Colored Noises Commutate Calcium Wave in Intracellular Calcium Oscillation

Wei-Long Duan and Ze-Bin Fan

City college, Kunming University of Science and Technology, Kunming 650051, China
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The revised role of colored noises in the intracellular calcium oscillation (ICO) system are investigated by means of a first-order algorithm for the stochastic simulation of colored noises. The simulation results showed clearly that the colored noises commutate a calcium wave. Concretely, for a correlation time of colored noise τ_1 there exists a threshold value τ_c which plays an important role in shifting a calcium wave from negative to positive, however, the calcium wave will show negative regardless of any noise's correlation time taking any value, so long as $\tau_1 < \tau_c$. So considering colored noises in the ICO could explain reasonably the ICO phenomenon.

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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 oscillations play 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 intracellular calcium oscillation (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. This autocatalytic amplification is called calcium-induced calcium release [6]. There are a variety of channels showing calcium-induced calcium release and a variety of models to describe the ICO as in [6–9]. In intracellular Ca^{2+} dynamics stochastic backfiring [10], dispersion gap and localized spiral waves [11], stochastic resonance [12], coherence resonance [13, 14], bistability solutions with hysteresis [15], calcium puffs [16], various spontaneous Ca^{2+} patterns [17], non-Gaussian noise-optimized ICO in cytosol [18], and so forth, have been found. Subsequently, intracellular calcium responses to signals [19–22] were also observed.

Colored noise is widespread in many stochastic systems, instead of white noise. In stochastic systems, colored noise can induce some significant phenomenon, for instance, stochastic resonance [23, 24], coherence resonance [25], synchronization [26–28], asymmetry [29], discontinuous transitions [30], stability [31], and so on. Oppositely, colored noise can also reduce the fluctuations [32] and the population extinction [33]. In Refs. [34–36], the stochastic simulation has been used to study the stochastic Kuramoto model and gene regulatory networks. In research on the ICO, however, except for Li and Wang [37] taking account of colored noise, the other researchers have considered only white noise, including our investigations [38–40]. Although we considered time delay in the transmission of Ca^{2+}, the model still can't explain rationally the phenomenon of the ICO, so that considering colored noises in the intracellular Ca^{2+} dynamics with time delay will be more reasonable for explaining the phenomenon of the ICO.

In this paper, considering colored noises in intracellular Ca^{2+} dynamics with time delay is studied. In Sec. II, based on the model revised in Ref. [39], in view of colored noises, a new model for the ICO is presented. Then the time series of the intracellular Ca^{2+} concentration is analyzed by means of a first-order algorithm for the stochastic simulation of colored noises [41] in Sec. III. Conclusions are drawn in Sec. IV.

II. THE MODEL FOR INTRACELLULAR CALCIUM OSCILLATION WITH COLORED NOISES

The ICO system driven by both unit-variation external and internal noises, and considering the same time delay in the active uptake and release of intracellular Ca^{2+}, the system's Langevin equations can be transformed into equivalent Stratonovich stochastic differential equations [39]:

$$d_t x = A_1(x, y; x_\tau, y_\tau) + B_1(x, y; x_\tau, y_\tau)\epsilon(t), \tag{1}$$

$$d_t y = A_2(x, y; x_\tau) + B_2(x, y; x_\tau)\Gamma(t), \tag{2}$$

with

$$A_1(x, y; x_\tau, y_\tau) = v_0 + v_1\beta_0 - v_2 + v_{3\tau} + k_f y - kx, \tag{3}$$

$$A_2(x, y; x_\tau) = v_{2\tau} - v_3 - k_f y, \tag{4}$$

$$B_1(x, y; x_\tau, y_\tau) = \sqrt{v_1^2\beta_0^2 + 2v_1\beta_0\lambda W + W^2}, \tag{5}$$

