Using Math in Cell Biology
How Do Calcium Channels Work?

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This work was done in collaboration with:

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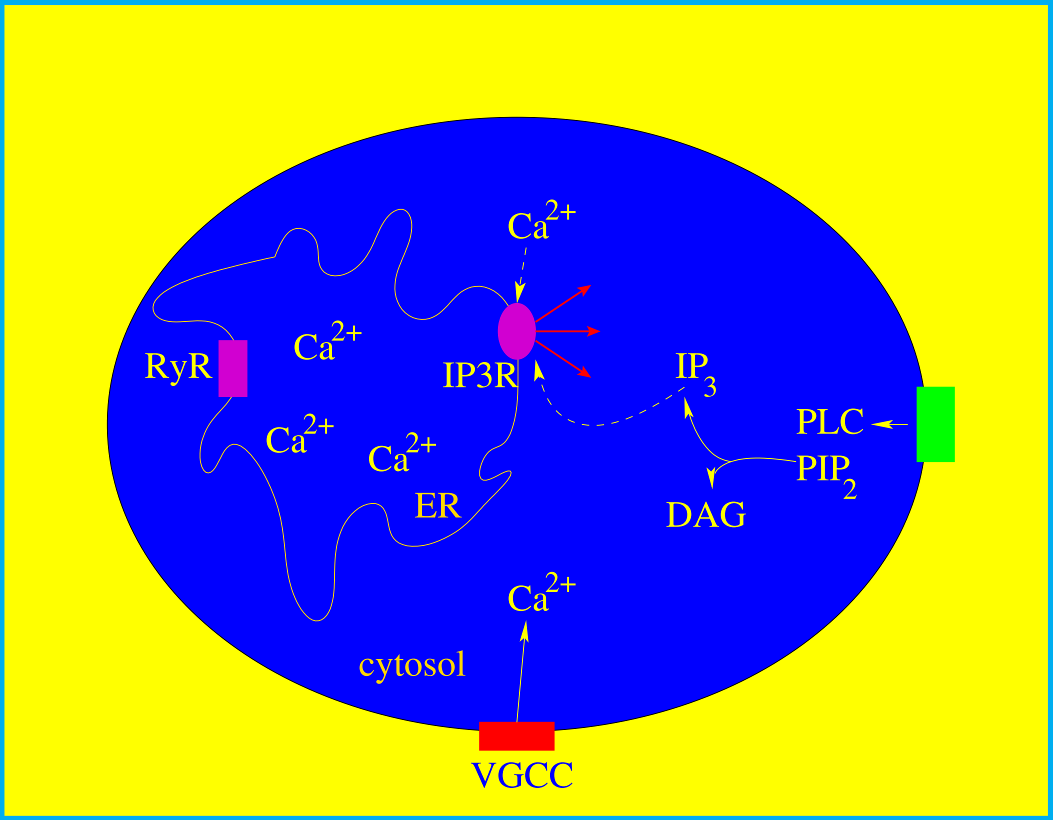
College of William and Mary

Ca^{2+} signalling in cells



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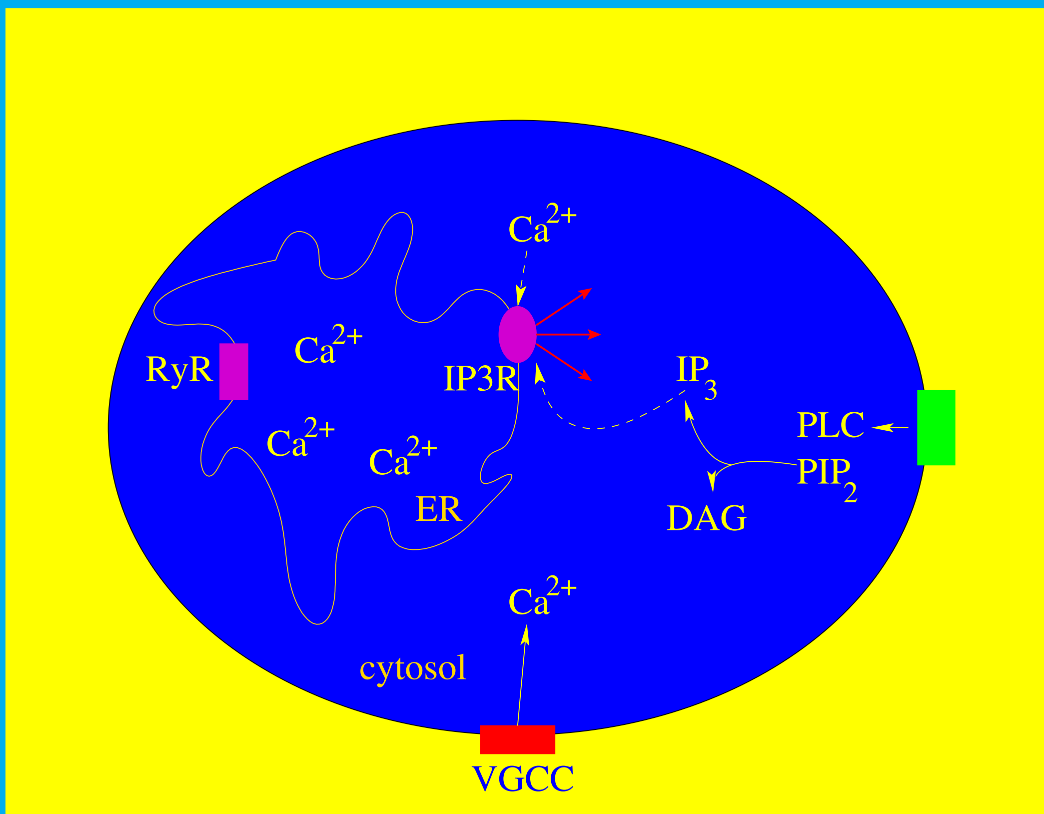
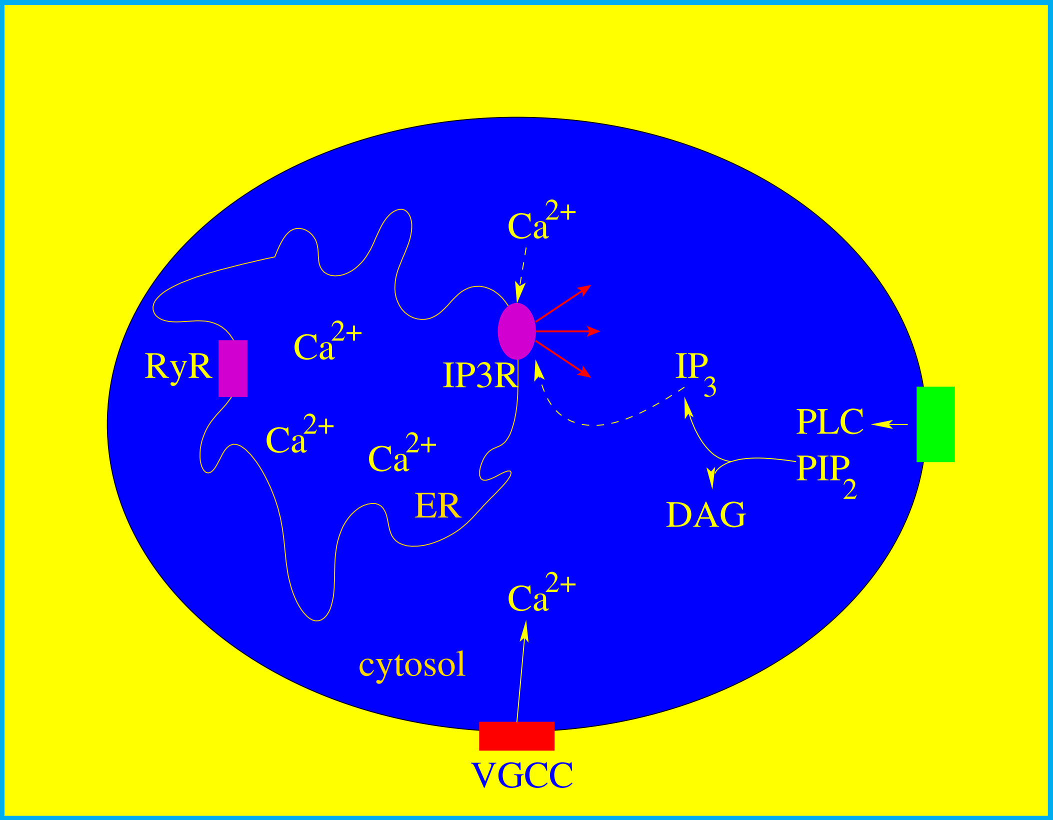


