Stochastic Calcium Oscillations

J. P. Keener

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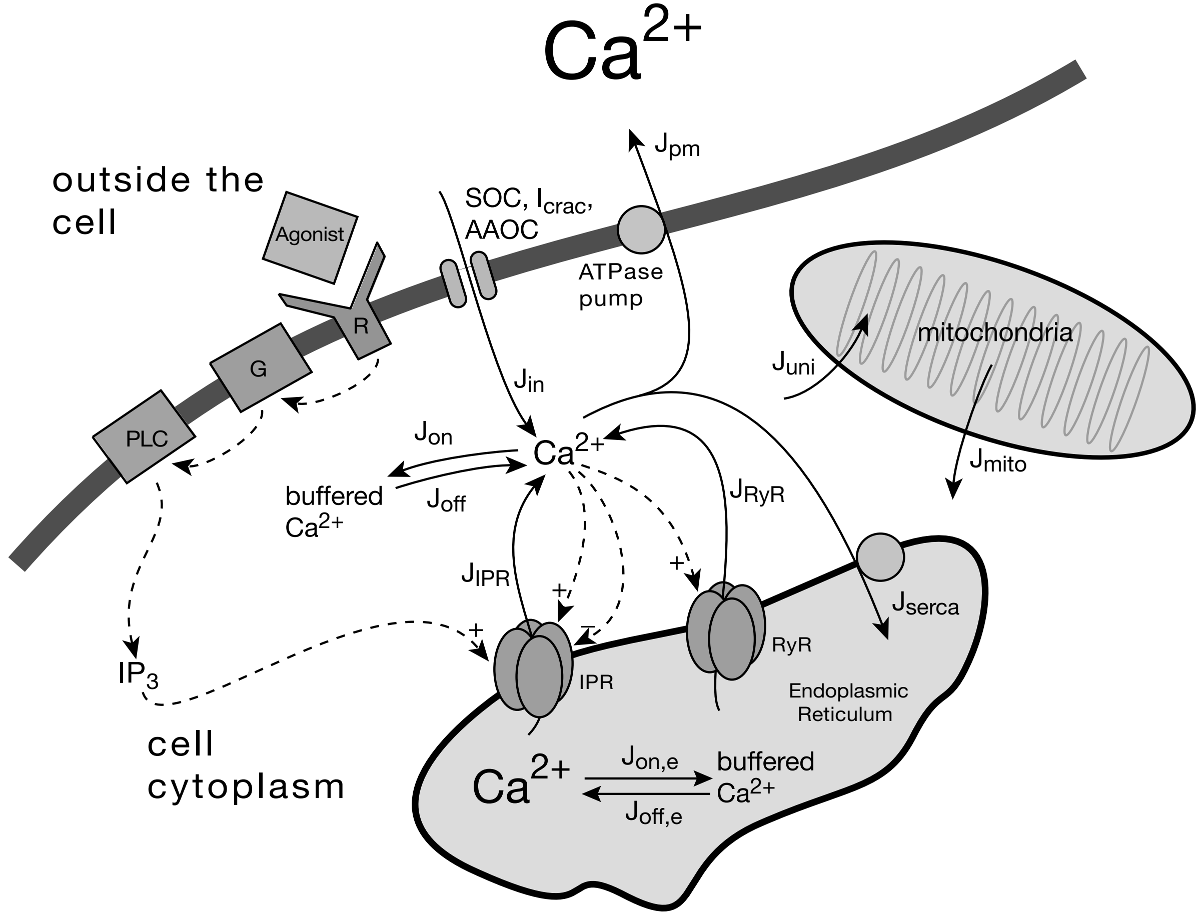
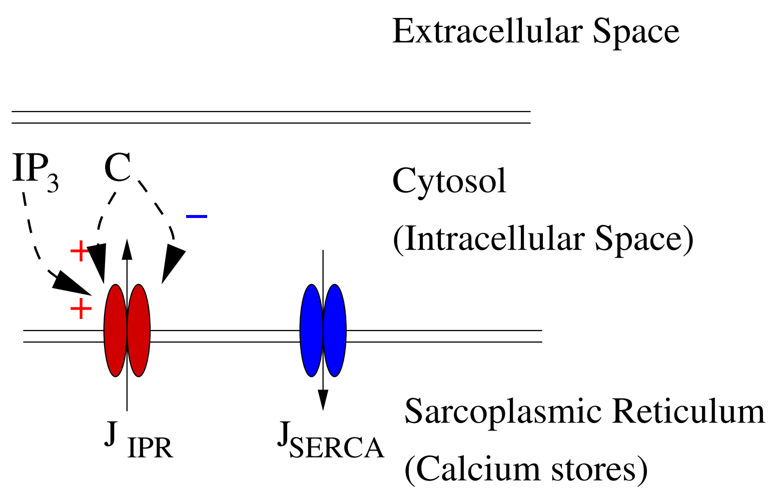
Calcium Handling



Basic Calcium Model

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



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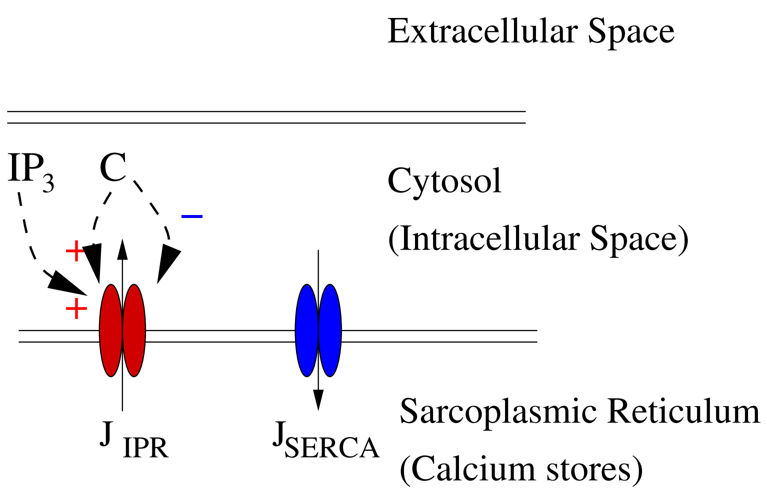

