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Two types of coherence resonance in an intracellular calcium oscillation system

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A B S T R A C T

Two types of noise induced oscillations (NIOs) near Hopf bifurcation and coherence resonance (CR) have been studied analytically in a calcium system. One is NIOs with small amplitude and internal signal stochastic resonance (CR type I) occurs, and the other is noise induced spike and the regularity of which reaches a maximum at an optimal noise level (CR type II). For the first type, stochastic normal form theory is employed to analyze the signal to noise ratio of the NIOs depending on the noise intensity. For the second type, based on the independent assumption, activation time and excursion time have been split, and the sum of which reach a minimum with the variation of noise intensity. The theoretical evidence is also explained in detail. Numerical simulations show good agreements with the theoretical results. It may indicate some kind of transmit mechanism involved in stochastic calcium dynamics.

1. Introduction

Stochastic oscillation (SR) and related phenomena have gained extensive attention in the last two decades [1]. Among these, coherence resonance (CR) is of particular interest, in that nonlinear systems driven by external or internal noise can produce a coherent response even in the absence of an external signal. Originally termed 'autonomous SR' since its introduction by Hu et al. [2], CR effects have been demonstrated theoretically and experimentally in many systems [3–6]. Typically, there are two types of CR behavior: in the systems where the oscillation results from supercritical Hopf bifurcation (HB), harmonic noise induced oscillations (NIOs) with small amplitude can be observed, even when the control parameter is located in the steady state region. The performance of the NIOs, characterized by an effective signal-to-noise ratio (*SNR*), also shows maxima with the variation of the noise intensity. This type of CR has been termed 'internal signal stochastic resonance (SR)' [7]; in the excitable systems such as a neuron, noise can induce large amplitude relaxation oscillation known as 'spikes' in the sub-threshold region, the regularity of which reaches a maximum at an optimal noise level [4,5]. Since oscillations are of ubiquitous importance in many physical, chemical and biological systems, both types of CR have gained a lot of attention in many scientific disciplines.

It is well known that intracellular calcium (Ca^{2+}) is one of the most important second messengers in the cytosol of living cells [8–9]. Many physiological processes [9–11], such as intracellular and extracellular signaling processes, muscle contraction, cell fertilization, gene expression, and so on, are all controlled by the oscillatory regime of the cytosolic calcium concentration. The information about environmental stimuli is encoded with the frequency or amplitude of calcium oscillations, which can effectively transmit many kinds of complex physiological information [12]. It has also been proposed that even at the cellular level, Ca^{2+} dynamics are intrinsically stochastic [13–15]. The effects of noise on the dynamics of calcium oscillations, from experimental data, shown directly that noise and other stochastic effects indeed play a central role [16–20] in system. For instance, Matjaž Perc group suggested that noise may be beneficial for the stability and robustness of calcium oscillations [17] and could induce periodic calcium waves [18]. Chunhua Zeng et al. [20] has studied the effect of time delay on intracellular calcium dynamics which driven by non-Gaussian noises. The CR phenomenon has also been discovered in intracellular calcium oscillation [21–25], however, the underlying mechanism of CR in calcium oscillation system is still unknown to us.

In the present paper, we will investigate how noise would influence two types of CR phenomenon near supercritical Hopf bifurcation in the calcium system. To be different from many previous works, our analysis is mainly theoretical which can give a systematic understanding. On one hand, if the noise intensity is small

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enough, the first CR phenomenon is occur. According to the standard bifurcation method [26], the system's dynamics near the bifurcation point can be reduced to a normal form equation governing the evolution of a complex magnitude on the two-dimensional center manifold associated with the two conjugate eigenvalues of the Jacobi matrix of the vector field. After a "stochastic averaging procedure", a simplified stochastic normal form was finally obtained from which analytical expressions for the probability distribution function of the oscillation amplitude and correlation time, and *SNR* (defined as height of the peak in the power spectral density divided by its half-height width) of the stochastic oscillation were all obtained. These theoretical expressions make it quite straightforward to predict the effects of the noise on the CR phenomenon in calcium oscillation system. On the other hand, if the noise intensity is large enough, spike can be induced and the second CR phenomenon can be observed. The squared *CV* can split into two parts (independent assumption): activation time and excursion time. The sum of the two parts attains a minimum with the variation of noise intensity. The numerical simulations are also performed here, and the results show rather good agreement with the theoretical calculation.

2. Model and simulation results

Stochastic models of intracellular calcium oscillations and waves observed in the experiments for a variety of cell types have been studied previously. According to the model of intercellular calcium oscillations proposed by Höfer [27], there are only considering the interaction of calcium fluxes from and into the endoplasmic reticulum (ER) and across the plasma membrane of the calcium signaling dynamics in a single cell. In the case of the agonists noradrenalin and vasopressin there exists a critical agonist dose above which a hepatocyte responds with regular calcium oscillations. Cytoplasmic oscillations are accompanied by phase-shifted oscillations in ER calcium content. The deterministic model for time evolution of concentration of the cytosolic Ca^{2+} (denoted by x) and total Ca^{2+} in the cell (denoted by z) are as following:

$$\frac{dx}{dt} = \rho\left(v_0 + v_c\frac{P}{k_0+P} - v_4\frac{x^2}{k_4^2+x^2} + \frac{\alpha k_r(x,P)}{\beta}(z-(1+\beta)x) - \alpha v_3\frac{x^2}{k_3^2+x^2}\right) \tag{1a}$$

$$\frac{dz}{dt} = \rho\left(v_0 + v_c\frac{P}{k_0+P} - v_4\frac{x^2}{k_4^2+x^2}\right) \tag{1b}$$

