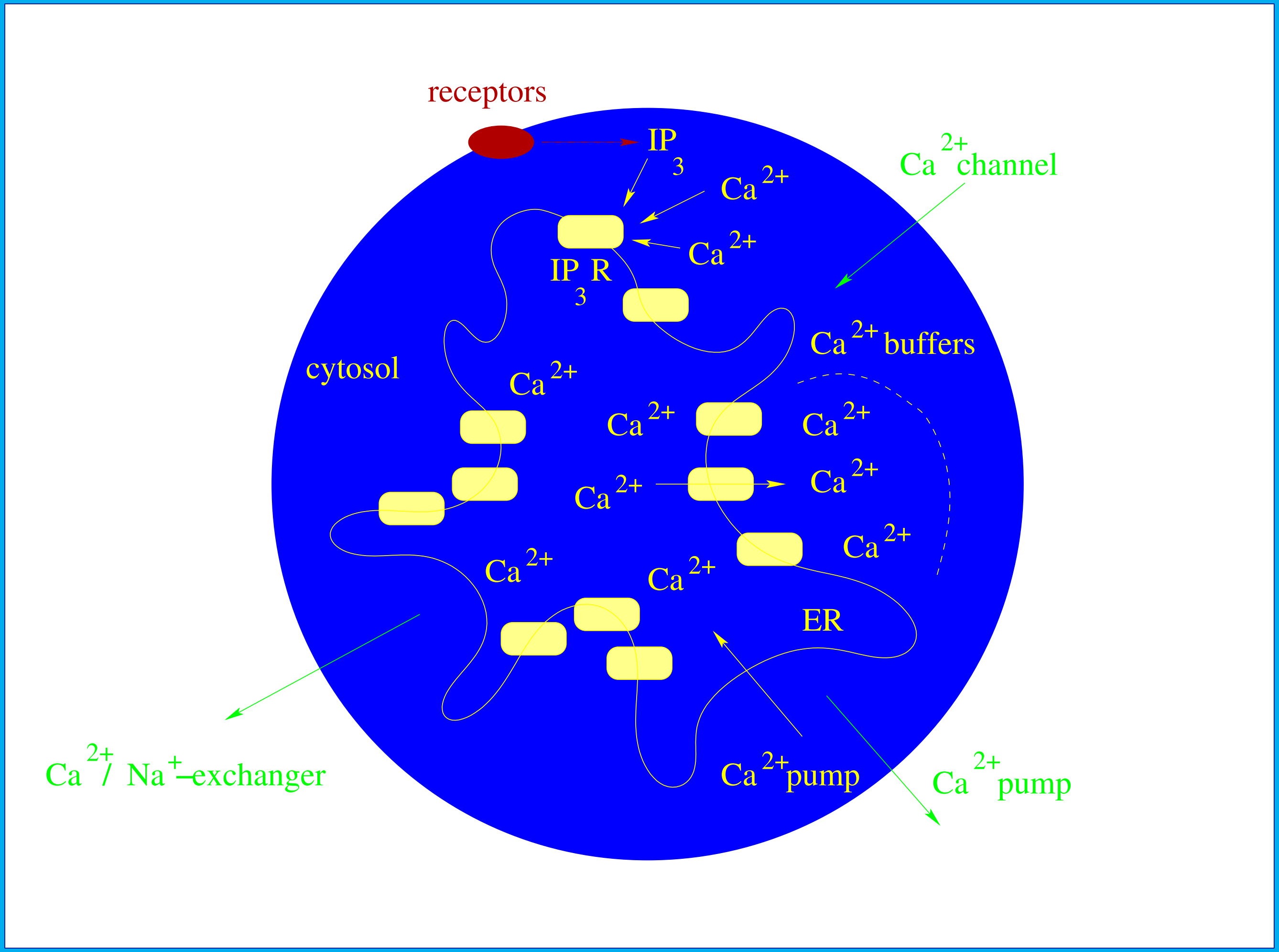
The localized dynamics of a Ca^{2+}channel (30-minute talk)

Bori Mazzag
Graduate Seminar
Sep 5, 2006

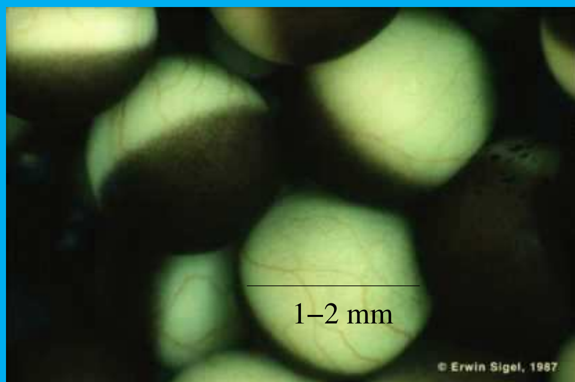
This work was done in collaboration with:

Christopher Tignanelli
&
Gregory D. Smith
Applied Science Department
College of William and Mary

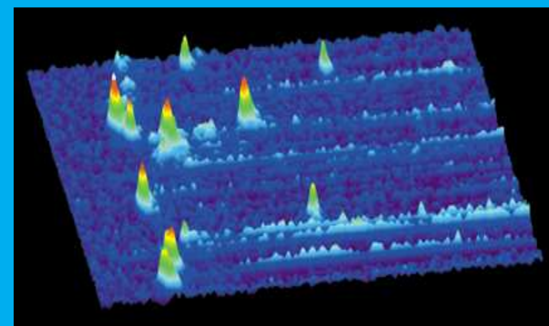
Ca^{2+} signalling in cells

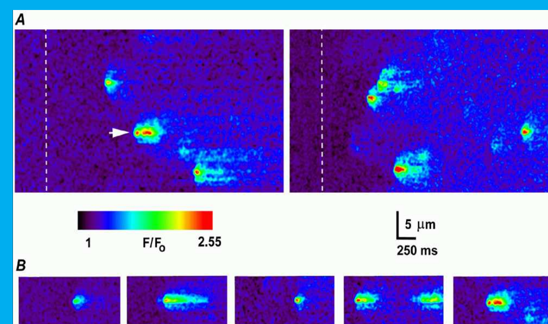


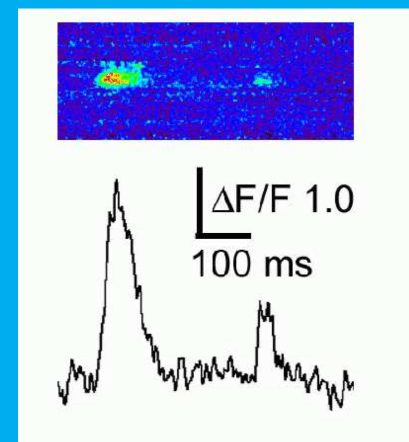
Model organism: *Xenopus oocyte*



(Erwin Sigel, University of Bern, 1987)

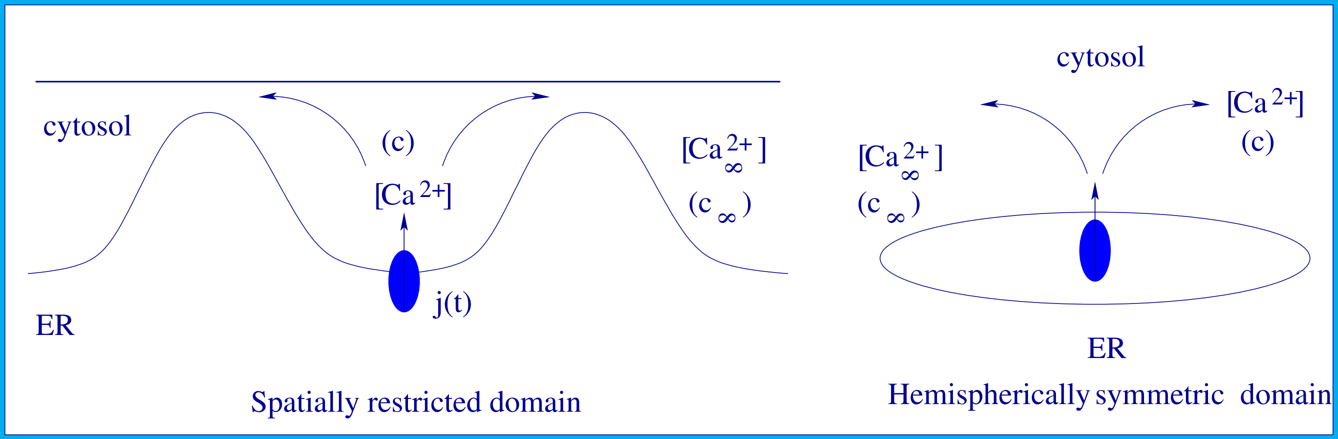






Figures from the Parker lab: Sun, et al., J. Physiol.1998, Parker and Callamaras, cover of Molecular Probes

