Lattice model for calcium dynamics

Nara Guisoni* and Mario José de Oliveira
Instituto de Física, Universidade de São Paulo, C.P. 66318, Cep 05315-970, São Paulo, SP, Brazil
(Received 30 November 2004; published 22 June 2005)

We present a simplified lattice model to study calcium dynamics in the endoplasmic reticulum membrane. Calcium channels and calcium ions are placed in two interpenetrating square lattices which are connected in two ways: (*i*) via calcium release and (*ii*) because transitions between channel states are calcium dependent. The opening or closing of a channel is a stochastic process controlled by two functions which depend on the calcium density on the channel neighborhood. The model is studied through mean field calculations and simulations. We show that the critical behavior of the model changes drastically depending on the opening/closing functions. For certain choices of these functions, all channels are closed at very low and high calcium densities and the model presents one absorbing state.

DOI: 10.1103/PhysRevE.71.061910 PACS number(s): 87.16.−b, 05.70.Ln, 05.50.+q, 82.20.−w

I. INTRODUCTION

Calcium ions (Ca^{2+}) play an important physiological role in living cells, acting as a second messenger to regulate multiple cellular functions, such as muscle contraction and synaptic transmission [1]. Changes in the cytosolic free calcium concentration are often used for signaling. In *Xenopus laevis* oocytes (frog eggs), for instance, penetration of a sperm into the egg increases cytosolic calcium, inducing cortical contraction, cell division, and structural rearrangement [1–3].

In cells that are not electrically excitable, calcium is stored in the endoplasmic reticulum (ER) [3]. Part of the sequestered calcium can be released by binding of inositol 1,4,5-triphosphate (IP_3) to a receptor that controls the permeability of a calcium channel in the ER membrane [2,3]. Experimental findings suggest that the opening of the channel occurs when both IP_3 and Ca^{2+} are bound to the activating sites and at the same time Ca^{2+} is not bound to the inhibiting site. This means that low calcium levels in the cytosol favor channel opening while high levels close the channel or inhibit its opening, rendering a nonlinear process [3]. This autocatalytic amplification is called calcium-induced calcium release and is present in a variety of channels [3,4]. Calcium release is terminated by the closure of calcium channels, after which Ca^{2+} is removed from the cytosol by the action of the Ca^{2+} ATPases and pumps [5].

There is a vast literature devoted to modeling calcium dynamics. Deterministic models consider a large population of channels and can be based on partial differential equations [3,6–10]. In the kinetic models [3,6–9] a different number of states for the channel-receptor is possible, depending on the rules for IP_3 and Ca^{2+} binding and the number of subunits of a calcium channel. Since experimental results showed that calcium release exhibits a high degree of stochasticity [11], different stochastic versions of the kinetic models have been proposed. These models present fourteen [12], eight [13], four [5,13,14], or two [15] possible states for the channel-receptor. In fact, in order to reproduce some experimental aspects of calcium release it is mandatory to take into account the binding processes of Ca^{2+} and IP_3 as stochastic events [5,12]. Both deterministic and stochastic models can be classified as temporal and spatio-temporal. The temporal models [5–9,15] can reproduce calcium oscillations in time. On the other hand, a spatial distribution of channels must be considered in order to study calcium wave patterns [3,10,12–14].

Some works use a reaction-diffusion equation with a simplified model for calcium release [16–19]. Bär *et al.* [4] propose a simplified stochastic model for clusters of calcium channels. In any case IP_3 is considered explicitly. Despite the fact that these models do not provide information about kinetics of channels, they are useful, for example, to study propagation of calcium waves.

In this paper we propose a simplified lattice model to study Ca^{2+} dynamics in the ER membrane. Calcium channels and calcium ions are considered in two interpenetrating square lattices that are connected in two ways: (*i*) via calcium release and (*ii*) because transitions between channel states are calcium dependent. For simplicity IP_3 is not considered in our model and we use a two-state model for the channel: it can be open or closed. Changes in the channel state are stochastic processes controlled by two functions, for opening and closing, which depend on the calcium density on the channel neighborhood. The model is studied through mean-field calculations (master equation) and simulations. We show that the critical behavior of the model changes drastically depending on the opening/closing probability functions. For certain choices of these functions, all channels are closed at very low and high calcium densities, as shown by experimental results [20], and the model presents one absorbing state. The critical behavior of the model is in the directed percolation universality class [21].

