The feedback of a localized calcium domain on calcium-gated channels

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This work was done in collaboration with:

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&
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Applied Science Department
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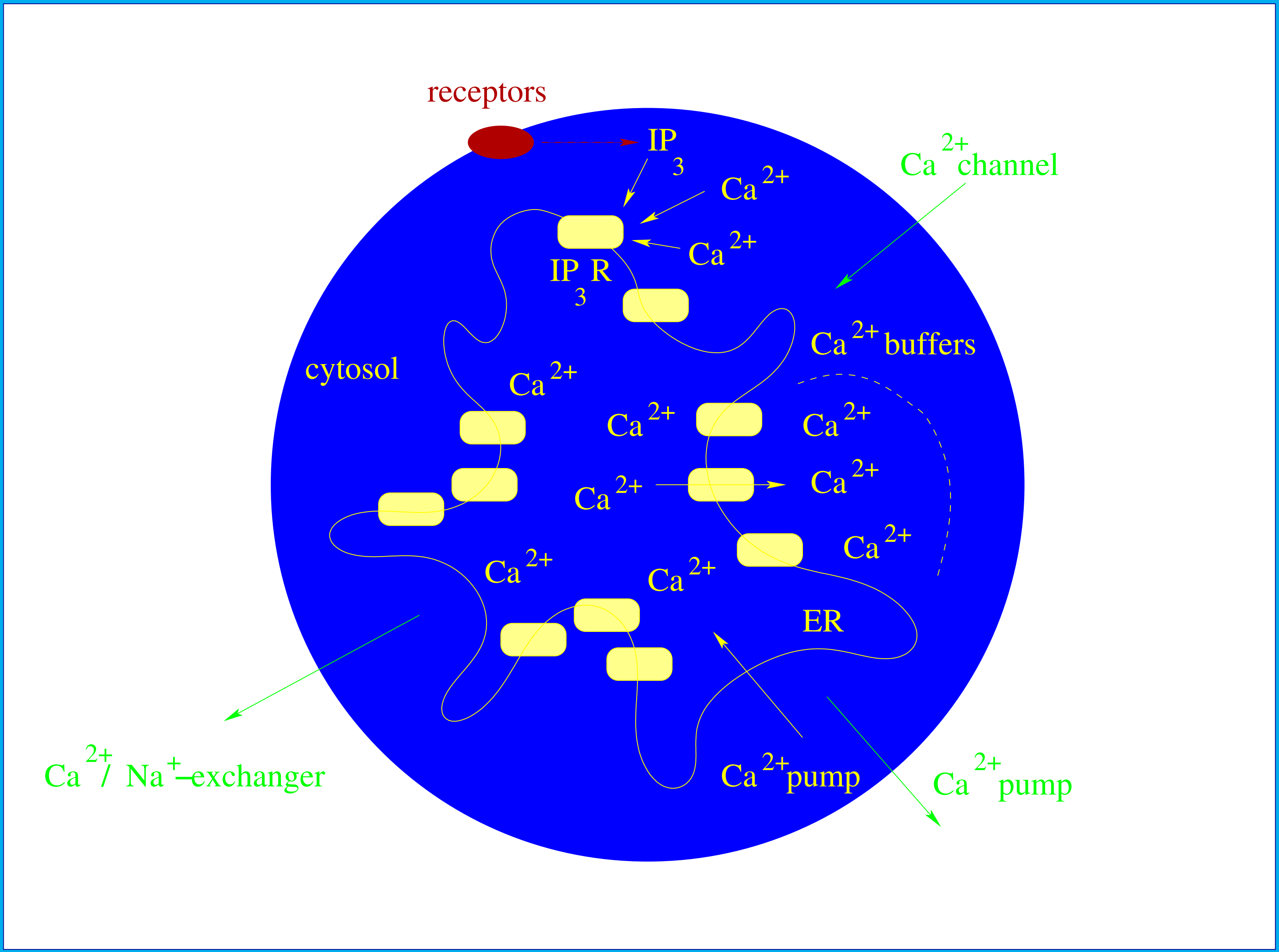
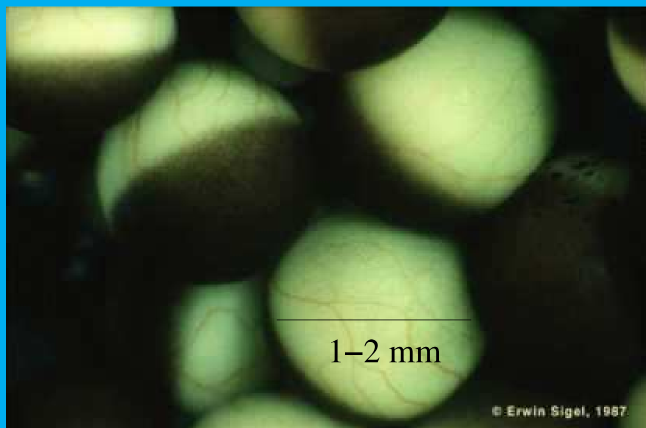
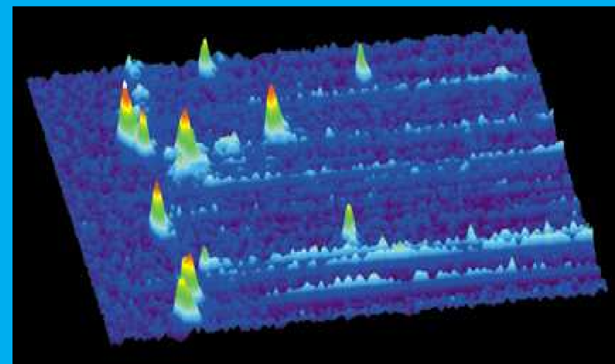
Ca^{2+} signalling in cells

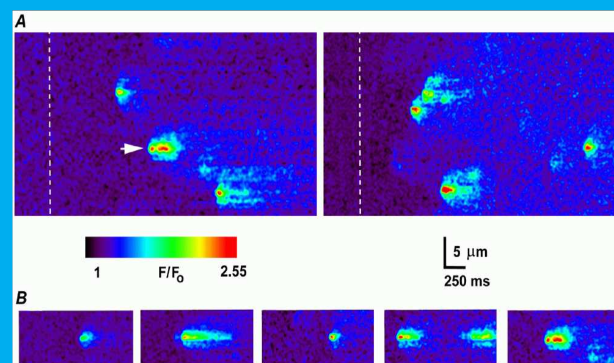


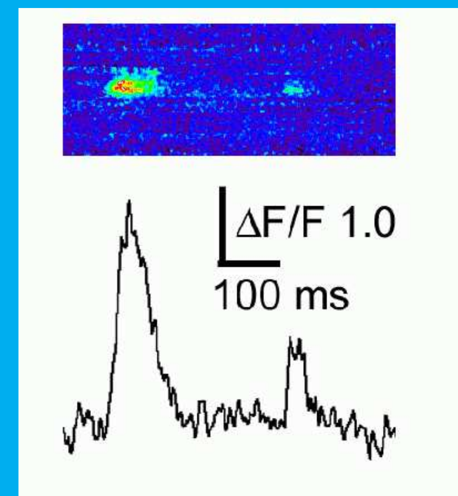
Model organism: *Xenopus oocyte*



(Erwin Sigel, University of Bern, 1987)