Model - Description of channels



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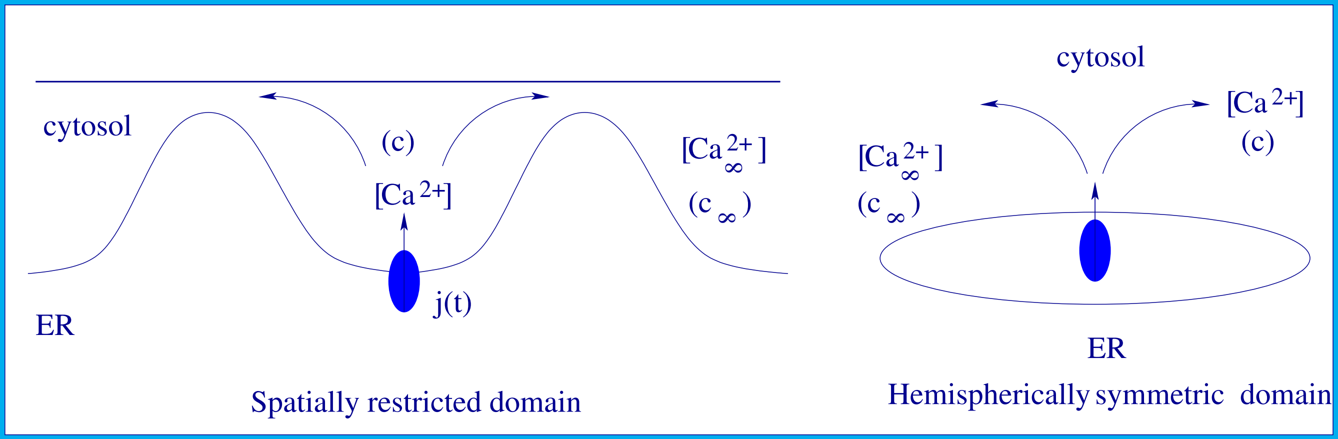

Ca-activated channel: $C\,(\text{closed}) \underset{k_-}{\overset{k_+c^\eta}{\rightleftharpoons}} O\,(\text{open})$

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

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

Model - calcium domains

Spatially restricted domain:

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

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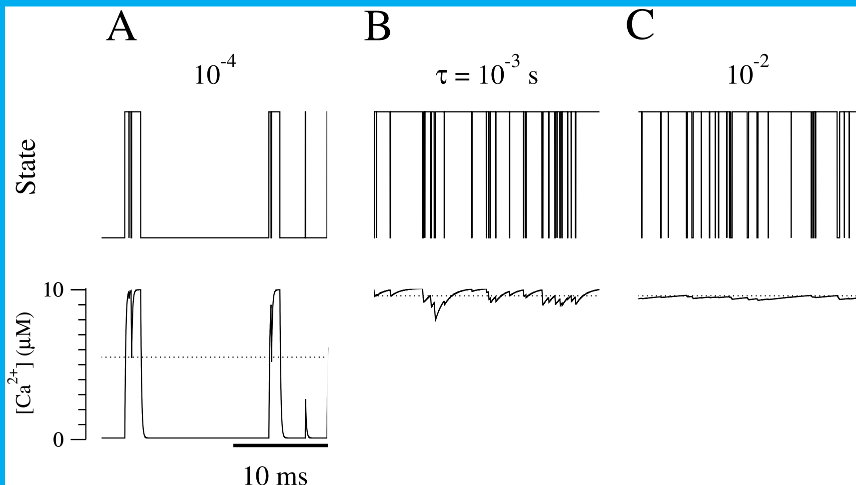
Spherically symmetric domain:

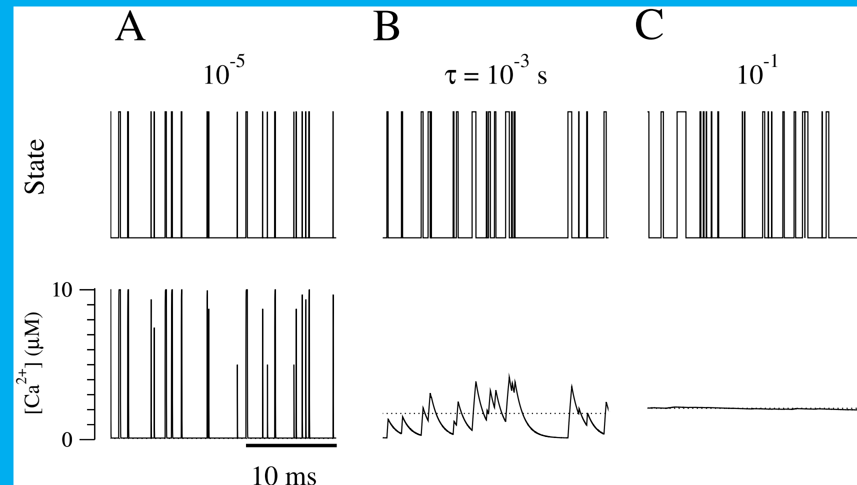
$$\frac{\partial c}{\partial t} = D_c \nabla^2 c - \frac{c - c_\infty}{\theta} \quad \text{with} \quad \theta = 1/k_{on}^{buf} b_\infty \quad \text{and} \quad b_\infty = b_t - (cb)_\infty$$