II. MODEL

In our model, the ER membrane is represented by a two-dimensional lattice which contains the calcium channels and the calcium ions. The dynamics of calcium ions on the membrane is performed in two stages. In the first one, calcium

*Corresponding author. Electronic address: nara@if.usp.br

ions are released from the ER through calcium channels and remain on the membrane. In the second stage, they spontaneously leave the membrane into the cytosol. The ER acts as a reservoir source and the cytosol as a reservoir sink of calcium ions. For simplicity IP_3 is not considered in our model.

We consider a two-dimensional square lattice with two interpenetrating sublattices A and B, which represent the ER membrane. Calcium channels are located only on the sites of the sublattice B and calcium ions coming from the reservoir source occupy only the sites of the sublattice A. A site i of the sublattice A can either be empty ($\eta_i=0$) or occupied ($\eta_i=1$) by one calcium ion. A calcium channel on the site j of the sublattice B can either be closed ($\sigma_j=0$) or open ($\sigma_j=1$).

The dynamic rules connect the calcium ions on the sublattice A and the calcium channels on the sublattice B in two ways: (*i*) calcium release into a site i of the sublattice A depends on the number $\alpha_i=\Sigma_\delta \sigma_{i+\delta}$ of open channels in its neighborhood which is composed by the four nearest neighbor sites belonging to the sublattice B, and (*ii*) the probability functions for the opening/closing of a calcium channel j are assumed to depend on the number $\gamma_j=\Sigma_\delta \eta_{j+\delta}$ of calcium ions in the channel neighborhood which is composed by the four nearest neighbor sites belonging to the sublattice A.

At each time step the sublattice A is updated with probability p_a and so is the sublattice B with probability $1-p_a$:

(1) If one decides to update the sublattice A, then the following rules are used. One calcium site i is randomly chosen. If it is occupied, then it is vacated with probability p_b. If it is empty, then a calcium ion is created with the normalized probability $(1-p_b)\alpha_i/4$. The first process represents a calcium ion leaving the ER membrane into the cytosol and the second one represents the calcium release from the ER through a calcium channel. In our model these processes correspond to a spontaneous annihilation and catalytic creation of calcium ions, respectively.

(2) If the sublattice B is to be updated, the rules are as follows. One channel site j is randomly chosen. If it is open, then it is closed with probability $f_{cl}(\gamma_j)$. If it is closed, then it is opened with probability $f_{op}(\gamma_j)$. The probabilities $f_{cl}(\gamma_j)$ and $f_{op}(\gamma_j)$ are normalized functions of the number of calcium ions γ_j in the neighborhood of the channel site j, to be defined shortly.

If the sets of probabilities for the opening/closing of a calcium channel, $f_{op}(n)$ and $f_{cl}(n)$, are given, the stochastic process defined by the above rules involves two parameters, p_a, related to the update of the sublattice A or B, and p_b, related to spontaneous annihilation of calcium ions.

The autocatalytic amplification (calcium-induced calcium release) found in calcium channels is represented in our model by nonlinear functions for opening/closing probabilities of a calcium channel. These functions mimic the experimental fact that low calcium levels favor channel opening while high levels close the channel or inhibit its opening [3]. In particular we focus our attention on the three sets of probabilities shown in Table I. One of the simplest choices for the functions $f_{op}(n)$ and $f_{cl}(n)$ (named as set 3 on Table I) is

$$f_{op}(n) = \delta_{n,2},$$

TABLE I. Sets 1, 2, and 3 for the opening $f_{op}(n)$ and closing $f_{cl}(n)$ probabilities of a calcium channel.

Function	Set 1	Set 2	Set 3
$f_{op}(0)$	0.0	0.0	0.0
$f_{op}(1)$	0.5	0.5	0.0
$f_{op}(2)$	1.0	1.0	1.0
$f_{op}(3)$	0.3	0.3	0.0
$f_{op}(4)$	0.0	0.0	0.0
$f_{cl}(0)$	0.1	0.0	0.0
$f_{cl}(1)$	0.2	0.2	0.25
$f_{cl}(2)$	0.5	0.5	0.5
$f_{cl}(3)$	0.8	0.8	0.75
$f_{cl}(4)$	1.0	1.0	1.0

$$f_{cl}(n) = \frac{n}{4}. \tag{1}$$

III. MASTER EQUATION

The probability $P(\eta,\sigma,t)$ of a state $(\eta,\sigma)=(\eta_1,\eta_2,\ldots,\eta_N,\sigma_1,\sigma_2,\ldots,\sigma_N)$ at time t is governed by the master equation. Denoting by $w_i^{ca}(\eta,\sigma)$ the transition probability from η_i to $1-\eta_i$, and by $w_j^{ch}(\eta,\sigma)$ the transition probability of a channel from σ_j to $1-\sigma_j$, the master equation reads

