Calcium dynamics on a stochastic reaction-diffusion lattice model

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We study a stochastic reaction-diffusion lattice model for describing the calcium dynamics in the endoplasmic reticulum (ER) membrane. Calcium channels and calcium ions are placed in two interpenetrating square lattices which are connected by calcium release and diffusion. Calcium ions are released from the ER through the channels and they can both remain in the membrane or spontaneously leave the membrane into the cytosol. The state of the channel is modulated by calcium ions: a channel can be open, closed, or inactive. The model is studied by numerical simulations and mean field theory and exhibits a phase transition from an active state to an absorbing state which is the result of the catalytic calcium release. The critical behavior of the model is in the directed percolation universality class.

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I. INTRODUCTION

Calcium ions (Ca^{2+}) play an important physiological role as second messenger for several cellular functions, ranging from muscle contraction to the activation of egg cells by fertilization [1–3]. In order to control this variety of functions Ca^{2+} needs to be precisely regulated in space and time. In fact, the nonlinear propagation of cytosolic free calcium are often used for signaling in cells, transmitting information over distances much longer than the diffusion process, and in more versatile ways [4].

The increase of intracellular calcium concentration occurs by the release from internal sources. Particularly, in cells that are not electrically excitable, calcium is stored in the endoplasmic reticulum (ER) and can be released through the calcium channels [2,3]. A calcium channel has a receptor with several binding sites. Experimental findings suggest that the opening of the channel occurs when the inositol 1,4,5-triphosphate (IP_3) and only one Ca^{2+} are bound to the receptor [5]. Calcium release is terminated by closure of calcium channels, when a calcium ion is bound to the other binding site. For this reason, the two binding sites for calcium are called activating and inhibiting sites. Therefore, low calcium levels in the cytosol favor channel opening while high levels close the channel, rendering a highly nonlinear behavior [3]. This autocatalytic amplification is called calcium-induced calcium release and it is present in a variety of channels [3,6]. Exceeding Ca^{2+} is removed from the cytosol to the ER by the action of the pumps [7]. An important aspect of the closing and the opening of the channel is its stochastic nature due to the random binding and unbinding of calcium ions into the activating and inhibiting sites [8]. Indeed, experimental observations of the release of a single channel or of a cluster of channels showed that a high degree of stochasticity is present [9].

There is much literature devoted to modeling calcium dynamics. The kinetic models present a different number of states for the channel receptor, depending on the rules for IP_3 and Ca^{2+} binding and on the number of subunits of a calcium channel. The kinetic deterministic models [3,10–13] consider a large population of channels and use partial differential equations in order to describe the calcium concentration and the channel states. Stochastic versions of the kinetic models have also been proposed [7,8,14–17]. In fact, in order to reproduce some important experimental aspects of calcium release (such as the statistics of puffs) it is mandatory to take into account the binding processes of Ca^{2+} and IP_3 as stochastic events [1,7,16].

Reaction-diffusion equations coupled to simplified models for calcium release have also been used in the analysis of calcium dynamics [18–22]. Other simplified stochastic models for calcium dynamics consider local coupling between the state of the channel and the calcium density in its neighborhood [6,23]. In any case IP_3 is considered explicitly. Several of these models are in the directed percolation universality class [6,19,20,23]. Based on these results some authors agree that intracellular calcium waves could be an experimental realization of the direct percolation [6,20,24], although there are examples contradicting this behavior [25]. In addition to that, some of these simplified models allow the study of calcium waves [6,18–21].

In this paper we propose a stochastic reaction-diffusion lattice model to study Ca^{2+} dynamics in the ER membrane. Calcium channels and calcium ions are considered in two interpenetrating sublattices which are connected via calcium release and by diffusion. Calcium ions remain in the membrane or spontaneously leave the membrane into the cytosol. The state of channel is modulated by calcium ions: a channel can be in one of three states, open, closed, or inactive, which depends on the calcium ions bound to the activating and inhibiting sites. In this way, we incorporated into the model, in a simplified way, the dependence of the calcium channel state on the density of calcium ions on its neighborhood. For simplicity IP_3 is not considered in our model.

