

Numerical simulation of intracellular calcium dynamics

S. Rüdiger, M. Falcke

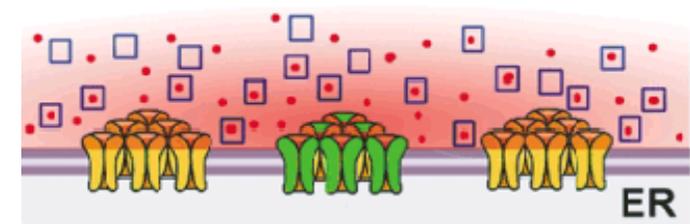
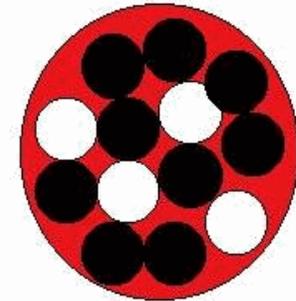
Hahn-Meitner Institut Berlin

G. Warnecke, N. Chamakuri

Math. Fakultät, Uni Magdeburg

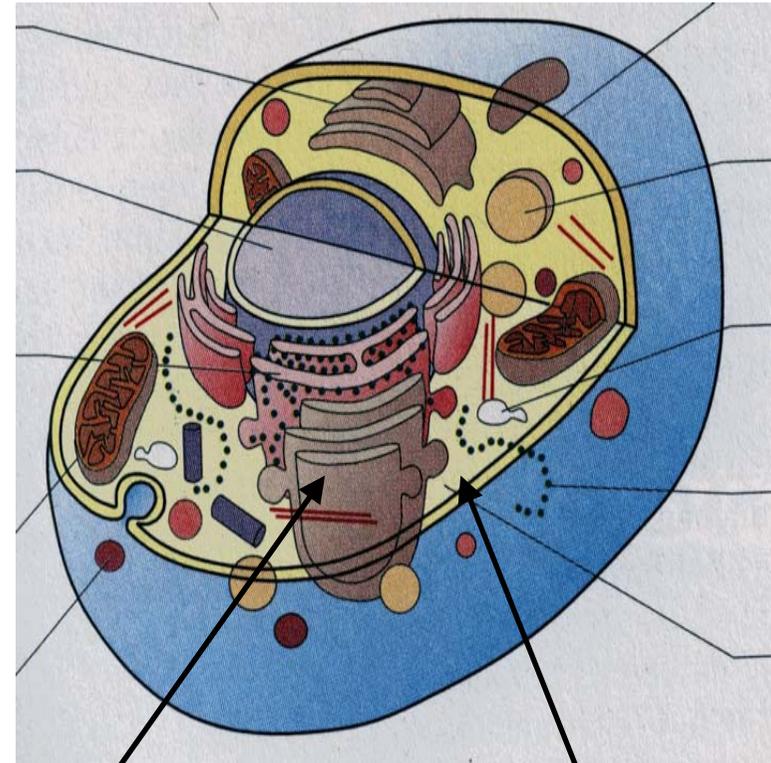
Overview

- ▶ Transitions of single release sites (channels) – DeYoung-Keizer model
- ▶ Release sites cluster – stochastic calcium dynamics
- ▶ Coupling of clusters generates waves/coherent oscillations
- ▶ Hybrid stochastic/deterministic solver for models with time dependent diffusion
- ▶ Effect of buffers



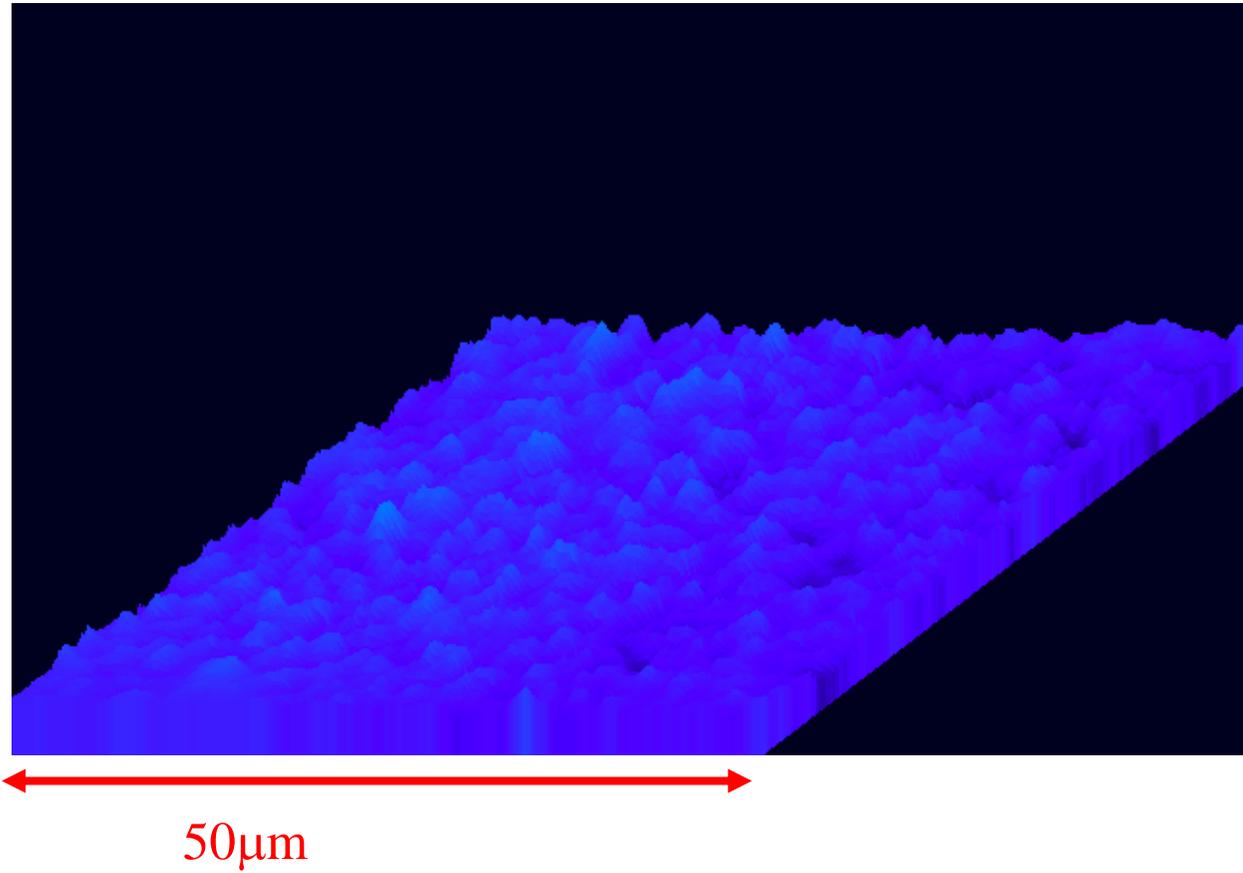
I. Introduction

- ▶ The endoplasmic reticulum (ER) has a high calcium concentration
- ▶ Channels: ER→cytosol, pumps: cytosol→ER
- ▶ Ca^{2+} is released by transient openings of channels
- ▶ Channels are activated by IP_3 and Ca^{2+}