$$\begin{aligned}\frac{d}{dt}P(\eta,\sigma;t) = &\sum_i [w_i^{ca}(\eta^i,\sigma)P(\eta^i,\sigma,t) - w_i^{ca}(\eta,\sigma)P(\eta,\sigma,t)] \\ &+ \sum_j [w_j^{ch}(\eta,\sigma^j)P(\eta,\sigma^j,t) \\ &- w_j^{ch}(\eta,\sigma)P(\eta,\sigma,t)],\end{aligned} \tag{2}$$

where (η^i,σ) and (η,σ^j) denote the states obtained from (η,σ) by changing η_i to $1-\eta_i$ and σ_j to $1-\sigma_j$, respectively. The first summation is performed over the sites of the sublattice A whereas the second is performed over the sites of the sublattice B. According to the local rules of the model, defined above, we have

$$w_i^{ca}(\eta,\sigma) = p_a\left[p_b\eta_i + \tfrac{1}{4}(1-p_b)\alpha_i(1-\eta_i)\right],$$

$$w_j^{ch}(\eta,\sigma) = (1-p_a)[f_{cl}(\gamma_j)\sigma_j + f_{op}(\gamma_j)(1-\sigma_j)]. \tag{3}$$

The average of a generic state function $F(\eta,\sigma)$ is defined by

$$\langle F(\eta,\sigma)\rangle = \sum_{\eta,\sigma} F(\eta,\sigma)P(\eta,\sigma;t). \tag{4}$$

From the master equation [Eq. (2)] and the transition probabilities [Eqs. (3)], its time evolution is given by

$$\frac{d}{dt}\langle F(\eta,\sigma)\rangle = \sum_i \langle [F(\eta^i,\sigma) - F(\sigma,\eta)] w_i^{ca}(\eta,\sigma)\rangle + \sum_j \langle [F(\eta,\sigma^j) - F(\eta,\sigma)] w_j^{ch}(\eta,\sigma)\rangle. \quad (5)$$

We are especially interested in the expressions for the time evolution of the density of calcium ions $\langle \eta_i \rangle$ and the density of open channels $\langle \sigma_j \rangle$, given, respectively, by

$$\frac{d}{dt}\langle \eta_i\rangle = \langle (1-2\eta_i) w_i^{ca}(\eta,\sigma)\rangle = p_a\left[\tfrac{1}{4}(1-p_b)\langle (1-\eta_i)\alpha_i\rangle - p_b\langle \eta_i\rangle\right],$$

$$\frac{d}{dt}\langle \sigma_j\rangle = \langle (1-2\sigma_j) w_j^{ch}(\eta,\sigma)\rangle = (1-p_a)[\langle (1-\sigma_j) f_{op}(\gamma_j)\rangle - \langle \sigma_j f_{cl}(\gamma_j)\rangle]. \quad (6)$$

IV. MEAN FIELD APPROXIMATION

In order to obtain approximative solutions for Eqs. (6) we use a truncation scheme. Its simplest version consists in writing the probability of a cluster of sites as the product of the probability of each site (e.g., $\langle \eta_i\alpha_i\rangle \sim \langle \eta_i\rangle\langle \alpha_i\rangle$). Using this approximation Eqs. (6) become

$$\frac{d}{dt}\rho_{ca} = p_a[(1-p_b)(1-\rho_{ca})\rho_{ch} - p_b\rho_{ca}],$$

$$\frac{d}{dt}\rho_{ch} = (1-p_a)[(1-\rho_{ch})\langle f_{op}(\gamma_j)\rangle - \rho_{ch}\langle f_{cl}(\gamma_j)\rangle], \quad (7)$$

where $\langle \eta_i\rangle = \rho_{ca}$, $\langle \sigma_j\rangle = \rho_{ch}$, and $\langle \alpha_i\rangle = 4\rho_{ch}$, since we are looking for homogeneous solutions.

