) to 0.08 and vary the IPR density (k_{IPR}) between [0.71,270],and simulate the model with the different agonists' fluxes i.e. $[75,80,85,90,95]nMs^{-1}$. It was found that calcium oscillates in cytosol with higher frequency and small amplitudes. It is consistent with the prediction that an increase in IPR density results in fast oscillations and decrease in time to

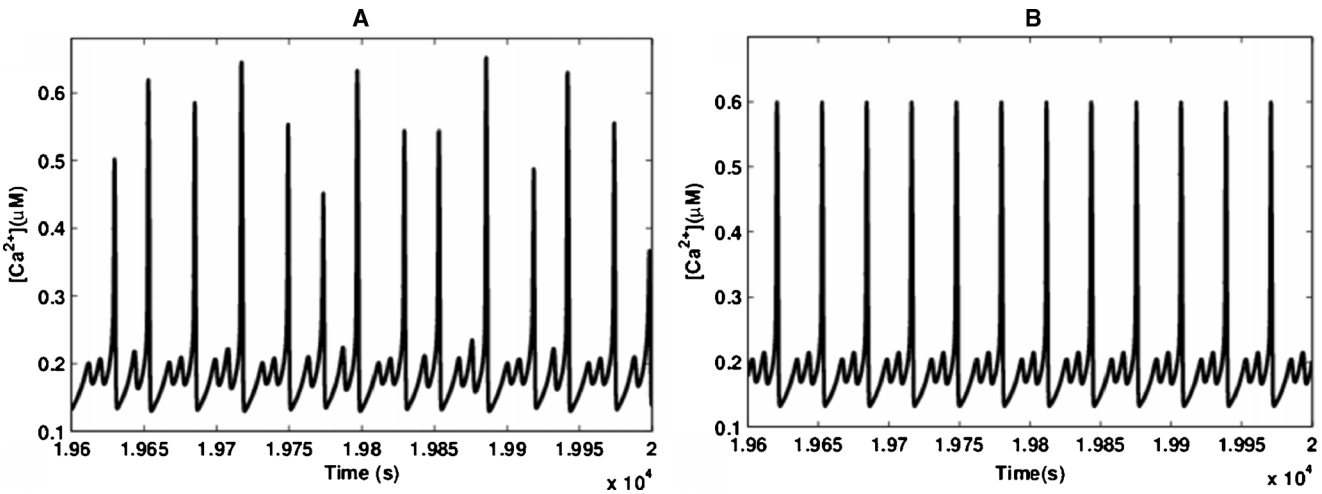

Fig. 8 At VPLC=87nMs−1, Panel A shows Calcium response without mitochondria (no uptake and no release). Panel B shows calcium response with mitochondria