Growth cone guidance

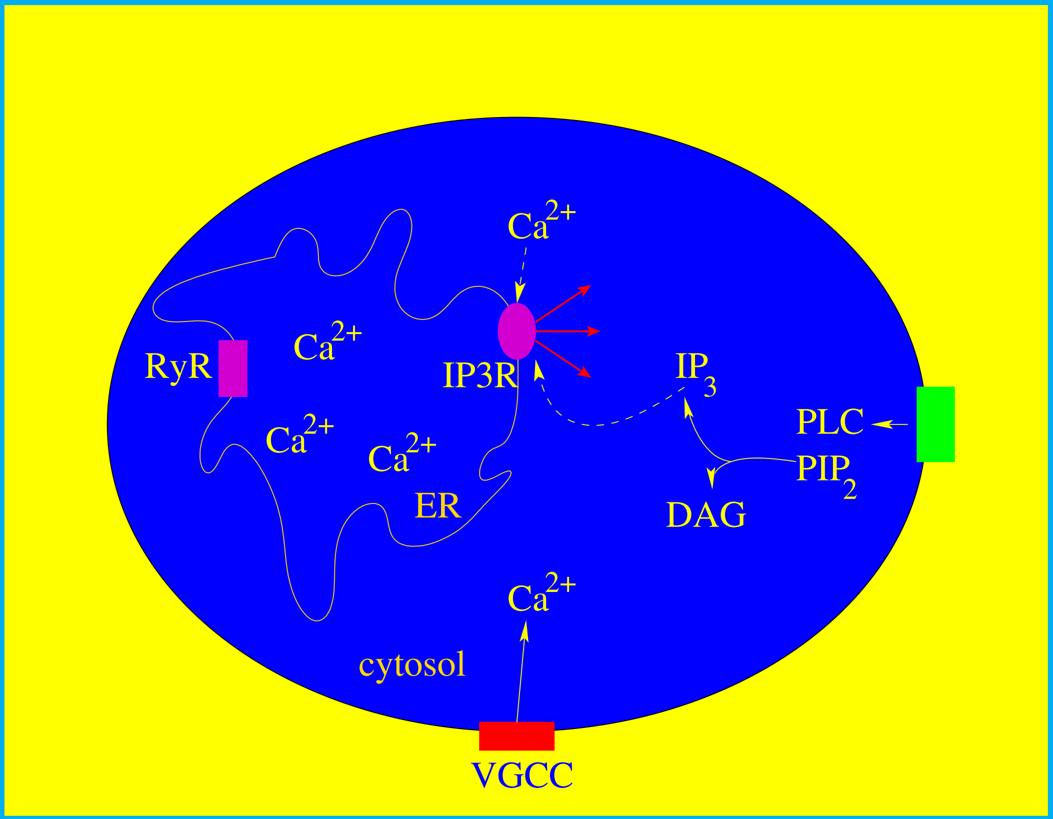
Ca^{2+} **signalling in cells**



Growth cone guidance

Ca^{2+}waves during fertilization of *Xenopus oocytes*

Ca^{2+} signalling in cells

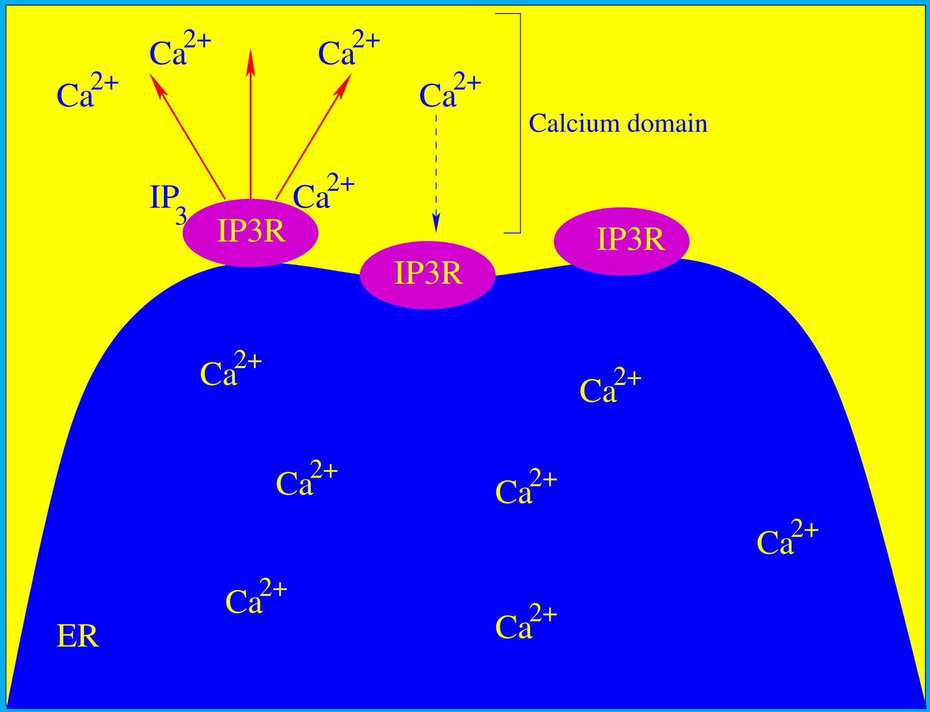


Growth cone guidance

Ca^{2+} waves during fertilization of *Xenopus oocytes*

Influx of Ca^{2+} through VGCC in cardiac cells

Release sites and Ca^{2+}-channels

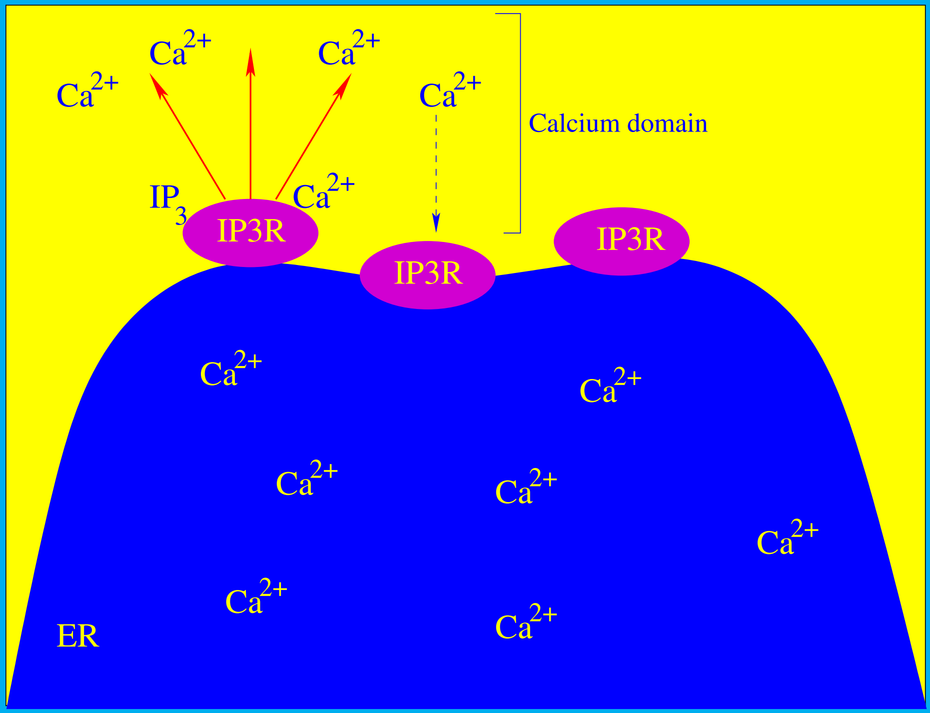


IP_3 potentiation

Ca^{2+} activation

Ca^{2+} inactivation

Release sites and Ca^{2+}-channels



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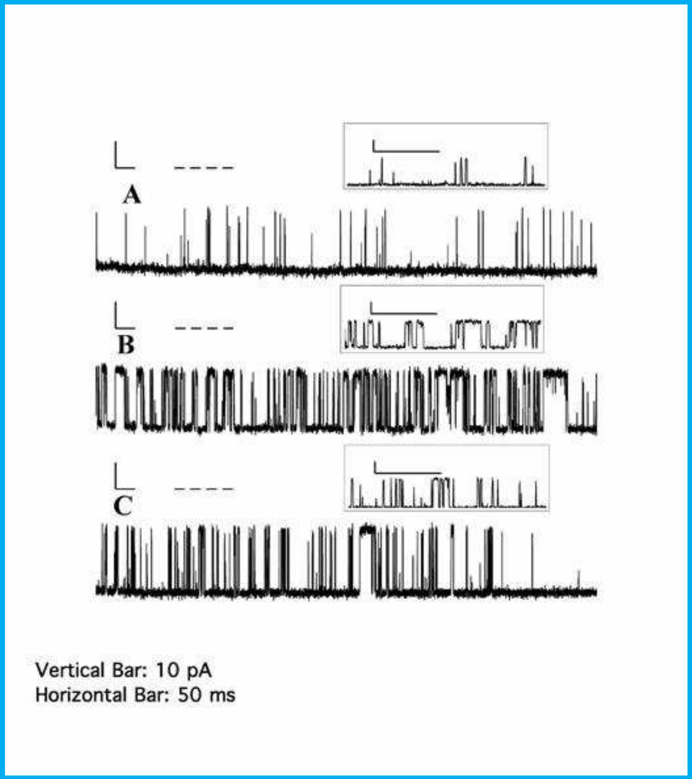

Single channel recording of cardiac Ca^{2+} channels

Cannon, et al. (2003)

Localized Ca^{2+} dynamics

Goal: Determine the effect of residual Ca^{2+} on the equilibrium open probability of a single channel

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Model assumptions

- Stochastic channel gating
- Incorporation of effects 'residual Ca^{2+}'

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Model assumptions

- Stochastic channel gating
- Incorporation of effects 'residual Ca^{2+}'
- Ca^{2+} activation or Ca^{2+} inactivation only
- Simplifying assumptions about Ca^{2+} domain

Modeling stochastically gated channels

Ca^{2+}-activated channel:

$$C\,\text{(closed)} \quad \underset{k_-}{\overset{k_+[\mathrm{Ca}^{2+}]_d}{\rightleftharpoons}} \quad O\,\text{(open)}$$