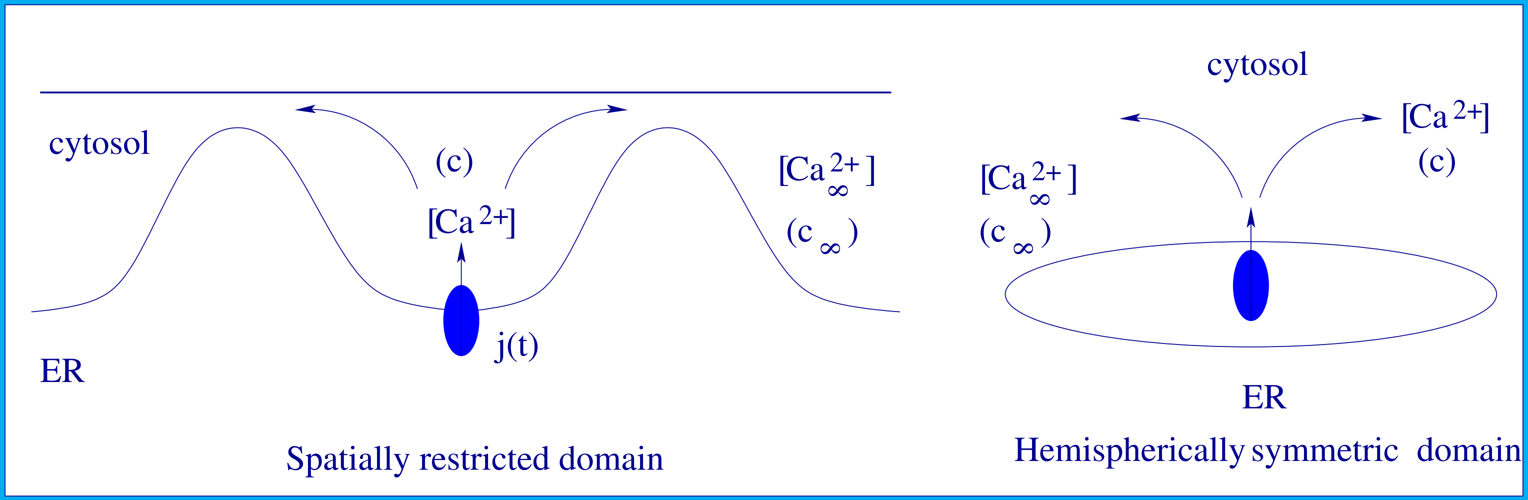






Figures from the Parker lab: Sun, et al., J. Physiol.1998, Parker and Callamaras, cover of Molecular Probes

Model - Description of channels



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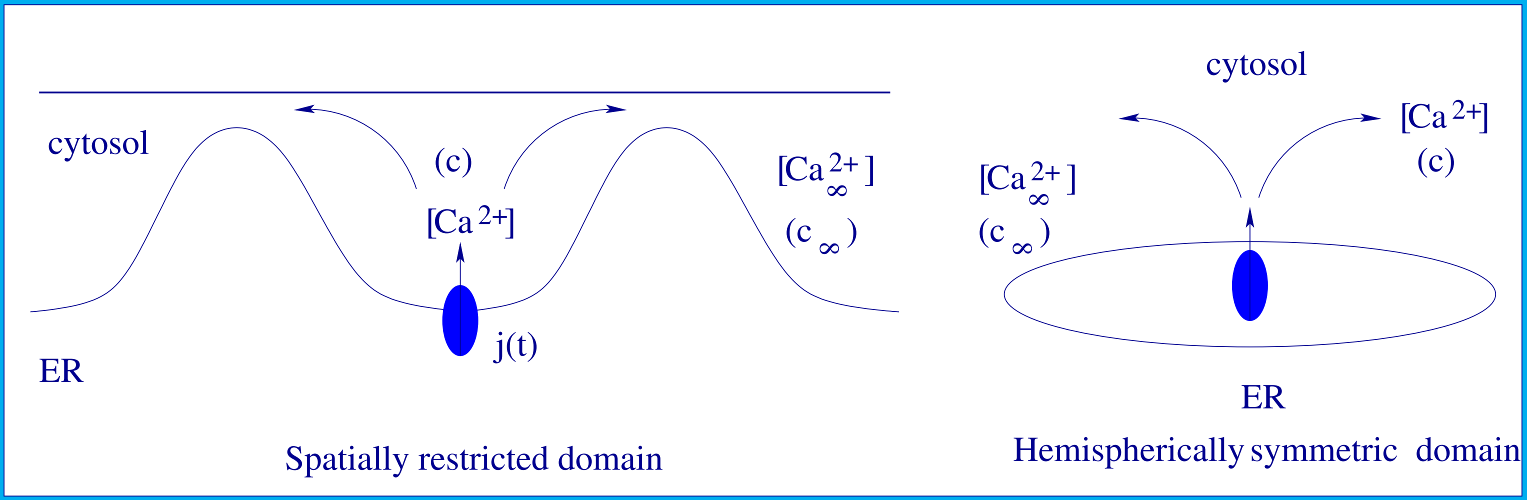

Ca-activated channel: $C\,\text{(closed)} \underset{k_-}{\overset{k_+ c^\eta}{\rightleftharpoons}} O\,\text{(open)}$

Transition probability matrix: $W = \begin{bmatrix} 1 - k_+ c^\eta \Delta t & k_+ c^\eta \Delta t \\ k_- \Delta t & 1 - k_- \Delta t \end{bmatrix}$

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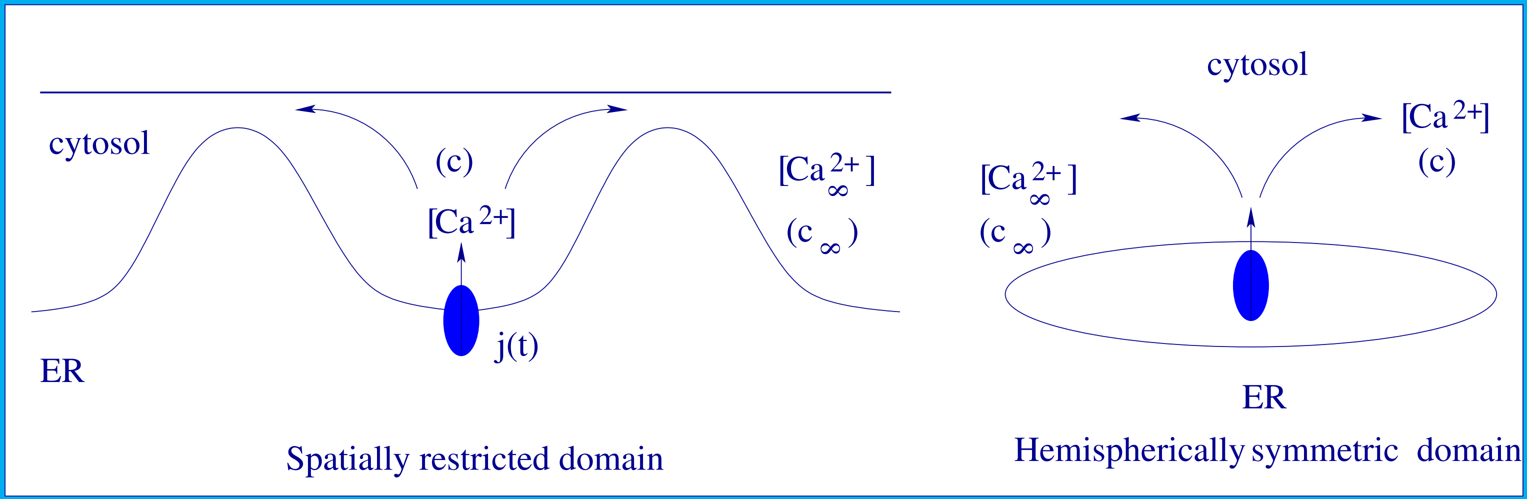

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Transition probability matrix: $W = \begin{bmatrix} 1 - k_+c^\eta\Delta t & k_+c^\eta\Delta t \\ k_-\Delta t & 1 - k_-\Delta t \end{bmatrix}$

Generator matrix: $Q = K_- + c^\eta K_+$ (so $W = I + Q\Delta t$).

Model - calcium domains

Spatially restricted domain:

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

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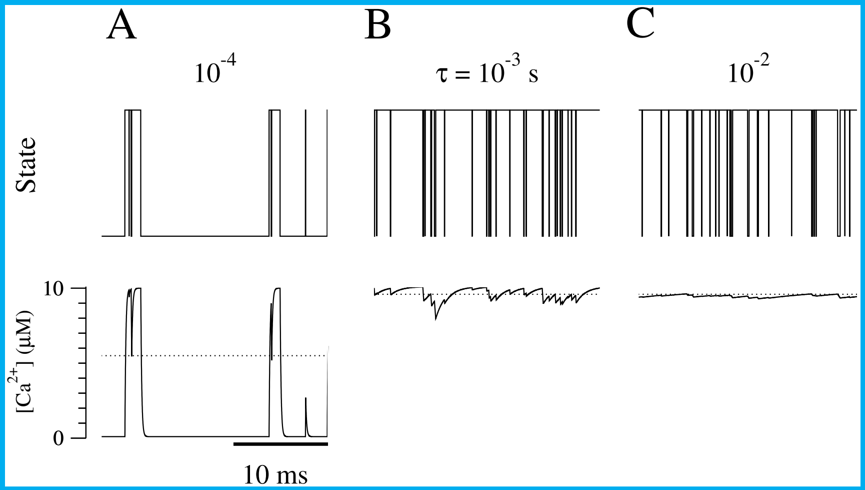
Spherically symmetric domain:

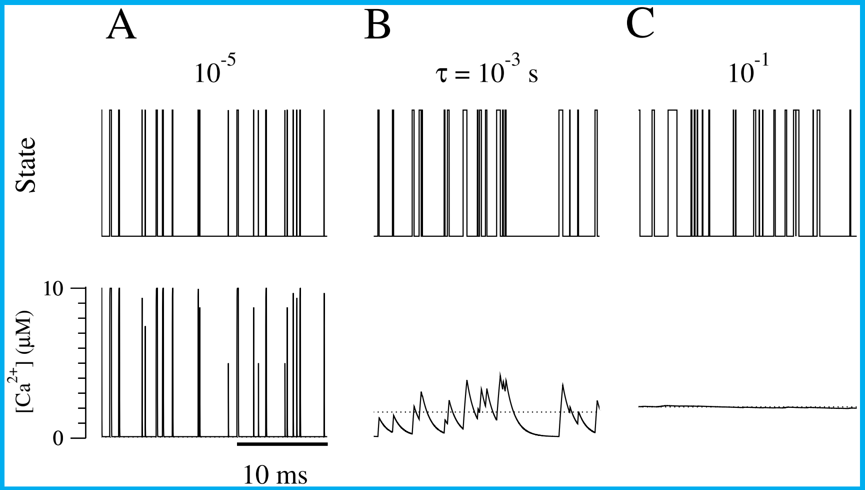
$$\frac{\partial c}{\partial t} = D_c \nabla^2 c - \frac{c - c_\infty}{\theta} \quad \text{with} \quad \theta = 1/k_{on}^{buf} b_\infty \quad \text{and} \quad b_\infty = b_t - (cb)_\infty$$

$$\lim_{r \to 0} \left\{ -2\pi r^2 D_c \frac{\partial c}{\partial r} \right\} = \sigma(t) \qquad \lim_{r \to \infty} c = c_\infty$$

Monte Carlo simulation results



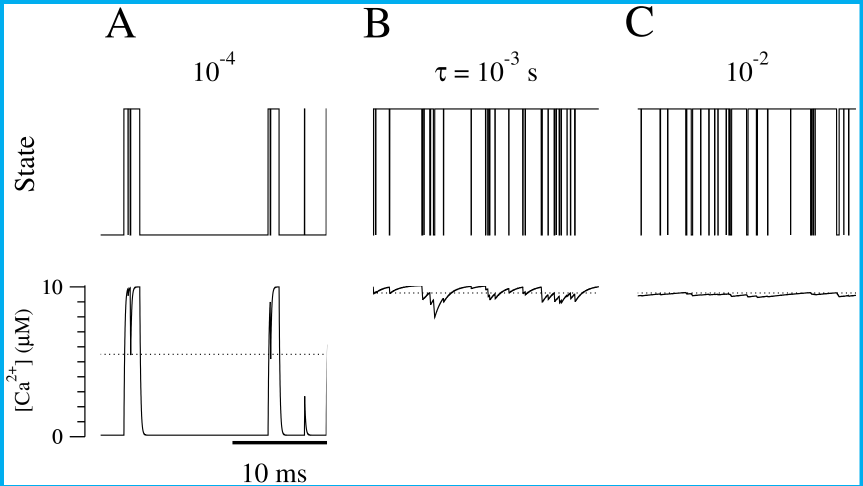
Ca^{2+}-activated channel



Ca^{2+}-inactivated channel

Parameters: $k_+ = 2\mu\mathrm{M}^{-1}\mathrm{ms}^{-1}$, $k_- = 1\mathrm{ms}^{-1}$, $\eta = 1$

Monte Carlo simulation results



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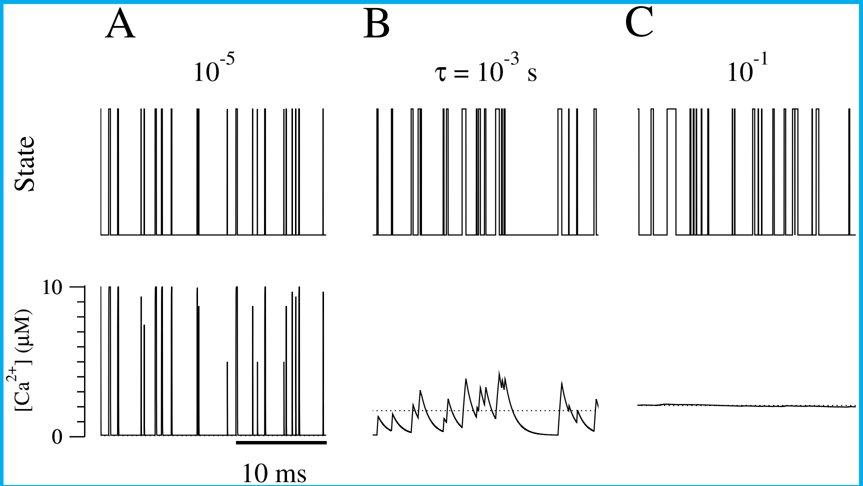

Ca^{2+}-inactivated channel

Parameters: $k_+ = 2\mu M^{-1}ms^{-1}$, $k_- = 1ms^{-1}$, $\eta = 1$

Fast domain (small τ): $$p_{open} = \frac{k_+ c_\infty}{k_+ c_\infty + k_-} = \frac{c_\infty}{c_\infty + K}$$

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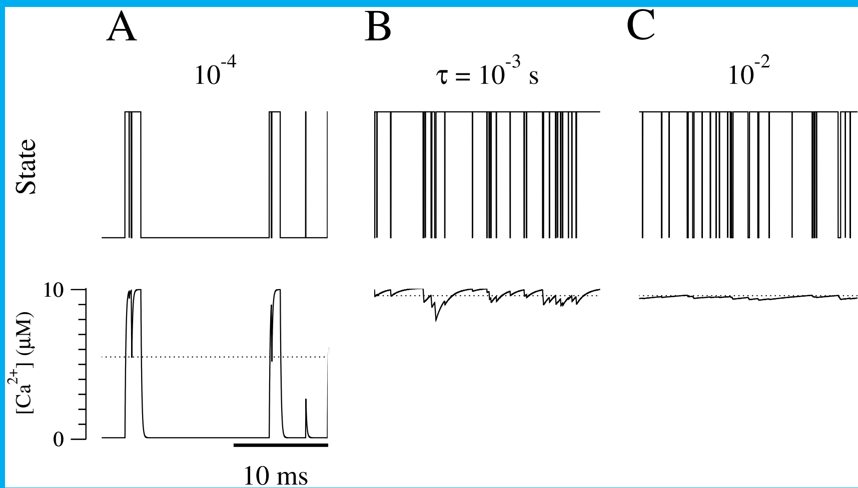

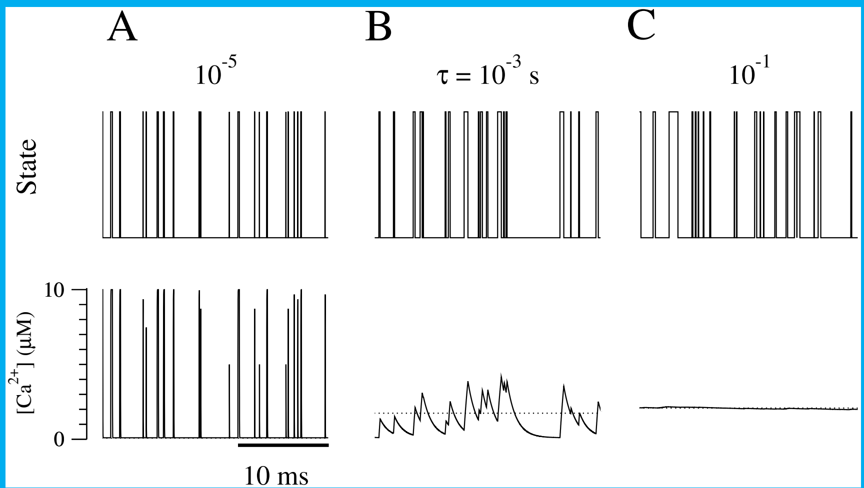

Ca^{2+}-activated channel $\qquad$ Ca^{2+}-inactivated channel

Parameters: $k_+ = 2\mu\mathrm{M}^{-1}\mathrm{ms}^{-1}$, $k_- = 1\mathrm{ms}^{-1}$, $\eta = 1$

