Time Delay Induces Resonant Activation in Intracellular Calcium Oscillations

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The role of time delay of the active transmission processes with colored noises of the intracellular Ca\(^{2+}\) on the intracellular calcium oscillation (ICO) is investigated by means of a first-order stochastic simulation algorithm. By simulating the time series and stationary probability distribution (SPD) of the ICO system, as the time delay and colored noises increase periodicity is respectively strengthened and destroyed; bistable and monostable states appear as the time delay varies. Then, from the statistics of the mean first-passage time (MFPT) of the system from the secondary peak to the main peak of the SPD, the results indicate: as colored noises strengthen, time delay induces a resonant activation (RA) in the ICO system.

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I. INTRODUCTION

It is well known that intracellular calcium(Ca\(^{2+}\)) is one of the most important second messengers in the cytosol of living cells [1, 2]. Cytosolic calcium oscillation plays a vital role as a communication mechanism between distinct parts of the cell or between adjacent cells in the tissue. Many processes [2–5], like intracellular and extracellular signaling processes, muscle contraction, cell fertilization, gene expression, and so on, are all controlled by the oscillatory regime of the cytosolic Ca\(^{2+}\) concentration. In many studies on the ICO, a cell has been simplified into a cytosol and a calcium store in the center, where Ca\(^{2+}\) is released from the calcium store through channels. This process is nonlinear since, as a general pattern, increased Ca\(^{2+}\) concentration in the cytosol favors channel opening, so that Ca\(^{2+}\) is pumped into the calcium store again. This autocatalytic amplification is called calcium-induced calcium release [6]. In many studies on the ICO, there are a variety of channels showing calcium-induced calcium release and a variety of models to describe the ICO as in [6–9]. Many interesting phenomena have been found, such as stochastic backfiring [10], a dispersion gap and localized spiral waves [11], stochastic resonance [12], coherence resonance [13, 14], bistability solutions with hysteresis [15, 16], calcium puffs [17], various spontaneous Ca\(^{2+}\) patterns [18], non-Gaussian noise-optimized ICO in the cytosol [19], and so forth. Subsequently, intracellular calcium responses to signals [20–23] were also observed.

For intracellular Ca\(^{2+}\), in active transmission processes between the cytosol and the calcium store, it must take time due to the finite transmission speed of matter, energy, and
information. Previous investigations, however, either only considered time delay and white noise, or they only considered colored noise. In this paper, thus, we consider simultaneously time delay and colored noises. Interestingly, in our research [16, 24–26], the bistable and monostable states appear in the structure of the stationary probability distribution (SPD) of the ICO system as the density of the colored noises and time delay vary. Thus, we make a study on the effects of time delay and colored noises on the conversion dynamics between the secondary peak and main peak of the SPD, i.e., the MFPT taken by this conversion process from the secondary peak to the main peak of the SPD of the ICO system.

In this paper, in view of the time delay of active transmission processes with colored noises of intracellular Ca$^{2+}$, the phenomenon of the ICO is studied. In Sec. II, based on the model revised in Ref. [16], taking into account the time delay and colored noises, a new model for the ICO is presented, then the time series and SPD of the intracellular Ca$^{2+}$ concentrations are analyzed by a first-order algorithm for stochastic simulation with colored noises. In Sec. III, the MFPT from the secondary peak to the main peak of the SPD is counted and studied. Finally, conclusions are drawn in Sec. IV.

II. SPD OF THE ICO SYSTEM WITH TIME DELAY AND COLORED NOISES

II-1. The model for the ICO system with time delay and colored noises

In this paper, $x$ and $y$ denote the concentration of free Ca$^{2+}$ of the cytosol and calcium store in a cell, respectively. Taking into account of the same time delay $\tau$ in processes of active uptake and release of Ca$^{2+}$ in a real cell, under conditions of unit-variation external and internal noises, by the random equivalent method [27], the Langevin equations of the ICO system can be transformed into the following Stratonovich stochastic differential equations according to [25]:

$$\begin{align*}
d_t x &= A_1(x, y; x_\tau, y_\tau) + B_1(x, y; x_\tau, y_\tau) \epsilon(t), \\
d_t y &= A_2(x, y; x_\tau) + B_2(x, y; x_\tau) \Gamma(t),
\end{align*}$$