The model is studied through mean field calculations and numerical simulations. We show that the fraction of open channels as a function of the density of calcium ions has a bell shape reflecting the experimental result [26] that at very low and very high calcium concentration all channels are closed. The present model exhibits an absorbing state in which all channels are closed and the lattice is depleted of

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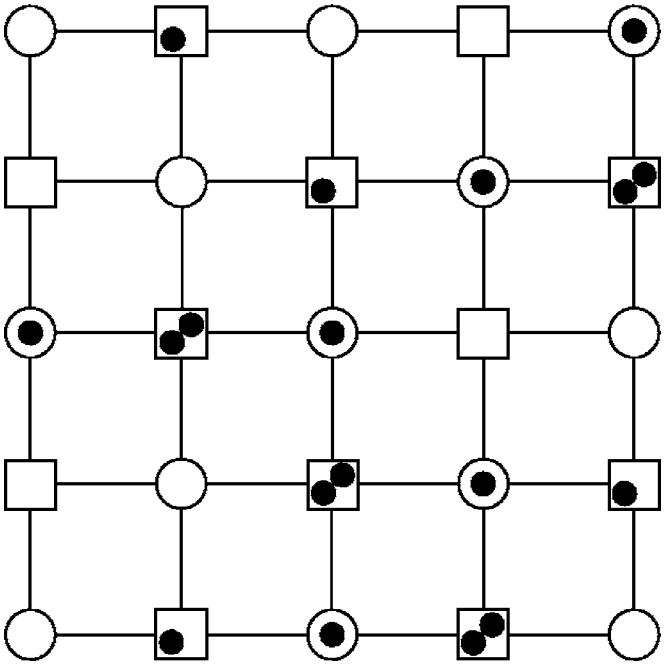

FIG. 1. Two-dimensional lattice representing the ER membrane. The channels are located at the sites of the sublattice B (squares). The calcium ions (full circles) can be either on the sites of the sublattice A (open circles) or on the sites of the sublattice B. A site of sublattice A can have at most one calcium ion whereas a site of B can have at most two calcium ions. Periodic boundary conditions are considered.

calcium ions. The phase transition to the absorbing state occurs when the rate of leaving the ER membrane into the cytosol is sufficiently high. The critical behavior of the model is in the directed percolation universality class [24,27,28].

II. MODEL

We consider a two-dimensional square lattice with two interpenetrating sublattices A and B, as shown in Fig. 1, which represent the ER membrane. 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. If we denote by η_i the number of calcium ions at site i, then $\eta_i=0$ or $\eta_i=1$ according to whether the site $i \in A$ is vacant or has one calcium ion, respectively. Let us define the variable σ_j as the number of calcium ions on the binding sites of a channel at a site $j \in B$. A calcium channel has two binding sites for calcium ions, corresponding to the activating and to the inhibiting sites, therefore the variable σ_i will take the values 0, 1, or 2. Since $IP_3$is not considered in our model, σ_i will also describe the three possible states of a channel. The channel is open only when a calcium ion is bound to the activating site and there is no calcium bound to the inhibiting site $\sigma_j=1$. The state $\sigma_j=2$ corresponds to the inhibited state, and the state $\sigma_j=0$ refers to the closed state. Note that we consider a sequential bind of calcium ions in the channel, as made before in other theoretical works [3,7].

The dynamics of calcium ions on the membrane occurs in three stages. In the first, ions are released from the ER through calcium channels and remain in the membrane. In our model this is represented by the process of catalytic creation of calcium ions on the sites of sublattice A. In the second, they leave the membrane into the cytosol. This is represented by a spontaneous annihilation of calcium ions presented on the sites of sublattice A. The ER then acts as a source and the cytosol as a sink of calcium ions. In the third stage diffusion of calcium ions between sublattices A and B is considered. Diffusion and calcium release connect the calcium ions on sublattice A and the calcium at the channels on sublattice B. Let us consider two independent parameters in order to implement the dynamic rules: p, related to the diffusion probability, and a, related to the annihilation process. In this way, the diffusion, annihilation, and creation, are assumed to occur with probabilities p, $q=(1-p)a$, and $r=(1-p)(1-a)$.

