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Modified Langevin approach for a stochastic calcium puff model

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Abstract. In many cell types, intracellular calcium is released from internal stores through calcium release channels. Because these channels are distributed in clusters with a few tens of channels, the clusters show a strongly stochastic open and close dynamics, resulting in noisy localized Ca^{2+} signals called puffs. Using the Li-Rinzel model we compare the stochastic channel simulations for the Markov method and three different Langevin approaches. We suggest that a modified Langevin approach should be considered in order to more accurately simulate Markov channel noise for puff dynamics.

1 Introduction

Calcium signaling is one of the most important and versatile signaling mechanisms in cell biology [1]. Ca^{2+} triggers life at fertilization and controls the development and differentiation of cells into specialized types. It mediates the subsequent activity of cells and is also involved in cell death. Calcium ions can be released from the endoplasmic reticulum (ER), an internal store in cells with high calcium concentration, through inositol 1,4,5-trisphosphate receptors (IP_3R) [2] or Ryanodine receptors (RyR) [3].

Recently, high-resolution fluorescence experiments suggested that the Ca^{2+} releasing IP_3R channels are spatially organized in clusters with only 20−50 channels and a size of about 400 nm [4,5]. The cluster distance is about 2 μm. Upon the binding of inositol 1,4,5-trisphosphate (IP_3) messengers and calcium ions, the IP_3R channels become open to release calcium from the ER into cytosolic space. Such localized Ca^{2+} releases are called puffs [4–6] or sparks [7] for release from a cluster of IP_3Rs or RyRs, respectively. Ca^{2+} blips arising from the opening of single release channels have been observed as well [4,8]. It has been shown that the clustered channels show a strongly stochastic open/close dynamics, resulting in noisy puffs with broad distributions of amplitude, lifetime and inter-puff interval [9].

Different stochastic methods have been employed to simulate the stochastic channel dynamics. A simple computer implementation of the stochastic process is based on a fixed small time step and from here on called Markov method [9,10]. A statistically exact method was proposed by Gillespie [11,12]. The drawback of these methods is that they become computationally very demanding as one wishes to describe an entire cell with thousands of release clusters or even networks of cells. Stochastic differential equations in the Langevin approach have been suggested where the gate variables are modulated by Gaussian noise [9,13]. Such a gate-kinetic Langevin approach (gate-LA) is easy to implement and computationally efficient. This line of Langevin approach was first discussed by Fox and Lu in the Hodgkin-Huxley neuron model [14,15], which is widely used as an approximation for stochastic channel dynamics [16–19].

With the Hodgkin-Huxley neuron model at small channel number it has been suggested that the gate-LA does not accurately replicate the stochastic response properties of the Markov models and should be modified to correctly reflect the channel noise [16,17,20]. For the calcium system with Li-Rinzel model [21], the comparison between the exact Markov method and the Langevin approach in the calcium system has also shown that the gate-LA does not accurately replicate the stochastic response properties of the Markov models at small channel number [9,22]. Moreover, there has been proposed another Langevin approach for stochastic Hodgkin-Huxley model based on the channel kinetic dynamics [14,17], which has seldom been discussed for neuronal models and never been applied to the calcium system. In the paper we introduce this channel-kinetic Langevin approach (channel-LA) for the Li-Rinzel model [21], and compare the moments of the noisy calcium signals obtained with the gate-LA, the channel-LA and the Markov method. We show that the Langevin approaches agree with the Markov model at large channel number.

In fact, Langevin approaches are obtained by expanding the master equation of the Markov model in terms of the inverse of the channel number and truncating the resulting infinite orders after the second term. Thus, the Langevin approaches cannot accurately replicate

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the properties of Markov model at small channel number, because the truncated noise terms are not negligible. These Langevin approaches then provide less accurate properties for puff dynamics where there are only a few tens of channels in the cluster [5,8]. Our goal here is to present an improved Langevin approach, which is valid for puff dynamics. We suggest a modified Langevin approach which can represent channel noise much better in the Li-Rinzel model for puff simulation. Such a modified Langevin approach will be helpful for the simulations of global calcium waves with puffs from many clusters by generating reasonable noise amplitudes with a fast computation method.