with

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

Basic Calcium Model

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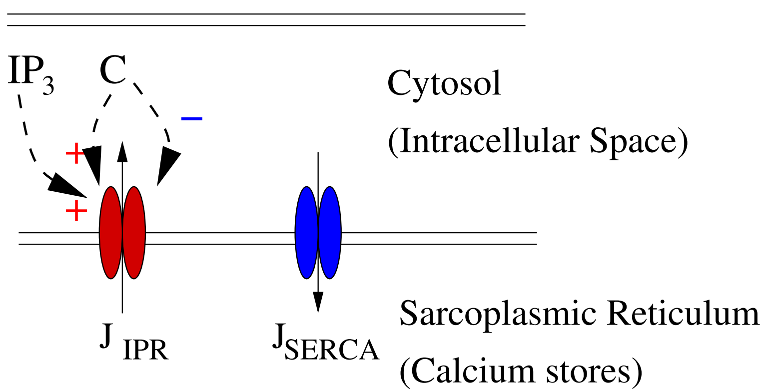

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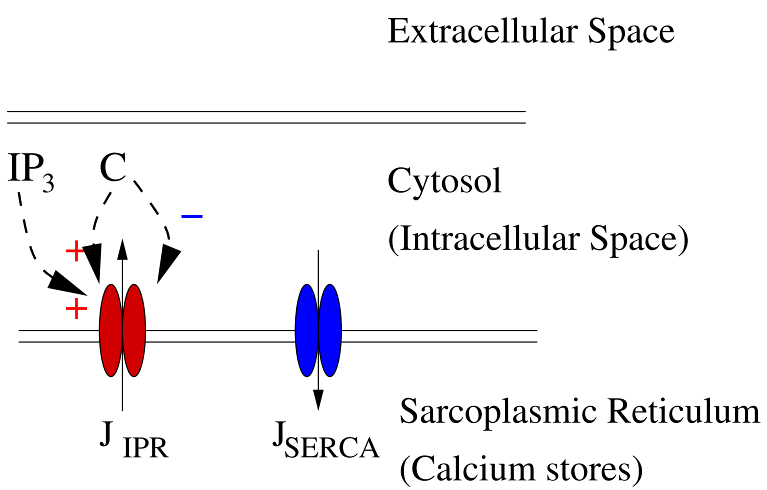

with

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

J_{SERCA} Sarco- and Endoplasmic Reticulum Calcium ATPase,

What are the flux terms?

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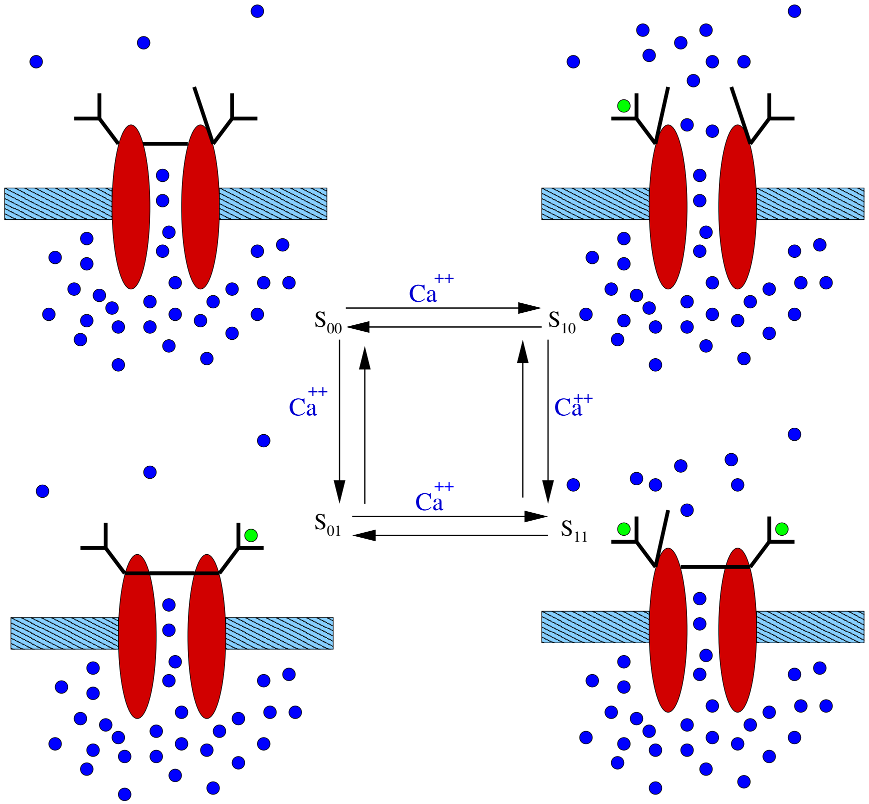
CICR in IP_3 Receptors



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

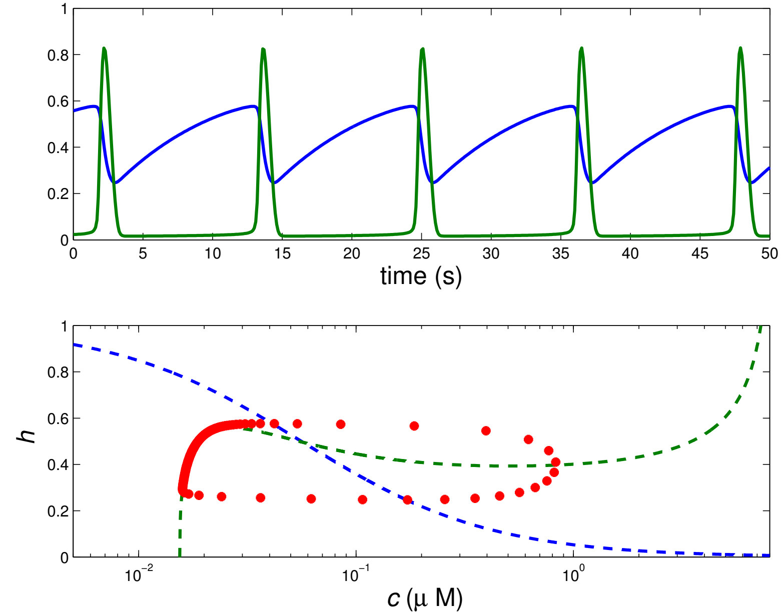
$$\frac{dc}{dt} = (g_{max}P_o + J_{er})(c_{sr} - c) - J_{SERCA},$$

