Using math in cell biology: A tale of two channel types

Bori Mazzag
Occidental College

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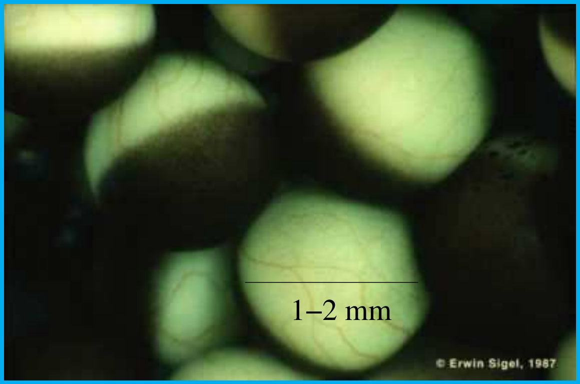
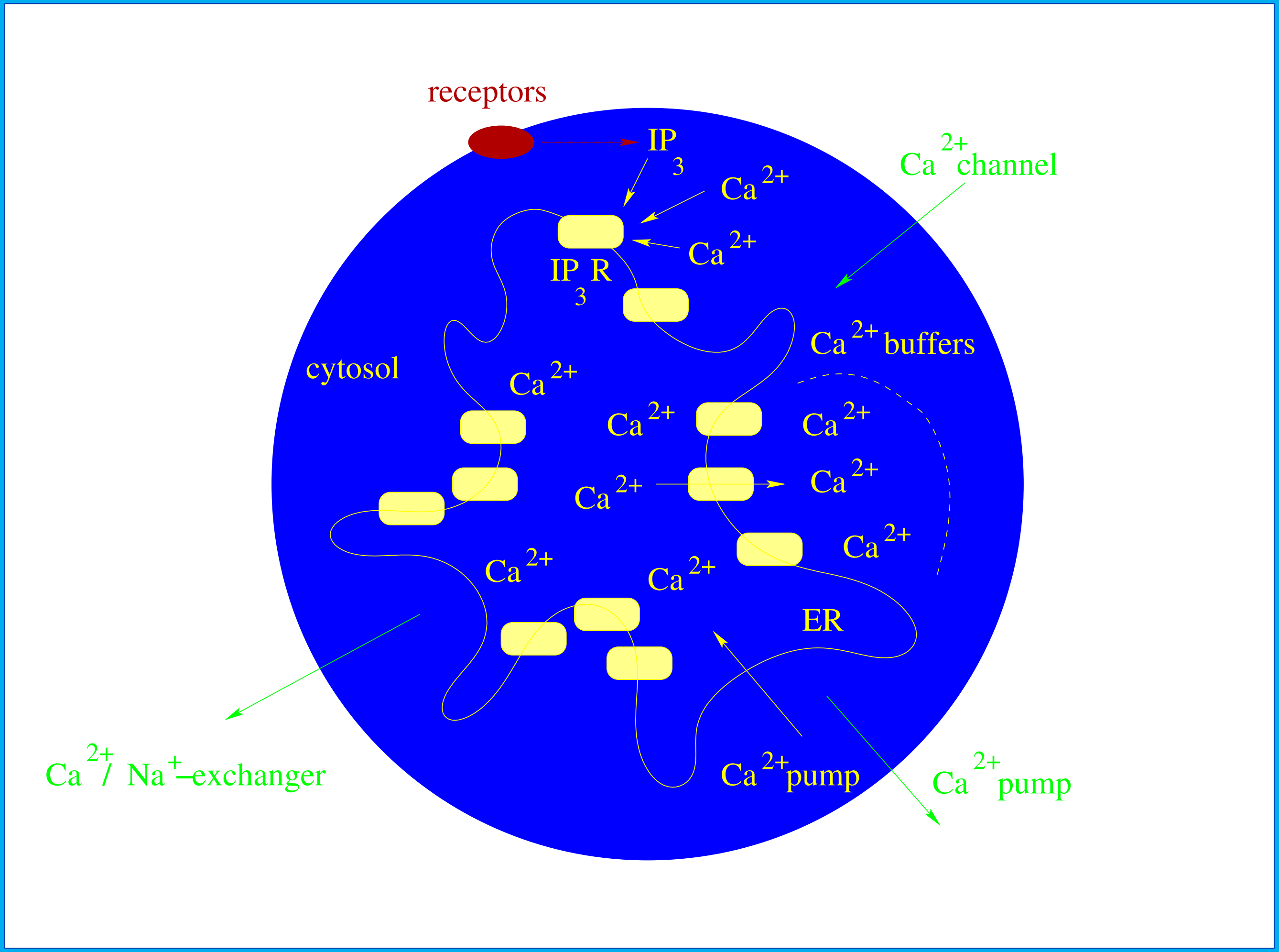
- Fertilization of *Xenopus oocytes*

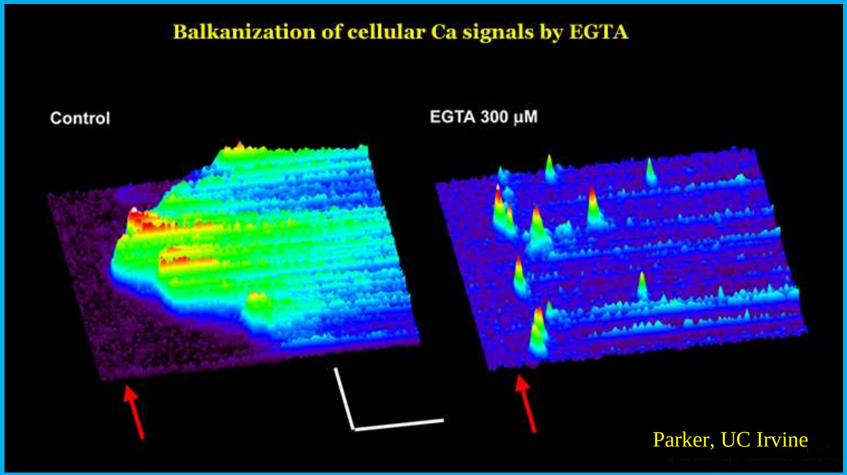


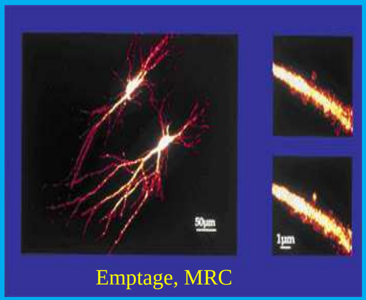
(Erwin Sigel, University of Bern, 1987)

Ca^{2+} signaling in cells



Diversity of Ca^{2+} signals





- Appearance of signals: size (blips, puffs, waves) and domain

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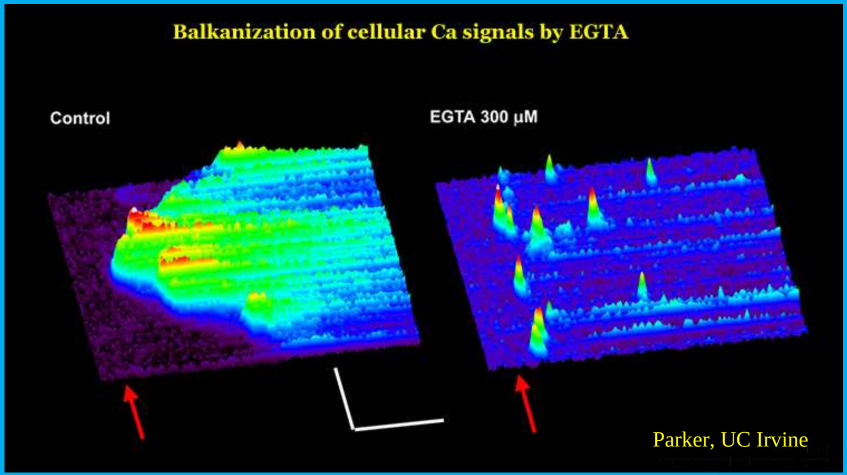