endoplasmic
reticulum

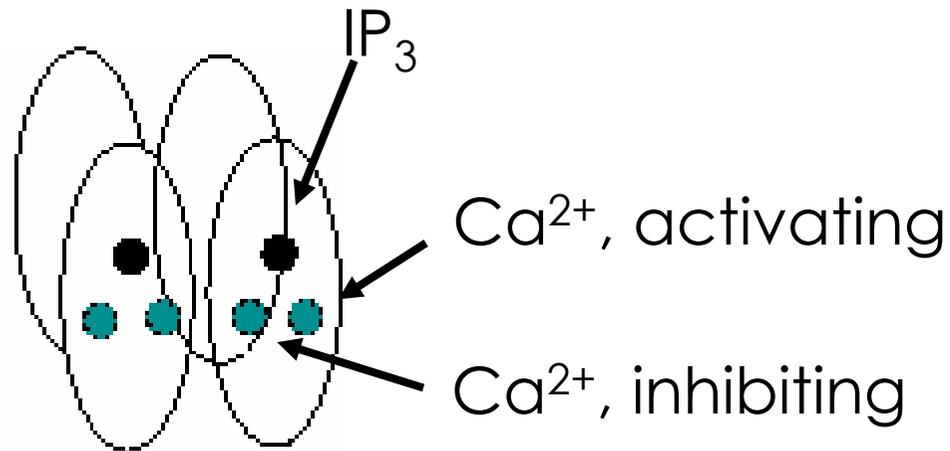
cytosol



Puffs and waves in the stochastic regime
(I. Parker, UC Irvine)

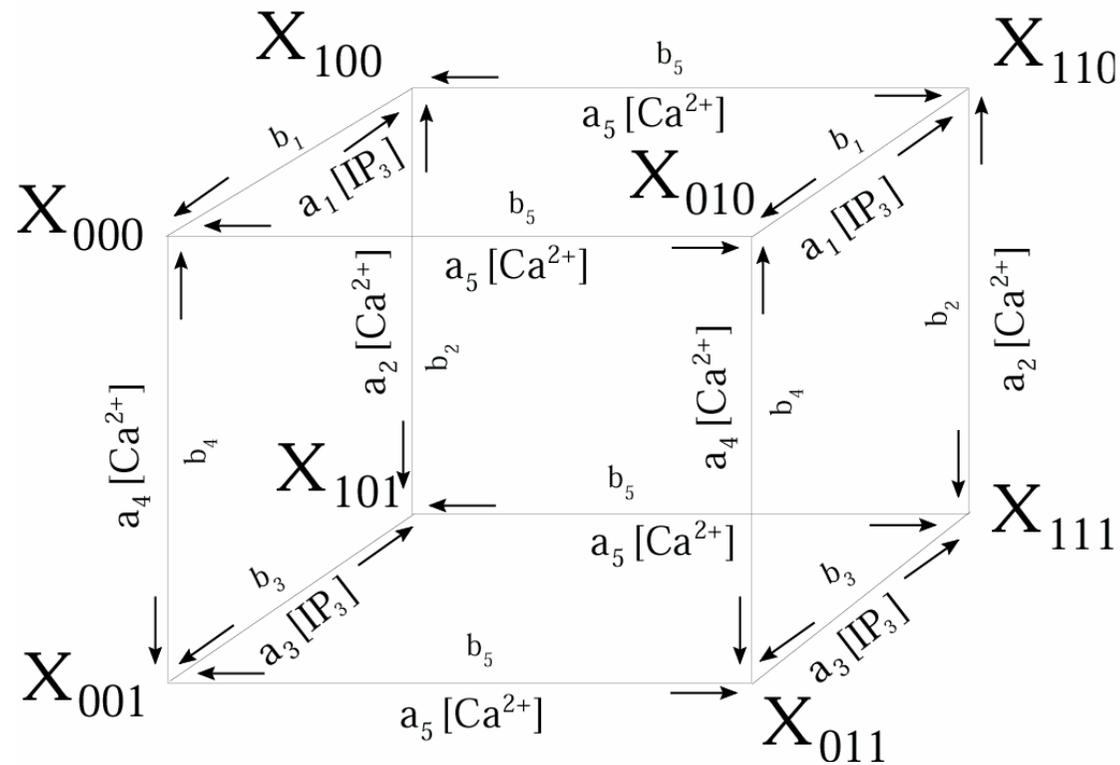
II. Channel dynamics

- Channels are sensitive to IP_3 and Ca^{2+} (calcium induced calcium release)
- Biphasic modulation, optimal response for $[Ca^{2+}] = 300nM$
- De Young-Keizer model: a channel has four subunits



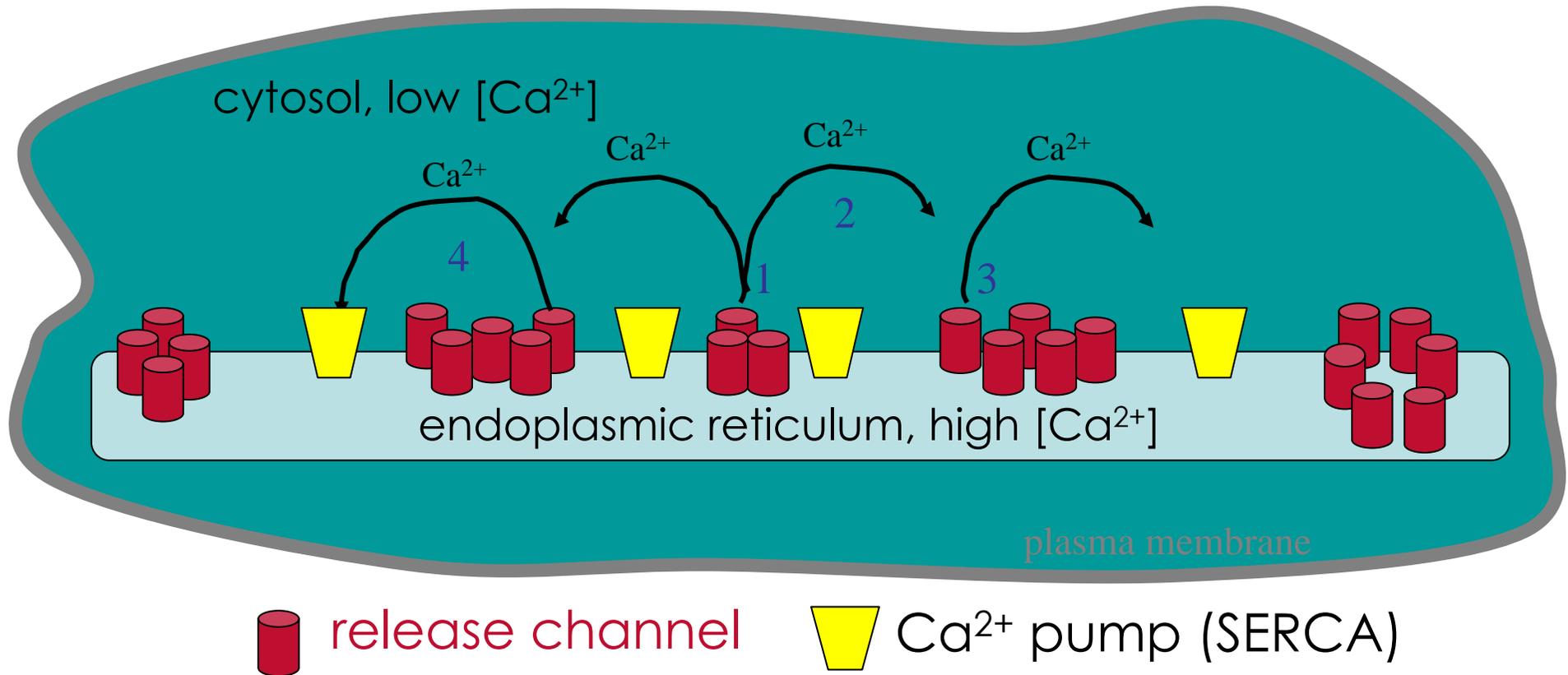
- Each subunit with 8 states.
- Transition rates depend on $[IP_3]$ and local Ca^{2+} concentration.

