EMBL-EBI

Simulations in Systems Neurobiology

EMBL-EBI

European Bioinformatics Institute

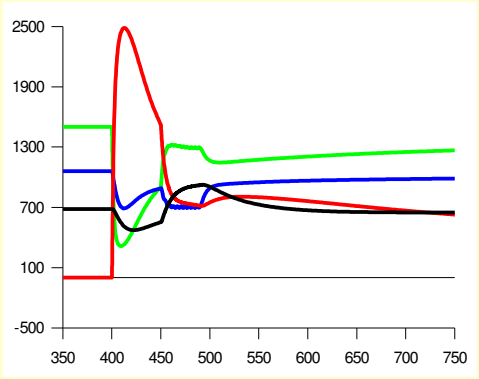
British outstation of the European Molecular Biology Laboratory

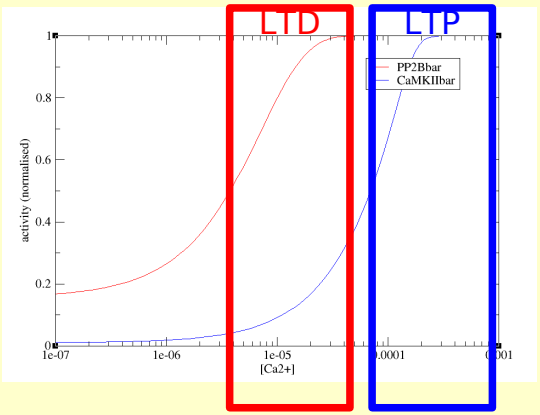
- Databases
  - Sequences, structures
  - Transcriptomics, Proteomics pathways, models
  - Controlled vocabularies and dictionaries

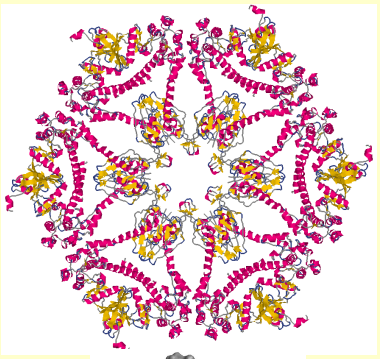
- Research groups
  - Structural Genomics (Thornton)
  - Molecular Evolution (Goldman)
  - Text-Mining (Rebholz-Schumman)
  - Computational Systems Biology (Le Novère)
  - Statistical array analysis (Huber)
  - Genomic analysis of regulatory systems (Luscombe)
  - Systems Biology of ES cells (Bertone)
  - Bioinformatics of microRNA (Enright)

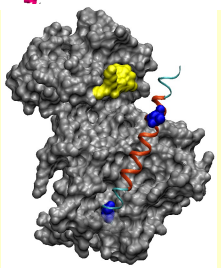
Group themes and projects

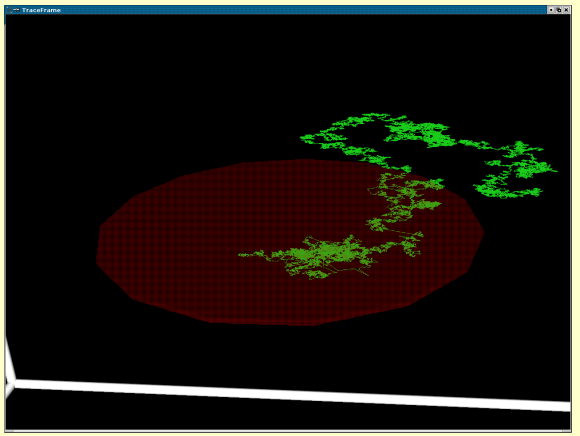
Computational Neurobiology











Systems Biology

SBML

SBGN
Systems Biology Graphical Notation

SBO

TEDDY

KISAO

e-MeP

Ligand-Gated Ion Channel database

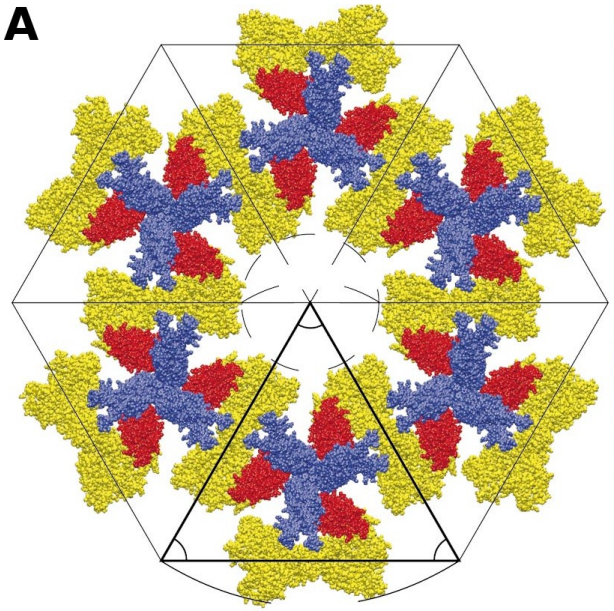
MIRIAM

MIASE

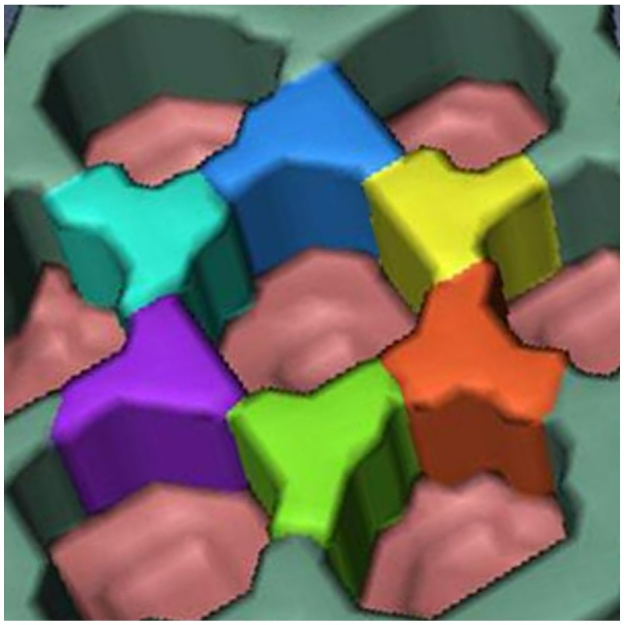
BioModels

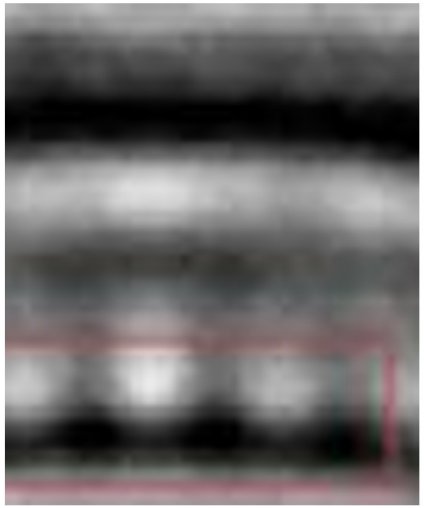
Computational modeling works!

Shimizu et al (2000) *Nat Cell Biol*.



Briegel et al (2008) *Mol Microbiol*.

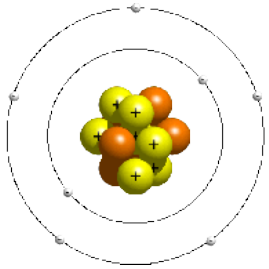


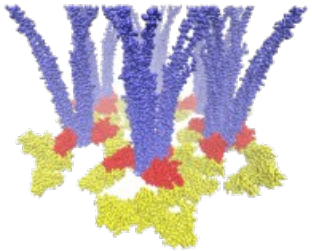


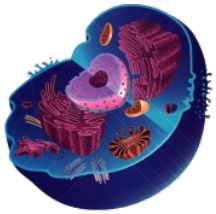
A multiscale problem

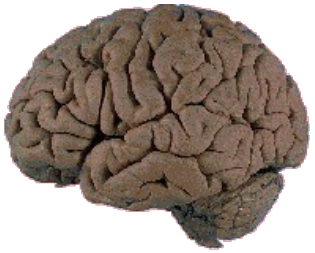
10^{-10} 10^{-8} 10^{-7} 10^{-5} 10^{-2} 10^{-0} m

spatial scale problem









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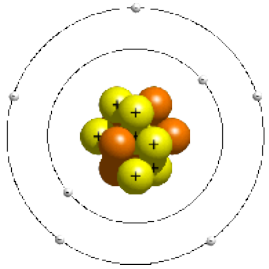
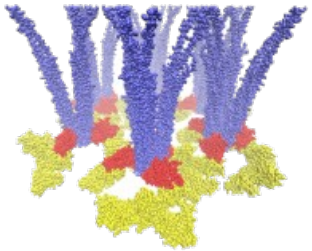
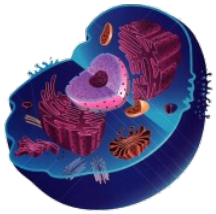
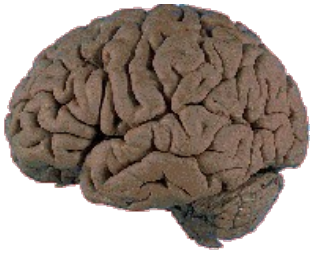


10^{-12} 10^{-6} 10^{-1} 10^{1} 10^{3} 10^{5} 10^{7} 10^{9} s

time scale problem

molecular dynamics
conformational transition
molecule diffusion
nerve signal
signalling cascade
gene regulation
circadian rhythm
cell cycle
reproduction
life cycle

A simulation problem

- Molecular dynamics: to simulate $\propto 10^{-12}$ s requires $\propto$ 1 s
- Particle diffusion: to simulate $\propto 10^{-6}$ s requires $\propto$ 1 s
- Stochastic chemical kinetics: to simulate $\propto$ 1 s requires $\propto$ 1 s
- Continuous ODE: to simulate $\propto 10^{3}$ s requires $\propto$ 1 s

⇒ **Very large stiffness: the speed of the whole simulation is determined by the quickest event**

A cell at atomic resolution?

1) The size of the problem

- Largest simulations so far: 1 millions atoms during 50 nsec (tobacco mosaic virus capside), 10000 atoms during 500 usec (>30 years CPU)
- E coli contains roughly 1 000 000 000 000 atoms
- Simulation of 1 sec would requires $\mathbf{10^{14}}$ more power
- => in one century if corrected Moore law stays valid

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2) Theoretical problems

- We don't know how to model secondary structure element creation, movement and destruction
- We don't know how to simulate global rearrangements
- We do not know how to take into account adequately prot-prot interactions

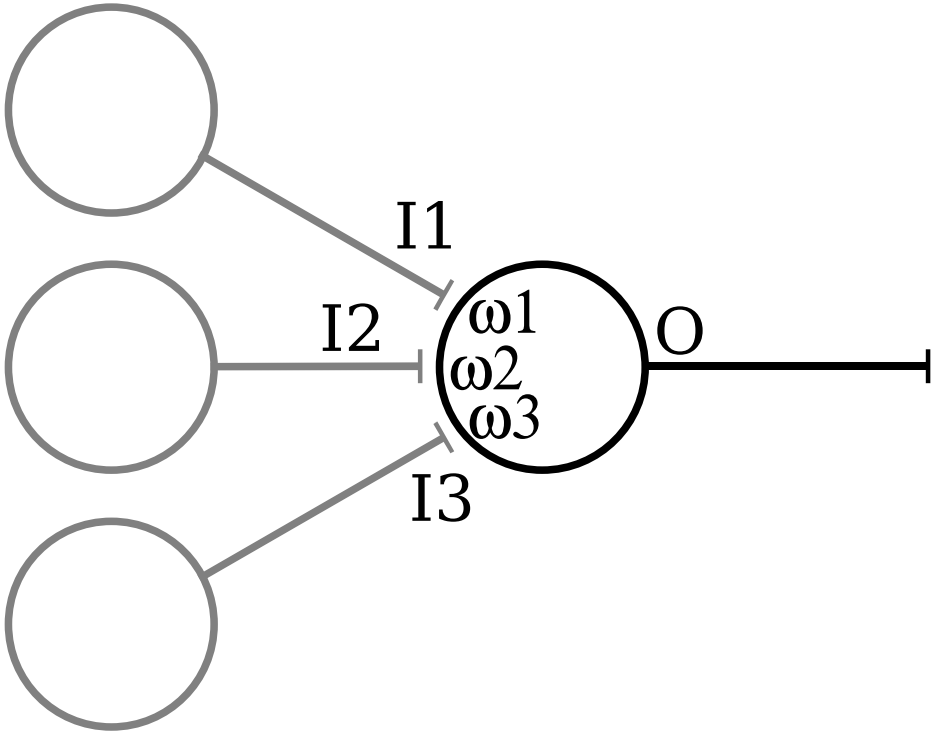
A cell at atomic resolution?

LET'S FORGET THE BRUTE FORCE! THAT IS NOT LIKELY TO HAPPEN
(and if it does, the answers provided are likely to be irrelevant)

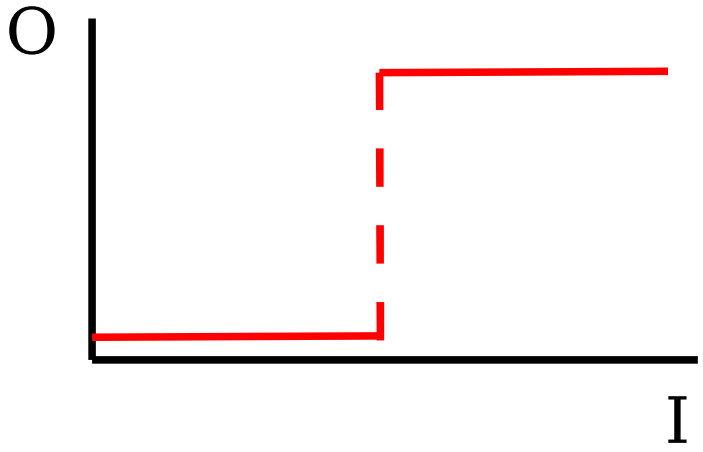
→ Pick the right scale for the right question

→ The mechanistic description of a level generates the phenomenologic description used in the higher level ...

Artificial neuron: theoretical

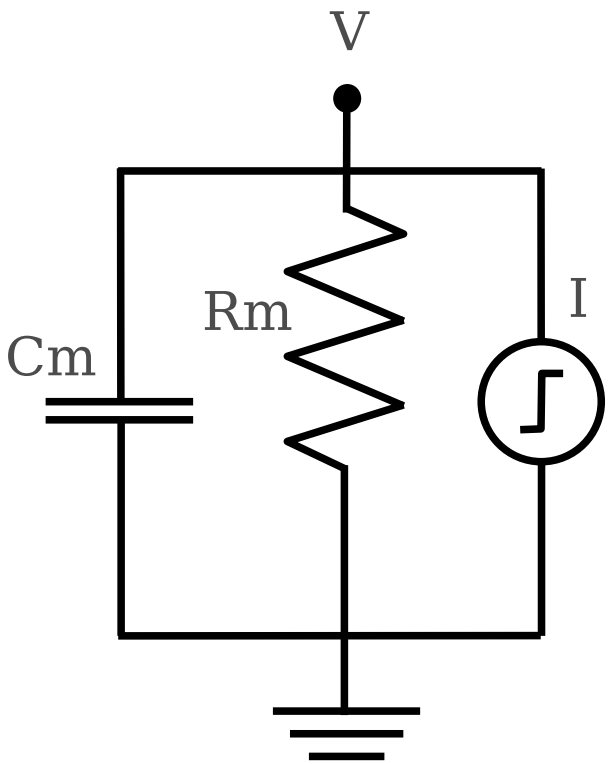


$$O = H\sum_i \omega_i I_i$$

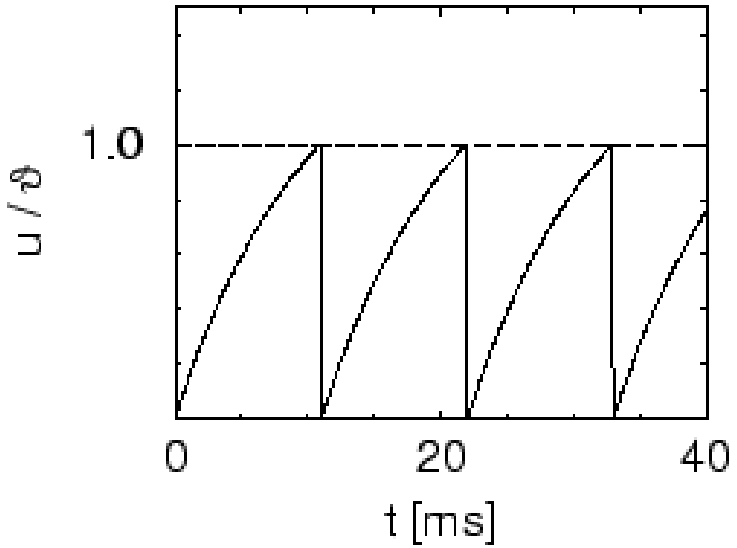


McCulloch, Pitts (1943) *Bull Math Biophys* 5: 115-133.

Leaky integrate and fire: phenomenological



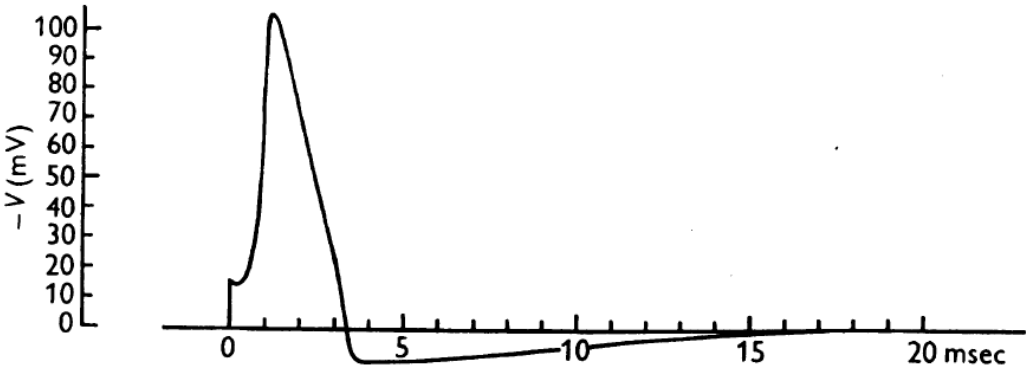
$$Cm\frac{dV}{dt} = -\frac{V}{Rm} + I$$

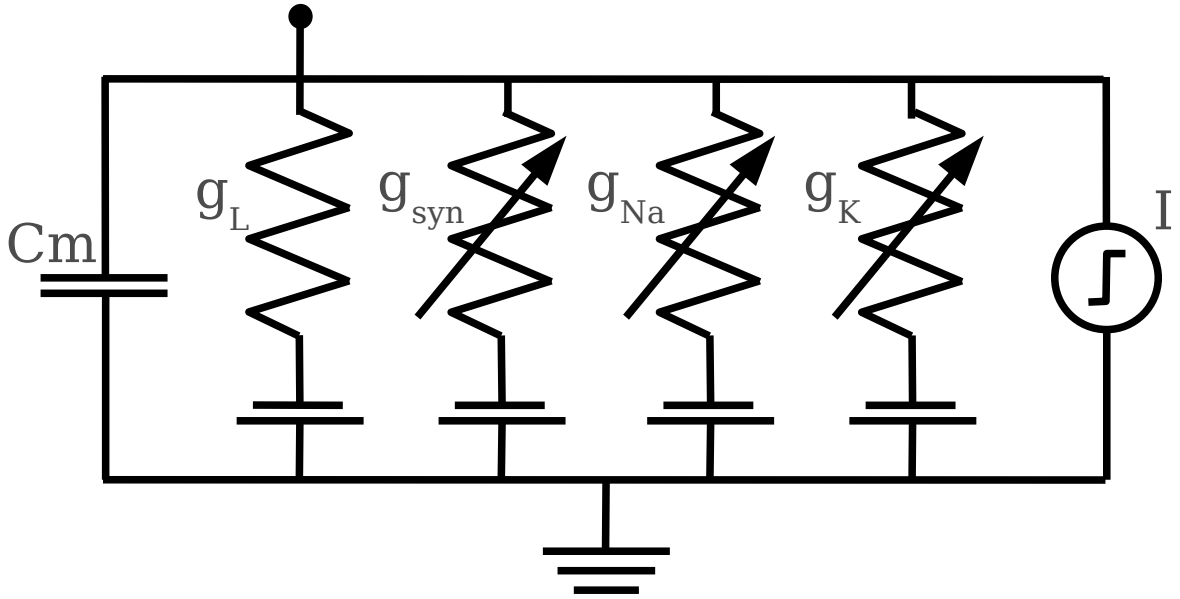


Lapicque (1907) *J Physiol Pathol Gen* 9: 620-635.