Modeling stochastically gated channels

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Transition probability matrix:

$$W = \left[\begin{array}{cc} \Pr\{\mathrm{C}, t+\Delta t|\mathrm{C}, t\} & \Pr\{\mathrm{O}, t+\Delta t|\mathrm{C}, t\} \\ \Pr\{\mathrm{C}, t+\Delta t|\mathrm{O}, t\} & \Pr\{\mathrm{O}, t+\Delta t|\mathrm{O}, t\} \end{array} \right]$$

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$$= \begin{bmatrix} 1 - k_+[\mathrm{Ca}^{2+}]_d \Delta t & k_+[\mathrm{Ca}^{2+}]_d \Delta t \\ k_- \Delta t & 1 - k_- \Delta t \end{bmatrix}$$

Transition probability matrix

Let $\pi_C = \Pr\{\mathrm{C}, t\}$, $\pi_O = \Pr\{\mathrm{O}, t\}$ and $\boldsymbol{\pi} = [\pi_C \quad \pi_O]$.

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$$\bar{\pi}_C = \Pr\{\mathrm{C}, t + \Delta t | \mathrm{C}, t\} \Pr\{\mathrm{C}, t\} + \Pr\{\mathrm{C}, t + \Delta t | \mathrm{O}, t\} \Pr\{\mathrm{O}, t\}$$

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So, $\boldsymbol{\pi}(t) W = \boldsymbol{\pi}(t + \Delta t)$.

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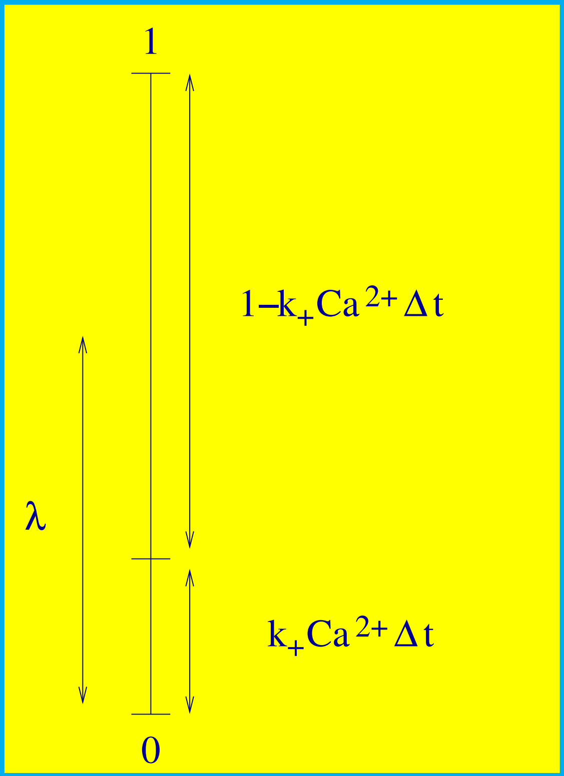
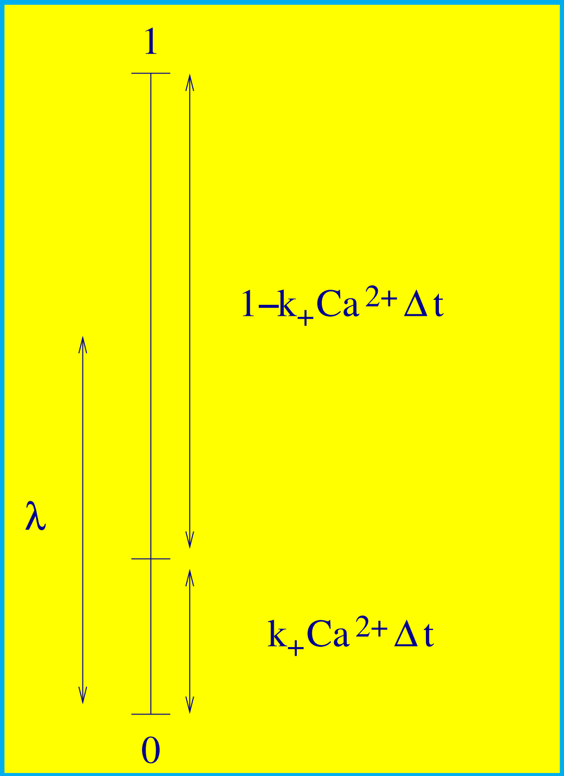
So, $\boldsymbol{\pi}(t) W = \boldsymbol{\pi}(t+\Delta t)$.
The equilibrium probability is the vector $\tilde{\boldsymbol{\pi}}$ such that $\tilde{\boldsymbol{\pi}} = W \tilde{\boldsymbol{\pi}}$.