Subunit dynamics



A **channel opens** if at least three of the four subunits are activated, i.e. each subunit has:

- ▶ IP_3 bound
- ▶ activating Ca^{2+} bound
- ▶ inhibiting Ca^{2+} not bound

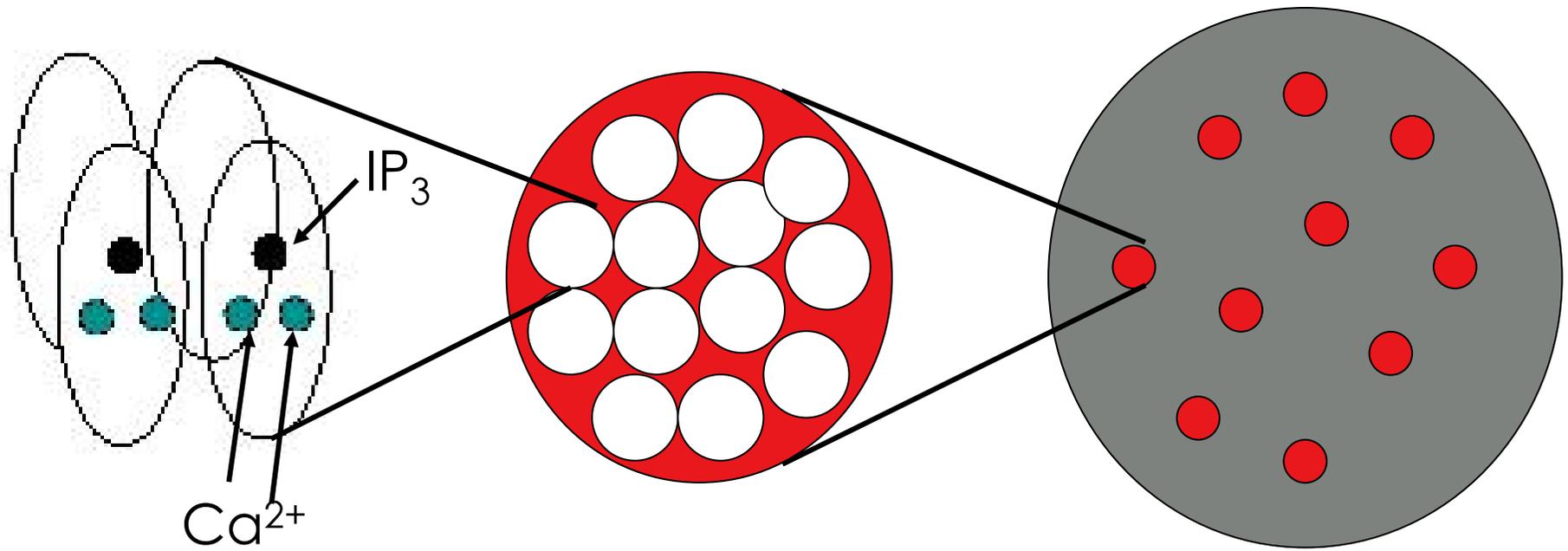


- 1 channel opens, releases Ca^{2+} from the ER into the cytosol
- 2 Ca^{2+} diffuses to neighboring channels
- 3 increase of Ca^{2+} favors opening: amplification,
very high Ca^{2+} decreases opening probability: inhibition
- 4 Ca^{2+} is pumped back from the cytosol into the ER

