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Different Types of Periodic Activities in a Calcium Oscillation Model

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Abstract: In this paper, a model proposed by Marhl et al. is considered to investigate the effect of several parameters on the calcium bursting oscillation behavior. Different types of bursting are presented. Fast-slow burster analysis and first return map are used to explain the mechanism of the four types of bursting. The results are instructive for understanding the role of these parameters played in complex dynamics in the Marhl-Haberichter calcium oscillation model.

Keywords: Calcium oscillation, bursting, fast-slow dynamics, return map.

1 Introduction

In excitable as well as in non-excitable cells, many processes, such as cell secretion and egg fertilization, are performed by the oscillatory changing of free cytosolic calcium concentration. Calcium oscillations were found experimentally in the 1980s [1]. A large number of experimental works have confirmed the significant role of bursting oscillations in cell signaling. Due to the importance of oscillations, several mathematical models were established in order to explain the mechanism [2–10].

The first model was established by Shen and Larter [5], and its functioning bases on two main mechanisms, i.e. the calcium-induced calcium release (CICR) and the inositol trisphosphate crosscoupling (ICC). A more detailed research in explaining the complex calcium oscillations in non-excitable cells have been given by Borghans et al. [6] and Houart et al. [7] followed. In this paper, we focus on effects of different parameters to study their physiological roles in generating complex Ca^{2+} oscillations. Another model demonstrating bursting oscillations was proposed by Kummer et al. [8], which incorporates the feedback inhibition on the initial agonist receptor complex by Ca^{2+} and activated phospholipase C (PLC), as well as receptor type-dependent self-enhanced behavior of the activated G_a subunit. In the present article, the Marhl-Haberichter Ca^{2+} oscillation model [2, 3, 9, 10] is analyzed by using the so-called fast-slow burster analysis and first return map [11, 12]. The dynamic mechanism of different calcium oscillations in non-excitable cells has been extensively investigated. For more details and analysis about these results see Ref. [13].

2 Materials and methods

The mathematical model we used was proposed by Marhl et al. [2]. The model is described by the following differential equations:

$$\frac{dCa_{\rm cyt}}{dt} = J_{\rm ch} - J_{\rm pump} + J_{\rm leak} + J_{\rm out} - J_{\rm in} + J_{\rm CaPr} - J_{\rm Pr} \quad (1)$$

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

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

where $J_{\rm ch} = k_{\rm ch}\frac{Ca_{\rm cyt}^2}{Ca_{\rm cyt}^2+K_1^2}(Ca_{\rm er} - Ca_{\rm cyt})$, $\mathrm{Pr}_{\rm tot} = \mathrm{Pr} + Ca\,\mathrm{Pr}$, $J_{\rm pump} = k_{\rm pump}Ca_{\rm cyt}$, $J_{\rm Pr} = k_+ Ca_{\rm cyt}\,\mathrm{Pr}$, $J_{\rm CaPr} = k_- Ca\,\mathrm{Pr}$, $J_{\rm leak} = k_{\rm leak}(Ca_{\rm er} - Ca_{\rm cyt})$, $J_{\rm out} = (k_{\rm m}\frac{Ca_{\rm cyt}^2}{Ca_{\rm cyt}^2+K_1^2} + k_{\rm mit})Ca_{\rm m}$,

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$Ca_{\text{tot}} = Ca_{\text{cyt}} + \frac{\rho_{\text{er}}}{\beta_{\text{er}}}Ca_{\text{er}} + \frac{\rho_{\text{m}}}{\beta_{\text{m}}}Ca_{\text{m}} + Ca\,\text{Pr}$, $J_{\text{in}} = k_{\text{in}}\frac{Ca_{\text{cyt}}^8}{Ca_{\text{cyt}}^8+K_2^8}$.

Three variables in the system are: the free Ca^{2+} concentration in the cytosol (Ca_{cyt}), free Ca^{2+} concentration in the endoplasmic reticulum(ER) (Ca_{er}), and the free Ca^{2+} concentration in the mitochondria (Ca_m).