In order to obtain expressions for $\langle f_{op}(\gamma_j)\rangle$ and $\langle f_{cl}(\gamma_j)\rangle$, we should remember that γ_j is the number of calcium ions in the channel neighborhood, and it can take values between 0 and 4, since the lattice has coordination four and each site of sublattice A can be empty or occupied by one calcium ion. Let us consider $P_j(\alpha_1,\alpha_2,\alpha_3,\alpha_4)$ as the probability of a particular cluster configuration of calcium ions in the channel j neighborhood. We can write

$$f_{op}(\gamma_j) = f_{op}(0)P_j(0,0,0,0) + 4f_{op}(1)P_j(1,0,0,0) + 6f_{op}(2)P_j(1,1,0,0) + 4f_{op}(3)P_j(1,1,1,0) + f_{op}(4)P_j(1,1,1,1),$$

where the degeneracy is correctly considered. Using the truncation scheme defined above we can write $\langle P_j(1,0,0,0)\rangle \sim \rho_{ca}(1-\rho_{ca})^3$ for homogeneous solutions, and we have

$$\langle f_{op,cl}(\gamma_j)\rangle = \sum_{n=0}^{4} f_{op,cl}(n)(1-\rho_{ca})^{4-n}(\rho_{ca})^n \binom{4}{n}. \quad (8)$$

To simplify the notation we define $\rho_{ca}=x$ and $\rho_{ch}=y$, so that Eqs. (7) are rewritten as

$$\frac{dx}{dt} = p_a[(1-p_b)(1-x)y - p_b x], \quad (9)$$

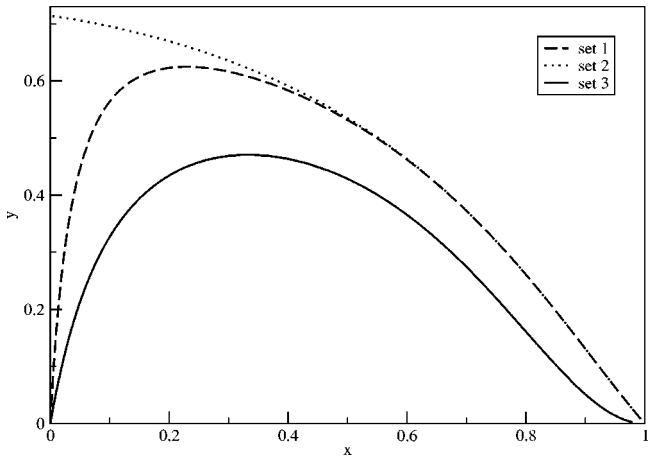

FIG. 1. The mean field results for the fraction of open channels y as a function of calcium density x. Sets 1, 2, and 3 are according to definition in Table I. Despite great similarities between sets 1 and 2, the absorbing state ($x=y=0$) exists just in the first case. For set 3 the absorbing state is also present.

$$\frac{dy}{dt} = (1-p_a)\{(1-y)[f_{op}(0)(1-x)^4 + 4f_{op}(1)x(1-x)^3 + 6f_{op}(2)x^2(1-x)^2 + 4f_{op}(3)x^3(1-x) + f_{op}(4)x^4] - y[f_{cl}(0)(1-x)^4 + 4f_{cl}(1)x(1-x)^3 + 6f_{cl}(2)x^2(1-x)^2 + 4f_{cl}(3)x^3(1-x) + f_{cl}(4)x^4]\}. \quad (10)$$

In the particular case in which the functions $f_{op}(n)$ and $f_{cl}(n)$ are given by set 3 [Eqs. (1)] the time evolution for x and y [Eqs. (9) and (10)] assume a simple form:

$$\frac{dx}{dt} = p_a[(1-p_b)(1-x)y - p_b x],$$

$$\frac{dy}{dt} = (1-p_a)[(1-y)6x^2(1-x)^2 - yx]. \quad (11)$$

In Fig. 1 we present the density of open channels y as a function of calcium density x obtained from numerical solution of Eqs. (9) and (10) in the stationary state. Note that the solutions do not depend on p_a, but only on p_b, which is an artifact of the simplest mean field approximation we used. One can observe that the probability functions for the opening/closing of a calcium channel changes drastically the critical behavior of the model. Despite great similarities between sets 1 and 2 [the only difference is $f_{cl}(0)$, see Table I], its behavior is completely different, since the absorbing state exists just in the first case. For set 3 the absorbing state is also present.

It is possible to find analytical expressions for the relation between the density of open channels y and the calcium density x in the regions of low and high calcium density ($x \to 0$ and $x \to 1$, respectively). This analysis for low calcium density allows us to establish the conditions that must be satisfied by the functions $f_{op}(n)$ and $f_{cl}(n)$ so that the absorbing state exists. Consequently, we understand why the absorbing state is present for sets 1 and 3 but not for set 2.

Furthermore, when the absorbing state is present, we obtain the critical exponent associated with the order parameter of the model. For convenience we define $r=p_b/(1-p_b)$.

