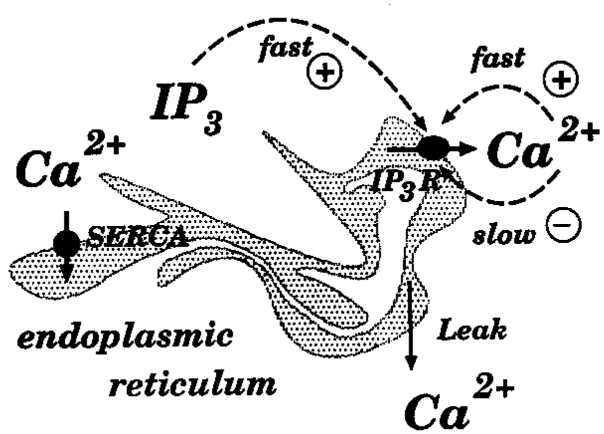
Stochastic Modeling of Local and Global Intracellular Calcium Dynamics



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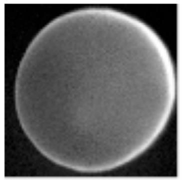
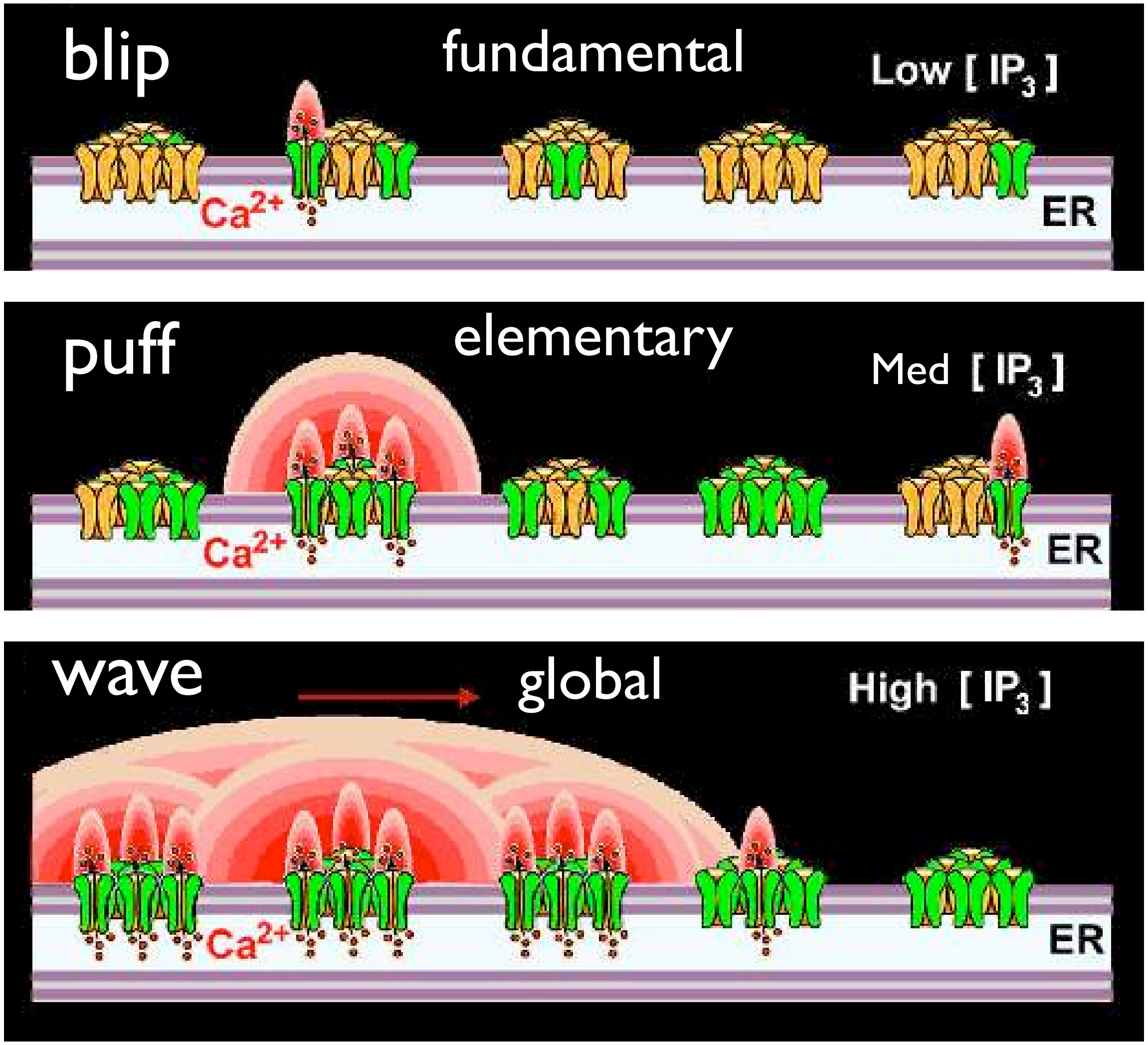
IP_3Rs are clustered in *Xenopus laevis* oocytes

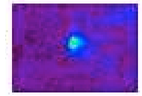


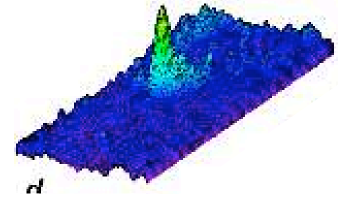
1.2 mm
(Nuccitelli)



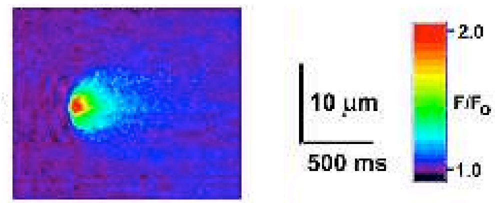
Three “modes” of Ca^{2+} release
(Parker, Bootman, Berridge)

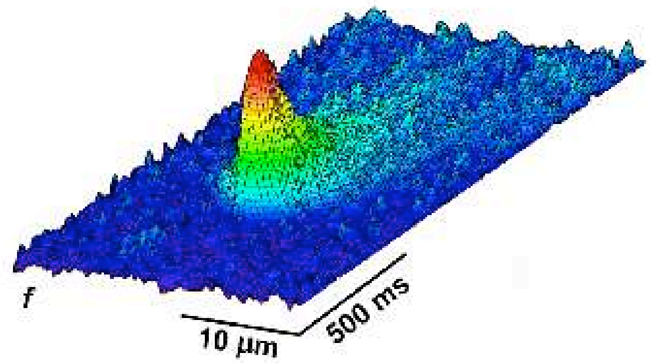
blip



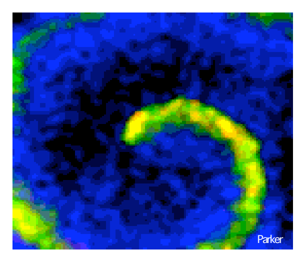


puff





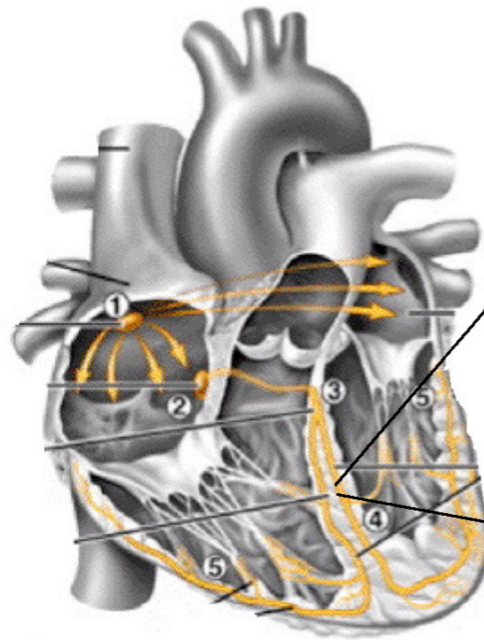
wave

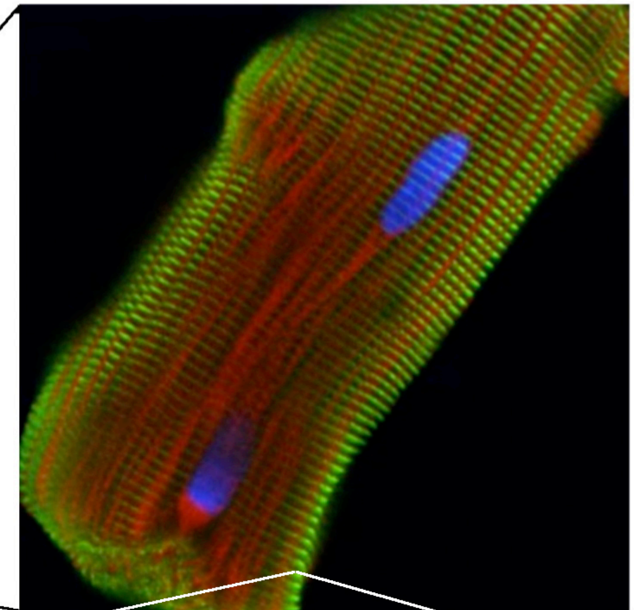


(Parker)

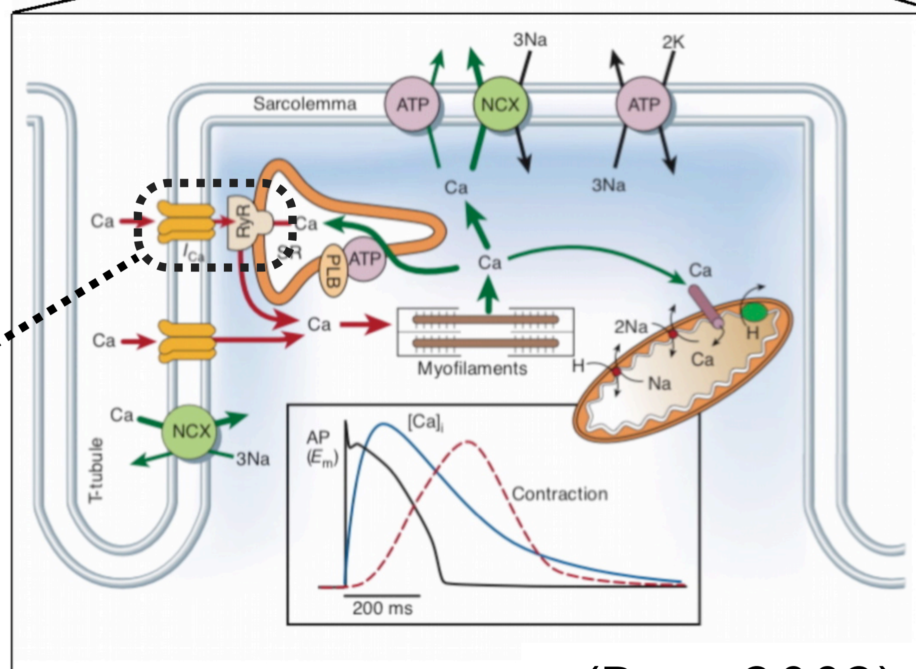
RyRs are clustered in cardiac myocytes (quarks, sparks, waves)

- Depolarization
- Ca influx (DHPRs)
- Ca release (RyRs)
- Elevated Ca in myoplasm
- Contraction of sarcomere





“Common pool” models of excitation-contraction coupling do not properly account for local Ca signaling in the diadic space and junctional SR



(Bers 2002)

?

single channel gating ⇔ calcium puffs/sparks

~~allosteric coupling~~

arrangement of channels

buffered calcium diffusion

buffered Ca diffusion

near point source
for free Ca

$$\mathrm{Ca}^{2+} + \mathrm{B} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{CaB}$$

$$\frac{\partial[\mathrm{Ca}^{2+}]}{\partial t} = D_{Ca}\nabla^2[\mathrm{Ca}^{2+}] - k_f[\mathrm{Ca}^{2+}][\mathrm{B}] + k_r[\mathrm{CaB}] + \sigma(t)\delta(r)$$

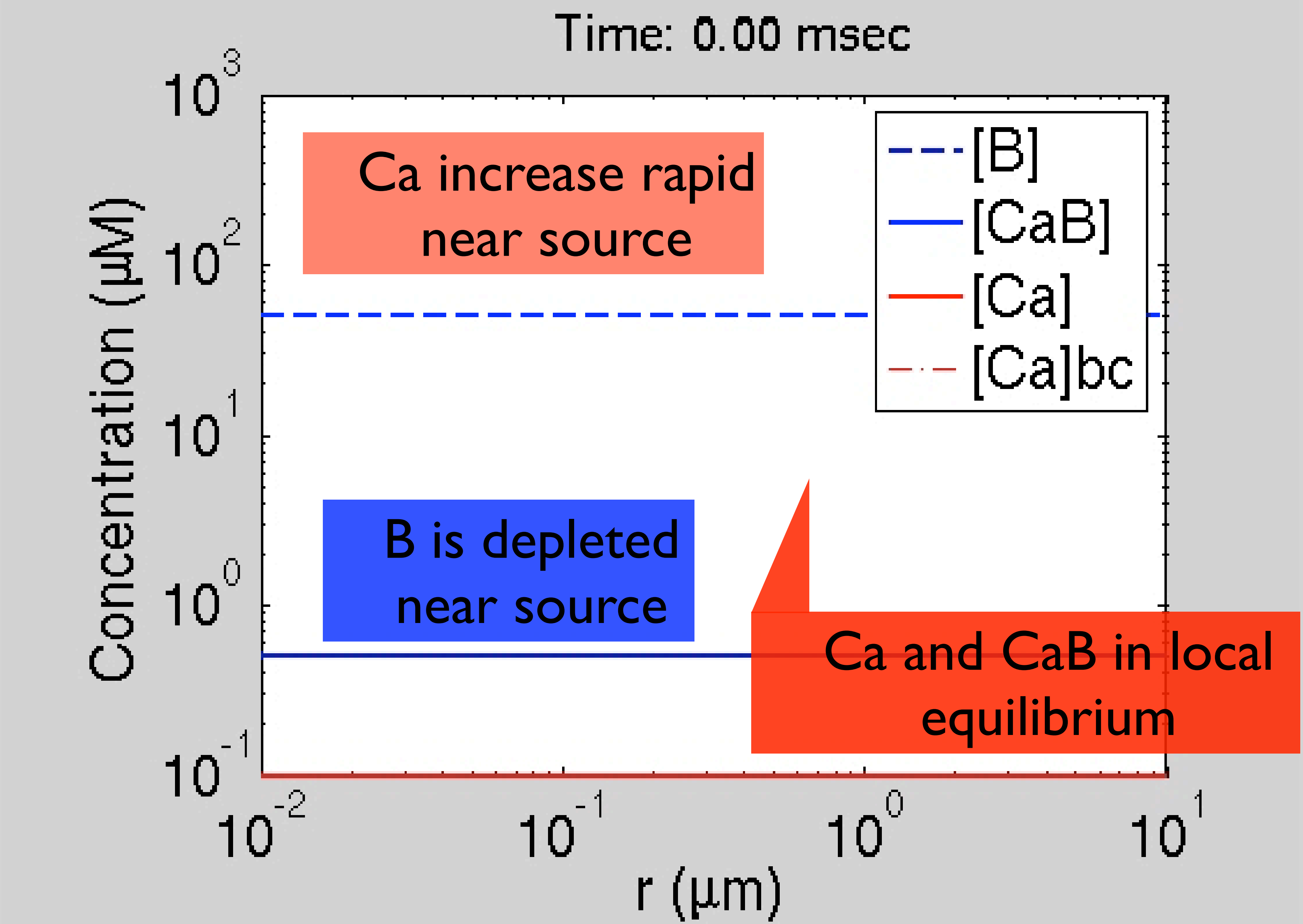
$$\frac{\partial[\mathrm{B}]}{\partial t} = D_B\nabla^2[\mathrm{B}] - k_f[\mathrm{Ca}^{2+}][\mathrm{B}] + k_r[\mathrm{CaB}]$$

$$\frac{\partial[\mathrm{CaB}]}{\partial t} = D_{CaB}\nabla^2[\mathrm{CaB}] + k_f[\mathrm{Ca}^{2+}][\mathrm{B}] - k_r[\mathrm{CaB}]$$

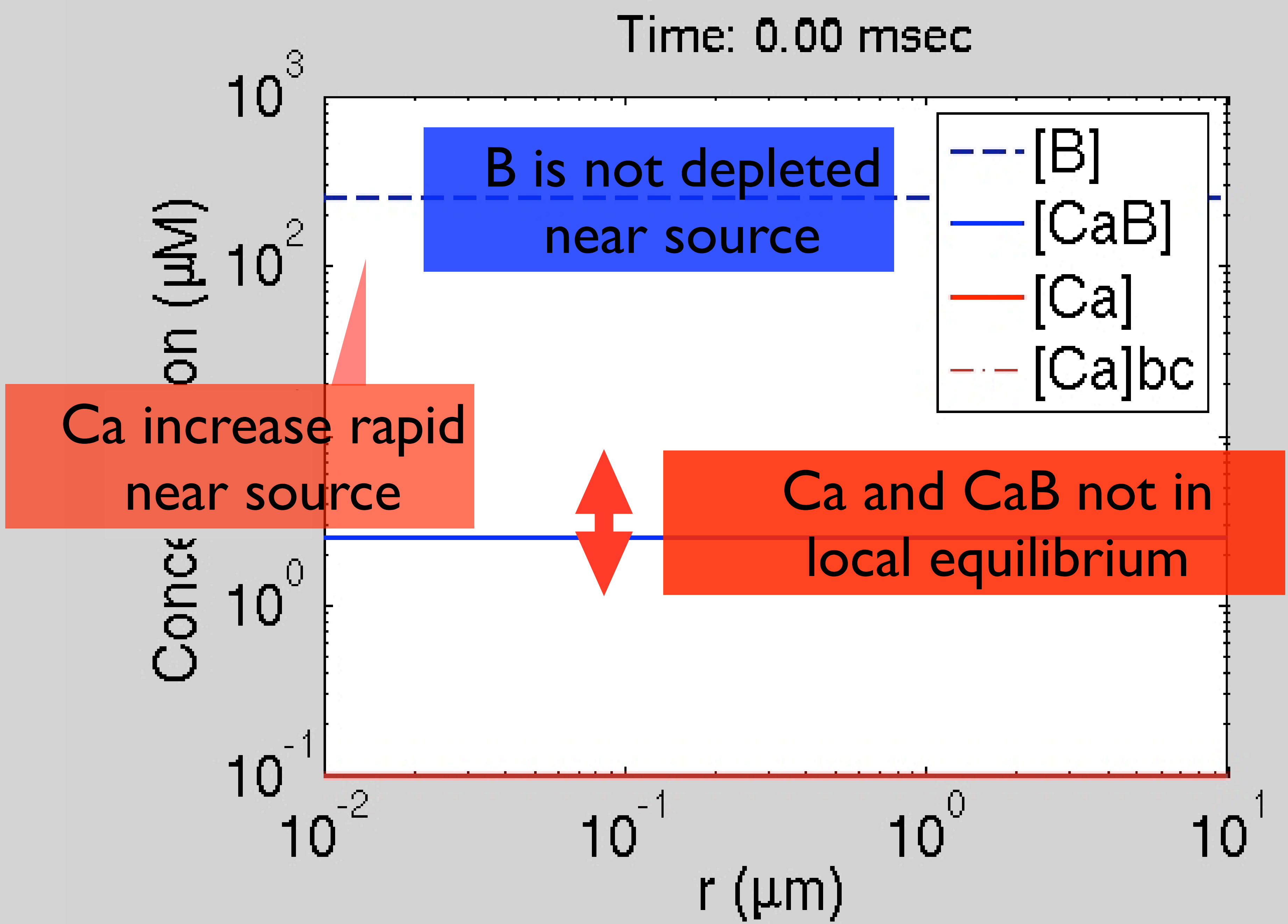
$r = 0$: flux for Ca turns "on" at $t = 0$ (no flux for buffer)

