The Effect of Discreteness in Calcium Handling

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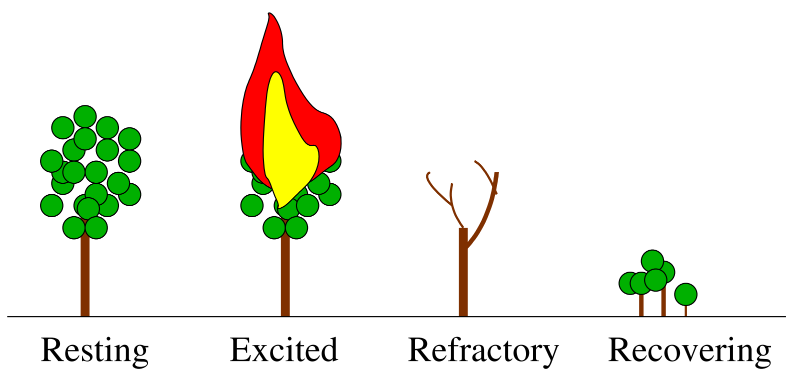
Introduction - Excitability

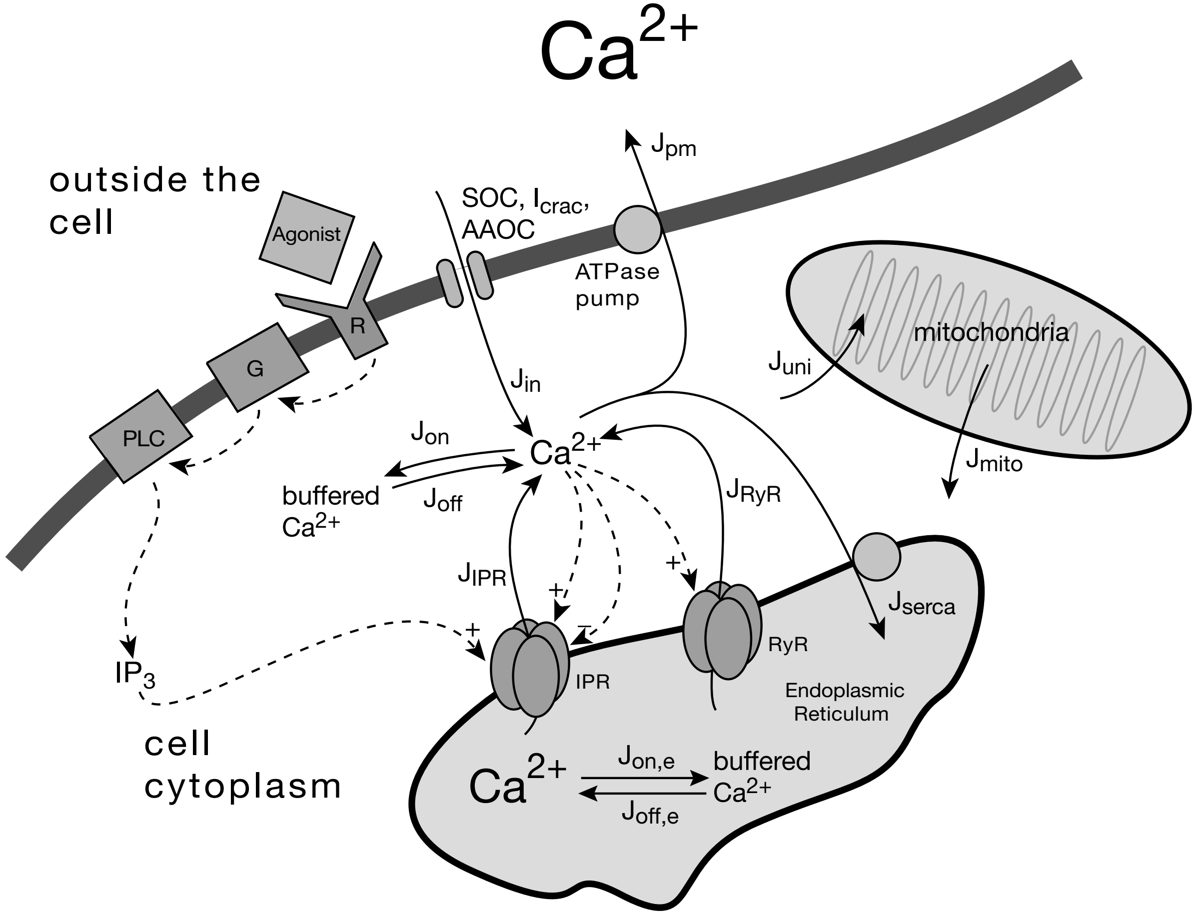
- B-Z reagent
- Nerve cells
- cardiac cells, muscle cells
- Slime mold (*dictystelium discoideum*)
- CICR (Calcium Induced Calcium Release)
- Forest Fires

