

Discrete Stochastic Modeling of Calcium Channel Dynamics

Markus Bär,¹ Martin Falcke,^{2,3,*} Herbert Levine,² and Lev S. Tsimring⁴

¹Max-Planck Institut für Physik komplexer Systeme, Dresden 01187, Germany

²Department of Physics, University of California at San Diego, La Jolla, California 92093-0319

³Department of Molecular Medicine, Institute of Biotechnology, University of Texas Health Science Center at San Antonio, 15355 Lambda Drive, San Antonio, Texas 78245-3207

⁴Institute for Nonlinear Science, University of California at San Diego, La Jolla, California 92093-0402

(Received 5 October 1999)

We propose a discrete stochastic model for calcium dynamics in living cells. A set of probabilities for the opening/closing of calcium channels is assumed to depend on the calcium concentration. We study this model in one dimension, analytically in the limit of a large number of channels per site N , and numerically for small N . As the number of channels per site is increased, the transition from a non-propagating region of activity to a propagating one changes from one described by directed percolation to that of deterministic depinning in a spatially discrete system. Also, for a small number of channels a propagating calcium wave can leave behind a novel fluctuation-driven state.

PACS numbers: 87.16.Xa, 05.40.-a, 82.20.Mj

It has become clear that the intracellular nonlinear dynamics of calcium plays a crucial role in many biological processes [1]. The nonlinearity of this problem is due to the fact that there exist calcium stores inside the cell which can be released via the opening of channels which themselves have calcium-dependent kinetics. Typically, these processes are modeled using a set of coupled equations for the calcium concentration (the diffusion equation with sources and sinks) and for the relevant channels; the latter is often described by a rate equation for the fraction of open channels per unit of area. More elaborate models take into account the discrete nature of these channels, their spatial clustering, and fluctuations in the process of their opening and closing [2,3].

In this paper, we will propose and analyze a set of models which operate just with the channel dynamics alone. The justification for this is that the calcium field equilibrates quickly, with a diffusion time of perhaps 0.1 s, as compared to the channel transition times, perhaps on the order of 1 s for activation of a subunit to several seconds for its deactivation. One can then imagine solving for the quasistationary calcium concentration and thereafter using it to determine the conditional probabilities of channel opening or closing. With this perspective, the most important determinants of the calcium concentration at any specific site, and hence the aforementioned probabilities, are the states of the channels at that specific location and at nearby locations. Hence, we will assume this type of local coupling and investigate *general* features of this class of models in a one dimensional geometry. In a subsequent paper [4], we will show how one can derive in detail a model of this form starting from a specific fully coupled model (the DeYoung-Keizer model [5,6]).

For specificity, we will focus on systems that have IP₃ (inositol 1,4,5-trisphosphate) channels. Each of these channels consists of a number of subunits. Here we assume that h subunits have to be activated for the channel

to be open; experiments indicate that $h = 3$ [7]. A subunit is activated when IP₃ ion is bound to its corresponding domain and Ca²⁺ is bound to its activating domain and *not* bound to its inhibiting site. The characteristic time of binding and unbinding of IP₃ is typically so fast (more than 20 times faster than other binding steps [5]) that we can assume that this reaction is always at equilibrium; thus, the varying IP₃ is equivalent to varying the number of available channels. Furthermore, we assume that the channels are spatially organized into clusters [8,9], with a fixed number of channels N per cluster and a fixed intercluster distance.

Our model is as follows. We introduce two stochastic variables for each channel cluster: n_i , the number of activated subunits, and m_i , the number of inhibited subunits. At every time step, the number of activated subunits n_i at site i is changed due to three stochastic processes: activation of additional subunits by binding available Ca²⁺ to their activation domains, deactivation by unbinding Ca²⁺ from active subunits, and inhibition by binding available Ca²⁺ to their inhibition domains. Transitions involving binding (but not those involving unbinding) depend on local Ca²⁺; hence we take these transition rates to depend on the number of open channels at site i , c_i , and on the number of open channels at the nearest neighboring sites $i \pm 1$, $c_{i \pm 1}$. Similarly, there will be binding and unbinding to the inhibitory domain, changing m_i . We neglect direct transitions from the inhibited state back to an activated state, since the unbinding of Ca²⁺ from the activating site is very fast once the subunit is inhibited. We denote by $p_{0(1)}^{\pm}$ the probability to activate/inhibit a subunit per number of open channels at the same site (0) or the neighboring site (1). To compute the actual probabilities, we need to multiply these by the number of open channels. Here, we use the simple expedient of taking this to equal n_i^h/hN_s^{h-1} where the total number of subunits $N_s = hN$; this is easily shown to be the expected number of open channels for large enough N .