$$B_2(x, y; x_\tau) = \sqrt{\frac{1}{V}(v_{2\tau} + v_3 + k_f y)}, \tag{6}$$

$$W(x, y; x_\tau, y_\tau) = \sqrt{\frac{1}{V}(v_0 + v_1\beta_0 + v_2 + v_{3\tau} + k_f y + kx)}, \tag{7}$$

and

$$v_2 = \frac{V_2 x^2}{x^2 + k_1^2}, \tag{8}$$

$$v_3 = \frac{V_3 x^4 y^2}{(x^4 + k_2^4)(y^2 + k_3^2)}, \tag{9}$$

$$v_{2\tau} = \frac{V_2 x_\tau^2}{x_\tau^2 + k_1^2}, \tag{10}$$

$$v_{3\tau} = \frac{V_3 x_\tau^4 y_\tau^2}{(x_\tau^4 + k_2^4)(y_\tau^2 + k_3^2)}. \tag{11}$$

Here, x and y denote the concentration of free Ca^{2+} of the cytosol and calcium store in a cell, respectively. 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 that store into the cytosol in a process activated by cytosolic Ca^{2+}. $v_{2\tau}$ is v_2 with time delay, and $v_{3\tau}$ is v_3 with time delay. $W = W(x, y; x_\tau, y_\tau)$, $x_\tau = x(t-\tau)$, $y_\tau = y(t-\tau)$, λ denotes the cross-correlation degree of internal and external noise before merger [39]. Besides, $\epsilon(t)$ and $\Gamma(t)$ are noises. The value of the parameters are set as in Ref. [13]: $v_0 = 1$ μM/s, $v_1 = 7.3$ μM/s, $\beta_0 = 0.287$, $k_f = 1$ s^{-1}, $k = 10$ s^{-1}, $V_2 = 65$ μM/s, $V_3 = 500$ μM/s, $k_1 = 1$ μM, $k_2 = 0.9$ μM, $k_3 = 2$ μM, and $V = 1000$.

In previous studies, the noises in intracellular Ca^{2+} dynamics are almost all Gaussian white noises rather than colored noises. In practicality, the noise of stochastic dynamics often isn't white, but is colored. Thus, the noises $\epsilon(t)$ and $\Gamma(t)$ should be Gaussian colored noises with the following statistical properties:

$$\begin{aligned}
&\langle \epsilon(t) \rangle = \langle \Gamma(t) \rangle = 0, \\
&\langle \epsilon(t)\epsilon(t') \rangle = D\lambda_1 \exp(-\lambda_1 |t-t'|), \\
&\langle \Gamma(t)\Gamma(t') \rangle = D\lambda_2 \exp(-\lambda_2 |t-t'|),
\end{aligned} \tag{12}$$

here, we suppose that the noises $\epsilon(t)$ and $\Gamma(t)$ have the same strength D, λ_1 and λ_2 are reciprocals of the correlation time τ_1 and τ_2 of the colored noises $\epsilon(t)$ and $\Gamma(t)$, respectively.

III. THE TIME SERIES OF CA^{2+} CONCENTRATION

The analytical expressions of x and y are difficult to obtain. But Eqs. (1) and (2) can be stochastically simulated by means of a first-order algorithm with colored noises [41]:

$$\begin{aligned}
x(t+\Delta) = {} & x(t) + A_1\Delta + B_1[\Gamma_0(t+\Delta) - \Gamma_0(t)] + \frac{1}{4}\frac{\partial B_1^2}{\partial x}[\Gamma_0(t+\Delta) - \Gamma_0(t)]^2 \\
& + \frac{B_2}{2B_1}\frac{\partial B_1^2}{\partial y}[\Gamma_0(t+\Delta) - \Gamma_0(t)][\Gamma_0^{'}(t+\Delta) - \Gamma_0^{'}(t)],
\end{aligned} \tag{13}$$