The three processes are described as follows. At each time step one site i of the A sublattice is chosen at random.

(a) *Spontaneous annihilation*. If the site i is occupied then it becomes empty with probability q. This process represents a calcium ion leaving the ER membrane into the cytosol. It is depicted as

η_i	$\rightarrow$	η_i'
1	$\rightarrow$	0,

where η_i and η_i' are the initial and final state, respectively.

(b) *Diffusion*. One of the four nearest neighbor of site i, say site j 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. If we denote the initial and final states of these two sites by η_i, σ_j, and η_i', σ_j' then the possible processes are

η_i	σ_j	$\rightarrow$	η_i'	σ_j'
0	1	$\rightarrow$	1	0
1	0	$\rightarrow$	0	1
0	2	$\rightarrow$	1	1
1	1	$\rightarrow$	0	2

For initial states 00 and 12, diffusion is not possible. Notice that diffusion occurs between a site of one sublattice and a site of the other sublattice.

(c) *Catalytic creation*. One of the four nearest neighbor of site i, say site j of sublattice B, is chosen at random. If calcium channel j is open ($\sigma_j=1$) then a calcium ion is created at site i with probability r. This process represents a calcium release from the ER and occurs only if the calcium channel is open. It is depicted as

η_i	σ_j	$\rightarrow$	η_i'	σ_j'
0	1	$\rightarrow$	1	1.

Note that this process (that represents a release of calcium) is

not a diffusion since the creation of a calcium ion on sublattice A does not change the channel state on sublattice B. The channel is open when there is one calcium ion bound in the activating site, and it depends on the diffusion between calcium ions at the membrane (sublattice A) and on the channel (sublattice B). Therefore the state of the channel depends on the calcium concentration on the neighborhood of the channel.

III. MASTER EQUATION

The evolution of the probability $P(\eta,\sigma,t)$ of a configuration

$$(\eta,\sigma) = (\eta_1, \eta_2, \ldots, \eta_N, \sigma_1, \sigma_2, \ldots, \sigma_N) \tag{1}$$

at time t is governed by the master equation

$$\begin{aligned}\frac{d}{dt}P(\eta,\sigma,t) = &\sum_{i\in A}\{w_i^a(\eta^i)P(\eta^i,\sigma,t) - w_i^a(\eta)P(\eta,\sigma,t)\} \\ &+ \sum_{i\in A}\sum_{j\in B}\{w_{ij}^d(\eta^i,\sigma^j)P(\eta^i,\sigma^j,t) \\ &- w_{ij}^d(\eta,\sigma)P(\eta,\sigma,t)\} + \sum_{i\in A}\sum_{j\in B}\{w_{ij}^c(\eta^i,\sigma) \\ &\times P(\eta^i,\sigma,t) - w_{ij}^c(\eta,\sigma)P(\eta,\sigma,t)\},\end{aligned} \tag{2}$$

where $w_i^a(\eta,\sigma)$, $w_{ij}^d(\eta,\sigma)$, and $w_{ij}^c(\eta,\sigma)$ are the annihilation, diffusion and creation transition rates, respectively. According to the rules defined above they are given by

$$w_i^a = q\,\eta_i, \tag{3}$$

$$w_{ij}^d = \frac{p}{4}\left[\eta_i(1-\sigma_j) + \frac{1}{2}\sigma_j(3-\sigma_j)\right], \tag{4}$$

$$w_{ij}^c = \frac{r}{4}(1-\eta_i)\sigma_j(2-\sigma_j). \tag{5}$$

Note that w_{ij}^d and w_{ij}^c are zero if the site i of sublattice A and the site j of sublattice B are not first nearest neighbors. The notation η^i stands for the configuration obtained from η by changing η_i to $1-\eta_i$ and (η^i,σ^j) stands for the configuration obtained from (η,σ) according to the diffusion rule, as defined in item b of Sec. II. That is, if $(\eta,\sigma)=(\eta_1,\ldots,\eta_i,\ldots,\eta_N,\sigma_1,\ldots,\sigma_j,\ldots,\sigma_N)$ then $(\eta^i,\sigma^j)=(\eta_1,\ldots,\eta_i',\ldots,\eta_N,\sigma_1,\ldots,\sigma_j',\ldots,\sigma_N)$ where η_i,σ_j and η_i',σ_j' are connected according to the rules in item b of Sec. II.