$r \rightarrow \infty$: buffers in equilibrium with background Ca

5 pA source — cluster of channels — fast buffer kinetics



0.5 pA source — single channel — slow buffer kinetics

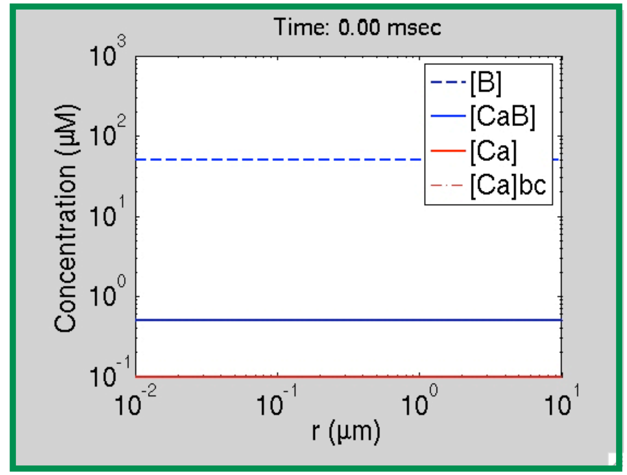


- Steady-state rapid buffer limit (large source)

$$t \rightarrow \infty$$

$$D_{Ca}[\mathrm{Ca}^{2+}] + D_{CaB}\frac{[\mathrm{Ca}^{2+}][\mathrm{B}]_\mathrm{T}}{[\mathrm{Ca}^{2+}] + K} = \frac{\sigma}{2\pi r} + const$$

$$K = k_r/k_f \qquad [\mathrm{B}]_\mathrm{T} = [\mathrm{B}] + [\mathrm{CaB}]$$



Buffer is nearly saturated near source

Local equilibrium between Ca^{2+} and buffer everywhere

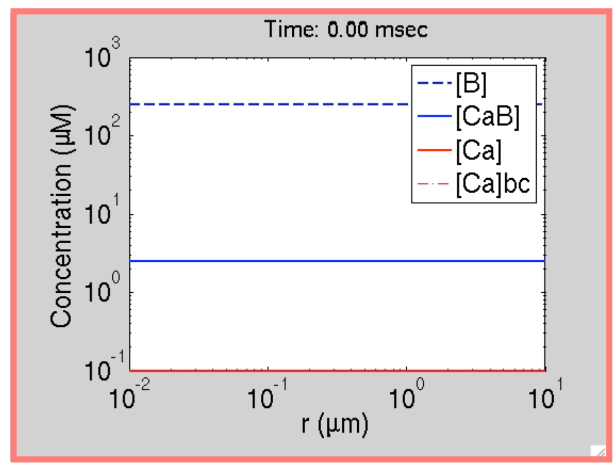
(Wagner & Keizer 1994)
(Smith 1996)

- Steady-state excess buffer limit (small source)

$$t \rightarrow \infty$$

$$[\mathrm{Ca}^{2+}] = \frac{\sigma}{2\pi D_{Ca} r} e^{-r/\lambda} + [\mathrm{Ca}^{2+}]_\infty$$

$$\lambda = \sqrt{D_{Ca}/k_f[\mathrm{B}]_\infty} \qquad [\mathrm{B}]_\infty = \frac{K[\mathrm{B}]_\mathrm{T}}{[\mathrm{Ca}^{2+}]_\infty + K}$$

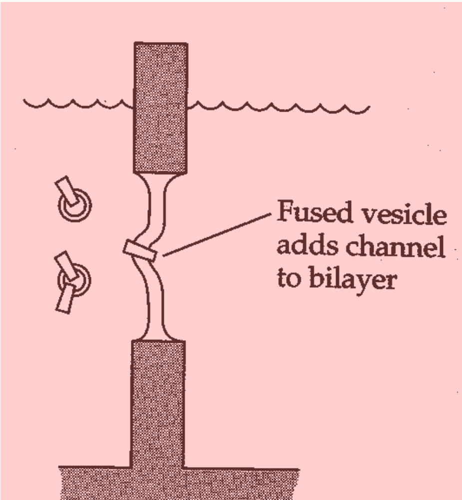


Buffer profile is only slightly perturbed near source

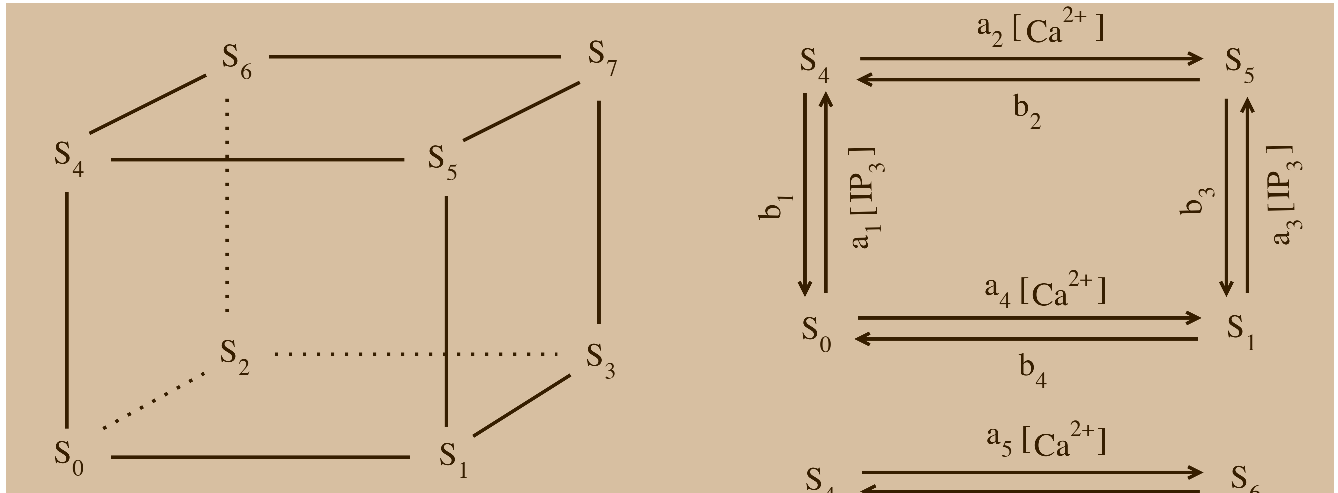
No local equilibrium between Ca^{2+} and buffer near source

(Neher 1986)

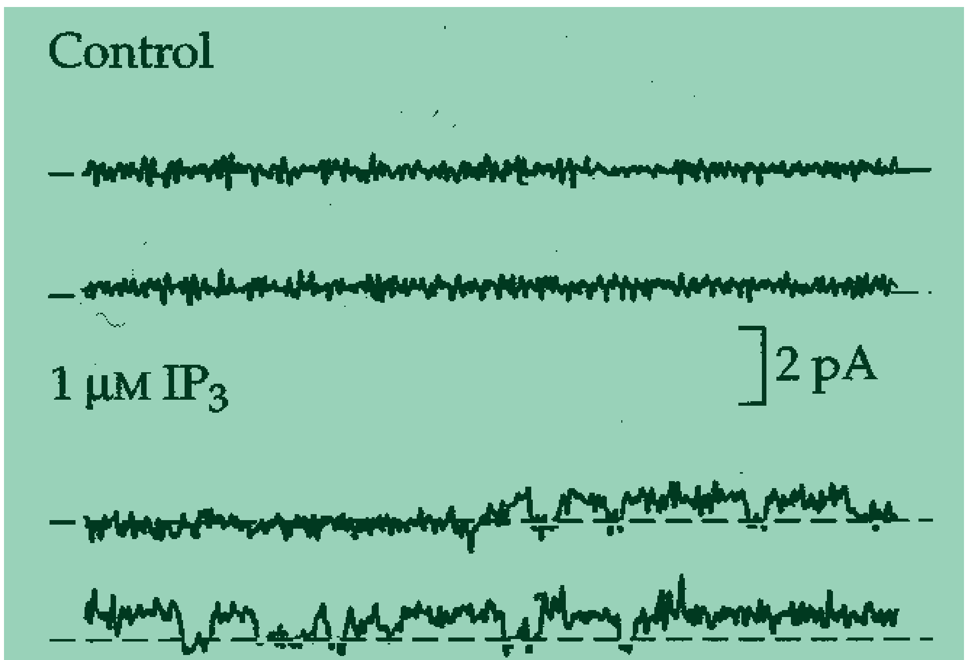
IP3R and RyR gating modeled as a Markov chain



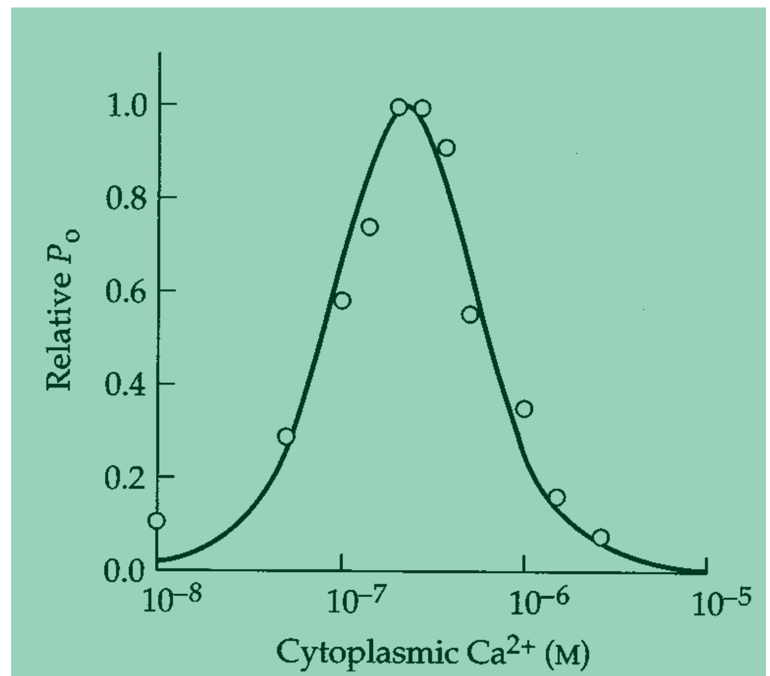
(Hille)



(DeYoung & Keizer 1992)



(Ehrlich & Watras 1988)



(Bezprozvanny et al. 1991)

intracellular channels are modeled as Markov chains

$$X(t) \in \{1, 2, \cdots, M-1, M\}$$

each state is "open" or "closed"

cooperativity of Ca^{2+} binding

$$Q(t) = K_- + c(t)^\eta K_+$$

infinitesimal generator

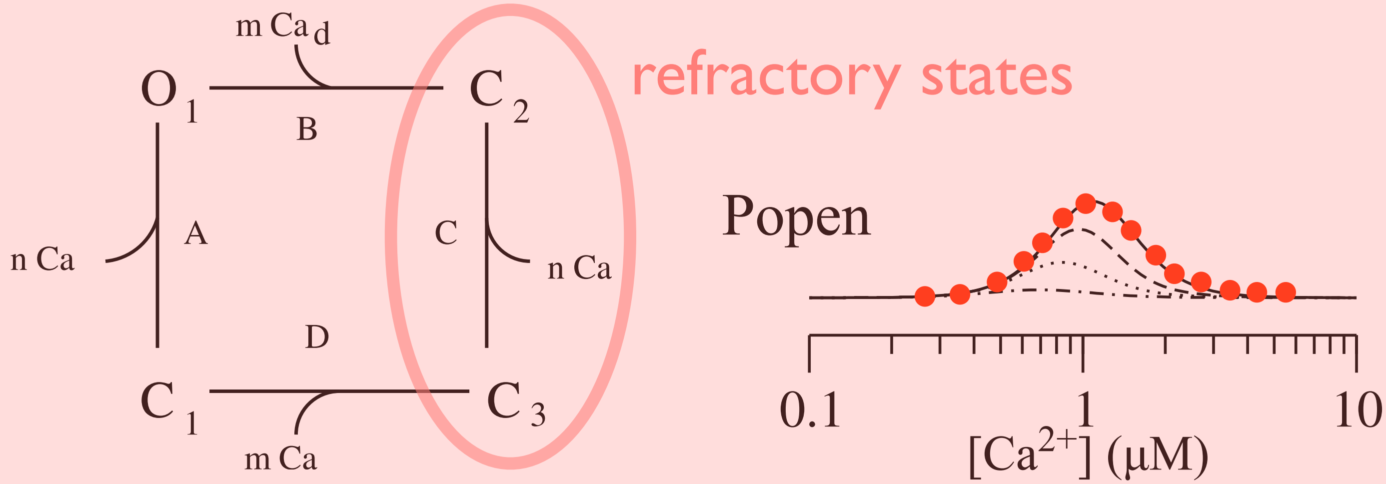
dissociation rate constants

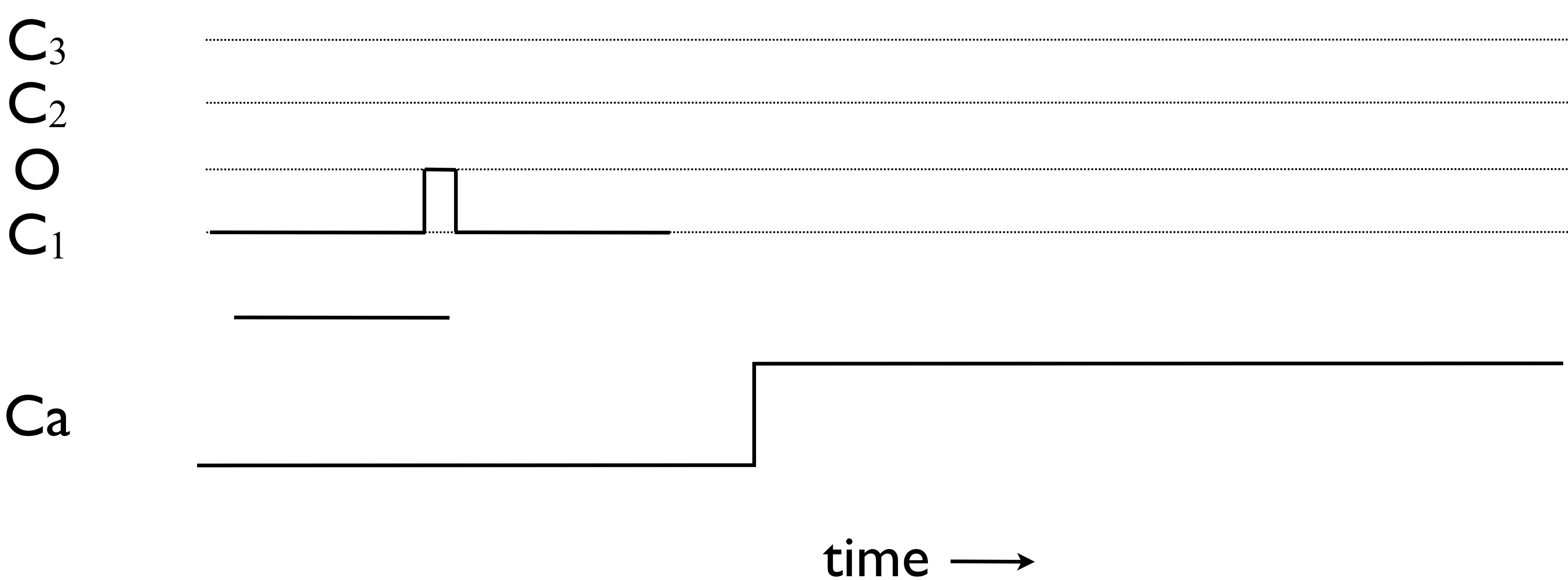
local [Ca]

association rate constants

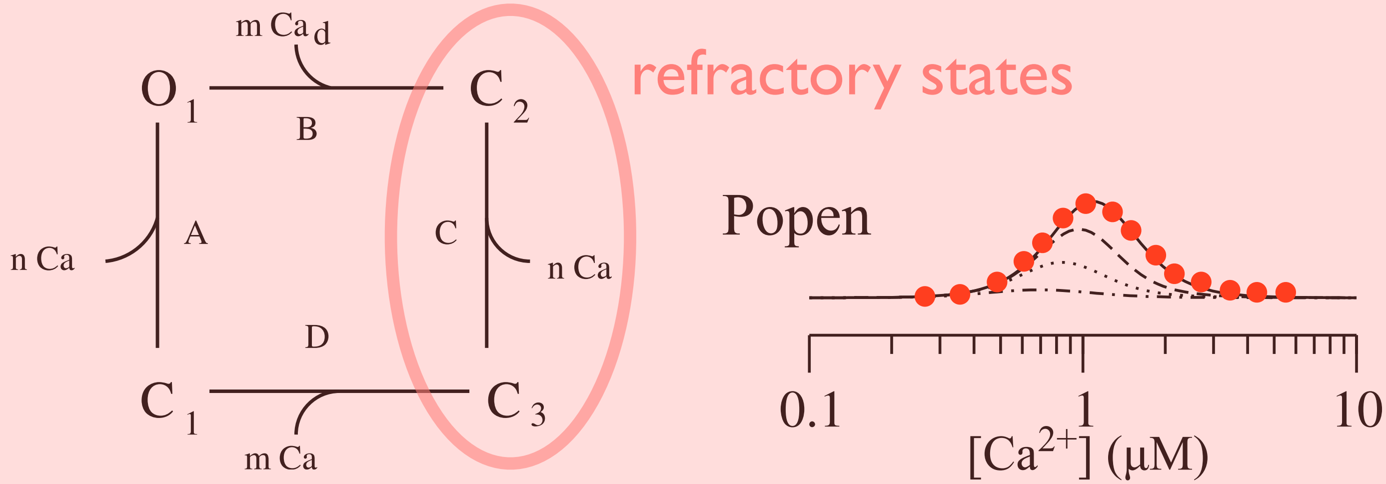
improve
next slide

four-state model with fast Ca activation and slow Ca inactivation

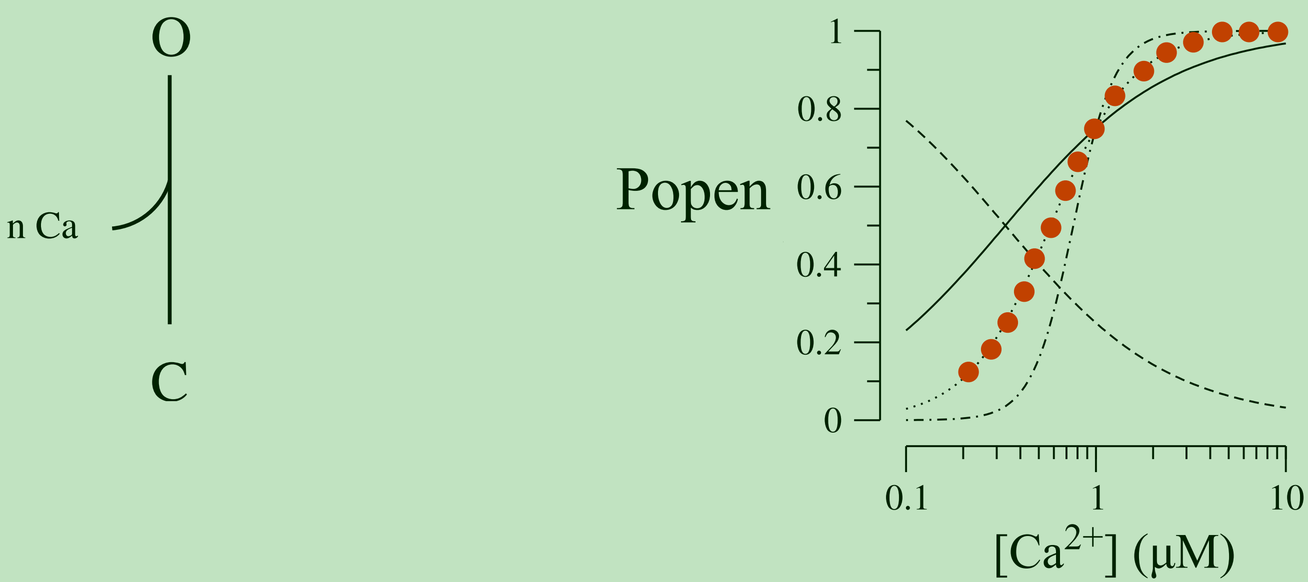




four-state model with fast Ca activation and slow Ca inactivation



two-state model with Ca activation but no inactivation



channels are coupled assuming excess buffer limit

$$C = (c_{ij})$$

N×N coupling matrix

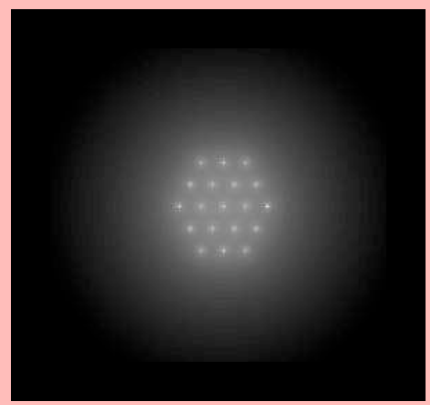
$$c_{ij} = \frac{\sigma_O}{2\pi D r_{ij}} e^{-r_{ij}/\lambda}$$