Conductance-based: mechanistic

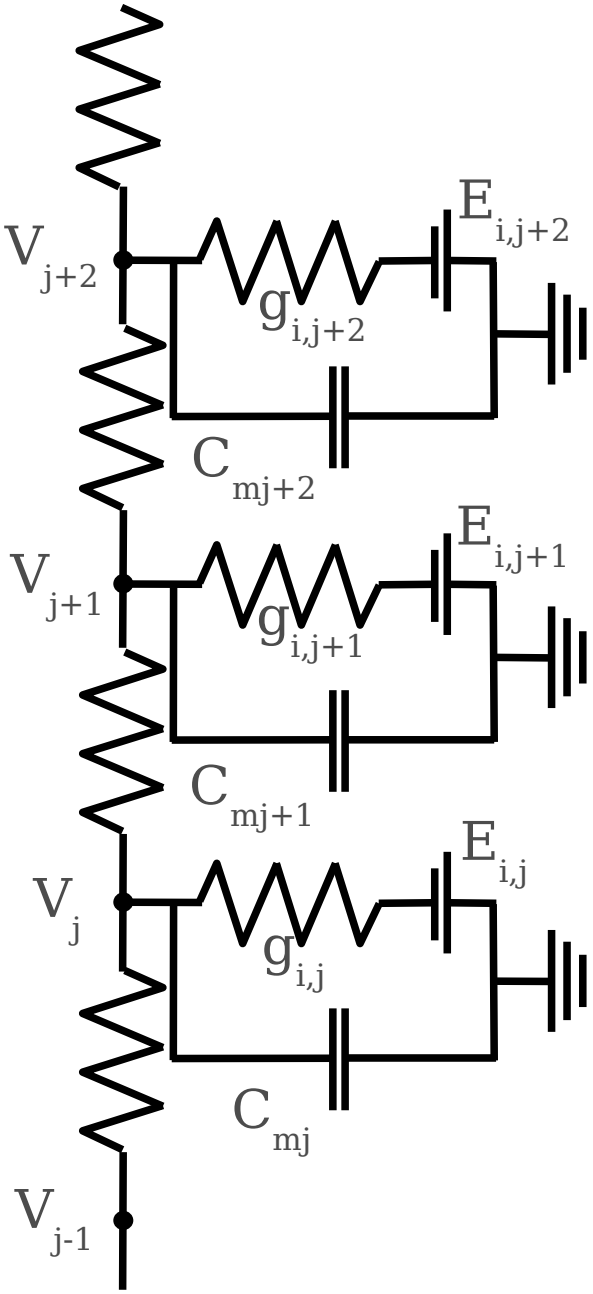
$$
\begin{aligned}
Cm\frac{dV}{dt} &= -g_L(V - E_L) - \bar{g}_{Na}m^3h(V_V - E_{Na}) - \bar{g}_K n^4(V - E_K) \\
\frac{dm}{dt} &= \alpha_m(V)(1 - m) - \beta_m(V)m \\
\frac{dh}{dt} &= \alpha_h(V)(1 - h) - \beta_h(V)h \\
\frac{dn}{dt} &= \alpha_n(V)(1 - n) - \beta_n(V)n
\end{aligned}
$$



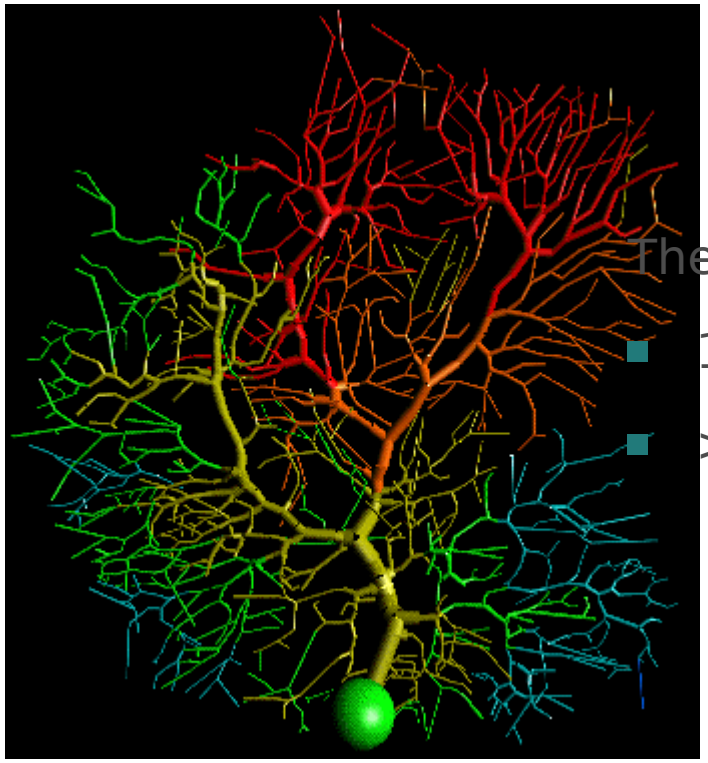


Hodgkin, Huxley (1953) *J Physiol* 117: 500-544

Cable approximation



Rall (1959) *Exp Neurol* 1: 491-527.



The Purkinje Neuron

- 1 Neuron
- > 3000 compartments

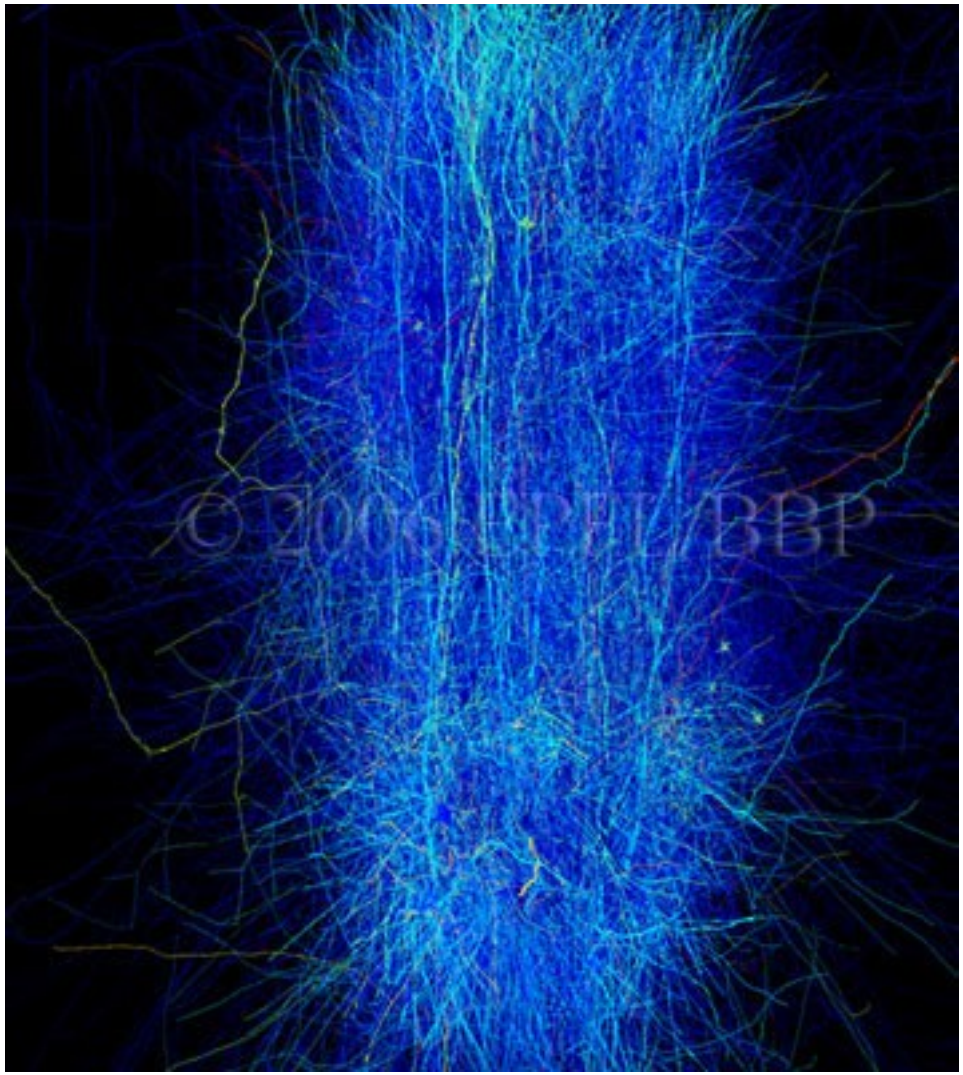
De Schutter (1994) *J Physiol* 71: 375-400.

$$Cm\frac{dV_j}{dt} = -\sum_i g_i j[V_j - E_i] + \sum_k \frac{V_k - V_j}{R_j k} + I$$

Functional assembly

- 10 000 Neurons
- ~100 compartments

The neocortical column of the blue-brain project

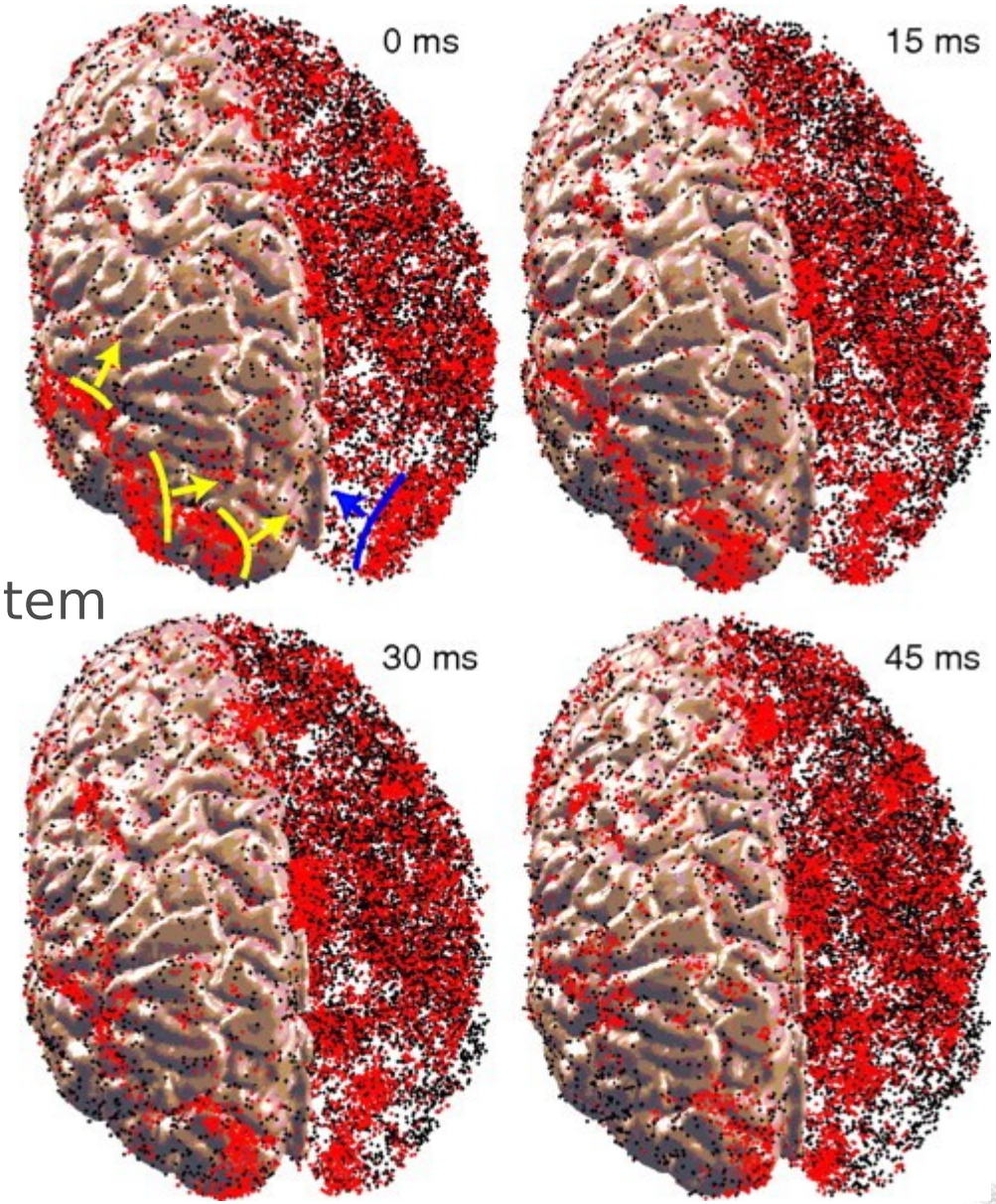


Markram (2006) *Nat Rev Neurosci* 7: 153-160.

A whole organ

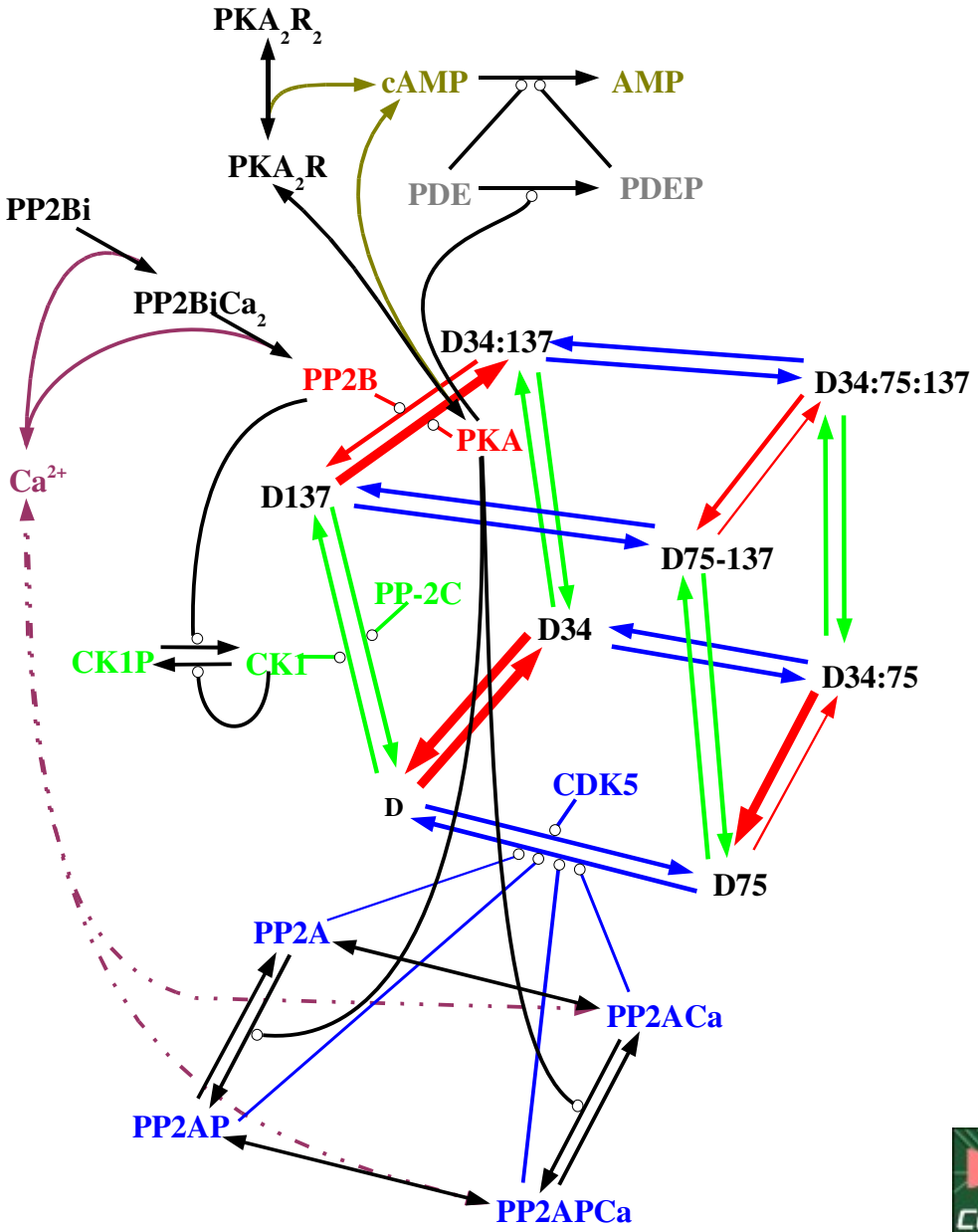
- 1 000 000 Neurons
- 10-50 compartments
- 1 000 000 000 synapses

The thalamo-cortical system

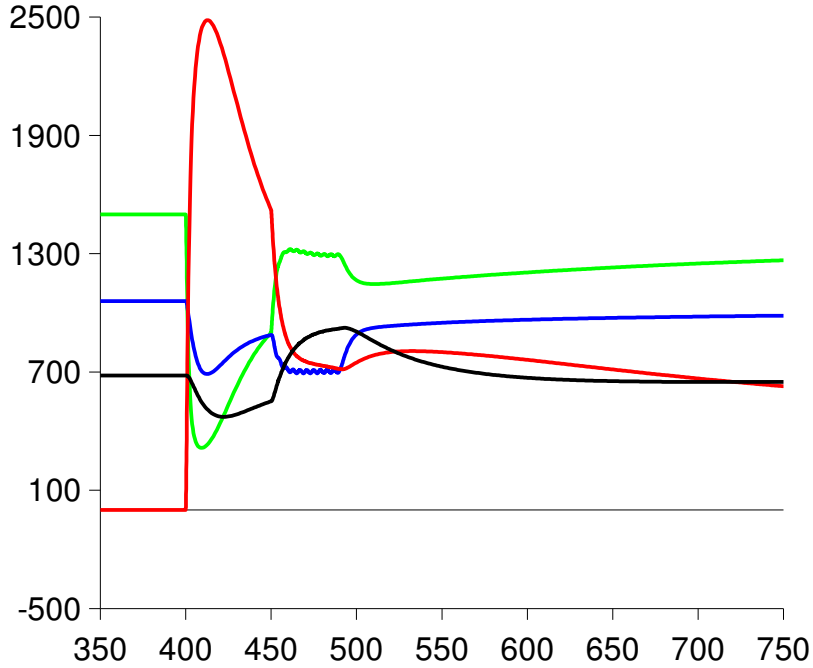


Izhikevich, Edelman (2008) *PNAS* 105: 3593-3598

Signalling pathways: ODEs



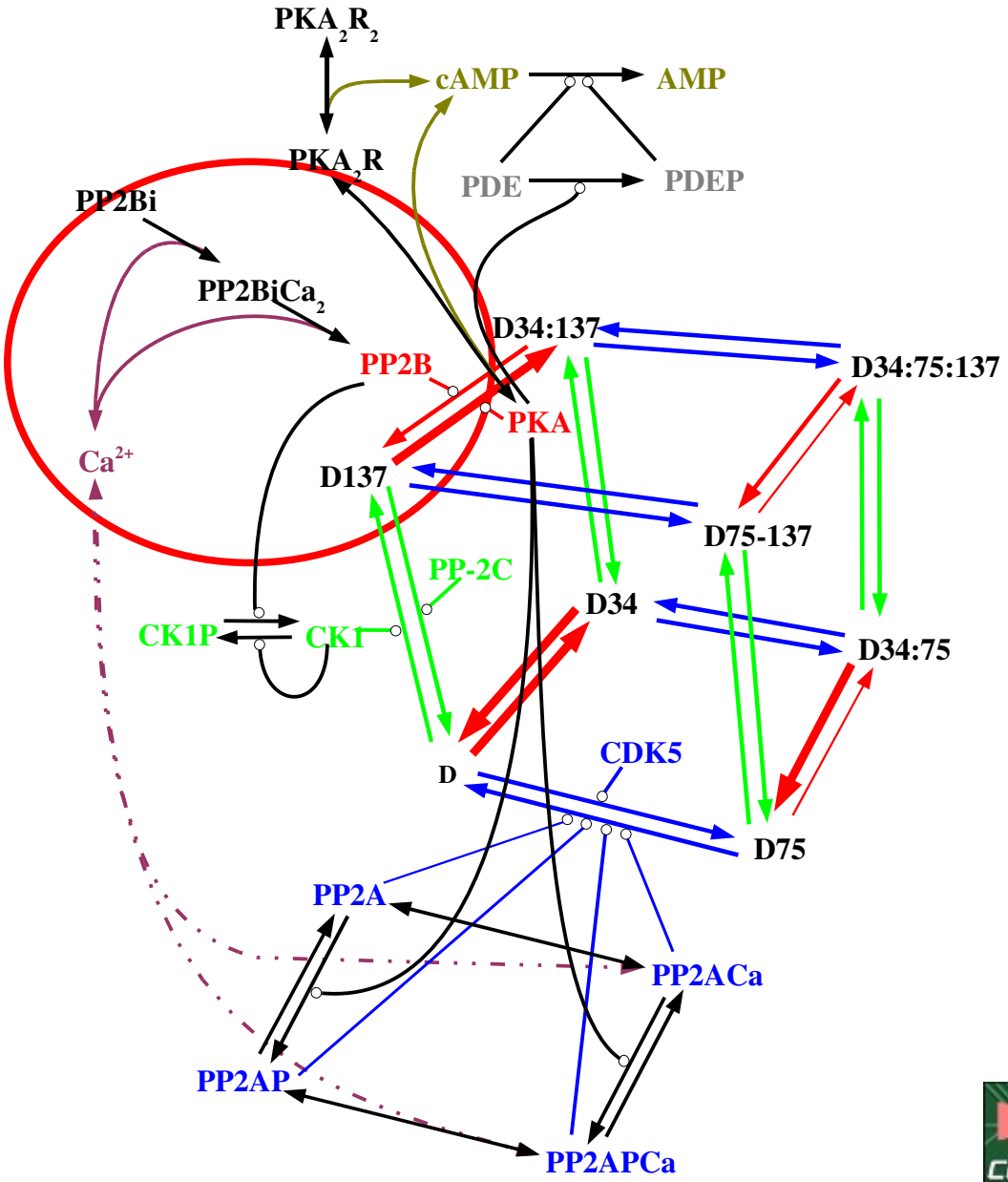
$$\frac{dX_i}{dt} = \sum_j n_{ij} f(X_0, X_1, ..., X_n)$$