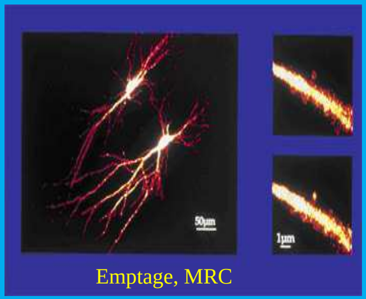

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- Regulation of channels

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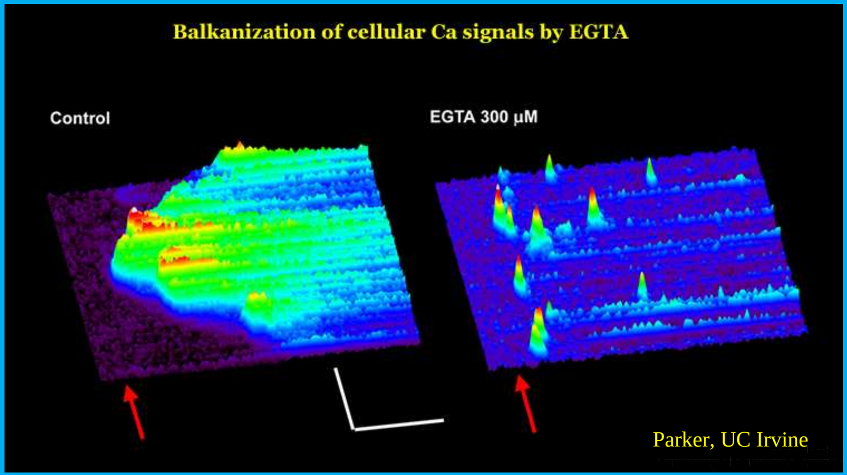
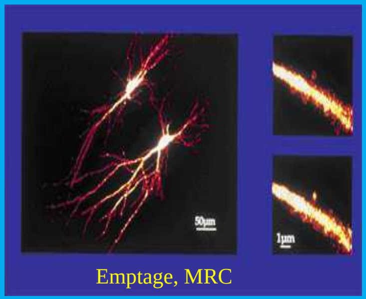


Parker, UC Irvine


Clapham, Harvard



Emptage, MRC

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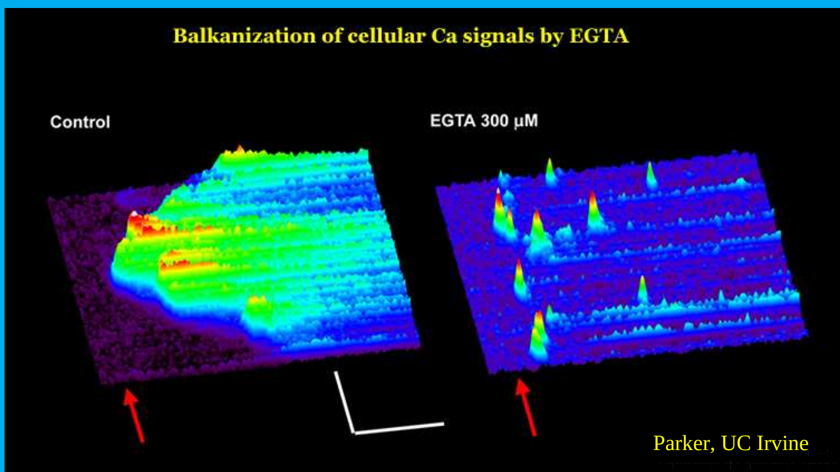
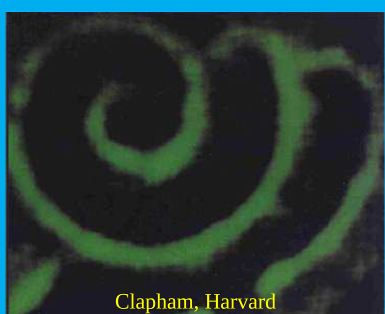
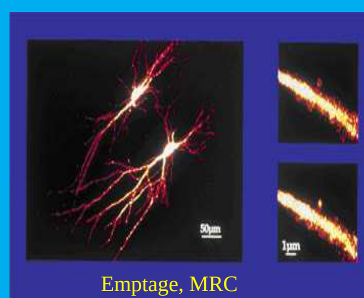
Diversity of Ca^{2+} signals







