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Coarse-graining Calcium Dynamics on Stochastic Reaction-diffusion Lattice Model

Chuan-sheng Shen[a*], Han-shuang Chen[b]

a. Department of Physics, Anqing Normal University, Anqing 246011, China
b. School of Physics and Material Science, Anhui University, Hefei 230039, China

We develop a coarse grained (CG) approach for efficiently simulating calcium dynamics in the endoplasmic reticulum membrane based on a fine stochastic lattice gas model. By grouping neighboring microscopic sites together into CG cells and deriving CG reaction rates using local mean field approximation, we perform CG kinetic Monte Carlo (kMC) simulations and find the results of CG-kMC simulations are in excellent agreement with that of the microscopic ones. Strikingly, there is an appropriate range of coarse proportion m, corresponding to the minimal deviation of the phase transition point compared to the microscopic one. For fixed m, the critical point increases monotonously as the system size increases, especially, there exists scaling law between the deviations of the phase transition point and the system size. Moreover, the CG approach provides significantly faster Monte Carlo simulations which are easy to implement and are directly related to the microscopics, so that one can study the system size effects at the cost of reasonable computational time.

Key words: Calcium dynamics, Kinetic Monte Carlo simulation, Lattice model, Coarse-graining

I. INTRODUCTION

As a second messenger in living cells, calcium ions (Ca^{2+}) play a vital role in providing the intracellular signaling. Many important cellular processes and biological function, such as muscle contraction and synaptic transmission, are regulated by Ca^{2+} signals [1−4]. Ca^{2+} release is an inherently multi-scale problem, for instance, in cardiac myocytes, the majority of the control of calcium-induced-calcium-release (CICR) [5, 6] happens in the microdomain of the so-called diadic cleft, this microdomain is between the L-type voltage-gated Ca^{2+} channels and the ryanodine receptors. The ryanodine receptors sense local $[Ca^{2+}]$ in the diadic cleft positioned between the t-tubules and the sarcoplasmic reticulum. The length scale of aforementioned occurrences is on the order of nanometers and relevant time scales range from micro- to milliseconds [7]. However, each cell contains approximately 10,000 diadic spaces which act independently [8]. Typically, one is interested in Ca^{2+} currents at the whole cell level and higher. This is a multi-scale problem. Given the limits of computational power, hardly can we model an entire cellular cytoplasm by incorporating detailed structural information.

Some multi-scale models of CICR have been developed that successfully reproduced experimental observations, as well as save computation largely [7−9]. However, these models are based upon deterministic coupled ordinary differential equations derived from biophysical mechanisms [10], and lack accurate description of microscopic dynamics of calcium ion channels. In fact, fluctuations always exist in ion channels and play a crucial role in Ca^{2+} release mechanism [11, 12]. Recently, Vlachos and coworkers proposed a multiscale approach for coarse graining stochastic processes and associated Monte Carlo (MC) simulations in surface reaction systems [13−15]. The method is efficient in describing much larger length scales than conventional MC simulations while still incorporating microscopic details, and resulting in significant computational savings. An overview of the method is given in Ref.[16].

In the present work, the multiscale approach was applied to a relatively simple stochastic reaction-diffusion lattice model for calcium dynamics in the endoplasmic reticulum (ER) membrane, proposed by Guisoni et al. [17, 18]. We coarse grain the model and processes, and derive the coarse-grained (CG) surface diffusion transition probability rates. By numerical simulations, it is found that the results of CG kinetic MC (kMC) simulations are in excellent agreement with that of the microscopic ones corresponding to the optimal coarse proportion. Secondly, we study the system size effects by fixing the coarse proportion, and find the phase transition point increases monotonously as the system size increases. Especially, there exists a scaling law between

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*Author to whom correspondence should be addressed. E-mail: schuansheng@aqtc.edu.cn

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TABLE I The processes and transition probability rates for CG-kMC.