Computational Neurobiology

Fernandez et al (2006)
PLoS Comp Biol 2: e176

Signalling pathways: ODEs



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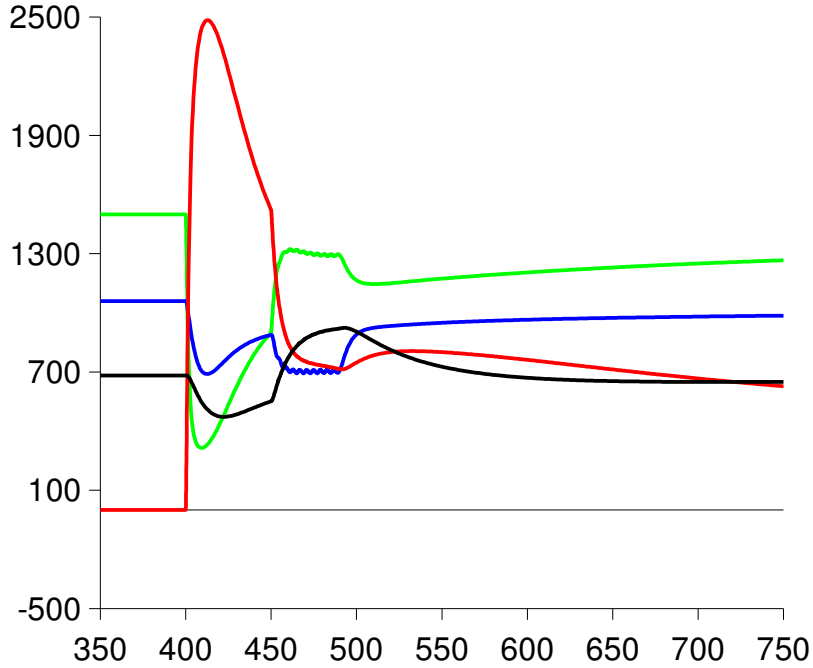
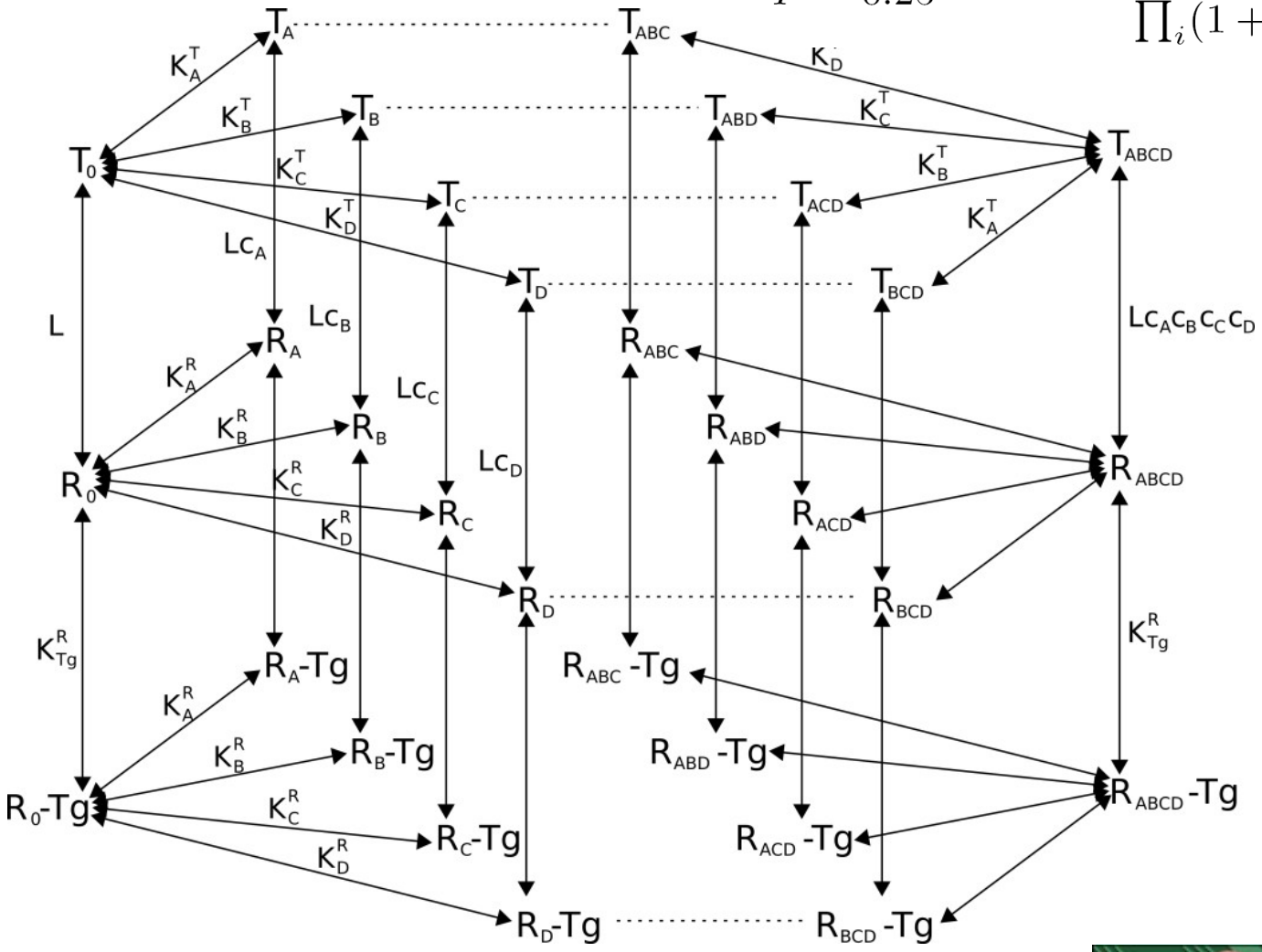


Computational Neurobiology

Fernandez et al (2006)
PLoS Comp Biol 2: e176

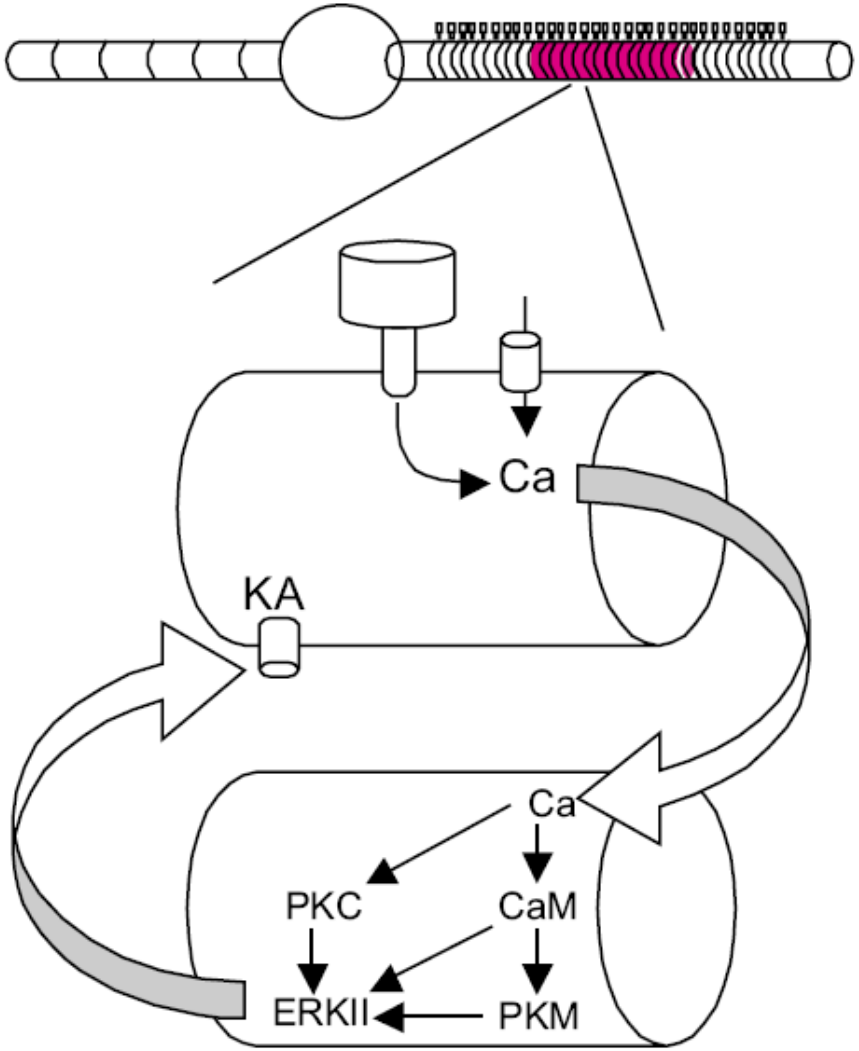
Biophysical models of signalling

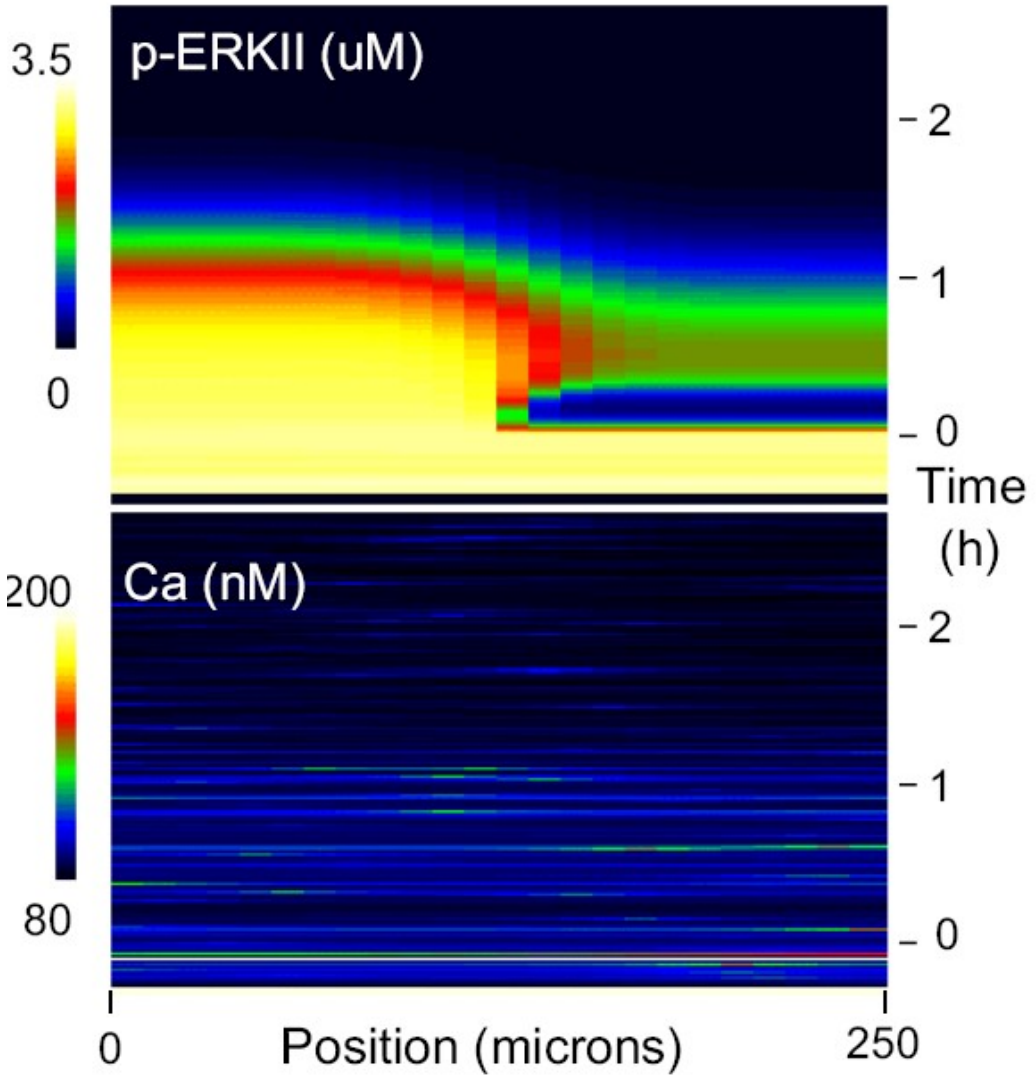
$$\bar{Y} = 0.25 \frac{\sum_i \left(\alpha_i \prod_j (1+\alpha_j)\right) + L \sum_i \left(c_i \alpha_i \prod_j (1+c_j \alpha_j)\right)}{\prod_i (1+\alpha_i) + L \prod_i (1+c_i \alpha_i)}$$



Stefan et al (2008)
PNAS, AOP 31 Jul

Signalling in multi-compartment models



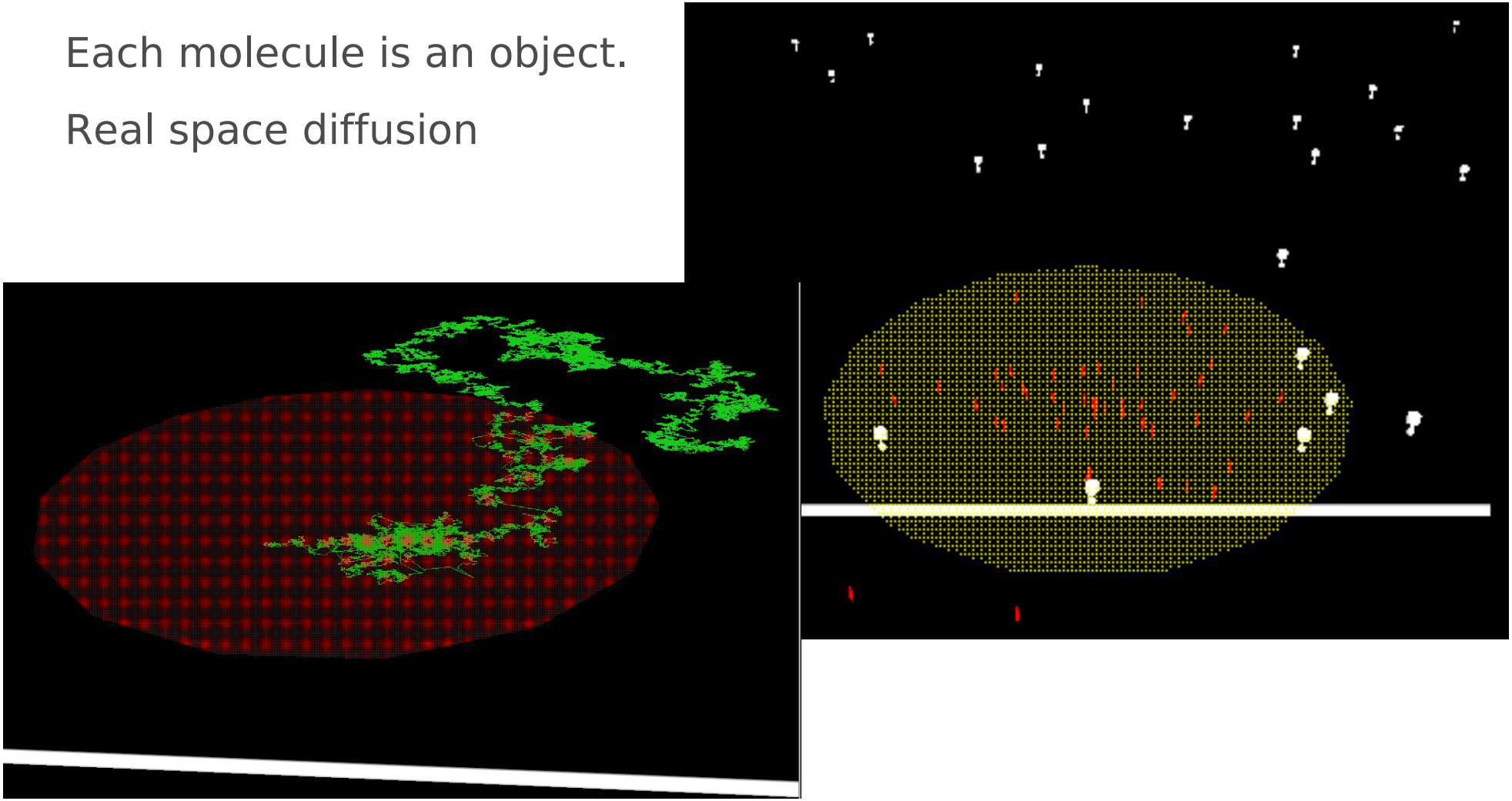


Upinder Bhalla (personal communication)

Agent-based models

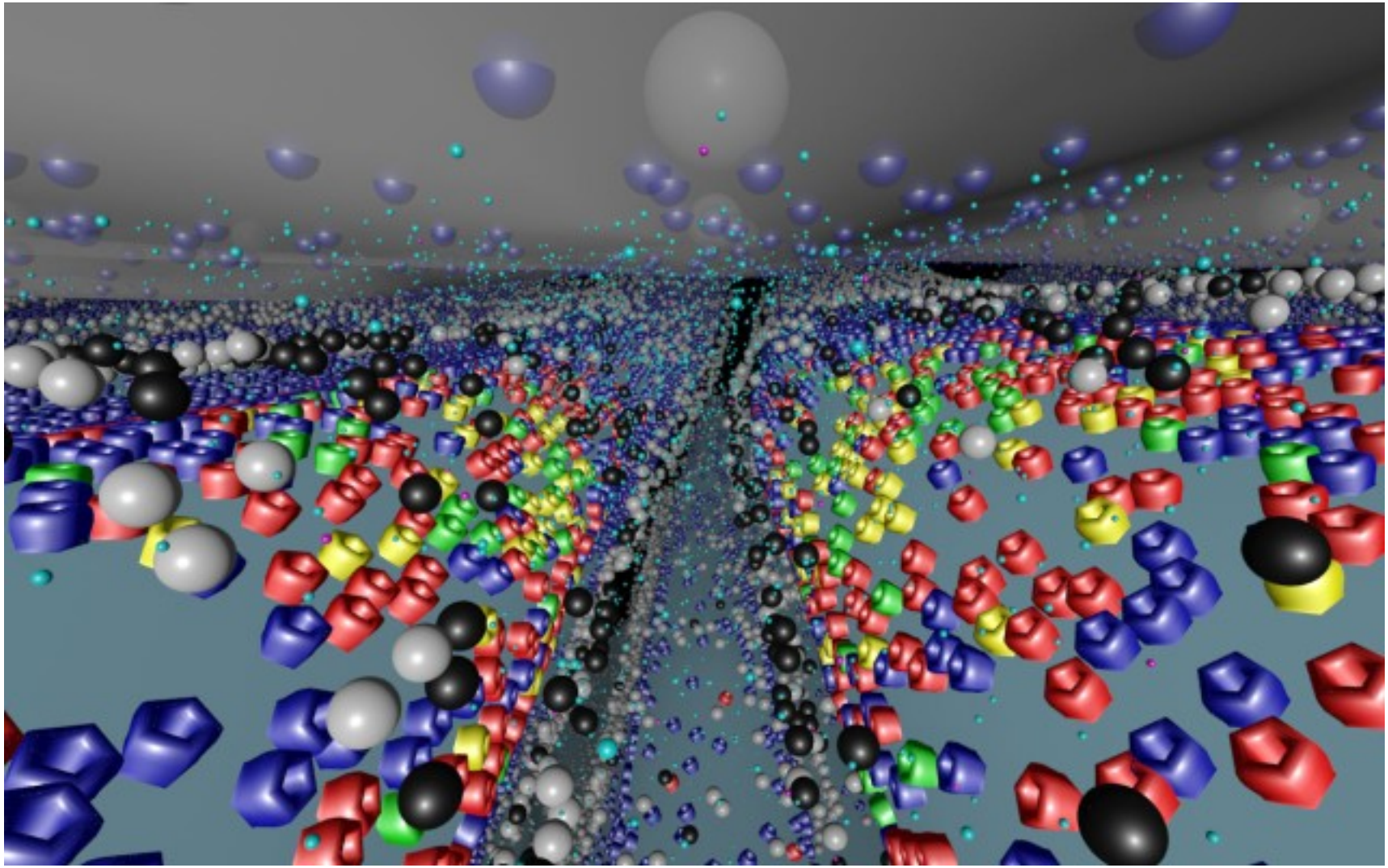
Each molecule is an object.