peak. The oscillations are not seen for higher values of k_{IPR} i.e. ≥270. However, it is unlikely that high value of k_{IPR} are realistic, so most of the analysis is focused on the lower values of k_{IPR} i.e. [0.71,100]. Our results demonstrate that large increase in $[Ca^{2+}]$m are parallel to the Ca^{2+} signals evoked in the cytoplasm by IPR receptors through CICR and the strength of extracellular agonists applied. Secondly, to see whether CICR mechanism from the RyR receptors is important phenomenon to elevate the calcium concentration in the mitochondria, we fix the value of k_{IPR} and vary the value of k_{RyR}. In Fig. 9, we see the time series of cytosolic calcium and mitochondrial calcium concentration: when the model is stimulated with $85nMs^{-1}$ agonist flux, the k_{IPR} is fixed to 0.71, and k_{RyR} is varied to different values. Figure 9 panel A shows the time series of $[Ca^{2+}]$ when k_{RyR} is slightly increased from 0.08 to 0.09.As predicted the amplitude and frequency of oscillation in cytosol increases and sustained oscillation are seen as compared with the oscillation in Fig. 5 Panel A. The CICR from RyR enhances the calcium concentration in the cytosol, which in turn amplitude. Simultaneously, the calcium in the mitochondria increases and it oscillates with high amplitude as shown in Fig. 9 Panel B. If the k_{RyR} is further increased to 0.12, the amplitude of oscillations increases from $\approx 0.9\mu M$ to $\approx 1.4\mu M$. The corresponding enhancement in the mitochondrial calcium is seen, and the amplitude of $[Ca^{2+}]$m is increased from $\approx 0.6\mu M$ to $\approx 1.5\mu M$. On comparing panel A and panel C of Fig. 9, it was found that there is significant change in the amplitude of $[Ca^{2+}]$ as k_{RyR} is increased from 0.12 to 3,and $[Ca^{2+}]$ reaches maximum up to $\approx 5.7\mu M$. The mitochondrial uniporter up takes calcium and the calcium in the mitochondria rises up to $\approx 2.7\mu M$.We vary the density of RyR between [0.08–100] and fix IPR density to 0.71, and observe the behavior of calcium oscillation in cytosol and mitochondria. We observe that on increasing the value of k_{RyR} the amplitude of calcium oscillations increases, and it doesn't put so much impact on the frequency of oscillations as shown in Fig. 9 for two values of RyR (0.09 and 3). It also explains the fact that most of the calcium released through the RyR is rapidly sequestered by mitochondria leading to transient rise of $[Ca^{2+}]$m. This shows RyR activations (through CICR) produce local micro domain and Ca^{2+} increase in the opposing mitochondria. Our finding indicates that, in conjunction with the IPR, the RyR must also be in a close apposition and functionally coupled to mitochondria. In the present study the mechanism of regenerative