Features of Excitability

- Threshold Behavior
- Refractoriness
- Recovery

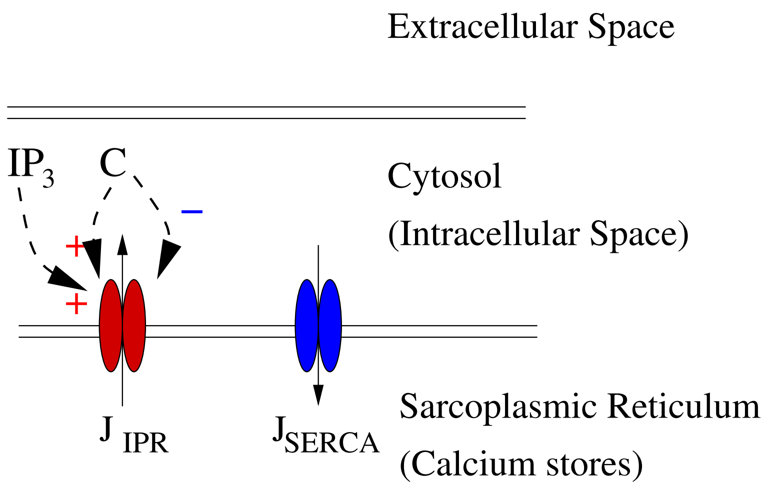


Calcium Handling



Basic Calcium Model

$$\frac{dc}{dt} = J_{IPR} - J_{SERCA}$$



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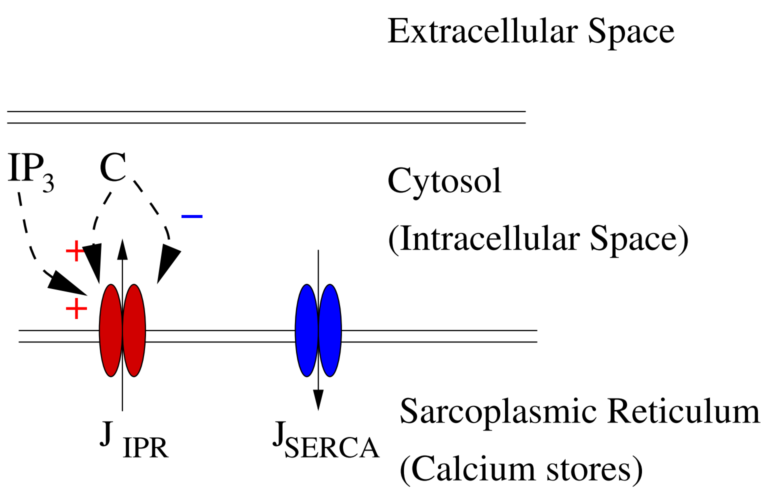

with

J_{IPR} IP$_3$ Receptor - IP$_3$ and calcium regulated calcium channel,

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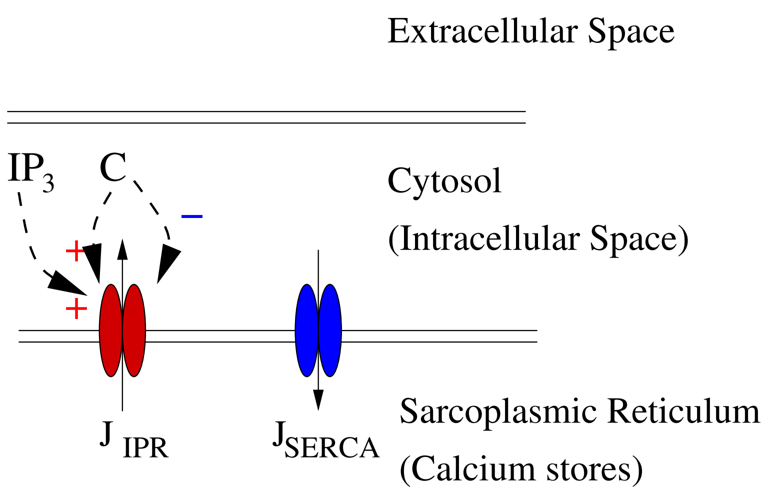

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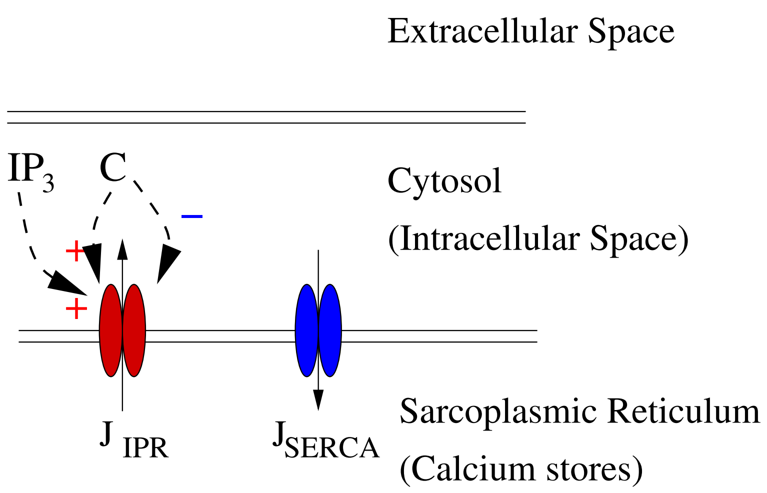

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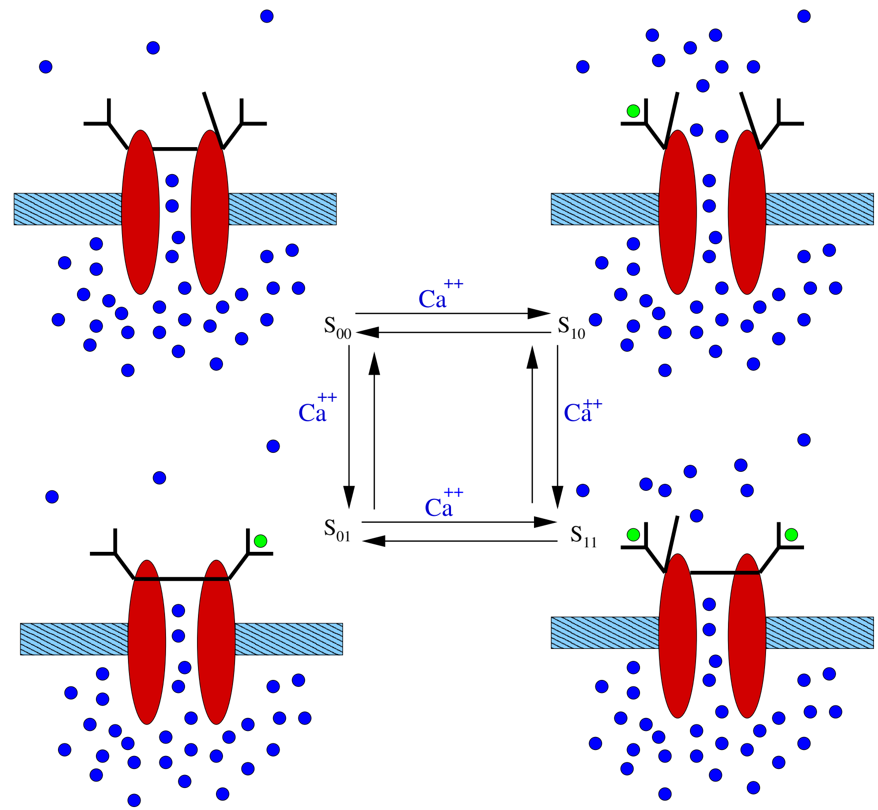
What are the flux terms?

