EMBL-EBI

Multi-scale modelling of neuronal signalling

Nicolas Le Novère, EMBL-EBI

6th Conference on Computational Methods in Systems Biology,
Warnemünde, Rostock, 13-15 Oct 2008

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Modelling of neuronal signalling at multiple scales

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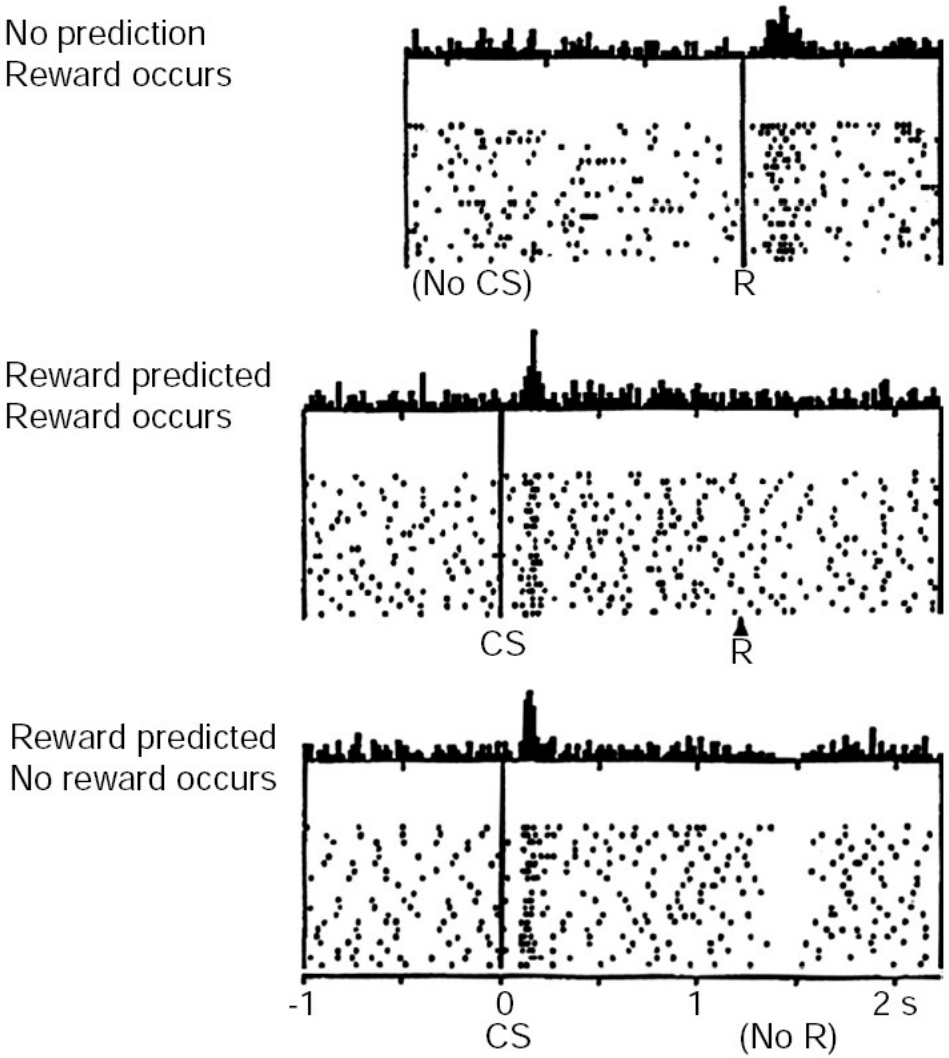
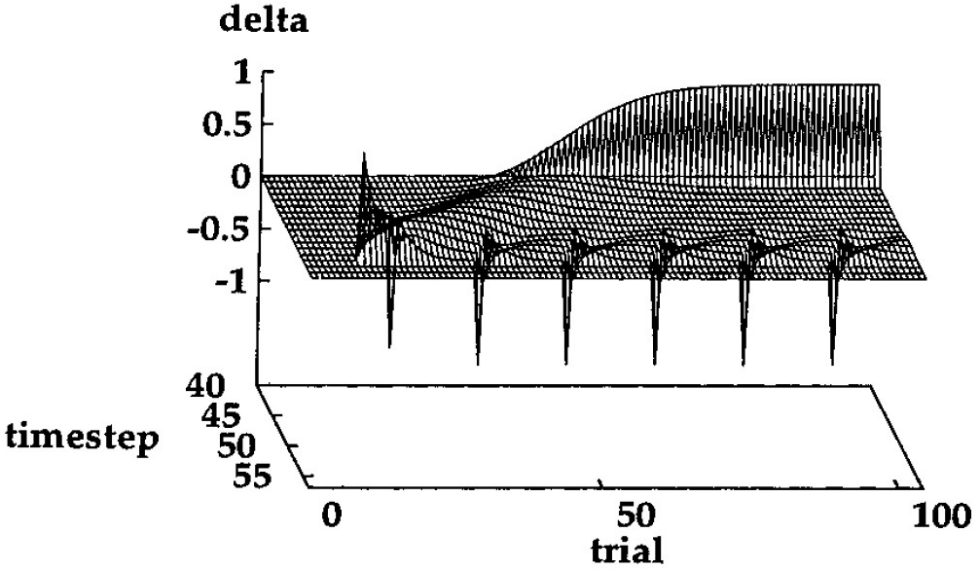
Dopamine, reward and learning

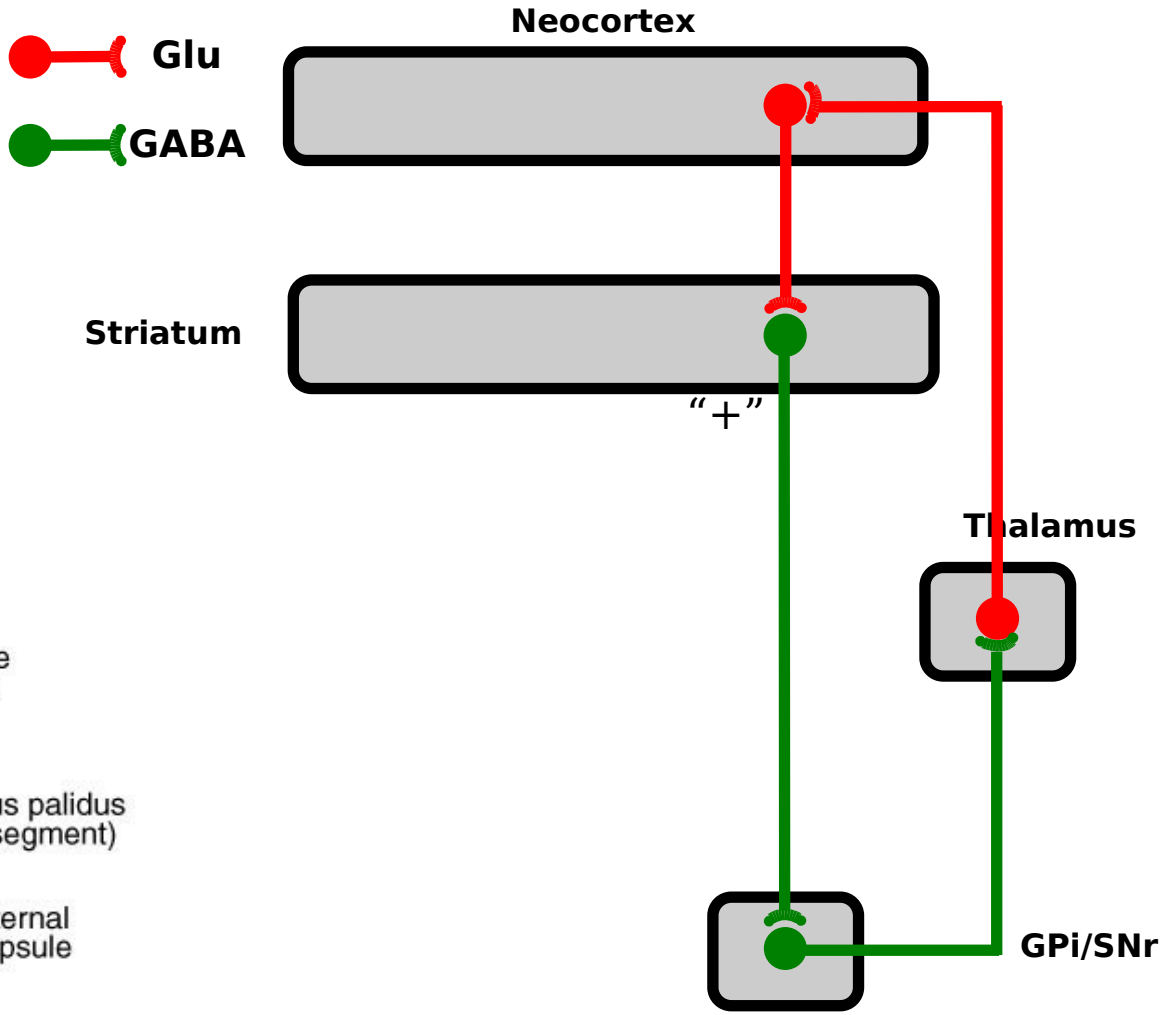


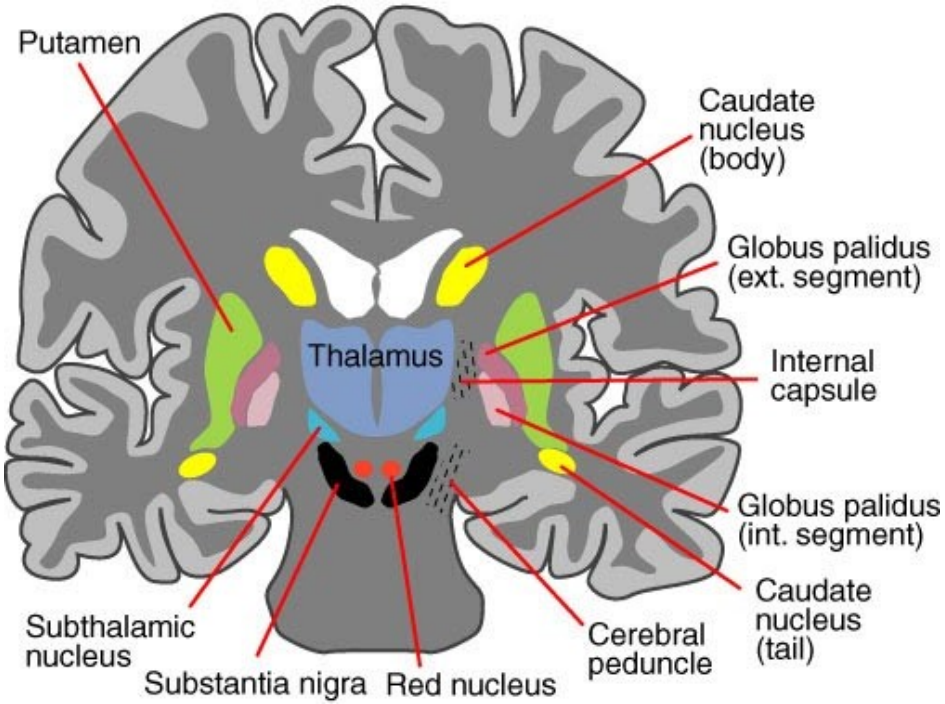
Schultz W, Dayan P, Montague PR (1997)
A neural substrate of prediction and reward.
Science 275:1593-1599.



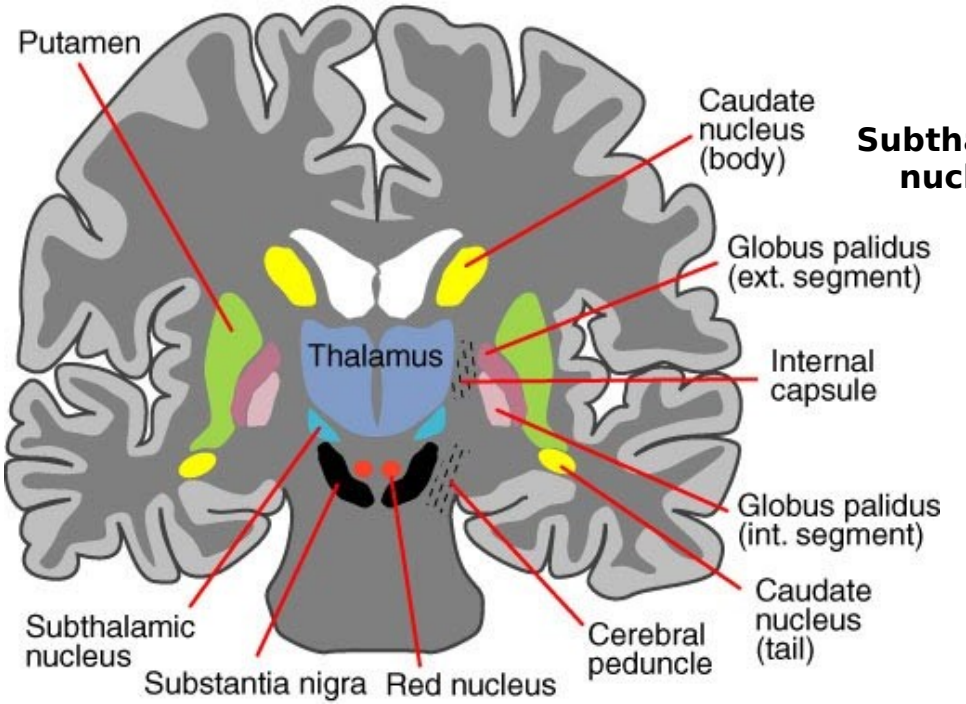
Montague PR, Dayan P, Sejnowski TJ (1996)
A framework for mesencephalic dopamine systems based on predictive Hebbian learning.
J Neurosci 16: 1936-1947

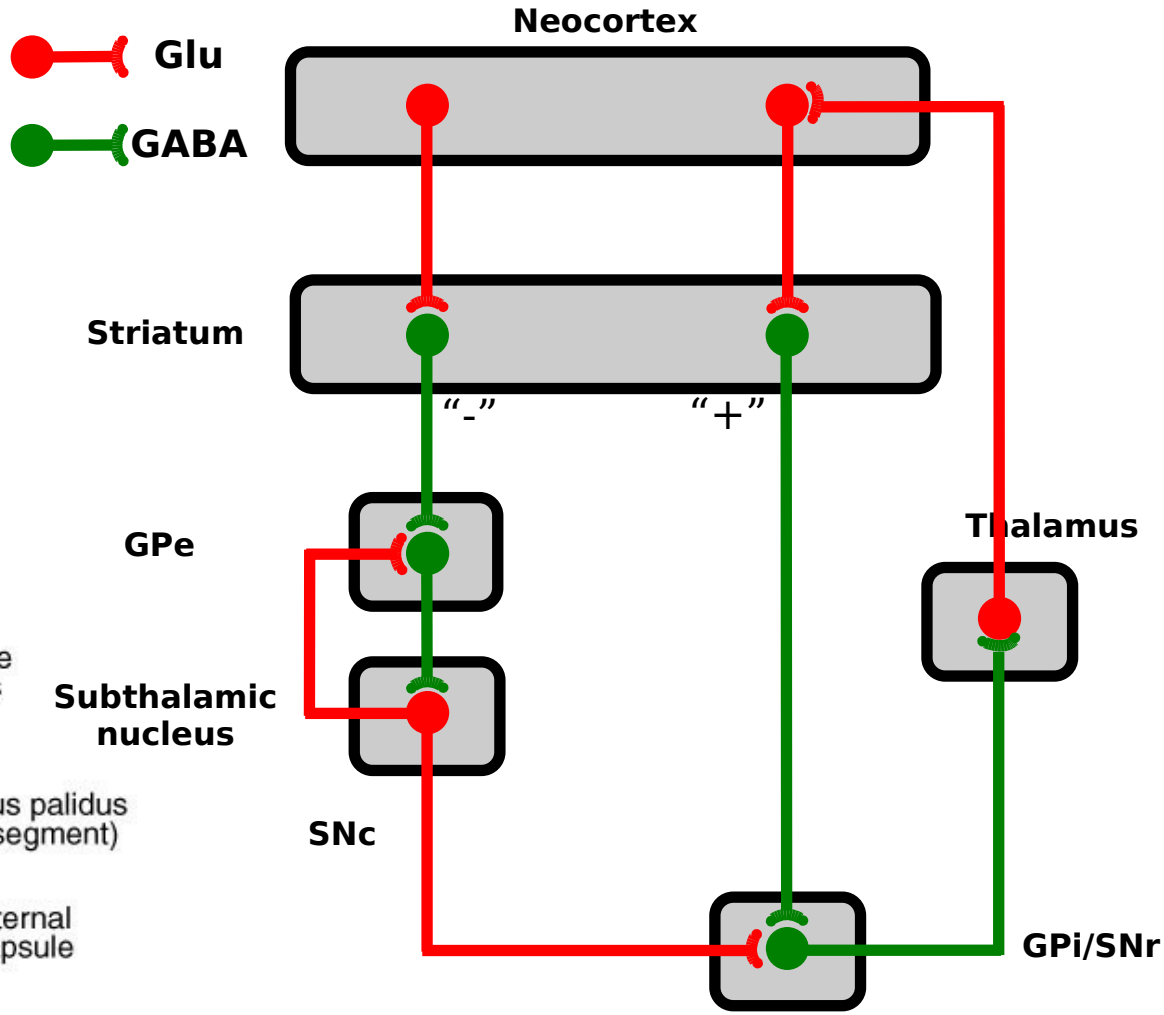
Dopamine mesotelencephalic pathway





Dopamine mesotelencephalic pathway





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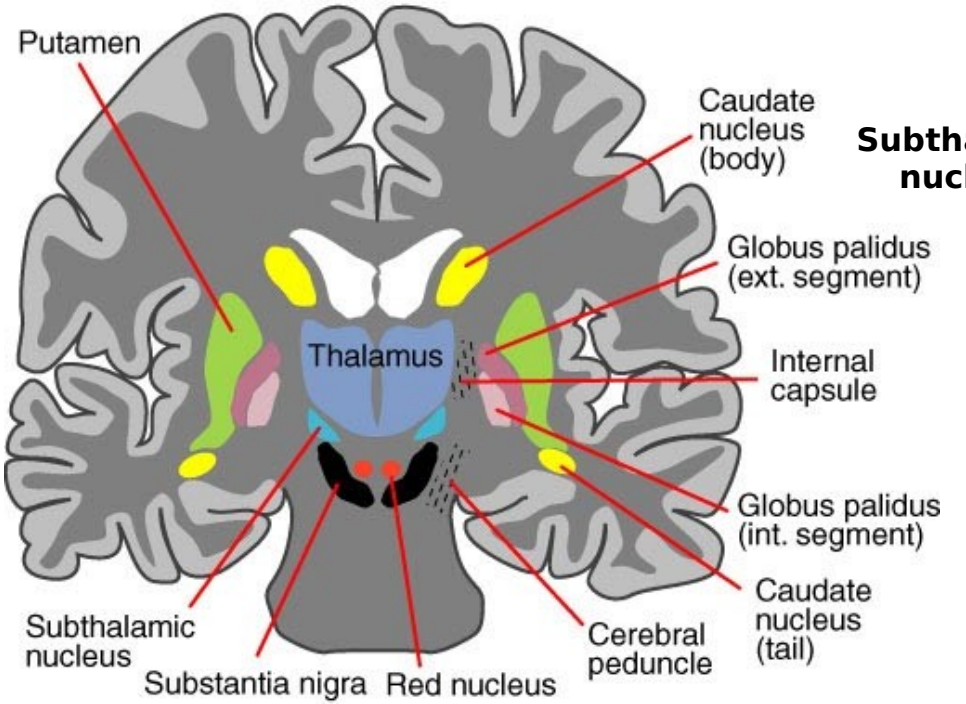
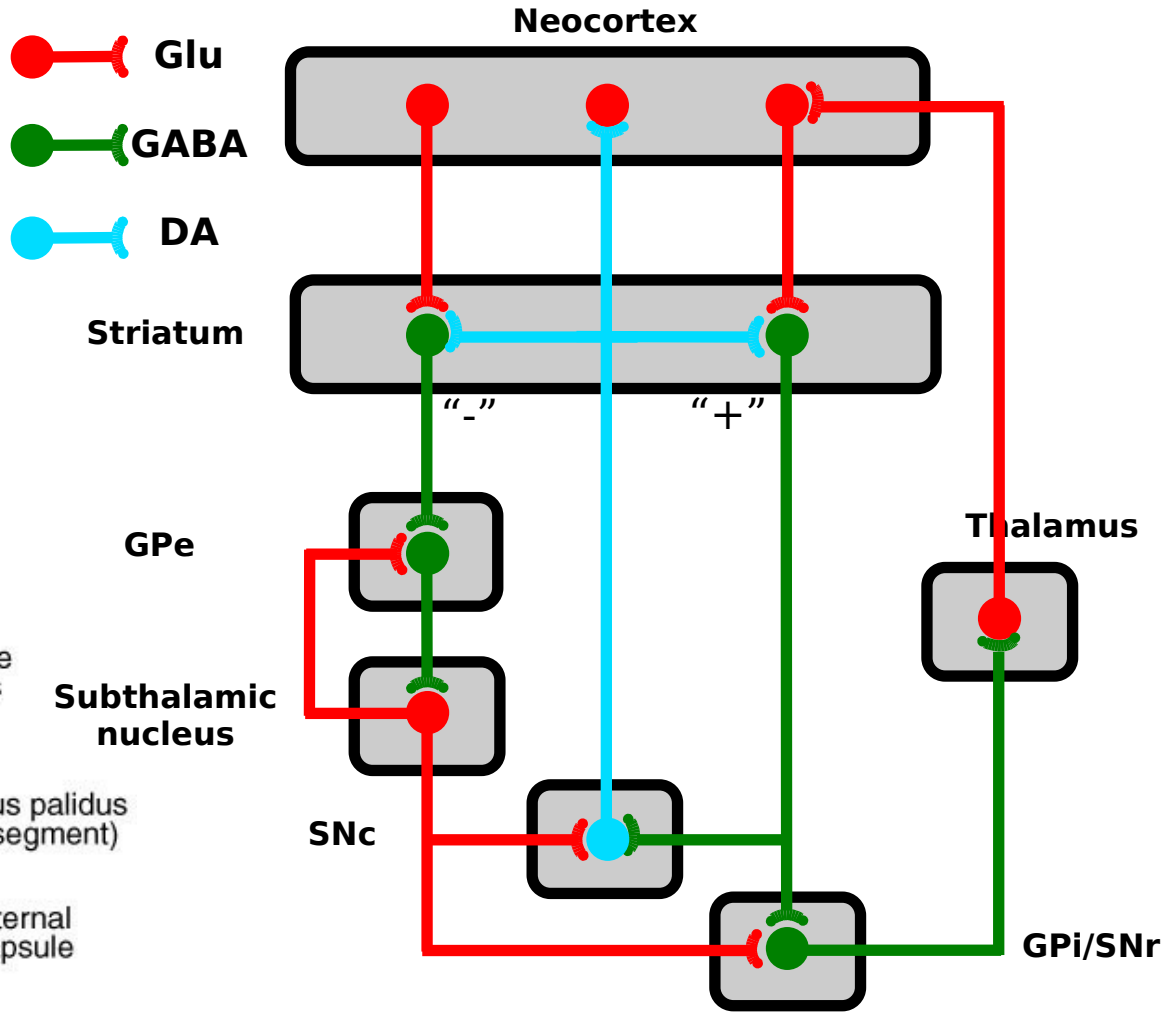
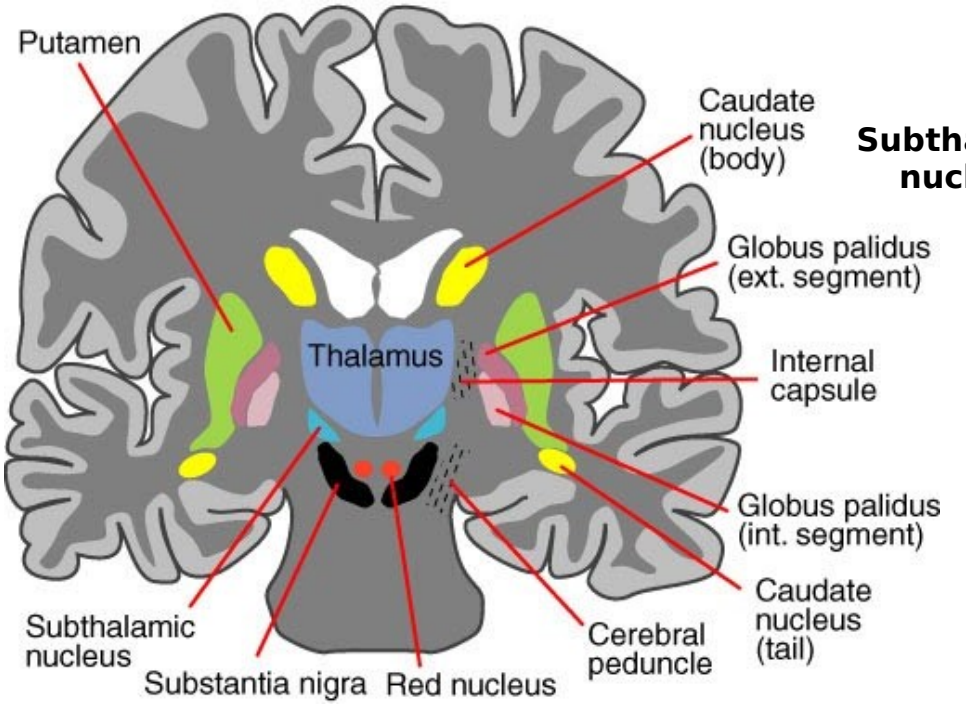
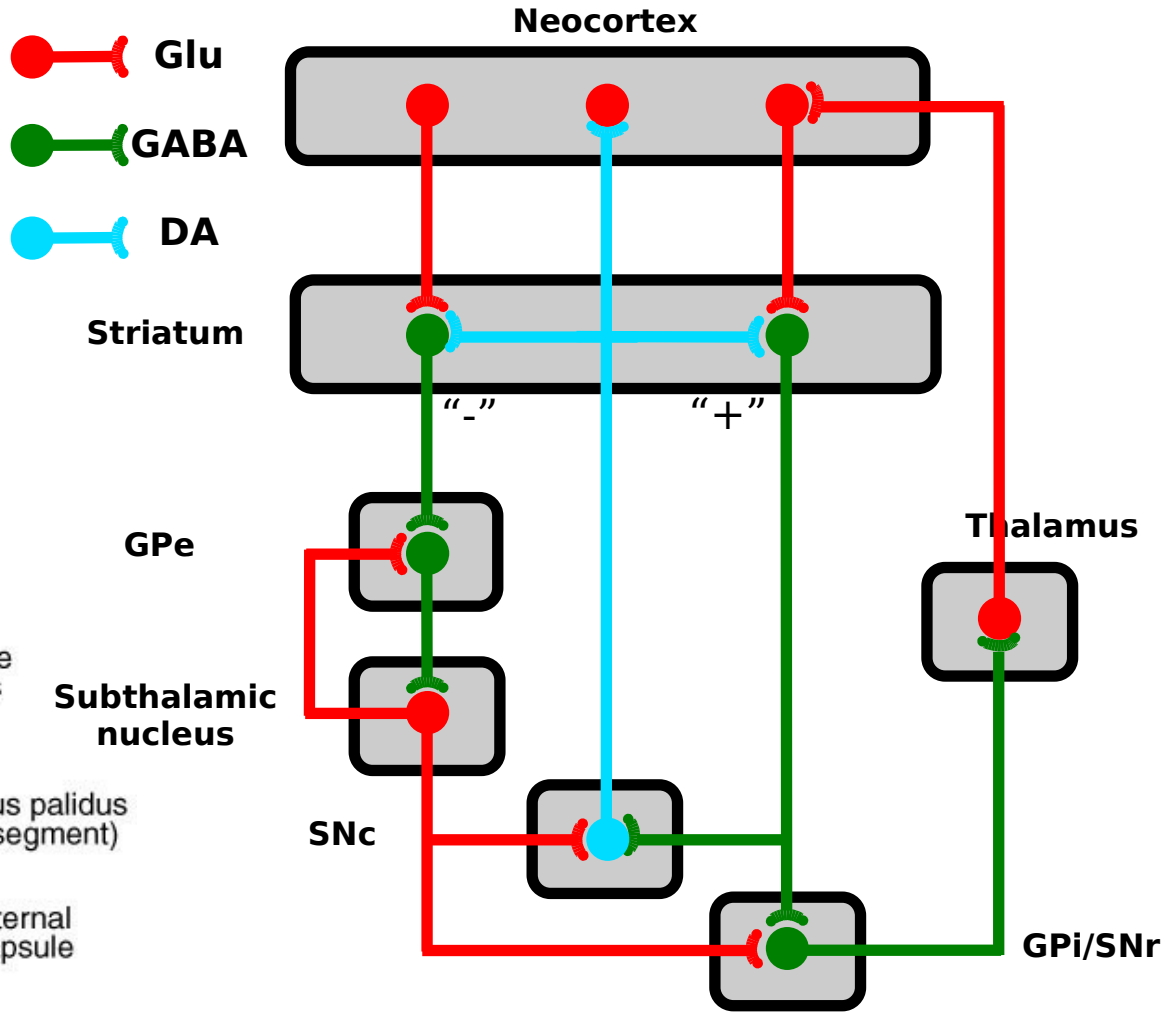




Dopamine mesotelencephalic pathway

Voluntary motion
Emotional control
Reward
Learning

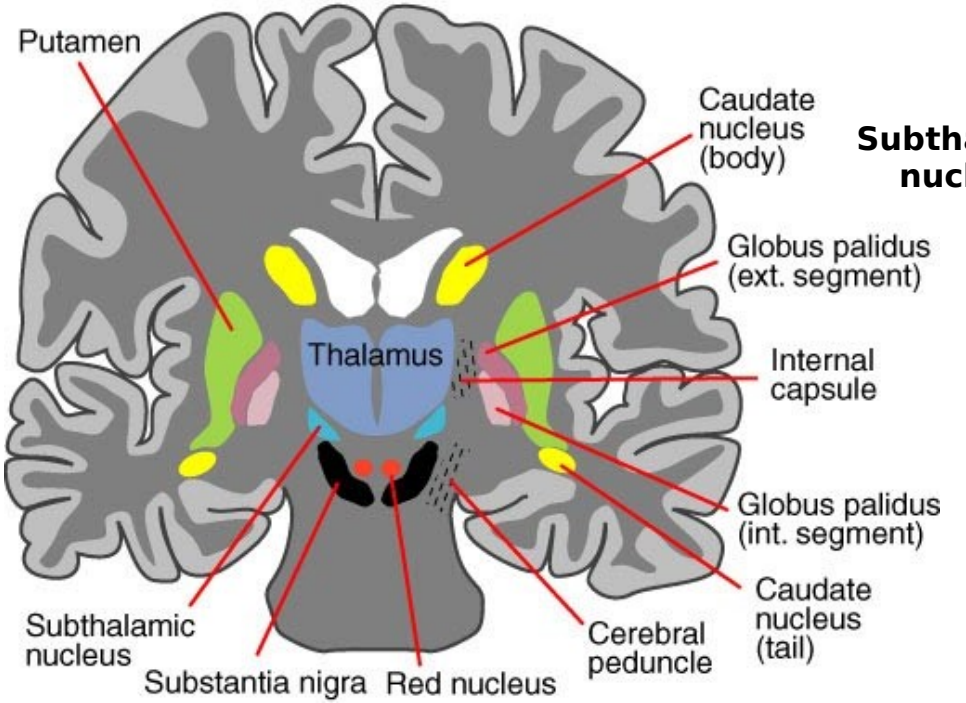


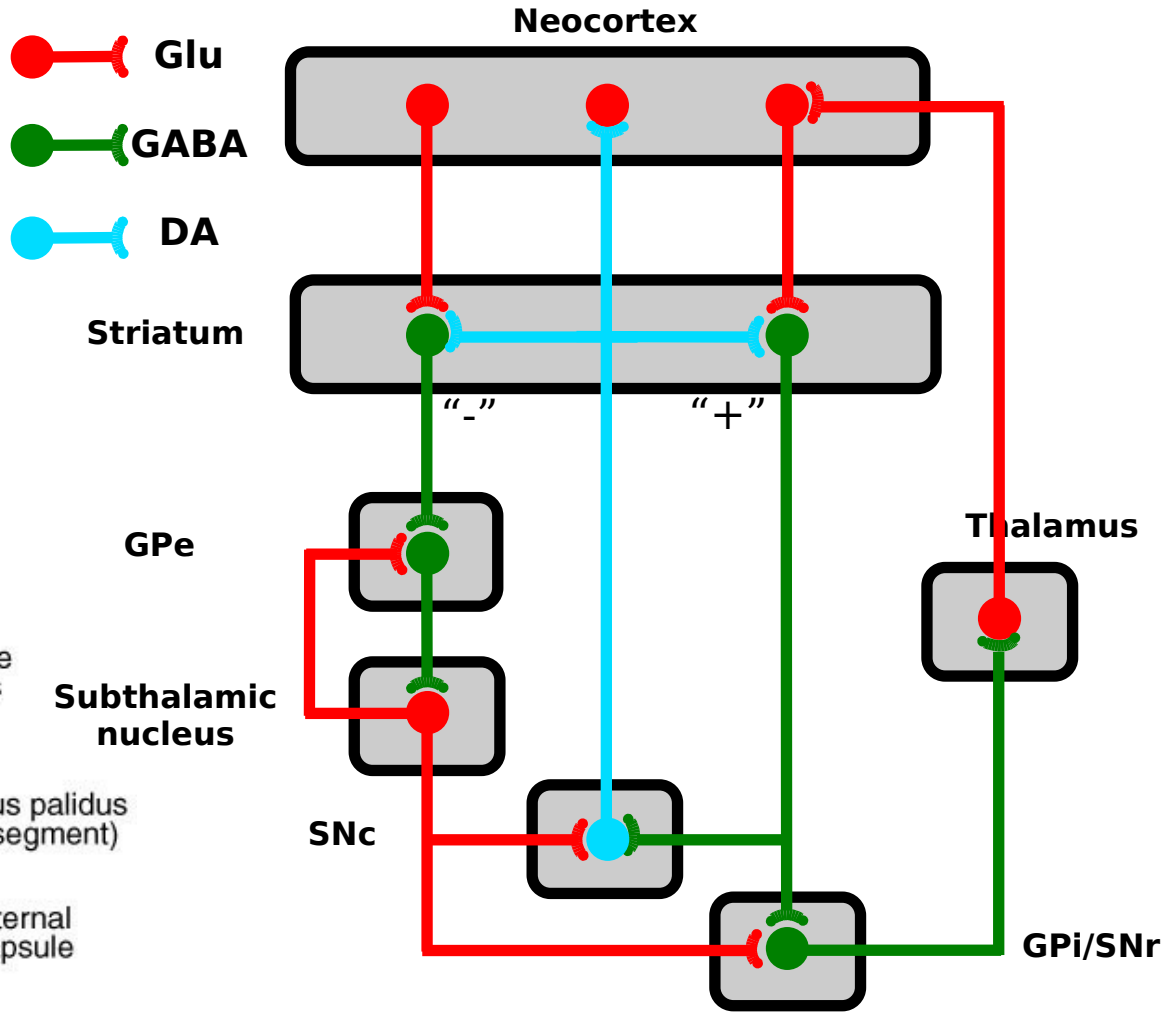


Dopamine mesotelencephalic pathway

Voluntary motion
Emotional control
Reward
Learning

Parkinson's disease
Huntington's chorea
Hemibalism
Schizophrenia
Drug addiction
Depression
Obsessive-Compulsive Disorder
Tourette syndrome
ADHD





Dopamine mesotelencephalic pathway

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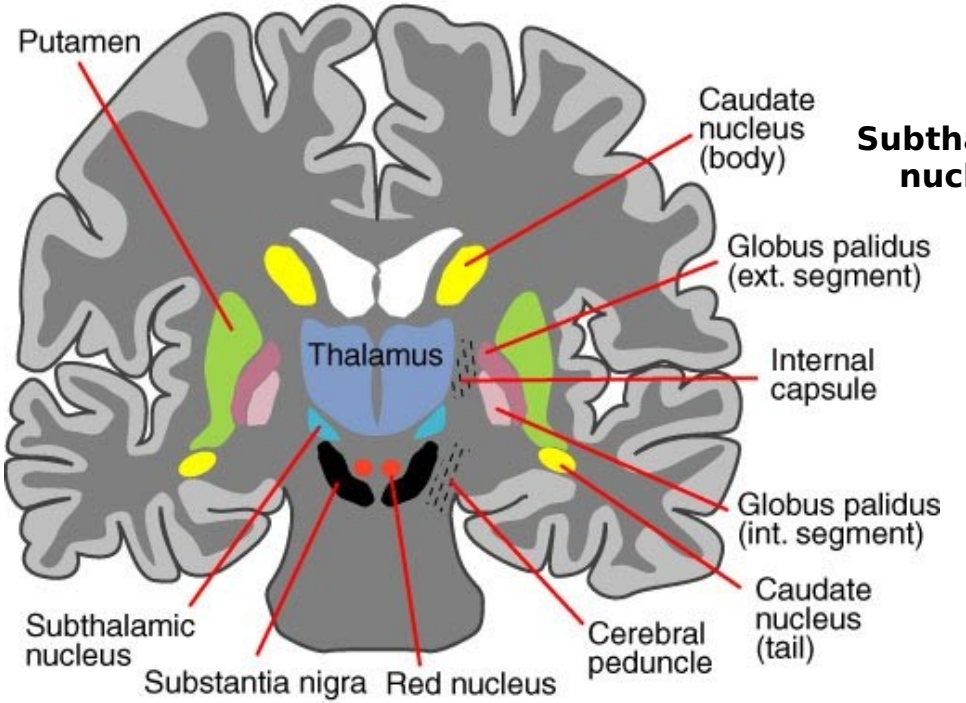
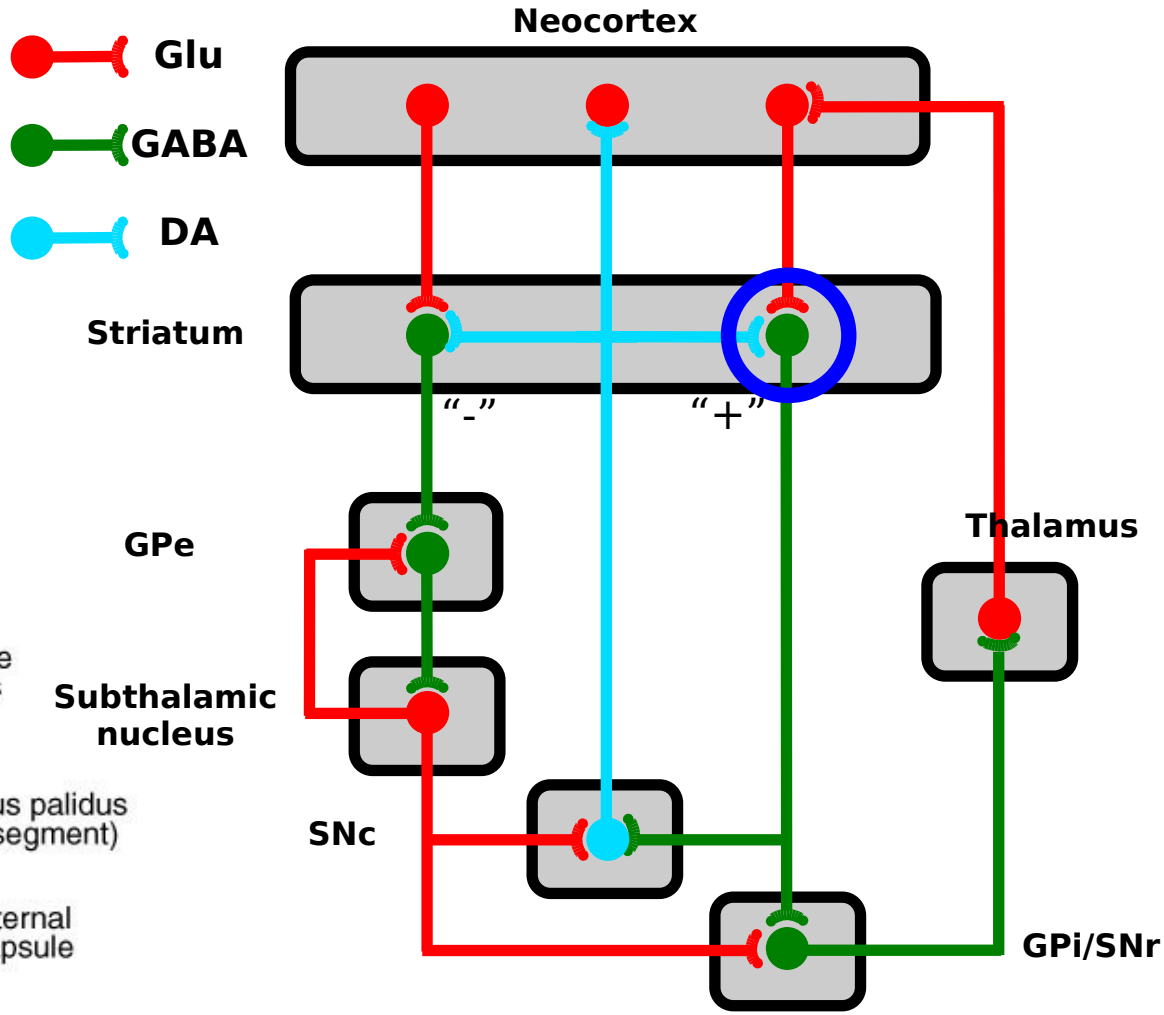
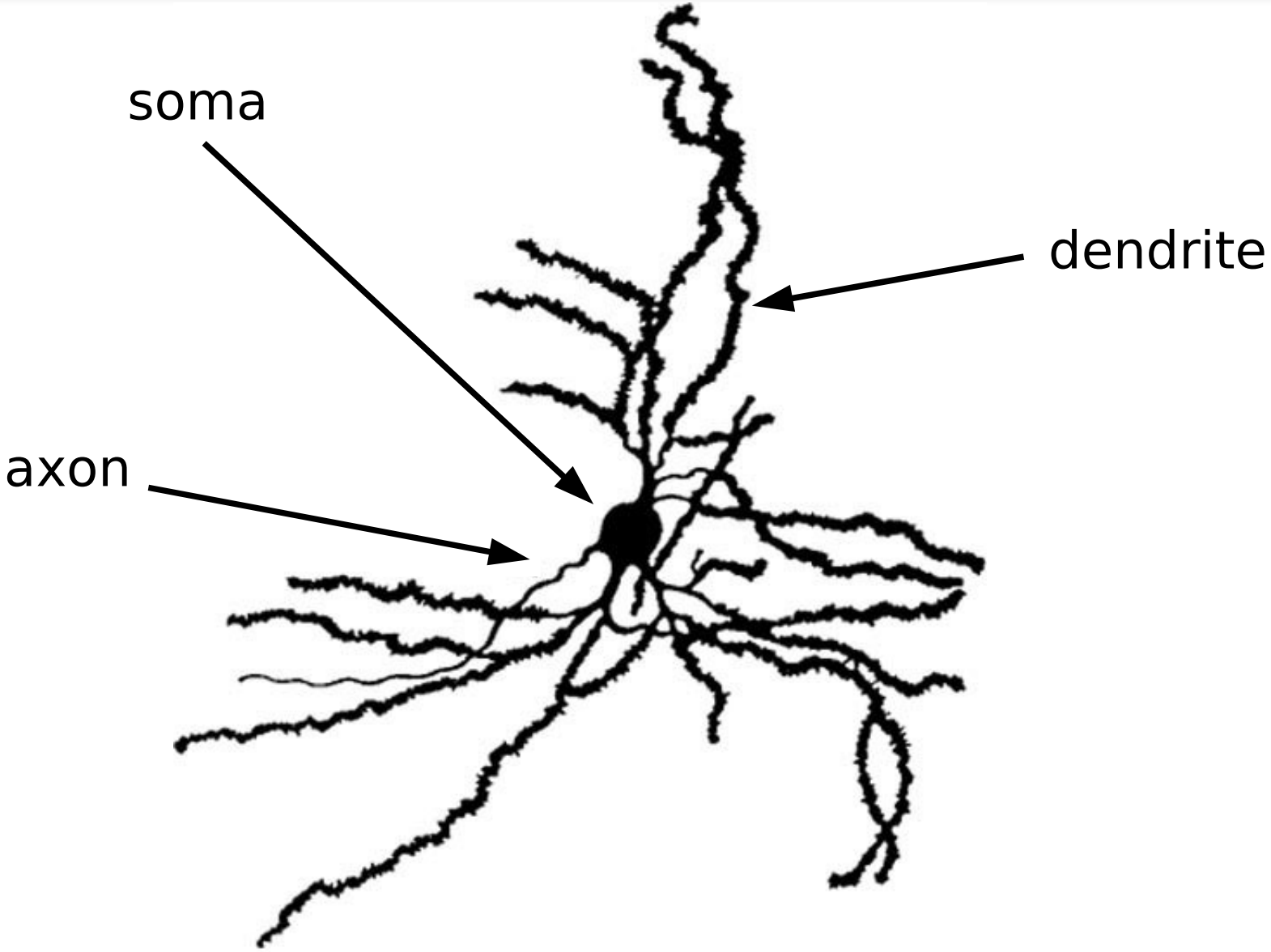
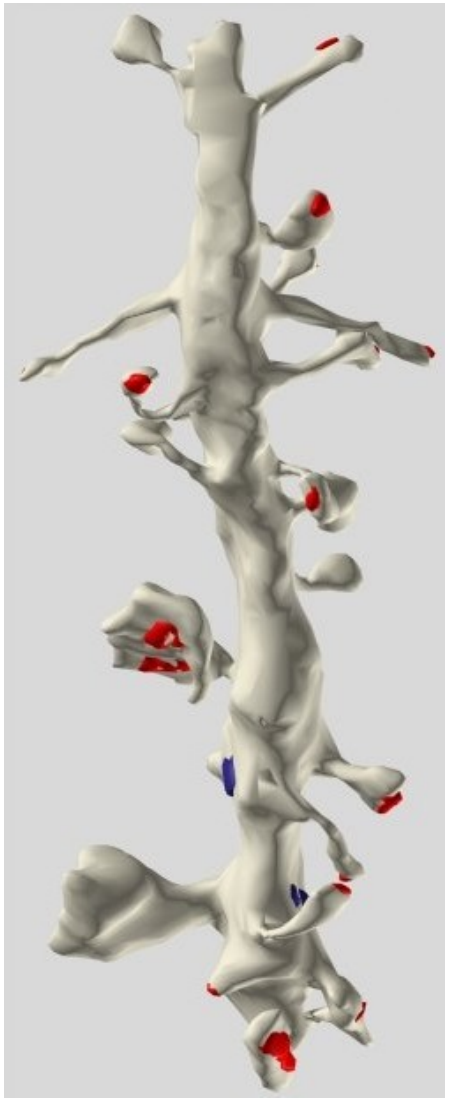


