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Semi-Discrete Systems and Intracellular Calcium Dynamics

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Abstract

Intracellular calcium is sequestered in closed membranes such as the sarcoplasmic or endoplasmic reticula and released at discretely distributed protein/receptor channels. The release kinetics can result in the propagation of waves of elevated calcium concentration. The main physical processes are reactions at the release sites and diffusion between the sites. The theory of chemical wave propagation in reaction-diffusion systems is in large part devoted to the study of systems in which there are no extrinsic inhomogeneities. The discrete distribution of the release sites plays a key role in determining the nature of the propagating wave. We analyze some simple reaction-diffusion models in order to elucidate the role of discreteness for chemical wave propagation.

1 Calcium Signaling

Calcium is a universal second messenger that is used to activate and moderate a large variety of cellular processes among which are muscle contraction, sensory perception and mitosis [1, 2]. Ca$^{2+}$ is stored intracellularly in the endoplasmic or sarcoplasmic reticulum (ER or SR) at millimolar levels. The calcium in these internal stores can be released into the cytosol where the concentrations range from 10nM to 1μM. The release process which is known as calcium induced calcium release (CICR), involves Ca$^{2+}$ release through specialized Ca$^{2+}$ channels that are activated at slightly elevated levels of cytosolic Ca$^{2+}$ and then inactivated as the level of Ca$^{2+}$ rises further. After an open channel closes via inactivation, it cannot reopen for some time during which it is in a "refractory" state. Thus the release of Ca$^{2+}$ by intracellular stores is self-regulating. This mechanism can result in the propagation of Ca$^{2+}$ waves [1, 3, 4, 5].

The characteristic spacing for the release sites is a few microns. The release events are the elementary processes underlying Ca$^{2+}$ waves so it is important to understand how their spatial arrangement influences wave propagation. To this end we shall now look at two mathematical models of wave propagation in reaction-diffusion systems. The first, "fire-diffuse-fire" was directly motivated by calcium dynamics and the second, "the semi-discrete cubic model", is a semi-discrete version of the cubic model, the paradigmatic model for nonlinear wave propagation in reaction diffusion systems. In both cases the
nature of the propagating wave front is determined by a dimensionless number, \( \beta = \frac{D \tau}{d^2} \) where \( D \) is the diffusion coefficient, \( \tau \) is a chemical time scale and \( d \) is the site spacing. When \( \beta \gg 1 \) discreteness is not important and when \( \beta \ll 1 \) then discreteness plays a large role in the wave propagation.

2 The Fire Diffuse Fire Model

The “fire-diffuse-fire” (FDF) model [3, 4, 5] consists of a regular array of point source release sites with spacing, \( d \), embedded in a continuum in which \( Ca^{2+} \) ions diffuse with diffusion coefficient \( D \). In cells in which release sites do not occur in regular arrays, \( d \) should be thought of as a mean spacing. Whenever the cytosolic \( Ca^{2+} \) concentration in the vicinity of a release site reaches a threshold value, \( [Ca^{2+}]_T \), the site begins releasing \( Ca^{2+} \) ions at a rate \( \sigma/\tau \). It remains open for a time \( \tau \) and then closes after having released a quantity, \( \sigma \), of \( Ca^{2+} \). In dimensionless units the evolution equations are given by:

\[
\begin{align*}
\frac{u_t}{u_{xx}} &= \Gamma \sum_{i=-\infty}^{\infty} \delta(x-i)H(t-t_i)H(t_i+1-t)
\end{align*}
\]

where \( H(x) \) is the Heaviside function \( H(x) = 1 \) for \( x \geq 0 \) and \( H(x) = 0 \) for \( x < 0 \) and \( \delta(x-i) \) is Dirac’s delta function. In these units, the threshold concentration is unity and the \( t_i \) are determined by demanding that \( u(i,t_i) = 1 \) where \( u(x,t) \) is the formal solution to eq. 1. Traveling wave solutions of the “fire-diffuse-fire” model for both large and small \( \beta \) are illustrated in Fig 1. We remark here that for large \( \beta \) the velocity scales as \( v \propto \sqrt{D/\tau} \) and that for small \( \beta \) we have \( v \propto D/d \). The scaling here can be understood in terms of the following fact. The velocity of a reaction diffusion wave must scale as the square root of a diffusion coefficient divided by some time scale. In the fire-diffuse-fire model there are traveling wave solutions provided \( \Gamma > 1 \). For large \( \beta \), the release of \( Ca^{2+} \) from the sites is...
Figure 2: A sequence of snapshots of the solutions of the semi-discrete cubic (SDC) model in the small \( \beta \) regime.

the rate limiting process and the time scale is \( \tau \). Then the wave appears continuous as in Fig \( 1b \). For small \( \beta \), intersite diffusion is the rate-limiting process and the time scale is \( D^2/\mu \). Then the waves appear as a sequence of bursts as in Fig \( 1a \). The situation is somewhat different in the semi-discrete cubic model which we now discuss.