Monte Carlo simulations



Starting from closed state

Monte Carlo simulations

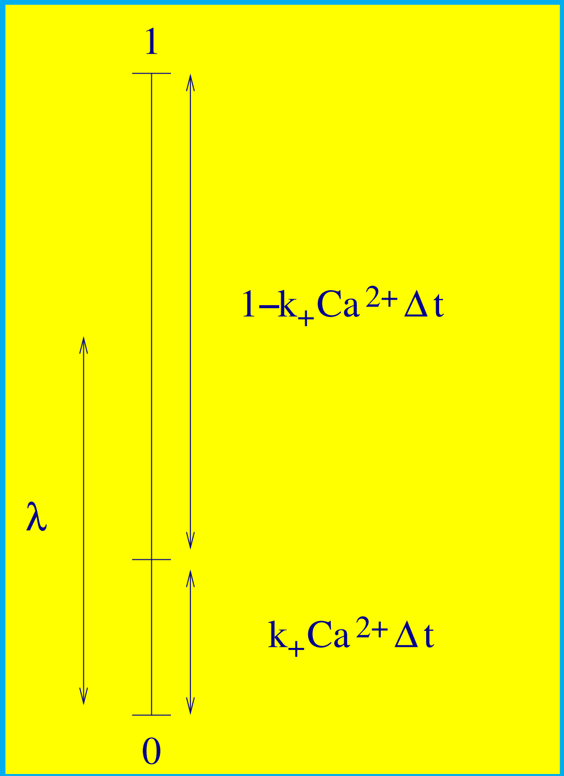


Starting from closed state

In general (n states):

$$W = \begin{bmatrix} \mathrm{k}_{i1} & \mathrm{k}_{i2} & \ldots & \mathrm{k}_{in} \\ & & & \end{bmatrix}$$

Monte Carlo simulations



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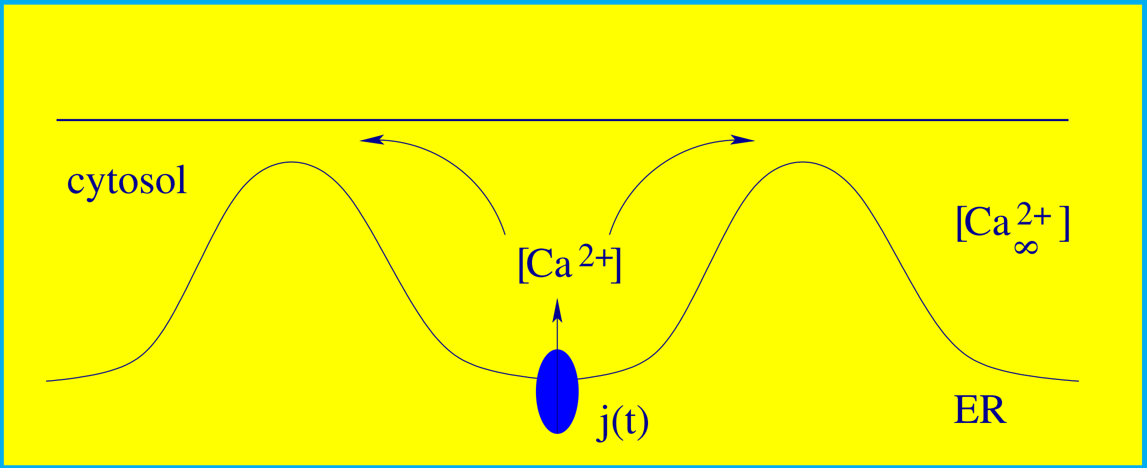
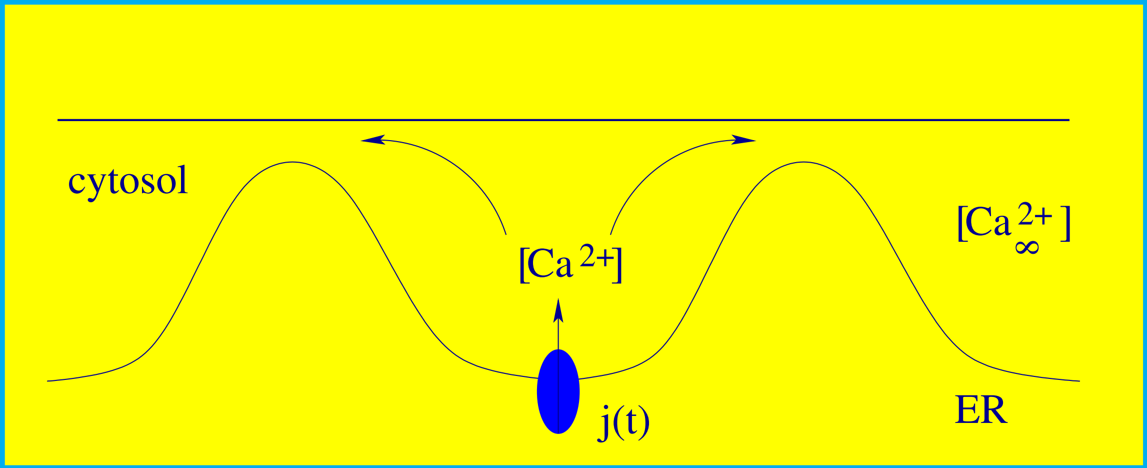
where $k_{ii} = 1 - \sum_j k_{ij}$.

To use Monte Carlo method: divide unit interval into n subintervals corresponding to k_{ij}, and choose λ as before.