Process	Change of coarse variable			Coarse transition probability rate
	$\Delta\tilde{\eta}$	$\Delta\tilde{\sigma}_1$	$\Delta\tilde{\sigma}_2$	
Annihilation	-1	0	0	$\tilde{W}^1 = a(1-p)\tilde{\eta}$
Diffusion	$+1$	-1	0	$\tilde{W}^2 = pq^2(1-\eta)\sigma_1/2$
	-1	$+1$	0	$\tilde{W}^3 = p\tilde{\eta}(1-\sigma_1-\sigma_2)$
	$+1$	$+1$	-1	$\tilde{W}^4 = pq^2(1-\eta)\sigma_2/2$
	-1	-1	$+1$	$\tilde{W}^5 = p\tilde{\eta}\sigma_1$
Creation	$+1$	0	0	$\tilde{W}^6 = (1-p)(1-a)q^2(1-\eta)\sigma_1/2$

the deviations of the phase transition point and the system size. Finally, we investigate CPU time and find the approach provides significantly faster MC simulations which are easy to implement and are directly related to the microscopic one.

II. COARSE-GRAINING THE LATTICE MODEL

A. Microscopic model

We consider a two-dimensional square lattice with two interpenetrating sublattices A and B [17, 18] in ER membrane, as shown in Fig.1. Calcium channels are located only on the sites of the sublattice B and calcium ions occupy not only the sites of the sublattice A but also the sites of the sublattice B. A site i of the sublattice A can either be empty or occupied by at most one calcium ion, the sublattice B take the values 0, 1, or 2 corresponding to the closed, activating(open), and inhibiting state respectively.

The dynamics of calcium ions in the model exhibit three stages. In the first stage of spontaneous annihilation, if the site of the A sublattice is occupied then it becomes empty with probability $q=(1-p)a$, here p is related to the diffusion probability, a, related to the annihilation process. In the second stage of diffusion, one of the four nearest neighbor of site of the A sublattice, say site i of sublattice B, is chosen at random. A calcium ion then hops from a site of one sublattice to a site of the other sublattice with probability p. In the third stage of catalytic creation, one of the four nearest neighbor of site of the A sublattice, say site j of sublattice B, is chosen at random. If calcium channel j is open then a calcium ion is created at site i with probability $r=(1-p)(1-a)$.

B. Coarse-graining process

In the work, neighboring microscopic sites $q{\times}q$ are grouped together into a CG cell, one can obtain a CG-lattice model with coarse cells. Figure 1 shows an example of a coarse-graining lattice model with q=2 and
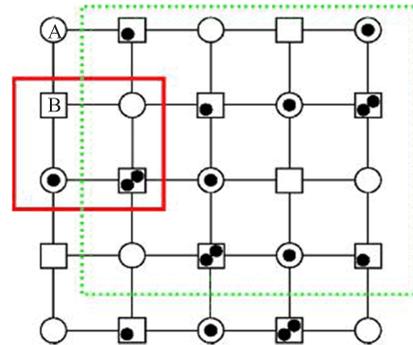

FIG. 1 Schematic illustration of coarse-graining lattice model. Circle sites denote sublattice A and square cites denote sublattice B. The solid symbols represent Ca^{2+}.

q=4, denoted by solid square and dotted square respectively, here, q is even because of two kind of sublattice A and B.

We define CG variables:

$$\tilde{\eta} = \sum_{i \in D_k} s_i \tag{1}$$

$$\tilde{\sigma}_1 = \sum_{j \in D_k} \delta(x_j - 1) \tag{2}$$

$$\tilde{\sigma}_2 = \sum_{j \in D_k} \delta(x_j - 2) \tag{3}$$

here, microscopic variable s_i and x_j denote the number of calcium ions at the A and B respectively, and satisfy the constraint $0<\tilde{\eta}<q^2/2$, $0<\tilde{\sigma}_1<q^2/2$, $0<\tilde{\sigma}_2<q^2/2$. Since each coarse cell contains q^2 microcells. Equivalently we may also consider the averaged version (termed below as coverage), $s=2\tilde{s}/q^2$, $(s=\eta, \sigma_1, \sigma_2)$. The dynamics of calcium ions on the CG model has also three processes: spontaneous annihilation, diffusion, and catalytic creation. Table I gives summary of processes and transition probability rates for CG-kMC.

