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A Stochastic Fire-Diffuse-Fire Model of Ca^{2+} Release

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Abstract. Calcium ions are an important second messenger in living cells transmitting signals in the form of waves. It is now well established that these waves are composed of elementary stochastic release events (calcium puffs) from spatially localised calcium stores. Here we develop a mathematical model of calcium release based upon a stochastic generalisation of the fire-diffuse-fire (FDF) threshold model for calcium release. Our model retains the discrete characteristic of the FDF model (spatially localised stores) but also incorporates a notion of release probability, via the introduction of threshold noise. It is possible to identify a critical level of noise defining a non-equilibrium phase-transition between abortive and propagating waves. This transition is shown to belong to the directed percolation universality class.

1. Introduction

Calcium signals in the form of sparks and propagating waves are observed in a wide range of cell types. Experiments have shown the stochastic nature of release events both in systems based on the inositol (1,4,5)-trisphosphate (IP_3) receptor (MARCHANT and PARKER, 2001) and the ryanodine receptor (RyR) (CHENG *et al*., 1996). The importance of stochasticity for the initiation and propagation of calcium waves has been a subject of limited theoretical investigation. Notable exceptions are the work of KEIZER and SMITH (1998) on stochastic RyR release sites in cardiac myocytes, and the work of BÄR *et al*. (2000) on stochastic IP_3 channels.

In this paper we introduce a stochastic version of the FDF threshold model for calcium release of KEIZER *et al*. (1998). One of the main advantages of our model is that it is biophysically realistic and computationally cheap to solve. Simulation results are presented for both a one and two dimensional cell model. We demonstrate that different noise intensities can lead to a variety of different structures, including noisy travelling circular fronts, spiral waves, target patterns and large scale coherent periodic rhythms. Moreover, a statistical analysis shows that the model exhibits a non-equilibrium phase transition belonging to the directed percolation universality class.

2. The FDF Threshold Model

The FDF model of KEIZER *et al*. (1998) was originally introduced as a minimal model of spark-mediated Ca^{2+} waves. In one dimension the model may be written in the form:

$$\frac{\partial u}{\partial t} = -\frac{u}{\tau_d} + D\frac{\partial^2 u}{\partial x^2} + \sigma \sum_{n\in\mathbb{Z}} \sum_{m\in\mathbb{Z}} \delta(x - nd)\eta\left(t - T_n^m\right), \quad x \in \mathbb{R}, \quad t > 0, \tag{1}$$

where $u(x, t)$ denotes the concentration of Ca^{2+} ions in the cytosol. The first term in Eq. (1) models a linear Ca^{2+} pump which operates at a rate τ_d^{-1}. Ca^{2+} puffs are triggered from the release site at positions $x = nd$ at times T_n^m. These release times are defined in terms of a threshold process according to

$$T_n^m = \inf\left\{t \middle| u(nd, t) > u_c,\ u_t(nd, t) > 0,\ T_n^m > T_n^{m-1} + \tau_R\right\}, \tag{2}$$

where release events are separated by at least a time τ_R. The function $\eta(t)$ describes the shape of the Ca^{2+} puff and is considered to be a rectangular pulse shape $\eta(t) = \Theta(t)\Theta(\tau - t)/\tau$ with duration τ and strength σ. It is convenient to define a *release function* $a_n(p)$, where $a_n(p) = 1$ if $T_n^m = p\tau$ and is zero otherwise. We now restrict the system so that release times occur on a regular temporal lattice. Choosing the refractory time as $\tau_R = R\tau$ for some $R \in \mathbb{Z}$ we use the approximation

$$a_n(p) = \Theta\left(u_n(p) - u_c\right) \prod_{m=1}^{\min(R,p)} \Theta\left(u_c - u_n(p - m)\right), \tag{3}$$

where $u_n(p) \equiv u(nd, p\tau)$. The first term on the right in Eq. (3) is a simple threshold condition for the determination of a release event whilst the second term ensures that release events are separated by at least τ_R. Using the above restriction, the FDF model takes the simple form