Fast domain (small τ): $\quad p_{open} = \frac{k_+ c_\infty}{k_+ c_\infty + k_-} = \frac{c_\infty}{c_\infty + K}$

Slow domain (large τ):

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

Analytical method

$$\rho_O(c,t)\Delta c = \Pr\{c < [\mathrm{Ca}^{2+}] < c + \Delta c \text{ and } S(t) = O\}$$
$$\rho_C(c,t)\Delta c = \Pr\{c < [\mathrm{Ca}^{2+}] < c + \Delta c \text{ and } S(t) = C\}$$

$$\frac{\partial \rho_C}{\partial t} = -\frac{\partial}{\partial c}\left[-\frac{c - c_\infty}{\tau}\rho_C\right] + k_-\rho_O - k_+ c\rho_C$$
$$\frac{\partial \rho_O}{\partial t} = -\frac{\partial}{\partial c}\left[\left(j_o - \frac{c - c_\infty}{\tau}\right)\rho_O\right] - k_-\rho_O + k_+ c\rho_C$$
$$\text{B.C.}\begin{cases} \rho_C(c_{ss},t) = 0 \\ \rho_O(c_\infty,t) = 0 \end{cases}$$
$$\int_{c_\infty}^{c_{ss}} (\rho_O + \rho_C)\,dc = 1$$

Analytical results

Analytical solution for ρ_O steady state:

$$\rho_{O,ss} = \bar{\rho_O} e^{\tau k_+ c} \left(c_{ss} - c\right)^{\tau k_- - 1} \left(c - c_\infty\right)^{\tau k_+ c_\infty}$$

$$p_{open} = \int_{c_\infty}^{c_{ss}} \rho_{O,ss}(c) dc$$

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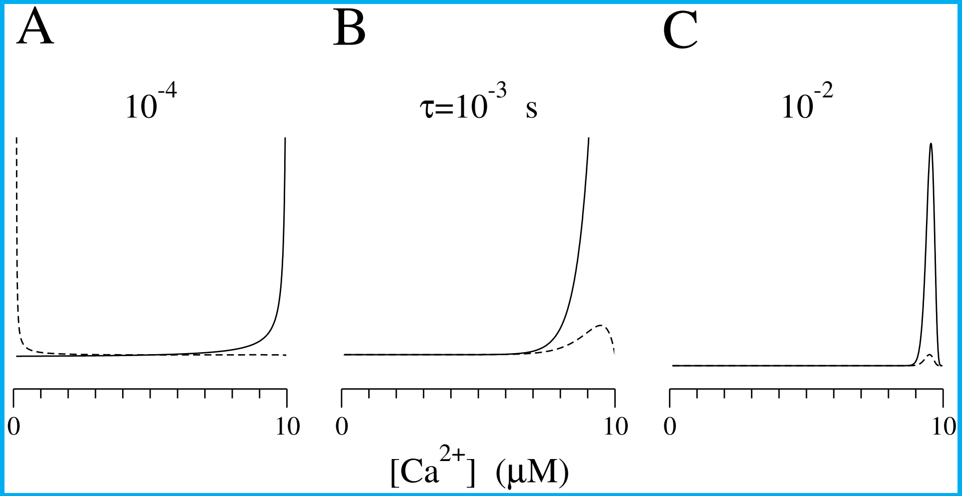
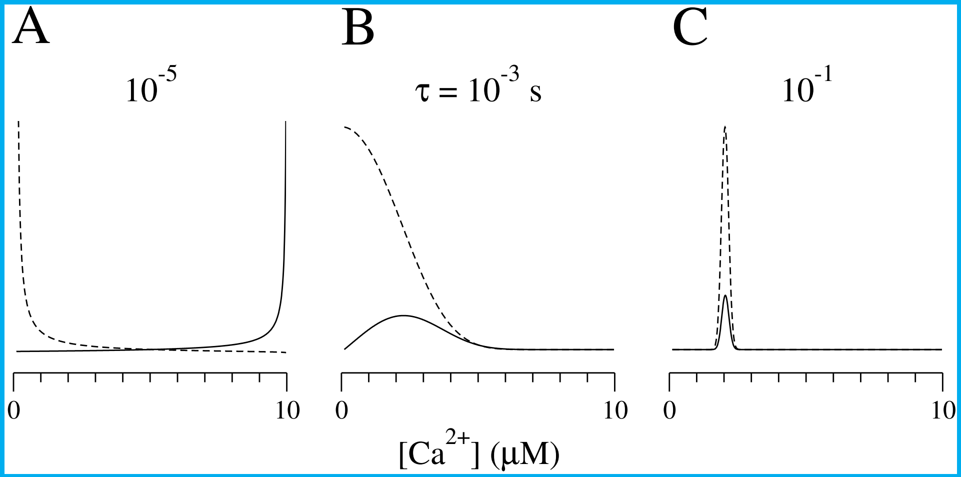
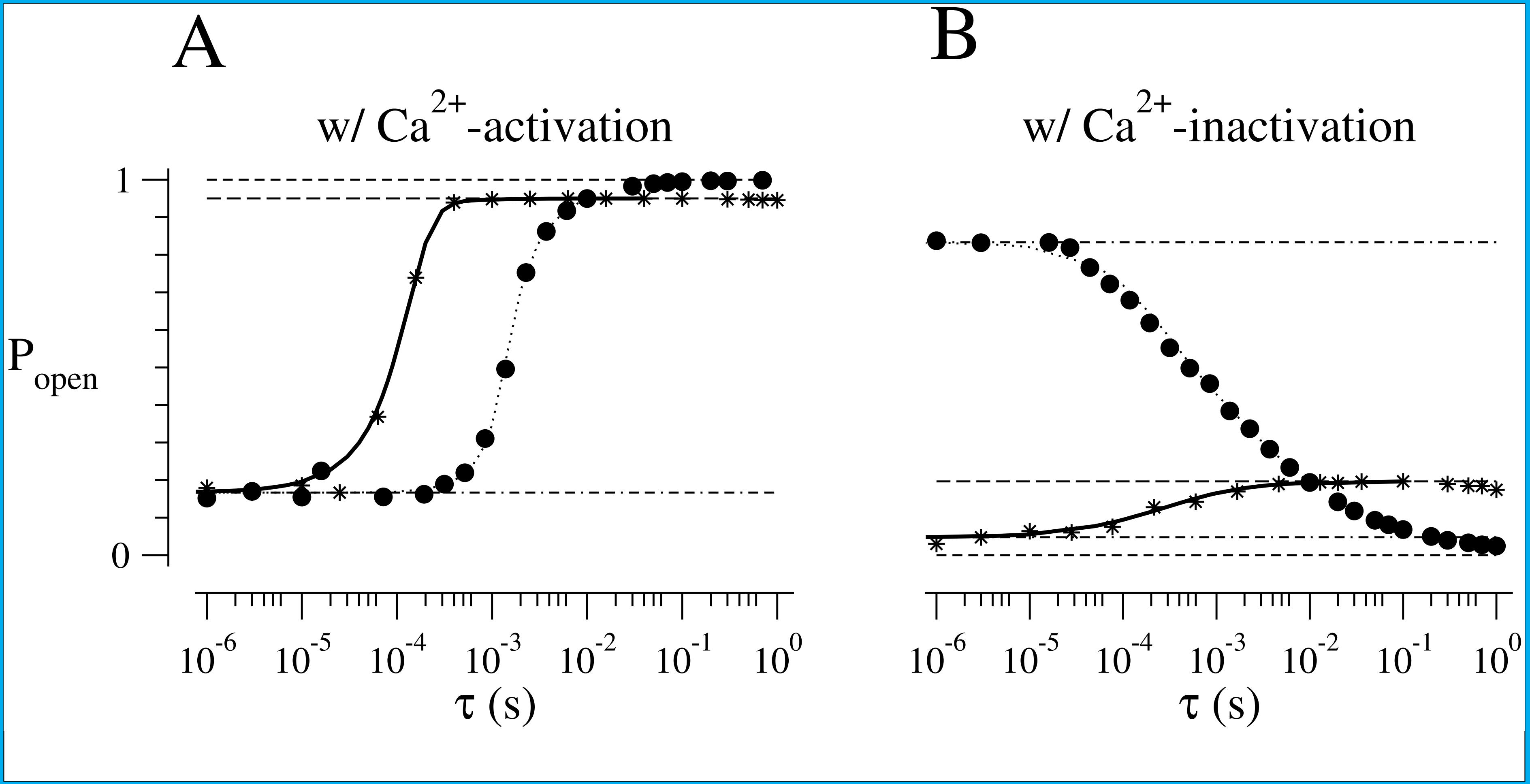
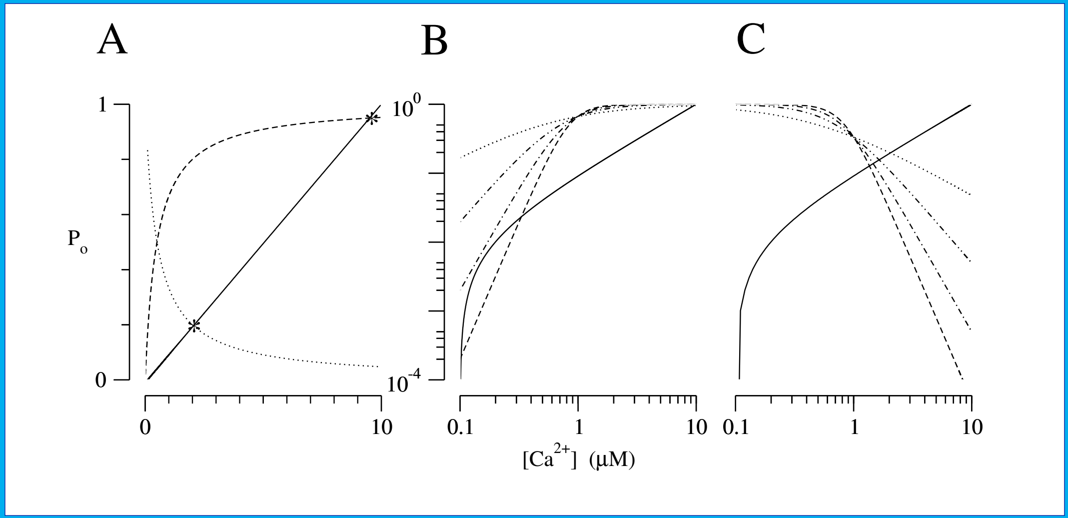