Parameters for which all calculations are made if not otherwise stated: $k_{\text{leak}} = 0.01s^{-1}$, $k_{\text{pump}} = 20.0s^{-1}$, $k_{\text{in}} = 300\mu Ms^{-1}$, $k_{\text{m}} = 125s^{-1}$, $k_{+} = 0.09\mu Ms^{-1}$, $k_{-} = 0.01s^{-1}$, $K_1 = 5.0\mu M$, $K_2 = 0.8\mu M$, $Ca_{\text{tot}} = 90\mu M$, $Pr_{\text{tot}} = 120\mu M$, $\rho_{\text{er}} = 0.01$, $\beta_{\text{er}} = 0.0025$, $\rho_{\text{m}} = 0.01$, $\rho_{\text{m}} = 0.0025$.

Equations (1)-(3) construct a full system with the fast subsystem (FS.) and the slow subsystem (SS.). In the fast-slow analysis, we determine the type of bursting by behavior of FS, where the slow variable Ca_m is considered as bifurcation parameter.

3 Results

When $k_{\text{ch}} = 1500$, there is a point-cycle bursting of subHopf-suHopf type, as shown in Fig.1 and 2. HB and LPC are subcritical Hopf bifurcation and fold limit cycle bifurcation respectively. Solid and doted lines (right and left side of HB) are stable and unstable steady state. Dash (thin solid) lines are stable (unstable) periodic solutions. The closed line represents the limit cycle trajectory of the complete system.

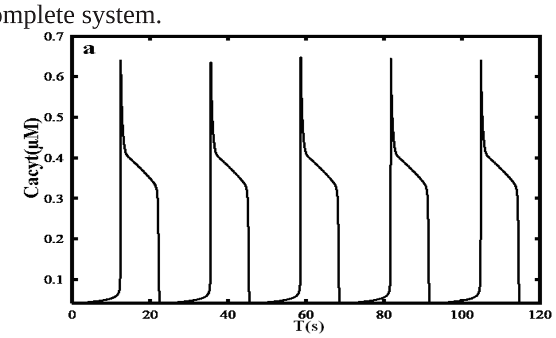

Fig. 1. Time series of Ca_{cyt} with $k_{ch} = 1500$ of point-cycle bursting.

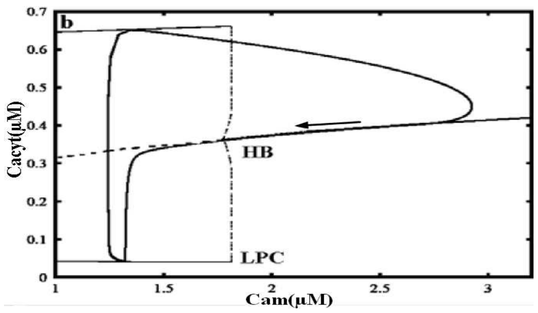

Fig. 2. Fast-slow dynamical analysis of point-cycle bursting.

The main character of this type is the active and silent phases of bursting depend on a stable steady state and a stable limit cycle related to a subHopf bifurcation at HB, see Fig.2. When the trajectory passes the subcritical Hopf bifurcation (HB), the stable steady state branch turns unstable. Therefore, the trajectory unfolds from the unstable steady state to stable periodic attractors. This starts the active phase of bursting. As time progresses the trajectory passes through the unstable limit cycle. Due to the attractive stable foci, the trajectory turns to the stable steady state on the other side of the subcritical Hopf bifurcation. The silent phase of bursting starts again.

When $k_{\text{ch}} = 2225$ and $k_{\text{leak}} = 0.03$, this system has two attractors. The trajectory tends to one of them, depending on the different initial conditions. This phenomenon is called birhythmicity. For one initial condition $(Ca_{\text{cyt}} = 0.5, Ca_{\text{er}} = 0.5, Ca_{\text{m}} = 0.85)$, there is only regular spiking of Ca_m shown in Fig.3, so the trajectory is a simple unfolded limit cycle, as illustrated in Fig.4. However, for another initial condition $(Ca_{\text{cyt}} = 0.5, Ca_{\text{er}} = 0.5, Ca_{\text{m}} = 1)$ one period of oscillations of Ca_m composes of two spikes differed in the amplitude (as shown in Fig.5, which leads to a double folded limit cycle (see Fig.6. Bifurcation analysis is similar to the above and omitted here).