superpose interactions

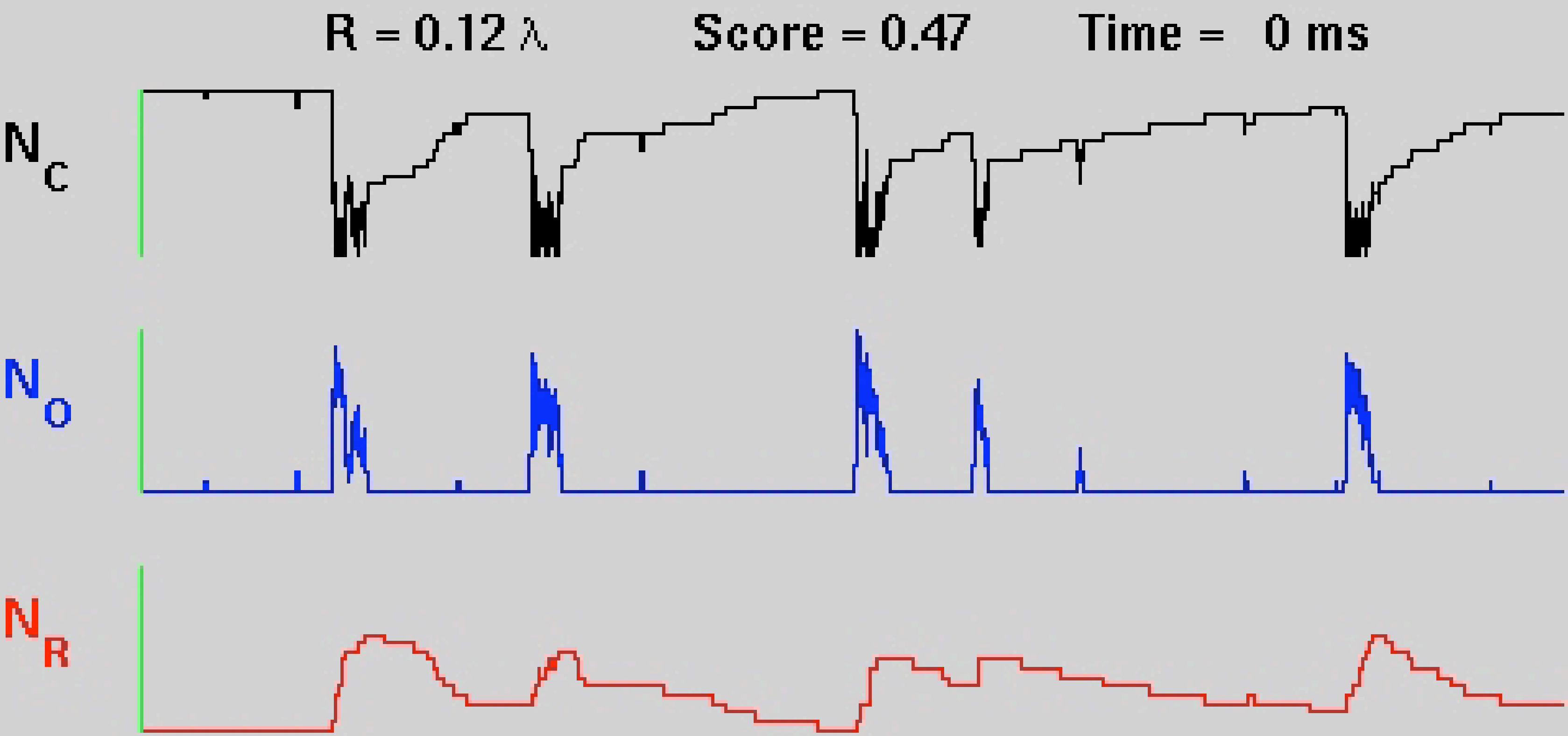
instantaneous coupling

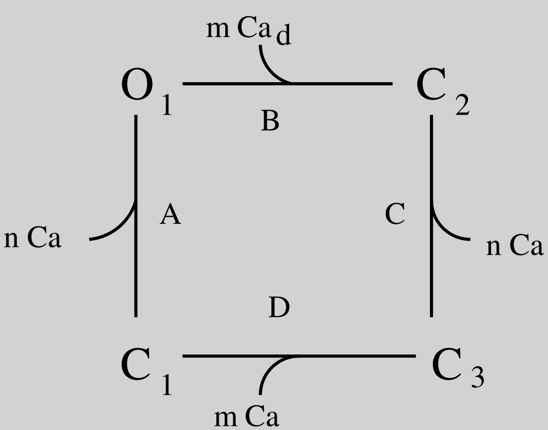
$$\tau_{chan} << \tau_{diff}$$

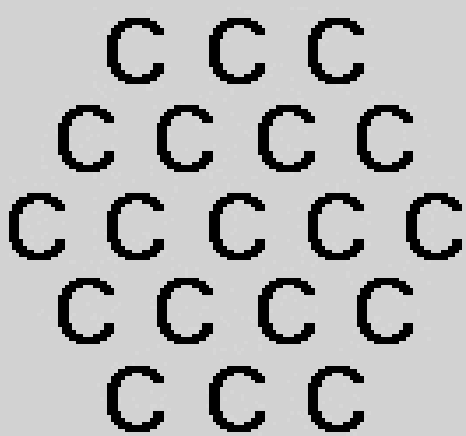
arrangement of channels

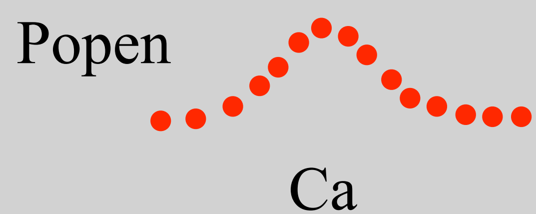


Four-state model with Ca^{2+} activation and Ca^{2+} inactivation

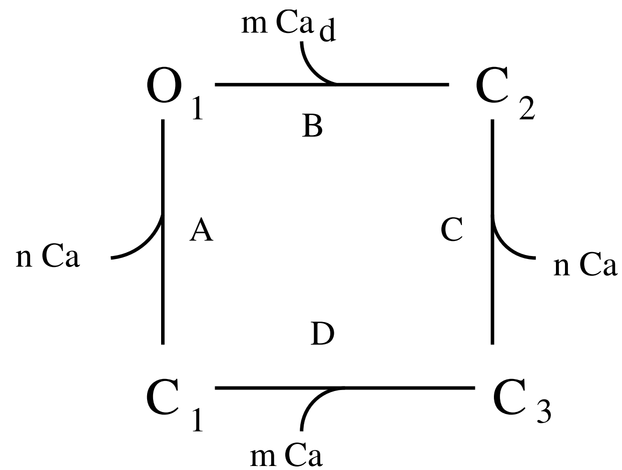


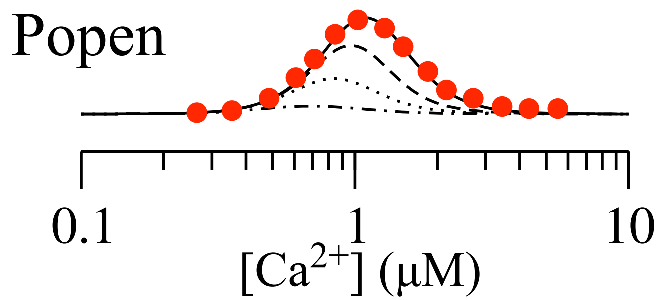


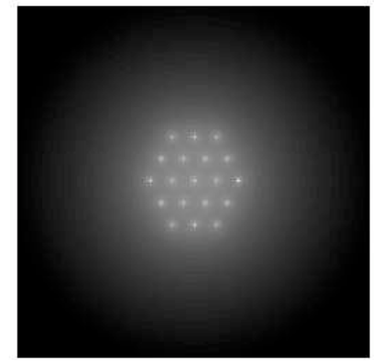


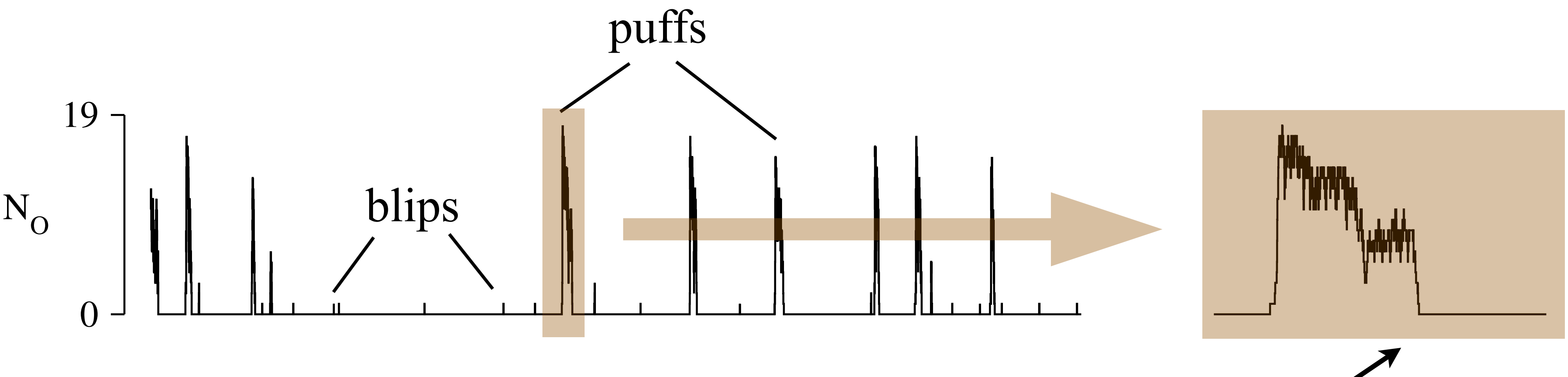


Four-state model with Ca^{2+} activation and Ca^{2+} inactivation



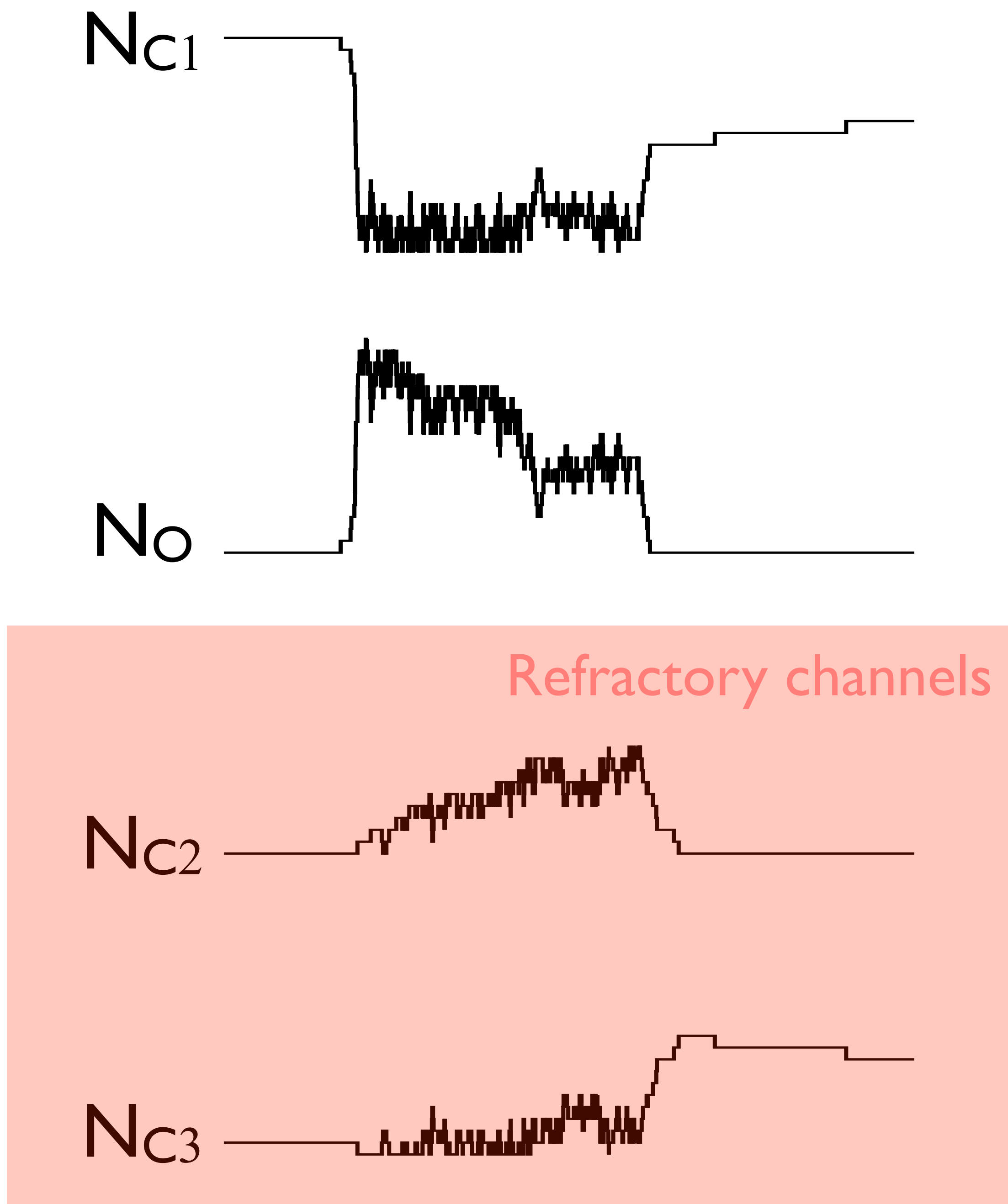




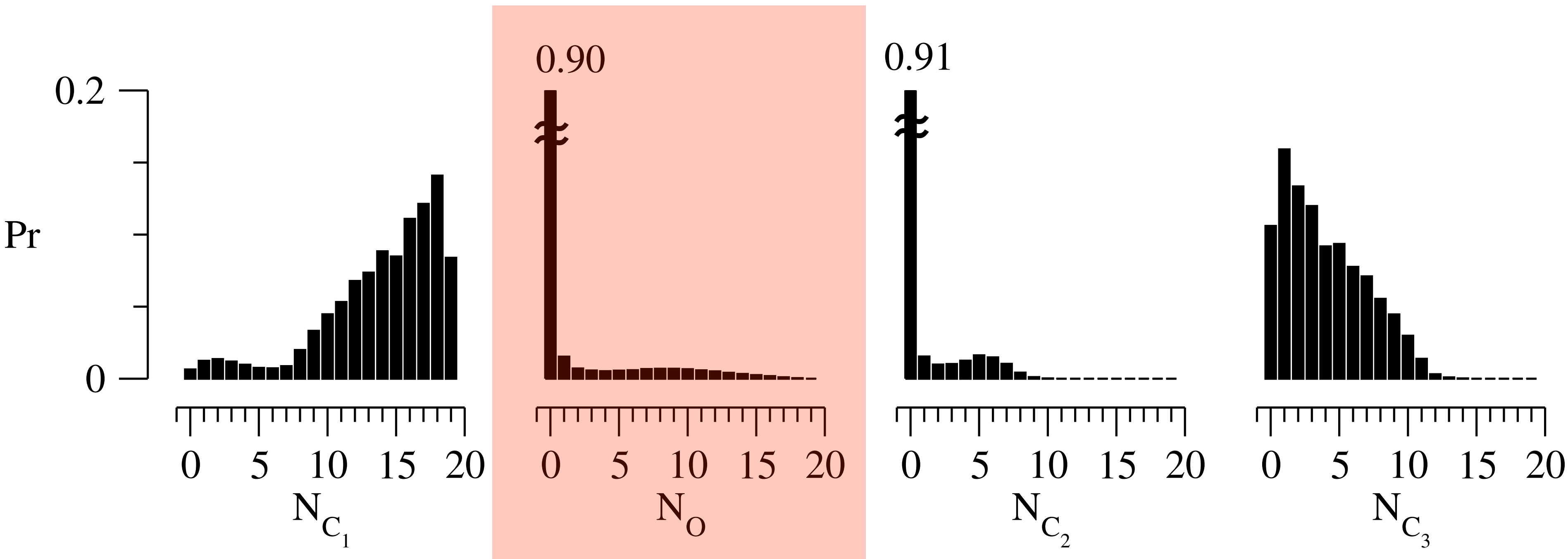


What leads to the termination of these Ca^{2+} puffs?

accumulation of Ca inactivation leads to termination of these puffs



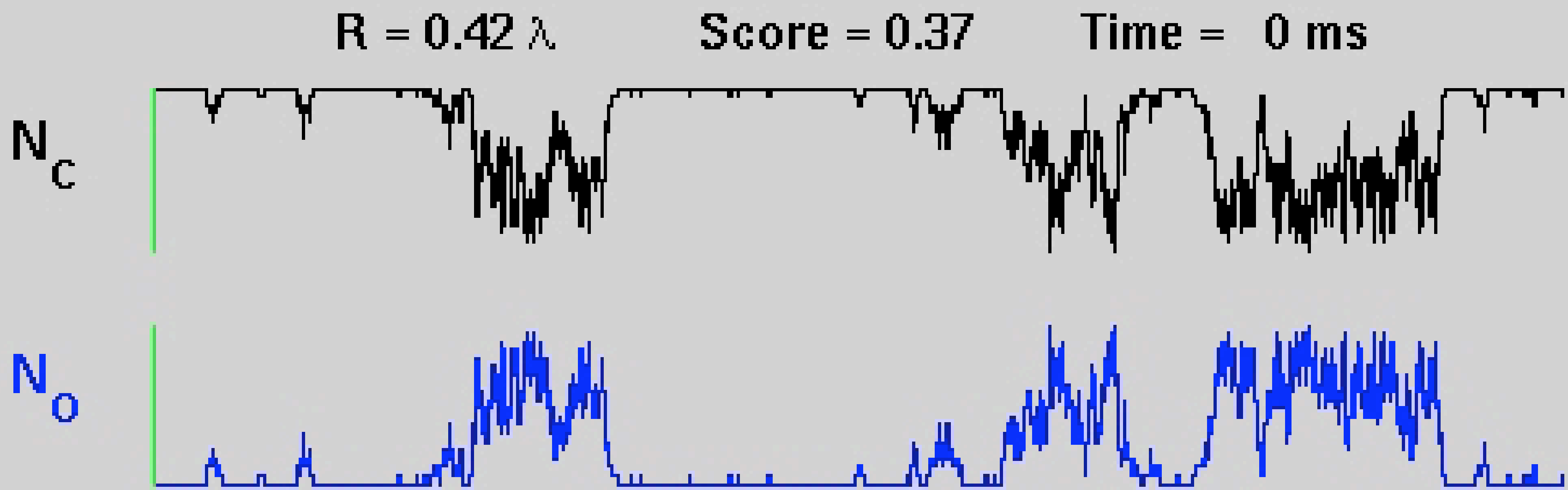
Limiting probability distributions

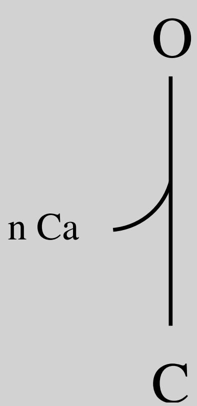


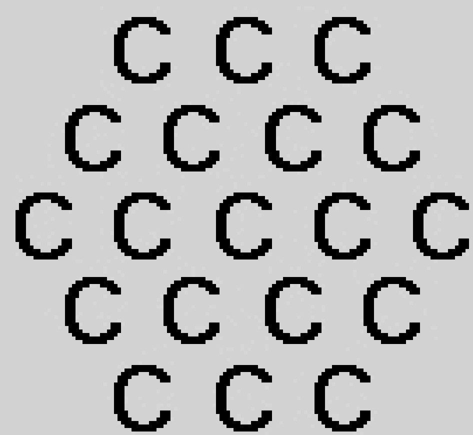
$$f_O = \frac{N_O}{N} \qquad Score = \frac{\mathrm{Var}[f_O]}{\mathrm{E}[f_O]} \approx 0.5$$

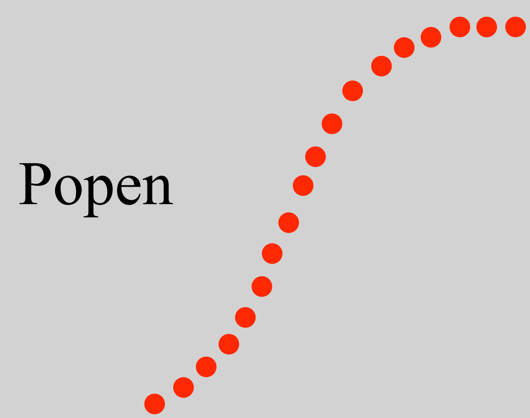
Not all parameters lead to puffs ($Score > 0.3$)
but parameters leading to puffs are easy to find