$$\partial_t u + \frac{u}{\tau_d} - D\partial_{xx} u = \frac{\sigma}{\tau} \sum_{n\in\mathbb{Z}} a_n(p)\delta(x - nd), \quad p\tau < t < (p + 1)\tau, \tag{4}$$

with Green's function $G(x, t) = \exp[-t/\tau_d - x^2/4Dt]/\sqrt{4\pi Dt}\ \Theta(t)$. The dynamics for $p\tau < t < (p+1)\tau$ may then be determined in terms of initial data $u_p(x) = u(x, p\tau)$ as

$$u(x, t) = \frac{\sigma}{\tau} \sum_{n\in\mathbb{Z}} a_n(p) H(x - nd, t - p\tau) + \left(G \otimes u_p\right)(x, t), \tag{5}$$

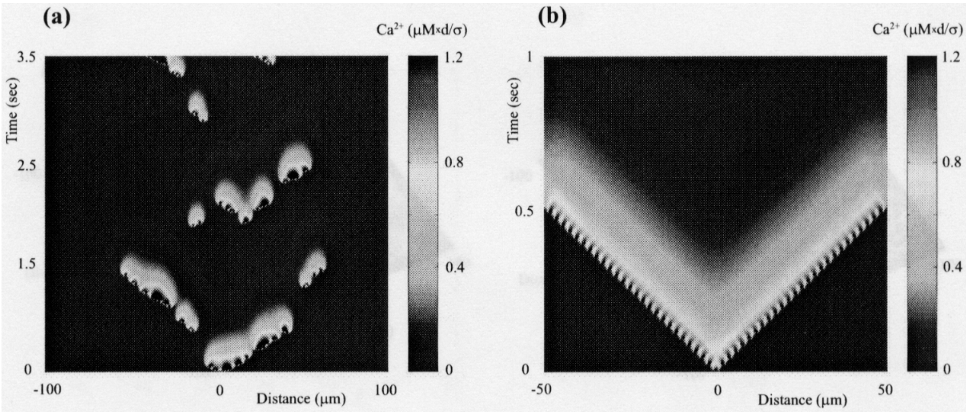

Fig. 1. (a) Stochastic travelling wave in one dimension with the following parameters d = 2 μm, D = 30 $\mu m^2/s$, $\tau = 0.01$ s, $\tau_d = 0.2$ μM/s, $u_c d/\sigma = 0.1$, $\tau_R = 50\tau$ and $\beta = 10$. (b) Deterministic travelling wave with speed s = 100 μm/s (the same parameters and $\beta \to \infty$). Lurching pulses propagate both left and right from a central sites, giving rise to a saw wave-like front. Regions between saw teeth are occupied by material with a high density of Ca^{2+}.

where $H(x, t) = \int_0^t G(x, t - s)\mathrm{d}s$ and $(G \otimes u_p)(x, t) = \int_{-\infty}^{\infty} G(x - y, t - p\tau)u_p(y)\mathrm{d}y$. A closed form expression for $H(x, t)$ is given in COOMBES (2001). Compared to the original FDF model the one we have described here is computationally cheap to solve. The solution $u(x, p\tau)$ is a sum of two terms that are both amenable to fast numerical evaluation. In particular the first term in Eq. (5) with $t = p\tau$ depends on the *basis* functions $H_n(x) = \sigma H(x - nd, \tau)/\tau$ which are fixed for all time. Hence, they need only be computed once. The convolution operation arising in the second term may be performed effciently using Fast Fourier Transform (FFT) techniques. Once again the FFT of $G(x, \tau)$ need only be computed once, so the computational burden is shifted to the evaluation of the FFT of $u_p(x)$ and the construction of $G \otimes u_p$ as $\mathcal{F}^{-1}(\mathcal{F}[G]\mathcal{F}[u_p])$, where $\mathcal{F}$ denotes the FFT.