This approach allows us to avoid keeping explicit account of each of the independent subunits. Also, we let p_d^\pm be the deactivation and deinhibition probabilities which are c independent.

Let us define the total probabilities $p^\pm = p_0^\pm + 2p_1^\pm$ and the ‘‘diffusion constant’’ $\alpha = p_1^\pm / (p_0^\pm + 2p_1^\pm)$. We also denote $C_i(t) = (1 - 2\alpha)c_i(t) + \alpha c_{i-1}(t) + \alpha c_{i+1}(t)$, which mimics the amount of calcium at site i due to open channels at sites $i, i \pm 1$. Our model explicitly consists of the following coupled stochastic processes. n_i is updated,

$$n_i(t + \Delta t) = n_i(t) + \Delta_n^+ - \Delta_n^- - \delta_+, \quad (1)$$

where Δ_n^+ is a random integer number drawn from the binomial distribution $B(\Delta_n^+, N_s - n_i(t) - m_i(t), p^+ C_i(t))$, Δ_n^- is drawn from $B(\Delta_n^-, n_i(t), p^- C_i(t))$, and δ_n^+ is drawn from $B(\delta_n^+, n_i(t), p_d^+)$. The equation for m_i reads

$$m_i(t + \Delta t) = m_i(t) + \Delta_m^+ - \delta_m^+, \quad (2)$$

where Δ_m^+ is drawn from $B(\Delta_m^+, N_s - m_i(t), p^- C_i(t))$, and δ_m^+ is drawn from $B(\delta_m^+, m_i(t), p_d^-)$. In all these formulas, $B(x, y, p) \equiv yx p^x (1 - p)^{y-x}$. Note that the probability that IP₃ is bound is included by rescaling the number of subunits.

As a first step, we consider a simplified version of the channel dynamics with the inhibition process excluded (all $p^- = 0$), i.e., a subunit is activated whenever Ca^{2+} is attached to its activating site. Thus we take $m_i = 0$, and arrive at the one-variable model for the number of activated subunits n_i . Let us first focus on fairly small N_s . Examples of the stochastic dynamics for several values of parameters are shown in Fig. 1. At small α , an initial seed almost always ultimately dies giving rise to so-called abortive calcium waves. At larger values of α the region of activated channels typically expands at a finite rate. This transition mirrors what has been seen in many experimental systems [9].

As is well known for statistical models such as the contact process [10], the critical value of α can be accurately determined by computing the distribution of

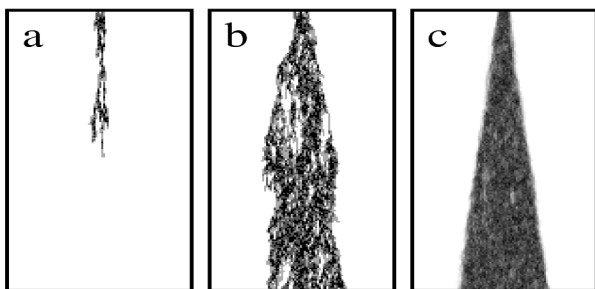


FIG. 1. Evolution of an initial seed of five clusters of open channels in the middle of the lattice for $p^+ N_s / h = 1$, $p_d^+ = 0.2$, $h = 3$, and $N_s = 3$, and $N_s = 3$, $\alpha = 0.1$ (a), $N_s = 3$, $\alpha = 0.25$ (b), and $N_s = 30$, $\alpha = 0.25$ (c). The horizontal axis is the spatial coordinate (100 sites), and the vertical axis is time (1000 iterations).