with

$$\begin{align*}
A_1(x, y; x_\tau, y_\tau) &= v_0 + v_1 \beta_0 - v_2 + v_3 \tau + k_f y - k x, \\
A_2(x, y; x_\tau) &= v_2 - v_3 - k_f y, \\
B_1(x, y; x_\tau, y_\tau) &= \sqrt{v_1^2 \beta_0^2 + 2v_1 \beta_0 \lambda W + W^2}, \\
B_2(x, y; x_\tau) &= \sqrt{\frac{1}{V} (v_2 + v_3 + k_f y)}, \\
W(x, y; x_\tau, y_\tau) &= \sqrt{\frac{v_0 + v_1 \beta_0 + v_2 + v_3 \tau + k_f y + k x}{V}},
\end{align*}$$

where $\epsilon(t)$ and $\Gamma(t)$ are independent white and colored noises, respectively.
and 

\[ v_2 = \frac{V_2 x^2}{x^2 + k_1^2}, \]
\[ v_{2r} = \frac{V_2 x^2}{x^2 + k_1^2}, \]
\[ v_3 = \frac{V_3 x^4 y^2}{(x^2 + k_1^2)(y^2 + k_3^2)}, \]
\[ v_{3r} = \frac{V_3 x^4 y^2}{(x^2 + k_1^2)(y^2 + k_3^2)}. \]  

Here \( v_0 \) is the steady flow of \( Ca^{2+} \) to the cytosol, \( v_1 \) is the maximum rate of the stimulus induced influx of \( Ca^{2+} \) from the extracellular medium, \( \beta_0 \) is the external control parameter that denotes the degree of extracellular simulation. The rates \( v_2 \) and \( v_3 \) refer, respectively, to the pumping of \( Ca^{2+} \) into the calcium store and to the release of \( Ca^{2+} \) from the store into the cytosol in a process activated by cytosolic \( Ca^{2+} \). \( v_{2r} \) is \( v_2 \) with time delay, and \( v_{3r} \) is \( v_3 \) with time delay. \( k_{fy} \) is a diffusional flow of \( Ca^{2+} \) from store to cytosol, \( k_z \) denotes the uptake from the cytosol, \( V \) is the system size. \( v_2 \) and \( v_3 \) denote the maximum values of the rates \( v_2 \) and \( v_3 \), respectively. The parameters \( k_1, k_2, \) and \( k_3 \) are threshold constants for pumping, release, and activation of release by \( Ca^{2+} \) and by inositol 1,4,5-trisphosphate. \( W = W(x, y; x_r, y_r), x_r = x(t - \tau), y_r = y(t - \tau) \). \( \lambda \) denotes the cross-correlation degree of internal and external noise before merger [16]. The value of the parameters are set as in Ref. [13]: \( v_0 = 1 \text{ \mu m/s}, \ v_1 = 7.3 \text{ \mu m/s}, \ \beta_0 = 0.287, \ k_f = 1/s, \ k = 10/s, \ V_2 = 65 \text{ \mu m/s}, \ V_3 = 500 \text{ \mu m/s}, k_1 = 1 \mu m, k_2 = 0.9 \mu m, k_3 = 2 \mu m, \) and \( V = 1000 \).

In previous studies, \( \epsilon(t) \) and \( \Gamma(t) \) are almost Gaussian white noises rather than colored noises. In practicality, the noise of a stochastic dynamics system is often not white, but is colored. Thus, the noises \( \epsilon(t) \) and \( \Gamma(t) \) are considered as Gaussian colored noises with the following statistical properties:

\[
\langle \epsilon(t) \rangle = \langle \Gamma(t) \rangle = 0, \\
\langle \epsilon(t) \epsilon(t') \rangle = D \lambda_1 \exp(-\lambda_1 |t - t'|), \\
\langle \Gamma(t) \Gamma(t') \rangle = D \lambda_2 \exp(-\lambda_2 |t - t'|).
\]

In order to make the study easier, we suppose that the noises \( \epsilon(t) \) and \( \Gamma(t) \) have the same strength \( D \), and that \( \lambda_1 \) and \( \lambda_2 \) are reciprocals of the correlation times \( \tau_1 \) and \( \tau_2 \) of the colored noises \( \epsilon(t) \) and \( \Gamma(t) \), respectively.