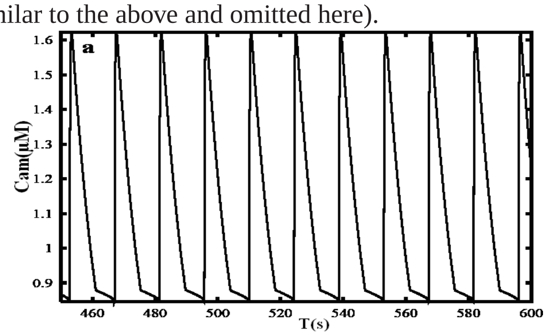

Fig. 3. Time series of birhythmic bursting with $k_{ch} = 2225$ and $k_{leak} = 0.03$.

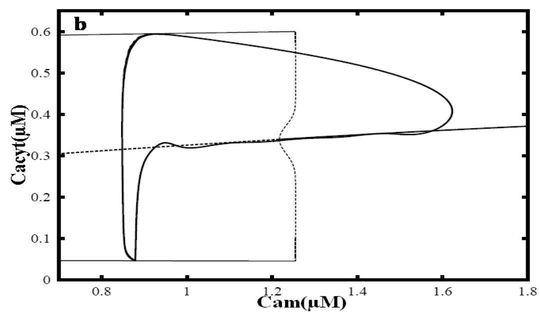

Fig. 4. Unfolded limit cycle trajectory of the complete system in (Ca_{cyt}, Ca_m)-plane.

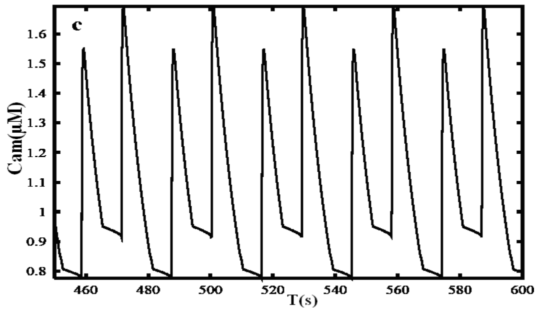

Fig. 5. Time series of Ca_m with $k_{ch} = 2225$ and $k_{leak} = 0.03$ for different initial conditions.

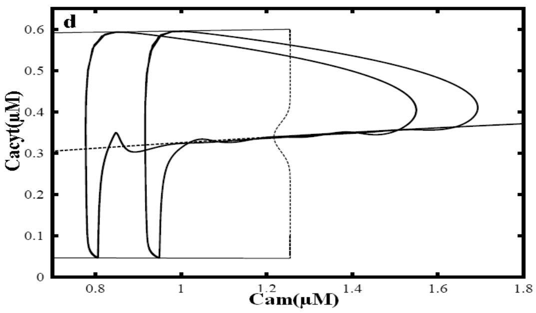

Fig. 6. Folded limit cycle trajectory of the complete system in (Ca_{cyt}, Ca_m)-plane.

When $k_{\mathrm{ch}} = 2000$ and $k_{\mathrm{pump}} = 17.8$, the full system has four attractors. We call this phenomenon quadric-rhythmicity (see Fig.7). For some strict conditions, the trajectory of the complete system can show quadruple folded limit cycle (as shown in Fig.8). Fig.9 shows such a return map for an example of quadric-rhythmic bursting. In this figure, the successive maxima of Ca_m are plotted against their predecessors. Points of the bisector line represent cycles of constant amplitudes. Each single point of the return map represents one cycle of the system trajectory.

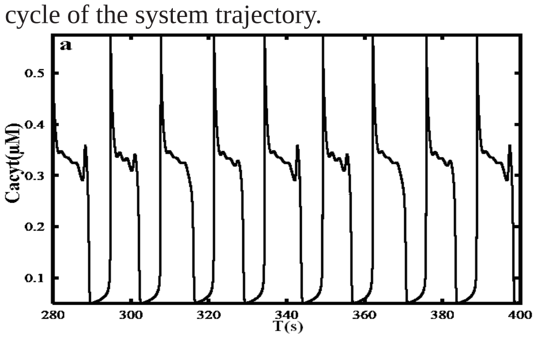

Fig. 7. Time series of quadric-rhythmic bursting with $k_{ch} = 2000$ and $k_{pump} = 17.8$.