survival times $\Pi(t)$ for the activation process started from a single active site. For $\alpha < \alpha_c$, the distribution falls exponentially at large t as the wave of activation eventually dies out. On the contrary, at $\alpha > \alpha_c$, $\Pi(t)$ asymptotically reaches a constant value Π_∞ , since a nonzero fraction of runs produce ever-expanding active regions. At $\alpha = \alpha_c$, the distribution function exhibits a power-law asymptotic behavior with the slope determined by the universality class of the underlying stochastic process. Our data (not shown) indicate that α_c is inversely proportional to the number of subunits per site N_s . We have checked that our data are in the *directed percolation* (DP) [11] class. For example, in Fig. 2 we show $\Pi(t)$ of a cluster of open channels at the critical value of α_c for $h = 3$, $N_s = 10$, and $\gamma = 0.1$. The power-law dependence is consistent with the DP prediction of $\Pi(t) \propto t^{-0.159}$. This is perhaps not too surprising. According to the Janssen-Grassberger DP conjecture [12], any spatiotemporal stochastic process with short range interactions, fluctuating active phase and unique non-fluctuating (absorbing) state, single order parameter and no additional symmetries, should belong to the DP class. This result does open up the exciting possibility that intracellular calcium dynamics could be an experimental realization of the DP process.

Figure 1(c) shows the opposite limit where the dynamics becomes almost deterministic. If we take $N_s \rightarrow \infty$ and fix $p N_s / h \rightarrow P$, we can use a mean-field description in terms of the fraction of activated subunits $\rho_i = n_i / N_s$,

$$\dot{\rho}_i = [(1 - 2\alpha)\rho_i^h + \alpha\rho_{i-1}^h + \alpha\rho_{i+1}^h](1 - \rho_i) - \gamma\rho_i, \quad (3)$$

and where we rescaled time $t' = Pt / \Delta t$ and introduced $\gamma = p_d / P$. For all $h \geq 2$, if $\gamma < \gamma_{cr}$ [Eq. (3)] the system possesses two stable uniform solutions, $\rho = 0$ and $\rho = \rho_0$ and one unstable solution ρ_u , where $\rho_{0,u}$ are real roots of the algebraic equation $\rho^{h-1}(1 - \rho) = \gamma$. The front is a solution connecting these two stable fixed points; it is easy to show that this front has a unique propagation velocity.

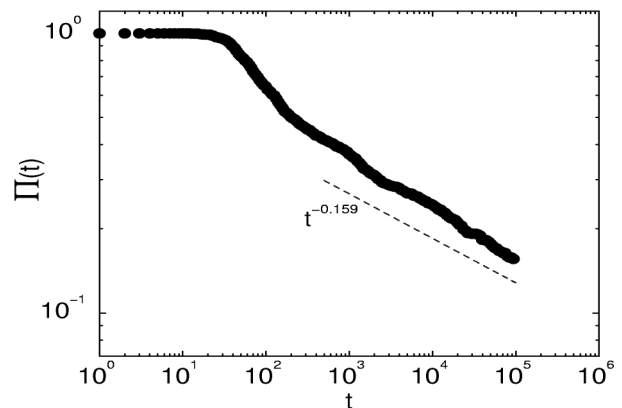


FIG. 2. The distribution of survival time for the stochastic model with $h = 3$, $\gamma = 0.1$, $N_s = 10$, and $\alpha = \alpha_c = 0.359$. Dashed line indicates the power-law scaling $\propto t^{-0.159}$.