IP_3 Receptors



Flux through IP_3 receptor is diffusive,

$$J_{IPR} = g_{max} P_o (c_{sr} - c)$$

where $P_o = S_{10}^3$ is the open probability.

Calcium Dynamics

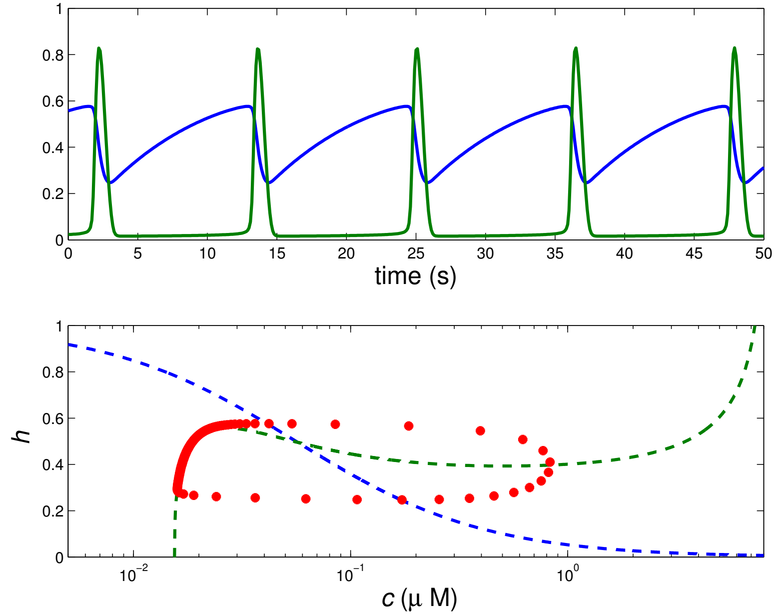
$$\frac{dc}{dt} = (g_{max} P_o + J_{er})(c_{sr} - c) - J_{SERCA},$$

$$\frac{dh}{dt} = \phi_h(c)(1-h) - \psi_h(c)h,$$

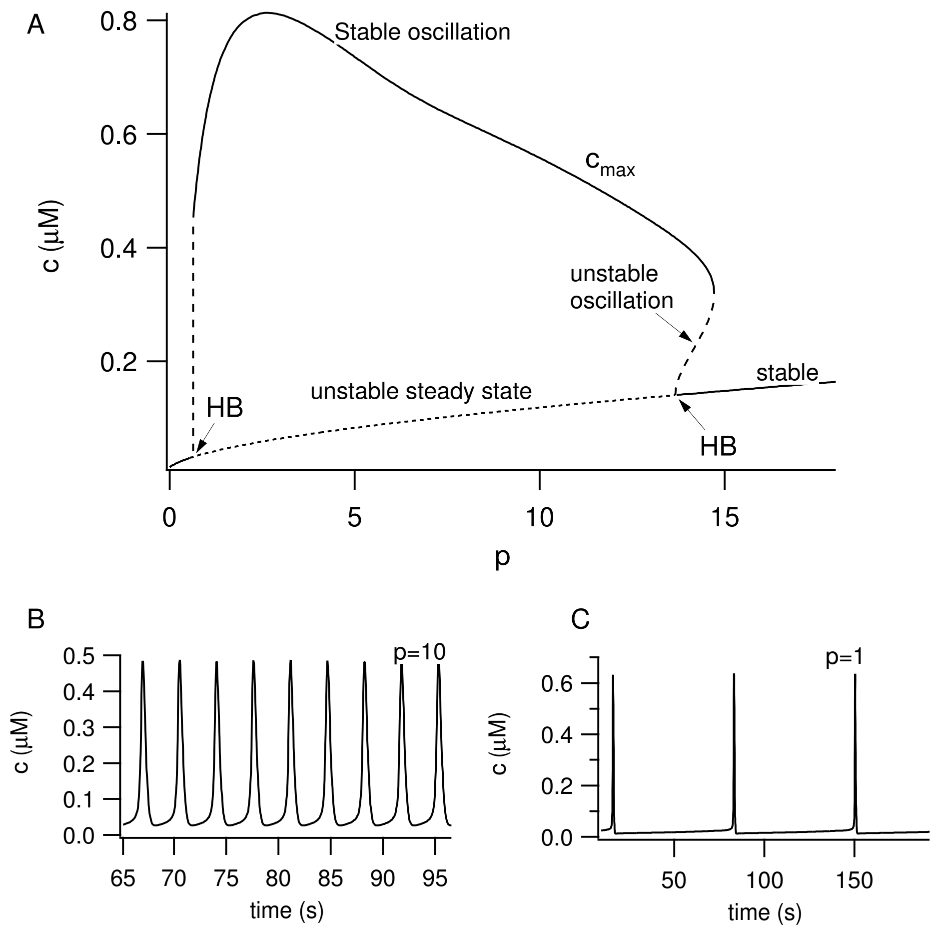
where

$$J_{SERCA} = V_{max} \frac{c^2}{K_s^2 + c^2},$$

$$P_o = h^3 f(c)$$



Bifurcation Diagram



But the data do not look like this at all!

Onset of Oscillations

- At low IP_3 concentrations, calcium release is infrequent and highly irregular.

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- At medium IP_3, calcium release is less rare and less irregular.
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The data show no Hopf Bifurcations or sharp onset of oscillations.

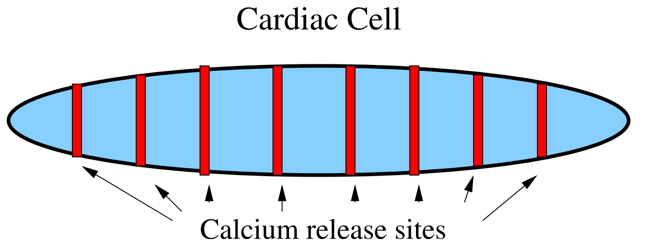
Problems

What went wrong?