Dependence of p_{open} on τ



Interesting dynamics for $\eta > 1$



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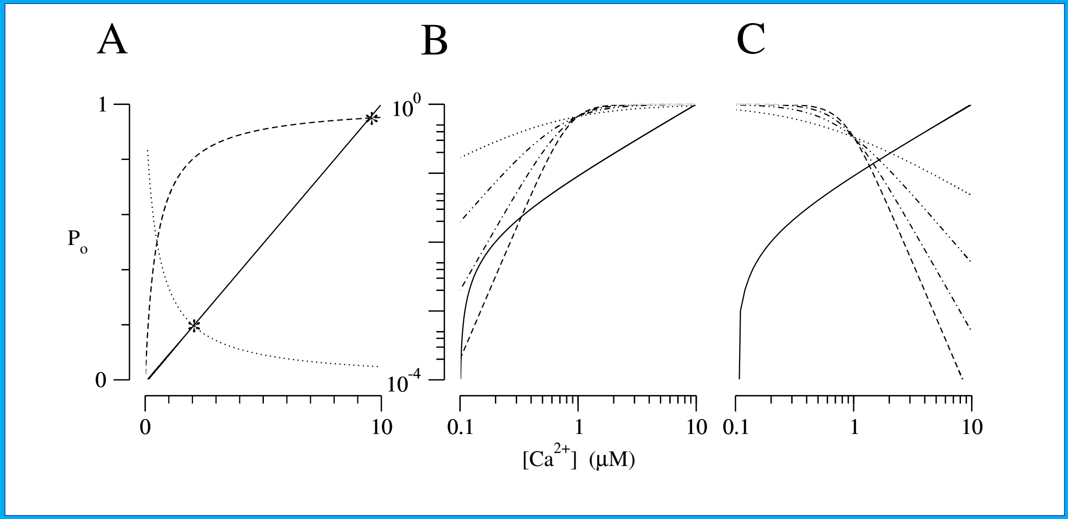
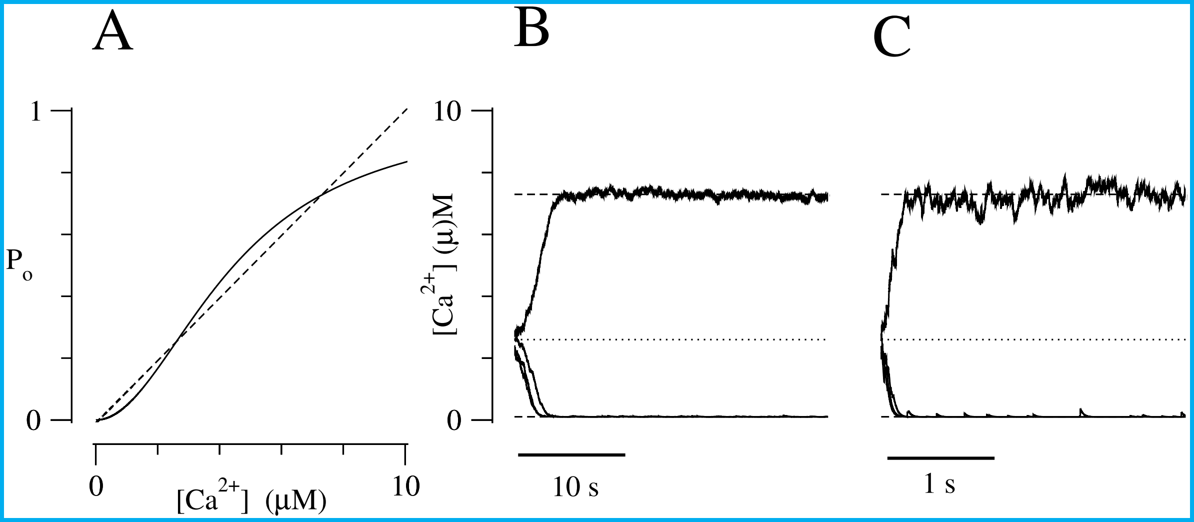
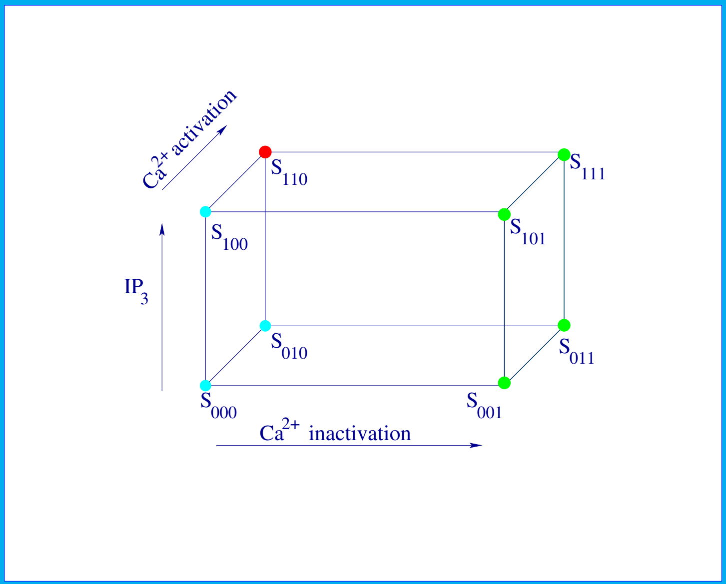




$k_+ = 200\mu M^{-2} ms^{-1}$, $k_- = 4000\mathrm{ms}^{-1}$, $\tau = 300, 30$ ms

Results for a more complex channel model



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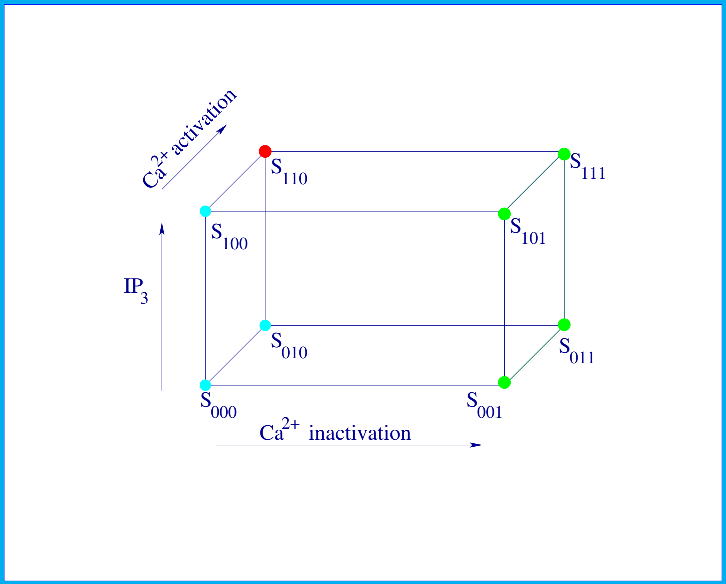