Two-state model with Ca^{2+} activation but no Ca^{2+} inactivation

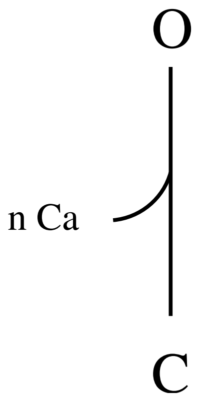


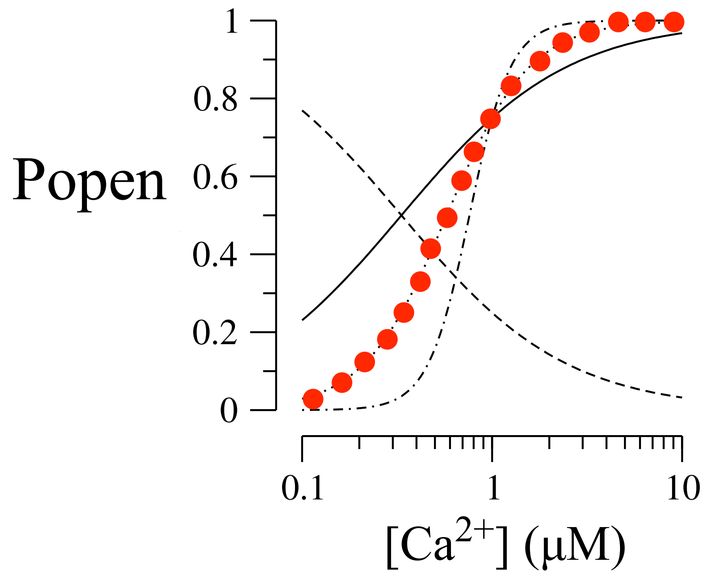


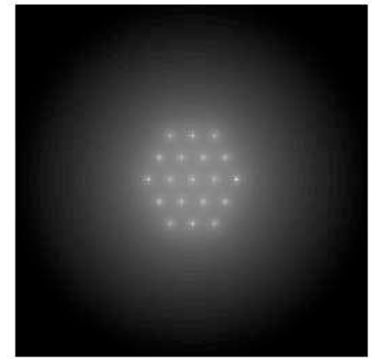


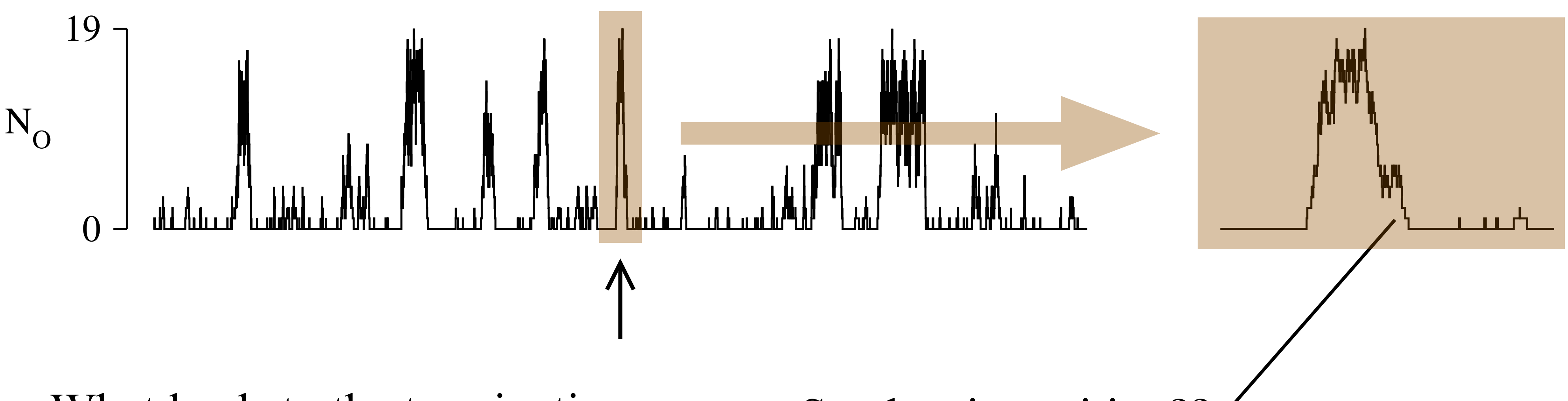


Two-state model with Ca^{2+} activation but no Ca^{2+} inactivation









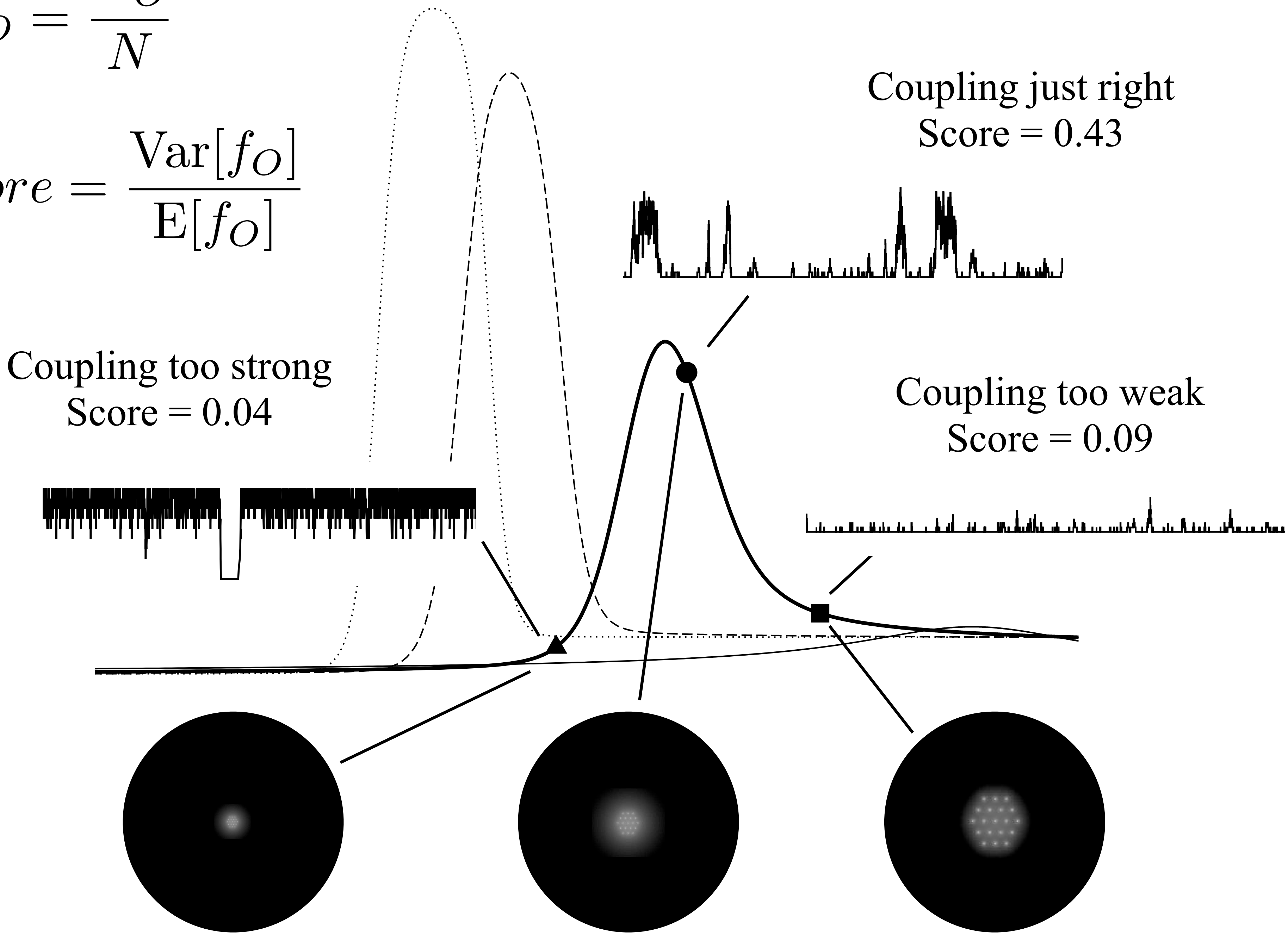
What leads to the termination of these Ca^{2+} puffs?

Stochastic attrition??
(cf. Cheng and Stern 2005)

Puffs are sensitive to channel density (w/o Ca inactivation)

$$f_O = \frac{N_O}{N}$$

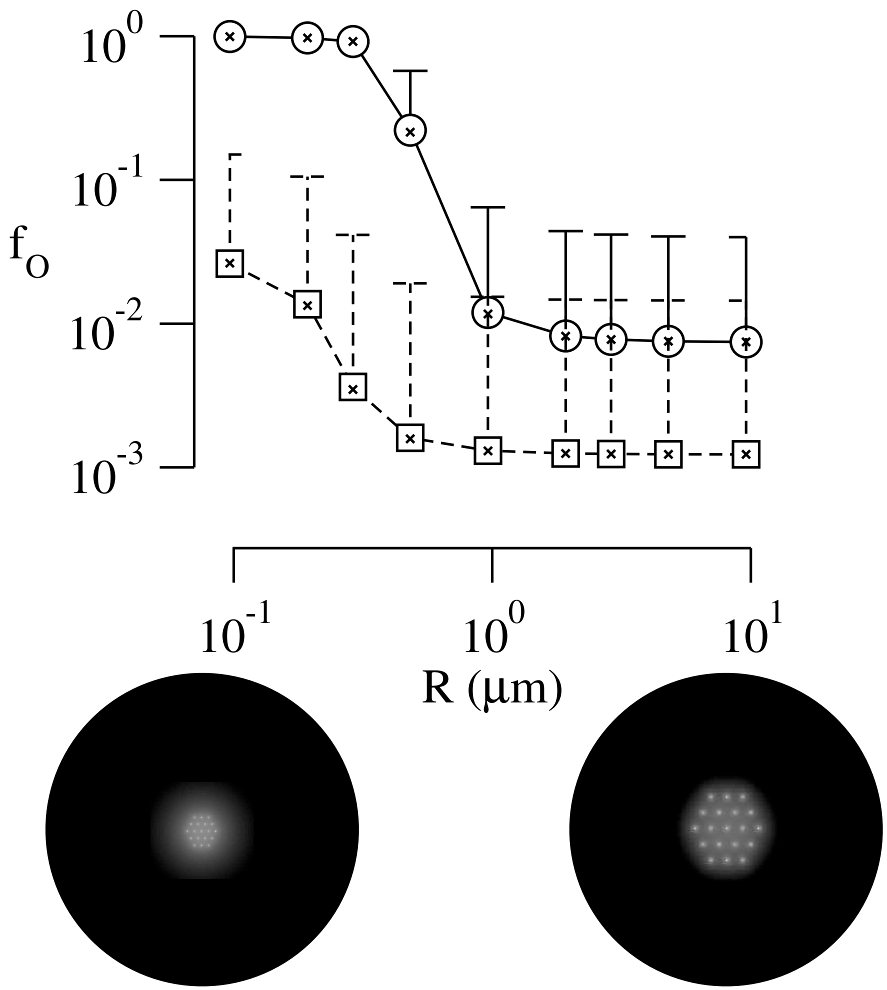
$$Score = \frac{\mathrm{Var}[f_O]}{\mathrm{E}[f_O]}$$

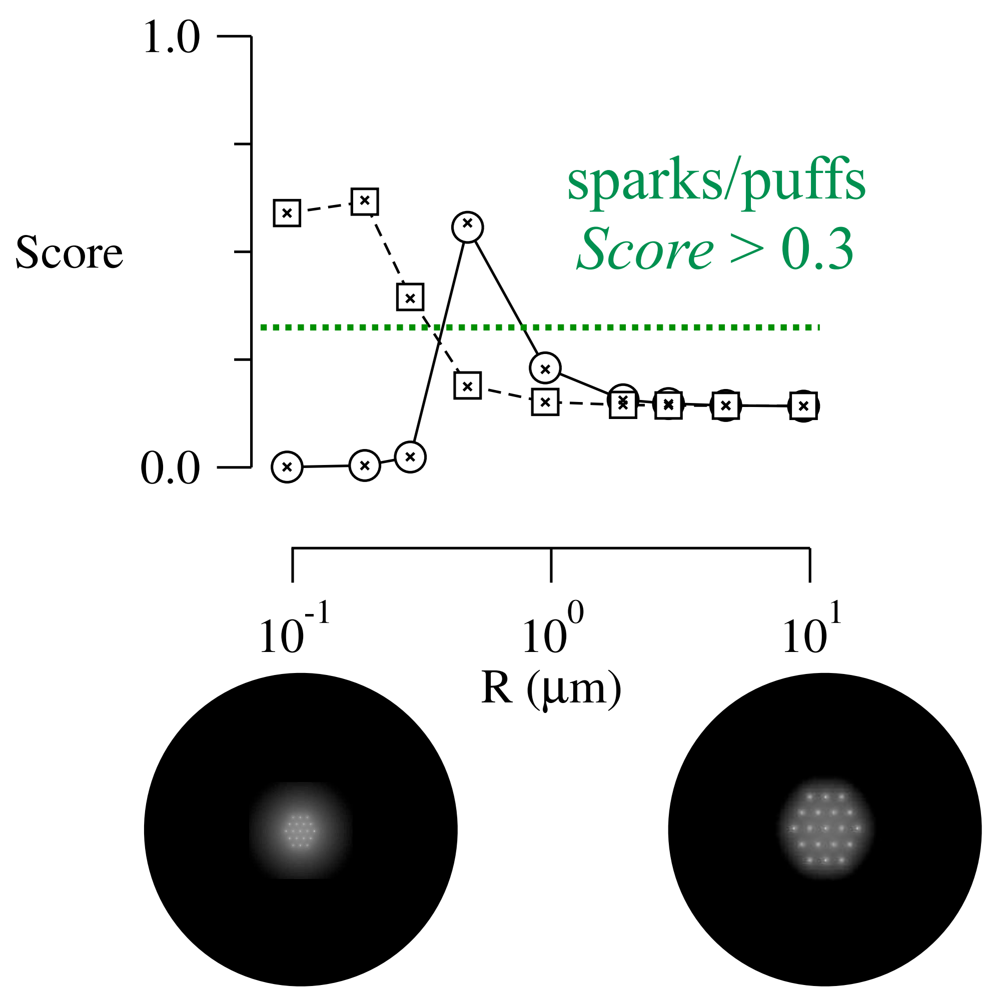


Puffs terminating via Ca inactivation are not sensitive to channel density

$$f_O = \frac{N_O}{N}$$

$$Score = \frac{\mathrm{Var}[f_O]}{\mathrm{E}[f_O]}$$





R < λ　　R > λ　　R < λ　　R > λ

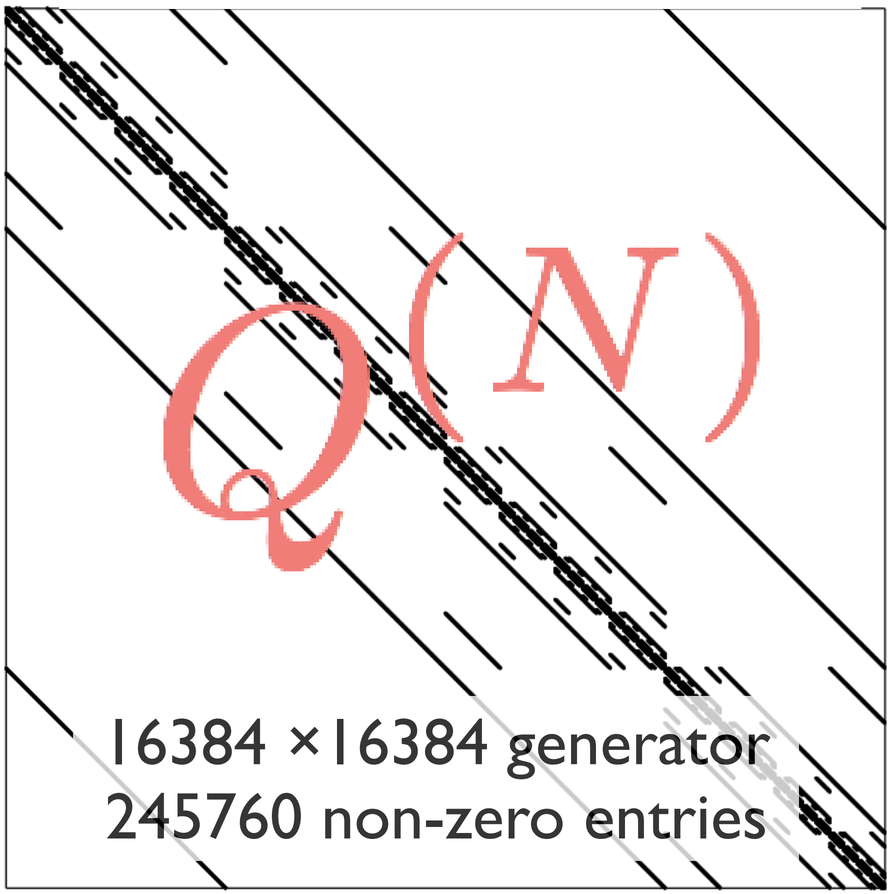
Parameter studies are performed using direct methods

$$\pi^T Q^{(N)} = 0 \text{ subject to } \pi^T e = 1$$

— faster than Monte Carlo estimates —

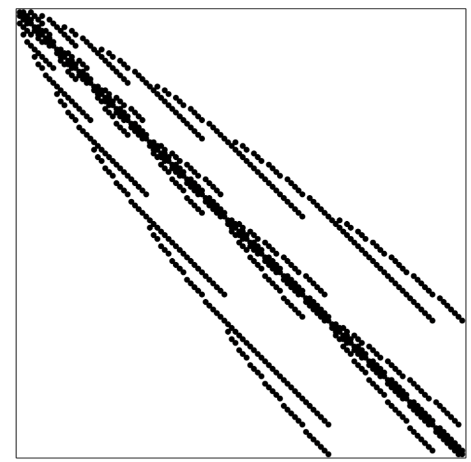
— nontrivial due to state space explosion —

seven four-state channels



assume mean-field coupling

neighboring channels indistinguishable



N terms

120 ×120 generator
792 non-zero entries

for computational efficiency

“mean-field” approximation for channel coupling

Coupling matrix $C = (c_{ij})$ gives [Ca] increase experienced by channel j when channel i is open

c_{11}	c_{12}	c_{13}	c_{14}
c_{21}	c_{22}	c_{23}	c_{24}
c_{31}	c_{32}	c_{33}	c_{34}
c_{41}	c_{42}	c_{43}	c_{44}

general form

➡

c_d	c_{12}	c_{13}	c_{14}
c_{21}	c_d	c_{23}	c_{24}
c_{31}	c_{32}	c_d	c_{34}
c_{41}	c_{42}	c_{43}	c_d

channels identical

➡

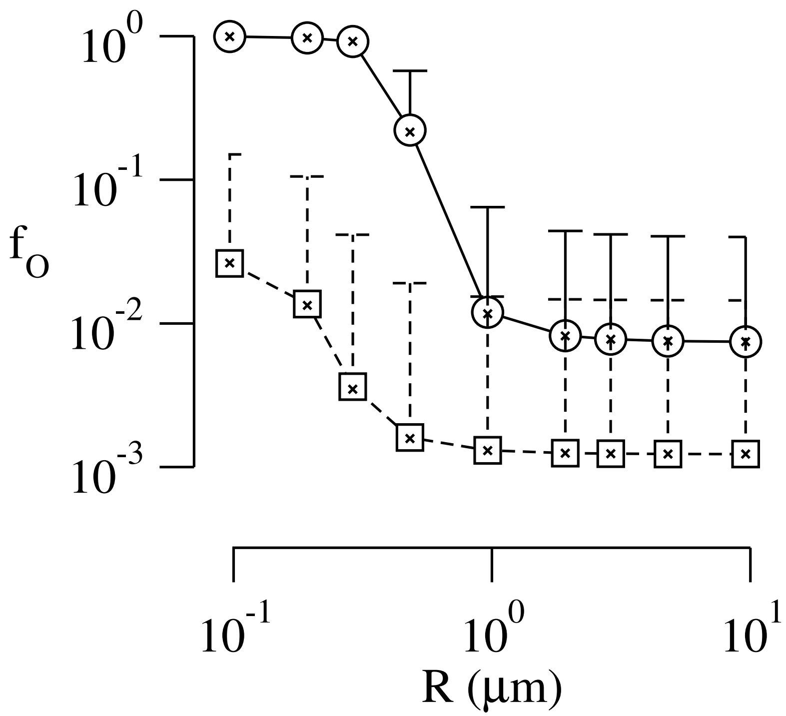
c_d	c_*	c_*	c_*
c_*	c_d	c_*	c_*
c_*	c_*	c_d	c_*
c_*	c_*	c_*	c_d

mean field

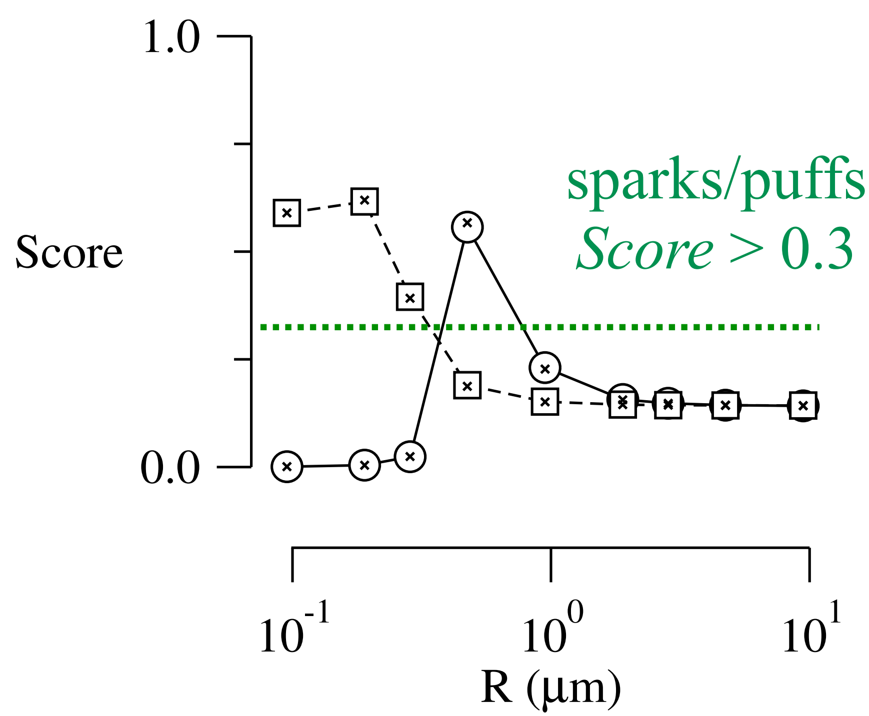
Mean-field approximation usually works well
(see next slide)