Equations (9) and (10) have a fixed point $(x,y)=(0,0)$ just for $f_{op}(0)=0$. We are interested in the behavior of x and y near to this fixed point. From the stationary condition on Eq. (9) we obtain the relation $y=rx/(1-x)$, which can be approximated by $x=y/r$ when $x\to 0$. Using this approximation and the condition $f_{op}(0)=0$ in Eq. (10) we obtain the stationary condition for y near the fixed point:

$$y\left(\frac{4}{r}f_{op}(1)-f_{cl}(0)\right)+y^2\left(\frac{4}{r}[f_{cl}(0)-f_{op}(1)-f_{cl}(1)]+\frac{6}{r^2}[f_{op}(2)-2f_{op}(1)]\right)+O(y^3)+O(y^4)+O(y^5)=0, \tag{12}$$

whose first nonzero coefficient determines the critical parameter r_c. For sets 1 and 2 the linear coefficient of Eq. (12) is nonzero and

$$r_c=\frac{4f_{op}(1)}{f_{cl}(0)}, \tag{13}$$

therefore the absorbing state exists for set 1 ($r_c=20$, which corresponds to $p_b^c\simeq 0.95$) but does not exist for set 2, as we can see from Table I and Fig. 1. For set 3 we must consider the quadratic coefficient of Eq. (12), since the linear coefficient is zero, and the critical parameter is

$$r_c=\frac{3f_{op}(2)}{2f_{cl}(1)}. \tag{14}$$

Consequently the absorbing state is present for set 3, with $r_c=6$ and $p_b^c\simeq 0.857$ (see Table I and Fig. 1). As expected, the critical behavior of the model depends on the functions $f_{op}(n)$ and $f_{cl}(n)$ for small values of n.

Therefore, from the analytical results, we confirm that the absorbing state is present just for sets 1 and 3. For $r<r_c$ the trivial solution $(x,y)=(0,0)$, which corresponds to the absorbing state, is stable. At $r=r_c$ there is a phase transition since an active state with $x\neq 0$ and $y\neq 0$ takes place for $r>r_c$.

In the vicinity of the fixed point $(x\to 0)$ we have shown that $y=r_c x$ with r_c defined by Eq. (13) (set 1) or Eq. (14) (set 3). In the region of high calcium density, when $x\to 1$, from the stationary condition on Eq. (10), and considering $f_{op}(0)=0$ (a condition to exists the absorbing state) and $f_{op}(4)=0$ (which is filled by sets 1, 2, and 3), we can also find the relation between y and x. Therefore, when $x\to 1$, for sets 1 and 2 we have $y=4f_{op}(3)(1-x)/[xf_{cl}(4)]$, whereas for set 3 we obtain $y=6f_{op}(2)(1-x)^2/[x^2f_{cl}(4)]$ [22]. The asymptotic behaviors for $x\to 0$ and $x\to 1$ are confirmed by the numerical solution presented in Fig. 1.

In the critical region ($x\to 0$ and $y\to 0$) the relation between the density of open channels y and the order parameter r is given by Eq. (12). From this equation we can obtain the critical exponent of the model in the mean field approximation. Considering two nonzero terms of Eq. (12) for sets 1 and 3, we find that $y(r)=(r-r_c)^\beta/A$, with the critical exponent $\beta=1$, as expected. For set 1 $A=1+3f_{op}(2)/[2f_{op}(1)]-4[f_{op}(1)+f_{cl}(1)]/f_{cl}(0)$ and for set 3, $A=1-3[f_{op}(2)+f_{cl}(2)]/[2f_{cl}(1)]$.

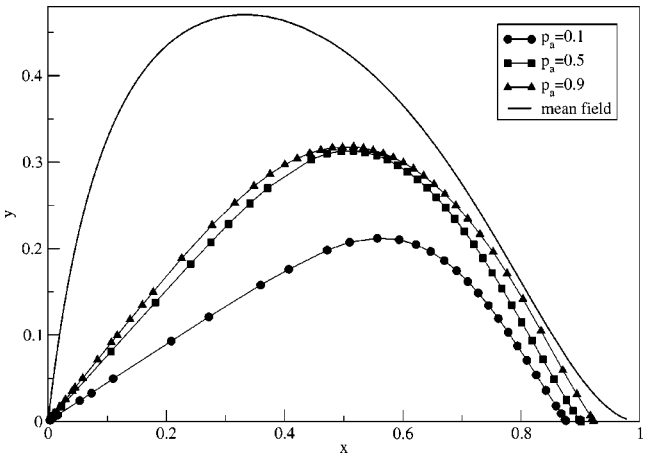

FIG. 2. The simulation results for the fraction of open channels y as a function of calcium density x using set 3 for $p_a=0.1$, $p_a=0.5$, and $p_a=0.9$ and lattice size $L=40$. Comparison with mean field solution.