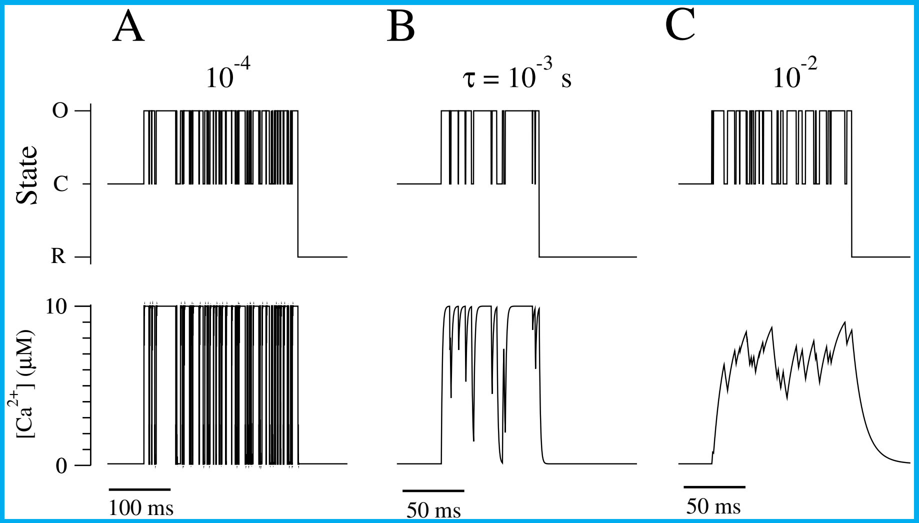

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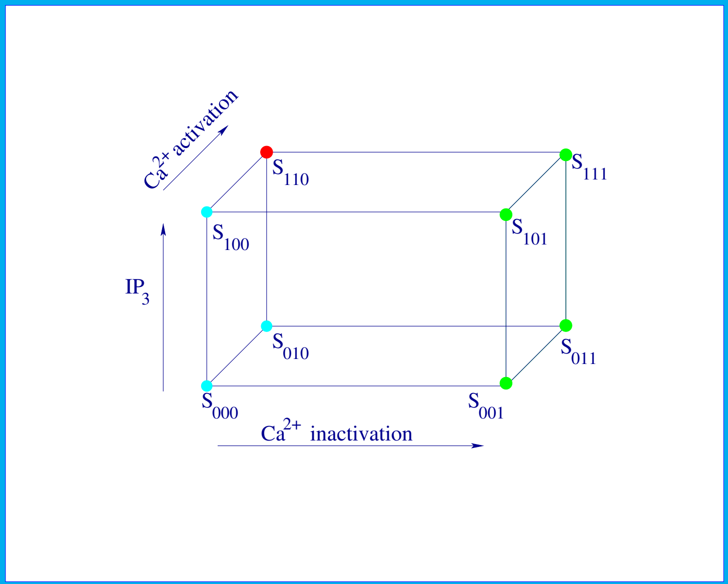

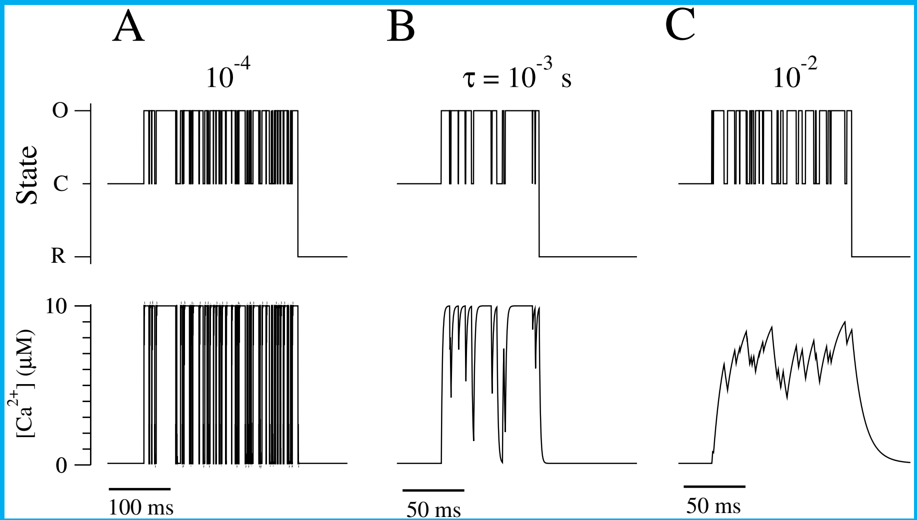

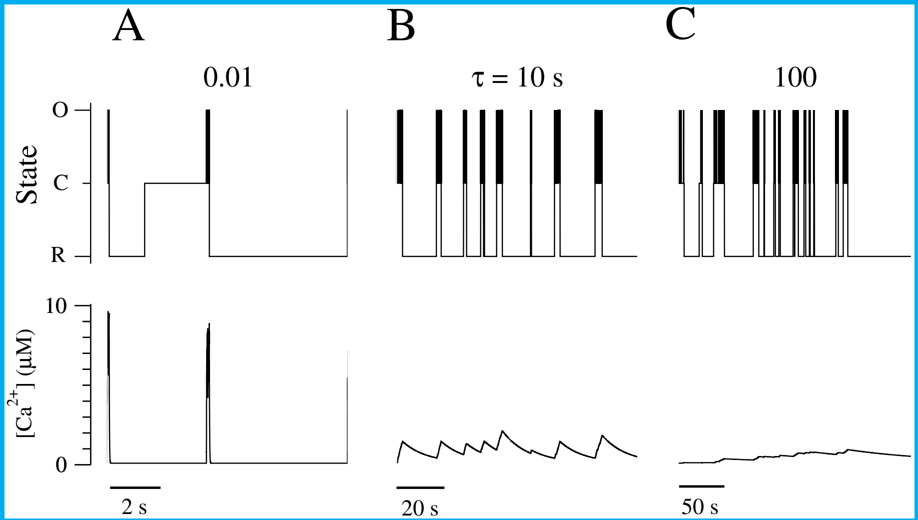

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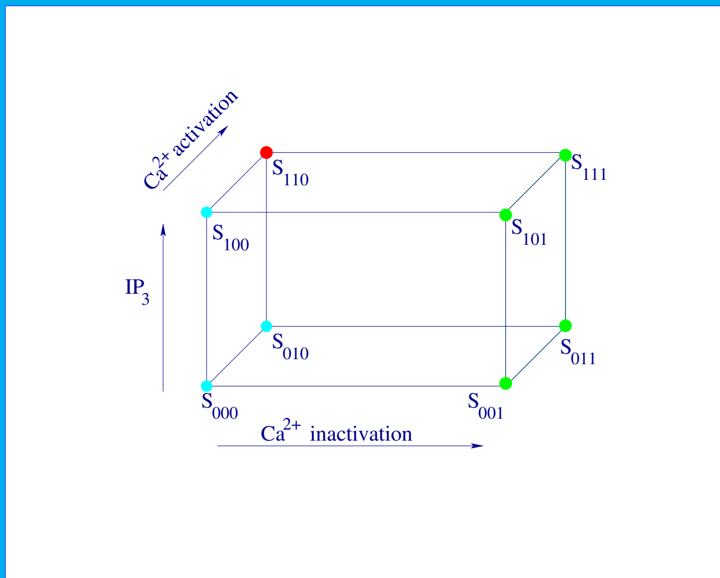