$$\begin{aligned}
y(t+\Delta) = {} & y(t) + A_2\Delta + B_2[\Gamma_0^{'}(t+\Delta) - \Gamma_0^{'}(t)] + \frac{1}{4}\frac{\partial B_2^2}{\partial y}[\Gamma_0^{'}(t+\Delta) - \Gamma_0^{'}(t)]^2 \\
& + \frac{B_1}{2B_2}\frac{\partial B_2^2}{\partial x}[\Gamma_0(t+\Delta) - \Gamma_0(t)][\Gamma_0^{'}(t+\Delta) - \Gamma_0^{'}(t)],
\end{aligned} \tag{14}$$

here,

$$\frac{\partial B_1^2}{\partial x} = \frac{1}{V}\left(1+\frac{v_1\beta_0\lambda_0}{W}\right)\left[k+\frac{2V_2k_1^2x}{(x^2+k_1^2)^2}\right], \tag{15}$$

$$\frac{\partial B_1^2}{\partial y} = \frac{k_f}{V}\left(1+\frac{v_1\beta_0\lambda_0}{W}\right), \tag{16}$$

$$\frac{\partial B_2^2}{\partial x} = \frac{4V_3k_2^4y^2x^3}{V(x^4+k_2^4)^2(y^2+k_3^2)}, \tag{17}$$

$$\frac{\partial B_2^2}{\partial y} = \frac{1}{V}\left[k_f+\frac{2V_3k_3^2x^4y}{(x^4+k_2^4)(y^2+k_3^2)^2}\right], \tag{18}$$

$$\Gamma_0(t+\Delta)-\Gamma_0(t) = \frac{1}{\lambda_1}(1-e^{-\lambda_1\Delta})\epsilon(t)+G_1, \tag{19}$$

$$\Gamma_0'(t+\Delta)-\Gamma_0'(t) = \frac{1}{\lambda_2}(1-e^{-\lambda_2\Delta})\Gamma(t)+G_1', \tag{20}$$

$$\epsilon(t+\Delta) = e^{-\lambda_1\Delta}\epsilon(t)+\sqrt{D\lambda_1(1-e^{-2\lambda_1\Delta})}\Psi_1, \tag{21}$$

$$\Gamma(t+\Delta) = e^{-\lambda_2\Delta}\Gamma(t)+\sqrt{D\lambda_2(1-e^{-2\lambda_2\Delta})}\Psi_1, \tag{22}$$

$$G_1 = \frac{D(1-e^{-\lambda_1\Delta})^2}{\sqrt{D\lambda_1(1-e^{-2\lambda_1\Delta})}}\Psi_1 + \sqrt{2D(\Delta-\frac{3}{2\lambda_1}+\frac{2}{\lambda_1}e^{-\lambda_1\Delta}-\frac{e^{-2\lambda_1\Delta}}{2\lambda_1})-\frac{4D(\frac{1-e^{-2\lambda_1\Delta}}{2\lambda_1}-\Delta e^{-\lambda_1\Delta})^2}{\lambda_1(1-e^{-2\lambda_1\Delta})}}\Psi_2, \tag{23}$$

$$G_1' = \frac{D(1-e^{-\lambda_2\Delta})^2}{\sqrt{D\lambda_2(1-e^{-2\lambda_2\Delta})}}\Psi_1 + \sqrt{2D(\Delta-\frac{3}{2\lambda_2}+\frac{2}{\lambda_2}e^{-\lambda_2\Delta}-\frac{e^{-2\lambda_2\Delta}}{2\lambda_2})-\frac{4D(\frac{1-e^{-2\lambda_2\Delta}}{2\lambda_2}-\Delta e^{-\lambda_2\Delta})^2}{\lambda_2(1-e^{-2\lambda_2\Delta})}}\Psi_2. \tag{24}$$