2 Li-Rinzel calcium model

One of the first kinetic models for the IP_3R was proposed by DeYoung and Keizer [23]. The Li-Rinzel IP_3R model [21] is a simplified DeYoung-Keizer model. According to the Li-Rinzel model, the IP_3R channel is modeled by three identical subunits that each have three binding sites: one for the IP_3 messenger (m-gate), one activating site (n-gate) for Ca^{2+} and one inactivating site (h-gate) for Ca^{2+}. In order for a subunit to be open, only the IP_3 and the activating Ca^{2+} binding sites need to be occupied. The IP_3R is conducting if three subunits are open. In the Li-Rinzel model, the gating variables m and n have been replaced by their quasi equilibrium values m_∞ and n_∞ due to their fast kinetics. Then the calcium signaling model is given by [21],

$$\begin{aligned} \frac{dC}{dt} &= J_C - J_P + J_L \\ \frac{dh}{dt} &= \alpha(1-h) - \beta h \end{aligned} \tag{1}$$

with

$$\begin{aligned} J_C &= c_1 v_C m_\infty^3 n_\infty^3 h^3 (C_{ER} - C) \\ J_P &= v_P \frac{C^2}{k^2 + C^2} \\ J_L &= v_L (C_{ER} - C). \end{aligned} \tag{2}$$

Here, C denotes the localized Ca^{2+} concentration released from a cluster of channels, C_{ER} the Ca^{2+} concentration in the ER, and h the slow inactivation variable. J_C denotes Ca^{2+} efflux from intracellular stores through clustered IP_3R channels, J_P the ATP-dependent Ca^{2+} flux from the intracellular space back to the stores, and J_L the leakage flux.

The slow unbinding and binding rates for Ca^{2+} inactivation are given by

$$\begin{aligned} \alpha &= a d_2 \frac{p + d_1}{p + d_3} \\ \beta &= aC \end{aligned} \tag{3}$$

in which p denotes the concentration of IP_3. The quasi-equilibrium states of m and n are

$$\begin{aligned} m_\infty &= \frac{p}{p + d_m} \\ n_\infty &= \frac{C}{C + d_n}. \end{aligned} \tag{4}$$

According to reference [21], the model parameters are $c_1 = 0.185$, $v_C = 6\ s^{-1}$, $v_L = 0.11\ s^{-1}$, $v_P = 0.9\ \mu M\ s^{-1}$, $k_3 = 0.1\ \mu M$, $d_1 = 0.13\ \mu M$, $d_2 = 1.049\ \mu M$, $d_3 = 0.9434\ \mu M$, $d_5 = 0.08234\ \mu M$, and $a_2 = 0.2\ \mu M^{-1}\ s^{-1}$. The total amount of Ca^{2+} is conserved via the Ca^{2+} concentration in ER with $C + c_1 C_{ER} = c_0$ with $c_0 = 2.0\ \mu M$.

3 Simulations of stochastic channel dynamics

In this paper the Li-Rinzel model is used to simulate calcium release from small clusters of IP_3Rs [9,13]. Assuming the clustered channels to be close enough, the Ca^{2+} concentration can be considered homogeneous throughout the cluster [24,25]. Thus we neglect spatial aspects of the formation and collapse of localized Ca^{2+} concentration in the cluster [26]. Supposing there are N channels in the cluster, we discuss the stochastic channel dynamics which can be simulated by the Markov method, gate-LA or channel-LA.

In a deterministic Li-Rinzel model, h^3 represents the fraction of un-inhibited IP_3Rs, i.e. $h^3 \equiv N_{uninhibition}/N$. Here the un-inhibited IP_3R is the channel with three inhibiting Ca^{2+}-binding sites all unbound and $N_{uninhibition}$ is the number of uninhibited channels in the cluster. Hence, the channel flux density can be written as

$$J_C = c_1 v_C m_\infty^3 n_\infty^3 \left(\frac{N_{uninhibition}}{N} \right) (C_{ER} - C). \tag{5}$$

An accurate method of stochastic channel dynamics is the two-state Markov method where the binding/unbinding state of each h-gate is calculated in detail with sufficiently small time step [9,13].