II-2. Time series of intracellular \( Ca^{2+} \) concentrations

The analytical expressions of \( x \) and \( y \) are difficult to obtain, but Eqs. (1) and (2) can be stochastically simulated by a first-order algorithm with colored noises [28] (for the specific simulation process see Ref. [25]). In the following simulation, it is necessary to set initial values. Experimentally, \( x \) is on the order of 100~200 nm in the basal state [29] and \( y = 5 \mu m \) [30], therefore, the initial values \( x(0) \) and \( y(0) \), respectively, take uniformly random values from \( 0.1 \sim 0.2 \mu m \), and \( 5 \sim 6 \mu m \). For the case of time delay, it is rational to let \( x(t - \tau) = x(0) \) and \( y(t - \tau) = y(0) \) as \( t < \tau \). For the initial values of the colored noises, \( \epsilon(0) \) and \( \Gamma(0) \), take them respectively to be uniformly random from \( 0 \sim 1 \). According to a previous stochastic simulation, \( \tau_1 = 4 \text{ s} \) and \( \tau_2 = 1 \text{ s} \) are a reasonable choice. In addition, in this paper, the time step is \( \Delta = 0.001 \text{ s} \) and \( \lambda = 0.1 \).
FIG. 1: The time series of the Ca\(^{2+}\) concentrations in the cytosol \(x(t)\) (solid line) and calcium store \(y(t)\) (dotted line) with different delay times \(\tau=0.001\text{s}\) and 0.4s. Here in the left column \(D = 0.1\) and in the right column \(D = 1\).

The time series of the Ca\(^{2+}\) concentrations in the cytosol \(x(t)\) and in the calcium store \(y(t)\) are plotted in Fig. 1 with different time delays \(\tau = 0.001\text{s}\) and 0.4\text{s}, here in the left column \(D = 0.1\) and in the right column \(D = 1\). They exhibit anti-synchronous oscillation as time evolves, and periodicity increases as the time delay prolongs but disappears as the colored noises strengthen.

II-3. SPD of the ICO system

By using the above method, one can firstly obtain the long time series of the cytosolic Ca\(^{2+}\) concentration \(x(t)\) and of the calcium store’s Ca\(^{2+}\) concentration \(y(t)\). Then, by means of the statistics of the number ratios of data belong to different value zones of the variables and normalizing them, the SPD of the ICO system is obtained under different conditions. Specifically, in the two-dimensional plane constituted with \(x\) and \(y\), the statistics for the frequency \(n\) of the simultaneous occurrence of \(x\) and \(y\) coordinates of each point in a long time series, can be represented in a three-dimensional graphics constituted by \((x, y, n)\); we compute its volume. Then we normalized this volume, the SPD with a stable structure is obtained.

Our results indicate that, for the case of strong colored noises, the SPD shows a conversion between a bistable state and monostable state as the time delay varies, see Fig. 2. Where the SPD emerges at a critical value of the time delay \(\tau \approx 0.1\text{s}\), i.e., as \(\tau \to 0.1\text{s}\), the SPD shifts into a monostable state (see Fig. 2(b)). Otherwise, the SPD shows a bistable state (see Fig. 2(a) and (c)), now there are double peaks in the structure of the SPD, where the highest peak is named as the main peak and the other peak is named
as the secondary peak. When SPD appears as a bistable state, here the secondary peak is always unstable, because it always disappears slowly as the time delay varies; however, the main peak is always stable and only corresponds to the case for the Ca\(^{2+}\) concentration in the calcium store being much higher than the cytosolic. This case is reasonable owing to the Ca\(^{2+}\) concentration of the calcium store being much higher than the cytosolic in the cell forever, so that the state of an unstable secondary peak will shift into the state of a stable main peak. As stated in the above analysis of the SPD of the ICO system, the nominal estimate of a typical delay time for a typical living cell might be not less than 0.1 s.

III. MFPT FROM THE SECONDARY PEAK TO THE MAIN PEAK OF THE SPD

In this section, in order to study the transient process from the secondary peak to the main peak of the system, it is important to analyze the structure of the SPD of the system. The SPD of the ICO system appears with double peaks, the region between the double peaks is a concave well, like a potential well. Moreover, a system making a transition from the secondary peak to the main peak must pass this potential well, thus the mean time taken by this conversion process of the system passing through the potential well is called the MFPT.

