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-Schumann)
  - Computational Systems Biology (Le Novère)
  - Statistical array analysis (Huber)
  - Genomic analysis of regulatory systems (Luscombe)
  - Systems Biology of ES cells (Bertone)

EMBL-EBI

Group themes and projects

Neurobiology

Allosteric molecules

(European Membrane Protein Consortium)

Structural modelling

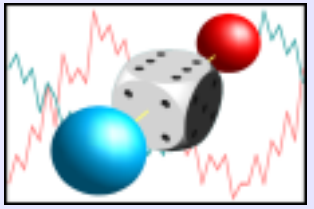
Databases

Functional modelling

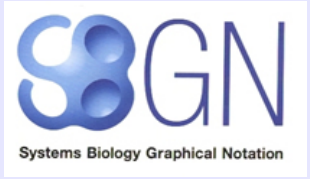
Standards in Systems Biology

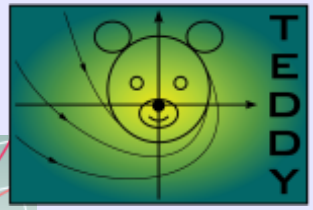
Post-synaptic density

Integration of signals

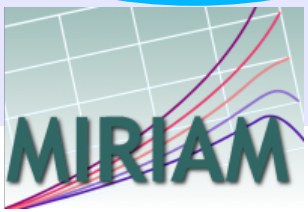


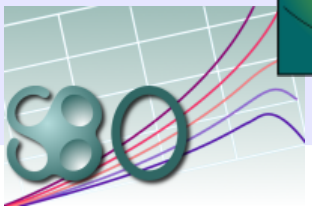
StochSim





Systems Biology





REVIEW ARTICLE

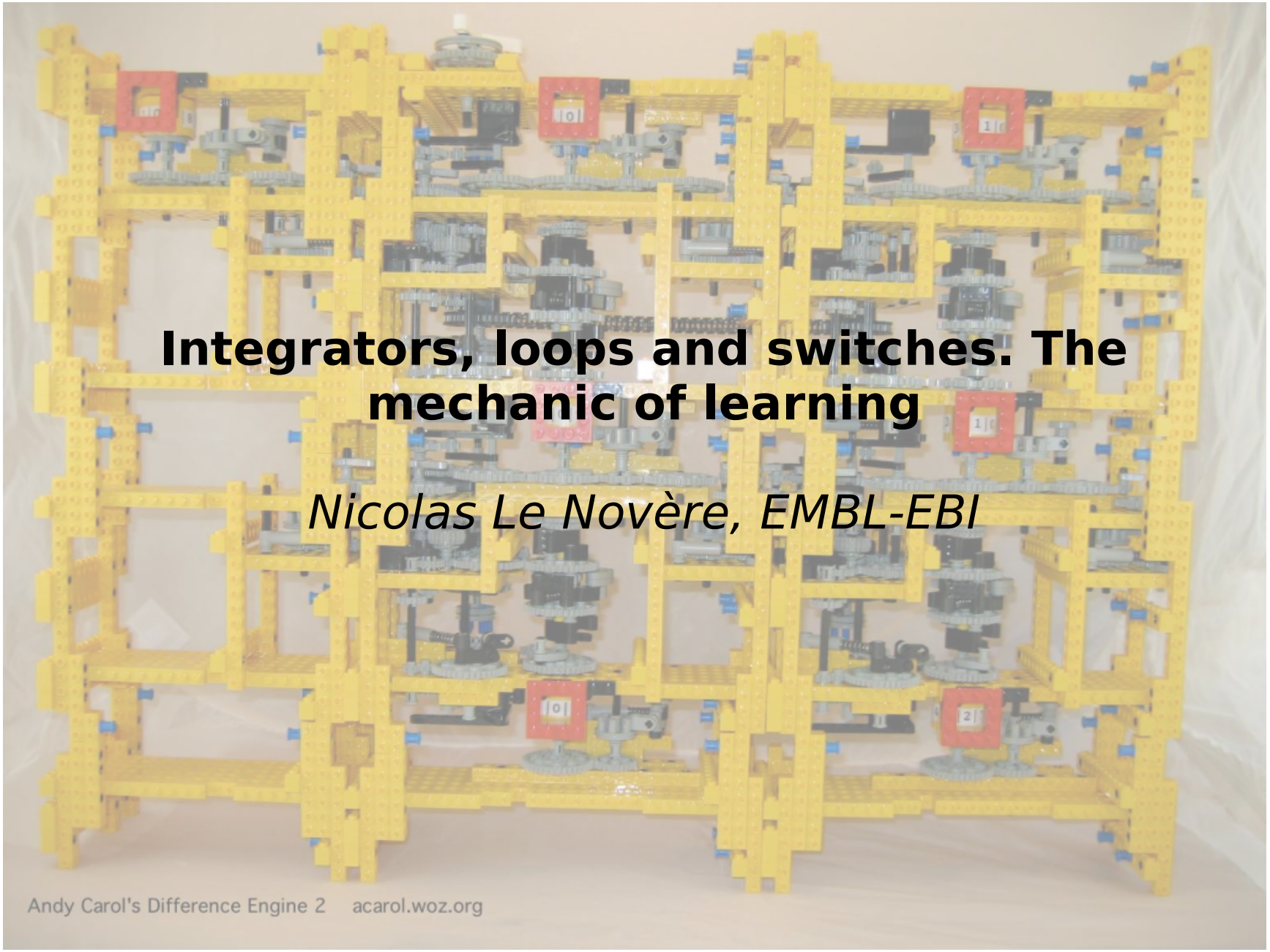
Protein molecules as computational elements in living cells

Dennis Bray

Many proteins in living cells appear to have as their primary function the transfer and processing of information, rather than the chemical transformation of metabolic intermediates or the building of cellular structures. Such proteins are functionally linked through allosteric or other mechanisms into biochemical 'circuits' that perform a variety of simple computational tasks including amplification, integration and information storage.

In unicellular organisms, protein-based circuits act in place of a nervous system to control behaviour; in the larger and more complicated cells of plants and animals, many thousands of proteins functionally connected to each other carry information from the plasma membrane to the genome. The imprint of the environment on the concentration and activity of many thousands of proteins in a cell is in effect a memory trace, like a 'random access memory' containing ever-changing information about the cell's surroundings. Because of their high degree of interconnection, systems of interacting proteins act as neural networks trained by evolution to respond appropriately to pat-

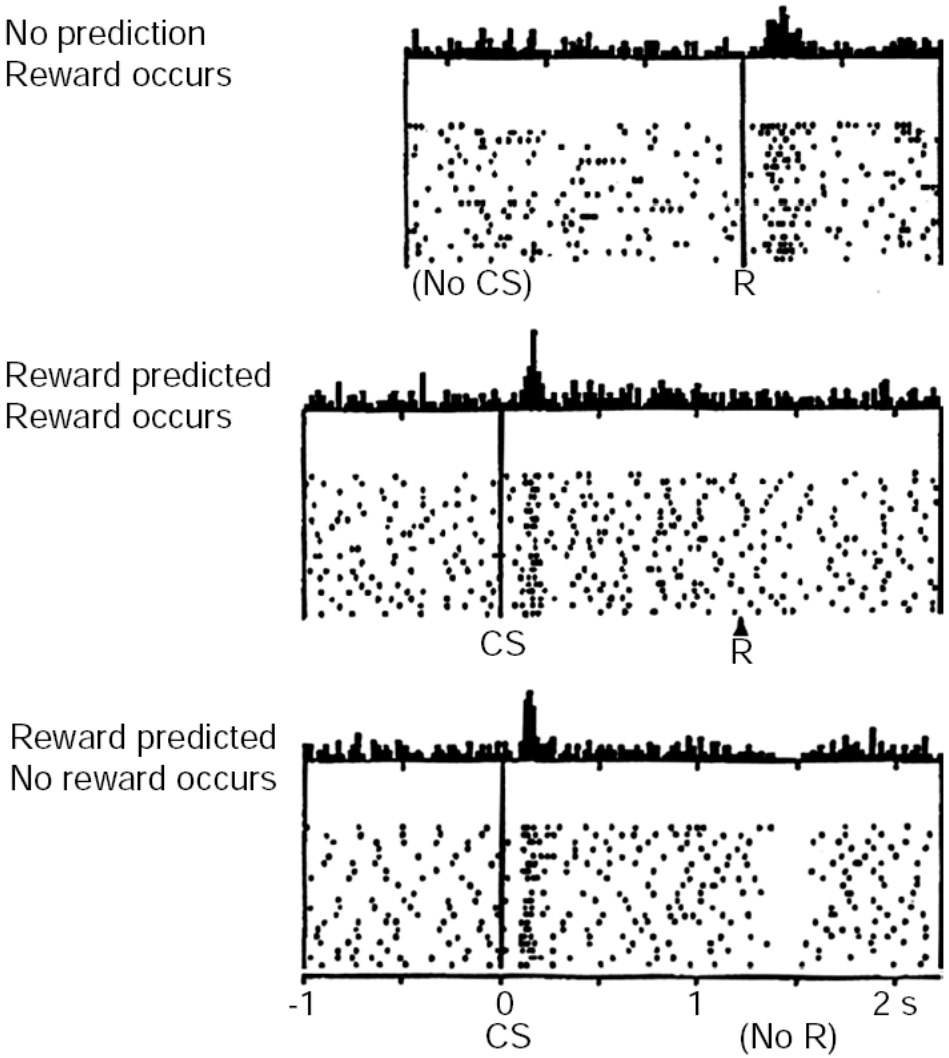
the protein. In some cases protein modification changes the three-dimensional structure of the protein and, by altering the interactions with adjoining subunits, thereby causes a cooperative, or sigmoidal, response. The enzyme glycogen phosphorylase, for example, could be represented symbolically in a similar way to aspartate transcarbamoylase in Fig. 1*c* simply by replacing the inputs with (1) the concentration of its substrate, glycogen, (2) the activity of phosphorylase kinase, which adds a phosphate group to a site that is remote from the catalytic site, and (3) the activity of a protein phosphatase that removes this phosphate group[2].

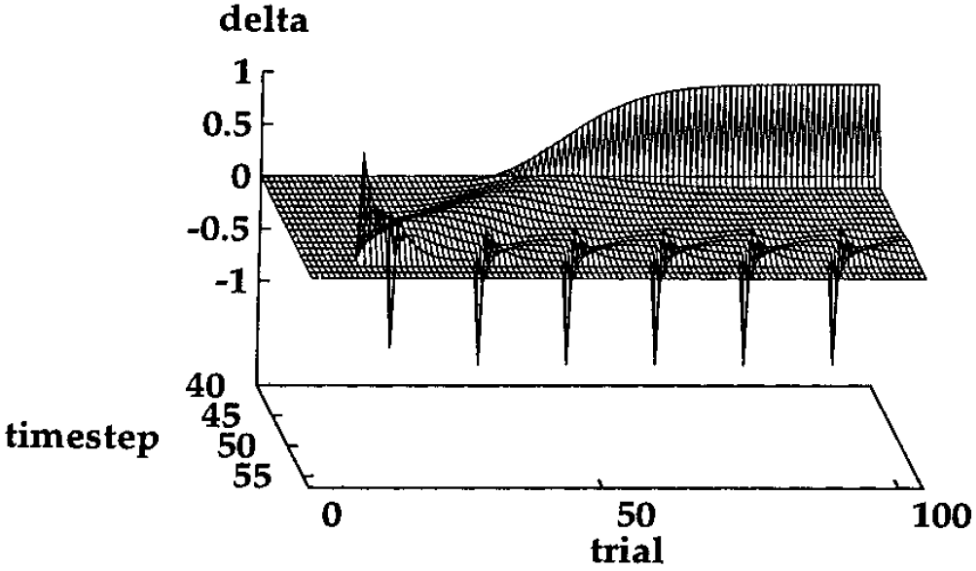


Integrators, loops and switches. The mechanic of learning

Nicolas Le Novère, EMBL-EBI

Dopamine, reward and learning

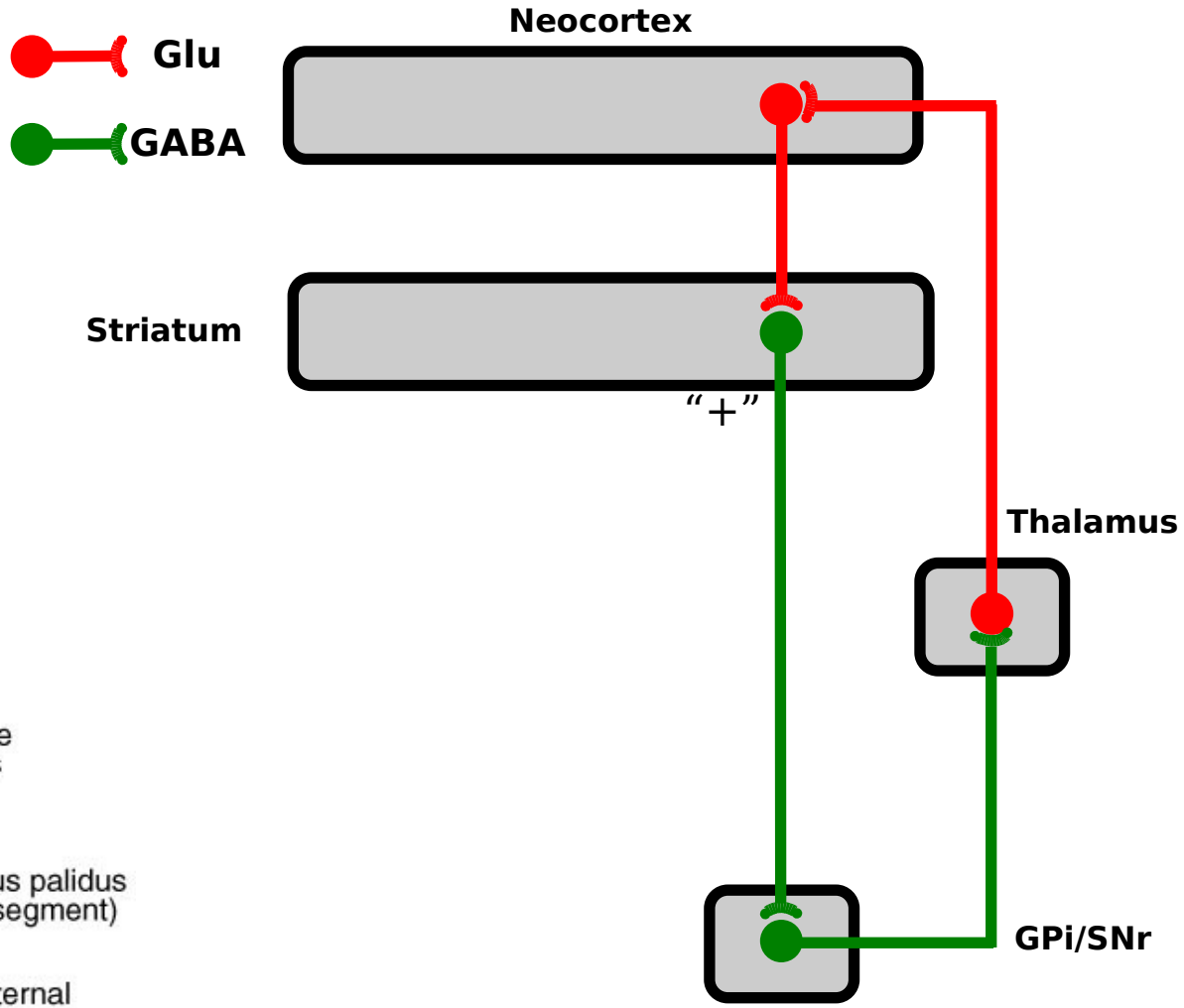


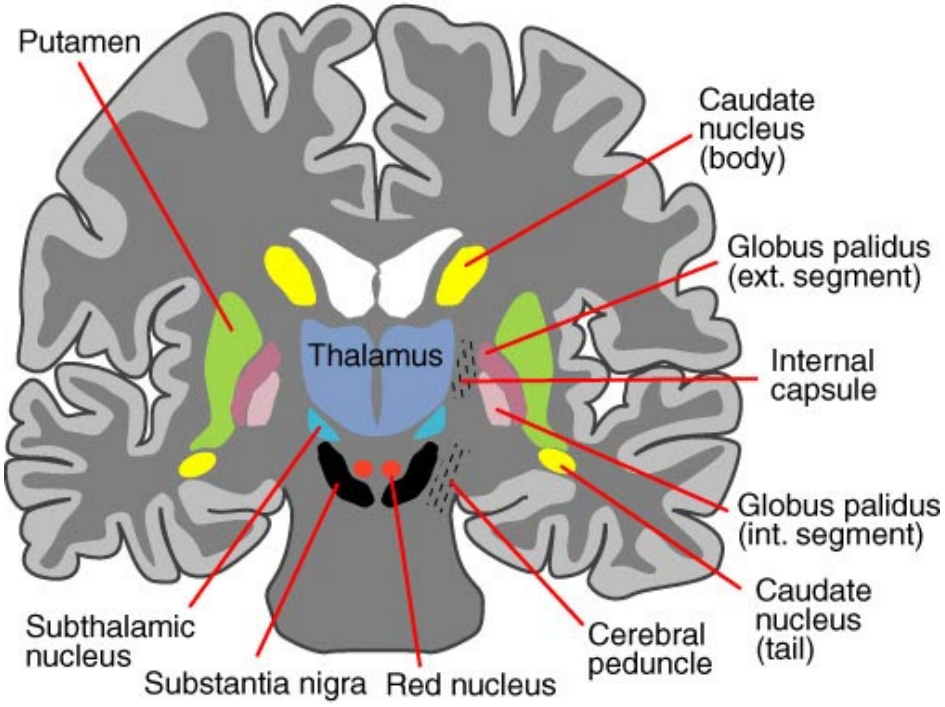


Schultz W, Dayan P, Montague PR (1997)
A neural substrate of prediction and reward.
Science 275:1593-1599.

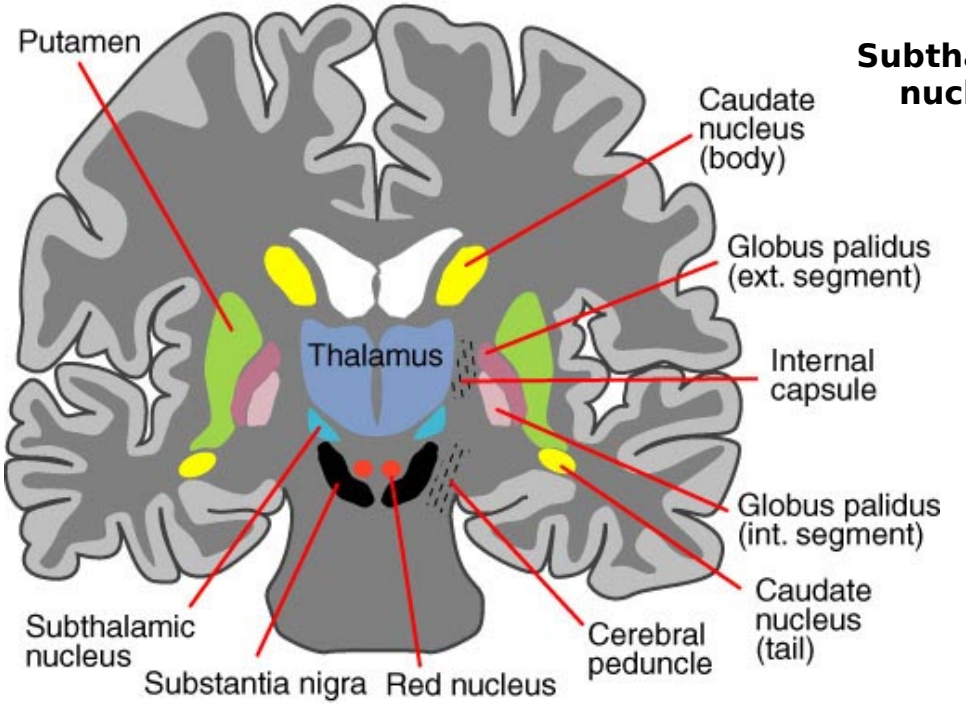
Montague PR, Dayan P, Sejnowski TJ (1996)
A framework for mesencephalic dopamine systems based on predictive Hebbian learning.
J Neurosci 16: 1936-1947

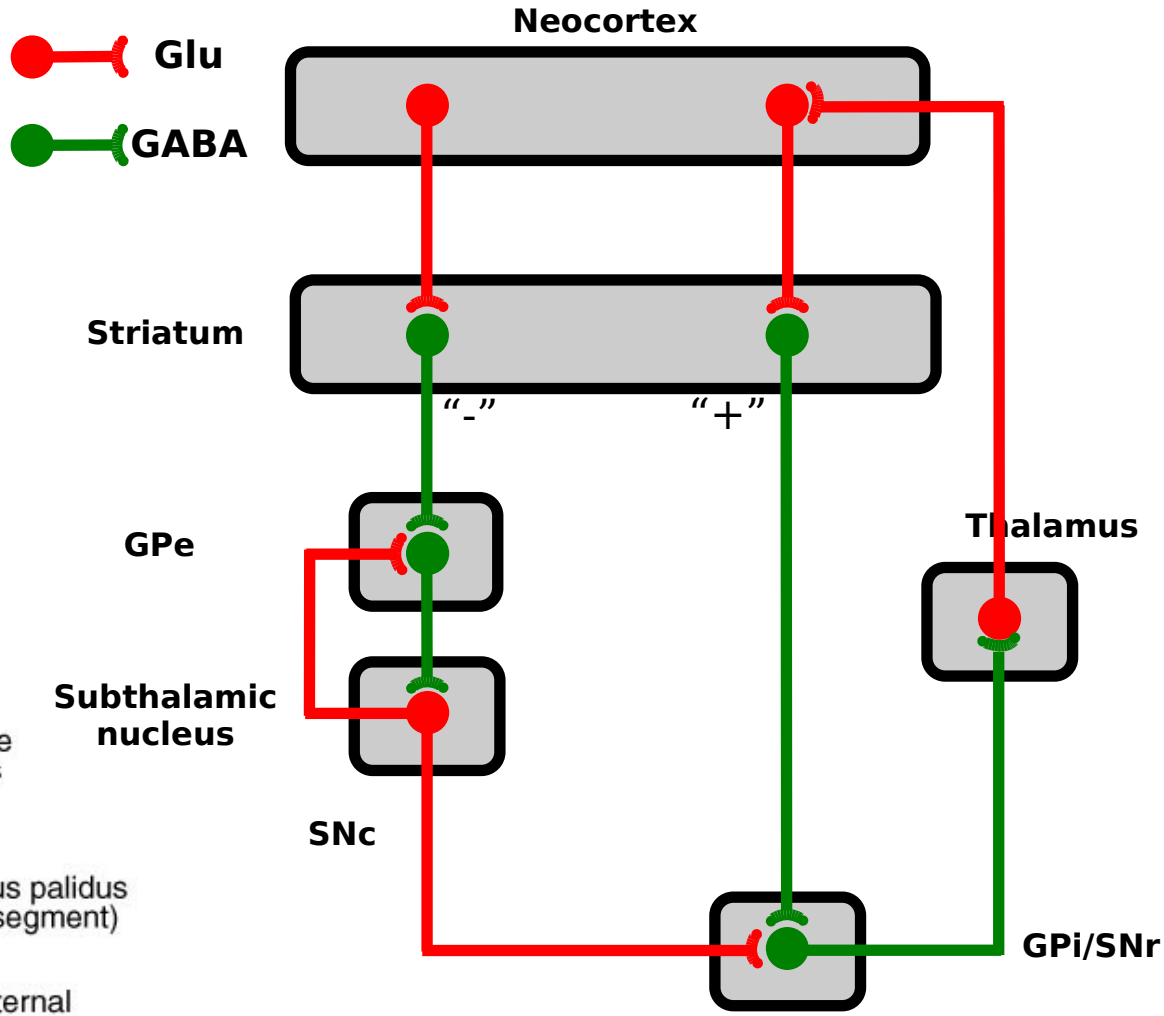
Dopamine mesotelencephalic pathway



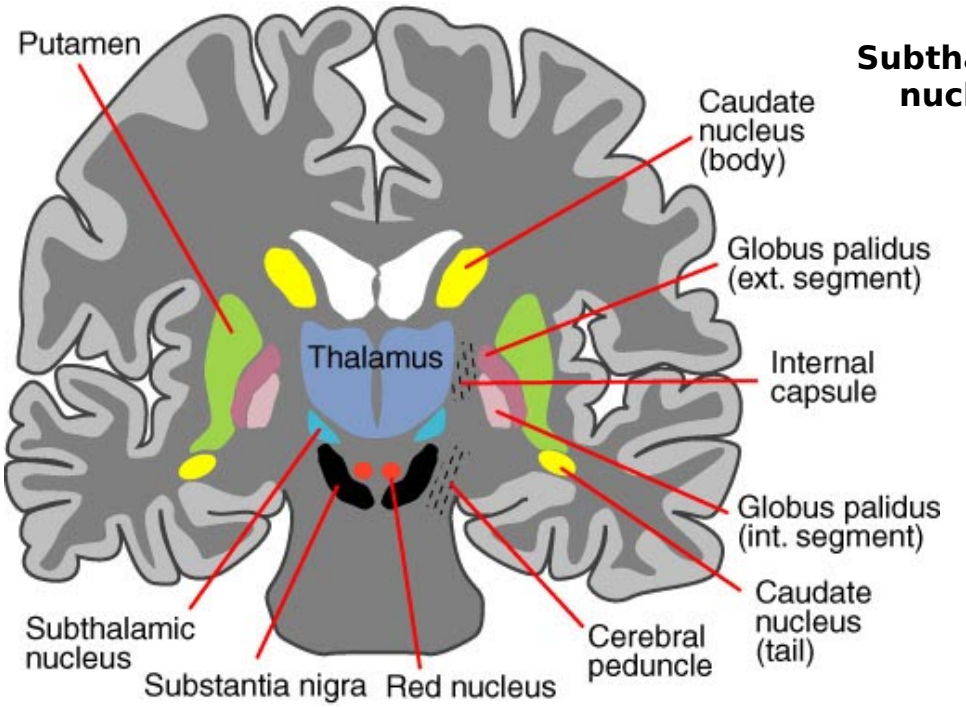


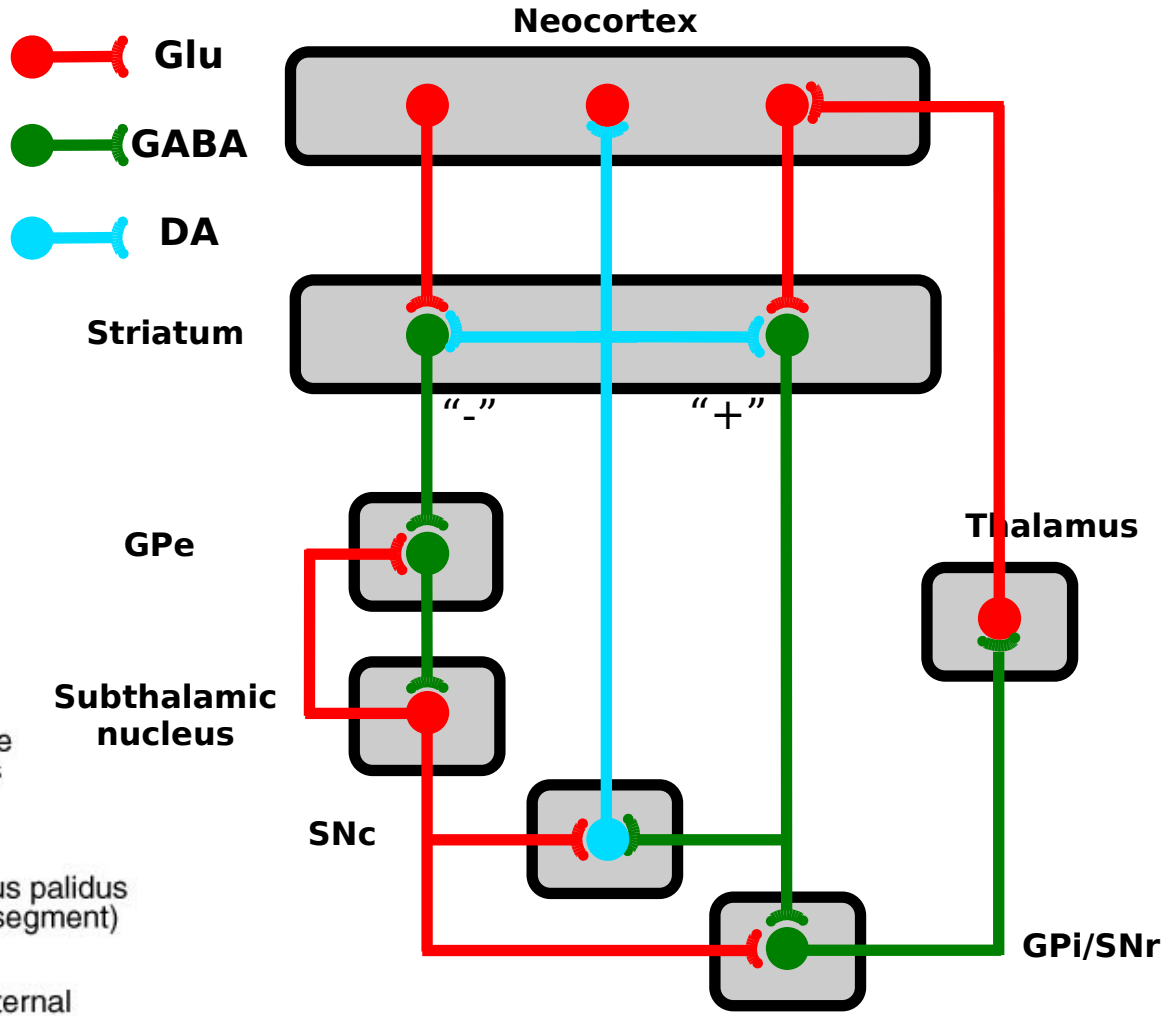
Dopamine mesotelencephalic pathway





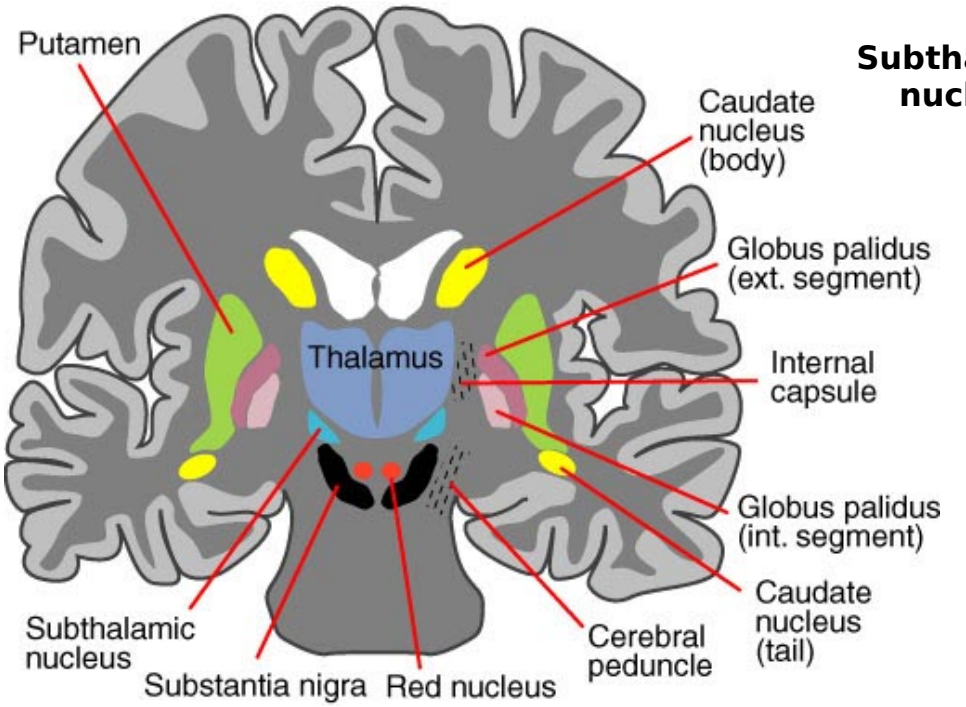
Dopamine mesotelencephalic pathway

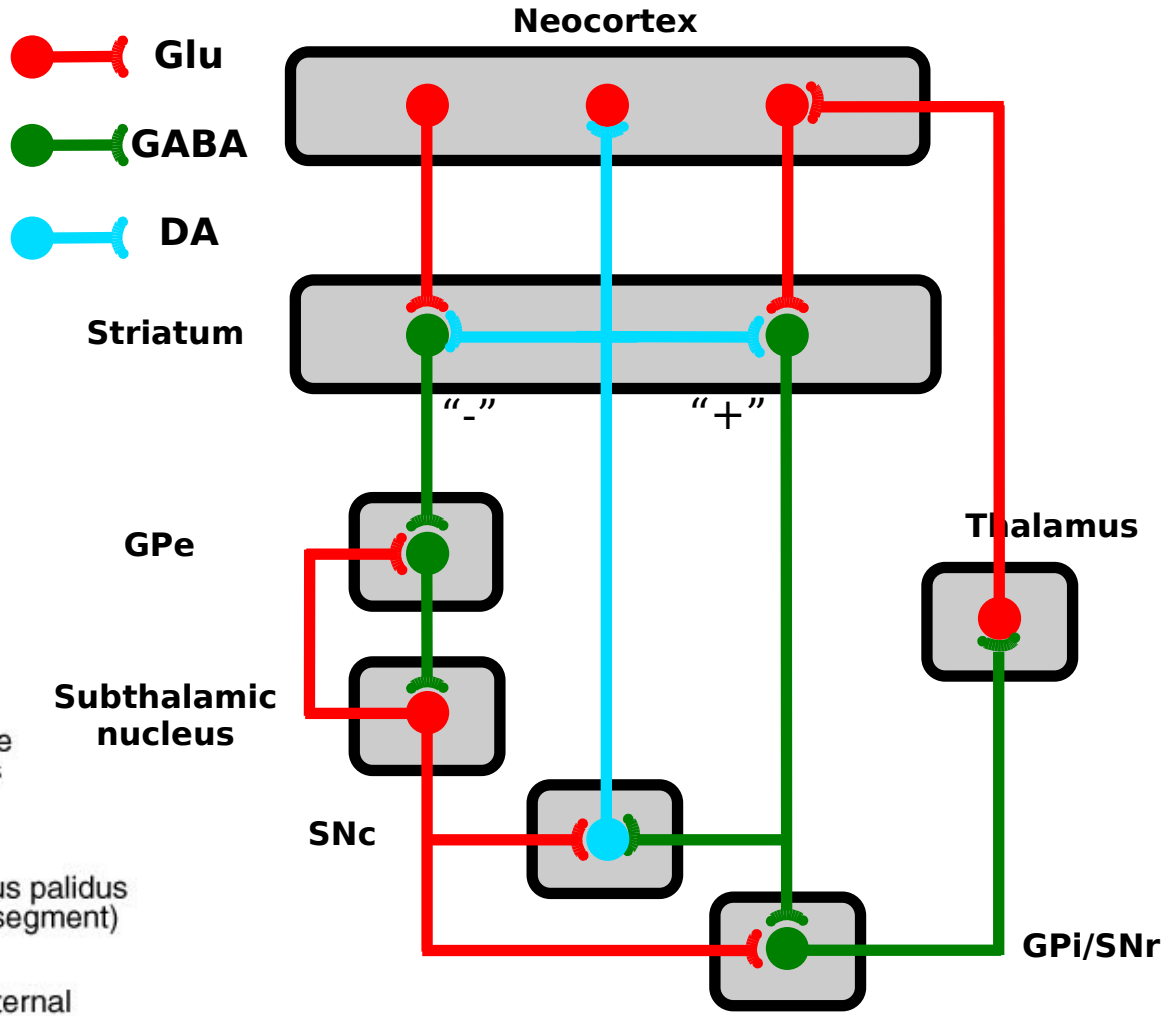




Dopamine mesotelencephalic pathway

Voluntary motion
Emotional control
Reward
Learning

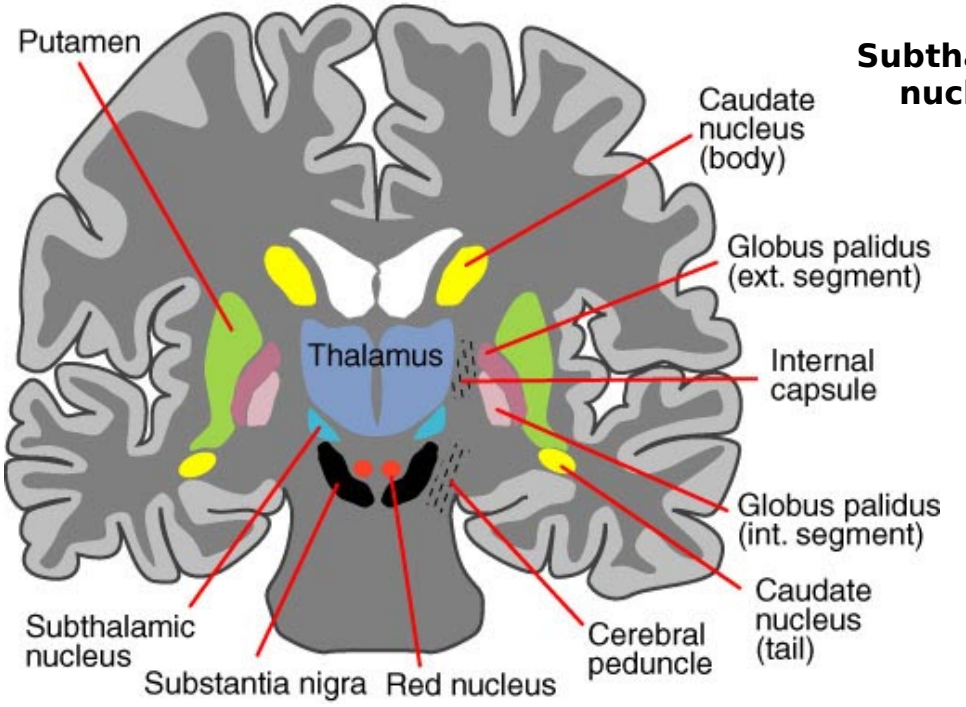


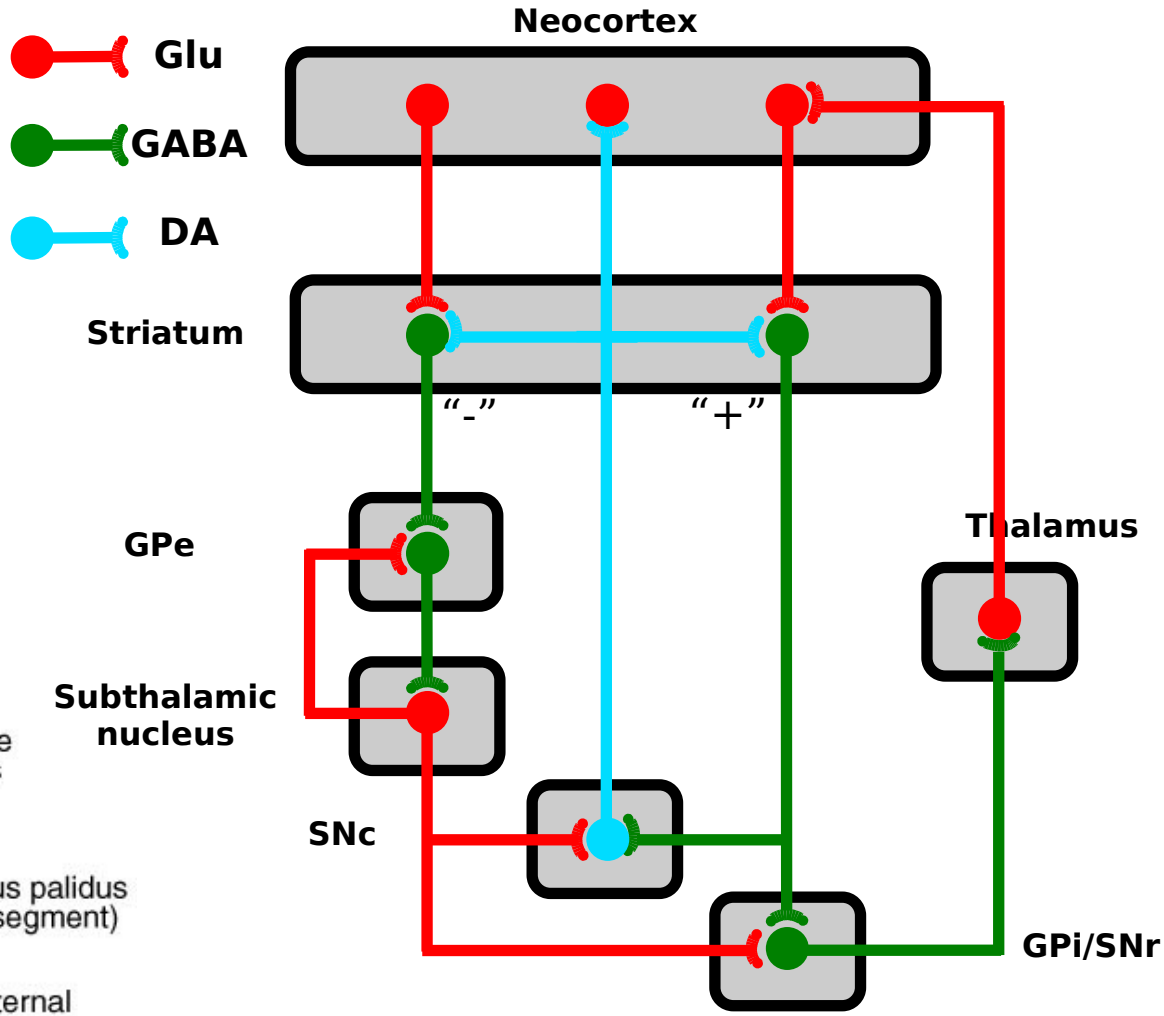


Dopamine mesotelencephalic pathway

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

Voluntary motion
Emotional control
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Learning