Real space diffusion



Computational Neurobiology

Tolle (2006)
Curr Bioinfo 1: 315-320



Cellular network

Molecular network

Electrical behaviour

Multi-compartment model

Biochemical processes

Neuronal system

Geometry and topology

Space and diffusion

Quantitative representation

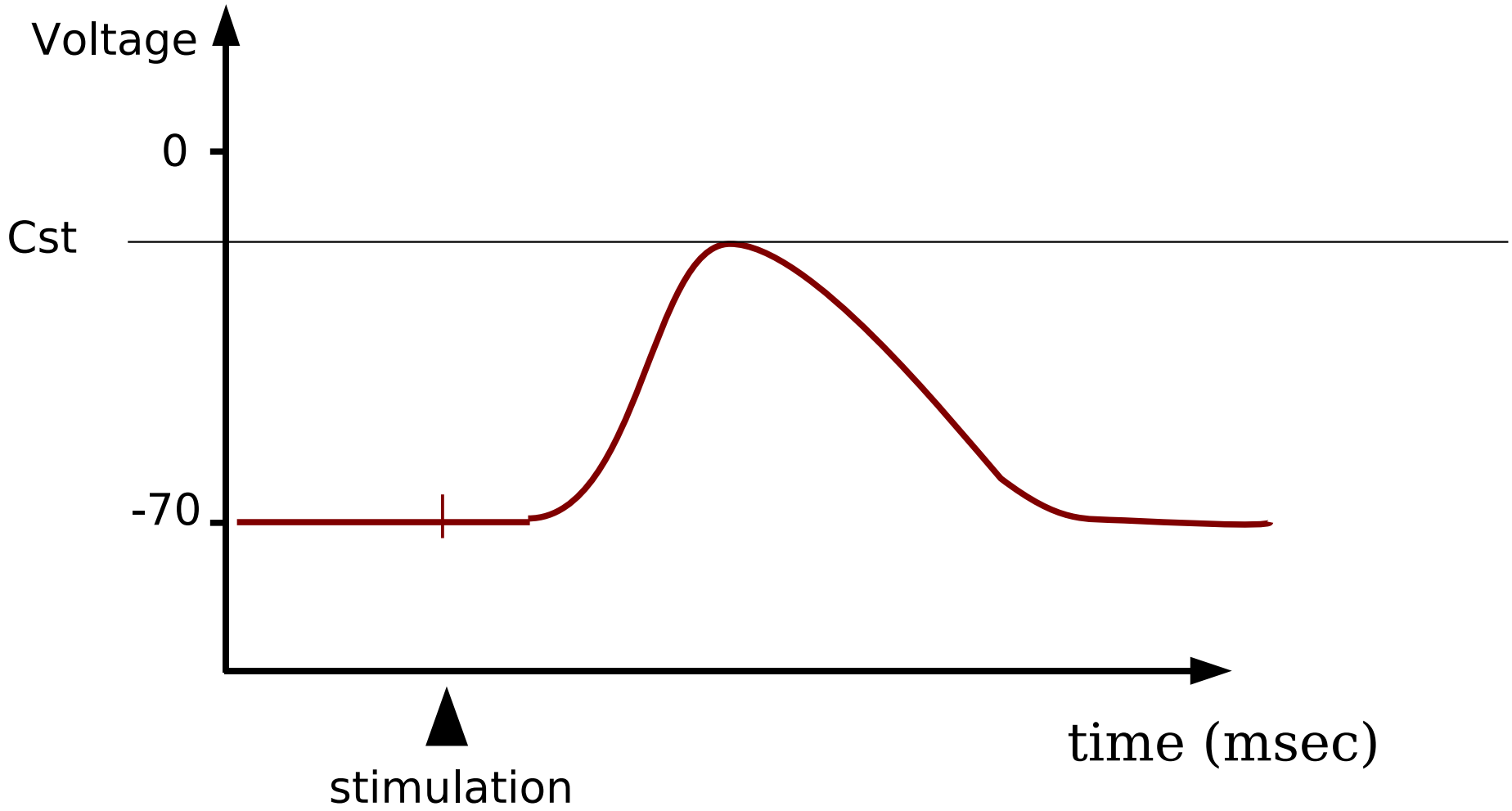
Logical interactions and inferences

Qualitative representation

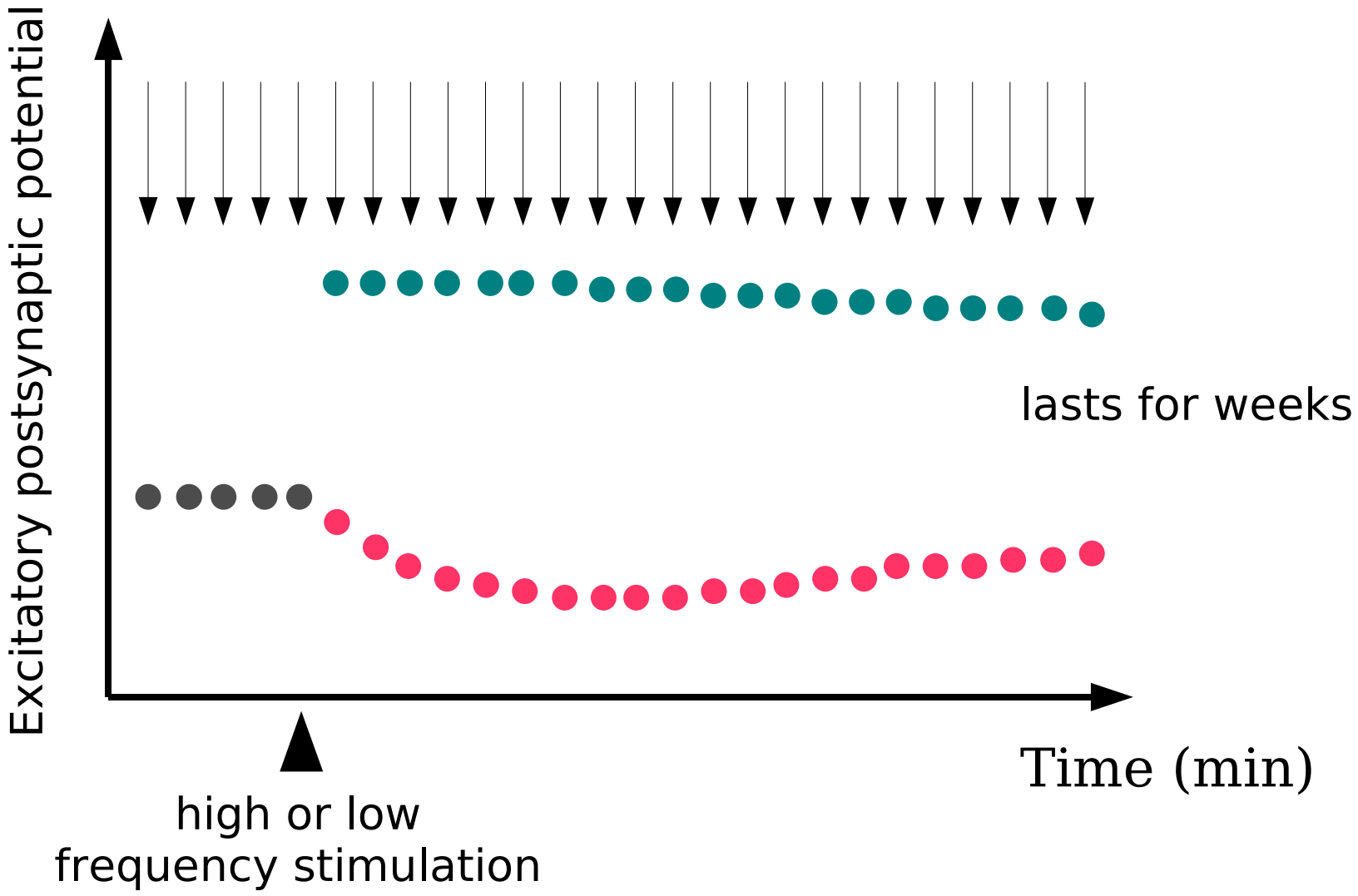
Parameter space exploration

Stefan, Edelstein, Le Novere (2008) An allosteric model of calmodulin explains differential activation of PP2B and CaMKII. *PNAS* Advanced online publication July 31st

Excitatory post-synaptic potential

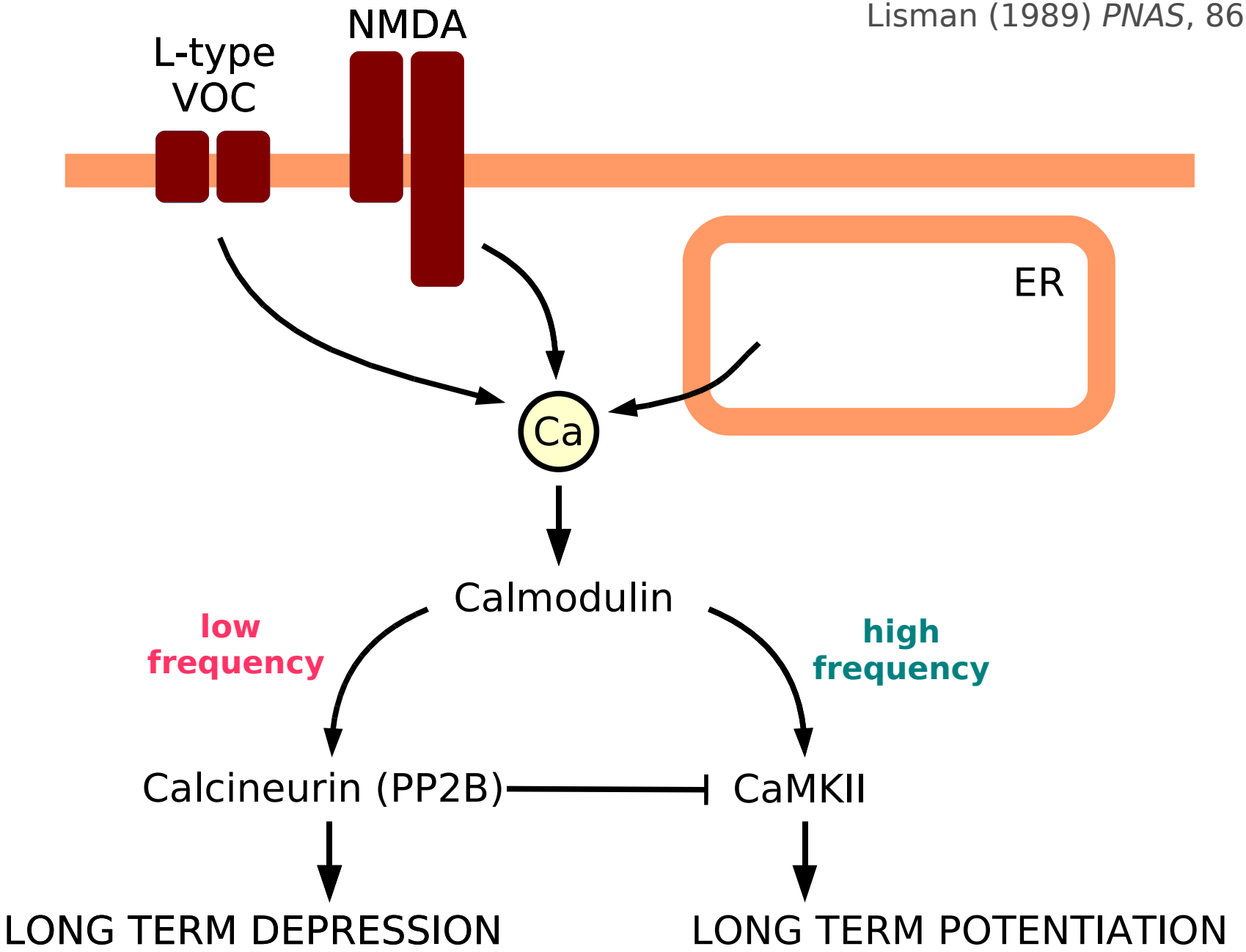


Bidirectional synaptic plasticity

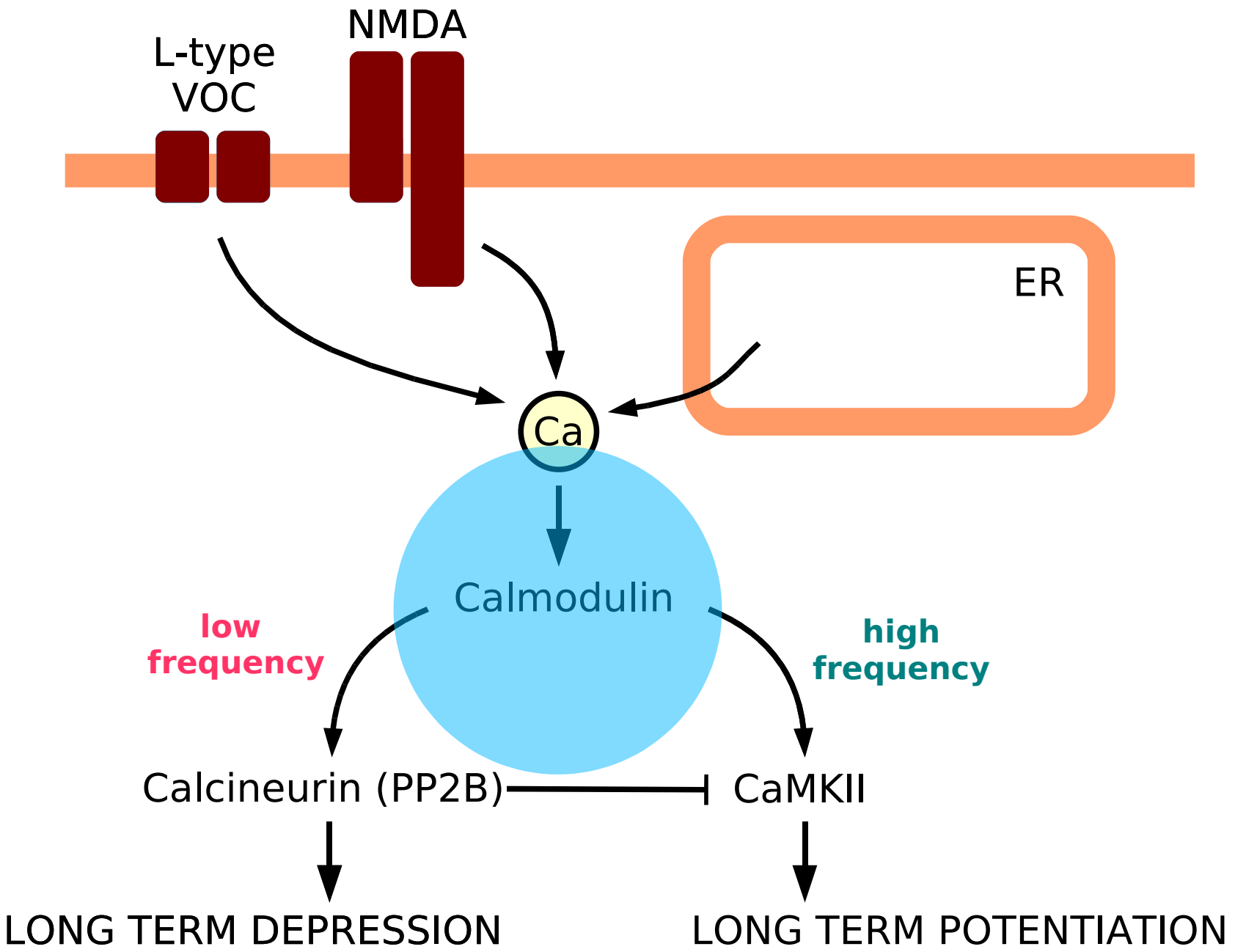


Calcium theory of Synaptic Plasticity

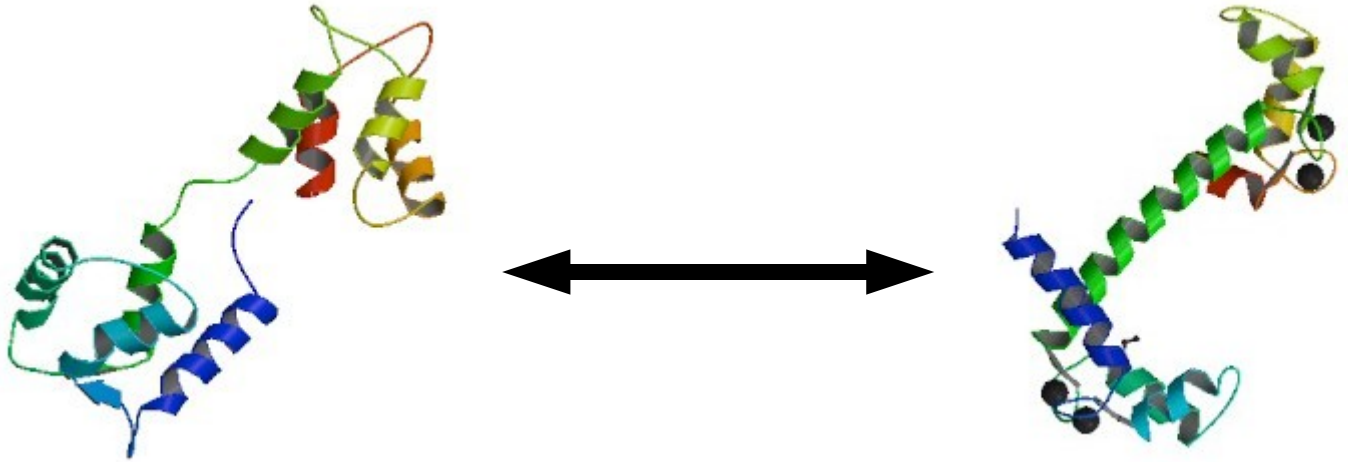
Lisman (1989) *PNAS*, 86: 9574-8



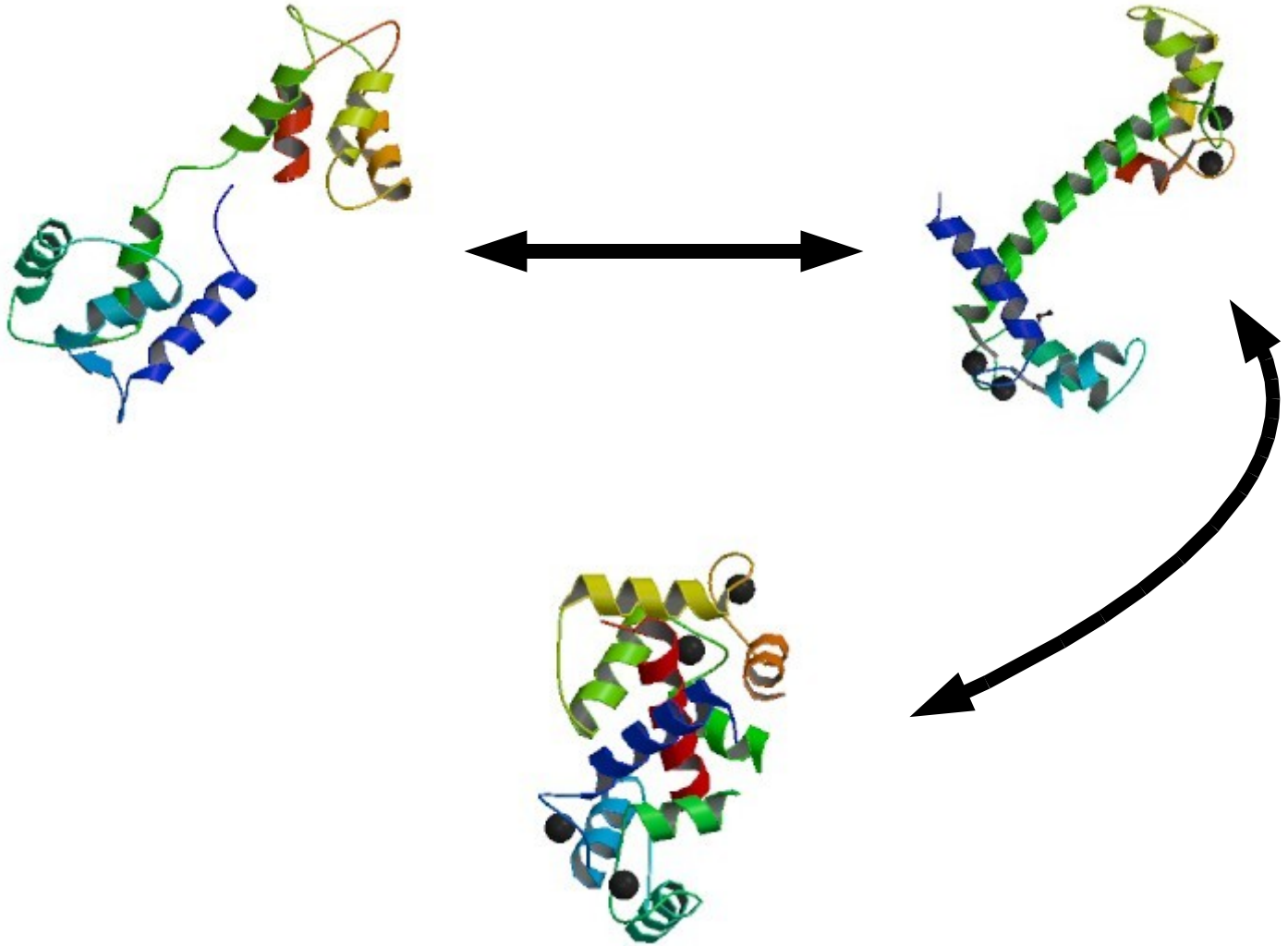
Calmodulin as a switch



Alternative structures of calmodulin



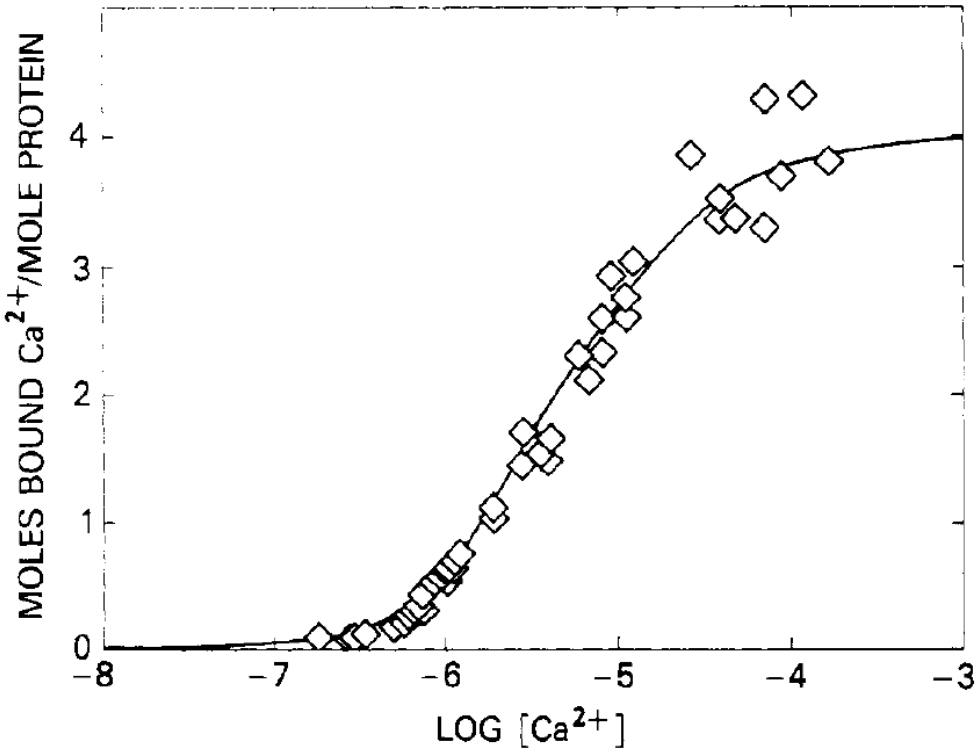
Alternative structures of calmodulin



Fitting of experimental results

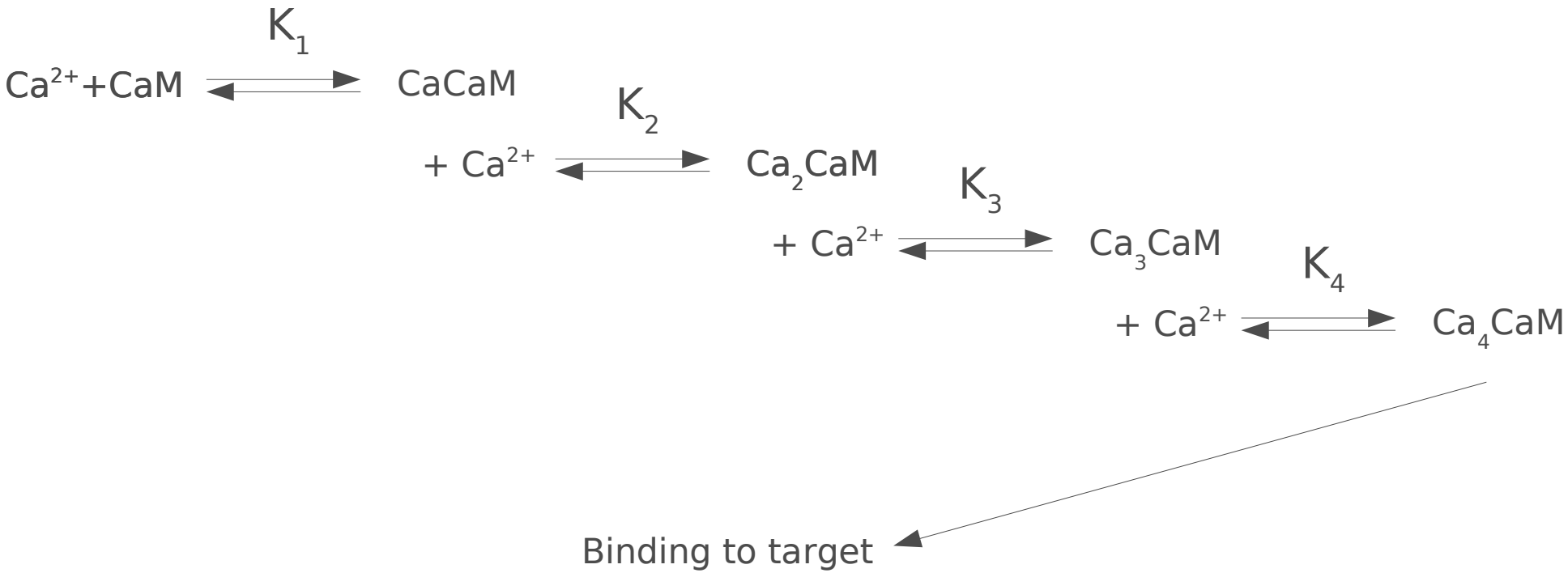
$$\overline{Y} = \frac{K_1[Ca]+2K_1K_2[Ca]^2+3K_1K_2K_3[Ca]^3+4K_1K_2K_3K_4[Ca]^4}{1+K_1[Ca]+K_1K_2[Ca]^2+K_1K_2K_3[Ca]^3+K_1K_2K_3K_4[Ca]^4}$$