with

$$k_r(x,P) = k_1\left(\frac{d_2(d_1+P)Px}{(d_p+P)(d_a+x)(d_2(d_1+P)+x(d_3+P))}\right)^3 + k_2$$

where P is the inositol 1,4,5-trisphosphate (IP_3) concentration in the cell, and the IP_3 receptors (IP_3R) release function $k_r(x,P)$ describes the gating kinetics of IP_3 receptor R. The parameter ρ, α and β denote the ratios of the total areas of plasma membrane and the effective cytosolic volume, the total areas of the ER membrane and the plasma membrane, and the effective volumes of the ER and the cytoplasm, respectively. According to Ref. [27], the effect of a change in ρ is straightforward to evaluate by realizing that it corresponds to a rescaling of time in Eq. (1). Changes in α leave the period practically constant, even when α changes ~10-fold. By contrast, the period increases appreciably when β is increased, and it indicates that the refilling process of the ER is crucial in determining the oscillation period. Besides, we choose values for the rate constants that yield results consistent with experimental observations. It is note that a crude expression is chosen for calcium-release activated calcium entry by assuming that the average store concentration of calcium decreases with the level of activation, and hence calcium entry increases with P, up to a maximal rate v_c.

The parameter values are chosen as follows: $\alpha = 2.0$, $\beta = 0.1$, $\rho = 0.02$, $v_0 = 0.2\ \mu M\ s^{-1}$, $v_c = 4.0\ \mu M\ s^{-1}$, $v_3 = 9.0\ \mu M\ s^{-1}$, $v_4 = 3.6\ \mu M\ s^{-1}$, $k_0 = 4.0\ \mu M$, $k_3 = 0.12\ \mu M$, $k_4 = 0.12\ \mu M$, $d_1 = 0.3\ \mu M$, $d_2 = 0.4\ \mu M$, $d_3 = 0.2\ \mu M$, $d_p = 0.2\ \mu M$, $d_a = 0.4\ \mu M$, $k_1 = 40.0\ s^{-1}$, $k_2 = 0.02\ s^{-1}$. See Fig. 1 for the bifurcation diagram in the vicinity of the HB point and the frequency $f = 1/T$ (denote by star), where T is the period of the limit cycle. With the variation of the control parameter P, the system has a supercritical Hopf bifurcation (HB) points at $P_H \approx 1.450\ \mu M$ and a canard point at $P_C \approx 1.446\ \mu M$.

The small oscillation appears when $P_H < P < P_C$ and relaxation oscillation occurs when $P > P_C$.

For simplicity, the system we considered in above model subjected to additive noise as Eq. (2). It is worthy to note that the following theoretical analysis in the present letter can be extended to more general cases.

$$\frac{dx}{dt} = \rho\left(v_0 + v_c\frac{P}{k_0+P} - v_4\frac{x^2}{k_4^2+x^2} + \frac{\alpha k_r(x,P)}{\beta}(z-(1+\beta)x) - \alpha v_3\frac{x^2}{k_3^2+x^2}\right)$$

$$\frac{dz}{dt} = \rho\left(v_0 + v_c\frac{P}{k_0+P} - v_4\frac{x^2}{k_4^2+x^2}\right) + \sqrt{2D'}\varepsilon(t) \tag{2}$$

where $\varepsilon(t)$ stands for Gaussian white noise with zero mean and unit variance, and D' denotes noise intensity. Our analysis is focused on the parameter region outside but close to the supercritical HB, where two types of NIOs and CR can be found with the variation of noise intensity. Assuming that the control parameter $P = 1.44$ which is sub-threshold for the deterministic calcium oscillations, however, when the noise is considered, the results altered. If the noise is too weak (Fig. 2(a)), for instance, $2D = 10^{-8}$, there would be small calcium oscillations. On the contrary, if the noise is large enough (Fig. 2(b)), $2D = 10^{-3}$, continuous calcium spikes appear, and $x_c = 0.25$ is taken as the critical value of spike. Furthermore, the phase portrait of small oscillations are shown in Fig. 2(c); the phase portrait of spikes and nullcline for the system are plotted in Fig. 2(d).

In this paper, we are mainly focus on the underline mechanism of two different types of CR which influenced by noise intensity. On one hand, to measure the relative regularity of the stochastic small

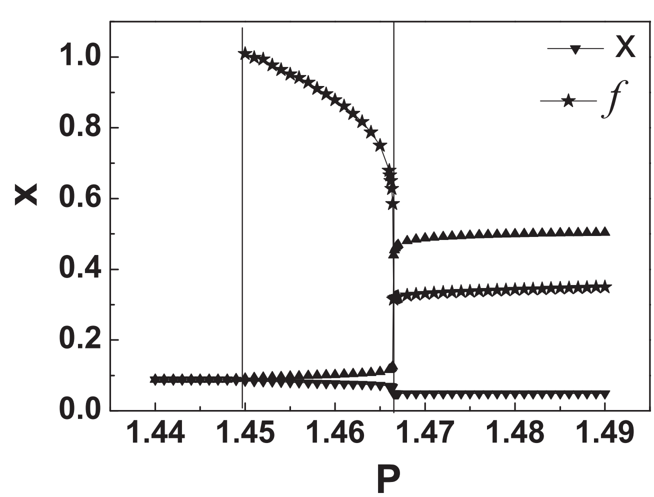

Fig. 1. Bifurcation diagram for x (denote by triangle), and the frequency $f = 1/T$ (denote by star), where T is the period of the limit cycle. The Hopf bifurcation point is $p_H \approx 1.450$, and the canard point is $p_C \approx 1.466$.