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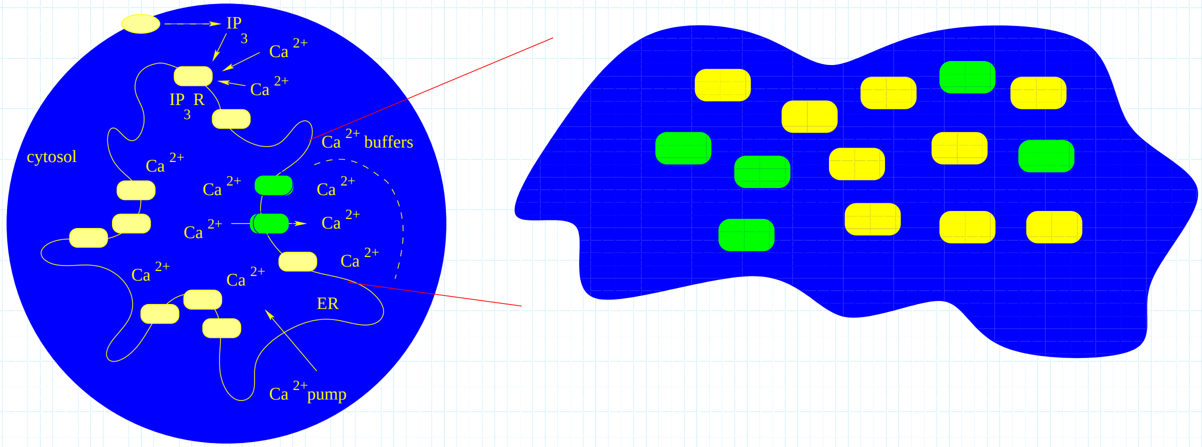
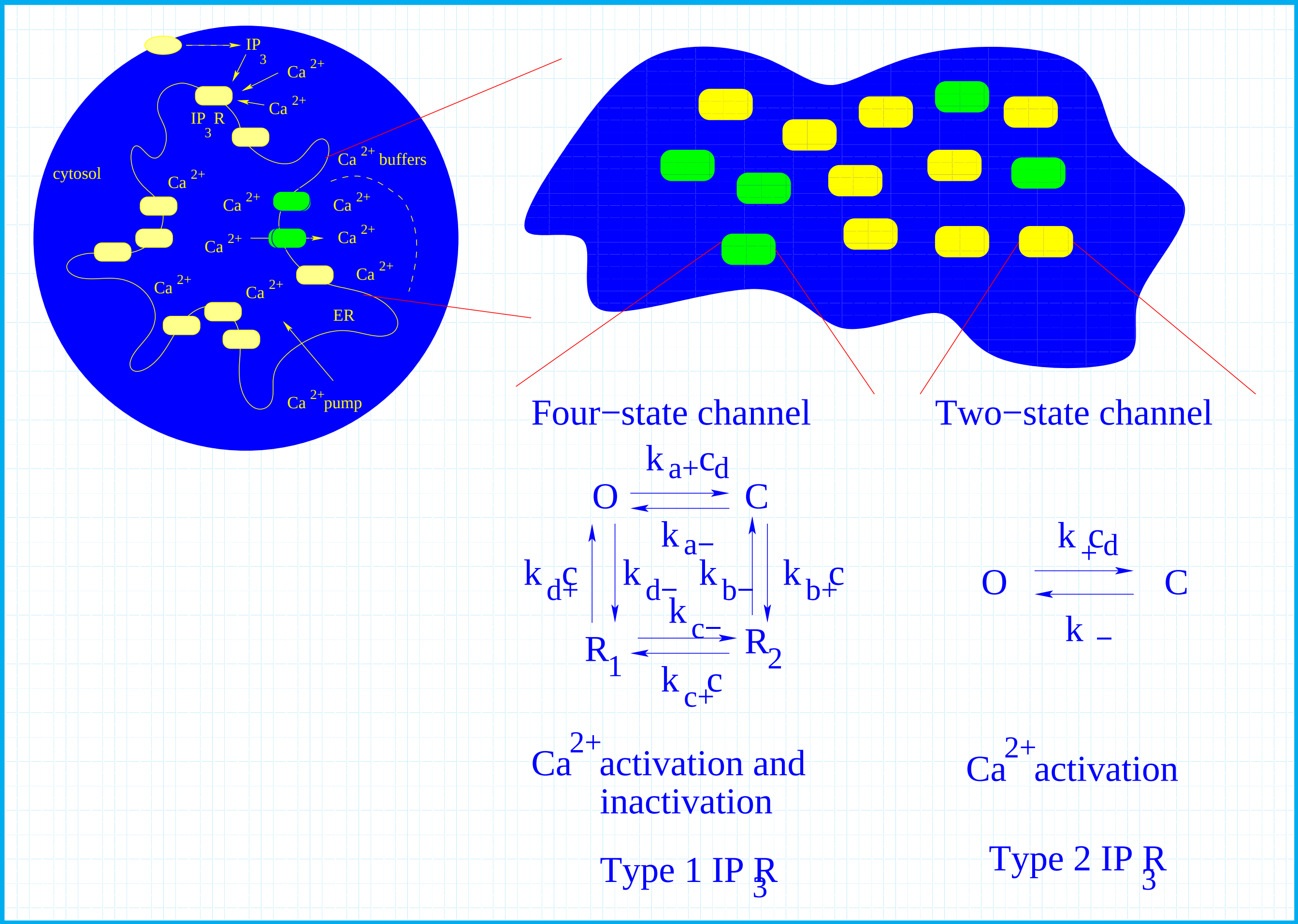
- Spatial organization

Heterogeneous IP$_3$R Release Sites



Heterogeneous IP_3R Release Sites



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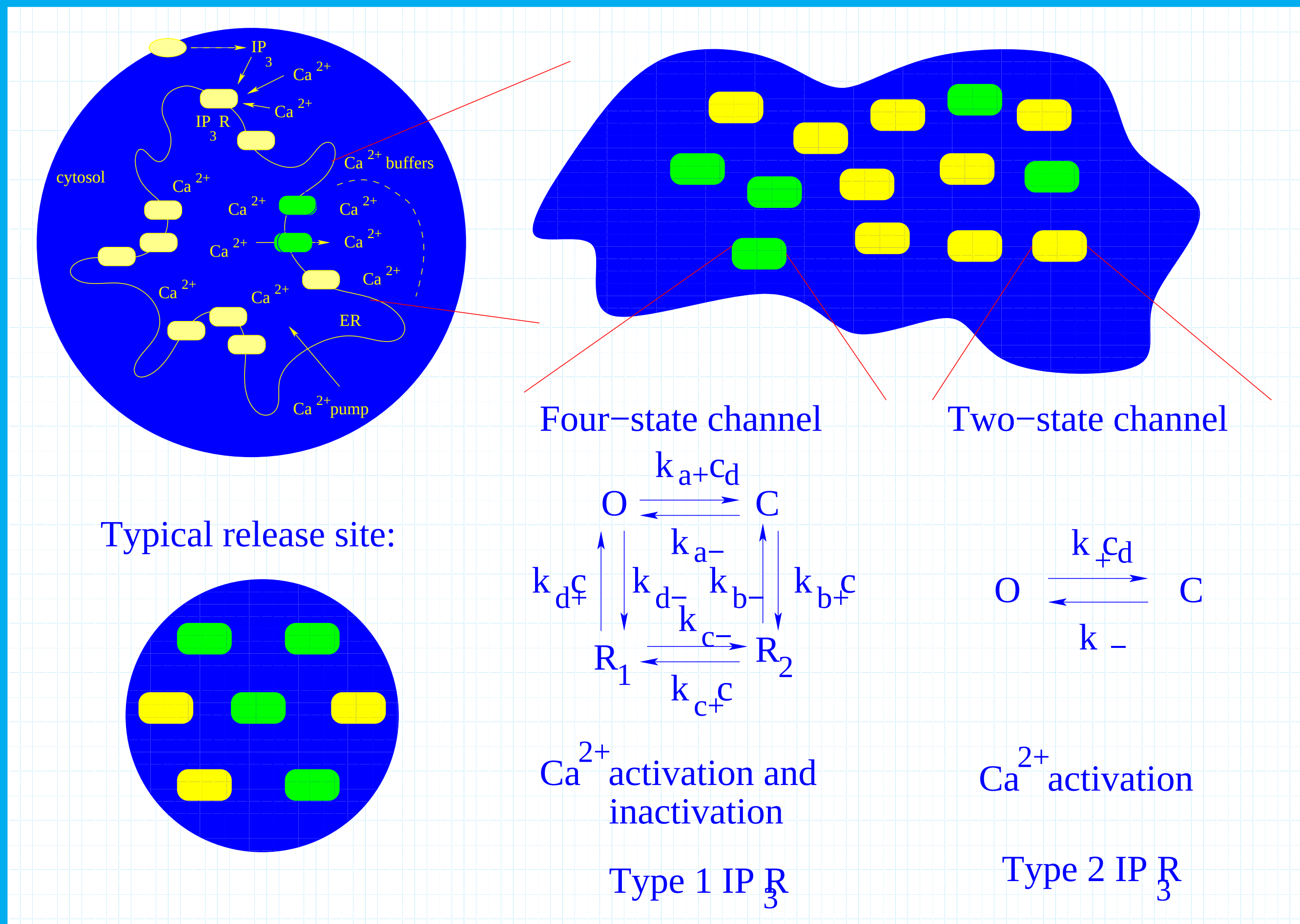

