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Simulations to Evaluate the Impact of Ca^{2+} release from Endoplasmic Reticulum on Intracellular Ca^{2+} Oscillations

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***Abstract*—The role of Ca^{2+} release from endoplasmic reticulum (ER) in influencing intracellular Ca^{2+} oscillation is elucidated. Various types of oscillations in a two-pool model are discussed, based on fast-slow dynamic analysis. Three types of burster are obtained by varying the parameter affecting Ca^{2+} release from ER, namely, subHopf-subHopf of point-cycle type, subHopf-cycle of point-cycle type with multiple rhythms and fold-fold of point-point type. The results may help us better understand the role of Ca^{2+} release played in complex intra- and inter-cellular Ca^{2+} signaling.**

Keywords-bifurcation; calcium oscillation; fast-slow dynamic analysis

I. INTRODUCTION

Ca^{2+} is the most widely used second messenger in both excitable and non-excitable cells [1]. In response to adequate agonist stimuli, Ca2+ concentration increases, oscillates and decreases, leading to regulate many cellular events, such as fertilization of oocytes, cell division and secretion [2].

Among these oscillations, burst is highly correlated with encoding of information processing [3]. Many literatures are presented to reveal the dynamics underlying burst Ca^{2+} oscillations and their transitions in experimental observations [4].

It is known that topological classification of burst mentioned above can be carried out by means of the fast-slow dynamic analysis [5-7]. For understanding the computational properties of bursting behaviors, the geometry of the phase plane, which is depicted in case of the fast-slow dynamic analysis, should be discussed.

Marhl et al. proposed a two-pool model of calcium-induced calcium release (CICR) with a focus on the role of calcium binding proteins and mitochondria. With associated calcium pumps and calcium leak fluxes, this model is presented to explain calcium oscillation that occurs without IP_3, which have similar characteristics as those observed in the experiments in cell biology [8-13].

Bifurcation analysis of a theoretical model, proposed by Borghans and co-authors, was conducted by Zhang [8]. Regular and chaotic bursting calcium oscillations were investigated in a wide range of parameter values. A mathematical model is considered to reveal the impact of the calcium pump. Regular and quasi-periodic calcium oscillations are obtained by varying the calcium pump parameter. Perc investigated the flexibility and sensitivity of the calcium oscillation comparatively for chaotic calcium oscillations, and the results showed that the complexity of calcium oscillations did not directly imply sensitivity or flexibility [10].

However, to the best of our knowledge, we believed that insufficient attention was being paid to the role of rate factor of calcium leak flux through ER membrane (k_{leak}). Such a factor can vary according to the various environmental conditions. It is known that calcium leak flux out of ER is described by plausible rate laws. Once the IP_3 receptor is open, the calcium ions leak out of ER into cytoplasm before inactivation by Ca^{2+} occurs. A special interest is how the factor influences the level on the calcium oscillation behavior.

II. MODEL DESCRIPTION

The model we considered here is mainly concerned with the functioning of two possible mechanisms (that is CICR and the mitochondrial CICR). In addition, cytosolic calcium binding proteins is also taken into account [9].

This model can be described by the following equations:

$$dCa_{cyt} / dt = J_{ch} - J_{pump} + J_{leak} - J_{out} + J_{in} + J_{Ca\mathrm{Pr}} - J_{\mathrm{Pr}} \quad (1)$$

$$dCa_{er} / dt = \beta_{er} / \rho_{er} (J_{pump} - J_{ch} - J_{leak}) \quad (2)$$

$$dCa_{m} / dt = \beta_{m} / \rho_{m} (J_{in} - J_{out}) \quad (3)$$

where

$$J_{ch} = k_{ch} \frac{Ca_{cyt}^2}{Ca_{cyt}^2 + K_1^2} (Ca_{er} - Ca_{cyt}), J_{pump} = k_{pump} Ca_{cyt},$$

$$J_{leak} = k_{leak} (Ca_{er} - Ca_{cyt}),\ J_{Ca\mathrm{Pr}} = k\_Ca\,\mathrm{Pr},$$

