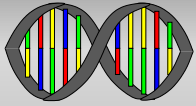


# ***The Effect of Discreteness in Calcium Handling***

J. P. Keener

Department of Mathematics  
University of Utah

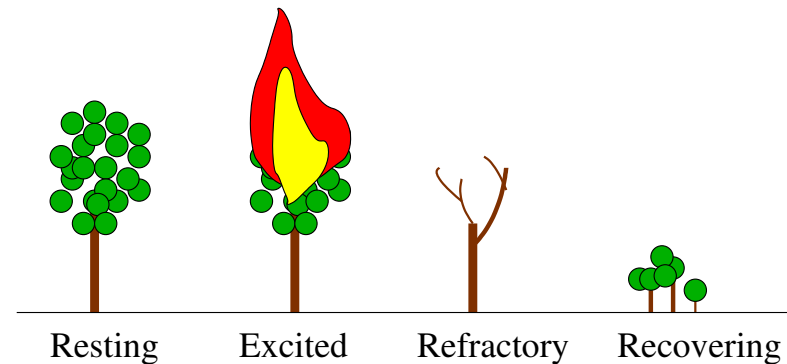


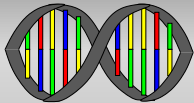
# Introduction - Excitability

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

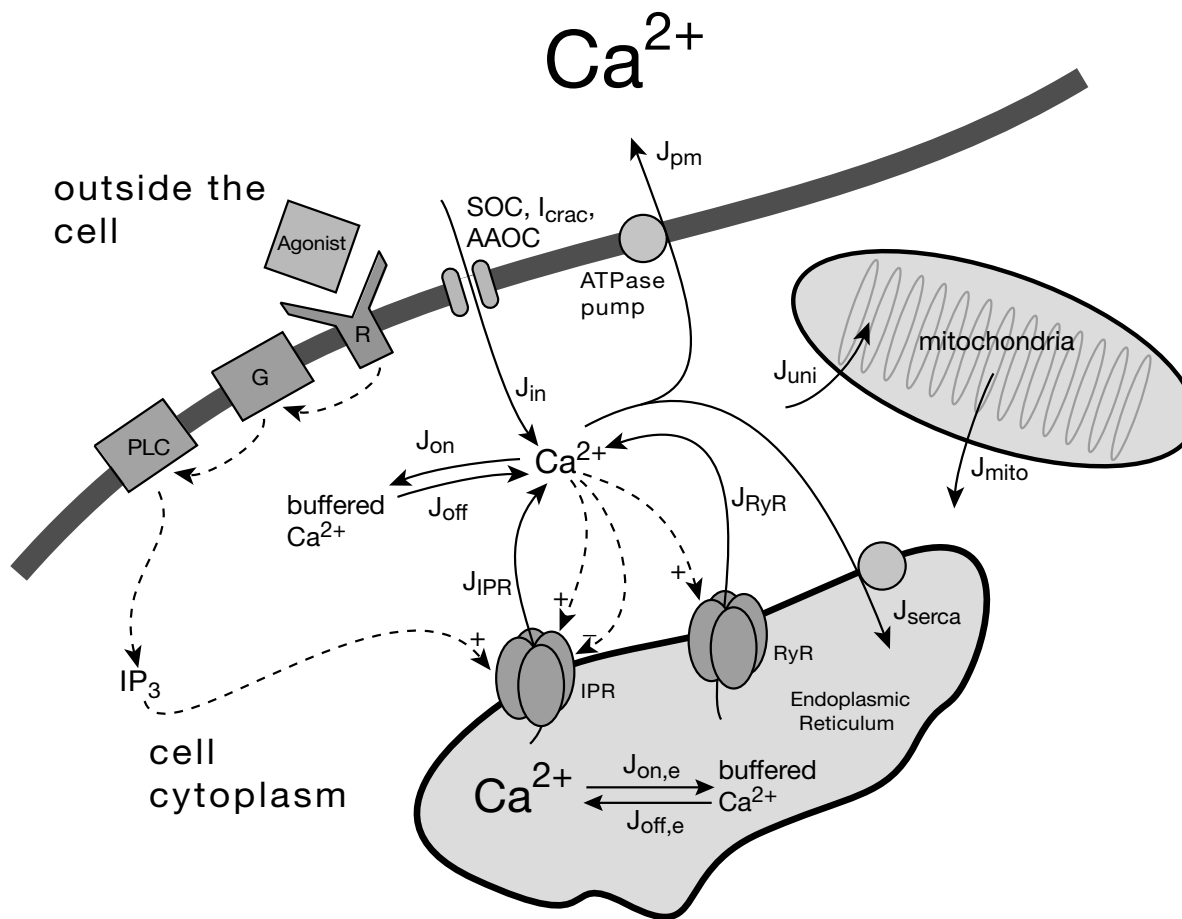
## Features of Excitability

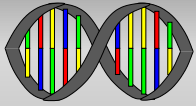
- Threshold Behavior
- Refractoriness
- Recovery