Modeling assumptions and goals

Assumptions

- Channel gating is stochastic
- Channel kinetics are much slower than domain time scale

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Goals: Examine the dynamics generated by

- heterogeneous release sites
- homogeneous release sites (natural variation among channels)

Two-state channels

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

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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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$$\begin{aligned} \bar{\pi}_C &= \Pr\{\mathrm{C}, t+\Delta t|\mathrm{C}, t\}\Pr\{\mathrm{C}, t\} + \Pr\{\mathrm{C}, t+\Delta t|\mathrm{O}, t\}\Pr\{\mathrm{O}, t\} \\ &= \pi_C(t+\Delta t) \end{aligned}$$

Modeling release sites

Transition probability matrix for two coupled Ca^{2+}-activated channels:

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$$I + \Delta t \begin{bmatrix} -k_+c^\eta - k_+c^\eta & k_+c^\eta & k_+c^\eta & 0 \\ k_- & -k_- - k_+c^\eta & 0 & k_+c^\eta \\ k_- & 0 & -k_- - k_+c^\eta & k_+c^\eta \\ 0 & k_- & k_- & -k_- - k_- \end{bmatrix}$$

How can we find the appropriate $[\mathrm{Ca}^{2+}]$?

Modeling the calcium-dependence

$$\frac{\partial[\mathrm{Ca}^{2+}]}{\partial t} = D_c \nabla^2 [\mathrm{Ca}^{2+}] - \frac{[\mathrm{Ca}^{2+}] - [\mathrm{Ca}^{2+}]_\infty}{\tau}$$

$$\text{with} \quad \mathrm{BCs}: \quad \lim_{r \to 0} \left\{ -2\pi r^2 D_c \frac{\partial c}{\partial r} \right\} = \sigma(t) \quad \lim_{r \to \infty} c = c_\infty$$

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Steady state of the equation: $c(\boldsymbol{r}) = \frac{\sigma}{2\pi D |\boldsymbol{r}_{ch} - \boldsymbol{r}|} e^{-|\boldsymbol{r}_{ch} - \boldsymbol{r}|/\lambda}$

$$\text{where} \quad \sigma = \begin{cases} 0 & \text{if} \quad \text{channel} \quad \text{is} \quad \text{closed} \\ \sigma_0 & \text{if} \quad \text{channel} \quad \text{is} \quad \text{open} \end{cases}$$

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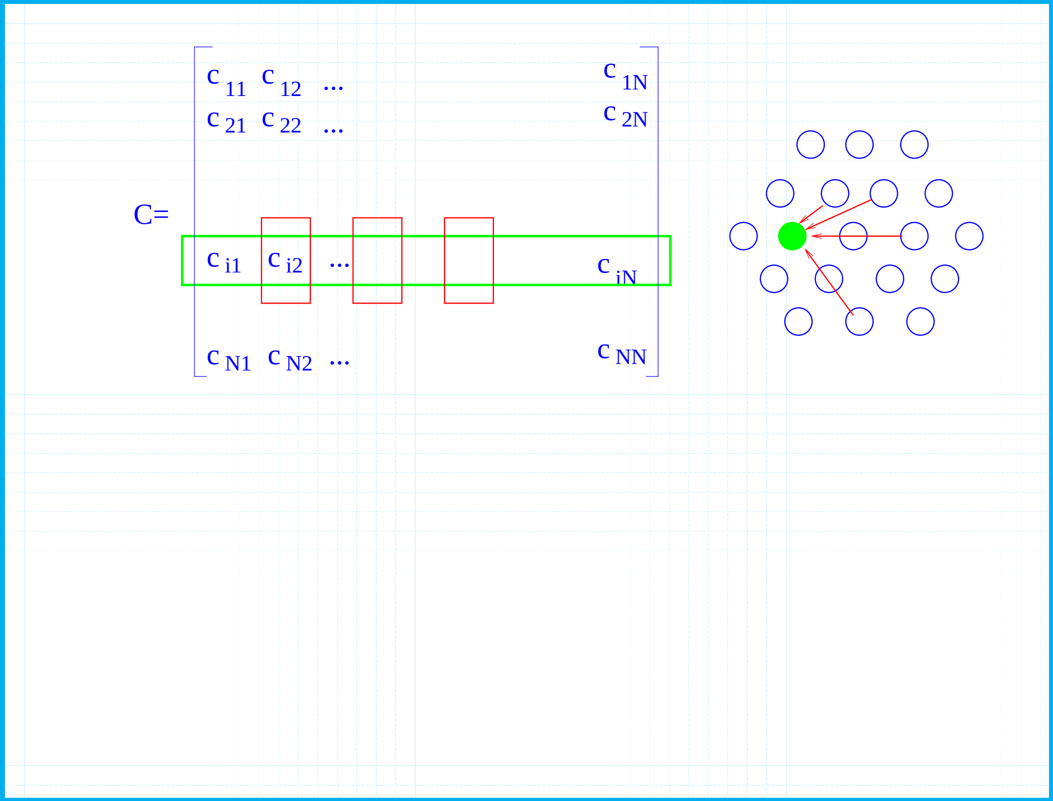

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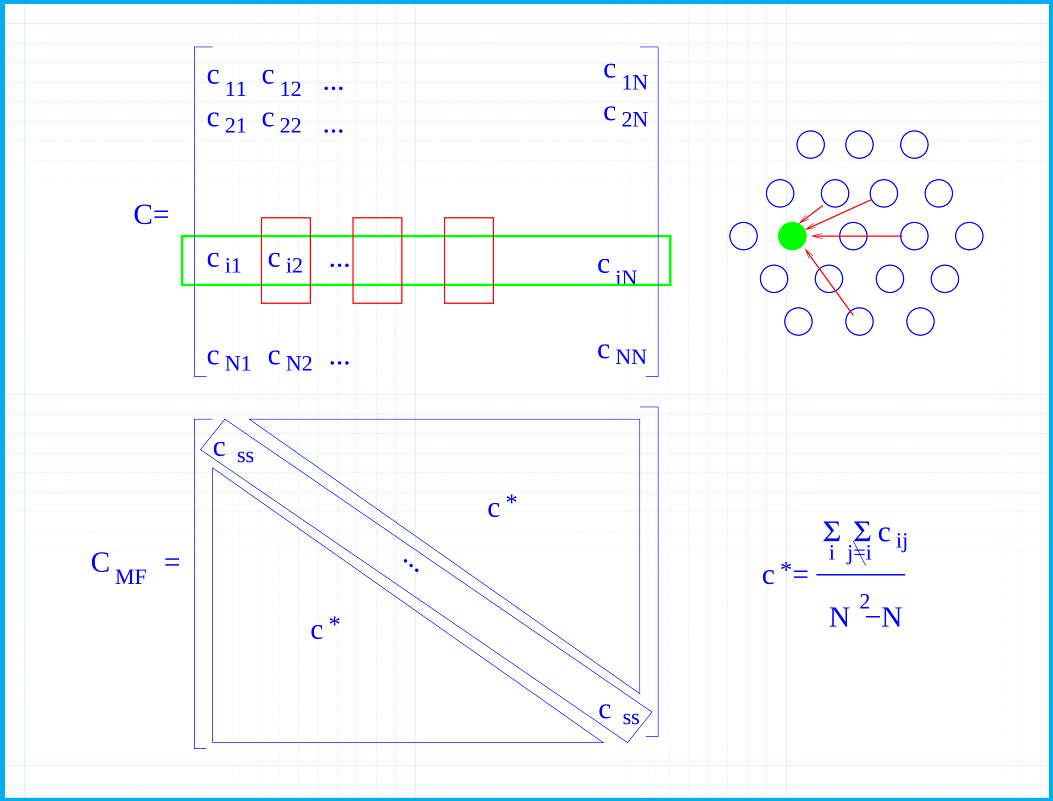
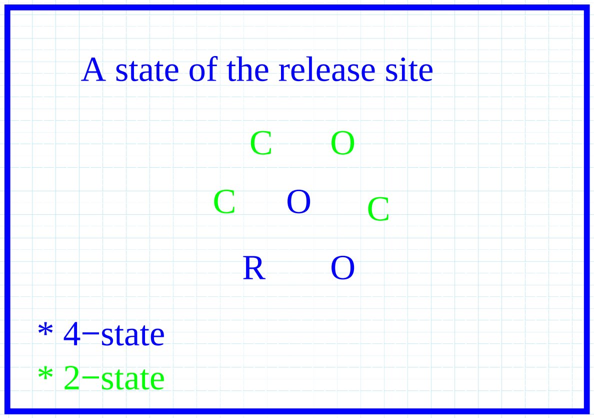