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

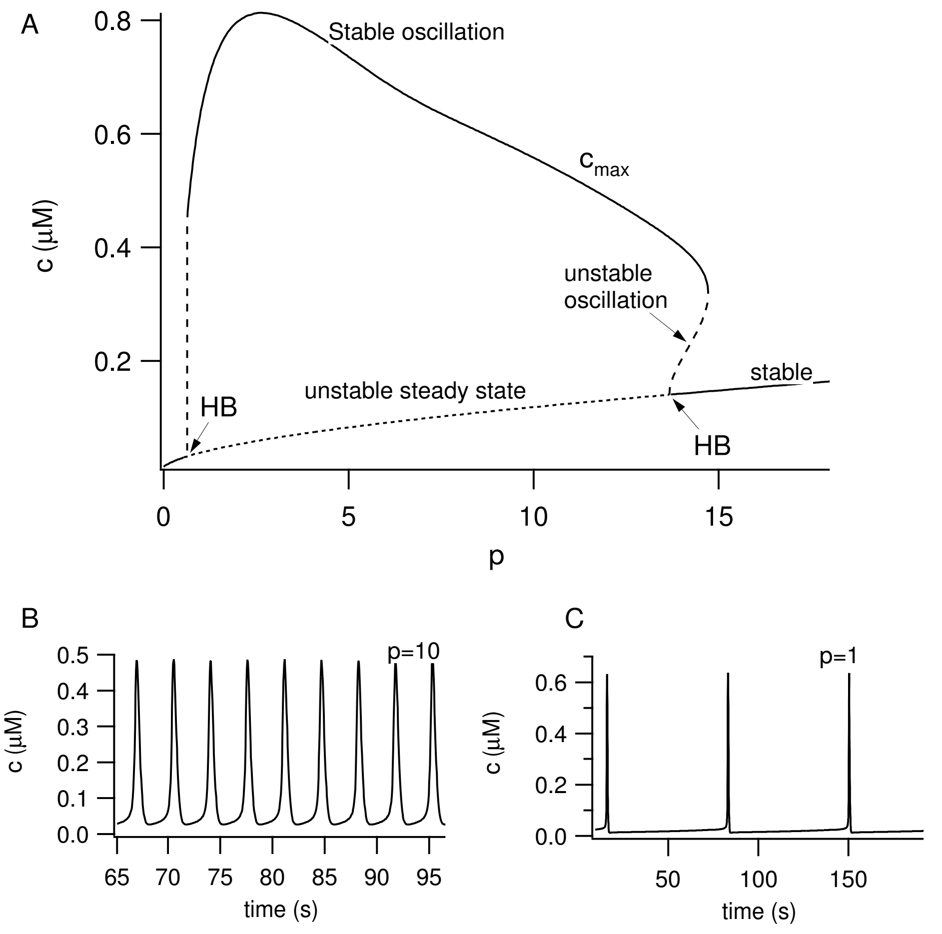
where

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

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



Bifurcation Diagram



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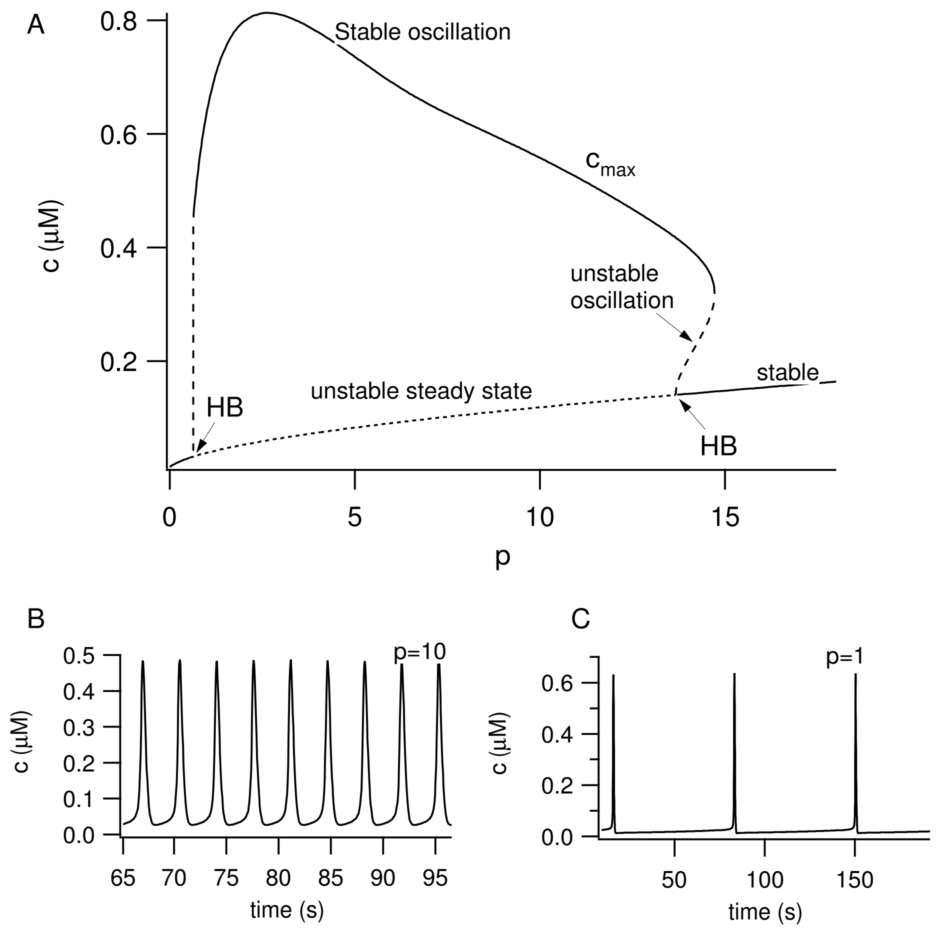

But the data do not look like this at all!

Onset of Oscillations

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

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- At high IP_3, calcium release is frequent and regular (a periodic oscillation).

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- At low IP_3 concentrations, calcium release is infrequent and highly irregular.
- At medium IP_3, calcium release is less rare and less irregular.
- At high IP_3, calcium release is frequent and regular (a periodic oscillation).