There are two problems with this model:

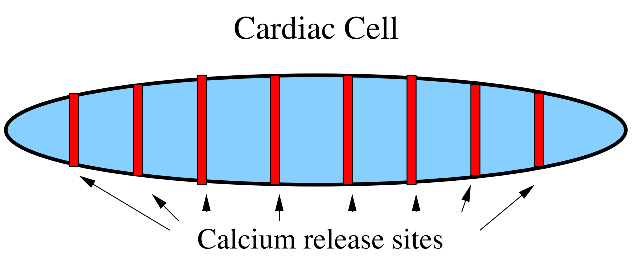
1. Calcium is not spatially homogenious; channels are controlled by **local** calcium concentration.
2. Channel openings are not deterministic.

Discrete Release Sites



$$\frac{\partial c}{\partial t} = \frac{1}{L}\sum_n \delta(x - x_n)\ J_{IPR} - J_{SERCA} + D\frac{\partial^2 c}{\partial x^2}$$

Discrete Release Sites



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with

x_n location of release sites separated by distance L,

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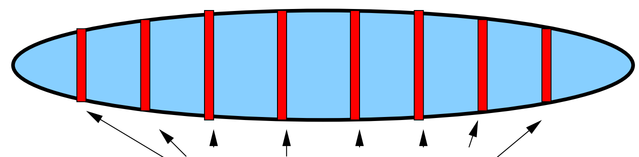
Discrete Release Sites



$$\frac{\partial c}{\partial t} = \boxed{\frac{1}{L}\sum_n \delta(x - x_n)} J_{IPR} - J_{SERCA} + \boxed{D\frac{\partial^2 c}{\partial x^2}}$$

with

x_n location of release sites separated by distance L,

$D\frac{\partial^2 c}{\partial x^2}$ spatial diffusion of calcium

Apply Homogenization

Standard homogenization theory applied to

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + g(\frac{x}{\epsilon})f(u) - h(u)$$

yields

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + Gf(u) - h(u)$$

where $G = \frac{1}{L}\int_0^L g(x)dx$, so that $F(u) = Gf(u) - h(u)$ is the effective release/uptake function.

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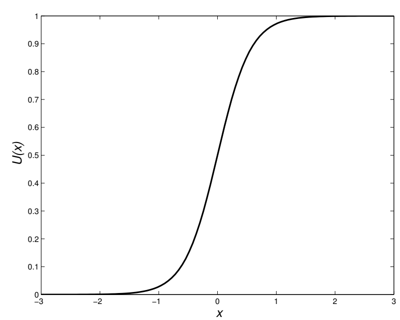
This is the well-known Bistable Equation.

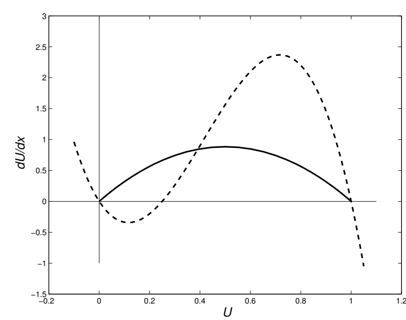
The Bistable Equation

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + F(u)$$

with $F(0) = F(a) = F(1) = 0$, $0 < a < 1$.

- There is a unique traveling wave solution $u = U(x - ct)$,
- The solution is stable up to phase shifts,
- The speed scales as $c = c_0\sqrt{D}$,
- U is a homoclinic trajectory of $DU'' + cU' + F(U) = 0$



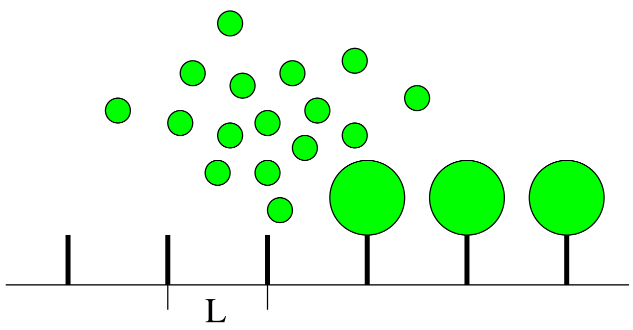


Problems

There can be propagation failure (also called pinning) with discrete release. What happens is shown in this movie with Discrete Release Sites.

How to fix this? cf. J. P. Keener, Propagation of Waves in an Excitable Medium with Discrete Release Sites, SIAM J. Appl. Math., 61, 317-334 (2000).

Fire-Diffuse-Fire Model



Suppose calcium c is released from

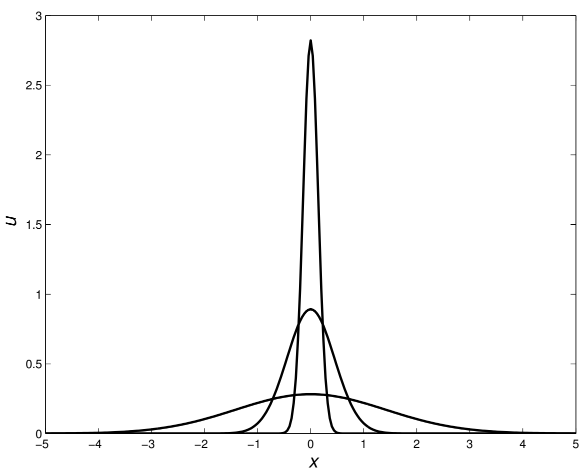
- a long line of evenly spaced release sites;
- Release of full contents σ occurs when the local concentration c reaches threshold θ.