For small α , the discreteness of our spatial lattice causes the front to become pinned, as the probability of activating subunits at the neighboring site $O(\alpha\rho_0^h)$ becomes smaller than the threshold value for excitation probability $O(\rho_u)$. The stationary front solution is described by the recurrence relation,

$$(1 - 2\alpha)\rho_i^h + \alpha\rho_{i-1}^h + \alpha\rho_{i+1}^h = \frac{\gamma\rho_i}{1 - \rho_i}. \quad (4)$$

The bifurcation line which separates pinned and moving fronts can be found in the limit of small α by using the ideas of Ref. [13]. Indeed, in this limit, the values of ρ_i quickly (as α^i) approach 0 and ρ_0 away from the front at $i \rightarrow \pm\infty$, respectively. We can thus replace ρ_i by ρ_0 and 0 everywhere to the left and to the right of the front position except for ρ_{\pm} at the two sites nearest to the front, $i - 1$ and $i + 1$. Solving the resulting set of two algebraic equations up to α^2 , one can obtain the values of ρ_{\pm} . At any γ , there is a critical value of α_m at which the real solution ρ_{\pm} vanishes. The family of these values α_m forms the bifurcation line for front pinning in (γ, α) plane. At large α , discreteness of the mean-field model (3) becomes insignificant, and (3) can be replaced by its continuum limit

$$\partial_t \rho = (\rho^h - \alpha \partial_x^2 \rho^h)(1 - \rho) - \gamma \rho, \quad (5)$$

which of course has no front pinning. Instead, α can be scaled out and there is a specific value of γ at which the system goes from forward to backward propagating fronts. Figure 3 shows the phase diagram of the mean-field equation (3) for $h = 3$. All the data (except possibly at the nongeneric case $\gamma = 0$) are consistent with expected [13] $(\alpha - \alpha_m)^{1/2}$ scaling.

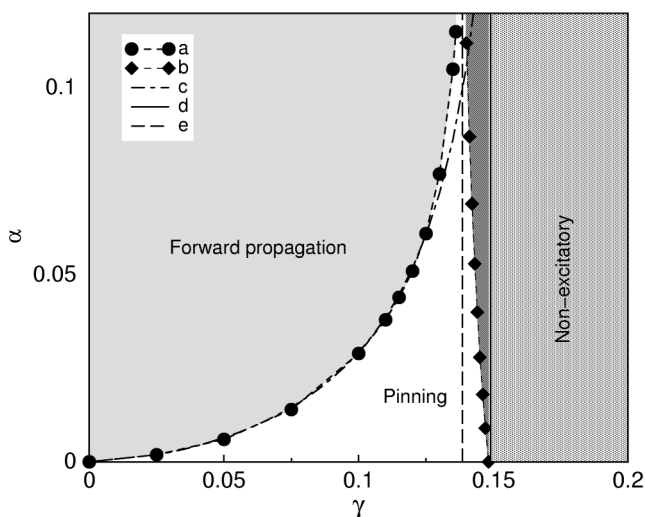


FIG. 3. Phase diagram of the mean-field equation (3) for $h = 3$: Curve (a): bifurcation line separating forward propagating fronts from pinning region; (b): same for backward propagating fronts; (c): small- α approximation of pinning line; (d): line $\gamma = 4/27$ separating the region of nonexistence of the excited state; (e): Maxwell line $\gamma = 0.138, \dots$ separating forward and backward front propagation in the continuum limit.

How does one get from DP behavior to deterministic pinning/depinning? To investigate this issue, we have performed simulations for the front speed as a function of α at various finite values of N_s , with the results given in Fig. 4. At large N_s , the velocity approaches the mean-field prediction as long as $\alpha > \alpha_m$. Close to critical value α_m , the velocity deviates from the mean-field dependence $V \propto (\alpha - \alpha_m)^{1/2}$ because of thermally activated “creep”; fluctuations allow the front to overcome potential barriers associated with finite site separation, and lead to exponentially slow front propagation (see, e.g., [14]). Directed percolation regime is not observed at large N_s since the DP critical value α_c is less than α_m . At smaller N_s , the relative magnitude of the fluctuations grows, and the DP threshold value α_c exceeds α_m . Now, the front propagation is determined by fluctuations rather than discreteness, and the critical state exhibits the properties of directed percolation.