Let us denote by $P_A(\eta_i)$ the probability that the site $i\in A$ be in state η_i and by $P_B(\sigma_i)$ the probability that the site $j\in B$ be in state σ_j. From the master equation it is straightforward to obtain the following time evolution for these probabilities:

$$\begin{aligned}\frac{d}{dt}P_A(1) = &rP_{AB}(01) - qP_A(1) + p[P_{AB}(01) \\ &+ P_{AB}(02) - P_{AB}(10) - P_{AB}(11)],\end{aligned} \tag{6}$$

$$\frac{d}{dt}P_B(1) = p[P_{AB}(10) + P_{AB}(02) - P_{AB}(01) - P_{AB}(11)], \tag{7}$$

$$\frac{d}{dt}P_B(2) = p[P_{AB}(11) - P_{AB}(02)], \tag{8}$$

where $P_{AB}(\eta_i,\sigma_j)$ is the joint probability that sites $i\in A$ and $j\in b$ be in states η_i and σ_j, respectively.

We are interested in determining the stationary state. Particularly, we wish to determine the average number $\langle N_{B1}\rangle$ of channels with one calcium (open channels), the average number $\langle N_{B2}\rangle$ of channels with two calcium ions (inhibited channels), and the average number $\langle N_{A1}\rangle$ of calcium ions on sublattice A. From these quantities we may determine the density of open channels $\chi=\langle N_{B1}\rangle/N$, the density of calcium ions on the lattice $\rho=\langle(N_{B1}+2N_{B2}+N_{A1})\rangle/N$ and the flux of calcium ions per site $\phi=a\langle N_{A1}\rangle/N$. These quantities are related to the densities $x=P_B(1)$, $y=P_B(2)$, and $z=P_A(1)$ by $\rho=(x+2y+z)/2$, $\chi=x/2$, and $\phi=az/2$.

IV. MEAN FIELD APPROXIMATION

The simplest version of a truncation scheme consists in writing the probability of a cluster of sites as the product of the probability of each site so that $P_{AB}(\eta_i,\sigma_j)=P_A(\eta_i)P_B(\sigma_j)$. Using this approximation and the notation $P_A(1)=z$, $P_B(1)=x$, and $P_B(2)=y$, we get the following approximate equations:

$$\frac{dz}{dt} = r(1-z)x - qz + p[(1-z)(x+y) - z(1-y)], \tag{9}$$

$$\frac{dx}{dt} = p[z(1-x-y) + (1-z)y - x], \tag{10}$$

$$\frac{dy}{dt} = p[zx - (1-z)y]. \tag{11}$$

This set of equations admits a trivial stationary solution $x=0$, $y=0$, and $z=0$, and a nontrivial stationary solution, given by

$$x = \frac{a}{2(1-a)}(c-1), \tag{12}$$

$$y = \frac{a}{4(1-a)}(c-1)^2, \tag{13}$$

$$z = \frac{c-1}{c+1}, \tag{14}$$

where the auxiliary quantity c is given by

$$c = \sqrt{\frac{4}{a} - 7} \tag{15}$$

occurring when $a<a_c=1/2$. When $a>a_c$, the only solution is the trivial solution corresponding to the absorbing state.

