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Effects of Time Delay on Intracellular Ca^{2+} Concentration Oscillations *

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Based on the SS-model [Somogyi R and Stucki J W J. Biol. Chem. 266 (1991) 11 068] for the generation of intracellular Ca^{2+} concentration oscillations, we consider a time delay for the binding kinetics of the Ca^{2+} channel and find a significant phenomenon that the oscillation takes two quite different modes when a parameter of the system crosses a threshold. One is a quick oscillation mode and the other is a slow oscillation mode. The oscillation frequencies of these modes differ from each other by more than ten times. The change of oscillation form with parameters and its critical behaviour are illustrated by numerical simulation results.

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It is now widely recognized that biological systems are ideally constituted for the generation of oscillations since they are not thermodynamically closed. Biochemical and physiological processes within single cells can be considered to form nonlinear non-equilibrium dissipative structures with many opportunities for feedback mechanisms required for the generation of oscillations. Ca^{2+} is a crucial second messenger in cells. It responds to external stimuli by sustained oscillations and the signal is encoded through either frequency modulation or amplitude modulation.[1,2] Since the first discovery of the oscillation phenomena of cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) in 1986,[3] various models have been proposed based on different biochemical mechanisms.[4]

Somogyi and Stucki[5] proposed a model (SS-model) of $[Ca^{2+}]_i$ oscillations in which there are three Ca^{2+} pools: the extra-cellular pool, the cytosolic Ca^{2+} compartment, and the intracellular store. Based on some experimental results, the Hill function was used in this model to describe the dependence of the opening probability of channels on Ca^{2+} concentration at a modulatory site. Like many other models, this system shows sustained oscillations or steady states under different parameter values.[4] As we know, the Ca^{2+} release from the intracellular store results from the structure change of channel proteins. Experiments show that the responses of non-excitable cells to Ca^{2+}-mobilizing stimuli often occur after a latent period or time lag. The relation between agonist dose and time delay of $[Ca^{2+}]_i$ responses can be observed in several types of cells.[6,7] Ca^{2+} acts as a co-agonist of inositol-(1,4,5)-trisphosphate (IP_3) induced Ca^{2+} release,[8] but the Ca^{2+} binding dynamics and the multiple steps of conformational changes due to the phosphorylation and dephosphorylation of the pump states are not yet known clearly. These processes are expected to need some time to proceed. However, up to now to our knowledge, this factor not has been considered in all models of Ca^{2+} oscillations. In this letter, we try to improve the SS-model by introducing a time delay for the opening of Ca^{2+} release channels that depend sensitively on the Ca^{2+} concentration at a modulatory site. By numerical simulations, we show how the time delay, i.e. the calcium-binding dynamics of the channel protein, will affect intracellular Ca^{2+} oscillations.

Considering the time cost for the Ca^{2+} bindings and conformation changing, we adjust the equations of the SS-model as follows:

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= A-(b+c)\,x+\left(\alpha+\beta\frac{x'^h}{K^h+x'^h}\right)(y-x)\,,\\ \frac{\mathrm{d}y}{\mathrm{d}t} &= cx-\left(\alpha+\beta\frac{x'^h}{K^h+x'^h}\right)(y-x)\,,\end{aligned} \tag{1}$$

with $x'=x'(t)\equiv x(t-\tau)$. When the time delay $\tau=0$, these equations return to the original SS-model. Here x is the cytosolic Ca^{2+} concentration, y the free Ca^{2+} concentration of intracellular store, A the inward Ca^{2+} flux across the plasma membrane which is presumed to be a constant, b the rate constant of the plasma membrane Ca^{2+} pumps which serve to keep the low resting Ca^{2+} level, c the rate constant of the pump at the surface of intracellular pool and cytosol, and α the leak rate constant of intracellular pool. The release of Ca^{2+} from an IP_3-sensitive intracellular pool to cytosol is controlled by the product of the rate constant β (implicit function of IP_3) and the function $f(x)$ [Ca^{2+} dependence according to the Hill equation, $f(x)=x^h/(K^h+x^h)$], for which the Hill coefficient $h>1$ implies positive co-operativity, while K represents the half saturation Ca^{2+} concentration of the modulatory site sensitive to Ca^{2+}. In this model, IP_3 and Ca^{2+} appear as co-agonists governing the opening probability of exit channels of the intracellular store. Cytosolic Ca^{2+} exerts a positive

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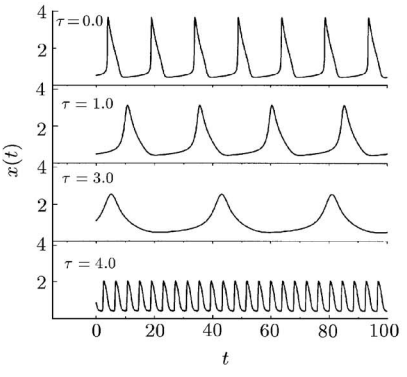

Fig. 1. Oscillation forms of $x(t)$ for $\tau = 0,\ 1.0,\ 3.0,\ 4.0$ when $A = 1, b = 1, c = 2, \alpha = 0.05, \beta = 8, K = 2, h = 4$.