Now we return to the full two-variable stochastic model which describes both activation and inhibition. Since the probability of Ca^{2+} binding to the inhibition domain is typically much smaller than those for the activation domain, the inhibitor dynamics is slow. In the mean-field limit $N_s \rightarrow \infty$, this model is similar to the FitzHugh-Nagumo model often used to describe waves propagating in excitable systems. One therefore expects that for a certain range of binding/unbinding probabilities, the model gives rise to pulse propagation; that is, once the wave passes, the system goes into a state dominated by inhibition from which it slowly recovers as the inhibitory domains slowly unbind. This is indeed what we find for large enough N_s , as shown in Fig. 5(a). Behind the pair of outgoing pulses, the channels stay refractory for a certain time $O(1/p^-)$ and then return to the quiescent state.

However, we find that having only a modest number of channels N leads to fluctuations which strongly affect the spatiotemporal behavior of the model. In fact, a new

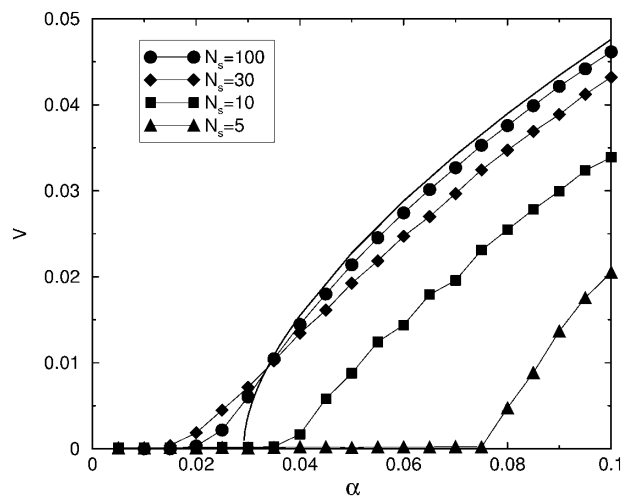


FIG. 4. The average front speed as a function of α for stochastic model at $h = 3$, $\gamma = 0.1$, $p^+N_s/h = 1$, $p_d^+ = 0.1$, and different values of N_s . Solid line indicates the mean-field limit $N_s \rightarrow \infty$.

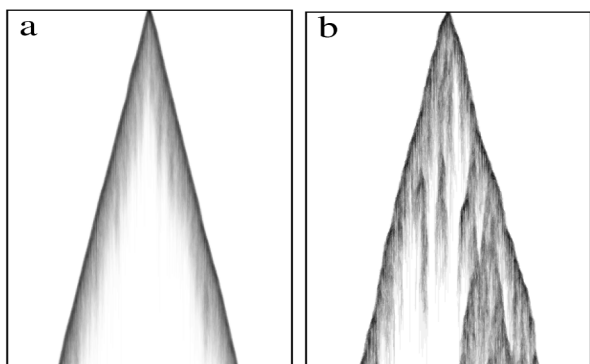


FIG. 5. Space-time evolution initiated by opening channels at a single cluster in the middle of the lattice of 300 sites for the full activation/inhibition model with $p^+ = 1$, $p_d^+ = 0.04$, $p^- = 0.1$, $p_d^- = 0.12$, $h = 3$, $\alpha = 0.7$, and $N_s = 200$ (a) and $N_s = 20$ (b), 500 iterations.

dynamical state is formed behind the outgoing fronts, a state which remains active at all subsequent times [see Fig. 5(b)]. This state is catalyzed by backfiring, i.e., the creation of oppositely propagating waves behind a moving front. In the deterministic limit of our model, this cannot occur as the system is completely refractory once the front has passed. At finite N however, propagation of the front does not lead to the activation and subsequent inhibition of all the channels. Instead, a finite number of these remain inactivated, providing a supply of active elements that can still support wave propagation. There exist more complicated deterministic models [15], such as one proposed for CO oxidation on single crystal surfaces [16], which also appear to have pulse-induced backfiring. There, however, this effect is due to the loss of pulse stability which occurs due to the rather complex nonlinear dynamics of the inhibitory field. Here, it is the fluctuations which allow for this phenomenon.

We have checked that this backfiring-induced state occurs as well in more realistic and more complex models which solve for the calcium concentration together with the channel dynamics. Again, the mechanism appears to be the lack of complete inhibition in the wake of the propagating pulse. Hence, our result that one should find this behavior in intracellular calcium dynamics is not an artifact of any of the simplifying assumptions used here. Also, this state persists when the model is studied in higher dimensions [4].