Monte Carlo simulations



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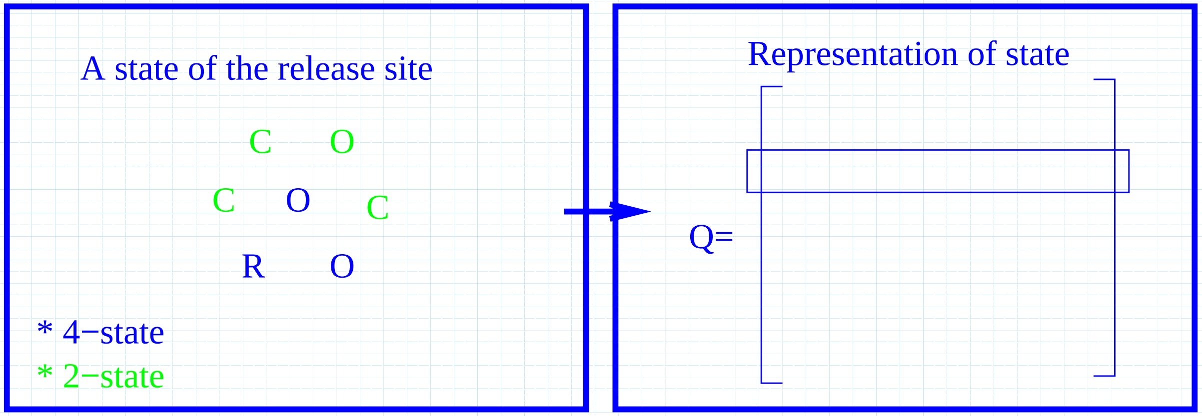

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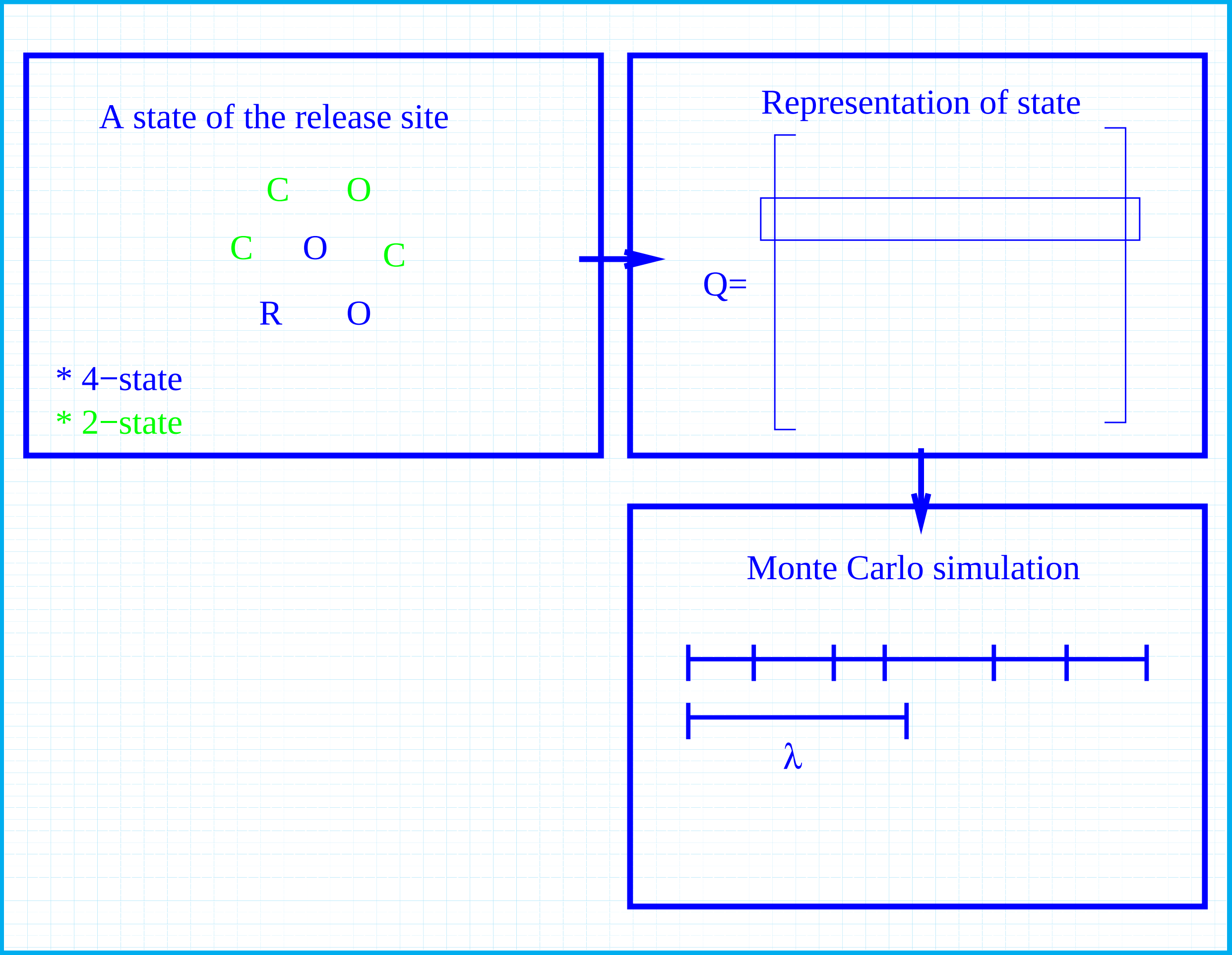