The Gaussian random variables Ψ_1 and Ψ_2 are generated by the Box-Mueller algorithm [42] from two random numbers η_1 and η_2, which are uniformly distributed on the unit interval:

$$\Psi_1 = \sqrt{-2\ln(\eta_1)}\cos(2\pi\eta_2), \tag{25}$$

$$\Psi_2 = \sqrt{-2\ln(\eta_1)}\sin(2\pi\eta_2). \tag{26}$$

In the following, it is important to set the initial values . Experimentally, x is on the order of 100–200 nM in the basal state [43] and $y = 5$ μM [44], therefore, the initial values $x(0)$ are taken randomly from $0 \backsim 1$ μM, and $y(0)$ are taken randomly from $5 \backsim 10$ μM. In the condition 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 $\Gamma(0)$ all take values randomly between

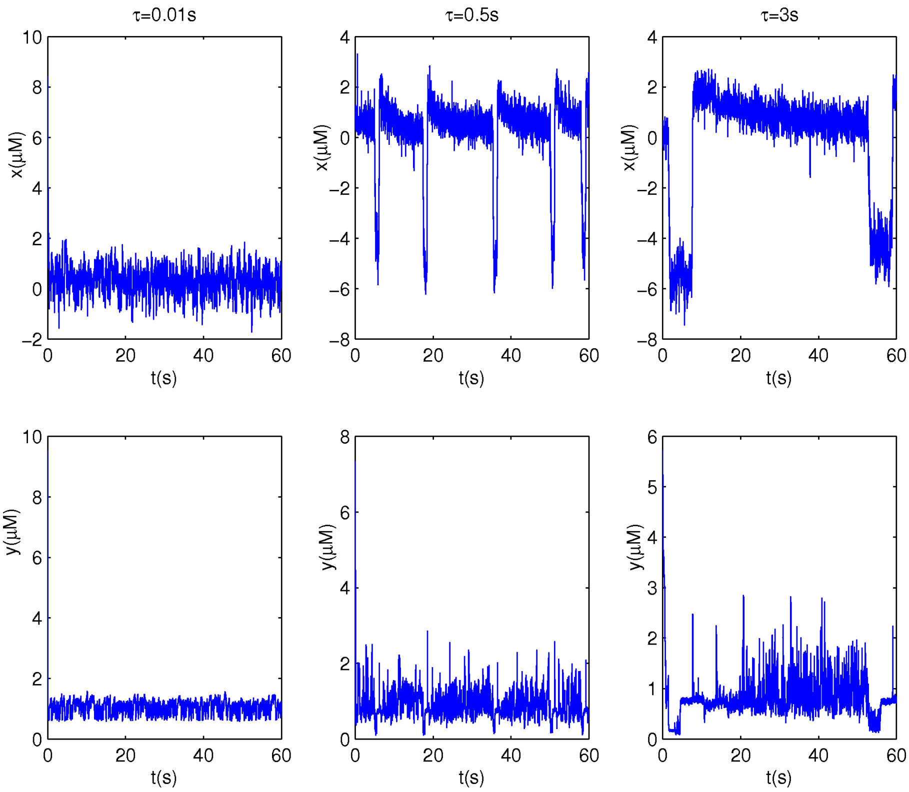

FIG. 1: The time series of Ca^{2+} concentrations in the cytosol x and in the calcium store y variation with delay time τ under the condition of white noises. $D = 1$ and $\lambda = 0.1$.

0 and 1. In addition, in the following investigation, we take time step $\Delta = 0.001$s, $\lambda = 0.1$, and $D = 1$.

The variation of the model for the ICO are simulated as follows. In order to compare the rationality of colored noises rather than white noises being in the ICO, it is necessary to simulate firstly the case for limit $\tau_1 = \tau_2 = 0$, i.e., white noises. The simulation results of x and y at different time delay τ are plotted in Fig. 1. One can see that in the concentration of cytosolic Ca^{2+} x there often appears a negative value, regardless of the time delay τ taking any value, which is impossible in a real cell, even though the concentration of calcium store Ca^{2+} y is all positive values. Obviously, the model for the ICO with white noises has a defect.