The gate-LA is a widely applied approach where the h-gate dynamics is simply modulated by a Gaussian noise [9,13]. There are two ways to consider the Gaussian noise for the three h-gates: one either simply assumes three identical h-gates or one assumes three independent h-gates. For the identical gate-LA, we have

$$J_C = c_1 v_C m_\infty^3 n_\infty^3 h^3 (C_{ER} - C) \tag{6}$$

and

$$\frac{dh}{dt} = \alpha(1-h) - \beta h + \frac{G}{\sqrt{N}} \zeta(t). \tag{7}$$

For the independent gate-LA, we have

$$J_C = c_1 v_C m_\infty^3 n_\infty^3 h_1 h_2 h_3 (C_{ER} - C) \tag{8}$$

and

$$\frac{dh_i}{dt} = \alpha(1-h_i) - \beta h_i + \frac{G}{\sqrt{N}} \zeta_i(t) \ (i = 1, 2, 3) \tag{9}$$

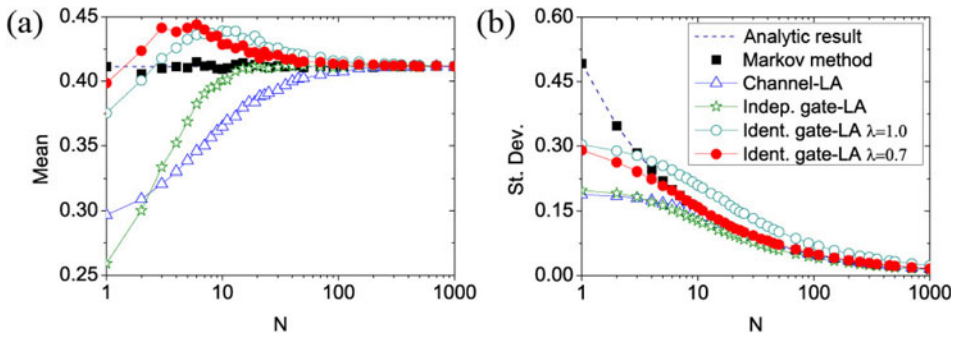

Fig. 1. (Color Online) The mean fraction (a) and the standard deviation (b) of uninhibited IP_3R as a function of channel number N at the equilibrium state with $C = 0.125$ μM and $p = 0.3$ μM, obtained with the analytic result (dashed lines), Markov method (squares), channel-LA (triangles), independent gate-LA at $\lambda = 1$ (open stars), identical gate-LA at $\lambda = 1$ (open circles) and modified identical gate-LA at $\lambda = 0.7$ (solid circles). Note that λ is introduced in equation (20). For the standard derviation such as in equation (7), $\lambda = 1$.

$$D = \begin{pmatrix} 3\alpha x_0 + \beta x_1 & -(3\alpha x_0 + \beta x_1) & 0 & 0 \\ -(3\alpha x_0 + \beta x_1) & 3\alpha x_0 + (\beta + 2\alpha)x_1 + 2\beta x_2 & -(2\alpha x_1 + 2\beta x_2) & 0 \\ 0 & -(2\alpha x_1 + 2\beta x_2) & 2\alpha x_1 + (\alpha + 2\beta)x_2 + 3\beta x_3 & -(\alpha x_2 + 3\beta x_3) \\ 0 & 0 & -(\alpha x_2 + 3\beta x_3) & \alpha x_2 + 3\beta x_3 \end{pmatrix} \quad (16)$$

where $\zeta(t)$ is uncorrelated Gaussian white noise with zero mean and unit variance. The term G is a time-dependent noise strength with

$$G^2(t) = \alpha(1 - h) + \beta h. \quad (10)$$

In the simulation, we use the simple Euler method to solve the equations, where the h-gate is given by [15]

$$h(t+\Delta t) = h(t)+\Delta t\,(\alpha(1 - h(t)) - \beta h(t))+\frac{G}{\sqrt{N}}\Delta\kappa \quad (11)$$

with

$$\Delta\kappa = \sqrt{-2\Delta t \lg(a)}\cos(2\pi b) \quad (12)$$

in which a and b are two white noises homogeneously distributed from 0 to 1.