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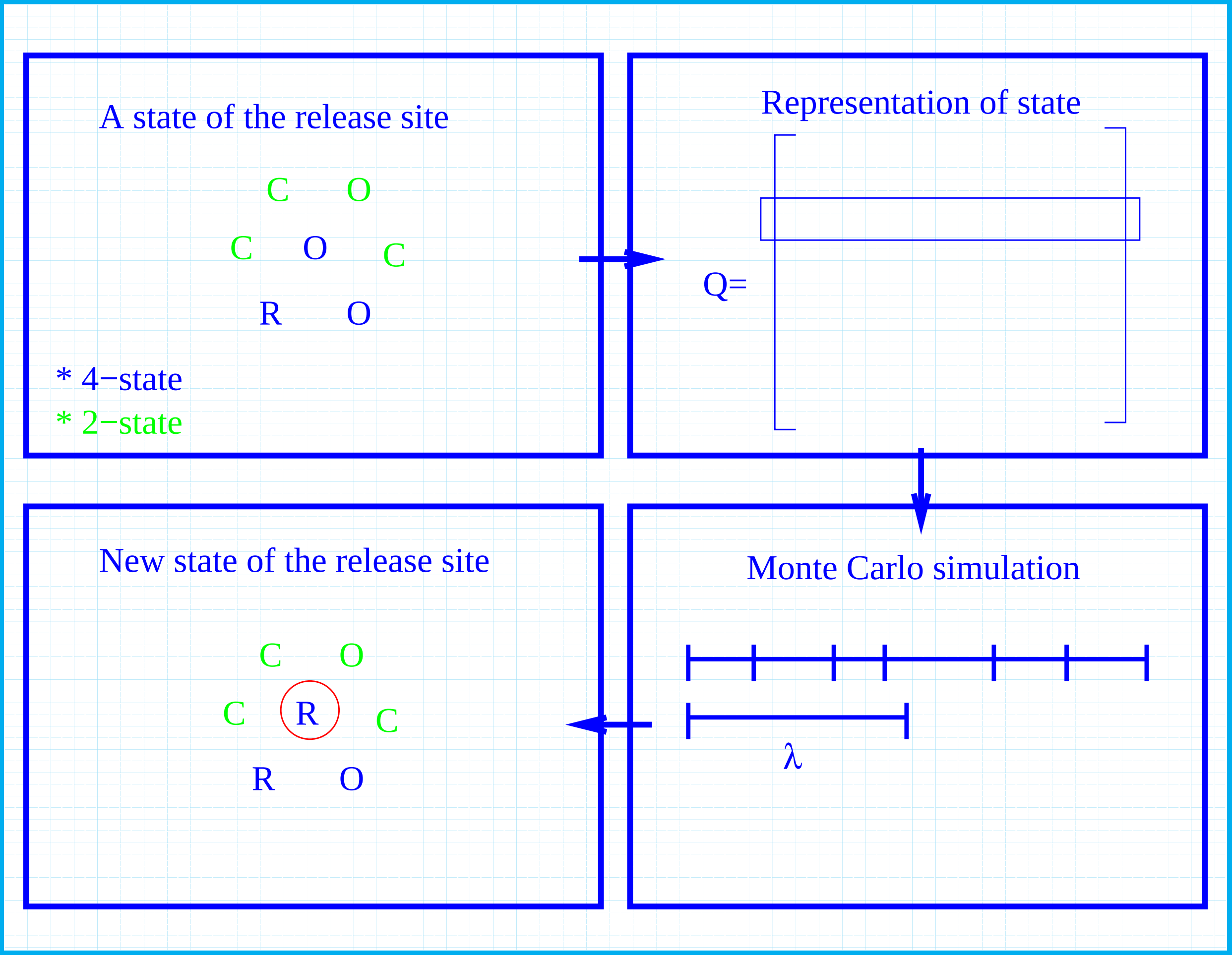
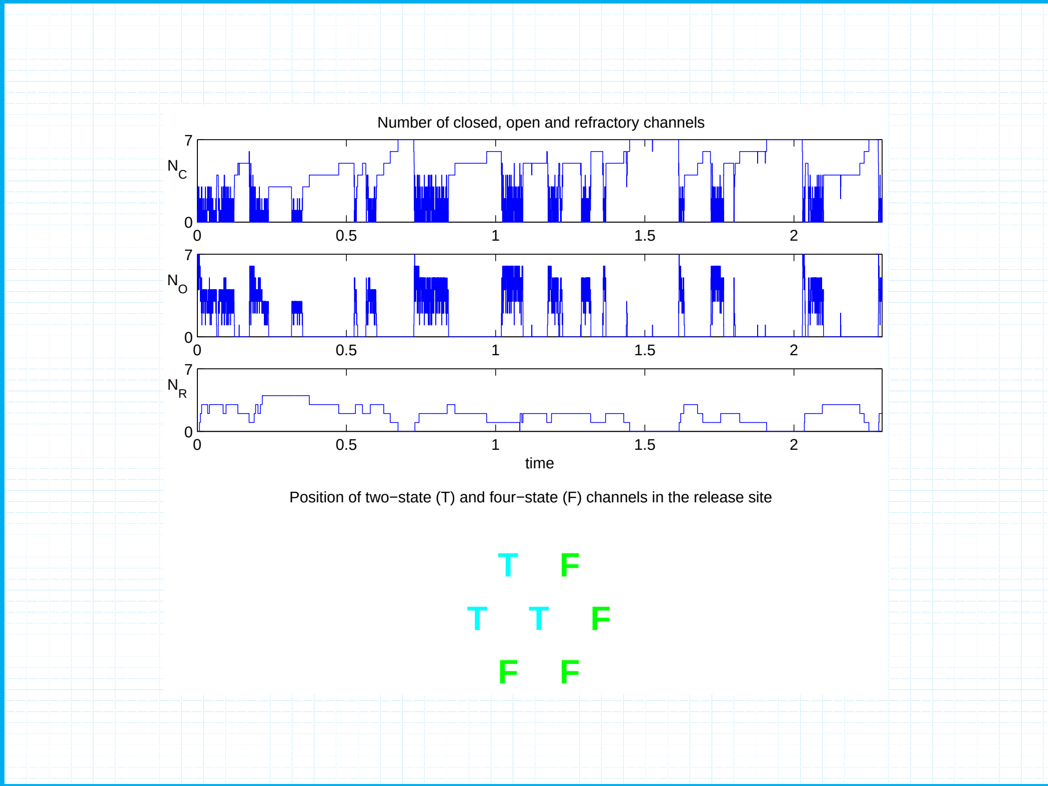