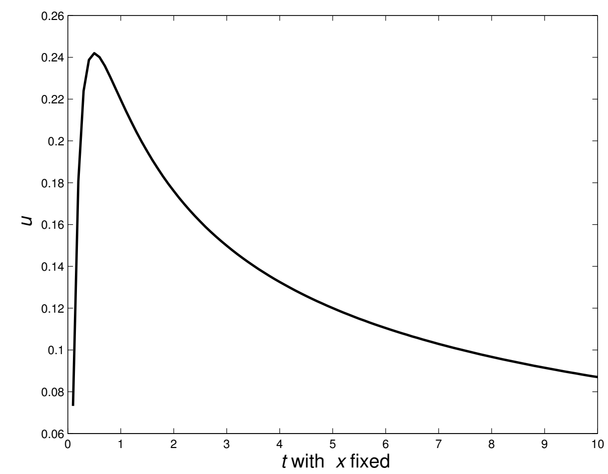
$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - k_s c + \frac{\sigma}{L}\sum_n \delta(x - nL)\delta(t - t_n)$$

Fire-Diffuse-Fire-II

Recall that the solution of the heat equation with δ-function initial data at $x = x_0$ and at $t = t_0$ is

$$c(x,t) = \frac{1}{\sqrt{4\pi D(t-t_0)}} \exp\left(-\frac{(x-x_0)^2}{4D(t-t_0)} - k_s(t-t_0)\right)$$



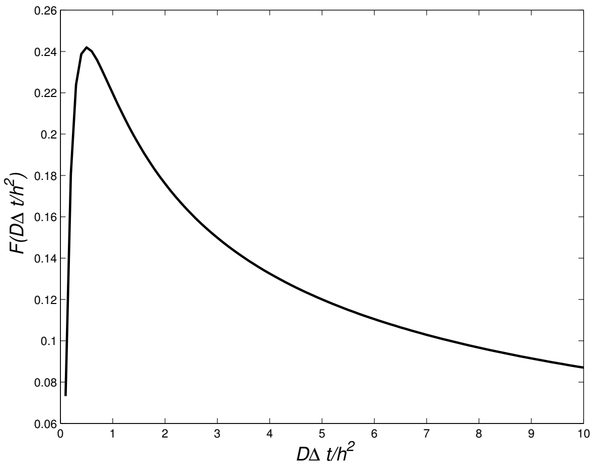


Fire-Diffuse-Fire-III

Suppose known firing times are $t_j = j\Delta t$ at position $x_j = jL$, $j = -\infty, \cdots, n-1$. Find t_n.

At $x = x_n = nL$,

$$c(nL,t) = \frac{1}{L}\sum_{j=-\infty}^{n-1} \frac{\sigma}{\sqrt{4\pi D(t-t_j)}} \exp\left(-\frac{(n-j)^2L^2}{4D(t-t_j)} - k_s(t-t_j)\right) \equiv \frac{\sigma}{L} F\left(\frac{D\Delta t}{L^2}\right)$$

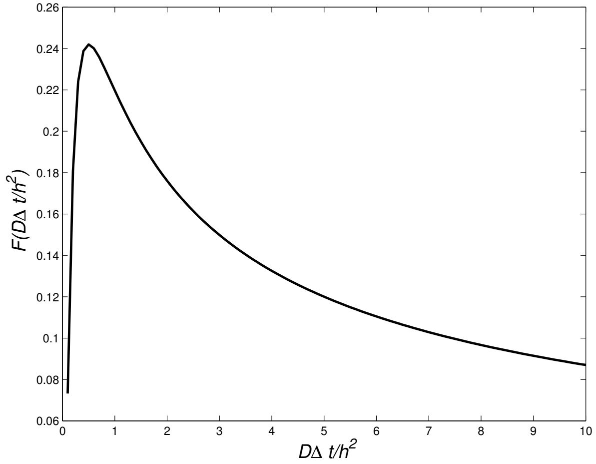


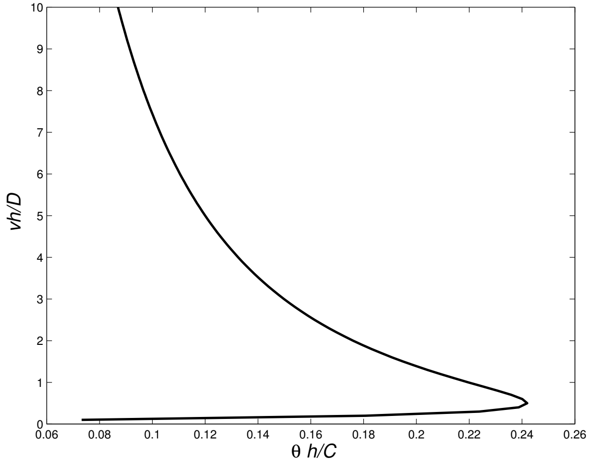
Fire-Diffuse-Fire-IV

To find the delay Δt, solve the equation

$$\frac{\theta L}{\sigma} = f(\frac{D\Delta t}{L^2}).$$

This is easy to do graphically:





Conclusion: Propagation fails for $\frac{\theta L}{\sigma} > \theta^*$ (i.e. if L is too large, θ is too large, or σ is too small.)

Problems

What went wrong?