Now we introduce the channel-LA. Consisting of three identical and independent subunits, the channel kinetics can be modeled as a 4-state Markov chain, where each state indicates the number of h-uninhibited subunits:

$$0 \underset{\beta}{\overset{3\alpha}{\rightleftarrows}} 1 \underset{2\beta}{\overset{2\alpha}{\rightleftarrows}} 2 \underset{3\beta}{\overset{\alpha}{\rightleftarrows}} 3.$$

We define x_i $(i = 0, 1, 2, 3)$ to be the proportion of IP_3Rs that have i h-uninibited subunits among the total channel number. Following Fox and Lu method [14] by applying a system-size expansion, one can derive a channel-LA for the master equation

$$\frac{dX}{dt} = AX + \frac{S}{\sqrt{N}}\xi(t) \quad (13)$$

with X being the vector of x_{i-s}

$$X = \begin{pmatrix} x_0 \\ x_1 \\ x_2 \\ x_3 \end{pmatrix}, \quad (14)$$

and the transition matrix A

$$A = \begin{pmatrix} -3\alpha & \beta & 0 & 0 \\ 3\alpha & -2\alpha - \beta & 2\beta & 0 \\ 0 & 2\alpha & -\alpha - 2\beta & 3\beta \\ 0 & 0 & \alpha & -3\beta \end{pmatrix}. \quad (15)$$

The matrix S is the matrix square root of the diffusion matrix D:

(*see equation (16) above*)

and $\xi(t)$ is a noise vector with each element an uncorrelated Gaussian white noise with zero mean and unit variance.

The entry x_3 is the probability of the uninhibited channels. In other words, we have

$$J_C = c_1 v_C m_\infty^3 n_\infty^3 x_3 (C_{ER} - C). \quad (17)$$

In the simulation we keep the boundary limitation of $0 \leqslant h, x_i \leqslant 1$ by simply putting h or $x_i = 0$ or 1 once they are out of the bound and calculate $x_0 = 1 - \sum_{i>0} x_i$ to ensure $\sum x_i = 1$.

4 Simulation results

First we consider the equilibrium state of the IP_3R at constant concentrations of calcium and IP_3 and compare the statistical results derived with different simulation methods. Figure 1a shows the mean fraction of uninhibited IP_3R as a function of channel number N at $C = 0.125$ μM and $p = 0.3$ μM. The standard deviation of the fraction is also given in Figure 1b. Assuming that all N channels are identical and independent statistically, the distribution of the total number of uninhibited channels at any given time is a binomial distribution

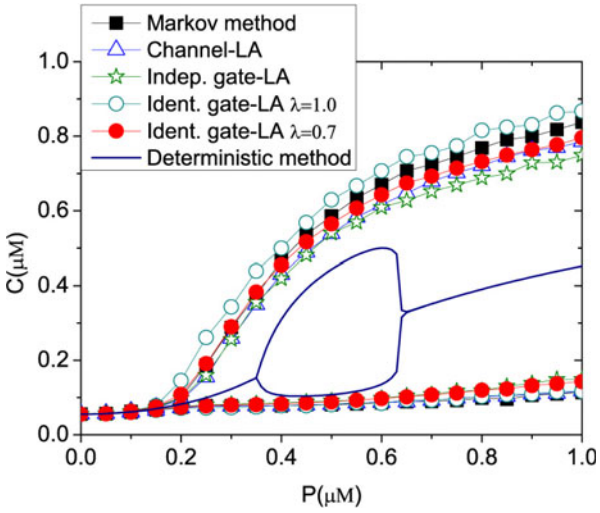

Fig. 2. (Color Online) The bifurcation diagrams of C as a function of p. The solid line is for deterministic model at infinite N. For a cluster of $N = 20$, the averaged maximal and minimal are plotted with Markov method (squares), channel-LA (triangles), independent gate-LA at $\lambda = 1$ (stars), identical gate-LA at $\lambda = 1$ (open circles) and modified identical gate-LA at $\lambda = 0.7$ (solid circles).

with the h-open probability $P_h = h_\infty^3$ as the bias value with $h_\infty = \alpha/(\alpha + \beta)$. Thus, the analytic solution of the mean is the bias value of h_∞^3 and the analytical standard deviation is $\sqrt{P_h(1-P_h)/N} = \sqrt{h_\infty^3(1-h_\infty^3)/N}$ [17], given by dashed lines in the figure. One can see that, the mean $\langle N_{uninhibition}/N\rangle$ obtained with the Markov method (squares) represents the deterministic result of h_∞^3 even at small channel number. While the identical gate-LA ($\langle h^3\rangle$ given by open circles), the independent gate-LA ($\langle h_1 h_2 h_3\rangle$ given by stars) and the channel-LA ($\langle x_3\rangle$ given by triangles) could not reproduce the result of Markov method at small N. The independent gate-LA gives smaller mean than the identical gate-LA at a few tens of N, suggesting that the identical gate approach causes additional noise beyond the Kramers-Moyal truncation for the independent gate approach at small N.