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

Monte Carlo simulation results

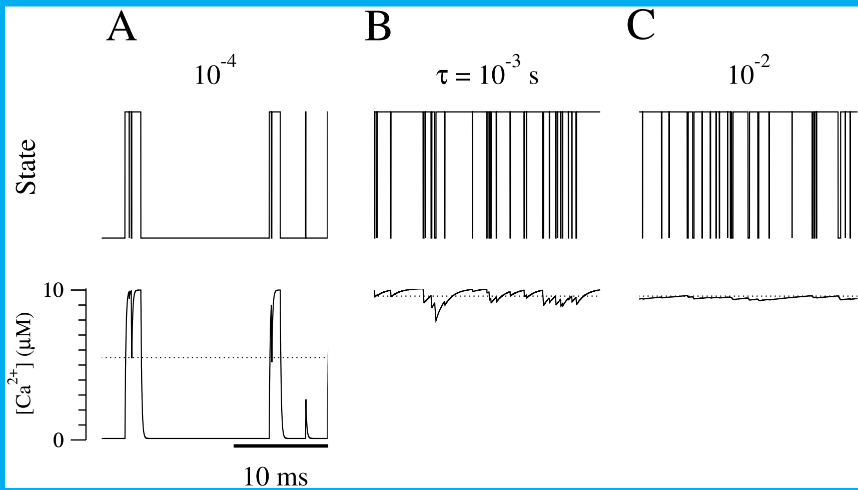


Ca^{2+}-activated channel



Ca^{2+}-inactivated channel

Monte Carlo simulation results



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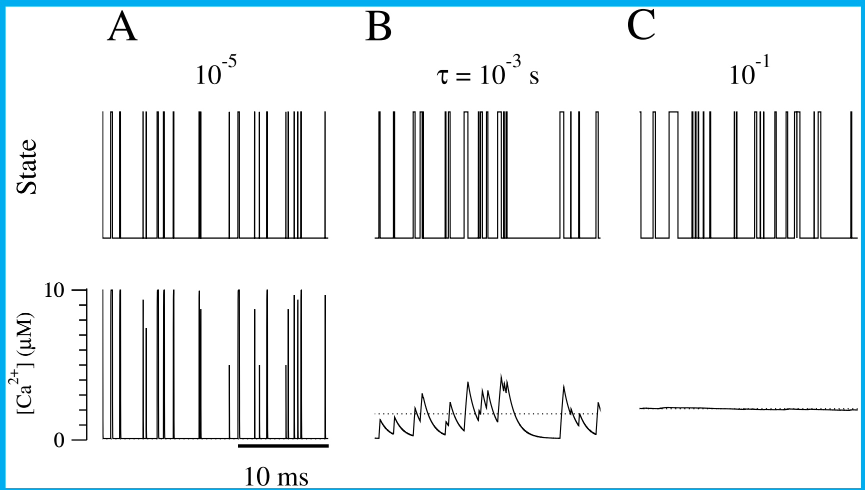

Ca^{2+}-inactivated channel

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

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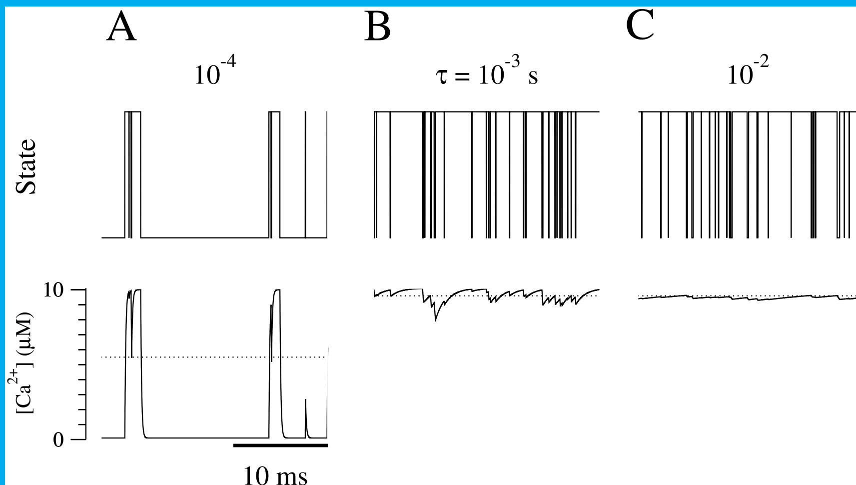