Parkinson's disease
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Drug addiction
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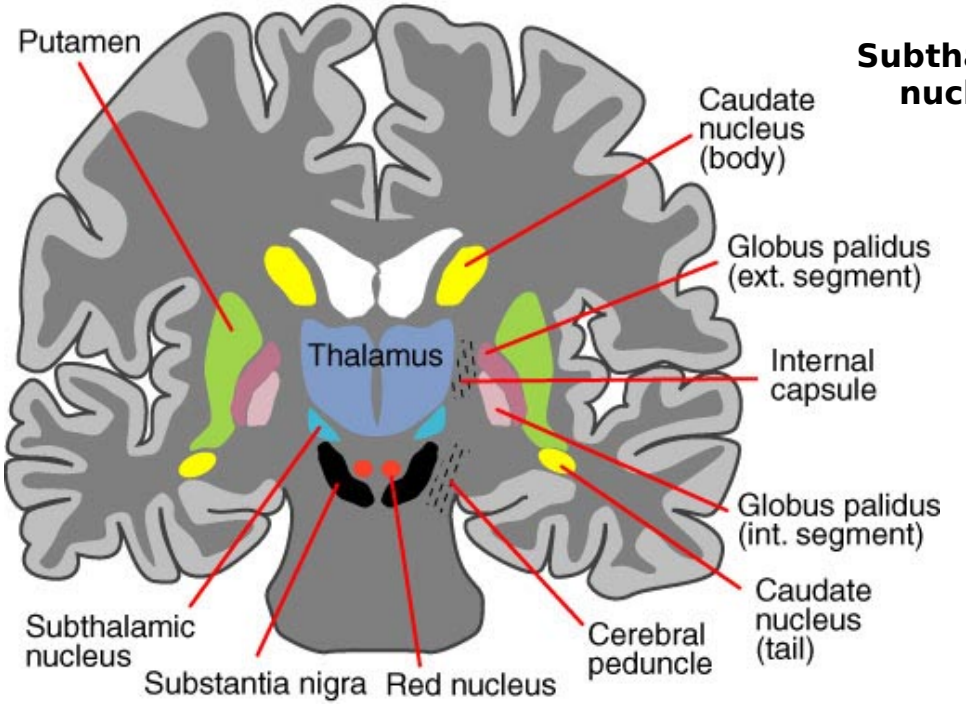
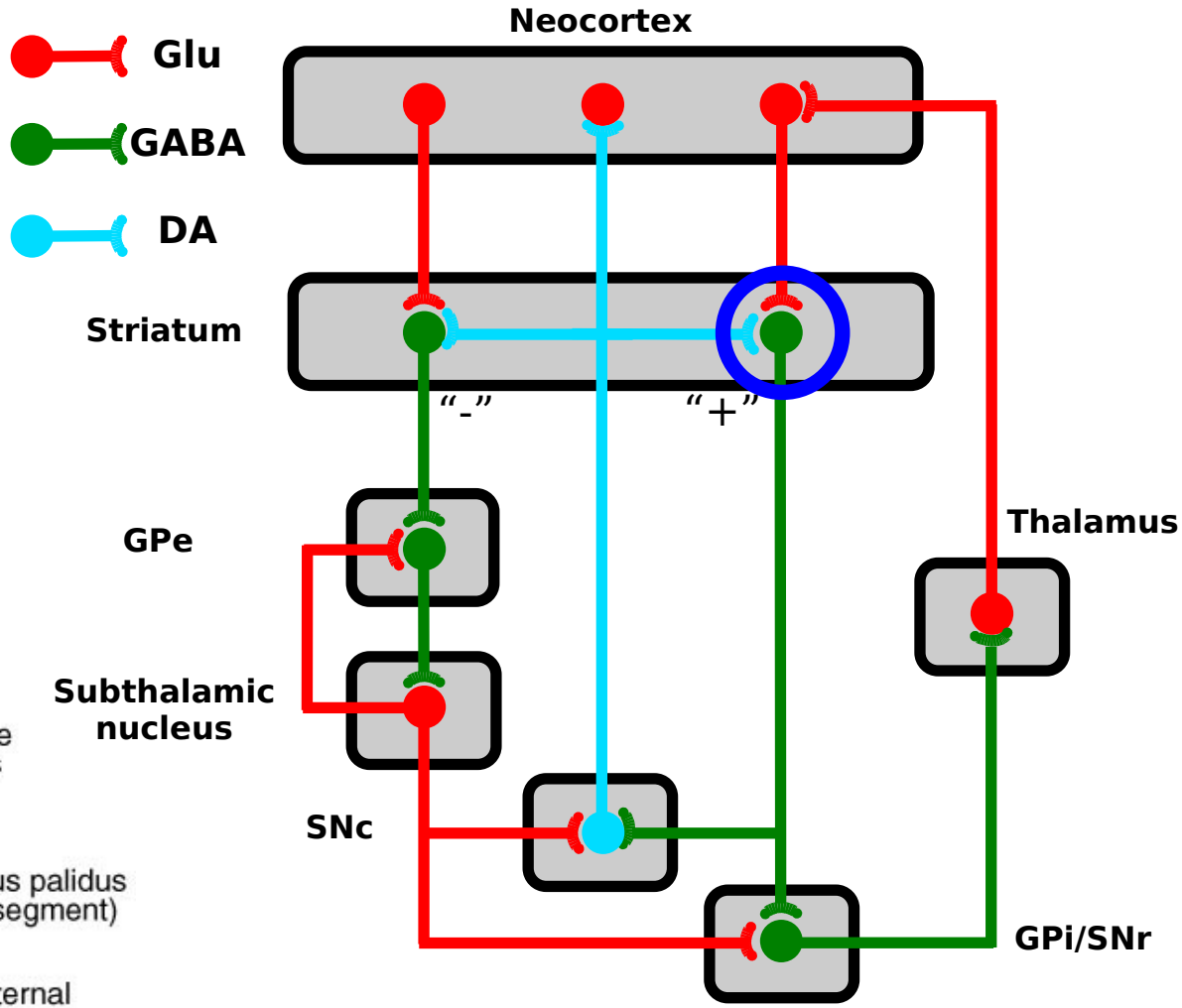
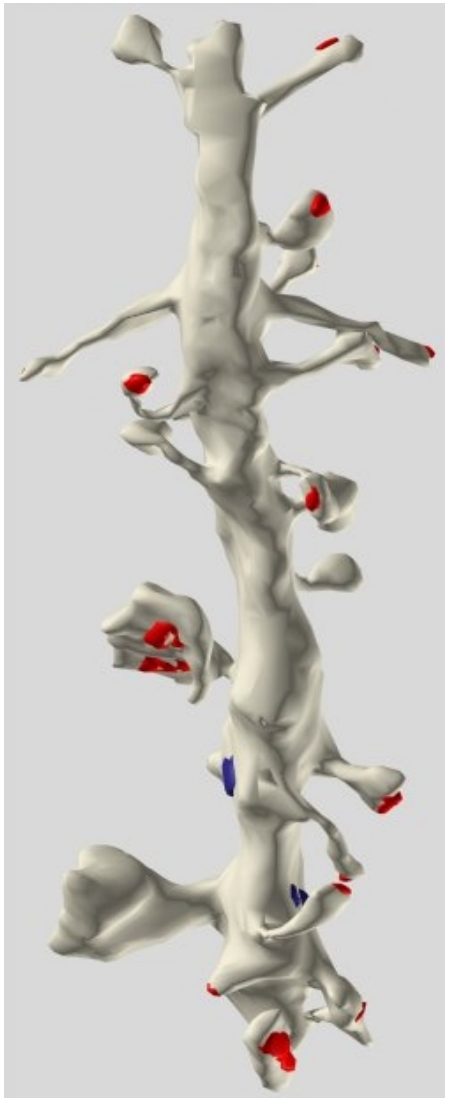
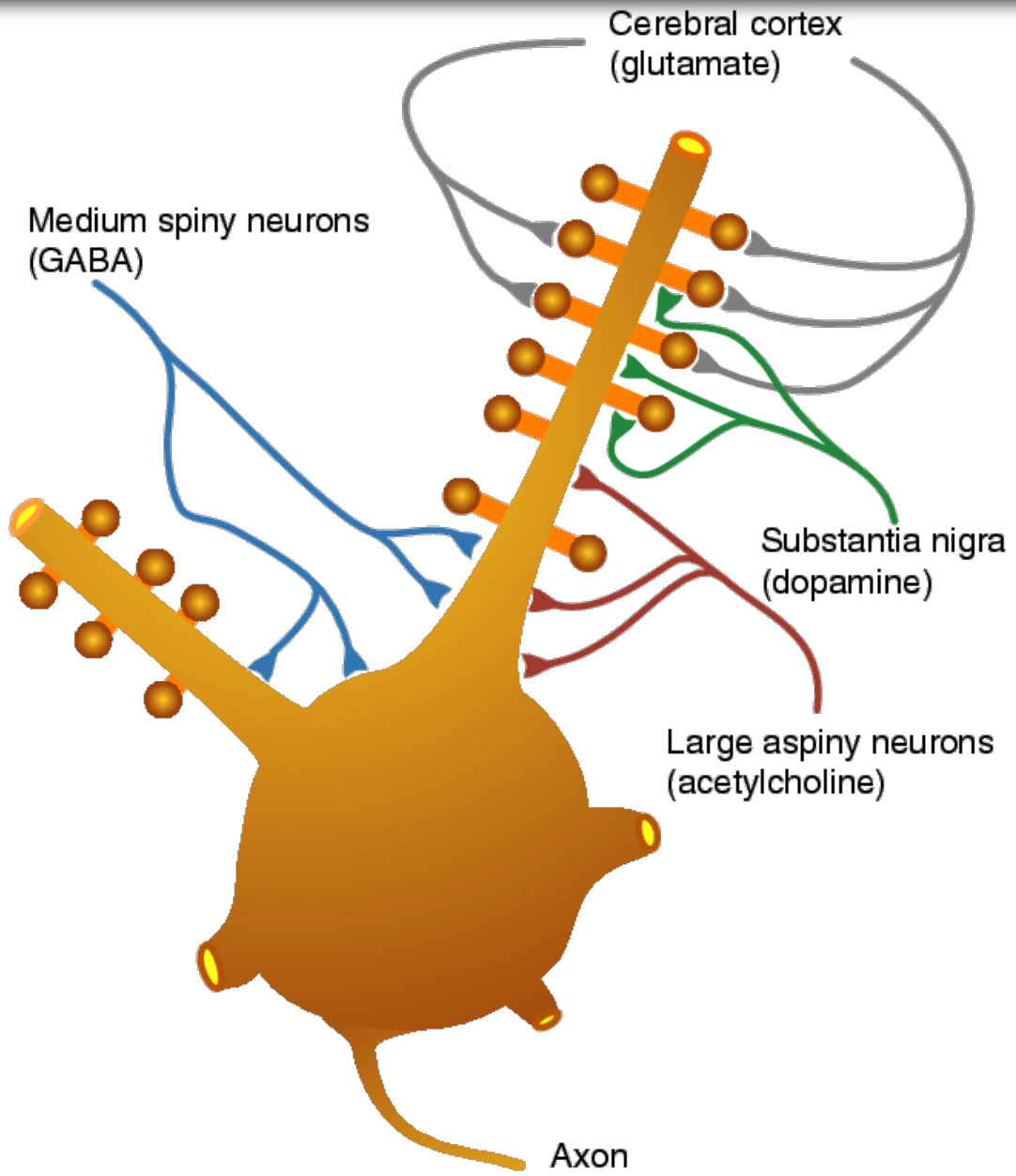




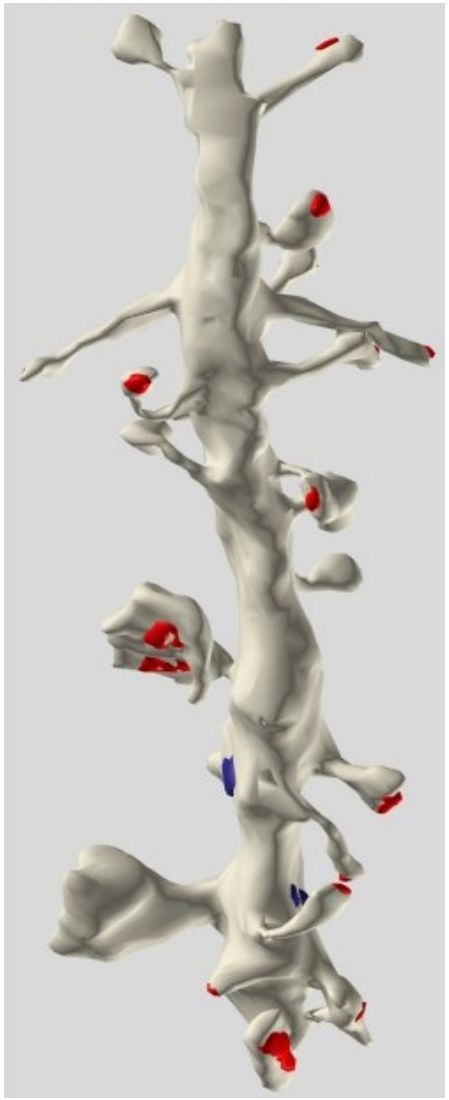
Multiple afferent signals

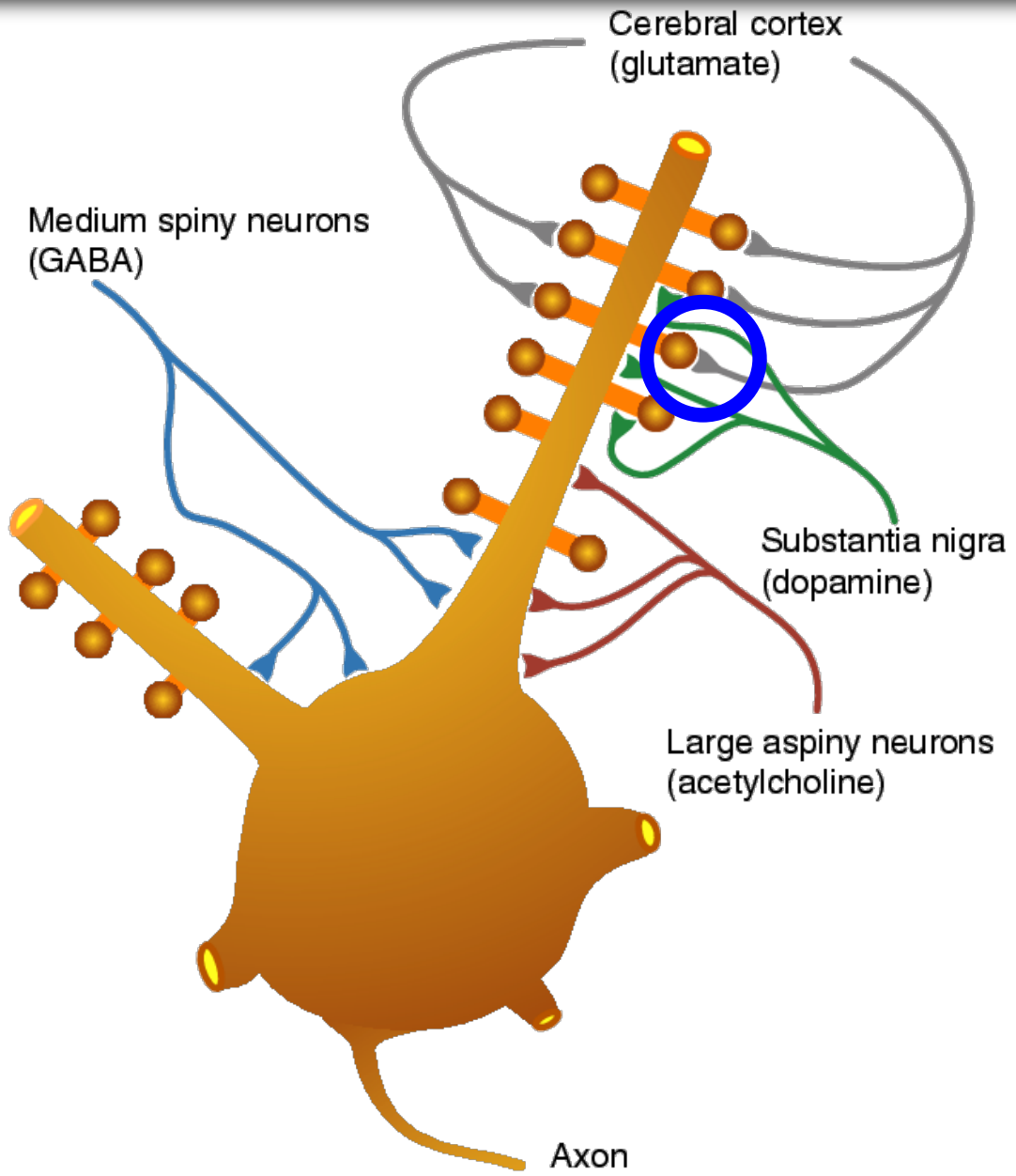




Fundamental Neuroscience
Squire et al. 2nd ed(2003)

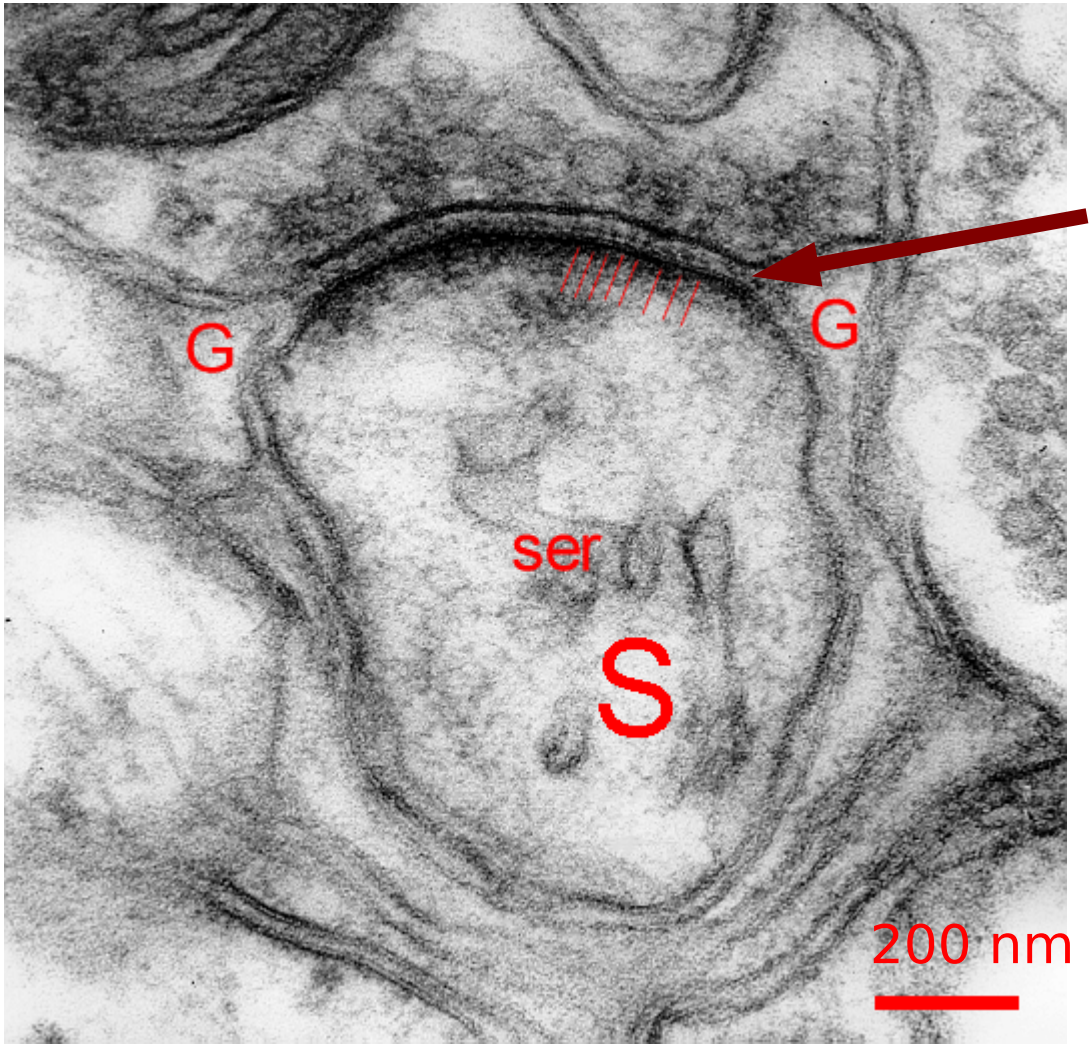
Multiple afferent signals





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

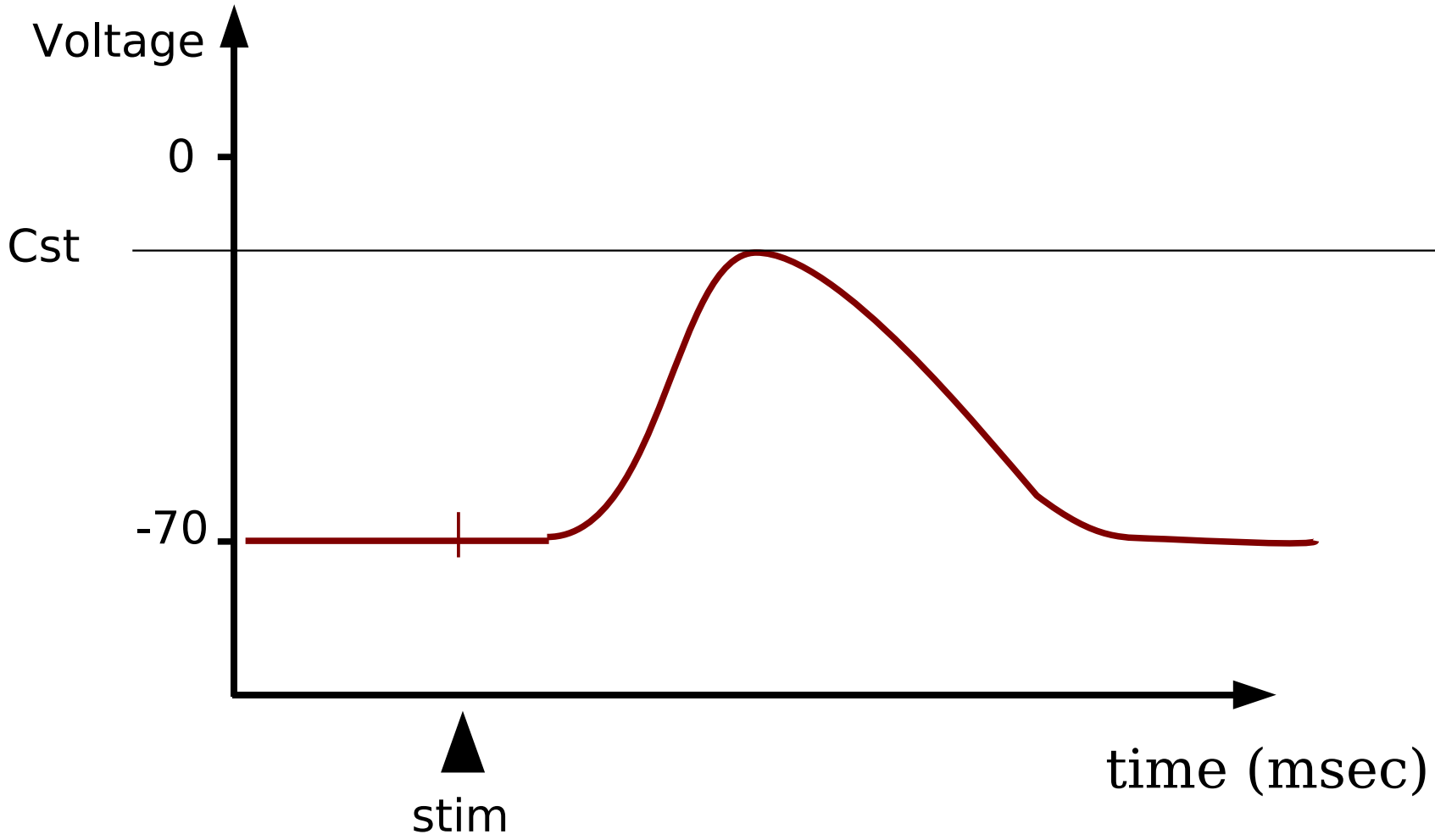
The spine as a “mini-cell”