Channel

Cluster

Cell



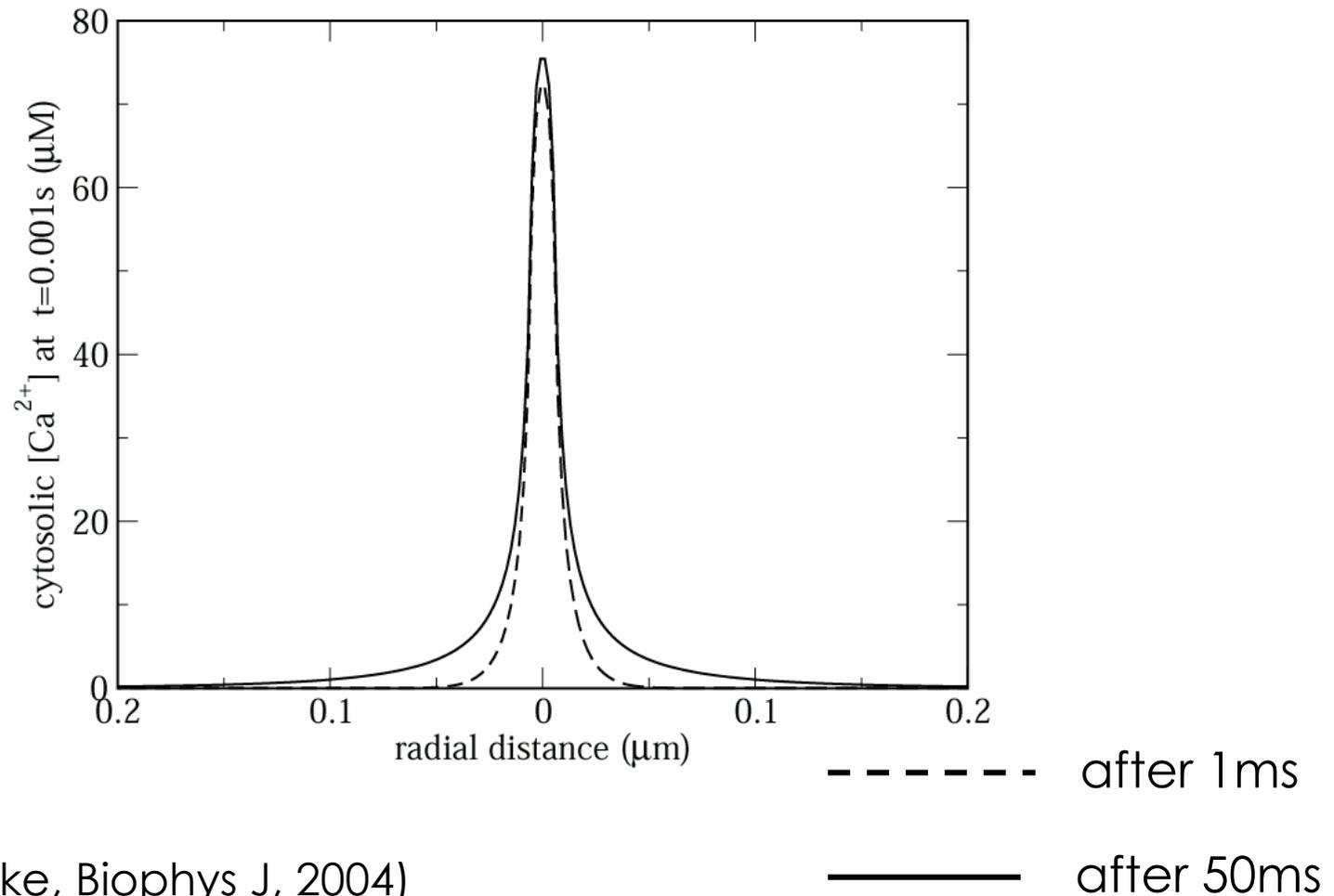
6nm

20-100nm

20-1000μm

III. Stochastic calcium oscillations

Radial cluster concentration profile
(3D simulation for a single channel)



(Thul and Falcke, Biophys J, 2004)

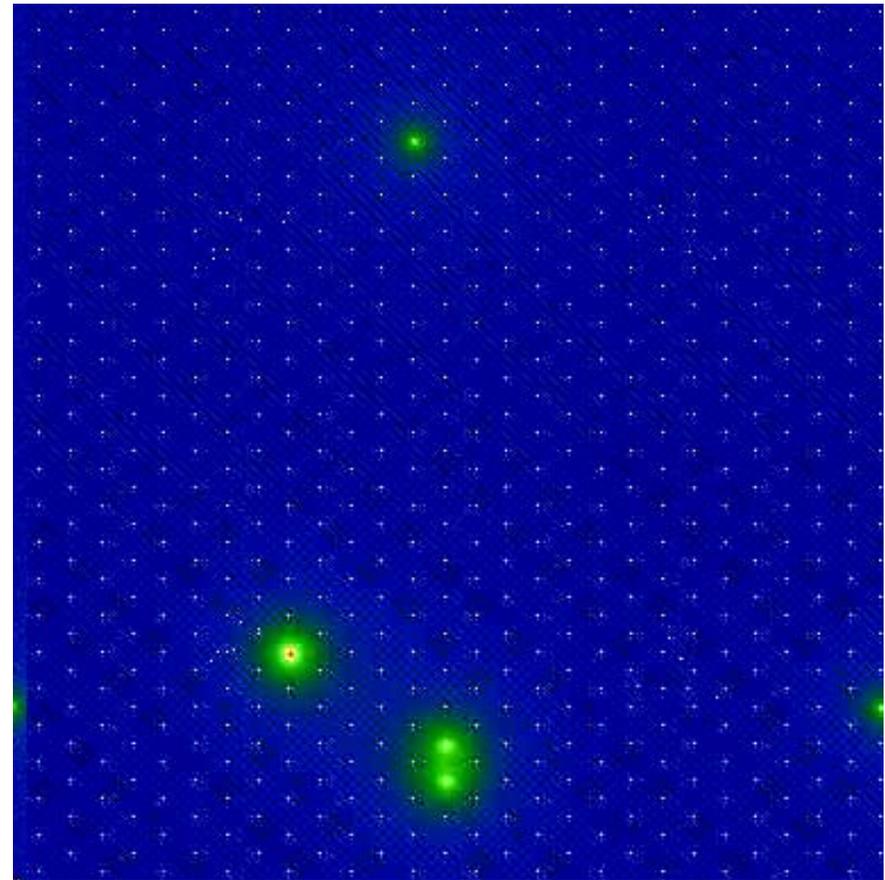
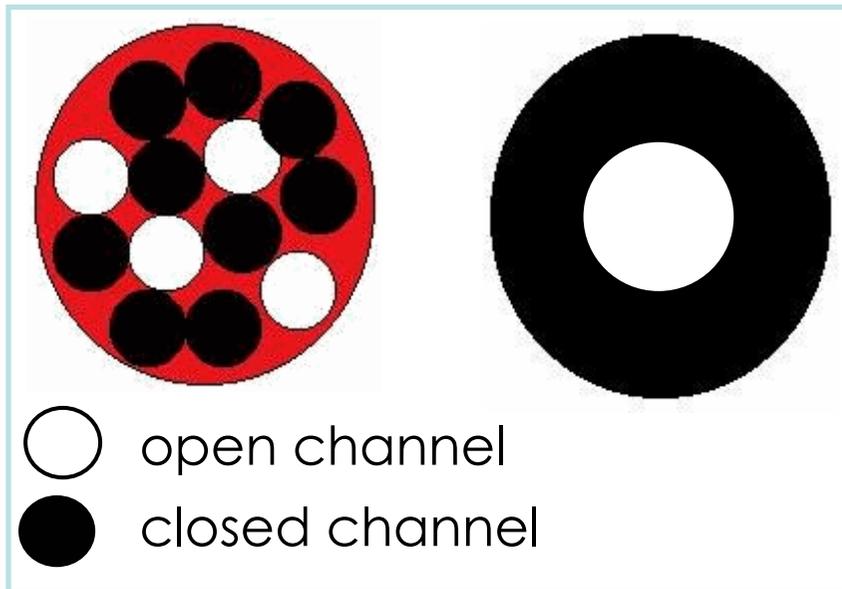
- ▶ Early models are based on very low (spatially averaged) Ca^{2+} concentrations.
- ▶ Adjusting the Ca^{2+} levels leads to an excitable local dynamics of subunit states. Ca^{2+} oscillations are driven by fluctuations (Thul & Falcke 2004).
- ▶ For sufficiently strong coupling of clusters one finds nucleation and propagation of waves. This can be seen in purely stochastic simulations of channel transitions of coupled clusters.