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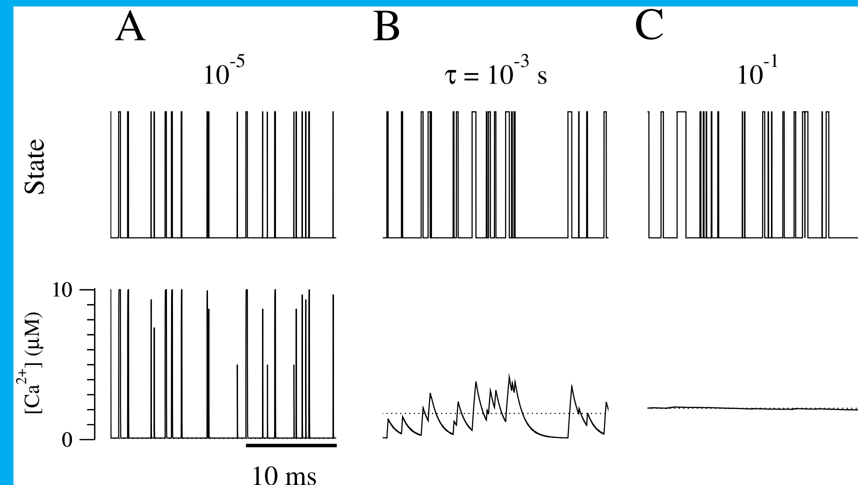