The time evolution of the concentration of Ca^{2+} in a cell are shown in Figs. 2 and 3 after changing into colored noises, where the time delay $\tau = 0.1$ s. In the process of simulating the time series variation with a correlation time τ_1 of colored noise $\epsilon(t)$, one finds that there is a threshold value $\tau_c = 4$ s of τ_1 (see Fig. 2, here, $\tau_2 = 0.1$ s), i.e., as $\tau_1 < \tau_c$ (e.g., $\tau_1 = 0.05$ s and 1 s), the concentration of cytosolic Ca^{2+} often appears to have a negative value as time evolves, however, it can all convert to a positive value when $\tau_1 \geq \tau_c$ (e.g., $\tau_1 = 4$ s and 5s). More importantly, the threshold value really exists, this is

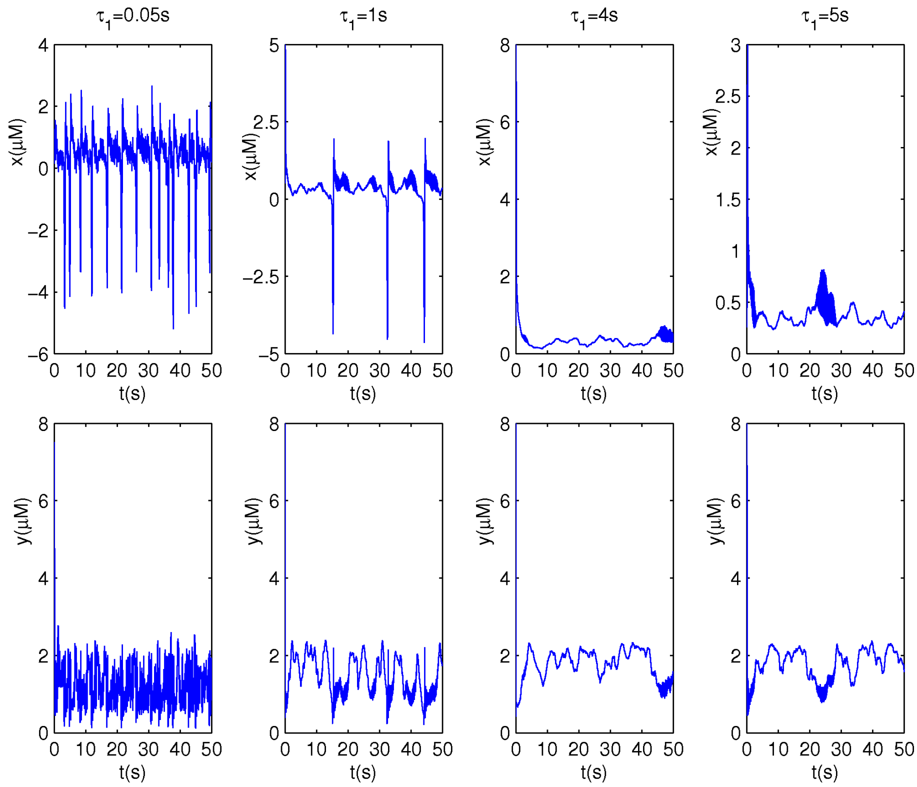

FIG. 2: The time series of Ca^{2+} concentrations in the cytosol x and in the calcium store y, variation with correlation time τ_1 of the colored noise $\epsilon(t)$. $\tau = 0.1$ s, $\tau_2 = 0.1$ s, the other parameters are the same as in Fig. 1.

proved by simulating the variation of the time series with a correlation time τ_2 of colored noise $\Gamma(t)$ (see Fig. 3). In the above Fig. 3(a), $\tau_1 = 0.1$ s, i.e., $\tau_1 < \tau_c$, the concentration of the cytosolic Ca^{2+} all appears to have a negative value regardless of τ_2 taking any value. In Fig. 3(b) below, $\tau_1 = 4$ s, i.e., τ_1 is up to the threshold value, a pronounced feature is that the concentrations of Ca^{2+} in the cell have all become positive.