Next we would like to discuss the simulations for a dynamical situation where the calcium concentration changes with time. In Figure 2 we compare the bifurcation diagrams obtained with different methods. The solid line gives the values of C as a function of p with the deterministic Li-Rinzel model (limit of very large N). We also consider $N = 20$ in a cluster with stochastic channel dynamics. We calculate the maximal and minimal C during each time window of 10 s, and then plot the averaged maximal and minimal value in Figure 2 for the Markov method (squares), channel-LA (triangles), independent gate-LA (stars), and identical gate-LA (open circles). It can be seen that for a $N = 20$ cluster, the bifurcation diagram with the Markov method is quite different from the deterministic one. This is because the excitable behavior exists to the left and the right of the oscillatory region for the deterministic system. However, the three different stochastic methods give similar bifurcation diagrams.

We compare these different stochastic methods in detail. We calculate not only the mean $\langle C\rangle$ and the standard deviation D of calcium concentration, but also the third moment S, i.e. skewness, and the fourth moment K, i.e. kurtosis, which are defined as

$$S = \left\langle \left(\frac{C - \langle C\rangle}{D} \right)^3 \right\rangle \tag{18}$$

and

$$K = \left\langle \left(\frac{C - \langle C\rangle}{D} \right)^4 \right\rangle - 3. \tag{19}$$

These parameters as a function of channel number N at $p = 0.3$ and 0.5 μM are plotted in Figures 3 and 4, respectively. As shown in Figure 2, the deterministic system presents a fixed point at $p = 0.3$ μM and a periodic oscillation at $p = 0.5$ μM.

One can see that the identical gate-LA cannot give a reasonable approximation for the stochastic channel dynamics when $N < 1000$ at $p = 0.3$ μM, but the channel-LA and the independent gate-LA can give a valid approximation for the stochastic channel dynamics for $N > 200$ (Fig. 3). At $p = 0.5$ μM the three Langevin approaches cannot give a good approximation for the stochastic channel dynamics when $N < 100$ (Fig. 4).

The independent gate-LA and channel-LA give similar results of moments, indicating both approaches generate a noise of similar character. The mean values of calcium signals obtained with these two Langevin approaches are smaller than those obtained with the Markov method for small N (Figs. 3a and 4a). This is because these two Langevin approaches disregards the higher order noise terms in a $1/N$ expansion of the Markov master equation. In contrast, the identical gate-LA typically gives larger mean values of calcium signals than those obtained with the Markov method for small N (Figs. 3a and 4a), suggesting that the identical gate assumption causes additional noise and results in a larger total noise than the Markov channel noise.

This discussion indicates that these Langevin approaches cannot give accurate results for stochastic puff dynamics if there are not more a few tens of channels within the cluster, which are the reasonable number in biological puff cluster [5,8]. Considering the simplicity of the identical gate-LA, our goal in the paper is then to find a modified identical gate-LA which can give a better approximation for puff dynamics with a few tens of channels in the cluster.

Therefore we consider a modified identical gate-LA in which the strength of the Gaussian noise is rescaled:

$$\frac{dh}{dt} = \alpha(1-h) - \beta h + \lambda \frac{G}{\sqrt{N}} \zeta(t) \tag{20}$$

where λ is a rescaling parameter to modify the noise strength. In Figure 5 we show the mean and the deviation of calcium orbits as a function of parameter λ at

