Dynamics Analysis and Transition Mechanism of Bursting Calcium Oscillations in Non-Excitable Cells *

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A one-pool model with Ca^{2+}-activated inositol-trisphosphate-concentration degradation is considered. For complex bursting Ca^{2+} oscillation, point–cycle bursting of subHopf–subHopf type is found to be in the intermediate state from quasi-periodic bursting to point–point bursting of subHopf–subHopf type. The fast–slow burster analysis is used to study the transition mechanisms among simple periodic oscillation, quasi-periodic bursting, point–point and point–cycle burstings. The dynamics analysis of different oscillations provides better insight into the generation and transition mechanisms of complex intra- and inter-cellular Ca^{2+} signalling.

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Bursting was found to be the primary mode of electrical firing behaviour in neurons,[1,2] and has been described and classified within a framework of the theory of dynamical systems with fast and slow variables.[3,4] Recently, the role of bursting oscillations for intracellular Ca^{2+} signalling has become of interest. In excitable as well as non-excitable cells a significant part of signal transduction, controlling the complex behaviour of the biological systems, is performed by the oscillatory changing of free cytosolic calcium concentration. These oscillations regulate many cellular processes from egg fertilization to cell death.[5] Bursting oscillations of free cytosolic calcium were found experimentally in cells.[6,7] Here we consider a model about bursting Ca^{2+} oscillation in non-excitable cells.[8] There are three variables in this model: free Ca^{2+} concentration in the cytosol ($C_{\mathrm{Ca}_{cyt}}$), free Ca^{2+} concentration in the endoplasmic reticulum (ER) ($C_{\mathrm{Ca}_{\mathrm{er}}}$), and the inositol trisphosphate concentration in the cytosol (C_{IP_3}). The concentration C_{IP_3} most probably varies with time. Meyer and Stryer[9] proposed a theoretical model for simple periodic Ca^{2+} oscillations based on the activation of C_{IP_3} synthesis by cytosolic Ca^{2+}. Complex oscillations of Ca^{2+} have recently been observed in an extension of this model by Shen and Larter.[10] Here we focus on the well-documented effect of cytosolic Ca^{2+} on the degradation of C_{IP_3}.

Although the model for bursting Ca^{2+} oscillations has been introduced for several years, only a few types of bursting Ca^{2+} oscillations appearing in this model were reported,[11] including quasi-periodic, periodic (point–point) bursting Ca^{2+} oscillations. Therefore, more complex oscillations in this model is awaiting to discover. In this study it is found that there exist some new types of bursting Ca^{2+} oscillations, that is, including point–cycle bursting and simple periodic oscillations (spiking). The fast–slow burster analysis is used to study the transition mechanisms among different firings. Because Ca^{2+} and C_{IP_3} act as co-agonists to stimulate Ca^{2+} release through the C_{IP_3}R channel, we investigate the possibility that bursting can arise as a result of the Ca^{2+} activation of C_{IP_3} degradation.

A calcium oscillation model proposed by Borghans *et al.* in Ref. [8] concerned the dynamics of C_{IP_3}, by

$$\frac{dC_{\mathrm{Ca}_{cyt}}}{dt} = J_{\mathrm{in}} + J_{\mathrm{leak}} - J_{\mathrm{pump}} + J_{\mathrm{er}} - J_{\mathrm{out}}, \tag{1}$$

$$\frac{dC_{\mathrm{IP}_3}}{dt} = r \cdot k_p - J_D - J_C, \tag{2}$$

$$\frac{dC_{\mathrm{Ca}_{\mathrm{er}}}}{dt} = J_{\mathrm{pump}} - J_{\mathrm{leak}} - J_{\mathrm{er}}, \tag{3}$$