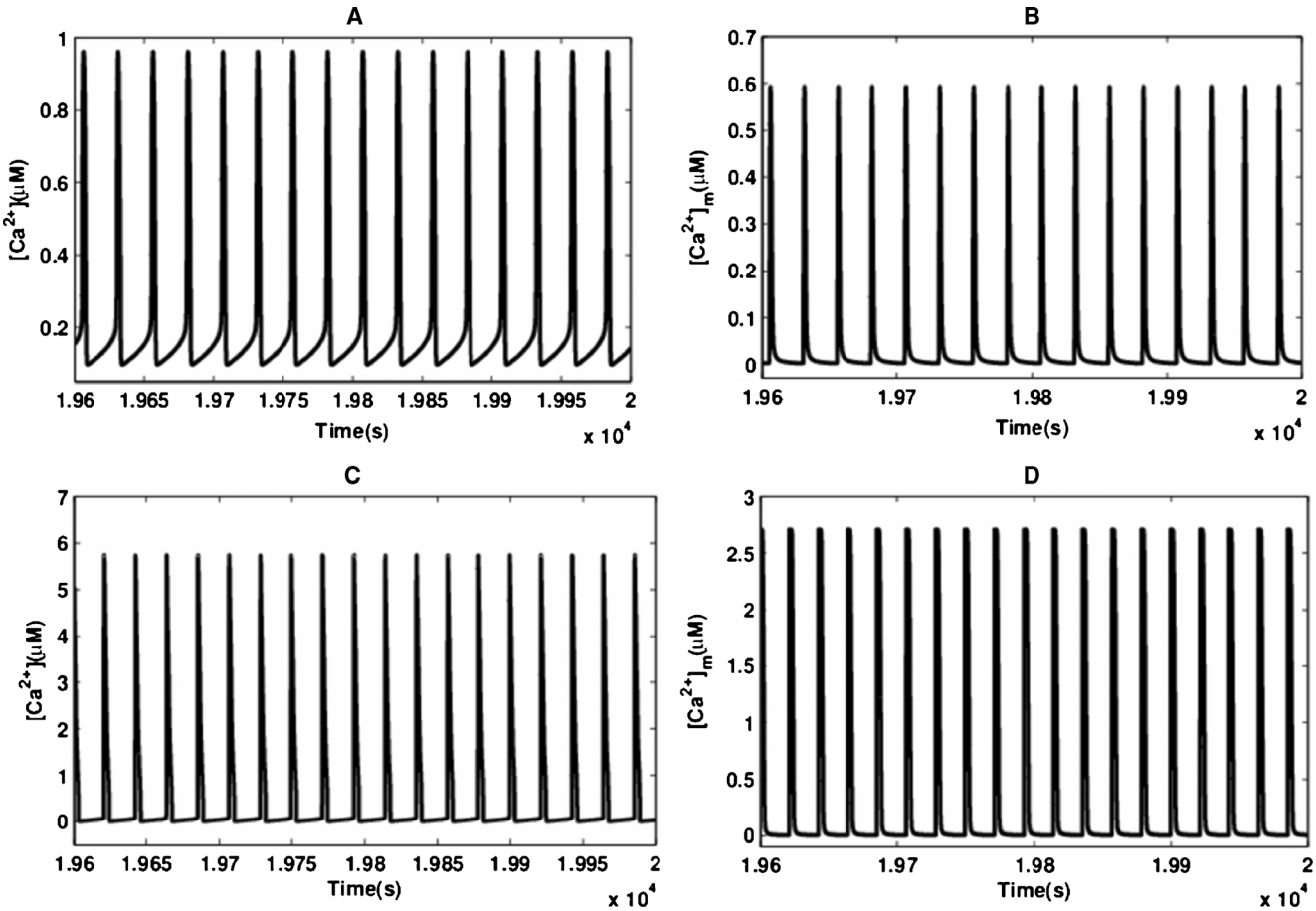

Fig. 9 Periodic sustained calcium oscillations when CICR from RyR are increased. Panel A shows calcium oscillations when k_{RyR}=0.09. The corresponding time series for [Ca2+]m is shown in panel B. The amplitude of oscillation is increased when k_{RyR}=3 (Panel C), and corresponding time series for [Ca2+]m is shown in panel D. All simulations are performed when VPLC=85nMs−1

calcium oscillations is well presented. Our results which give us better understanding of what derives the calcium oscillations in the pancreatic acinar cell, and how these oscillations are affected by the interplay among the different fluxes involved in this model. Our outcomes also suggest that the complex calcium oscillations (Figs. 5–8) are shifting between slow and fast motion and small and large amplitudes. Such types of oscillations are called mixed-mode oscillations (MMOs). These mixed-mode oscillations in which oscillatory behavior consists of number of large excursion combined with number of small peaks are frequently seen in various experiments and theoretical studies (Strizhak et al. 1995; Simpson et al. 2005; Harvey et al. 2010; Harvey et al. 2011), and our observations are consistent with that. Our results characterized although the simple Ca^{2+} oscillations are seen (Fig. 4), but the complex calcium oscillation in the form of MMOs should also be seen in the pancreatic acinar cells as shown in Figs. (5–8). On analyzing the model, the two types of regulation by Ca^{2+} have been observed. On one hand due to the activity of Ca^{2+} stimulation of PLC, increases the IP_3 production which upsurges the rate of Ca^{2+} release into the cytosol. On the other hand, due to 3-kinase stimulation by Ca^{2+}, it brings down the IP_3 concentration in the cytosol which as a result reduces the rate of Ca^{2+} release in to the cell. Simultaneously mitochondria uptakes and release calcium. These counteracting effects of Ca^{2+} and the mechanism involved in mitochondrial uptake and release are the source of MMOs in the present model. Indeed, CICR from both the receptors (IPR and RyR) can be ensured in the presence of constant IP_3 values and provide a mechanism for calcium oscillations in the pancreatic acinar cells (Sneyd et al. 2003; Simpson et al. 2005; Keener and Sneyd 2008). But in the present study the variable IP_3 that generate oscillations is itself modulated, as IP_3 raises the level $[Ca^{2+}]$, which in turn decreases that of IP_3 through the action of Ca^{2}+ dependent 3-kinase. Also the cytosolic calcium concentration is influenced by the IPR and RyR, and oscillation control switches between these two receptors. To derive the prescribed dynamic behavior we choose the parameter values in such a way that it gives such types of calcium oscillations. If we change the parameter values slightly there is a large shift in the qualitative behavior. However, our results match with the earlier findings (Keener and Sneyd 2008) that in response to different agonist concentrations (Yule and Gallacher 1988; Petersen et al. 1990; Mignen et al. 2005; Petersen and Tepikin 2008), the pancreatic acinar cells exhibit markedly different Ca^{2+} response. On the application of acetylcholine (ACh) the pancreatic acinar cells give rise to sinusoidal, raised baseline, high frequency while the cholecystokinin (CCK) gives low frequency baseline spiking (Petersen et al. 1990; Yule et al. 1991; Tepikin and Petersen 1992; Yule et al. 1996; LeBeau et al. 1999; Petersen and Tepikin 2008). Thus the temporal oscillations in this model match with experimental observations.