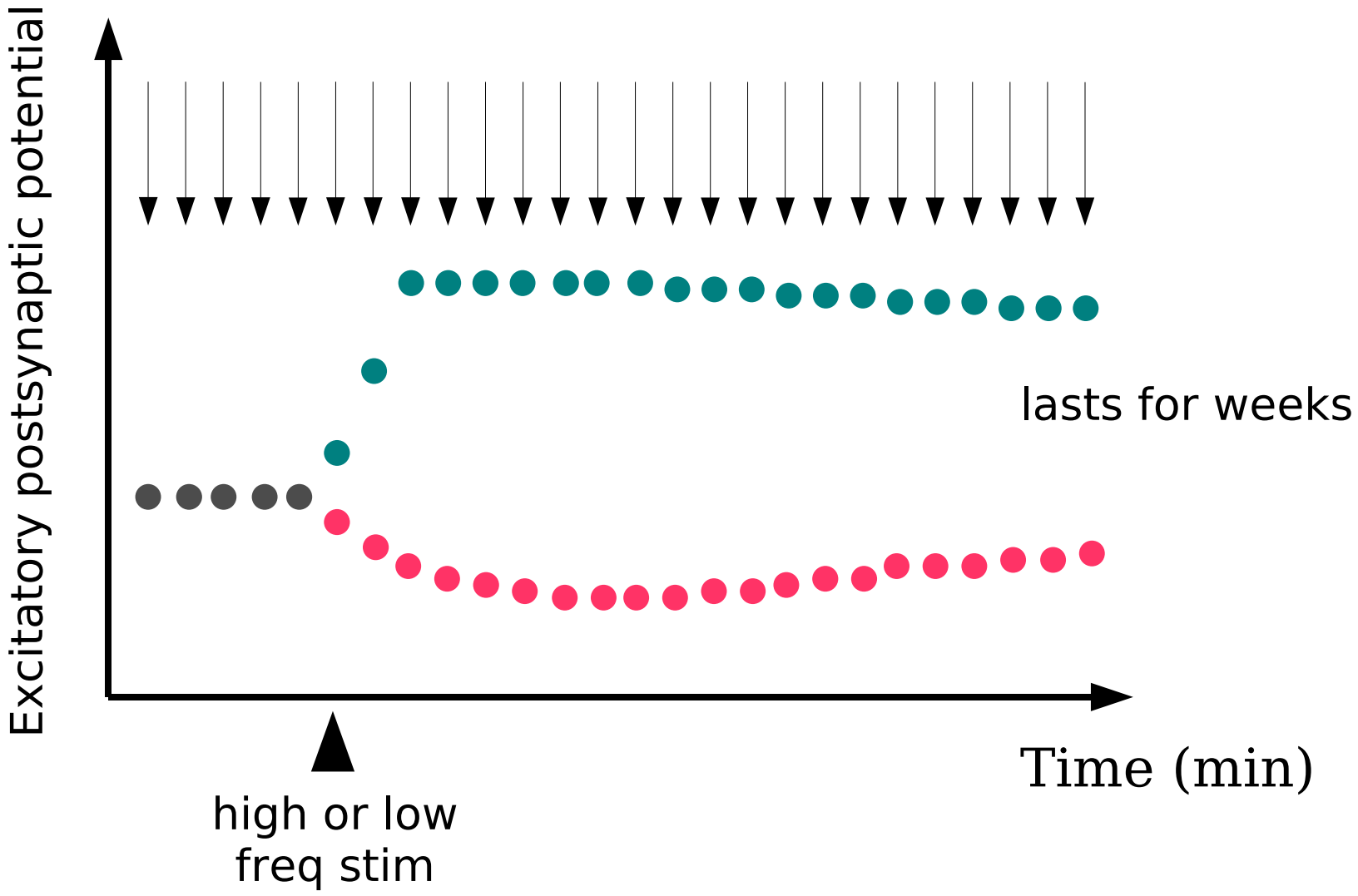
post-synaptic density

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

Excitatory post-synaptic potential

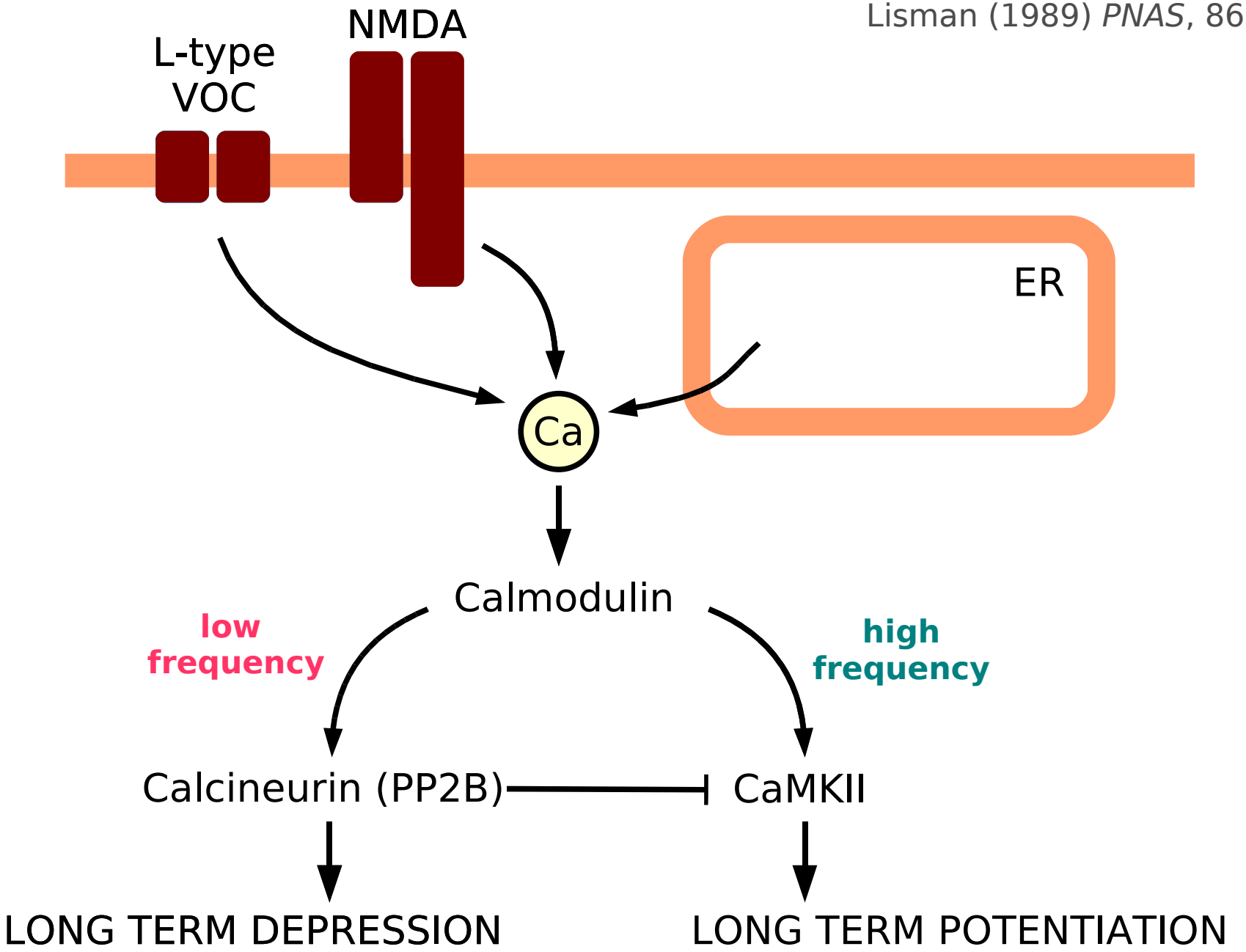


Bidirectional synaptic plasticity



Calcium theory of Synaptic Plasticity

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



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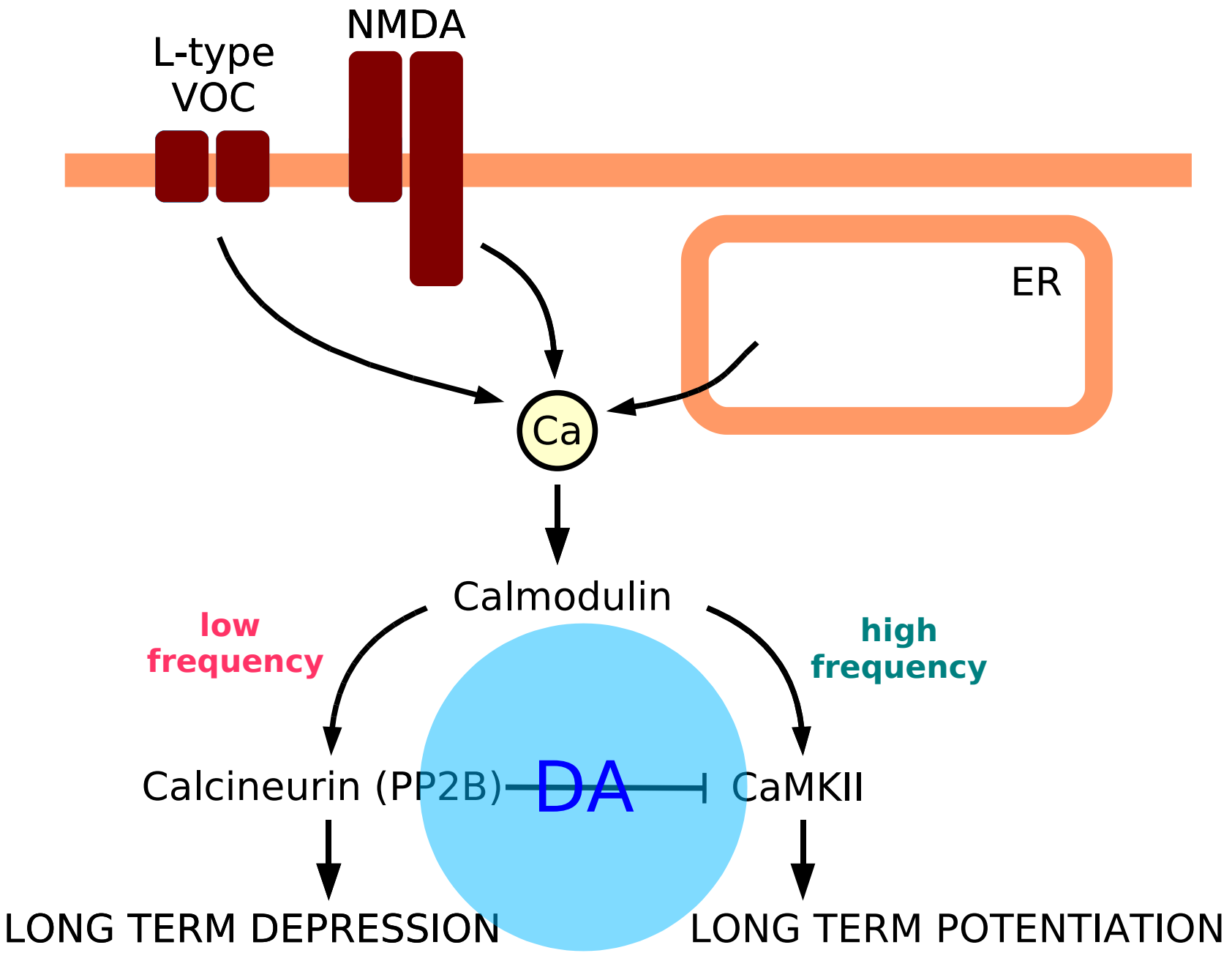
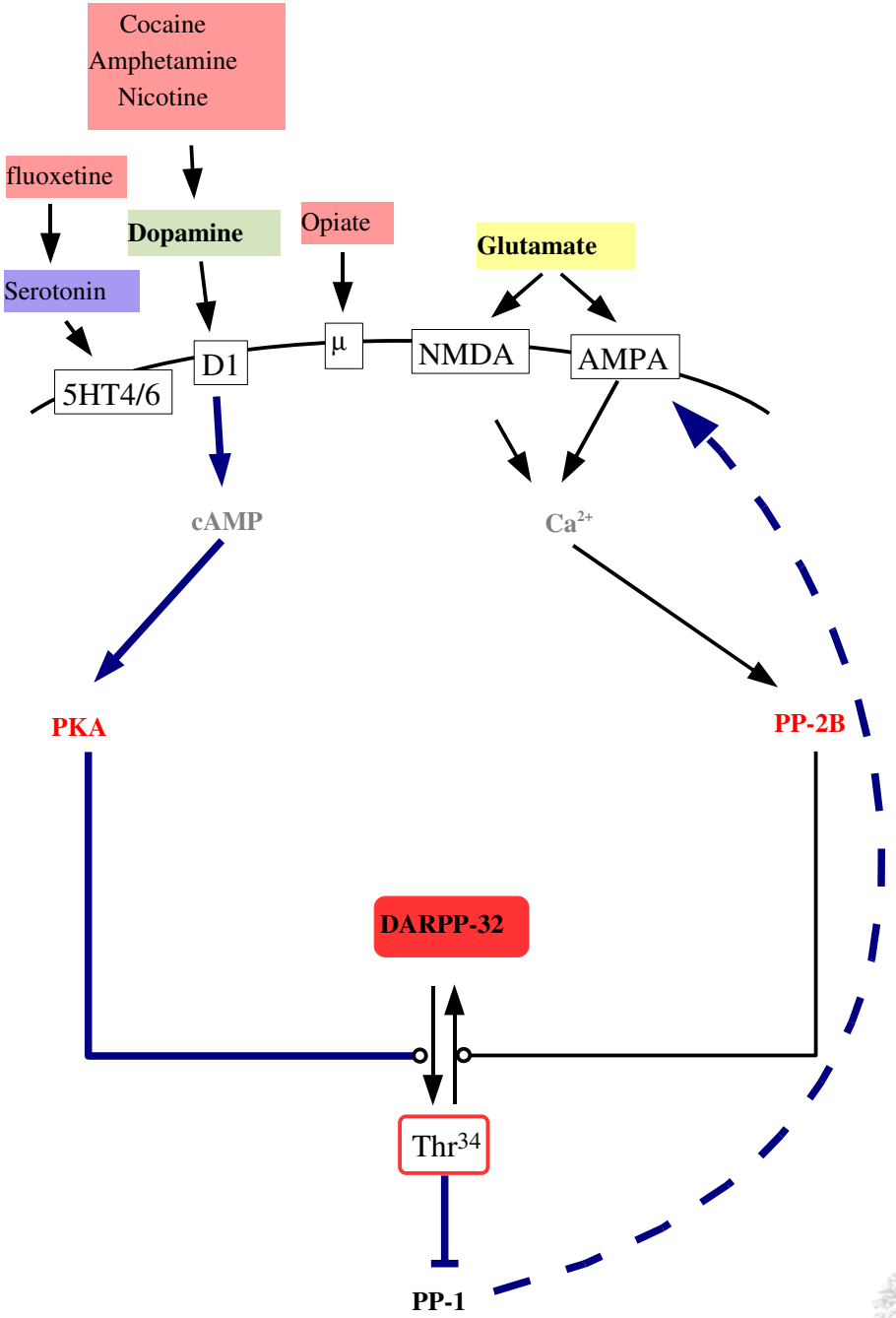


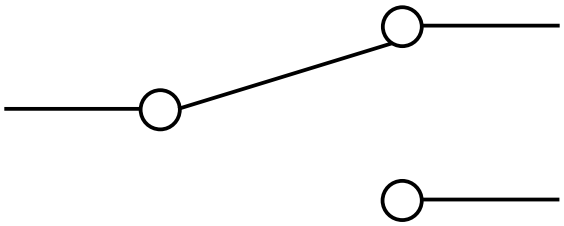
Is DARPP-32 a switch?

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.

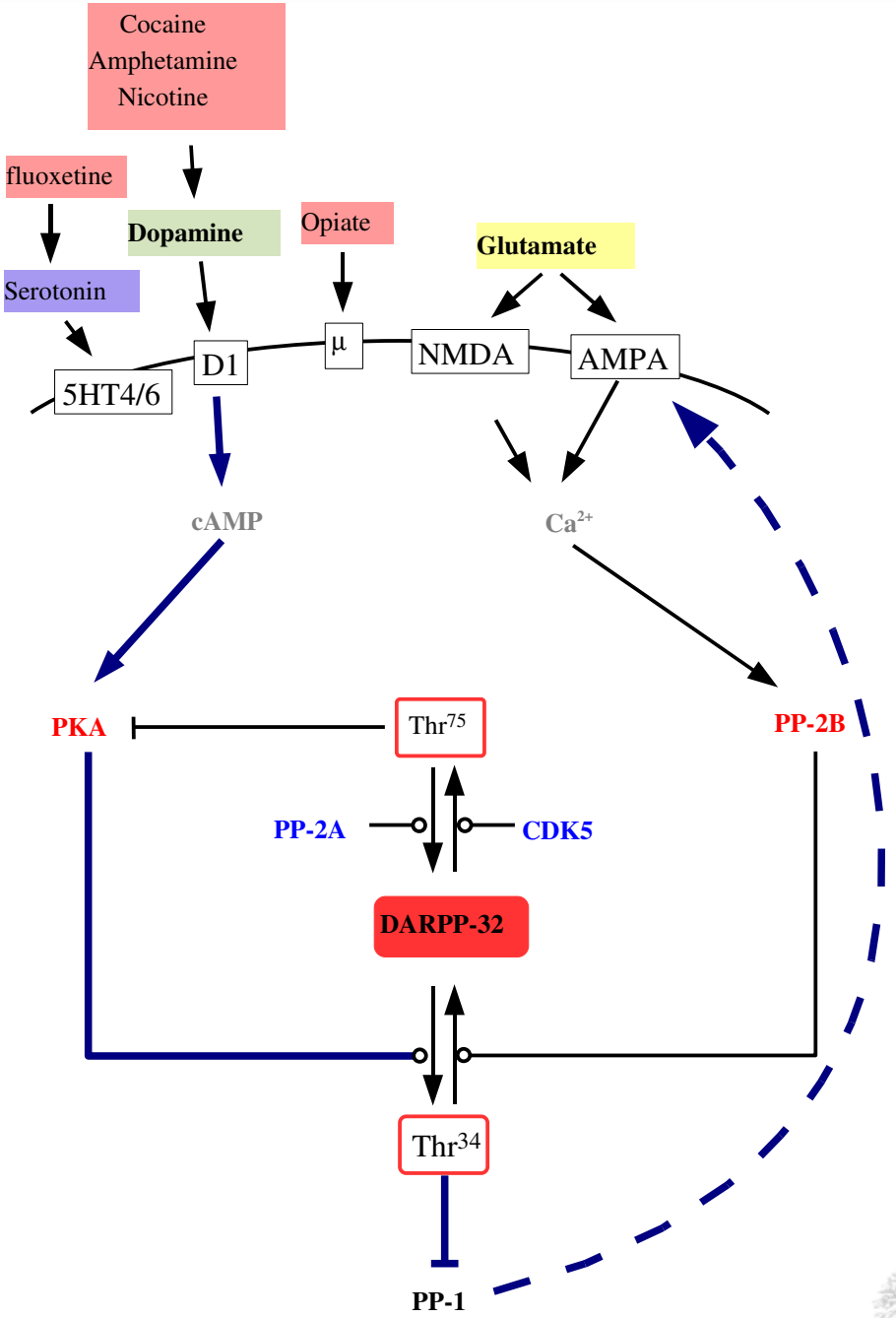
Textbook's view



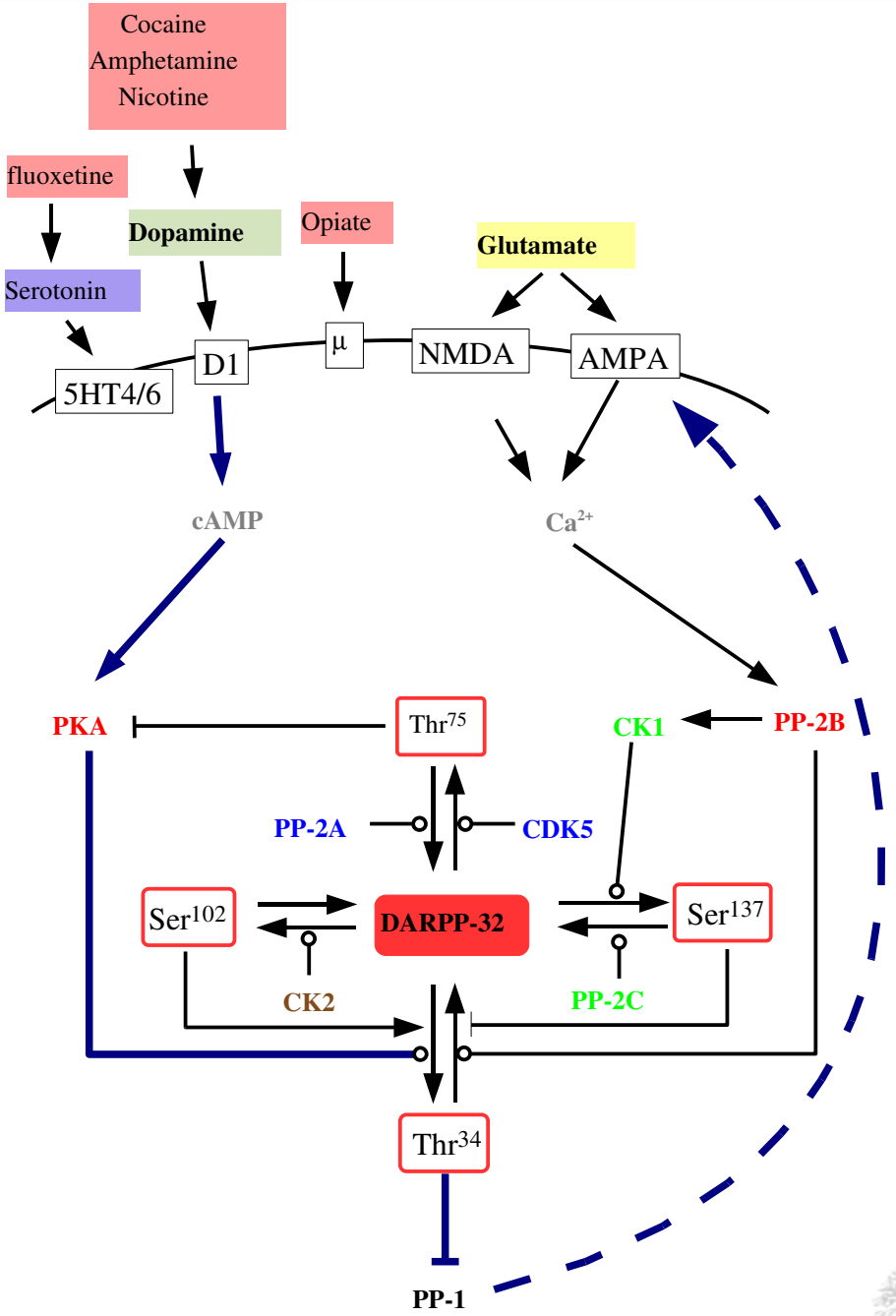
Is DARPP-32 a switch?

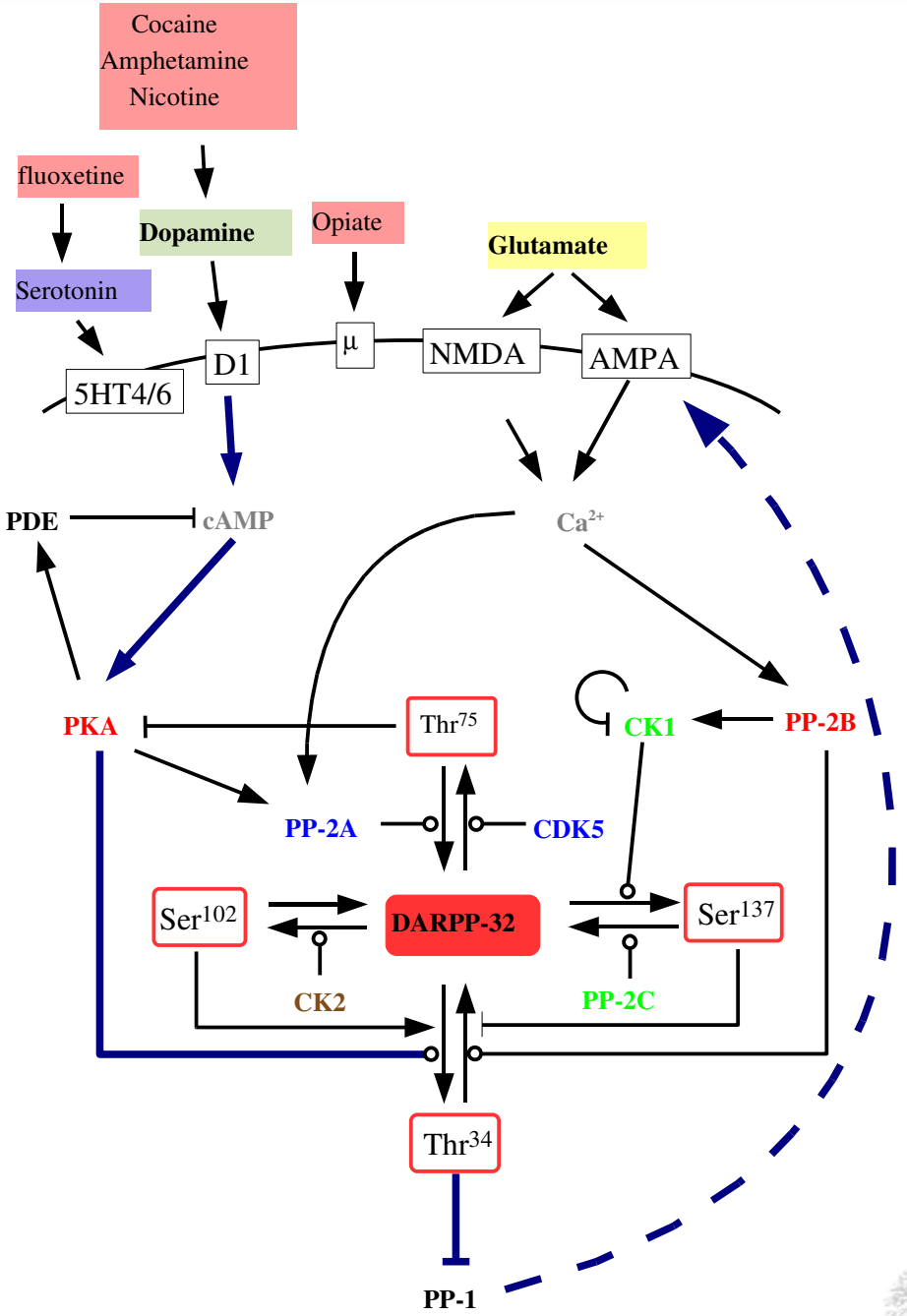


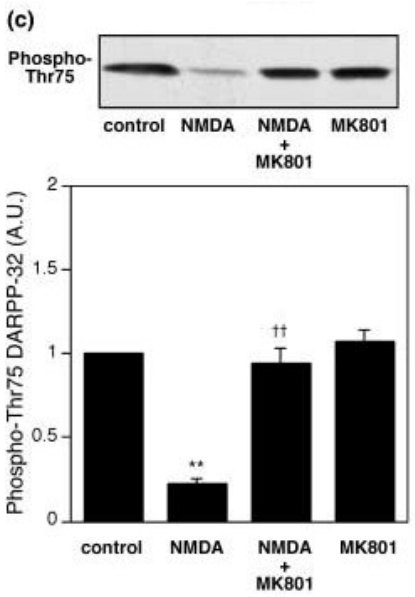
Review article's view



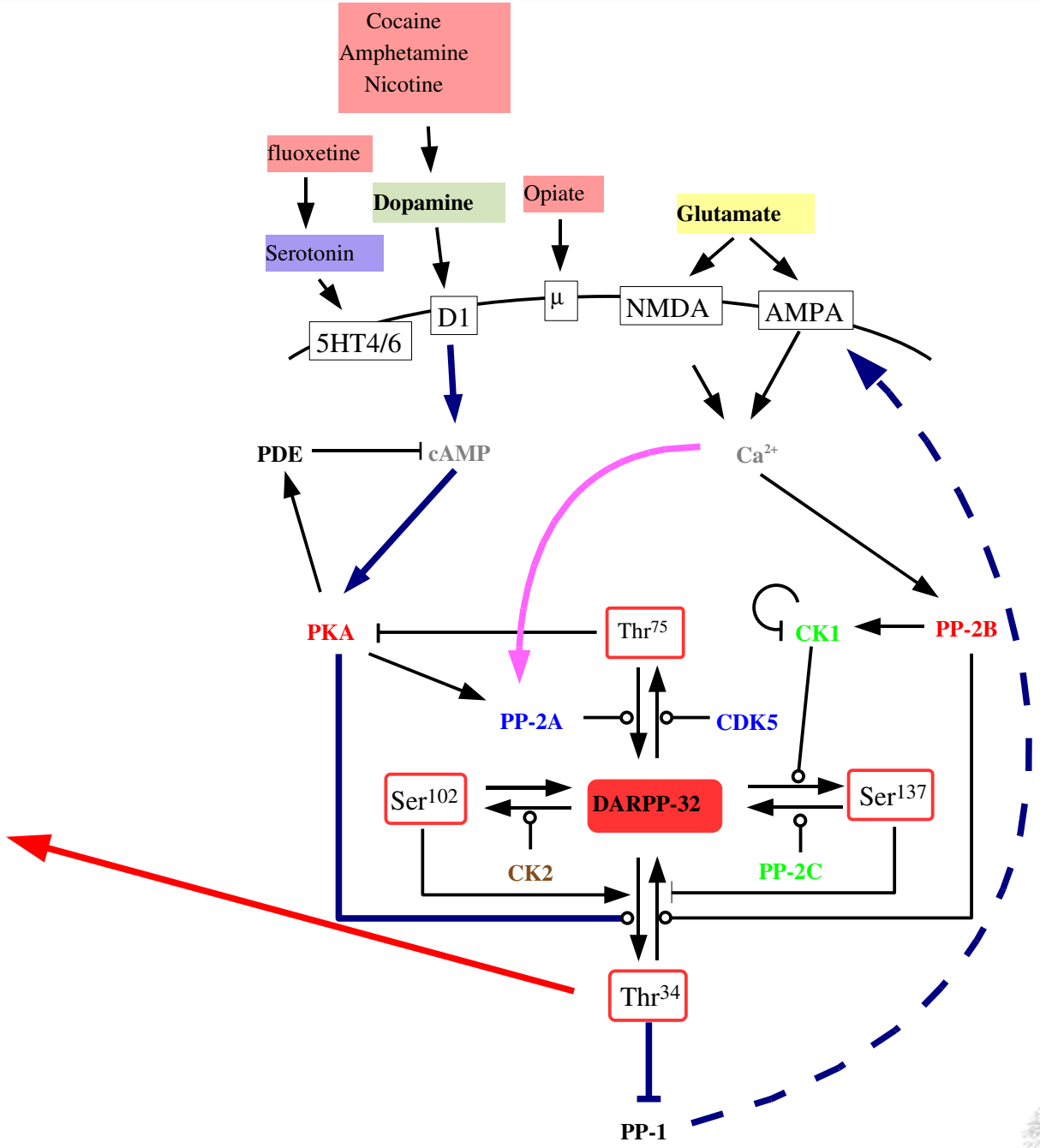
DARPP-32 is a “hub” for
phosphatases and kinases
in the post-synaptic compartment

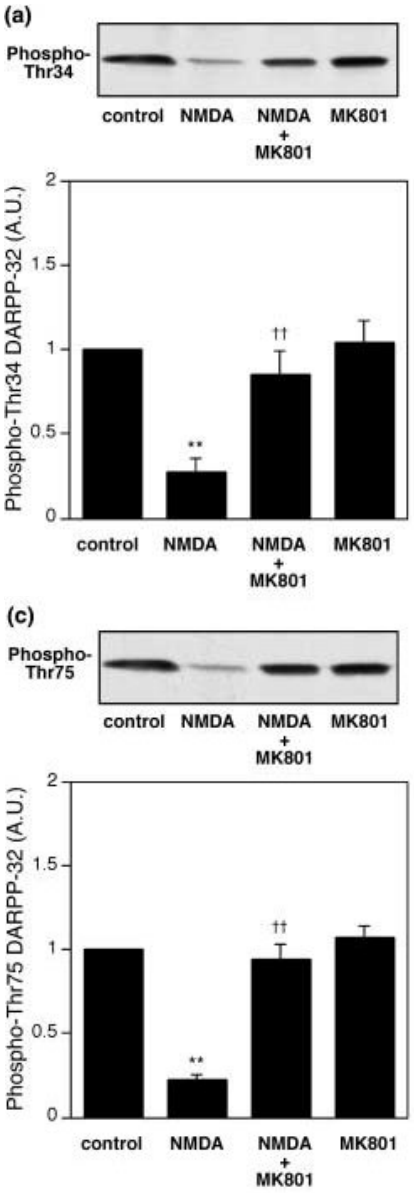



Cocaine
Amphetamine
Nicotine
fluoxetine
Dopamine
Opiate
Glutamate
Serotonin
D1
μ
NMDA
AMPA
5HT4/6
PDE
cAMP
Ca2+
PKA
Thr75
CK1
PP-2B
PP-2A
CDK5
Ser102
DARPP-32
Ser137
CK2
PP-2C
Thr34
PP-1



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





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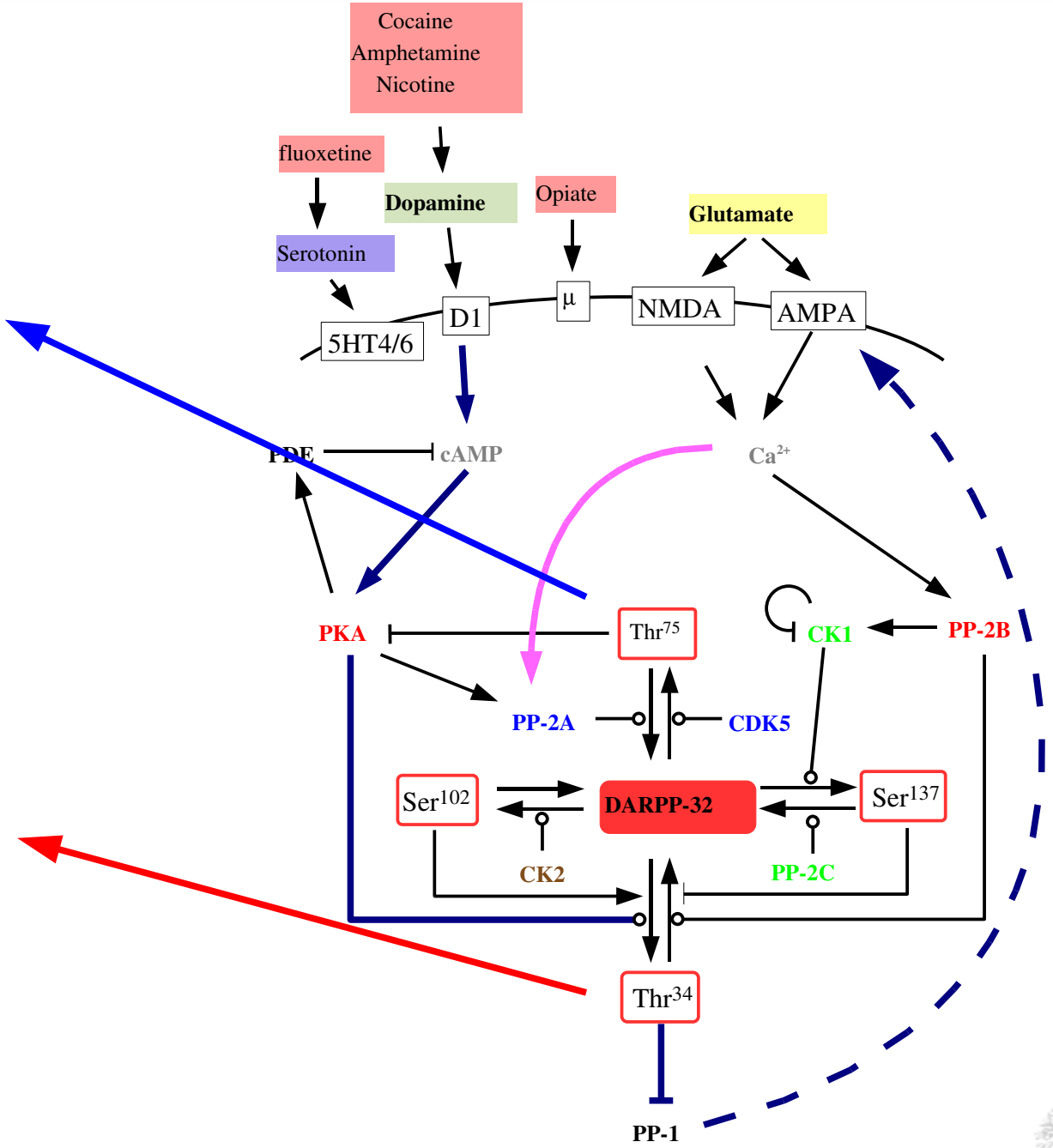
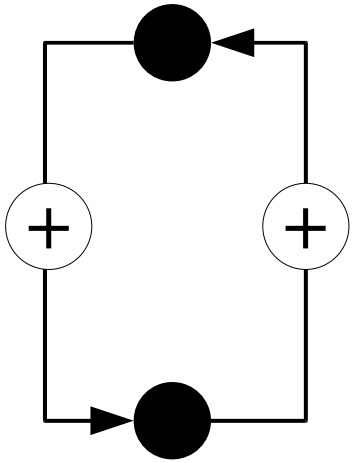
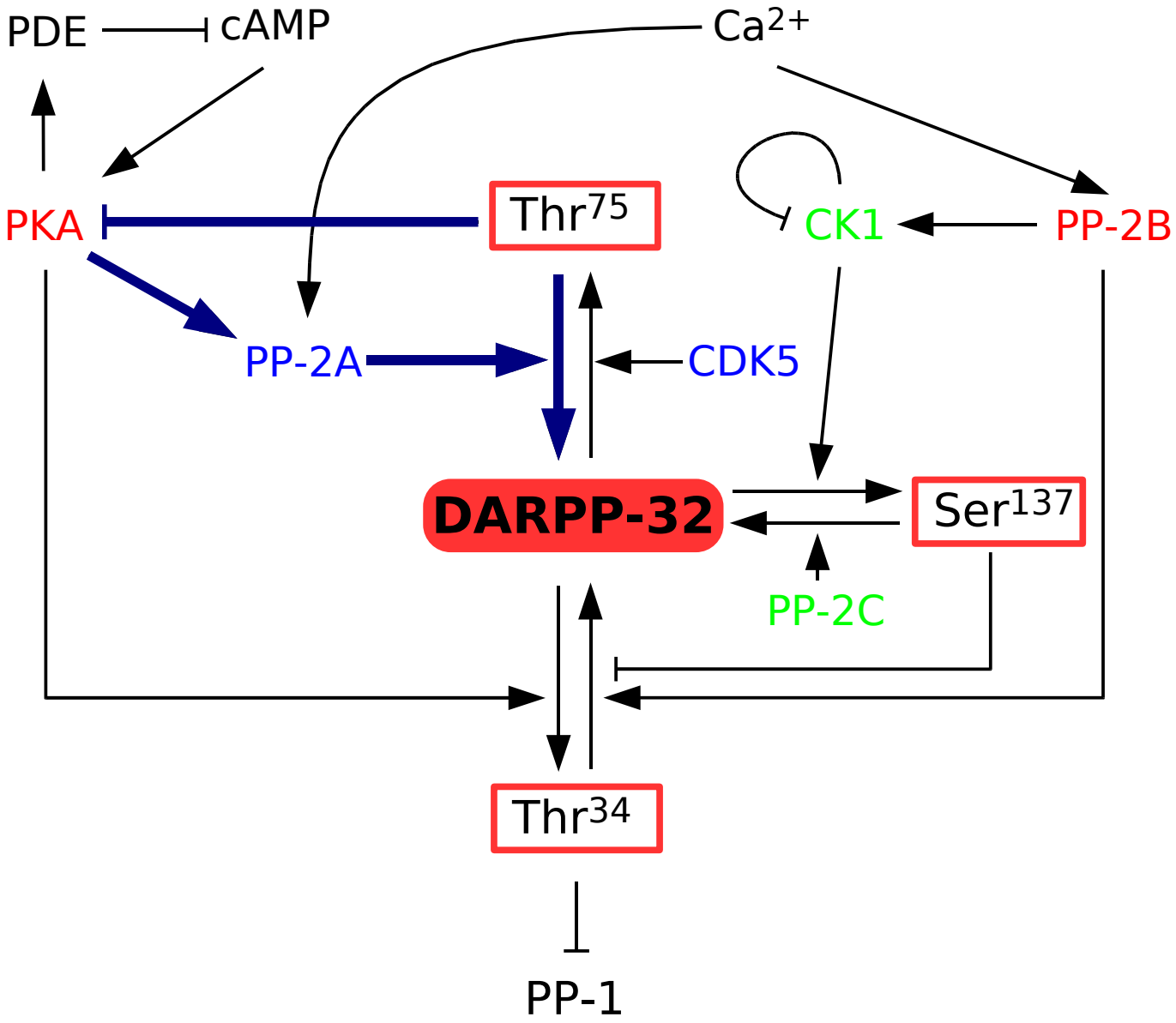