Adair (1925)
J Biol Chem, 63: 529-545

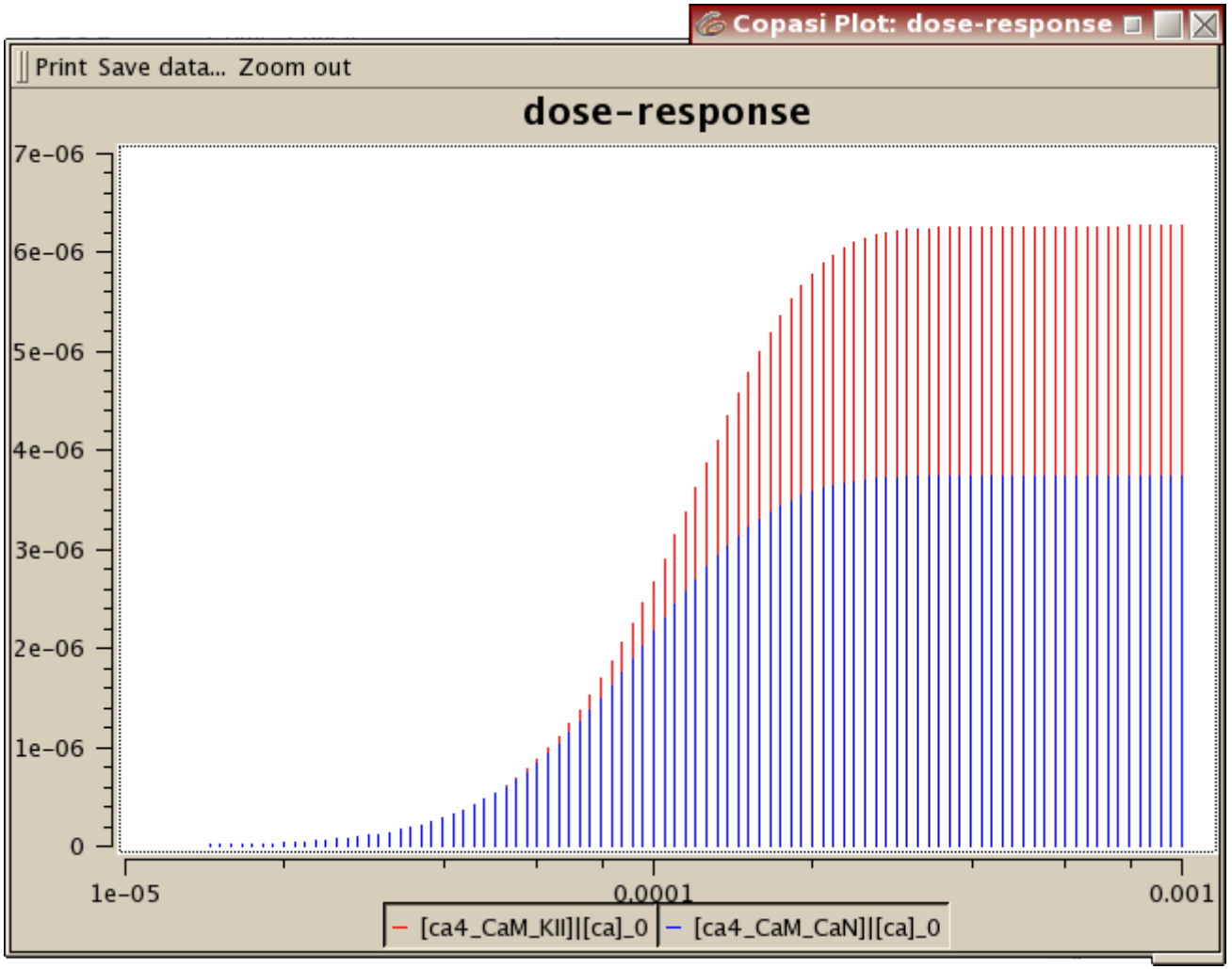


Crouch and Klee (1980)
Biochemistry, 19: 3692-3698

Phenomenological models



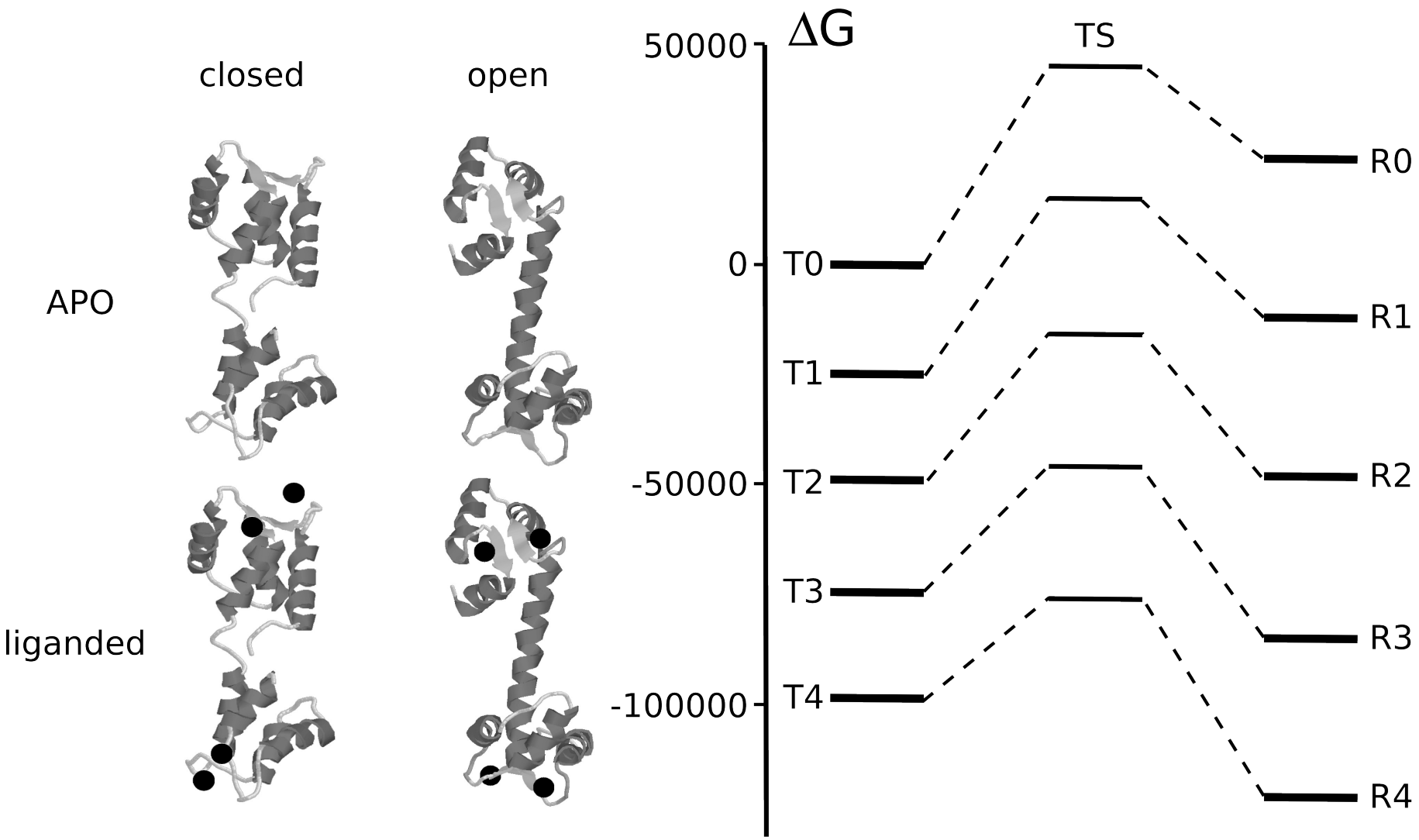
That does not work ...



That does not work ...

- Calmodulin bound to three calcium activates calcineurin
  - Kincaid and Vaughan (1986). *PNAS*, 83: 1193-1197
- Calmodulin bound to two calcium can bind CaMKII
  - Shifman et al (2006). *PNAS*, 103: 13968-13973
- Calmodulin affinity for calcium increases once bound to CaMKII
  - Shifman et al (2006) [but many previous reports on other targets: e.g. Burger et al (1983). *JBC*, 258: 14733-14739 ; Olwin et (1984). *JBC* 259: 10949-10955]
- Calcium activates both LTP and LTD through calmodulin
  - Lisman (1989) *PNAS*, 86: 9574-9578
  - High [Ca^{2+}] (high freq) ≅ CaMKII ; Low [Ca^{2+}] (low freq) ≅ Calcineurin

Concerted transition



Extended MWC model

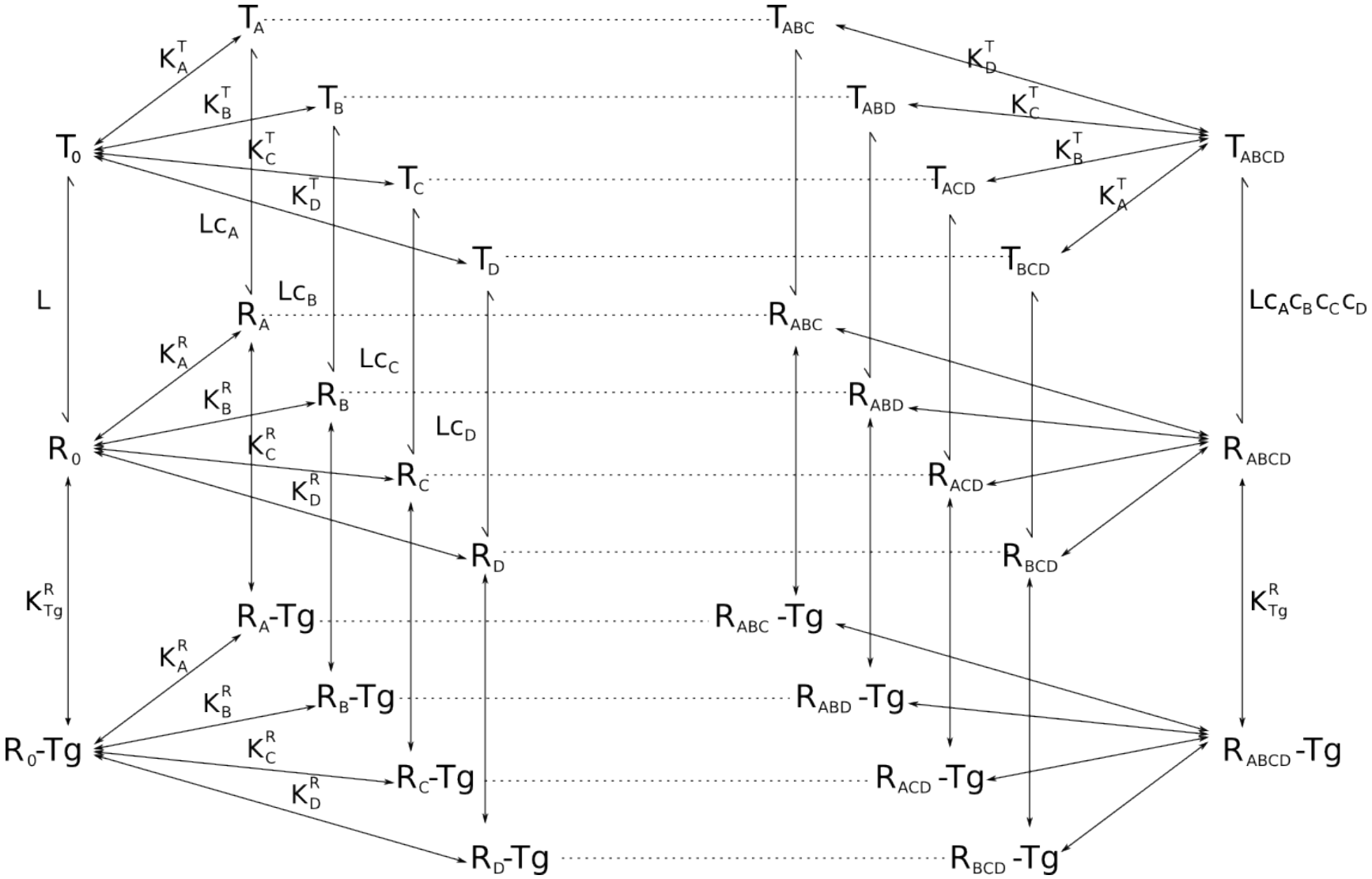
$$\bar{R} = \frac{\prod_i (1+\alpha_i)}{\prod_i (1+\alpha_i) + L \prod_i (1+c_i \alpha_i)}$$

$$\bar{Y} = 0.25 \frac{\sum_i \left(\alpha_i \prod_j (1+\alpha_j) \right) + L \sum_i \left(c_i \alpha_i \prod_j (1+c_j \alpha_j) \right)}{\prod_i (1+\alpha_i) + L \prod_i (1+c_i \alpha_i)} \quad [1]$$

where $i, j \in \{A, B, C, D\}$, and $j \neq i$. $\alpha_i = [Ca^{2+}]/K_i^R$, where K_i^R denotes the dissociation constant for calcium to site i in the R state.

Monod, Wyman, Changeux (1965). *J Mol Biol*, 12: 88-118

Full mechanistic thermodynamic model



$$L = \frac{[T0]}{[R0]} \qquad C_I = \frac{K^R_I}{K^T_I}$$

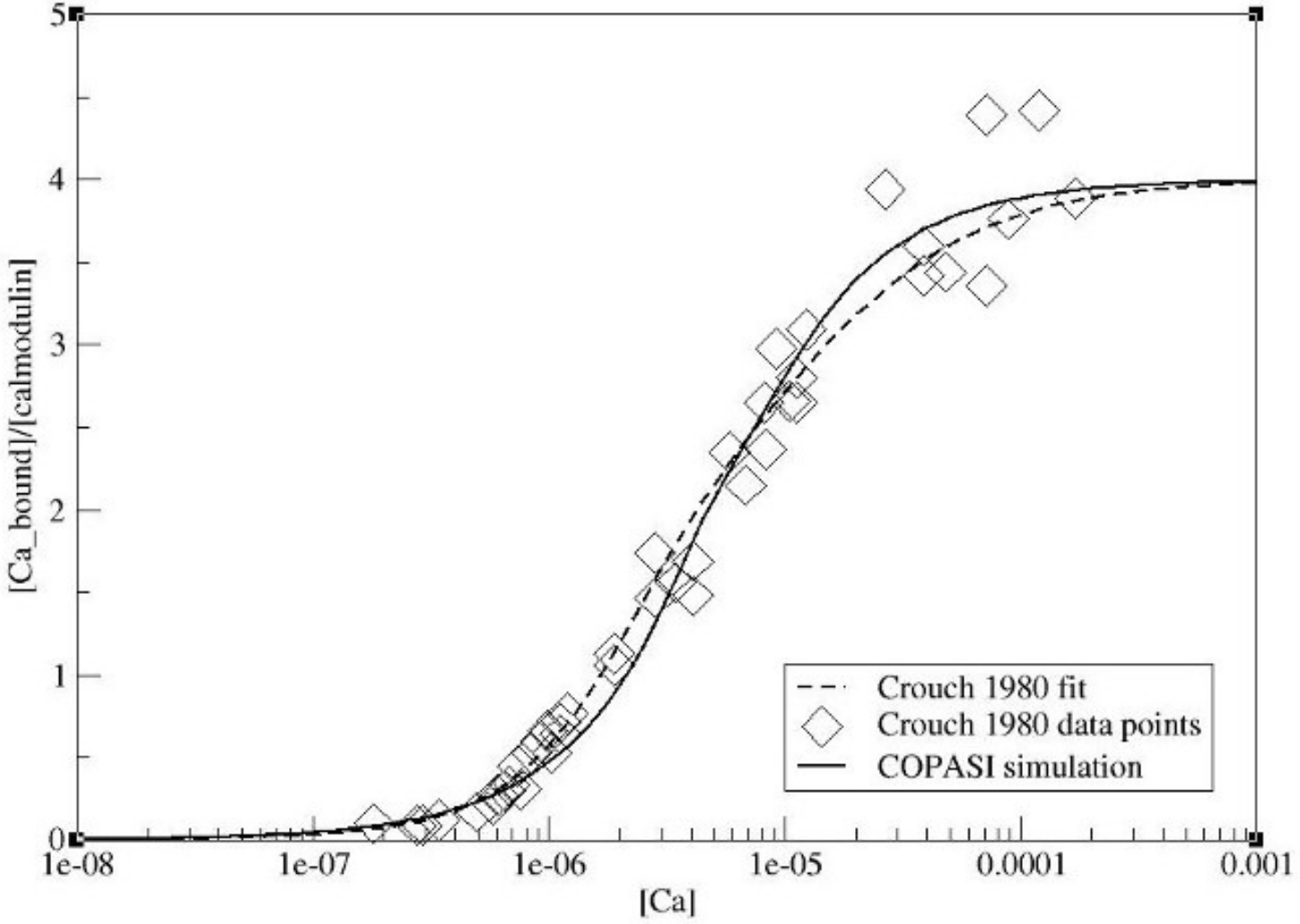
Model constraints

- Determination of c and L
  - Ca binding in presence of target: none, skMLCK, PhK5, CaATPase (Peersen et al (1997) Prot Sci 6: 794-807)
  - 100 000 simulations with different parameter sets plus least-square
- Calcium dissociation constants
  - Complete CaM (Bayley et al (1996) *Prot Sci* 5: 1215-1228)
  - N and C term Mutants (Shifman et al (2006) *PNAS*, 103: 13968-13973)
  - R-only - skMLCK(Peersen et al (1997) Prot Sci 6: 794-807)
  - Systematic logarithmic sampling of the affinity space (coarse-grained, 50 values per affinity, then refined 66 values per affinity) = 25 millions simulations

Simulations ran by COPASI (http://www.copasi.org)

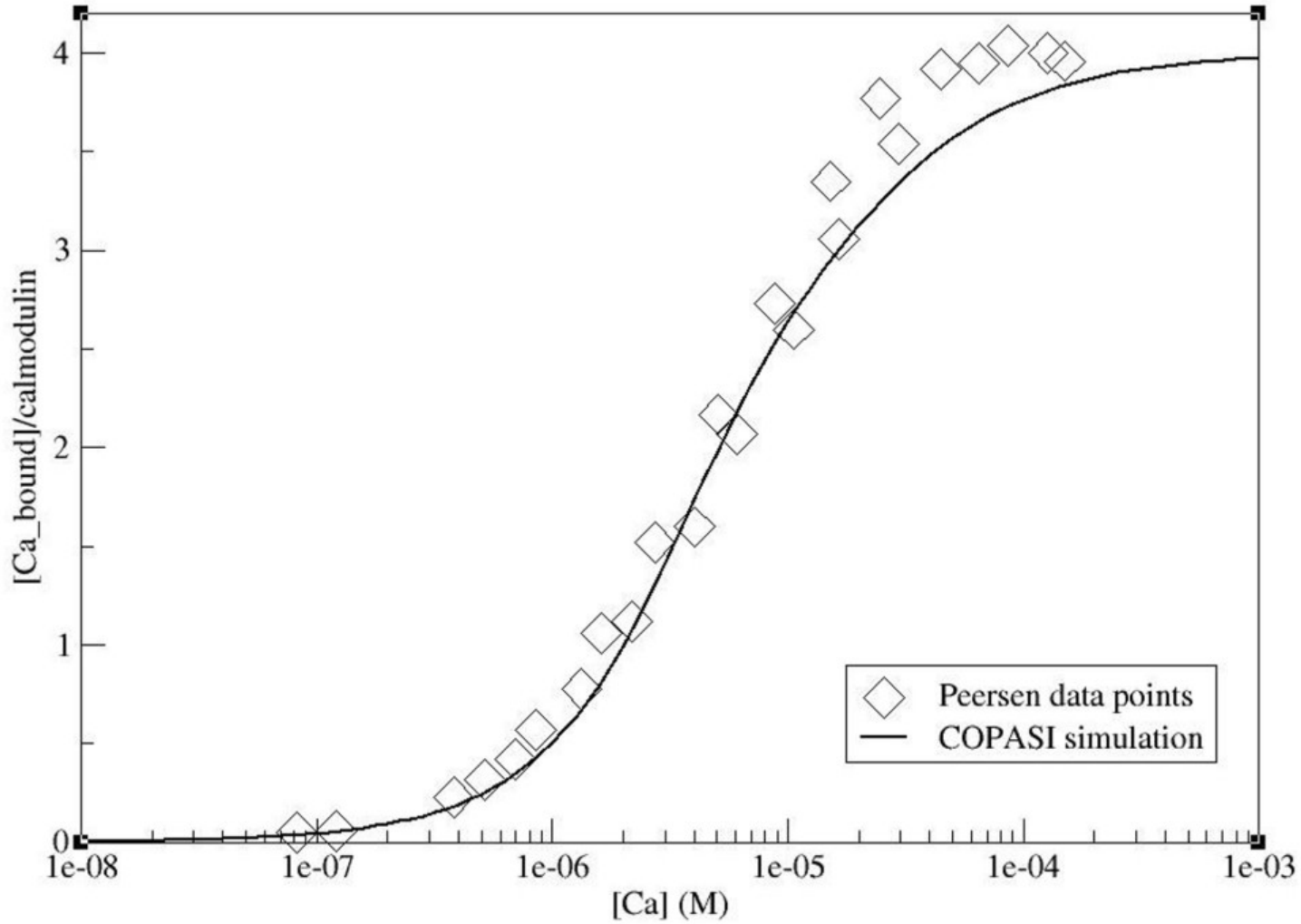
fit done with SciLab (http://www.scilab.org/)