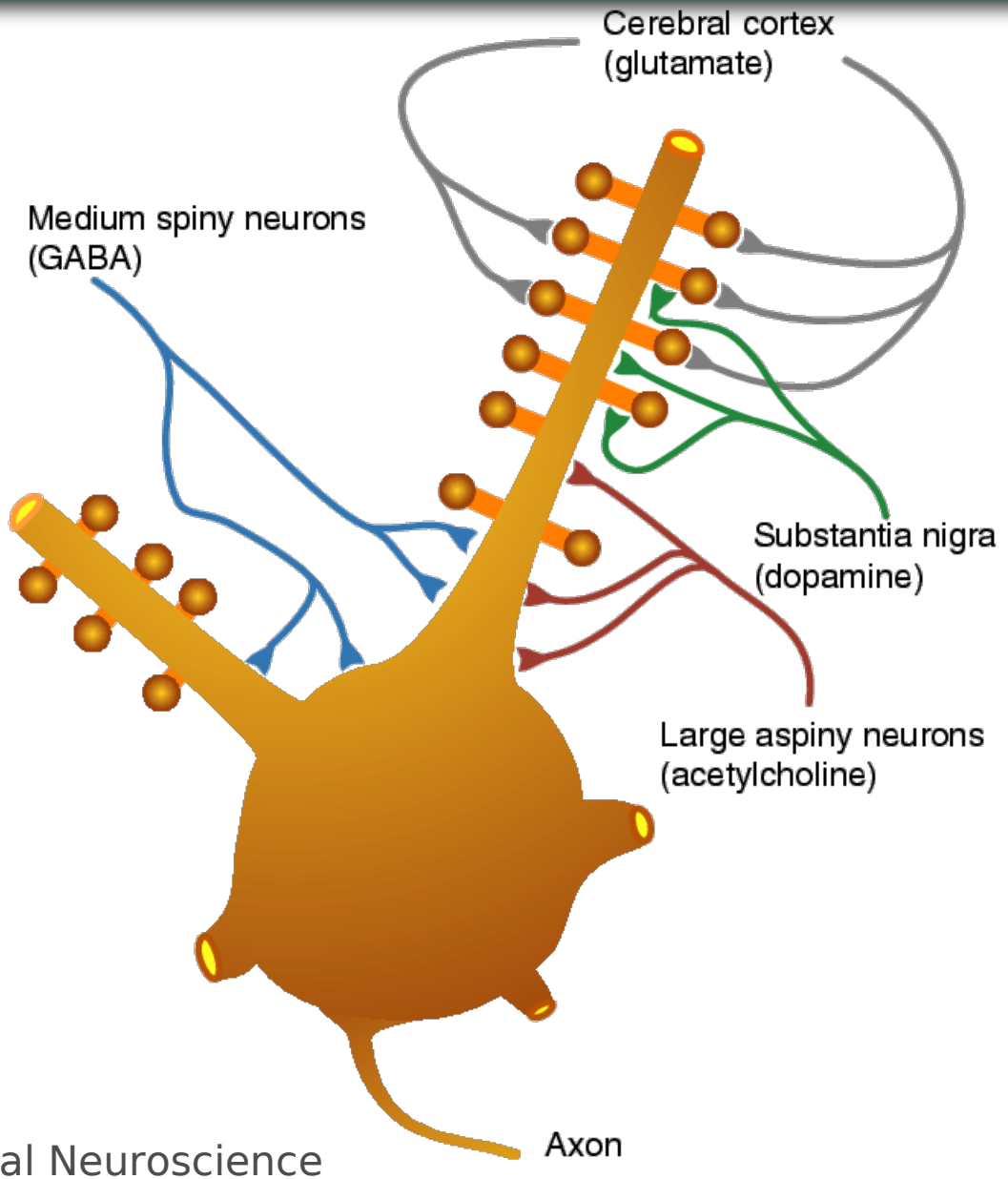


Structure of a medium-spiny neuron



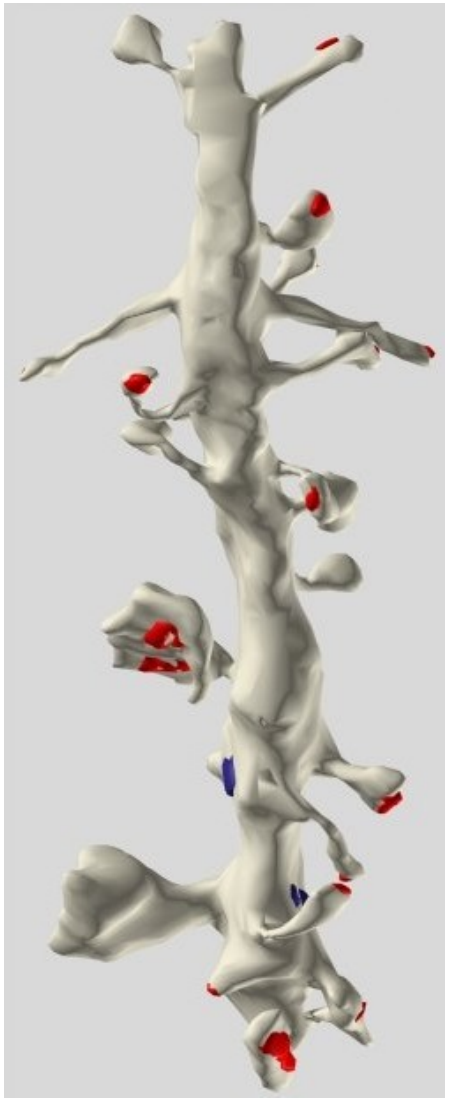
Multiple afferent signals

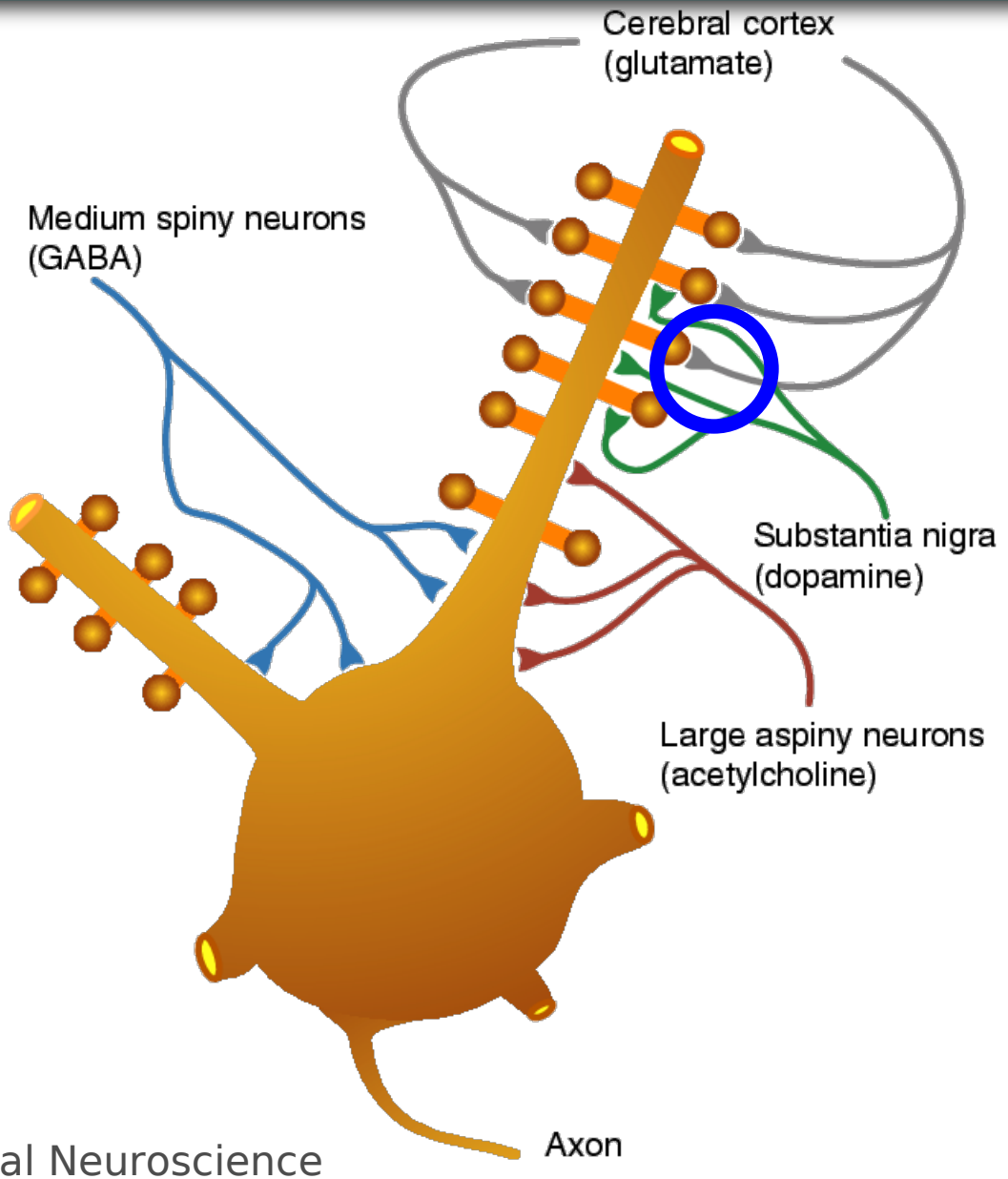




Fundamental Neuroscience
Squire et al. 2nd ed(2003)

Multiple afferent signals



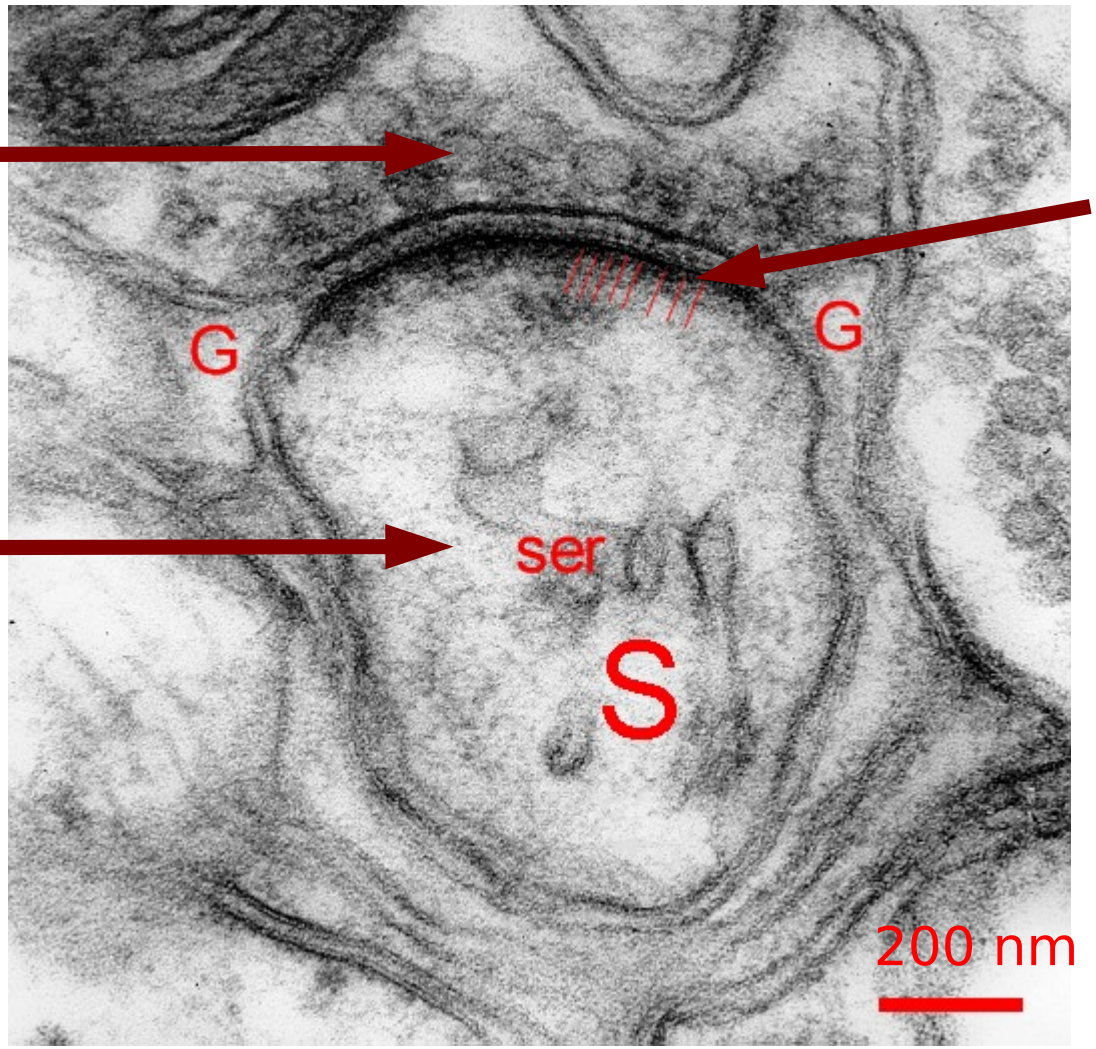


Fundamental Neuroscience
Squire et al. 2nd ed(2003)

The spine as a “mini-cell”

pre-synaptic neuron

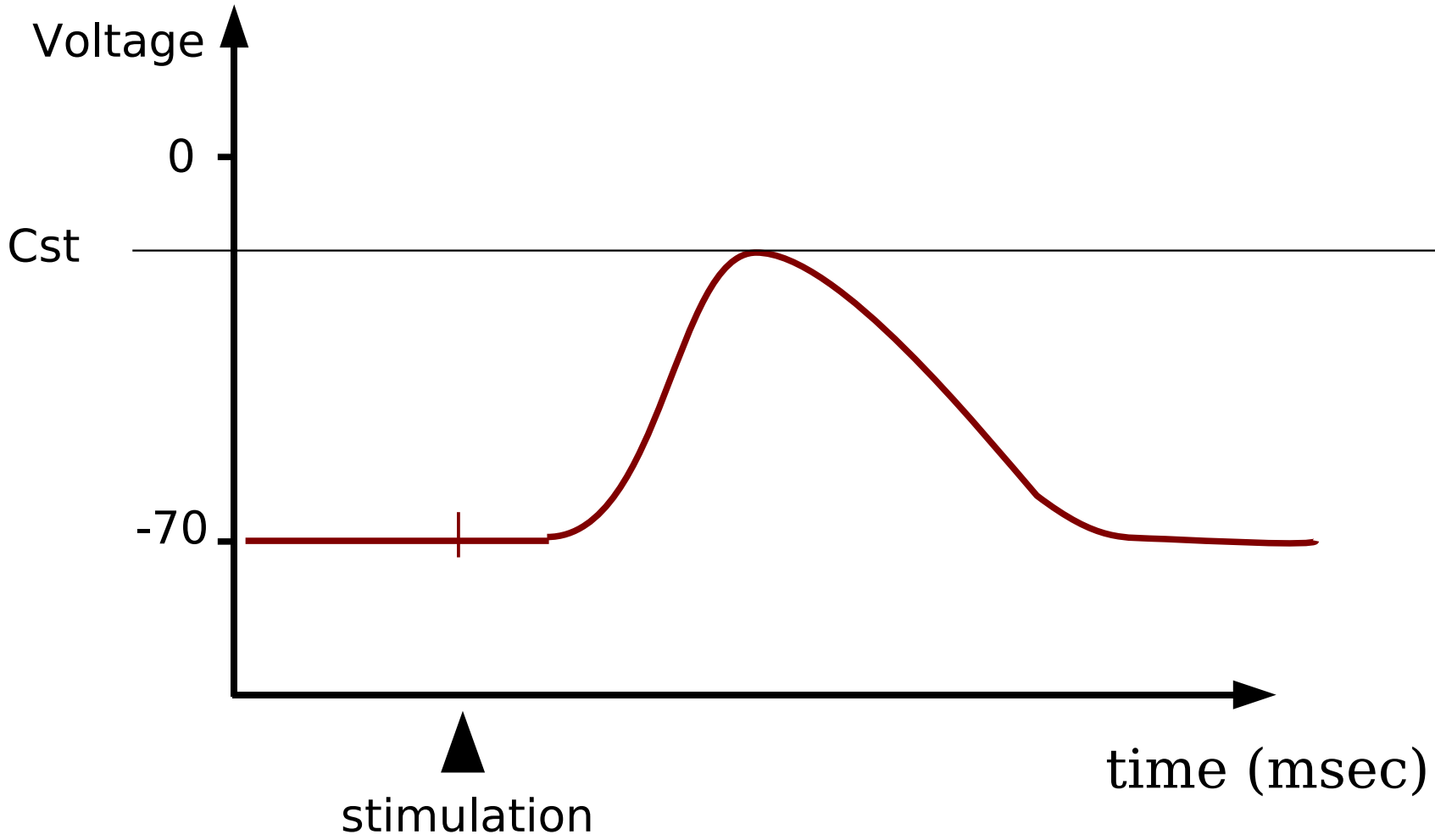
Dendritic spine



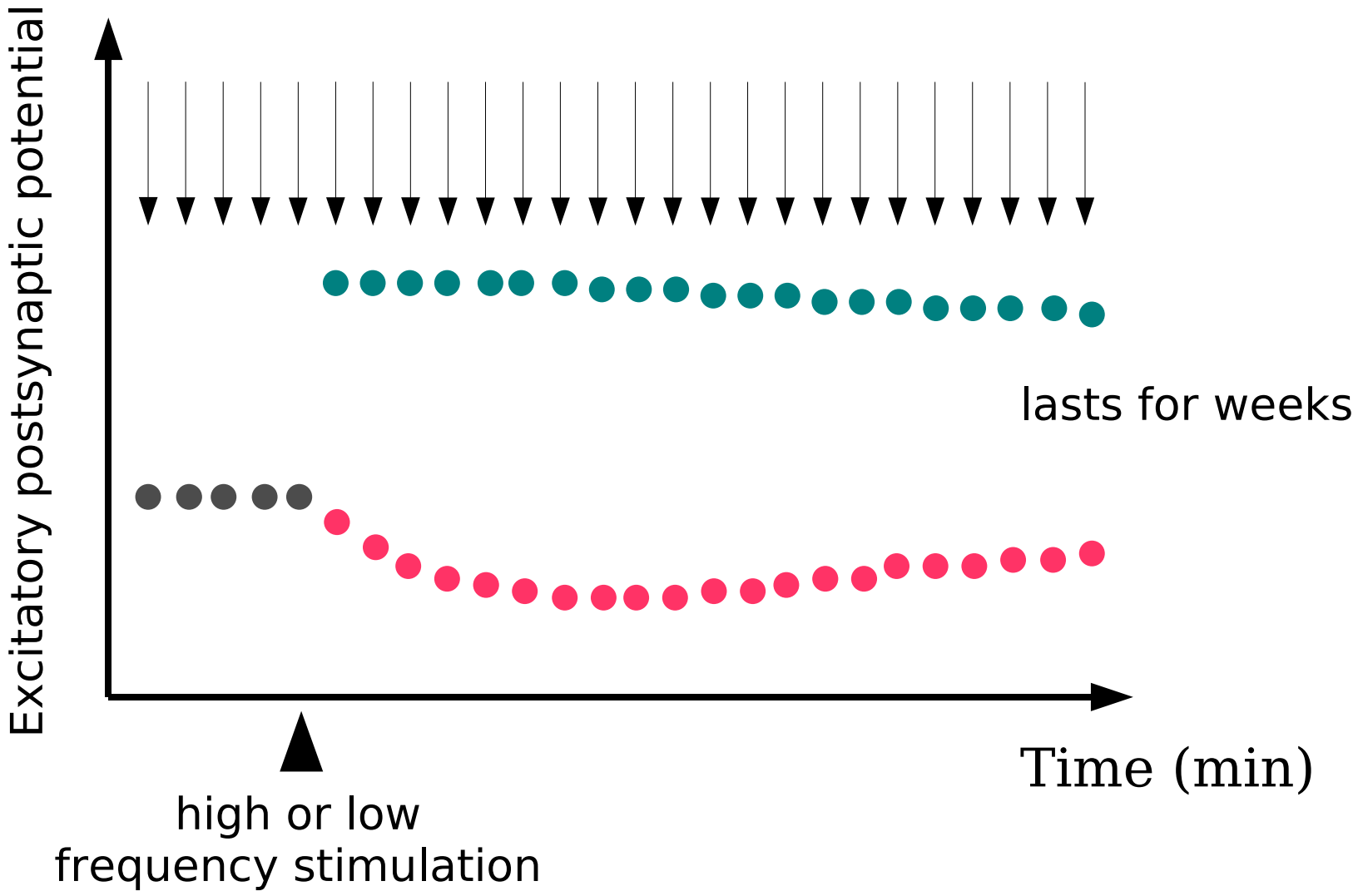
post-synaptic density

Atlas of ultrastructural neurocytology (http://synapse-web.org/)

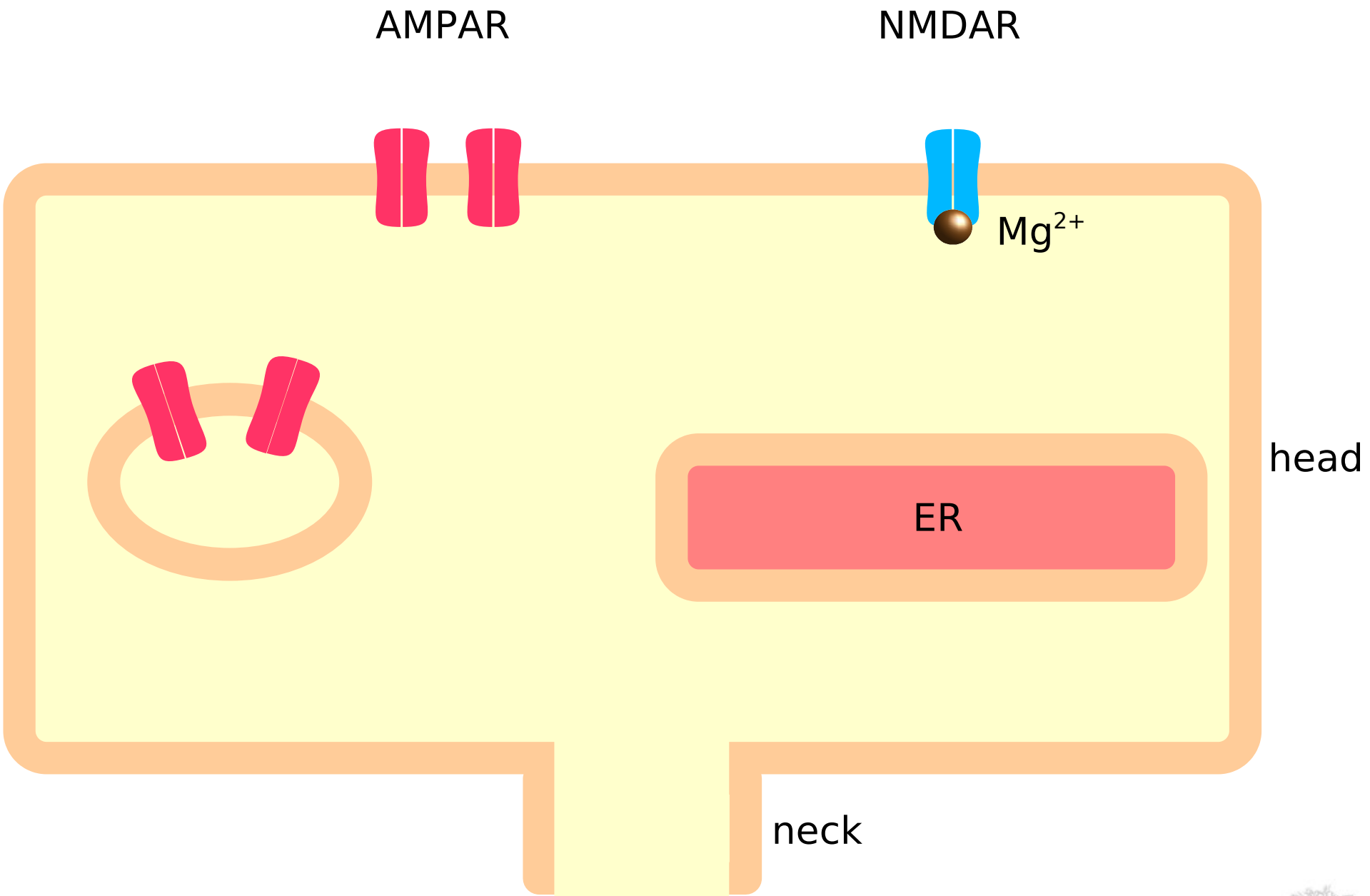
Excitatory post-synaptic potential



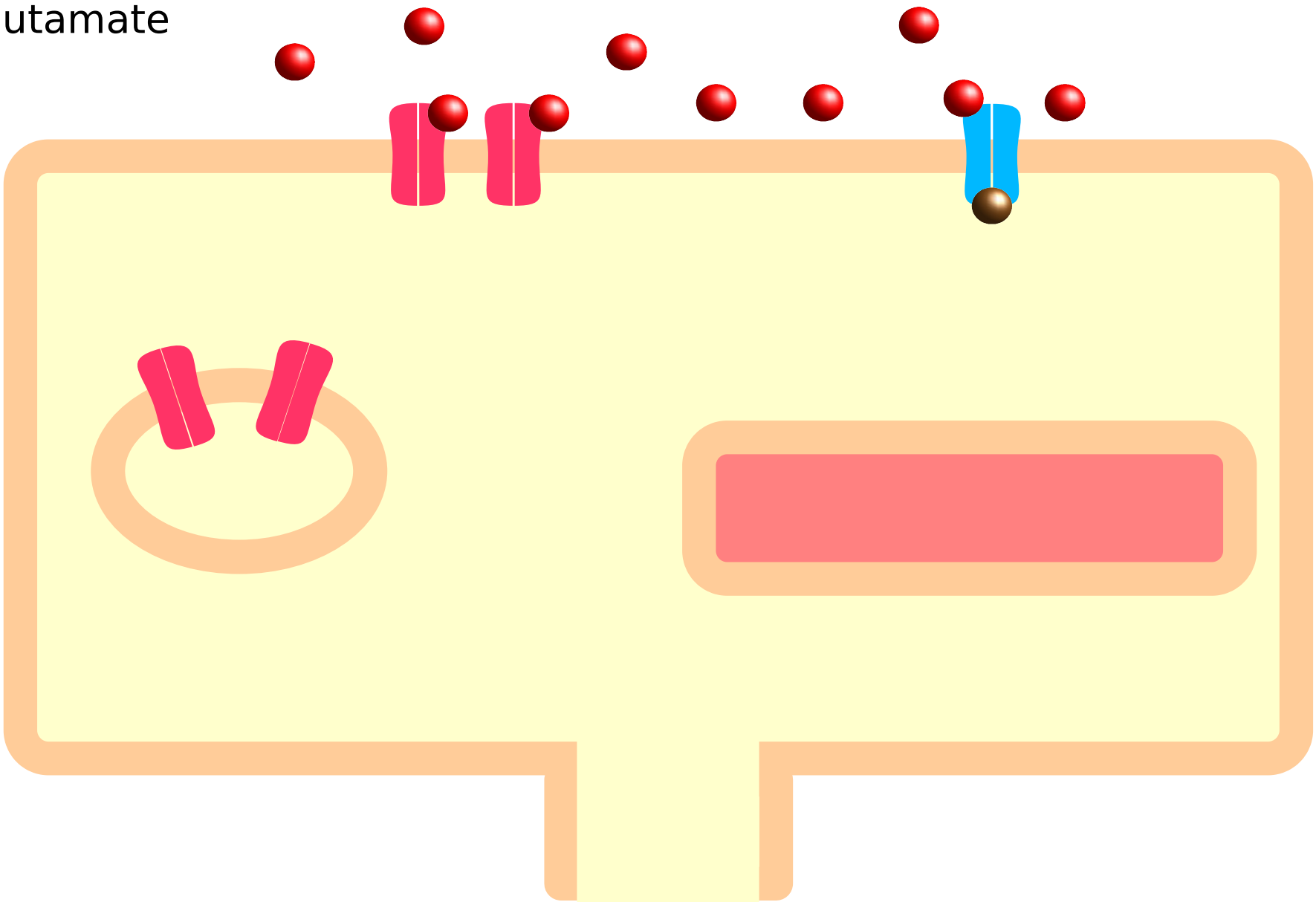
Bidirectional synaptic plasticity



Signalling at the dendritic spine



Signalling at the dendritic spine



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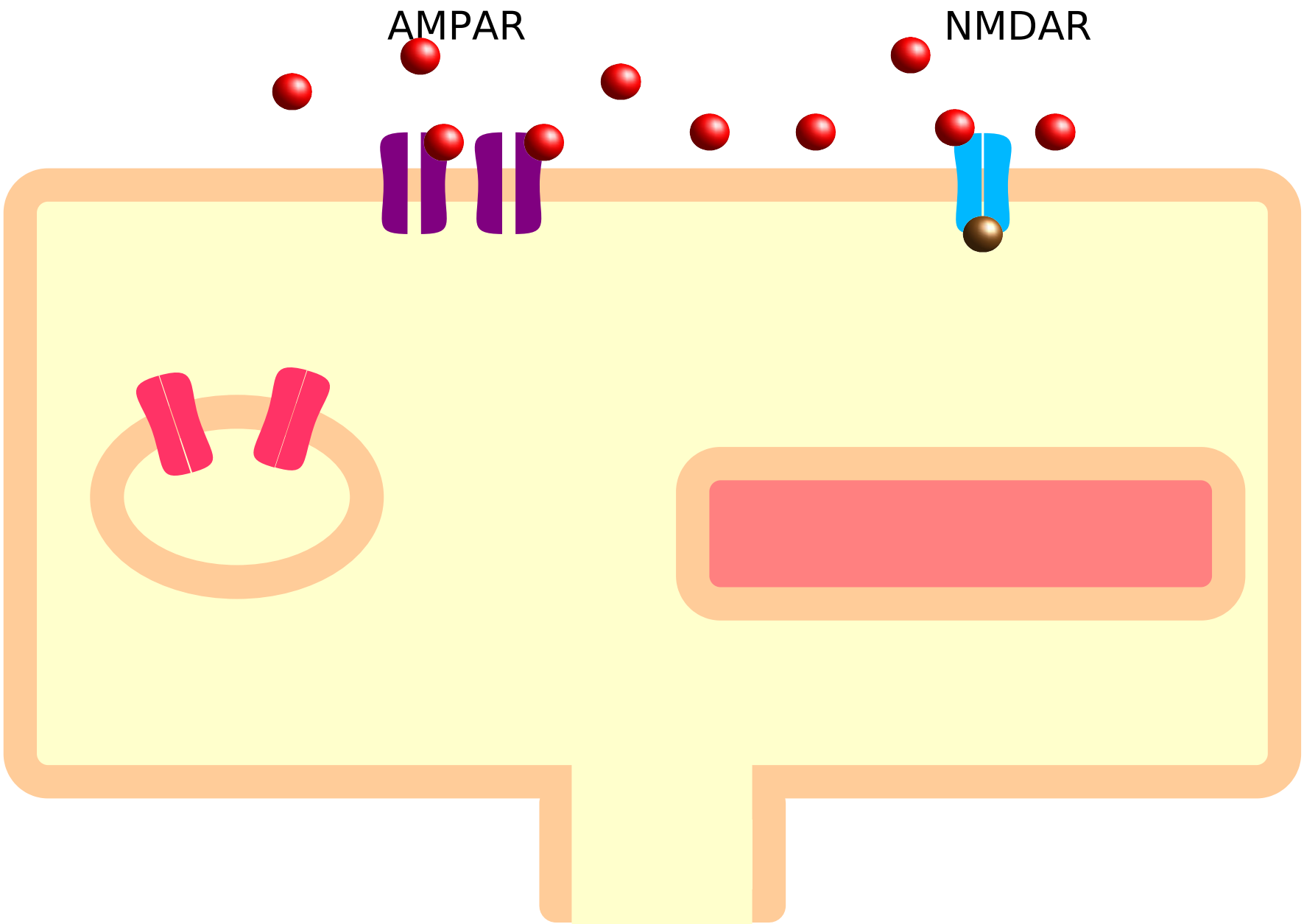
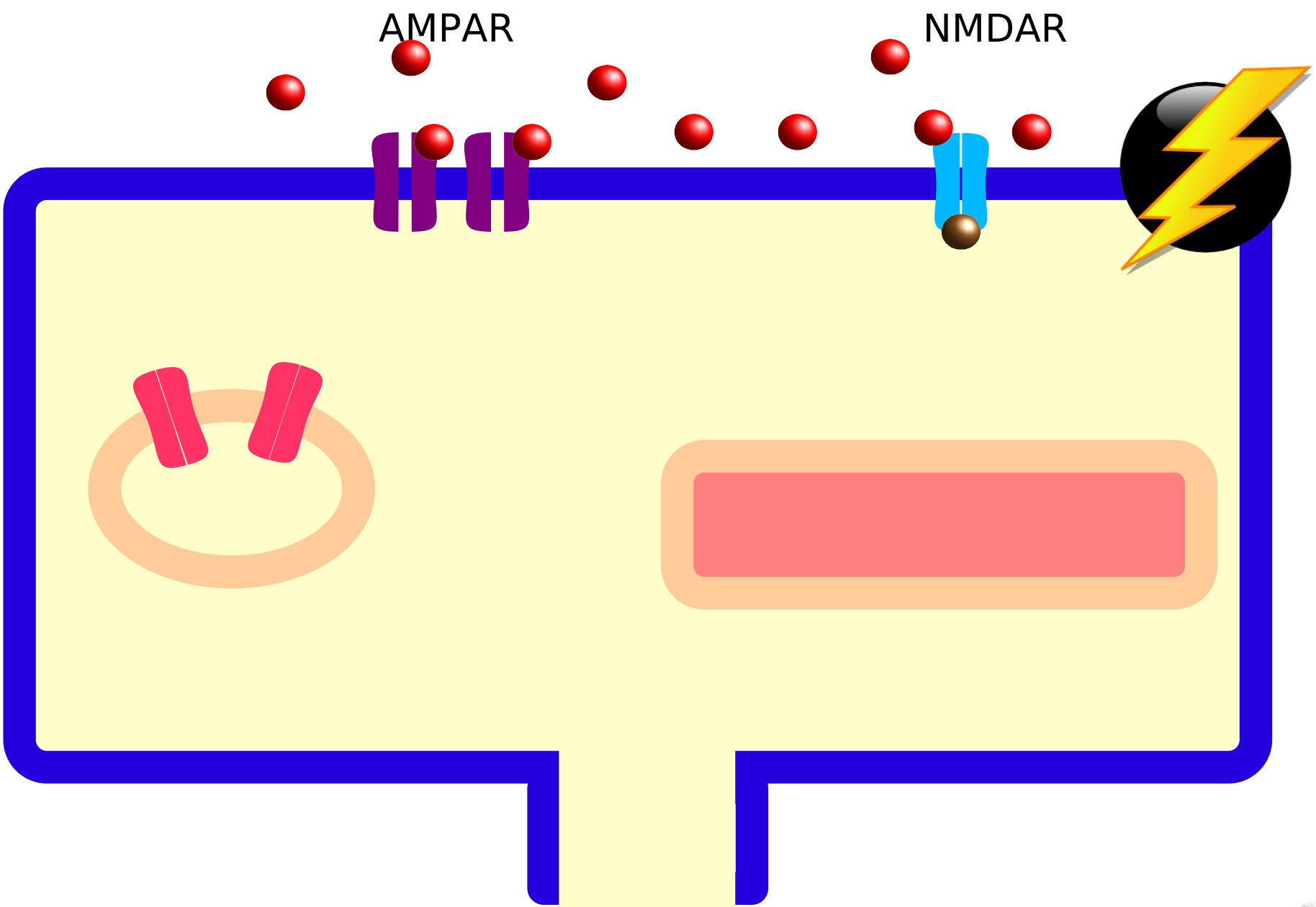
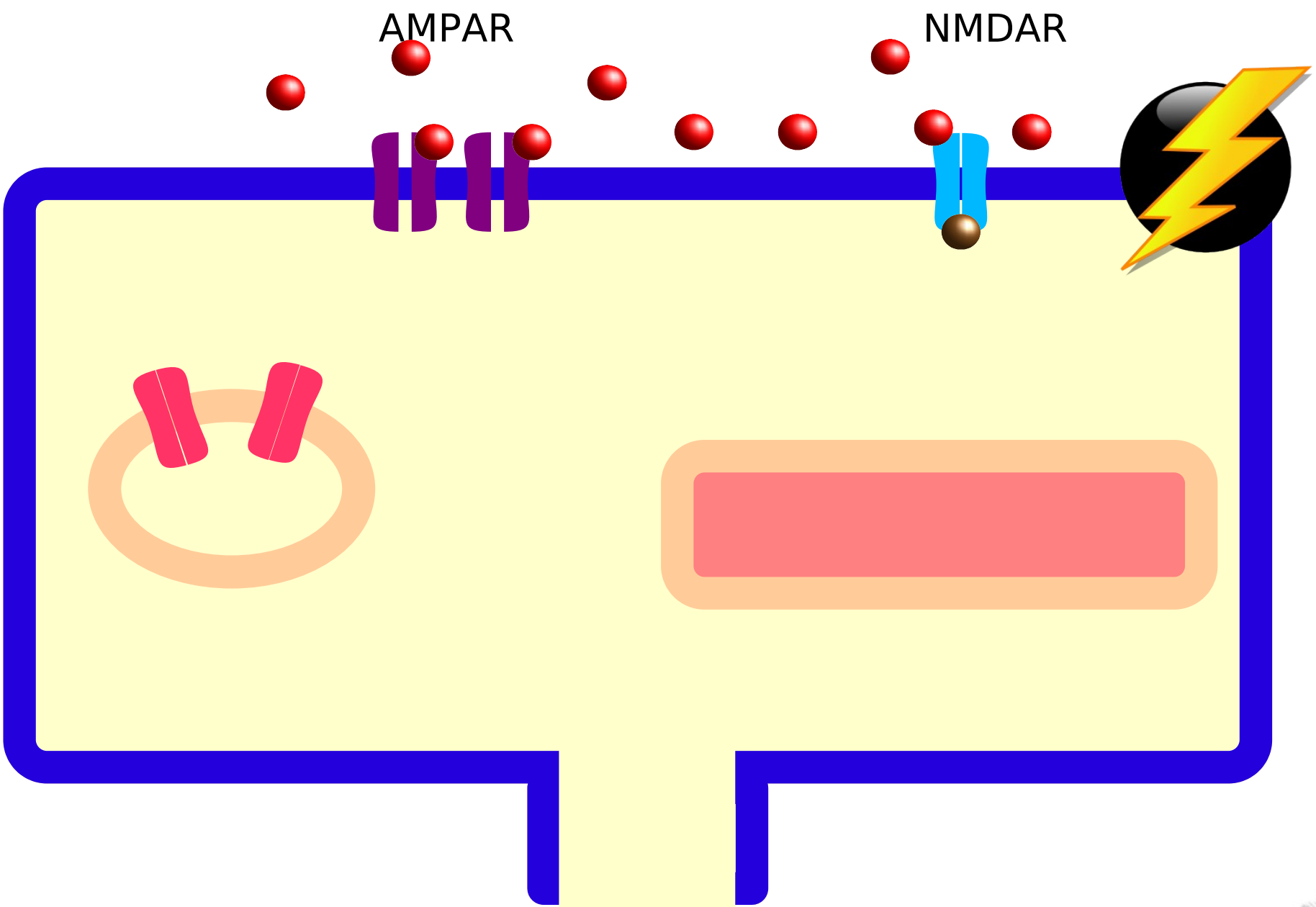


Signalling at the dendritic spine



Signalling at the dendritic spine



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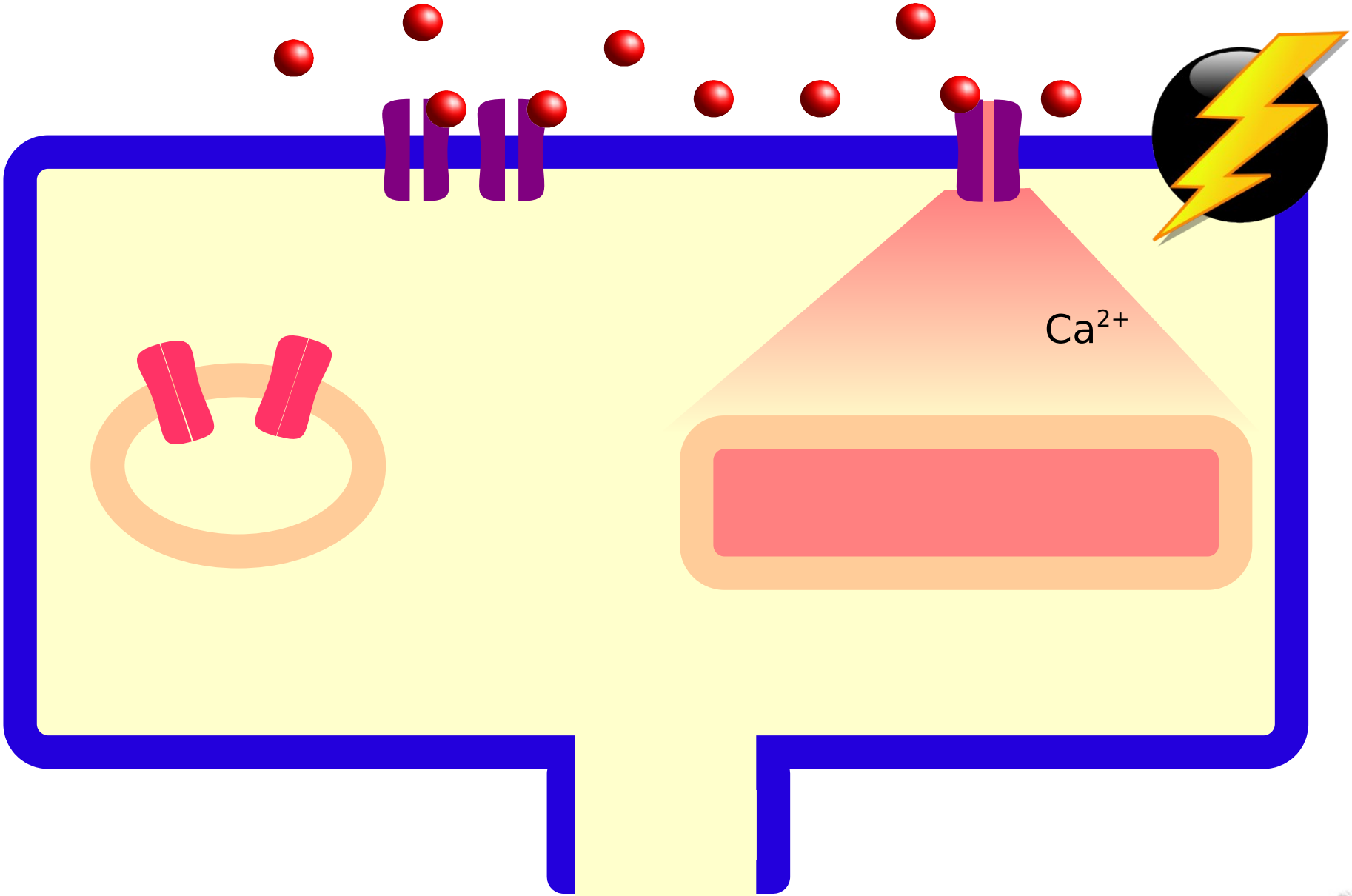