The method of computing the MFPT is summarized as follows. Dividing into two cases, for the case of the monostable state, i.e., there is only one stable state, now the system has no transitions, MFPT = 0. For the case of the bistable state, one measures firstly the corresponding coordinates of the peak values of the secondary peak \((x_0, y_0)\) and the main peak \((x_1, y_1)\) of the SPD. Suppose that \(z(t) = x(t) + y(t)i\) in long time series of \(x(t)\) and \(y(t)\), \(i\) is the imaginary unit, then one can find these points \(z_0 = x_0 + y_0i\) and \(z_1 = x_1 + y_1i\) in long time series. Thereby we can count the time difference between two adjacent points \(z_0\) and \(z_1\) in long time series, and the two points must be such that point \(z_1\) is later than point \(z_0\), this time difference is namely the first-passage time. Take the average value for the first-passage time for all long time series, then the MFPT is obtained.

Finally, take the average value of the MFPT for 1000 trajectories again, a more smooth curve of the MFPT \(\langle T \rangle\) vs time delay \(\tau\) at different densities of colored noises is obtained in Fig. 3.

From the figure, for the case of weak colored noises (e.g., \(D=0.1\)), the MFPT has a peak structure after maintaining a minimum. However, as the colored noise increases, the MFPT first declines, and then slowly goes up as the time delay prolongs. Namely, there is a structure of a concave trough of the MFPT vs \(\tau\), and the stronger the colored noises, the shallower the trough is. Importantly, the time delay is the time taken by Ca\(^{2+}\) active transmission between the cytosol and calcium store in a cell, and this time is similar to the intrinsic time of the system, i.e., the time delay is similar to the period of the ICO system, and the reciprocal of the period is the frequency. Thus, the time delay could be thought of as the reciprocal of the ICO system’s frequency.

In summary, the system’s transition process from secondary peak to main peak is
FIG. 2: The stationary probability distribution (SPD) as a function of the Ca$^{2+}$ concentrations in the cytosol $x$ and in the calcium store $y$ at strong density of colored noises for different time delays $\tau=0.001$ s, 0.1 s, and 0.4 s. Here $D=0.5$. 
equal to the process of escape from a potential well, the relative MFPT of the process has a minimum when the reciprocal of the frequency near resonance is added to the ICO system. In previous Refs., the authors described the resonant activation (RA) effect as the presence of a minimum of the speed-up of escape from a potential well when the forcing frequency near resonance is added to thermal forcing, namely added forcing induces the RA effect. In this way, according to the above description, time delay induces the RA effect in the ICO system as colored noises strengthens.

The phenomenon of RA is important for investigating the conversion dynamics in physical, chemical, and biological systems [31–41]. Therefore, it has been widely investigated not only in theory [31–36, 42–46] but also in experiment [38–41, 47]. Furthermore, the occurrence of RA together with other stochastic effects, such as noise-enhanced stability [48–51] and stochastic resonance [52, 53], have been also investigated. Very recently, the role of piecewise linear asymmetric potentials on RA [54], in a system of an overdamped Brownian particle in a potential undergoing dichotomic fluctuations in the appearance of RA [55], the RA of a synthetic antiferromagnet [56] and so on, were also proposed.

FIG. 3: The MFPT from the secondary peak to the main peak of the SPD as a function of time delay $\tau$ at different levels of colored noises $D = 0.1$, 0.5, and 0.8.
IV. CONCLUSIONS

In this paper, in view of the time delay in active transmission processes with colored noises of the intracellular Ca$^{2+}$, by means of first-order algorithm of stochastic simulation colored noises, the phenomenon of the ICO is investigated. The time series and SPD of the ICO system is simulated firstly, then the MFPT from the unstable secondary peak to the stably main peak of the SPD is investigated.

The time series vs time delay and strength of colored noises exhibit anti-synchronous oscillation as time evolves, and periodicity increases as time delay prolongs, but it is destroyed as colored noises strengthen. The simulation results show that in the ICO system some changes occur as time delay and the density of colored noises vary. For the case of strong colored noises, the bistable and monostable state all appear as time delay prolongs. Then for the MFPT vs time delay from an unstable secondary peak to the stable main peak of the SPD, it is clearly seen that the MFPT has a concave structure; this implies that the RA effect occurs in the ICO system in moderate time delay, namely time delay induces the RA effect. Thus, the RA effect not only can be induced by noise, but can also be induced by time delay. This is a new result for stochastic dynamical and biological systems.

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References