Open symbols are full model while X's are mean-field result

$$f_O = \frac{N_O}{N}$$



$$Score = \frac{\mathrm{Var}[f_O]}{\mathrm{E}[f_O]}$$

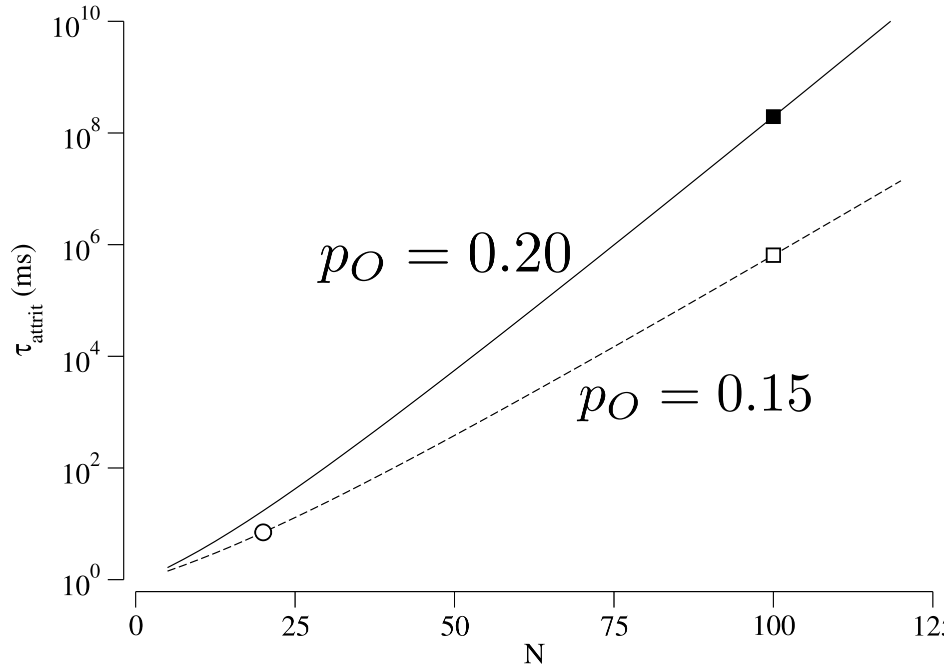


The details of channel position are important primarily through their effect on the average coupling stength (c*)

Isn't stochastic attrition an unlikely termination mechanism?

N two-state channels
identical
independent gating

$$C(\text{closed}) \underset{1/\tau_O}{\overset{1/\tau_C}{\rightleftharpoons}} O(\text{open})$$

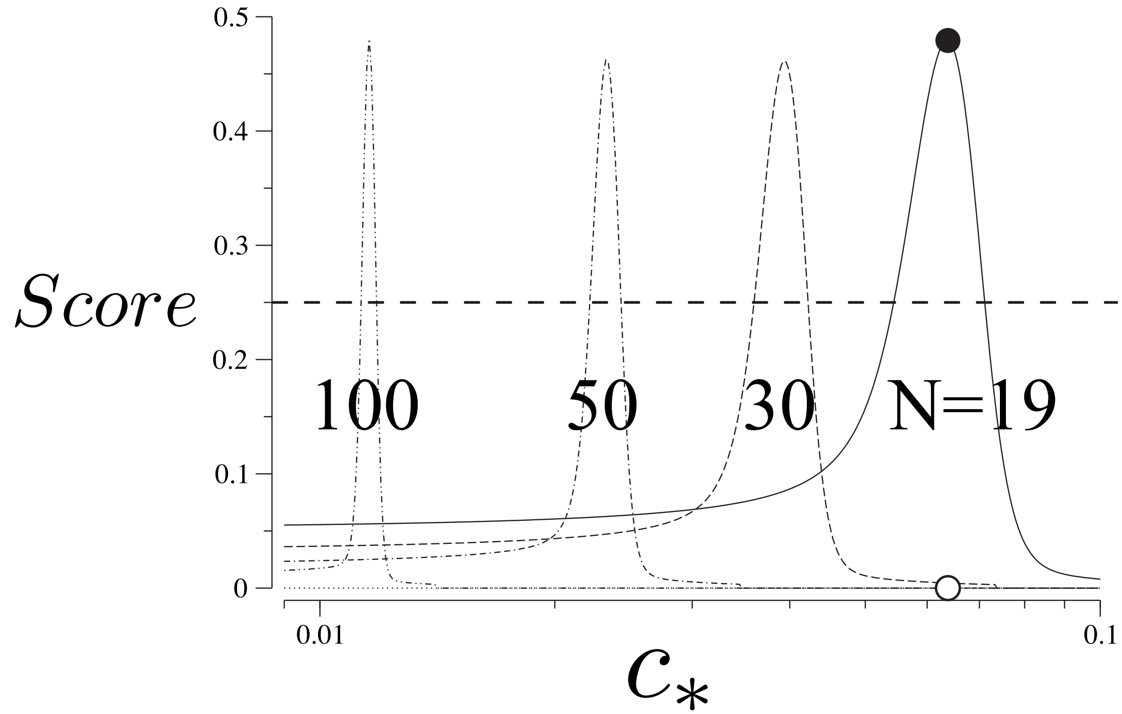


The time constant for stochastic attrition is an exponential function of the number of open channels

$$\tau_{attrit} = \frac{1}{k_{attrit}} = \tau_O \frac{1 - (1 - p_O)^N}{N (1 - p_O)^{N-1} p_O} \qquad p_O = \frac{\tau_O}{\tau_C + \tau_O}$$

(Stern)

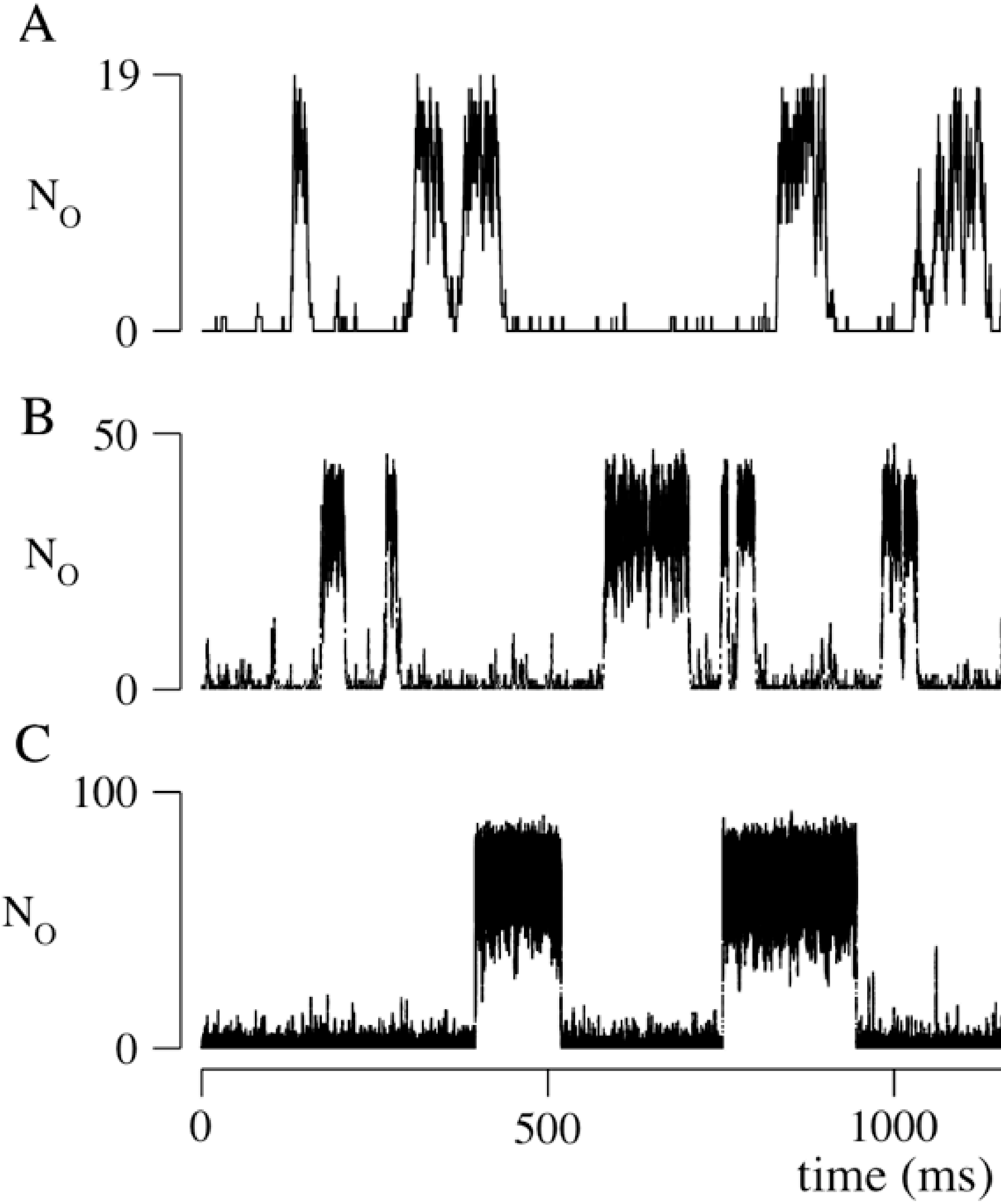
N two-state channels
identical
~~independent gating~~
mean-field instantaneously-coupled gating

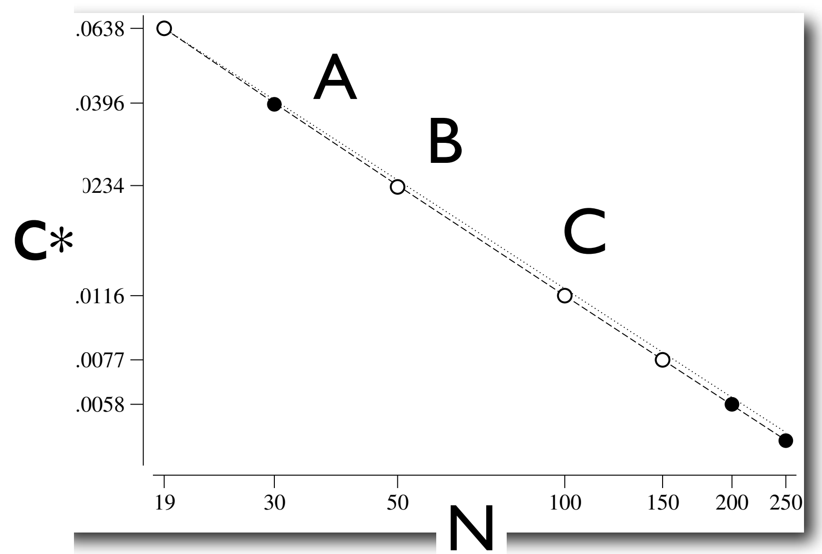


The time constant for stochastic attrition depends on the coupling strength (i.e., the density of the release site)

$$\tau_{attrit} = \frac{1}{k_{attrit}} = \frac{1}{k_-}\left\{1 + \sum_{i=1}^{N-1}\left[\frac{(N-1)!}{(i+1)!(N-1-i)!}\prod_{j=1}^{i}\left(\frac{c_\infty + jc_*}{K}\right)^{\eta}\right]\right\}$$

N can be large if coupling strength is appropriately reduced



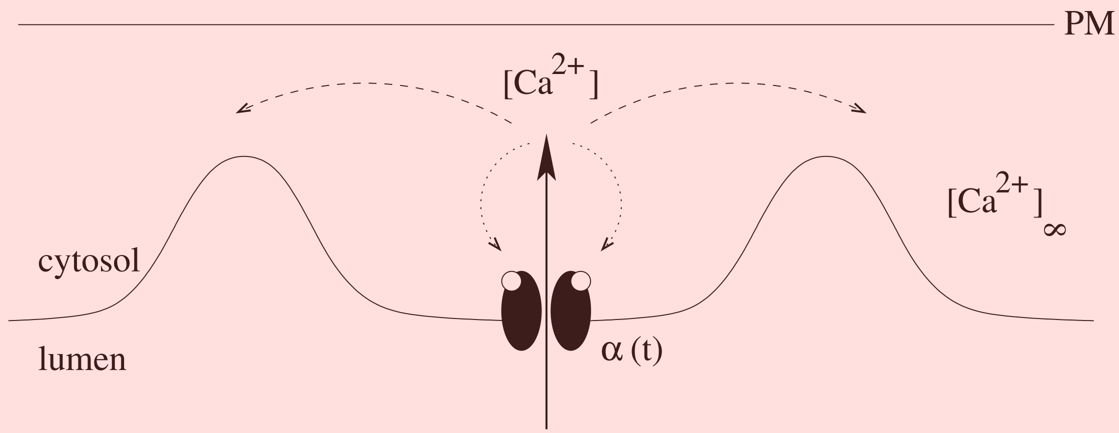


But stochastic attrition is not robust when the number of channels is large, that is, it requires channels with precisely the right density or source amplitude

One expects that the time constant for domain formation and collapse will influence puff/spark termination

Before considering Ca release sites, consider the effect of a time-dependent Ca domain on a single Ca-regulated channel

Effect of "residual calcium" on Ca-regulated channels



$$k^+ c^\eta$$

$$\text{(closed)} \quad C \quad \rightleftharpoons \quad O \quad \text{(open)}$$

$$k^-$$

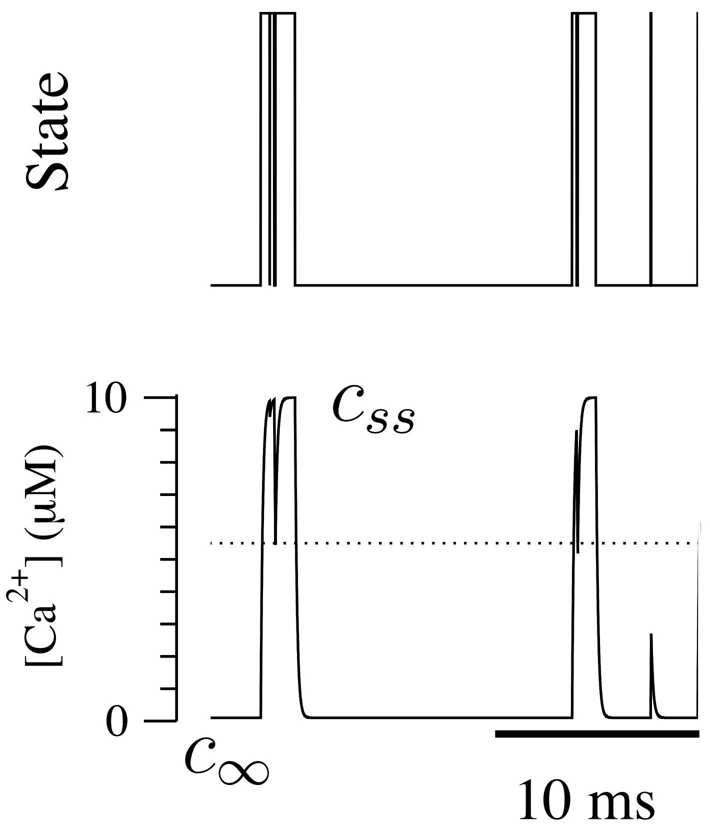
$$\frac{dc}{dt} = \alpha(t) - \frac{c - c_\infty}{\tau} \qquad \text{where} \qquad \alpha(t) = \begin{cases} 0 & \text{when} \quad S(t) = C \\ \alpha_0 & \text{when} \quad S(t) = O. \end{cases}$$

$$c_\infty < c < c_{ss} = \tau\alpha_0 + c_\infty$$

Effect of "residual Ca" on Ca-activated channel

fast domain
slow channel

$\tau = 10^{-4}$



increase τ

when domain is slow "residual calcium" from previous openings increases rate of C→O transitions leading to elevated open probability

Probability density approaches as an alternative to Monte Carlo

The joint distributions

$$\begin{aligned}\rho_C(c,t)dc &= \mathsf{P}\left\{c < [\mathrm{Ca}^{2+}] < c + dc \text{ and } S(t) = C\right\} \\ \rho_O(c,t)dc &= \mathsf{P}\left\{c < [\mathrm{Ca}^{2+}] < c + dc \text{ and } S(t) = O\right\}\end{aligned}$$

are time-dependent and satisfy

reaction (stochastic gating)

$$\begin{aligned}\frac{\partial \rho_C}{\partial t} &= -\frac{\partial \phi_C}{\partial c} - k^+ c^\eta \rho_C + k^- \rho_O \\ \frac{\partial \rho_O}{\partial t} &= -\frac{\partial \phi_O}{\partial c} + k^+ c^\eta \rho_C - k^- \rho_O\end{aligned}$$

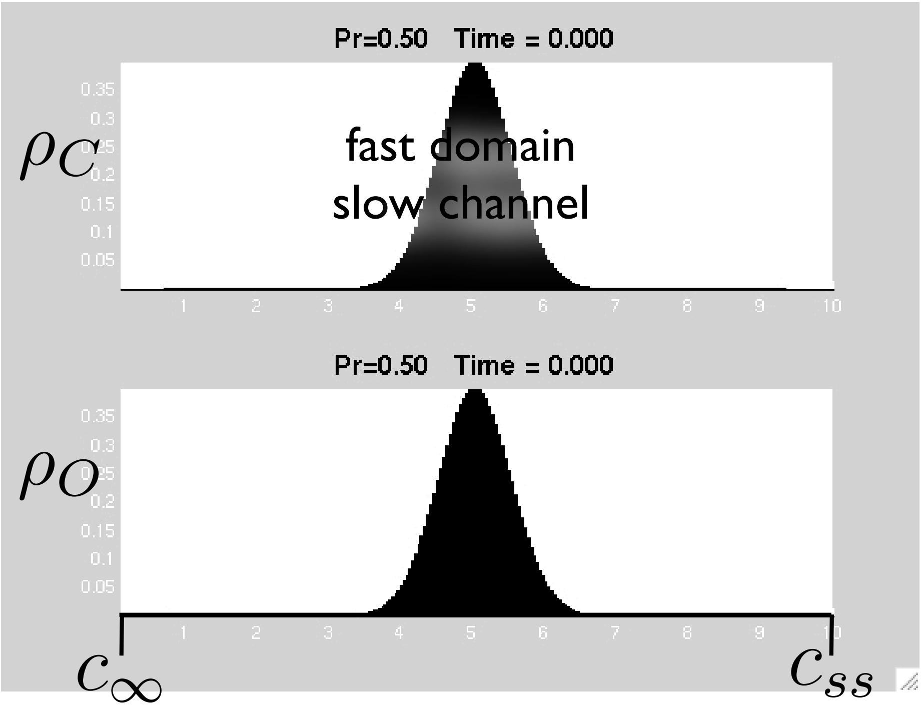
advection (deterministic dynamics of domain)