$$J_{out} = (k_m \frac{Ca_{cyt}^2}{Ca_{cyt}^2 + K_1^2} + k_{mit}) Ca_m, J_{\mathrm{Pr}} = k_+ Ca_{cyt}\,\mathrm{Pr},$$

$$Ca_{tot} = Ca_{cyt} + \frac{\rho_{er}}{\beta_{er}} Ca_{er} + \frac{\rho_m}{\beta_m} Ca_m + Ca\,\mathrm{Pr},$$

$$\mathrm{Pr}_{tot} = \mathrm{Pr} + Ca\,\mathrm{Pr},\ J_{in} = k_{in} \frac{Ca_{cyt}^8}{Ca_{cyt}^8 + K_2^8}.$$

This model consists of three variables, i.e. free Ca^{2+} concentration in cytosol (Ca_{cyt}), in ER (Ca_{er}), and in mitochondria (Ca_m). Parameters used in simulation are: k_{leak} = 0.01 s^{-1}, k_{pump} = 20.0 s^{-1}, k_{in} = 300 μMs^{-1}, k_m = 125 s^{-1}, k_+ = 0.09 μMs^{-1}, k_- = 0.01s^{-1}, K_1 = 5.0 μM, K_2 = 0.8 μM, Ca_{tot} = 90 μM, Pr_{tot} = 120 μM, $\rho_{er} = \rho_m$ = 0.01, $\beta_{er} = \beta_m$ = 0.0025.

Seeing equations (1)-(3) as the full system with fast subsystem and slow subsystem, we consider the burst patterns, where Cam is used as the bifurcation parameter [5-6].

III. SIMULATION

Fig.1 shows the corresponding time evolutions of Ca_{cyt} at different values of k_{leak}, that is, subHopf-subHopf burster for k_{leak} = 0.077 (Fig. 1(a)), the subHopf-cycle burster with multiple rhythms for k_{leak} = 0.2131 (Fig. 1(b)) and fold-fold burster for k_{leak} = 0.33 (Fig. 1(c)), are illustrated in the model.

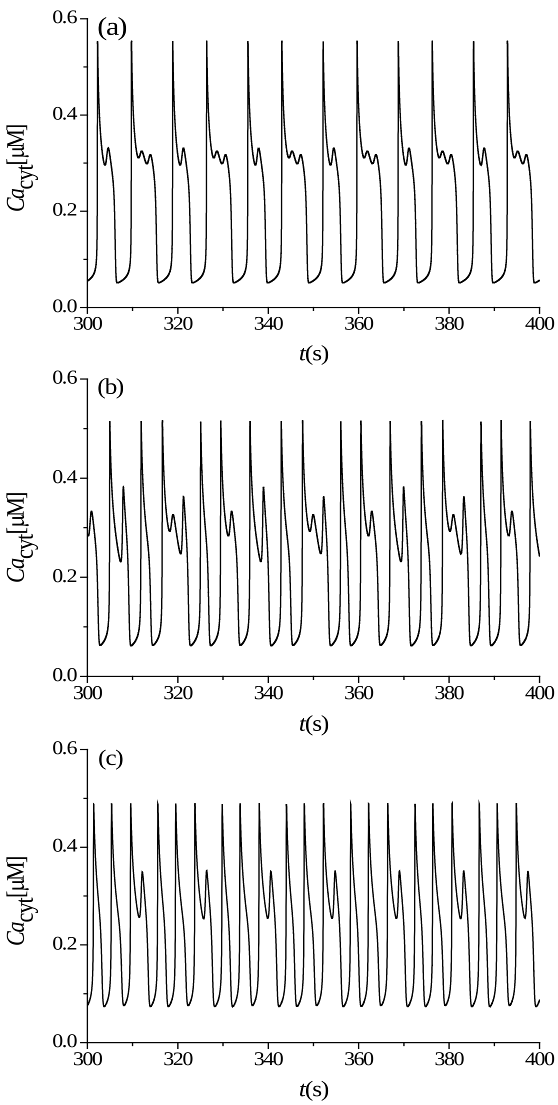

FIGURE I. TIME SERIES OF CALCIUM OSCILLATIONS: (A) SUBHOPF-SUBHOPF BURSER FOR KLEAK = 0.077. (B) SUBHOPF-CYCLE BURSTER FOR KLEAK = 0.2131. (C) FOLD-FOLD BURSTER FOR KLEAK = 0.33.

