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Dynamic analysis on the calcium oscillation model considering the influences of mitochondria

Xiang Li[a,b], Suxia Zhang[a,b,*], Xijun Liu[a,b], Xiaojing Wang[c], Anqi Zhou[a,b], Peng Liu[a,b]

[a] Department of Mechanics, School of Mechanical Engineering, Tianjin University, Tianjin 300354, PR China
[b] Tianjin Key Laboratory of Nonlinear Dynamics and Chaos Control, Tianjin 300354, PR China
[c] School of Chemical Engineering and Technology, Tianjin University, Tianjin 300354, PR China

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ABSTRACT

Based on the model considering the influences of mitochondria, a further theoretical study on the dynamic behaviors of calcium signals is made. First of all, the reason for the generation and disappearance of calcium oscillations is verified in theory. Second, an analysis on the model considering the influences of mitochondria and the model neglecting the influences of mitochondria is carried out. Third, β (representing calcium leak) is introduced and it can be found that with the increase of β, the Hopf bifurcation points of system move towards the decreasing direction of μ (representing stimulus intensity) and calcium oscillations region gradually decreases. Forth, the study on τ_h (representing relaxation time) indicates that with the increase of τ_h, the second Hopf bifurcation point of system moves towards the increasing direction of μ and calcium oscillations region gradually increases. Under certain stimulus intensity, when relaxation time increases, calcium oscillation peak rises rapidly and the period increases obviously. Fifth, two-parameter bifurcation diagram of V_{m1} (representing mitochondria activity) and μ contains three regions: stable region, oscillation region and unstable region. When the parameters fall in the unstable region Ca^{2+} gather towards mitochondria and further lead to cell apoptosis. With the increase of V_{m1}, calcium oscillations region shrinks gradually. V_{m1} and μ both play a key role in regulating cell apoptosis. Only when V_{m1} and μ are high enough can cells enter into programmed cell death and the higher V_{m1} is, the lower the stimulus intensity required by cell apoptosis is.

1. Introduction

Mitochondria belong to a kind of semi-autonomous organelles and universally exist in eukaryocyte. Studies have indicated that mitochondria in cells not only play a role as plant power or energy converter but also can control the basic functions of cells by regulating Ca^{2+} signals. They are key components in the signal transduction system of cells (Demaurex et al., 2009).

Ca^{2+} is an important second messenger in cells. It participates in and controls almost all the important physiological processes in form of calcium oscillations by frequency or amplitude encoding. For example, cell proliferation, secretion, genetic expression, metabolism and apoptosis are all related to Ca^{2+} signals (Berridge, 1993; Berridge et al., 1998; Ghosh and Greenberg, 1995; Müller et al., 1999). Since calcium oscillations were observed in cells in 1986 (Woods et al., 1986), researchers have found this phenomenon in many kinds of cells (Carroll and Swann, 1992; Hu et al., 1998; Huser et al., 2000; Prakash et al., 1997; Rooney et al., 1989). As an important part in the signal transduction process of cells, mitochondria play an important role in regulating calcium signals with complex space-time characteristics. Numerous experimental studies indicate that as buffer of Ca^{2+}, mitochondria can activate or inhibit plasma membrane channel by regulating the concentration of Ca^{2+}. As the transfer station of Ca^{2+}, mitochondria not only can transfer Ca^{2+} signals, but also can release Ca^{2+} into cytoplasm to regulate the concentration of Ca^{2+} in cytoplasm (Leo et al., 2005; Rizzuto et al., 1993).

Moreover, it is noteworthy that mitochondria can induce cell metabolism or apoptosis by regulating Ca^{2+} signals (Demaurex and Distelhorst, 2003; Satrustegui et al., 2007; Scorrano et al., 2003). The reason that the concentration of Ca^{2+} in cytoplasm can form complex time-space characteristics mainly relies on two important organelles, endoplasmic reticulum and mitochondria. The former can quickly and flexibly regulate the concentration of Ca^{2+} in cytoplasm and the latter can make lasting and high-capacity regulations

* Corresponding author at: Department of Mechanics, School of Mechanical Engineering, Tianjin University, Tianjin 300354, PR China.
E-mail addresses: axiang@tju.edu.cn (X. Li), zhangsux@tju.edu.cn (S. Zhang).