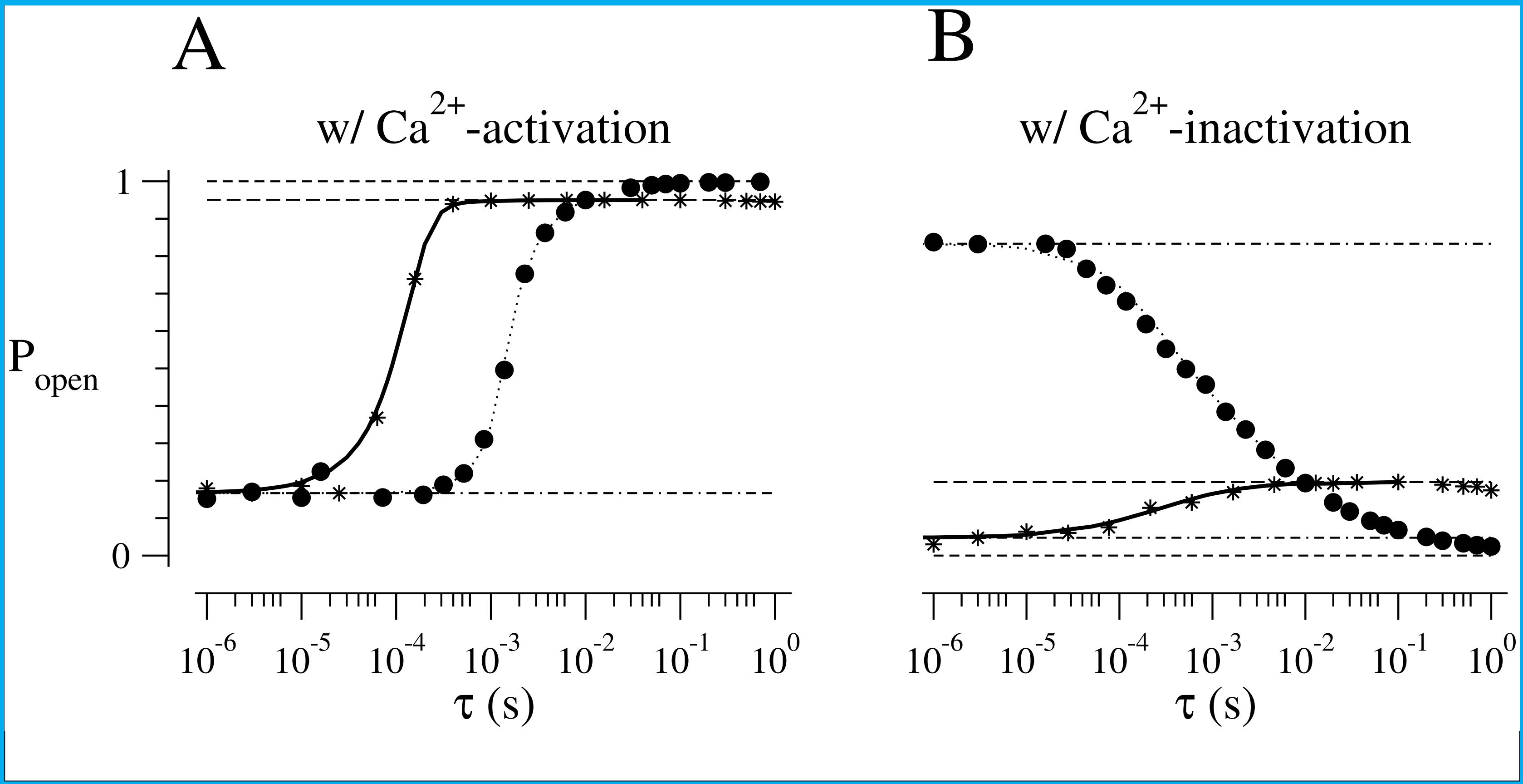
Ca^{2+}-inactivated channel

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

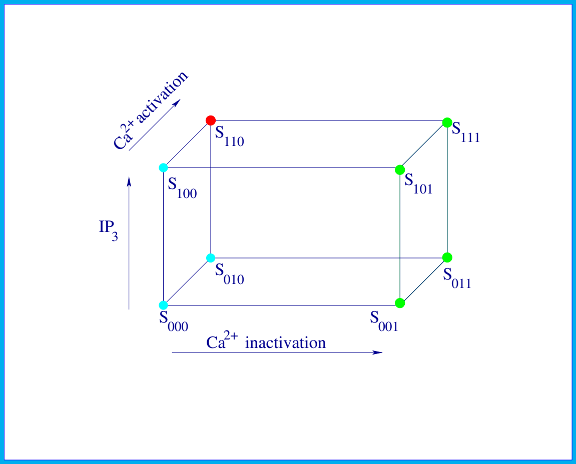
Slow domain (large τ):

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

Dependence of p_{open} on τ



Results for a more complex channel model



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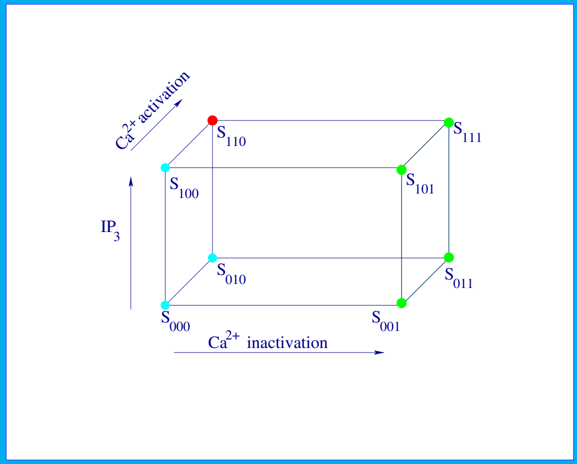

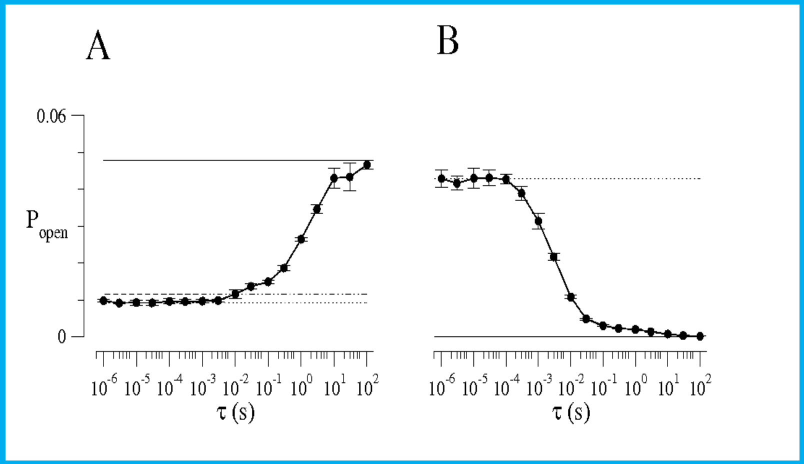

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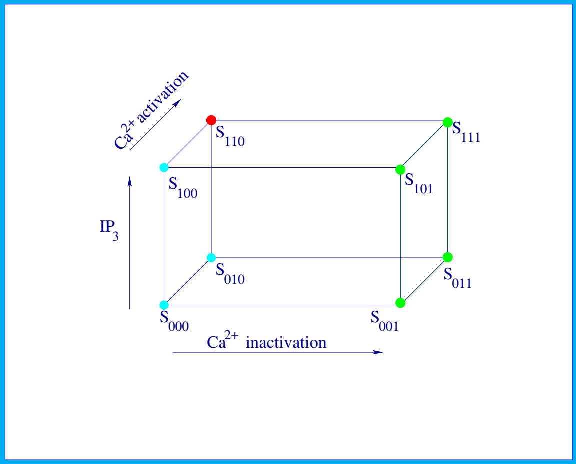