Modeling Ca^{2+}-dynamics

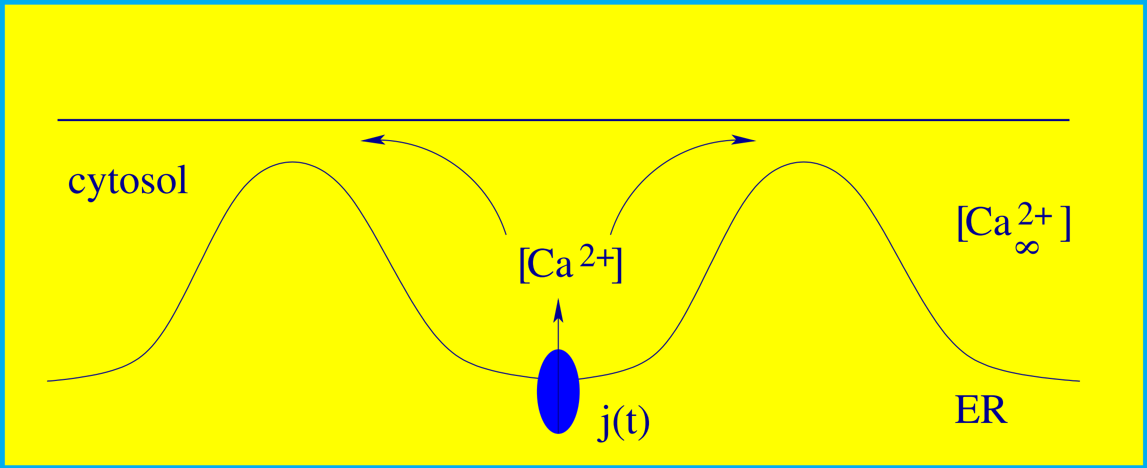


Modeling Ca^{2+}-dynamics



$$\frac{dc}{dt} = j - \frac{c - c_\infty}{\tau}$$

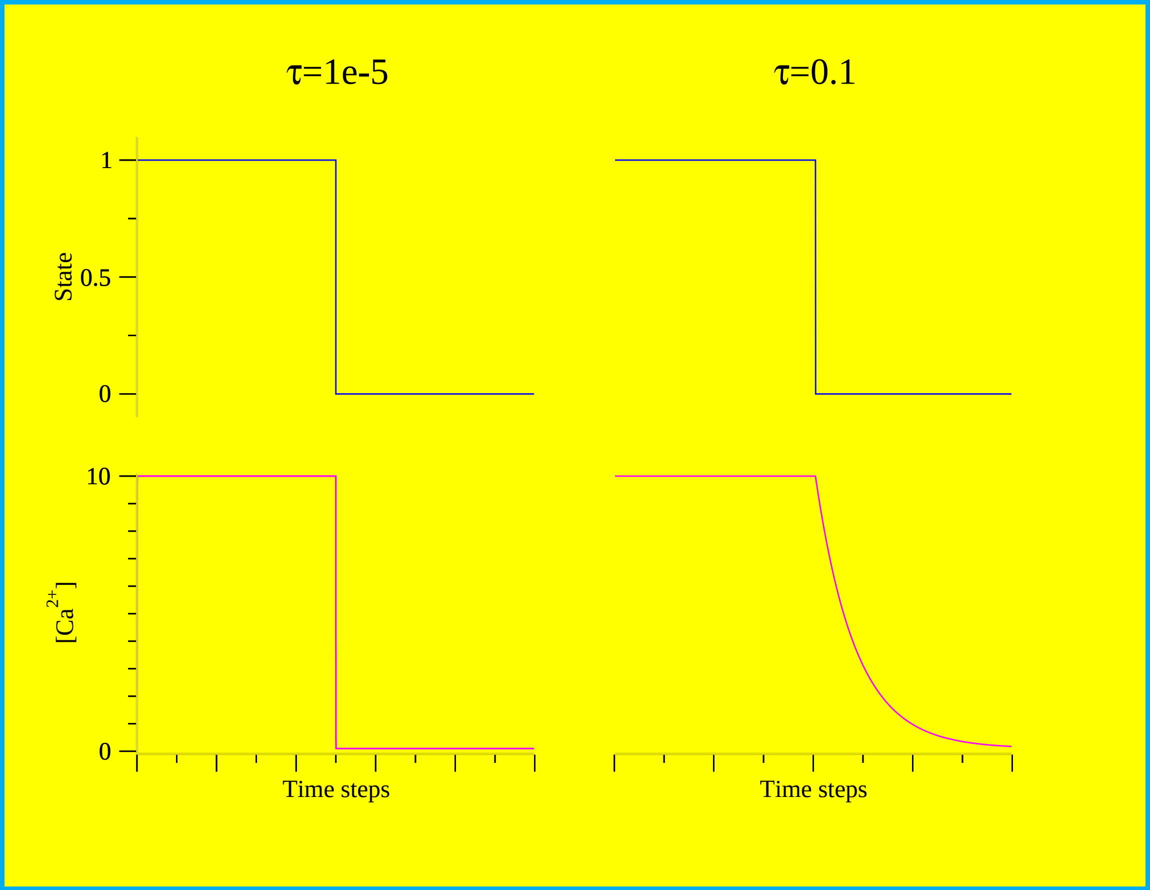
Modeling Ca^{2+}-dynamics



$$\frac{dc}{dt} = j - \frac{c - c_\infty}{\tau} \qquad j(t) = \begin{cases} 0 & \text{when} \quad S(t) = C \\ j_0 & \text{when} \quad S(t) = O \end{cases}$$