Discussion

In this paper a possible mechanism which explains the simple and complex calcium oscillations in pancreatic acinar cells is presented. We take into the account the IPR and RyR receptors which communicate through the process of CICR, the calcium transport into ER through SERCA pump, the uniporter calcium uptake by mitochondria, the slow release of calcium from mitochondria, and the inward/outward fluxes. With this model, we get varieties of pattern in calcium oscillations. On stimulation with different agonists fluxes, the period, amplitude, and frequency of cytosolic calcium changes, and are in the physiological range. The cytosolic Ca^{2+} oscillates with IP_3 oscillations. The oscillation in $[IP_3]$ signifies that the cytosolic calcium has significant effect on IP_3 production and degradation. The oscillations in $[Ca^{2+}]$ and $[IP_3]$ are exactly in same phase. Ca^{2+} release through the receptors (IPR & RyR) which are embedded in the ER membrane generate Ca^{2+} oscillation and load mitochondria with calcium. Before the another Ca^{2+} oscillation occurs, the Ca^{2+} release from mitochondria through $Na+/Ca^{2+}$ or $H+/Ca^{2+}$ exchanger causes a slow increase in the cytosolic Ca^{2+} concentration. It includes the regenerative ER calcium release, which generates the peak of Ca^{2+} oscillation and reloads the mitochondria. This series of events was continuous until the mitochondrial Ca^{2+} was depleted. Thus it was found that Ca^{2+} shuttles between ER and mitochondria in phase with calcium oscillations. Our results indicate that CICR can lead to a substantial elevation of $[Ca^{2+}]$m. Since mitochondria takes up calcium as a direct consequence of CICR, it is expected that in turn mitochondria influences the spread of ER calcium release as shown in Fig. 8. Thus, by local removal of Ca^{2+}, the mitochondria restricts the propagation of CICR, and this happens in pancreatic acinar cells (Tinel et al. 1999; Straub et al. 2000; Park et al. 2001; Petersen 2005). On stimulation with agonist, and due to the action of IP_3, Ca^{2+} is released through the IPR and the RyR receptors via CICR, causes the generation of similar Ca^{2+} micro domains adjacent to mitochondria. It appears that not only the IPR and RyR receptors independently act as a source of Ca^{2+} for the mitochondria, but the CICR process may be required to generate a sufficient local increase in $[Ca^{2+}]$ to enable efficient mitochondrial uptake of calcium. Although our results indicate that if the CICR from IPR receptors is increased the cytosolic calcium oscillates with high frequency but with smaller amplitude. The mitochondrial calcium increases parallel to the Ca^{2+} signals induced in the cytosol via CICR through IPR receptors. As predicted, if the CICR from the RyR is increased the amplitude of oscillation is increased and the frequency of calcium oscillations remains almost same. The mitochondria takes up calcium very fast and quickly filled with calcium, and thus the $[Ca^{2+}]$m oscillates with high frequency and amplitude. This implies that CICR from RyR receptors is very crucial mechanism for elevating the mitochondrial calcium.