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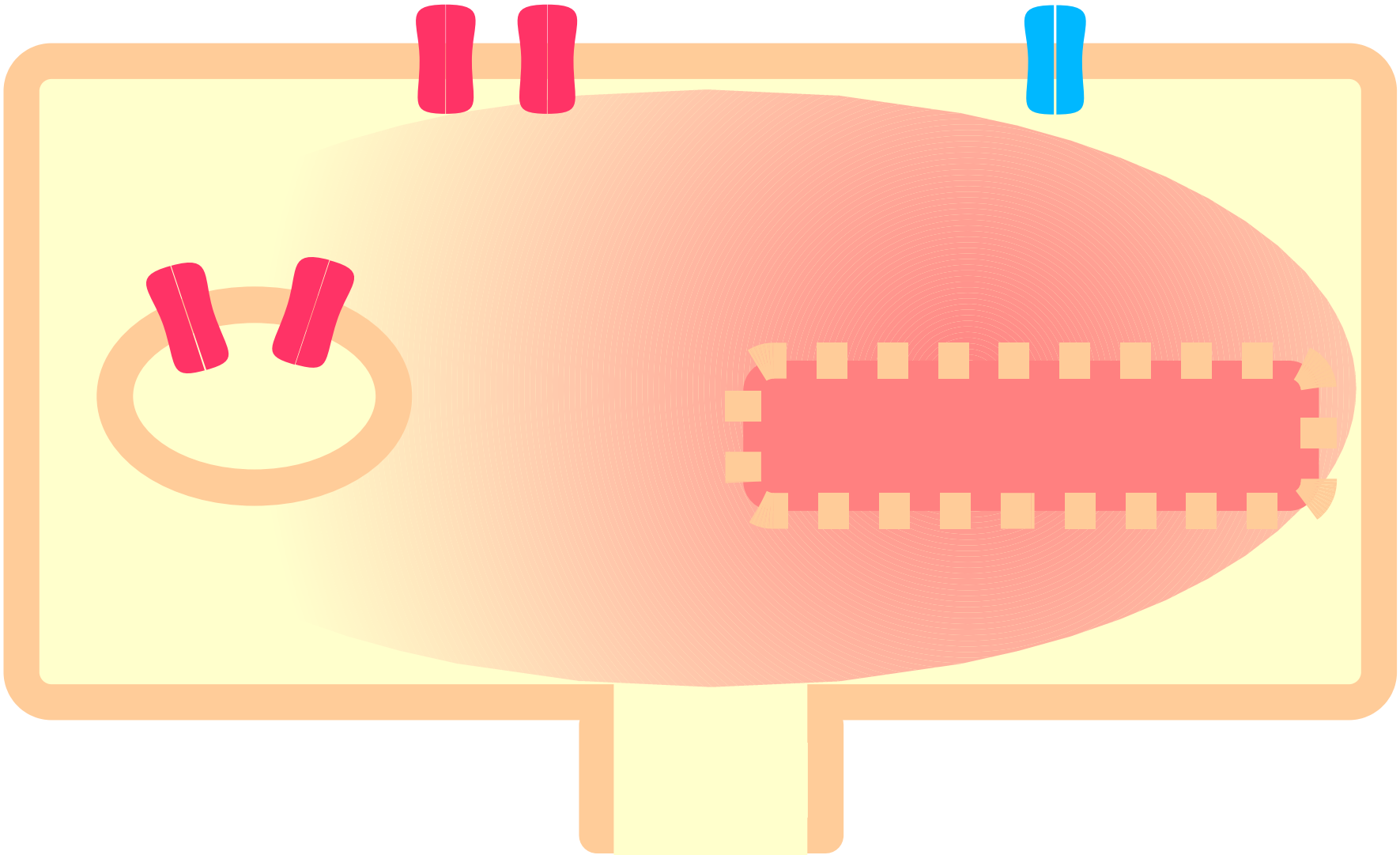
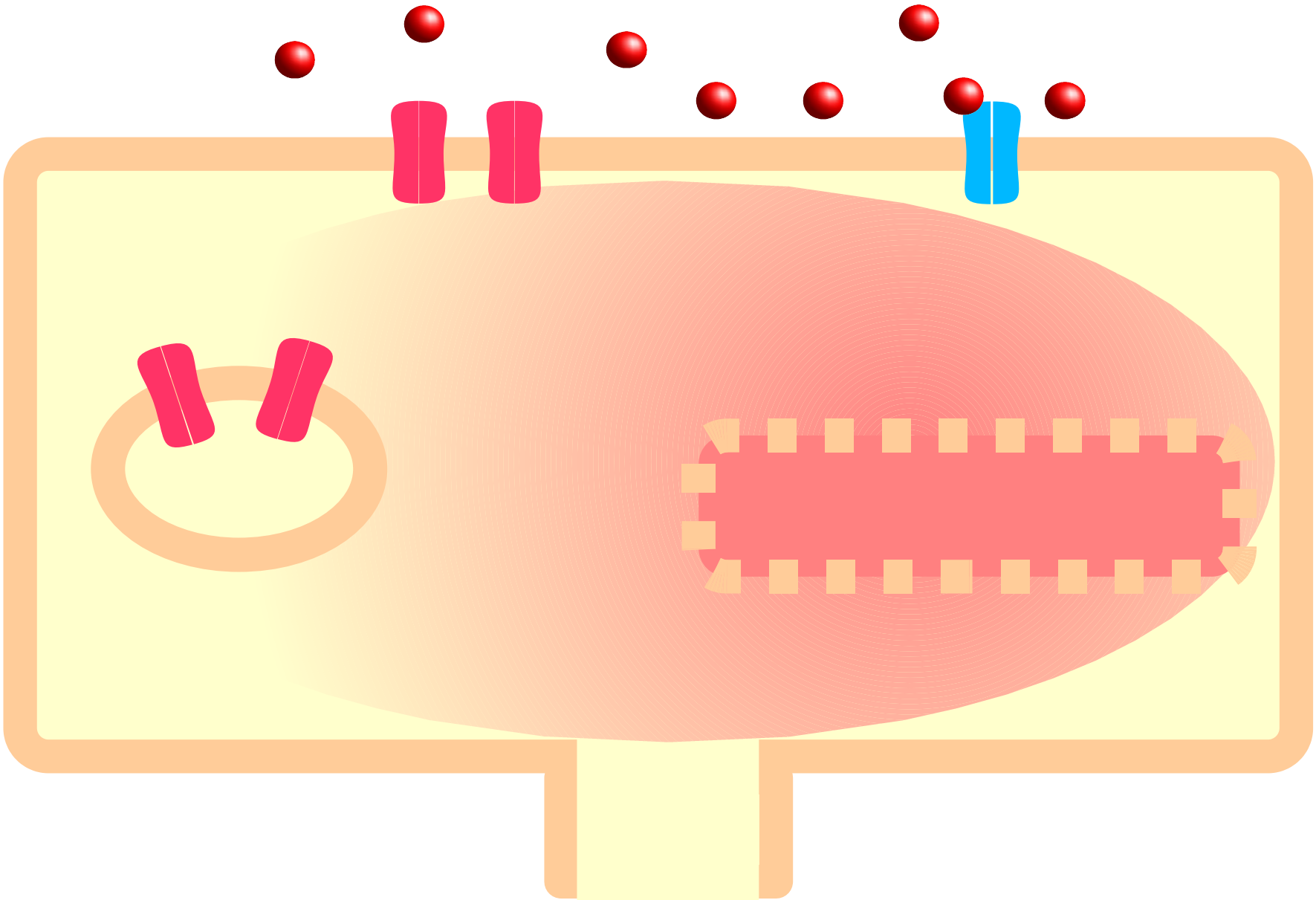
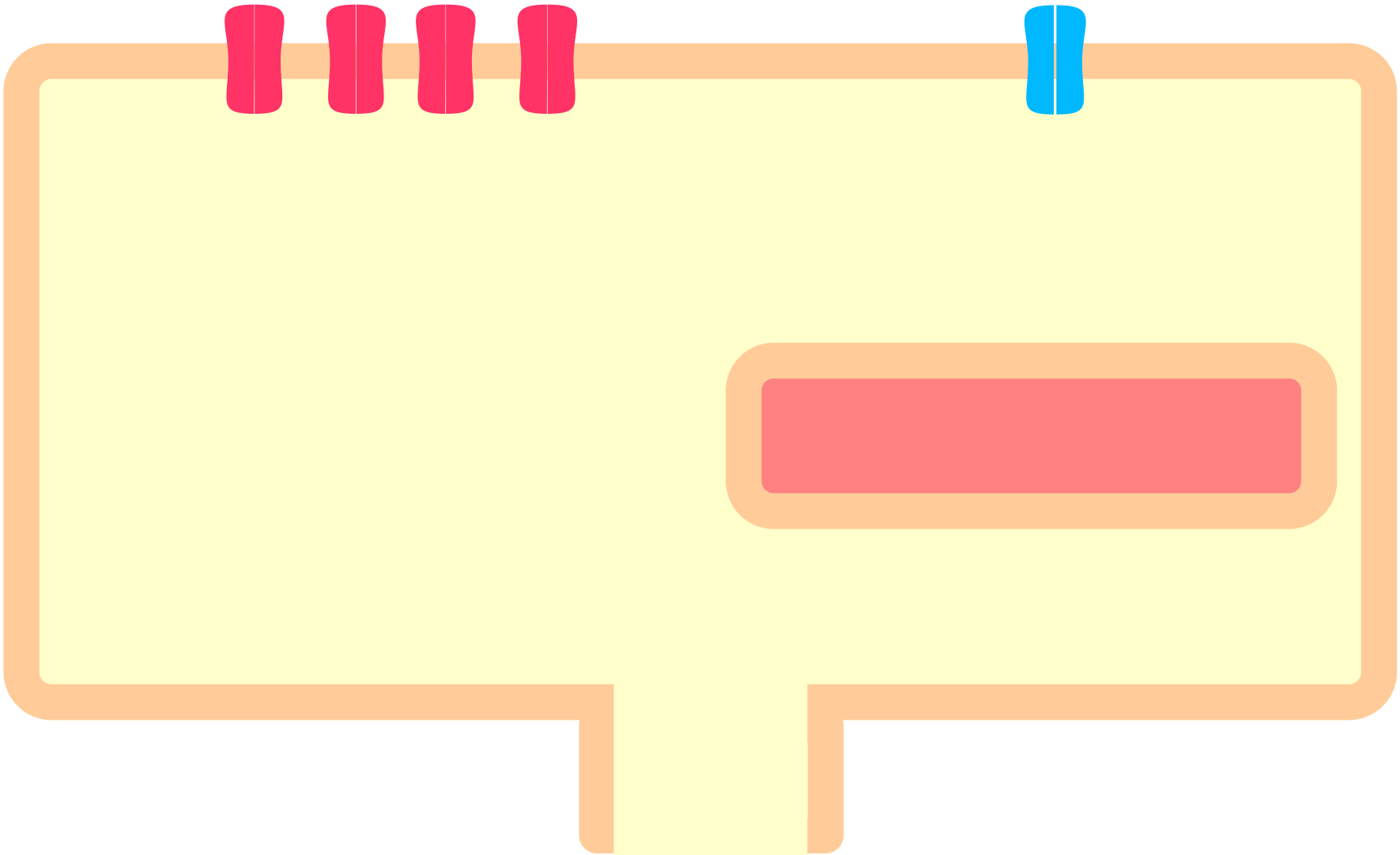


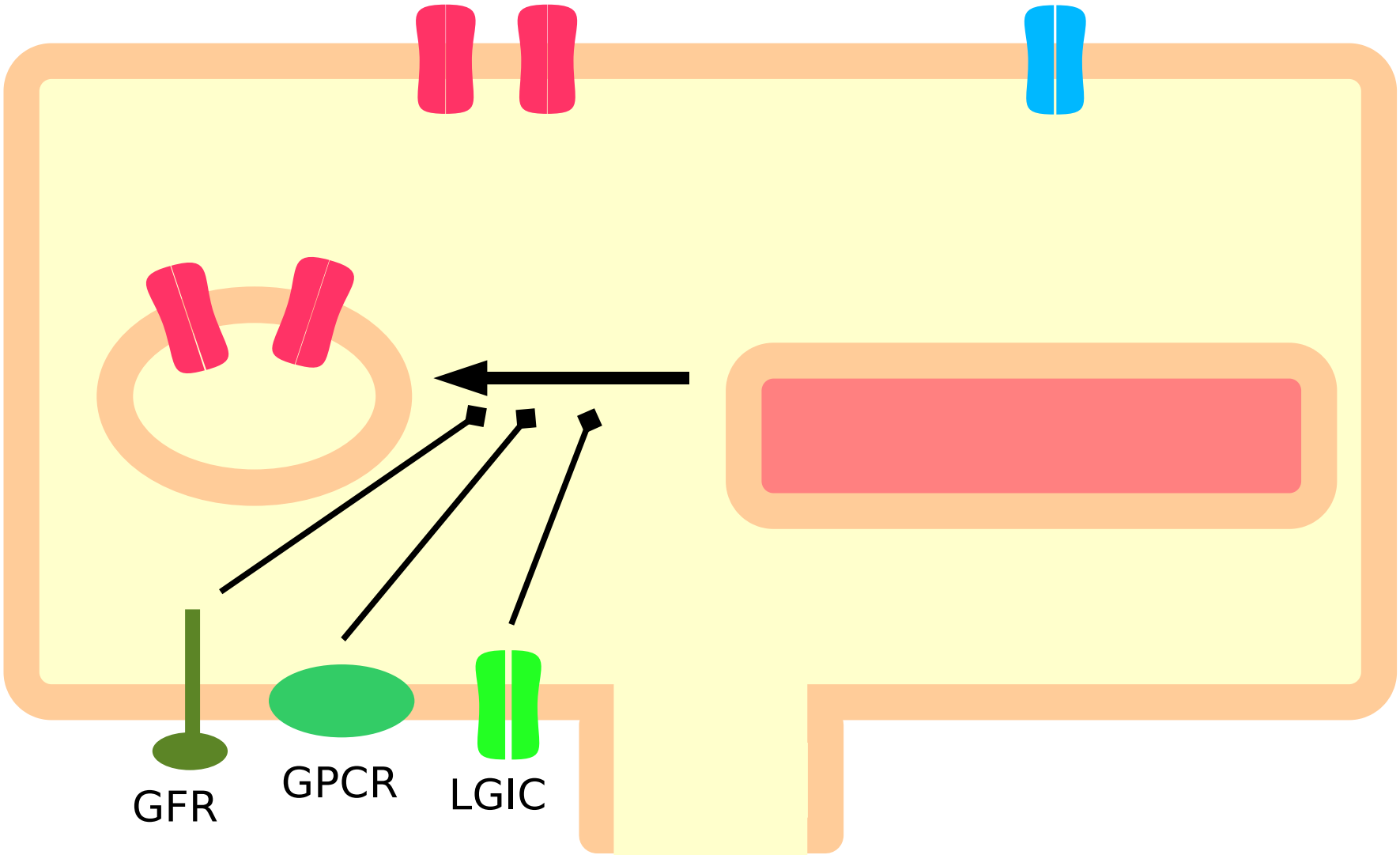
Signalling at the dendritic spine



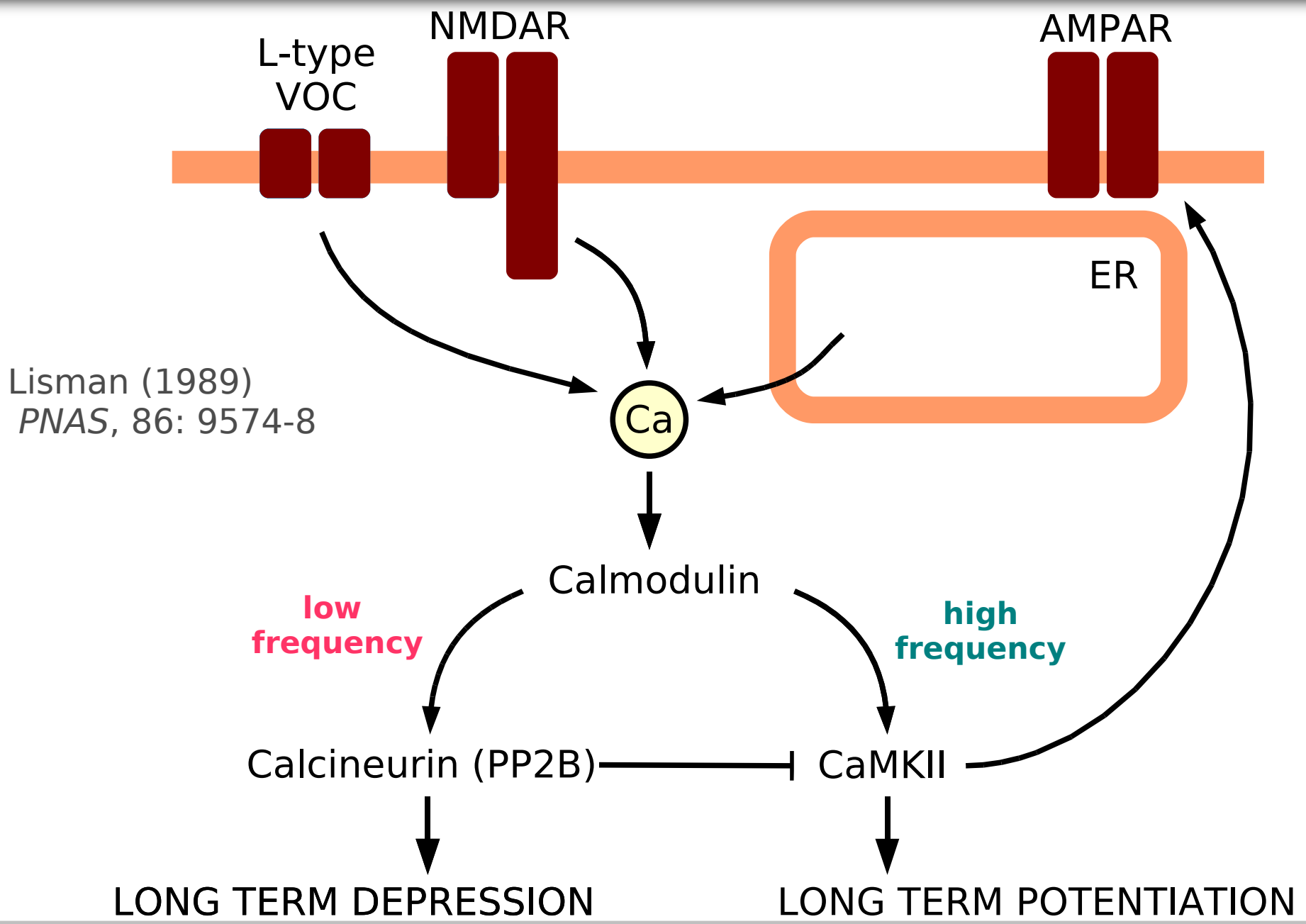
Signalling at the dendritic spine



Signalling at the dendritic spine

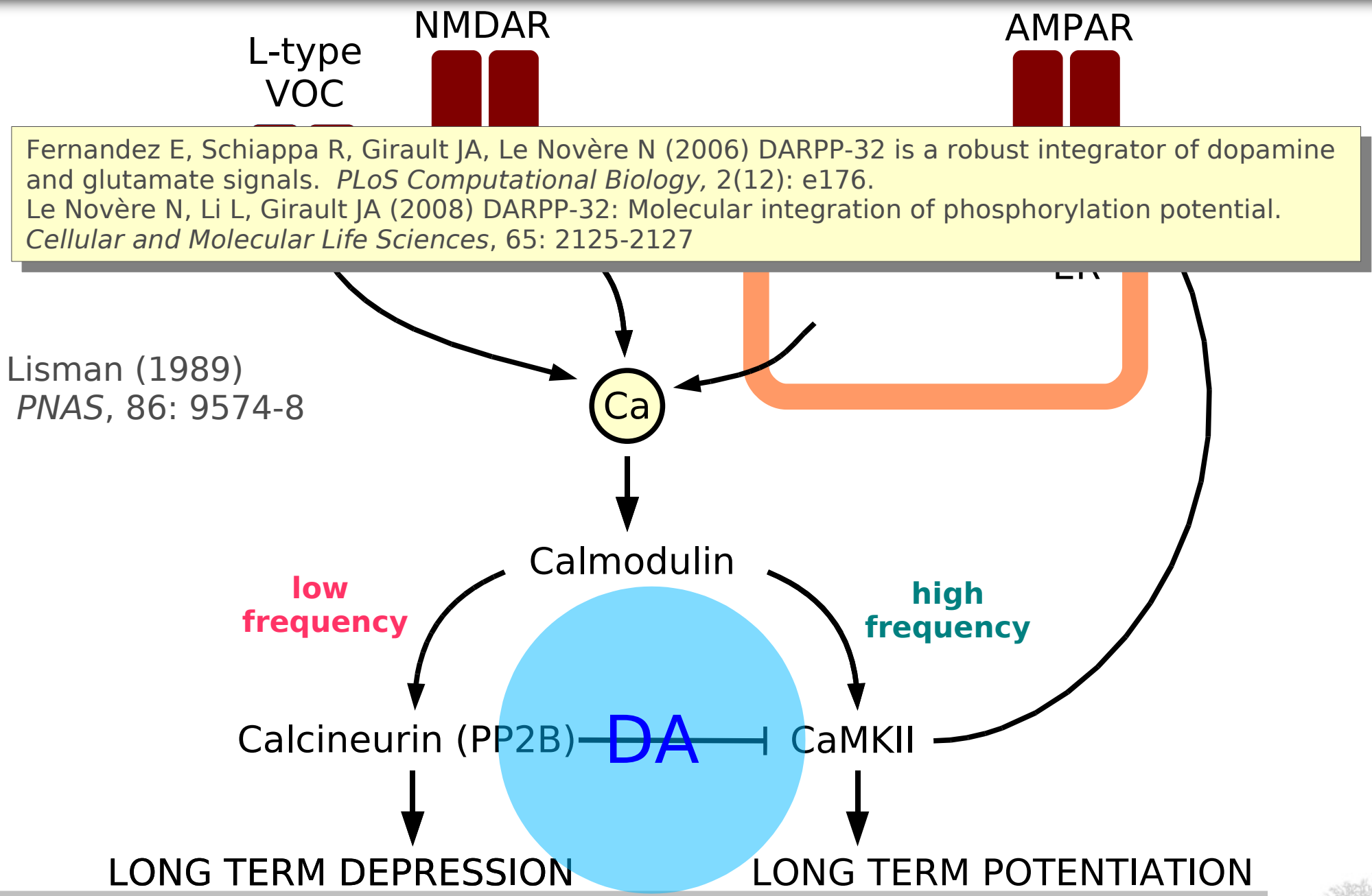


Calcium theory of Synaptic Plasticity



Lisman (1989)
PNAS, 86: 9574-8

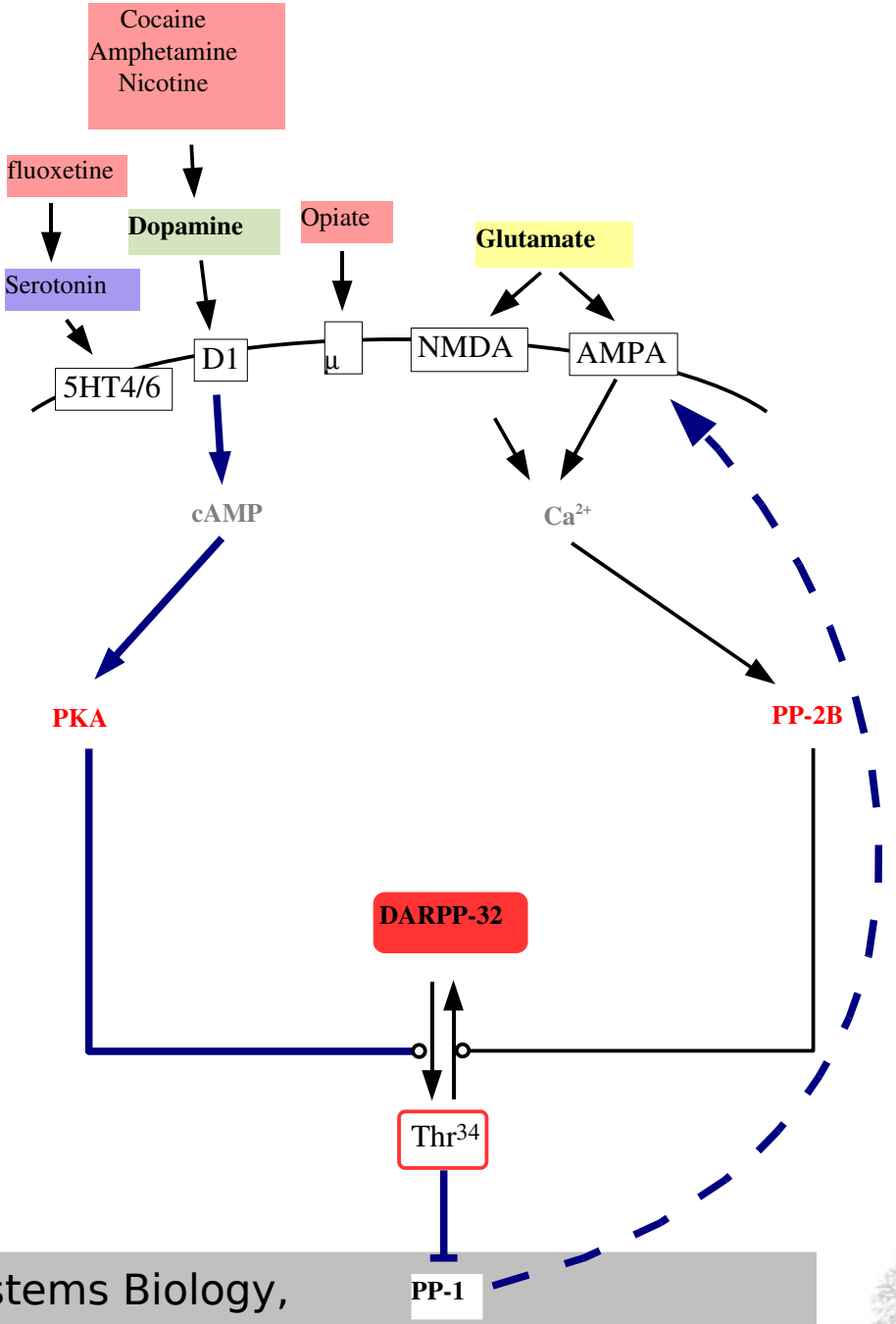
Calcium theory of Synaptic Plasticity



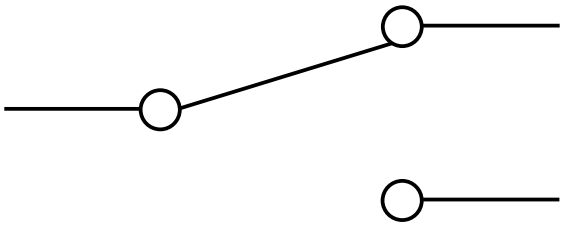
Is DARPP-32 a switch?

Fernandez E, Schiappa R, Girault JA, Le Novère N (2006) DARPP-32 is a robust integrator of dopamine and glutamate signals. *PLoS Computational Biology*, 2(12): e176.

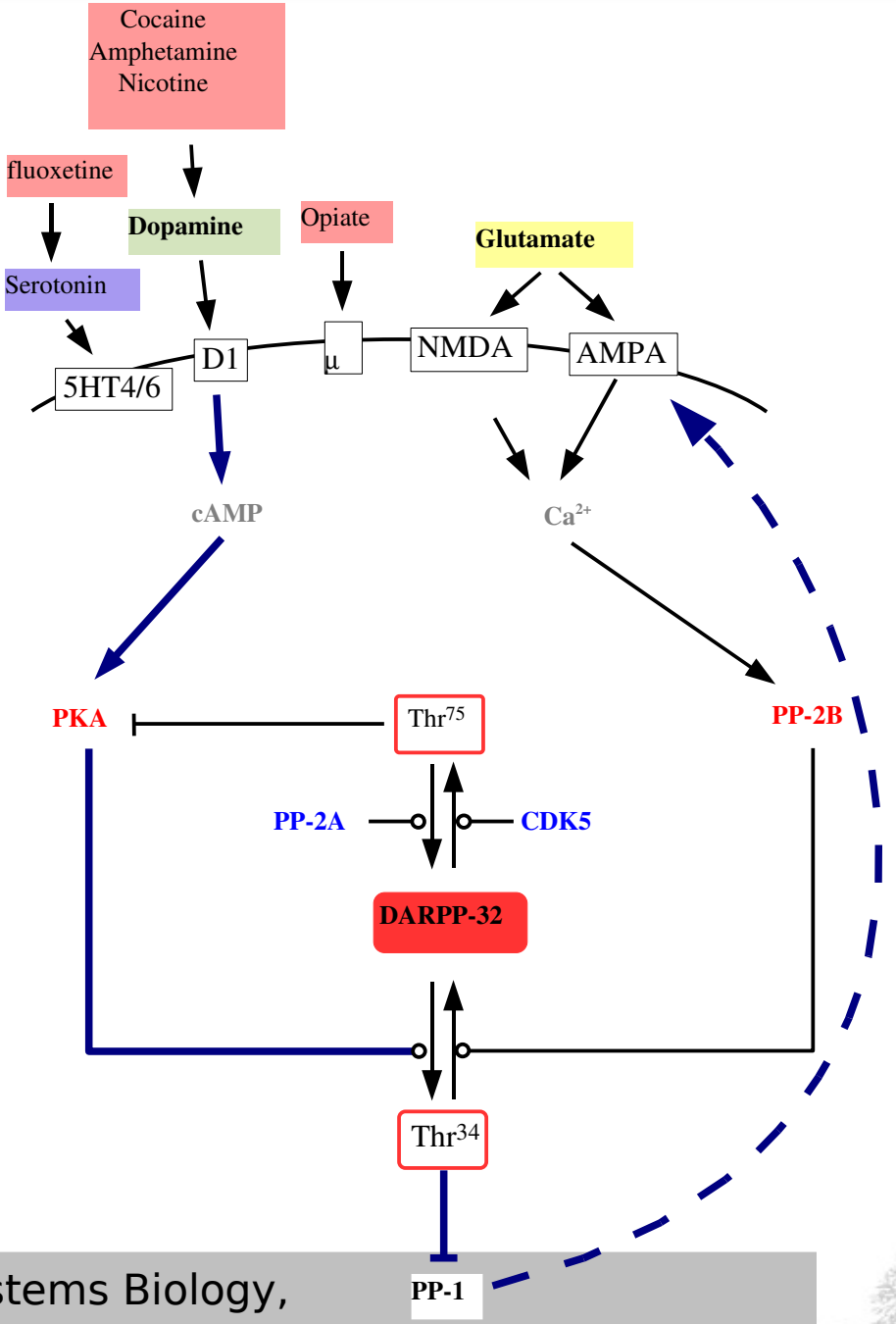
Textbook's view



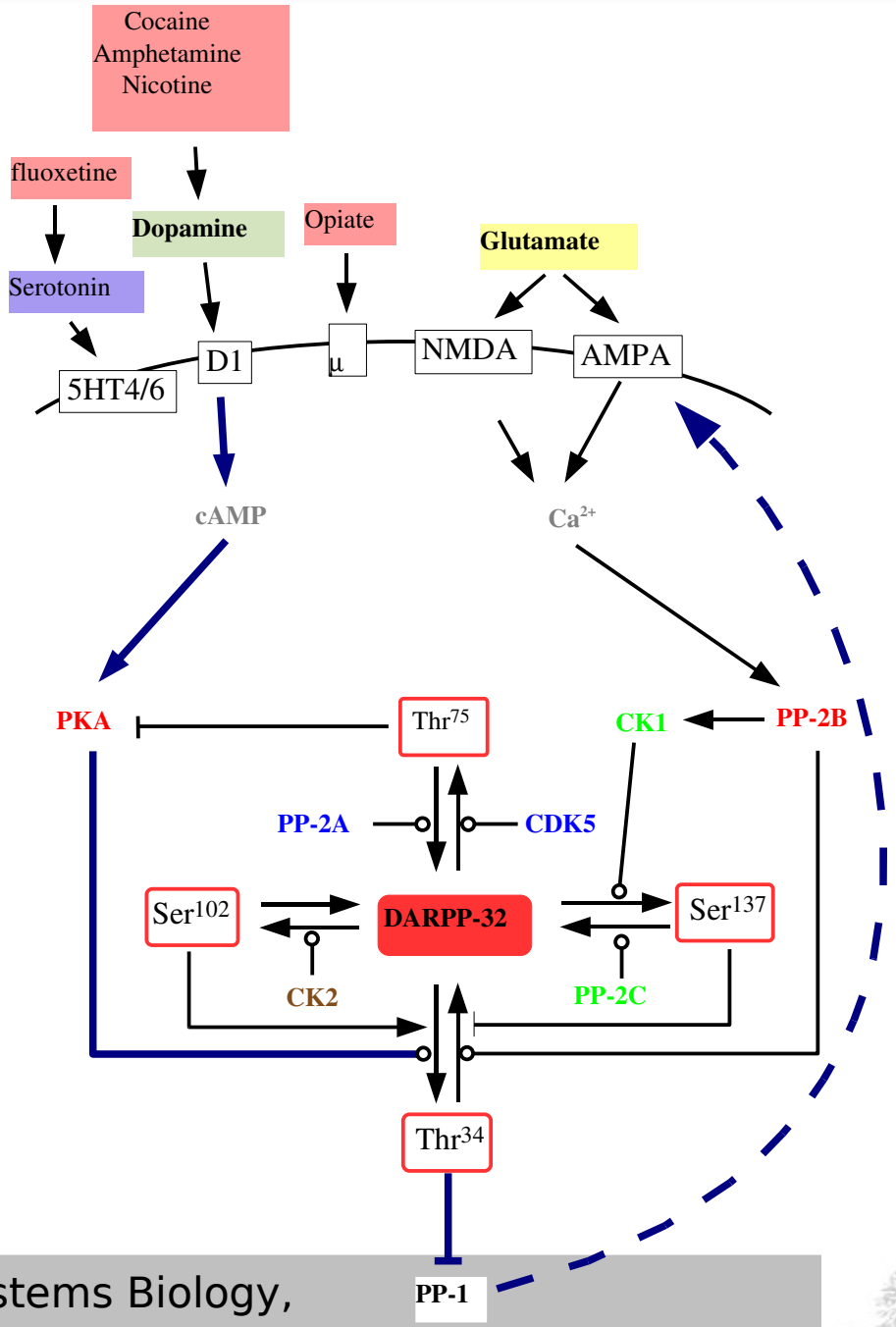
Is DARPP-32 a switch?

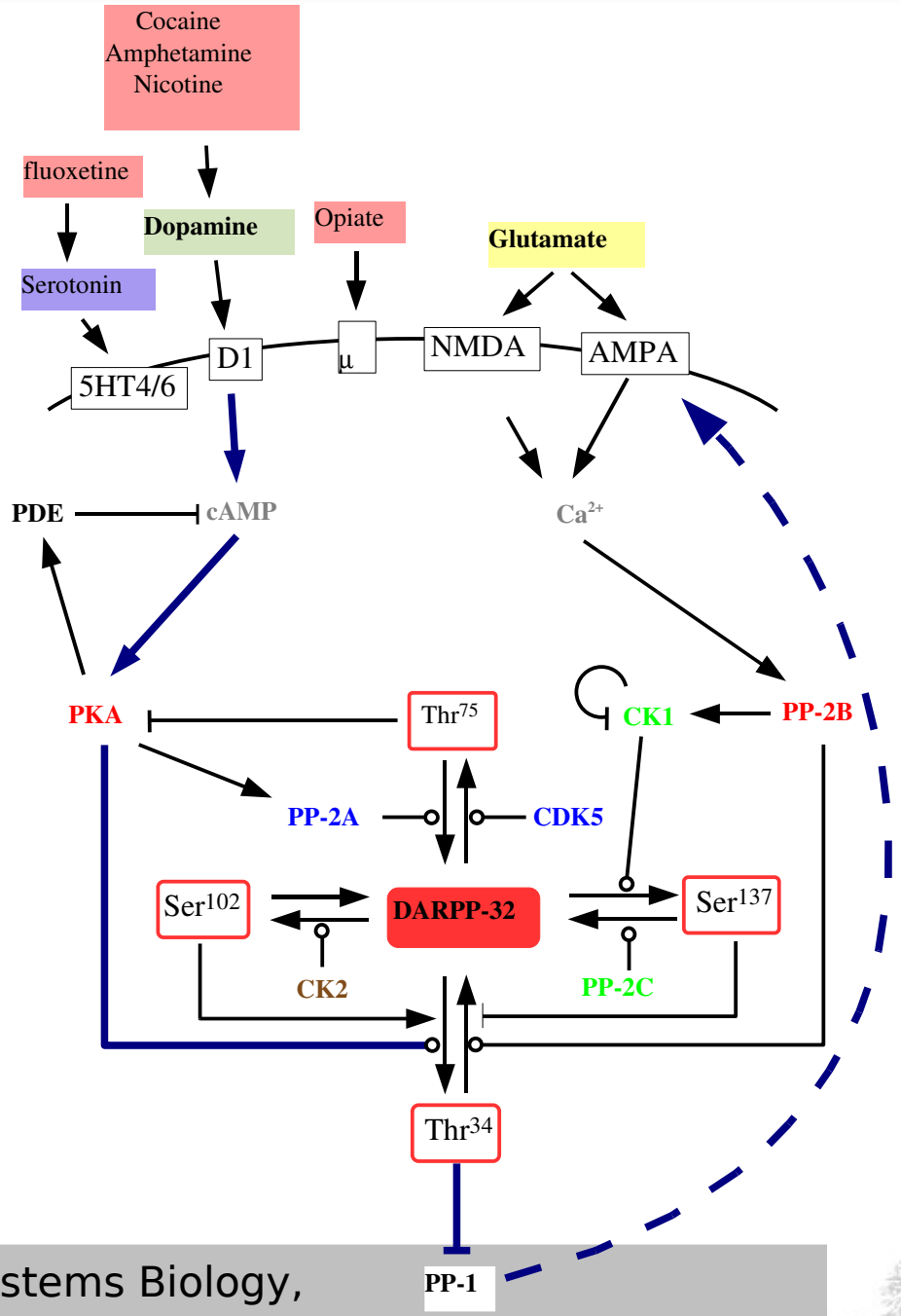


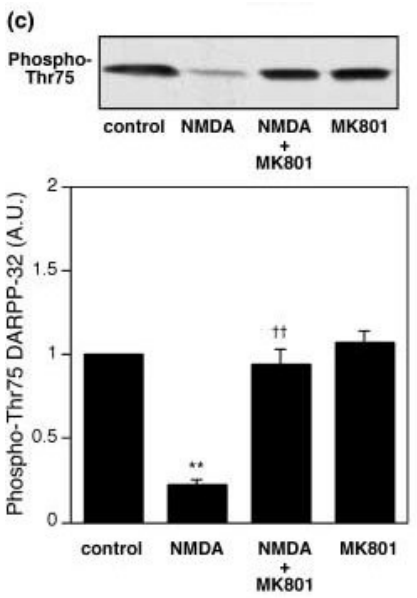
Review article's view

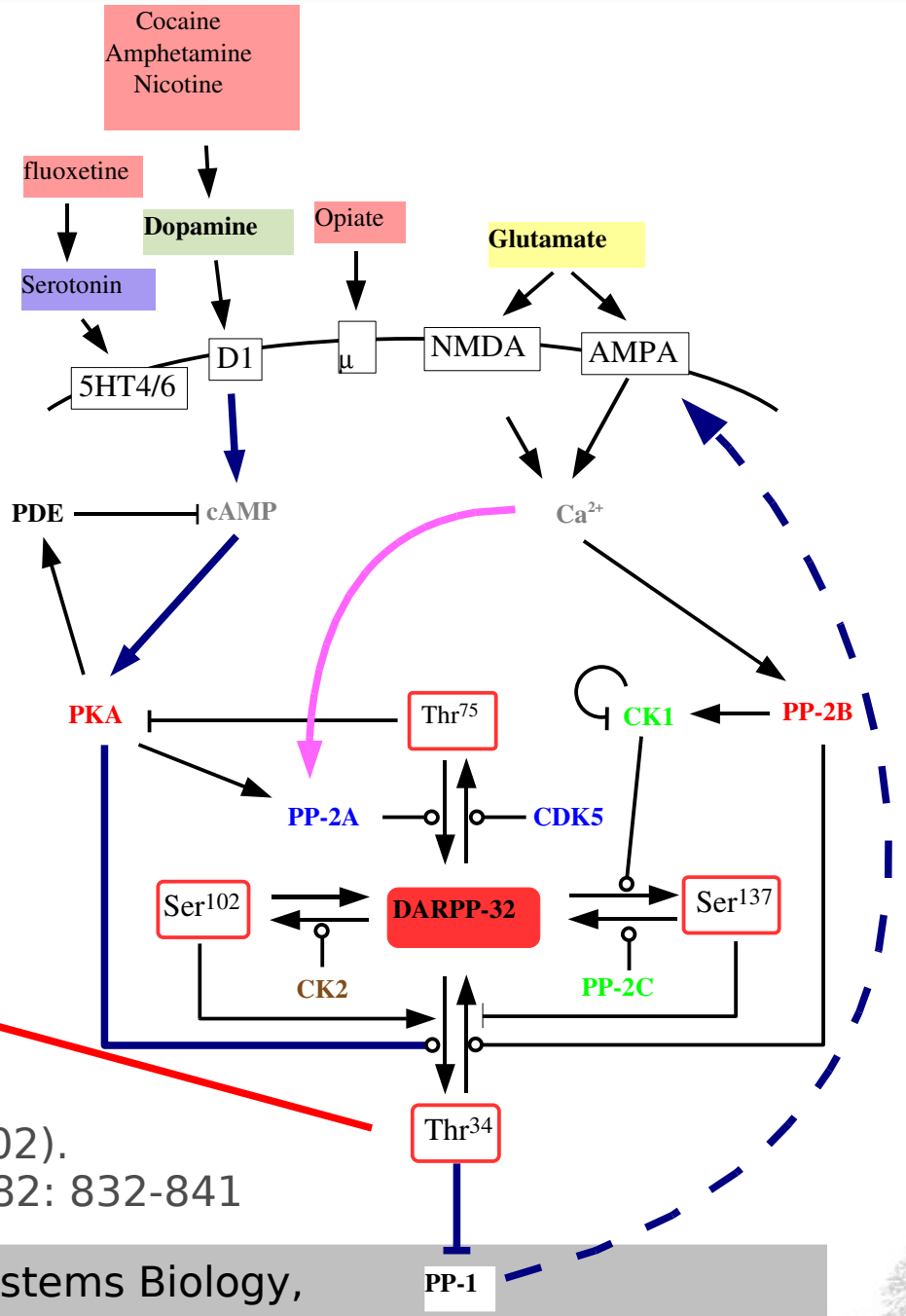


DARPP-32 is a “hub” for
phosphatases and kinases
in the post-synaptic compartment

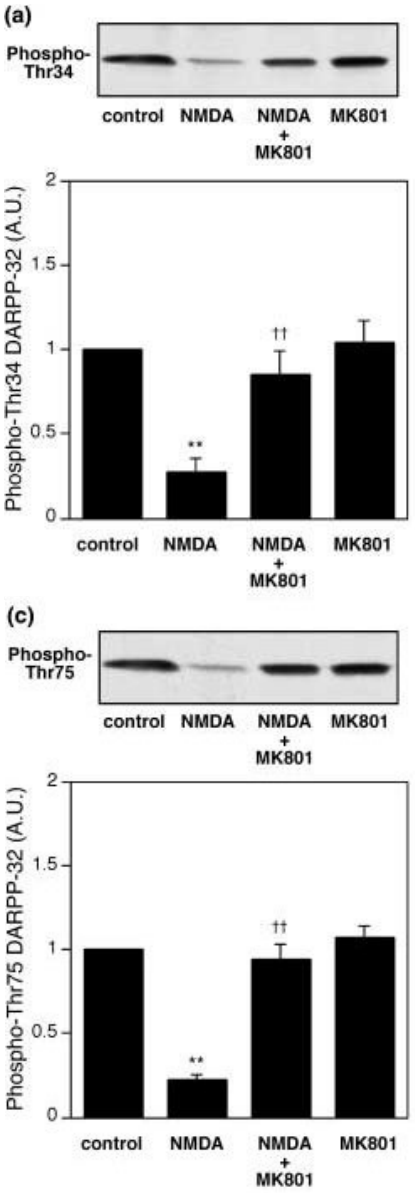


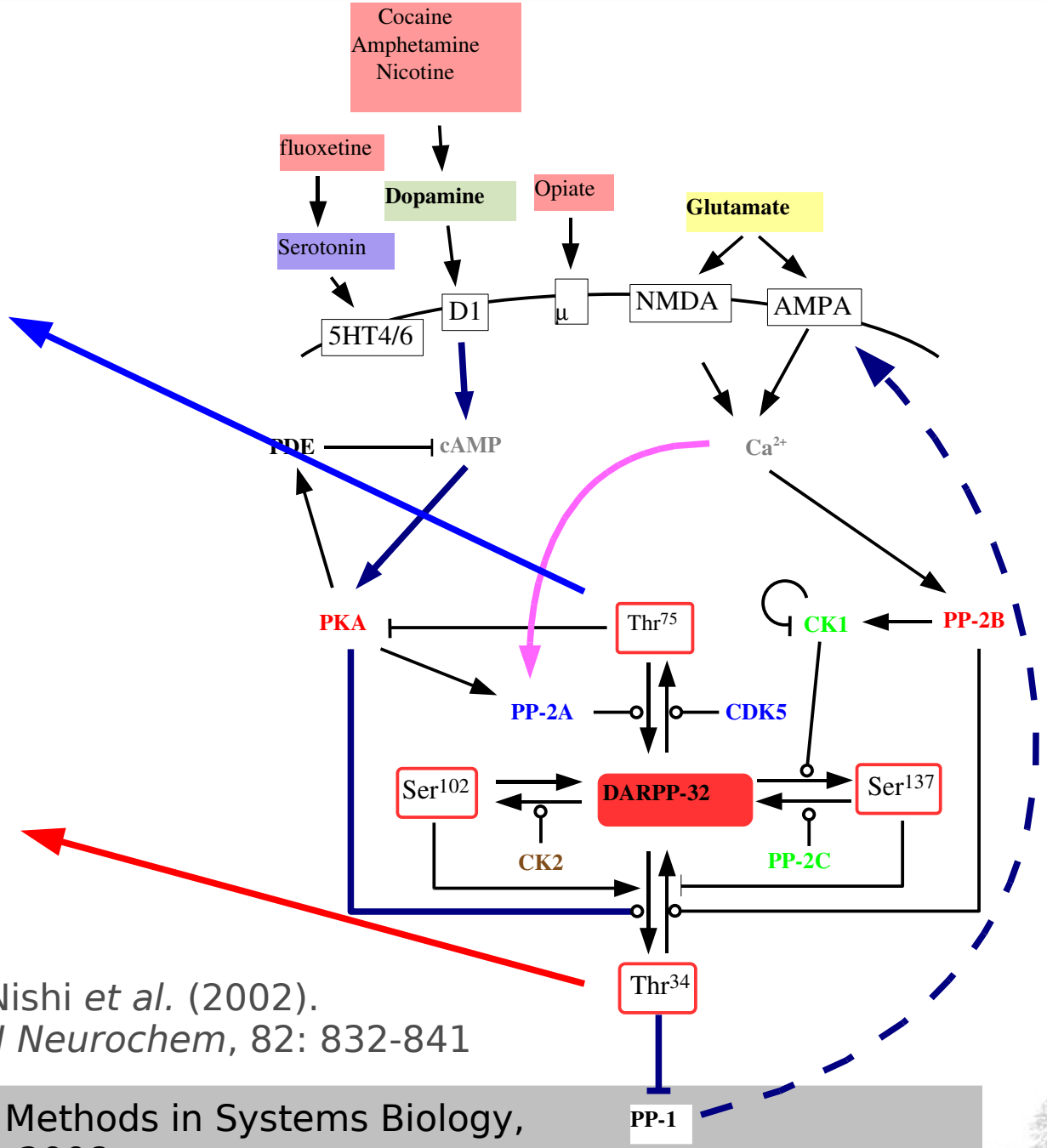

Cocaine
Amphetamine
Nicotine
fluoxetine
Dopamine
Opiate
Glutamate
Serotonin
D1
μ
NMDA
AMPA
5HT4/6
PDE
cAMP
Ca2+
PKA
Thr75
CK1
PP-2B
PP-2A
CDK5
Ser102
DARPP-32
Ser137
CK2
PP-2C
Thr34
PP-1