$$\text{with} \qquad j_0 = \frac{c_{ss} - c_\infty}{\tau}$$

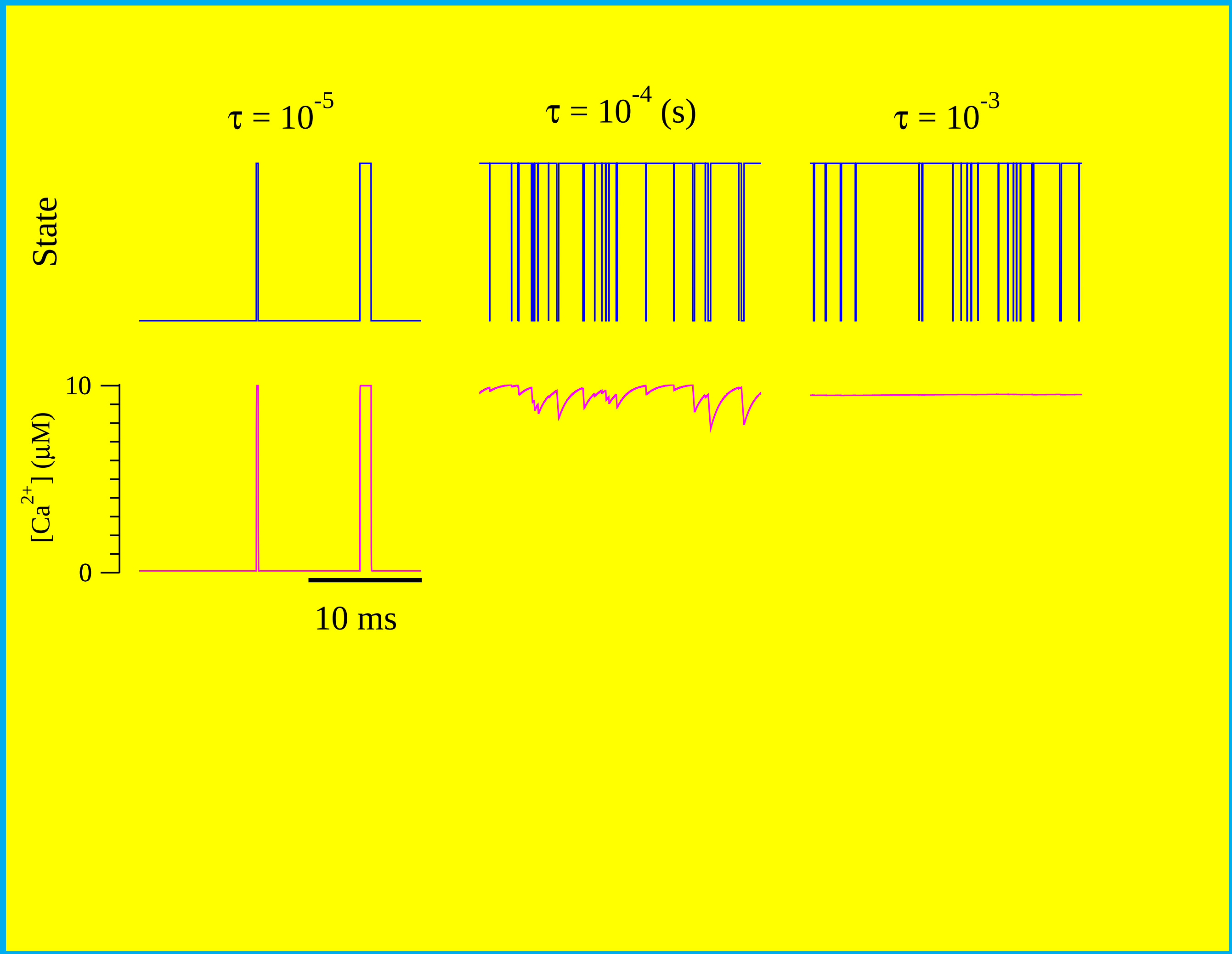
Ca^{2+} dynamics



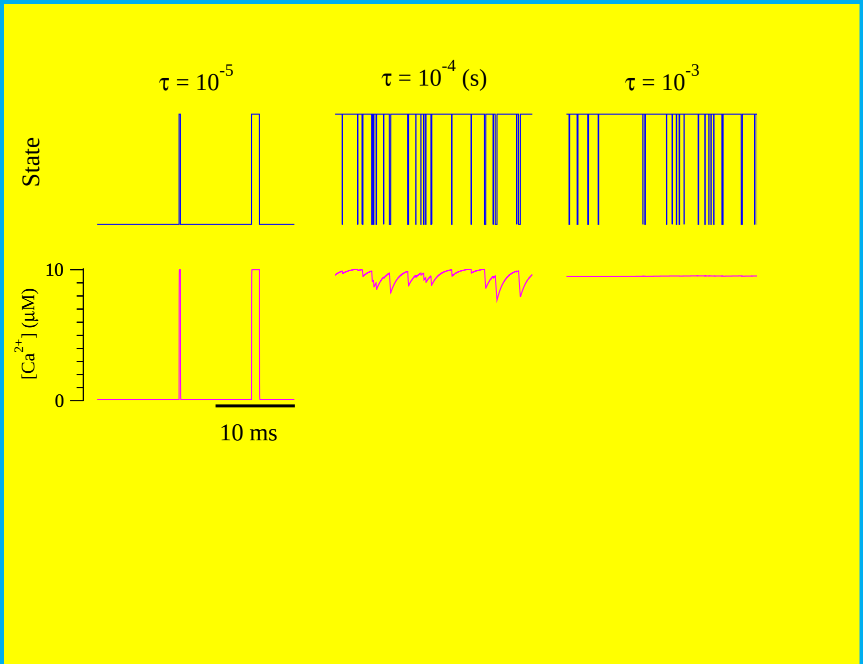
Increasing τ slows the formation and collapse of the Ca^{2+} domain

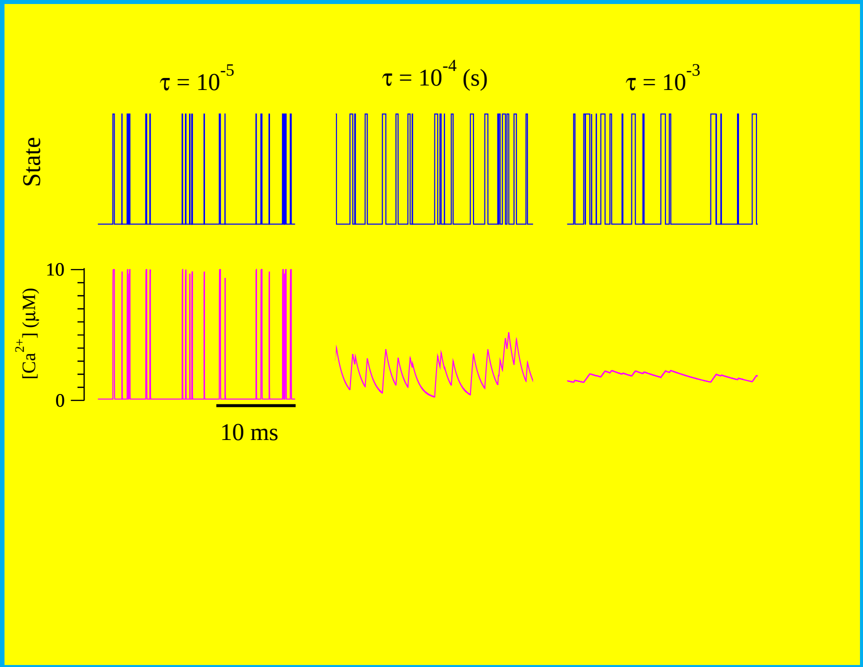
Simulations with $c_{ss} = c_\infty + j_O \tau$. Changing τ implies j_O is adjusted.

Monte Carlo simulation results I.



Monte Carlo simulation results II.





Ca^{2+}-activated channel

Ca^{2+}-inactivated channel

Analytical estimates of P_o

For the Ca^{2+} activated channel:

$$P_o = \frac{\mathrm{C} \longrightarrow \mathrm{O}}{\mathrm{C} \longrightarrow \mathrm{O} + \mathrm{C} \longleftarrow \mathrm{O}}, \qquad P_C = \frac{\mathrm{O} \longleftarrow \mathrm{C}}{\mathrm{C} \longrightarrow \mathrm{O} + \mathrm{C} \longleftarrow \mathrm{O}}$$

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Fast domain (small τ):

$$\lim_{\tau \rightarrow 0} P_o = \frac{k_+ c_\infty}{k_+ c_\infty + k_-} = \frac{c_\infty}{c_\infty + K}$$

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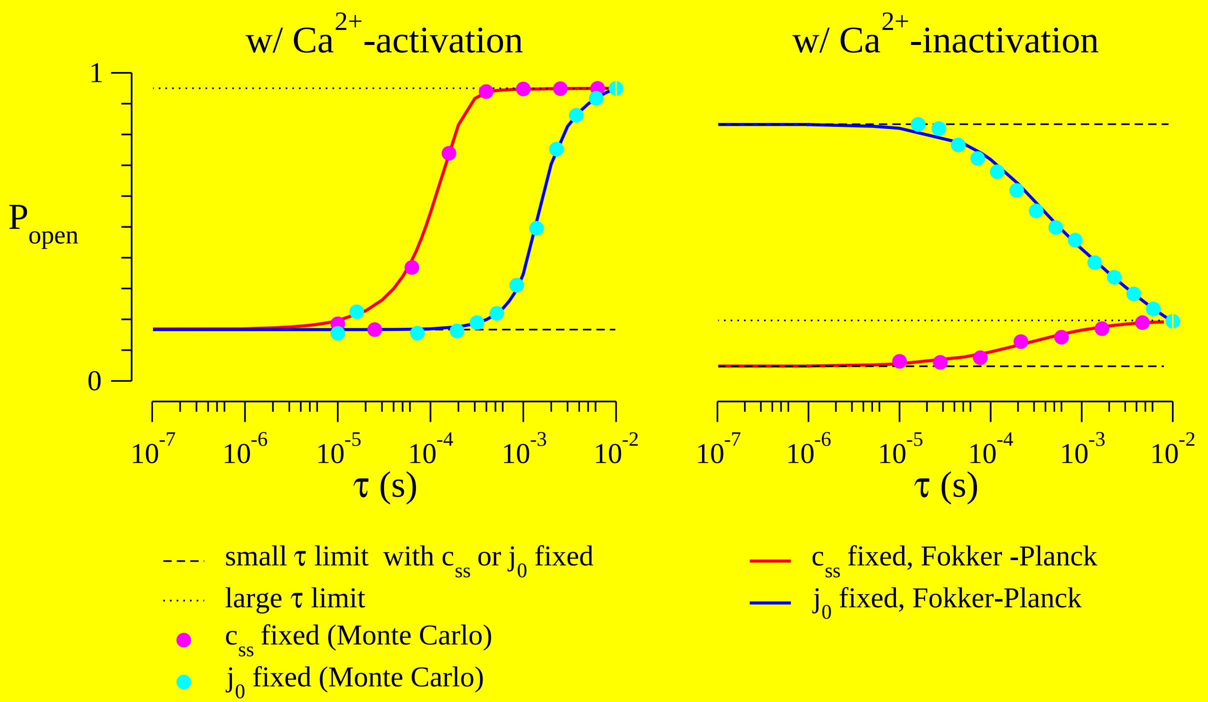
Fast domain (small τ):

$$\lim_{\tau \rightarrow 0} P_o = \frac{k_+ c_\infty}{k_+ c_\infty + k_-} = \frac{c_\infty}{c_\infty + K}$$