From these figures, one sees clearly that the colored noises filter the negative calcium wave, so that the negative calcium wave disappears and all becomes positive, this phenomenon is similar to commutating in electricity.

IV. CONCLUSIONS

In this paper, we investigated the revised role of colored noises on the ICO system. Especially, it is shown clearly that the colored noises commutate a calcium wave, namely make all the intracellular Ca^{2+} concentrations turn to positive values. In this process, there is a threshold value of the correlation time of the colored noise $\epsilon(t)$, this value plays an

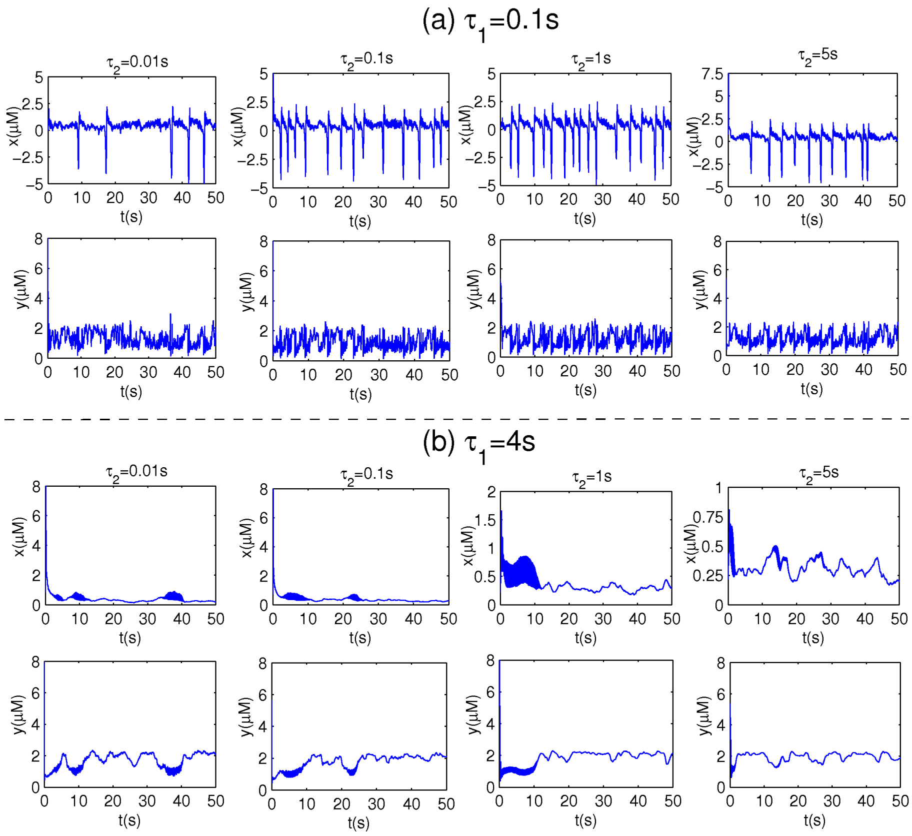

FIG. 3: The time series of the Ca^{2+} concentrations in the cytosol x and in the calcium store y, variation with correlation time τ_2 of the colored noise $\Gamma(t)$ for $\tau = 0.1$ s, (a) $\tau_1 = 0.1$ s and (b) $\tau_1 = 4$ s, the other parameters are the same as in Fig. 1.

important role in shifting the calcium wave from negative to positive, because the calcium wave will show a negative value if this colored noise's correlation time is less than the threshold value regardless of another noise's correlation time taking any value. Therefore, only by considering colored noises in the ICO could we explain reasonably the phenomenon of the ICO, because the concentration of the intracellular Ca^{2+} can only be a positive value.

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