3 The semi-discrete cubic model

Cubic kinetics provide the simplest example of a reaction-diffusion system with a traveling front solution. In dimensionless units the semi-discrete cubic (SDC) model is given by:

\[
\tag{2}
u_t = \beta u_{xx} + f(u) \sum_{i=-\infty}^{\infty} \delta(x - i)
\]

where \( f(u) = u(1 - u)(u - u_c) \). It is well known that the standard cubic model \( u_t = u_{xx} + f(u) \) has traveling wave solutions of the form \( u(x, t) = 1/2(1 - \tanh((x - ct)/\sqrt{2})) \) where \( c \) is given by \( c = \sqrt{2}(u_o - 1/2) \). This solution corresponds to a traveling front between the two spatially uniform stable steady states \( u = 0 \) and \( u = 1 \). Note that \( c = 0 \) only for a single parameter value, \( u_o = 1/2 \) which corresponds to equal heights of the extrema of the the potential \( \Phi(u) \) which satisfies \( \partial \Phi/\partial u = -f(u) \). We also remark that both the standard and semi-discrete versions of the cubic model are variational, i.e. their evolution equations can be written in the form:

\[
\tag{3}
u_t = -\delta E/\delta u
\]

where \( \partial \Phi/\partial u = -f(u) \). The novel feature in the semi-discrete cubic model is the existence of pinned states. That is, there exists a critical value of \( \beta, \beta_c \) below which there are static front solutions and no traveling solutions. For \( \beta > \beta_c \) there exist traveling fronts but no static fronts. The existence of static (pinned) fronts is an effect of discreteness. For small \( \beta \) but \( \beta > \beta_c \) the waves propagate with neither constant velocity nor constant shape as shown in figure 3. They do however have a well defined mean velocity \( v \propto \sqrt{\beta - \beta_c} \). The velocity is such that if \( u(x,t) \) is a traveling solution then \( u(x+1,t+1/v) = u(x,t) \). Along the solutions the energy functional can be parameterized by a single parameter, \( s \), which is a generalized arc length given by:

\[
\tag{4}
ds = \left( \int_{-\infty}^{\infty} \left( \frac{\partial u}{\partial t} \right)^2 dx \right)^{1/2} dt
\]

The functional has an infinity of minima for \( \beta < \beta_c \) which all disappear as \( \beta \) is increased through \( \beta_c \). This fact can understood in
terms of the following simplified evolution equation which contains the main ingredients of the semi-discrete cubic model:

$$\frac{dx}{dt} = 1 + (1 - \frac{\epsilon}{2}) \cos 2\pi x$$  \hspace{1cm} (5)

For $\epsilon < 0$ there are an infinity of fixed points. As $\epsilon$ is increased through 0 the fixed points disappear and a solution with the property that

$$x(t) + 1 = x(t + 1/v)$$  \hspace{1cm} (6)

with $v = \sqrt{\epsilon - \epsilon^2/4} \approx \sqrt{\epsilon}$. The Lyapunov function for 5 is given by $\bar{E}(x) = -(x + (1 - \epsilon/2) \sin (2\pi x)/(2\pi) + const$. has the same behavior as the energy functional $E(s)$.

4 Conclusions

We have discussed two different models of nonlinear wave propagation in semi-discrete reaction diffusion systems. The FDF model is directly motivated by the dynamics of intracellular calcium. Its parameters can be obtained from experimental data and the model used to explain experimentally observed wave dynamics and velocities. The SDC model was analyzed as a mathematical counter-point to the physically motivated FDF model. We make one general statement. The value of $\beta$ determines what role discreteness plays for calcium signal propagation. If $\beta$ is large compared to unity then the system can be modeled as if the Ca$^{2+}$ is released continuously throughout space. If $\beta$ is small then the discreteness is important and the waves have a burst-like character. The SDC model resulted in a pinned front which in which the velocity scaled as $v \propto \sqrt{\beta - \beta_c}$. There are no pinned fronts in the FDF model and the velocity scales as $\sqrt{D/\tau}$ for large $\beta$ and as $D/d$ for small $\beta$. General criteria for the occurrence of pinned fronts are needed. It is unknown whether it is possible for fronts to undergo pinning in physiologically relevant situations. The implications for intracellular signal processing are not known. It is widely held that information is encoded in the Ca$^{2+}$ signal [2, 6]. Thus, the distinction between burst waves and continuous waves likely has considerable physiological significance.

References

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