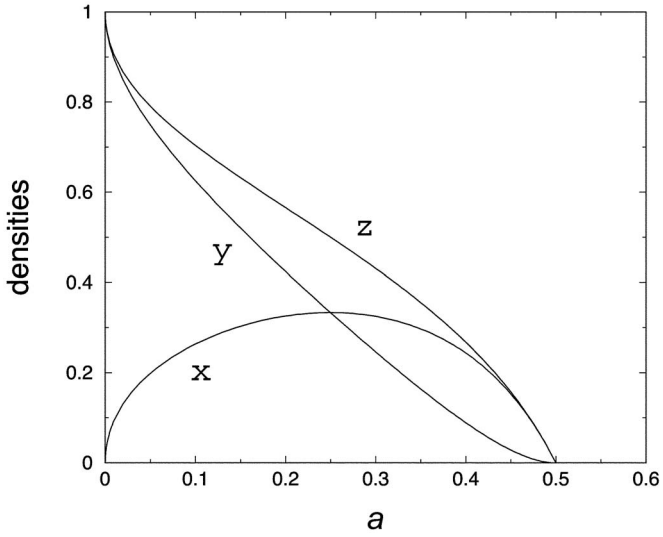

FIG. 2. Mean-field results for the densities x, y, and z as a function of the parameter a.

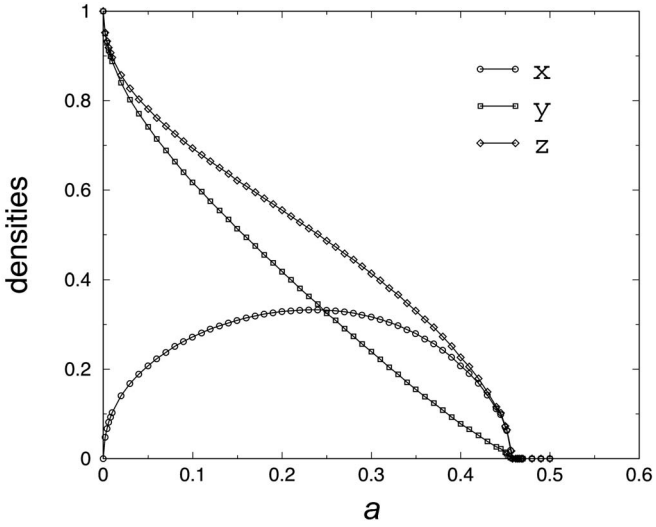

FIG. 3. Numerical simulation results for the densities x, y and z as a function of the parameter a for the case $p=0.5$. The densities vanish at the critical point $a_c=0.458$.

This state becomes unstable for $a<a_c$ making place to the nontrivial solution corresponding to the active state. The densities x, y, and z as a function of the parameter a is shown in Fig. 2. Note that the stationary behavior of the model in the mean field approximation [Eqs. (12)–(14)] does not depend on the parameter p. Around the critical point $a=a_c$ they behave as

$$x = 4(a_c - a), \tag{16}$$

$$y = 16(a_c - a)^2, \tag{17}$$

$$z = 4(a_c - a). \tag{18}$$

In this approximation, the critical exponent β associated to x and z equals 1. Note that the critical exponent associated with y is twice the critical exponent associated with x and z. The behavior of the densities when $a \to 0$ is given by

$$x = \sqrt{a}, \tag{19}$$

$$y = 1 - \sqrt{a}, \tag{20}$$

$$z = 1 - \sqrt{a}. \tag{21}$$

V. SIMULATION

We performed numerical simulations on a square lattice with $N=40\times 40$ sites with periodic boundary conditions. Each run started with an initial random configuration of calcium channels and calcium ions. The time evolution of the system follows the rules defined in Sec. II. That is, at each time step a site belonging to the A sublattice was chosen at random. A random variable ξ_1 uniformly distributed between 0 and 1 was generated. If $\xi_1 < p$ then an exchange of calcium ions between the two sublattices is attempted. Otherwise, another random variable ξ_2 was generated. If $\xi_2 < a$, the annihilation is performed. If $\xi_2 \geq a$, a calcium ion is created.

At each Monte Carlo step, we determined the number N_{B1} of channels with one calcium (open channels), the number N_{B2} of channels with two calcium ions (inhibited channels), and the number N_{A1} of calcium ions on sublattice A. The simulation results for the densities $x=\langle N_{B1}\rangle/N$, $y=\langle N_{B2}\rangle/N$, and $z=\langle N_{A1}\rangle/N$, as a function of the parameter a is shown in Fig. 3 for the case of $p=0.5$.