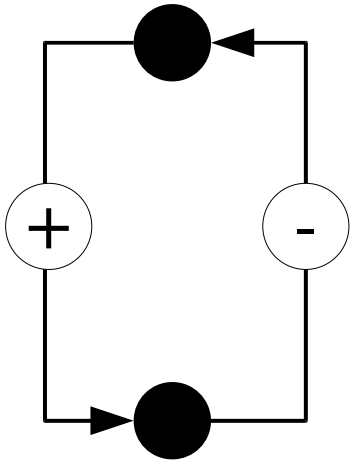
All the cybernetics in one system



positive feedback



All the cybernetics in one system



negative feedback

PDE — cAMP

Ca^{2+}

PKA — Thr^{75}

CK1

PP-2B

PP-2A

CDK5

DARPP-32

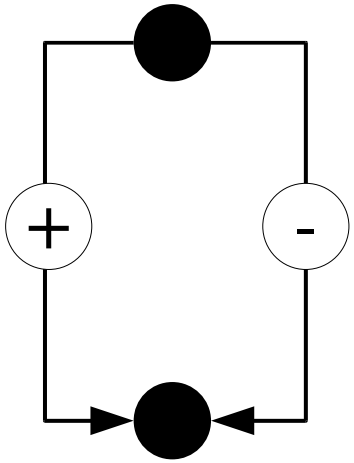
Ser^{137}

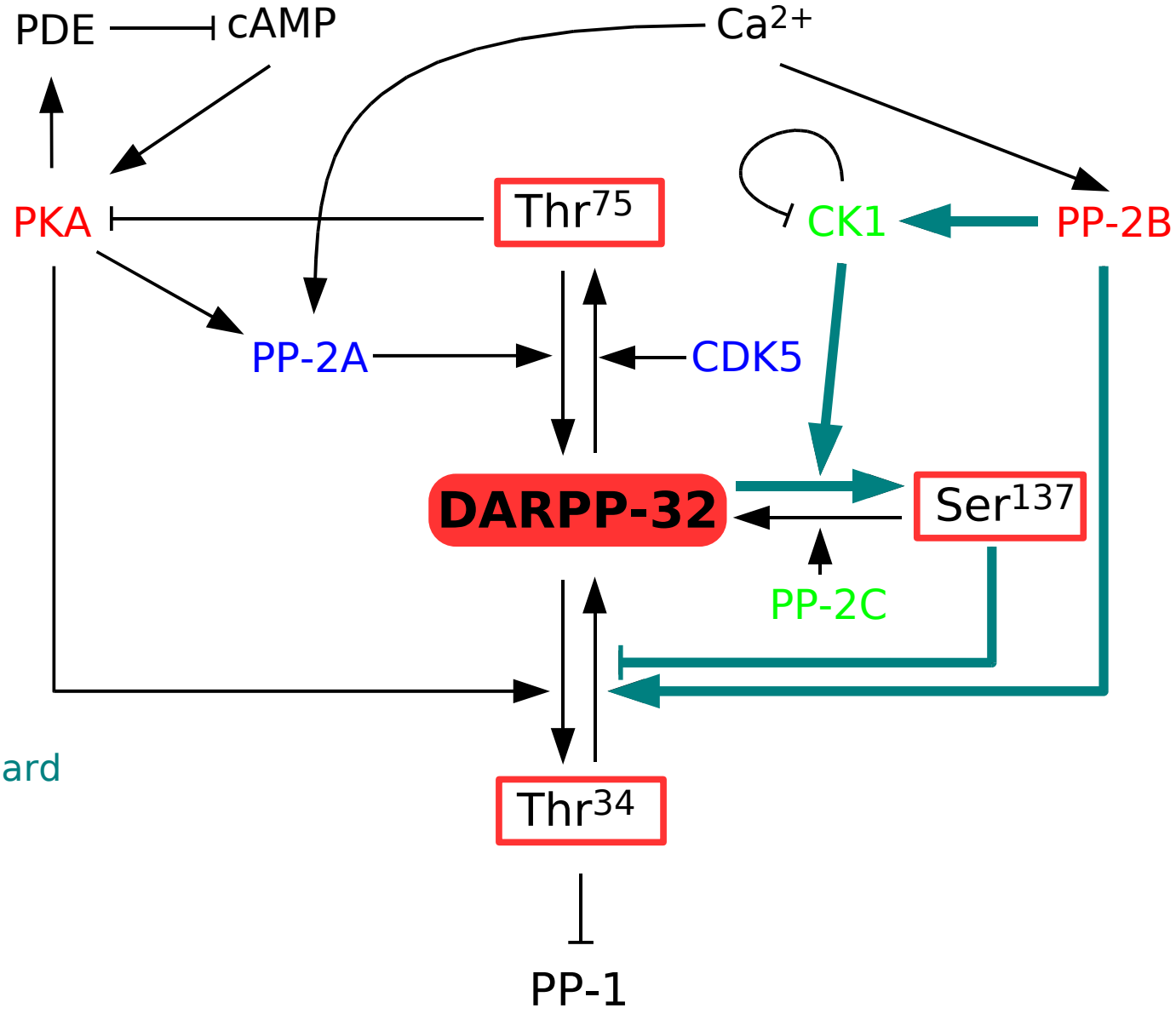
PP-2C

Thr^{34}

PP-1

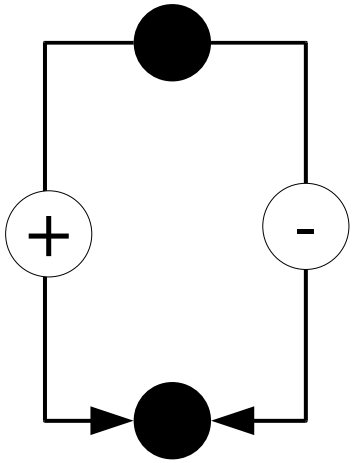
All the cybernetics in one system

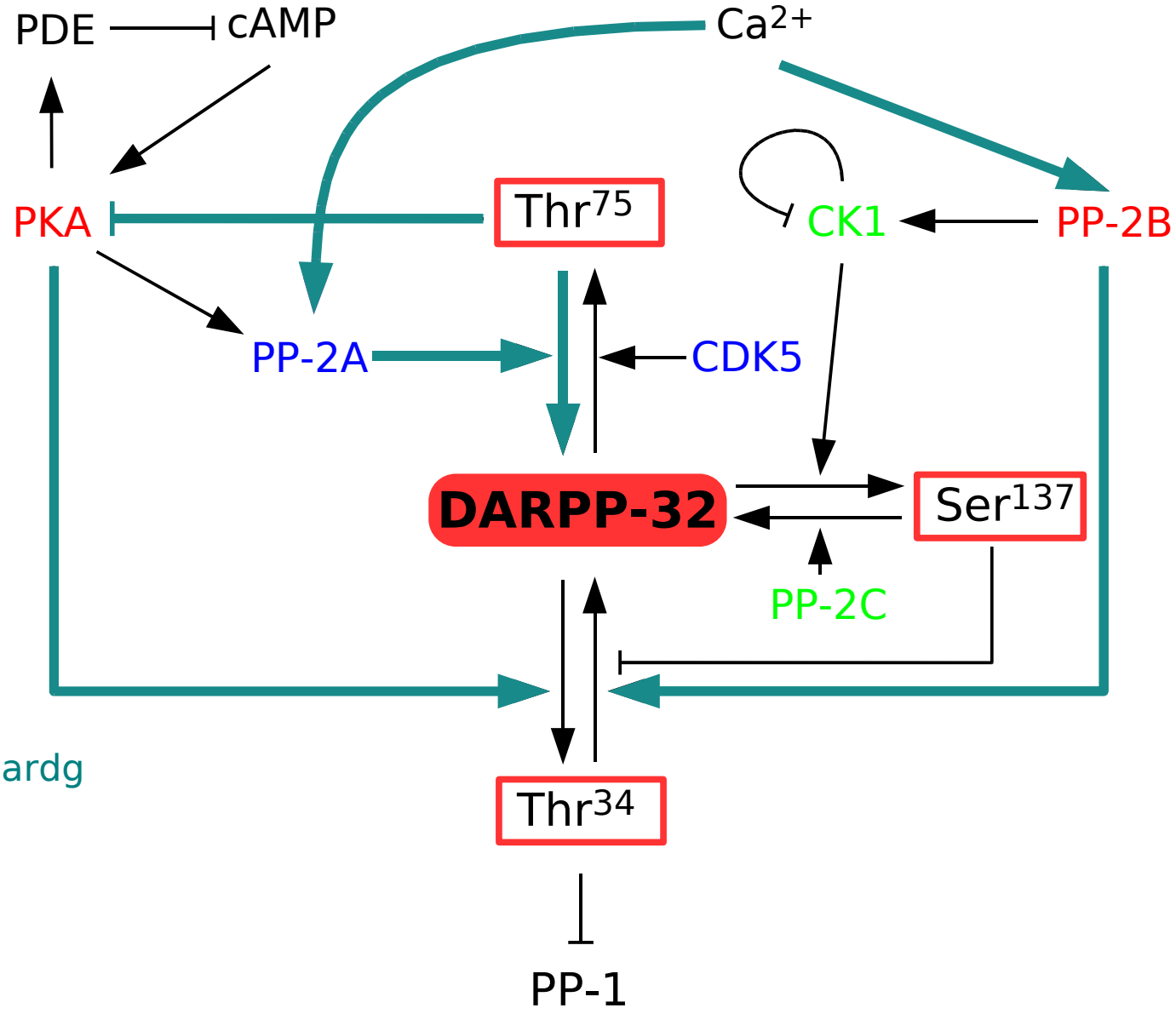




incoherent feedforward

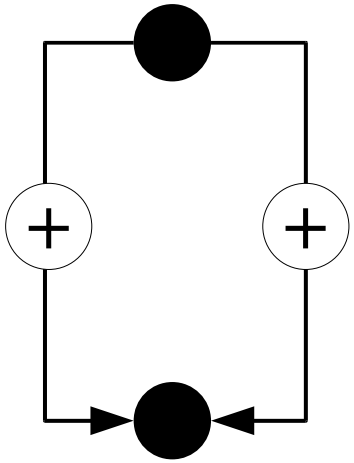
All the cybernetics in one system

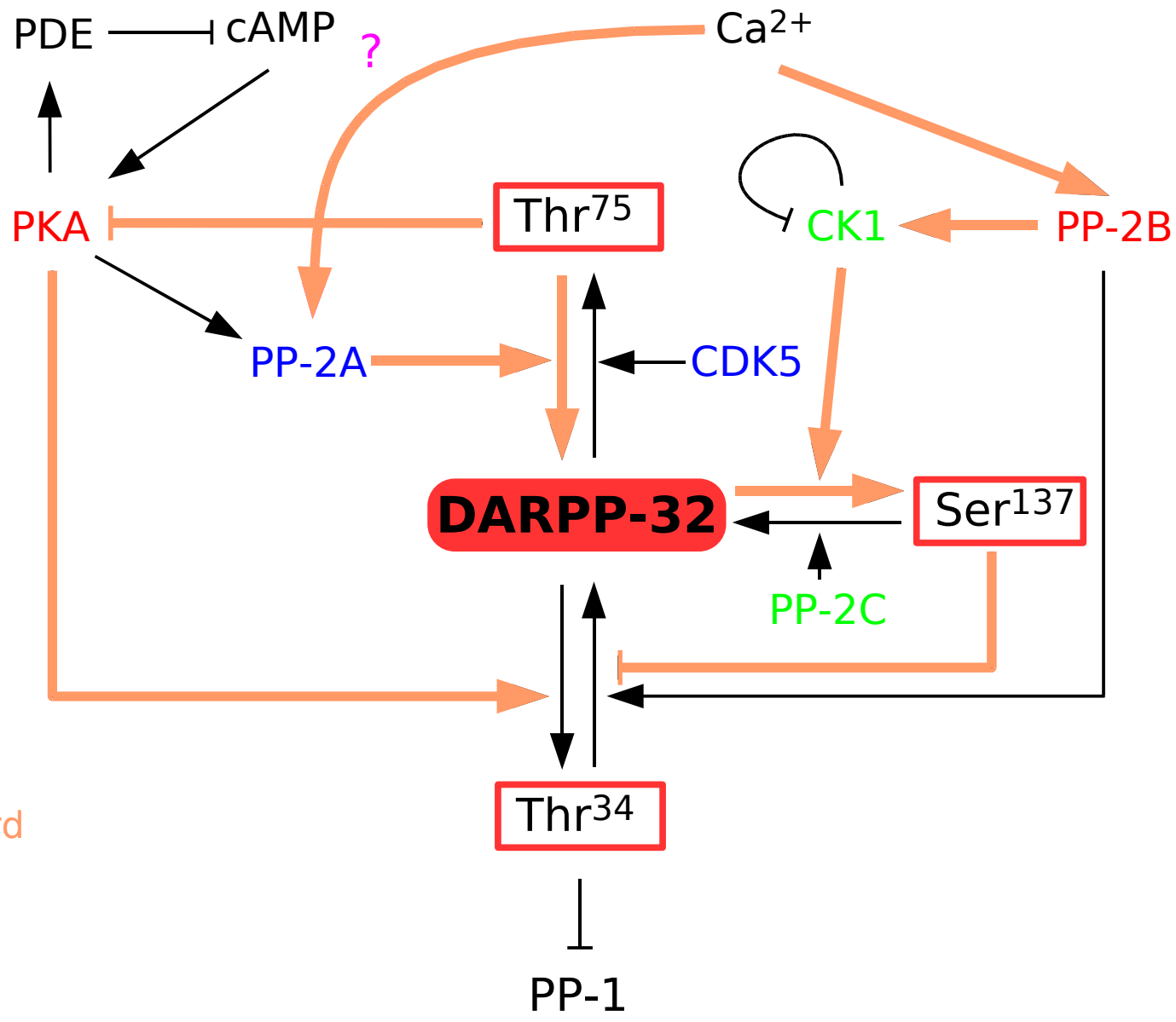




incoherent feedforwardg

All the cybernetics in one system



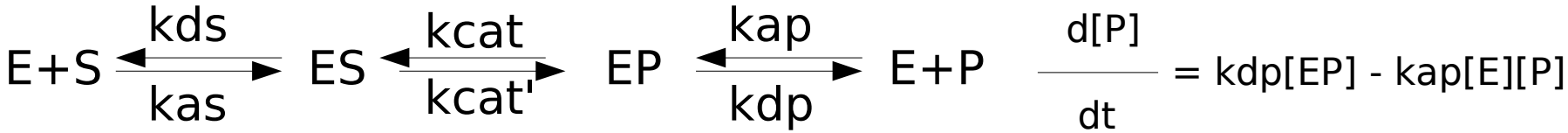


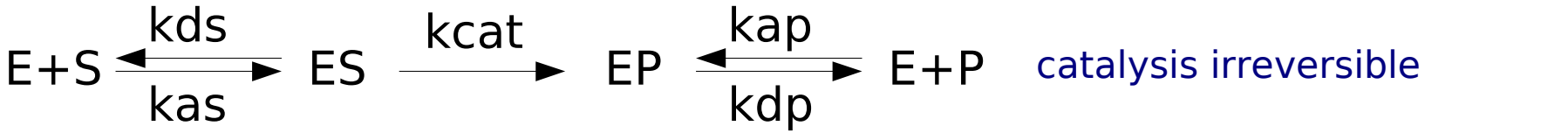
coherent feedforward

Choose the right formalism

$$E + S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \underset{kcat'}{\overset{kcat}{\rightleftharpoons}} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E + P \qquad \frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

Choose the right formalism





catalysis irreversible

Choose the right formalism

$$E+S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \underset{kcat'}{\overset{kcat}{\rightleftharpoons}} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E+P \qquad \frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

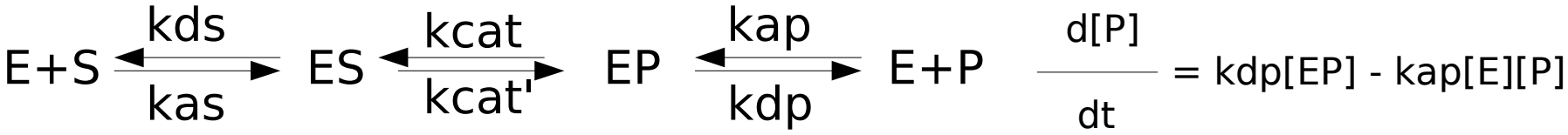
$$E+S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \xrightarrow{kcat} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E+P$$

catalysis irreversible

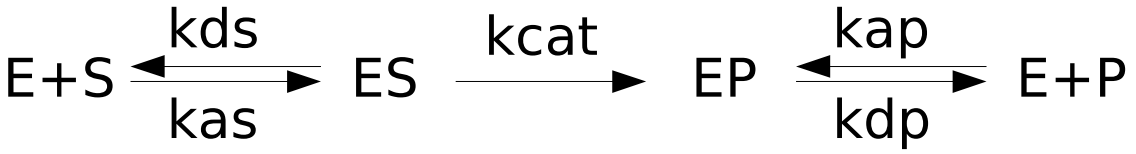
$$E+S \underset{ksd}{\overset{ksa}{\rightleftharpoons}} ES \xrightarrow{kcat} E+P$$

product is consumed before rebinding

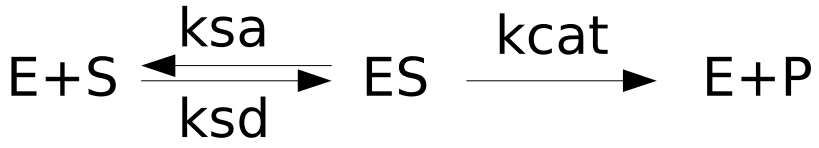
Choose the right formalism



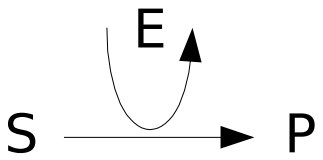
$$\frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$



catalysis irreversible



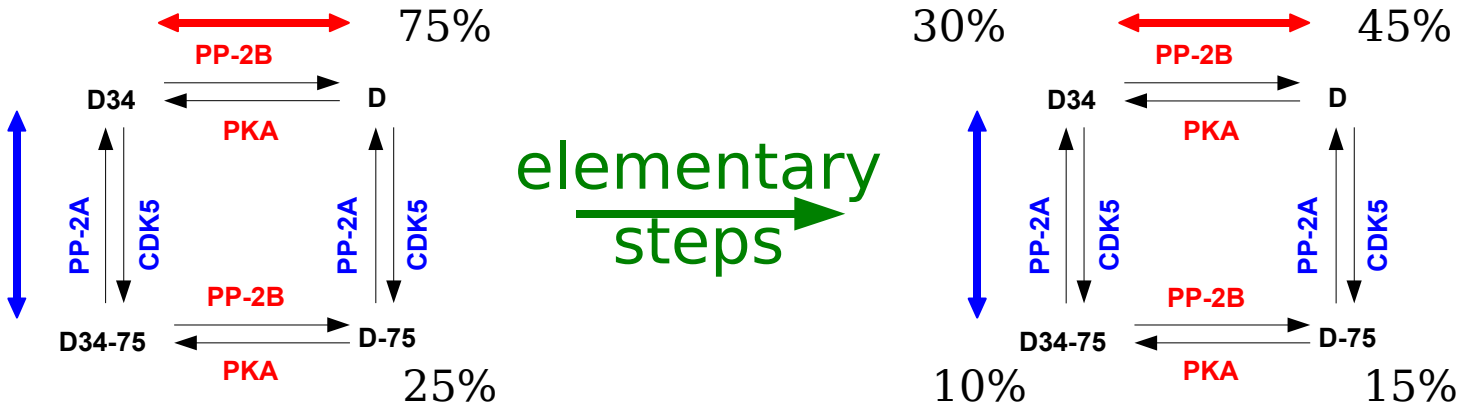
product is consumed before rebinding



steady-state

$$\frac{d[P]}{dt} = \frac{[E]\,kcat}{1 + \frac{Km}{[S]}}$$

Effect of the wrong choice



1) unbalance; 2) $\Sigma \neq 100\%$!!!

Briggs-Haldane

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E + P$$

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0$$

$$[ES] = \frac{k_1[E][S]}{k_{-1} + k_2}$$

$$K_m = \frac{k_{-1} + k_2}{k_1}$$

$$[ES] = \frac{[E][S]}{K_m}$$

$$\frac{d[P]}{dt} = k_2[ES]$$

$$[E]=[E_0]-[ES]$$

$$[ES] = \frac{([E_0] - [ES])[S]}{K_m}$$

$$[ES]\frac{K_m}{[S]} = [E_0] - [ES]$$

$$[ES](1 + \frac{K_m}{[S]}) = [E_0]$$

$$[ES] = [E_0]\frac{1}{1 + \frac{K_m}{[S]}}$$

$$\frac{d[P]}{dt} = k_2[E_0]\frac{[S]}{K_m + [S]} = V_{max}\frac{[S]}{K_m + [S]}$$

Briggs-Haldane

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E + P$$

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0$$

steady-state!!!

$$[ES] = \frac{k_1[E][S]}{k_{-1} + k_2}$$

$$K_m = \frac{k_{-1} + k_2}{k_1}$$

$$[ES] = \frac{[E][S]}{K_m}$$

$$\frac{d[P]}{dt} = k_2[ES]$$

$$[E]=[E_0]-[ES]$$

$$[ES] = \frac{([E_0] - [ES])[S]}{K_m}$$

$$[ES]\frac{K_m}{[S]} = [E_0] - [ES]$$

$$[ES](1 + \frac{K_m}{[S]}) = [E_0]$$

$$[ES] = [E_0]\frac{1}{1 + \frac{K_m}{[S]}}$$

$$\frac{d[P]}{dt} = k_2[E_0]\frac{[S]}{K_m + [S]} = V_{max}\frac{[S]}{K_m + [S]}$$

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

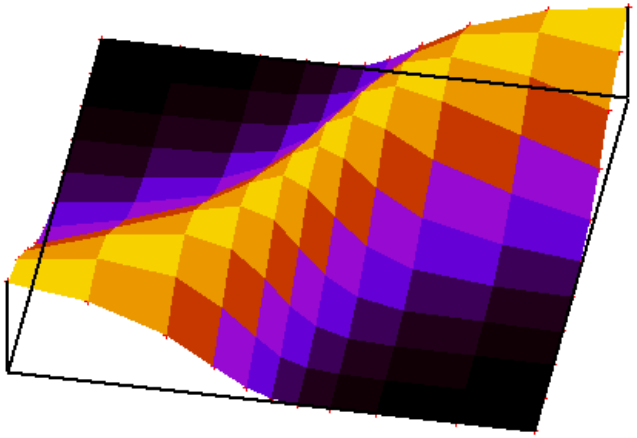
- D + CK1 ⇔ D_CK1 → D137 + CK1
- D137 + PP2C ⇔ D137_PP2C → D + PP2C
- D75 + CK1 ⇔ D75_CK1 → D75-137 + CK1
- D75-137 + PP2C ⇔ D75-137_PP2C → D75 + PP2C
- D34 + CK1 ⇔ D34_CK1 → D34-137 + CK1
- D34-75 + PP2C ⇔ D34-75_PP2C → D75 + PP2C
- D34-75 + CK1 ⇔ D34-75_CK1 → D34-75-137 + CK1
- D34-75-137 + PP2C ⇔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

79 species, 151 reactions

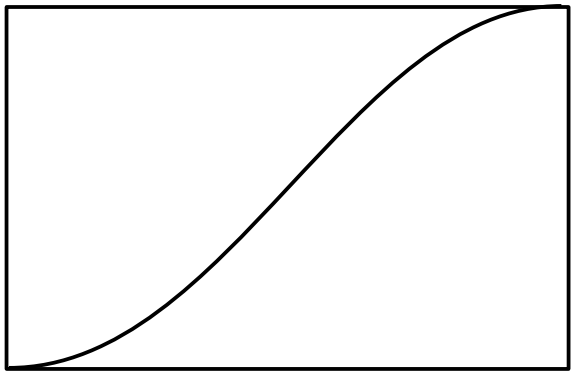
- D + PKA ⇔ D_PKA → D34 + PKA
- D34 + PP2B ⇔ D34_PP2B → D + PP2B
- D75 + PKA ⇔ D75_PKA → D34-75 + PKA
- D34-75 + PP2B ⇔ D34-75_PP2B → D75 + PP2B
- D137 + PKA ⇔ D137_PKA → D34-137 + PKA
- D34-137 + PP2B ⇔ D34-135_PP2B → D137 + PP2B
- D75-137 + PKA ⇔ D75-137_PKA → D34-75-137 + PKA
- D34-75-137 + PP2B ⇔ 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

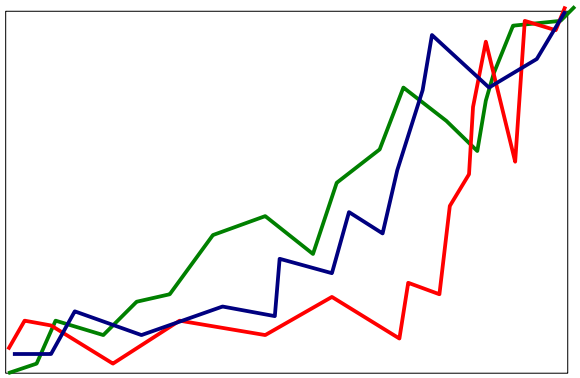
Different modelling approaches



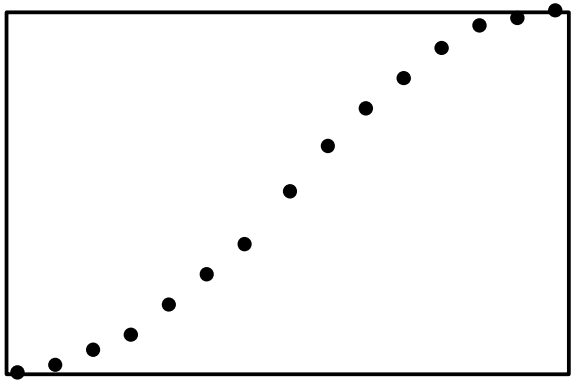
Grand Probability function: P(X,t)



typologic view of the world: (X)=f(t)



stochastic approach: P(X,t)/(X',t-1)



deterministic approach: (X,t)=f(X',t-1)

Mathematical model

Mathematical model

$$d[D]/dt = -k_1[CDK5][D] + k_2[D\_CDK5]$$

$$d[D\text{-}75P]/dt = +k_3[D\_CDK5]$$

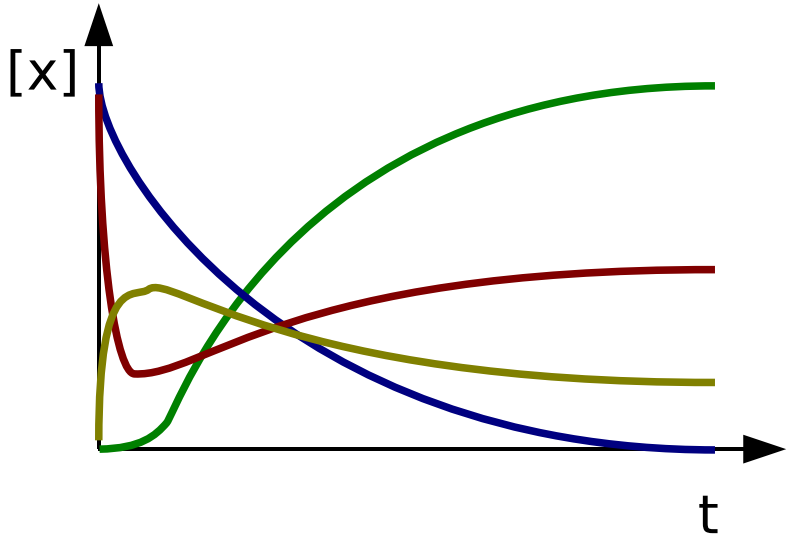
$$d[CDK5]/dt = -k_1[CDK5][D] + k_2[D\_CDK5] + k_3[D\_CDK5]$$

$$d[D\_CDK5]/dt = +k_1[CDK5][S] - k_2[D\_CDK5] - k_3[D\_CDK5]$$

Mathematical model

$$D + CDK5 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} D\_CDK5 \xrightarrow{k_3} D\text{-}75P + CDK5$$

$$\begin{aligned}
d[D]/dt &= -k_1[CDK5][D] + k_2[D_CDK5] \\
d[D\text{-}75P]/dt &= + k_3[D_CDK5] \\
d[CDK5]/dt &= -k_1[CDK5][D] + k_2[D_CDK5] + k_3[D_CDK5] \\
d[D_CDK5]/dt &= +k_1[CDK5][S] - k_2[D_CDK5] - k_3[D_CDK5]
\end{aligned}$$

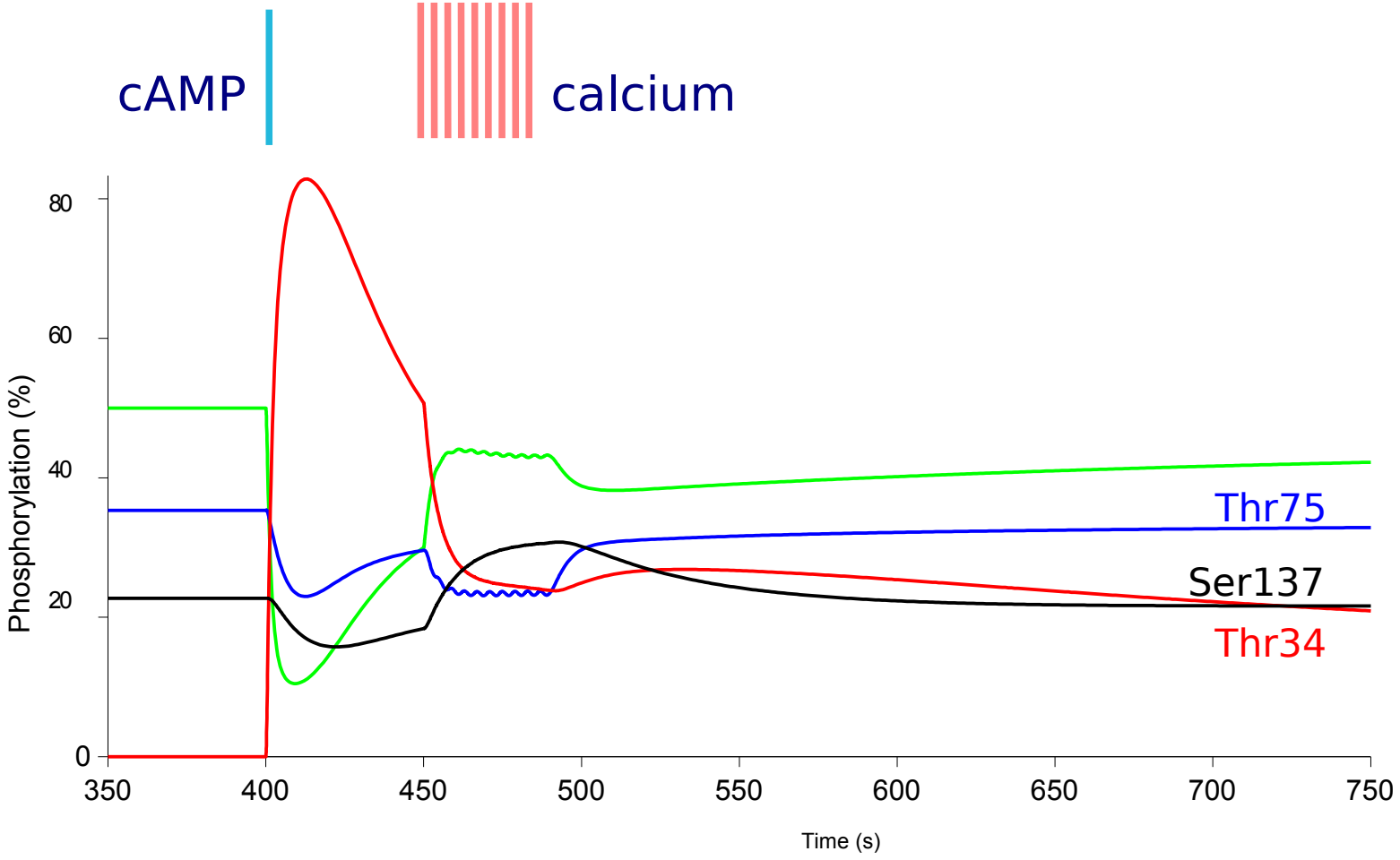


E-Cell3, a multi-algorithm simulator

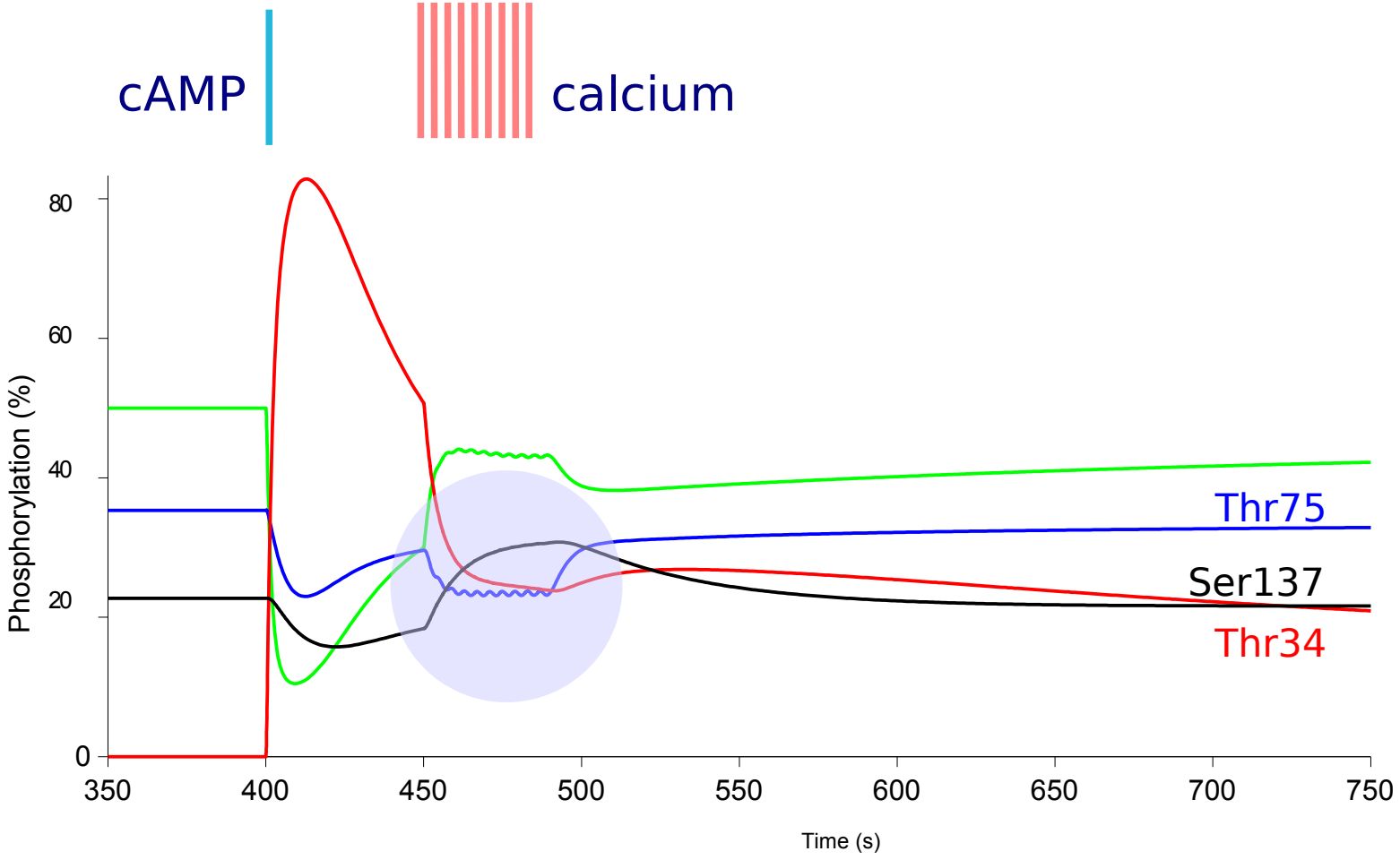
E-Cell

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

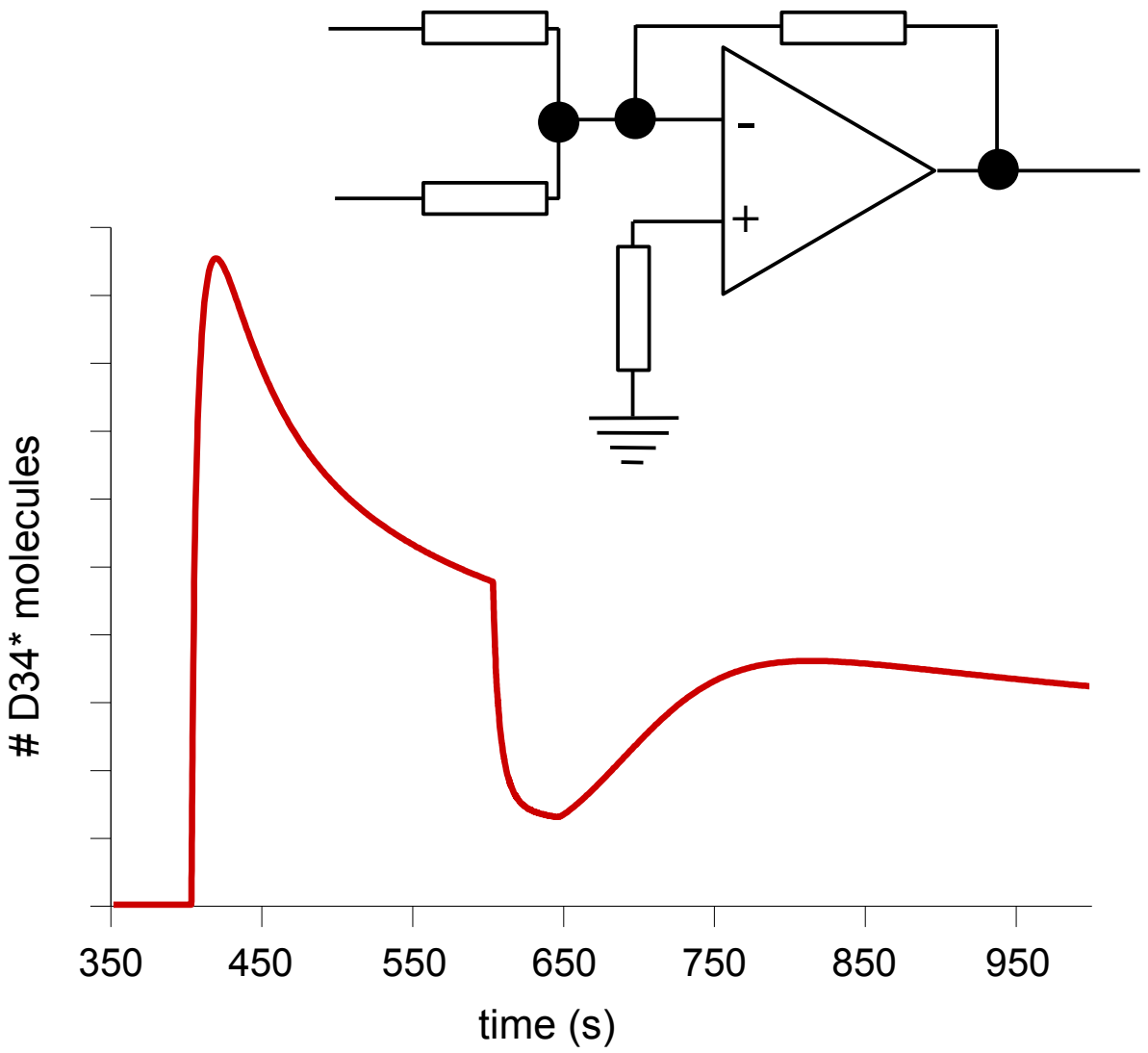
Dynamic simulations of DARPP-32 function