The dynamical behavior of calcium in pancreatic acinar cells is complex, so the major outcomes of this model are as follows:

a) The calcium oscillations in the cytosol are accompanied by the oscillations in the concentration of inositol- 1, 4, 5 trisphosphate [IP_3]. These oscillations in the intracellular calcium are driven because of calcium modulation of IP_3 level either through its production or/degradation. Calcium also modulates the open probability of both the IPR and the RyR receptors and acts as a messenger to communicate between these two receptors.
b) In absence of IPR, the increase in the agonist flux causes calcium oscillations. These oscillations depend upon the CICR from RyR, the slow release of calcium from mitochondria, and due to the increased influx of calcium. Such oscillations driven by increase in calcium influx are known to occur in muscle (both cardiac and smooth), and bullfrog sympathetic neuron cells, but not in pancreatic acinar cells.
c) In absence of RyR, the oscillations are totally abolished. Thus our model suggests that the functional coupling between these two receptors (IPR & RyR) is important phenomenon to cause calcium oscillation. Therefore in pancreatic acinar cells the Ca^{2+} oscillations are fully depending upon RyR receptors.
d) In presence of IPR, there are two types of oscillations. Firstly, due to the release of calcium from IPR, and secondly, depends upon the calcium release from RyR. These two mechanisms communicate via calcium through CICR.
e) On agonist stimulation, Calcium release from ER generated the first calcium oscillation and filled mitochondria with calcium. Before the second oscillation takes place, Ca^{2+} release from mitochondria via exchangers cause a gradual increase in cytoplasmic Ca^{2+} concentration, including the regenerative ER calcium release. It generates the peak of Ca^{2+} oscillations and partially reloads the mitochondria. These sequences of events are repeated until the mitochondrial calcium is depleted. Thus our results indicate that Ca^{2+} shuttling between ER and mitochondria is a crucial component of the Ca^{2+} oscillations mechanism, and has a pacemaker role in Ca^{2+} oscillations.
f) If the CICR from RyR is increased, (by increasing the density of RyR), the cytosolic calcium concentration increases, mitochondria uptakes calcium very quickly and oscillates with high amplitudes. Thus we conclude that mitochondrial calcium uptake is very much sensitive to RyR.
g) If CICR from IPR is increased, the frequency of oscillation is increased and amplitude of oscillation decreases. Also if CICR form RyR is increased, it enhances the amplitude of oscillations but frequency of oscillations remains almost the same. Thus CICR from both the receptors is important for calcium oscillations in the cell.

Calcium oscillation can take wide varieties of shape like baseline spikes, sinusoidal, transition from sinusoidal to transient oscillations, low-high frequency oscillations. These types of oscillations are seen at particular value of agonist applied. In this model there is intermediate value of agonist which shows calcium oscillations i.e. $[70 \leq V_{PLC} \leq 130] nMs^{-1}$, thus not even too low or too high agonist values produce calcium oscillations in a cell, and our results are consistent with various previous theoretical studies (Keizer and De Young 1992; Young and Keizer 1992; Gin et al. 2007; Palk et al. 2010).