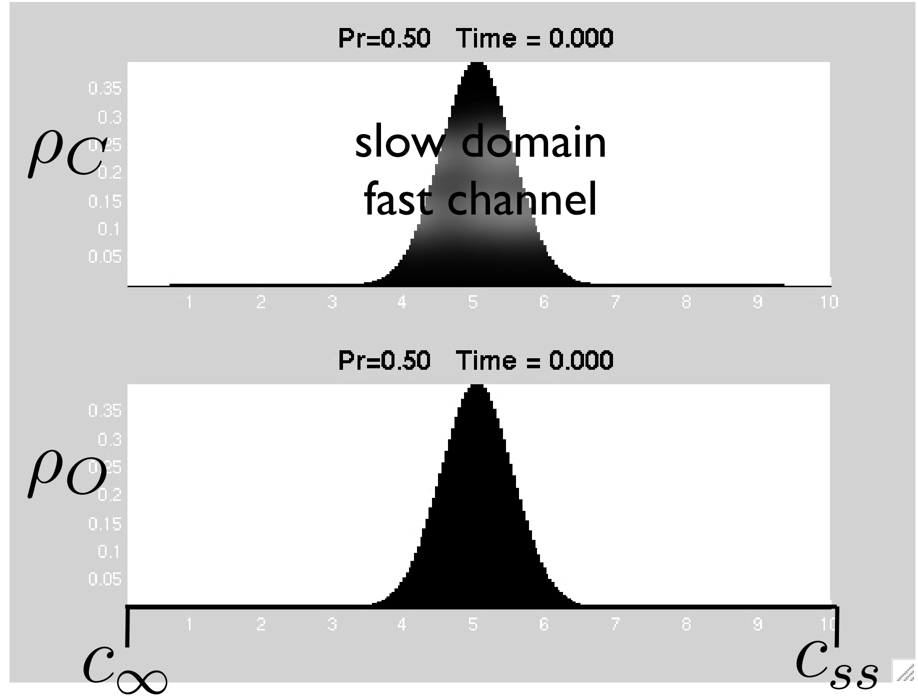
$$\begin{aligned}\phi_C(c,t) &= j_C(c)\,\rho_C(c,t) \\ \phi_O(c,t) &= j_O(c)\,\rho_O(c,t)\end{aligned}$$

$$j_C(c) = -\frac{c - c_\infty}{\tau}$$

$$j_O(c) = \alpha_0 - \frac{c - c_\infty}{\tau}$$

Time-dependent probability densities



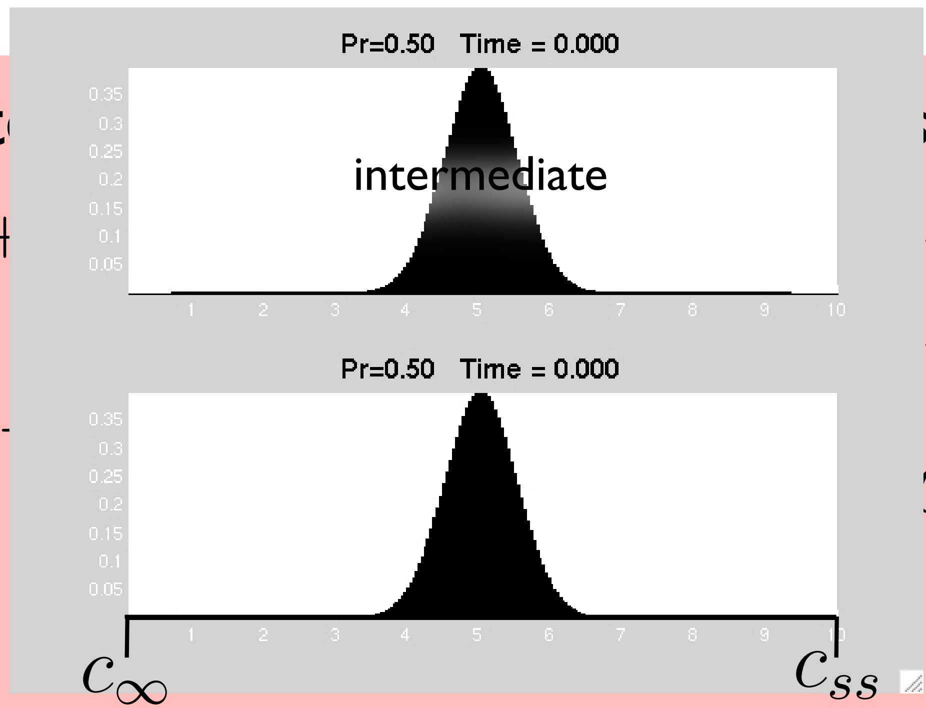


St… …s

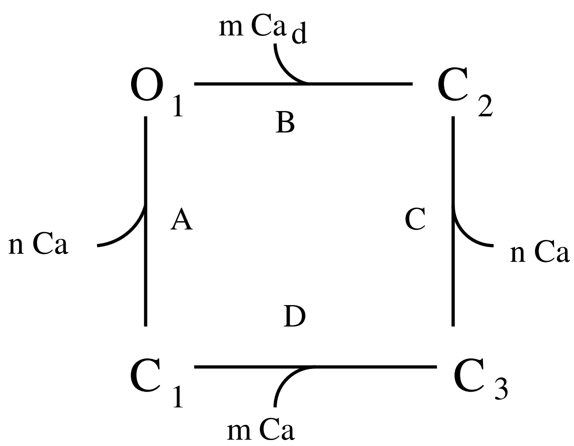
$\rho_C = \hat{\rho} e^{\tau^+ \cdots}$ … $)^{\tau^+ c_\infty - 1}$

$\rho_O = \hat{\rho} e^{\tau^{\cdots}}$ … $c_\infty)^{\tau^+ c_\infty}$

$\tau^\pm = \tau k^\pm$



The PD approach w/ more complicated single channel models

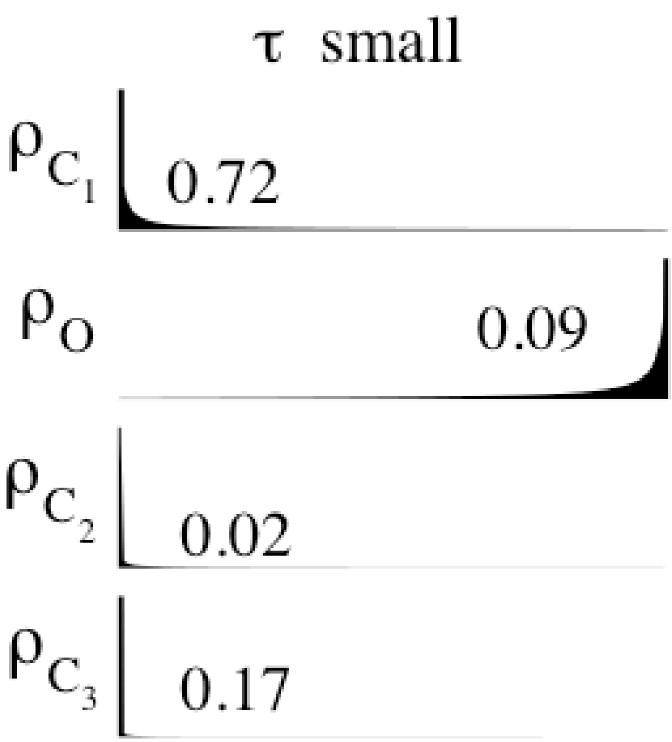


$$\rho_i(c,t)dc = \mathsf{P}\left\{c < [\mathrm{Ca}^{2+}] < c + dc \right.$$

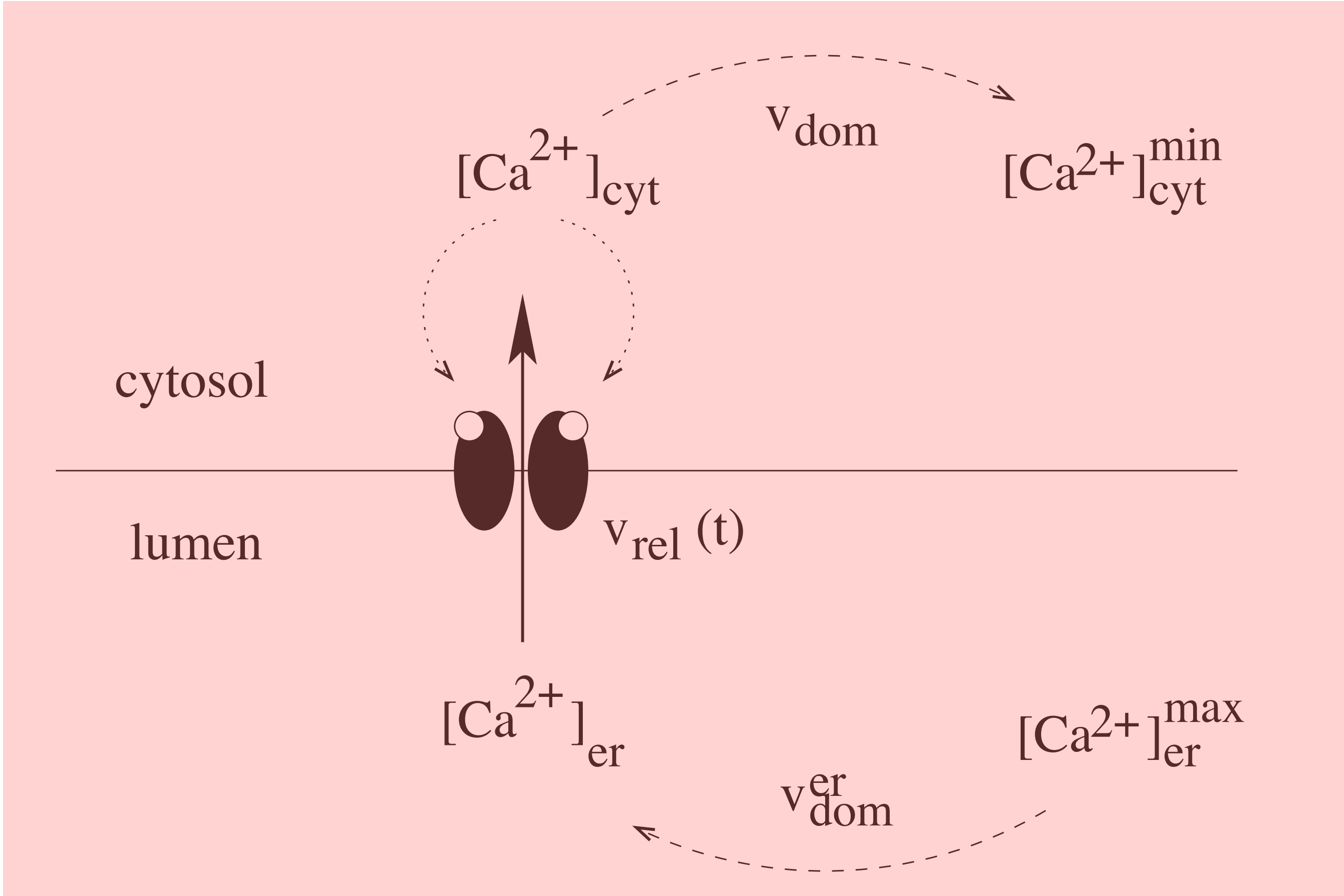
$$\left. \text{and } S(t) = \mathcal{S}_i \right\}$$

$$\frac{\partial \boldsymbol{\rho}}{\partial t} = -\frac{\partial}{\partial c}\left[\boldsymbol{\rho} J\right] + \boldsymbol{\rho} Q$$

$$\boldsymbol{\rho} = (\rho_1, \rho_2, \cdots, \rho_M)$$



The PD approach to study the effect of "lumenal depletion"



$$\frac{dC_{cyt}}{dt} = \gamma(t)\nu_{rel}(C_{er} - C_{cyt}) - \nu_{dom}(C_{cyt} - C_{min})$$

$$\frac{dC_{er}}{dt} = \frac{1}{\lambda}\left[-\gamma(t)\nu_{rel}(C_{er} - C_{cyt}) + \nu_{dom}^{er}(C_{max} - C_{er})\right]$$

The joint probability densities become multivariate

$$\rho_i(C_{cyt}, C_{er}, t)\ dC_{cyt}\ dC_{er} = \mathrm{Prob}\{C_{cyt} < \tilde{C}_{cyt} < C_{cyt} + dC_{cyt}\ \ \mathrm{AND}\ \ C_{er} < \tilde{C}_{er} < C_{er} + dC_{er}\ \ \mathrm{AND}\ \gamma(t) = i\}$$

but still satisfy a system of advection-reaction equations

$$\frac{\partial}{\partial t}\rho_i = \boxed{-\frac{\partial(F^i_{cyt}\rho_i)}{\partial C_{cyt}} - \frac{\partial(F^i_{er}\rho_i)}{\partial C_{er}}} + \boxed{[\vec{\rho}\mathbf{Q}]_i}$$

The probability flux has two components

$$F^i_{cyt} = \gamma_i\ \nu_{rel}(C_{er} - C_{cyt}) - \nu_{dom}(C_{cyt} - C_{min})$$

$$F^i_{er} = \frac{1}{\lambda}\left[-\gamma_i\nu_{rel}(C_{er} - C_{cyt}) + \nu^{er}_{dom}(C_{max} - C_{er})\right]$$

each of which depends on channel state

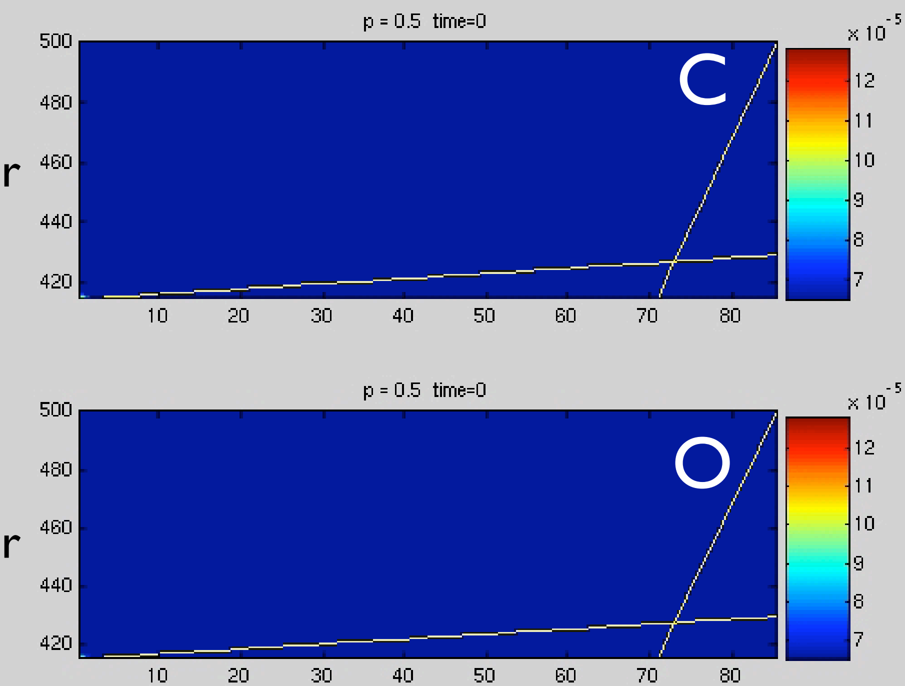
Cytosolic domain and lumenal depletion domain
Ca-activated channel

fast domain (large v's)

slow channel

Ca_{er}

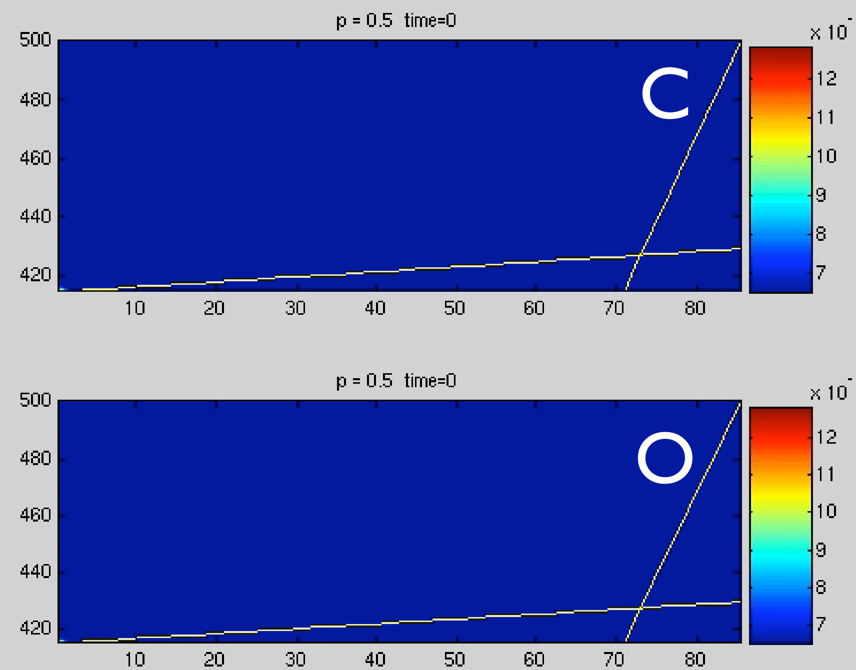
Ca_{er}



Ca_{cyt}

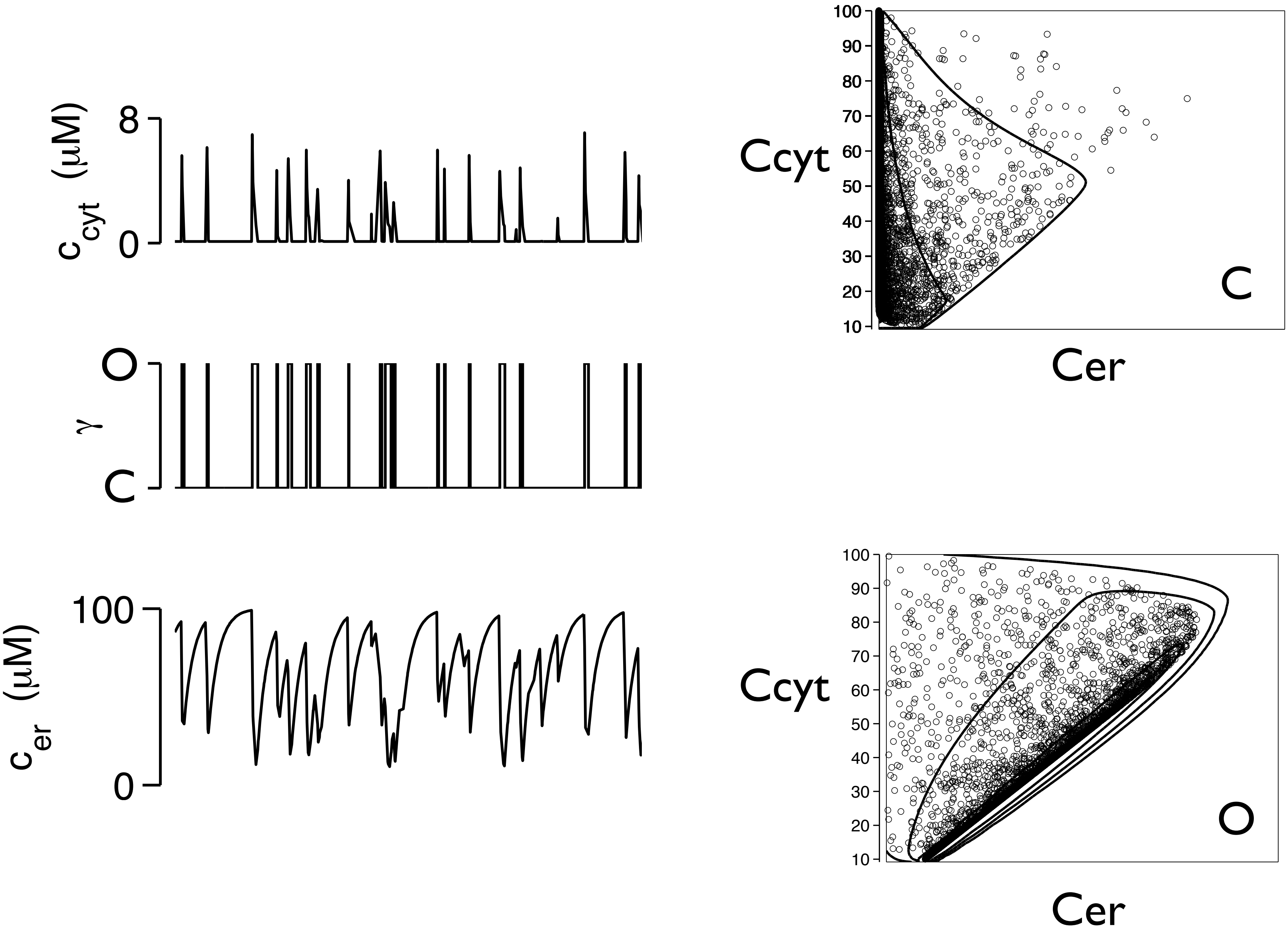
slow domain (small v's)