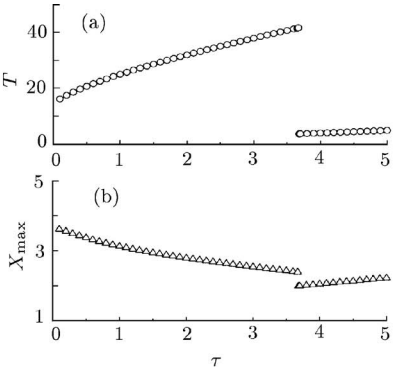

Fig. 2. Changes of the oscillation period (a) and the peak value of $x(t)$ (b) with τ.

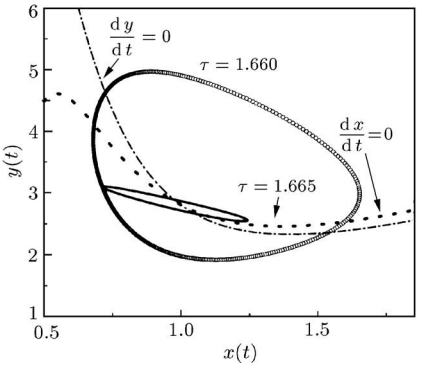

Fig. 3. Limit cycles of the system on the $x - y$ plane when $K = 1.6$, and with other parameters taking the same values as in Fig. 1.

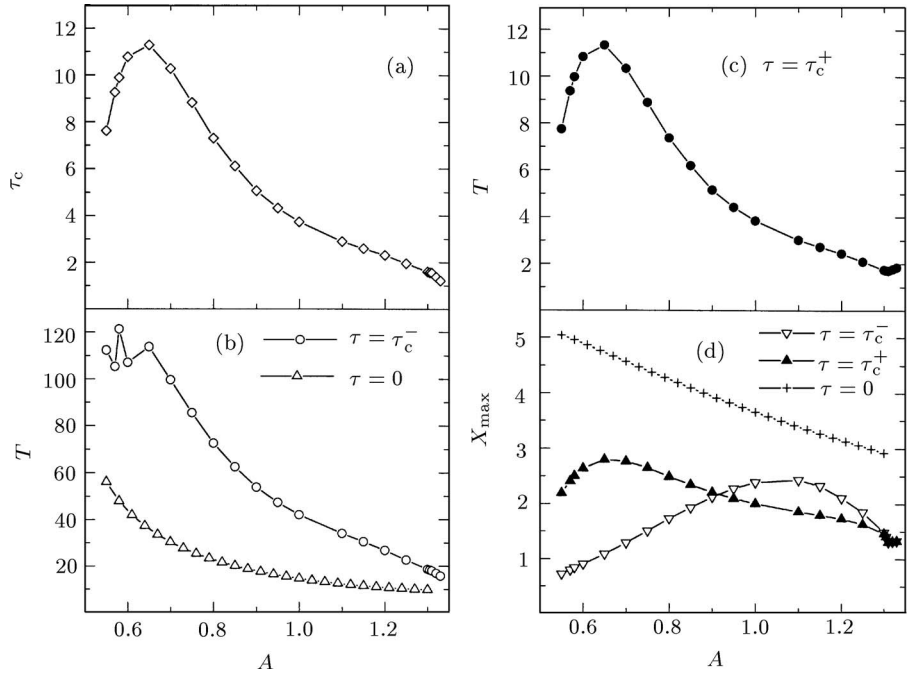

Fig. 4. (a) Critical value of time delay τ_c versus A when other parameters take the same values as in Fig.1. (b),(c) Oscillation period of the system when τ equals 0, approaches the critical value ($\tau = \tau_c^-$) and beyond the critical point ($\tau = \tau_c^+$). (d) Changes of the peak values of $x(t)$ for the three cases.

feedback on the activation of those channels.[8] Equation (1) means that the opening probability of exit channels of intracellular store at time t relies upon the cytosolic Ca^{2+} concentration a certain time earlier. The time interval τ can be taken as the Ca^{2+}-binding dynamics parameter. In what follows, let us study how this mechanism will affect the Ca^{2+} signalling in cells.

The system has the steady state $S(x_{ss}, y_{ss})$ which is given by $dx/dt = dy/dt = 0$. For example, when $A = 1.0$ and $b = 1.0$, we obtain $x_{ss} = A/b = 1.0$ and $y_{ss} = [(\alpha + c)(K^h + 1) + \beta]/[\alpha(K^h + 1) + \beta]$. Since an analytical solution probably does not exist or is impractical, we must integrate these equations numerically. In the following simulations, we take initial values of the system as $x|_{t=0} = 1.0$, $y|_{t=0} = 3.0$, and $x'|_{-\tau\ t\ 0} = 1.0$, and discard the transient period in the simulation.