Stochastic simulation of coupled clusters

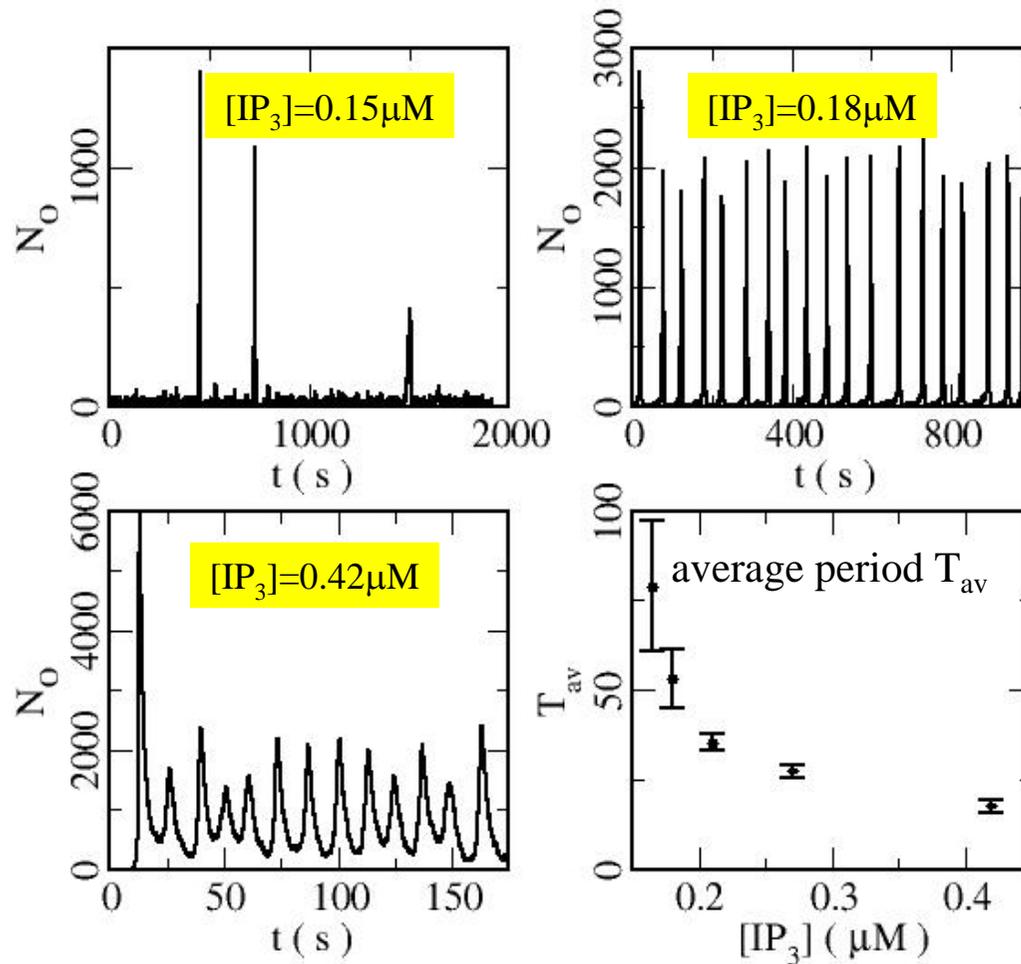
Approximations:

(Falcke, Biophys. J. 2003)

Steady-state approximation
for calcium transport and
diffusion



Oscillation characteristics in dependence on $[IP_3]$



- ▶ Period and its variance increase with decreasing $[IP_3]$!
- ▶ This can be understood from the smaller number of available channels for decreased $[IP_3]$.
- ▶ It agrees well with experimental observations (Marchant & Parker, EMBO J 2001).

V. Hybrid stochastic and deterministic simulations

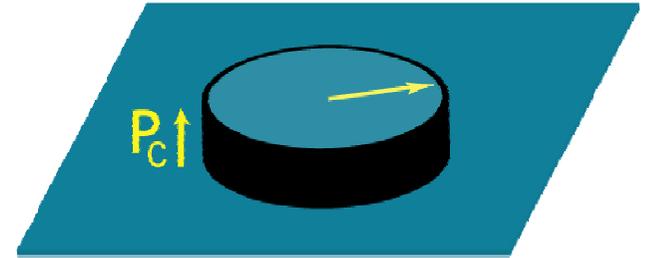
- ▶ Delay of diffusion, channels and pumps is needed for a correct simulation of cluster coupling and waves.
- ▶ Diffusion and reactions of Ca^{2+} and buffers are modelled with a deterministic reaction-diffusion equation.
- ▶ Coupling of deterministic processes and stochastic channel reactions necessitates a hybrid scheme.

Deterministic equations in two dimensions

$$c = [\text{Ca}^{2+}]_{\text{cyt}}$$

$$E = [\text{Ca}^{2+}]_{\text{ER}}$$

b_i, g_i – concentrations of buffer-bound Ca^{2+}



$$\frac{\partial c}{\partial t} = D_C \Delta c + (P_l + P_C(r))(E - c) - P_p \frac{c^2}{k_d^2 + c^2} + \sum_{i=1}^F B_i(c, b_i)$$

$$\frac{\partial E}{\partial t} = D_E \Delta E - \gamma \left[(P_l + P_C(r))(E - c) - P_p \frac{c^2}{k_d^2 + c^2} \right] + \sum_{i=1}^G G_i(E, g_i)$$

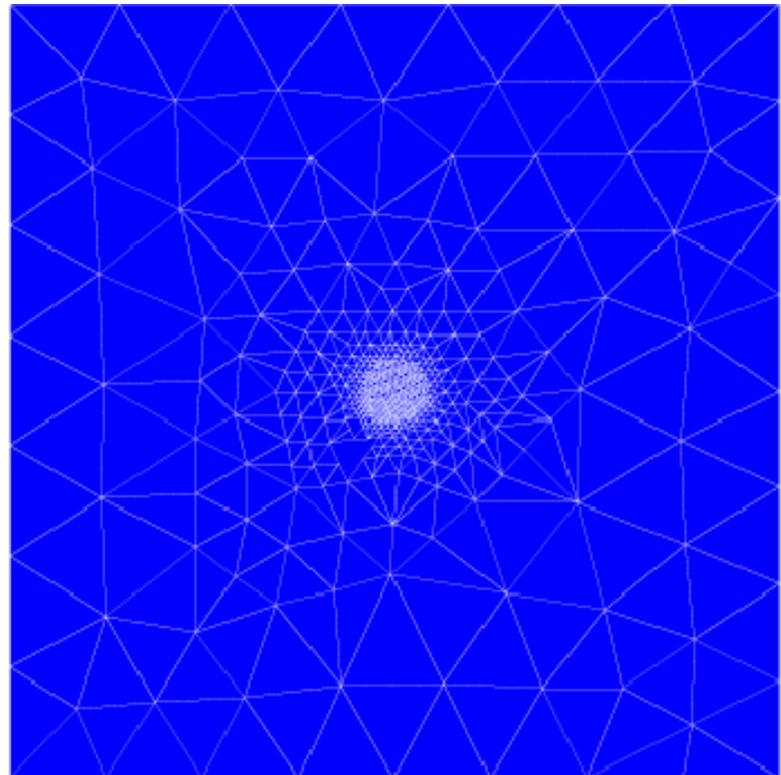
$$\frac{\partial b_i}{\partial t} = D_{b_i} \Delta b_i + k_{b,i}^+ (B_T - b_i)c - k_{b,i}^- b_i = D_{b_i} \Delta b_i - B_i(c, b_i)$$

$$\frac{\partial g_i}{\partial t} = D_{g_i} \Delta g_i + k_{g,i}^+ (G_T - g_i)E - k_{g,i}^- g_i = D_{g_i} \Delta g_i - G_i(E, g_i)$$

Implementation (deterministic part)