fast channel

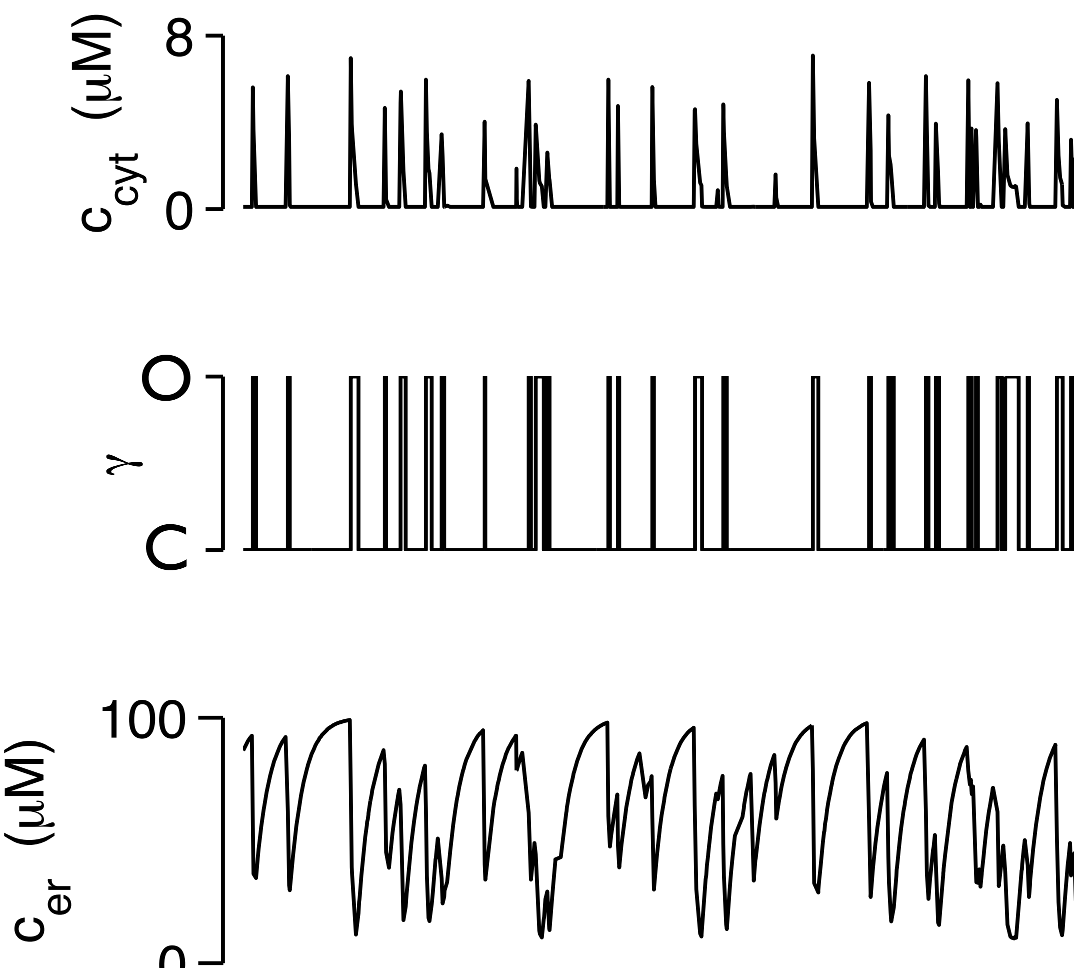


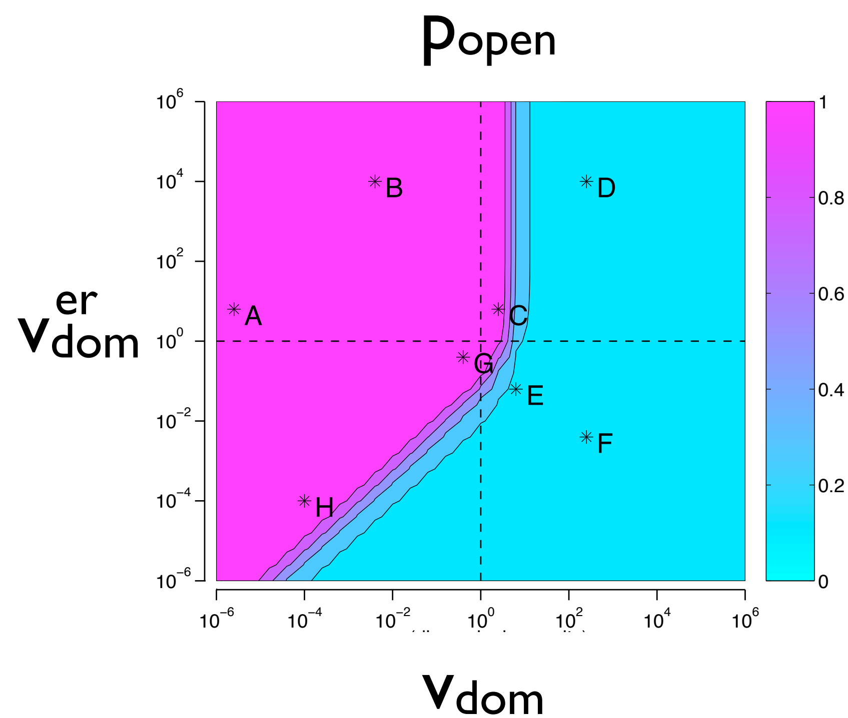
Ca_{cyt}

Comparison of Monte Carlo and probability density approaches



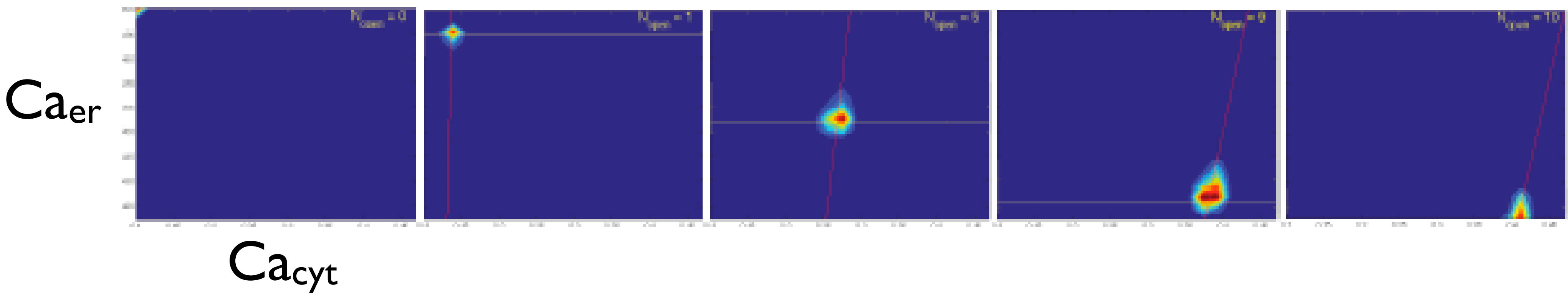
Calcium activated channel — effect of lumenal depletion

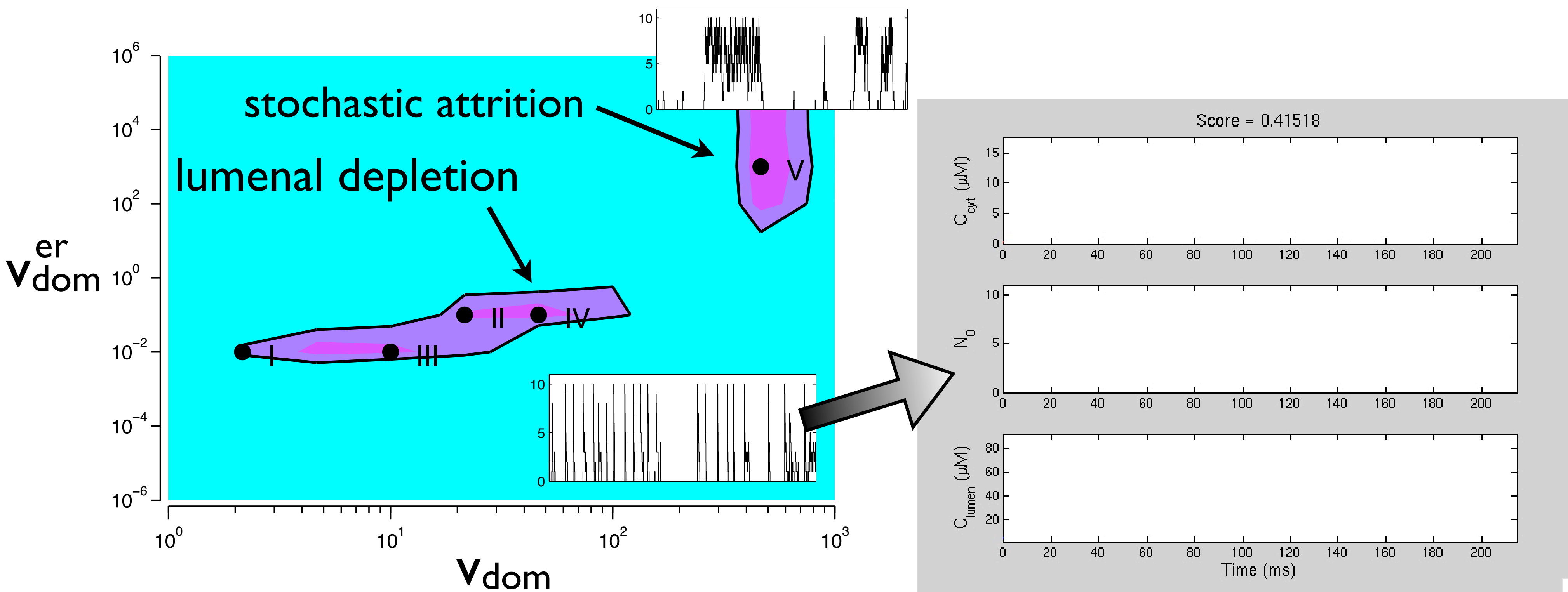




Dynamics of spark termination — effect of lumenal depletion

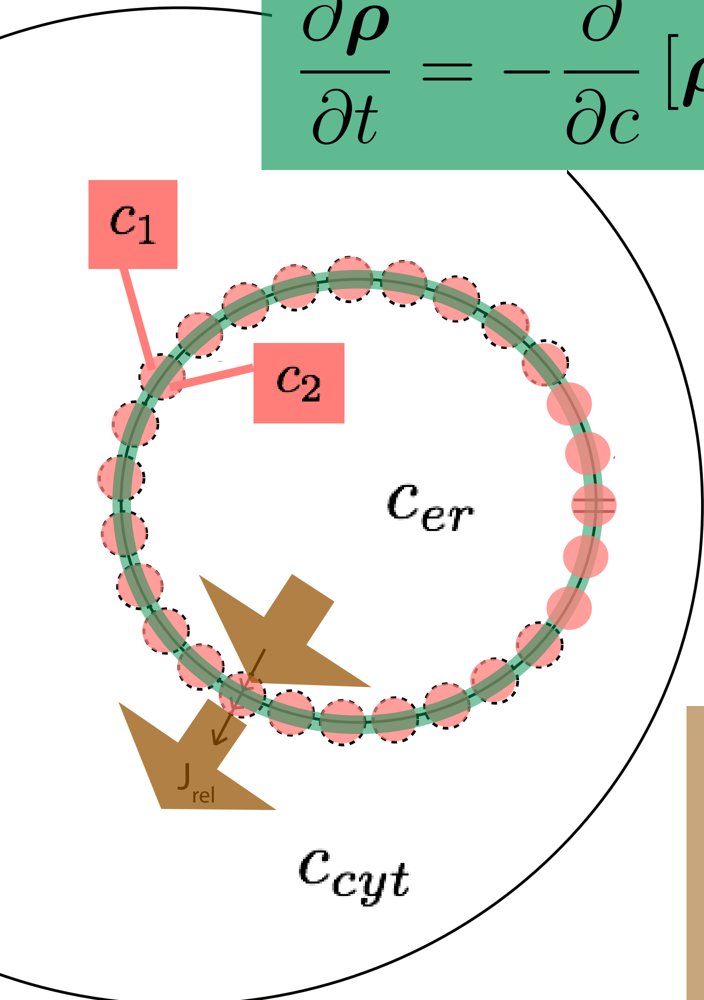
$$0 \underset{k^-}{\overset{Nk^+c_0}{\rightleftharpoons}} 1 \underset{2k^-}{\overset{(N-1)k^+c_1}{\rightleftharpoons}} 2 \underset{3k^-}{\overset{(N-2)k^+c_2}{\rightleftharpoons}} \cdots \underset{(N-1)k^-}{\overset{2k^+c_{N-2}}{\rightleftharpoons}} N-1 \underset{Nk^-}{\overset{k^+c_{N-1}}{\rightleftharpoons}} N$$





A new class of whole cell models

not explicitly spatial
but includes local signaling



$$\frac{\partial \boldsymbol{\rho}}{\partial t} = -\frac{\partial}{\partial c}\left[\boldsymbol{\rho} J\right] + \boldsymbol{\rho} Q$$

$$\frac{dc_{cyt}}{dt} = J^*_{cyt} + J_{leak} - J_{pump}$$

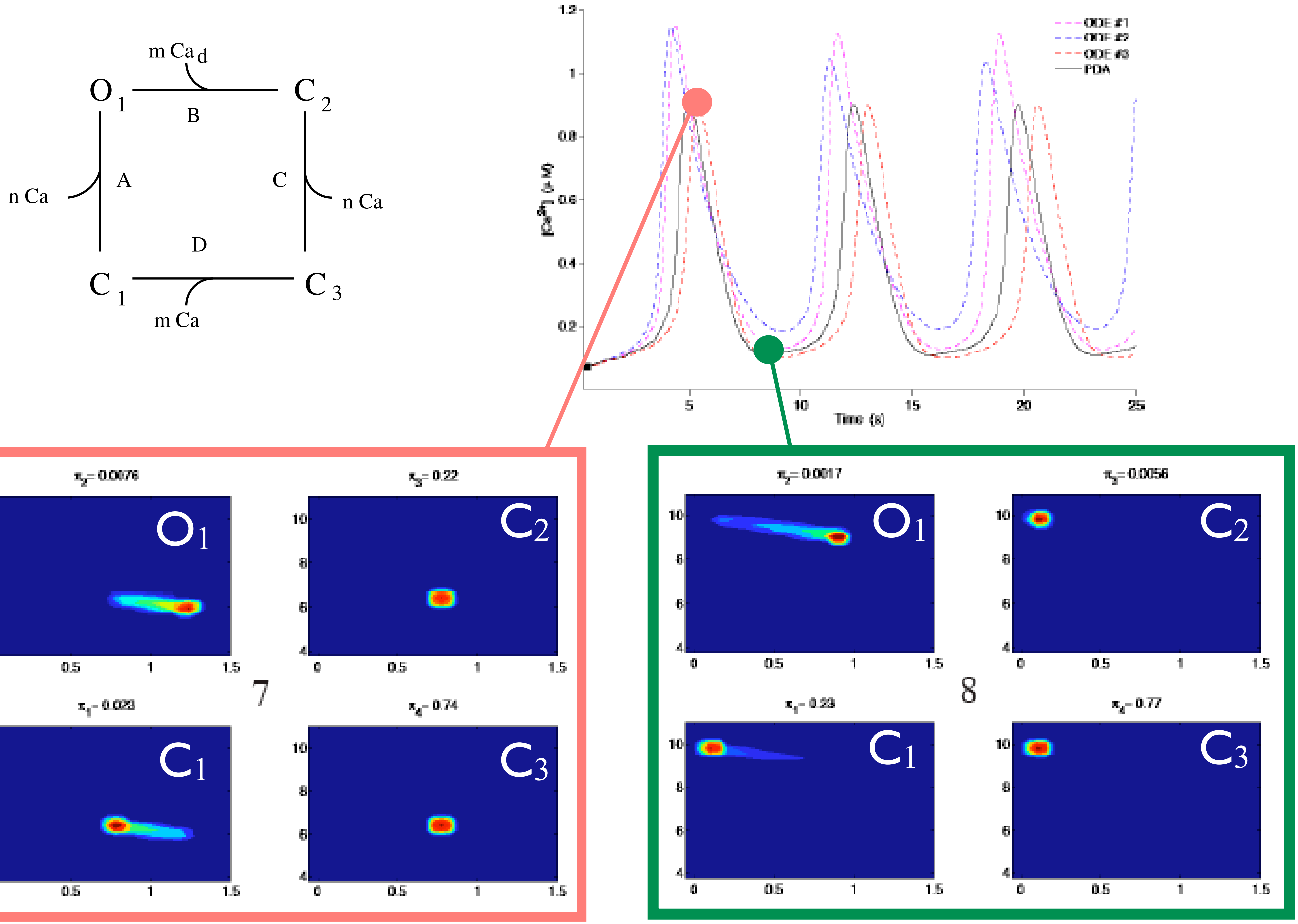
$$\frac{dc_{er}}{dt} = \frac{1}{\lambda_{er}}\left(J_{pump} - J_{leak} - J^*_{er}\right)$$

$$J^*_{cyt} = \sum_{i=1}^{M} \int_{c_2^{min}}^{c_2^{max}} \int_{c_1^{min}}^{c_1^{max}} v_{cyt}(c_1 - c_{cyt})\rho_i(c_1, c_2)dc_1dc_2$$

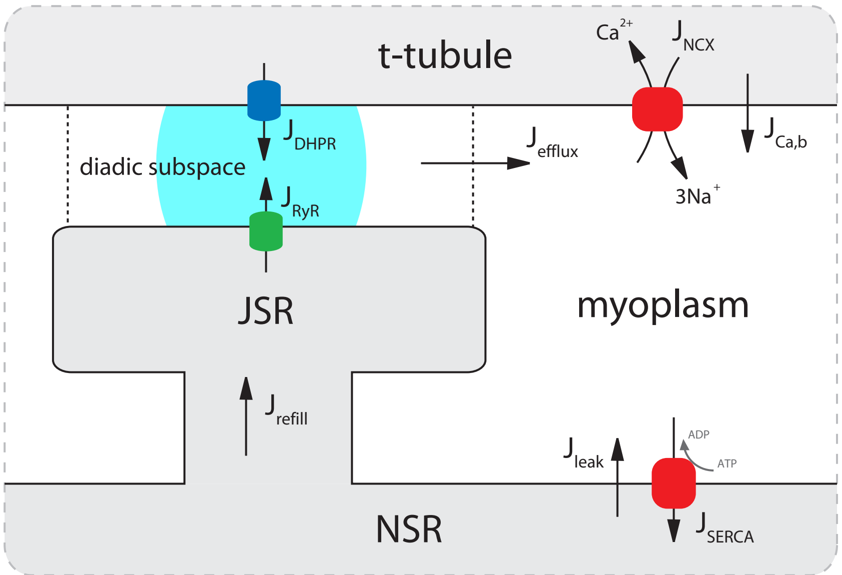
$$J^*_{er} = \sum_{i=1}^{M} \int_{c_2^{min}}^{c_2^{max}} \int_{c_1^{min}}^{c_1^{max}} v_{er}(c_{er} - c_2)\rho_i(c_1, c_2)dc_1dc_2$$