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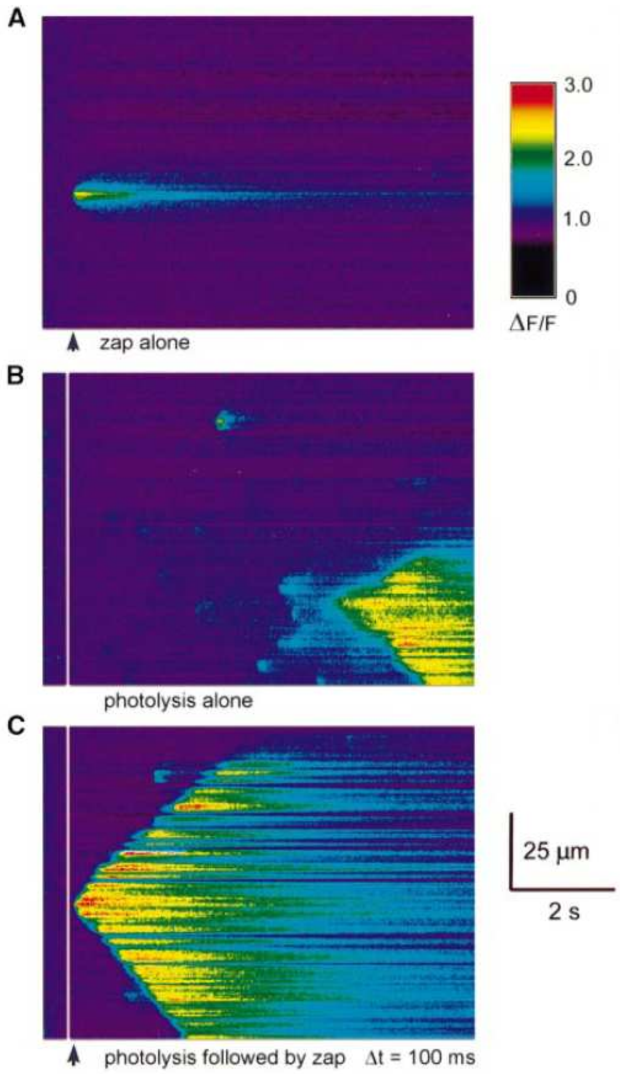
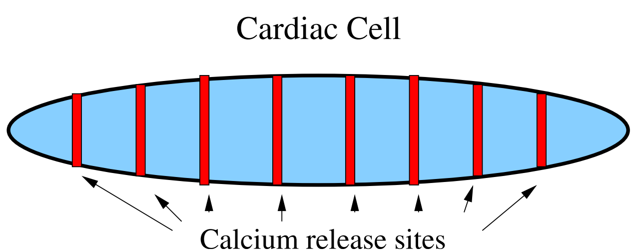
1. Calcium is not spatially homogenious; channels are controlled by **local** calcium concentration.
2. Channel openings are not deterministic.

Calcium Sparks and Waves



Discrete Release Sites



$$\frac{\partial c}{\partial t} = g_{max} \frac{1}{L} \sum_n \delta(x - x_n)\ y_n\ (c_e - c) - J_{SERCA} + D \frac{\partial^2 c}{\partial x^2}$$

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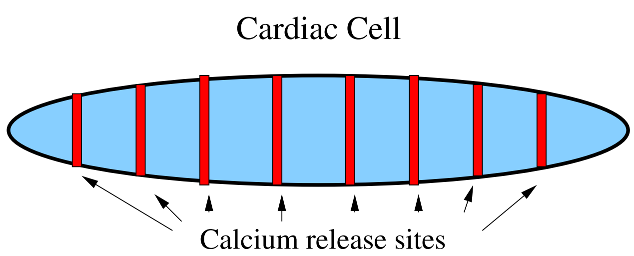
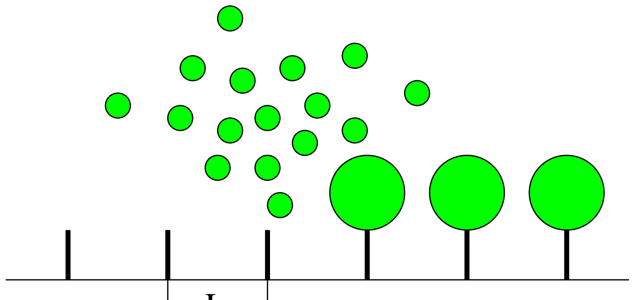


$$\frac{\partial c}{\partial t} = g_{max}\frac{1}{L}\sum_n \delta(x - x_n)\boxed{y_n}(c_e - c) - J_{SERCA} + D\frac{\partial^2 c}{\partial x^2}$$

with

y_n a random variable with values 0 or 1, with transition probability that depends on local calcium concentration.

Stochastic Fire-Diffuse-Fire Model



Suppose calcium c is released from

- a long line of evenly spaced release sites;
- Release of full contents σ is a stochastic process with probability depending on the local calcium concentration.

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - k_s c + \frac{\sigma}{L}\sum_n \delta(x - nL)\delta(t - t_n)$$