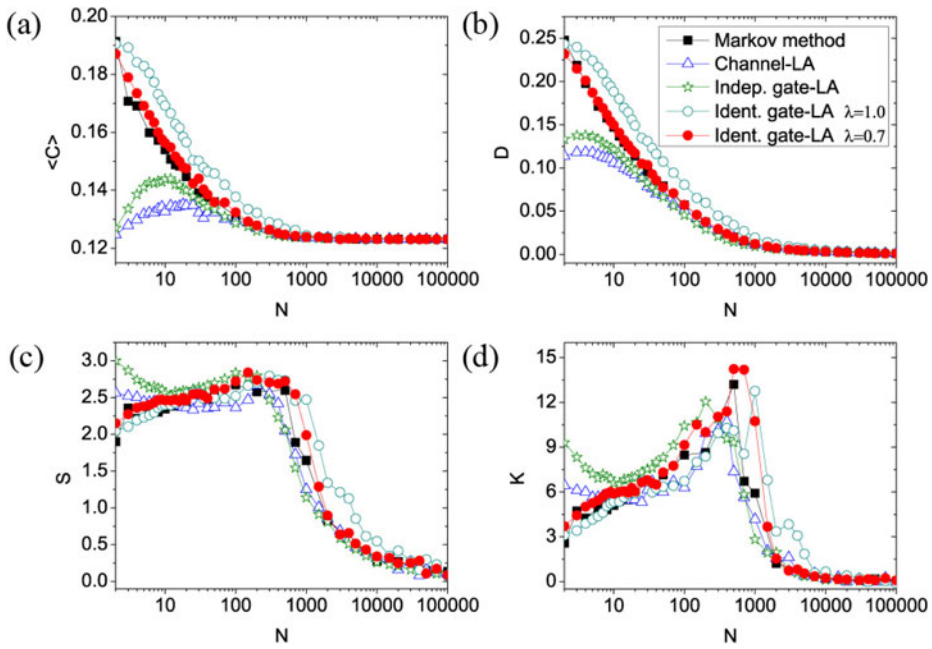

Fig. 3. (Color Online) The parameters of the mean (a), the standard deviation (b), the skewness (c) and kurtosis (d) as a function of N with Markov method (squares), channel-LA (triangles), independent gate-LA at $\lambda = 1$ (stars), identical gate-LA at $\lambda = 1$ (open circles) and modified identical gate-LA at $\lambda = 0.7$ (solid circles) at $p = 0.3$ μM.

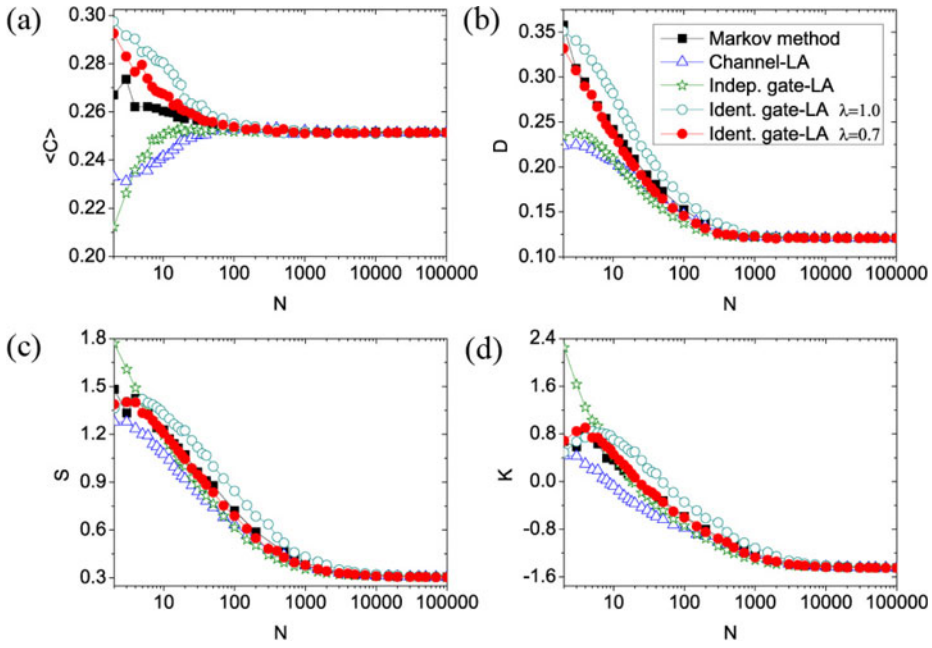

Fig. 4. (Color Online) The parameters of the mean (a), the standard deviation (b), the skewness (c) and kurtosis (d) as a function of N with Markov method (squares), channel-LA (triangles), independent gate-LA at $\lambda = 1$ (stars), identical gate-LA at $\lambda = 1$ (open circles) and modified identical gate-LA at $\lambda = 0.7$ (solid circles) at $p = 0.5$ μM.