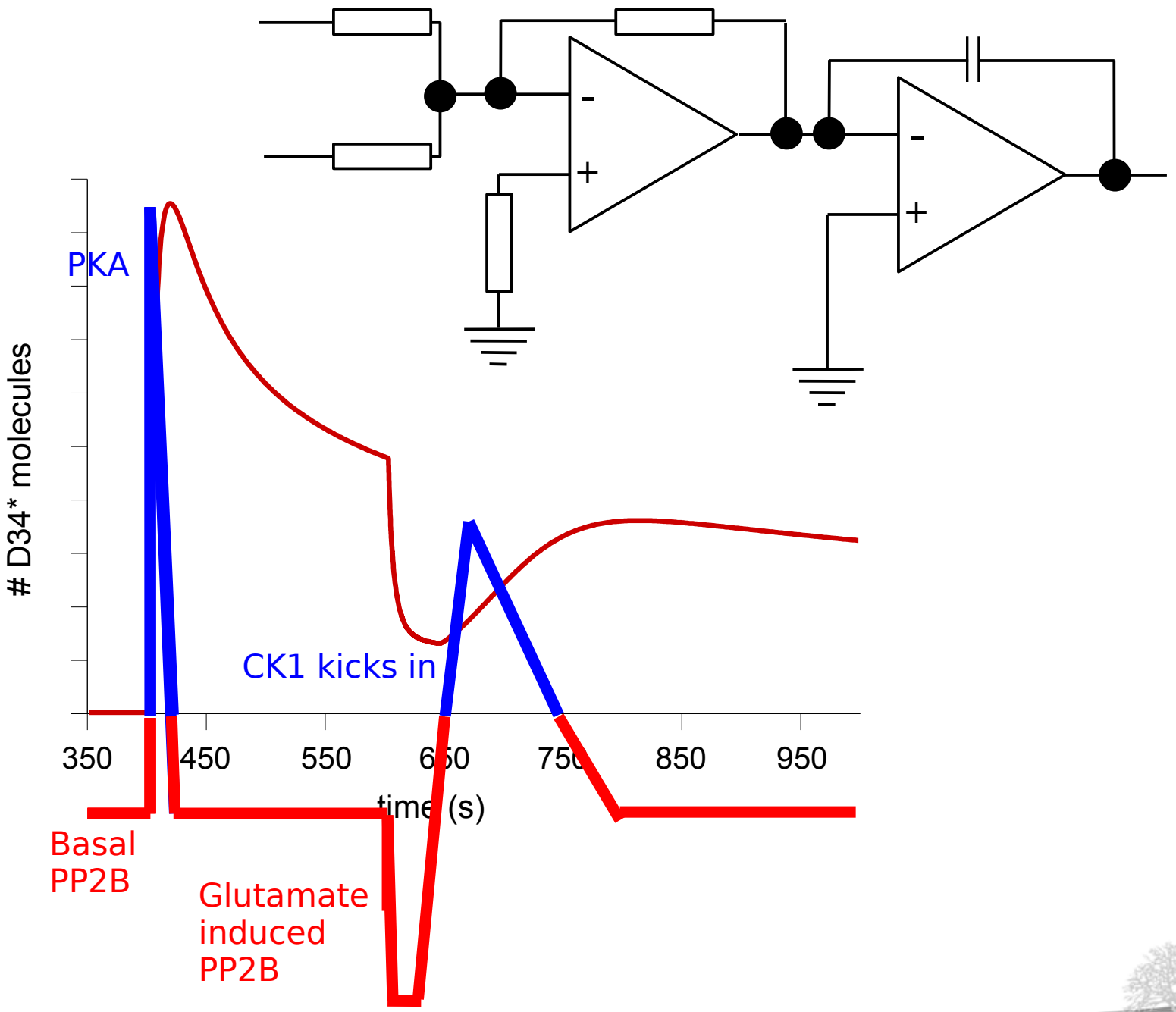
DARPP-32 is not a switch



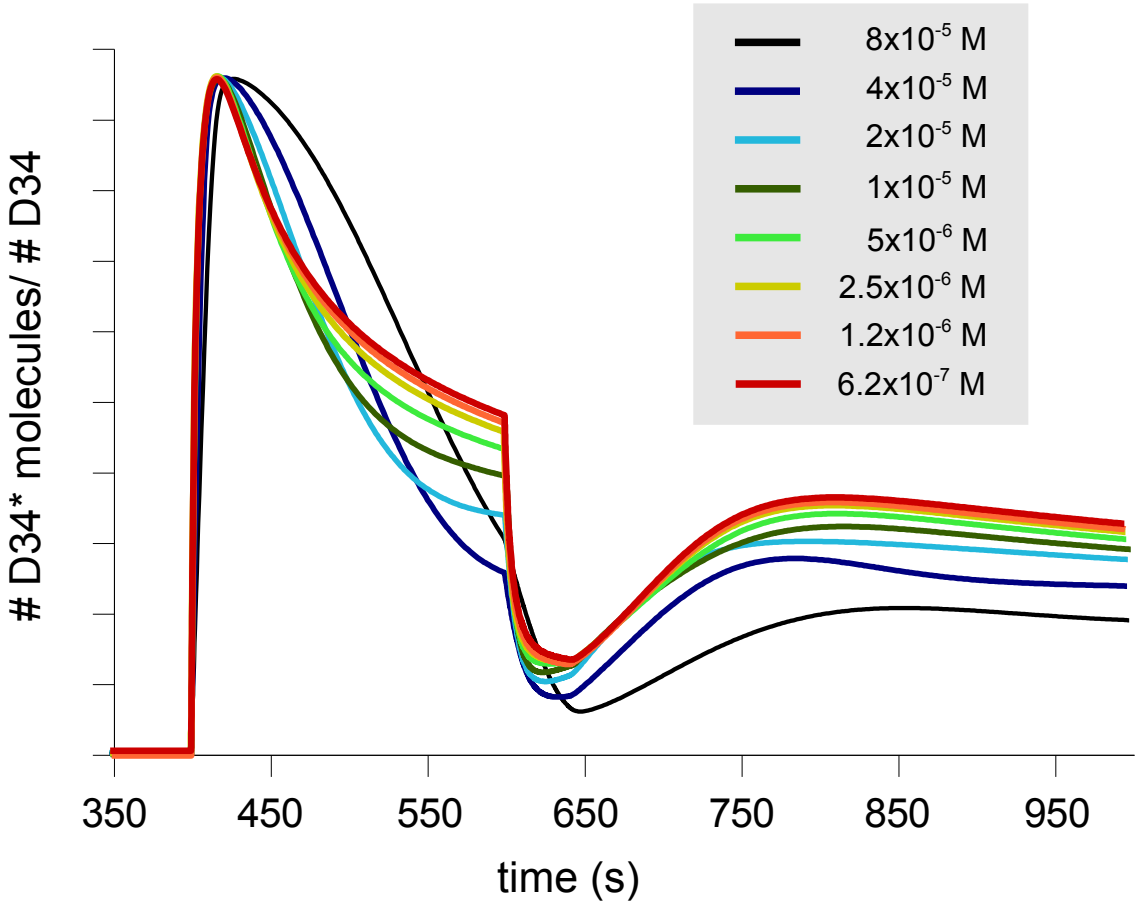
DARPP-32 is an integrator



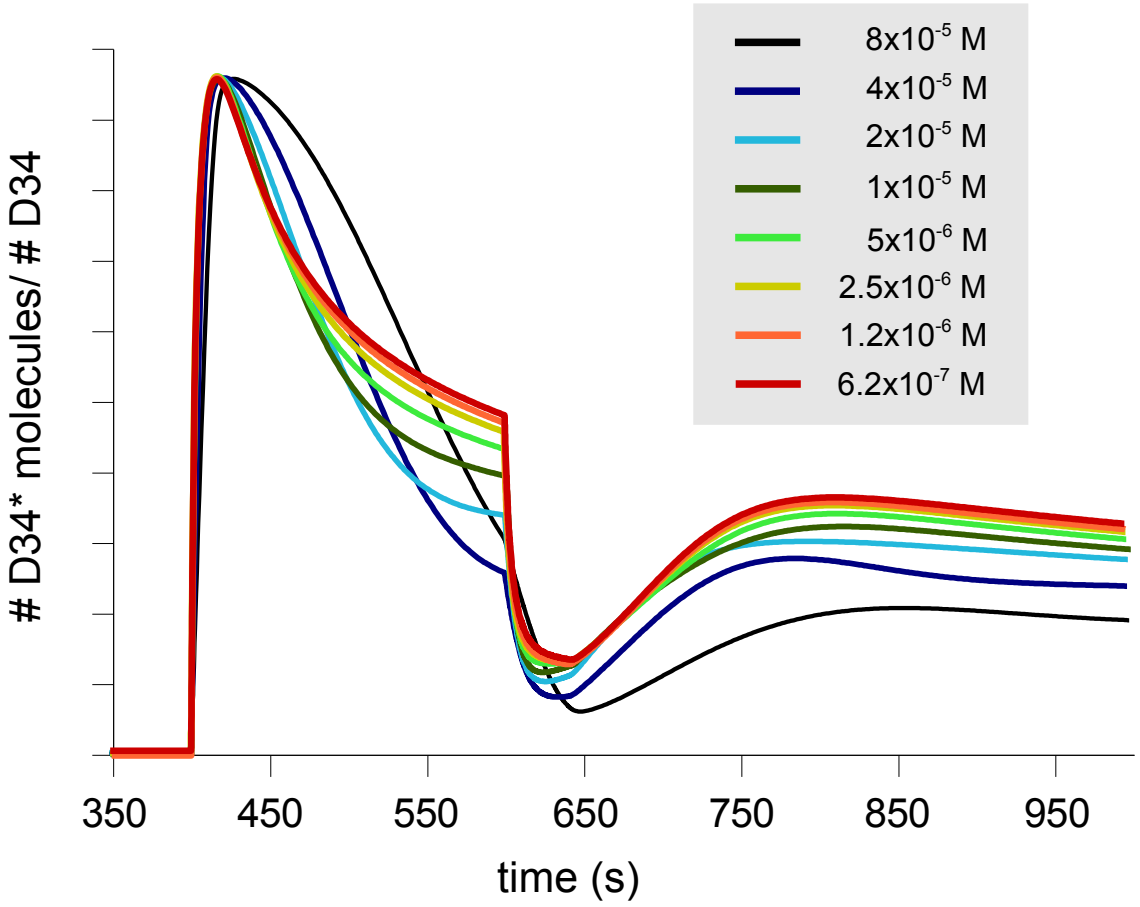
DARPP-32 is an integrator



DARPP-32 as a robust integrator

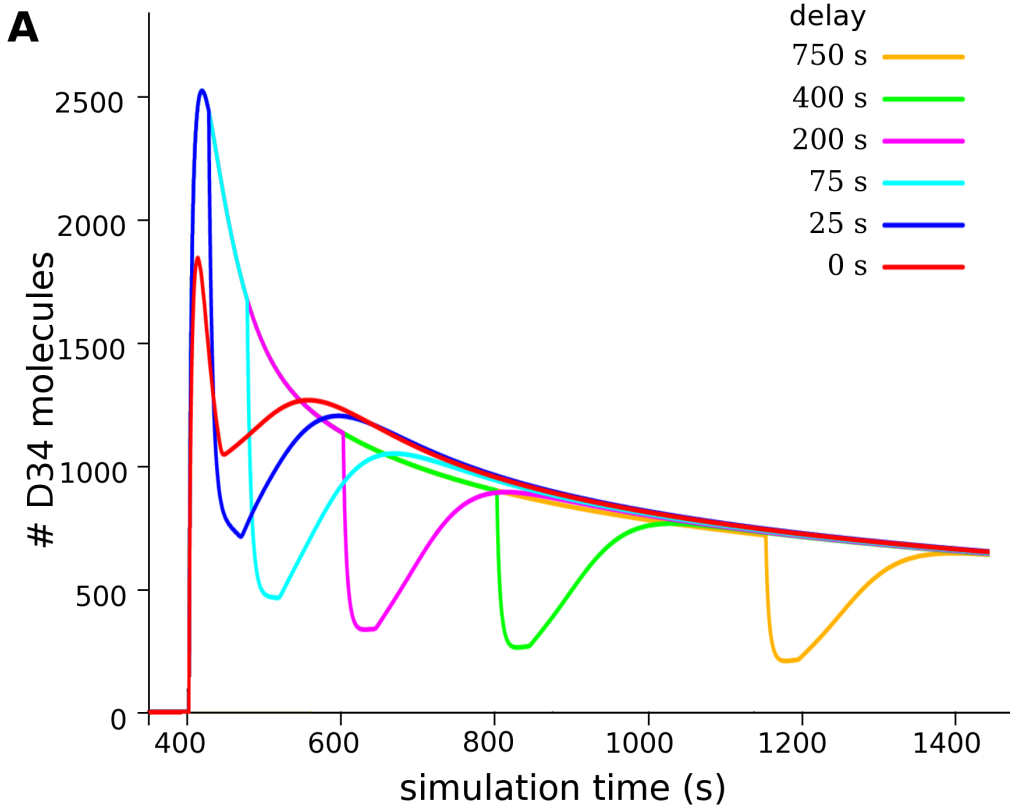


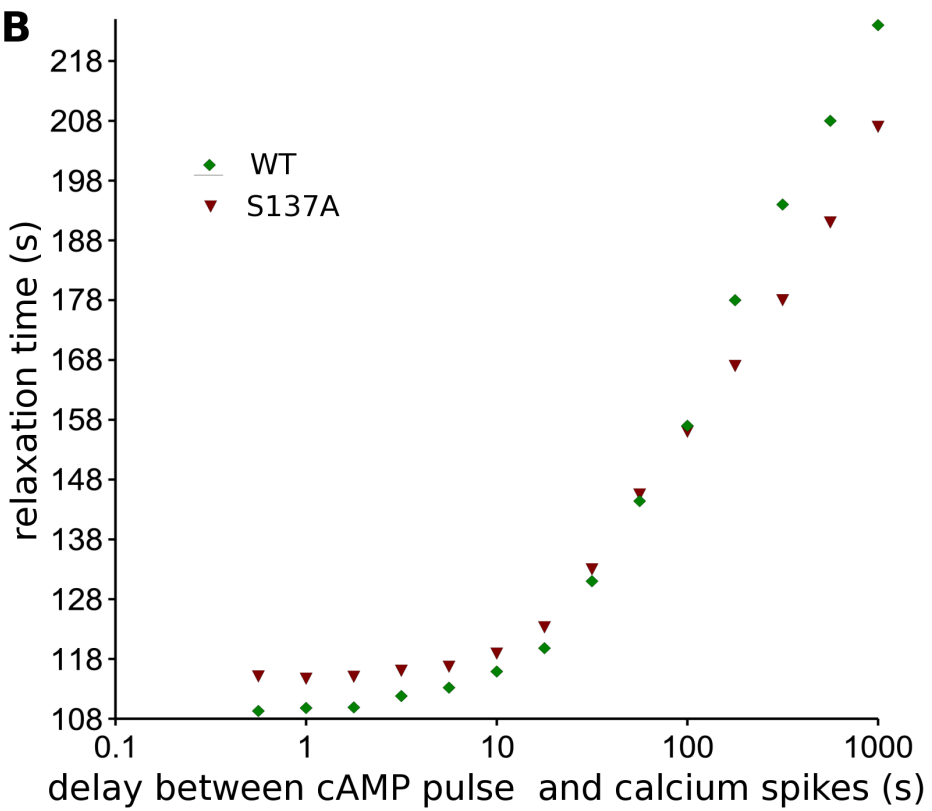
DARPP-32 as a robust integrator



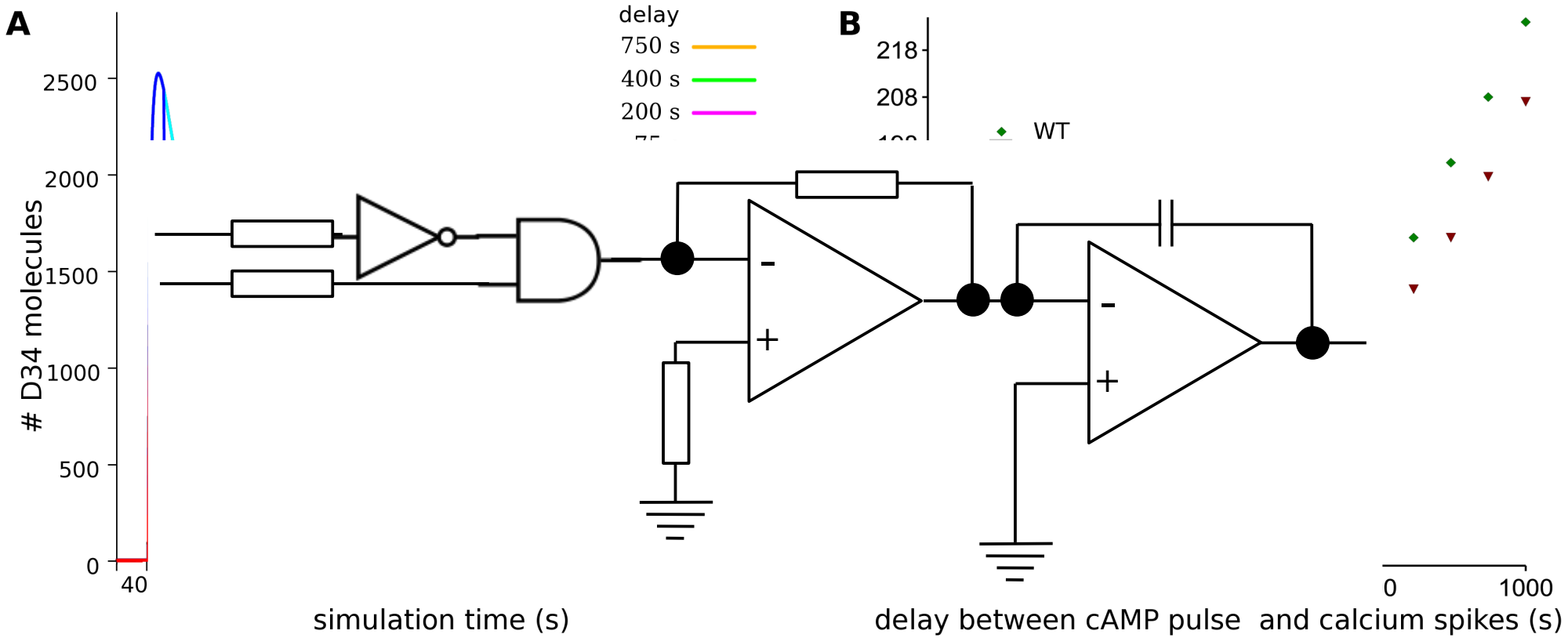
Heterozygous DARPP-32 +/- do not display phenotypes

Only an integrator?

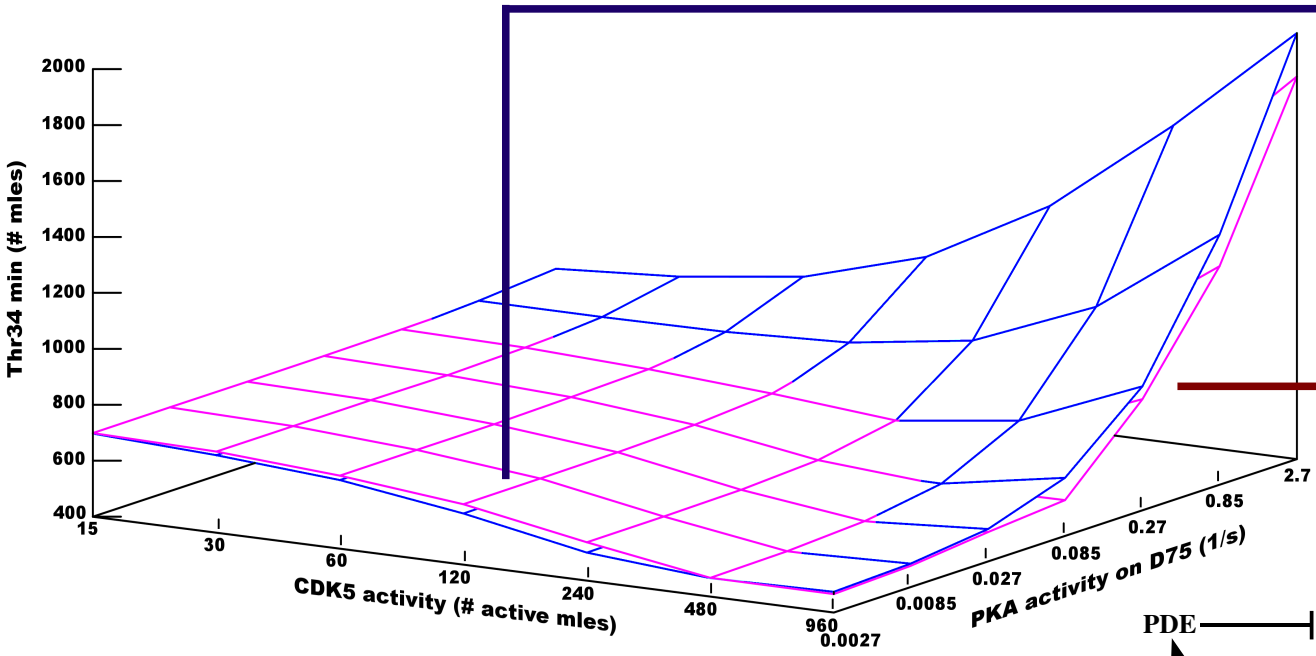


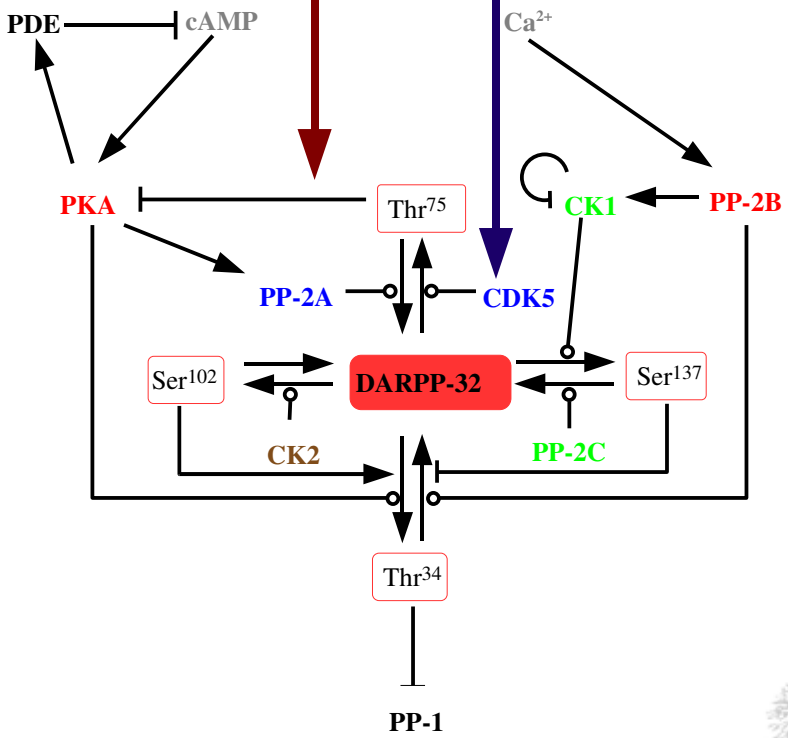


DARPP-32 is a coincidence detector

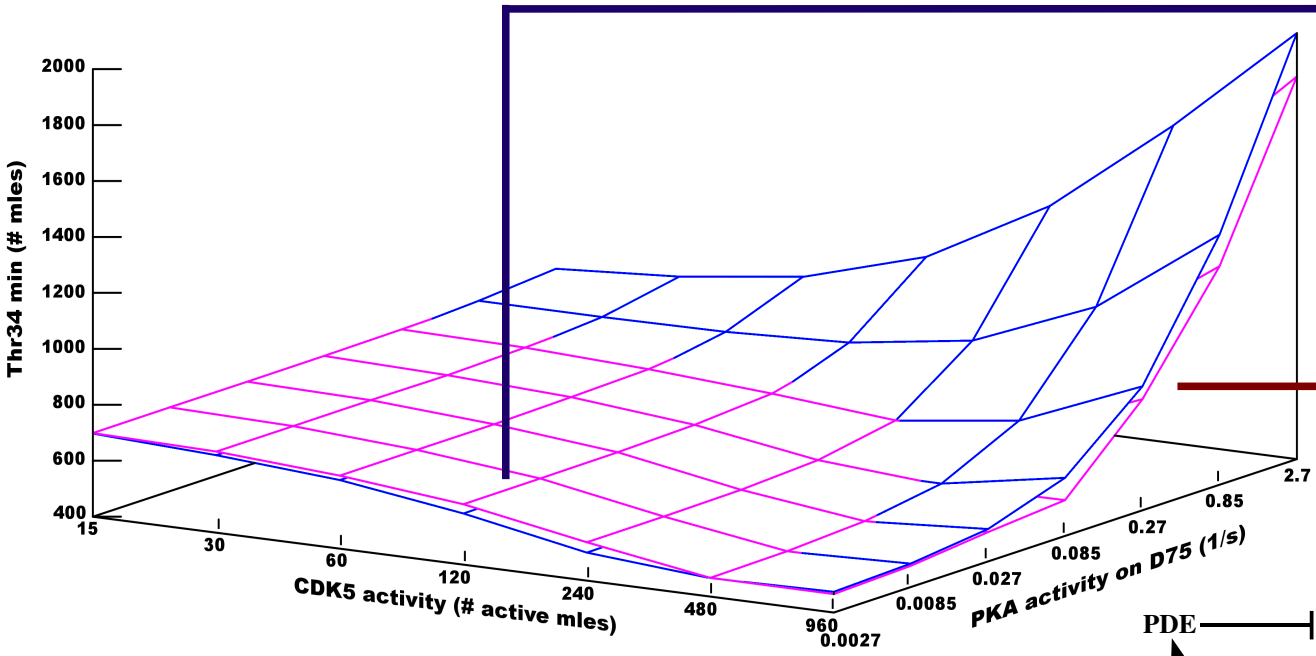


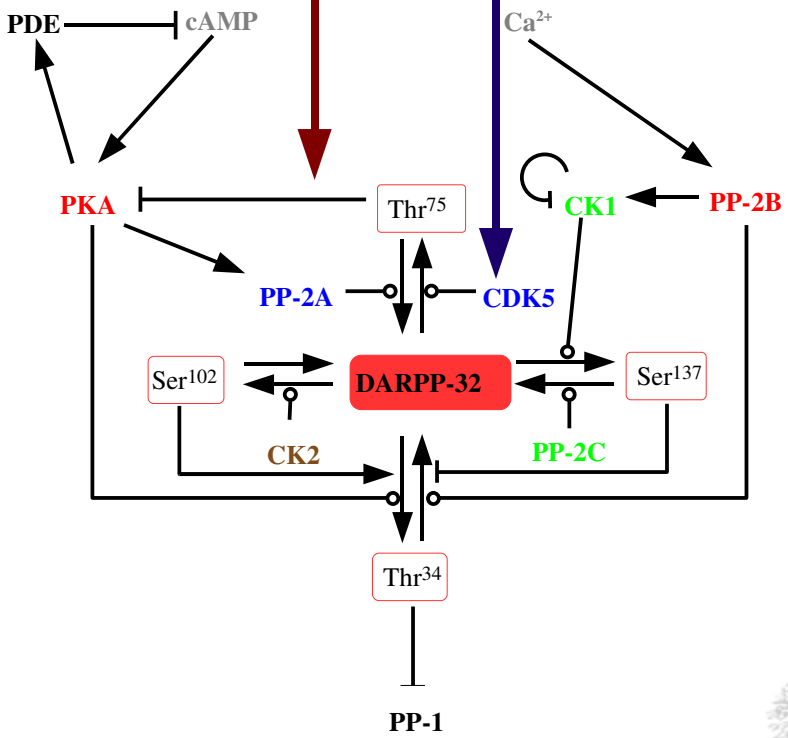
Some parameters are sensitive





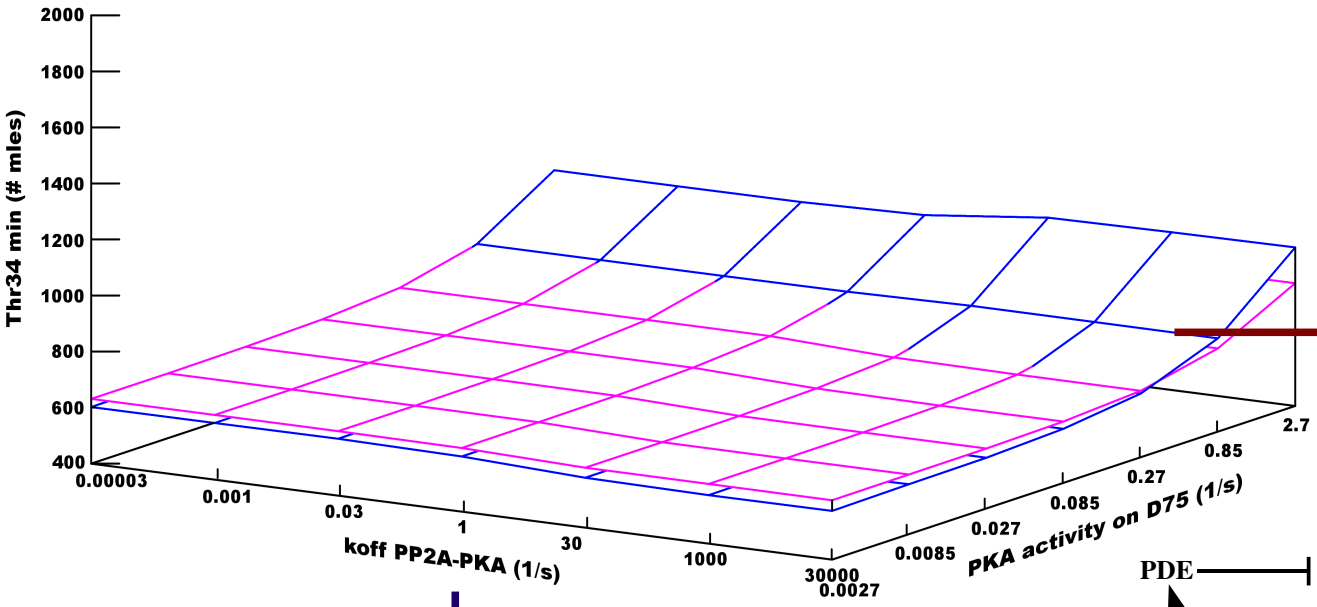
Some parameters are sensitive

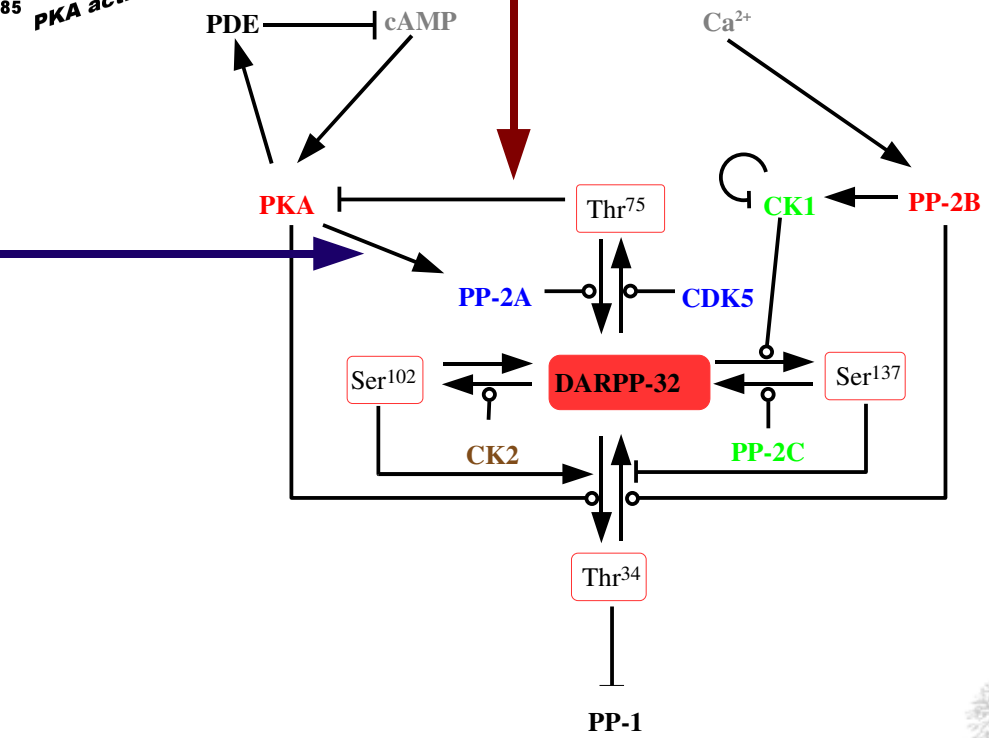




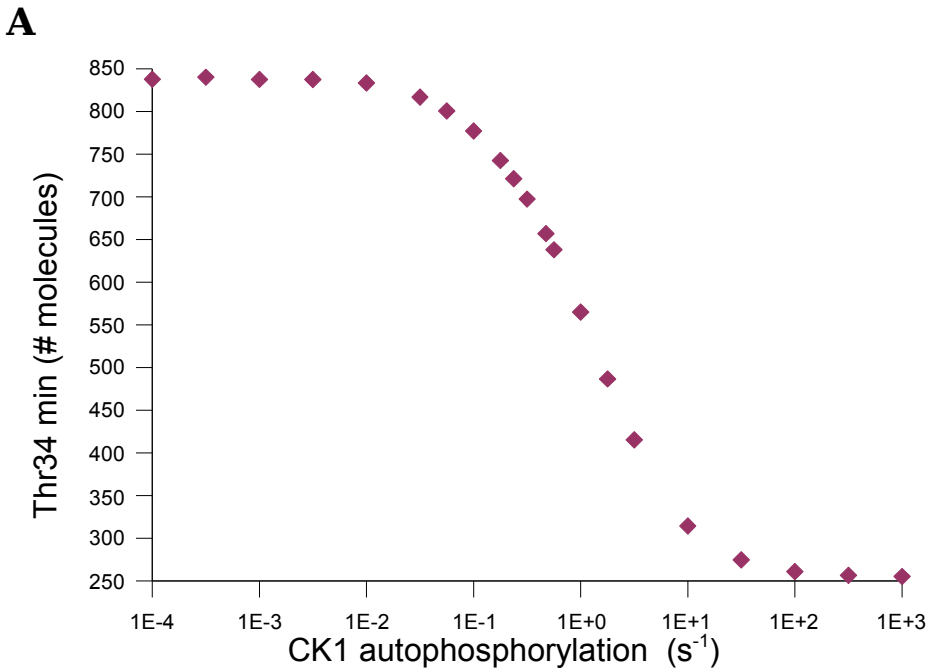
Takahashi et al (2005) Increased activity of cyclin-dependent kinase 5 leads to attenuation of cocaine-mediated dopamine signaling. PNAS 102: 1737–1742.

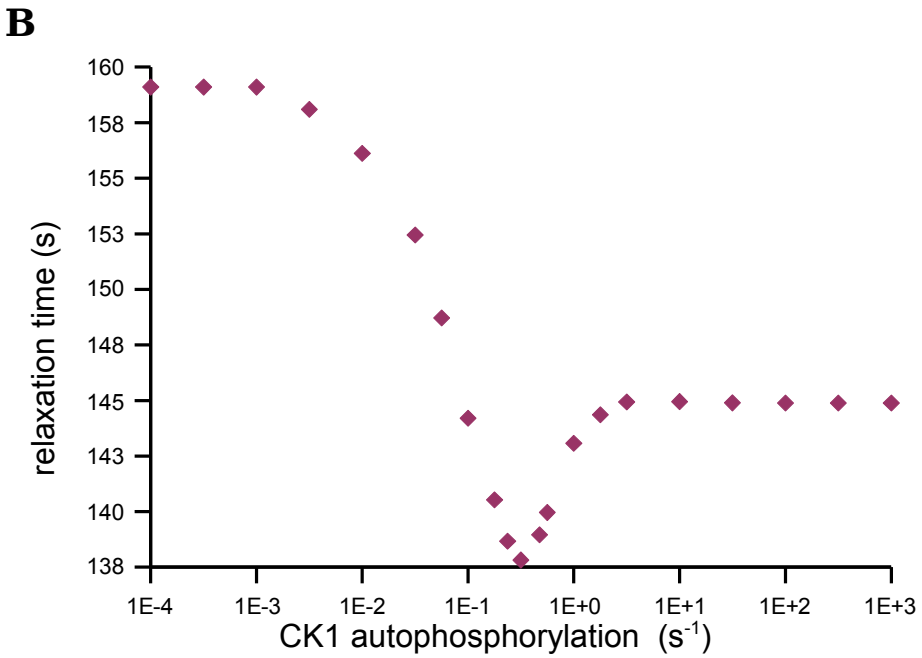
Some parameters are robust



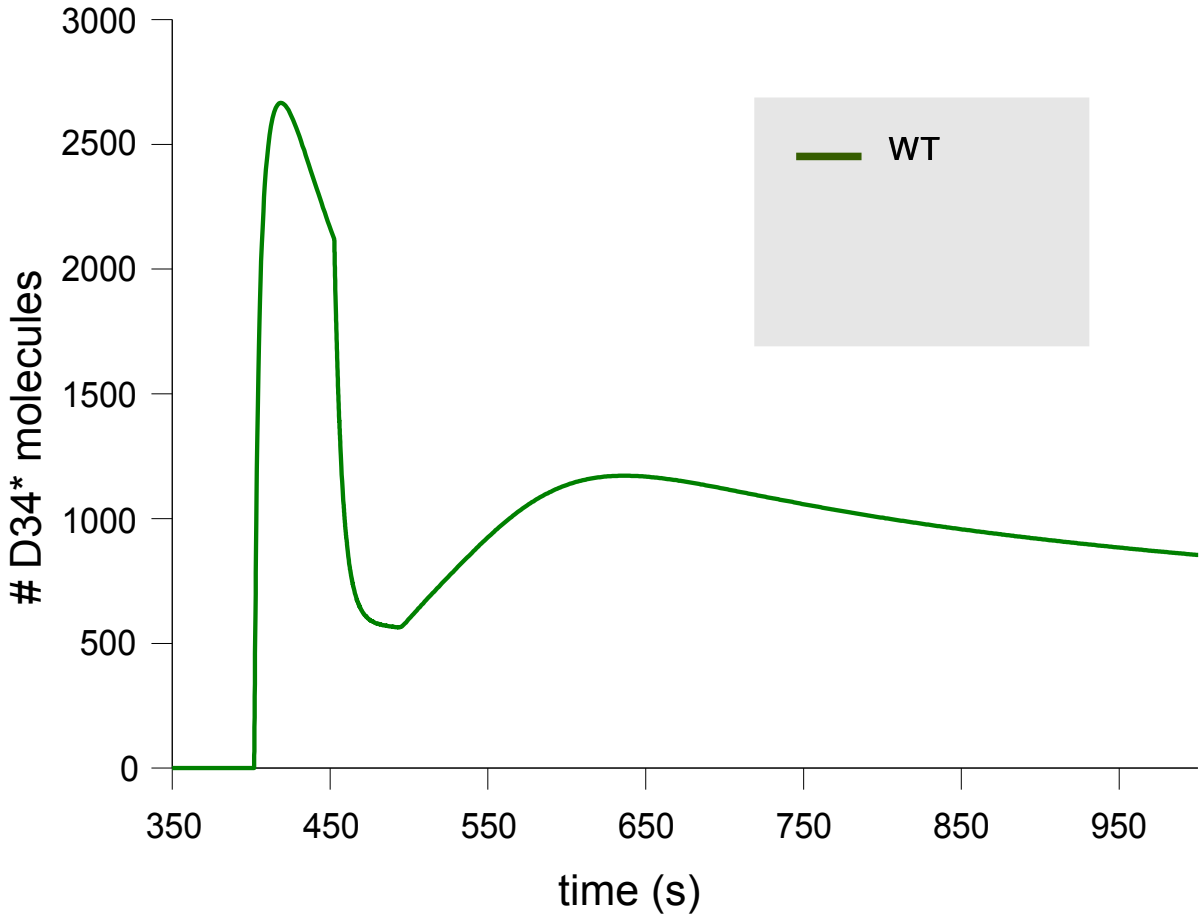


Optimality

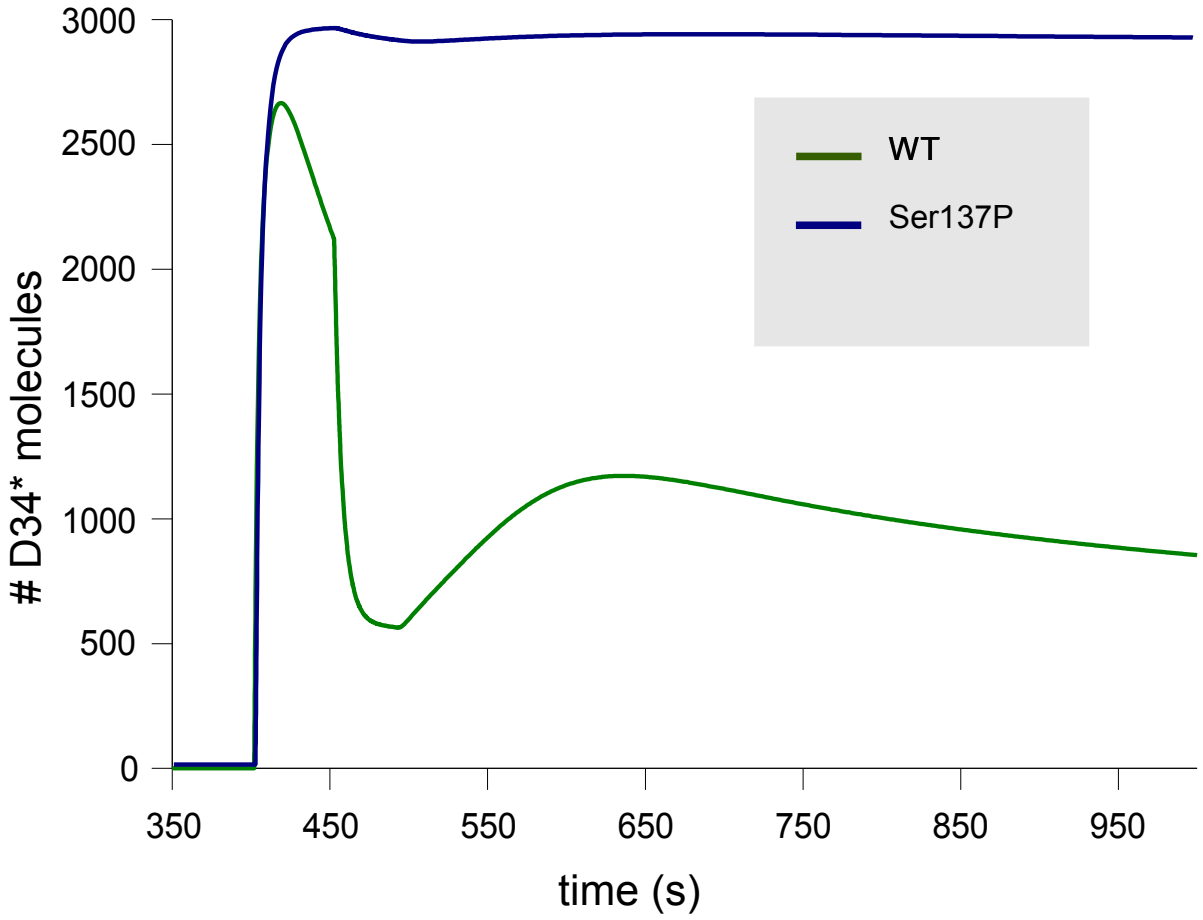

A
850
800
750
700
650
600
550
500
450
400
350
300
250
Thr34 min (# molecules)
1E-4
1E-3
1E-2
1E-1
1E+0
1E+1
1E+2
1E+3
CK1 autophosphorylation (s-1)