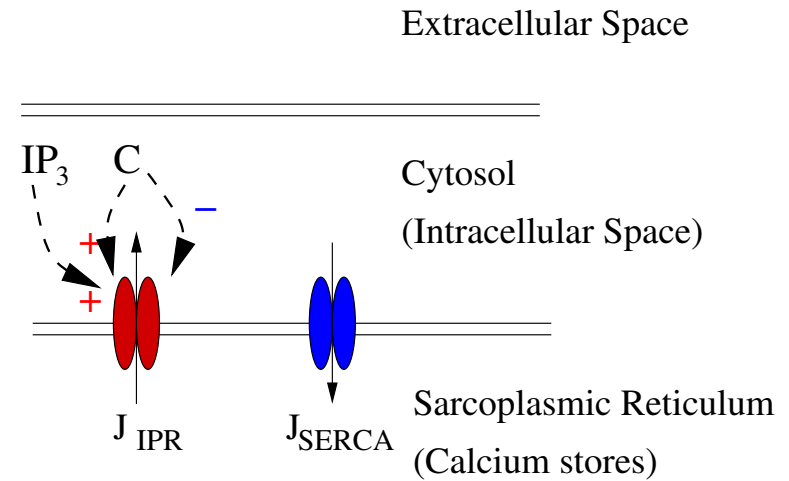
# Calcium Handling

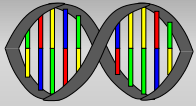




# Basic Calcium Model

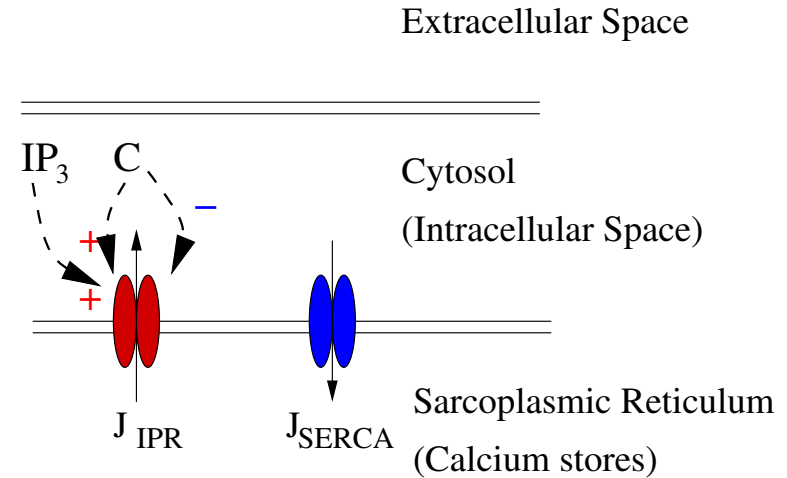
$$\frac{dc}{dt} = J_{IPR} - J_{SERCA}$$





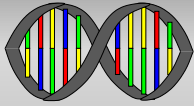
# Basic Calcium Model

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



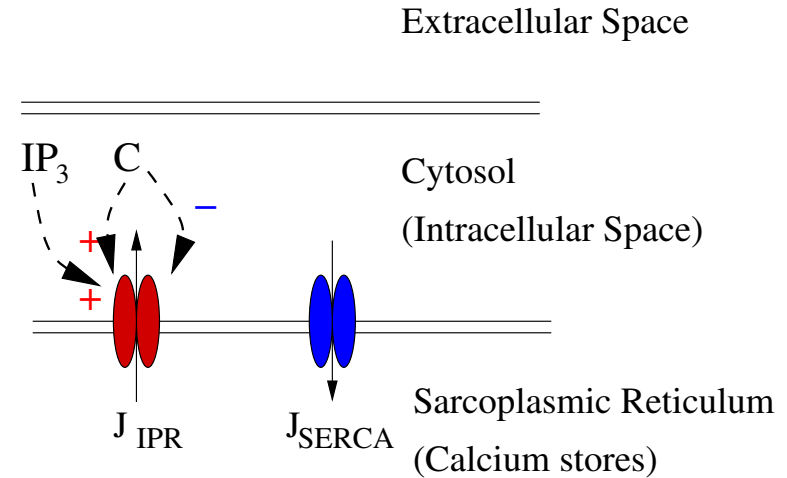
with

$J_{IPR}$  IP<sub>3</sub> Receptor - IP<sub>3</sub> and calcium regulated calcium channel,



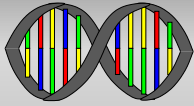
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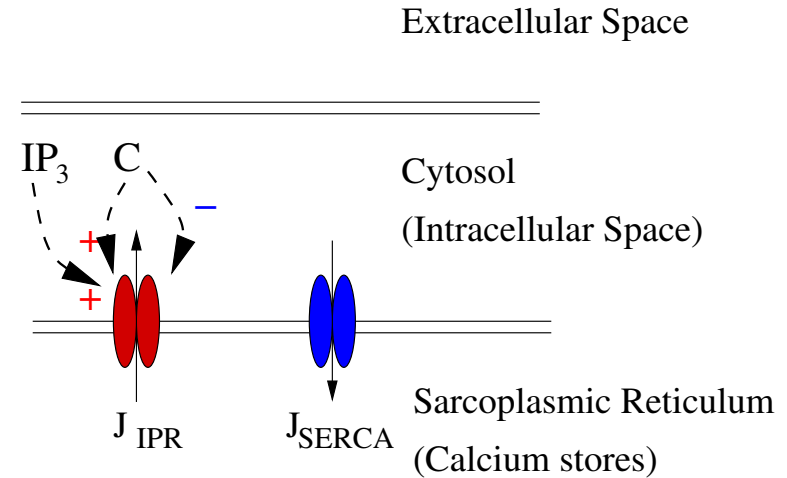
with