It is not possible to take all parameters from pancreatic acinar cells and construct such type of model. Therefore we take data from other sources to understand calcium oscillation in the pancreatic acinar cell. The pancreatic acinar cells contain all the three subtypes of IPR receptors (Type I, Type II, Type III) (Nathanson et al. 1994; Wojcikiewicz 1995; Thorn 1996; Lee et al. 1997; Yule et al. 1997; Williams and Yule 2012)which are distributed throughout the ER membrane. Although all the IPR subtypes show alike ion permeation properties, but differ significantly in there regularity properties due to the different interactions with proteins like regulation by ATP or phosphorylation (Wojcikiewicz and Luo 1997; LeBeau et al. 1999; Soulsby and Wojcikiewicz 2006). The exact nature of these difficulties remains controversial. But yet it is known that all the subtypes are differently regulated by IP_3 and Ca^{2+}. For instance type II has the greatest affinity for IP_3, as compared with type I and Type III receptors. They all have different open probabilities at steady state. The bell-shaped curve is concerned with the type II IPR, and its activity is modulated by cytosolic calcium, which leads to activating the channel, and then deactivating at high Ca^{2+} concentration. The Type III IPR shows similar behavior with Type II IPR. It is activated at low level of Ca^{2+} concentration and inhabited when calcium concentration is increased. In some studies, the central feature of oscillation is the kinetic properties of IPR. It is the sequential activation and deactivation of IPR, which plays an important role in controlling the oscillatory response. This time dependent data is fitted by Sneyd and Dufour (2002). The more review of different IPR models are found in (Sneyd and Falcke 2004; Sneyd et al. 2004). During realistic Ca^{2+} oscillations, the IPR is really at steady state. Thus to understand the behavior and function of IPR, it is important to construct a model which have both the correct steady state proprieties as well as the correct time dependence. However, yet it is not possible to construct a model of IPR that systematically represent both these properties. Thus we use a most recent model developed by Gin et al. (2009) for type I IPR, taking the steady-state single channel data, and this model is slightly modified by Palk et al. (2010). We use this model by assuming that IPR subtypes do not differ greatly in their dynamic response. For example type II IPR (Finch et al. 1991; Dufour et al. 1997) seems to have similar dynamic behavior to type I IPR receptors.

The rat pancreatic acinar cells express multiple isoforms of RyR (Ashby et al. 2002; Ashby and Tepikin 2002; Ashby et al. 2003) but predominance with type II RyR (Leite et al. 1999). The dynamic model of RyR has not been yet developed for pancreatic acinar cell. Therefore due to the unavailability of better model, we use the existing model of (Keizer and Levine 1996) which is originally developed for cardiac cell, and shows the dynamic behavior of type II RyR.

In our model, we include Ca^{2+} influx across the plasma membrane. This mechanism is owing because of arachidonic acid pathways (Mignen et al. 2005)or via the capacitive entry (Berridge 1995). Instead of taking these assumptions, we consider the Ca^{2+} influx from extracellular medium to intracellular medium is the increasing function of the maximal production rate of PLC. Thus we assume the agonist is linearly related to $[IP_3]$ and therefore the rate of production of PLC. The extrusion of Ca^{2+} from the cell is maintained by the plasma membrane pumps (PMCA). These functional units are modeled by Hill function of coefficient 2. Calcium is pumped back from cytosol into ER by SERCA pump. In some theoretical models (Atanasova et al. 2005; Keener and Sneyd 2008; Palk et al. 2010) the rate of SERCA pump solely depends upon cytosolic calcium concentration, and the pump activity is approximated by a Hill equation of coefficient two. In our model we use a common model of Sneyd et al. (2003) which is modulated by $[Ca^{2+}]$er. Although these fluxes are not static, similar expression have been used in earlier modeling work (Keener and Sneyd 2008).