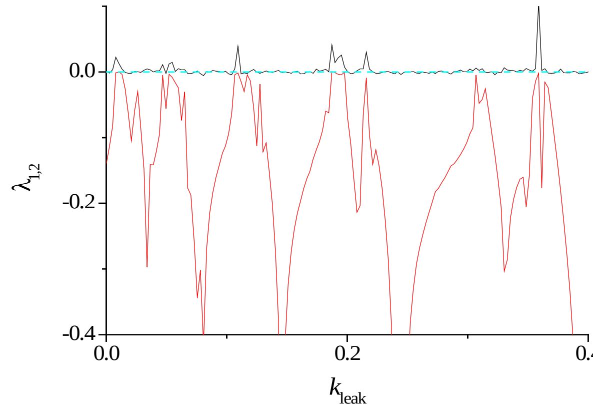

FIGURE II. THE FIRST (BLACK) AND THE SECOND (RED) LARGEST LYAPUNOV EXPONENTS Λ1, 2 OF THE WHOLE SYSTEM.

The diagram of the first and the second largest Lyapunov exponents is shown in Fig. 2. This system is considered chaos as the first largest Lyapunov exponent becomes positive.

Many theoretical studies of different bursting calcium oscillations have been published, treating Ca_{er} as the slow variable. In other theoretical studies, Ca_m is used as the slow variable. To investigate the bifurcation of various calcium oscillations we consider different time scales.

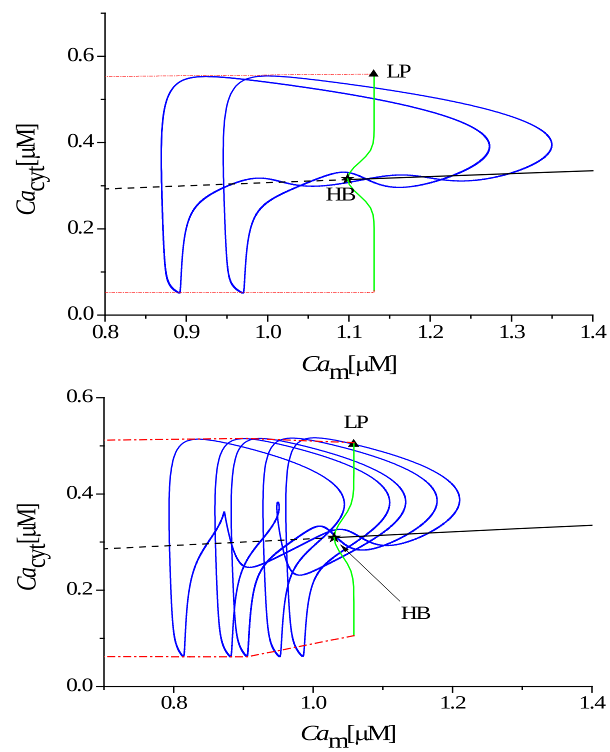

FIGURE III. BIFURCATION DIAGRAM OF FAST SUBSYSTEM. CAM IS TREATED AS THE BIFURCATION PARAMETER FOR THE SUBHOPF-SUBHOPF BURSTER OF POINT-CYCLE TYPE FOR KLEAK = 0.077 (A) AND THE SUBHOPF-CYCLE BURSTER WITH MULTIPLE RHYTHMS FOR KLEAK = 0.2131 (B). BLACK SOLID (BLACK DASHED) LINE IS THE STABLE (UNSTABLE) STEADY STATE. HB REFERS TO THE SUBCRITICAL HOPF BIFURCATION. LP (UP-TRIANGLE) IS THE FOLD BIFURCATION OF LIMIT CYCLE. THE THICK BLUE LINE IS 2D PROJECTION OF THE TRAJECTORY IN THE WHOLE SYSTEM.