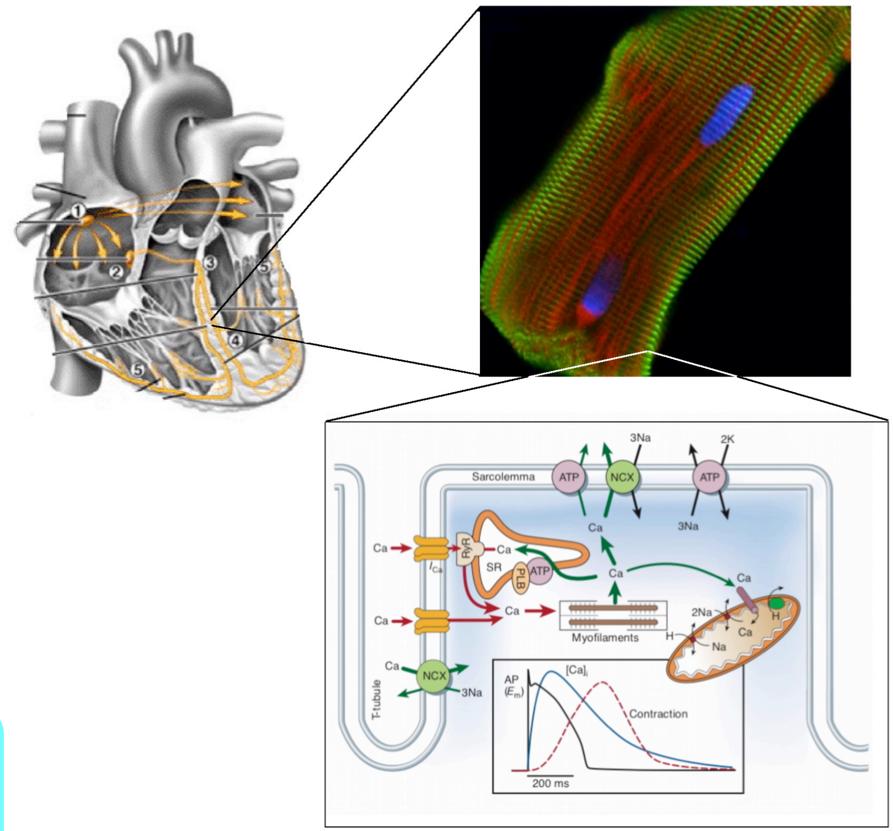
large number of channels
each with it’s own time-dependent domain

Diffuse IP3Rs with time-dependent domains



New approach for modeling "local control" during EC coupling





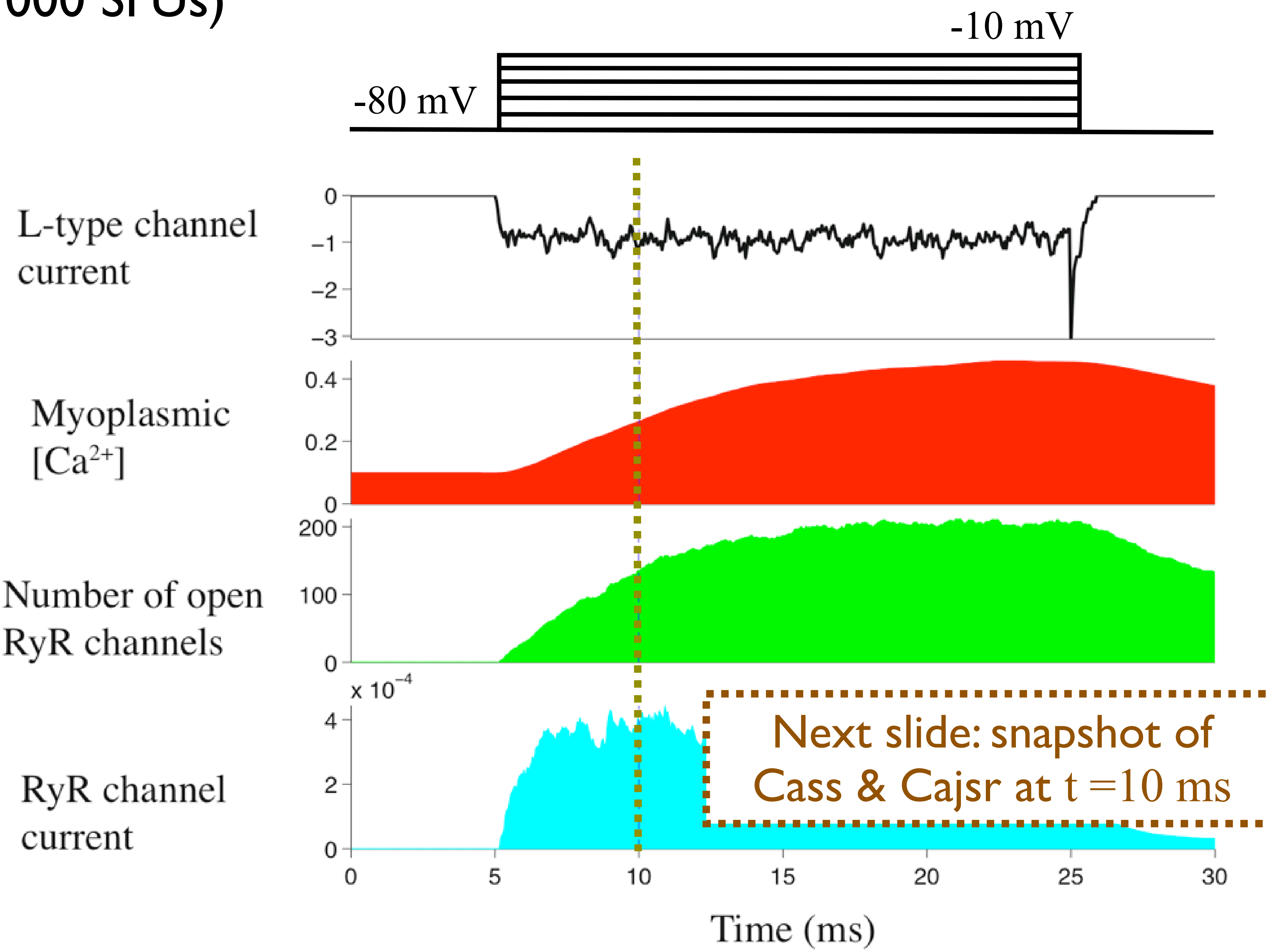
Bers 2002

SFU model

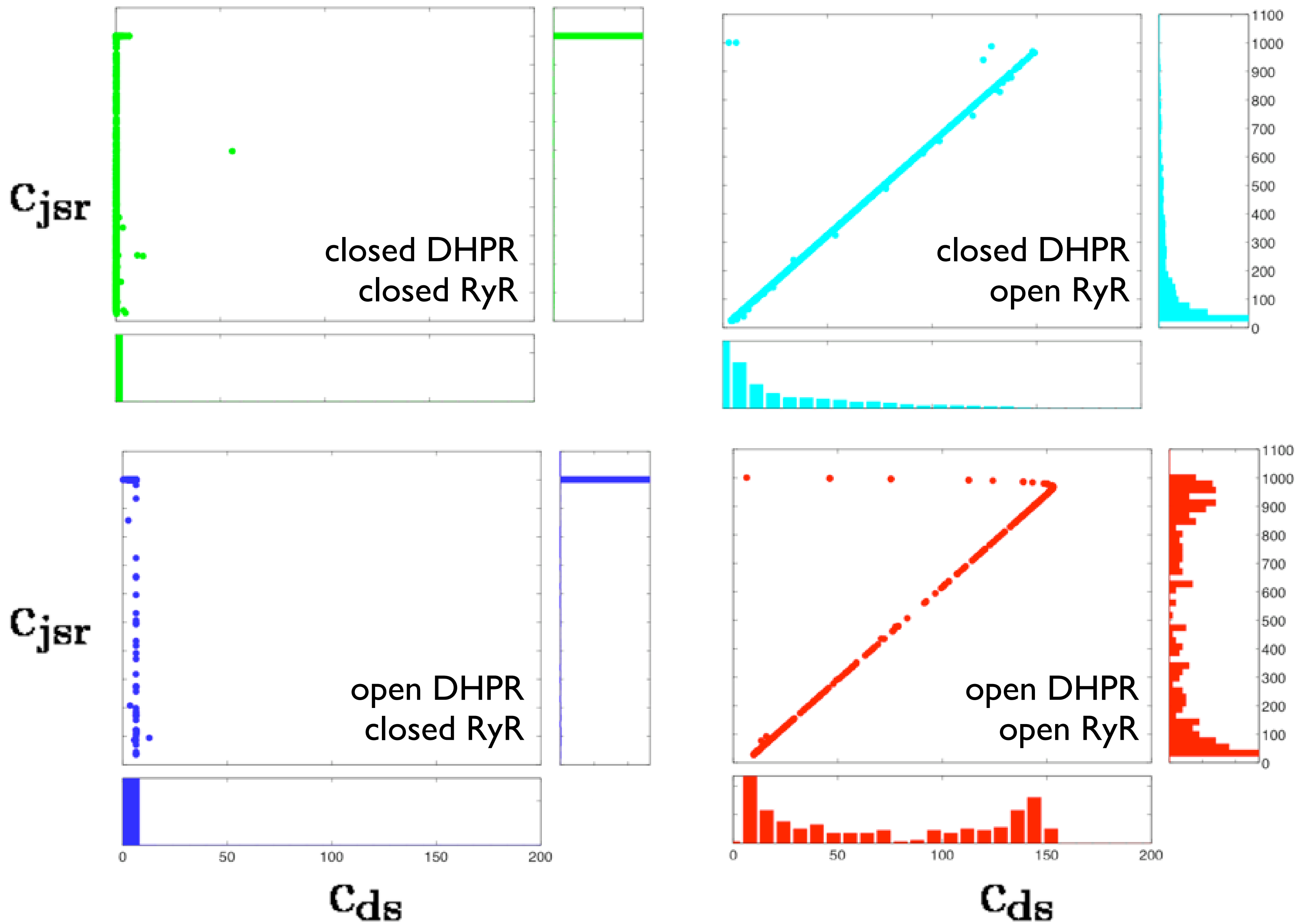
$$
\begin{array}{ccccccc}
\text{(both closed)} & CC & & \underset{k^-_{ryr}}{\overset{k^+_{ryr}}{\leftrightharpoons}} & & CO & \text{(RyR open)} \\
k^+_{dhpr} & \downarrow\uparrow & k^-_{dhpr} & & k^-_{dhpr} & \uparrow\downarrow & k^+_{dhpr} \\
\text{(DHRP open)} & OC & & \underset{k^+_{ryr}}{\overset{k^-_{ryr}}{\rightleftharpoons}} & & OO & \text{(both open)}
\end{array}
$$

Monte Carlo simulation of voltage-clamped cardiac myocyte

(1000 SFUs)

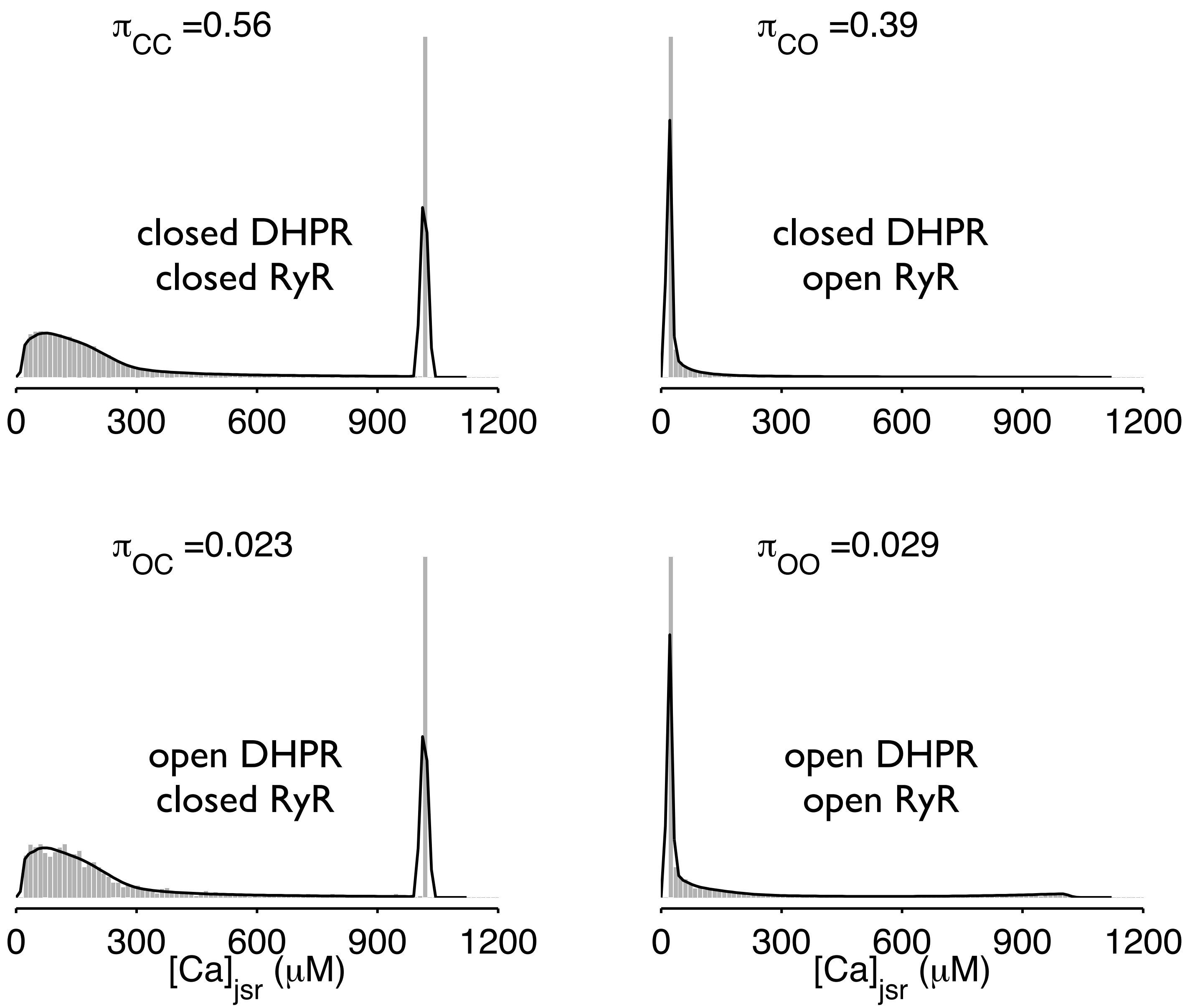


Marginal densities show lumenal depletion during voltage step

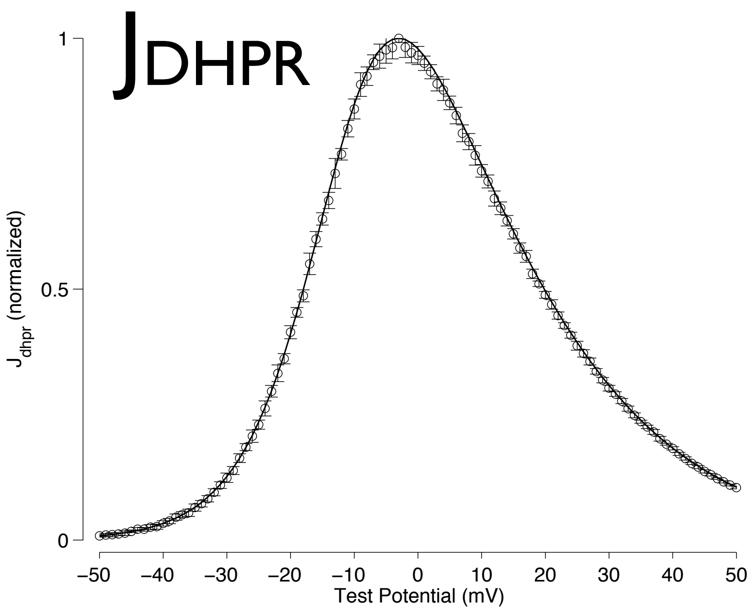


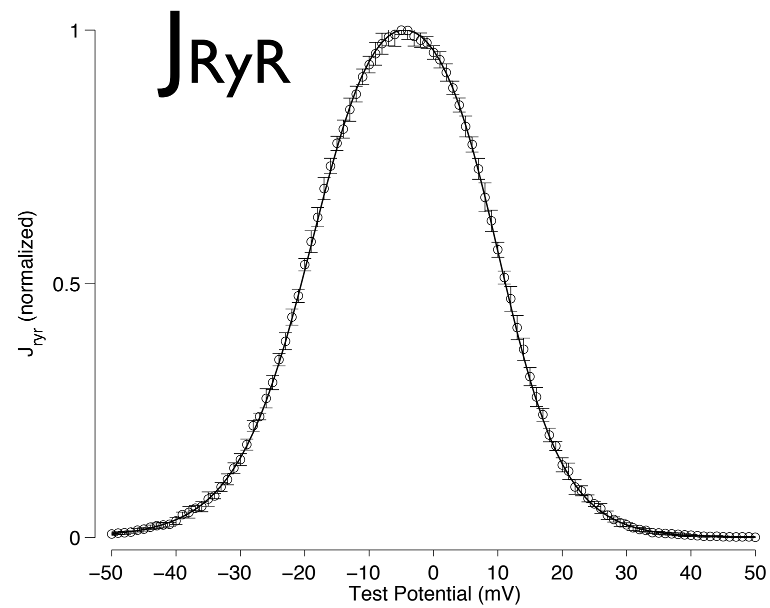
JSR is slow compared to diadic subspace...

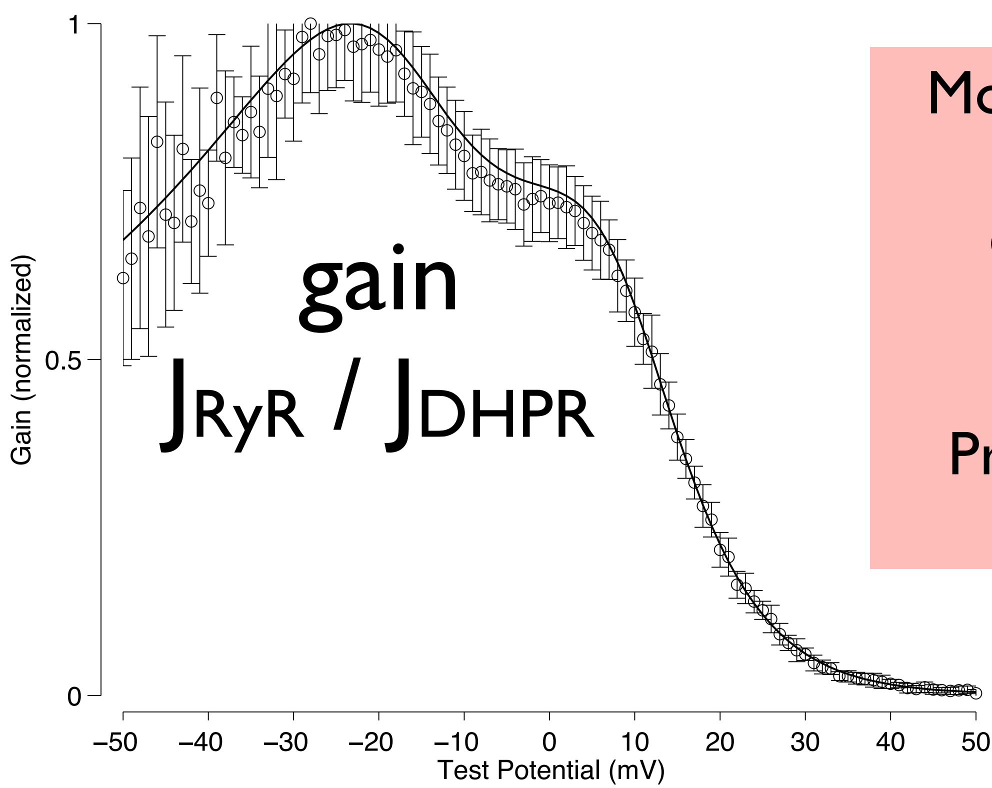
Because JSR is slow compared to diadic subspace, we can reduce to one-dimensional densities (in terms of Cajsr)



Probability density approach exhibits "gain and gradedness"







Monte Carlo using 1000 SFUs
each point is 10 runs
each run takes 3 minutes

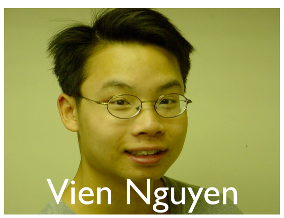
Probability density approach
each point takes 10 sec

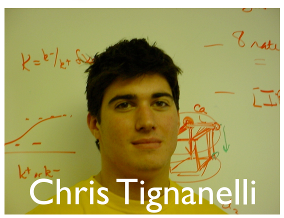
Computational efficiency of Monte Carlo and probability density approaches

Assuming the large N limit is of interest
(20,000 SFUs ≈ infinity)

Monte Carlo approach	Probability density approach
discretization error	discretization error
time step (Δt)	time step (Δt)
number of SFUs (N)	resolution of mesh (Δc)

Acknowledgments





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