At this value of p, the model shows a transition from the active state to an absorbing state occurring at $a_c=0.458$. The critical parameter found in the mean field calculations ($a_c=1/2$) is greater, as expected. The simulations were performed for various values of the diffusion probability. Since the results do not change qualitatively as one varies p, we have shown results only for $p=0.5$.

Around the critical point, we expect that the densities behave as

$$x \sim (a_c - a)^{\beta}, \tag{22}$$

$$y \sim (a_c - a)^{2\beta}, \tag{23}$$

$$z \sim (a_c - a)^{\beta}, \tag{24}$$

where β is the exponent associated to the order parameter.

From the double-log plot of x and z versus the deviation $(a_c - a)$ from the critical value, as shown in Fig. 4, we obtained the value $\beta=0.58$ in agreement with $\beta=0.583(4)$ [28], the expected value for two-dimensional models in the directed percolation universality class. For the quantity y the exponent obtained was 1.15 in accordance with 2β. We remark that the mean-field calculations are in agreement with this result, namely, that the critical exponent associated with y is twice that associated with x and z.

The density x of open channels as a function of the density of calcium ions on sublattice A y can be seen in Fig. 5, for $p=0.5$. We see that it has a bell shape reflecting the

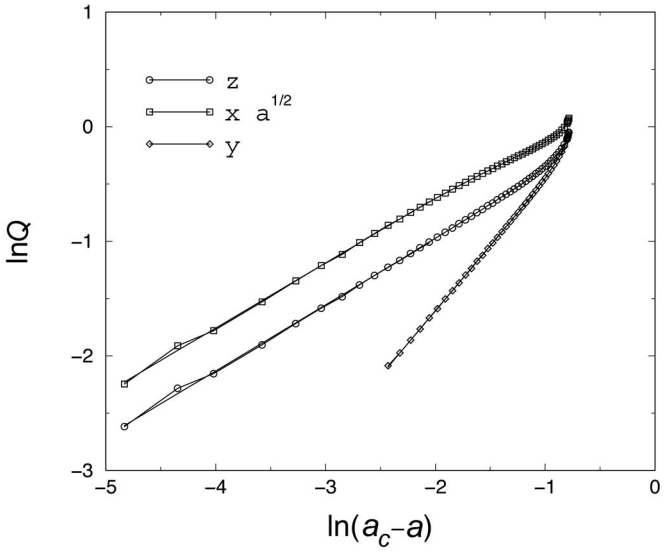

FIG. 4. Double-log plot of Q versus the deviation $a_c - a$ of the critical parameter, where the quantity Q can be z, $x\sqrt{a}$, or y. A linear fitting gives a slope 0.58 for the first two quantities and 1.15 for the third quantity.

experimental result [26] that at small and large calcium concentrations the number of open channels is very small. A relevant quantity related to the number of open channels is the flux ϕ of calcium ions through the ER membrane. In the stationary state the flux can be determined by the number of calcium ions leaving the ER membrane into the cytosol (or, in other words, the number of calcium ions that are annihilated) per unit time per site. This definition agrees with the expression $\phi = aP_A(1)/2 = az/2$, given before. In Fig. 6 we show the flux ϕ of calcium ions versus the density of calcium ions on sublattice A y, for $p=0.5$, and compare it with the mean field result. We see that the flux of calcium also decreases at small as well as at a large density of calcium.