B
160
158
155
153
150
148
145
143
140
138
relaxation time (s)
1E-4
1E-3
1E-2
1E-1
1E+0
1E+1
1E+2
1E+3
CK1 autophosphorylation (s-1)

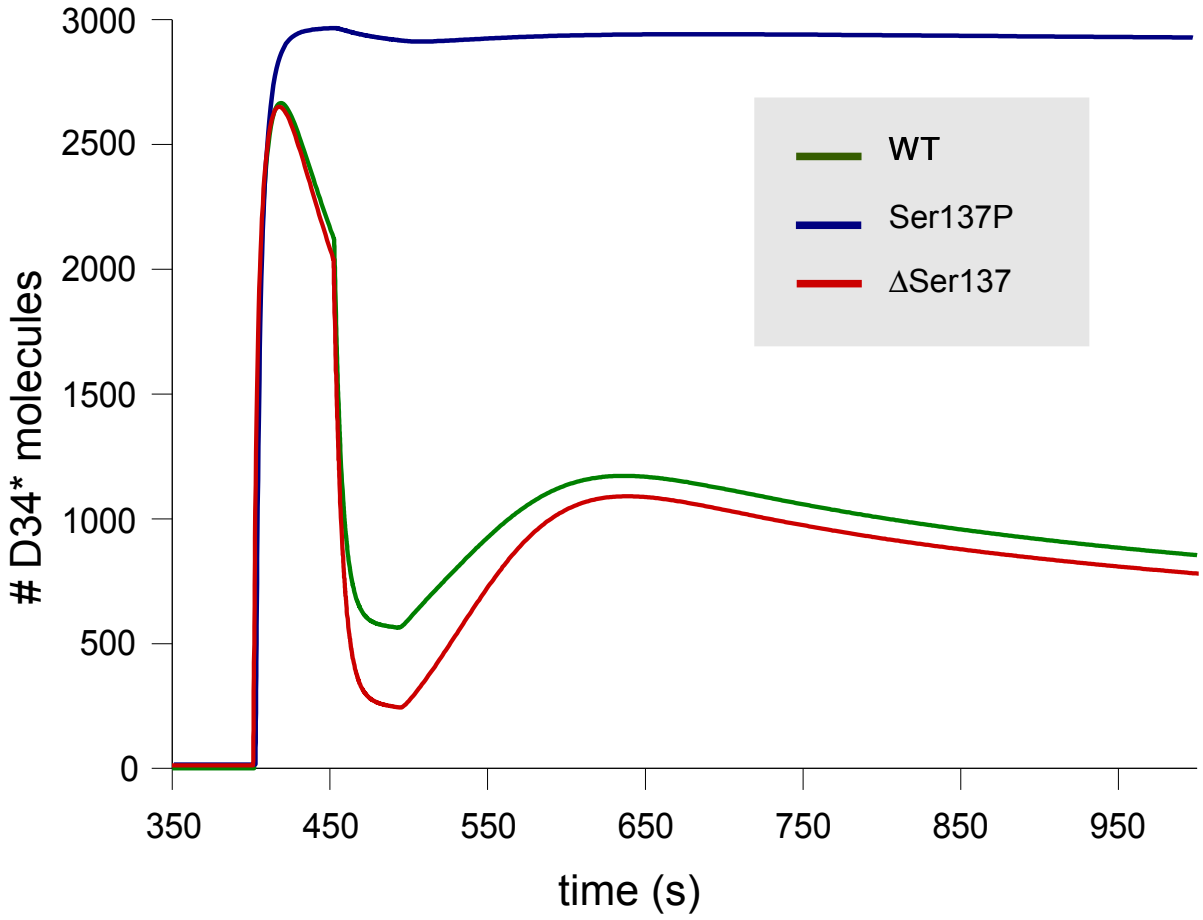
Mutation *in silico*



Mutation *in silico*



Mutation *in silico*



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

  Kouichi Takahashi

  Kazunari Kaizu

  Gabor Bereczki

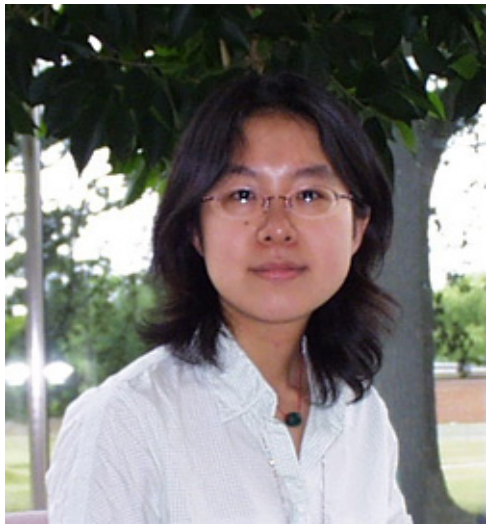
- Collaborators
  (INSERM U536, Paris)

  Jean-Antoine Girault

  Denis Herve

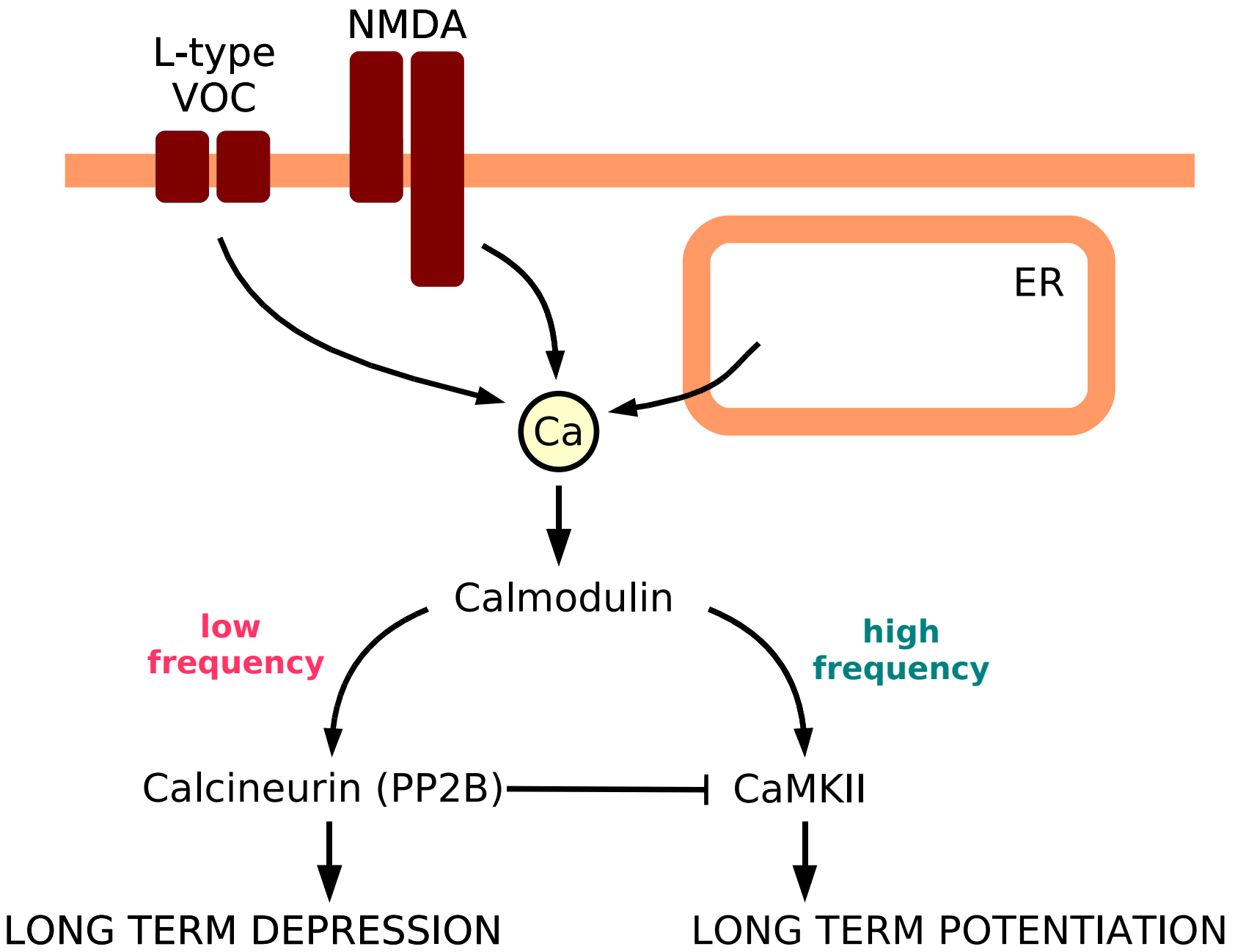
Eric Fernandez

Renaud Schiappa

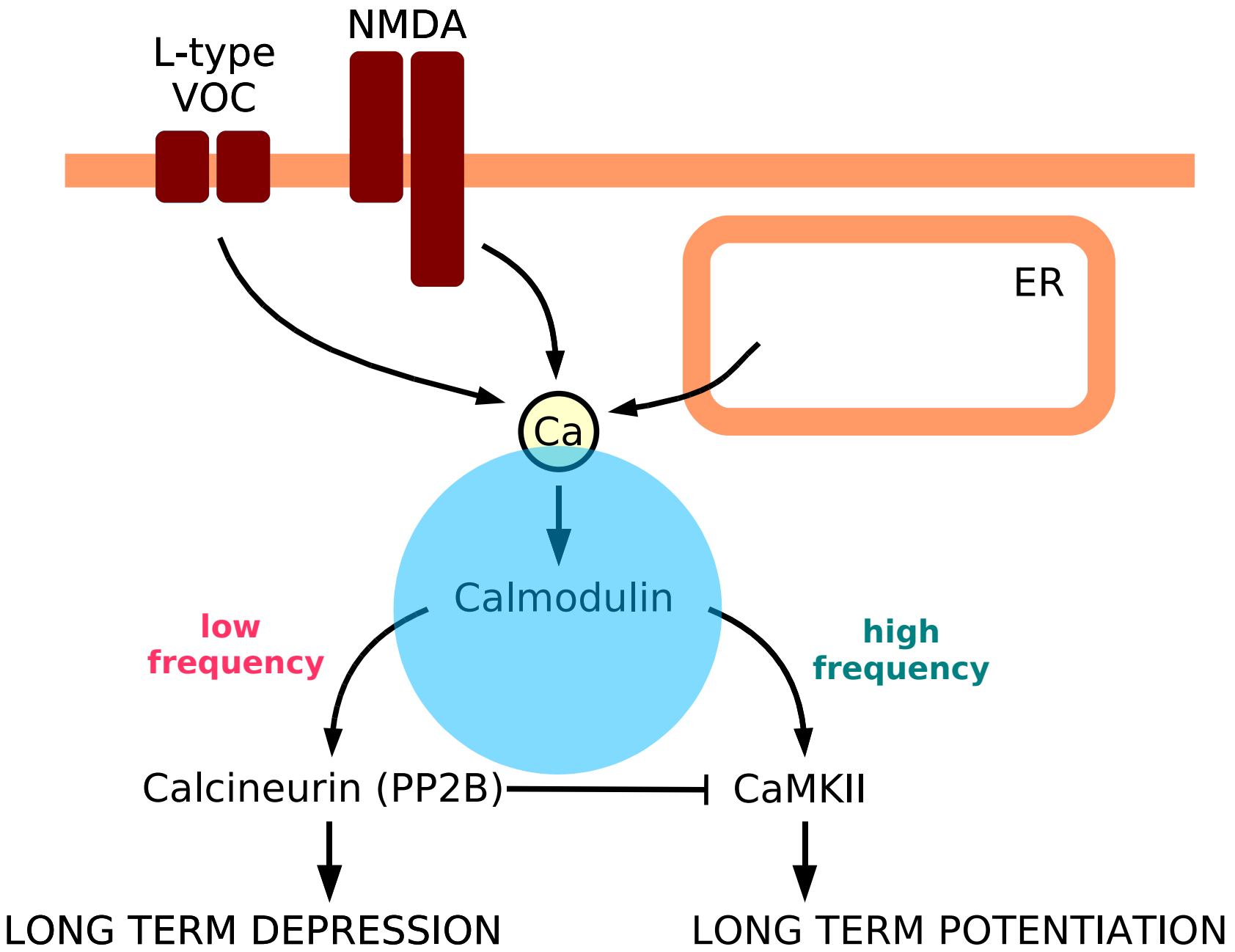


Lu Li

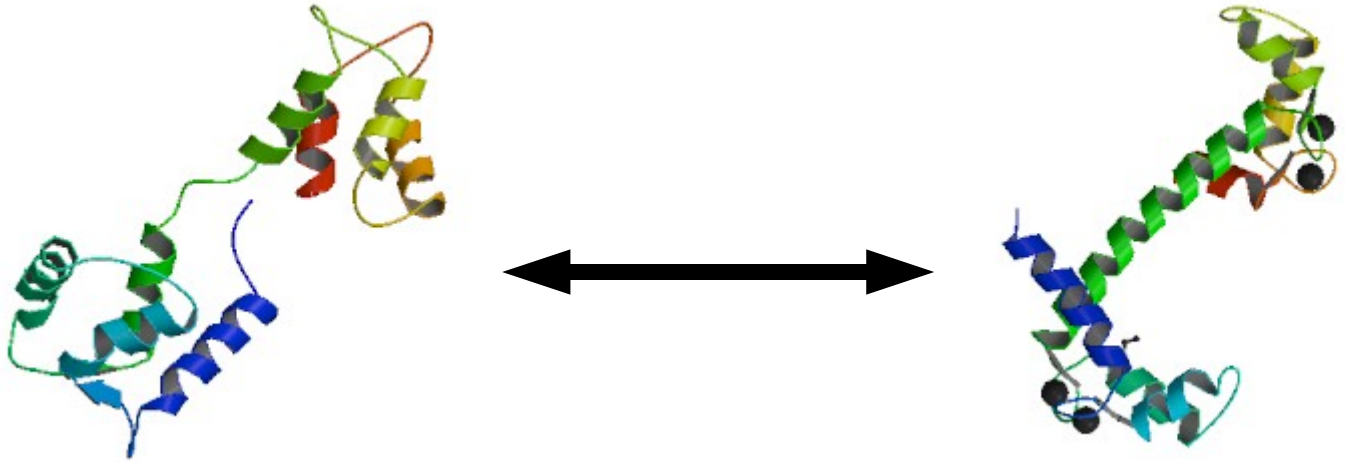
Calmodulin as a switch



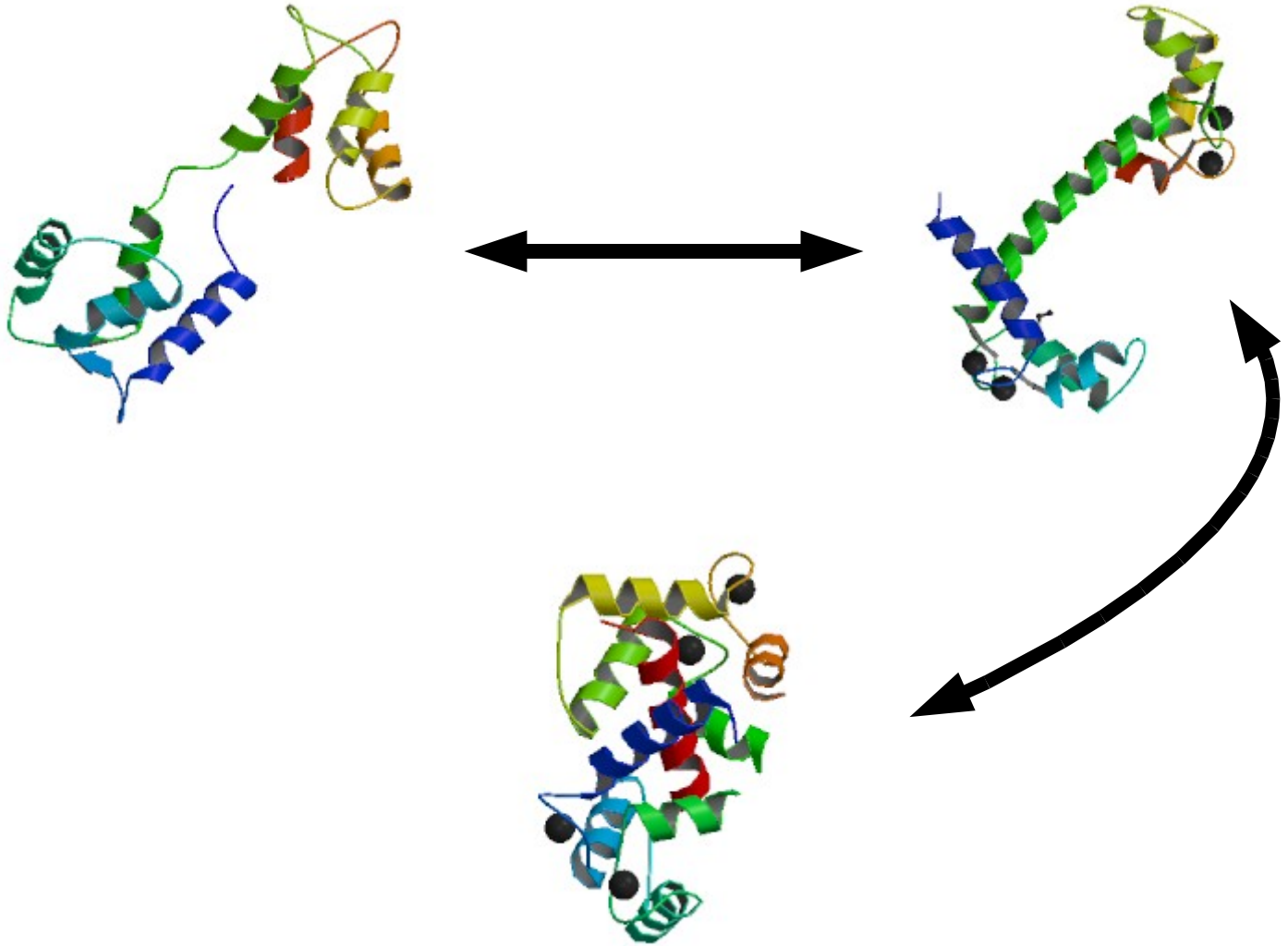
Calmodulin as a switch



Alternative structures of calmodulin



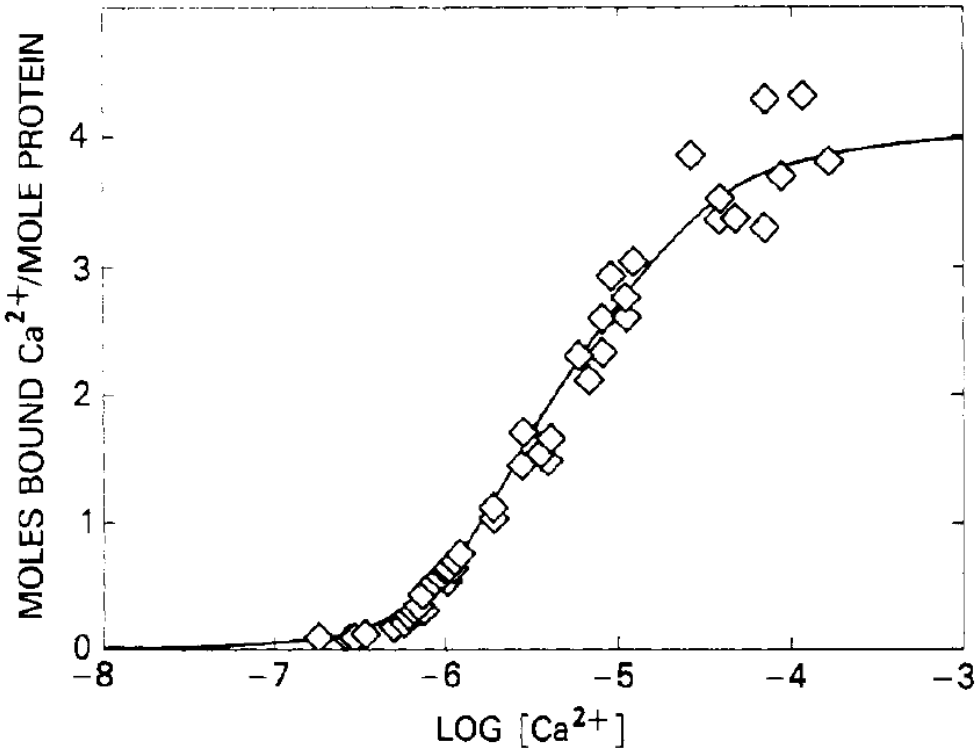
Alternative structures of calmodulin



Fitting of experimental results

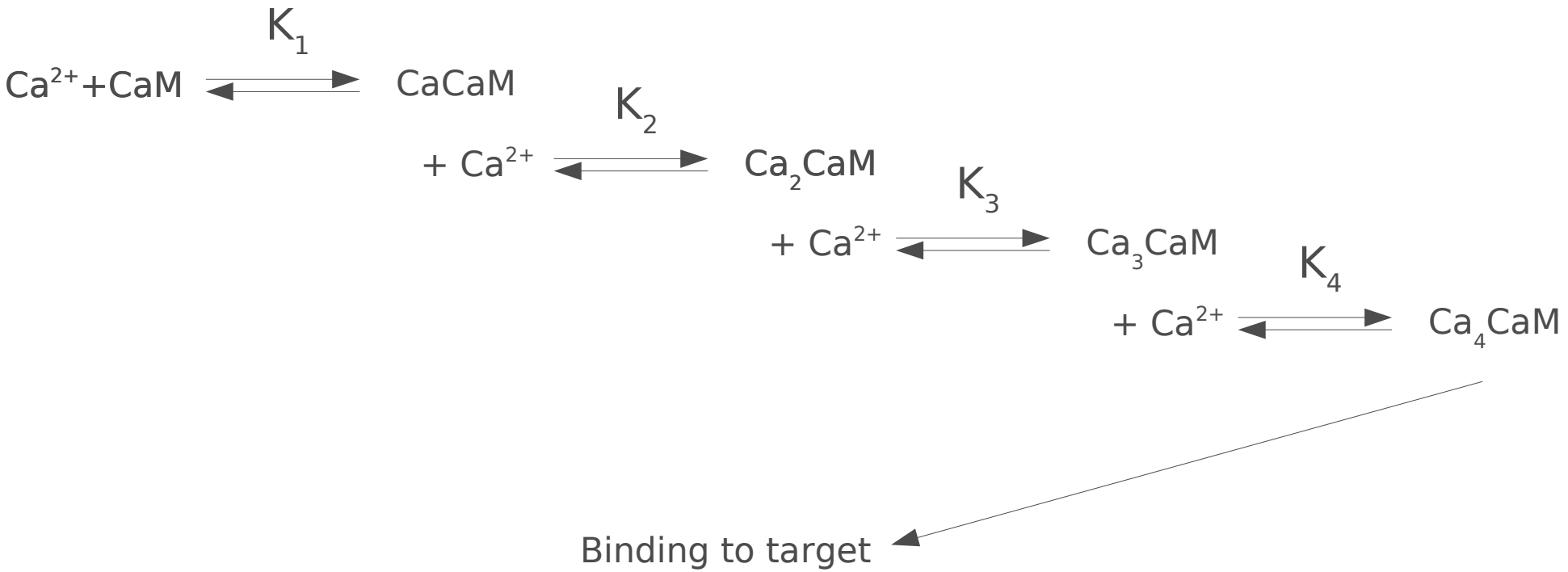
$$\overline{Y} = \frac{K_1[Ca]+2K_1K_2[Ca]^2+3K_1K_2K_3[Ca]^3+4K_1K_2K_3K_4[Ca]^4}{1+K_1[Ca]+K_1K_2[Ca]^2+K_1K_2K_3[Ca]^3+K_1K_2K_3K_4[Ca]^4}$$

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

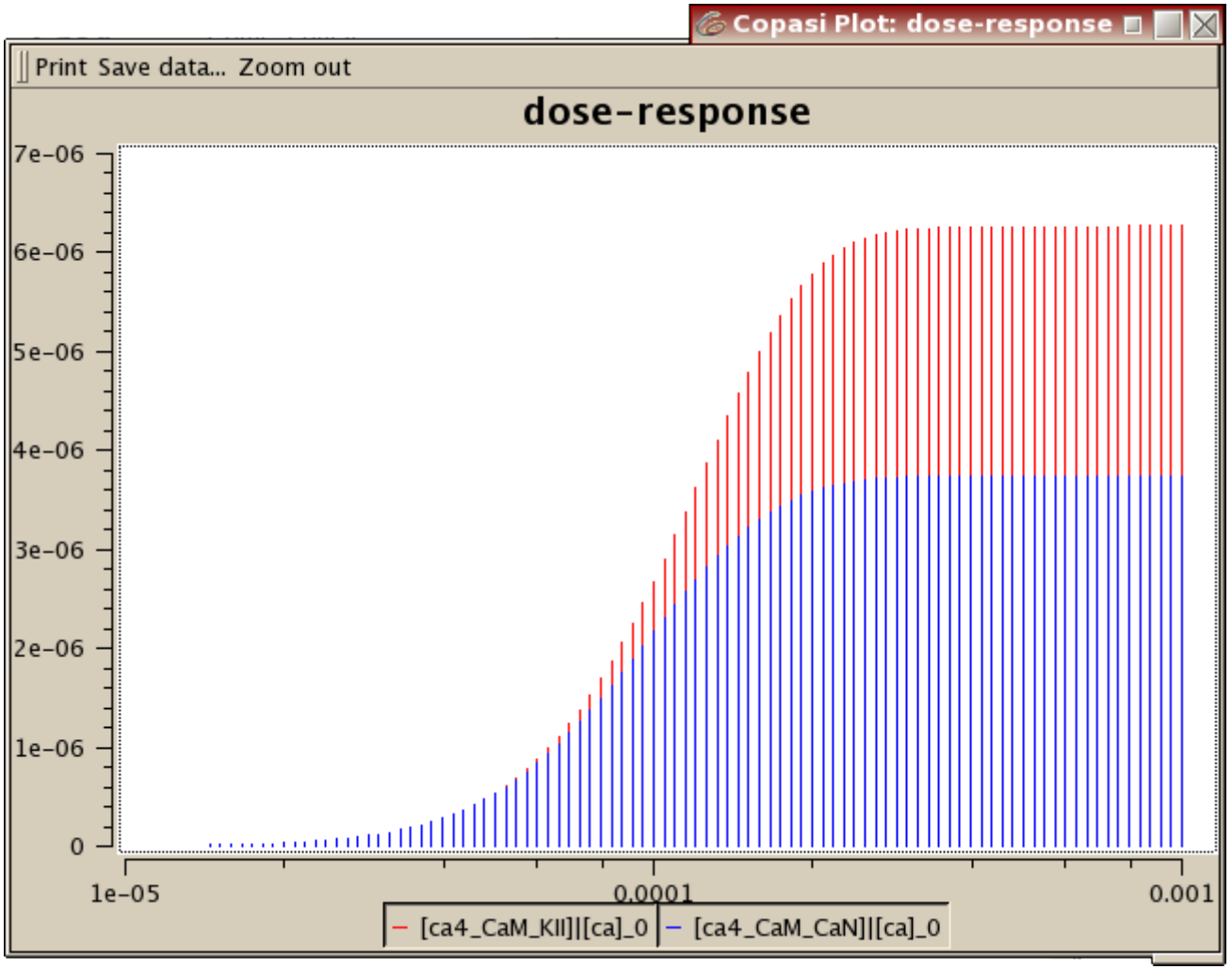


Crouch and Klee (1980)
Biochemistry, 19: 3692-3698

Phenomenological models



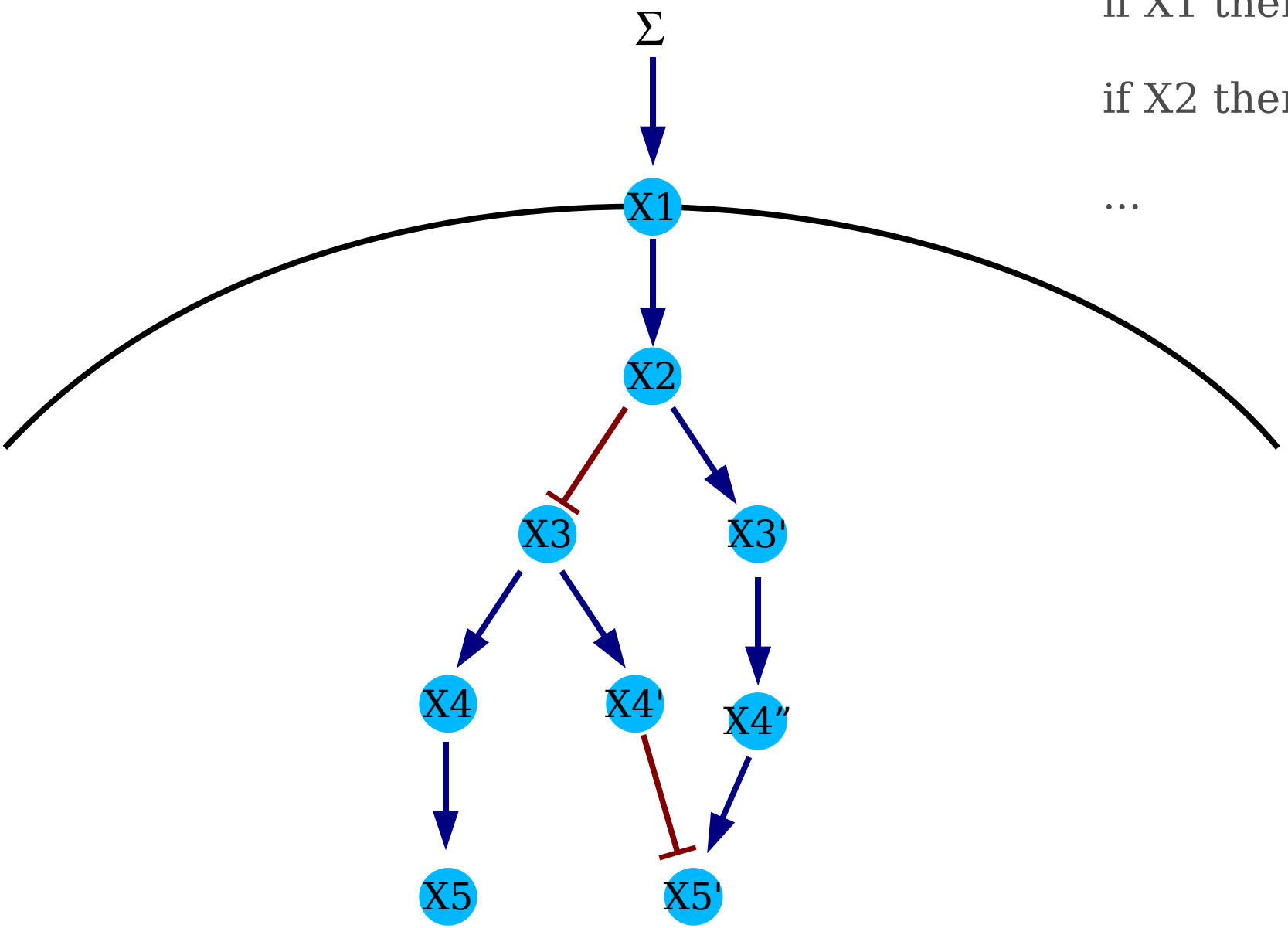
That does not work ...



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

Signals, fluxes and induction



if X1 then X2

if X2 then not X3

…

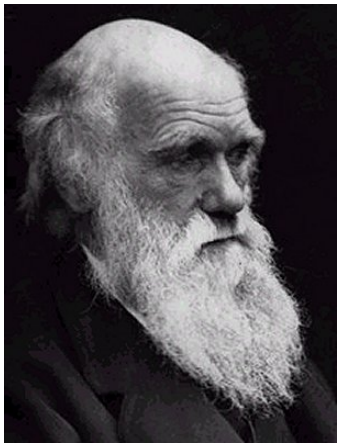
Induction Vs Selection

- Induction = BAD
  (intelligent design, Lamarck's first law, antibody moulding, directed axonal growth, induced-fit ...)

Induction Vs Selection

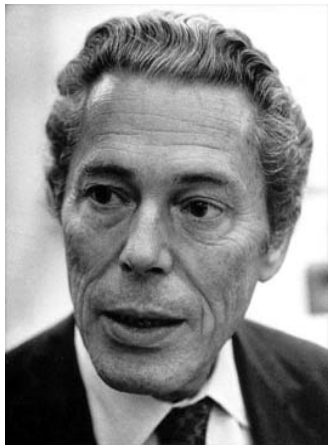
- Induction = BAD
  (intelligent design, Lamarck's first law, antibody moulding, directed axonal growth, induced-fit ...)

- Selection = GOOD
  (natural selection, clonal selection, synapse stabilisation, conformation stabilisation ...)