$p = 0.3$ μM and $N = 20$, 50 and 100. For comparison, the corresponding values obtained with the Markov method are also plotted in the figure as dashed lines. At $N = 50$ and 100 the identical gate-LA with $\lambda = 0.7$ can give a similar mean as given by the Markov method, but at $N = 20$ the identical gate-LA with $\lambda = 0.6$ can give a similar mean value as given by the Markov method.

Figure 5b shows that the identical gate-LA with $\lambda = 0.7$ can give a similar deviation as given by the Markov method. Thus, we suggest to use $\lambda = 0.7$ in the modified identical gate-LA model. Our simulation shows that at values around $\lambda = 0.7$ the modified identical gate-LA approach can give good results for the mean fraction and the standard deviation of uninhibited IP_3R at $N > 30$

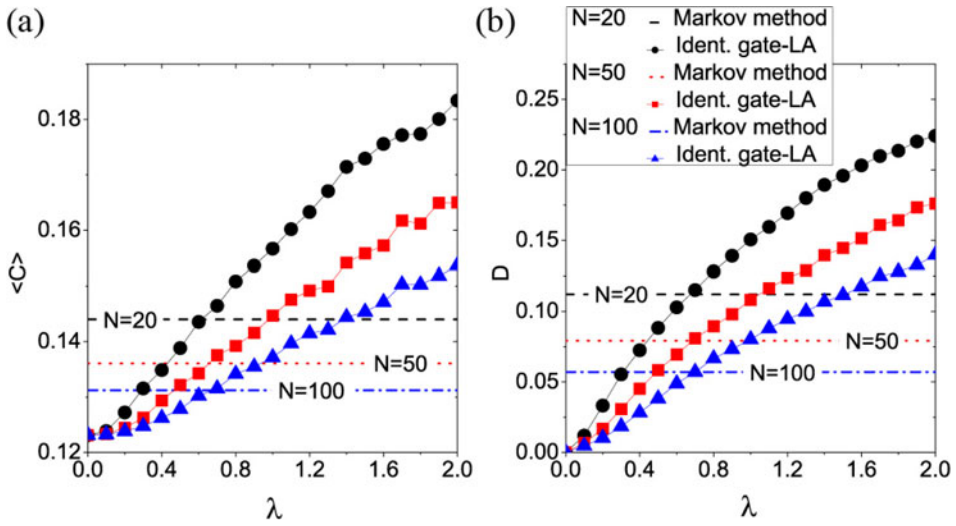

Fig. 5. (Color Online) The mean (a) and the standard deviation (b) of Ca^{2+} orbits obtained with the modified identical gate-LA as a function of λ at $p = 0.3$ μM and $N = 20$ (circles), 50 (squares) and 100 (triangles). The corresponding values obtained with the Markov method are given by dashed lines marked with channel numbers.

(solid circles in Fig. 1) at equilibrium state. The modified identical gate-LA can give a bifurcation diagram similar to that given by the Markov method (Fig. 2). Furthermore, Figures 3 and 4 indicate that not only the mean and the variance, but also the skewness and the kurtosis of the calcium orbits produced by the modified identical gate-LA are quite similar as those given with Markov method at $N > 10$.

A question is if the optimal parameter $\lambda = 0.7$, which is nearly a square root of 1/2, works for any gate-LA Li-Rinzel model. In order to answer this question we discuss the Li-Rinzel model with another set of model parameters given in reference [24]. Similarly, we show the mean and the deviation of calcium orbits as a function of parameter λ in Figure 6 at $p = 0.2$ μM and $N = 20$, 50 and 100. For comparison, the corresponding values obtained with the Markov method are plotted also in the figure as dashed lines. For this example $\lambda = 0.6$ is suggested. Thus the result indicates that the rescale parameter for Langevin noise is model-dependent.