Nishi *et al.* (2002).
J Neurochem, 82: 832-841





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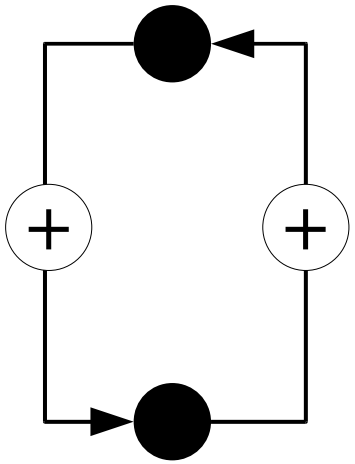
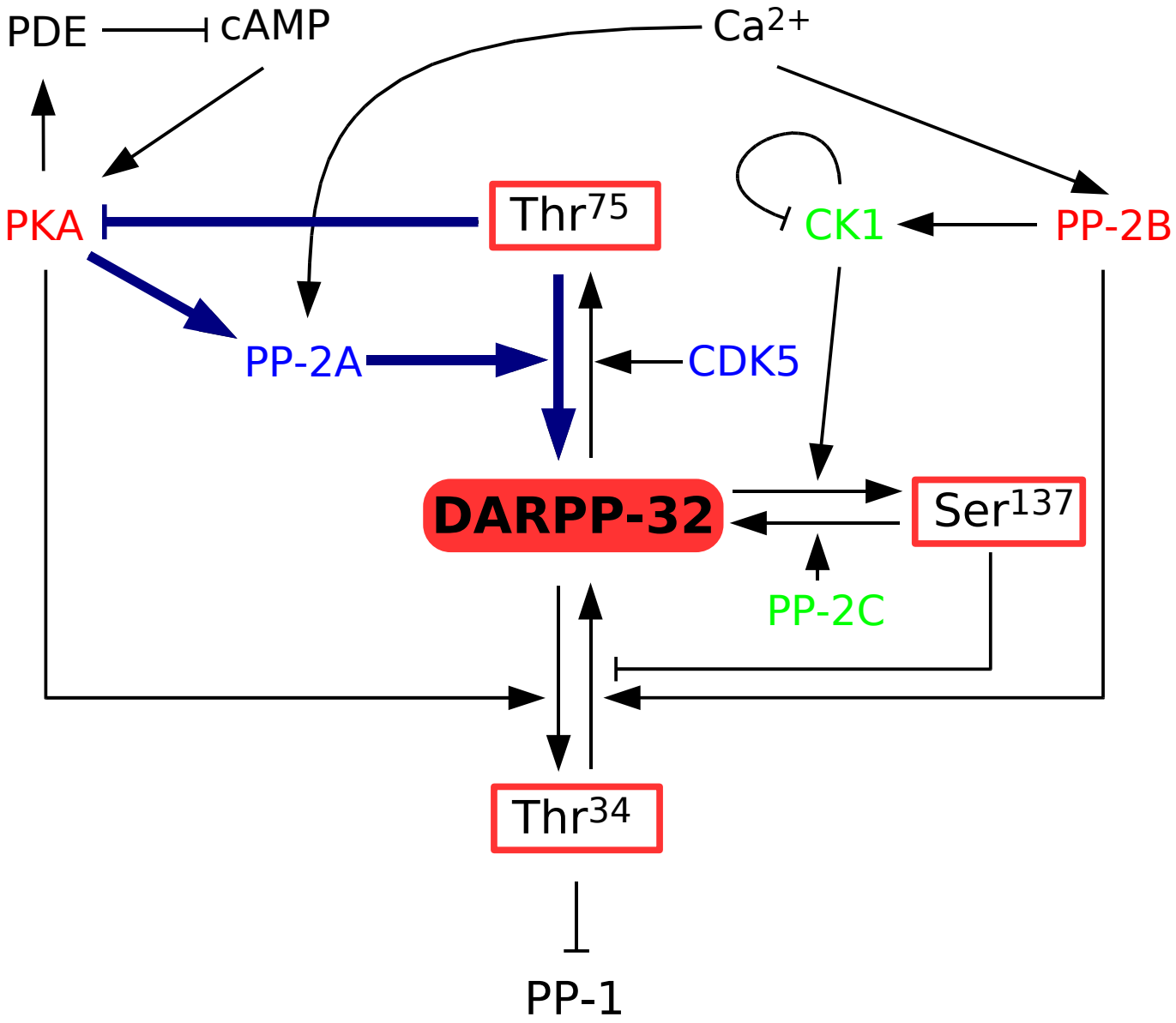
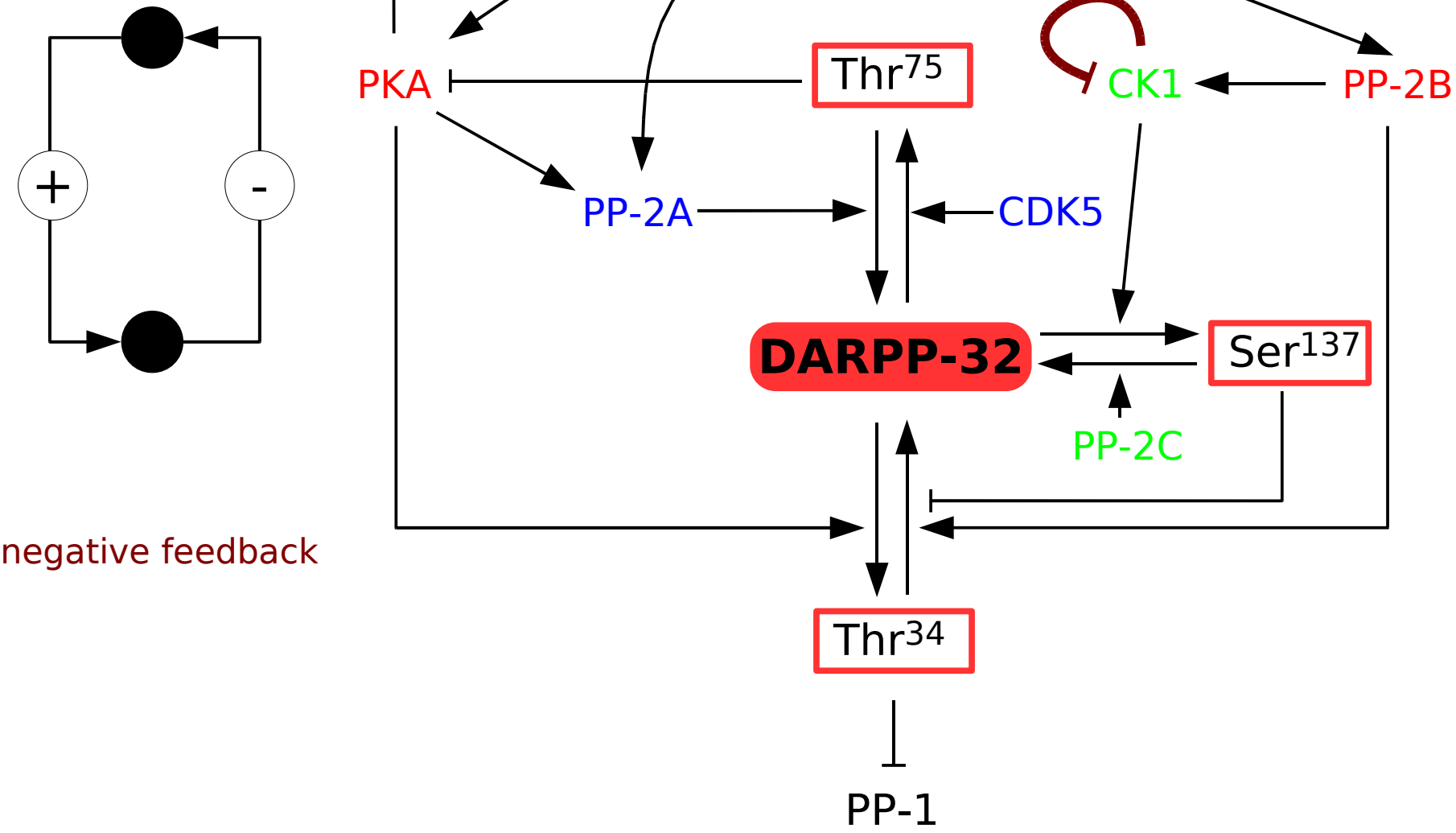
All the cybernetics in one system



positive feedback



All the cybernetics in one system



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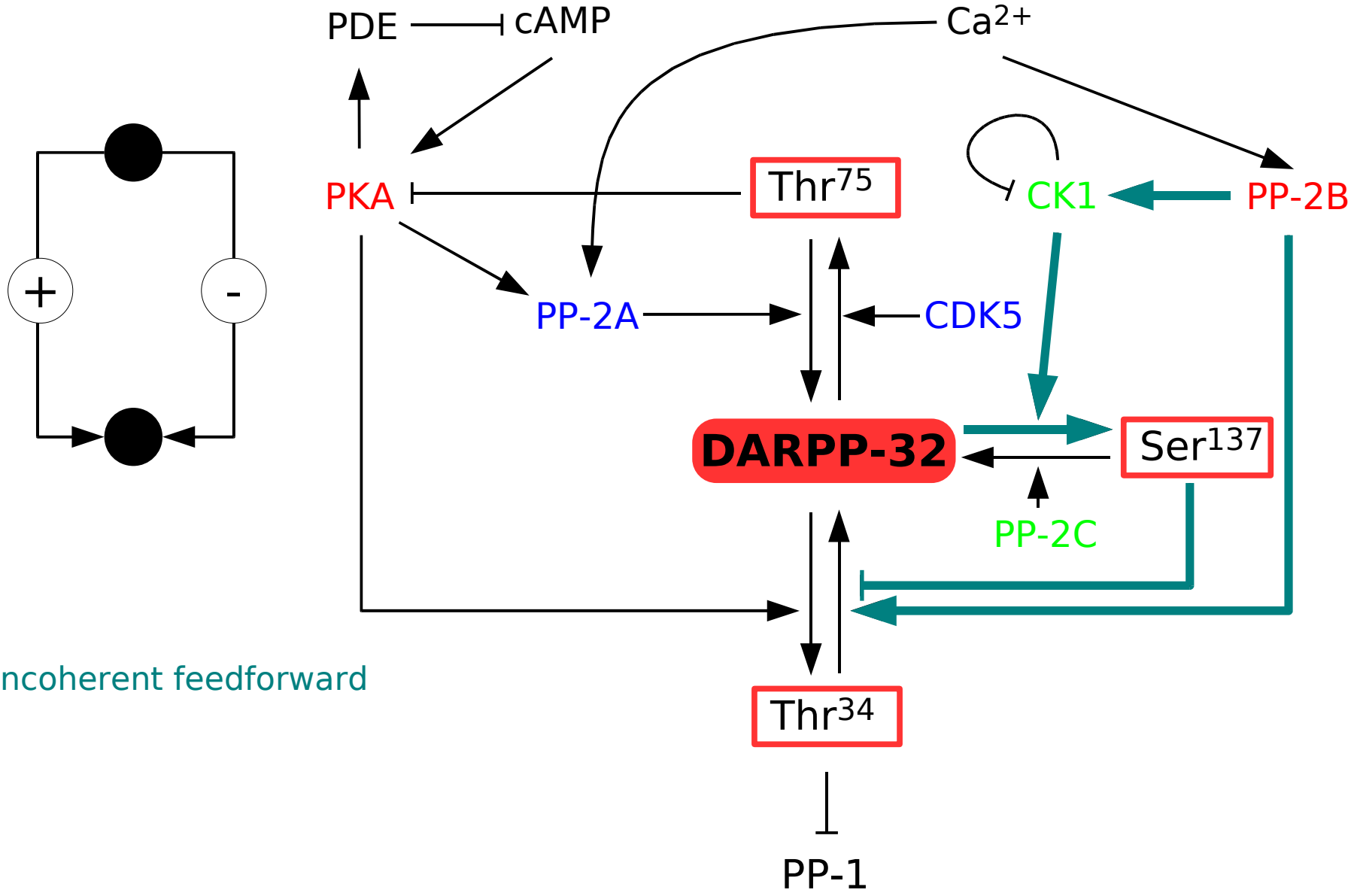
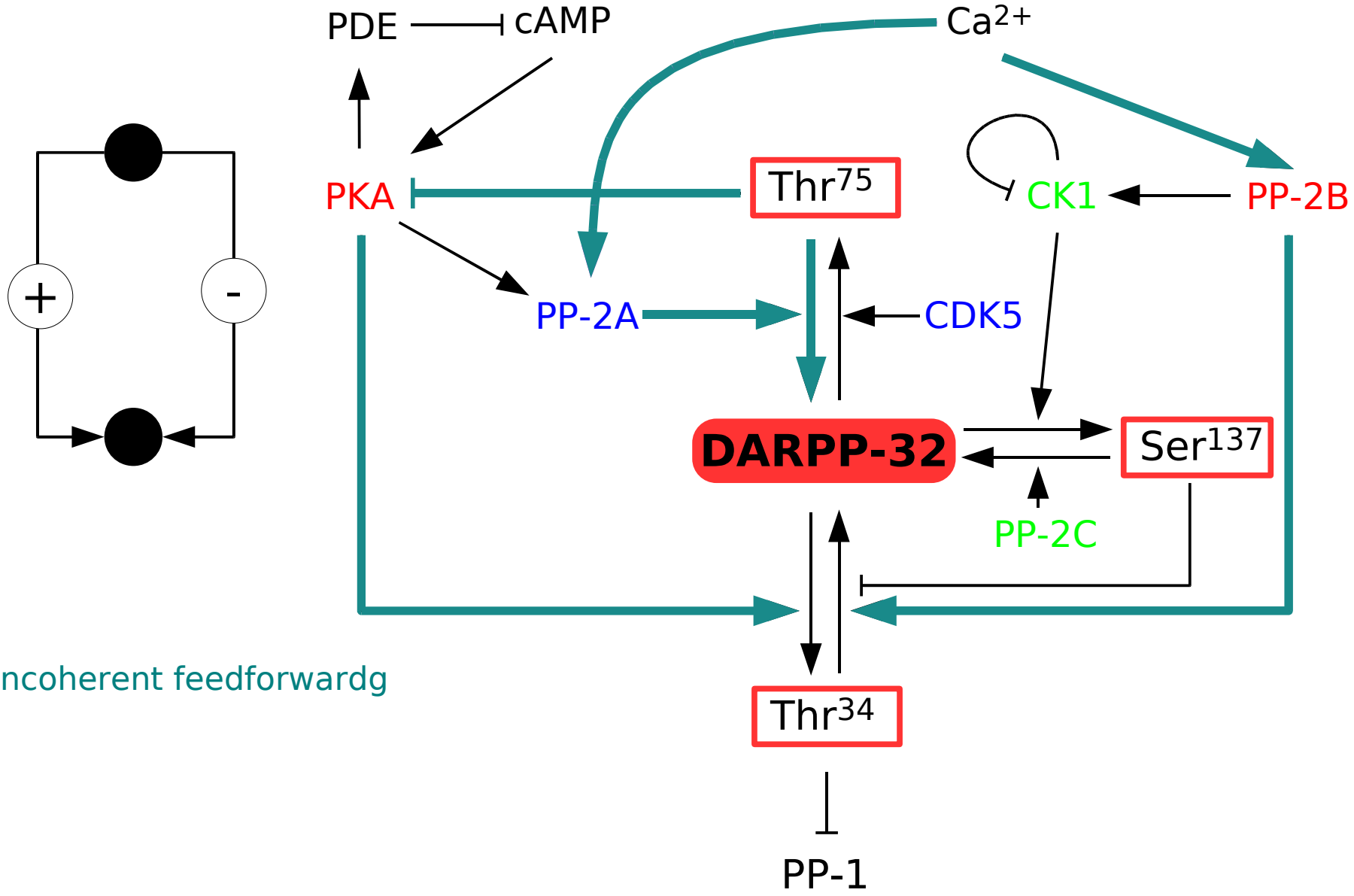


incoherent feedforward

All the cybernetics in one system



incoherent feedforwardg

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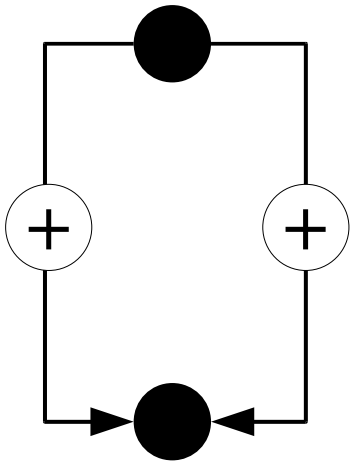
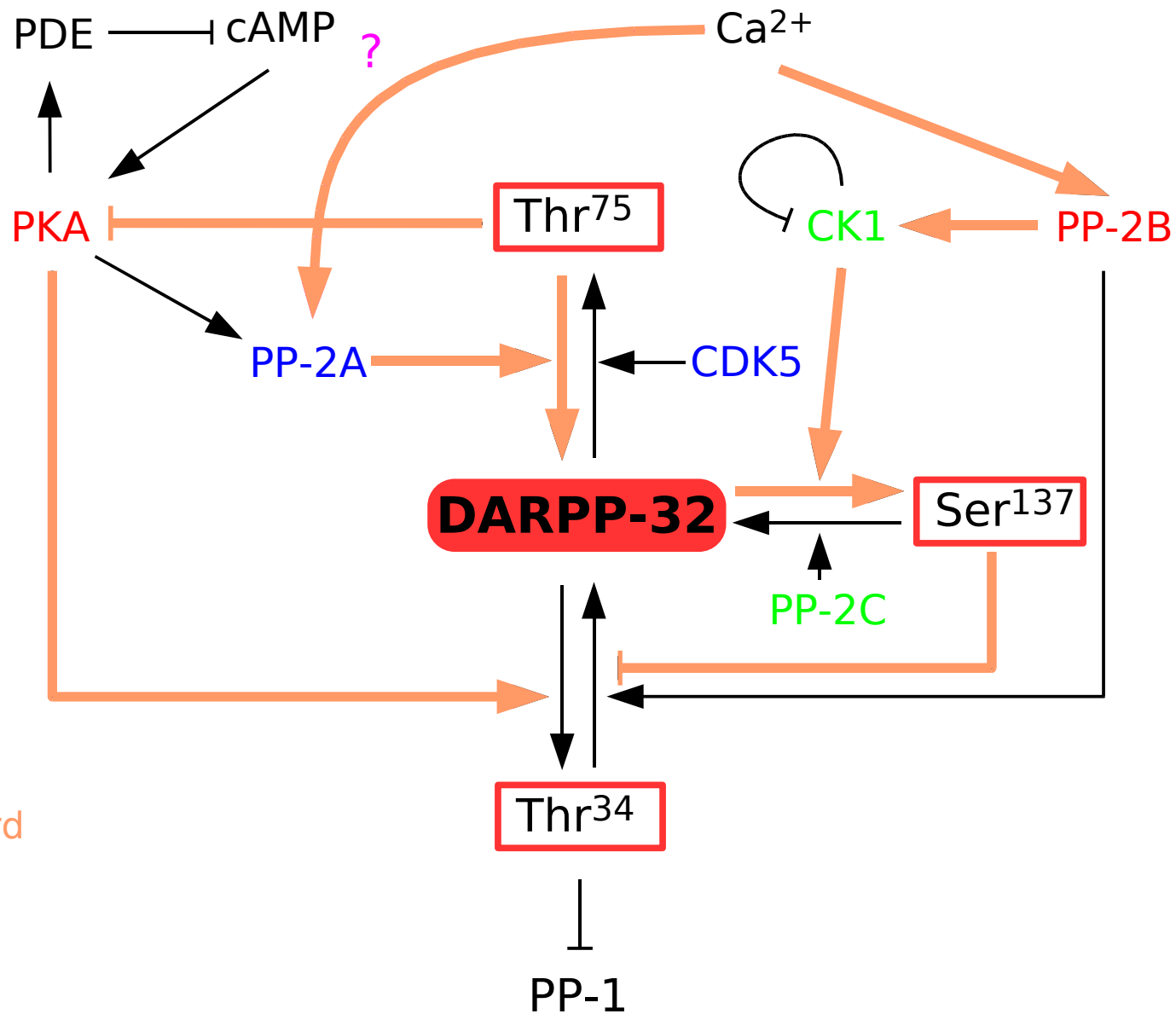
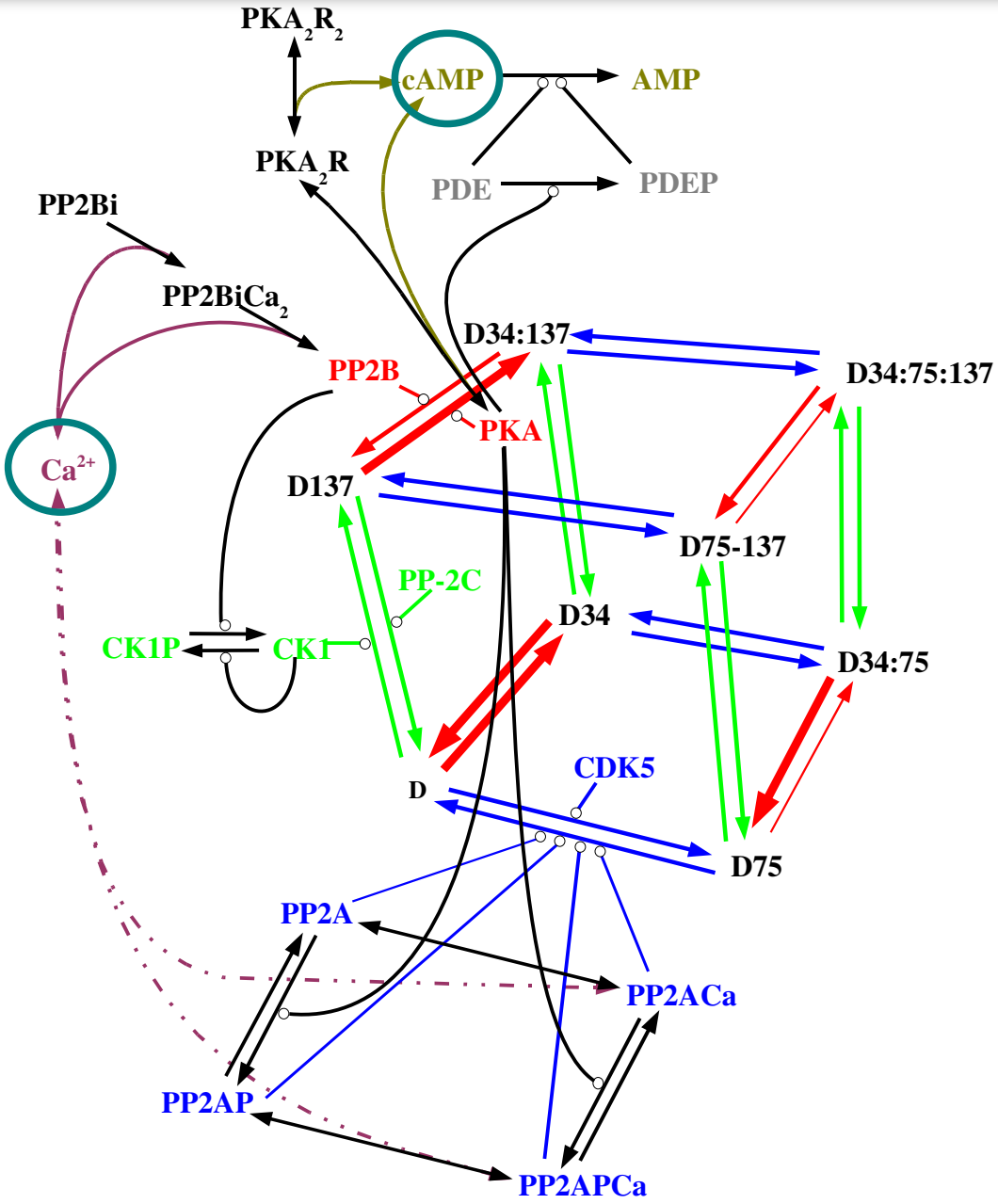




coherent feedforward

Chemical model of DARPP-32 regulation



Chemical model of DARPP-32 regulation

- D + CDK5 ⇔ D_CDK5 → D75 + CDK5
- D75 + PP2A ⇔ D75_PP2A → D + PP2A
- D75 + PP2ACa ⇔ D75_PP2ACa → D + PP2ACa
- D75 + PP2AP ⇔ D75_PP2AP → D + PP2AP
- D75 + PP2APCa ⇔ D75_PP2APCa → D + PP2APCa
- D137 + CDK5 ⇔ D137_CDK5 → D75-137 + CDK5
- D75-137 + PP2A ⇔ D75-137_PP2A → D137 + PP2A
- D75-137 + PP2ACa ⇔ D75-137_PP2ACa → D137 + PP2ACa
- D75-137 + PP2AP ⇔ D75-137_PP2AP → D137 + PP2AP
- D75-137 + PP2APCa ⇔ D75-137_PP2APCa → D137 + PP2APCa
- D34 + CDK5 ⇔ D34_CDK5 → D34-75 + CDK5
- D34-75 + PP2A ⇔ D34-75_PP2A → D34 + PP2A
- D34-75 + PP2ACa ⇔ D34-75_PP2ACa → D34 + PP2ACa
- D34-75 + PP2AP ⇔ D34-75_PP2AP → D34 + PP2AP
- D34-75 + PP2APCa ⇔ D34-75_PP2APCa → D34 + PP2APCa
- D34-137 + CDK5 ⇔ D34-137_CDK5 → D34-75_137 + CDK5
- D34-75-137 + PP2A ⇔ D34-75-137_PP2A → D34-137 + PP2A
- D34-75-137 + PP2ACa ⇔ D34-75-137_PP2ACa → D34-137 + PP2ACa
- D34-75-137 + PP2AP ⇔ D34-75-137_PP2AP → D34-137 + PP2AP
- D34-75-137 + PP2APCa ⇔ D34-75-137_PP2APCa → D34-137 + PP2APCa

- D + CK1 ⇔ D_CK1 → D137 + CK1
- D137 + PP2C ⇔ D137_PP2C → D + PP2C
- D75 + CK1 ⇔ D75_CK1 → D75-137 + CK1
- D75-137 + PP2C ⇔ D75-137_PP2C → D75 + PP2C
- D34 + CK1 ⇔ D34_CK1 → D34-137 + CK1
- D34-75 + PP2C ⇔ D34-75_PP2C → D75 + PP2C
- D34-75 + CK1 ⇔ D34-75_CK1 → D34-75-137 + CK1
- D34-75-137 + PP2C ⇔ D34-75-137_PP2C → D34-75 + PP2C
- CK1 + CK1 ⇔ CK1_CK1 → CK1P + CK1
- CK1P + PP2B ⇔ CK1P_PP2B → CK1 + PP2B

79 species, 151 reactions

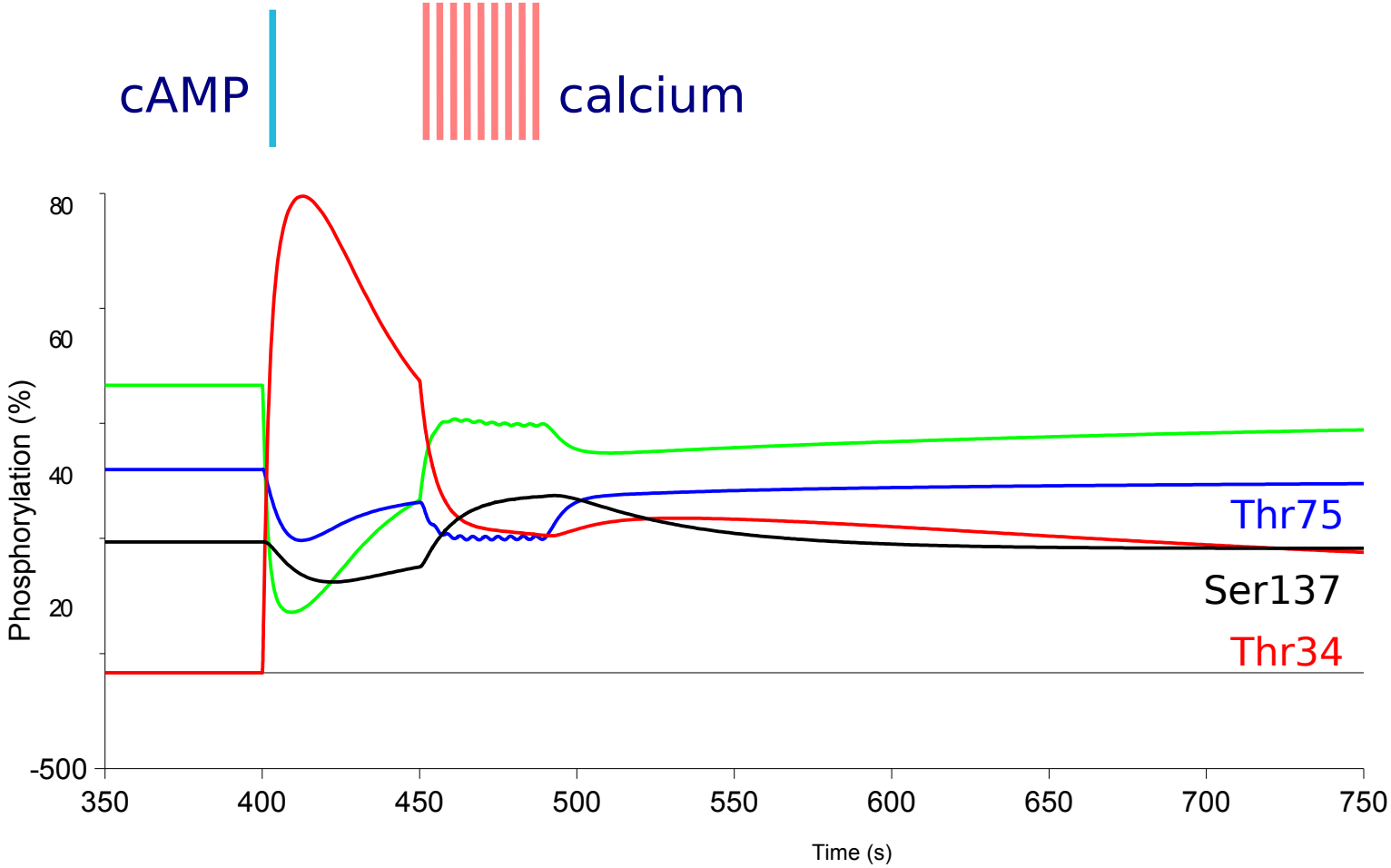
- D + PKA ⇔ D_PKA → D34 + PKA
- D34 + PP2B ⇔ D34_PP2B → D + PP2B
- D75 + PKA ⇔ D75_PKA → D34-75 + PKA
- D34-75 + PP2B ⇔ D34-75_PP2B → D75 + PP2B
- D137 + PKA ⇔ D137_PKA → D34-137 + PKA
- D34-137 + PP2B ⇔ D34-135_PP2B → D137 + PP2B
- D75-137 + PKA ⇔ D75-137_PKA → D34-75-137 + PKA
- D34-75-137 + PP2B ⇔ D34-75-135_PP2B → D75-137 + PP2B
- PP2A + PKA ⇔ PP2A_PKA → PP2AP + PKA
- PP2ACa + PKA ⇔ PP2ACa_PKA → PP2APCa + PKA
- Ø → Ca^{2+}
- Ca^{2+} → Ø
- PP2Bi + 2Ca ⇔ PP2Bi_Ca2
- PP2Bi_Ca + 2Ca ⇔ PP2B
- PP2A + Ca ⇔ PP2ACa
- PP2AP + Ca ⇔ PP2APCa

- R2_PKA2 + cAMP ⇔ cAMP_R2_PKA2
- cAMP_R2_PKA2 + cAMP ⇔ cAMP2_R2_PKA2
- cAMP2_R2_PKA2 + cAMP ⇔ cAMP3_R2_PKA2
- cAMP3_R2_PKA2 + cAMP ⇔ cAMP4_R2_PKA2
- cAMP4_R2_PKA2 ⇔ cAMP4_R2_PKA + PKA
- cAMP4_R2_PKA ⇔ cAMP4_R2 + PKA
- PKA + PDE ⇔ PKA_PDE → PKA + PDEP
- cAMP + PDE ⇔ cAMP_PDE → AMP + PDE
- cAMP + PDEP ⇔ cAMP_PDEP → AMP + PDEP

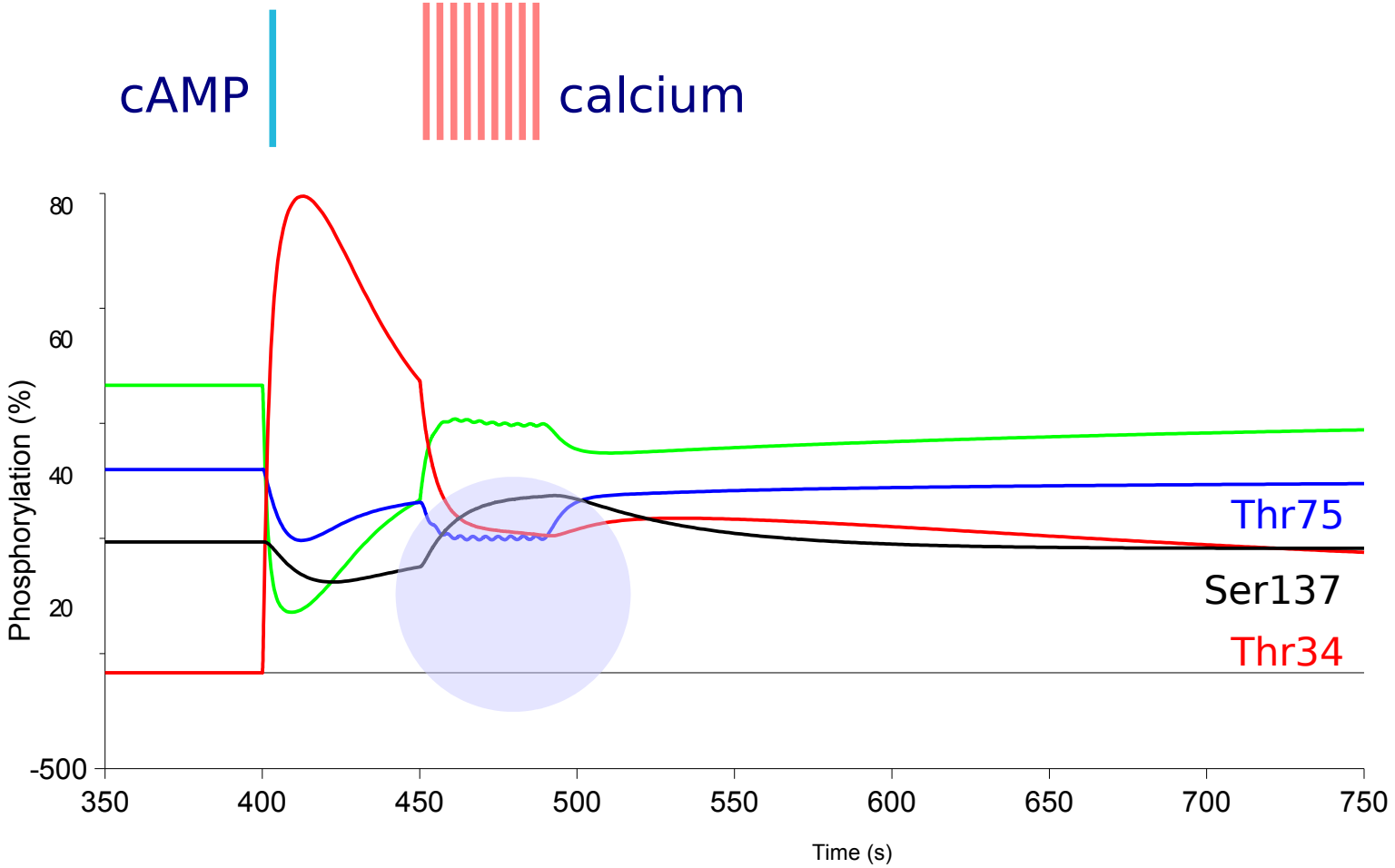
E-Cell3, a multi-algorithm simulator

- Discrete simulator (# molecules)
- Hybrid simulator (stochastic and deterministic)
- Advanced numerical solver
- multi-compartments
- Python scripting interface ⟶ arbitrary events
- Command-line + GUI

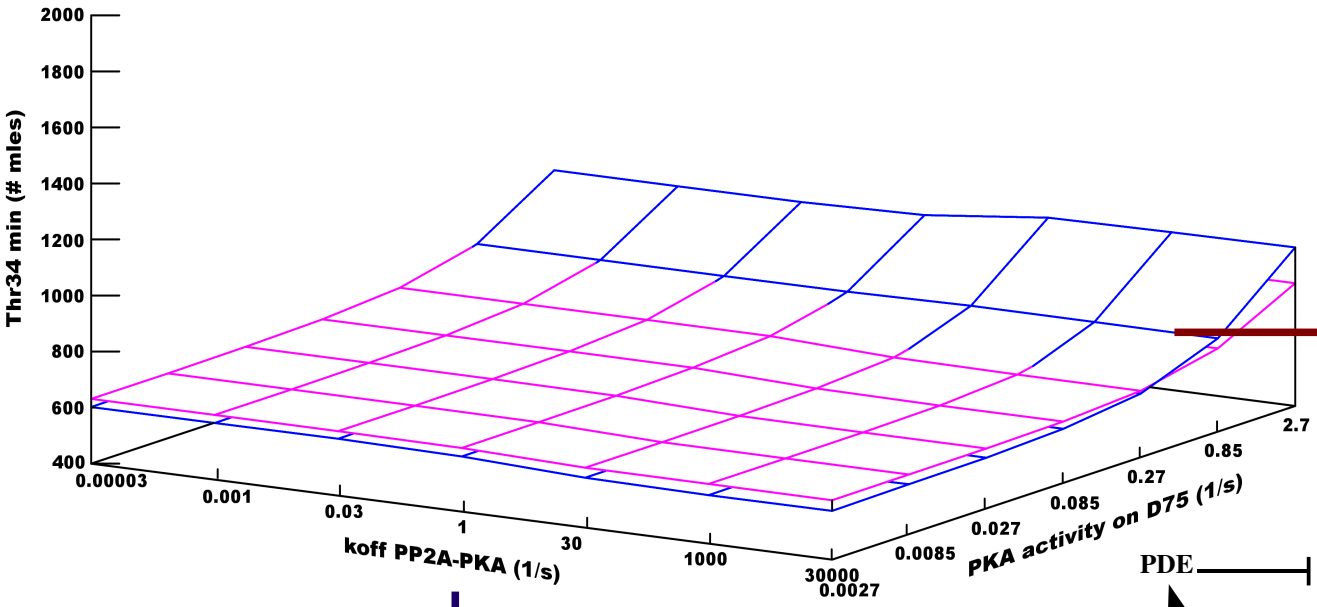
Dynamic simulations of DARPP-32 function