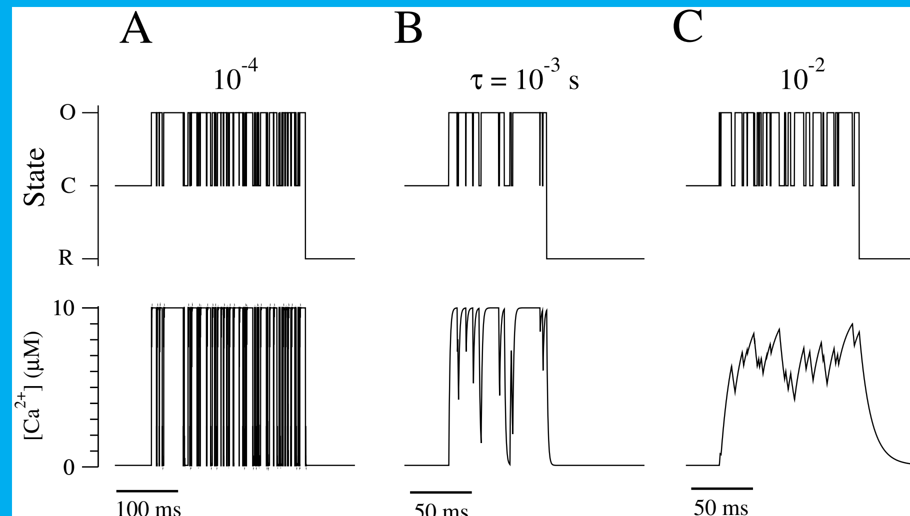

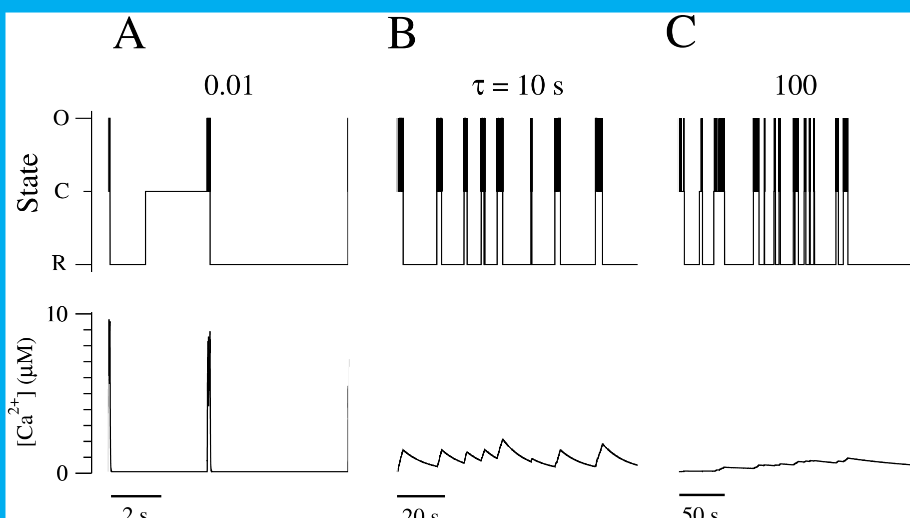

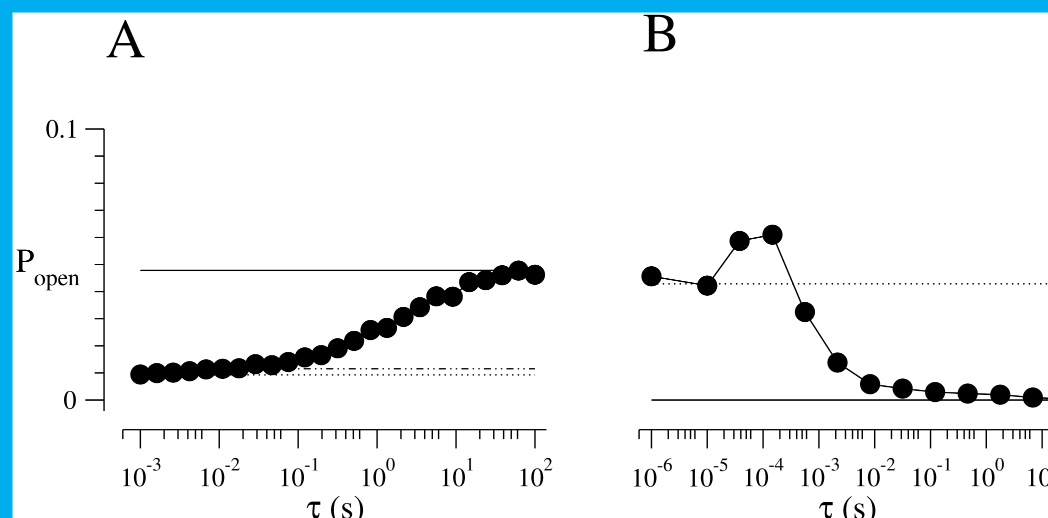

Generalized estimates for small and large $\boldsymbol{\tau}$

Small τ limit (fast domain):

$$\underline{Q} = K_{-} + \text{diag}\left\{c_{\infty}\boldsymbol{u}_C + c_{ss}\boldsymbol{u}_O\right\}^{\eta} K_{+},$$

$$\underline{p_{open}} = \underline{\boldsymbol{\pi}}\boldsymbol{u}_O \quad \text{where} \quad \underline{\boldsymbol{\pi}}\underline{Q} = \mathbf{0} \quad \text{and} \quad \underline{\boldsymbol{\pi}}\boldsymbol{e} = 1.$$

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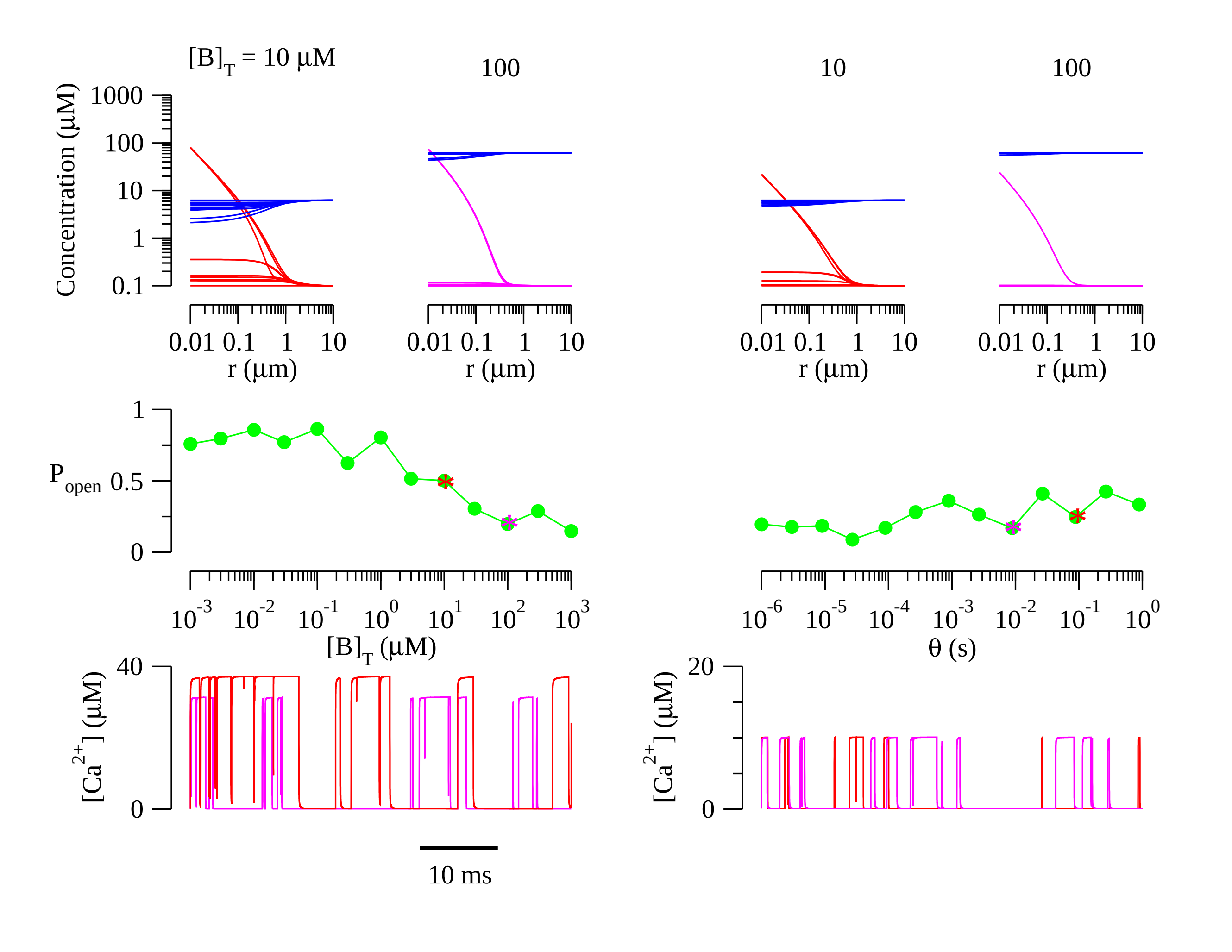
Large τ limit (slow domain):