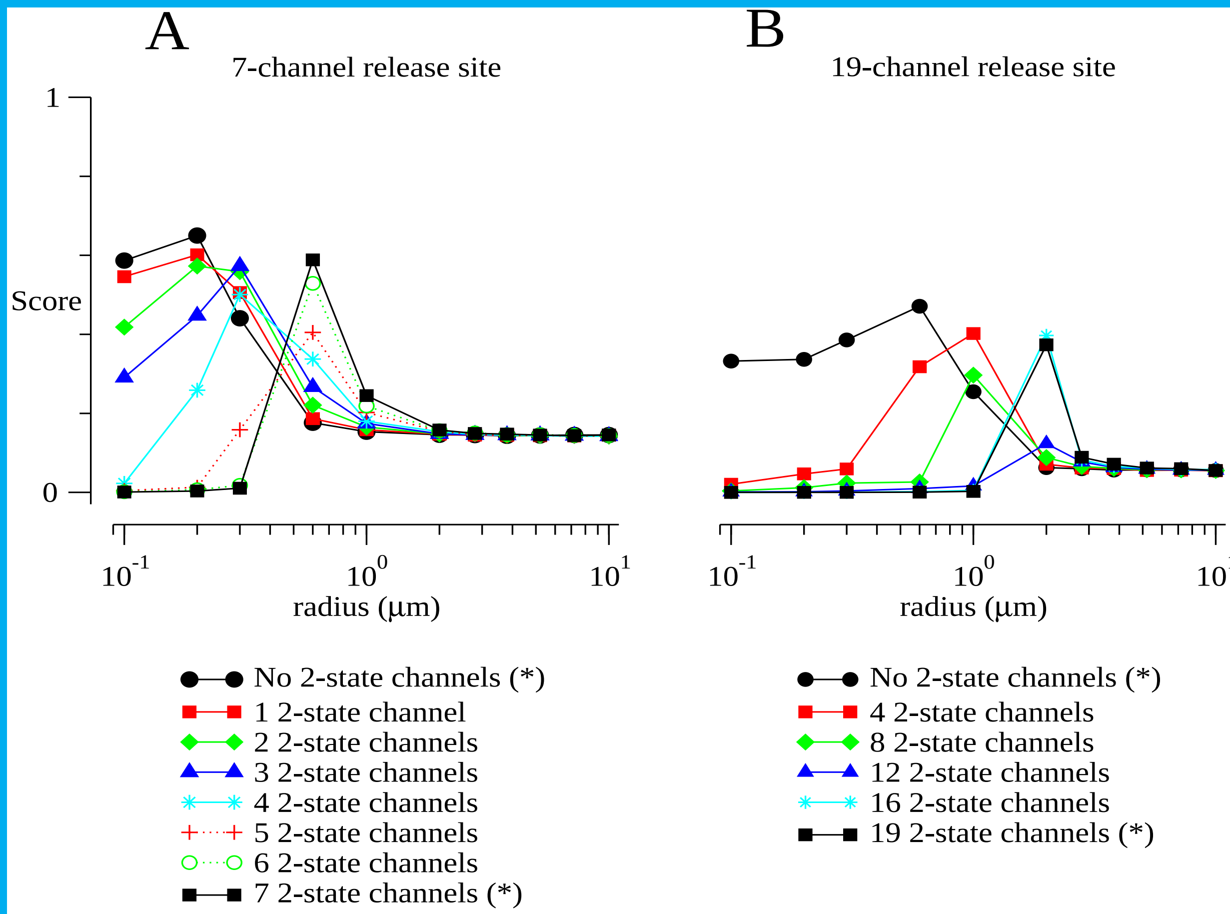
Visualisation of channel cluster Ca^{2+} dynamics



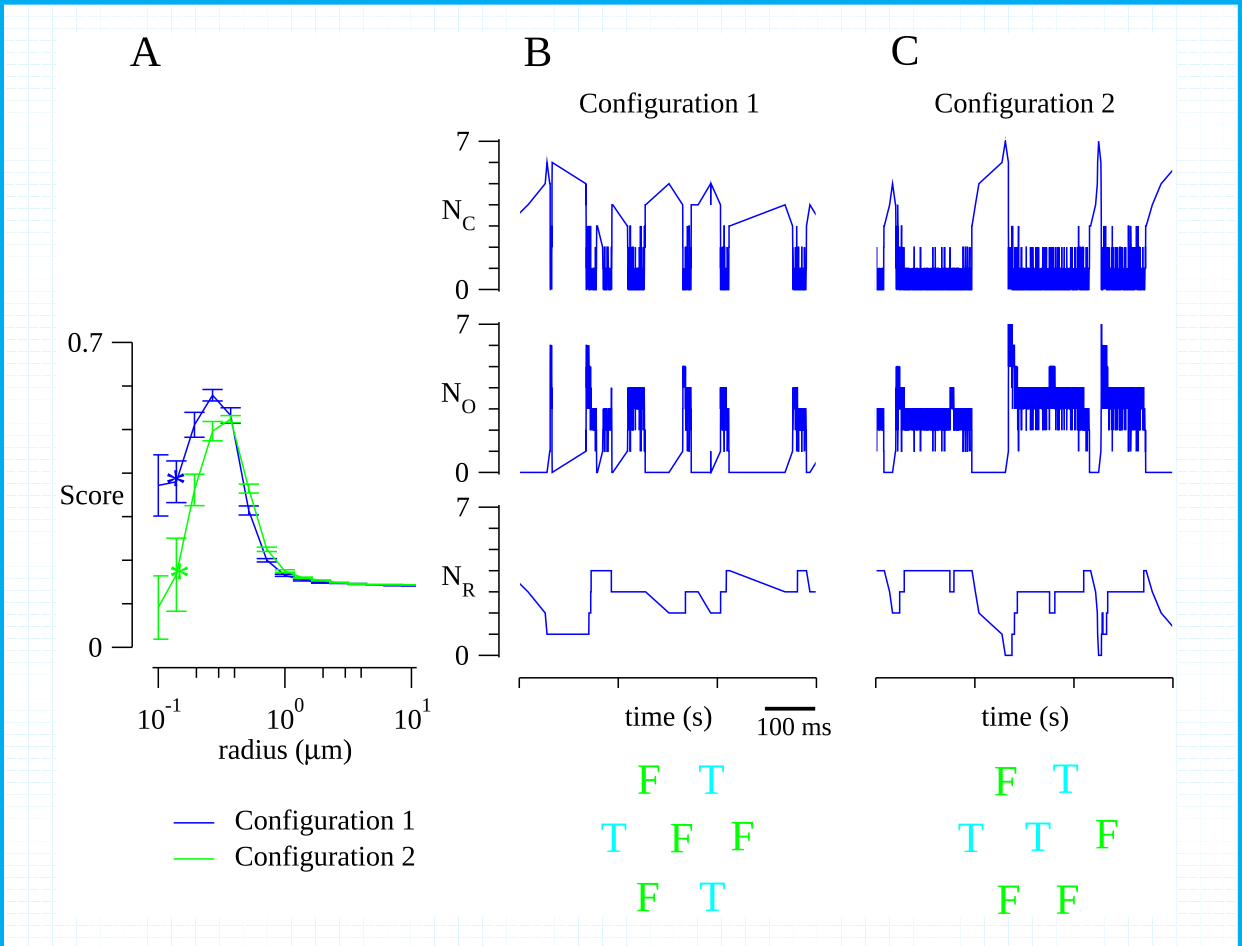
Measures: puff duration, inter-puff interval and score

$$\text{Score} = \frac{\mathrm{Var}[\mathrm{f_O}]}{\mathrm{E}[\mathrm{f_O}]} \text{ where } [f_O] : \text{fraction of open channels}$$