3. Stochastic Model

The FDF threshold model that we have described is easily extended to take into account the stochastic nature of Ca^{2+} release. We treat the threshold u_c as a random variable and consider the replacement $u_c \to u_c + \xi$ with some additive noise term ξ. The probability that $a_n(p) = 1$ and that there is a release event is given by

$$P\big(a_n(p)=1\big) = P\big(a_n(p) > u_c\big)\prod_{m=1}^{\min(R,p)} P\big(u_n(p-m) < u_c\big), \qquad (6)$$

for some probability distribution function $P(u > u_c) = f(u - u_c)$. From the work of IZU *et al.*

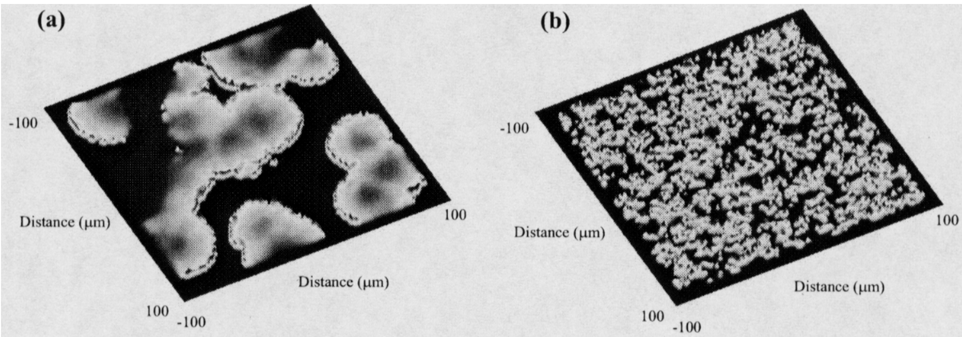

Fig. 2. Stochastic dynamics in two dimensions with the parameters from Fig. 1 and (a) $\beta = 100$ (intermediate noise), (b) $\beta = 10$ (high noise).

(2001), natural choices for the release probability functions are sigmoidal functions. Here we choose

$$f(\xi) = \left\{ \frac{1}{1+\mathrm{e}^{-\beta\xi}} - \frac{1}{1+\mathrm{e}^{\beta u_c}} \right\} \left(1 + \mathrm{e}^{-\beta u_c}\right), \tag{7}$$

so that the probability of release is zero when $u = 0$ and tends to one as $u \to \infty$. The stochastic FDF model is defined by Eq. (5) with $a_n(p) \in \{0, 1\}$ treated as a random variable. Numerical simulations of the model illustrate that stochastic calcium release can lead to the spontaneous production of calcium sparks that, under certain conditions, can merge to form saltatory waves. All numerical simulations start from a single active site. An example of a stochastic travelling wave is shown in Fig. 1(a). In the limit $\beta \to \infty$, the release probability function becomes a step function and we recover our original deterministic model. A saltatory wave in this deterministic case is shown in Fig. 1(b). Thus we interpret β as a parameter describing the level noise.

The generalisation of our stochastic FDF model to two dimensions is both natural and straight forward by introducing a continuous spatial coordinate $\mathbf{r} \in \mathbb{R}^2$ and a discrete set of vectors $\mathbf{r}_n \in \mathbb{R}^2$, $n \in \mathbb{Z}$, indicating the positions of release sites. Since the puff duration is very small compared to τ_R we have the useful approximation that $H(\mathbf{r}, t) \to G(\mathbf{r}, t)$, where $G(\mathbf{r}, t) = \exp[-t/\tau_d - r^2/4Dt]/4\pi Dt$, with $r = |\mathbf{r}|$. For simplicity we focus on a square lattice of release sites, with lattice spacing d. A single active site is placed in the centre of the square lattice at the beginning of simulations. It is possible to observe a well defined front of activity for large values of β (low noise), more irregular activity for intermediate levels of noise and a form of array enhanced coherence resonance for large values of noise. This leads to a high degree of synchronization between release events at different sites similar to that observed in the work by HEMPEL *et al*. (1999). Some examples of typical structures observed in the presence of intermediate and high noise are shown in Fig. 2.