The data show no Hopf Bifurcations or sharp onset of oscillations.

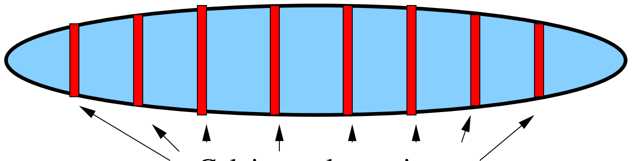
Problems

What went wrong?

There are (at least) two problems with this model:

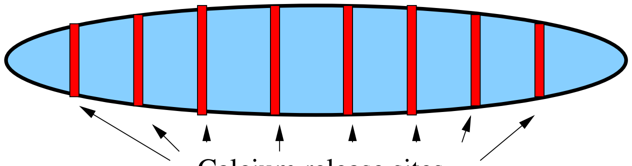
1. Calcium is not spatially homogenious; channels are controlled by **local** calcium concentration.
2. Channel openings are not deterministic.

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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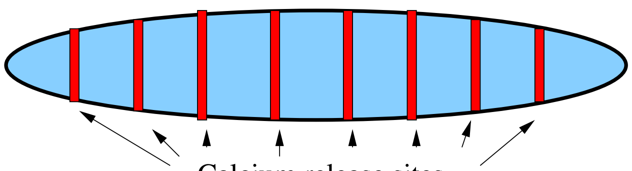


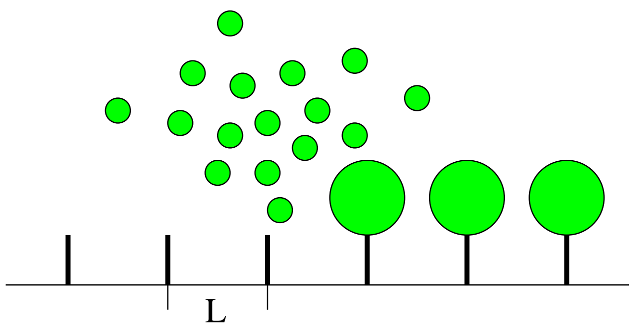
$$\frac{\partial c}{\partial t} = \boxed{\frac{1}{L}\sum_n \delta(x - x_n)} J_{IPR} - J_{SERCA} + \boxed{D\frac{\partial^2 c}{\partial x^2}}$$

with

x_n location of release sites separated by distance L,

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

Fire-Diffuse-Fire Model



Suppose calcium c is released from

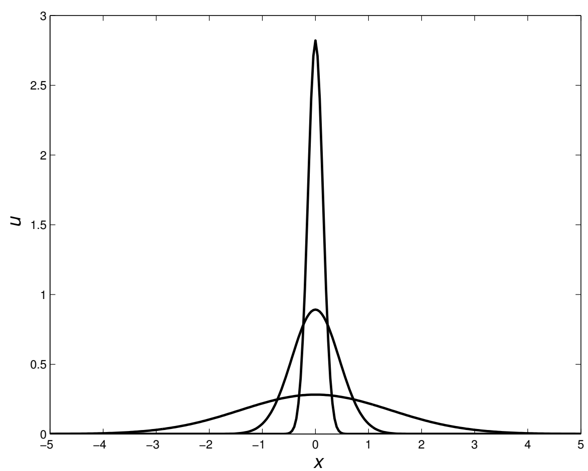
- a long line of evenly spaced release sites;
- Release of full contents σ occurs when the local concentration c reaches threshold θ.

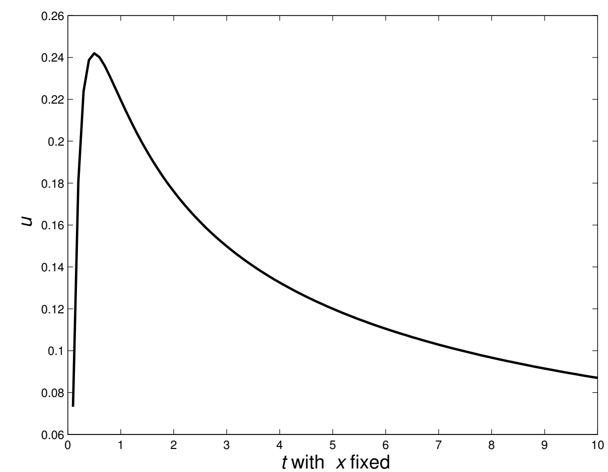
$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - k_s c + \frac{\sigma}{L}\sum_n \delta(x - nL)\delta(t - t_n)$$