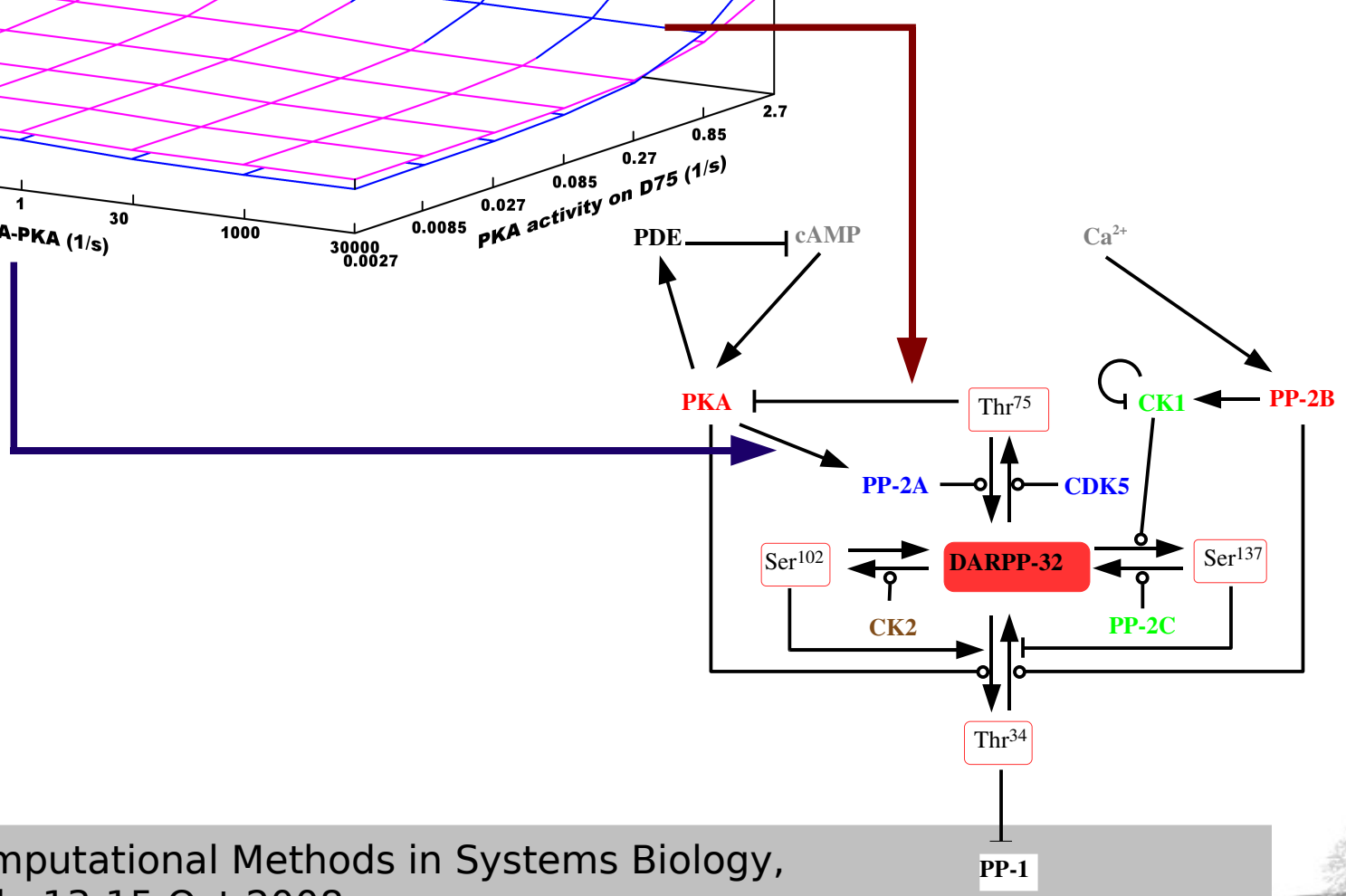


DARPP-32 is not a switch

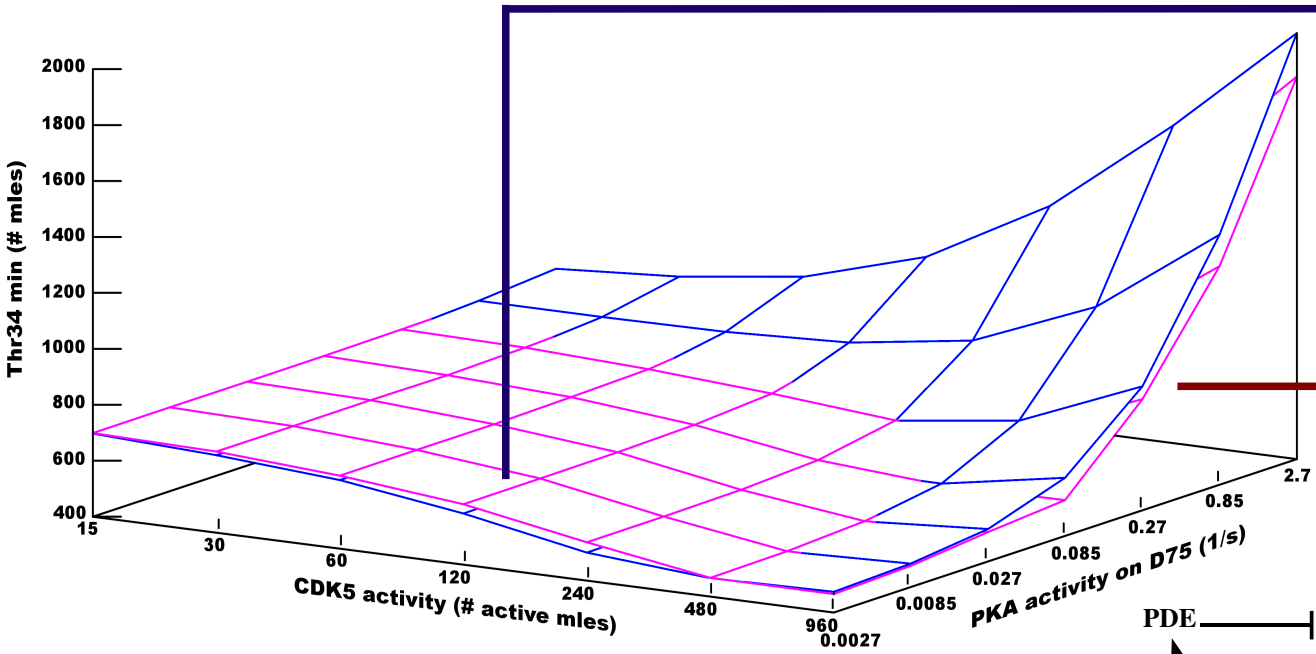


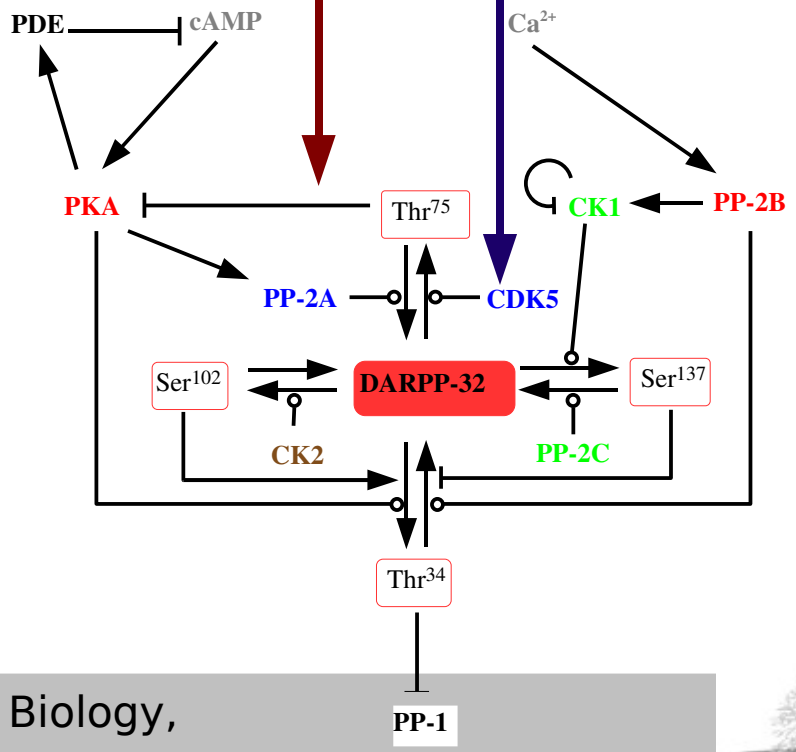
Some parameters are robust



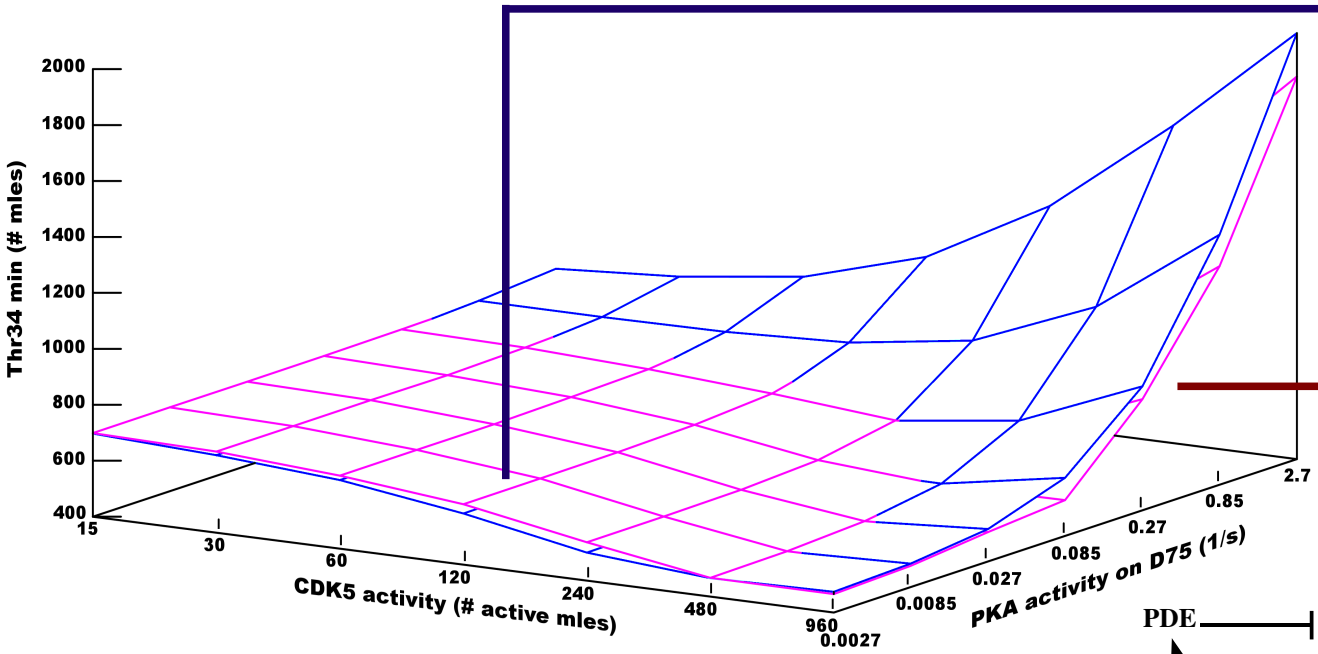


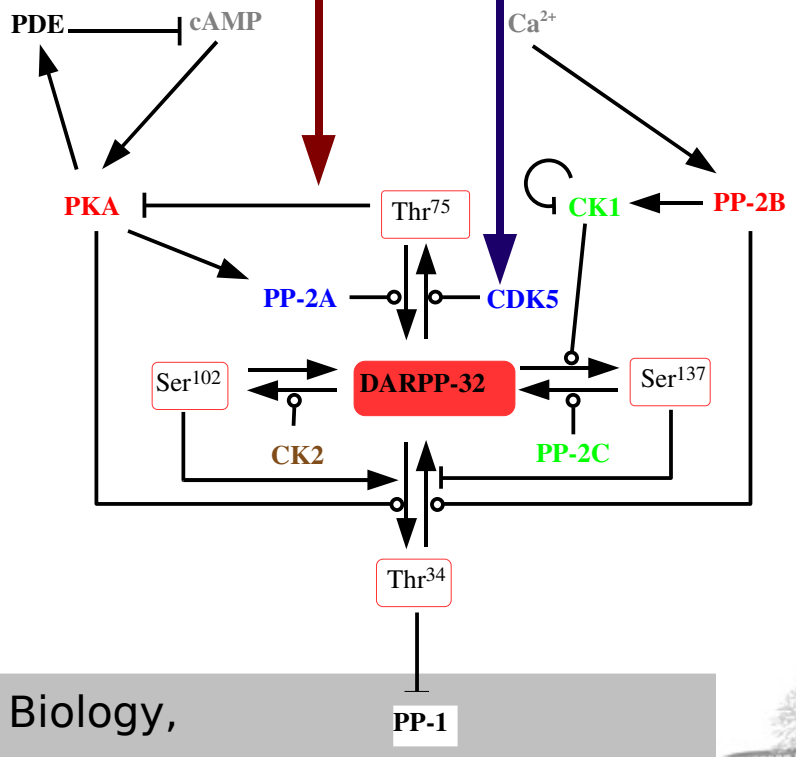
Some parameters are sensitive





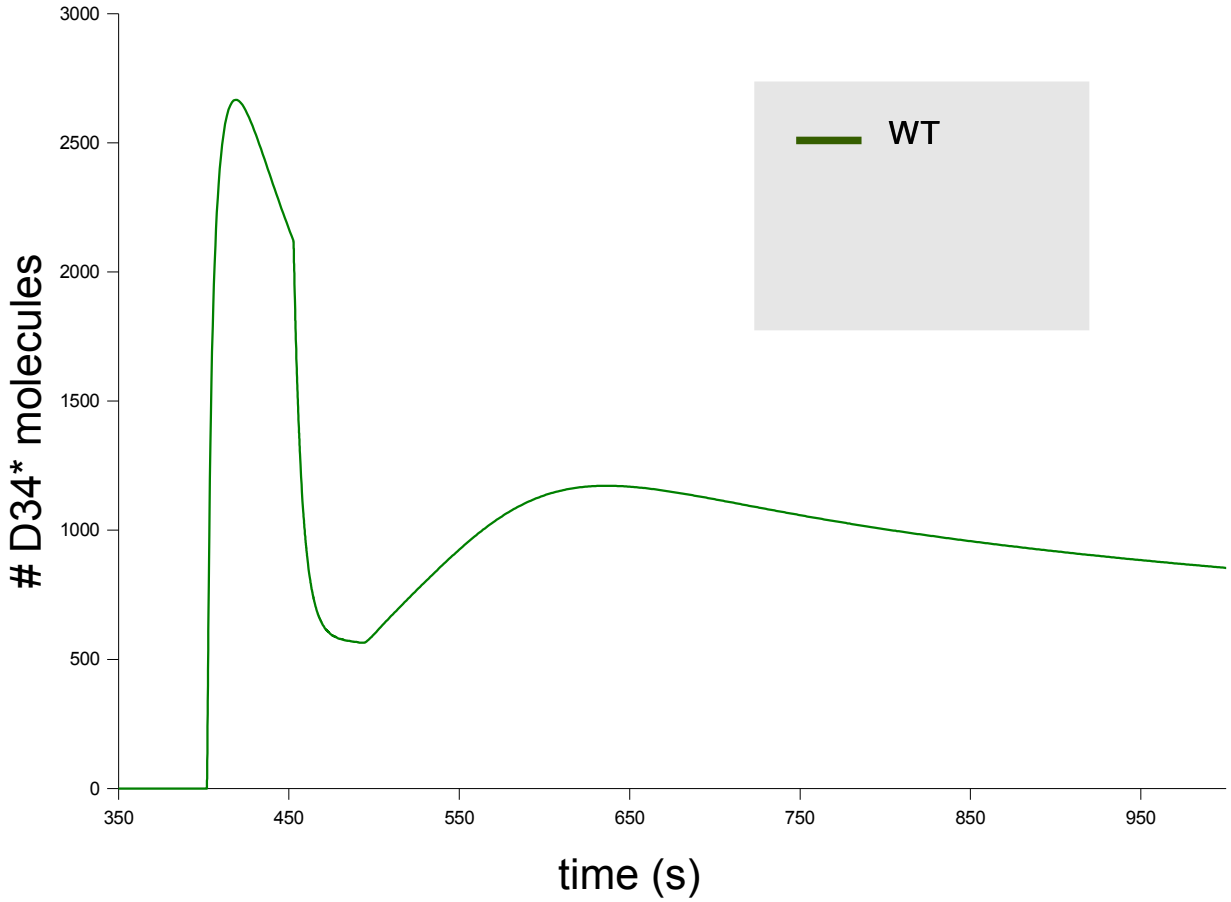
Some parameters are sensitive



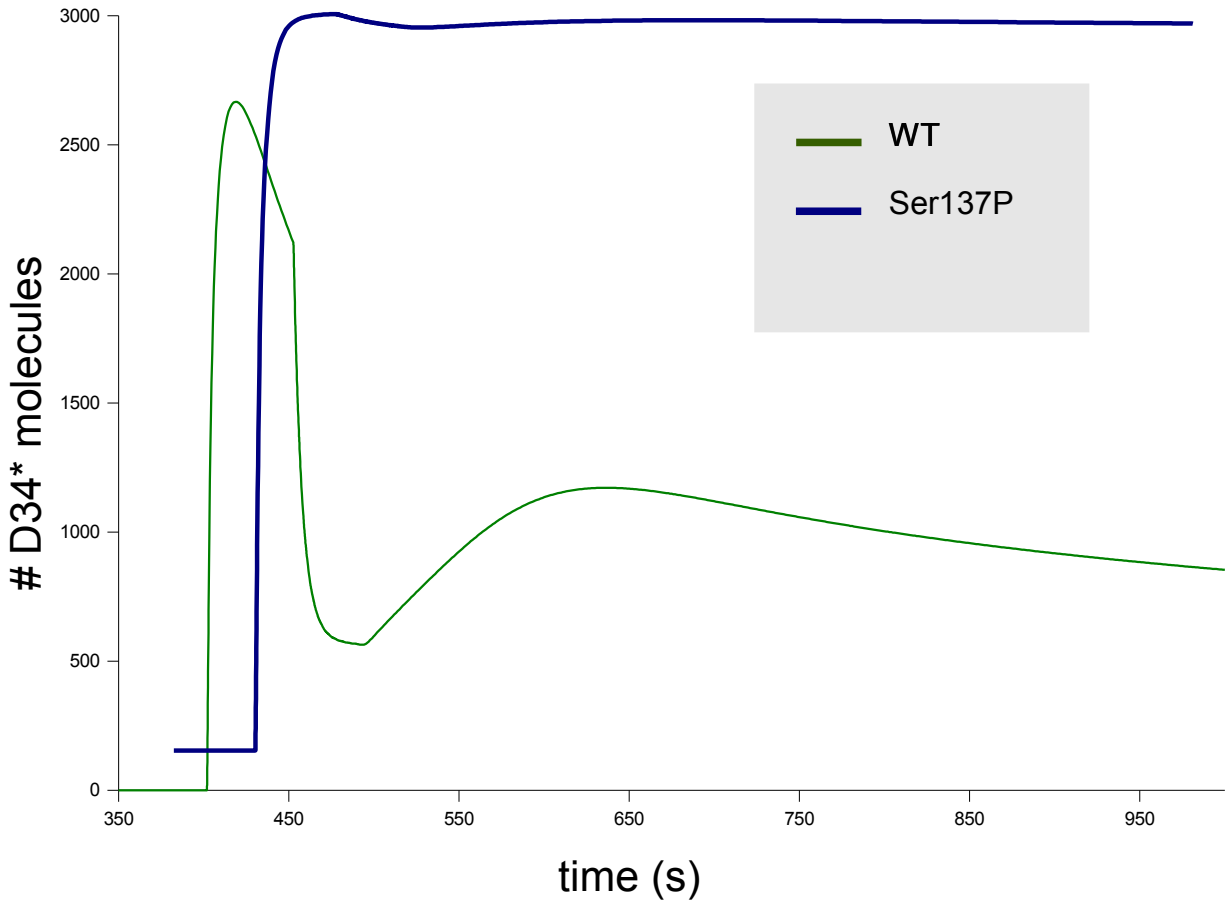


Takahashi et al (2005) Increased activity of cyclin-dependent kinase 5 leads to attenuation of cocaine-mediated dopamine signaling. PNAS 102: 1737–1742.

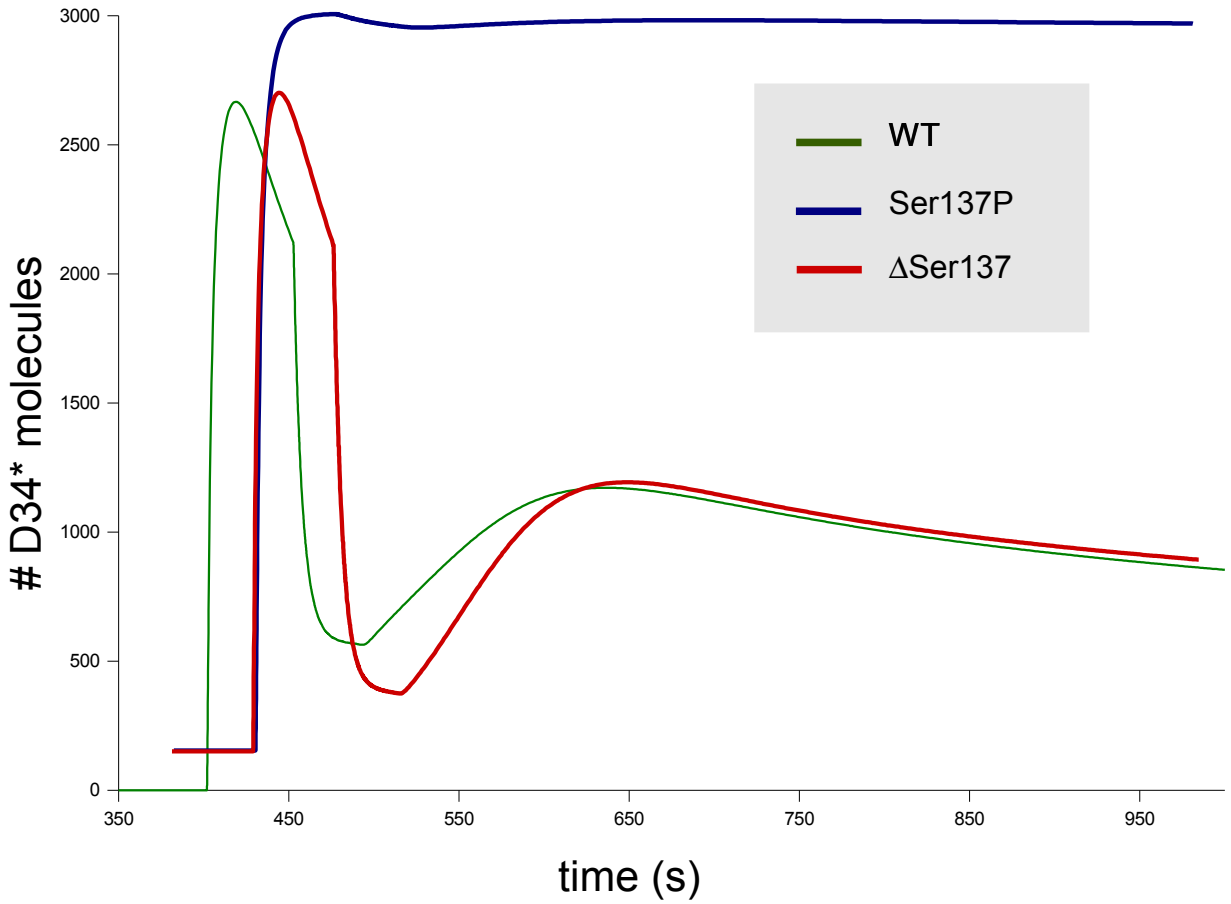
Mutation *in silico*



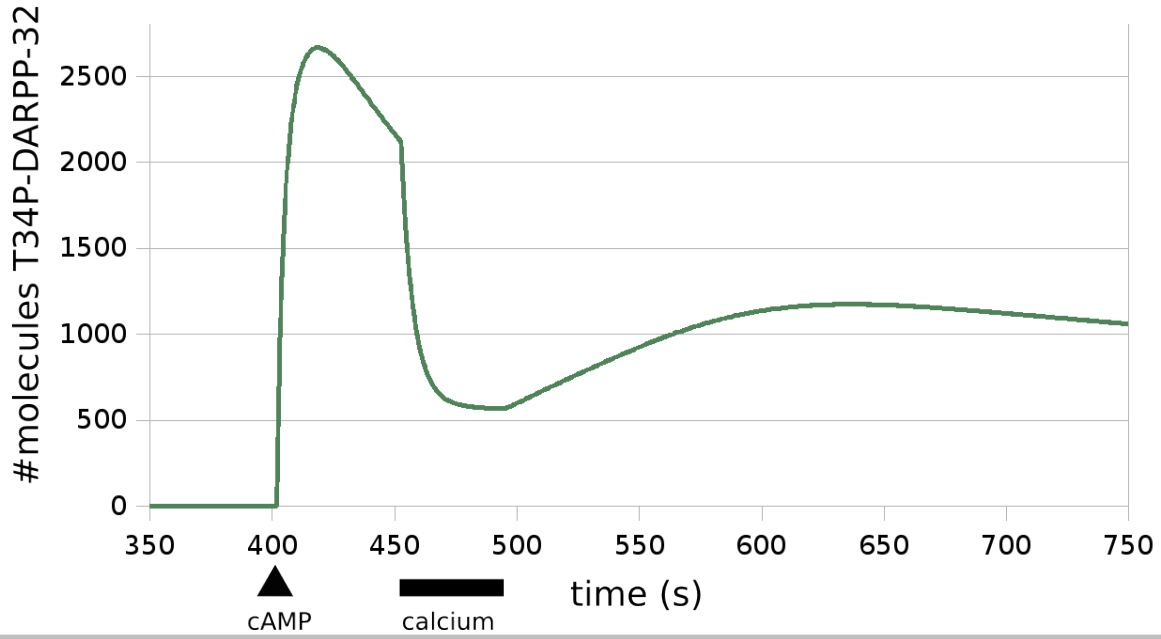
Mutation *in silico*



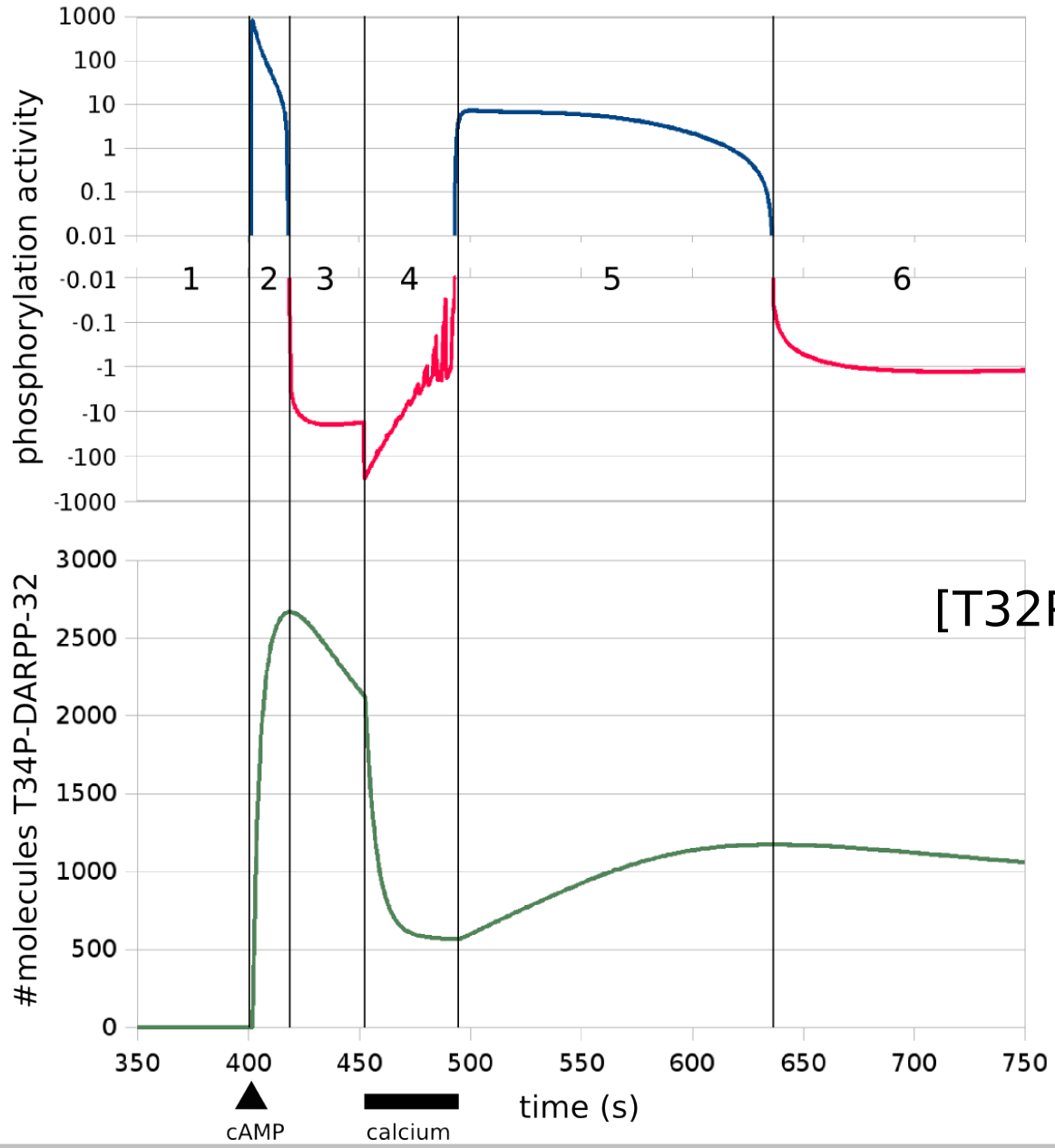
Mutation *in silico*



DARPP-32 is an integrator

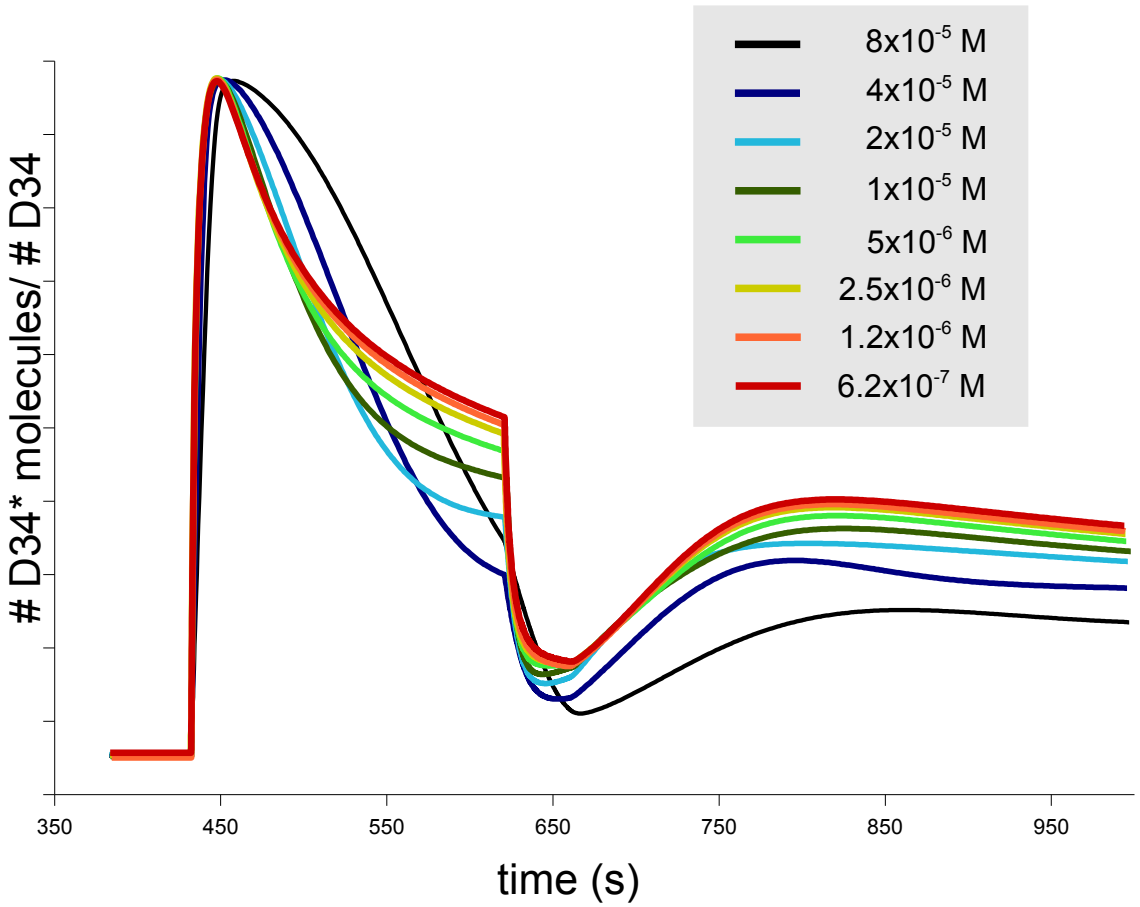


DARPP-32 is an integrator

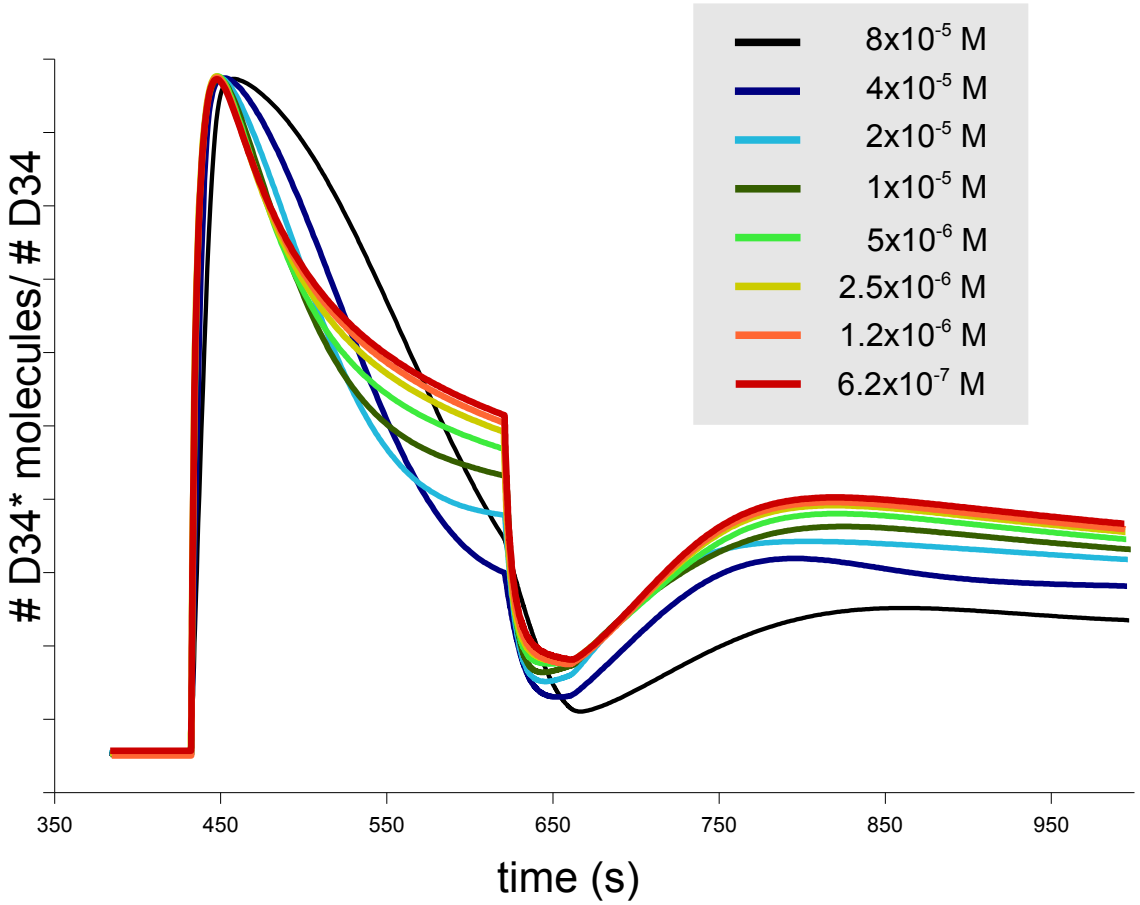


$$[T32P] = \int (\sum[kin] - \sum[ppase])\, dt$$

DARPP-32 as a robust integrator

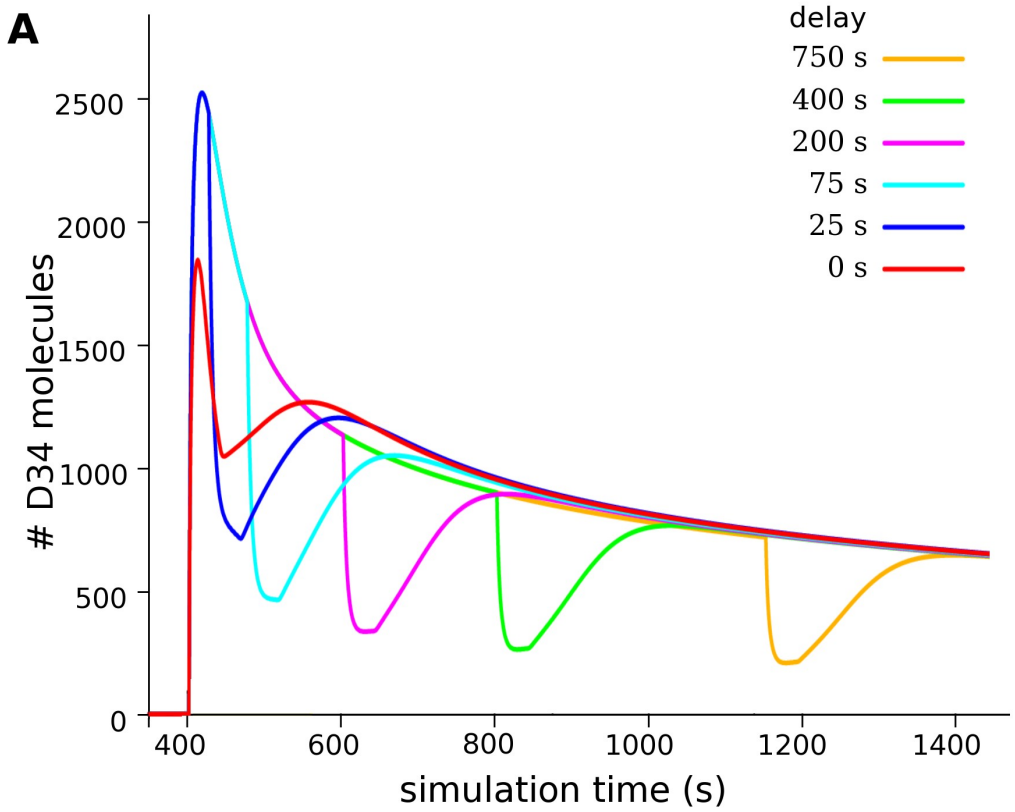


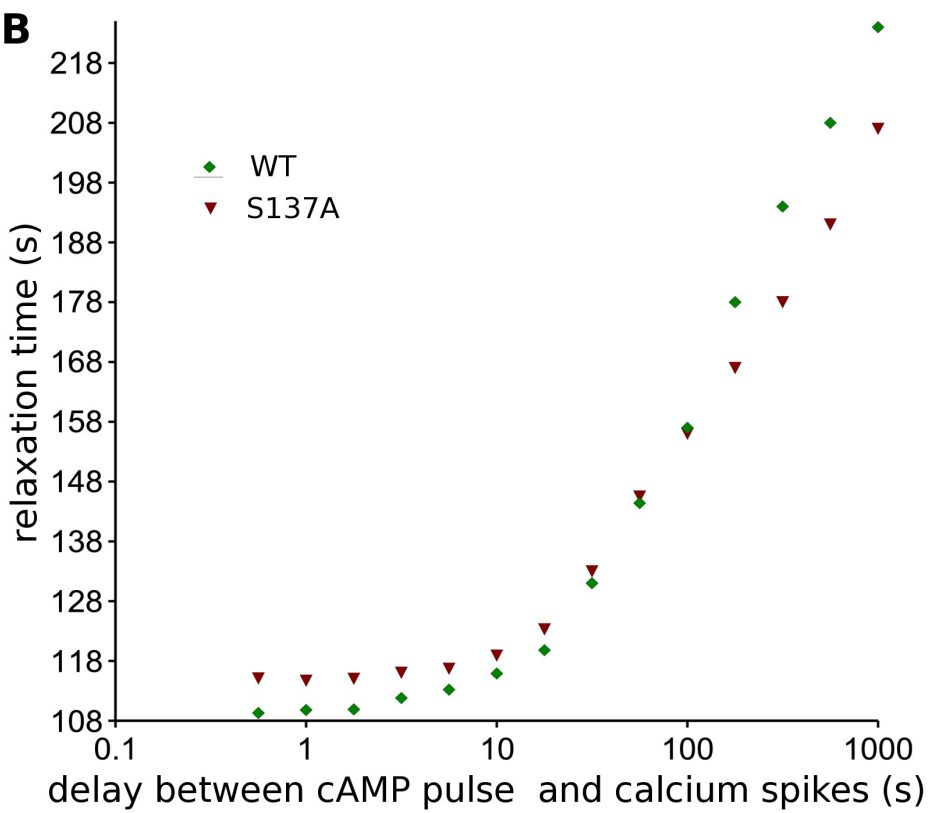
DARPP-32 as a robust integrator



Heterozygous DARPP-32 +/- do not display phenotypes

DARPP-32 is a coincidence detector





- E-cell developers
  (Institute of Advanced Biosciences, Tsuruoka)

  Kouichi Takahashi

  Kazunari Kaizu

  Gabor Bereczki

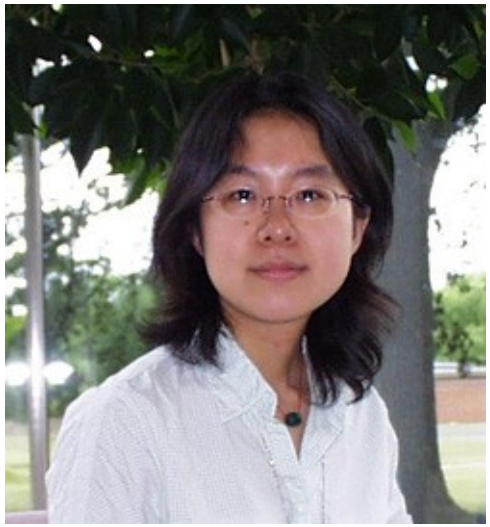
- Collaborators
  (INSERM U536, Paris)

  Jean-Antoine Girault

  Denis Herve

Eric Fernandez

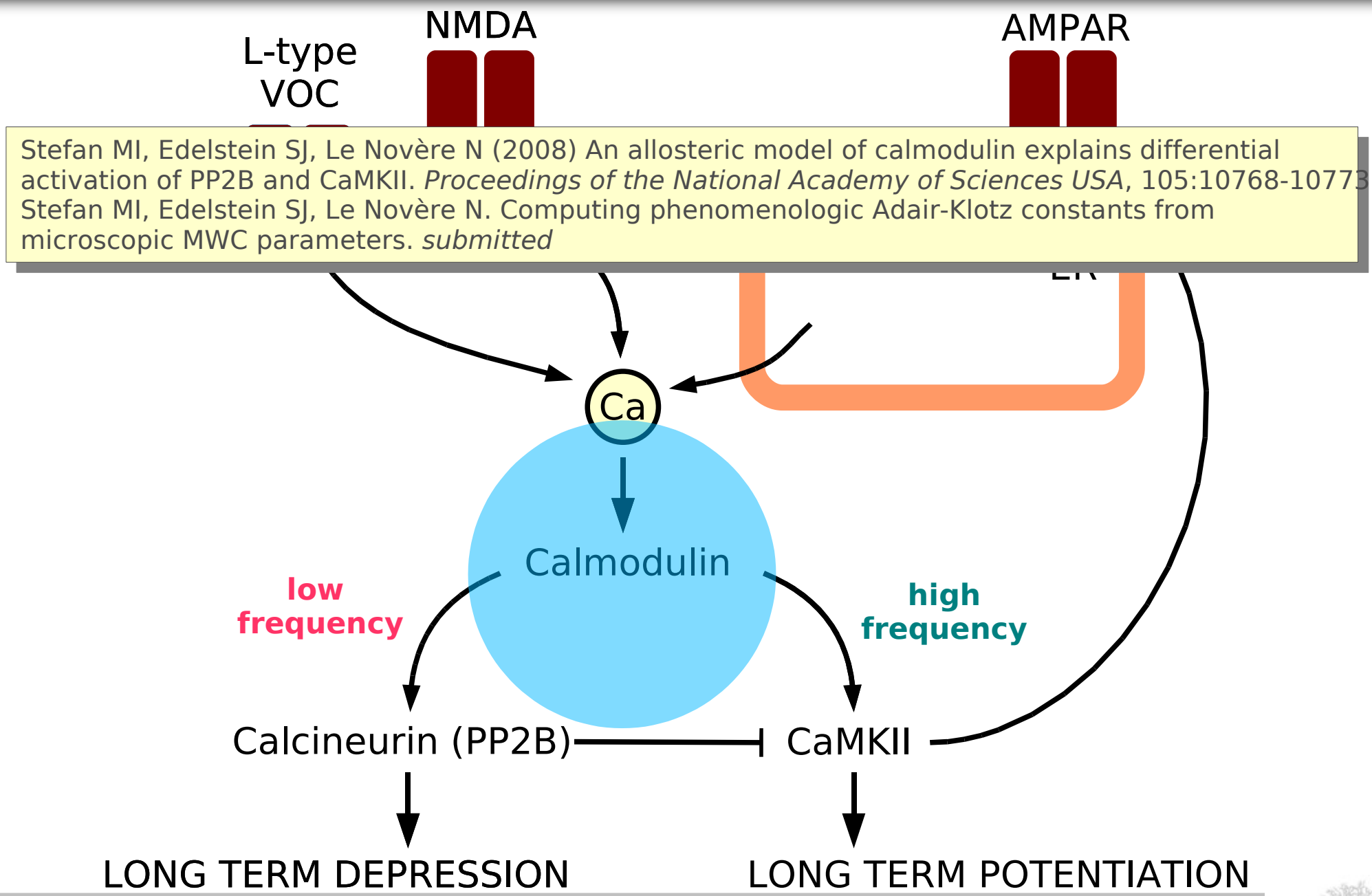
Renaud Schiappa



Lu Li

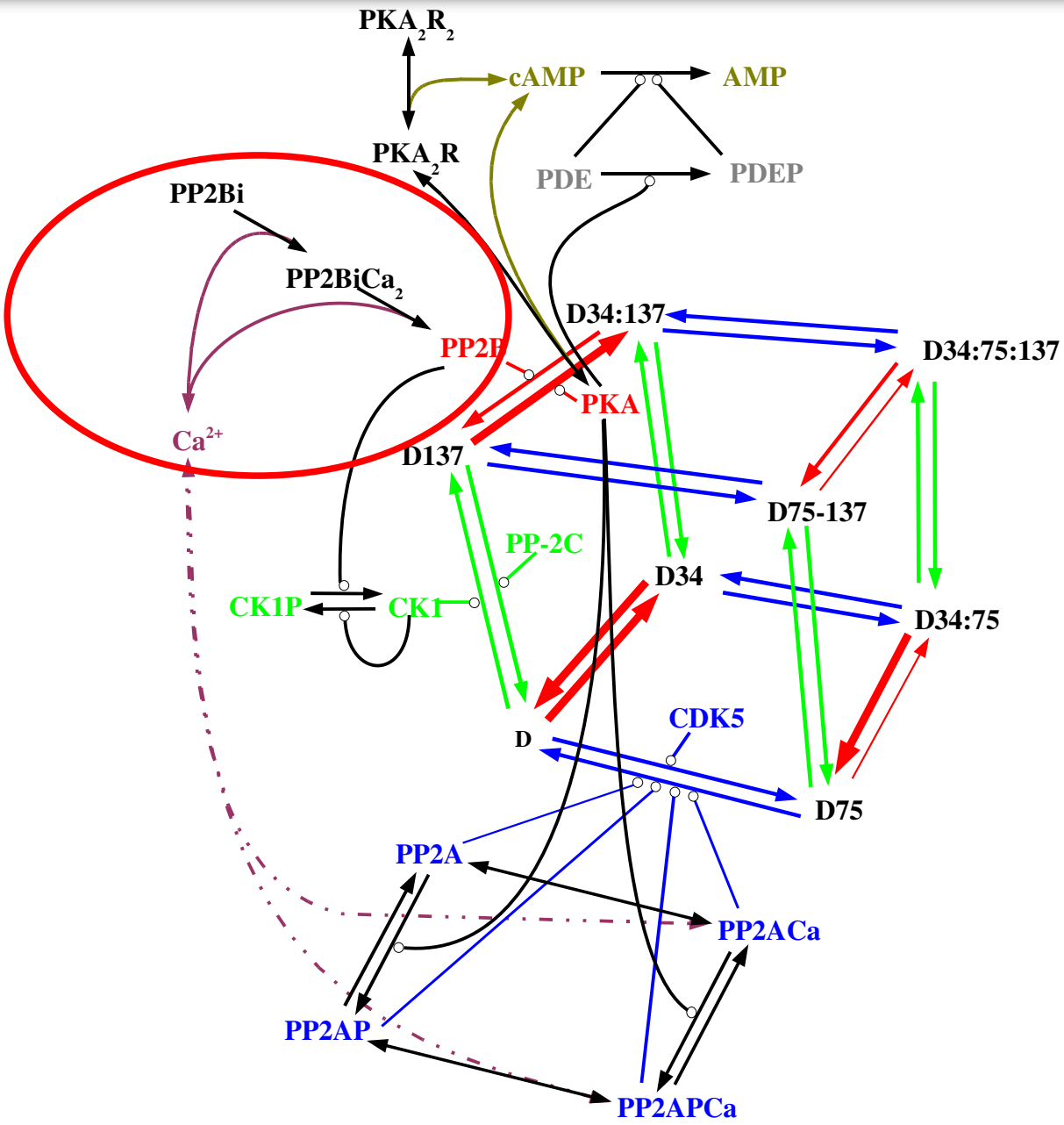
- Pros
  - Scale well-adapted to most available quantitative biochemical information
  - Can easily be extended and/or modularised
  - Extensive theoretical and computational toolkit
- Cons
  - Description of reactions is far from being realistic, and do not describe accurately the underlying mechanisms
  - Sensitive to combinatorial explosion
  - Dendritic spine is strongly anisotropic: Importance of distributions, gradients, crowding, scaffolding etc.

Allosteric signalling devices

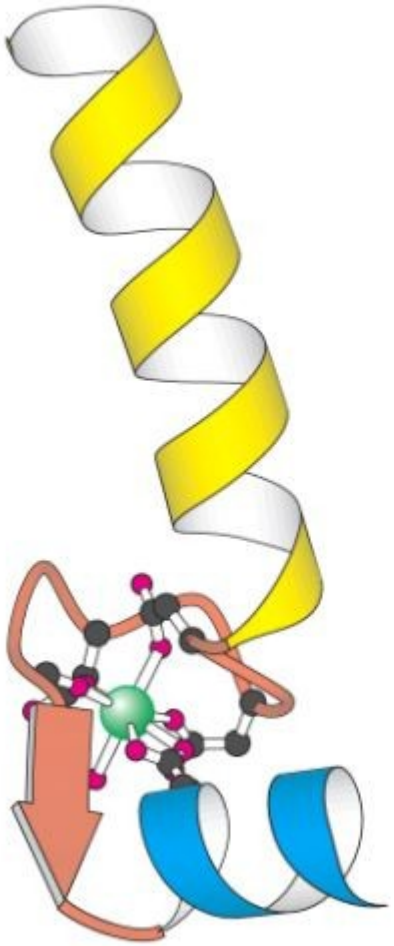


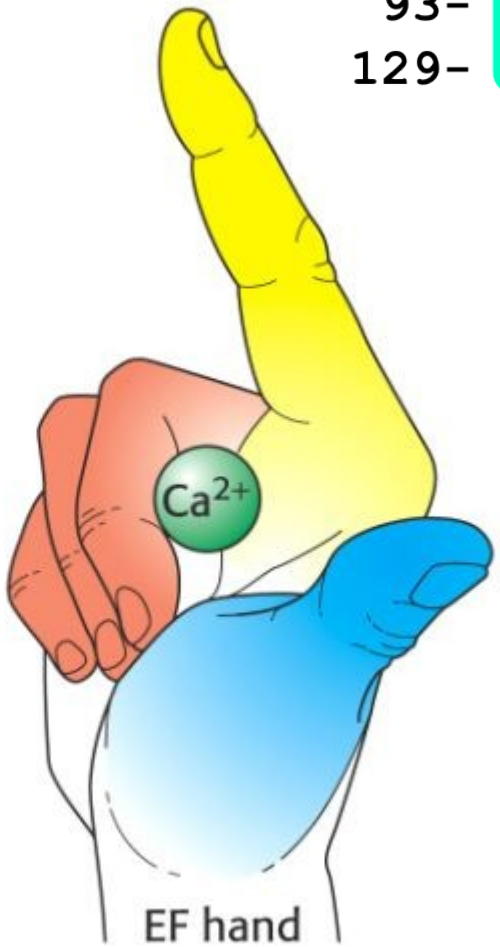
Stefan MI, Edelstein SJ, Le Novère N (2008) An allosteric model of calmodulin explains differential activation of PP2B and CaMKII. *Proceedings of the National Academy of Sciences USA*, 105:10768-10773
Stefan MI, Edelstein SJ, Le Novère N. Computing phenomenologic Adair-Klotz constants from microscopic MWC parameters. *submitted*

Let's zoom in

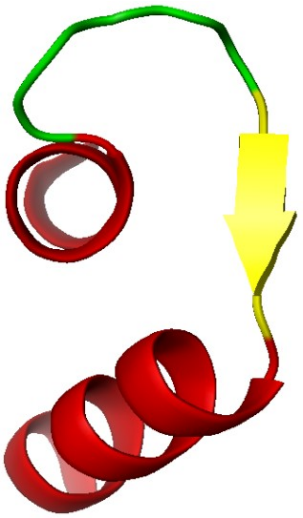

PKA2R2
cAMP
AMP
PKA2R
PDE
PDEP
PP2Bi
PP2BiCa2
D34:137
D34:75:137
PP2B
PKA
Ca2+
D137
D75-137
PP-2C
D34
CK1P
CK1
D34:75
CDK5
D
D75
PP2A
PP2ACa
PP2AP
PP2APCa

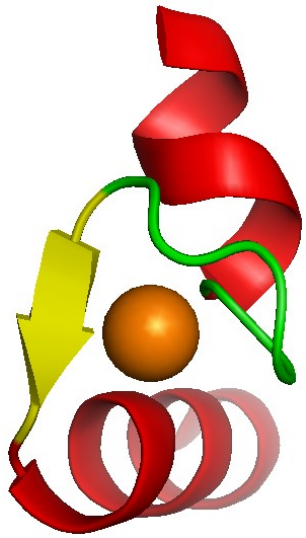
Structure of Calmodulin



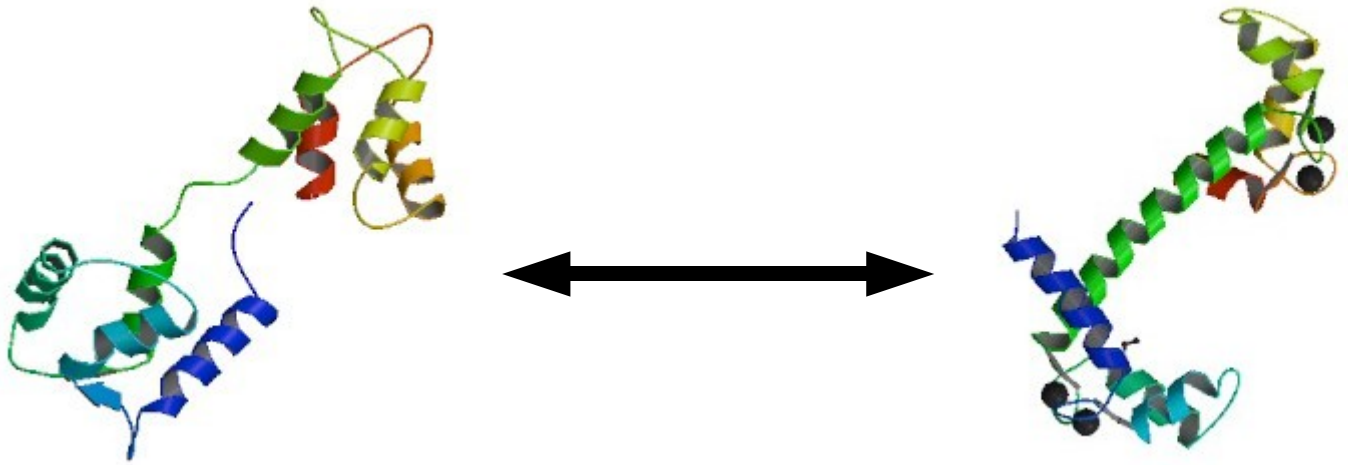


	X	Y	Z	-Y	-X	-Z	
20-	D	K	D	G	D	G	T	I	T	T	K	E	- 31
56-	D	A	D	G	N	G	T	I	D	F	P	E	- 67
93-	D	K	D	G	N	G	Y	I	S	A	A	E	-104
129-	D	I	D	G	D	G	Q	V	N	Y	E	E	-140