Comparison with experiment



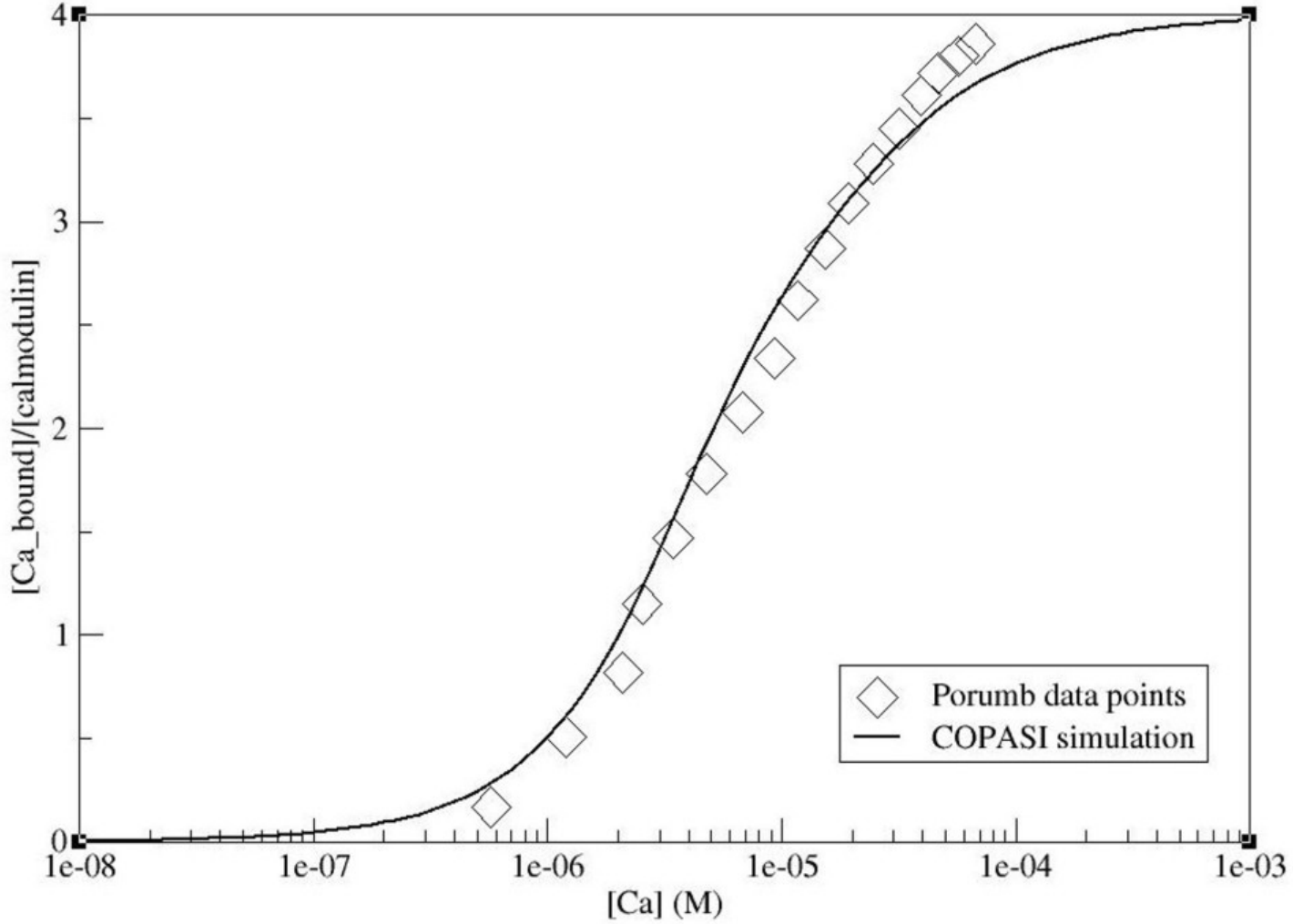
Crouch and Klee (1980) *Biochemistry*, 19: 3692-3698c

Comparison with experiment



Peersen et al (1997) Prot Sci 6: 794-807

Comparison with experiment



Porumb et al (1994) Anal Biochem 220: 227-237

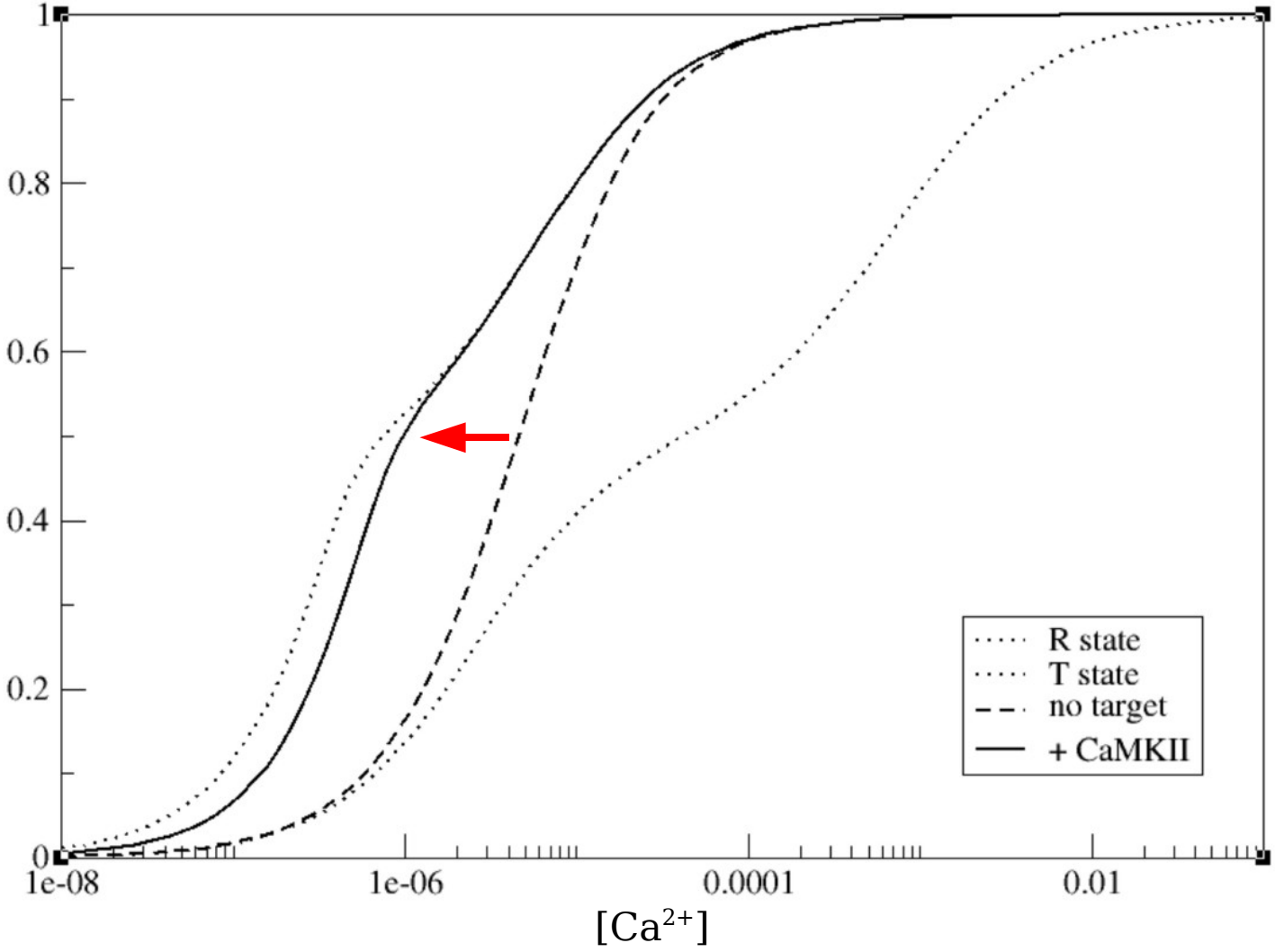
Activity of unsaturated calmodulin

- Fractional activity depends on the number of calcium ions bound. E.g.:

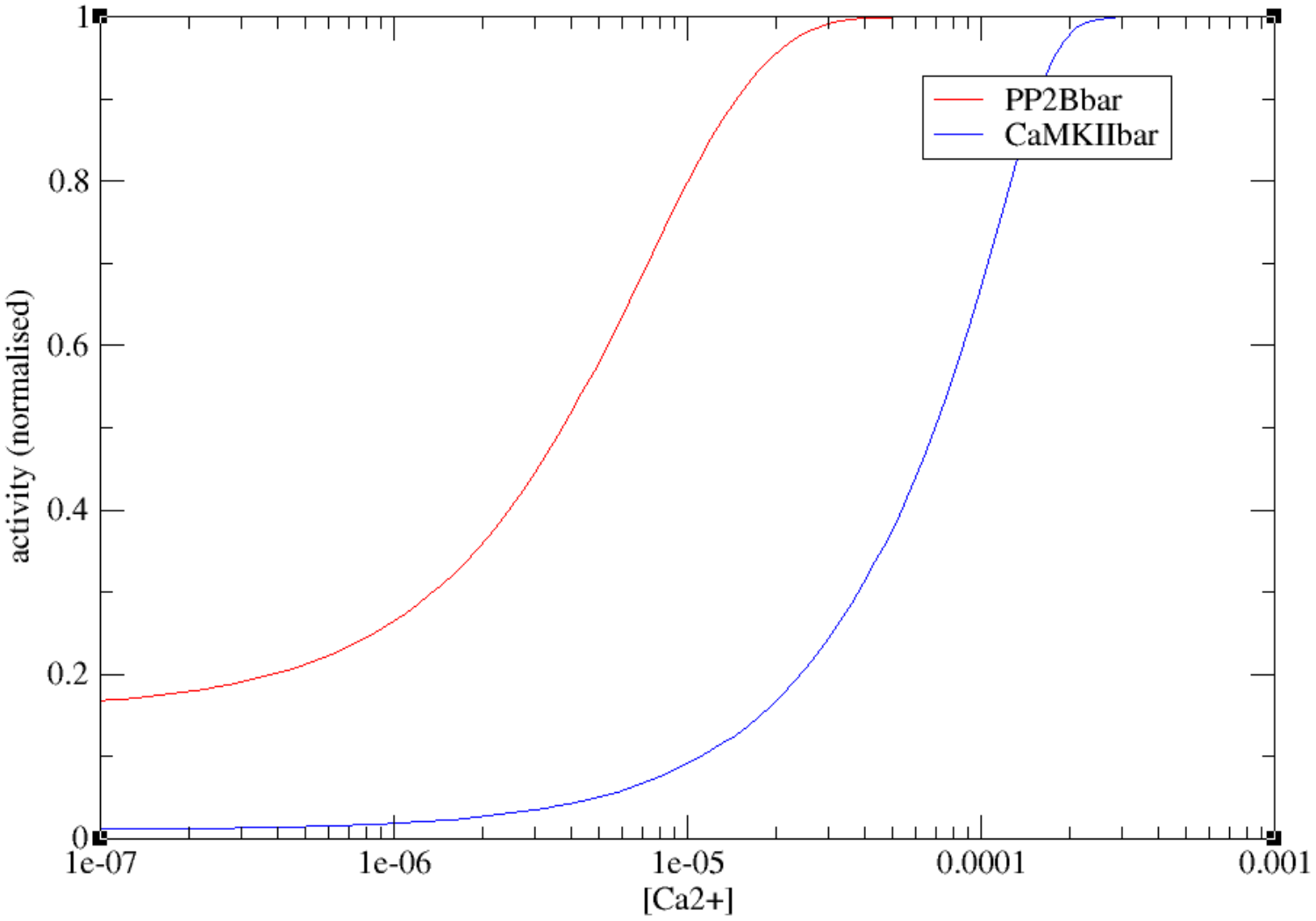
$$\frac{R_2}{T_2} = \frac{6}{L(c_A c_B + c_A c_C + c_A c_D + c_B c_C + c_B c_D + c_C c_D)}$$

- $R_0/T_0 = 1/20000$ (1/L)
- $R_1/T_1 = 1/170$
- $R_2/T_2 = 0.69$ → half-saturation = equi-probability
- $R_3/T_3 = 80$
- $R_4/T_4 = 10000$