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



# Basic Calcium Model

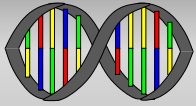
$$\frac{dc}{dt} = J_{IPR} - J_{SERCA}$$



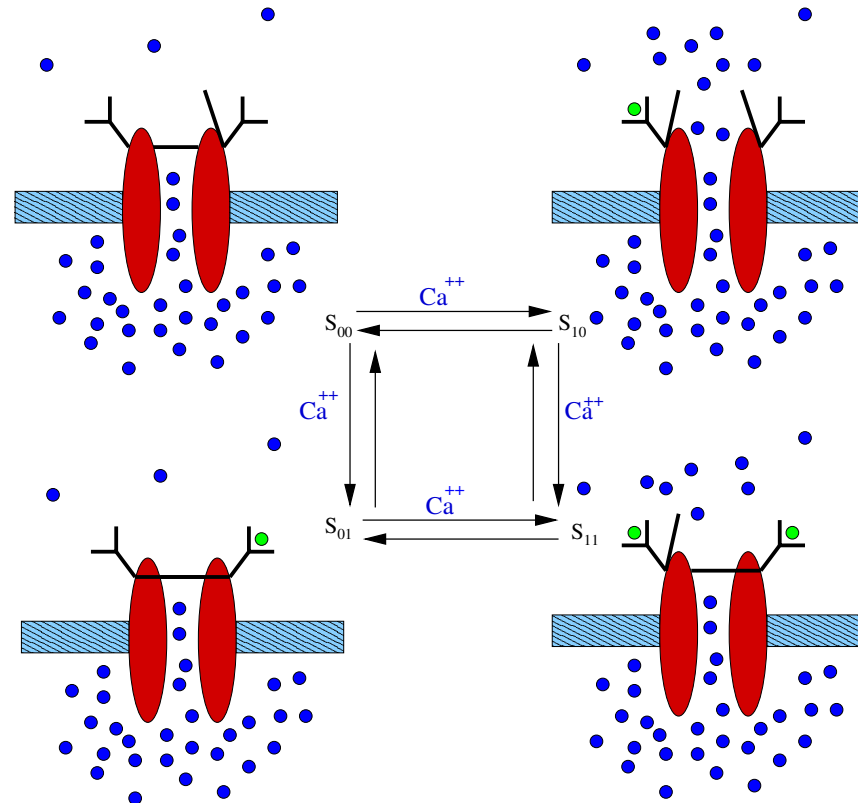
with

$J_{IPR}$   $IP_3$  Receptor -  $IP_3$  and calcium regulated calcium channel,  
 $J_{SERCA}$  Sarco- and Endoplasmic Reticulum Calcium ATPase,

What are the flux terms?



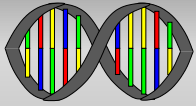
# $IP_3$ Receptors



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

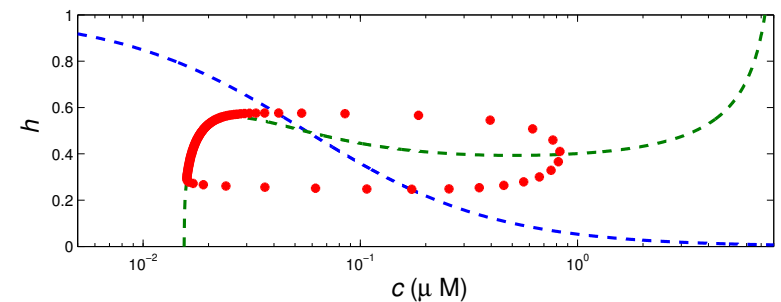
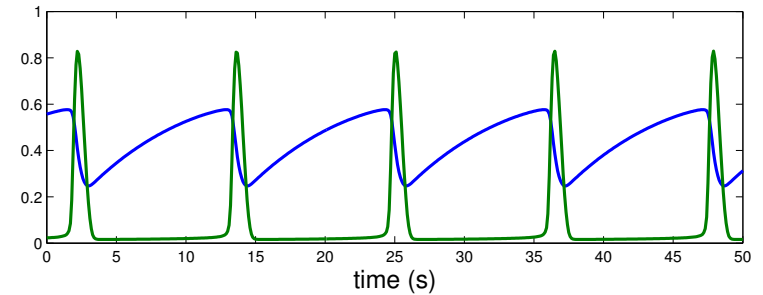
$$\frac{dc}{dt} = (g_{max}P_o + J_{er})(c_{sr} - c) - J_{SERCA},$$

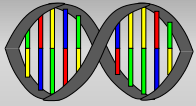
$$\frac{dh}{dt} = \phi_h(c)(1 - h) - \psi_h(c)h,$$

where

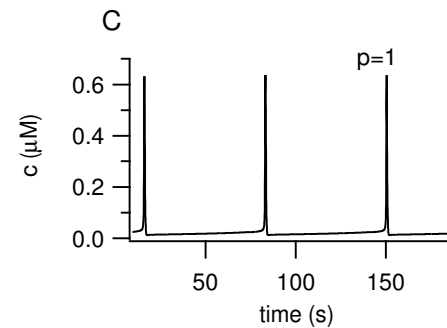
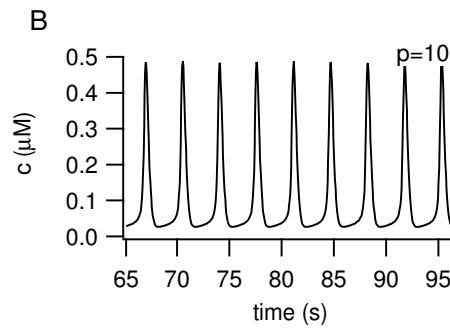
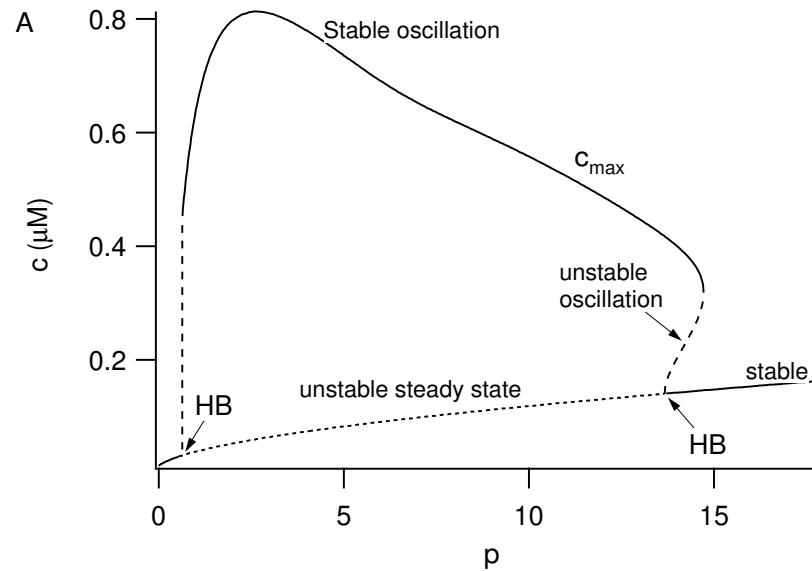
$$J_{SERCA} = V_{max} \frac{c^2}{K_s^2 + c^2},$$

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

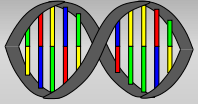




# Bifurcation Diagram



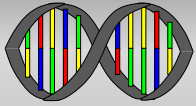
But the data do not look like this at all!