V. SIMULATION

Numerical simulations were performed on two interpenetrating square lattices with periodic boundary conditions. All figures in this section correspond to simulations using set 3 for the opening and closing functions (see Table I). Each run started with an initial configuration of open channels and calcium ions placed randomly on the lattice.

The results of the simulation for the density of open channels as a function of the calcium density are presented in Fig. 2, for lattice size $L=40$ and $p_a=0.1$, 0.5, and 0.9. For comparison we also show the mean field behavior. The agreement between simulation and mean field results is better for high values of p_a. Note that in the simulation, high levels of calcium density with $x<1$ result in the closing of all channels, which is more evident for small values of p_a. As discussed before, in the mean field approximation, when $x\to 1$ we have $y=6(1-x)^2/x^2$, and all channels are closed just for $x=1$.

In Figs. 3(a) and 3(b) we compare simulation and mean field calculations. Figure 3(a) shows the density of open channels and calcium ions as a function of p_b and in Fig. 3(b) we can see the flux (Φ) as a function of p_b, in both cases for $p_a=0.5$ and $L=40$. In the simulation, the flux is defined as the number of created or annihilated particles while in mean field it is given by $\Phi=xp_bp_a$. We can see that the critical parameter from mean field calculations [$p_b^c=0.857$, from Eq. (14)] is greater than that obtained from simulation ($p_b^c=0.292$), as expected. There is a good agreement between simulation and mean field results in the region of small p_b.

In Fig. 4 we present the calcium density x as a function of p_b for several values of p_a. The critical parameter p_b^c (for each value of p_a) is obtained from a linear regression in the

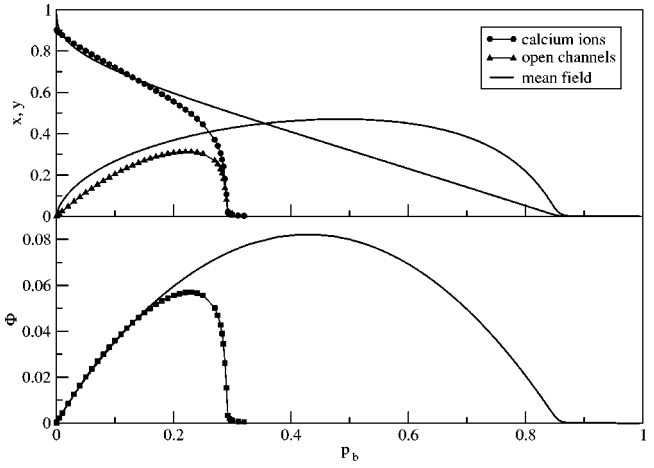

FIG. 3. The simulation results using set 3 for (a) the density of open channels y and of calcium ions x as a function of p_b for $p_a=0.5$ (lattice size $L=40$) and (b) the flux Φ as a function of p_b for $p_a=0.5$ (lattice sizes $L=40$). Comparison with mean field solution. We have $p_b^c \simeq 0.292$ for simulations and $p_b^c \simeq 0.857$ for mean field approximation.

region where density goes to zero ($x \to 0$). Results for p_b^c using calcium density or open channels density are exactly the same. The density of calcium ions x goes to zero continuously as p_b approaches p_b^c, as expected for the order parameter. The critical behavior of the order parameter follows $x \sim (p_b - p_b^c)^\beta$. We compute the critical exponent β fitting the data obtained by simulations and find that it is in agreement with $\beta=0.58$, the expected value for two-dimensional models in the directed percolation universality class [23].