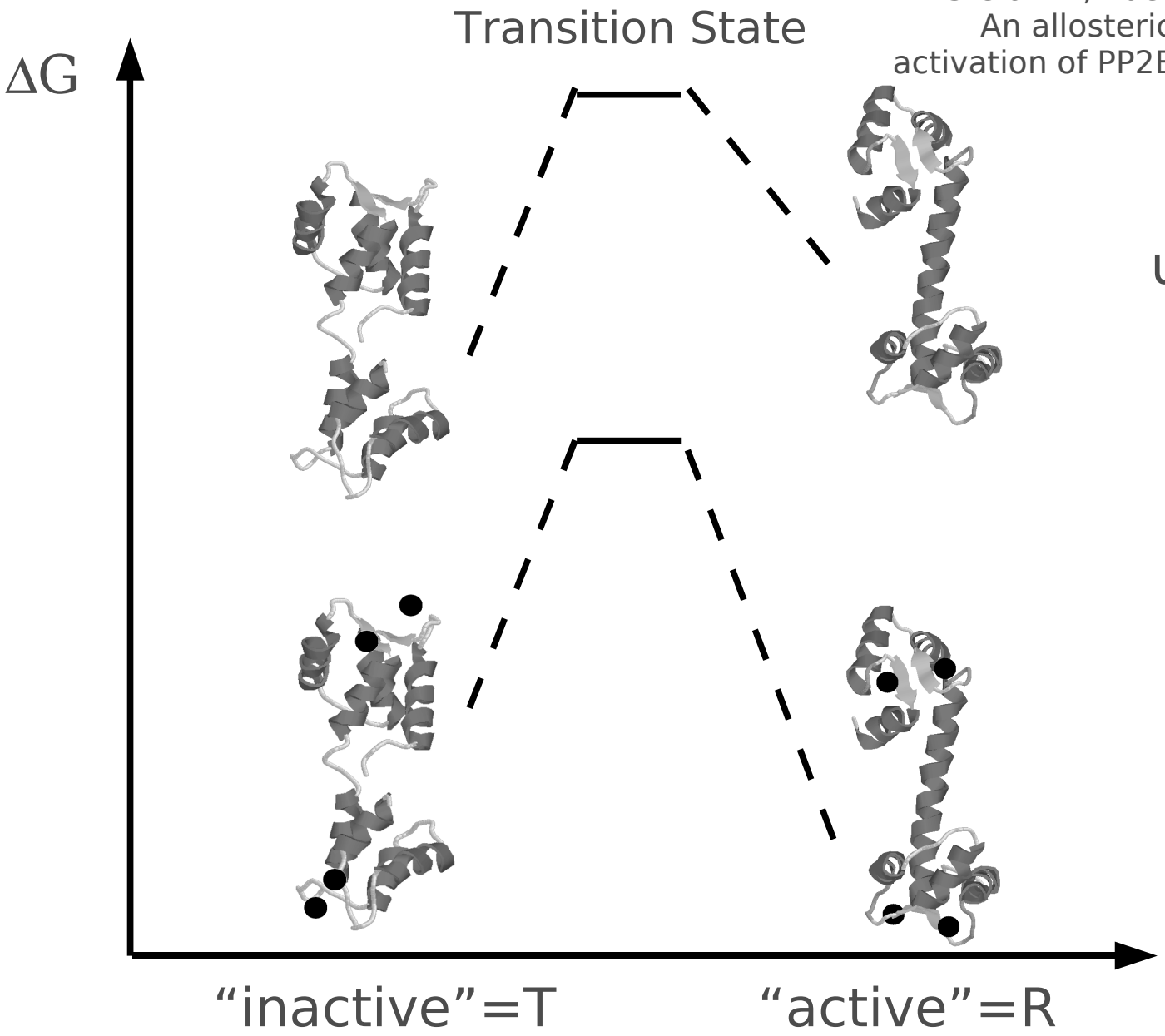
Allostery and state selection

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

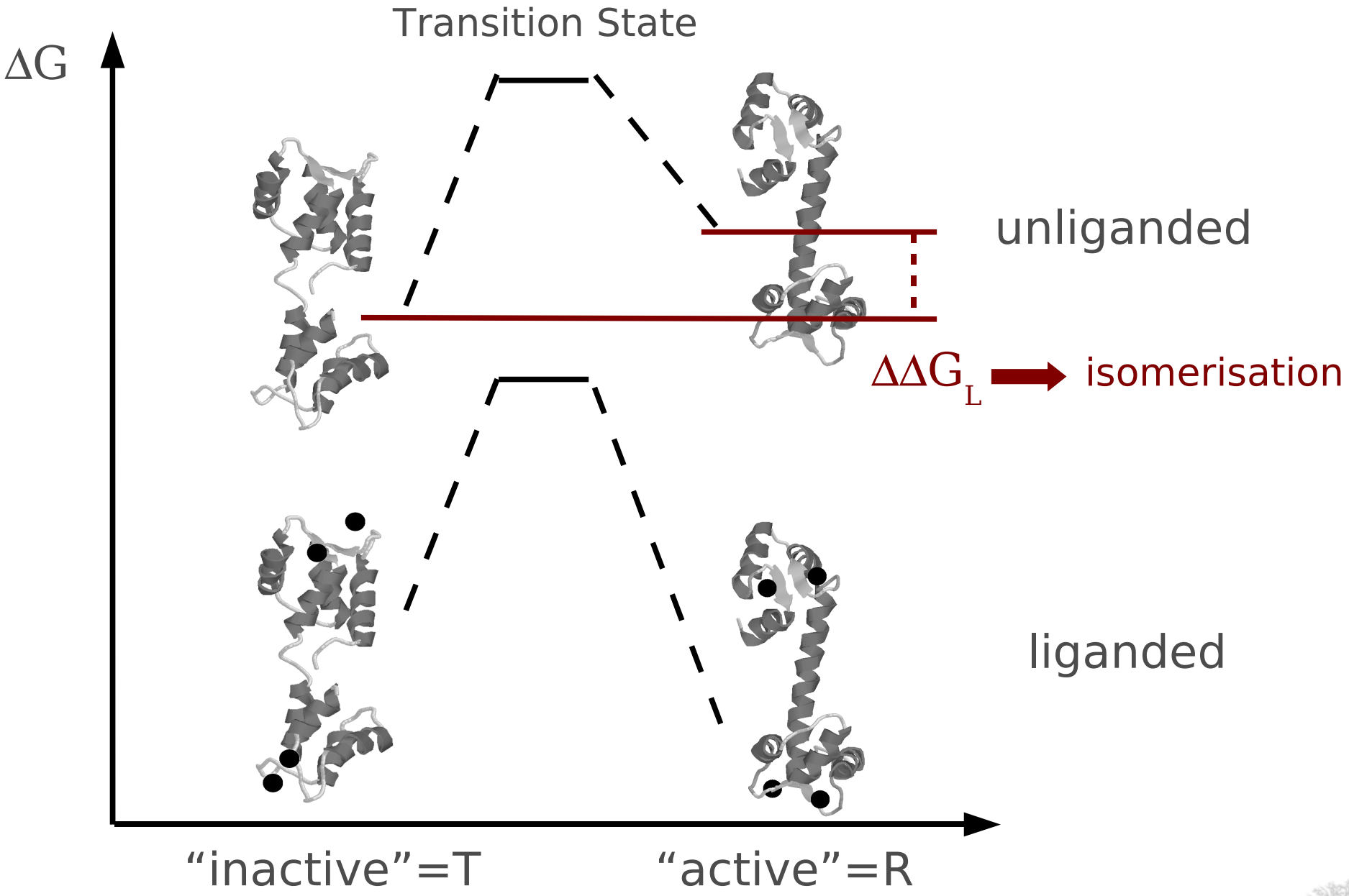


Free energy, ligand binding and isomerisation

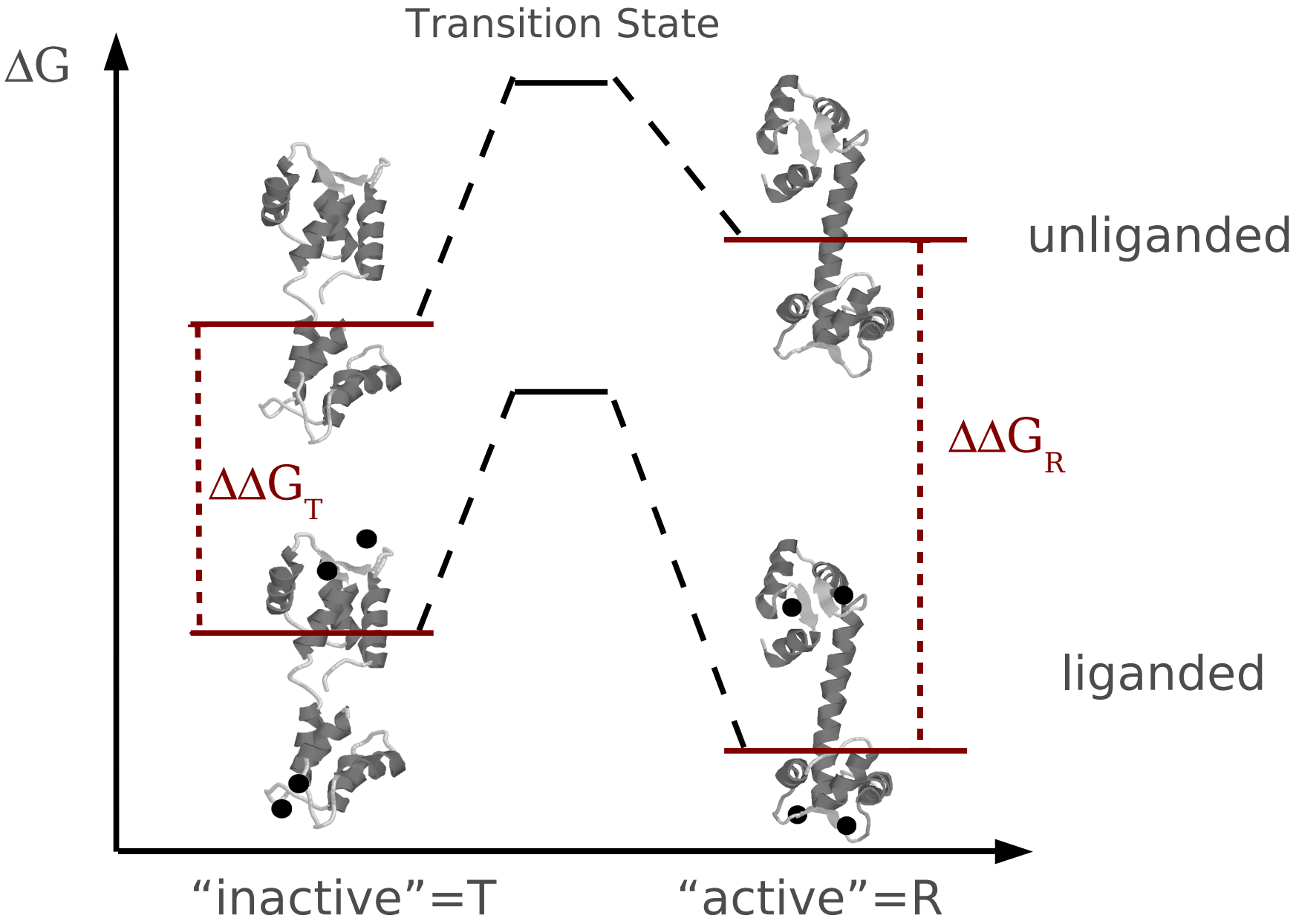
Stefan M, Edelstein S, Le Novère N (2008)
An allosteric model explains differential activation of PP2B and CaMKII by calmodulin.
Submitted



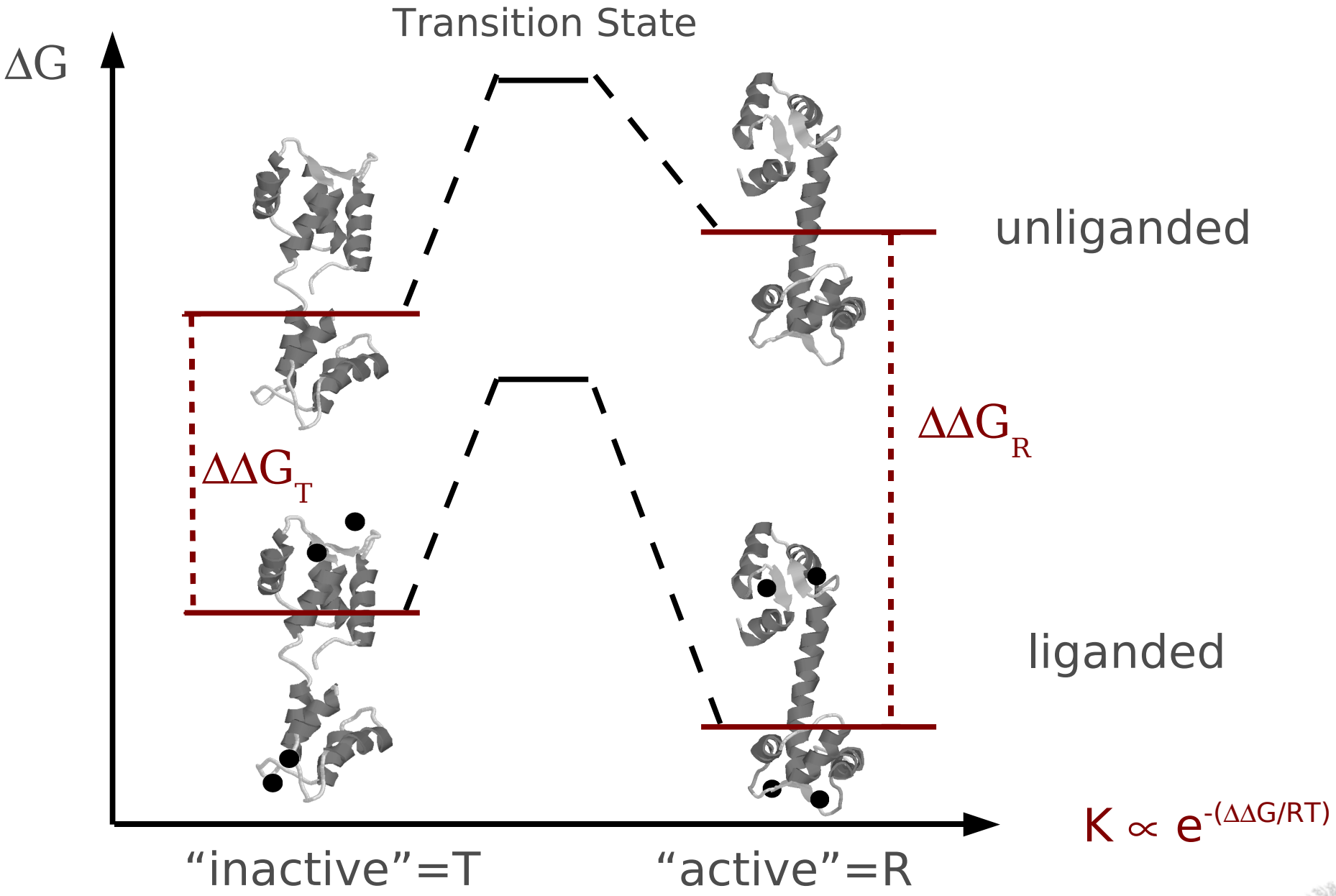
Free energy, ligand binding and isomerisation



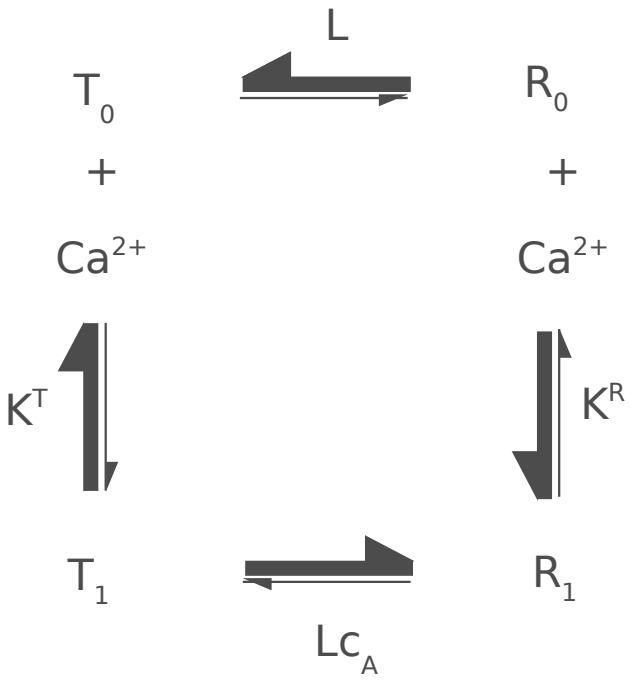
Free energy, ligand binding and isomerisation



Free energy, ligand binding and isomerisation



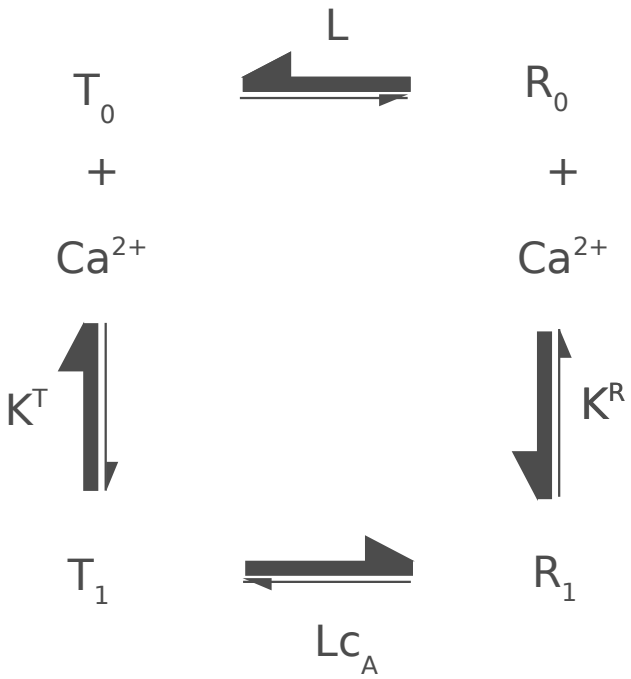
Allosteric regulation of calmodulin

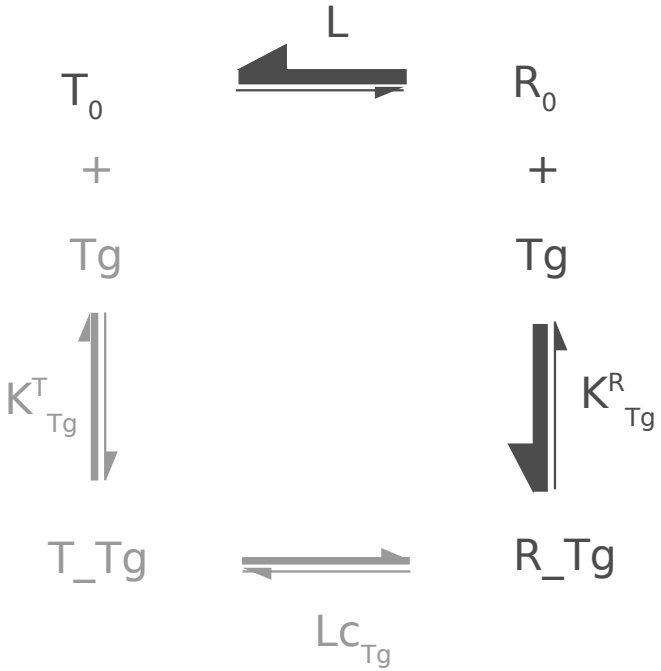


$$L = \frac{[T0]}{[R0]}$$

$$C_I = \frac{K^R_I}{K^T_I}$$

Allosteric regulation of calmodulin

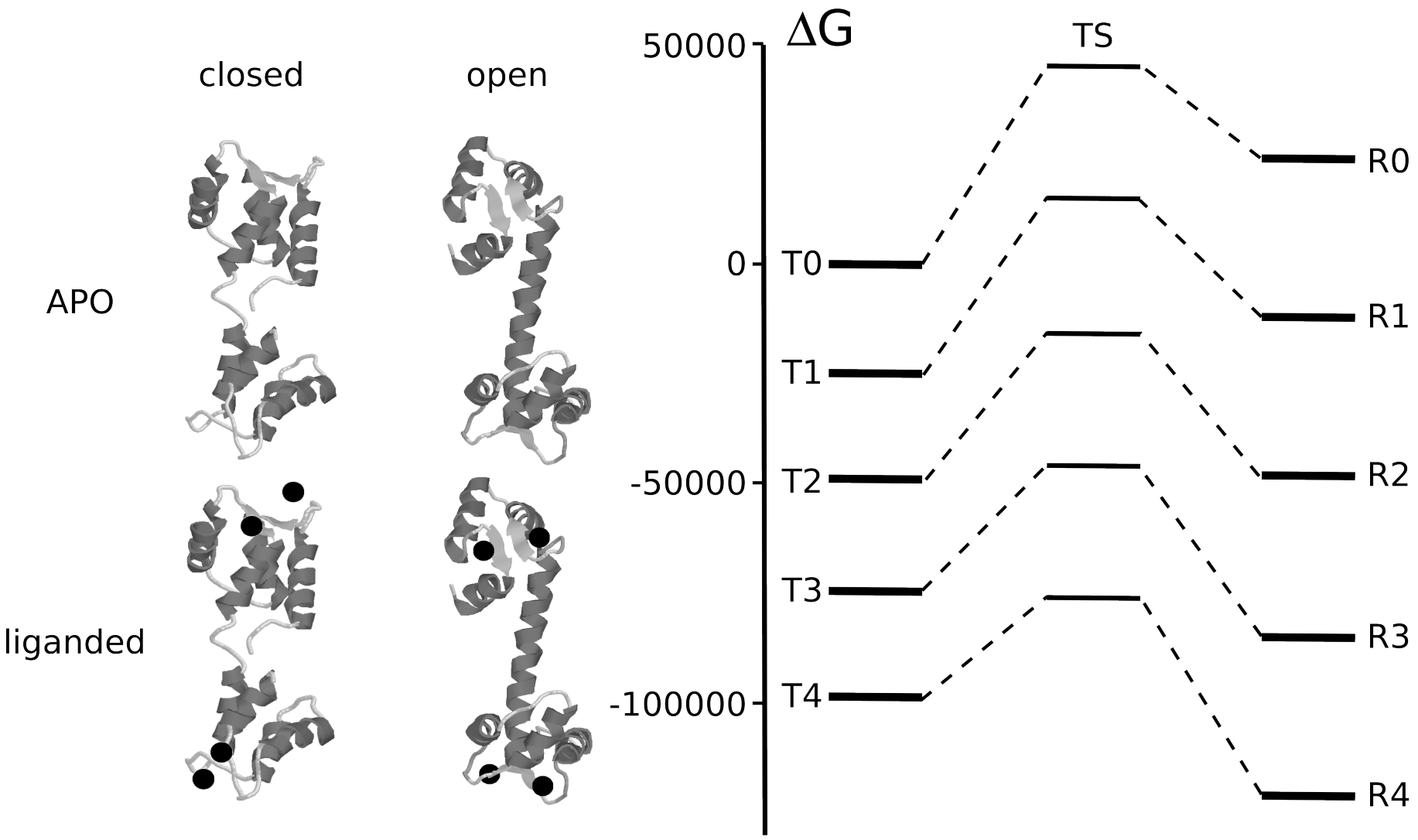




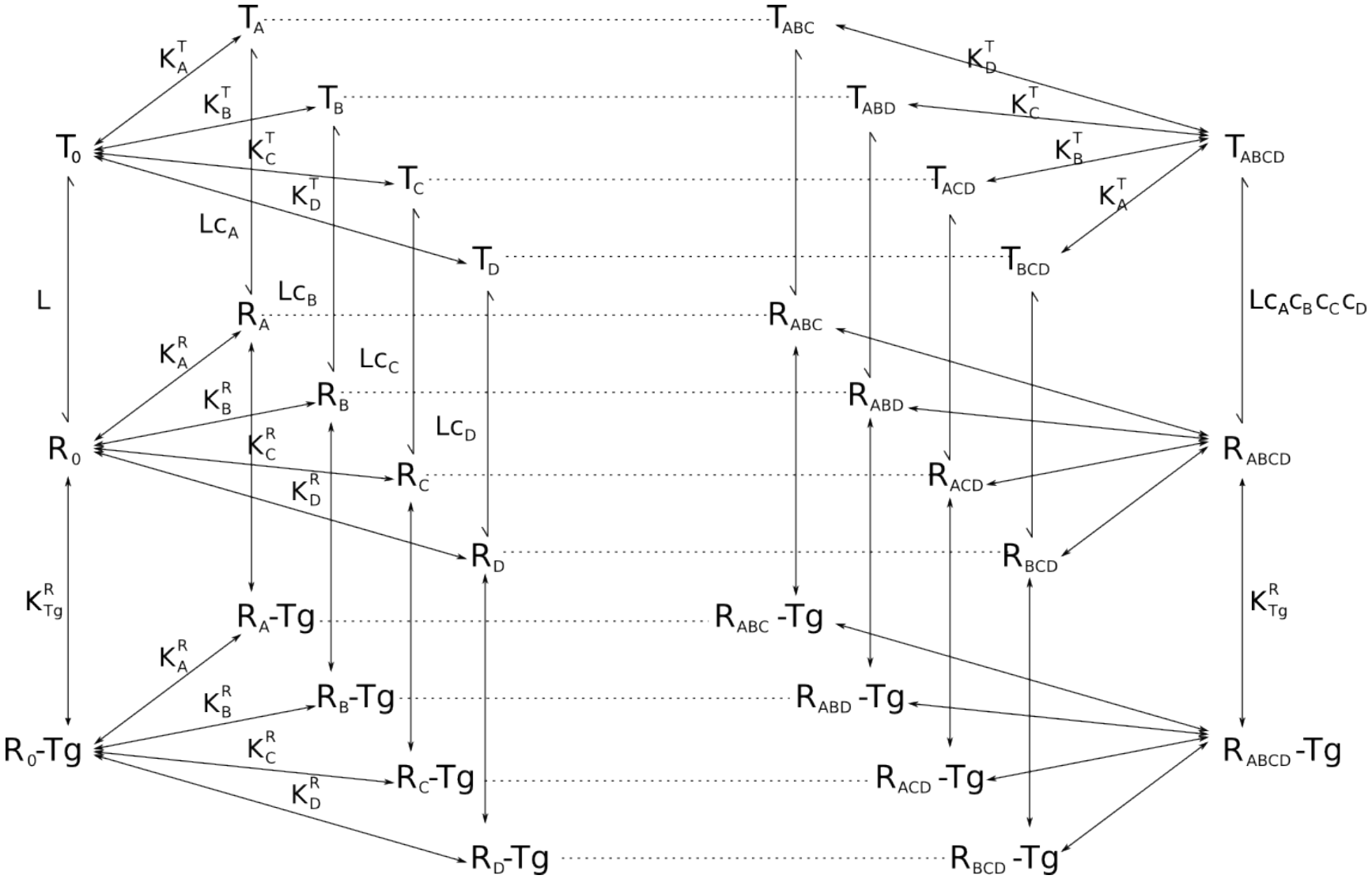
$$L = \frac{[T0]}{[R0]}$$

$$C_I = \frac{K^R_I}{K^T_I}$$

Four binding sites



Full mechanistic thermodynamic model



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

Model constraints

Parameter estimation constrained by:

- Calcium binding R and T states
  - Crouch and Klee (1980) *Biochemistry*, 19: 3692-3698
- Calcium binding R state only (locked by troponin) and isomerisation constant
  - Keller et al (1982). *Biochemistry*, 21: 156-162
- Calcium binding of N and C terminals
  - Shifman et al (2006) *PNAS*, 103: 13968-13973

- CaN affinity for CaM R state >> CaMKII one
- [CaMKII] >> [CaN]

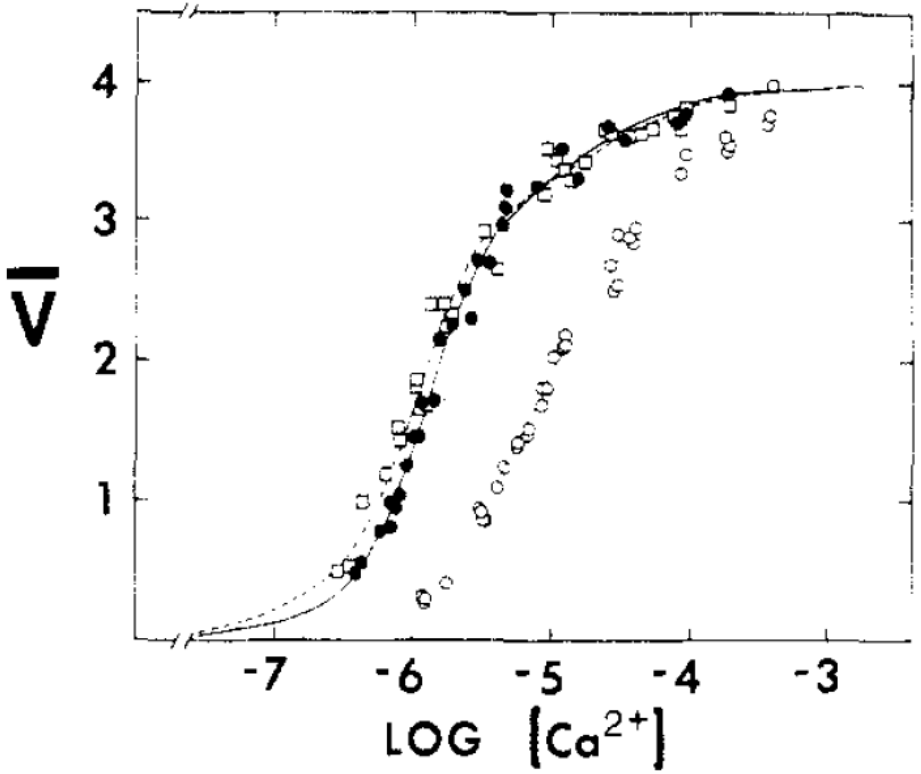


FIGURE 2: Ca^{2+} binding to CaM in the absence (○) and in the presence of stoichometric ● and higher (□) concentrations of TnI.

Keller et al (1982) *Biochemistry*, 21: 156-162

Getting L

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

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

- α = [ligand]/K^R_{lig}
- γ = [activator]/K^R_{act}
- n : number of ligand binding sites
- m : number of activator binding sites

- Make $\bar{Y}$ = 0.5 and replace α by $\alpha_{½}$ for both [troponin]

Getting L

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

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- α = [ligand]/K^R_{lig}
- γ = [activator]/K^R_{act}
- n : number of ligand binding sites
- m : number of activator binding sites

$L \approx 20\,000$

- Make $\bar{Y} = 0.5$ and replace α by $\alpha_{½}$ for both [troponin]

Getting c and K^R

MWC version:

$$\bar{Y} = \frac{Lc\alpha(1+\alpha)^3 + \alpha(1+\alpha)^3}{L(1+c\alpha)^4 + (1+\alpha)^4}$$

Our extended version:

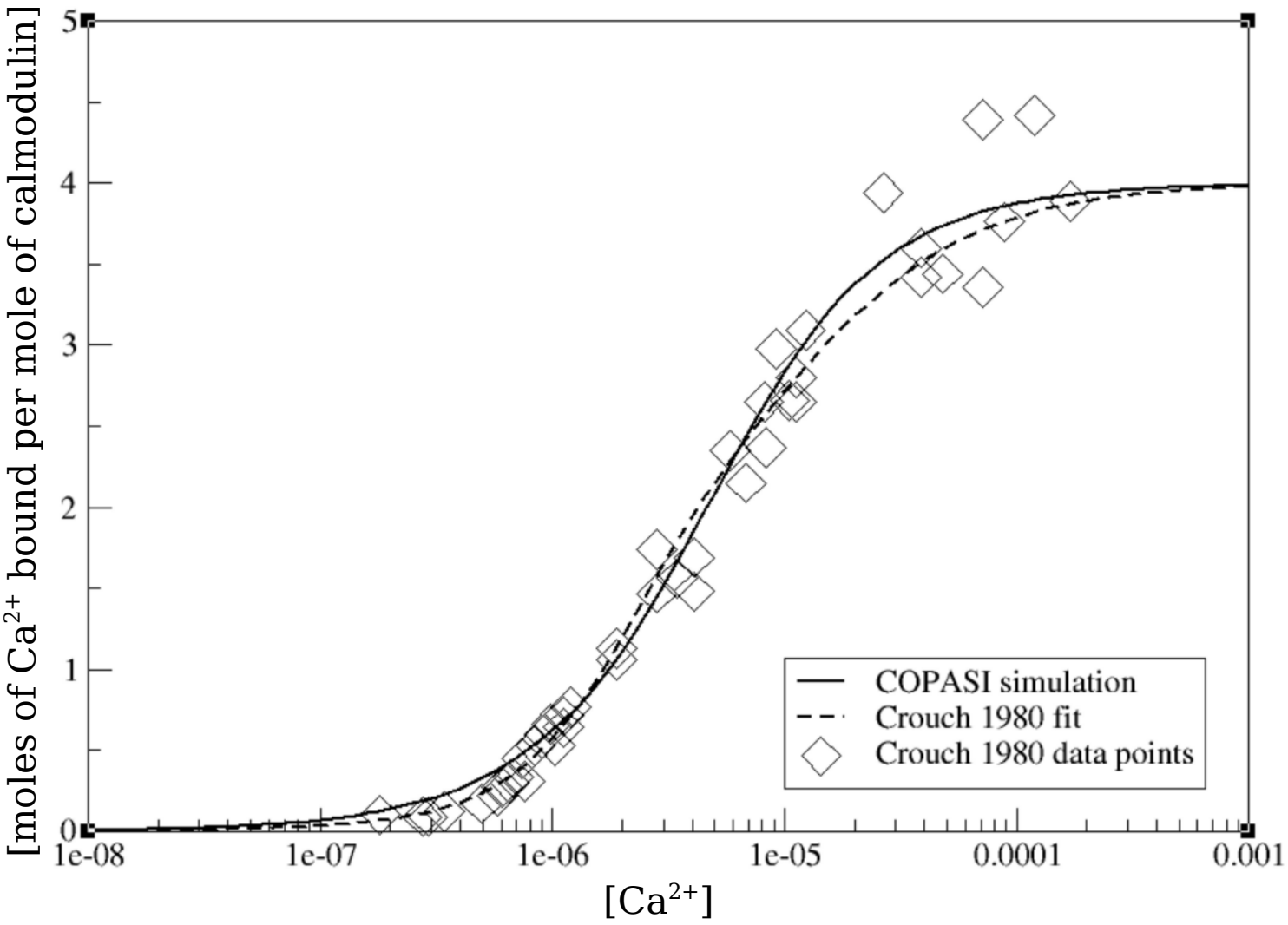
$$\bar{Y} = 0.25\frac{\sum_i \left(\alpha_i \prod_j (1+\alpha_j)\right) + L\sum_i \left(c_i\alpha_i \prod_j (1+c_j\alpha_j)\right)}{\prod_i (1+\alpha_i) + L\prod_i (1+c_i\alpha_i)}$$

$\alpha_i = [Ca]/K^R_i$

Use calmodulin with mutated Ca binding sites
(Shifman et al (2006) *PNAS*, 103: 13968-13973)

→ Reduced equation

Comparison with experiment



Derivation of Adair's constants

$$K_1 = 4\frac{1+L}{\frac{1}{K_A^R}+\frac{1}{K_B^R}+\frac{1}{K_C^R}+\frac{1}{K_D^R}+L\left(\frac{1}{K_A^T}+\frac{1}{K_B^T}+\frac{1}{K_C^T}+\frac{1}{K_D^T}\right)}$$

Derivation of Adair's constants

$$K_1 = 4\frac{1+L}{\frac{1}{K_A^R}+\frac{1}{K_B^R}+\frac{1}{K_C^R}+\frac{1}{K_D^R}+L\left(\frac{1}{K_A^T}+\frac{1}{K_B^T}+\frac{1}{K_C^T}+\frac{1}{K_D^T}\right)}$$

$$K_2 = \frac{3}{2}\frac{\frac{1}{K_A^R}+\frac{1}{K_B^R}+\frac{1}{K_C^R}+\frac{1}{K_D^R}+L\left(\frac{1}{K_A^T}+\frac{1}{K_B^T}+\frac{1}{K_C^T}+\frac{1}{K_D^T}\right)}{\frac{1}{K_A^RK_B^R}+\frac{1}{K_A^RK_C^R}+\frac{1}{K_A^RK_D^R}+\frac{1}{K_B^RK_C^R}+\frac{1}{K_B^RK_D^R}+\frac{1}{K_C^RK_D^R}+L\left(\frac{1}{K_A^TK_B^T}+\frac{1}{K_A^TK_C^T}+\frac{1}{K_A^TK_D^T}+\frac{1}{K_B^TK_C^T}+\frac{1}{K_B^TK_D^T}+\frac{1}{K_C^TK_D^T}\right)}$$

$$K_3 = \frac{2}{3}\frac{\frac{1}{K_A^RK_B^R}+\frac{1}{K_A^RK_C^R}+\frac{1}{K_A^RK_D^R}+\frac{1}{K_B^RK_C^R}+\frac{1}{K_B^RK_D^R}+\frac{1}{K_C^RK_D^R}+L\left(\frac{1}{K_A^TK_B^T}+\frac{1}{K_A^TK_C^T}+\frac{1}{K_A^TK_D^T}+\frac{1}{K_B^TK_C^T}+\frac{1}{K_B^TK_D^T}+\frac{1}{K_C^TK_D^T}\right)}{\frac{1}{K_A^RK_B^RK_C^R}+\frac{1}{K_A^RK_B^RK_D^R}+\frac{1}{K_A^RK_C^RK_D^R}+\frac{1}{K_B^RK_C^RK_D^R}+L\left(\frac{1}{K_A^TK_B^TK_C^T}+\frac{1}{K_A^TK_B^TK_D^T}+\frac{1}{K_A^TK_C^TK_D^T}+\frac{1}{K_B^TK_C^TK_D^T}\right)}$$

$$K_4 = \frac{1}{4}\frac{\frac{1}{K_A^RK_B^RK_C^R}+\frac{1}{K_A^RK_B^RK_D^R}+\frac{1}{K_A^RK_C^RK_D^R}+\frac{1}{K_B^RK_C^RK_D^R}+L\left(\frac{1}{K_A^TK_B^TK_C^T}+\frac{1}{K_A^TK_B^TK_D^T}+\frac{1}{K_A^TK_C^TK_D^T}+\frac{1}{K_B^TK_C^TK_D^T}\right)}{\frac{1}{K_A^RK_B^RK_C^RK_D^R}+L\frac{1}{K_A^TK_B^TK_C^TK_D^T}}$$