## ***Onset of Oscillations***

---

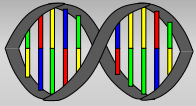
- At low  $IP_3$  concentrations, calcium release is infrequent and highly irregular.



# *Onset of Oscillations*

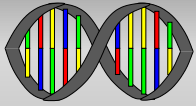
---

- At low  $IP_3$  concentrations, calcium release is infrequent and highly irregular.
- At medium  $IP_3$ , calcium release is less rare and less irregular.



# *Onset of Oscillations*

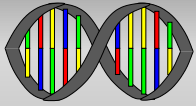
- At low  $IP_3$  concentrations, calcium release is infrequent and highly irregular.
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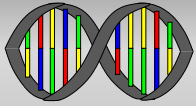
The data show **no** Hopf Bifurcations or sharp onset of oscillations.



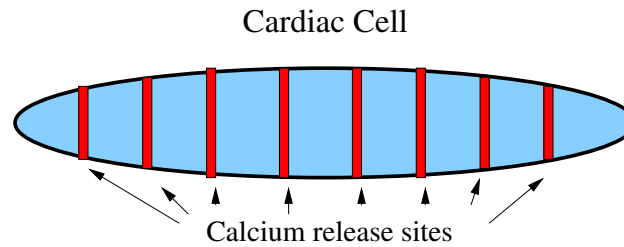
What went wrong?

There are two problems with this model:

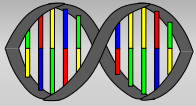
1. Calcium is not spatially homogenous; channels are controlled by local calcium concentration.
2. Channel openings are not deterministic.



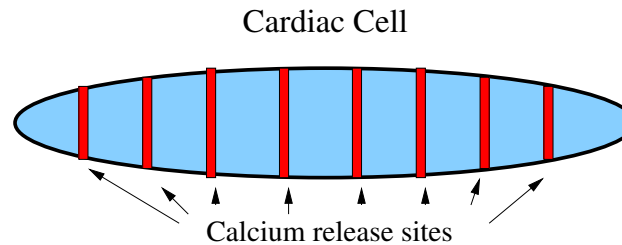
# Discrete Release Sites



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



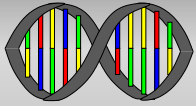
# Discrete Release Sites



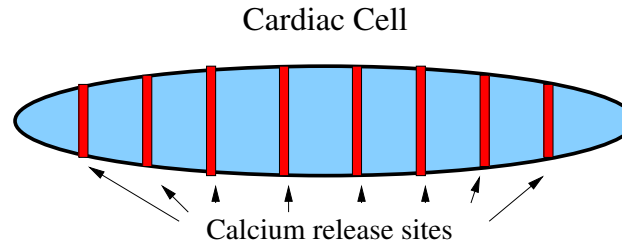
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with

$x_n$  location of release sites separated by distance  $L$ ,



# Discrete Release Sites

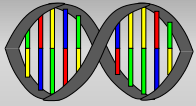


$$\frac{\partial c}{\partial t} = \frac{1}{L} \sum_n \delta(x - x_n) J_{IPR} - J_{SERCA} + D \frac{\partial^2 c}{\partial x^2}$$

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

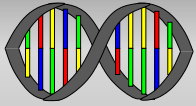
Standard homogenization theory applied to

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

yields

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

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



# Apply Homogenization

Standard homogenization theory applied to

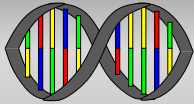
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where  $G = \frac{1}{L} \int_0^L g(x) dx$ , so that  $F(u) = G f(u) - h(u)$  is the **effective** release/uptake function.

This is the well-known **Bistable Equation**.

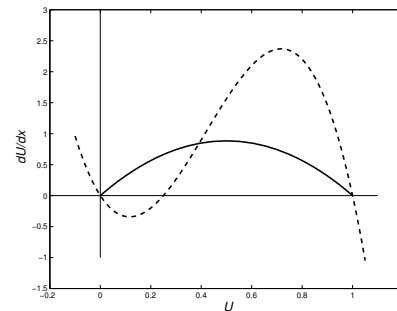
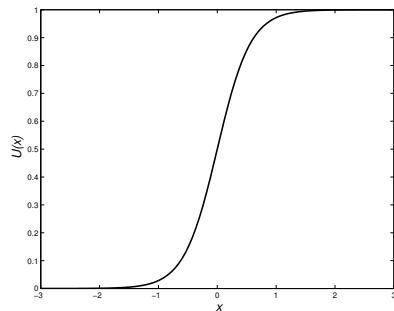


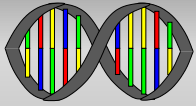
# The Bistable Equation

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

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  $DU'' + cU' + F(U) = 0$

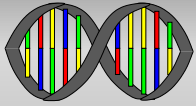




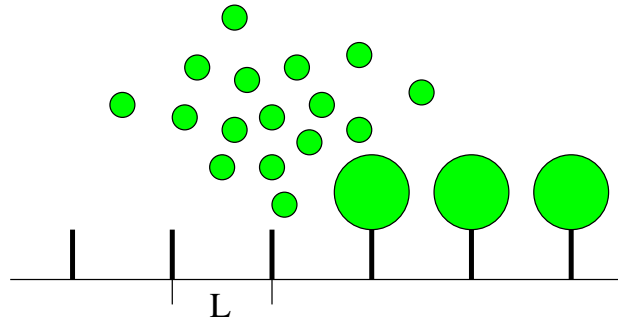
# *Problems*

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).



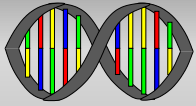
# Fire-Diffuse-Fire Model



Suppose calcium  $c$  is released from

- a long line of evenly spaced release sites;
- Release of full contents  $\sigma$  occurs when the local concentration  $c$  reaches threshold  $\theta$ .