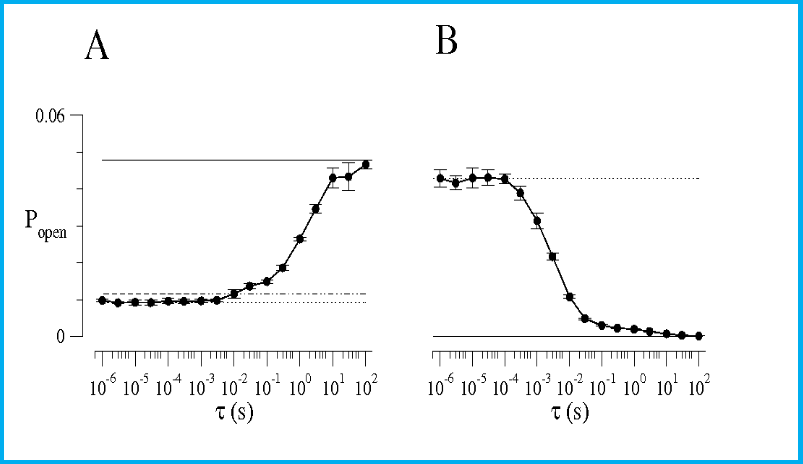

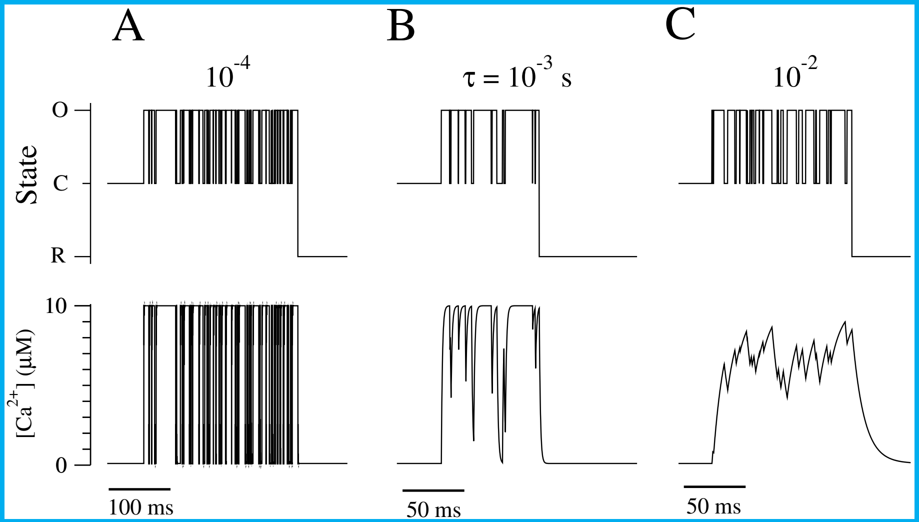

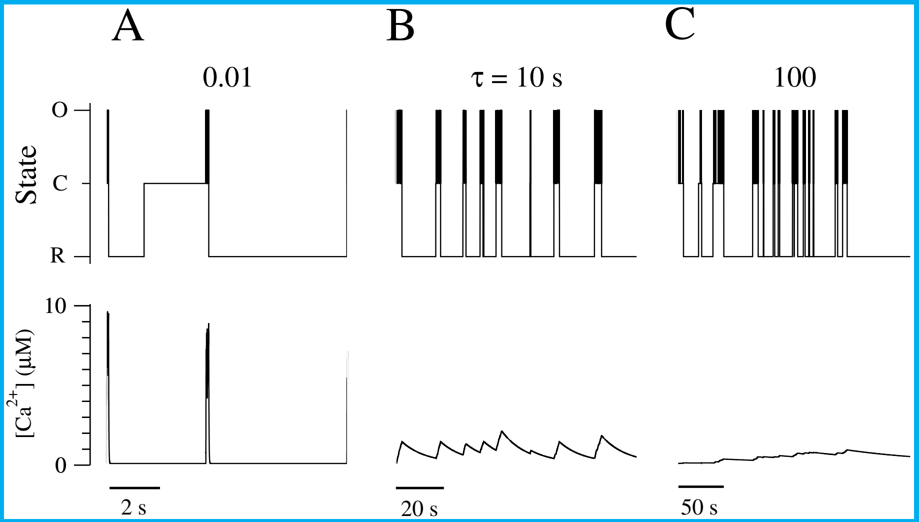

Generalized estimates for small and large $\boldsymbol{\tau}$

Small τ limit (fast domain):