- ▶ UG software (Universität Heidelberg)
- ▶ Finite elements in 2D and 3D
- ▶ Mesh reflects the highly localized concentrations

(per cluster: $4\mu\text{m} \times 4\mu\text{m}$,
~150 nodes, 5...500nm)



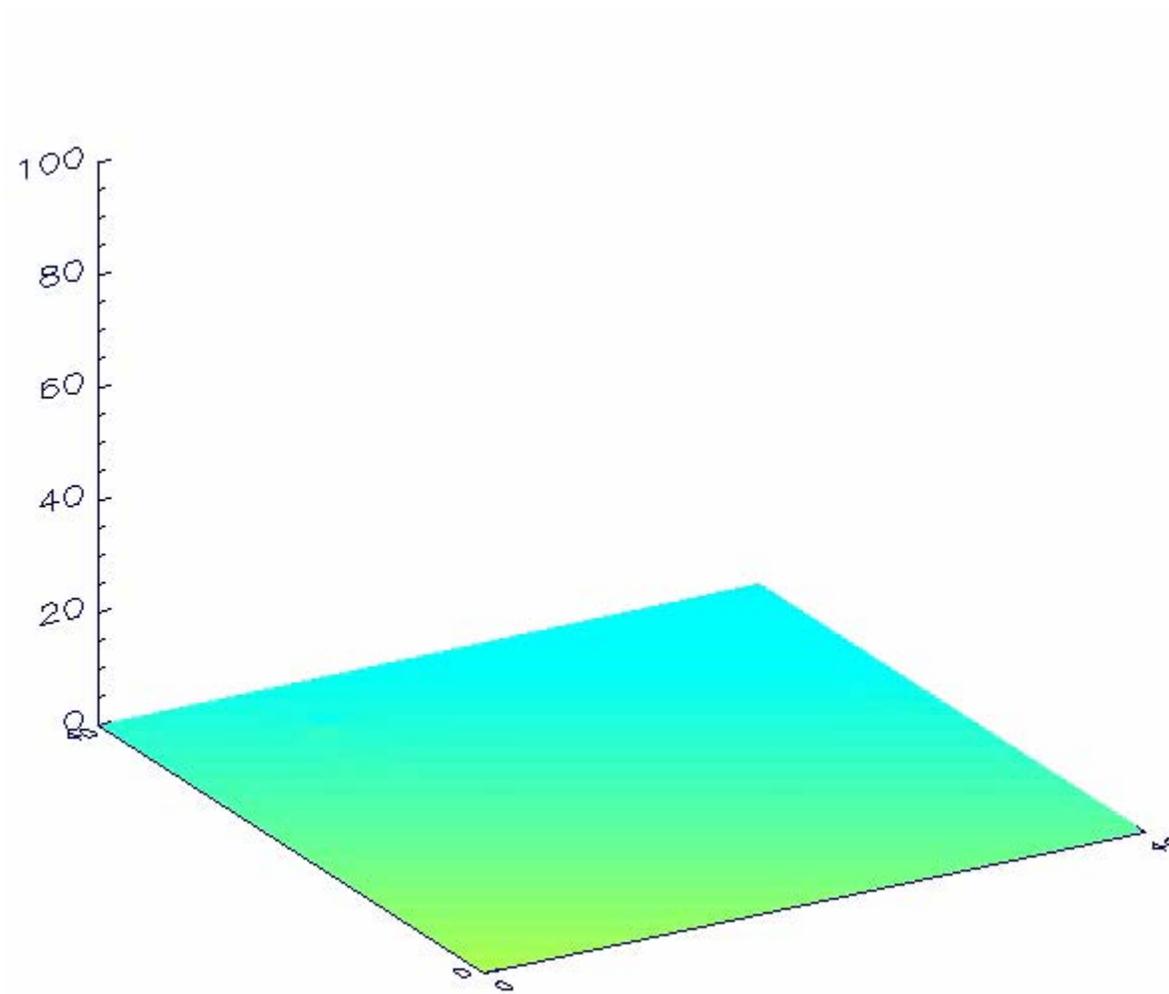
Stochastic scheme

- ▶ The probability of reaction i is given by the propensity a_i . The common Gillespie algorithm determines the time of the next reaction by using an exponential random number ξ : $\Delta t = \xi / \sum a_i(X_1, \dots)$
- ▶ Here the propensities depend on the deterministic dynamics and can change fast due to channel openings. The correct method is to integrate the propensities along with the deterministic dynamics (Alfonsi et al. 2005):

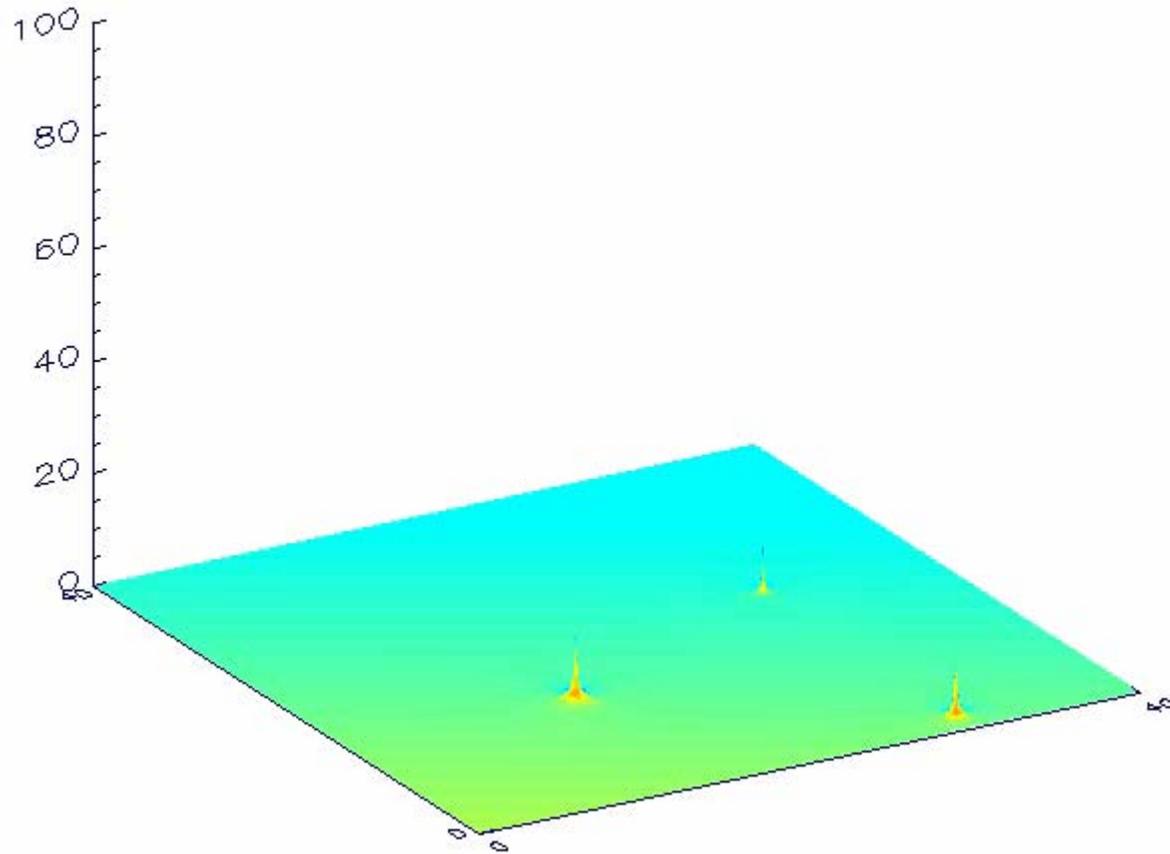
$$\frac{dc}{dt} = \Delta c + f(c, X_1, \dots), \quad \frac{dg}{dt} = \sum_i a_i(c, X_1, \dots)$$