In pancreatic acinar cells (Tinel et al. 1999; Straub et al. 2000; Albrecht et al. 2002., Petersen 2005; Kopach et al. 2011) the mitochondria play a great role in restricting the calcium waves in the granule region. Agonist evoked local calcium spiking, (Petersen 2005) and during each local calcium spike, the mitochondria uptakes calcium and restricts the calcium signal in the apical region. Recently (Csordas et al. 2001; Hajnoczky et al. 2002; Spat et al. 2008; Pan et al. 2011) the experimental studies demonstrate that the voltage-dependent anion channels (VDAC) of the outer mitochondrial membrane (OMM) and the uniporter on the internal mitochondrial membrane (IMM) allows Ca^{2+} to reach within the mitochondrial matrix along the electro-chemical gradient. However, further studies reveal that several other pathways exist for mitochondrial Ca^{2+} influx. For instance they are rapid mode of mitochondrial Ca^{2+} transport (RaM) (Gunter and Gunter 2001; Gunter et al. 2004; Friel and Chiel 2008; Bazil and Dash 2011), mitochondrial ryanodine receptors (mRyR) (Altschafl et al. 2007; Spat et al. 2008; Ryu et al. 2010; Pan et al. 2011),uncoupling proteins 2 and 3 (Trenker et al. 2007), and Letm1 mitochondrial Ca^{2+}/H+ antiporter (Spat et al. 2008; Jaing et al. 2009). We don't include these complexities in our model because these pathways are still not well understood and we do not have sufficient experimental and theoretical knowledge about their operation. However detailed consideration of these difficulties will have to wait for future work. In our model we just take an assumption that mitochondria uptakes calcium very fast through specific uniporter by RaM mechanism. Therefore, for the mitochondrial Ca^{2+} uptake is modeled by a Hill function with coefficient 8, which shows a step like kinetics (Marhl et al. 2000, Grubelnik et al. 2001; Dyzma et al. 2013). The balance between Ca^{2+} influx and efflux across the mitochondrial inner membrane establishes mitochondrial Ca^{2+} homeostasis. The slow release of calcium is take place through Na+/Ca^{2+} and H+/Ca^{2+} exchangers. For the sake of generality, in addition to these exchangers we also consider the mitochondrial permeability membrane pores (PTPs). The PTPs also contributed to Ca^{2+} efflux with exchangers. These flows are influenced by the transmembrane potential ($\Delta\psi_m$) (Nicholls 1978; Marhl et al. 1997b; Friel and Chiel 2008), but the change in $\Delta\psi_m$ is neglected in this model formulation. We also neglect the dependence on the concentration of Na+ ions. The more accurate model for IP_3 production and degradation would include the PLC isoforms (PLCβ & PLCδ), dephosphorylation and phosphorylation. We have taken only one isoform of PLC (PLCβ), and have specifically assumed that Ca^{2+} and agonist act on the same isoform of PLC (e.g. PLCβ). The removal of IP_3 in the cytosol is metabolized through two processes: Firstly, through 5- phosphate (IP_3P, dephosphorylation) whose activity is independent of Ca^{2+}. Secondly, the activity of 3-kinase (IP_3K, phosphorylation) that degrades IP_3 to IP_4 is an increasing function Ca^{2+}. It is well known that during Ca^{2+} oscillations, maximum IP_3 removal takes place predominantly via IP_3K rather than by IP_3P. About 70 % of the removal flux of IP_3 at high Ca^{2+} is carried by IP_3K. So, in our model we assume that IP_3 removal through IP_3P is least important as it is more sensitive to IP_3K.

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Appendix A

$$\frac{d[Ca^{2+}]}{dt} = \left(J_{IPR} + J_{RyR} + J_{ER}\right) - J_{SERCA} + \delta(J_{IN} - J_{PM}) + J_{m,out} - J_{m,in}, \quad \text{(A1)}$$

$$\frac{d[Ca^{2+}]_{er}}{dt} = \gamma\left(-\left(J_{IPR} + J_{RyR} + J_{ER}\right) + J_{SERCA}\right), \quad \text{(A2)}$$

$$\frac{d[IP_3]}{dt} = J_{IP_3prod} - J_{IP_3\deg}, \tag{A3}$$

$$\frac{d[Ca^{2+}]_m}{dt} = \tau\left(J_{m,in} - J_{m,out}\right), \tag{A4}$$

$$\frac{dw}{dt} = \frac{k_c^-(w^\infty[Ca^{2+}]-w)}{w^\infty[Ca^{2+}]}, \tag{A5}$$

$$P_{IPR} = \frac{q_{12}q_{32}q_{24}}{q_{12}q_{32}q_{24} + q_{42}q_{23}q_{12} + q_{42}q_{32}q_{12} + q_{42}q_{32}q_{21}}, (IPR\,open\,probability) \tag{A6}$$

$$P_{RyR} = \frac{w\left(1 + \left([Ca^{2+}]/K_b\right)^3\right)}{\left(1 + ([Ca^{2+}])^4 + \left([Ca^{2+}]/K_b\right)^3\right)}, (RyR\,open\,probability) \tag{A7}$$