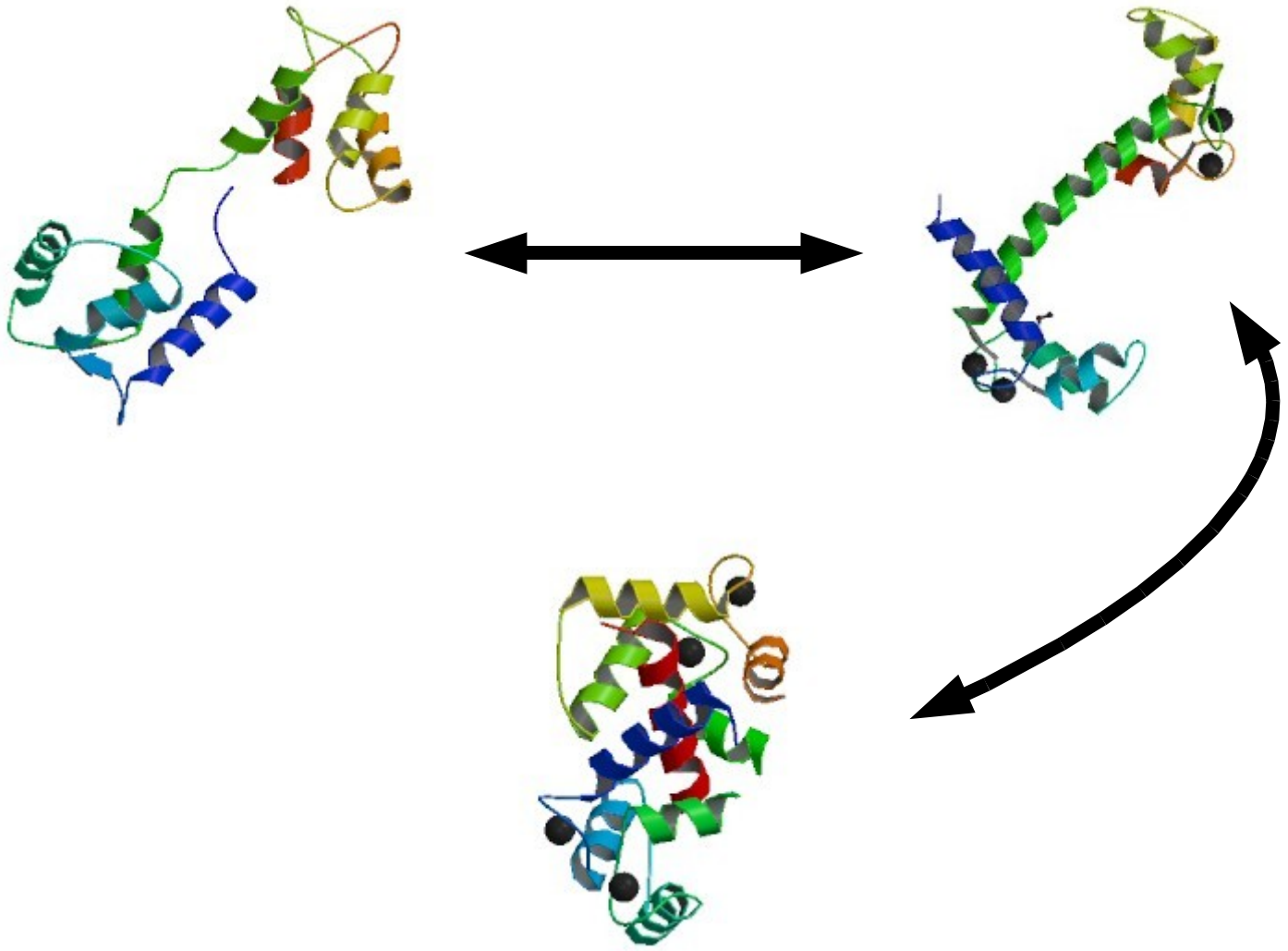




Alternative structures of calmodulin



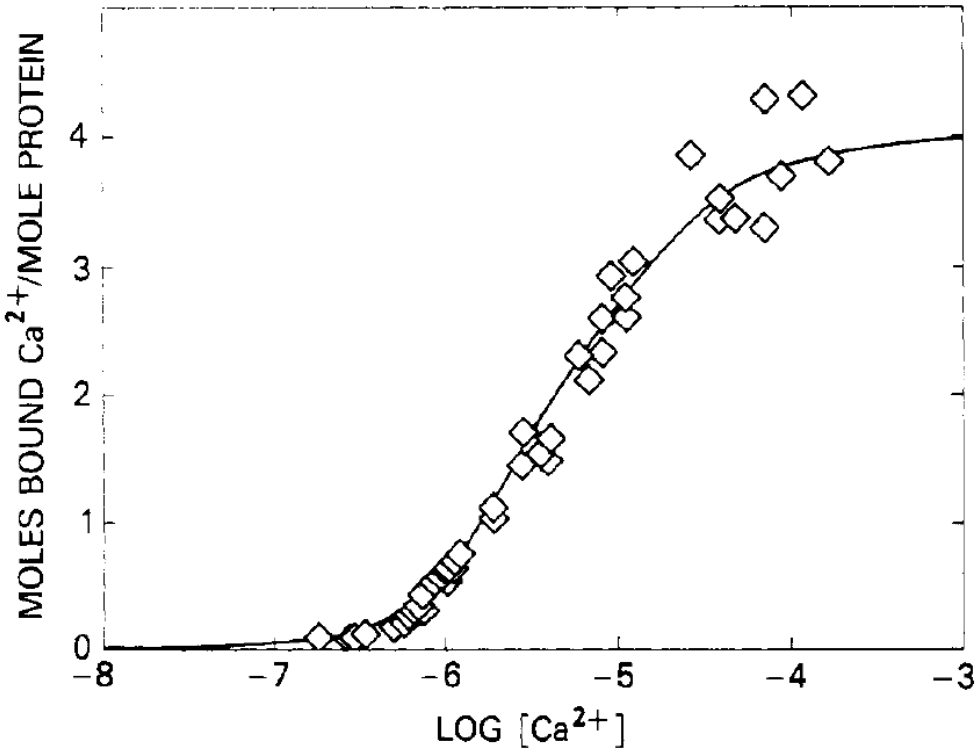
Alternative structures of calmodulin



Fitting of experimental results

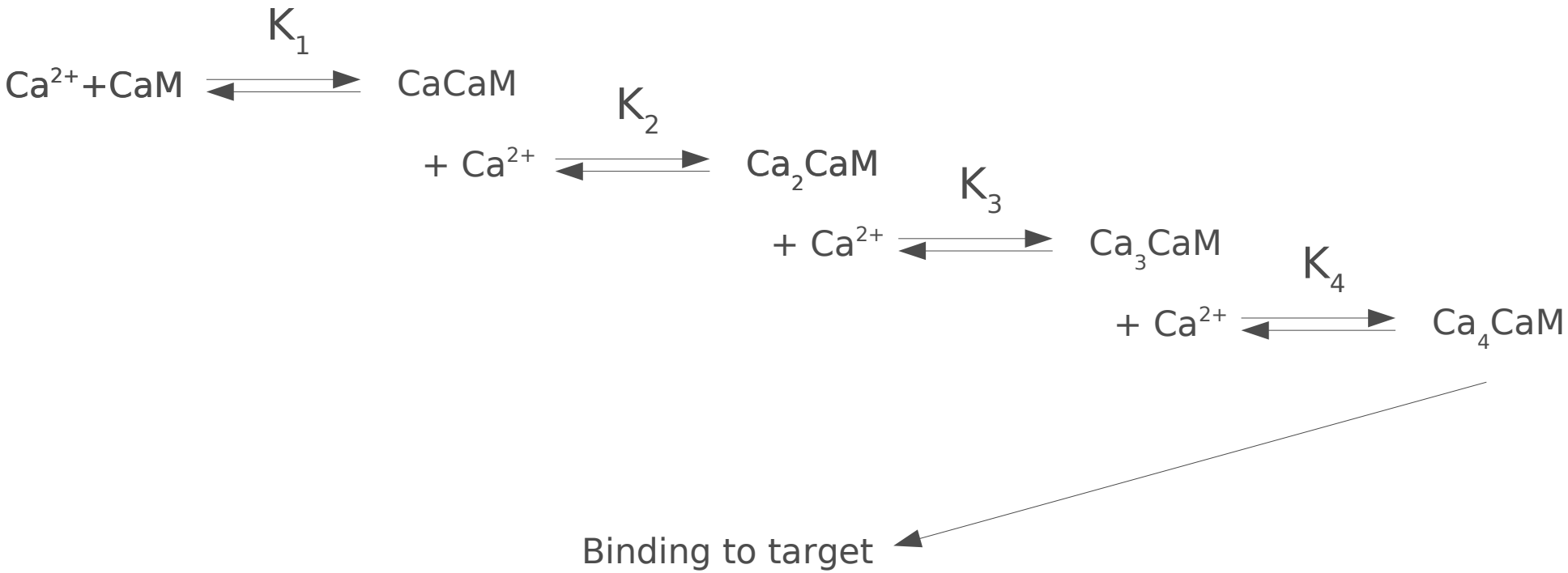
$$\overline{Y} = \frac{K_1[Ca]+2K_1K_2[Ca]^2+3K_1K_2K_3[Ca]^3+4K_1K_2K_3K_4[Ca]^4}{1+K_1[Ca]+K_1K_2[Ca]^2+K_1K_2K_3[Ca]^3+K_1K_2K_3K_4[Ca]^4}$$

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

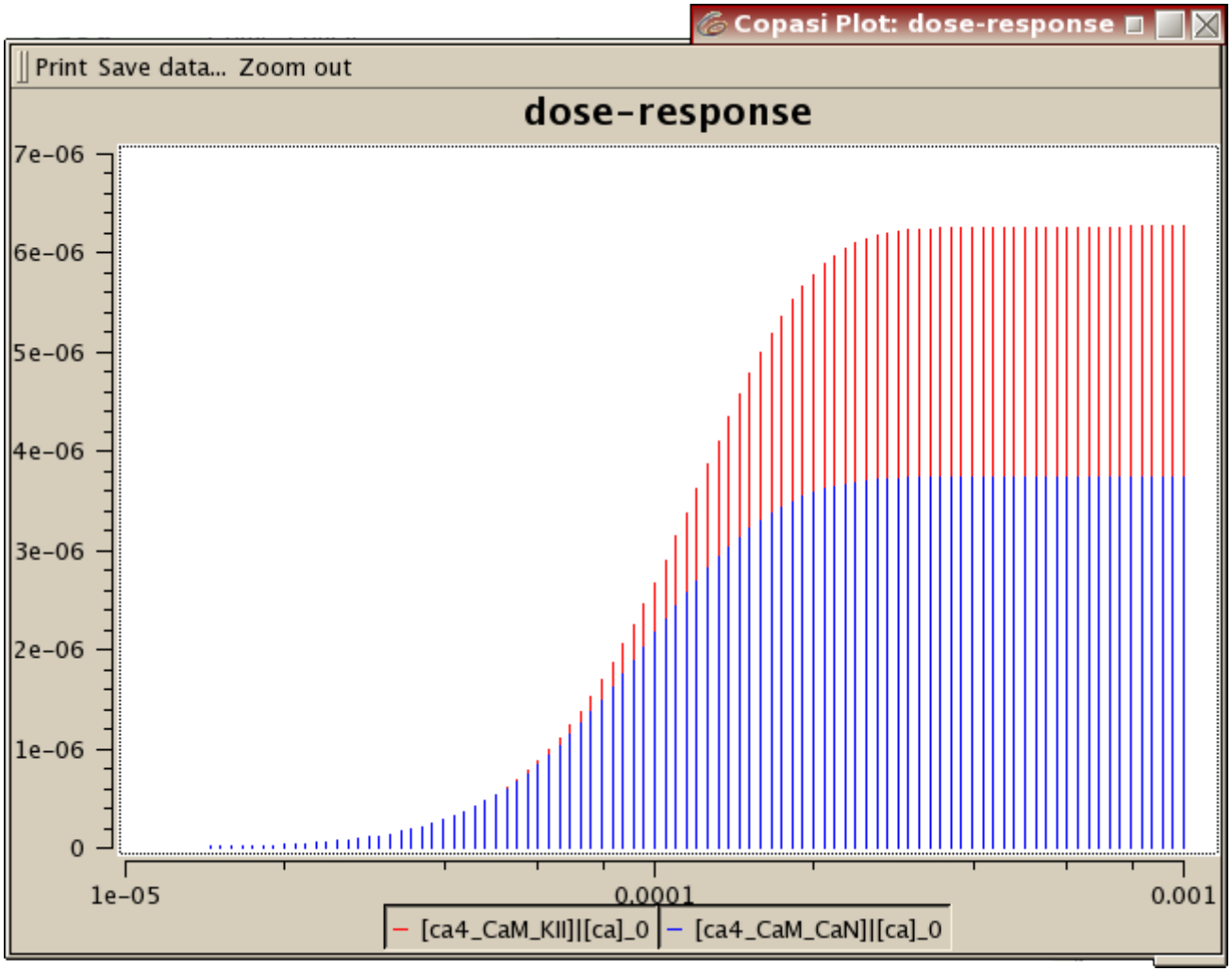


Crouch and Klee (1980)
Biochemistry, 19: 3692-3698

Phenomenological models



That does not work ...



That does not work ...

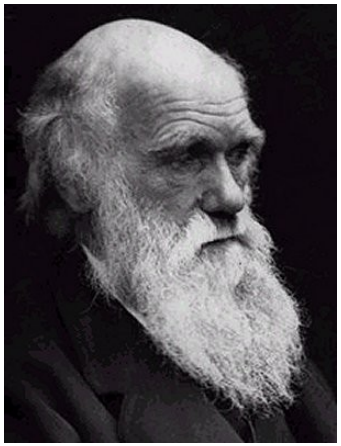
- Calmodulin bound to three calcium activates calcineurin
  - Kincaid and Vaughan (1986). *PNAS*, 83: 1193-1197
- Calmodulin bound to two calcium can bind CaMKII
  - Shifman et al (2006). *PNAS*, 103: 13968-13973
- Calmodulin affinity for calcium increases once bound to CaMKII
  - Shifman et al (2006) [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

Induction Vs Selection

- Induction = BAD
  (intelligent design, Lamarck's first law, antibody moulding, directed axonal growth, induced-fit ...)
- Physicaly non-sensical. Calcium has no inertia. Calcium cannot “trigger” a conformational change

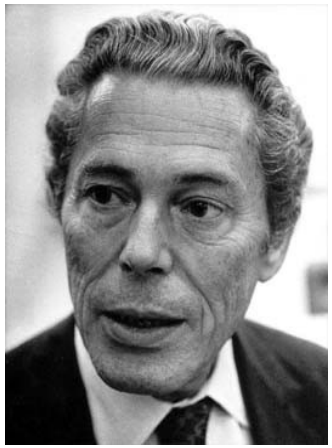
Induction Vs Selection

- Induction = BAD
  (intelligent design, Lamarck's first law, antibody moulding, directed axonal growth, induced-fit ...)
- Physicaly non-sensical. Calcium has no inertia. Calcium cannot "trigger" a conformational change
- Selection = GOOD
  (natural selection, clonal selection, synapse stabilisation, conformation stabilisation ...)

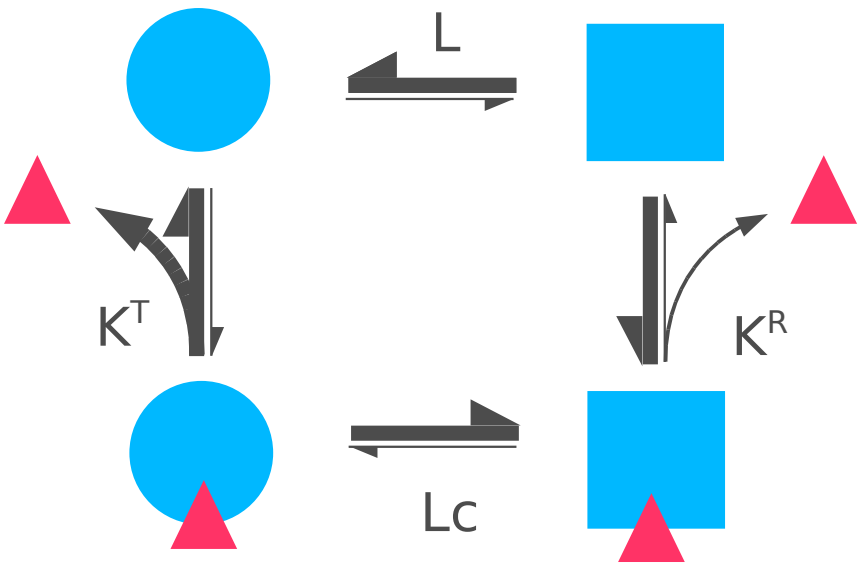


Allostery and state selection

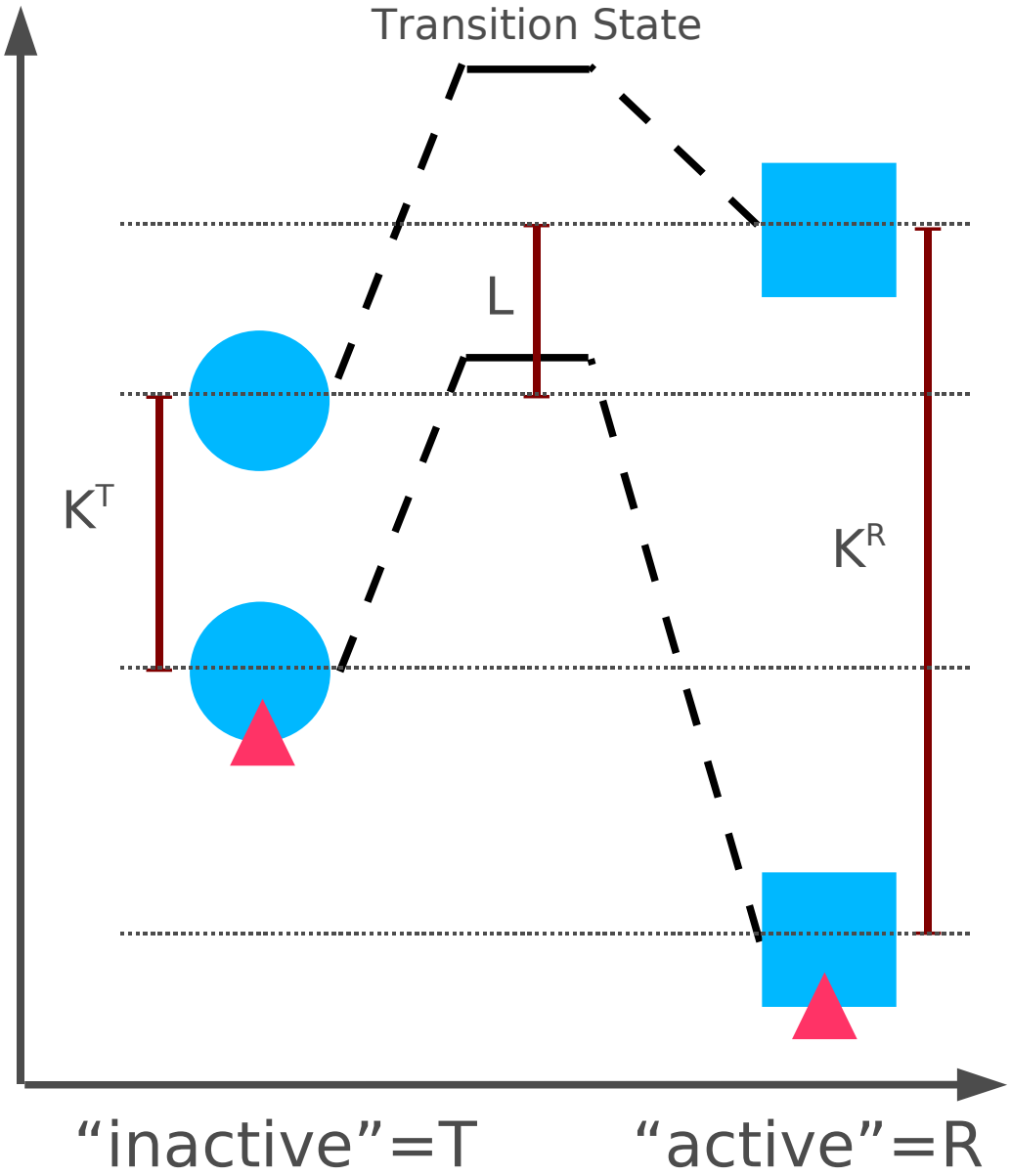
- Monod, Wyman, Changeux (1965). On the nature of allosteric transitions: a plausible model. *J Mol Biol*, 12: 88-118



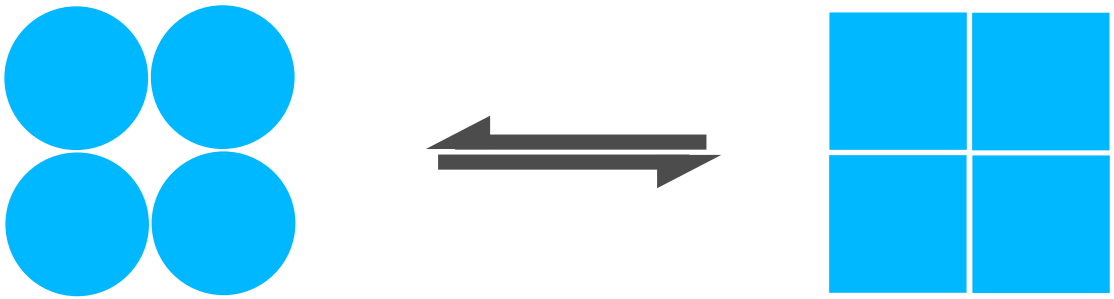
Modulation of thermal equilibria ≠ induced-fit



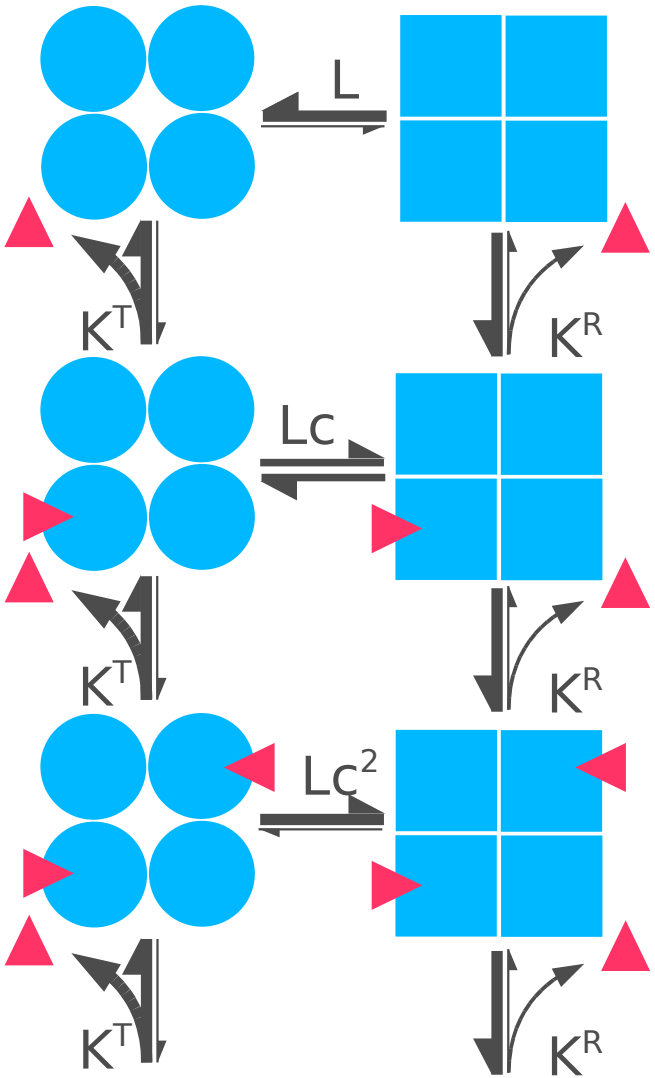
$$L = \frac{[T0]}{[R0]} \qquad C = \frac{K^R}{K^T}$$



Concerted transitions ≠ sequential model

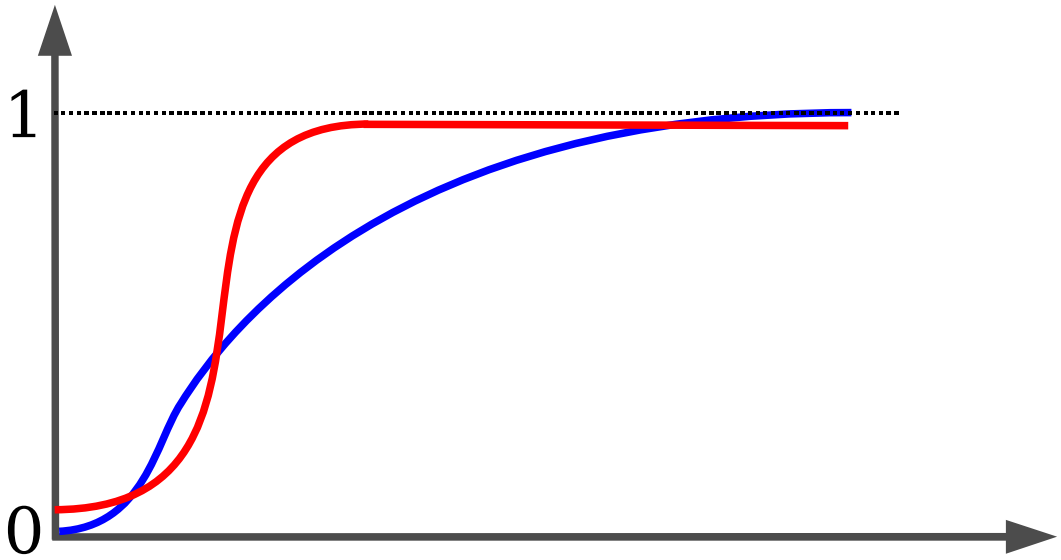


MWC model



$$\bar{Y} = \frac{Lc\alpha(1+c\alpha)^{n-1} + \alpha(1+\alpha)^{n-1}}{L(1+c\alpha)^n + (1+\alpha)^n}$$

$$\bar{R} = \frac{(1+\alpha)^n}{L(1+c\alpha)^n + (1+\alpha)^n}$$

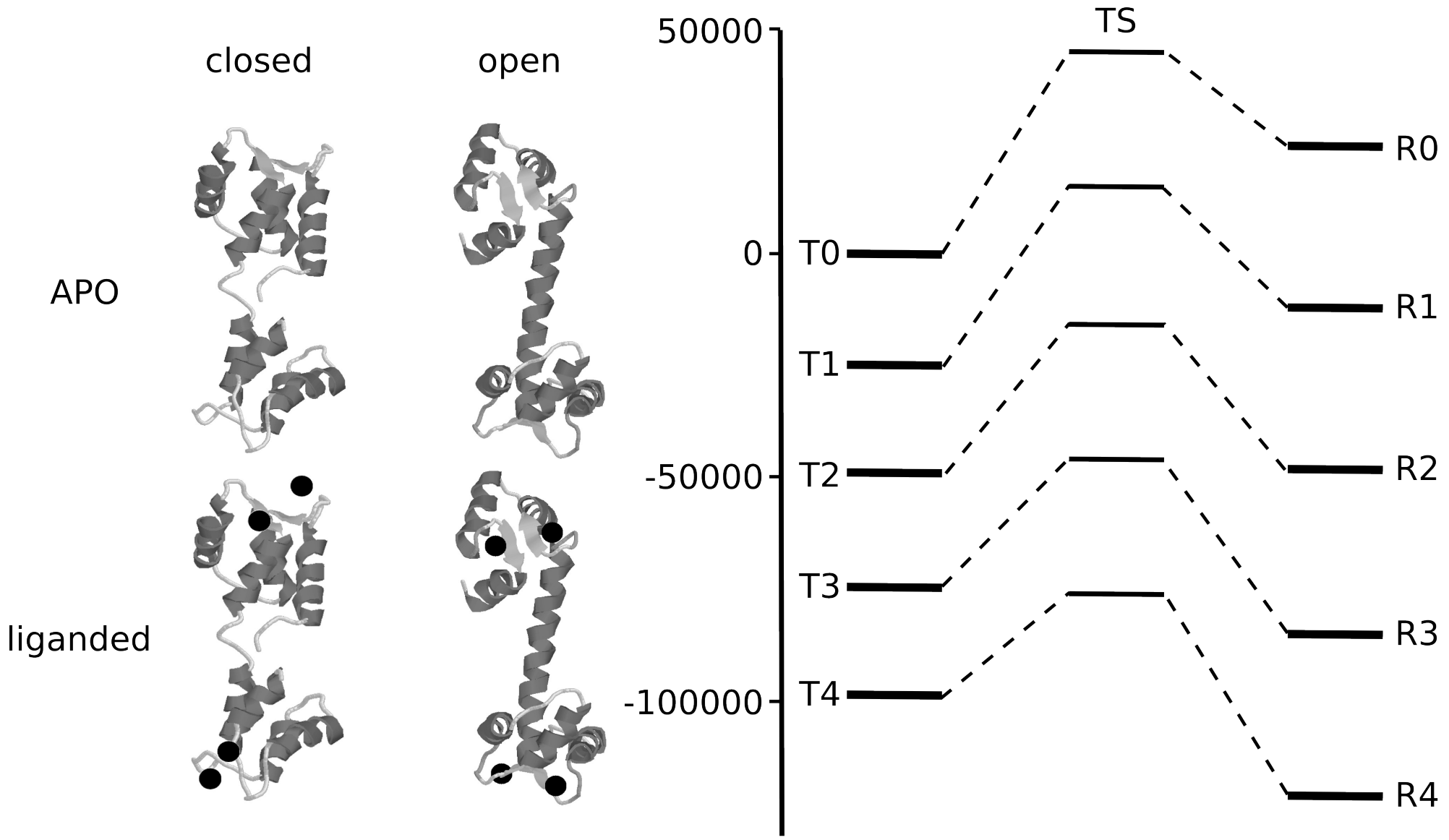


Extended MWC model

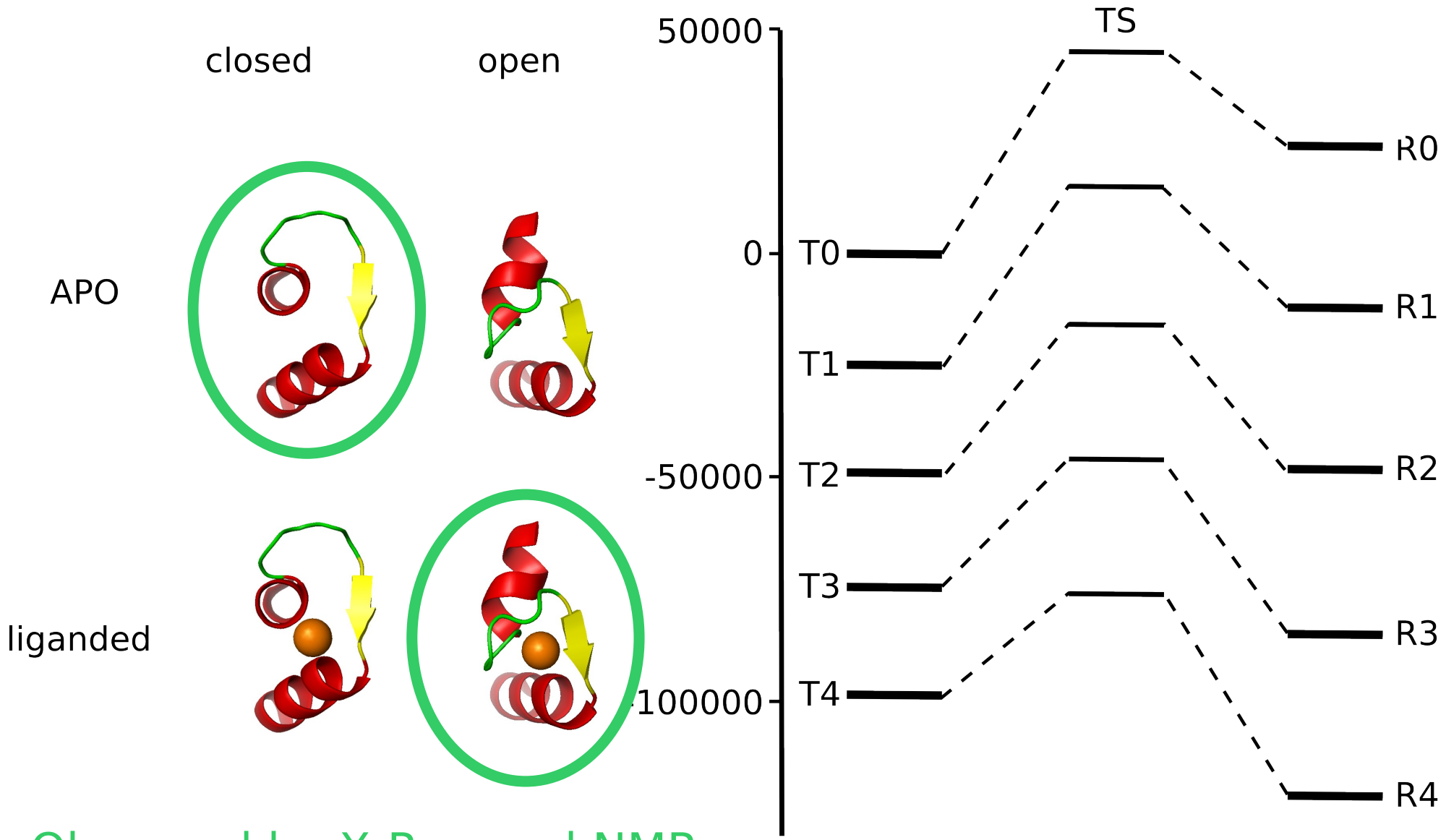
$$\bar{Y} = \frac{1}{n} \frac{\sum_i \left(\alpha_i \prod_{j \neq i} (1 + \alpha_j) \right) + L \prod_k \left(\frac{1 + e_k \gamma_k}{1 + \gamma_k} \right) \sum_i \left(c_i \alpha_i \prod_{j \neq i} (1 + c_j \alpha_j) \right)}{\prod_i (1 + \alpha_i) + L \prod_k \left(\frac{1 + e_k \gamma_k}{1 + \gamma_k} \right) \prod_i (1 + c_i \alpha_i)}$$

- αi = [ligand]/$K^R_{i,\text{lig}}$
- γk = [modulator]/$K^R_{k,\text{mod}}$
- $c i$ = $K^R_{i,\text{lig}}$ / $K^T_{i,\text{lig}}$
- $e k$ = $K^R_{k,\text{mod}}$ / $K^T_{k,\text{mod}}$

Four binding sites

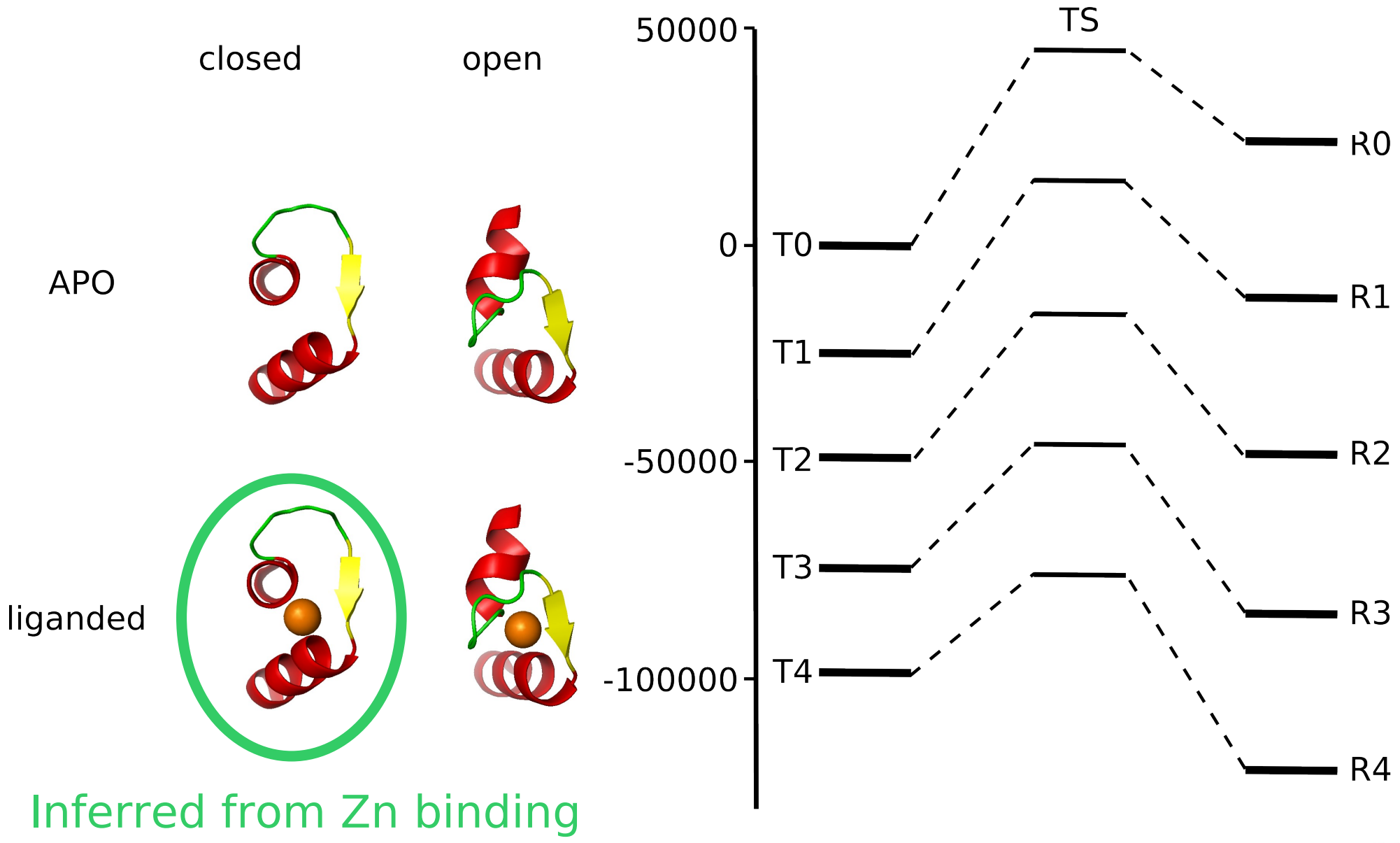


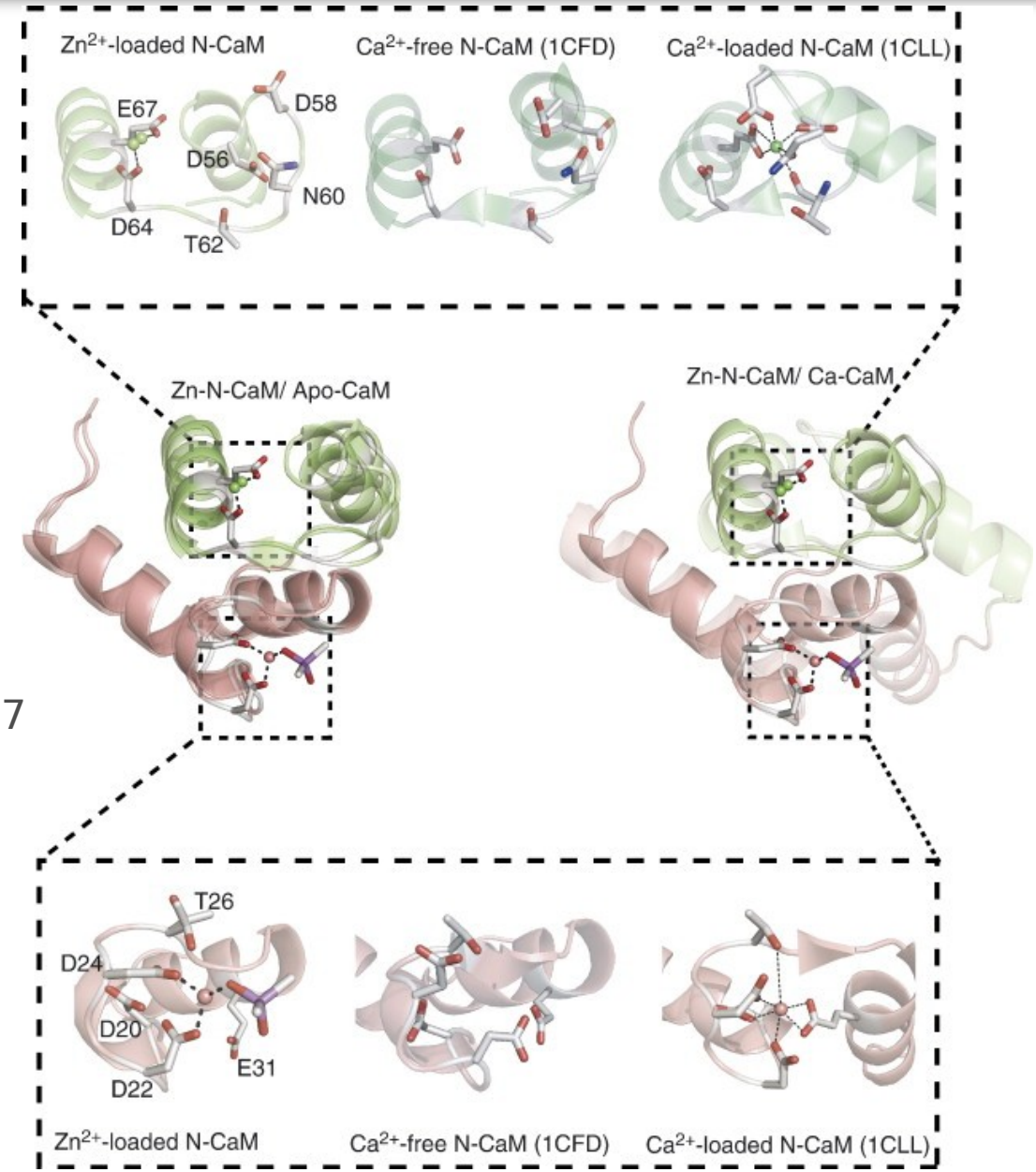
Concerted transition



Observed by X-Ray and NMR

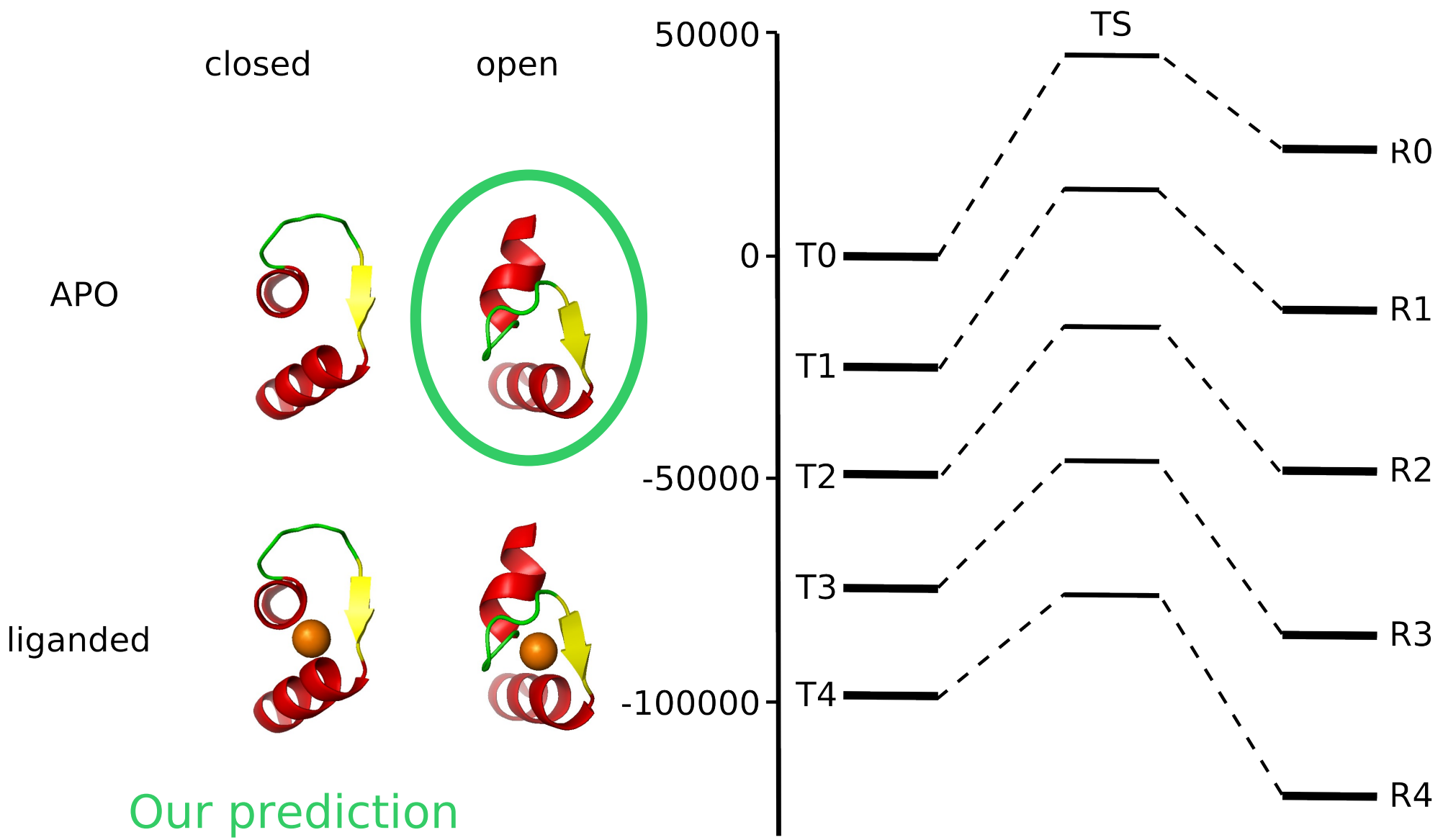
Concerted transition



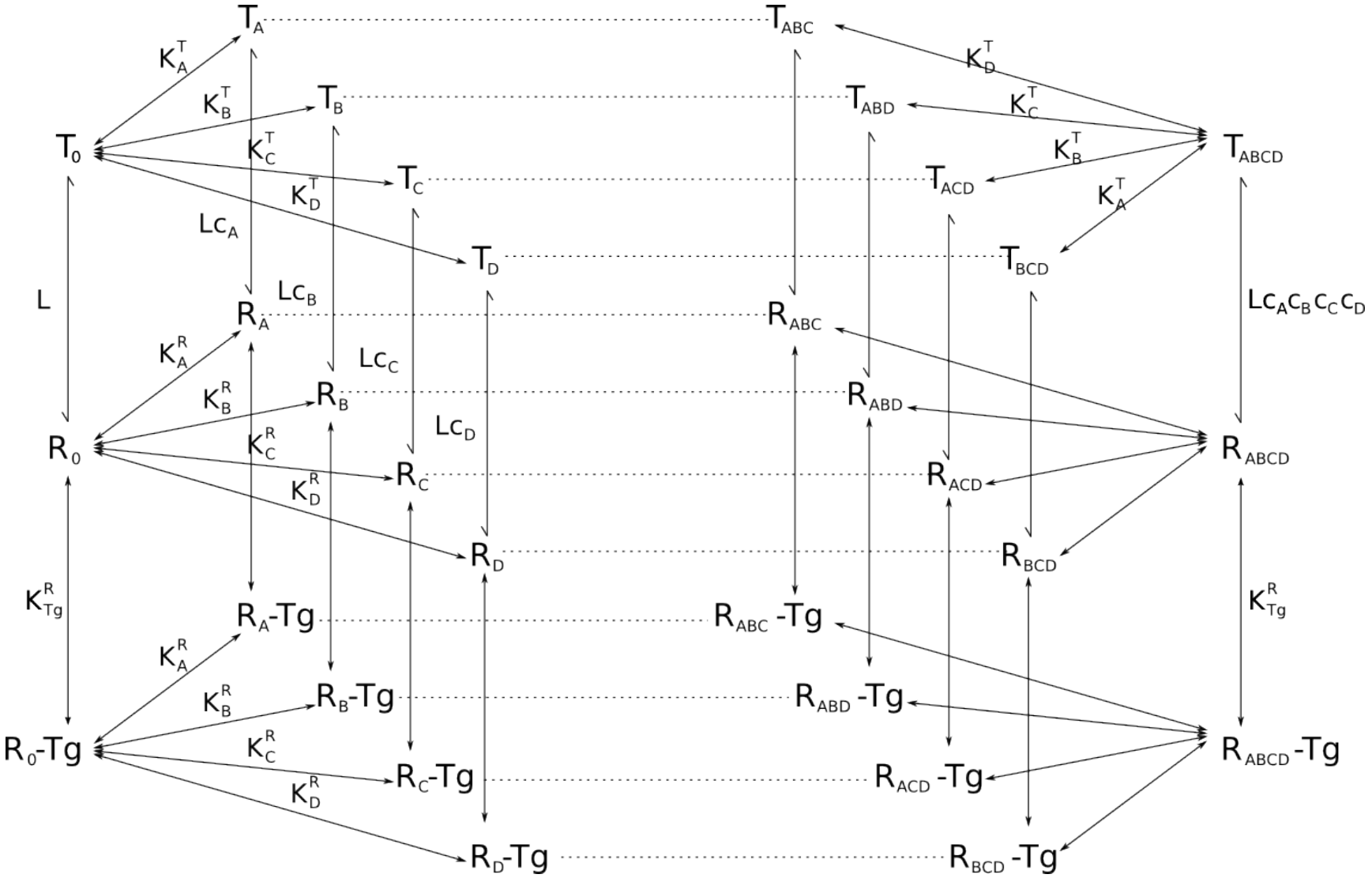


Warren *et al.* (2007).
J Mol Biol 374: 517-527

Concerted transition



Full mechanistic thermodynamic model



320 reactions

Restriction of the generalised model

- Hypothesis for the whole model: free energy of conformational transition is evenly distributed: c is unique
- Additional simplification to determine L: affinities are identical

$$\bar{Y} = \frac{\alpha(1+\alpha)^3 + L\left(\frac{1+\gamma e}{1+\gamma}\right)c\alpha(1+c\alpha)^3}{(1+\alpha)^4 + L\left(\frac{1+\gamma e}{1+\gamma}\right)(1+c\alpha)^4}$$

- Determination of individual affinities:

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

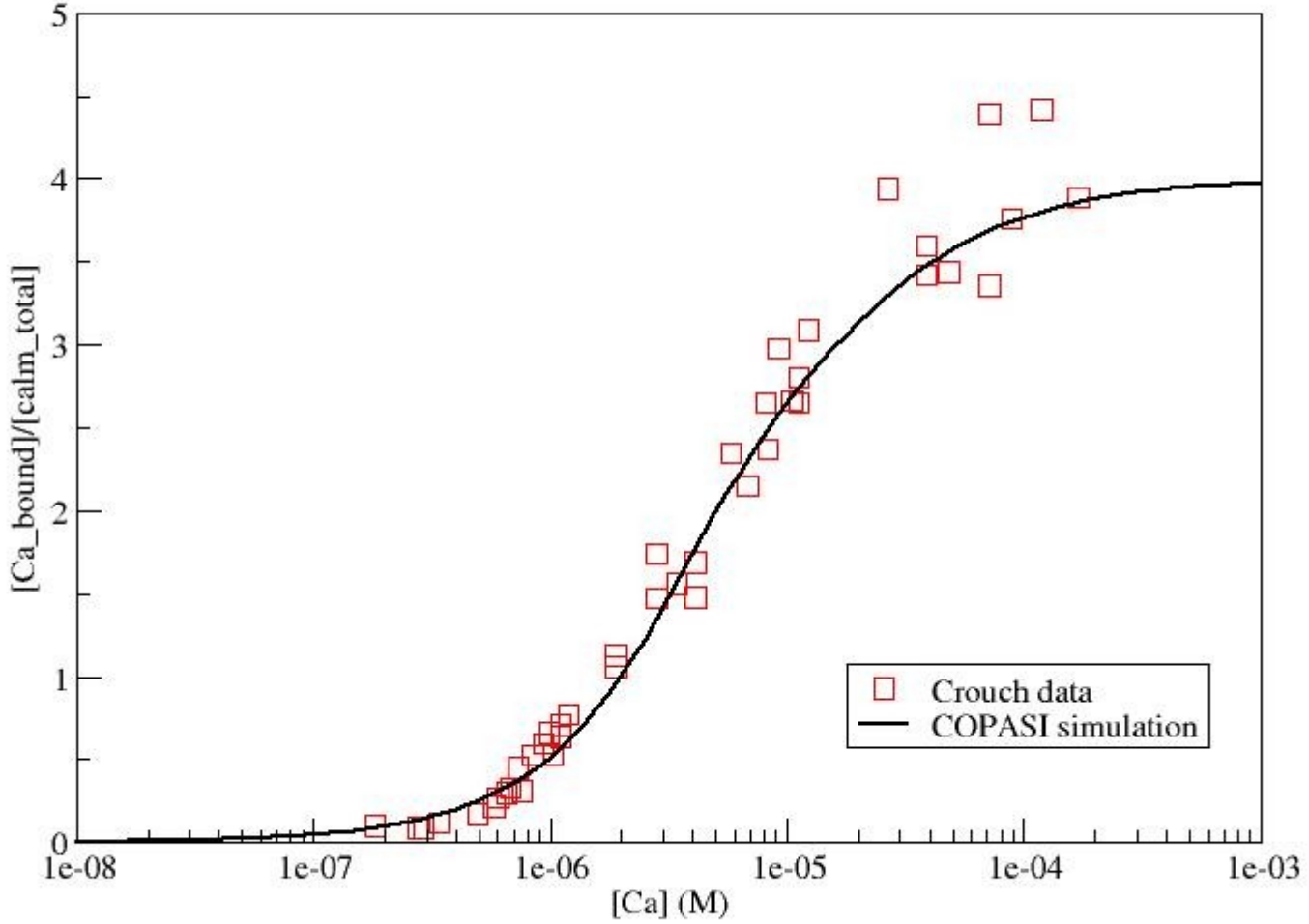
Model constraints

- 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 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 parameter sets

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

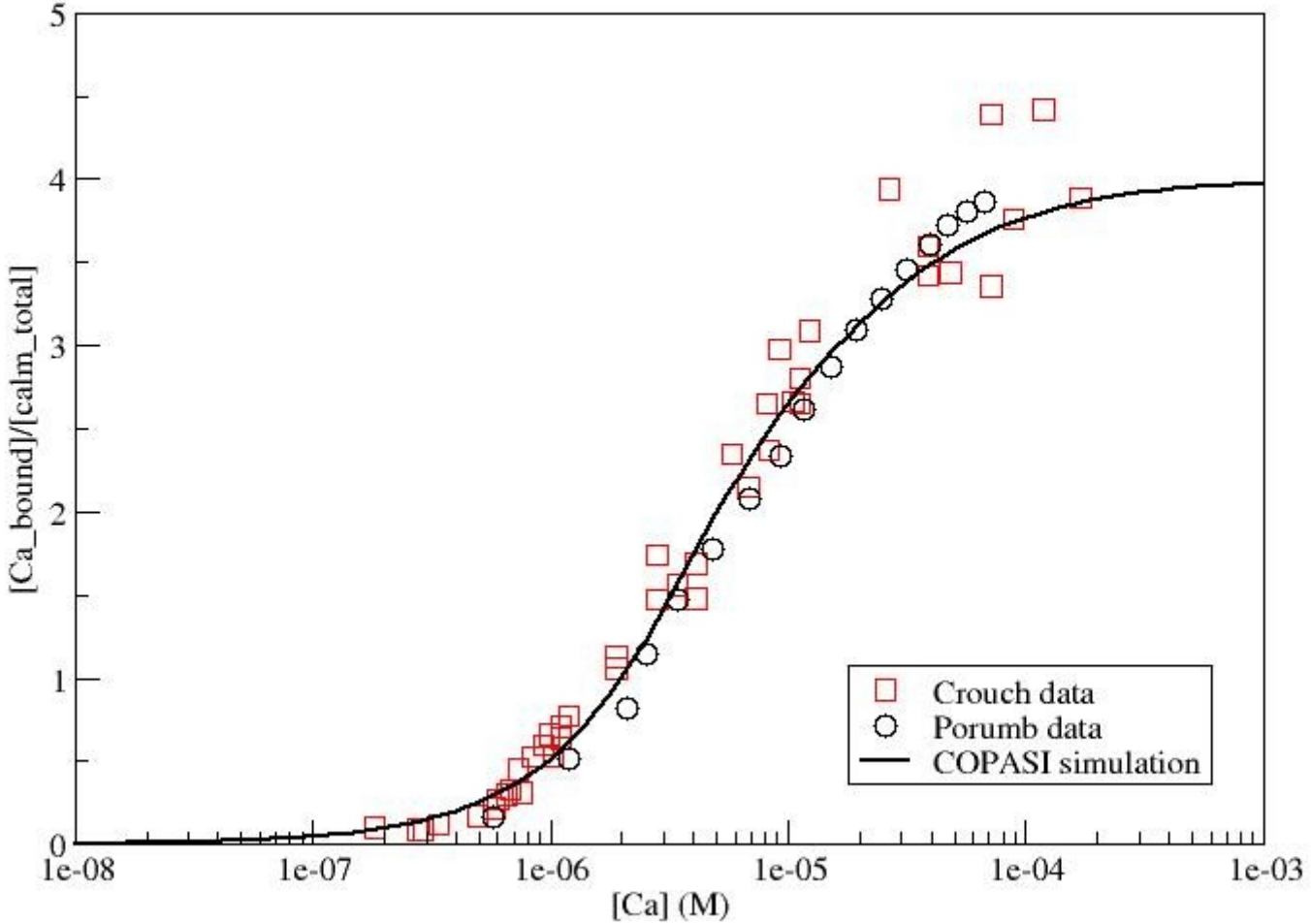
fit done with SciLab (http://www.scilab.org/)

Comparison with experiments



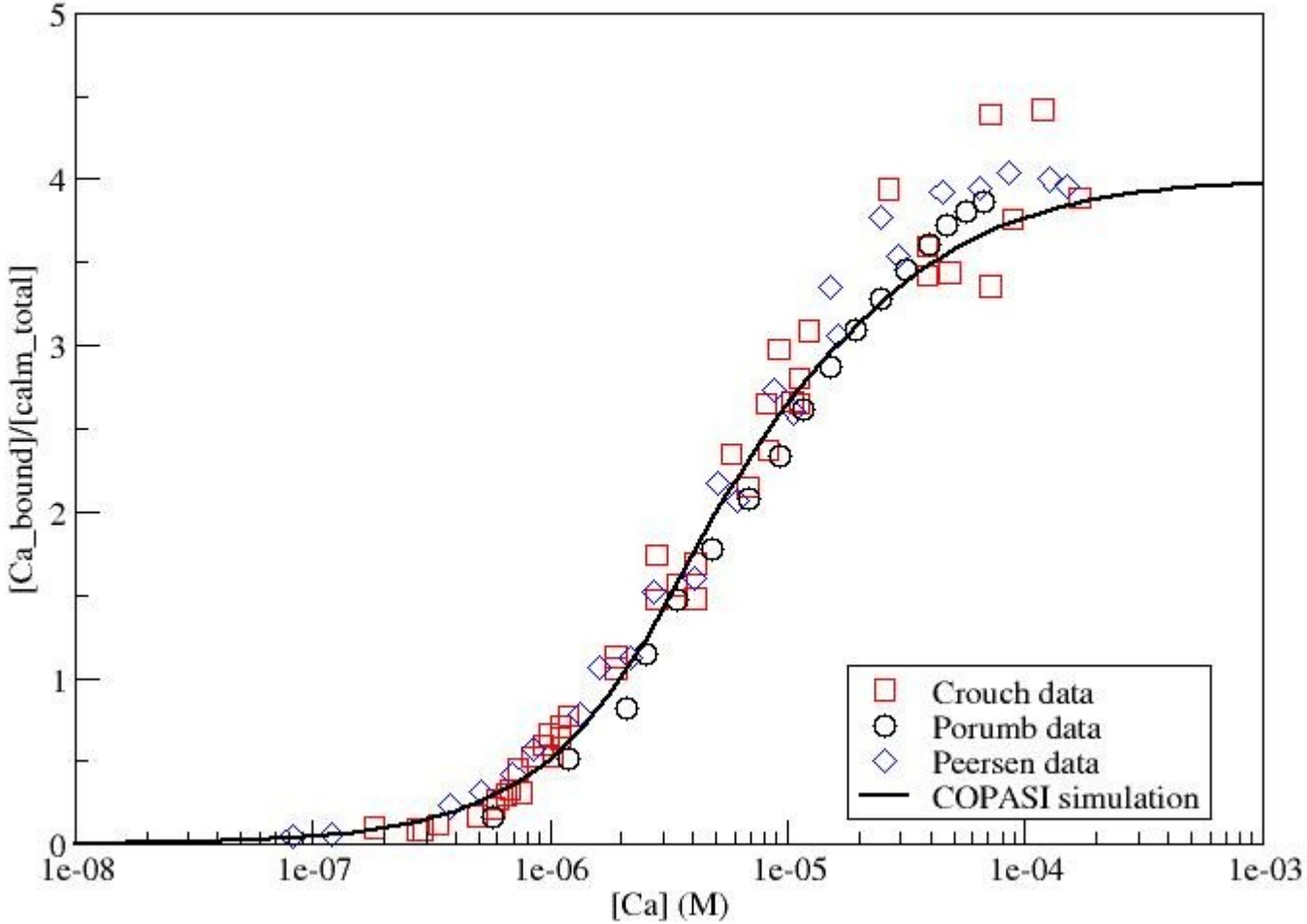
Crouch and Klee (1980) *Biochemistry*, 19: 3692-3698

Comparison with experiments



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

Comparison with experiments



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

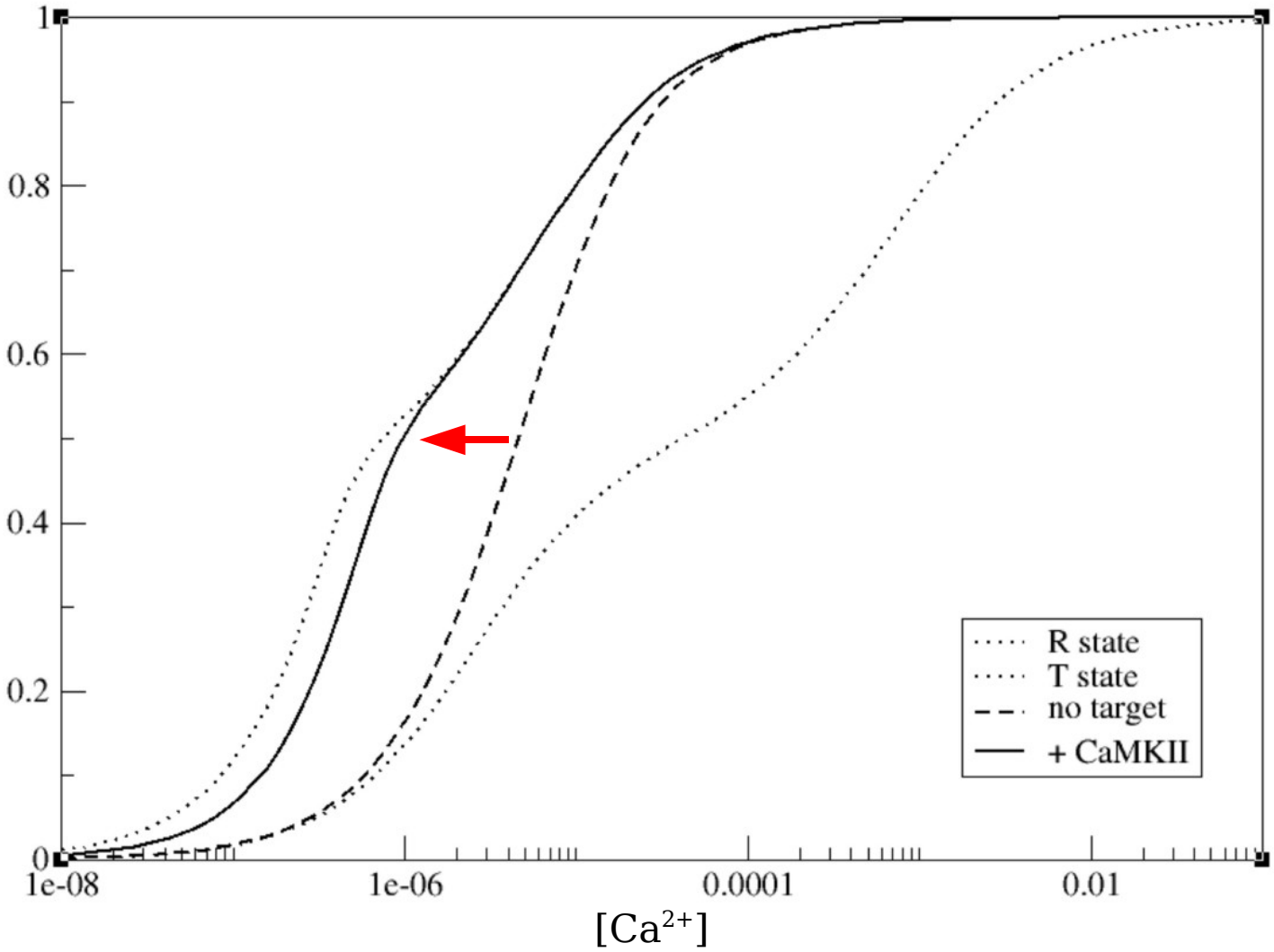
Activity of unsaturated calmodulin

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

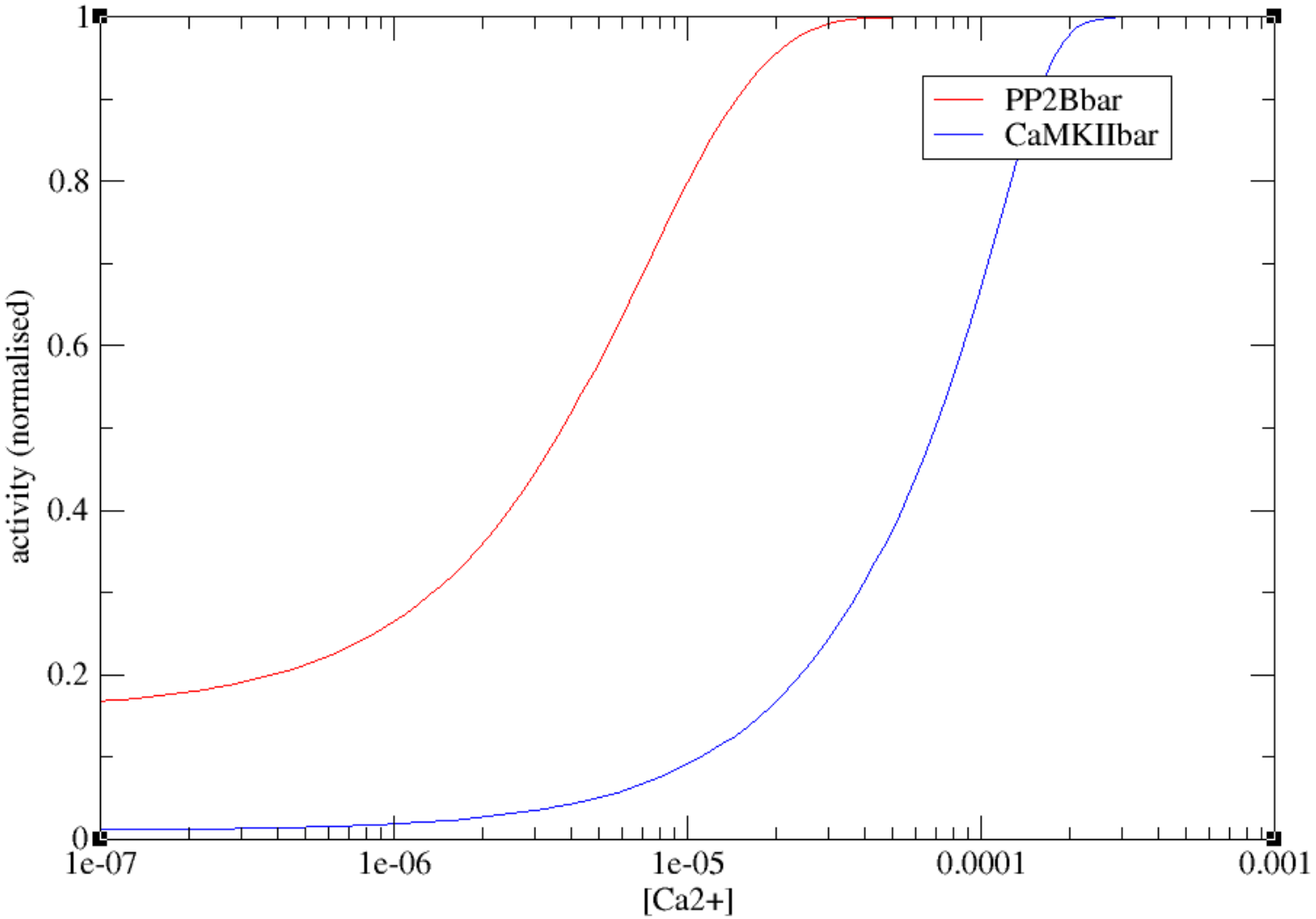
$$\frac{R_2}{T_2} = \frac{6}{L(c_A c_B + c_A c_C + c_A c_D + c_B c_C + c_B c_D + c_C c_D)}$$

- $R_0/T_0 = 1/20000$ (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+}

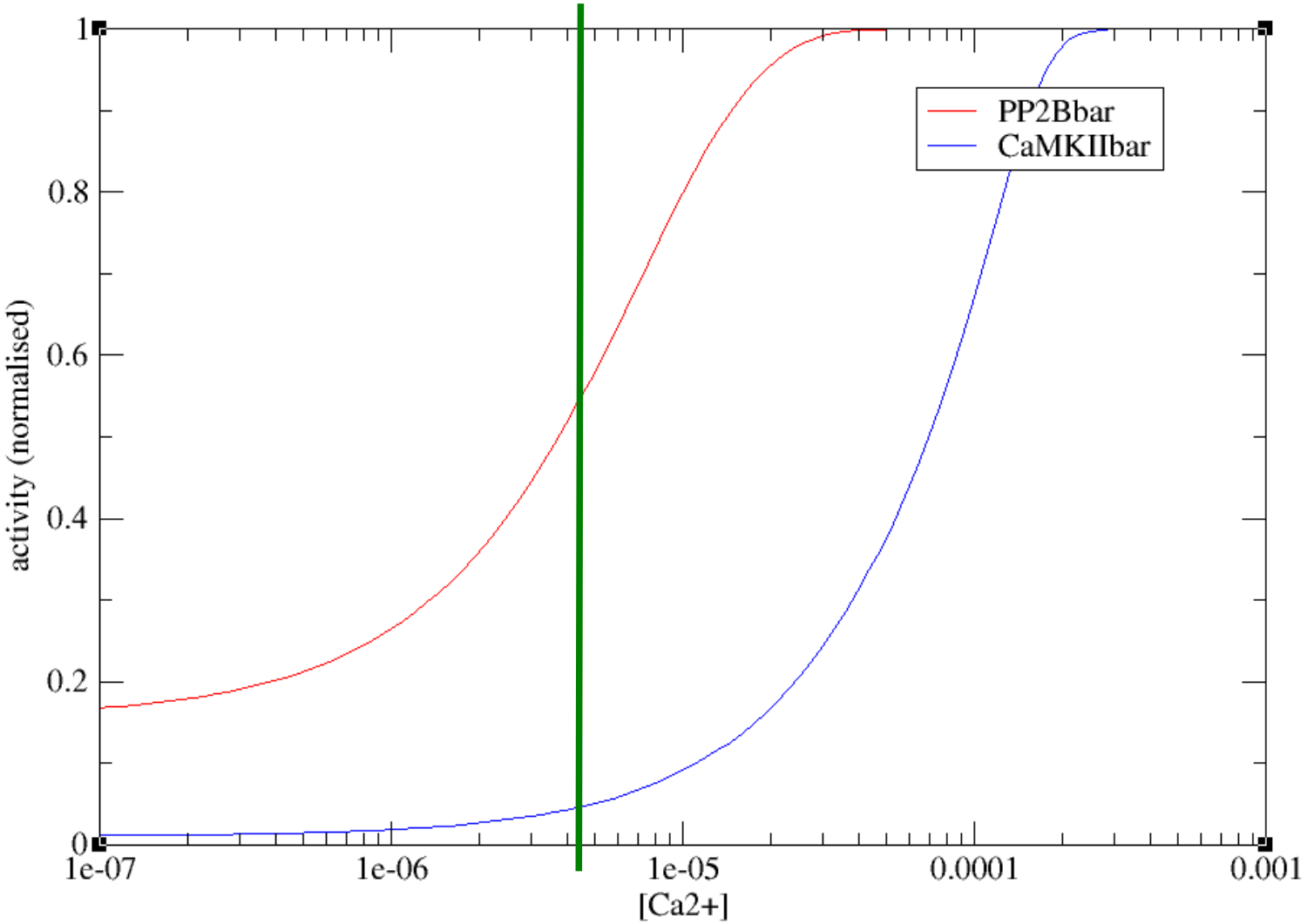


Bidirectional synaptic plasticity

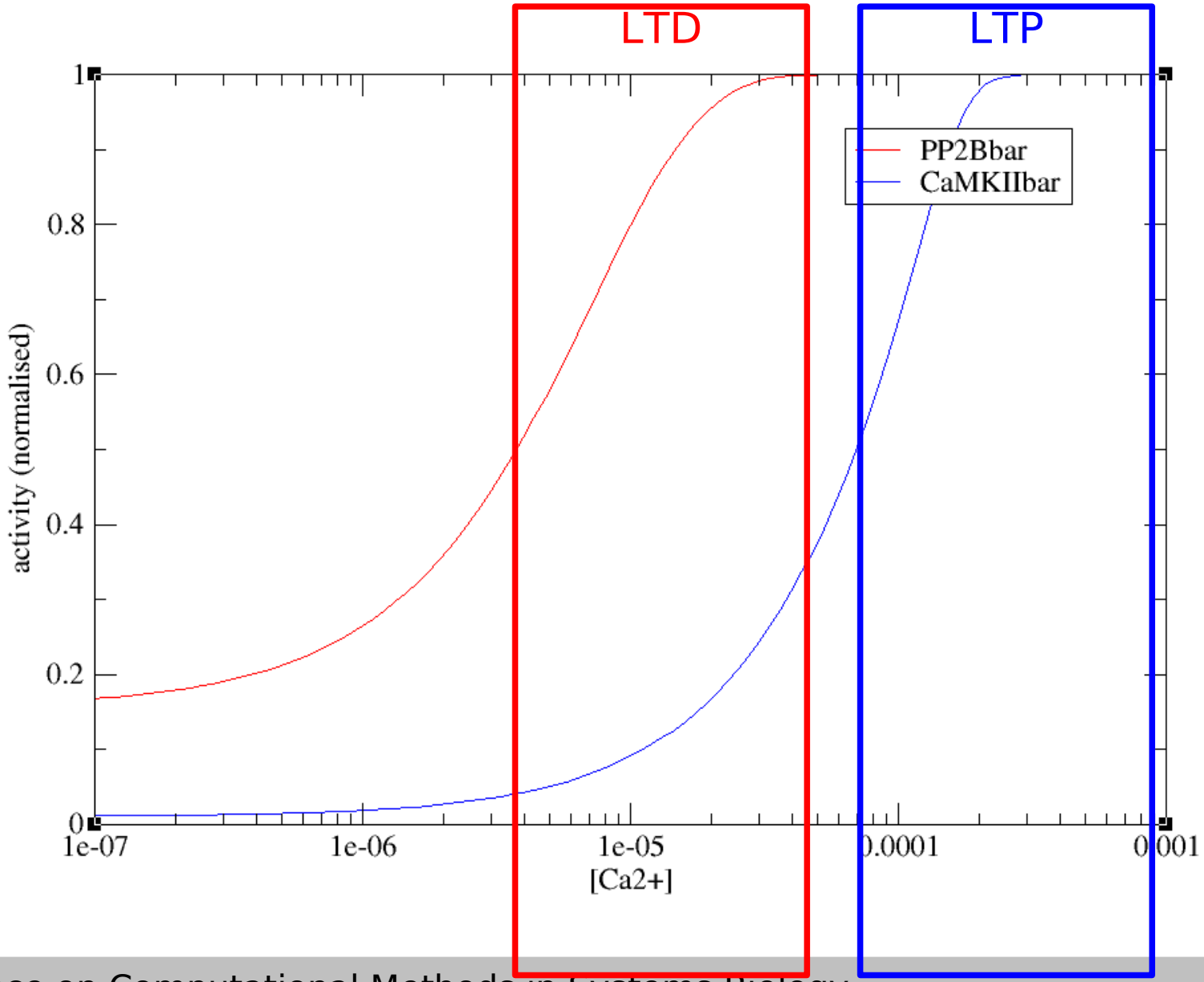


Bidirectional synaptic plasticity

half saturation of calmodulin



Bidirectional synaptic plasticity



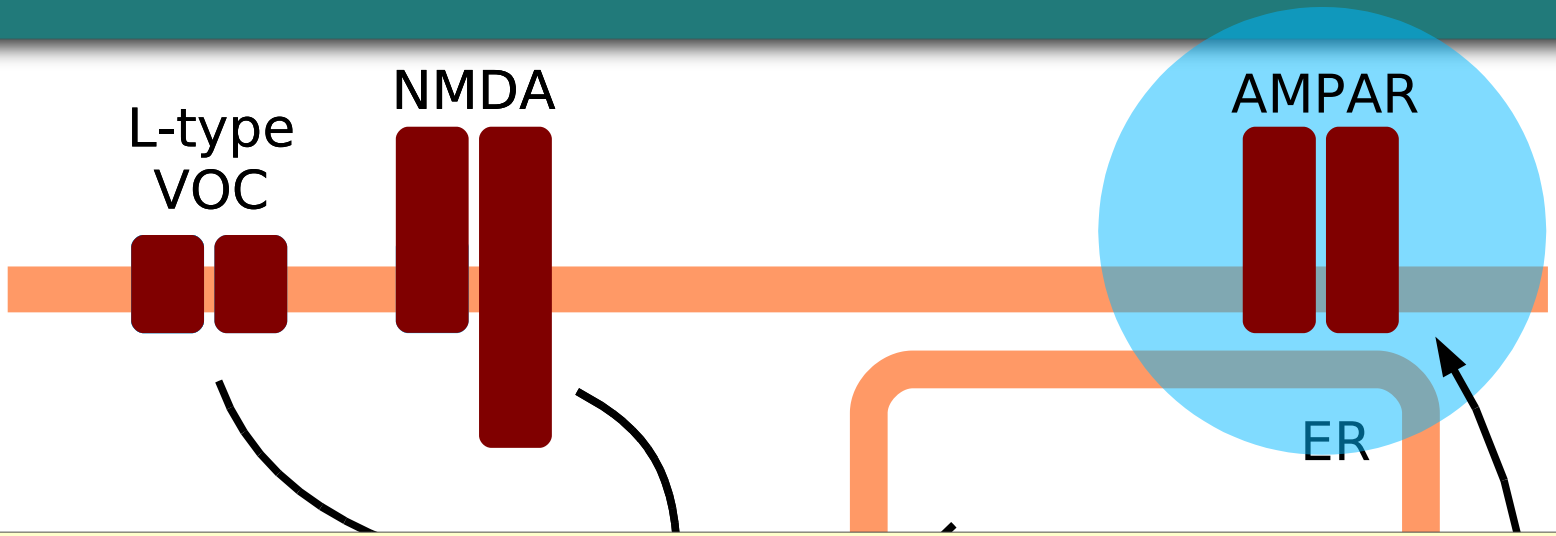
- Developers of COPASI
  - Sven Sahle
  - Stefan Hoops
  - Ursula Kummer
  - Pedro Mendes
- Developers of Scilab
- Annalisa Pastore
- Stephen Martins

Melanie Stefan

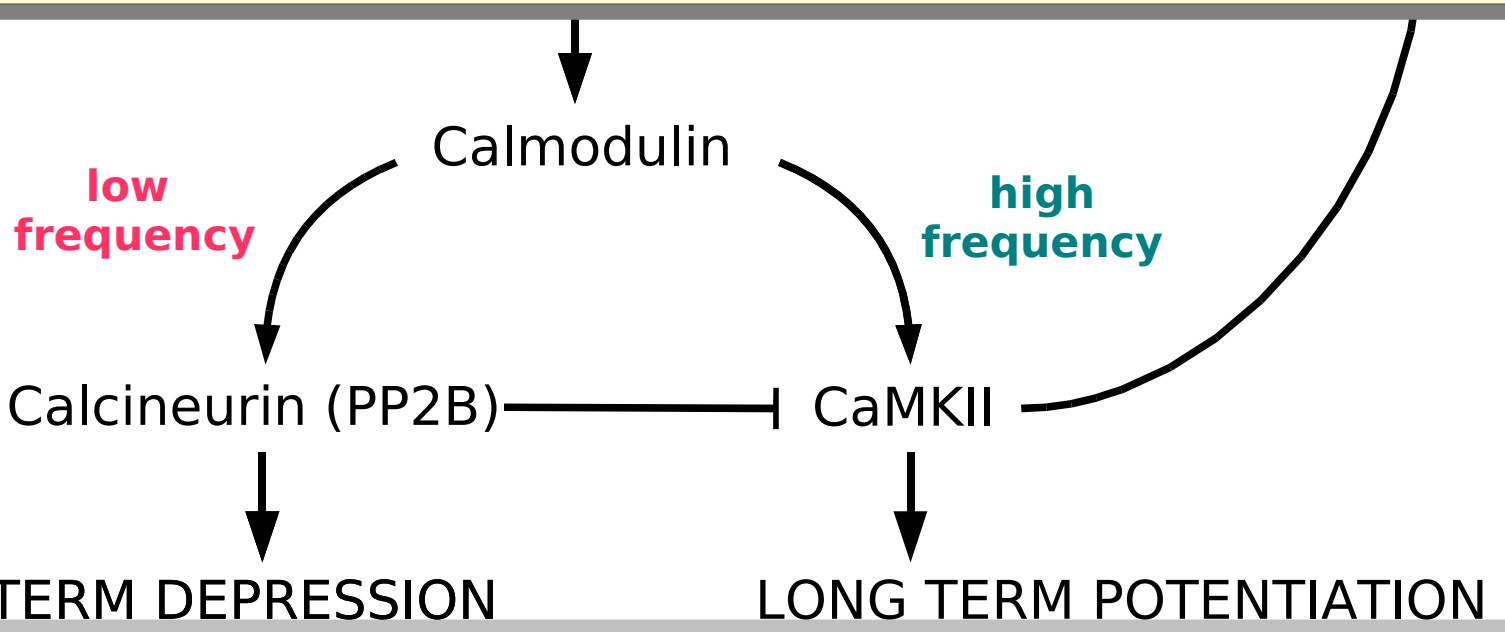
Stuart Edelstsein

- Pros
  - Trying to understand the “true” reaction mechanism
  - Able to generate non-trivial predictions
- Cons
  - Very sensitive to combinatorial explosion
  - Almost complete lack of adequate quantitative data
  - Cannot be easily embedded as such in larger models (but can be phenomenology abstracted)

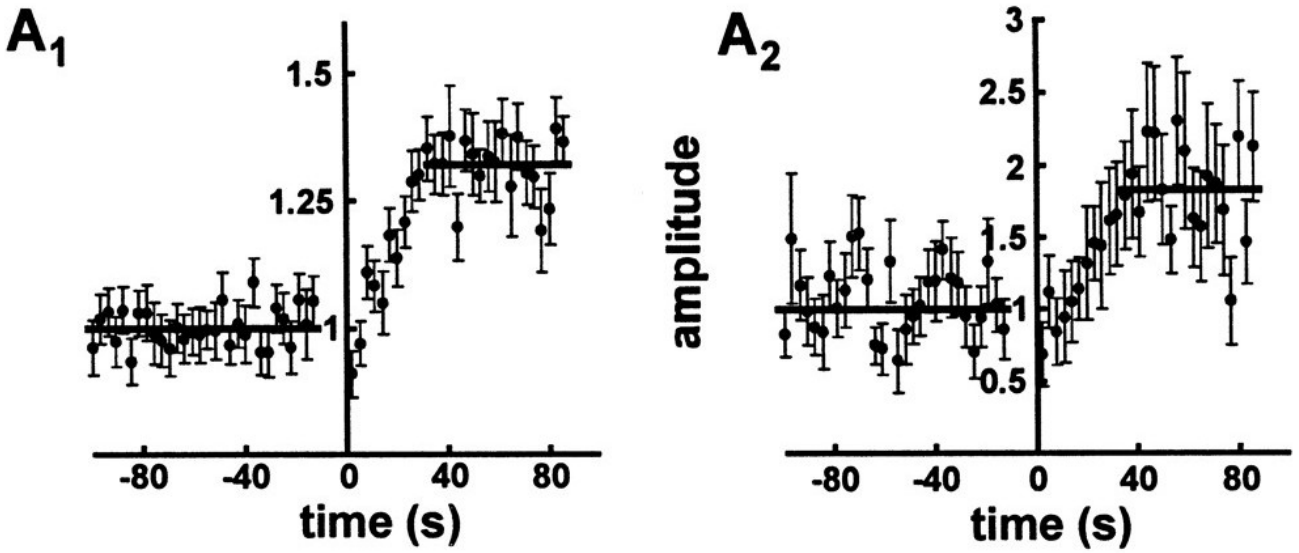
Allosteric signalling devices



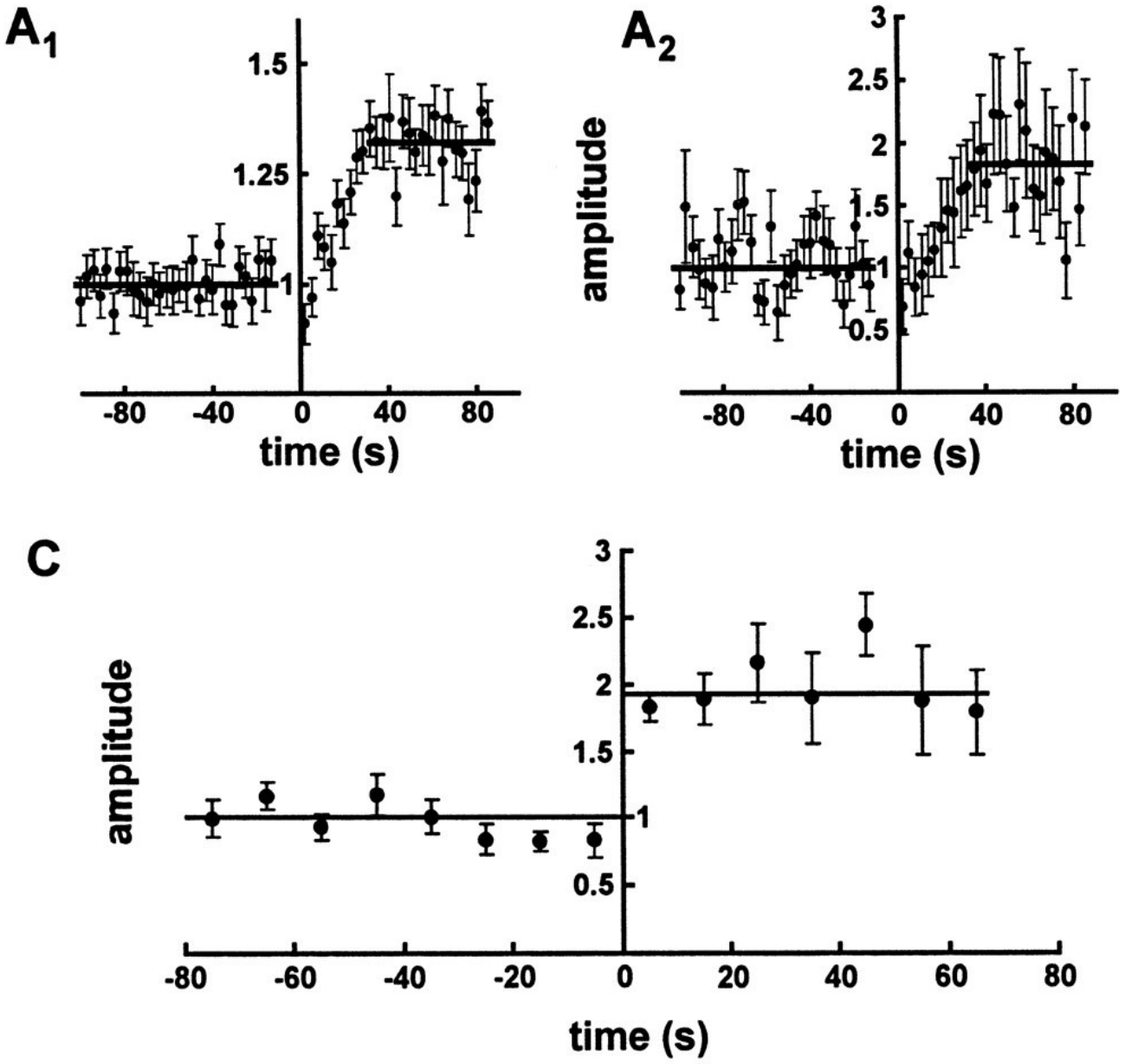
Tolle and Le Novère (2006) Particle-based Stochastic Simulation in Systems Biology. *Current Bioinformatics,* 1: 315-320
Tolle and Le Novère (2008) Brownian Diffusion of AMPA Receptors Is Sufficient to Explain Fast Onset of LTP. *Submitted*



Multi-synaptic LTP

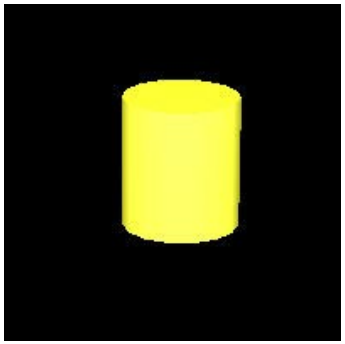


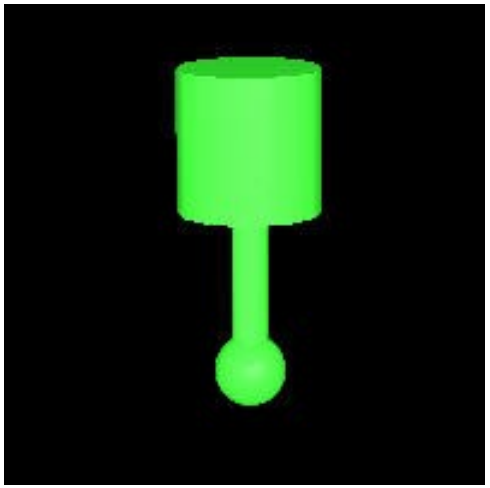
Single-synapse recording

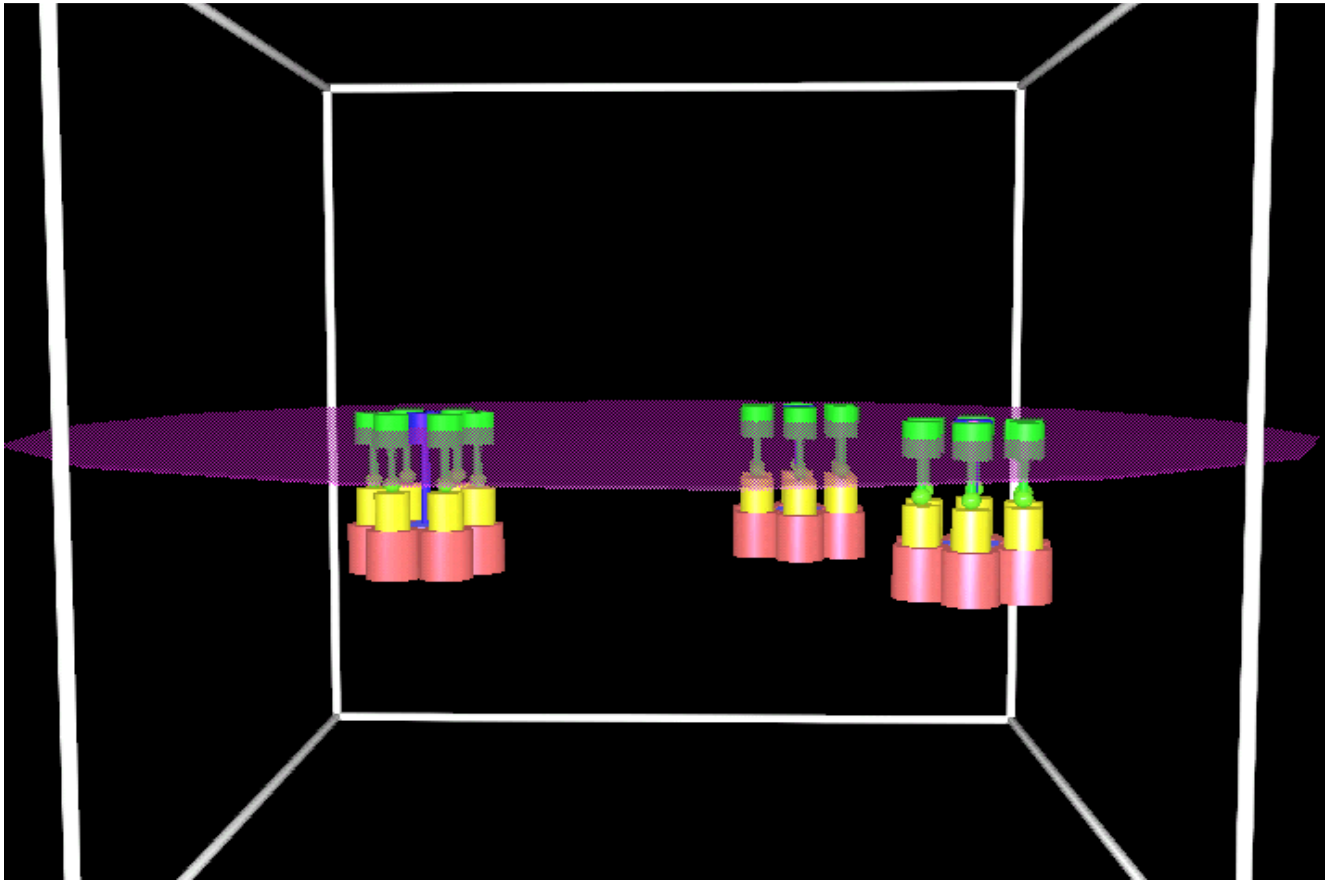


Petersen et al (1998)
PNAS 95: 4732-4737

Agent-based spatial simulations

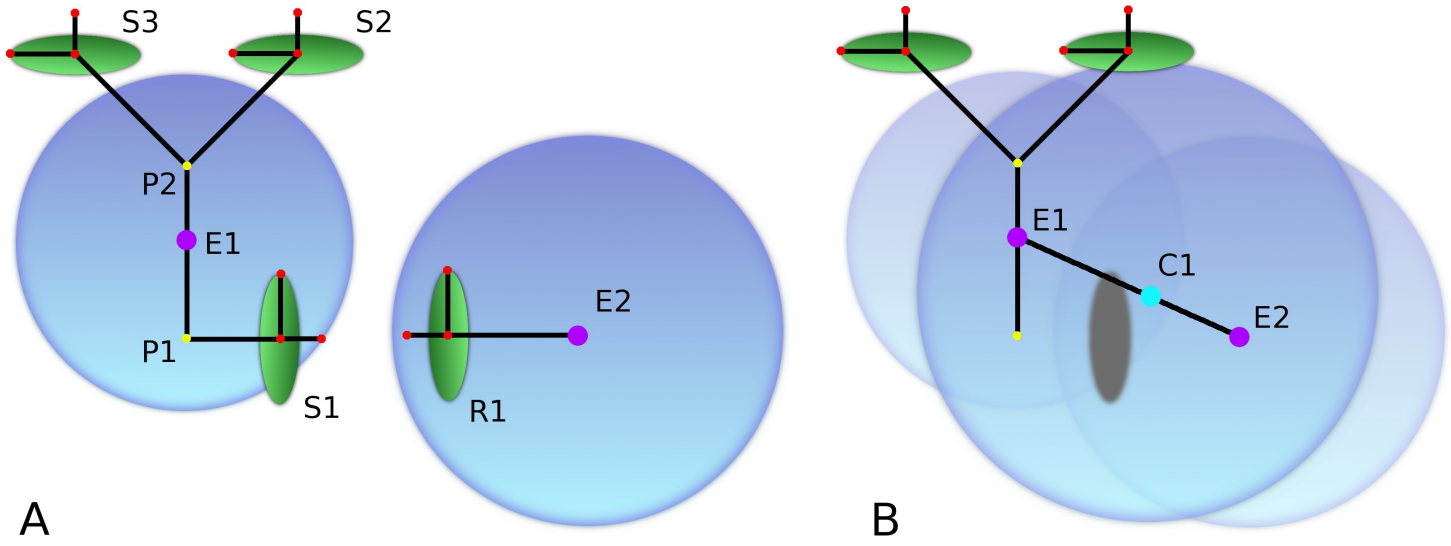






- Particles carry binding surfaces
- Cluster and entity classes allows recording of Center Of Mass, radius, RMS displacement, state
- Clusters are dynamically created and destroyed – transient
- State variables attached to entities and reacting surfaces

Binding ports on particles, entities and clusters



Molecule diffusion

- Different diffusion spaces:
  - Static; Free diffusion; Membrane diffusion; Above membrane; Below membrane
  - Membrane corrals, with different reflection properties
- 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 $\sigma^2 = 2Dt$