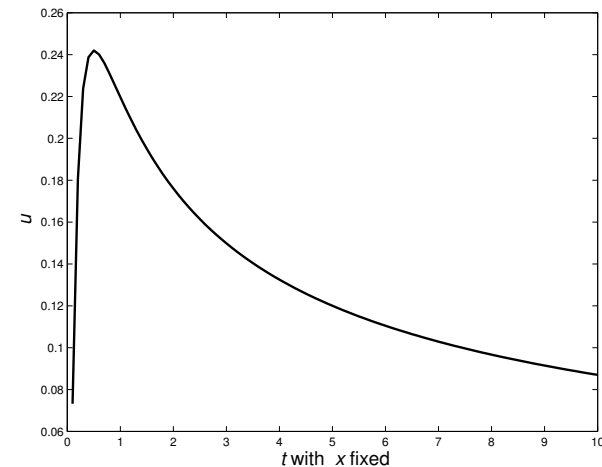
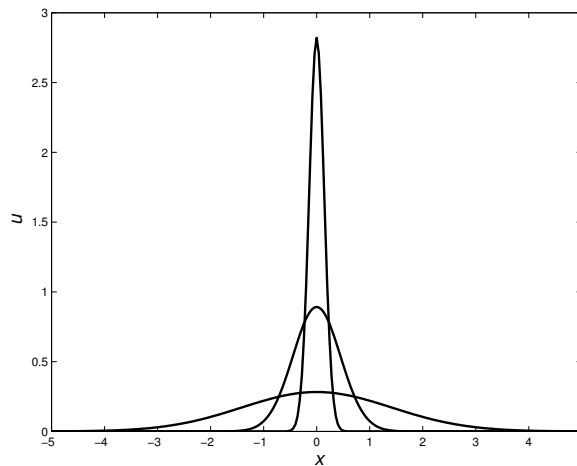
$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - k_s c + \frac{\sigma}{L} \sum_n \delta(x - nL) \delta(t - t_n)$$

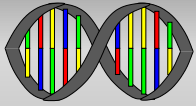


# Fire-Diffuse-Fire-II

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

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



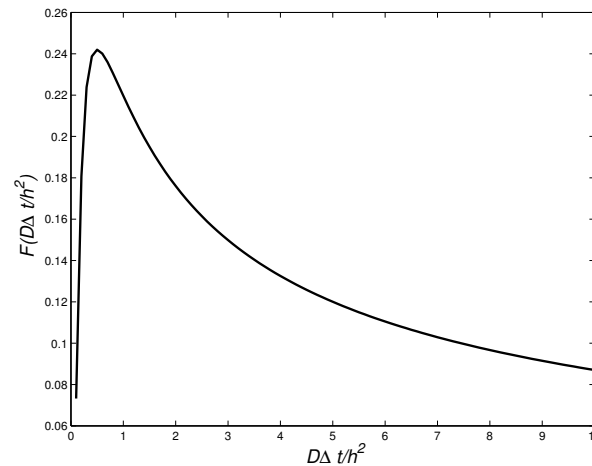


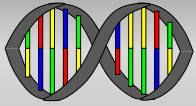
# Fire-Diffuse-Fire-III

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

At  $x = x_n = nL$ ,

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



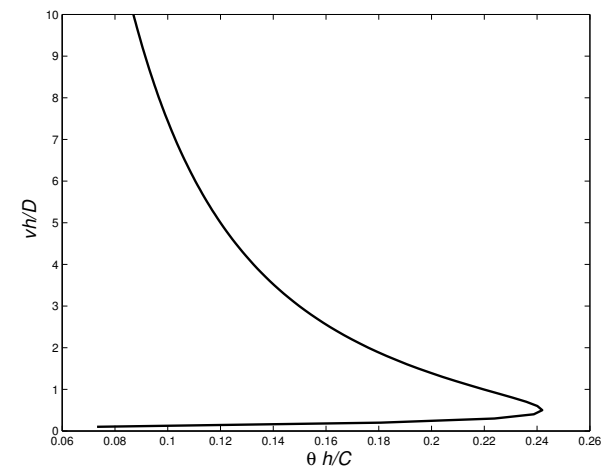
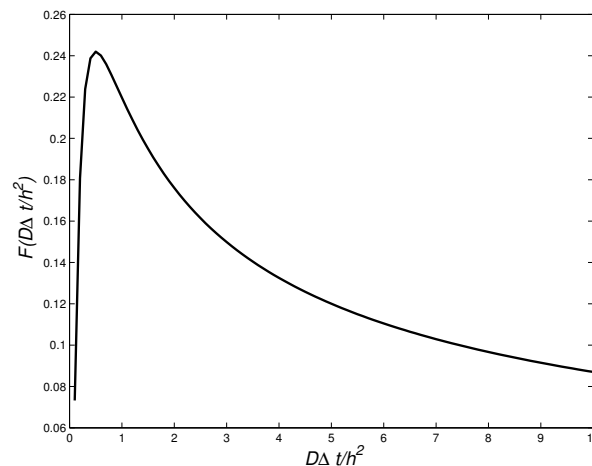


# Fire-Diffuse-Fire-IV

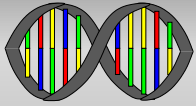
To find the delay  $\Delta t$ , solve the equation

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

This is easy to do graphically:



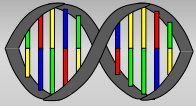
Conclusion: Propagation fails for  $\frac{\theta L}{\sigma} > \theta^*$  (i.e. if  $L$  is too large,  $\theta$  is too large, or  $\sigma$  is too small.)