$$J_{IPR} = k_{IPR}P_{IPR}\left(\left[Ca^{2+}\right]_{er} - \left[Ca^{2+}\right]\right), \tag{A8}$$

$$J_{RyR} = k_{RyR}P_{RyR}\left(\left[ca^{2+}\right]_{er} - \left[ca^{2+}\right]\right), \tag{A9}$$

$$q_{21} = \phi_{21}([IP_3])ms^{-1}, \tag{A10}$$

$$q_{23} = \alpha_{23}\psi_{23}\left(\left[Ca^{2+}\right]\right)\phi_{23}([IP_3])ms^{-1}, \tag{A11}$$

$$q_{32} = \alpha_{32}\psi_{32}\left(\left[Ca^{2+}\right]\right)\phi_{32}([IP_3])ms^{-1}, \tag{A12}$$

$$\phi_{21}([IP_3]) = \frac{VP_{21}}{1 + kp_{21}[IP_3]^3} + bp_{21}, \tag{A13}$$

$$\psi_{23}\left(\left[Ca^{2+}\right]\right) = a_{23} - \left(\frac{V_{23}}{k_{23}^2 + [Ca^{2+}]^2} + b_{23}\right)\left(\frac{Vm_{23}[Ca^{2+}]^5}{km_{23}^5 + [Ca^{2+}]^5} + bm_{23}\right), \tag{A14}$$

$$\phi_{23}([IP_3]) = \frac{VP_{23}}{1 + kp_{23}[IP_3]^3} + bp_{21}, \tag{A15}$$

$$\psi_{32}\left(\left[Ca^{2+}\right]\right) = \left(\frac{V_{32}}{k_{32}^3 + [Ca^{2+}]^3} + b_{32}\right)\left(\frac{Vm_{32}[Ca^{2+}]^7}{km_{32}^7 + [Ca^{2+}]^7} + bm_{32}\right), \tag{A16}$$

$$\phi_{32}([IP_3]) = \frac{VP_{32}[IP_3]^3}{1 + kp_{32}[IP_3]^3} + bp_{32}, \tag{A17}$$

$$w^\infty\left[Ca^{2+}\right] = \frac{\left(1 + \left(K_a/[Ca^{2+}]\right)^4 + \left([Ca^{2+}]/K_b\right)^3\right)}{\left(1 + \left(1/K_c\right) + \left(K_a/[Ca^{2+}]\right)^4 + \left([Ca^{2+}]/K_b\right)^3\right)}, \tag{A18}$$

$$J_{SERCA} = V_{SERCA}\frac{[Ca^{2+}]}{K_{SERCA} + [Ca^{2+}]} \times \frac{1}{[Ca^{2+}]_{er}}, \tag{A19}$$

$$J_{PM} = V_{PM}\frac{[Ca^{2+}]^2}{K_{PM}^2 + [Ca^{2+}]^2}, \tag{A20}$$

$$J_{IN} = \alpha_1 + \alpha_2 v_{PLC}, \tag{A21}$$

$$J_{m,in} = k_{in}\frac{[Ca^{2+}]^8}{K_2^8 + [Ca^{2+}]^8}, \tag{A22}$$

$$J_{m,out} = \left(K_{out}\frac{[Ca^{2+}]^2}{K_1^2 + [Ca^{2+}]^2} + K_m\right)\left[Ca_m^{2+}\right]^2, \tag{A23}$$

$$J_{IP_3prod} = V_{PLC}\frac{[Ca^{2+}]^2}{K_{PLC}^2 + [Ca^{2+}]^2}, \tag{A24}$$

$$J_{IP_3\deg} = k_{\deg}\frac{[Ca^{2+}]^2}{K_{\deg}^2 + [Ca^{2+}]^2}[IP_3], \tag{A25}$$

All parameters values are shown in Tables 1 and 2.

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