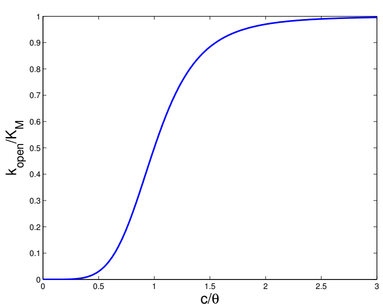
Stochastic Analysis

Let $P_n(t)$ be the probability that site n has fired before time t. Then

$$\frac{dP_n}{dt} = k_{open}(c(x_n, t))(1 - P_n)$$

where $P_n(0) = 0$, and

$$k_{open}(c) = K_M \frac{c^N}{\theta^N + c^N}.$$



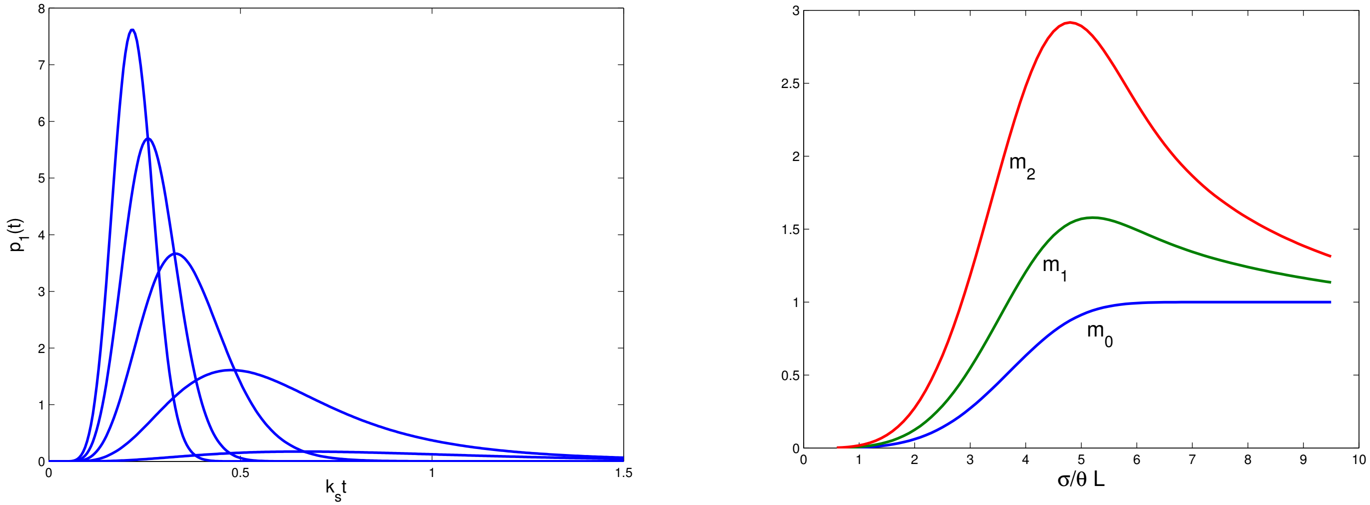
Remark: $c(x,t)$ is known as before

$$c(x,t) = \sum_{j=0}^{n-1} \frac{1}{\sqrt{4\pi D(t-t_j)}} \exp\left(-\frac{(x-x_j)^2}{4D(t-t_j)} - k_s(t-t_j)\right)$$

except that now the t_j are continuous random variables.

Site 1

Suppose site zero fires at time $t = 0$. What happens at site 1?



$p_1(t) = \frac{dP_1}{dt}$, and $m_k = \int_0^\infty t^k p_1(t) dt$ is the k^{th} moment.
Therefore, $m_0 = P_1(\infty)$ is the probability of firing at all.

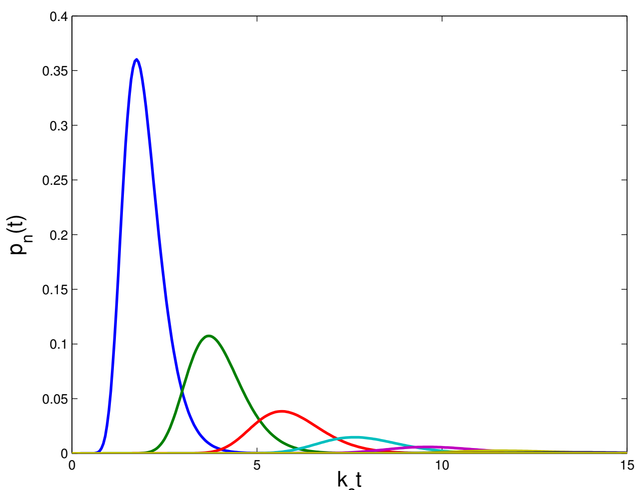
Observe: As $\frac{\sigma}{\theta L}$ increases, firing occurs sooner and with less variance.

Site n

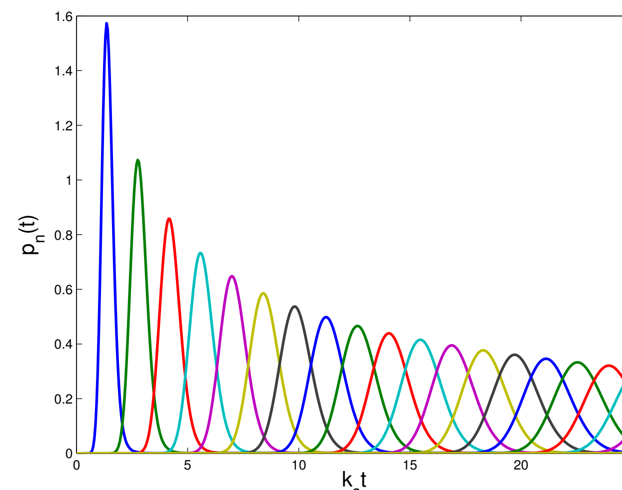
Suppose site zero fires at time $t = 0$. What happens at site $n > 1$?

$p_n(t)$ satisfies the renewal equation

$$p_n(t) = \int_0^\infty p_1(t-s)p_{n-1}(s)ds.$$



$\frac{\sigma}{\theta L}$ small - wave fails



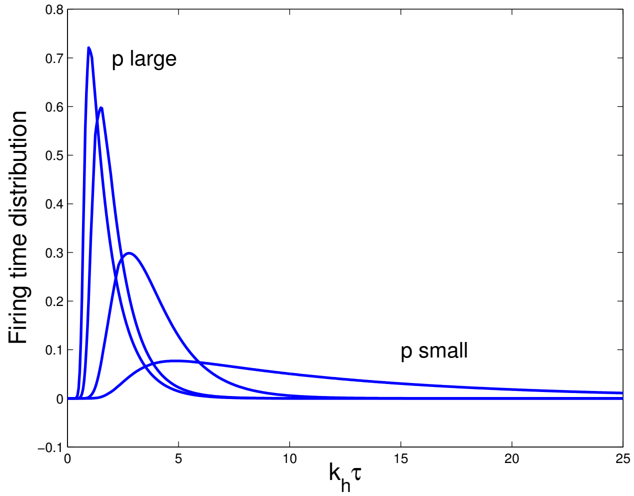
$\frac{\sigma}{\theta L}$ large - wave succeeds

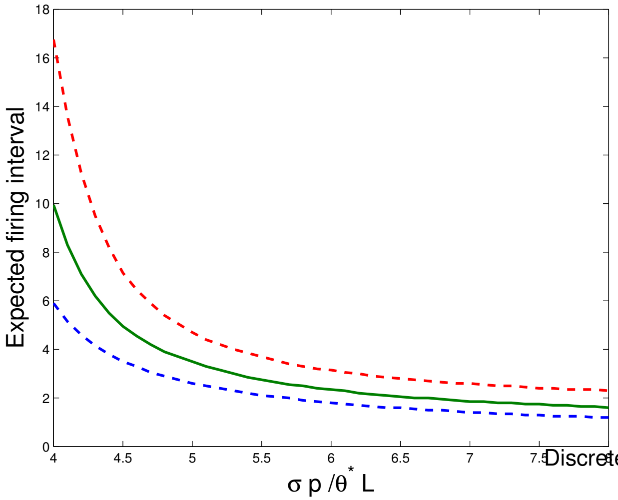
Whole Cell Calcium Release Events

Whole cell calcium release events are governed by three things:

- localized calcium release (sparks) - a Poisson process
- spark to wave transition - whole cell release
- resetting the threshold θ (time dependent recovery with time constant k_h).