Binding to target increases the affinity for Ca^{2+}

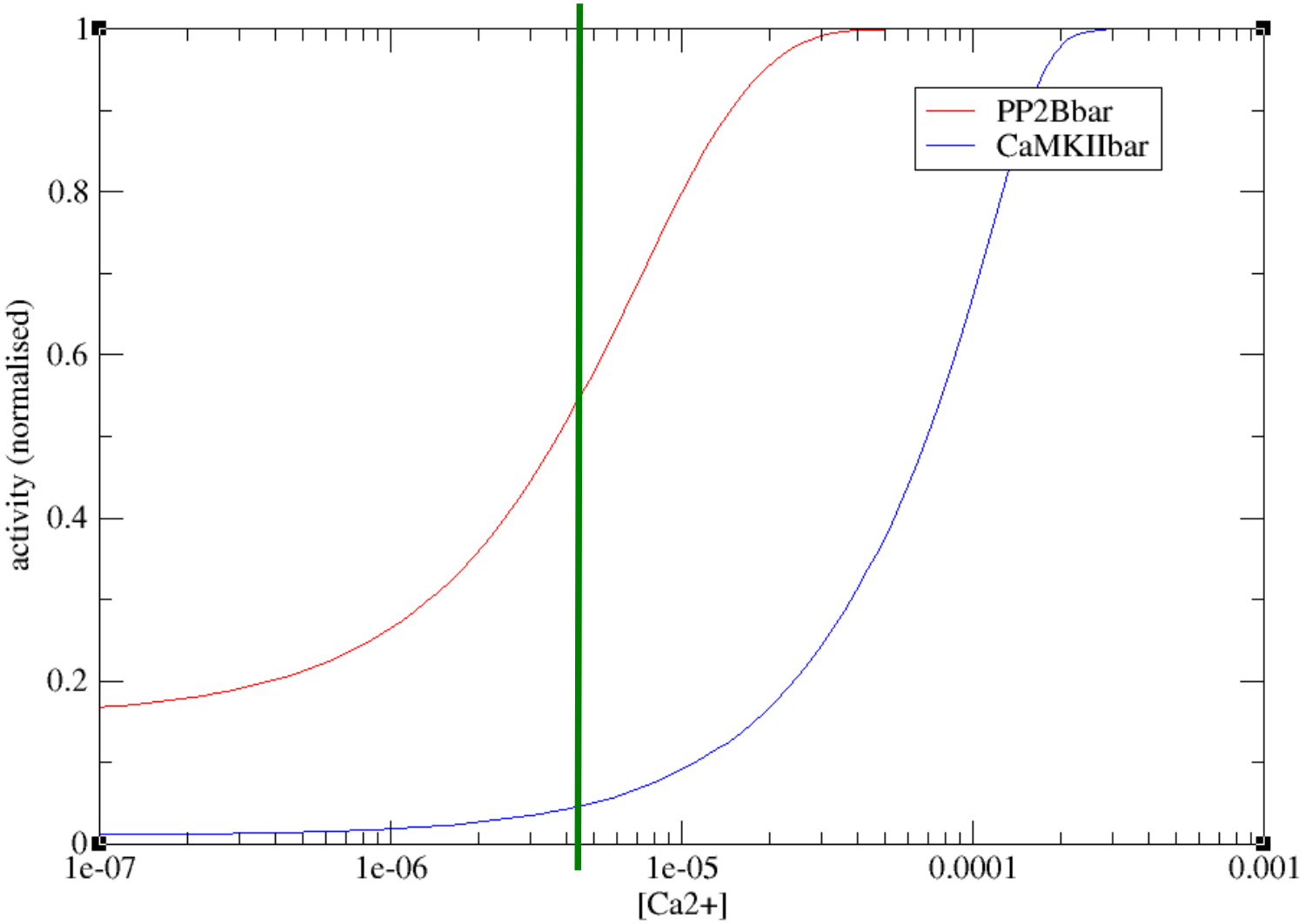


Bidirectional synaptic plasticity

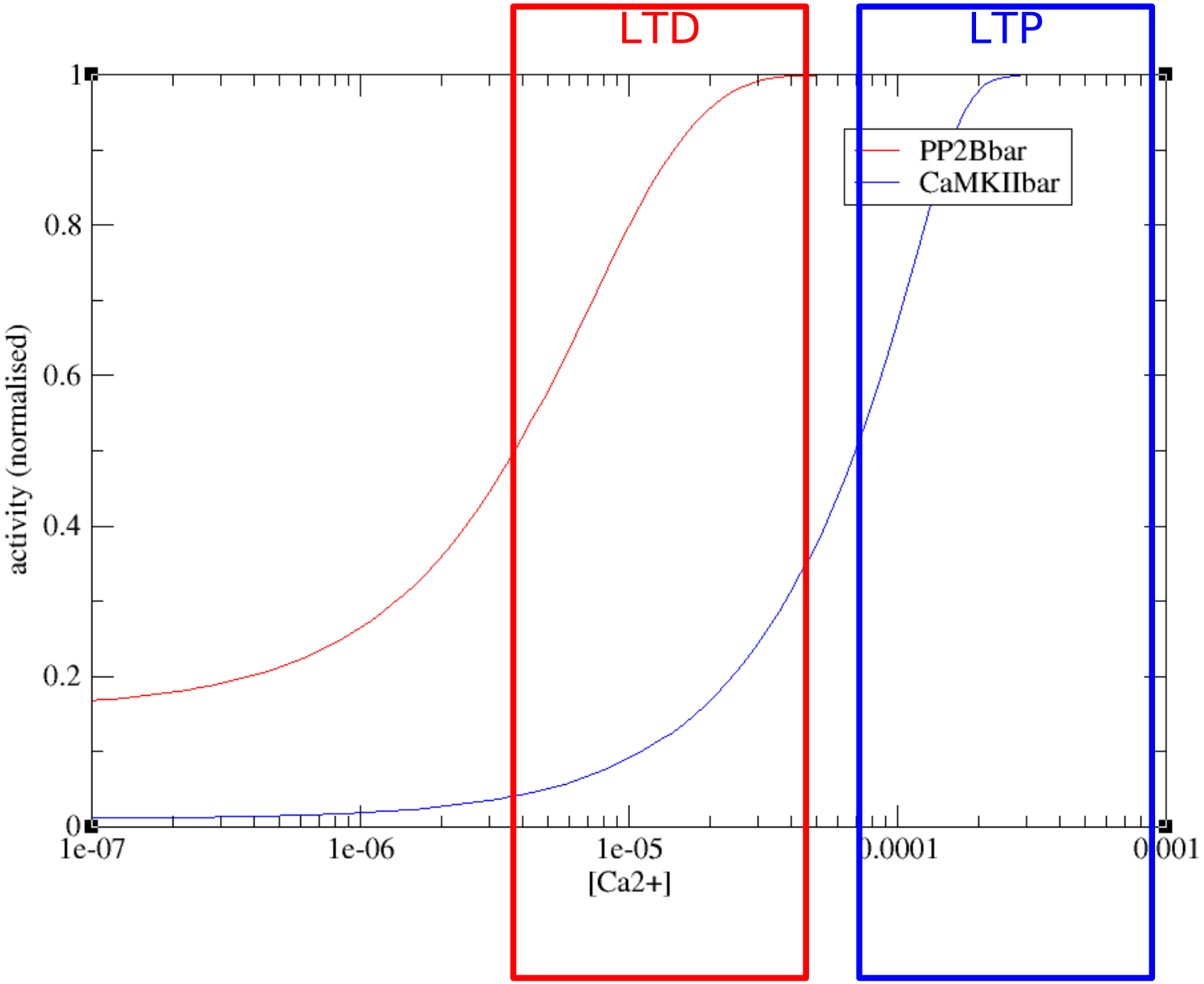


Bidirectional synaptic plasticity

half saturation of calmodulin



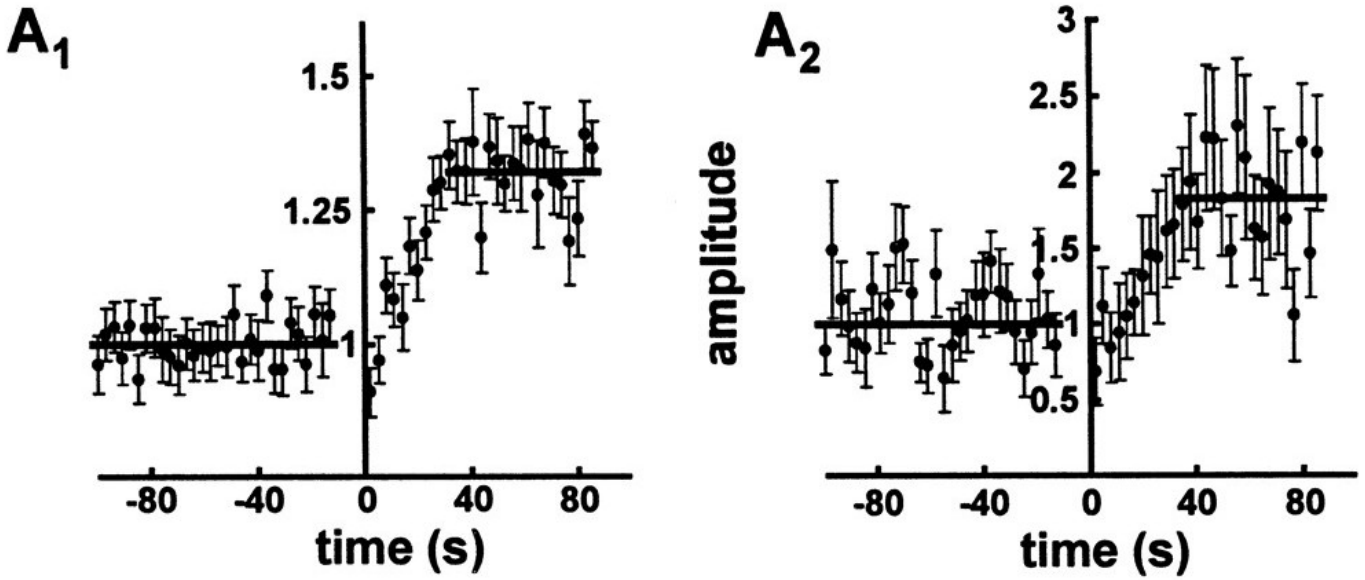
Bidirectional synaptic plasticity



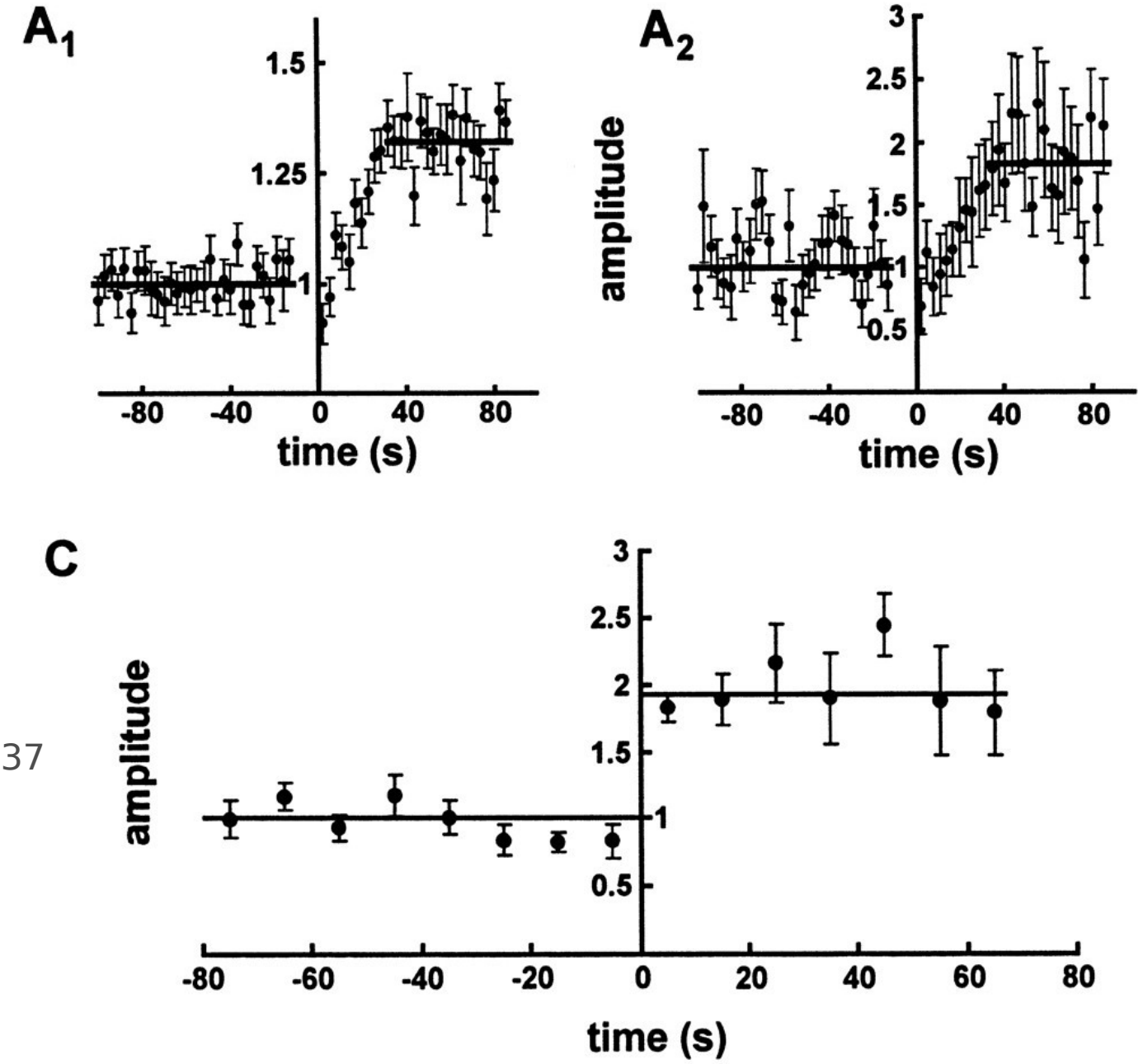
Reaction-diffusion problem

Tolle, Le Novere (2006) Particle-based Stochastic Simulation in Systems Biology *Curr Bioinfo*, 1: 315-320 .

Multi-synaptic LTP

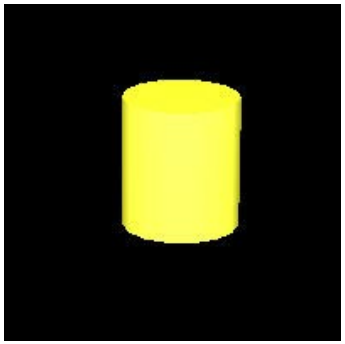


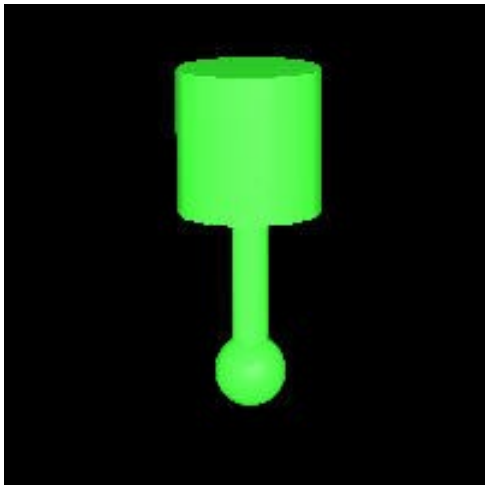
Single-synapse recording

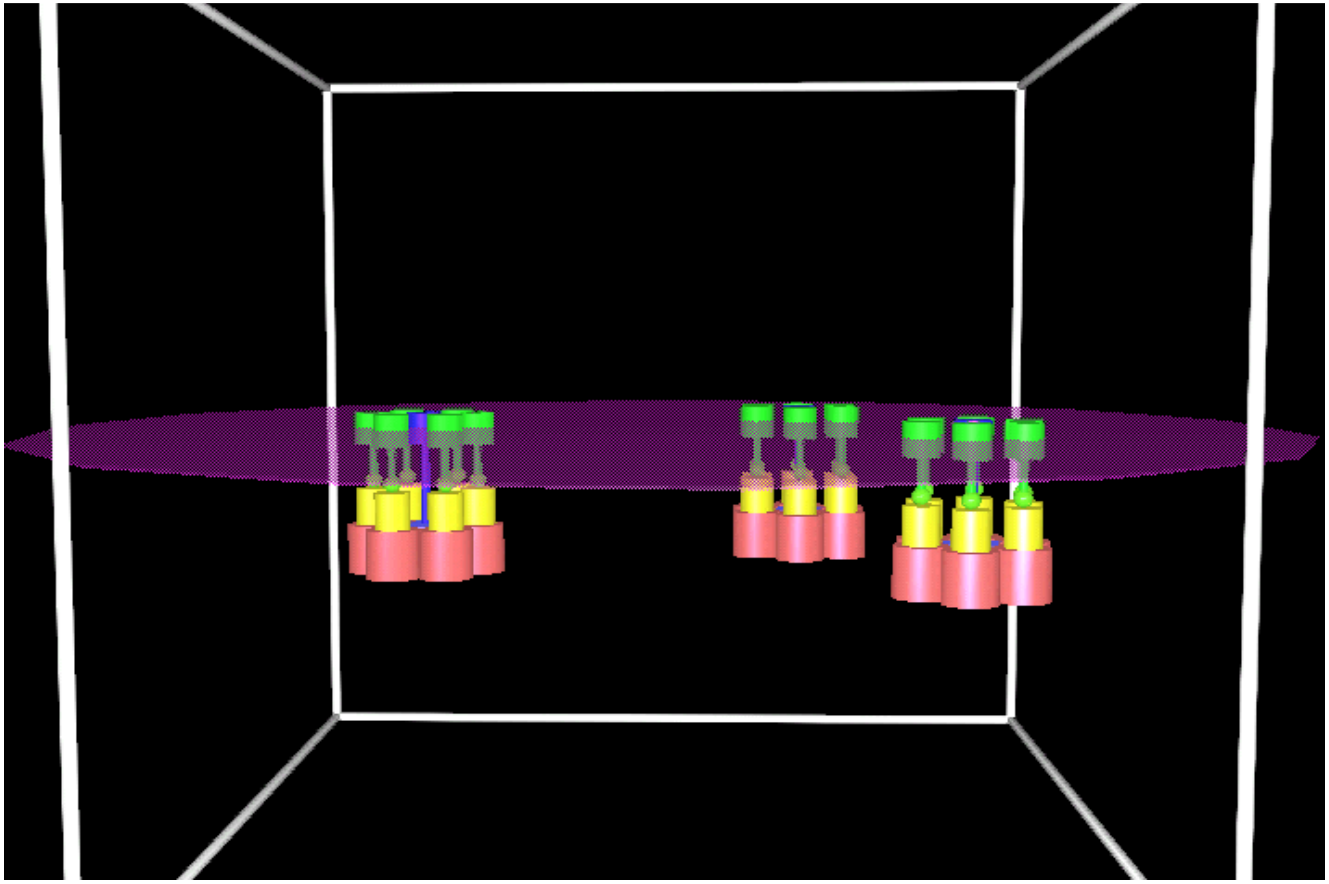


Petersen et al (1998)
PNAS 95: 4732-4737

Agent-based spatial simulations

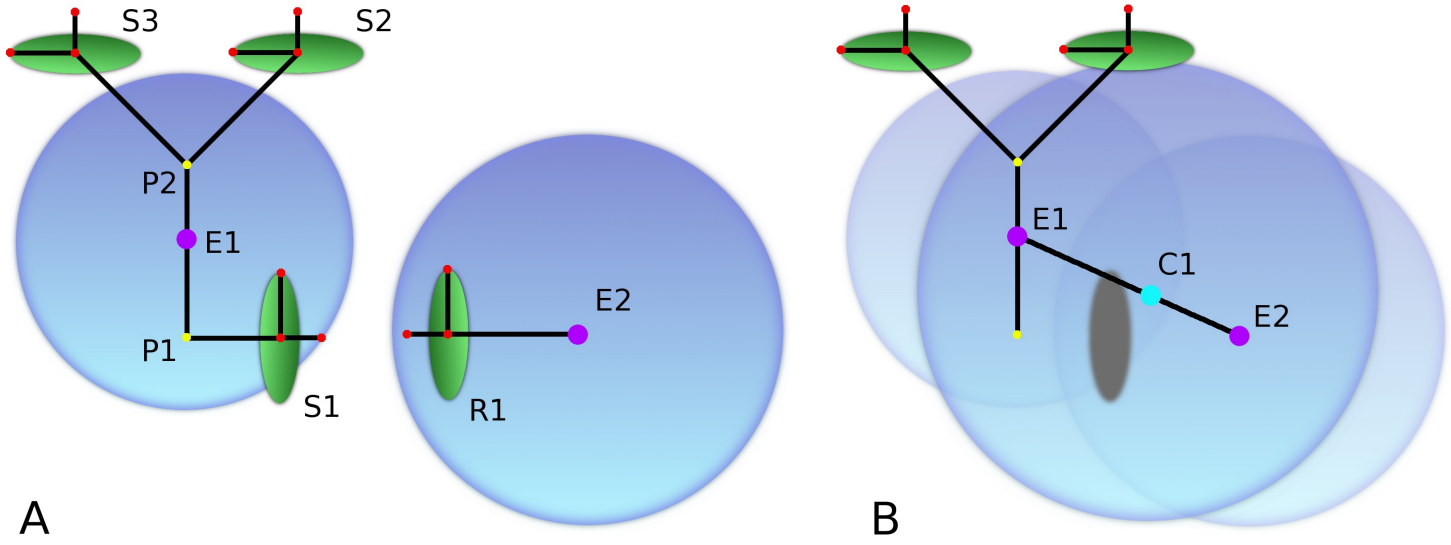






- Particles carry binding surfaces
- Cluster and entity classes allows recording of Center Of Mass, radius, RMS displacement, state
- Clusters are dynamically created and destroyed – transient
- State variables attached to entities and reacting surfaces

Binding ports on particles, entities and clusters



Molecule diffusion

- Different diffusion spaces:
  - Static; Free diffusion; Membrane diffusion; Above membrane; Below membrane
  - Membrane corrals
- Two types of motion:
  - Translational $\bar{r}^2 = 2\mathrm{D}_T t = 2\mathrm{kb}_T t$
  - Rotational $\bar{\theta}^2 = 2 D_R t = 2\mathrm{kb}_R t$
- random walk algorithm

$$p(x,t) = \frac{1}{\sqrt{4\pi Dt}} \exp - \frac{x^2}{4\mathrm{Dt}}$$ gaussian with $\sigma^2 = 2 \quad Dt$

  - Translational $\Delta(x,y,z) = \sqrt{2\mathrm{D}_T t} \times gaussRand$
  - Rotational $\Delta\theta = \frac{\sqrt{2\mathrm{D}_R t}}{r} \times gaussRand$
- Two types of diffusion equations:
  - unrestricted brownian motion – Low Trans/Rot
  - intra-membrane diffusion (Saffman and Delbrück 1975) – High Trans/Rot

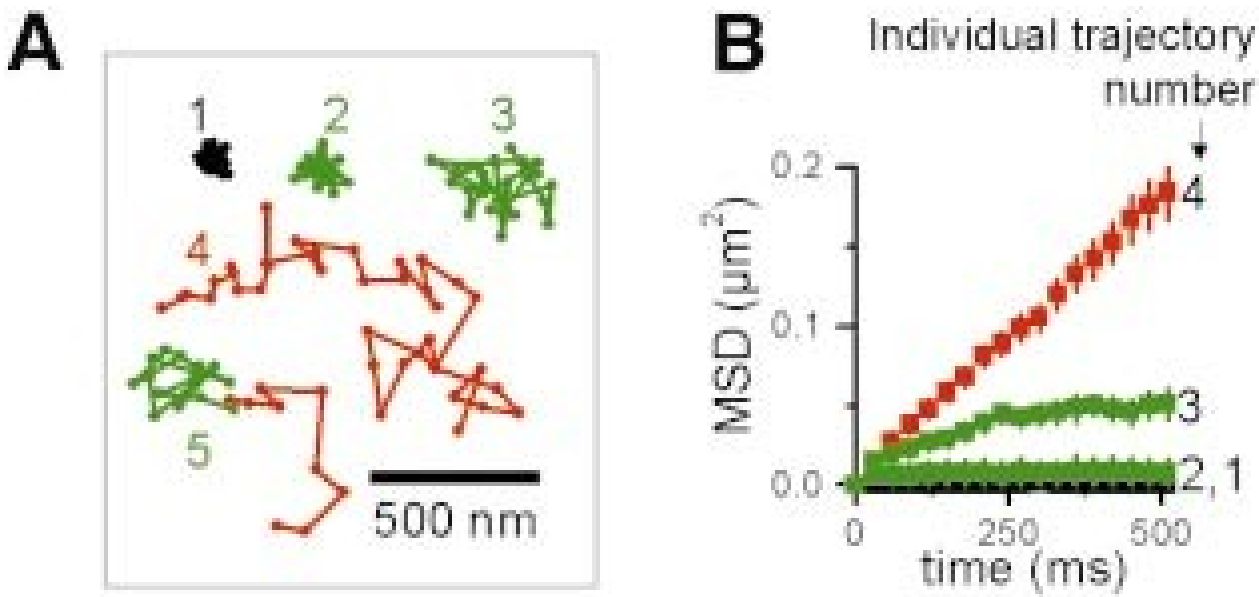
Molecule diffusion

- Unrestricted brownian motion – Low Translation/Rotational

$$b_T = \frac{1}{6\pi\mu r} \qquad b_R = \frac{1}{8\pi\mu r^3} \qquad \frac{b_T}{b_R} = \frac{4}{3} r^2$$

- Intra-membrane diffusion (Saffman and Delbrück 1975) High Translational/Rotational

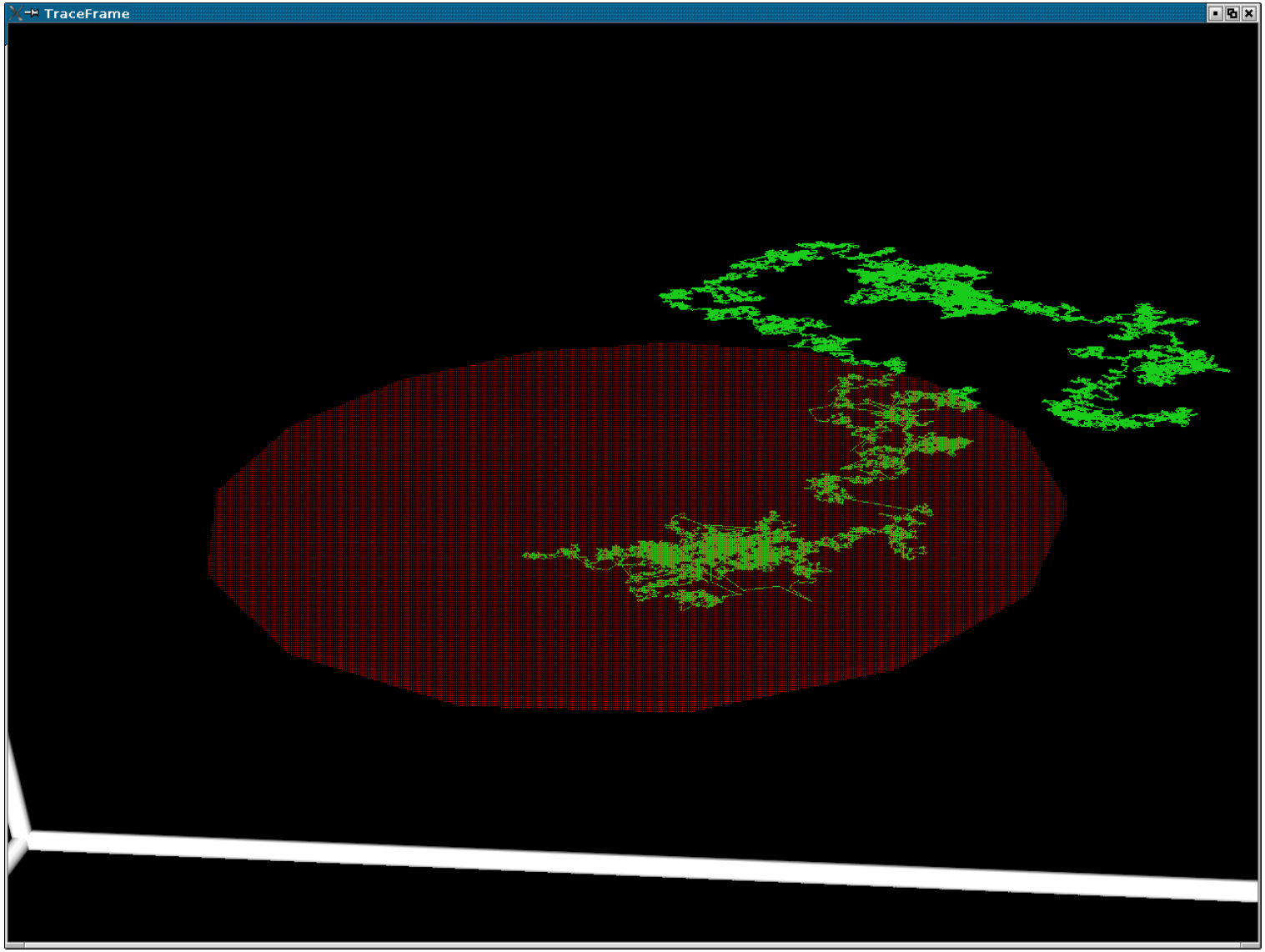
$$b_T = \frac{1}{4\pi\mu h}\left(\log\left(\frac{\mu h}{\mu' r}\right) - \gamma\right) \qquad b_R = \frac{1}{4\pi\mu r^2 h} \qquad \frac{b_T}{b_R} = \left(\log\left(\frac{\mu h}{\mu' r}\right) - \gamma\right) \times r^2$$