Simulation results are summarized in the phase diagram of Fig. 5, which depends on two parameters, p_a and p_b. Different lattice sizes results are shown for $p_a=0.1$, 0.5, and 0.9. Note that p_b^c is a crescent with p_a just for $p_a \leqslant 0.8$, as can also be seen in Fig. 4. For comparison we show the mean field results, which depend only on p_b. For simulation results region A represents the active states, where the densities of open channels and of calcium ions present a constant mean

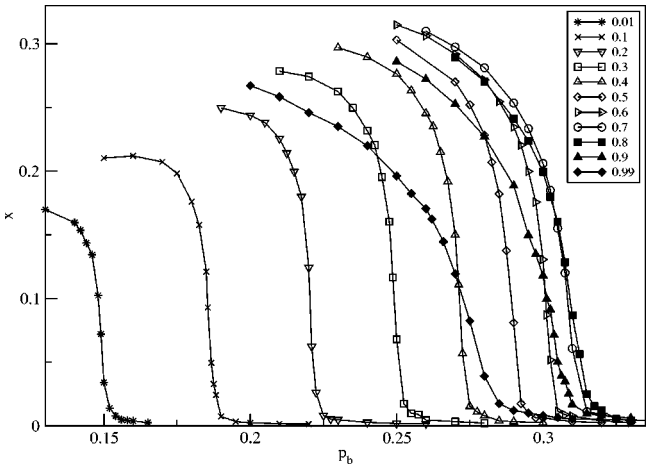

FIG. 4. The simulation results using set 3 for calcium density x as a function of p_b for several values of p_a (indicated in the figure). Lattice size $L=40$.

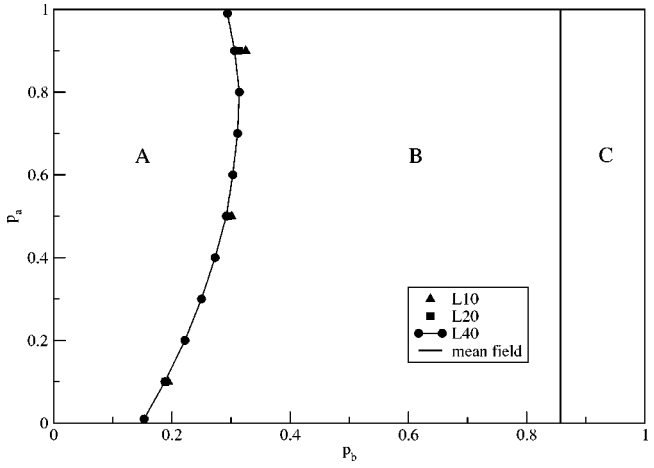

FIG. 5. The phase diagram for set 3 on the p_b-p_a plane, obtained from simulations for lattice sizes $L=10,20,40$ and mean field results. For simulations results region A represents the active states and regions B and C represent the absorbing states ($x=y=0$). For mean field results the active states are represented by regions A and B and the absorbing states are represented by region C.

value, and regions B and C represent the absorbing states ($x=y=0$). For mean field results the active states are represented by regions A and B and the absorbing states is represented by region C.

VI. DISCUSSION AND CONCLUSION

We propose a simplified 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 in two ways: (*i*) via calcium release and (*ii*) because transitions between channel states are calcium dependent. Changes in the channel state are stochastic processes controlled by two functions, for opening and closing, which depend on the calcium density in the channel neighborhood.

We found that the model can present one absorbing state depending on the choice of the opening/closing functions. As expected from Janssen-Grassberger conjecture [21] the phase transition between the active and the absorbing states in our model is in the direct percolation universality class. In fact, the critical exponent related with the order parameter in our model is in agreement with $\beta=0.58$, the expected value for a two-dimensional model [23]. Other simplified models [4,17,18] introduced for calcium wave propagation modeling are also in the directed percolation universality class. However, different from our model, these works were developed in one dimension [4,17] and just recently Timofeeva and Coombes [18] have showed that a two-dimensional model for calcium dynamics is in the direct percolation universality class. Particularly, in the model presented by Bär *et al.* [4], clusters of calcium channels are placed in a one-dimensional lattice with a fixed intercluster distance. The clusters are composed of several subunits, which can be open or closed. The amount of calcium released depends on the number of

open subunits in the cluster. Similarly to our model, changes between subunits states depend on the local calcium density. The model presents a nonequilibrium phase transition between propagating and abortive waves. Measurements of the critical exponent associated with this transition (the survival probability) show that it belongs to the directed percolation universality class. An important difference between our model and the one proposed by Bär *et al.* [4] is that they are focusing on wave propagation, differently from us, since we study only homogeneous solutions. In fact, our model is also capable of giving nonhomogeneous solutions which can be related to wave propagation. This will be a topic of future investigation. Thereby our result agrees with the possibility that intracellular calcium dynamics could be an experimental realization of the direct percolation process, as suggested by Bär *et al.* [4]. However, the measurement of the critical exponent in living cells could not be possible, as pointed out by Hinrichsen [24].