where

$$\begin{aligned}
J_{\mathrm{in}} &= k_{\mathrm{in1}} \cdot r + k_{\mathrm{in2}},\\
J_{\mathrm{leak}} &= r \cdot k_{\mathrm{leak}} \cdot \frac{C_{\mathrm{IP}_3}^4}{C_{\mathrm{IP}_3}^4 + K_a^4} \cdot \frac{C_{\mathrm{Ca}_{\mathrm{er}}}^2}{C_{\mathrm{Ca}_{\mathrm{er}}}^2 + K_y^2}\\
&\quad \cdot \frac{C_{\mathrm{Ca}_{cyt}}^4}{C_{\mathrm{Ca}_{\mathrm{cyt}}}^4 + K_z^4},\\
J_{\mathrm{pump}} &= k_{\mathrm{pump}} \cdot \frac{C_{\mathrm{Ca}_{\mathrm{cyt}}}^2}{C_{\mathrm{Ca}_{\mathrm{cyt}}}^2 + K_2^2},\\
J_{\mathrm{out}} &= k_{\mathrm{out}} \cdot C_{\mathrm{Ca}_{\mathrm{cyt}}}, \quad J_{\mathrm{er}} = k_f \cdot C_{\mathrm{Ca}_{\mathrm{er}}},\\
J_A &= r \cdot k_p,\\
J_D &= k_d \cdot \frac{C_{\mathrm{IP}_3}^2}{C_{\mathrm{IP}_3^2}^2 + K_p^2} \cdot \frac{C_{\mathrm{Ca}_{\mathrm{cyt}}}^4}{C_{\mathrm{Ca}_{\mathrm{cyt}}}^4 + K_d^4},\\
J_C &= \epsilon \cdot C_{\mathrm{IP}_3},
\end{aligned}$$

where three dynamical variables are $C_{\mathrm{Ca}_{\mathrm{cyt}}}$, C_{IP_3} and $C_{\mathrm{Ca}_{\mathrm{er}}}$. The values of parameters used here can

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seen in Ref. [11]. In what follows, we study this model by hanging the parameter r, which represents the stimulation level to affect both the Ca^{2+} entry from the extracellular medium ($k_{in1}r$) and the release of Ca^{2+} from the intracellular store (J_{leak}) as well as the effect of C_{IP_3} degradation on the concentration of Ca^{2+}. Thus, bursting can arise as a result of Ca^{2+} activation of C_{IP_3} degradation.

The one-pool model of calcium oscillation Eqs. (1)–(3) is a system with slow and fast time scales. The corresponding slow subsystem is Eq. (3), and Eqs. (1) and (2) consist of the fast subsystem. In the fast subsystem, the slow variable $C_{Ca_{er}}$ is considered to be a control parameter. The bifurcation diagrams of the fast subsystem with $C_{Ca_{er}}$ as the bifurcation parameter are plotted in Fig. 1, in which the phase trajectories of the whole system are also appended. Fast–slow burster analysis is used to study the generation mechanisms and types of different bursting oscillations. Furthermore, the bifurcation analysis of the whole system is carried out to investigate the parameter regions of different firings as well as their transition mechanism.

Firstly, the transition from simple periodic oscillation to quasi-periodicity is considered. Quasi-periodicity is a rather rare phenomenon in calcium oscillations, which can be revealed by calculating the first and second Lyapunov exponents[12] to be zero. It is seen that simple spiking turns to quasi-periodic bursting at $r \approx 0.9521$.

When $r = 0.95$, there is a simple periodic oscillation in Fig. 1(a). As r increases, for example when $r = 0.99$, there is a quasi-periodic bursting with a torus in the phase portrait appended in Fig. 1(b). The transition from the simple periodic oscillation to the quasi-periodic bursting is due to a supercritical Neimark–Sacker (NS) bifurcation in the whole system.