In summary, we proposed and studied a simple discrete model of calcium channel dynamics based on the assumption that calcium diffusion time is much smaller than the characteristic times of Ca^{2+} binding/unbinding. This model demonstrates familiar properties of deterministic reaction-diffusion systems in the limit $N \rightarrow \infty$ when fluctuations are small. For small N , we observed a transition in the directed percolation class, leading eventually to abortive waves. Inasmuch as there exists direct experimental evidence [8,9] for this type of fluctuation-

induced transition, we predict that one should be able to find DP behavior at a critical IP_3 concentration. For the full model including inhibition, we found at small N a novel persistent fluctuation-driven state which emerges behind a front of outgoing activation; this occurs in a parameter regime where the corresponding deterministic system exhibits only single outgoing pulses. Again, this will be observable if the relevant range of model parameters can be attained experimentally by varying the available controls. This issue will be addressed elsewhere [4].

The authors thank H. Hinrichsen, M. Or-Guil, and I. Mitkov for helpful discussions. L.S.T. thanks Max Planck Institut für Physik komplexer Systeme, Dresden, Germany for hospitality. L.S.T. was supported in part by the Engineering Research Program of the Office of Basic Energy Sciences at the U.S. Department of Energy under Grants No. DE-FG03-95ER14516 and No. DE-FG03-96ER14592. H.L. was supported in part by the U.S. NSF under Grant No. DMR98-5735. M.F. was supported in part by the DFG Grant No. Fa350/2-1.

*To whom correspondence should be addressed.

Email address: falcke@mpipks-dresden.mpg.de

- [1] M. J. Berridge, M. D. Bootman, and P. Lipp, *Nature* (London) **395**, 645 (1998).
- [2] J. Keizer and G. D. Smith, *Biophys. Chem.* **72**, 87 (1998).
- [3] J. Keizer, G. D. Smith, S. Ponce-Dawson, and J. E. Pearson, *Biophys. J.* **75**, 595 (1998).
- [4] M. Falcke, L. S. Tsimring, and H. Levine, *Phys. Rev. E* (to be published).
- [5] G. W. DeYoung and J. Keizer, *Proc. Natl. Acad. Sci. U.S.A.* **89**, 9895 (1992).
- [6] J. Keizer and G. W. DeYoung, *J. Theor. Biol.* **166**, 431 (1994).
- [7] I. Bezprozvanny, J. Watras, and B. E. Ehrlich, *Nature* (London) **351**, 751 (1991).
- [8] X. P. Sun, N. Callamaras, J. S. Marchant, and I. Parker, *J. Physiology* **509**, 67 (1998).
- [9] N. Callamaras, J. S. Marchant, X. P. Sun, and I. Parker, *J. Physiology* **509**, 81 (1998).
- [10] The contact process was first introduced by [E. T. Harris, *Ann. Prob.* **2**, 969 (1974)] a model for epidemic spreading. Infected species can either heal themselves or infect their nearest neighbors on a lattice.
- [11] S. R. Broadbent and J. M. Hammersley, *Proc. Cambridge Philos. Soc.* **53**, 629 (1957).
- [12] H. K. Janssen, *Z. Phys. B* **42**, 151 (1981); P. Grassberger, *Z. Phys. B* **47**, 365 (1982).
- [13] I. Mitkov, K. Kladko, and J. E. Pearson, *Phys. Rev. Lett.* **81**, 5453 (1999).
- [14] I. S. Aranson, B. Malomed, L. M. Pismen, and L. S. Tsimring, *Phys. Rev. E* (to be published).
- [15] M. G. Zimmerman, S. O. Firlre, M. A. Natiello, M. Hildebrand, M. Eiswirth, M. Bär, A. K. Bangia, and I. G. Kevrekides, *Physica* (Amsterdam) **110D**, 92 (1997).
- [16] M. Bär, N. Gottschalk, M. Eiswirth, and G. Ertl, *J. Chem. Phys.* **100**, 1202 (1994).