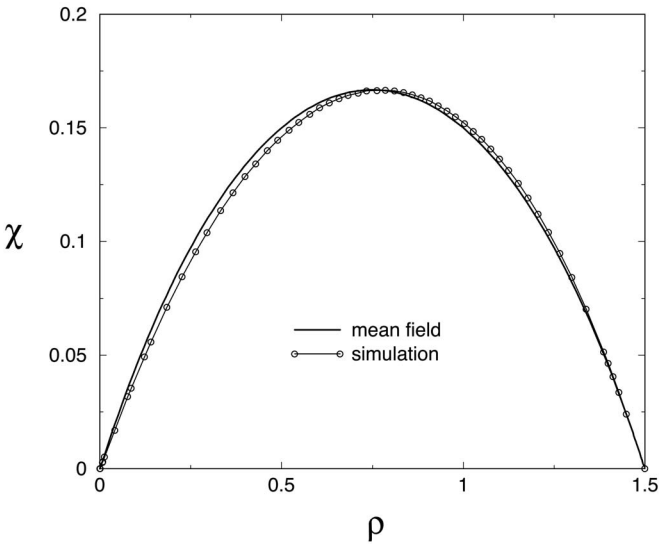

FIG. 5. Simulation results for the fraction of open channels χ as a function of calcium density ρ for $p=0.5$ obtained for a lattice size $N=40\times40$. For comparison we also show mean field calculations.

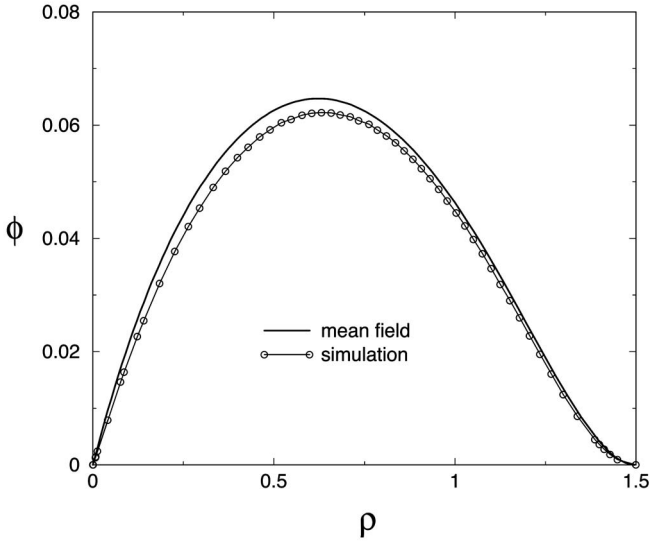

FIG. 6. The flux ϕ of calcium ions as a function of the density ρ from simulations for $p=0.5$ obtained for a lattice size $N=40\times40$. For comparison we also show mean field calculations.

VI. CONCLUSION

We have proposed a stochastic reaction-diffusion lattice model to study Ca^{2+} dynamics in the ER membrane. Calcium channels and calcium ions are placed in two interpenetrating square lattices which are connected via calcium release and by diffusion. Calcium ions are released from the ER through the channels and remain in the membrane or spontaneously leave the membrane into the cytosol. The state of the channel depends on the calcium concentration on its neighborhood. We have shown that the fraction of open channels as a function of the density of calcium ions has a bell shape (see Fig. 5) reflecting the experimental result that at very low and very high calcium concentration all channels are closed [26]. The present model exhibits an absorbing state in which all channels are closed and the lattice is depleted of calcium ions, whose critical behavior is in the directed percolation universality class [24,27,28].

Recently we have proposed a simplified stochastic model to study calcium release [23]. In that model two interpenetrating lattices were considered, one just for calcium ions, and other only for calcium channels. The density of calcium ions varies for two reasons: they could leave the membrane (spontaneous annihilation) or they could be released by the calcium channels. Particularly, we looked on the dependence of the critical behavior of the model as two functions (that describes the dependence on channel opening or closing) vary with the density of calcium ions on the neighborhood of the channel. We found that small variations on these functions strongly affected the critical behavior of the model. Consequently, for some choices of that functions, the fraction of open channels as a function of the density of calcium ions does not present a bell shape. In contrast, in the present model, where the dependence of the channel state on the density of calcium ions on its neighborhood is intrinsic to the model, the bell shape behavior is always observed. It is in-

teresting to note that both models are in the directed percolation universality class.

The behavior of the model is well described by mean field calculations. The simulation results do not change qualitatively as one varies the parameter p. This weak dependence on the diffusion is reflected on the mean-field calculations which show no dependence on that parameter [Eqs. (12)–(14). Both in mean field calculations as well as in simulations we found that the critical exponent associated with y is twice that associated with x and z.

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