  - 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

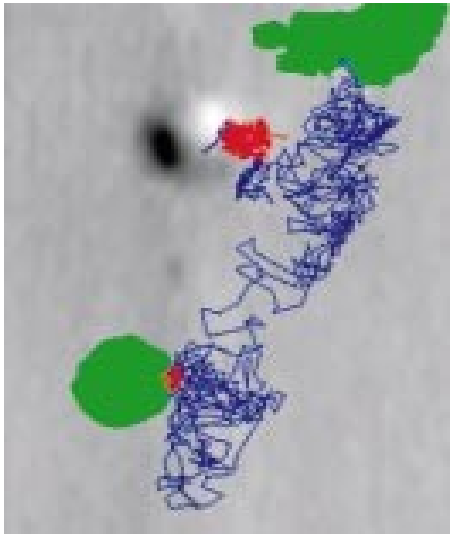
- Unrestricted brownian motion – Low Translation/Rotational

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

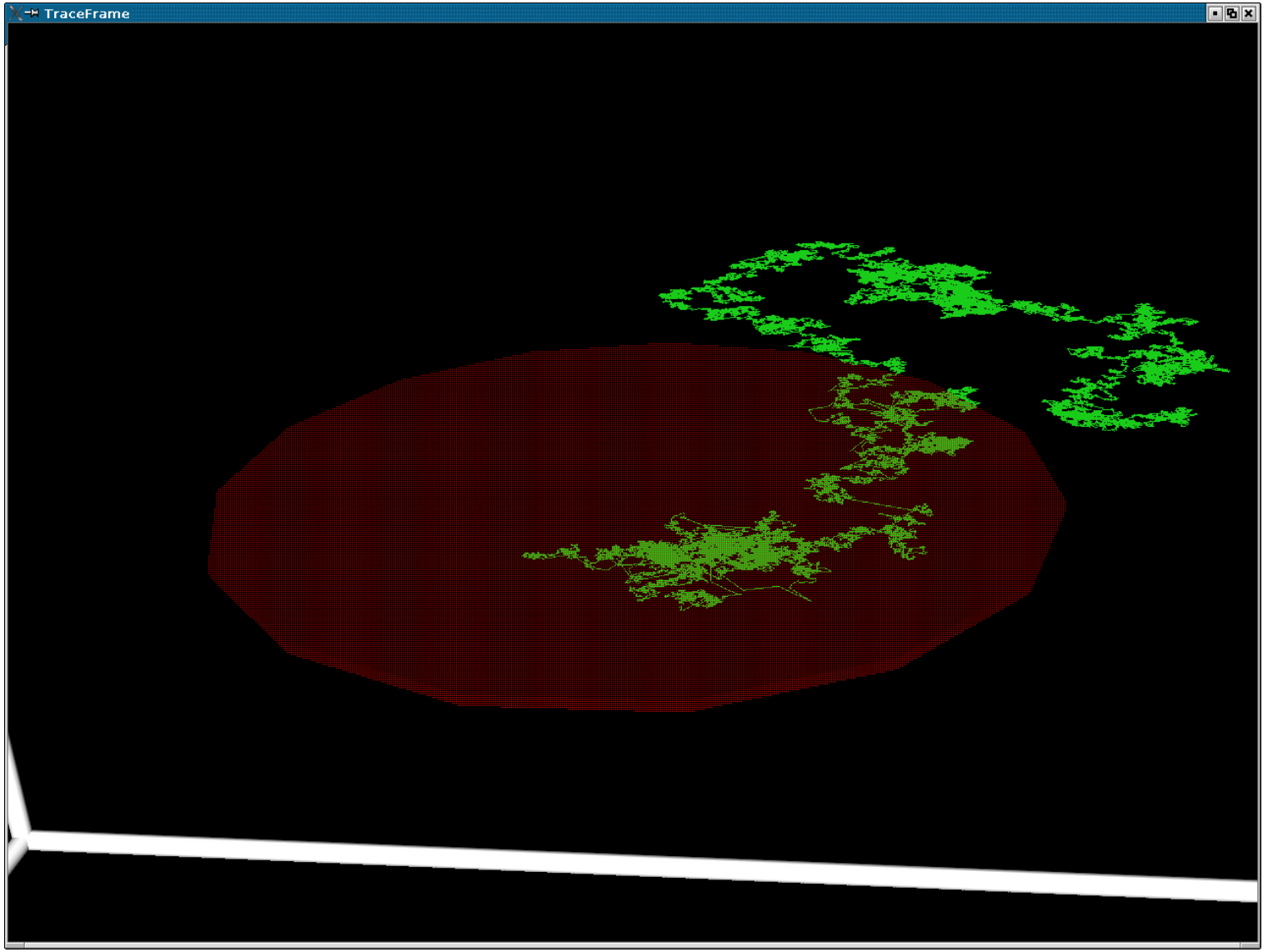
- Intra-membrane diffusion (Saffman and Delbrück 1975) High Translational/Rotational

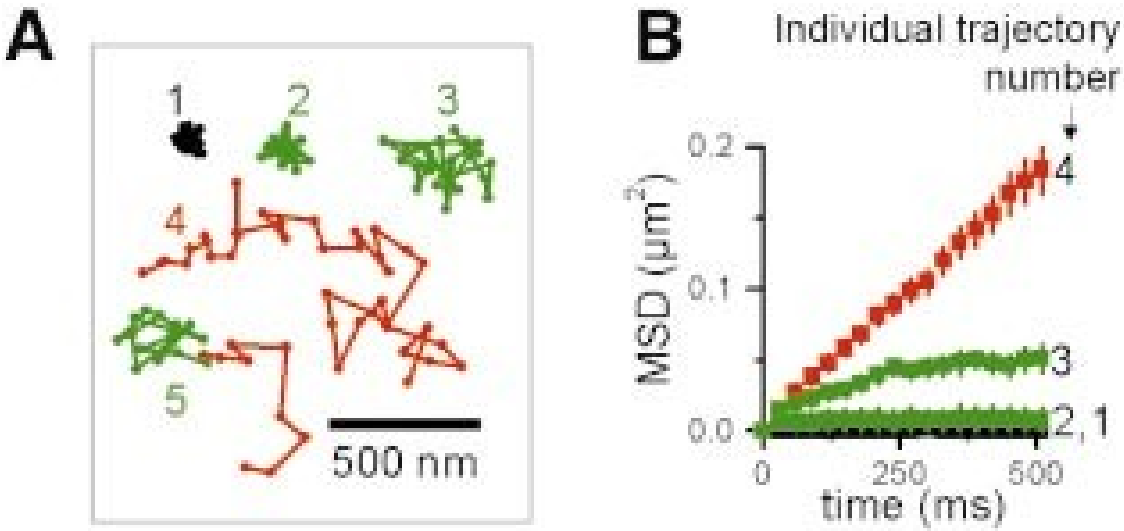
$$b_T = \frac{1}{4\pi\mu h}\left(\log\left(\frac{\mu h}{\mu' r}\right) - \gamma\right) \qquad b_R = \frac{1}{4\pi\mu r^2 h} \qquad \frac{b_T}{b_R} = \left(\log\left(\frac{\mu h}{\mu' r}\right) - \gamma\right) \times r^2$$

Simulations of receptor diffusion

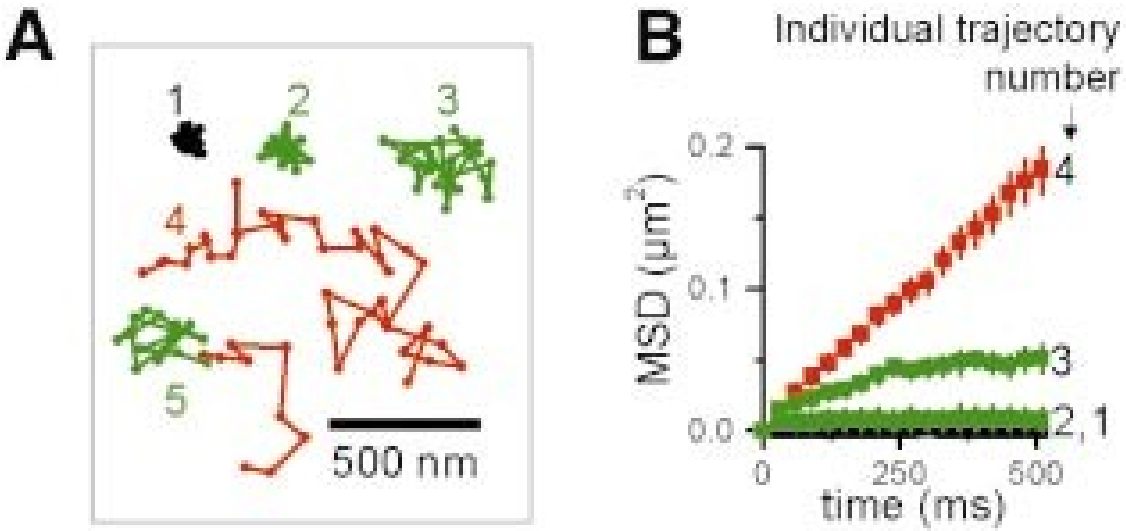


Borgdorrf et al (2002)
Nature 417: 649-653

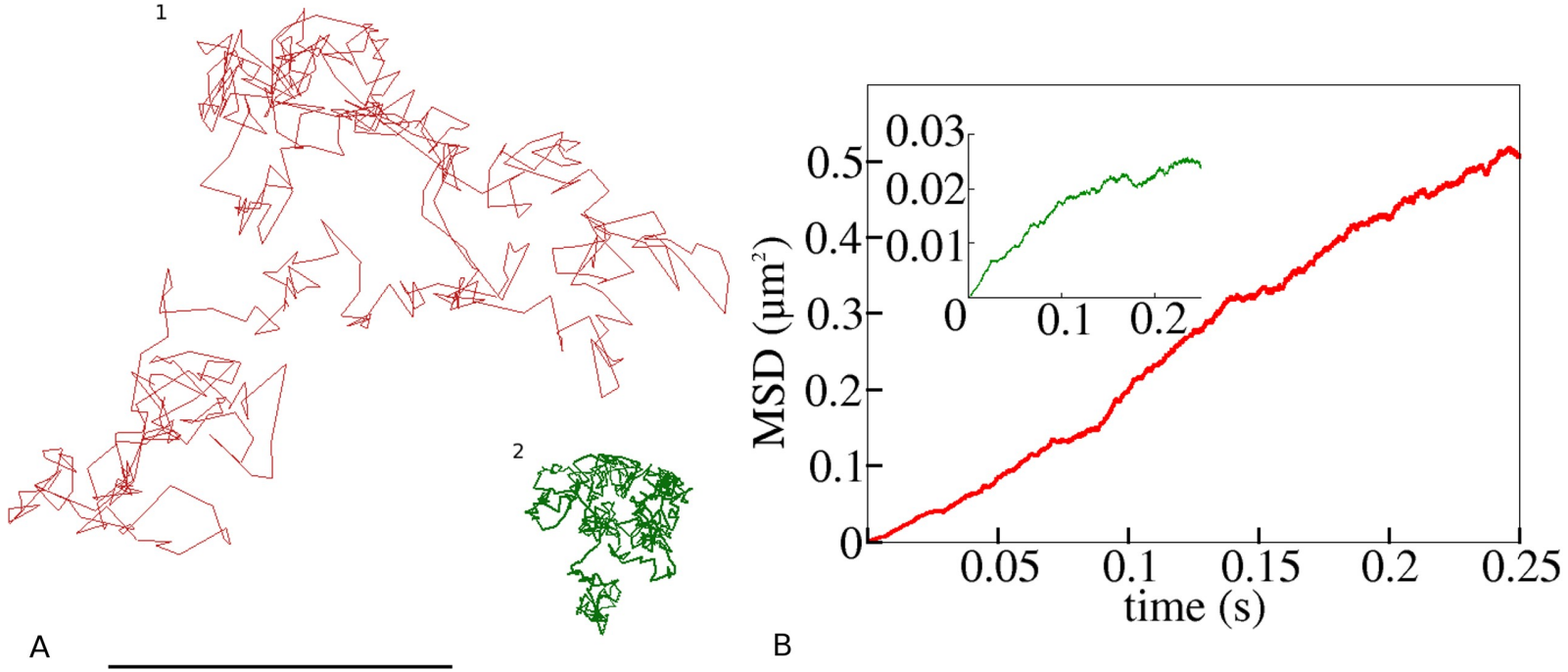




Tardin et al (2003)
EMBO J 22: 4656-4665

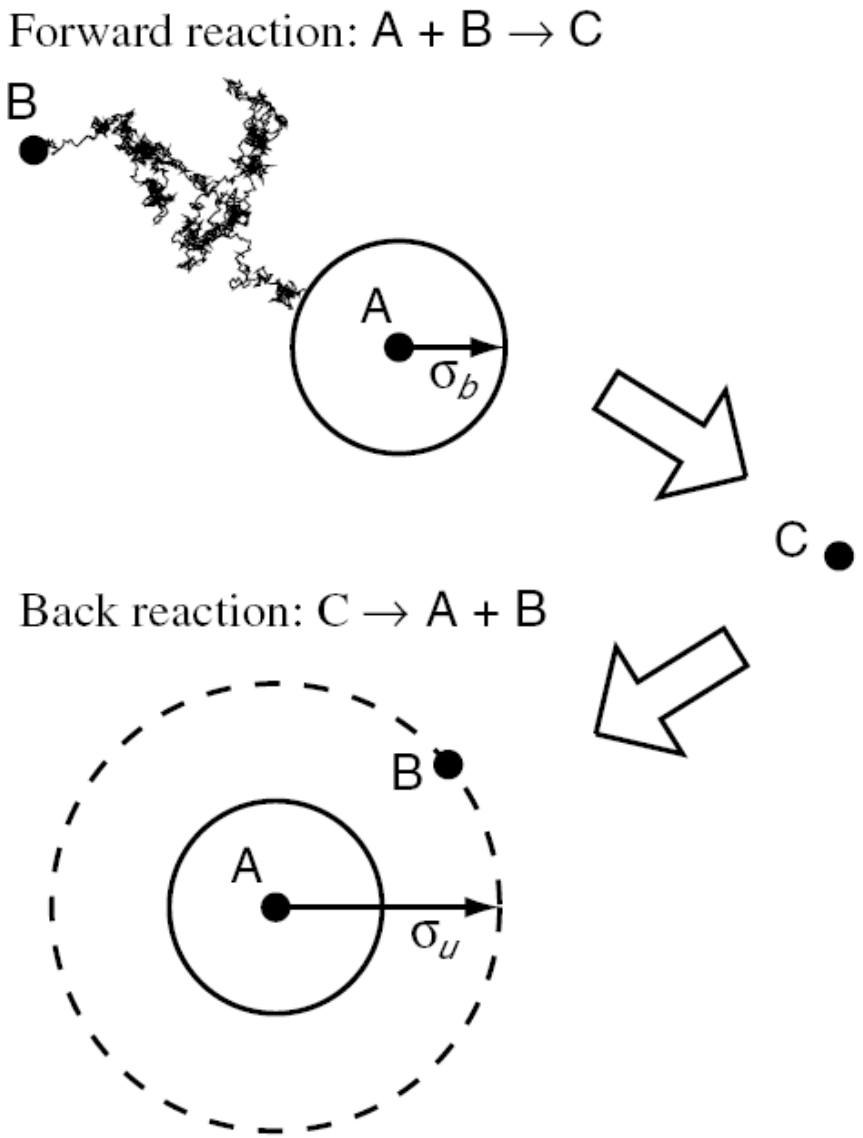


Tardin et al (2003)
EMBO J 22: 4656-4665

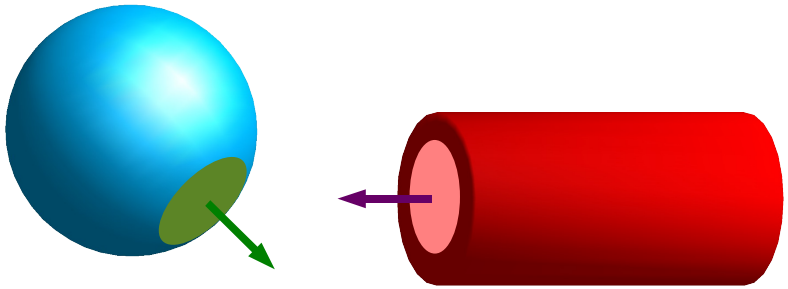


Smoluchovski model

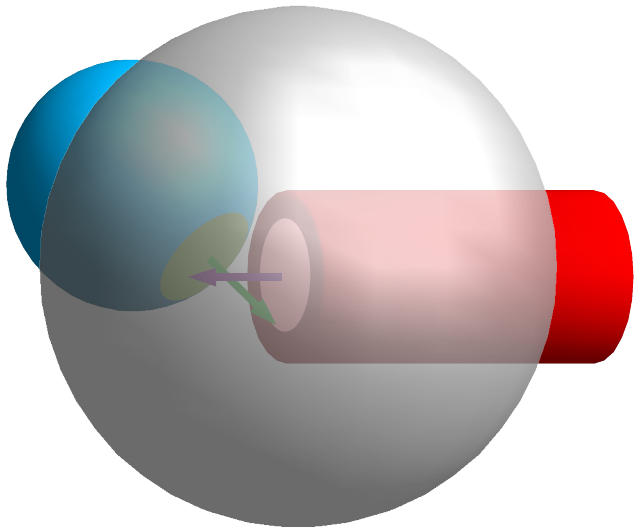
Andrews and Bray (2004)
Phys Biol 1: 137-151)



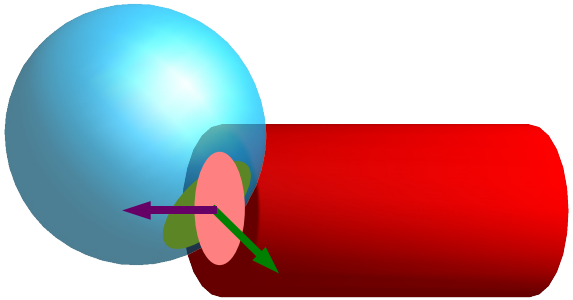
Reactions and complex formation



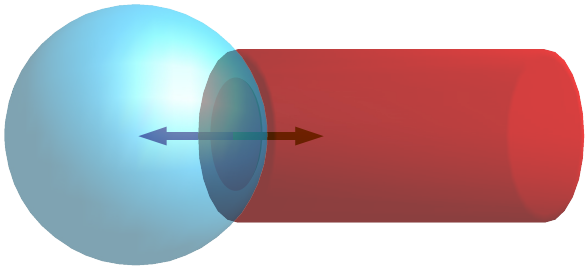
Reactions and complex formation



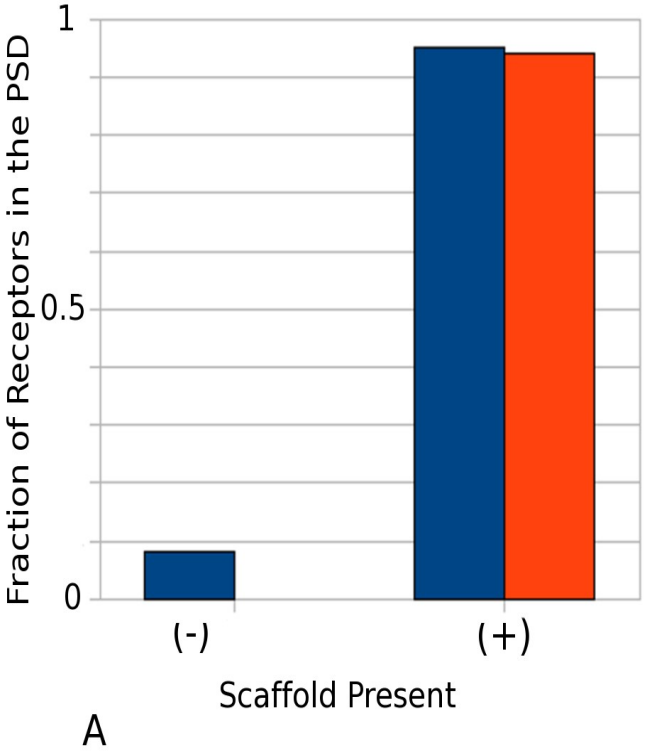
Reactions and complex formation



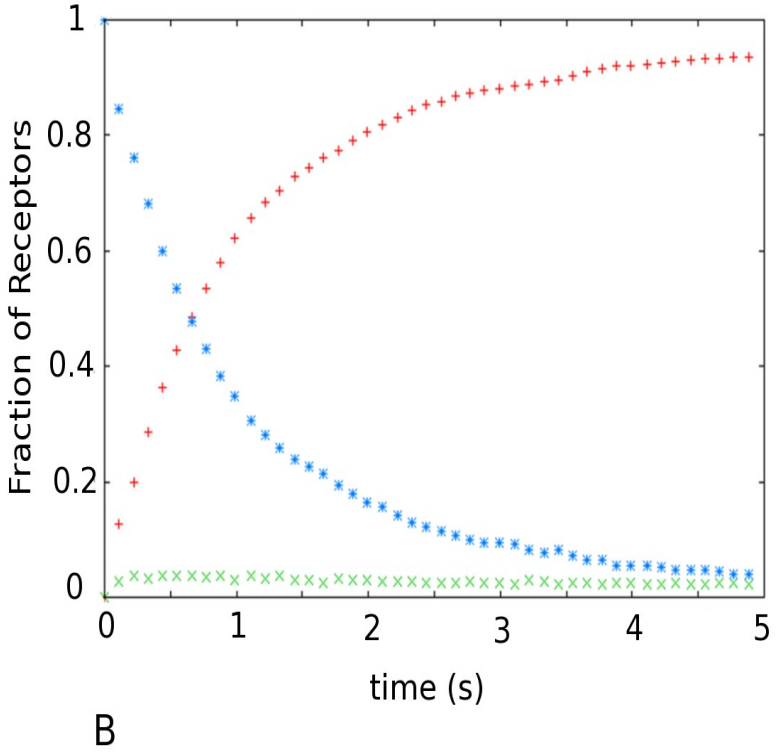
Reactions and complex formation



Aggregation of AMPAR at synapse after 5 sec



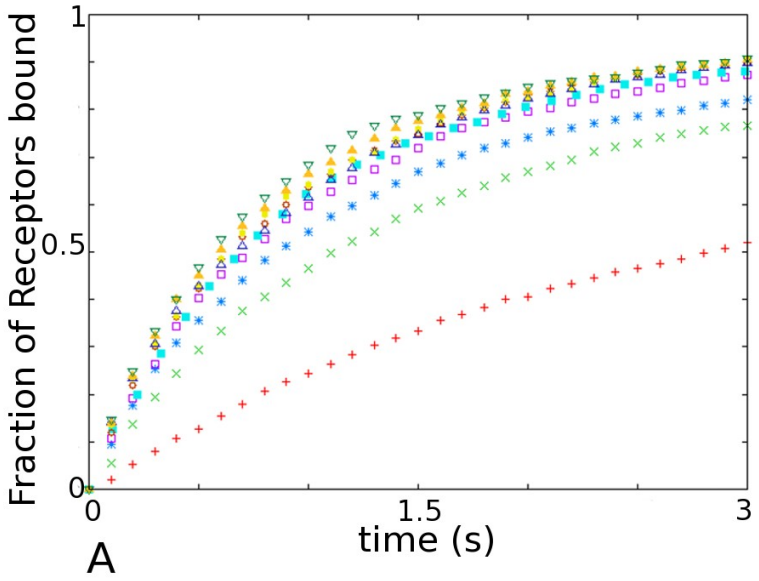
A

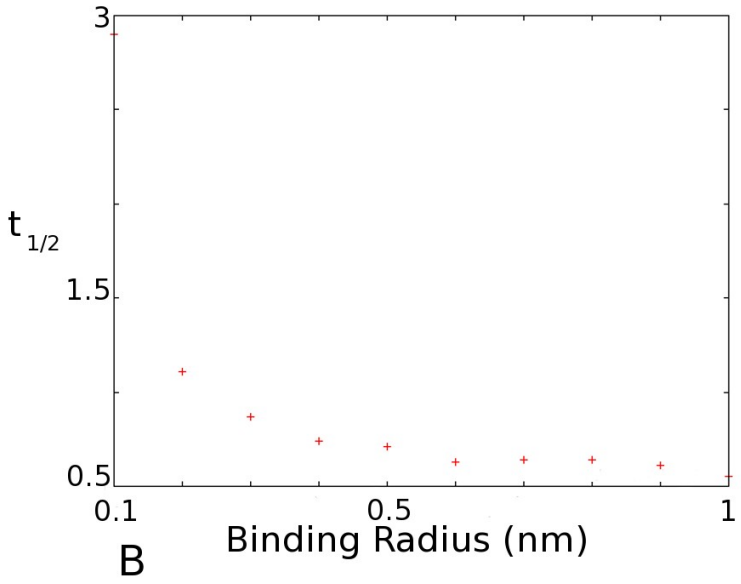


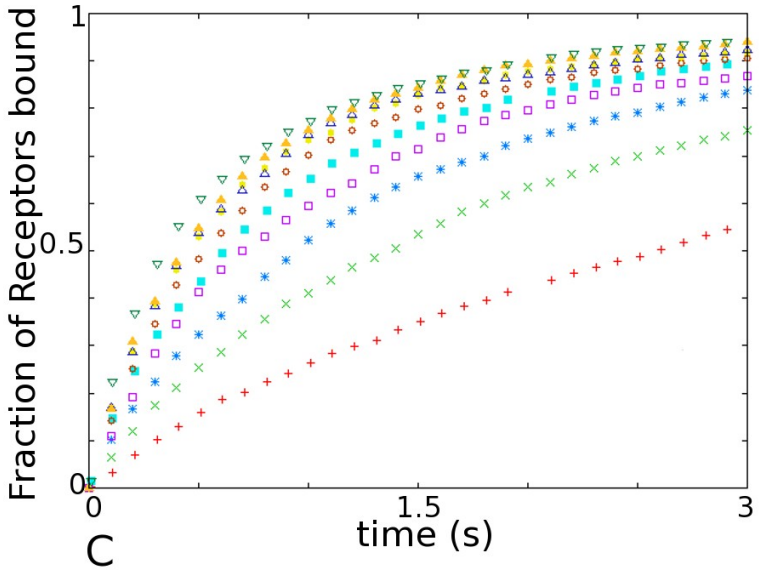
B

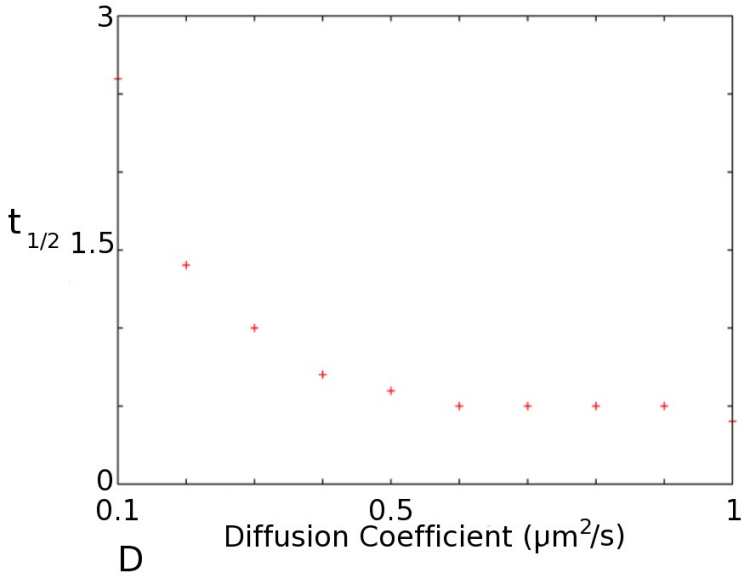
+ In PSD, bound
x In PSD, unbound
* In ESM

Effect of biophysical parameters

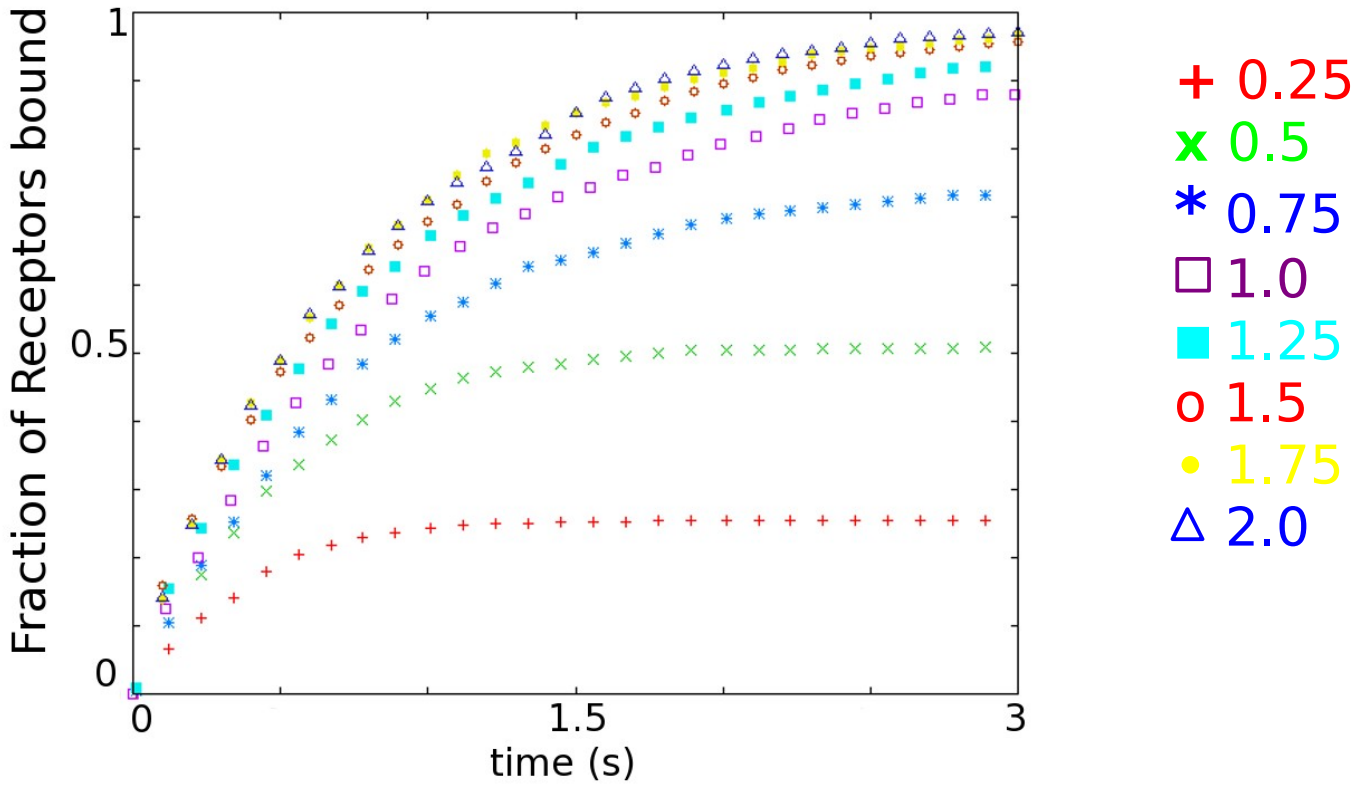




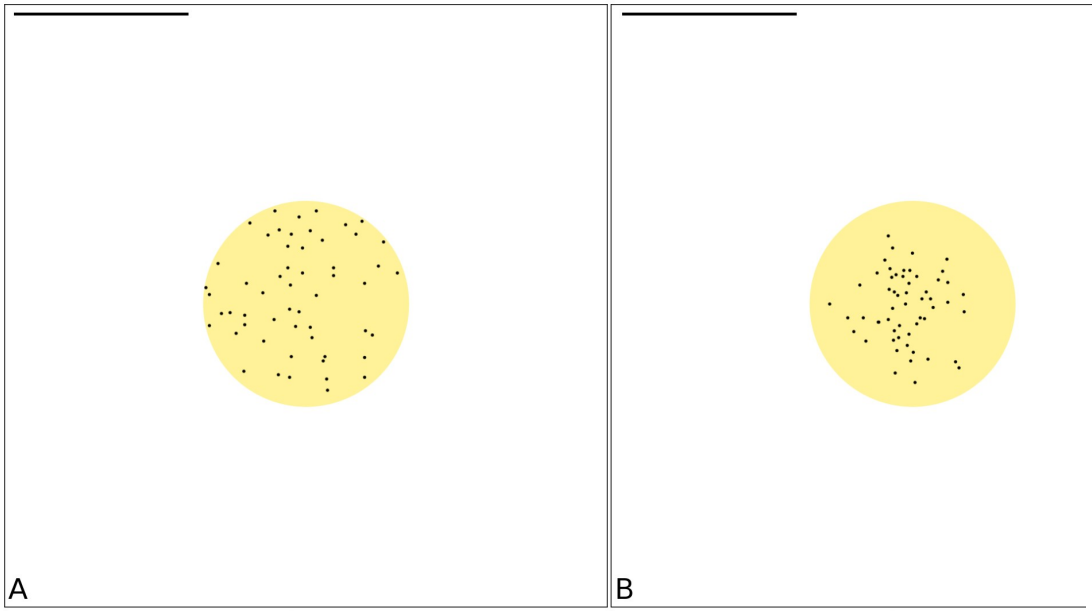


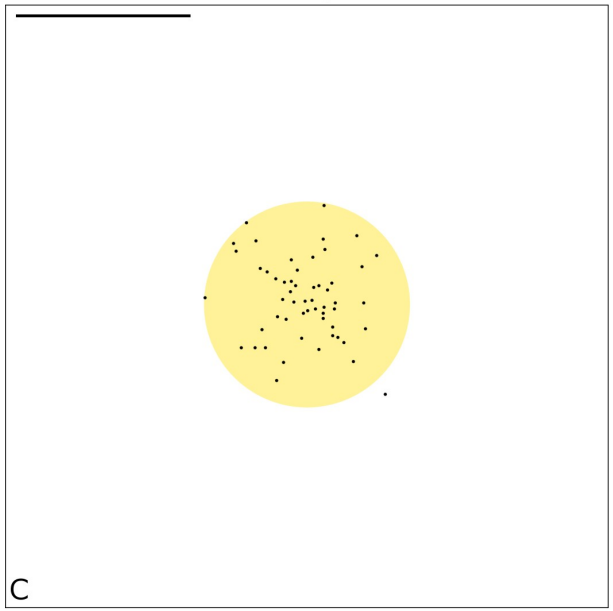


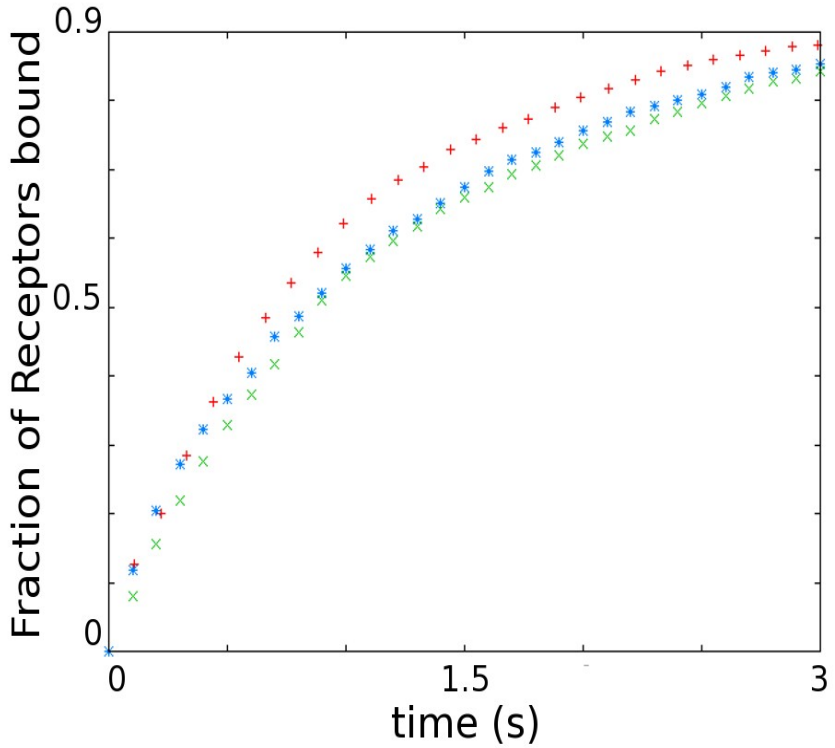
Effect of ratio scaffold Vs AMPAR



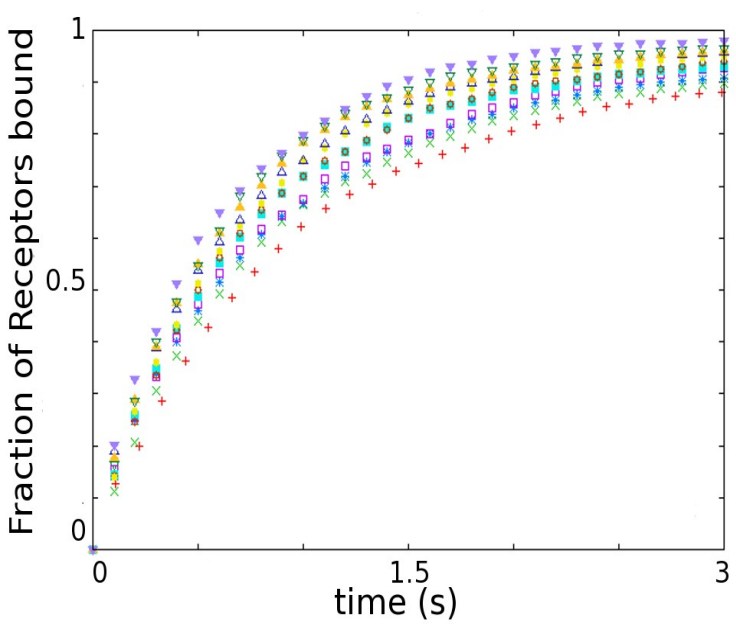
Effect of scaffold distribution

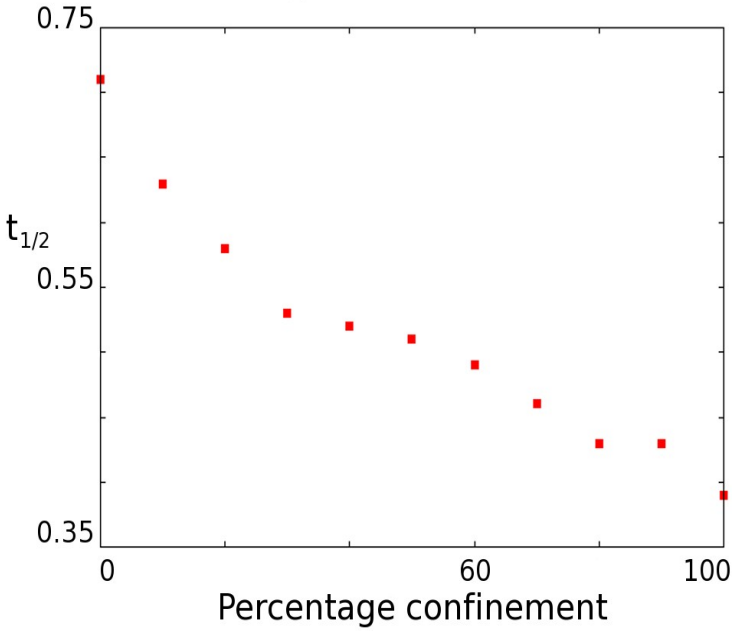




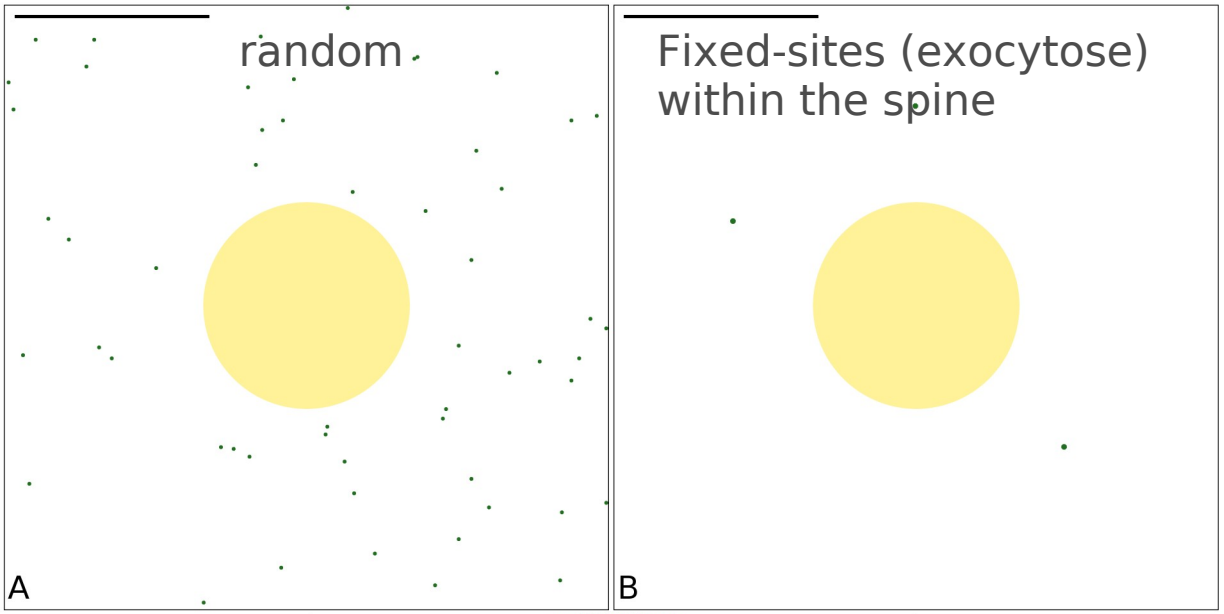


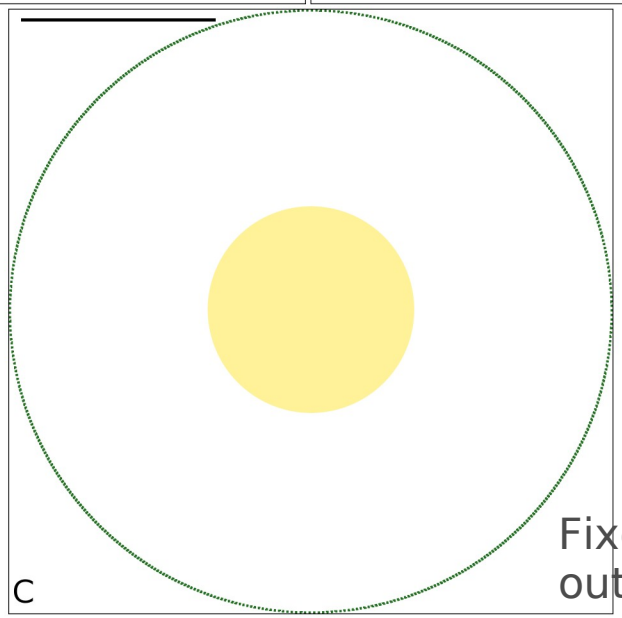
Effect of confinement



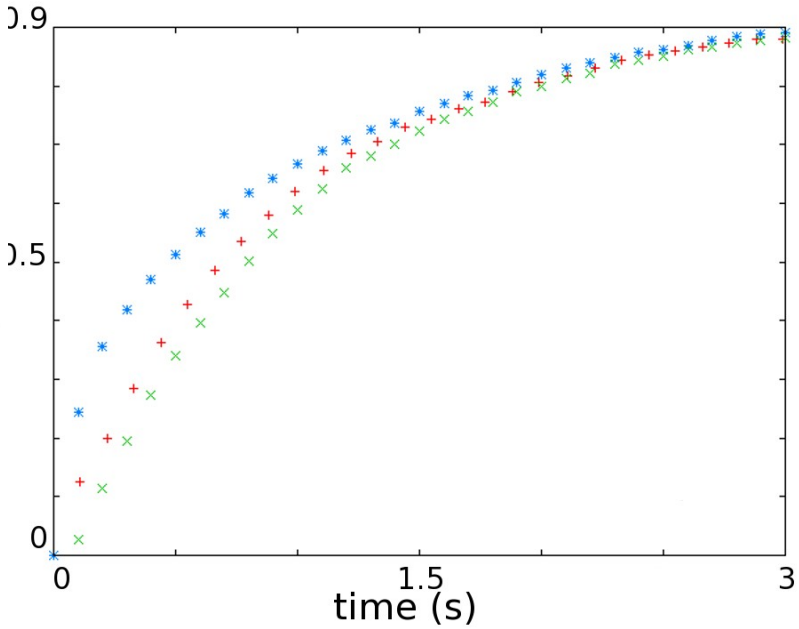


Release site does not affect clustering





Fixed distance
outside the spine



- If scaffolding proteins are present, 5 seconds are sufficient to cluster additional AMPA receptors to the post-synaptic density solely by “brownian” diffusion
- Distribution of scaffolding proteins, and initial position of inserted receptors does not affect outcome
- The crucial parameters are the ratio receptor/scaffold and the affinity of the scaffold proteins for the receptors

  => any process process modulating those characteristics will affect the plasticity of the synapse. This is the case of ... calmodulin-activated kinases ...

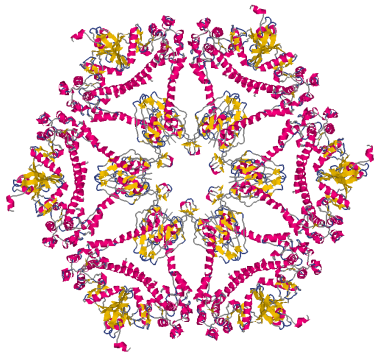
- Developers of APS
  - Fred Howell
  - Dan Mossop
- Steven Andrews

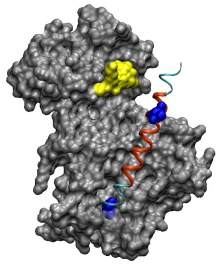
Dominic Tolle

- Pros
  - Able to accurately describe what is occurring in the cell (the spine)
  - One can embed crowding, gradients, anisotropy of conditions etc.
  - Agent-based approach avoid combinatorial explosion
- Cons
  - 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)

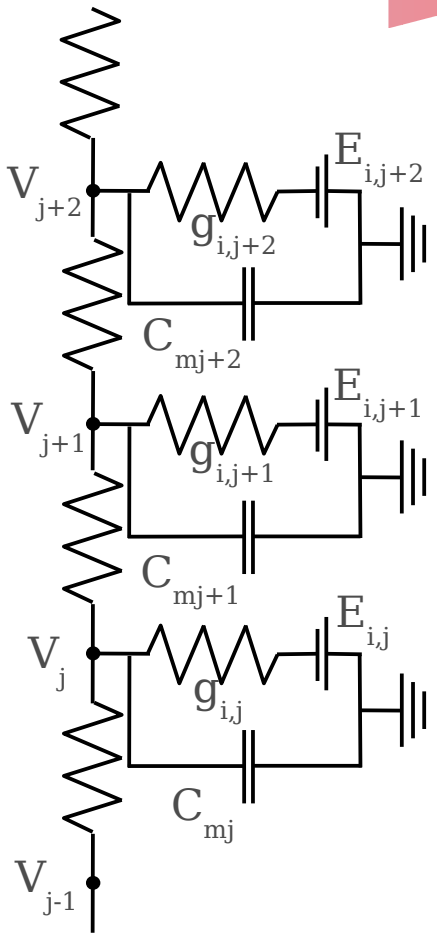
10^{-9} 10^{-6} 10^{-3} m

spatial scale





Scales presented today

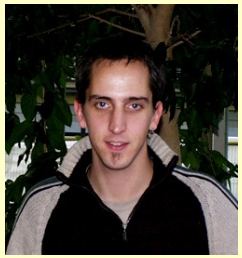


+Chemical kinetics

+diffusion

The team


Ranjita Dutta-Roy, SE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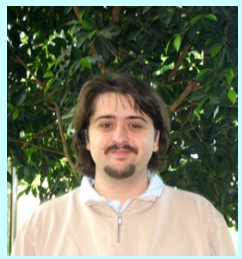
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