Fig. 3(a) shows the fast-slow dynamical analysis for the subHopf-subHopf burster of point-cycle type for k_{leak} = 0.077. In this case, the variable Ca_m was chosen as the bifurcation parameter. It is seen that the fast subsystem has a subcritical Hopf bifurcation point (HB). Unstable periodic branches originating from HB become stable through the fold limit cycle bifurcation point (LP).

The characteristic of this type of burster is that the active and silent phase depends on the stable limit cycle of the fast subsystem. Transition from the up-state to the down-state is due to LP. As k_{leak} increases, the subHopf-cycle burster with multiple rhythms occurs (see Fig. 3(b)).

To understand this type of burster, one can follow the trajectory of the whole system. The trajectories pass through HB and extend to the stable attractor, which contributes to the starting of the active phase.

It takes more time before reaching limit cycle due to the slow passage effect [9]. The trajectories reach LP. In the proposed scheme, this burster is of the subHopf-cycle type with multiple rhythms. The main difference between them is the stable periodic attractor corresponding to repetitive spiking disappears through LP in Fig. 3(b).

Model dynamics is investigated based on another slow variable Ca_{er}. Fig. 4 shows the fast-slow dynamical analysis of the fold-fold burster for k_{leak} = 0.33. Unlike the previous cases, the fast subsystem has two fold bifurcations (F1 and F2). This characteristic is that the rest state disappears through F2 and the active state disappears through F1. It is seen that the fast subsystem does not have a limit cycle for any value of Ca_{er}. So, this system displays the point-point type instead of point-cycle type.

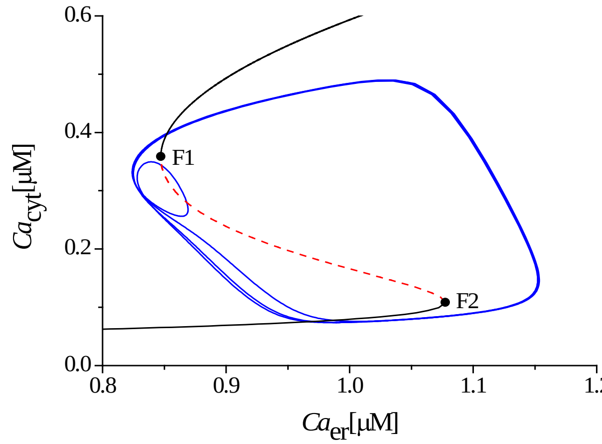

FIGURE IV. BIFURCATION DIAGRAM OF THE FAST SUBSYSTEM. THE SLOW VARIABLE CAER IS TREATED AS THE BIFURCATION PARAMETER FOR THE FOLD-FOLD BURSTER OF POINT-POINT TYPE FOR KLEAK = 0.33. BLACK SOLID (BLACK DASHED) LINE IS THE STABLE (UNSTABLE) STEADY STATE. F1 AND F2 REFER TO THE FOLD BIFURCATION. THE THICK BLUE LINE IS 2D PROJECTION OF THE TRAJECTORY IN THE WHOLE SYSTEM.

IV. CONCLUSIONS

The influence of rate factor of calcium release from the ER on Ca^{2+} oscillations in the two-pool model is investigated. Different effects of the slow variables Ca_m as well as Ca_{er} on the occurrence of bursting patterns are studied, based on the bifurcation theory and the fast-slow dynamical analysis.

A new subHopf-cycle burster of point-cycle type with multiple rhythms is found in our simulations. Transition mechanisms with the parameter k_{leak} varying are also explained. Our results show that the rate factor of calcium release from the ER and the slow variables on different time scales may simultaneously influence the complex calcium oscillations in biological cells. Meanwhile, the results in this paper indicate that the rate factor of calcium release from the ER could be of significant importance on various oscillating patterns of the biological cell systems.

The method proposed in this paper can be applied to other cell system or other bifurcation parameter. The rate factor of calcium release from the ER may be of great importance in intracellular calcium activities. We should point out that further studies of intercellular and intracellular synchronization of calcium oscillation are needed to reveal the importance of dynamics in propagating calcium signals.

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