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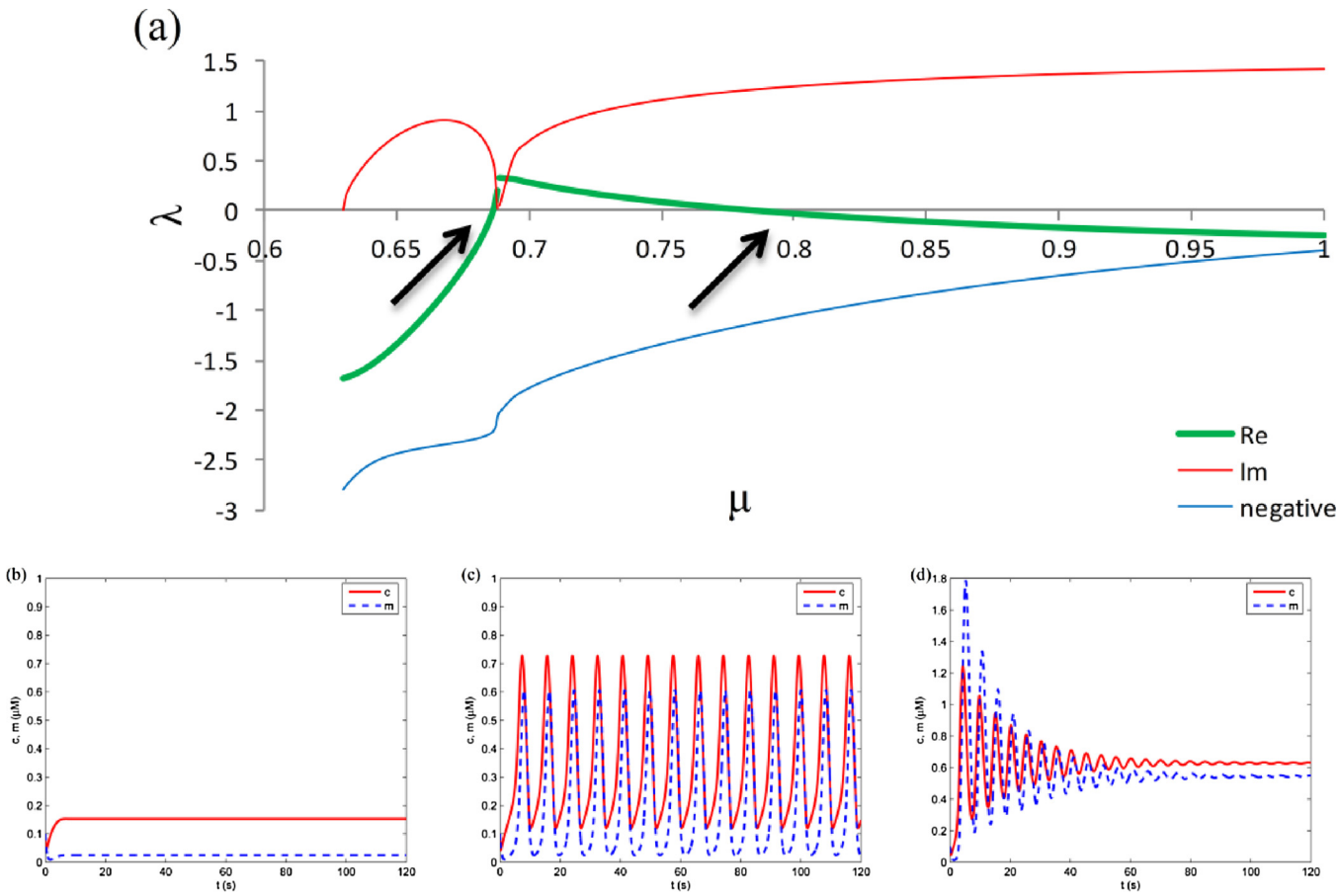

Fig. 1. The λ-μ plot and the time history plots as μ falling in different intervals. (a) λ-μ plot, negative roots-blue, imaginary part-red, real part-green, the arrows point out the non hyperbolic equilibrium points. The time history plots as (b) $\mu = 0.66$; (c) $\mu = 0.7$; (d) $\mu = 0.81$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Shi, 2003). Under general conditions, most Ca^{2+} linger in the cyst cavity of endoplasmic reticulum and only a small part flows into mitochondria. Once Ca^{2+} gather in mitochondria in large quantity, it will overload, leading to abnormal mitochondria metabolism. Then cytochrome c will be released from the intermembrane space of mitochondria, further causing programmed death of cells (Brookes et al., 2004; Hengartner, 2000; van Loo et al., 2002).

There have been a lot of experimental results on the action mechanism of mitochondria on cell calcium signals. However, reconstructing the development and evolution process of calcium oscillations by aid of the mathematical model is another important study method of calcium signals. Then the theoretical study of the calcium oscillations (Schuster and Marhl, 2001; Schuster et al., 2002) and calcium waves (Gosak, 2009) also gets great development. At present, most theoretical models describing calcium oscillations only consider the function of endoplasmic reticulum (Goldbeter et al., 1990; Hofer, 1999; Li and Rinzel, 1994) while few take the influences of mitochondria into consideration (Grubelnik et al., 2001; Marhl et al., 2000; Marhl et al., 1998). Based on the Ca^{2+} dynamics model proposed by Othmer-Tang et al., Falcke et al. added the Ca^{2+} cycle equation of mitochondria in it and presented the experimental findings of Jouaville et al., which is about the influences of mitochondria on intracellular calcium wave patterns (Falcke et al., 1999). Szopa et al. and Qi et al. respectively established the intracellular calcium oscillation model considering the influences of mitochondria. They studied the influences of the interaction between mitochondria and endoplasmic reticulum on calcium oscillations (Qi et al., 2015; Szopa et al., 2013). Shi also established a theoretical model considering the influences of mitochondria (Shi and Liu, 2005).

The model proposed by Atri et al. belongs to the kind of single-pool models, which has the property of calcium-induced calcium release. This model has a certain degree of universality and it is one of the most important theoretical models (Atri et al., 1993). Shi firstly made some improvements on this model and then added the calcium cycle equation of mitochondria to the improved model, so obtaining the calcium oscillation model considering the influences of mitochondria. Clear mechanism and simple form is the feature of this model. Through the numerical calculation, Shi obtained time series of calcium signals under some values of stimulus intensity and mitochondria activity and presented the cell apoptosis process caused by the gathering of Ca^{2+} in mitochondria (Shi and Liu, 2005).

However, the model proposed by Shi neglects the influences of calcium leak on the calcium oscillation system. Moreover, Shi calculated time history plots of this system under some isolated values of parameters but did not make a comprehensive and thorough kinetic analysis in theory. The influences of mitochondria activity on calcium oscillation were studied only under one value of stimulus intensity. Thus, it is impossible to analyze the dynamic characteristics of the system under the joint influences of two parameters.

In this paper, on the basis of the calcium oscillation model considering the influences of mitochondria proposed by Shi, the influences of calcium leak is added in the model. First of all, we prove the reasons for the appearance of oscillations in theory. Second, an analysis on the model considering the influences of mitochondria and the model neglecting the influences of mito-