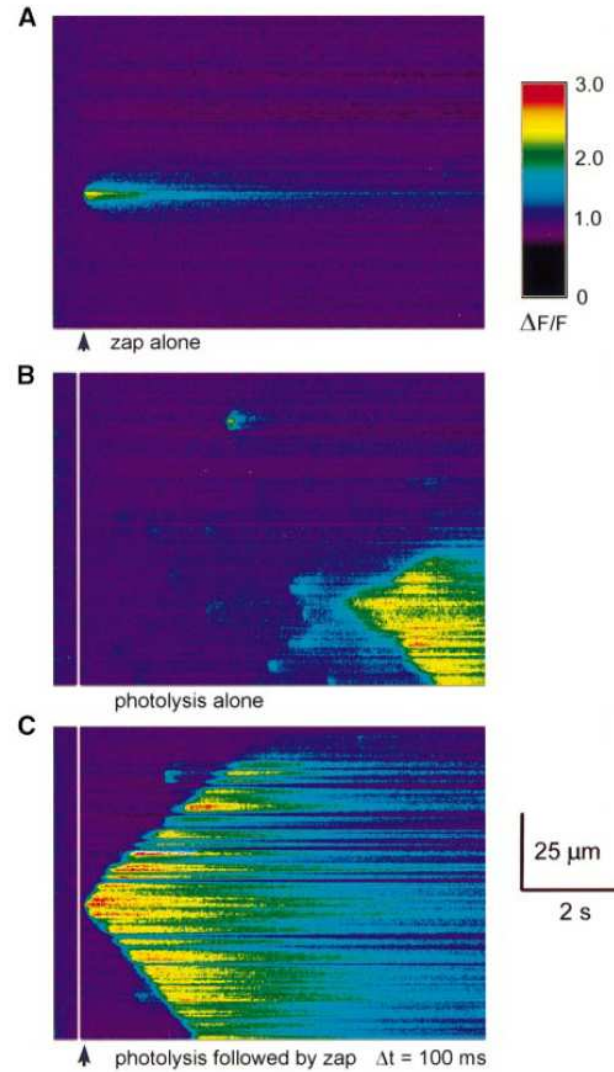
What went wrong?

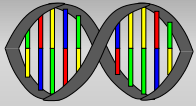
There are two problems with this model:

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

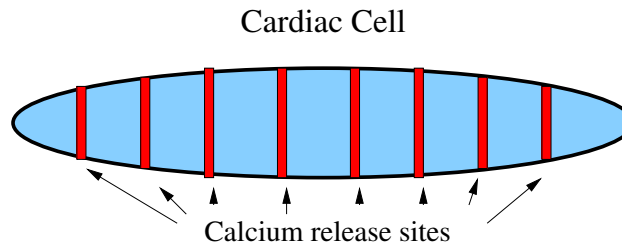


# Calcium Sparks and Waves

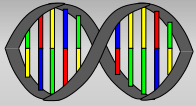




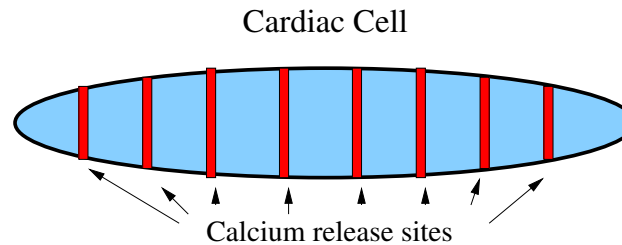
# Discrete Release Sites



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



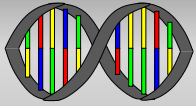
# Discrete Release Sites



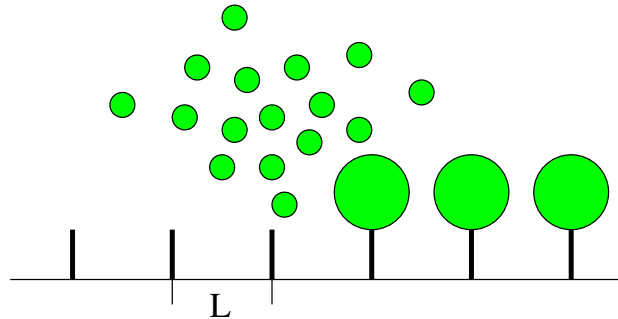
$$\frac{\partial c}{\partial t} = g_{max} \frac{1}{L} \sum_n \delta(x - x_n) y_n (c_e - c) - J_{SERCA} + D \frac{\partial^2 c}{\partial x^2}$$

with

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



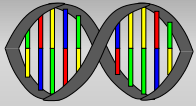
# Stochastic Fire-Diffuse-Fire Model



Suppose calcium  $c$  is released from

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

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



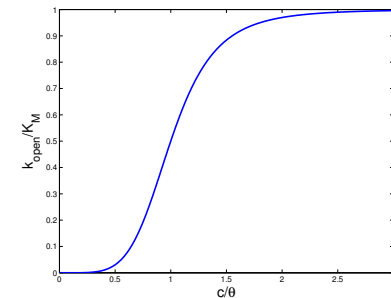
# Stochastic Analysis

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

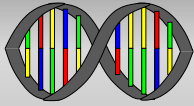
$$k_{open}(c) = K_M \frac{c^N}{\theta^N + c^N}.$$



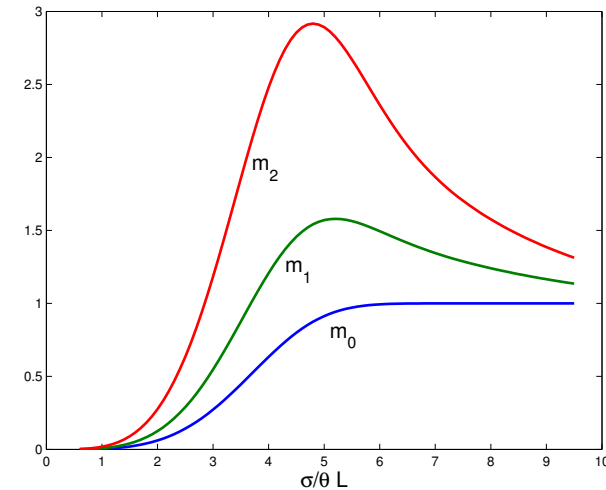
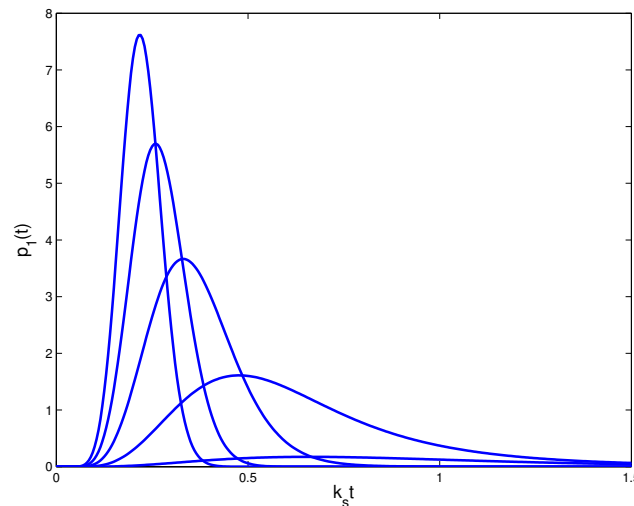
Remark:  $c(x, t)$  is known as before