5 Conclusions

In this paper we compare the stochastic Li-Rinzel model with a discrete representation to the identical gate-LA, the independent gate-LA and channel-LA. It is to our knowledge the first time that the channel-LA has been applied for calcium system. We show that the three Langevin approaches cannot accurately replicate the statistical properties of a discrete Li-Rinzel puff model in a cluster with a few tens of channels. This implies that the truncated noise terms of an $1/N$ expansion of the master equation in all the Langevin approaches becomes relevant at small N.

Our simulation results show that the mean values of calcium signals obtained with the independent gate-LA and channel-LA are smaller than those obtained with the Markov method for small cluster size. This is presumably because these two Langevin approaches neglects the noise terms represented by the higher order terms in the $1/N$ expansion due to the Kramers-Moyal truncation, which are large at small N. On the other hand, the identical gate-LA typically gives larger Ca^{2+} mean values than the independent gate-LA and channel-LA, suggesting that the identical gate assumption causes additional noise. With such the additional noise, the Ca^{2+} mean values obtained with identical gate-LA are even larger than those with the Markov method for small N. As a result, in order to approximate the Markovian channel noise, a rescale parameter $\lambda < 1$ has to be considered for identical gate-LA to reduce the Langevin noise.

With a Li-Rinzel model [21], the gating variables m and n of the IP_3R channel have been replaced by their quasi equilibrium values m_∞ and n_∞ due to their assumed fast kinetics and so the dimension of the master equation is only 4. The original model of the IP_3R was proposed by DeYoung and Keizer [23], where each subunit has eight states. Then for the DeYoung-Keizer channel model, the dimension of the master equation for channel-LA is 120. Thus it is computationally very demanding in order to solve the square root of matrix D with elements of 120×120 in equation (16).

Due to the simplicity of the identical gate-LA, we suggest a modified identical gate-LA which can well represent channel noise in Li-Rinzel model for $N > 10$. We show that, not only the parameters at equilibrium state but also the parameters at dynamic state of the Markov puff system can be reproduced better with the modified gate Langevin approach. Our results also suggest that the rescale parameters for Langevin noise is not universal but depends on the parameters of the Li-Rinzel model. Thus an empirical factor in the Langevin approach for puff dynamics has to be determined previously by comparing with the exact Markov solution. Such a modified

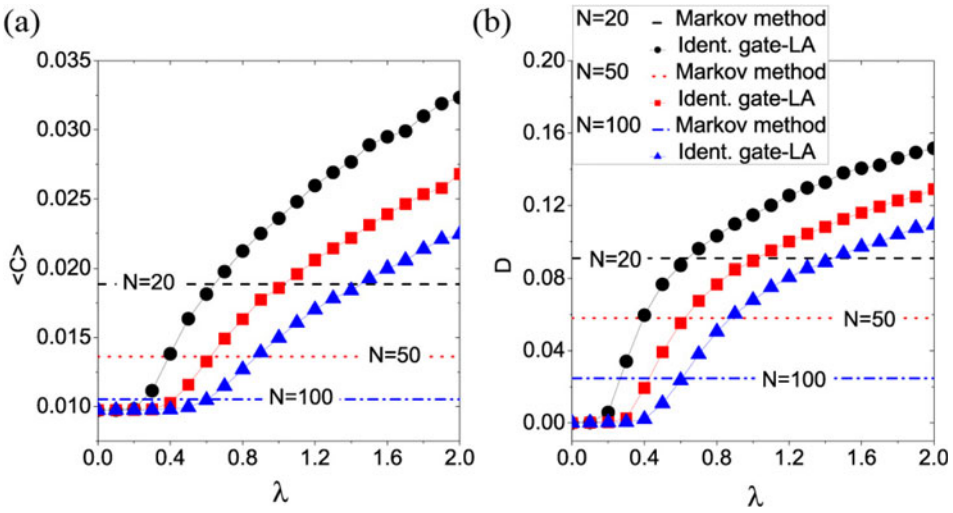

Fig. 6. (Color Online) The mean (a) and the standard deviation (b) of Ca^{2+} orbits obtained with the modified identical gate-LA as a function of λ with Li-Rinzel model given in reference [24] at $p = 0.2$ μM and $N = 20$ (circles), 50 (squares) and 100 (triangles). The corresponding values obtained with the Markov method are given by dashed lines marked with channel numbers.

Langevin approach will be helpful for the simulations of global calcium waves with puffs from many clusters by generating reasonable noise amplitudes with a fast computation method.

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