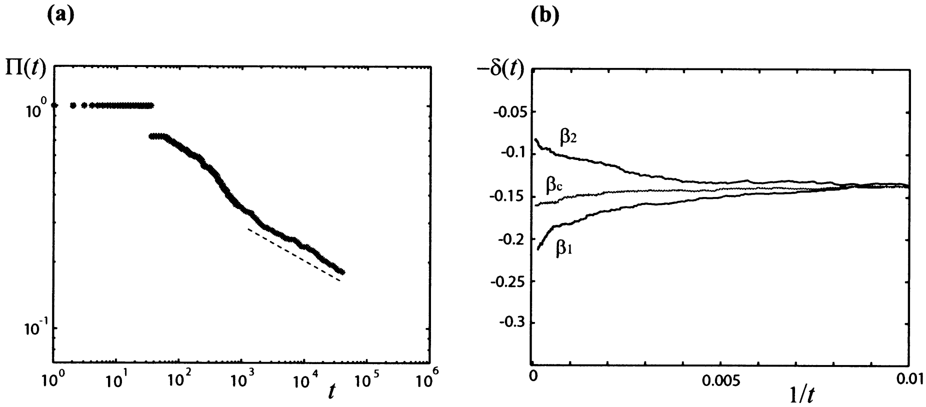

Fig. 3. (a) The distribution of survival times at the critical noise level β_c, showing that for large t there is a power law scaling of the form $\Pi(t) \sim t^{-\delta}$. The slope of the graph is used to predict that $\delta \sim 0.159$, as is expected for models in the universality class of directed percolation. (b) Plots of $\delta(t)$ used in the determination of β_c, showing that β_c lies between β_1 and β_2.

4. Directed Percolation

In common with many models which exhibit a non-equilibrium phase transition our model supports waves which *survive* or eventually go *extinct*. Similar to the stochastic model of calcium release proposed by BÄR *et al.* (2000) we demonstrate that our model belongs to the so-called directed percolation (DP) universality class. The DP model is the simplest model exhibiting a non-equilibrium transition (see HINRICHSEN (2000) for a review). At some critical noise level the survival probability, $\Pi(t)$, of a wave is expected to scale asymptotically as $t^{-\delta}$ with $\delta \sim 0.159464$. We shall treat the effective noise parameter β as the one controlling the DP phase transition and denote the critical value of β at the phase transition by β_c. To obtain a good estimate of the critical exponent δ, it is useful to consider the local slope of the survival probability curve by introducing the effective exponent $\delta(t) = \ln[\Pi(rt)/\Pi(t)]/\ln r$, where $\ln r$ is the distance used for estimating the slope. A plot of $\delta(t)$ for various choices of β may be used to predict the critical value β_c. A good estimate of δ can be obtained by extrapolating the behaviour of $\delta(t)$ to $t \to \infty$ and plotting the local slope as a function of t^{-1}. We plot $\delta(t)$ for various values of β in Fig. 3(b), showing that $\beta_c \sim 0.47$. The corresponding distribution of survival times $\Pi(t)$ for the activation process started from a single site is presented in Fig. 3(a). For our value of β_c we find $\delta \sim 0.159$ suggesting that our model also belongs to the DP universality class.

5. Discussion

This work introduces a stochastic generalisation of the FDF model for Ca^{2+} release. Our simulation results demonstrate that the model captures the main qualitative features of the experimentally observed calcium sparks and waves in a variety of cell types (CHENG *et al.*, 1996; MARCHANT and PARKER, 2001). One of the main advantages of our model is that it is computationally inexpensive. The stochastic nature of the release events is modelled by the inclusion of additive noise to the threshold. For high noise we observe spontaneous Ca^{2+} sparks and the possibility of global coherent signals in the form of simultaneous and periodic release from all sites. For low noise Ca^{2+} sparks can reinforce each other and propagate as waves. A statistical analysis of the model shows a non-equilibrium phase transition between propagating and non-propagating waves and that the model belongs to the directed percolation universality class.

The computational simplicity of our model makes it ideal for exploring the stochastic nature of Ca^{2+} sparks and waves in fully 3D model cells.

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