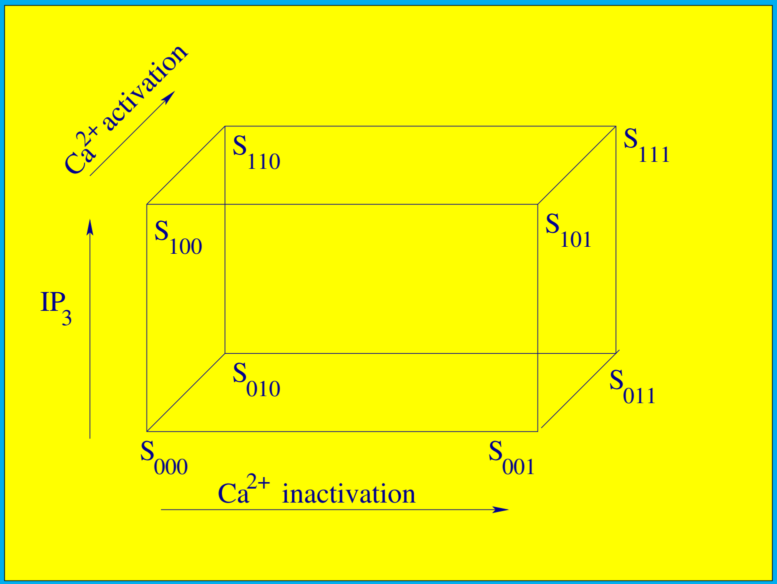
Slow domain (large τ):

$$P_o = \frac{c_*}{c_* + K} \qquad c_* = c_\infty (1 - P_o) + c_{ss} P_o.$$

Dependence of P_o on τ



Results for a more complex channel model



DeYoung-Keizer model

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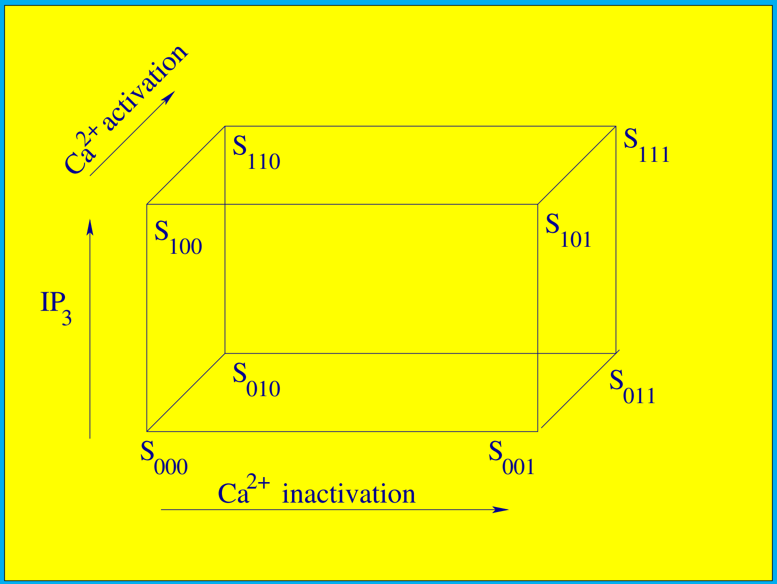
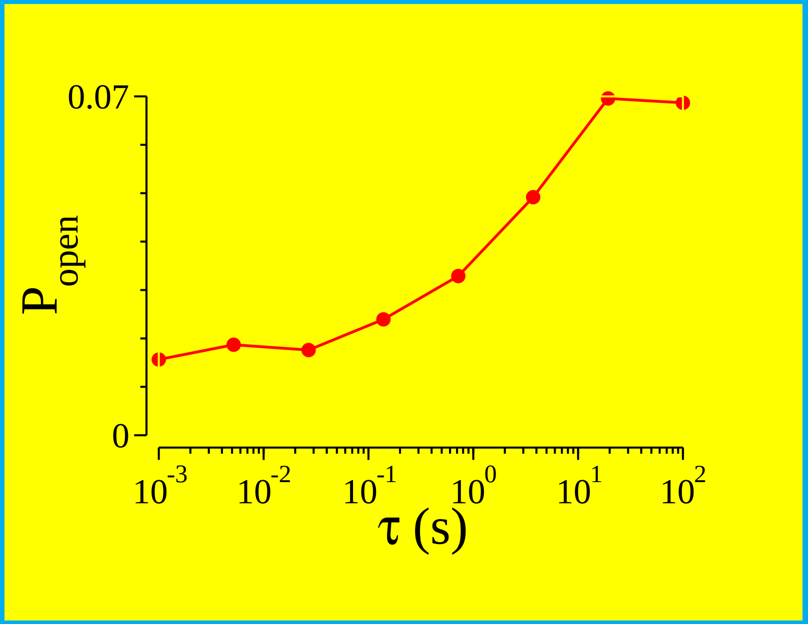
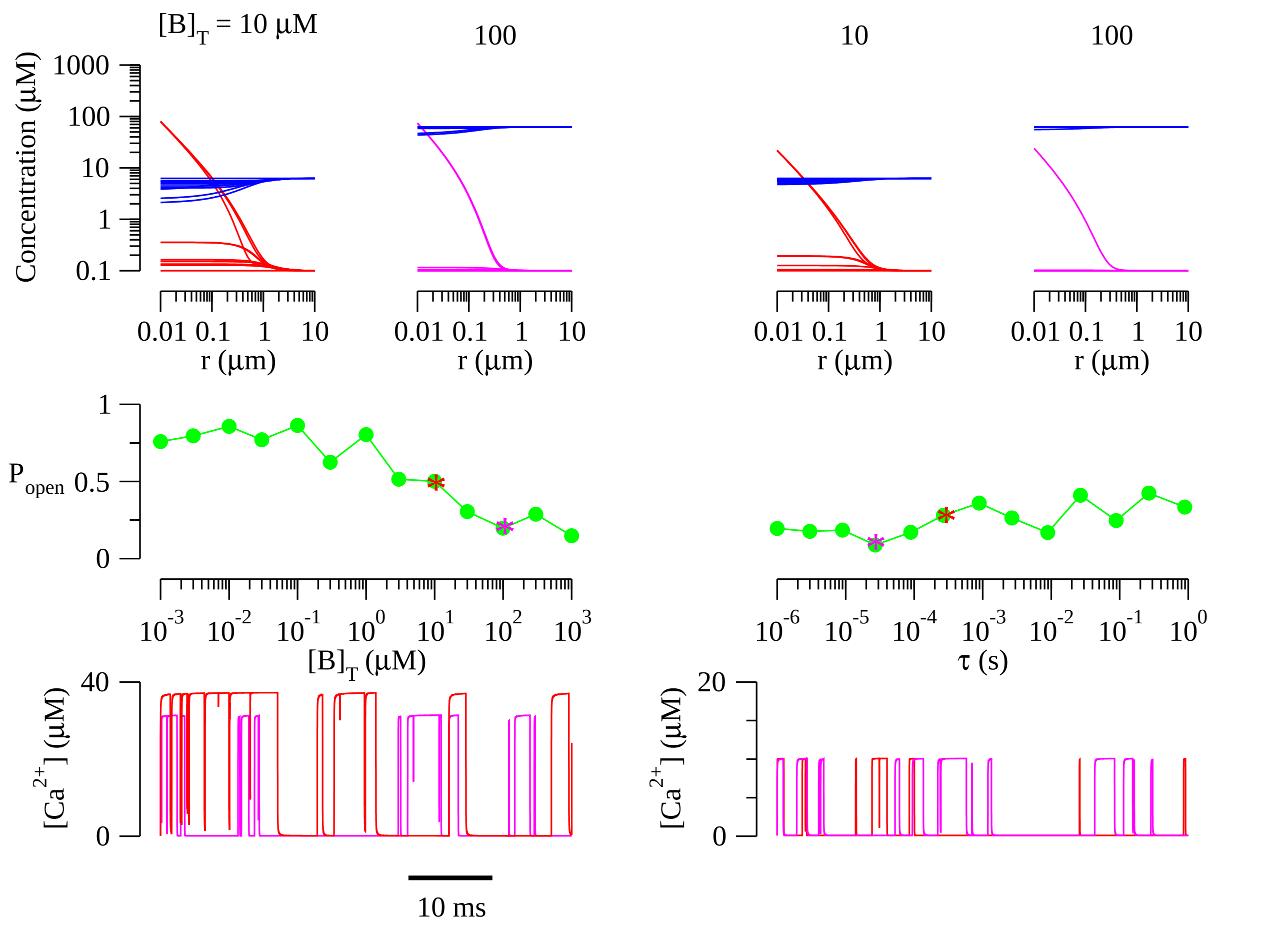