The critical behavior of the model is strongly affected by changes in the probabilities for the opening/closing of a calcium channel, as we can see in Fig. 1. For sets 1 and 3 the model presents one absorbing state, while for set 2 it does not exist. Note that the only difference between sets 1 and 2 is $f_{cl}(0)$, equal to 0.1 in the first case and 0 in the second one (see Table I). This result can be understood in the mean field approximation, since we establish the conditions that must be satisfied by the functions $f_{op}(n)$ and $f_{cl}(n)$ in order for the absorbing state to exist. As expected, the critical behavior of the model depends on the functions $f_{op}(n)$ and $f_{cl}(n)$ for low values of n.

Experimental results for cerebellar cells [20] show that the fraction of open channels as a function of the logarithm of calcium concentration corresponds to a bell-shaped curve. Despite the simplicity of our model, when the absorbing state exists, there is a qualitative agreement with this experimental result, since at very low and high calcium densities all channels are closed (Figs. 1 and 2).

ACKNOWLEDGMENTS

We would like to thank L. Diambra for helpful suggestions and discussions and M. Sabag for a careful reading of the manuscript. N.G. acknowledges financial support from the Brazilian Science Agency Fapesp (03/00831-8).

[1] M. Falcke, New J. Phys. **5**, 96 (2003).
[2] M. J. Berridge, M. D. Bootman, and P. Lipp, Nature (London) **395**, 645 (1998).
[3] H. G. Othmer and H. Tang, in *Experimental and Theoretical Advances in Biological Pattern Formation*, edited by H. G. Othmer, P. K. Maini, and J. D. Murray (Plenum Press, London, 1993).
[4] M. Bar, M. Falcke, H. Levine, and L. S. Tsimring, Phys. Rev. Lett. **84**, 5664 (2000).
[5] L. Diambra and N. Guisoni, Cell Calcium **37**, 321 (2005).
[6] G. W. De Young and J. Keizer, Proc. Natl. Acad. Sci. U.S.A. **89**, 9895 (1992).
[7] Y. Tang, J. L. Stephenson, and H. G. Othmer, Biophys. J. **70**, 246 (1996).
[8] Y. Li and J. Rinzel, J. Theor. Biol. **166**, 461 (1994).
[9] I. Bezprozvanny and B. Ehrlich, J. Gen. Physiol. **499**, 307 (1994).
[10] G. Dupont and A. Goldbeter, Biophys. J. **67**, 2191 (1994).
[11] M. Bootman, E. Niggli, M. Berridge, and P. Lipp, J. Physiol. (London) **499**, 307 (1997).
[12] S. Swillens, G. Dupont, L. Combettes, and P. Champeil, Proc. Natl. Acad. Sci. U.S.A. **96**, 13750 (1999).
[13] M. Falcke, L. S. Tsimring, and H. Levine, Phys. Rev. E **62**, 2636 (2000).
[14] M. Falcke, Biophys. J. **84**, 42 (2003).
[15] J. W. Shuai and P. Jung, Biophys. J. **83**, 87 (2002).
[16] J. Keizer, G. S. Smith, S. Ponce-Dawson, and J. E. Pearson, Biophys. J. **75**, 595 (1998).
[17] S. Coombes and Y. Timofeeva, Phys. Rev. E **68**, 021915 (2003).
[18] Y. Timofeeva and S. Coombes, Phys. Rev. E **70**, 062901 (2004).
[19] K. Wang, W. Rappel, and H. Levine, Phys. Biol. **1**, 27 (2004).
[20] I. Bezprozvanny, J. Watras, and B. Ehrlich, Nature (London) **351**, 751 (1991).
[21] H. K. Janssen, Z. Phys. B: Condens. Matter **42**, 151 (1981); P. Grassberger, *ibid.* **47**, 365 (1982).
[22] The expression $y=4f_{op}(3)(1-x)/[xf_{cl}(4)]$ obtained for sets 1 and 2 is not valid for set 3, since $f_{op}(3)=0$ (see Table I), and different terms in Eq. (10) must be considered. In order to obtain $y=6f_{op}(2)(1-x)^2/[x^2f_{cl}(4)]$ for set 3 one can also work with Eqs. (11) instead of Eq. (10).
[23] J. Marro and R. Dickamn, *Nonequilibrium Phase Transitions in Lattice Models* (Cambridge University Press, Cambridge, England, 1999).
[24] H. Hinrichsen, Braz. J. Phys. **30**, 69 (2000); H. Hinrichsen, Adv. Phys. **49**, 815 (2000).