Fire-Diffuse-Fire-II

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

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



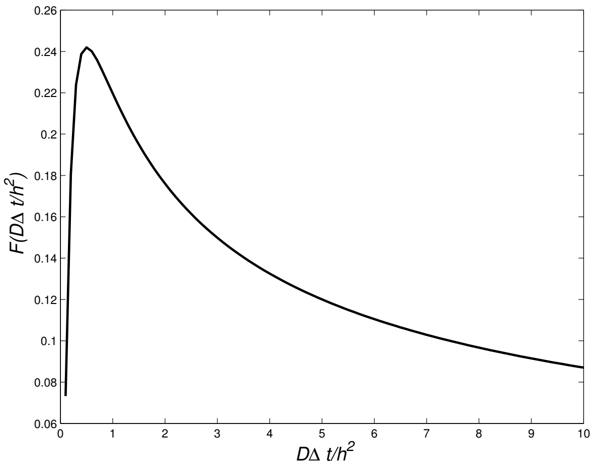


Fire-Diffuse-Fire-III

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

At $x = x_n = nL$,

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

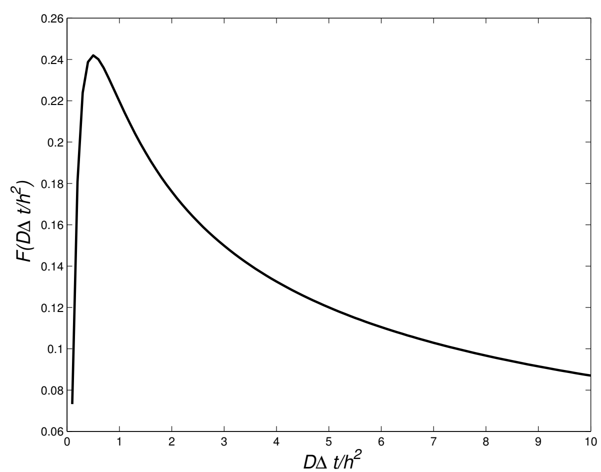


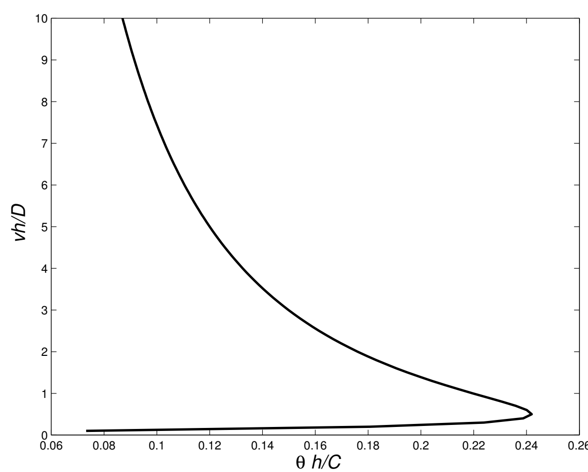
Fire-Diffuse-Fire-IV

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.)

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Problems

What went wrong?

There are two problems with this model:

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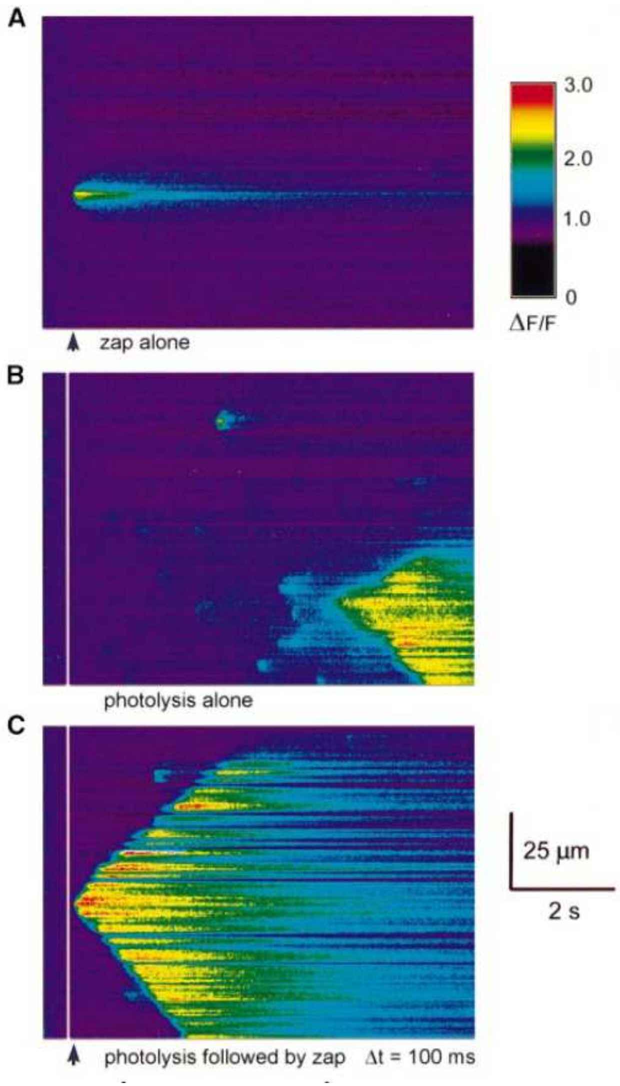
2. Channel openings are not deterministic.

Calcium Sparks and Waves



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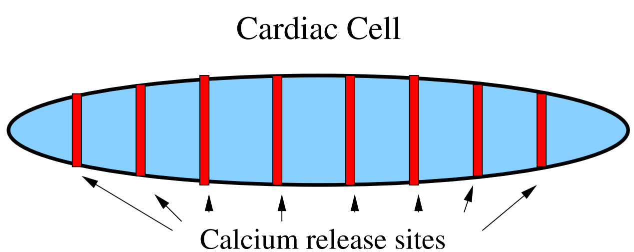
Discrete Release Sites



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

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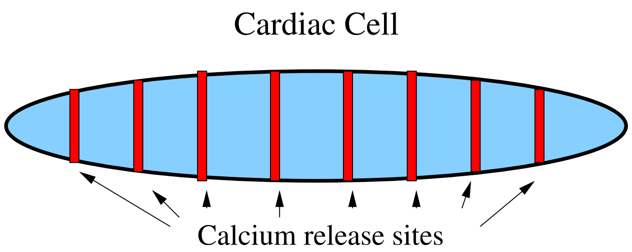
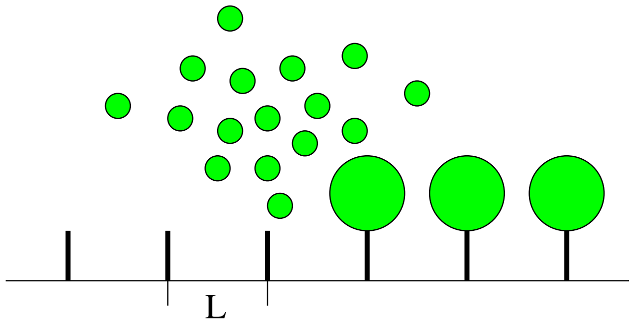


$$\frac{\partial c}{\partial t} = g_{max}\frac{1}{L}\sum_n \delta(x - x_n)\boxed{y_n}(c_e - c) - J_{SERCA} + D\frac{\partial^2 c}{\partial x^2}$$

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.