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

except that now the  $t_j$  are continuous random variables.

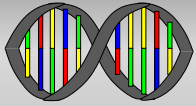


Suppose site zero fires at time  $t = 0$ . What happens at site 1?



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

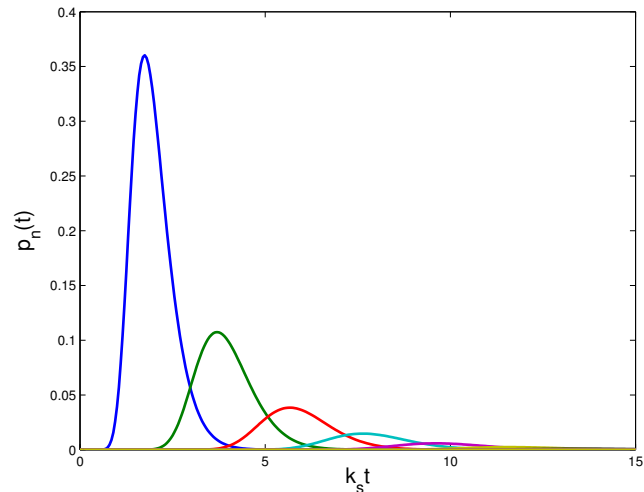
Observe: As  $\frac{\sigma}{\theta L}$  increases, firing occurs sooner and with less variance.



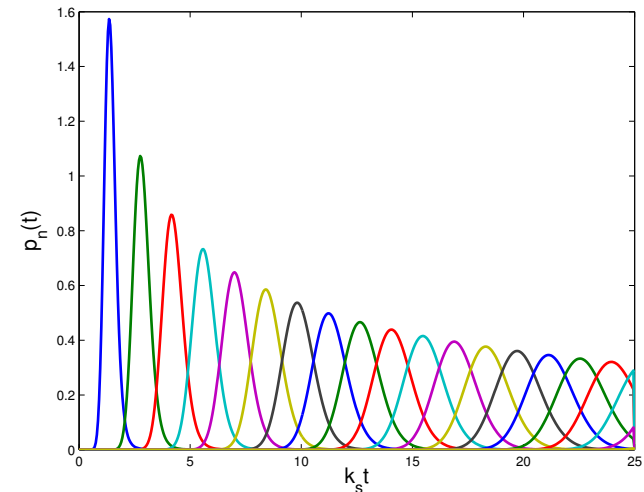
Suppose site zero fires at time  $t = 0$ . What happens at site  $n > 1$ ?

$p_n(t)$  satisfies the renewal equation

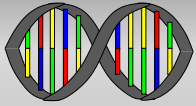
$$p_n(t) = \int_0^{\infty} p_1(t - s)p_{n-1}(s)ds.$$



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



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

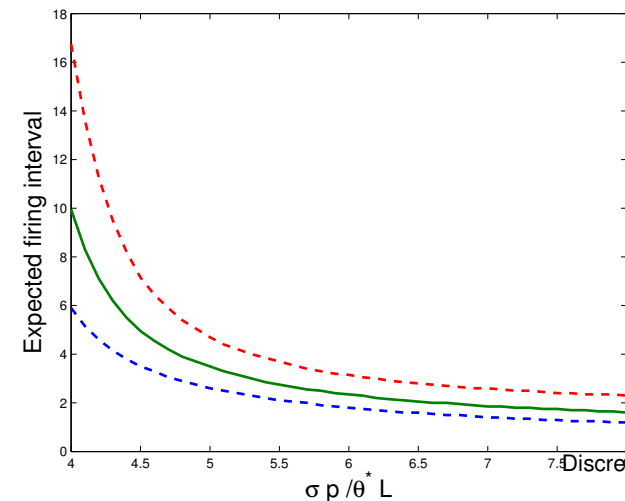
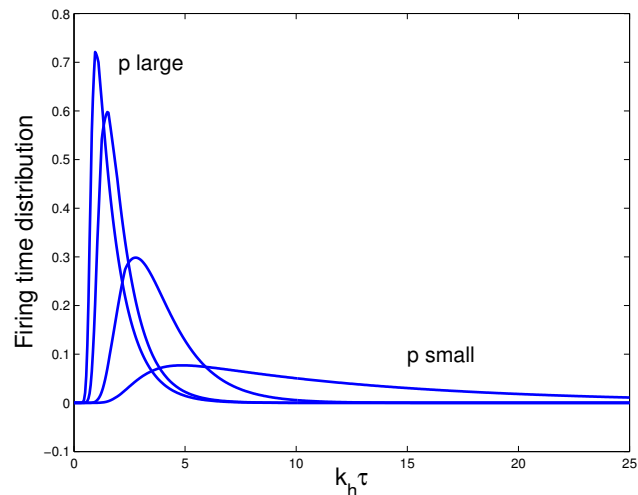


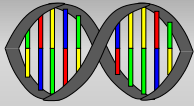
# Whole Cell Calcium Release Events

Whole cell calcium release events are governed by three things:

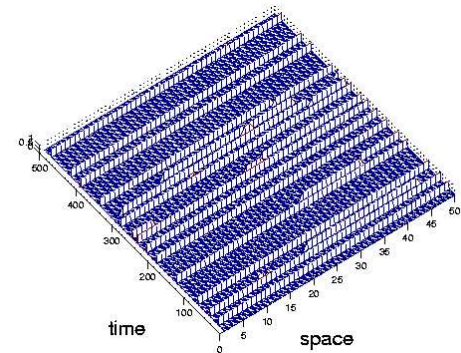
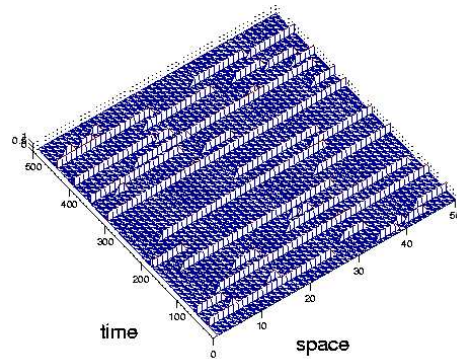
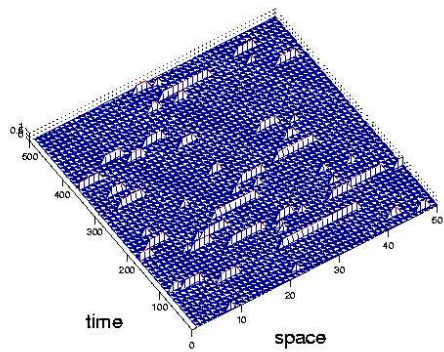
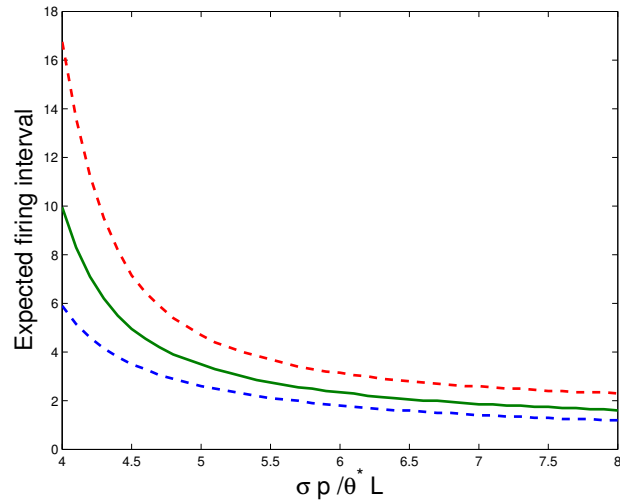
- localized calcium release (sparks) - a Poisson process
- spark to wave transition - whole cell release
- resetting the threshold  $\theta$  (time dependent recovery with time constant  $k_h$ ).

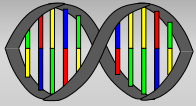
Putting it all together (using similar methods)





# Whole Cell Calcium Release Events



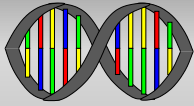


# *Conclusion*

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Whole cell calcium models fail because:

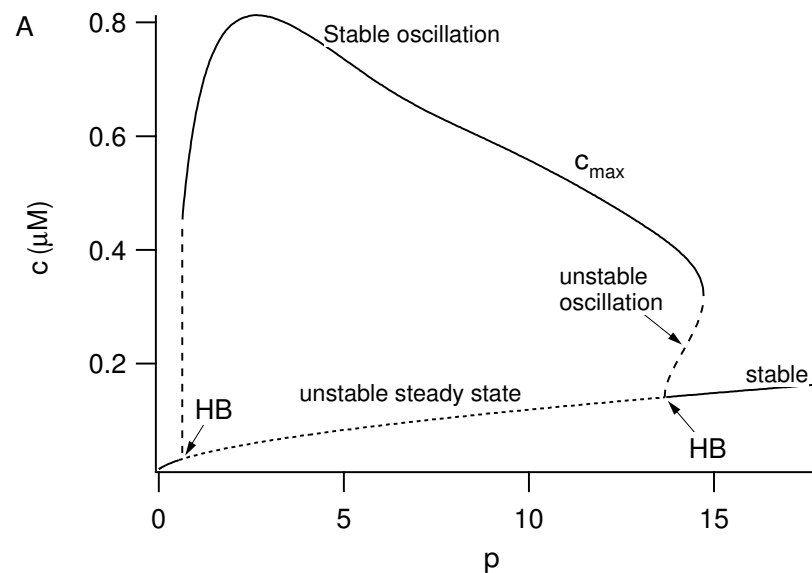
- Release sites are discrete and diffusion is too slow;
- Release is a stochastic event for which the law of large number does not apply.

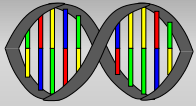


Whole cell calcium models fail because:

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

Consequently, not this



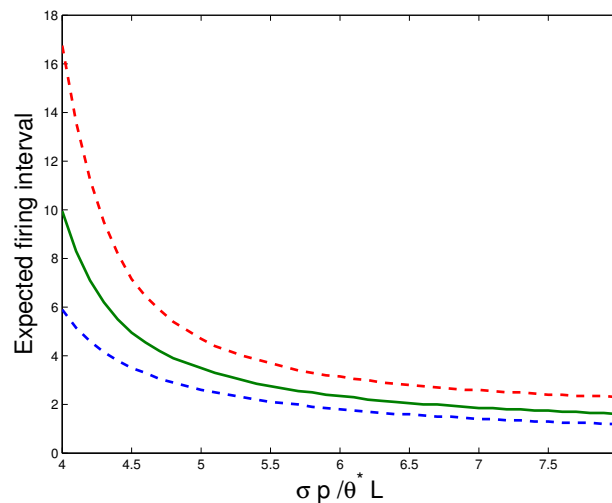


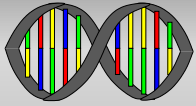
# Conclusion

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.

but this





# ***Acknowledgments***

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

The End