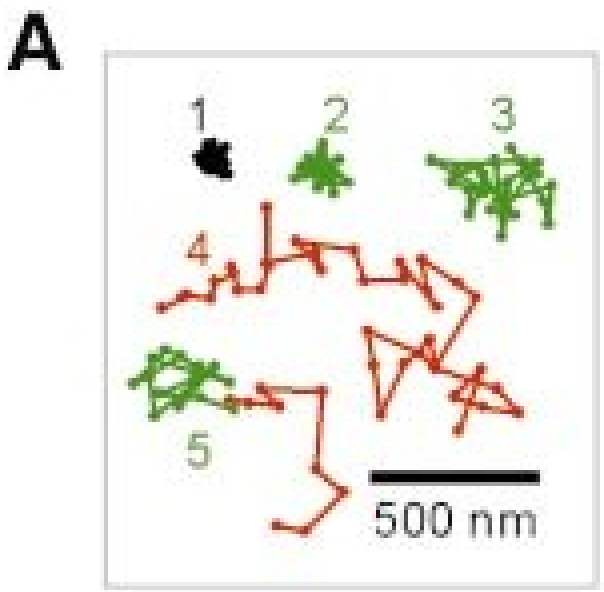


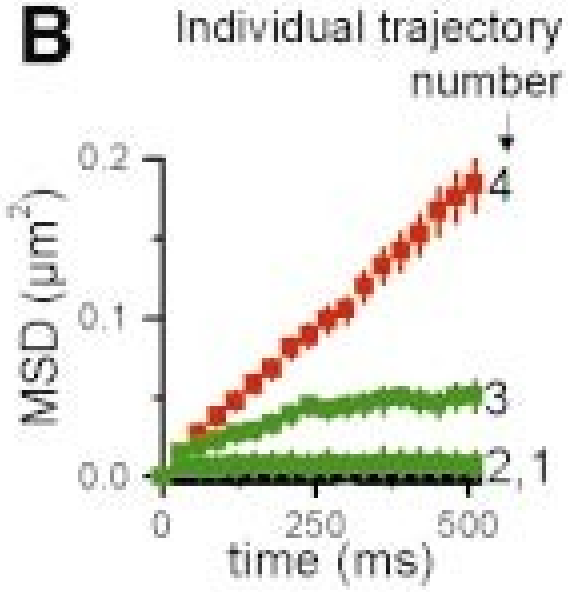
Tardin et al (2003)
EMBO J 22: 4656-4665

EMBL-EBI

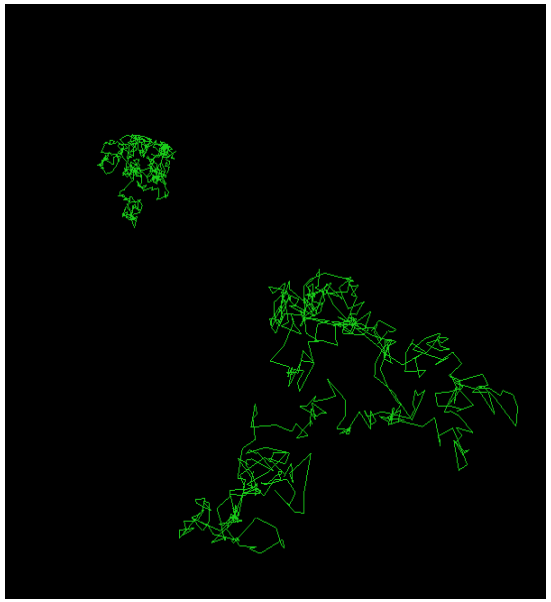
Simulations of receptor diffusion

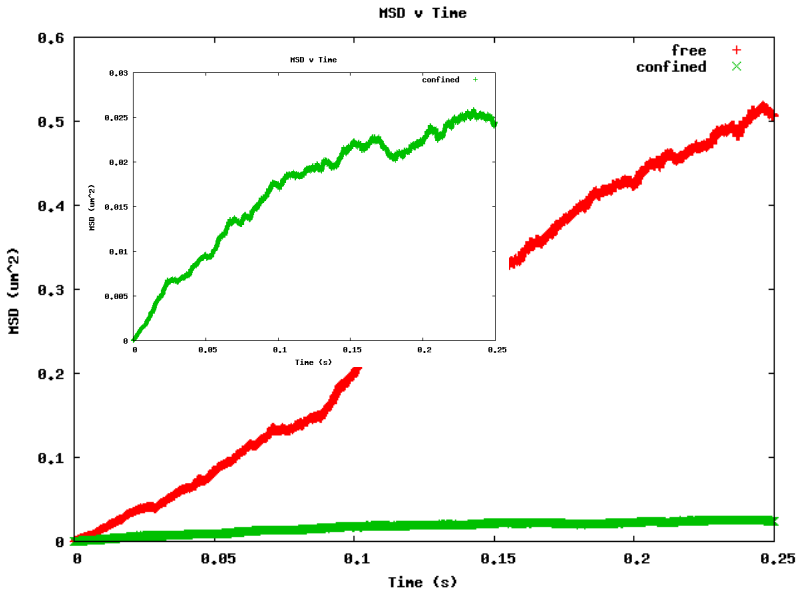






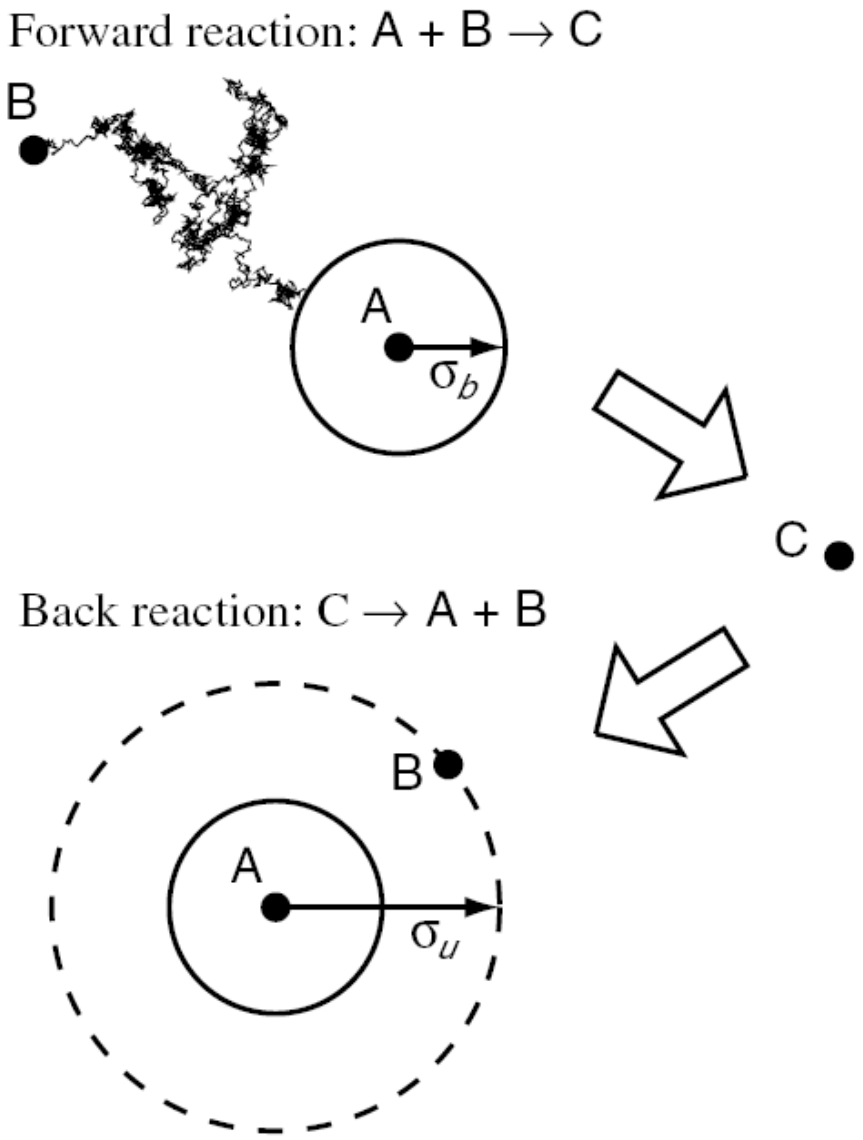
Tardin et al (2003)
EMBO J 22: 4656-4665



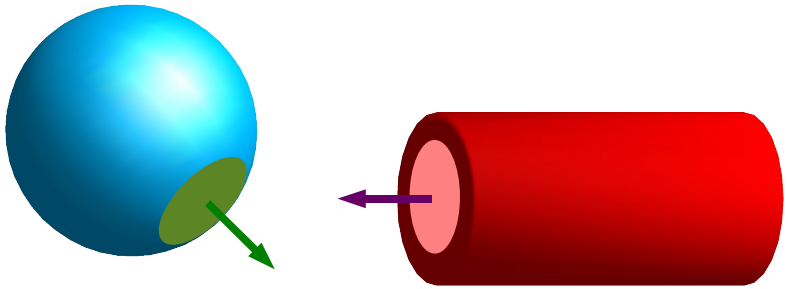


Smoluchovski model

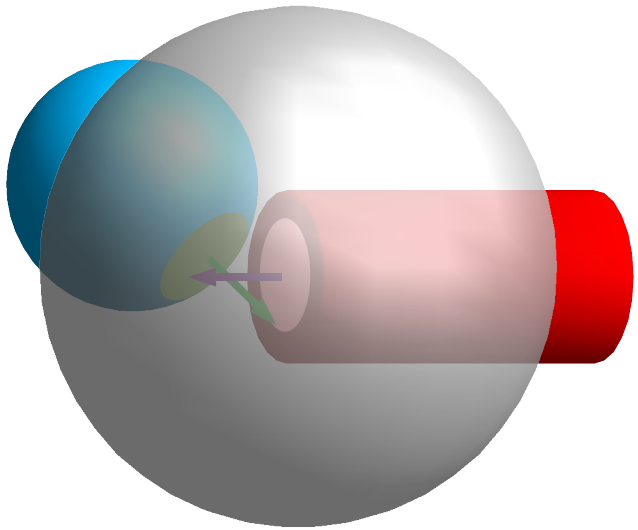
Andrews and Bray (2004)
Phys Biol 1: 137-151)



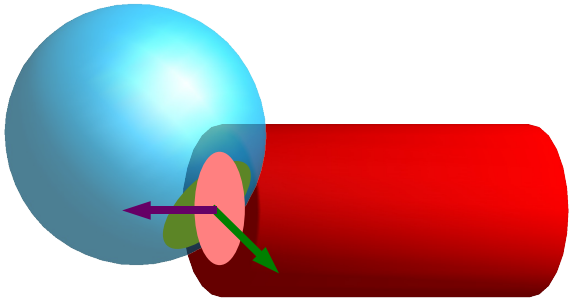
Reactions and complex formation



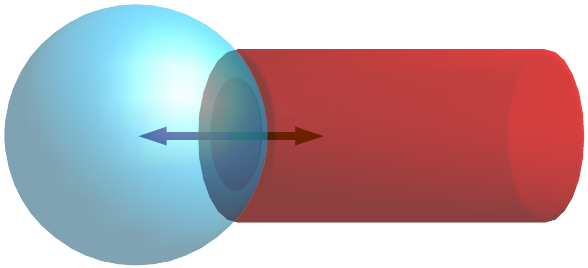
Reactions and complex formation

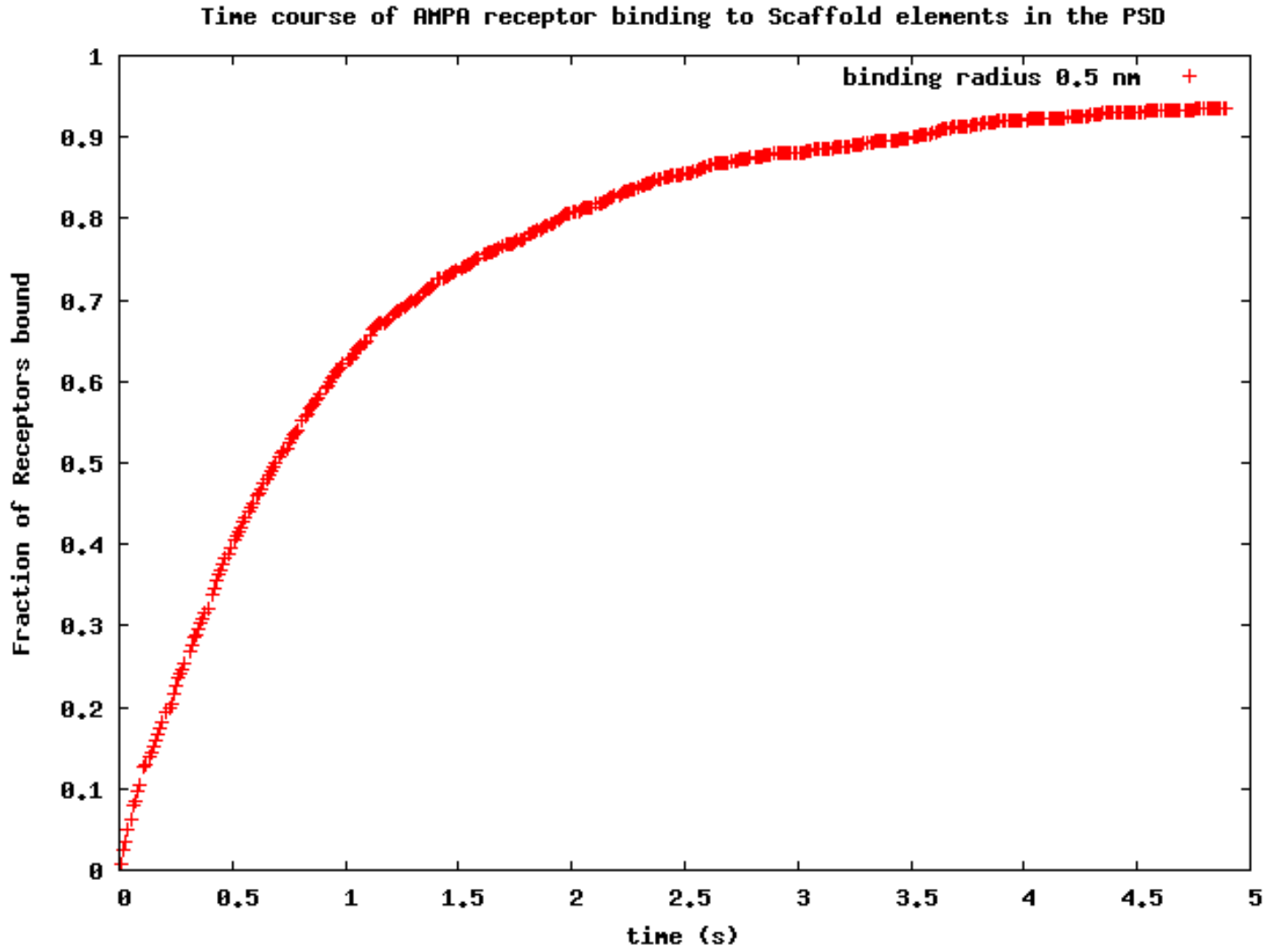


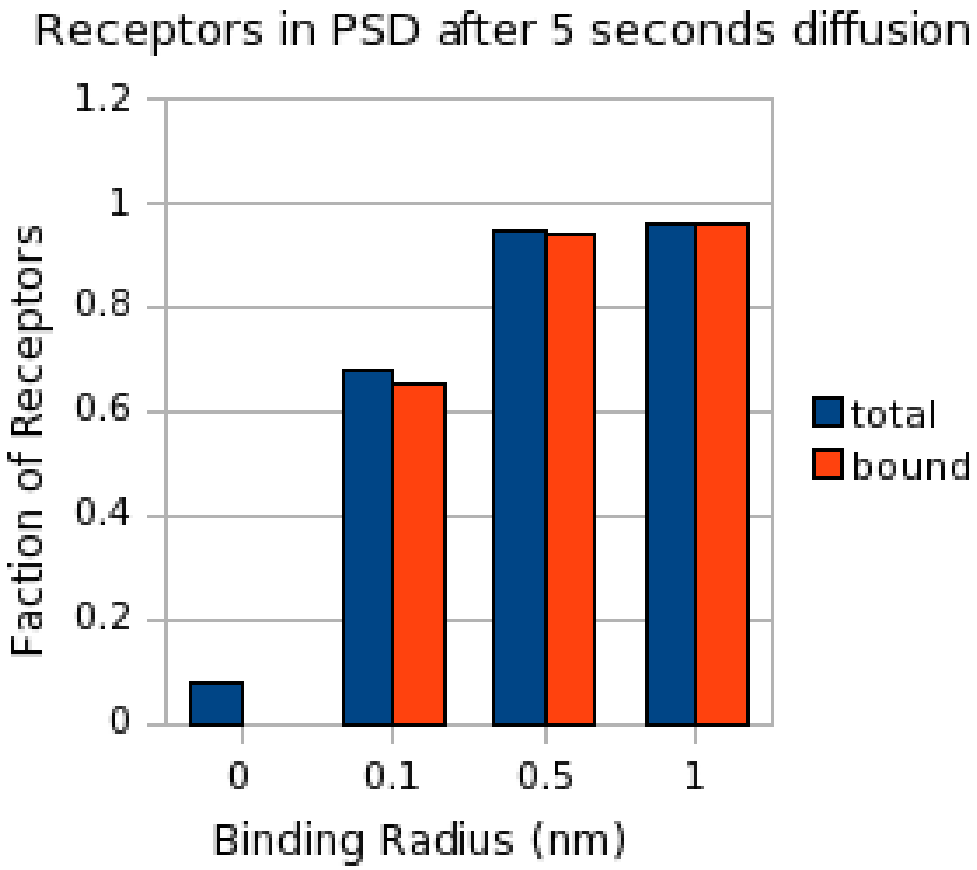
Reactions and complex formation



Reactions and complex formation



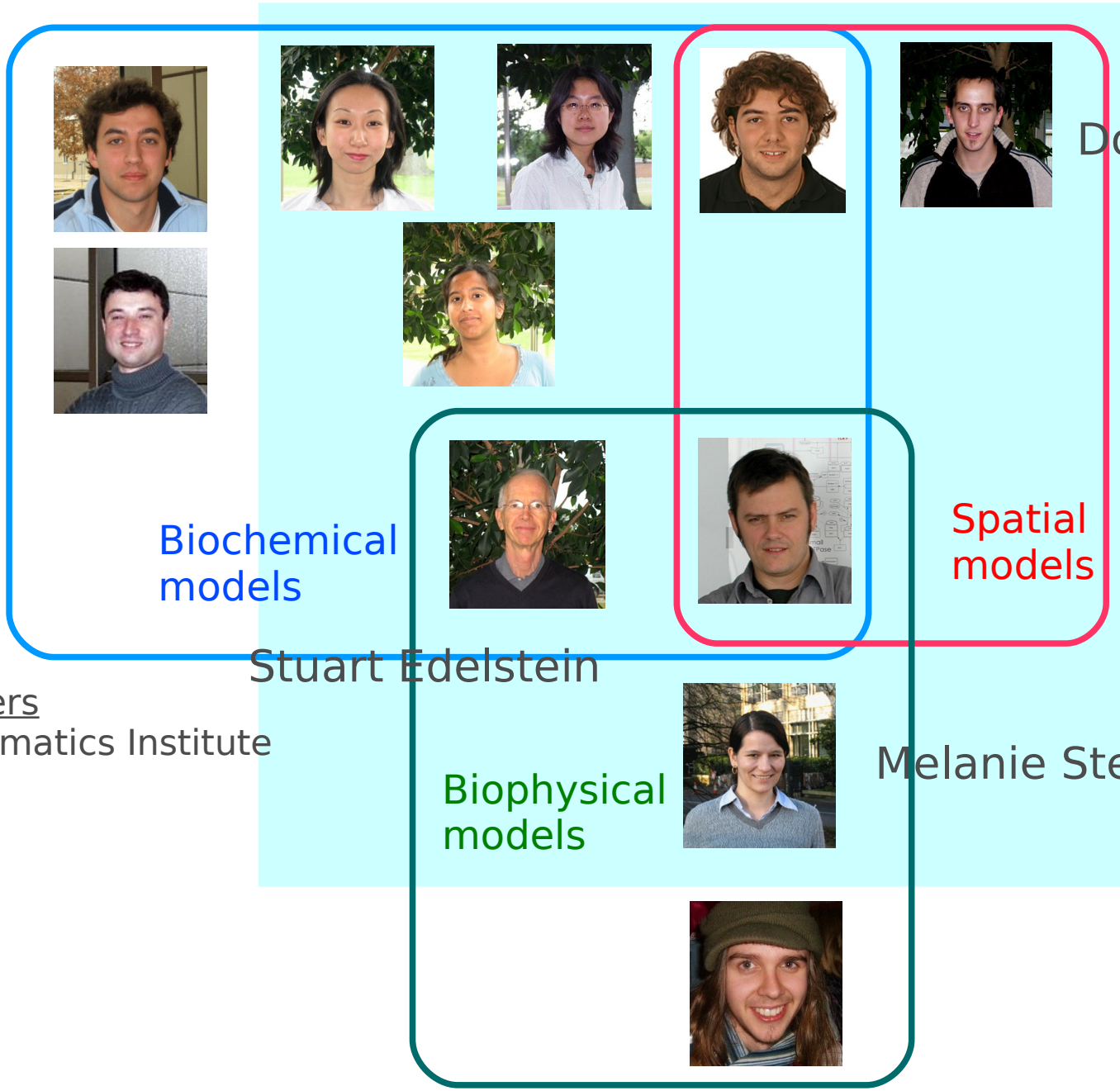

Time course of AMPA receptor binding to Scaffold elements in the PSD
binding radius 0.5 nm
Fraction of Receptors bound
time (s)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5


Receptors in PSD after 5 seconds diffusion
Faction of Receptors
1.2
1
0.8
0.6
0.4
0.2
0
0
0.1
0.5
1
Binding Radius (nm)
total
bound

Heavy ...

- 1 second of post-synaptic density with 100 receptors ~ 1 month CPU
- => Voxelisation and computing over a cluster
  1 second of synapse with 100 receptors ~ 1 day
- 1 second of synapse generates ... 10 Terabytes of data (positions and orientation of each cluster at each timepoint)

Acknowledgements



- COPASI developers
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  EML-research)

  Ursula Kummer
  Pedro Mendes
  Stefan Hoops
  Sven Sahle
  Ralf Gauges