III. RESULTS AND DISCUSSION

Given a microscopic initial condition at random, following the aforementioned rules Table I, the coarse-
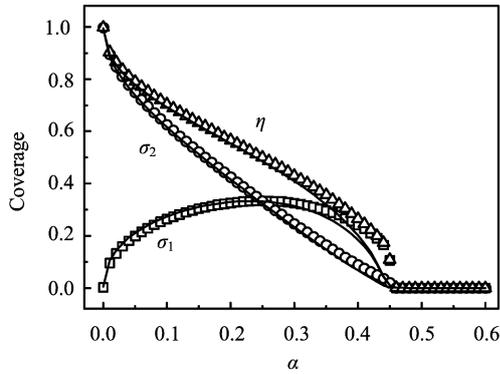
FIG. 2 CG-kMC simulation results for the coverage η, σ_1, σ_2 as a function of the parameter a for the case $p=0.5$ and $N\times N=200\times200$. The coverage vanishes at the critical point $a_c\approx0.47$. Lines indicate micro-simulations, symbols corresponds to CG ones with $q=40$.

grained calcium dynamics is computed with periodic boundary conditions. But it needs to make the computational demand of CG-kMC simulations per event the same as that of microscopic MC ones.

We perform CG-kMC simulations and microscopic simulations on a square lattice with $N\times N=200\times200$ sites, and plot the coverage η, σ_1, σ_2 as a function of the parameter a in Fig.2, where, σ_1 denotes the density of open channels on sublattice B, σ_2 denotes the density of inhibited channels on sublattice B, and η denotes calcium ions on sublattice A. Firstly we notice that the coverage predicted from the CG-kMC simulations is in reasonable agreement with that of the microscopic MC ones. Excitedly, the CG-kMC predicts the phase transition point is in good agreement with that of microscopic MC simulations. Indeed, small quantitative differences near the critical point also exist, probably due in part to the fluctuation, but still relatively small. These findings validate the CG approach works well in simulating calcium dynamics.

To detect the phase transition point accurately, we need to choose appropriate size $q\times q$ of coarse cell. But what a suitable q is? We define a coarse proportion m, $m=N/q$, namely, the square root of the number of coarse cells. Changing m we plot the deviation Δa_c of the phase transition points between CG-kMC and microscopic simulations for different system size $N\times N$, as shown in Fig.3. It can be seen that Δa_c begin to decrease and then increase with the increment of m, especially, the minimal Δa_c occurs near the same point $m=6$ for different $N\times N$. When $N\times N=720\times720$, there are two values of m corresponding to the minimal deviation, seeming to a small plain appears. Furthermore, the larger system size, the less deviation is. It is obvious that, there exists an appropriate range of m for coarse graining the system precisely. Therefore we can fix m and investigate the effects of system size on the phase transition point.

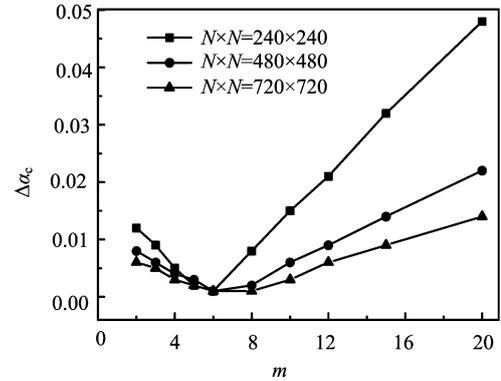For fixed $m=6$, we plot the critical point α_c as the

FIG. 3 The deviation $\Delta\alpha_c$ of the phase transition points between CG-kMC and microscopic simulations vs. the coarse proportion m for different system size $N\times N$.
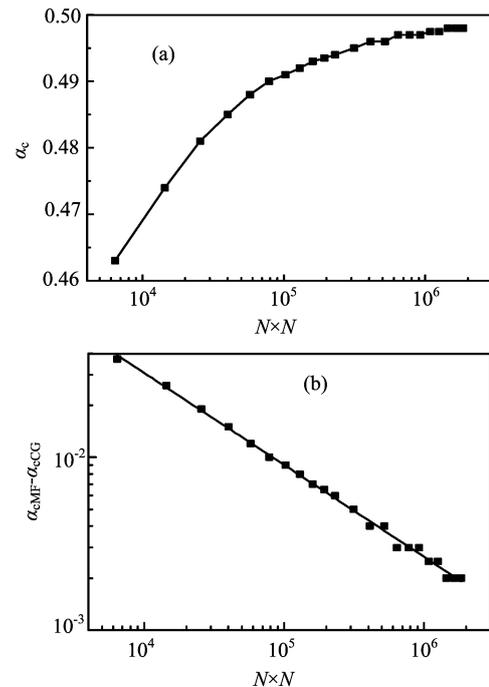