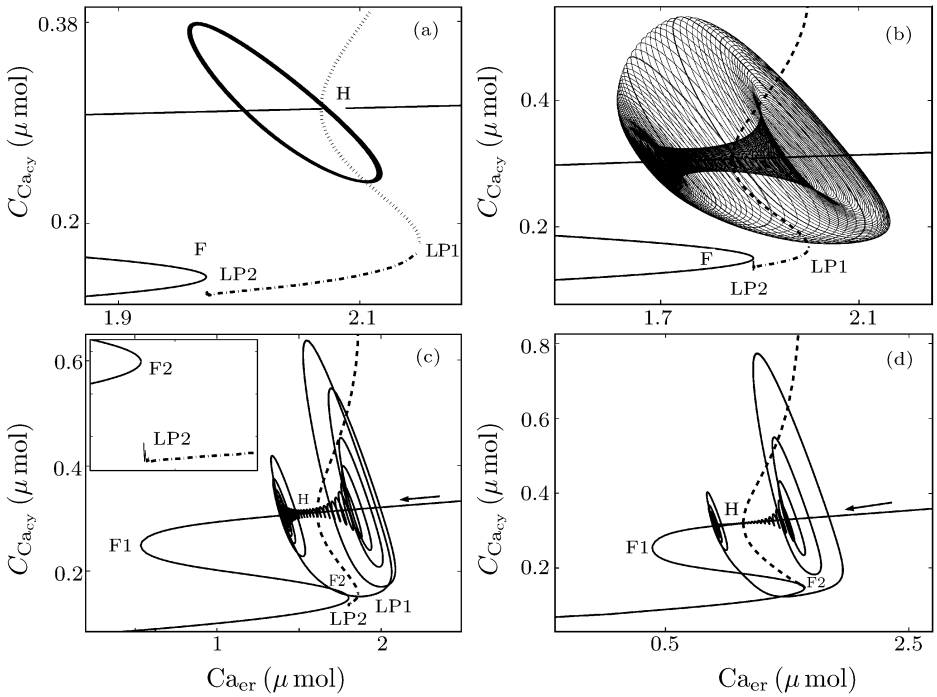


Fig. 1. Bifurcation diagrams of the fast subsystem, in which the slow variable $C_{Ca_{er}}$ is used as the bifurcation parameter. Solid lines represent steady equilibrium states, and dash-dotted (or dashed) lines represent stable (or unstable) periodic solutions. LP1 and LP2 are the fold limit cycle bifurcations; F1 and F2 are the fold bifurcations; H is the subcritical Hopf bifurcation. The appended thick solid curve represents the 2D projection of the trajectory of the whole system. (a) Simple periodic oscillation for $r = 0.95$; (b) quasiperiodic bursting for $r = 0.99$; (c) point–cycle bursting for $r = 1.03$, with the magnification of the region near the points F_2 and LP_2 on the left upper corner; (d) point–point bursting for $r = 1.11$.

Secondly, the transition from quasi-periodicity to point–cycle bursting is considered. From the above discussion, we know that there exists quasi-periodic bursting at $r = 0.99$. As r increases, the torus attractor experiences a fold limit cycle bifurcation with a homoclinic torus structure at $r \approx 1.0073$.

When $r = 1.03$, there is a point–cycle bursting of subHopf–subHopf type. The main character of point–cycle bursting is that the active and silent phases of bursting depend on a stable steady state (abbreviated as 'point') and a stable limit cycle (abbreviated as 'cycle') in the phase space of the fast subsystem. To explain the bursting pattern of subHopf–subHopf type, we start to follow the trajectory in the anti-clockwise direction at the upper steady state (marked by an arrow in Fig. 1(c)) and rotating in the anti-clockwise direction. When the trajectory passes the subcritical Hopf bifurcation point (H), the trajectory slowly ex-

pands from the unstable steady state to the stable periodic attractor. However, it takes considerable time before the trajectory reaches the stable limit cycle due to the slow passage effect. The trajectory is close to the rest state even after passing the subcritical Hopf bifurcation in a long time period, and then the transition to the stable limit cycle is delayed. As time progresses, the unstable steady branch from F1 to H gets increasingly repellent, which speeds up the transition to the stable limit cycle. Oscillations around the stable branch are damped due to attractive stable foci.