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

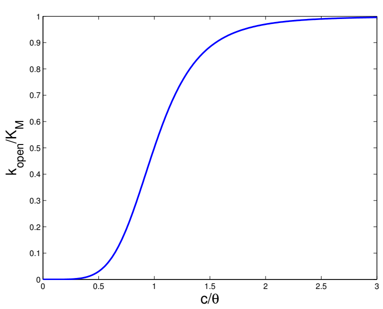
Stochastic Analysis

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

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



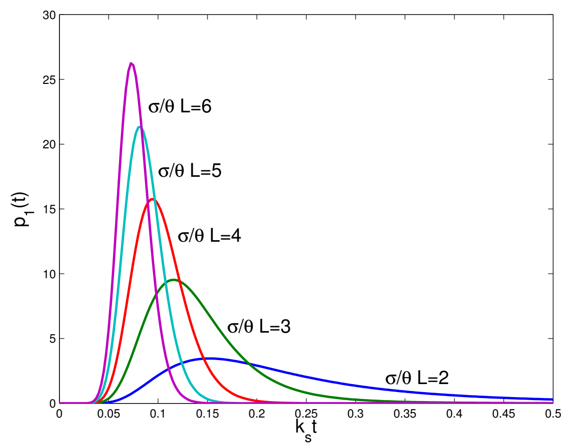
Remark: $c(x, t)$ is known as before

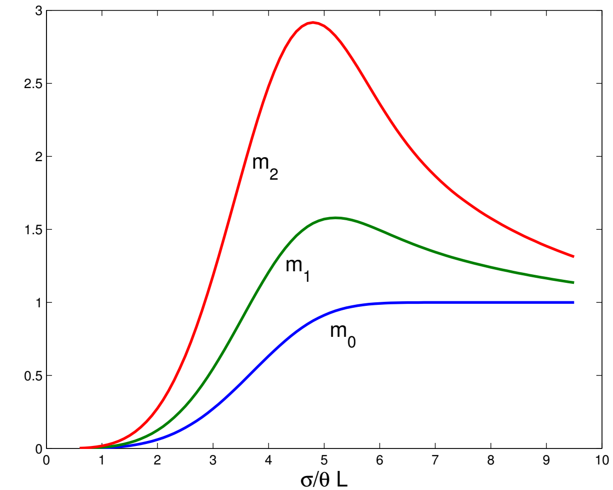
$$c(x,t) = \sum_{j=0}^{n-1} \frac{1}{\sqrt{4\pi D(t - t_j)}} \exp(-\frac{(x - x_j)^2}{4D(t - t_j)} - k_s(t - t_j))$$

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?





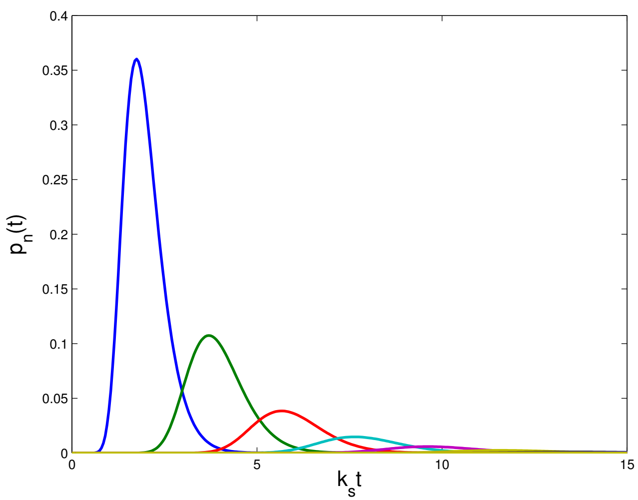
$p_1(t) = \frac{dP_1}{dt}$, and $m_k = \int_0^\infty t^k p_1(t) dt$ is the k^{th} moment. Therefore, $m_0 = P_1(\infty)$ is the probability of firing at all.

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

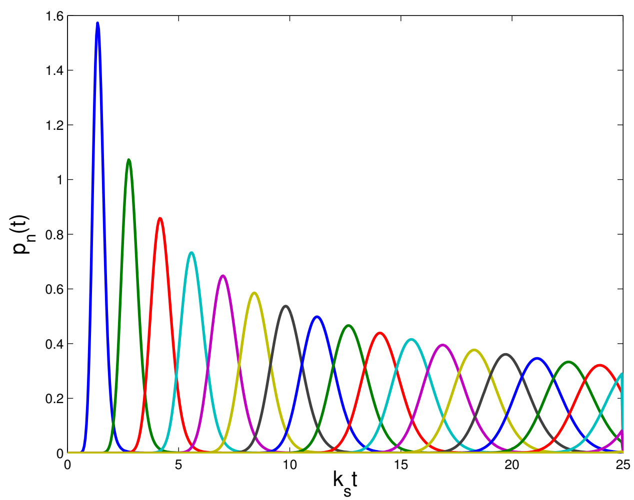
Site n

Suppose site zero fires at time $t = 0$. What happens at site $n > 1$? $p_n(t)$ satisfies the renewal equation (stochastic wave equation):

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



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

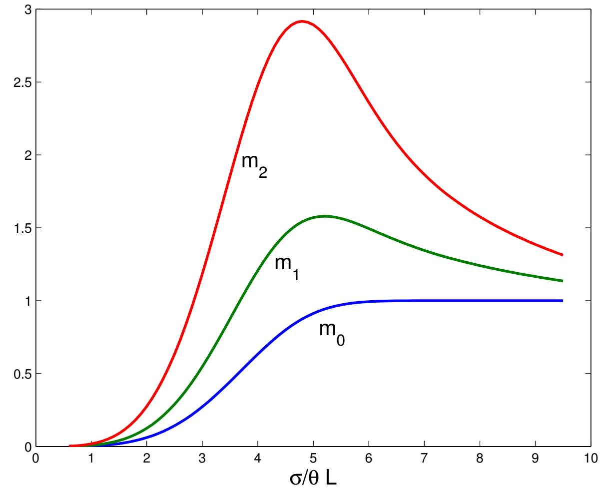


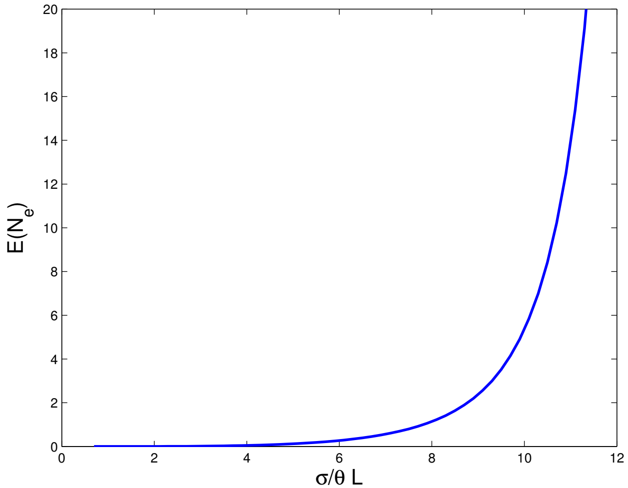
$\frac{\sigma}{\theta L}$ large - wave succeeds