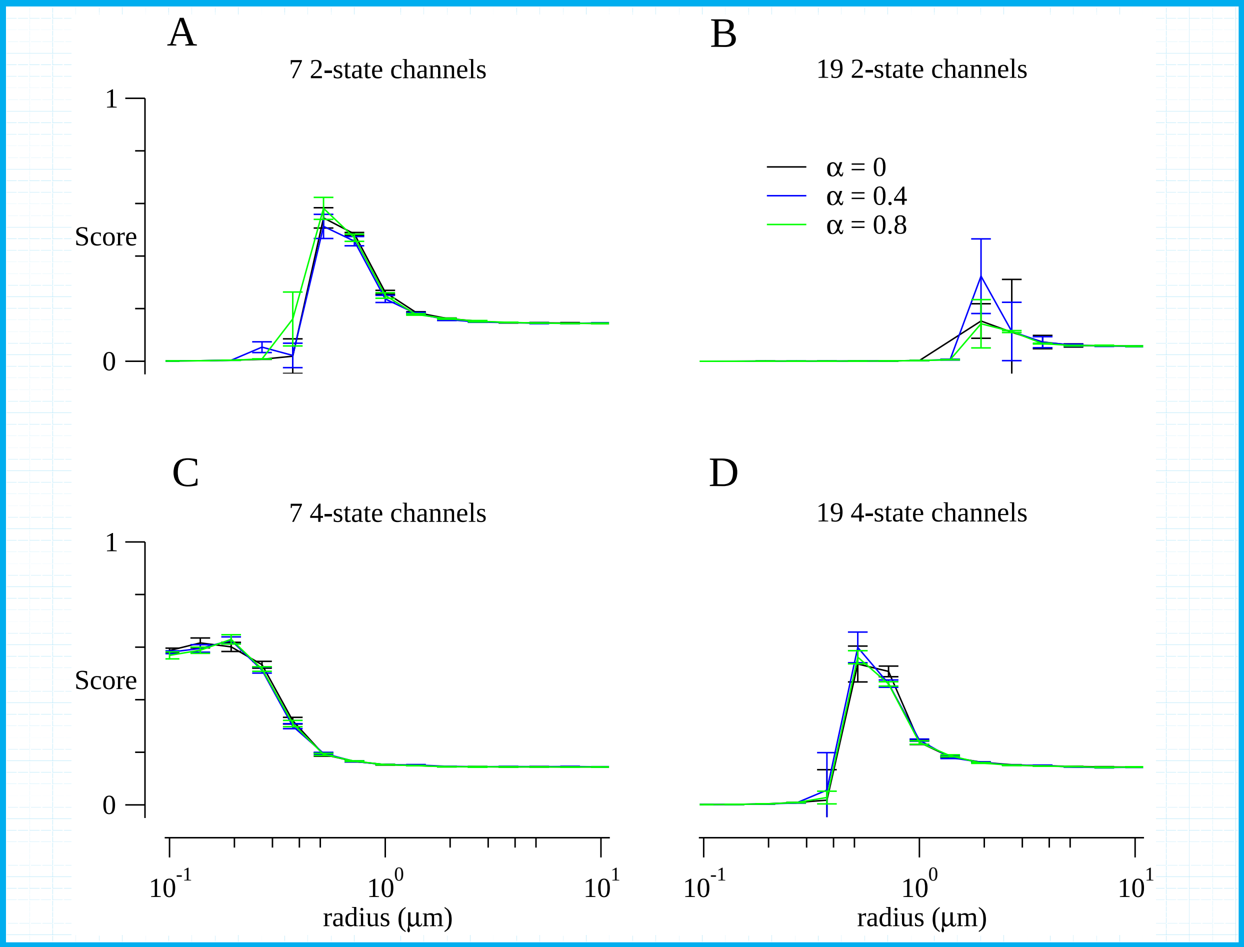
Varying the release site composition



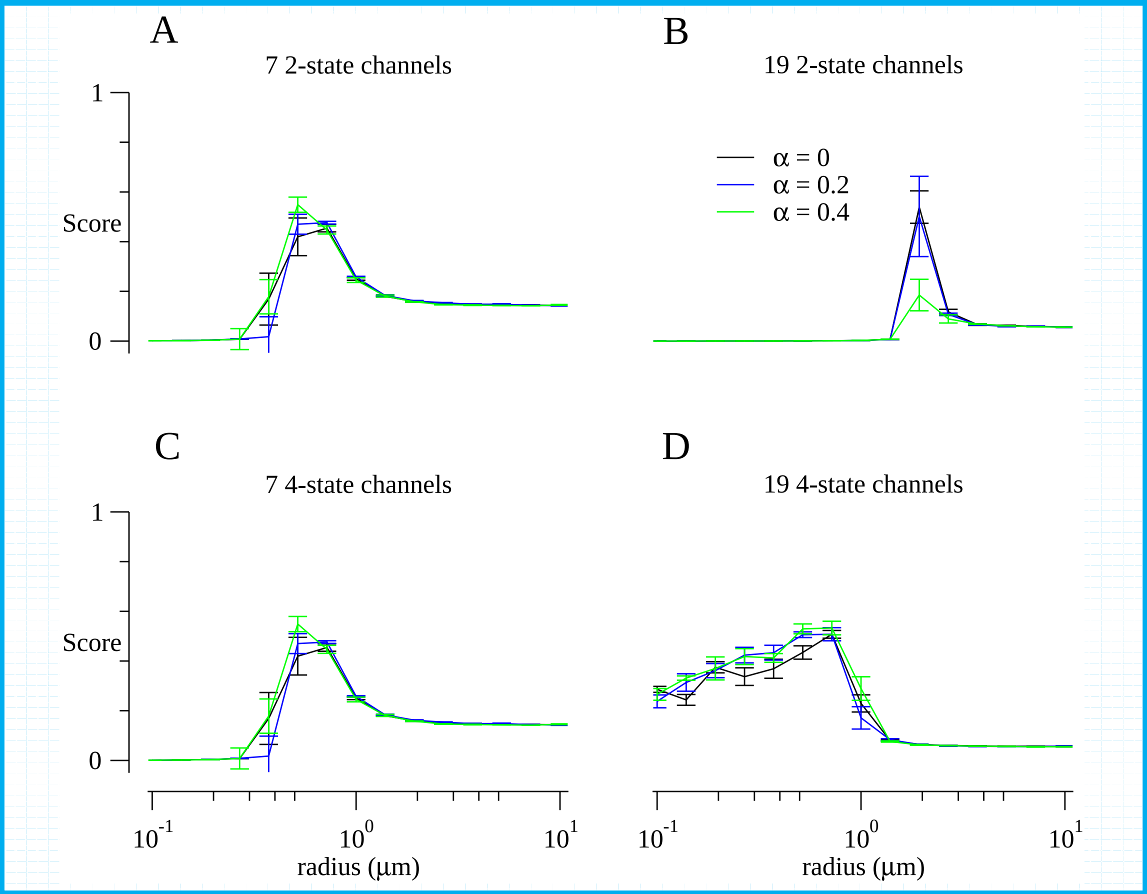
Heterogeneity and spatial positions



Variation in transition rates:



Variation in source amplitudes:



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- Spatial position of two-state and four-state channels matters
- Channel types located near center of release site have larger effect on the dynamics than channels near boundary
- Natural variation in the channel properties does not result in significant changes in calcium dynamics

Extensions of this work

- Showing other measures (puff duration and inter-puff interval)
- Specific examples:
  - ⋆ Growth of a heterogeneous release site
  - ⋆ Changing expression of IP3R in a release site

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- Specific examples:
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  - ⋆ Changing expression of IP3R in a release site
- Statistical analysis of heterogeneous and homogeneous release sites: is there an experimentally quantifiable difference?

Thank you!

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