- ▶ The stochastic event occurs if $g(t)$ approaches a value N : $g(t) = N$. N is updated after the event:
 $N := N + \xi$

Simulation in a $(40\mu\text{m})^2$ domain with 100 clusters, $[\text{IP}_3]=0.75\mu\text{M}$, $B_m=1\mu\text{M}$

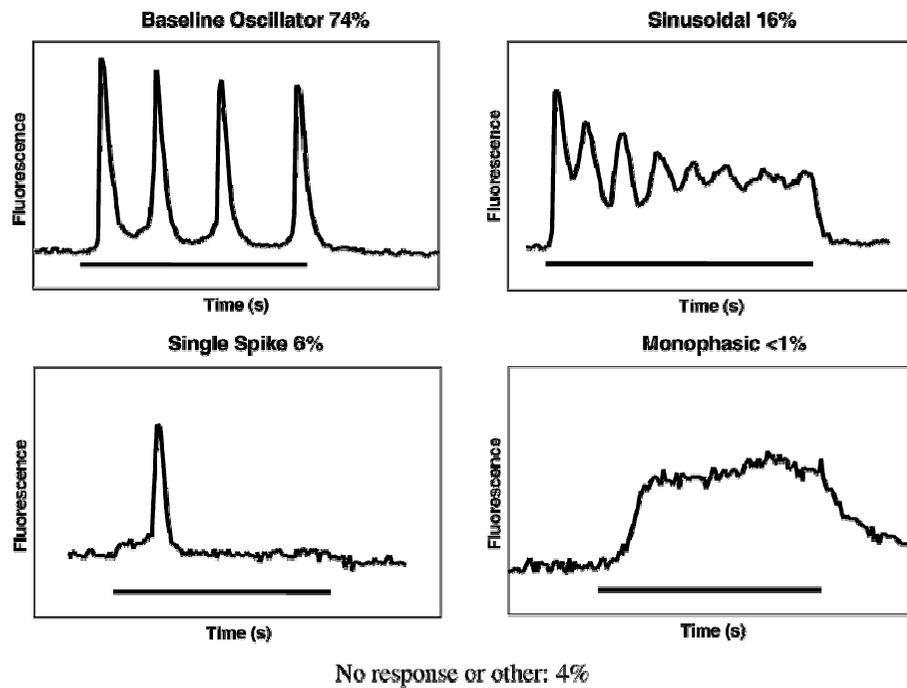


$$B_m = 100 \mu\text{M}$$

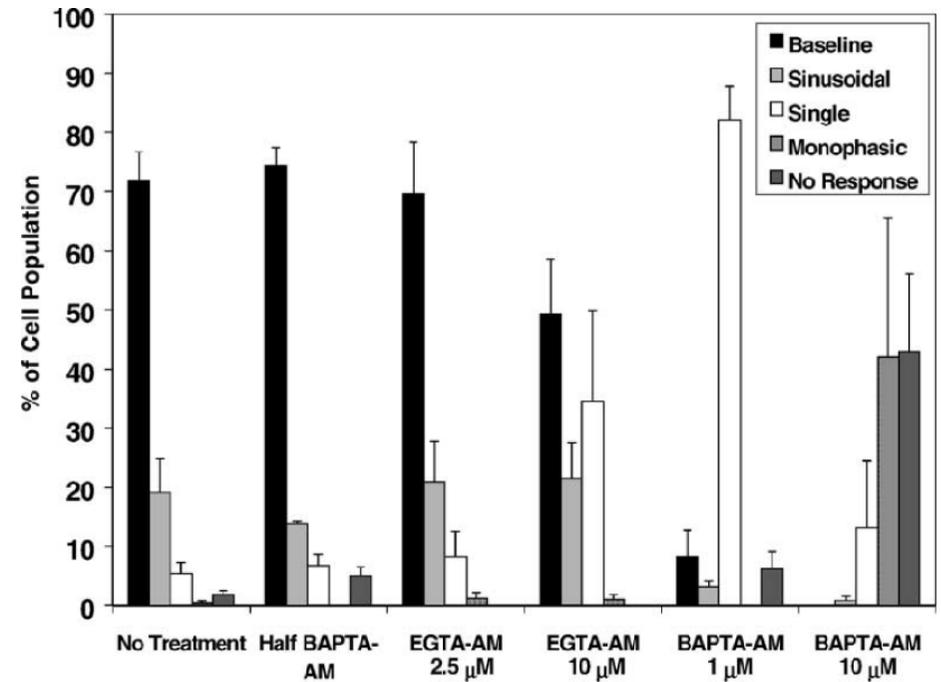


Strong localization of Ca^{2+} , small $[\text{Ca}^{2+}]$ at adjacent clusters.
No global oscillations, but: abortive waves