DeYoung-Keizer model

Monte Carlo simulations of the DYK model with 3 subunits



Buffered Ca^{2+} diffusion



Discussion of results

- For Ca^{2+} activated <u>and</u> inactivated channels, P_o increases with τ (if c_{ss} remains constant)

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- For Ca^{2+} activated <u>and</u> inactivated channels, P_o increases with τ (if c_{ss} remains constant)

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- Biological implications

Extensions of the project

- Using MC simulations of DKY model with realistic Ca^{2+} domain (buffered Ca^{2+} diffusion)

- Extend ideas to examine release sites
  - ⋆ How do channels interact through Ca^{2+} domain?
  - ⋆ What kind of emergent behavior of release sites can we predict?
  - ⋆ What are the quantitative differences between release sites made up of different Ca^{2+} channels?

Thank you!

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Fokker-Planck equations

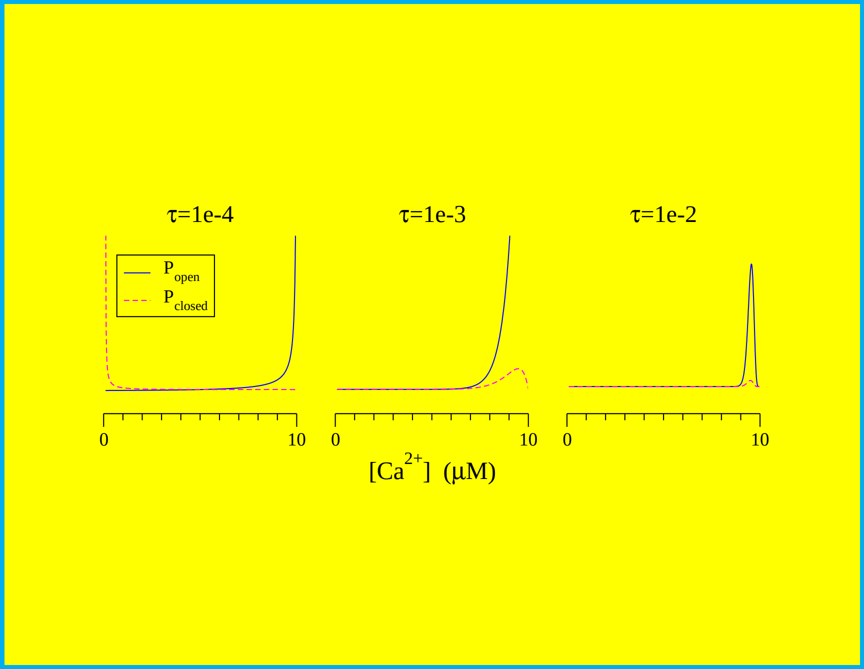
$\pi_O(c) = \{\Pr(c < C < c + \Delta c)$ and state $=$ open$\}$
$\pi_C(c) = \{\Pr(c < C < c + \Delta c)$ and state $=$ closed$\}$

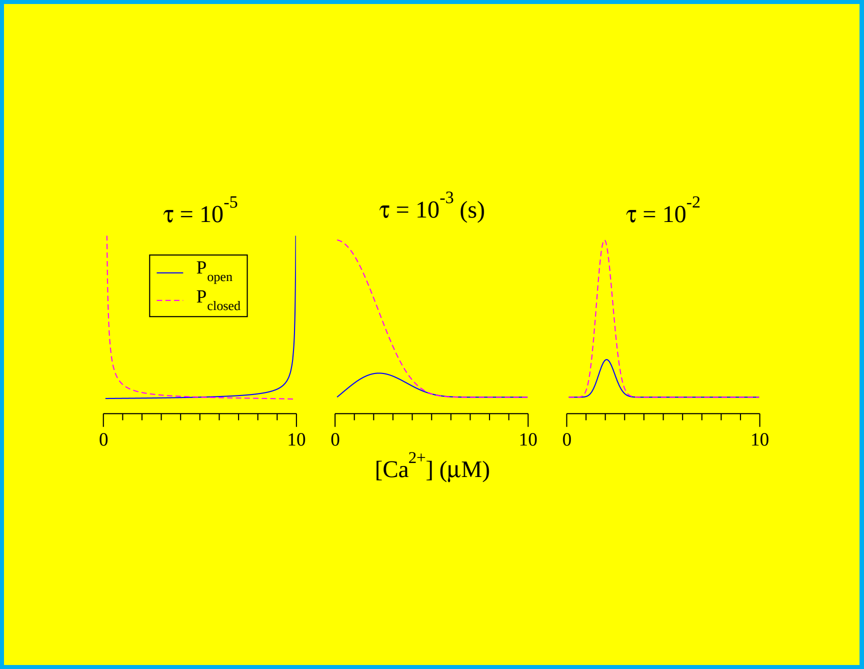
$$\frac{\partial \pi_C}{\partial t} = -\frac{\partial}{\partial c}\left[-\frac{c - c_\infty}{\tau}\pi_C\right] + k_-\pi_O - k_+ c\pi_C$$

$$\frac{\partial \pi_O}{\partial t} = -\frac{\partial}{\partial c}\left[\left(j_o - \frac{c - c_\infty}{\tau}\right)\pi_O\right] - k_-\pi_O + k_+ c\pi_C$$

$$\text{B.C.} = \begin{cases} \pi_C(c_\infty, t) = 0 \\ \pi_O(c_{ss}, t) = 0 \end{cases}$$

Fokker-Planck results





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