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

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

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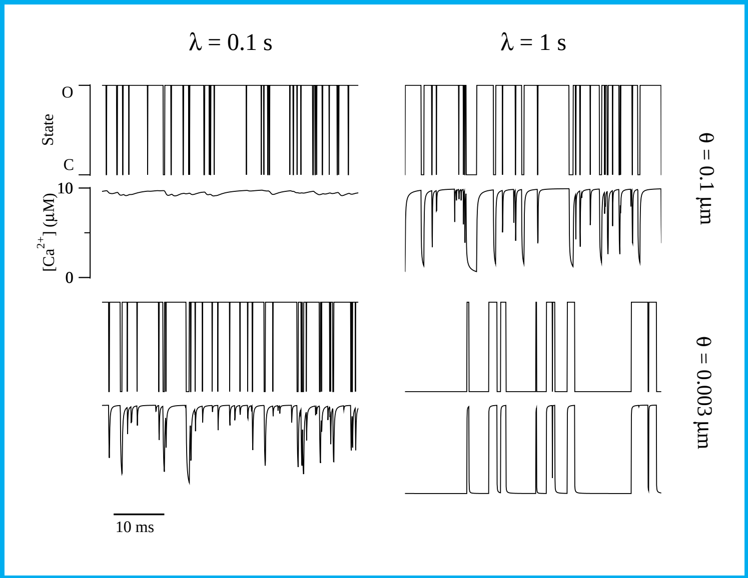
Large τ limit (slow domain):

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

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

Results for the spherically symmetric domain



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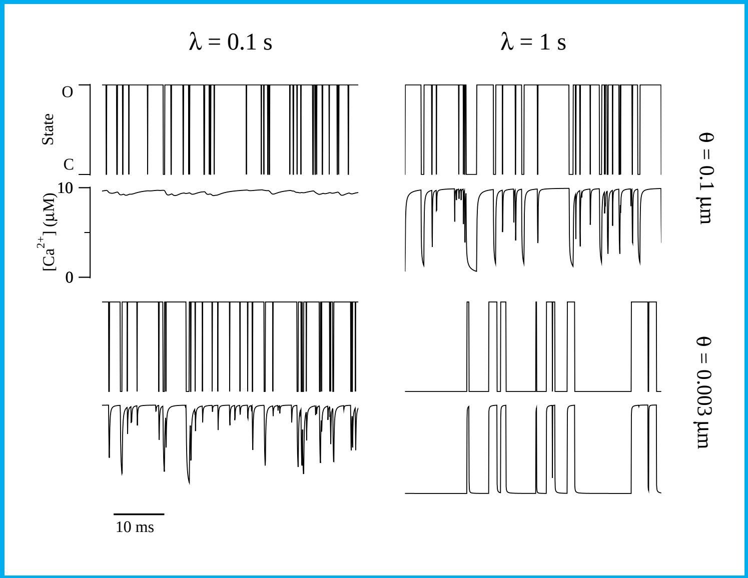

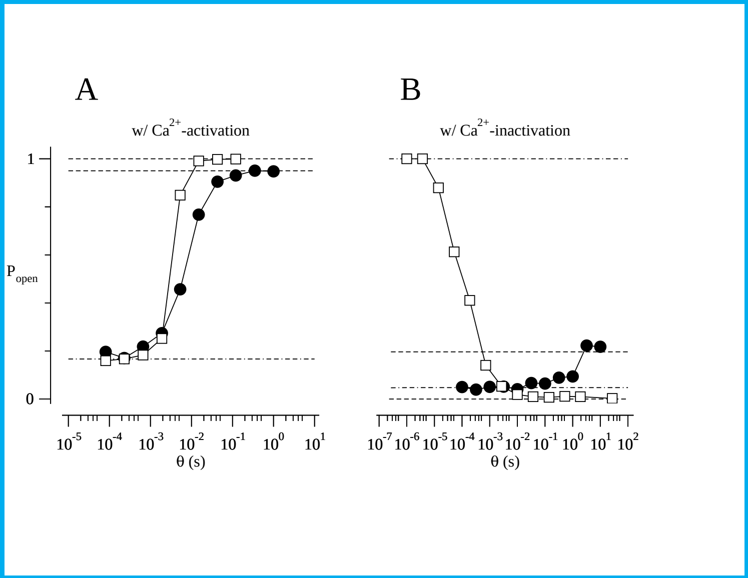

Discussion of results

- Computational methods and fast/slow domain estimates can be generalized for arbitrarily complicated channel models
- Results: understanding the dependence of p_{open} on the temporal scales of the problem

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- Results: understanding the dependence of p_{open} on the temporal scales of the problem
  - ⋆ p_{open} increases as domain becomes slow compared to channel gating
  - ⋆ More complicated behavior when channel model contains two different time scales
  - ⋆ Qualitatively similar behavior for PDE domain

Thank you!

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