FIG. 4 (a) The dependence of the critical point a_c on the system size $N\times N$ for fixed $m\times m=6\times6$. (b) The scaling law of the deviations $\alpha_{cMF}-\alpha_{cCG}$ and $N\times N$, where α_{cMF} denotes the critical point of the MF model and α_{cCG} denotes the critical point of the CG model, the scaling exponent is -0.531.

function of system size $N\times N$ in Fig.4. Apparently, α_c increases monotonously as $N\times N$ increases, and approaches to 0.5. Theoretically speaking, this asymptotic value corresponds to the critical point of mean field (MF). Figure 4(b) gives the scaling relation of the deviations and the system size, the scaling exponent is -0.531. To elucidate its accuracy, we have also carried out coarse grained simulations with $m=8$ (not shown here), and obtained a similar asymptote and power law. Therefore, we can analyze the effects of the system size
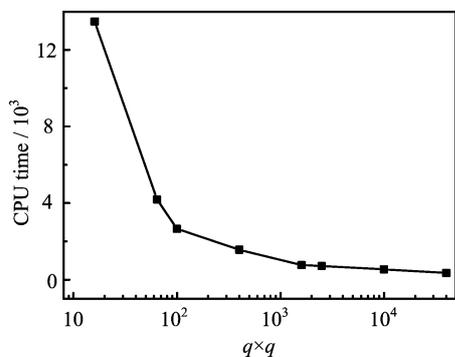
FIG. 5 CPU time for CG-kMC as a function of coarse cell size $q \times q$.

on the phase transition point according to the scaling law and detect the critical point accurately and rapidly.

Finally, we exhibit the significant computational savings resulting from coarse-graining, as shown in Fig.5. It can be seen that CPU time decreases monotonously as the size $q \times q$ of coarse cell increases. The larger size of coarse cell, the fewer CPU times. In this way, we can choose a bigger q to save computational time. In fact, the computer time in kMC simulation with global update, *i.e.*, searching the entire lattice to identify the chosen site, scales approximately as $O(N^2)$, but $O(m^2)$ in CG-kMC simulation. Accordingly, a q-fold reduction in the number of sites results in reduced computer time by a factor of $1/q^2$. Therefore, coarse-graining can render MC simulation for the large scales feasible.

IV. CONCLUSION

In this work, we propose an extensive CG model that can properly describe calcium dynamics on ER membrane. By a great deal of computer simulations, we demonstrate our model is highly effective because the results of CG-kMC simulations are in very good agreement with that of MC ones for a wide range of model parameters. Interestingly, it is shown that there exists an appropriate range of coarse proportion m, corresponding to the best estimation on the phase transition point compared to the microscopic counterpart, and such m is almost insensitive to the change of the system size. This make it possible to select an m without beforehand unwanted simulations for any real-world system size. Moreover, The CG-kMC method provides significant reduction in CPU while retaining very good accuracy in estimating the phase transition point. The larger the level of coarse-graining $q \times q$ is, the larger computational savings are, therefore we can obtain the phase transition point quickly. Using the CG model, we also found that the critical point increases monotonously as the system size increases. Especially, there exists a scal-

ing relation between the deviations of the phase transition point and the system size. A major advantage of the coarse model is that they have a direct connection to the microscopic dynamics and can provide valuable insights. Due to its reasonable accuracy and low computational requirements, we anticipate that the methods outlined in this work for simple systems will find widespread use in many realistic systems.

V. ACKNOWLEDGMENTS

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