The difference between Fig. 1(b) and Fig. 1(c) is explained as follows. In Fig. 1(c), the unstable limit cycle passing LP2 does not collide with the fold bifurcation F2 of the lower stable steady state branch, and the limit cycle passing LP2 tends to infinity in a fast manner. Therefore, there is a saddle homoclinic bifurcation in Fig. 1(c) but a homoclinic torus structure in Fig. 1(b), in which bursting changes from quasi-periodic to periodic.

Thirdly, the transition from point–cycle bursting to point–point bursting is considered. When $r = 1.11$, there is a point–point bursting of subHopf–subHopf type shown in Fig. 1(d). The main character of this type of bursting is that the active phase of bursting starts and ends with a subcritical Hopf bifurcation. The phenomenon of slow passage effect is the same as that for $r = 1.03$. Comparing with Fig. 1(c), two fold limit cycles disappear in Fig. 1(d). At the same time, there is a saddle homoclinic bifurcation of the fast subsystem, which arises when the fold bifurcation of the lower stable steady state branch collides with the lower unstable periodic branch originating from the subcritical Hopf bifurcation.

The main difference between Figs. 1(c) and 1(d) is described as follows. There are a stable limit cycle and two stable states in Fig. 1(c). When a trajectory appears near the Hopf bifurcation point, there are two stable steady states, i.e., a stable focus and a stable limit cycle, to be considered. The trajectory is attracted by the stable limit cycle, whereas it stays in the upper branch due to the slow passage effect after passing the Hopf bifurcation point. Therefore, the trajectory is a periodic oscillation in Fig. 1(c). With the parameter r increasing, there is only a stable steady state in Fig. 1(d) (that is, a stable focus in the lower branch), so the trajectory tends to the rest state after the Hopf bifurcation point, as seen from time course in Fig. 1(d). Therefore, they are called point–cycle bursting in Fig. 1(c) and point–point bursting in Fig. 1(d), respectively.

Finally, the bursting pattern does not change with r increasing until it turns to a simple oscillation. As time increases, the trajectory passes the subcritical Hopf bifurcation point H, and stays near the point H more time than that in Fig. 1(d). At the same time, the slow passage effect becomes weaker. By the fast-slow dynamics analysis, the bursting turns to a simple periodic oscillation when the slow passage effect disappears.

Table 1. Transition mechanism of different burstings.

Parameter	Bursting transition	Transition mechanism
$r \approx 0.9521$	(1)	Supercritical Neimark–Sacker bifurcation
$r \approx 1.0073$	(2)	Unstable limit cycle tending to infinity
$r \approx 1.0536$	(3)	Saddle homoclinic bifurcation
$r \approx 1.1925$	(4)	Slow passage effect disappearing

In conclusion, we have analysed complex bursting Ca^{2+} oscillations in the model (1)–(3). A new point–cycle bursting of subHopf–subHopf type is found, which is an intermediate state from quasi-periodic bursting to point–point bursting of subHopf–subHopf type. The transition mechanisms among different bursting are presented in Table 1, and summarized as follows:

(1) the transition from the simple periodic firing to the quasi-periodic bursting, which is due to a supercritical Neimark–Sacker bifurcation in the whole system;

(2) the transition from the quasi-periodic bursting to the periodic bursting, which is caused by the fact that the unstable limit cycle collides with the fold bifurcation of the lower stable steady state branch;

(3) the point–cycle bursting turns to the point-point bursting, which is resulted from the stable cycles from the subcritical Hopf bifurcation point disappearing;

(4) the point–point bursting turns to the simple oscillation. When the slow passage effect disappears, the complex periodic bursting turns to simple periodic oscillation.

The bifurcation diagrams were computed by using AUTO, as incorporated in XPPAUT.

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