We take the values of the parameters as $b = 1, c = 2, \alpha = 0.05,\ \beta = 8,\ K = 2, h = 4$. When $\tau = 0$ we can infer from the result of linear stability analysis made by Somogyi and Stucki in Ref. [5] that the system oscillates when A is changed from 0.55 to 1.33, and the system tends to a steady state when A takes values outside this region. Letting $A = 1.0$, we can see some change in the oscillation frequency with the time delay τ in Fig. 1. For small values of τ, considering

the Ca^{2+}-binding process, the oscillation frequency is lower than that of the immediate response. This is shown in the first three panels of Fig. 1 when τ takes values of 0, 1.0, 3.0. When $\tau = 4.0$, the oscillation was turned to a high frequency mode and the maximum of $x(t)$ decreases.

Figure 2 shows the oscillation period and the maximum of $x(t)$ as functions of τ. Compared with the oscillation mode of the original system without the time delay effect, the amplitudes of $x(t)$ decrease gradually with increasing τ in a certain range. What calls for attention is that the time delay has a critical value τ_c beyond which the mode of oscillation changes greatly. From Fig. 2, we can find $\tau_c \approx 3.67$.

The sustained periodic oscillating states of $x(t)$ and $y(t)$ correspond to the limit cycle of the system in the phase space. For the system without time delay, the limit cycle of Eq. (1) surrounds the unstable equilibrium state (x_0, y_0) satisfying both $dx/dt = 0$ and $dy/dt = 0$. The two curves of $dx/dt = f(x, y) = 0$ and $dy/dt = g(x, y) = 0$ on $x-y$ phase plane are called the null clines. In the case of $\beta = 8.0, K = 1.6$, oscillation frequency revulsion happens near $\tau = 1.660$. Figure 3 shows the limit cycles before and after oscillation frequency revulsion with the null clines of the original system. In this case, both limit cycles before and after frequency revulsion surround the original equilibrium state. The amplitudes of both $x(t)$ and $y(t)$ are narrowed by this frequency revulsion, especially for $y(t)$. The peak value or the changing range of $y(t)$ becomes smaller or narrower as τ passes its threshold. In other words, when τ is less than its threshold, the system demands large changes of $y(t)$ to support relatively small changes of $x(t)$. When τ is greater than τ_c, a relatively small change of free calcium concentration in intracellular stores can support a high-frequency mode of cytosolic calcium oscillations, or the requirement on the calcium mobilization of inner-store decreases.

In numerical simulations we find that the peak value of $x(t)$ increases for small values of A, and decreases for large values as τ passes its threshold. In order to obtain a more integrated understanding of the critical behaviour of delaying Ca^{2+}-binding effects on the cytosolic Ca^{2+} oscillations, we seek out the thresholds of the time delay versus the parameter A as shown in Fig. 4(a). Figure 4(b) illustrates the period of the oscillation before τ reaches the threshold ($\tau = \tau_c^-$), compared with the oscillation period of the system without the time delay effect ($\tau = 0$). Figure 4(c) shows the oscillation period after τ reaches its threshold ($\tau = \tau_c^+$). Figure 4(d) shows how the peak values of $x(t)$ change with A for the three cases.

From Fig. 4, we see that τ induces another intrinsic timescale or period into the system. Under suitable conditions, this intrinsic period will dominate the apparent oscillation of the system. When τ is larger than τ_c, the oscillation period of Fig. 4(c) is almost the same as the critical values of Fig. 4(a). If the Ca^{2+}-binding takes a time delay less than the critical value, Fig. 4(b) shows that time delay increases the period or decreases the frequency of oscillation. The original system has a tendency to decrease the peak values of $x(t)$ when the parameter A increases. Figure 4(d) shows that this tendency is changed by the time delay effect of Ca^{2+}-binding.

In conclusion, the results indicated above provide an interesting probable mechanism for the frequency encoding property of $[Ca^{2+}]_i$ oscillations. If the Ca^{2+}-binding dynamics for the channel of intracellular pool is stable, as represented by a constant parameter τ for a given cell type at a special evolution stage, a parameter of the system such as the influx across cell plasma membrane (value of A) can alter the oscillation mode. If the other components of a cell are relatively stable and the parameter A is kept constant, the Ca^{2+}-binding time property of the channel of inner pool changes with different stages of cell evolution, which determines the mode of $[Ca^{2+}]_i$ oscillations. These oscillations then closely reflect the process of cell evolution and can be taken as a trigger of the next steps. This result enlightens us on one possibility that the $[Ca^{2+}]_i$ oscillations might transfer some physiological information.

The model discussed here is quite simplified. We use only one parameter τ to describe the Ca^{2+}-binding dynamics of the Ca^{2+} channel. Actually the Ca^{2+}-binding dynamics may be more complex, and the agonist-sensitive release components may be a multi-timescale function. The nonlinear system with time delay feedback often shows complex dynamics.[9,10] This preliminary work is only an attempt of consideration in principle and the result we obtained seems to indicate some new prospect in understanding the cell Ca^{2+} signalling system.

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