Putting it all together (using similar methods)





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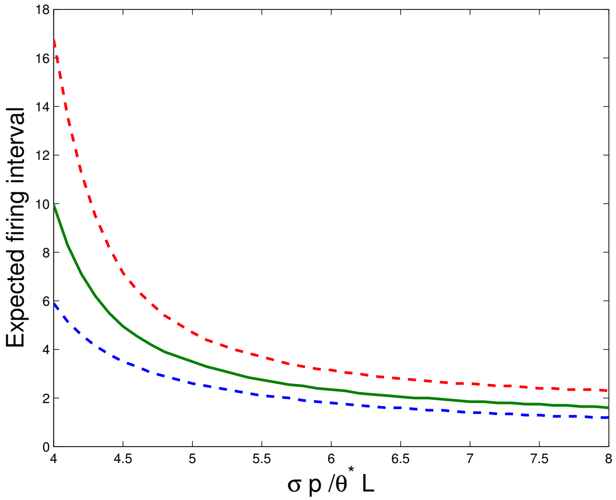

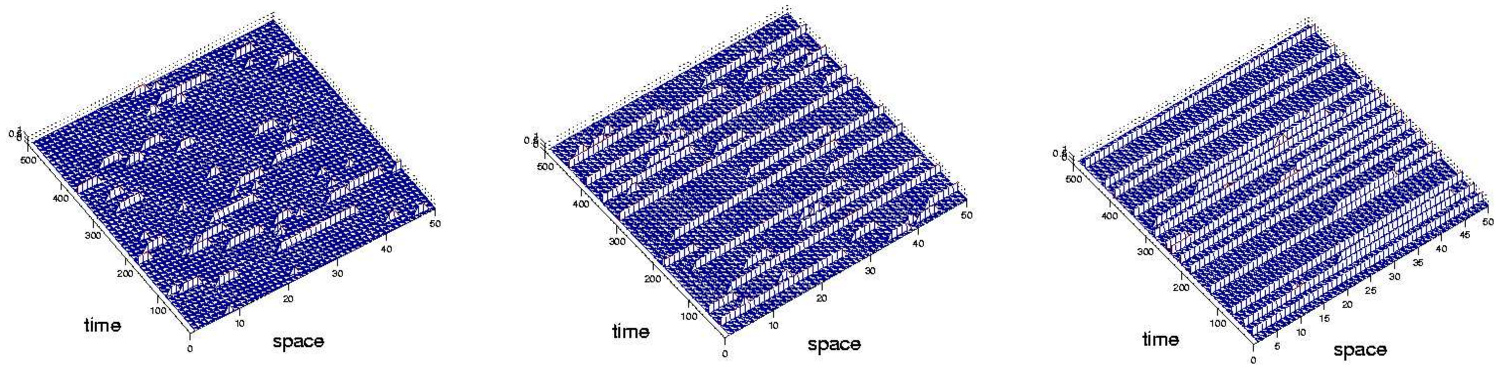

Conclusion

Whole cell calcium models fail because:

- Release sites are discrete and diffusion is too slow;
- Release is a stochastic event for which the law of large number does not apply.

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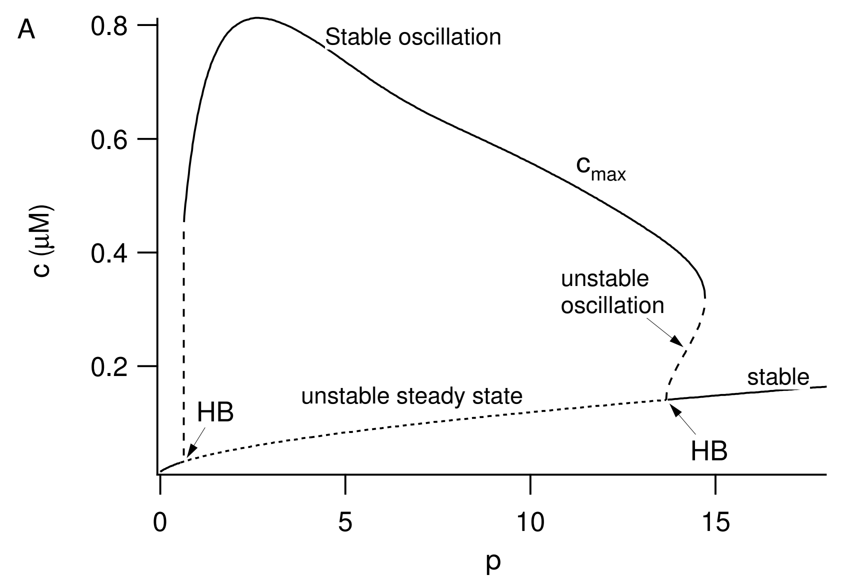
Consequently, not this



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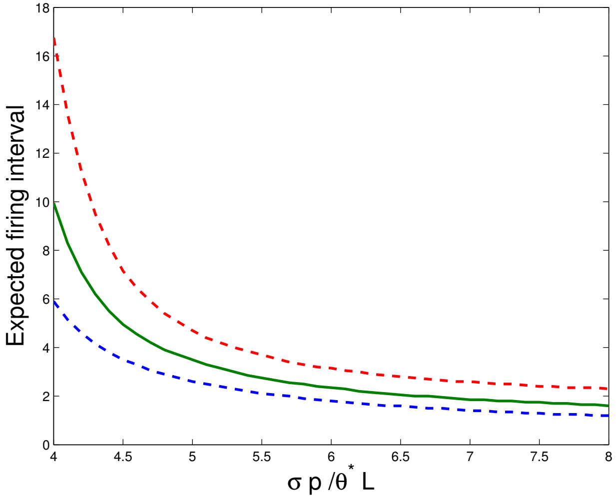
but this



Acknowledgments

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- No computers were harmed by Microsoft products during the production of this talk.

The End