Effects of buffers on calcium oscillations in experiments

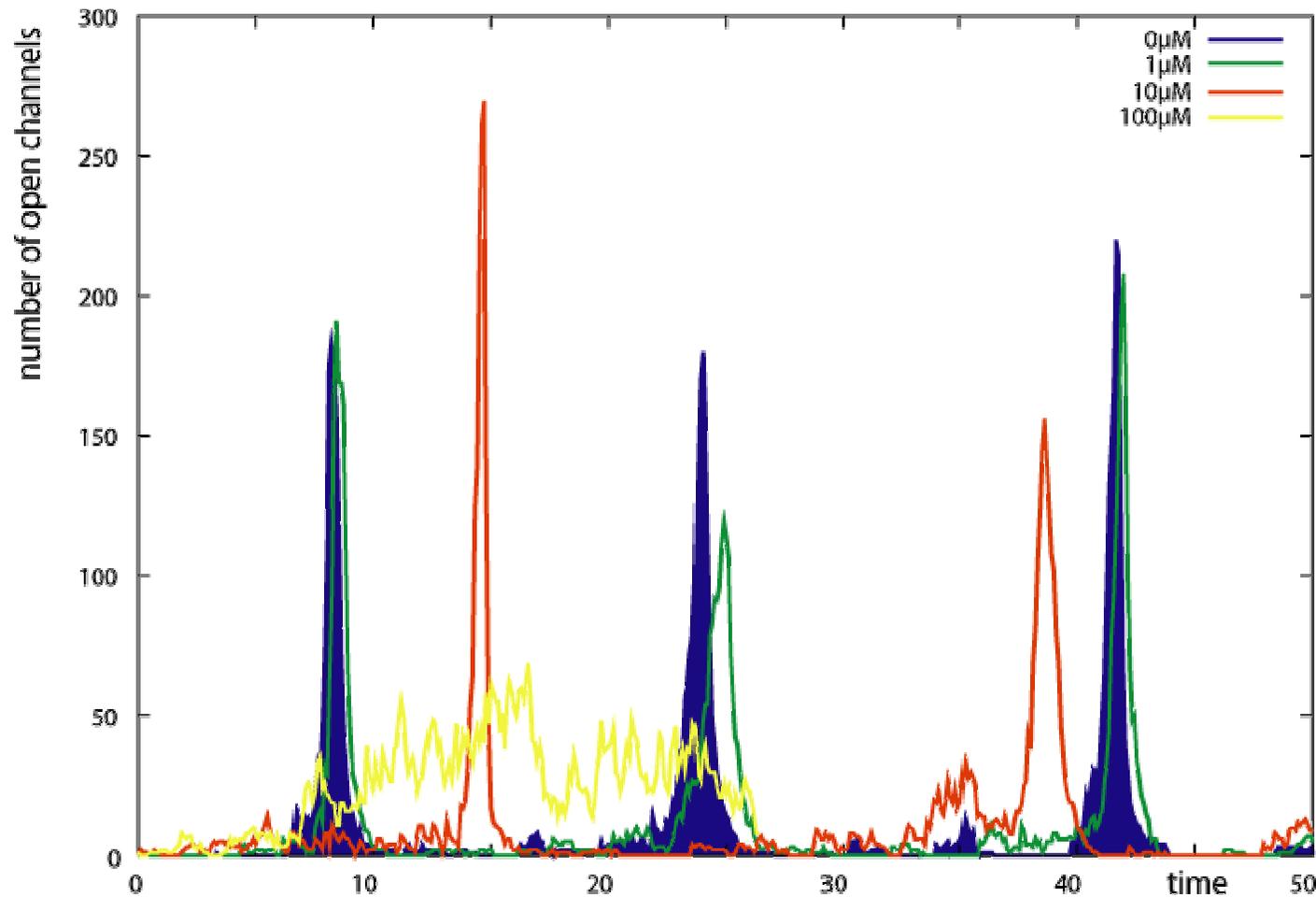


Without additional buffer

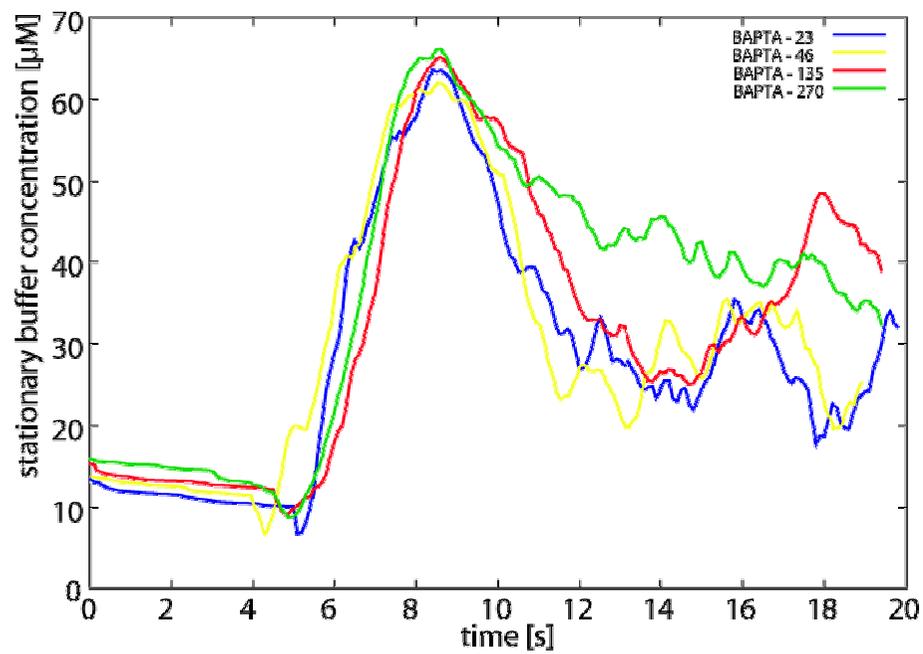


Additional buffer

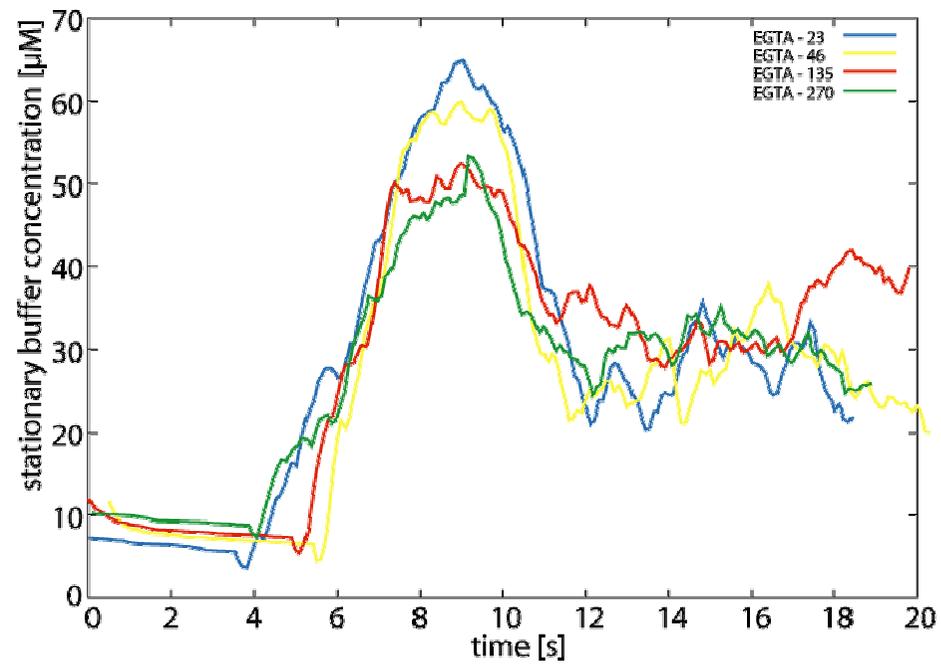
(Rintoul and Baimbridge, Cell Calcium 2003)



- ▶ For increased fast, mobile buffer concentration, the period of oscillations increases.
- ▶ For very large buffer concentration a non-oscillating state of high activity exists



BAPTA – fast kinetics



EGTA – slow kinetics

Summary

- ▶ We have introduced a hybrid method to efficiently simulate a new model of intracellular calcium dynamics with realistic localization and stochastic properties. The model shows puffs and global oscillations.
- ▶ Simulations with fast buffer show increased periods and suppression of oscillation in accordance with experiments. This loss of synchronization coincides with steeper Ca gradients and smaller cluster coupling.
- ▶ Outlook: 3D simulations of full channel dynamics.