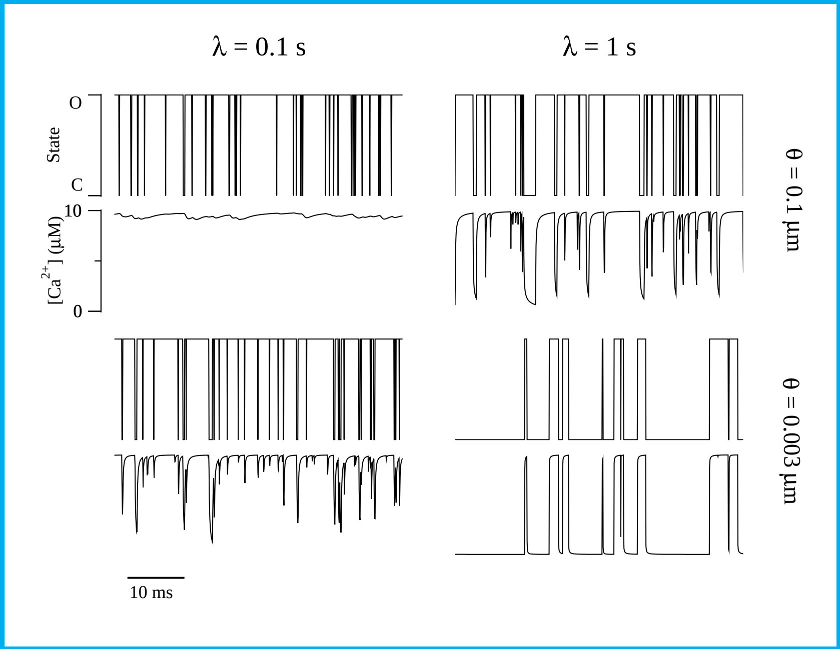
$$\overline{Q} = K_- + c_*^\eta K_+ \qquad \text{where} \qquad c_* = c_\infty\left(1 - \overline{p_{open}}\right) + \overline{p_{open}}c_{ss}.$$

$$\overline{p_{open}} = \overline{\boldsymbol{\pi}}\boldsymbol{u}_O \quad \text{where} \quad \overline{\boldsymbol{\pi}}\overline{Q} = \mathbf{0} \quad \text{and} \quad \overline{\boldsymbol{\pi}}\boldsymbol{e} = 1.$$

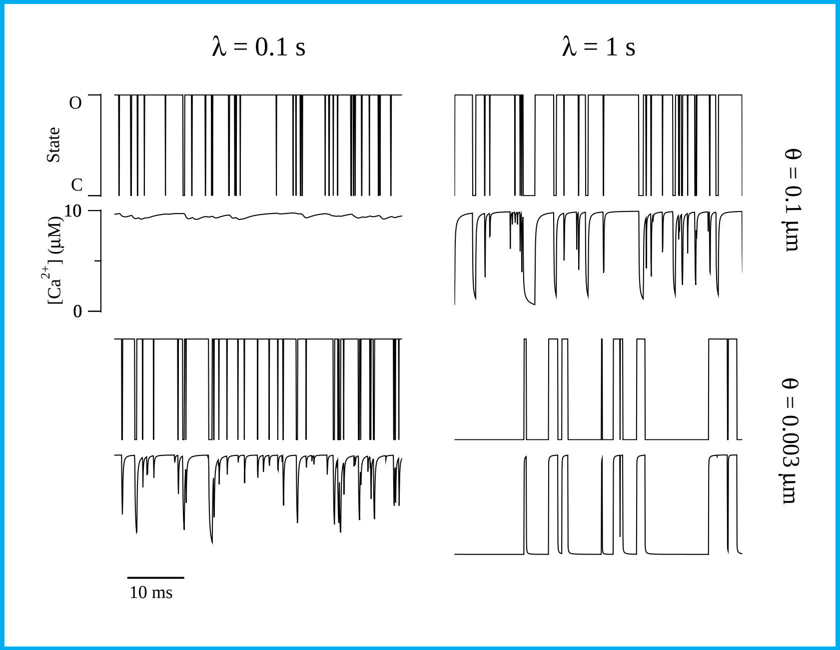
Buffered Ca^{2+} diffusion

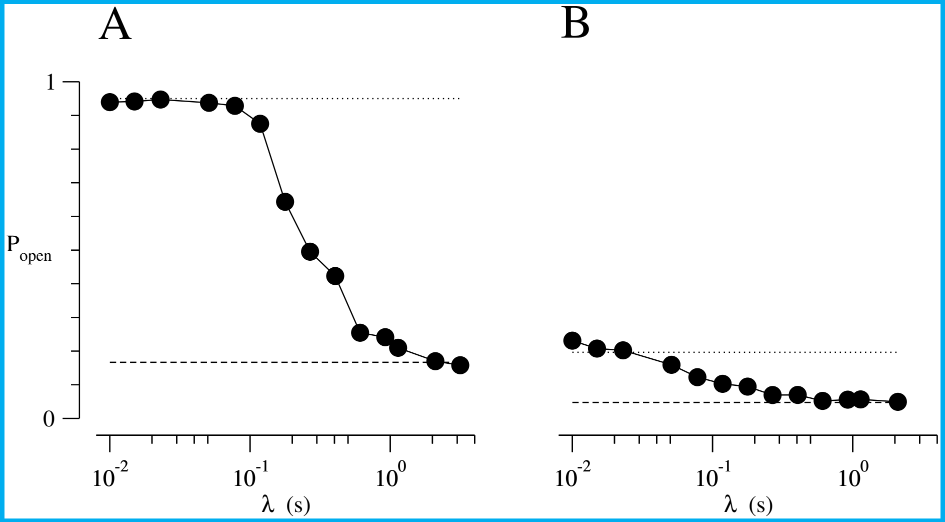


Results for the spherically symmetric domain



Results for the spherically symmetric domain





Discussion of results

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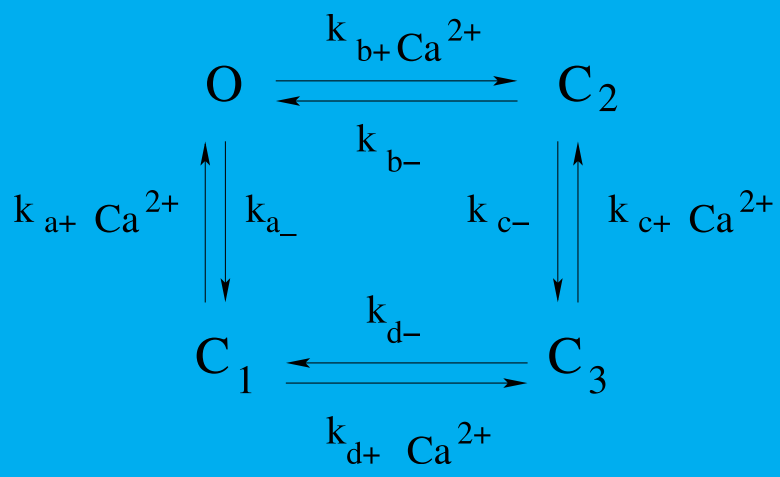
- For Ca^{2+} activated <u>and</u> inactivated channels, p_{open} increases with τ (if c_{ss} remains constant)

- PDE model for Ca^{2+} domain: although temporal and spatial scales change together, similar observation can be made when Ca^{2+} domain size is constant

- Biological implications: Using buffers to visualize $[\mathrm{Ca}^{2+}]$ effects open probability of channels, thus effects amount of Ca^{2+} released

Extensions of the project

- Simulations of release sites: instantaneous coupling (IC) and time dependent (TD) domain (four-state model)



- Question: When does the TD case converge to IC results?

Applications

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- What are the quantitative differences between release sites made up of different Ca^{2+} channels?
- How can channel models with calcium-dependent states be reduced?
- Applications to cardiac myocytes: coupling between L-type channels and RyR

Thank you!