Extent of Propagation

Extent of propagation N_e is exponentially distributed

$$P(N_e = n) = m_0^n(1 - m_0).$$

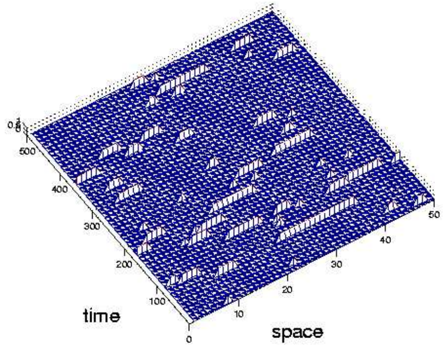


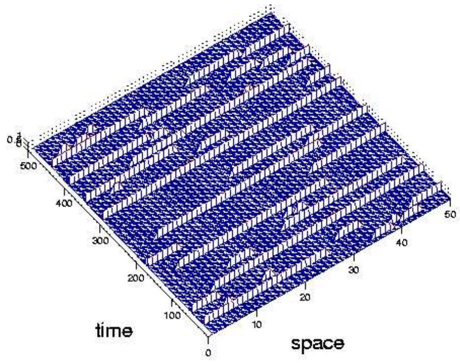


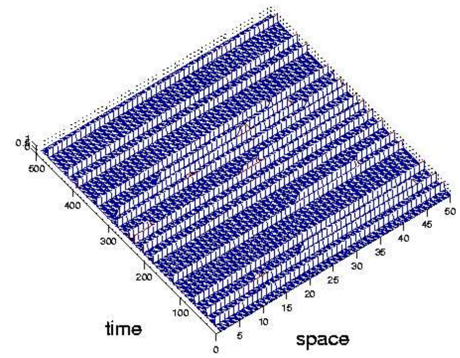
Whole Cell Calcium Release Events

Whole cell calcium release events are governed by three things:

- localized calcium release (sparks) - a Poisson process
- spark to wave transition - the rapid calcium transient
- removal of inactivation (a slow process).







A Chapman-Kolmogorov Equation

Let h be fraction of sites that are not inhibited ($0 \leq h < 1$),

$p(h,t)$ be the probability that fraction of uninhibited sites is h,

$\frac{\partial p}{\partial t} = -k_h \frac{\partial}{\partial h}((1-h)p) - \beta M h \, p + \int_h^1 W(\eta, h) \, p(\eta, t) d\eta,$

,

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For consistency,

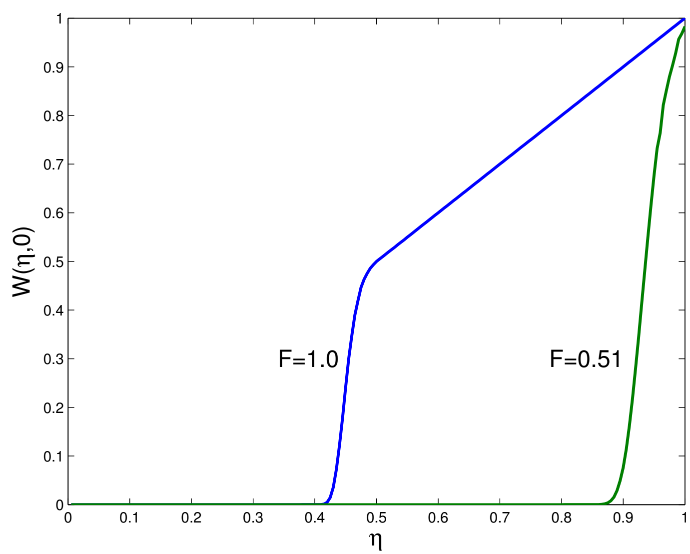
$$\beta M h = \int_0^h W(h, \eta) d\eta + W(h, 0).$$

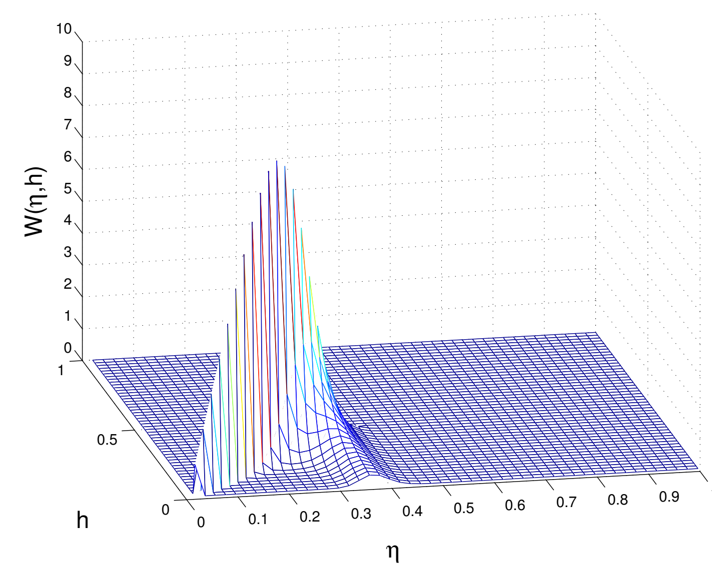
$W(h, 0) =$ probability of whole cell release.