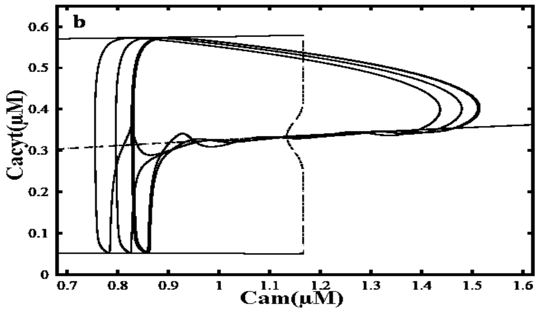

Fig. 8. Trajectory of the complete system in (Ca_{cyt}, Ca_m)-plane with $k_{ch} = 2000$ and $k_{pump} = 17.8$.

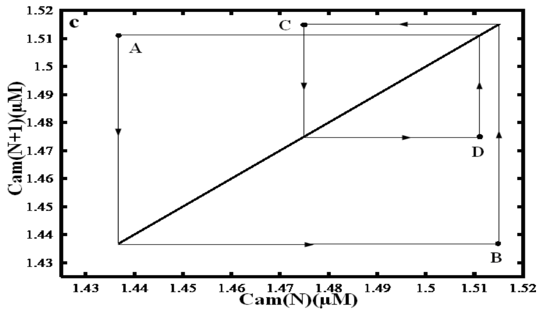

Fig. 9. Return map of Ca_m with $k_{ch} = 2000$ and $k_{pump} = 17.8$.

We start at the point A (marked by an arrow in the anti-clockwise direction), along the grey line, then we pass point B, C and D. At last we return to point A. This is a strong evidence for quadric-rhythmic bursting.

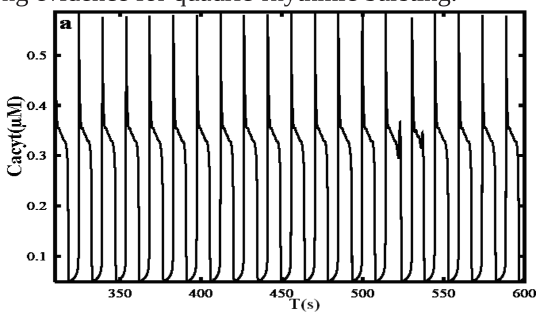

Fig. 10. Time series of chaotic bursting with $k_{ch} = 1800$ and $k_{pump} = 17.8$.

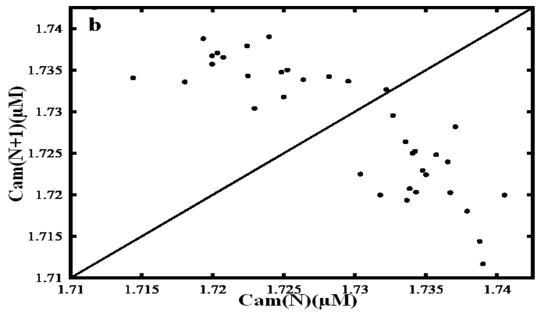

Fig. 11. Return map of Ca_m with $k_{ch} = 1800$ and $k_{pump} = 17.8$.

When $k_{\mathrm{ch}} = 1800$ and $k_{\mathrm{pump}} = 17.8$, the full system displays a chaotic bursting. These chaotic behaviors are characterized by a positive value of the largest Lyapunov exponent and neglected here. For $k_{ch} = 1800$ and $k_{pump} = 17.8$, the time course of chaos is shown in Fig.10. Note that the amplitudes of the Ca_{cyt} spikes keep almost constant all the time. The corresponding return map to the time series is presented in Fig.11. In this figure, the successive maxima of Ca_m are plotted against their predecessors. From this figure we can see that these points is very messy, which means the occurrence of chaos.

4 Discussion

In this paper, the effects of different parameters on the Ca^{2+} oscillations have been studied. Four types of bursting Ca^{2+} oscillations are given. Separately, we analyze point-cycle bursting of subHopf-subHopf type, birhythmicity, quadric-rhythmicity and chaos. Lots of studies show that frequency encoding and amplitude encoding play an extraordinary role in information processing and signal transduction in many biological systems. From this point of view, it is very important to analyze different types of bursting calcium oscillations, since different types of bursting behavior could reflect different encoding of biologically relevant information. Therefore, more types of bursting behavior should be found and further studies will be necessary to determine more precisely effects of different parameters on the Ca^{2+} oscillations.

Acknowledgement

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