Whole Cell Calcium Release Events

There are three behaviors:

- Small h: Sparks do not propagate; $(W(\eta, h)) \sim \delta(\eta - h))$
- Intermediate h: Truncated waves;
- Large h: Whole cell release



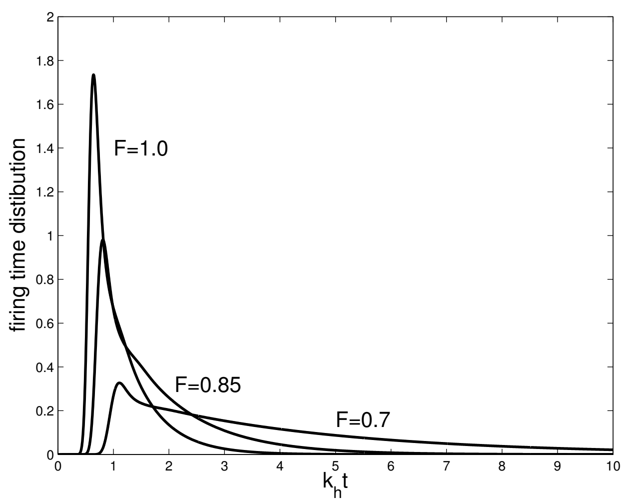


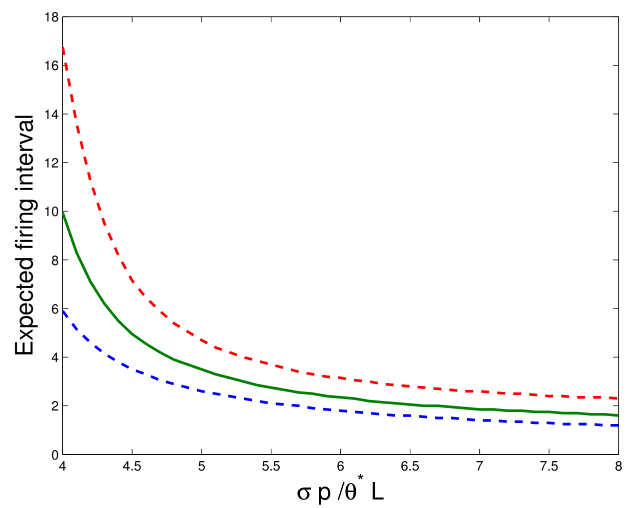
Whole Cell Calcium oscillations

Firing time distribution is

$$P(t) = 1 - \int_0^1 p(h,t)dt, \qquad p(h,0) = \delta(h).$$

Solving C-K equation numerically:





Spontaneous Spark Rate

Question: At what rate are spontaneous sparks produced?
One way to approach this question:

- Suppose the limiting deterministic dynamics are governed by the bistable equation

$$\frac{dc}{dt} = f(c).$$

  What is the appropriate Fokker-Planck equation

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial c}(f(c)p) + \frac{\partial^2}{\partial c^2}(D(c)p)?$$

- Since $f(c)$ is bistable it is the derivative of a double well potential $F'(c) = f(c)$. What is the mean rate of escape from the smaller of the two wells?

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Example

For the stochastic differential equation

$$\frac{dc}{dt} = \frac{1}{N}\sum_{n}^{Nh} y_n f(c) - g(c),$$

with

$$y_n : 0 \underset{\beta(c)}{\overset{\alpha(c)}{\rightleftarrows}} 1,$$

the deterministic limit is

$$\frac{dc}{dt} = h\frac{\alpha}{\alpha+\beta} f(c) - g(c),$$

but, what is the spark rate?

The Fast Transition Limit

Two approaches:

- Fast uptake (Hinch, Hinch and Chapman, Coombes, Hinch and Timofeeva), appropriate for cardiac cells;
- Fast transition rates:
  Fokker-Planck equation is

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial c}\left((h\frac{\alpha}{\alpha+\beta}f(c) - g(c))p\right) + \frac{\partial^2}{\partial c^2}\left(\frac{h}{N}\frac{\alpha\beta}{(\alpha+\beta)^3}f^2(c)p\right) +$$

This suggests a scaling law

$$k_{spark} \sim A\exp(-\frac{\lambda N}{h}),$$

for small h.

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Summary

Deterministic 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 numbers does not apply.

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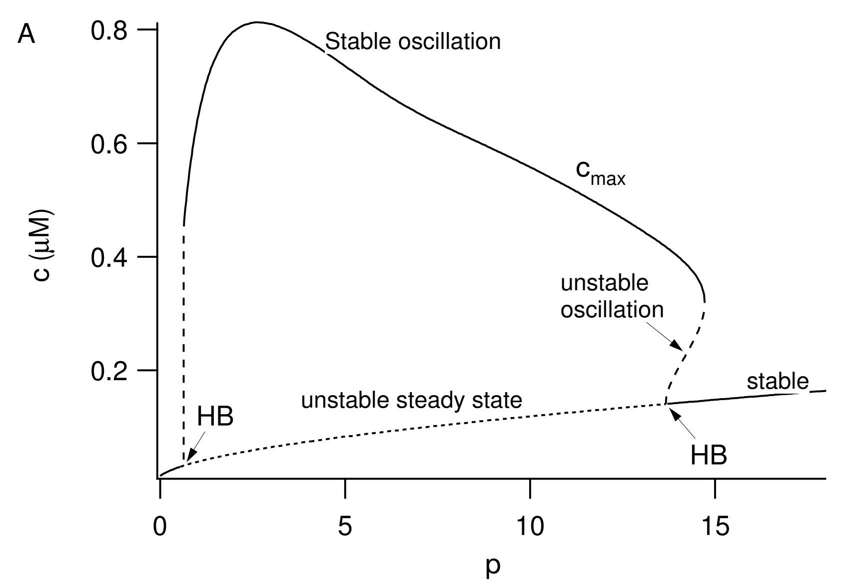
Consequently, not this



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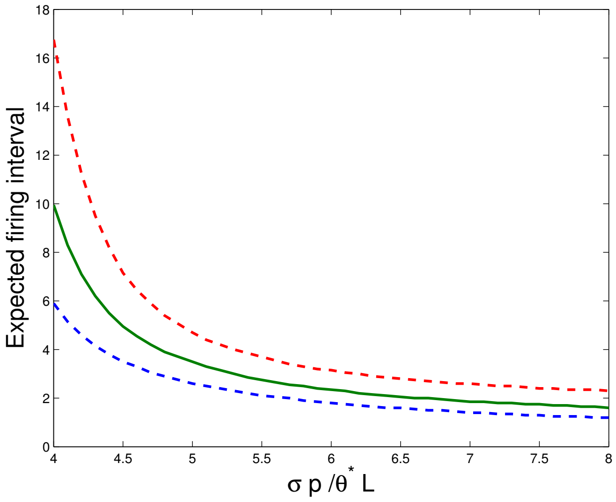

Acknowledgments

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

The End