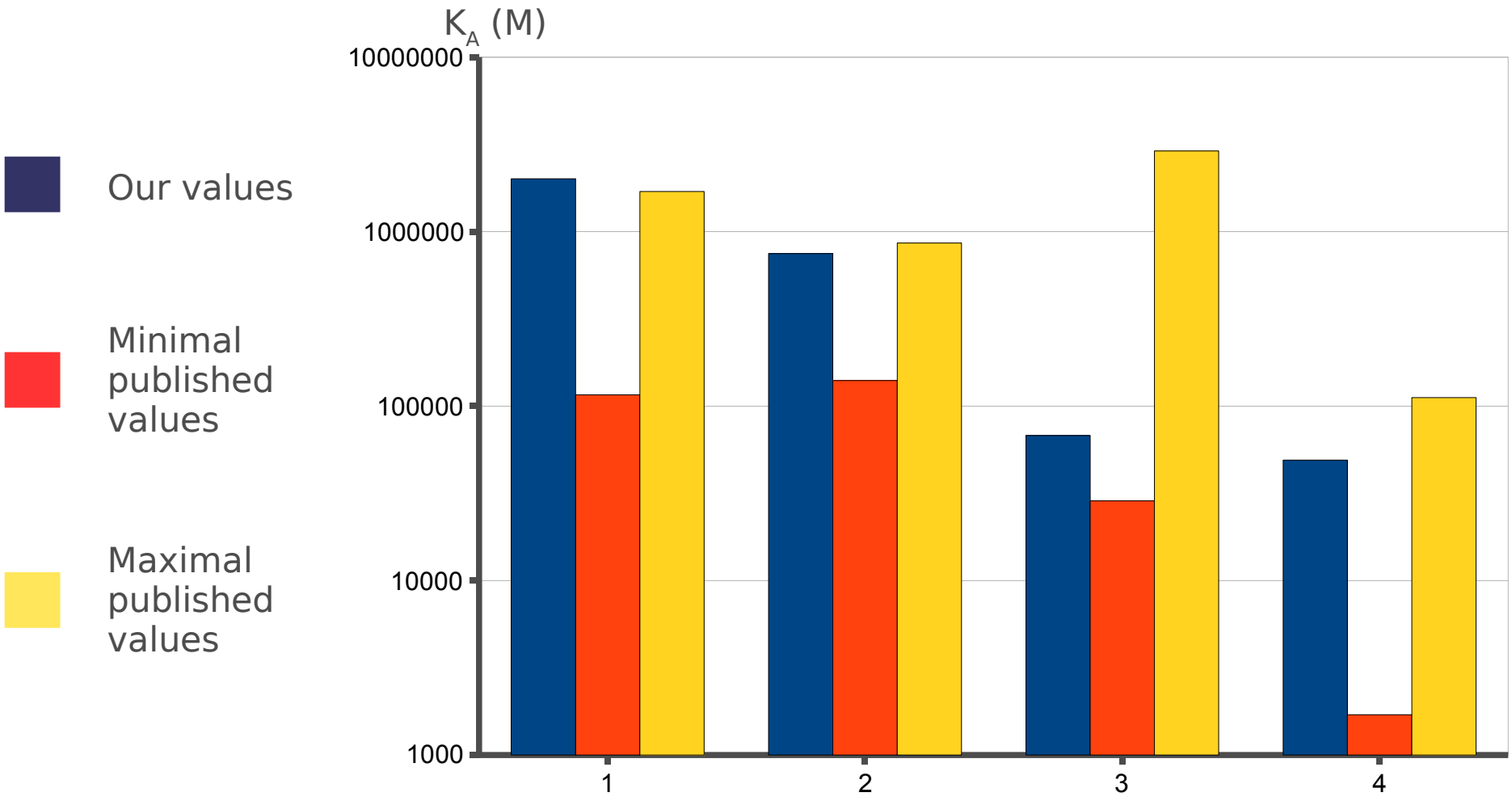
Derivation of Adair's constants

$$K_i = \frac{N - i + 1}{i} \frac{S_{i-1}^R + LS_{i-1}^T}{S_i^R + LS_i^T}$$

$$S_i^R := \sum_{K_j^R \in \{K_A^R, K_B^R, \dots\}, j_1 < j_2 < \dots < j_i} \frac{1}{K_{j_1}^R} \cdots \frac{1}{K_{j_i}^R}$$

$$S_i^T := \sum_{K_j^T \in \{K_A^T, K_B^T, \dots\}, j_1 < j_2 < \dots < j_i} \frac{1}{K_{j_1}^T} \cdots \frac{1}{K_{j_i}^T}$$

Comparison with measured K_A



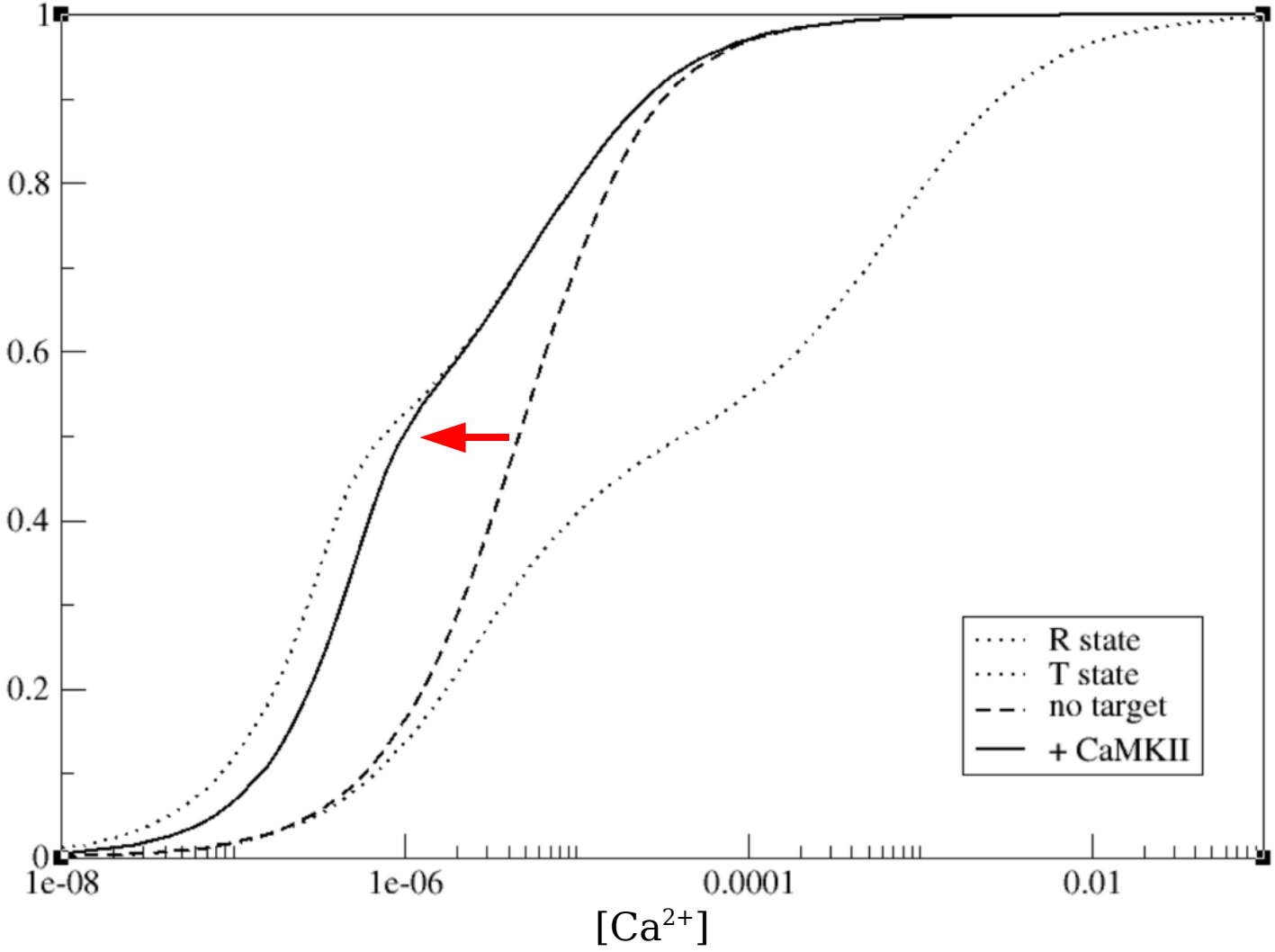
Activity of unsaturated calmodulin

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

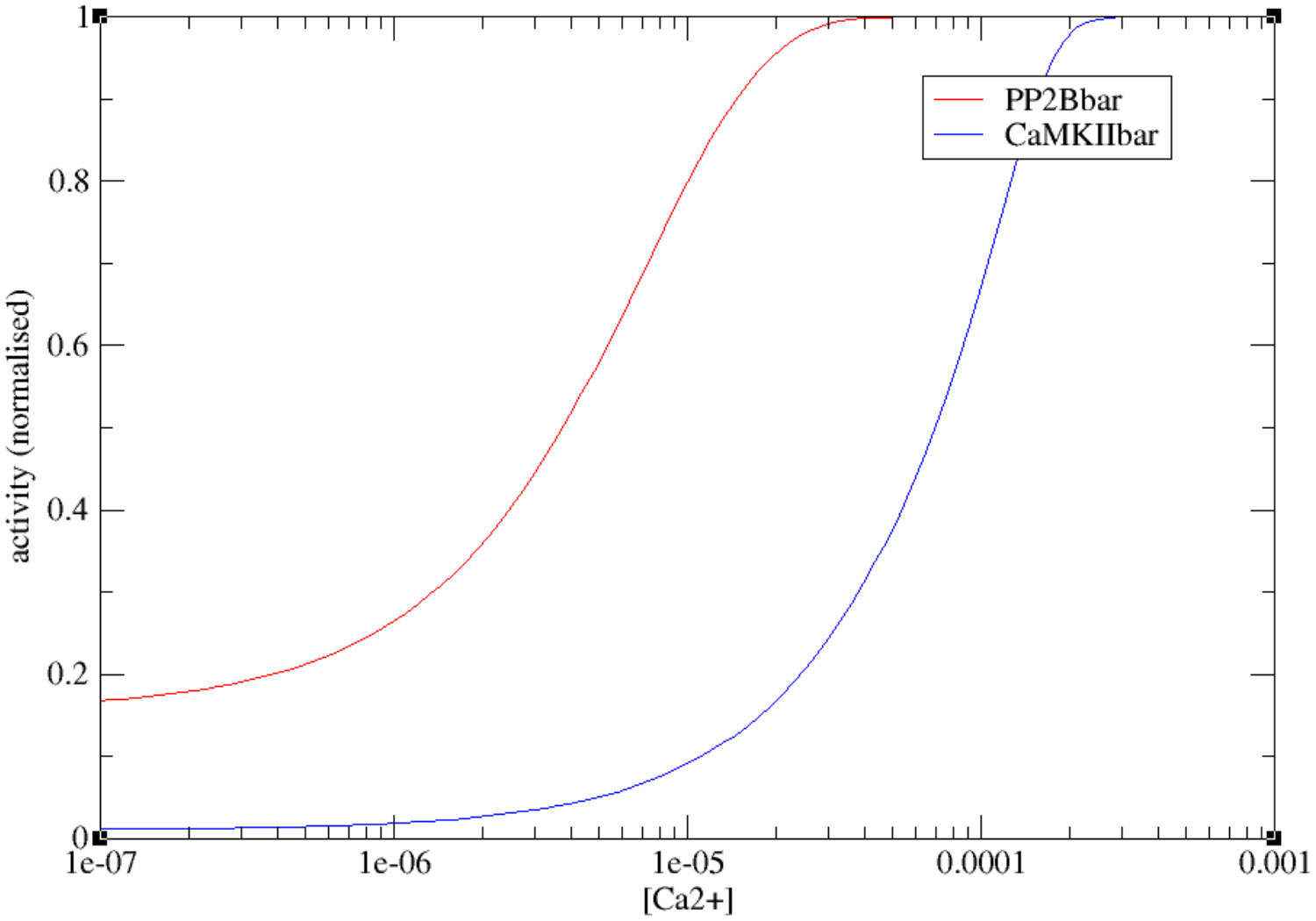
$$\frac{R_2}{T_2} = \frac{6}{L(c_A c_B + c_A c_C + c_A c_D + c_B c_C + c_B c_D + c_C c_D)}$$

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

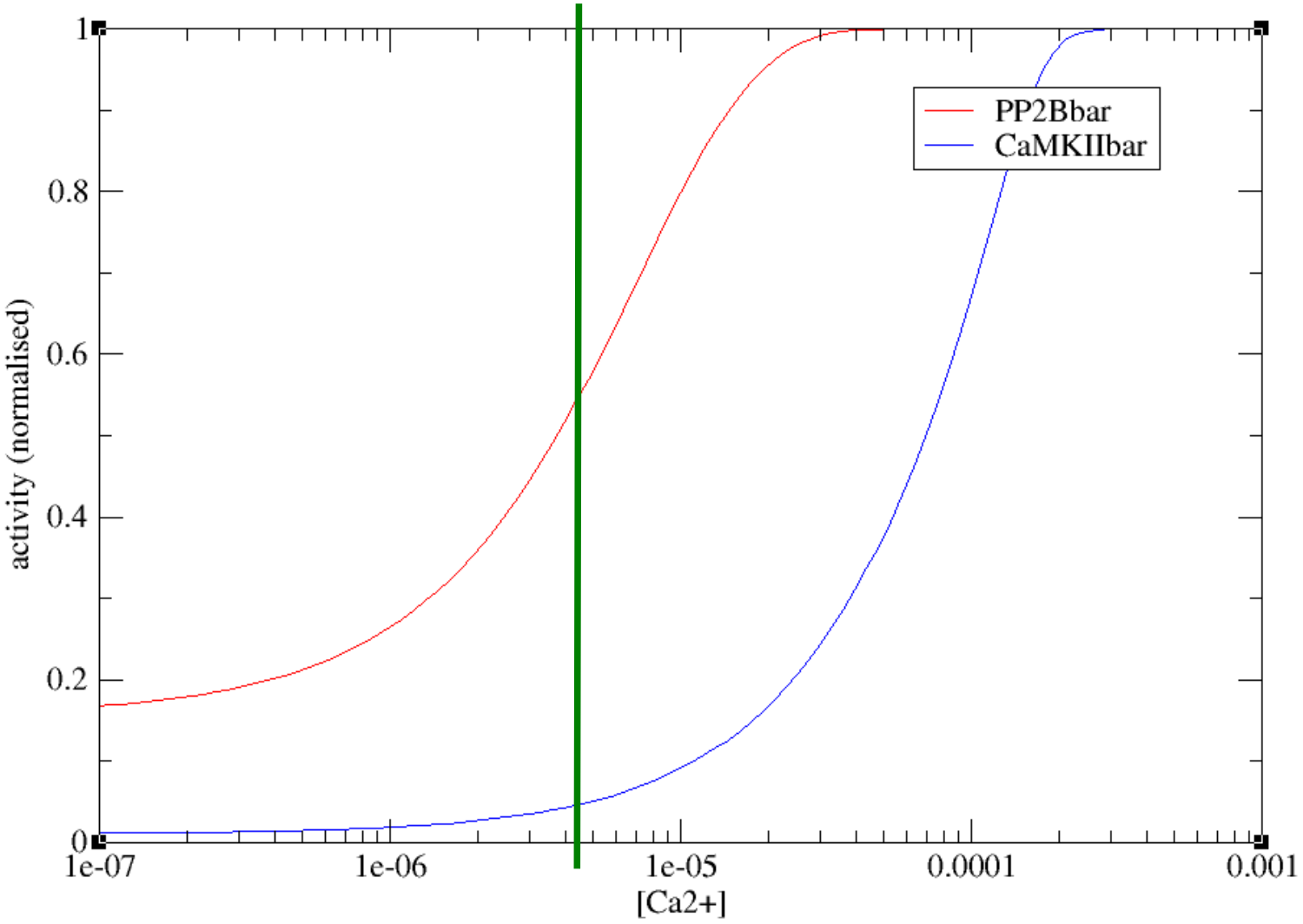


Bidirectional synaptic plasticity

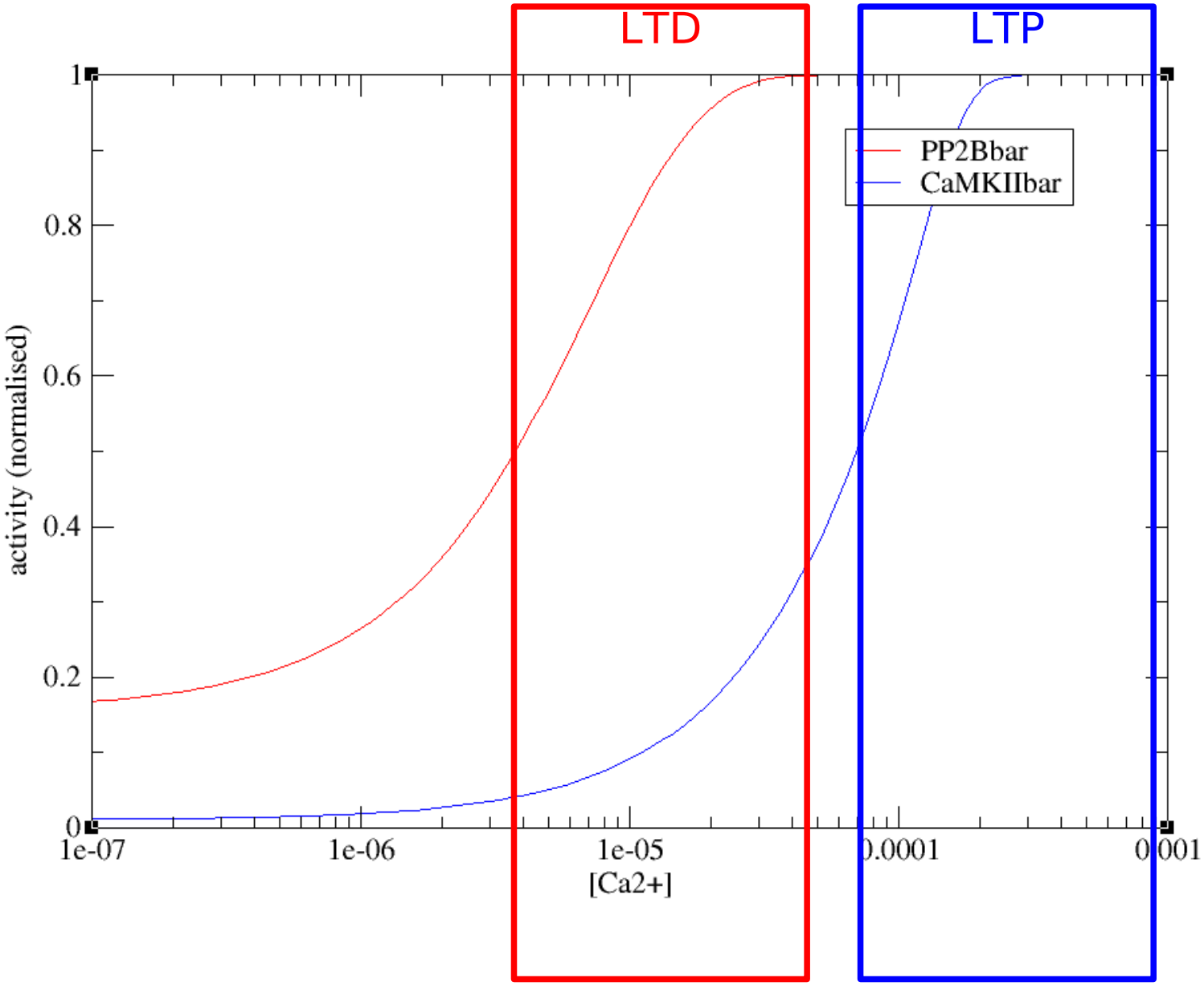


Bidirectional synaptic plasticity

half saturation of calmodulin



Bidirectional synaptic plasticity



- COPASI developers
  (Virginia Bioinformatics Institute
  EML-research)

  Ursula Kummer

  Pedro Mendes

  Stefan Hoops

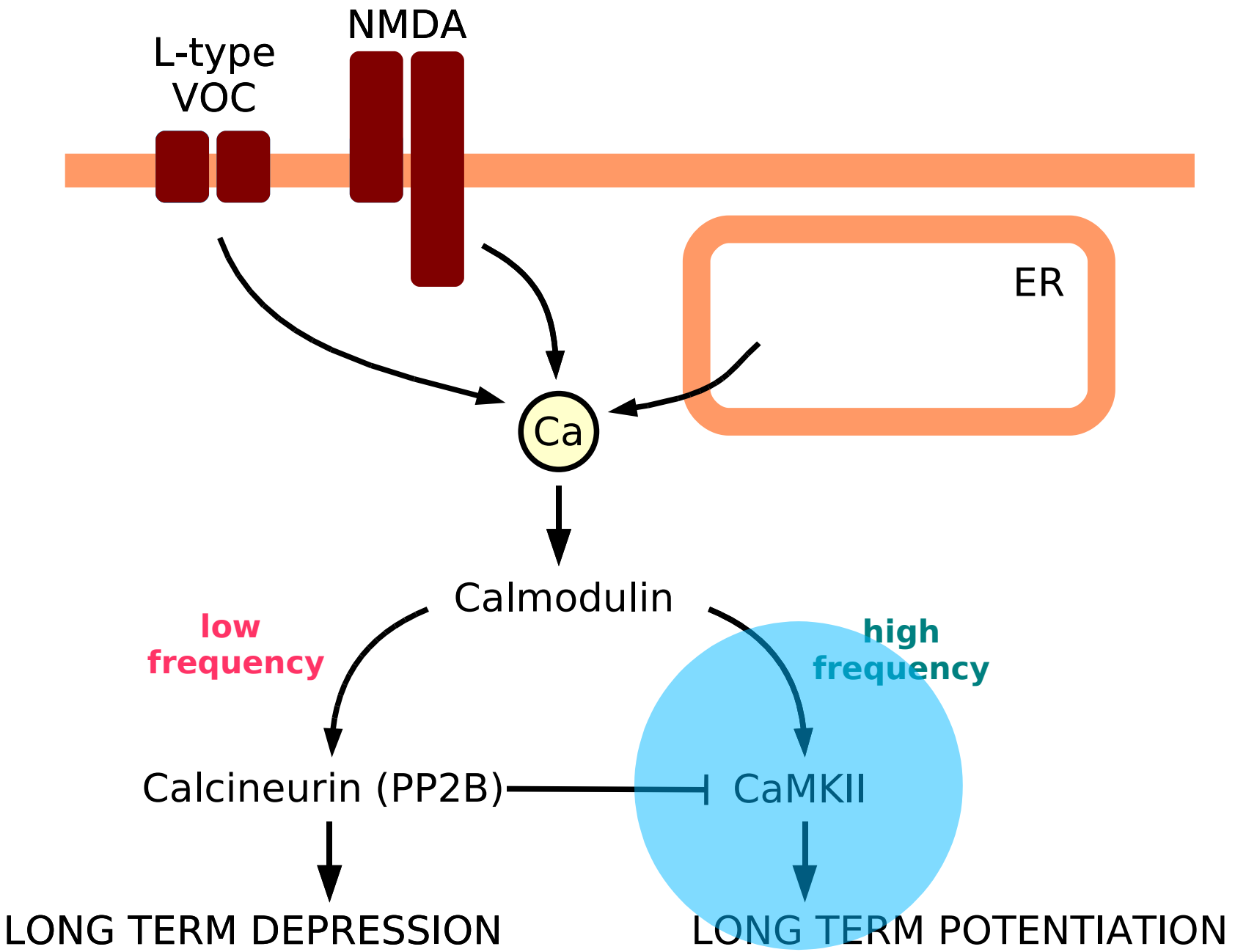
  Sven Sahle

  Ralf Gauges

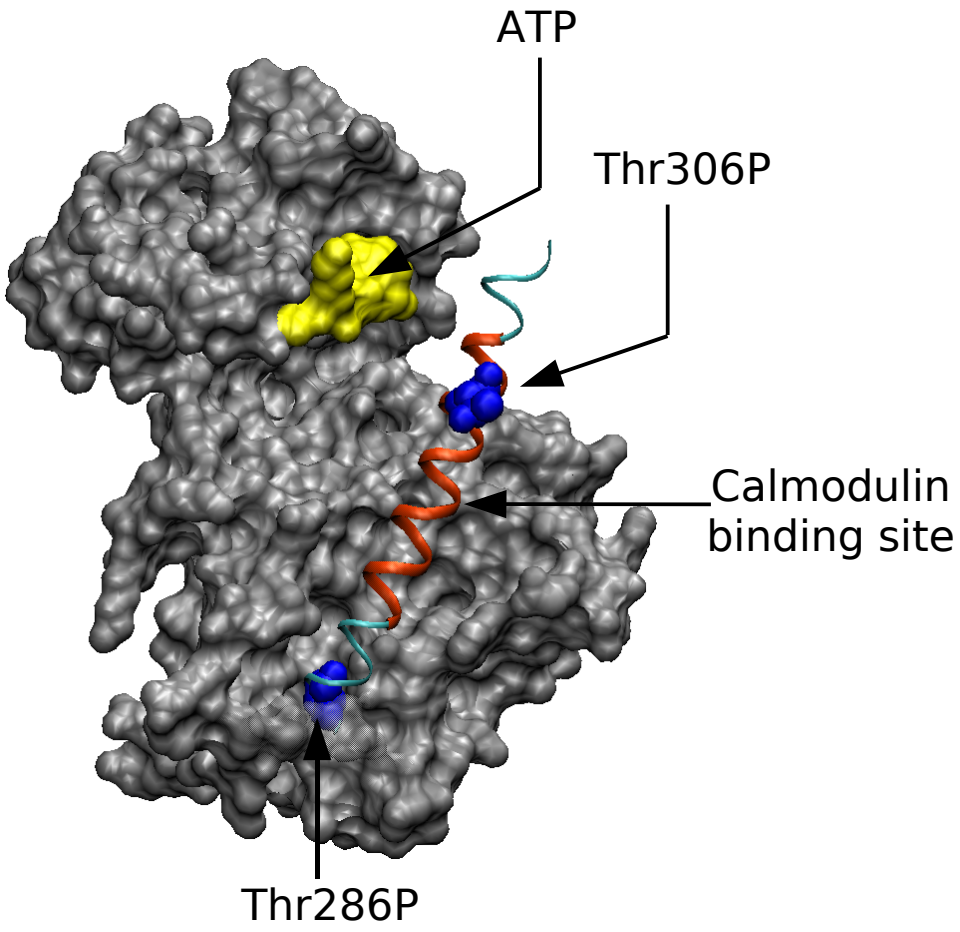
Melanie Stefan

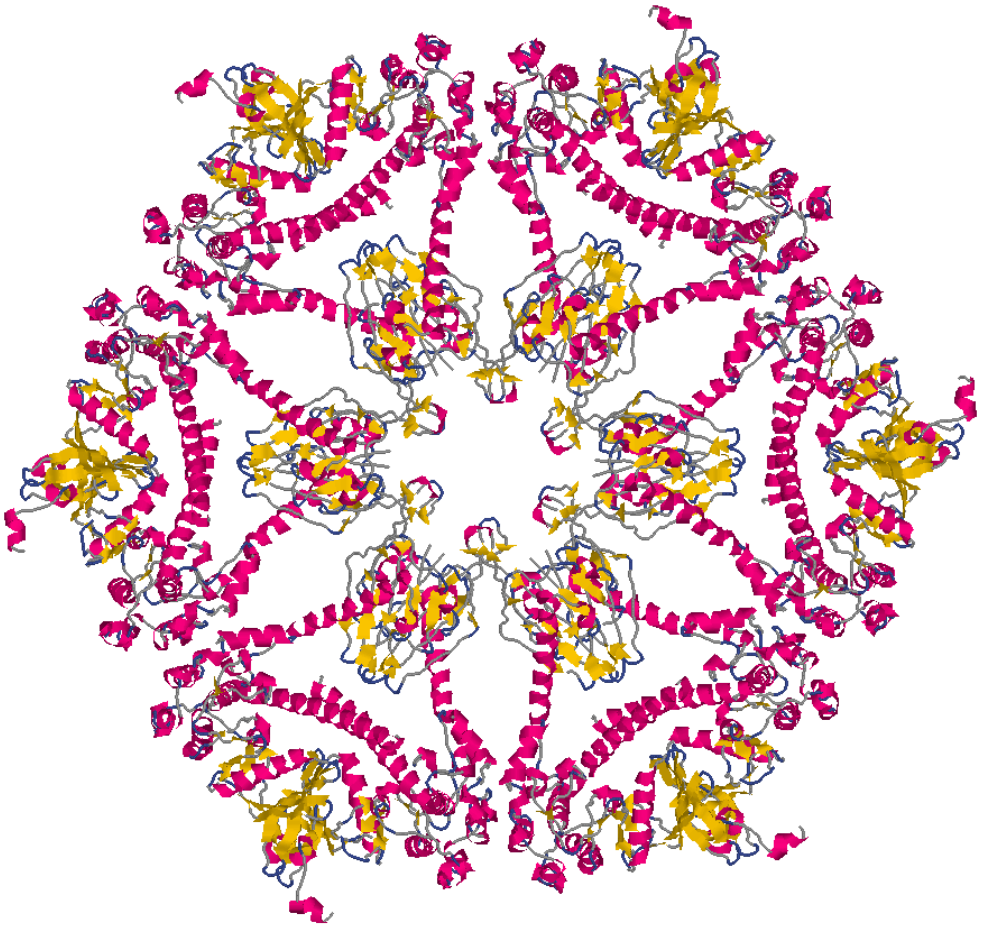
Stuart Edelstein

What next?


L-type
VOC
NMDA
ER
Ca
Calmodulin
low
frequency
high
frequency
Calcineurin (PP2B)
CaMKII
LONG TERM DEPRESSION
LONG TERM POTENTIATION

What next?





5x12 state variables=

1 152 900 000 000 000 000 states

(1 billion of billion)

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  Kouichi Takahashi
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  Gabor Bereczki

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  (Virginia Bioinformatics Institute
  EML-research)

  Ursula Kummer
  Pedro Mendes
  Stefan Hoops
  Sven Sahle
  Ralf Gauges

- Compneur group
  (EBI)

  Prof Stuart Edelstein, visitor
  Eric Fernandez, post-doc
  Lu Li, PhD student
  Renaud Schiappa, undergraduate
  Melanie Stefan, PhD student

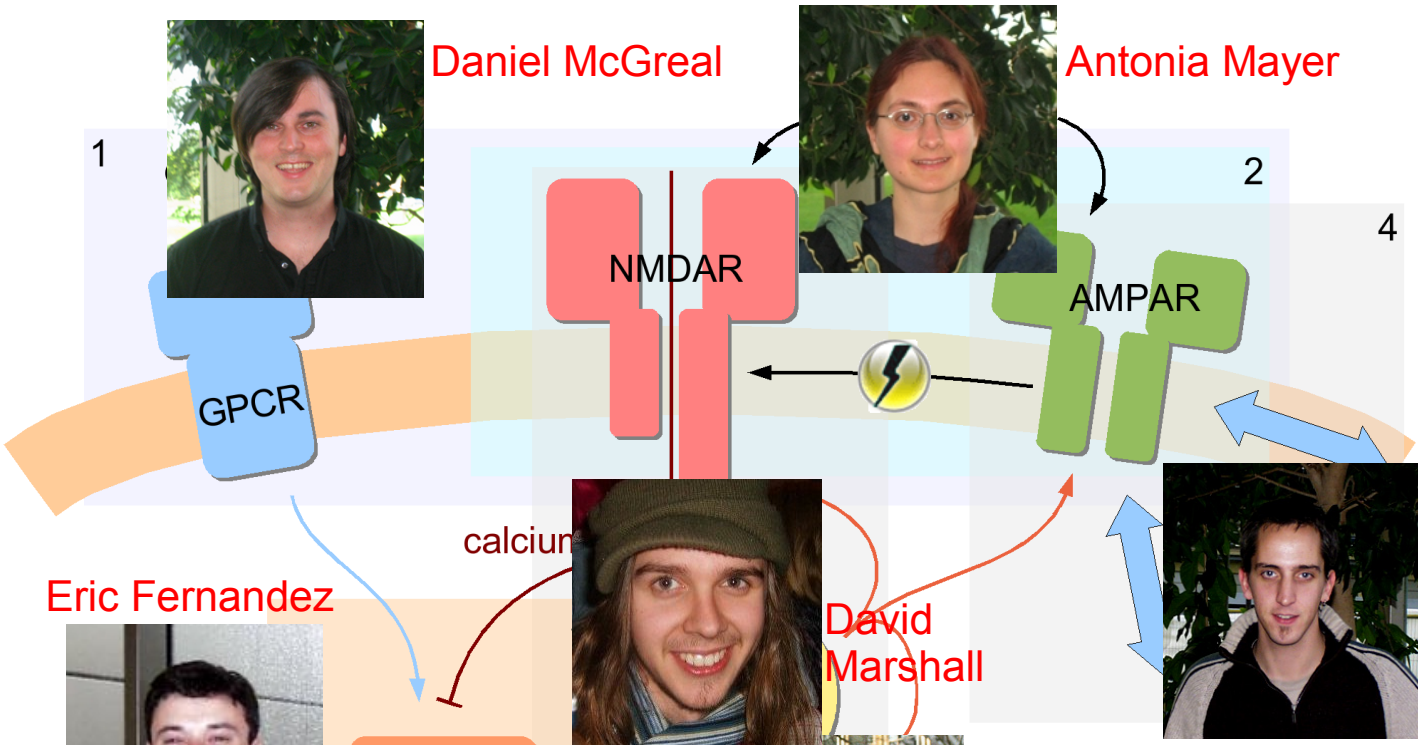
- Collaborators
  (INSERM U536, Paris)

  Jean-Antoine Girault
  Denis Herve

  (Weizmann Institute)

  Julia Shifmann

The “compneur” group



Daniel McGreal

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Camille Laibe

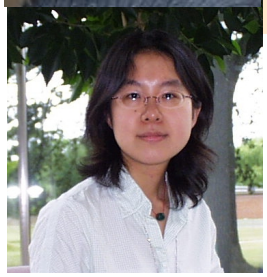


Dagmar Koehn

David Marshall

Dominic Tolle

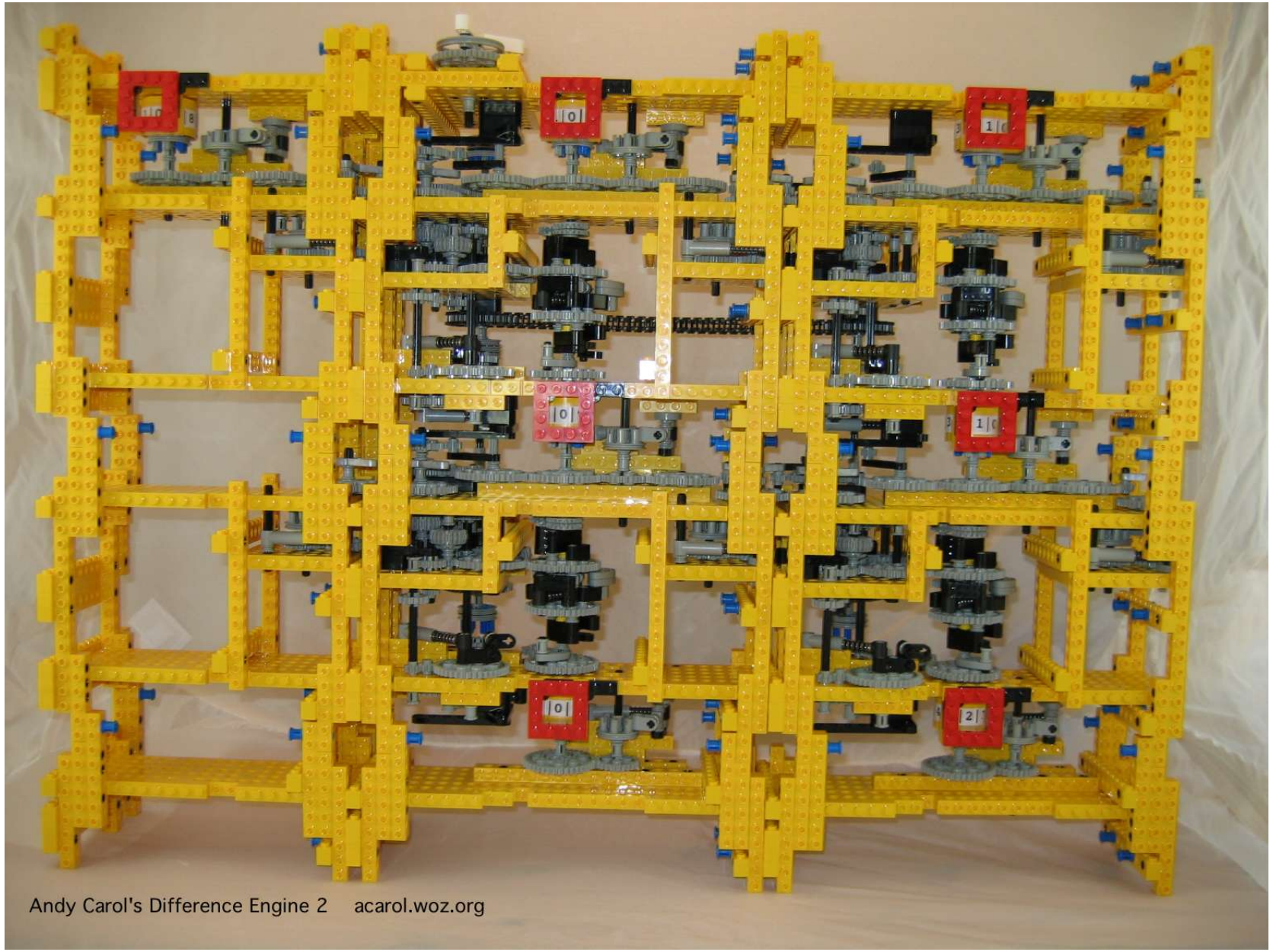
Eric Fernandez



Lu Li


Melanie Stefan


Stuart Edelstein


Anika Oellrich



Andy Carol's Difference Engine 2 acarol.woz.org

Derivation of Adair's constants

$$K_1 = \frac{\text{concentration of ligand binding sites} \times \text{ligand concentration}}{\text{concentration of protein bound to exactly one ligand molecule}}$$

$$= \frac{4[P_0][X]}{[P_1]}$$

Derivation of Adair's constants

$$K_1 = \frac{4([R_0] + [T_0])[X]}{[R_1] + [T_1]}$$

Derivation of Adair's constants

$$K_1 = 4\frac{([R_0] + [T_0])[X]}{([R_A] + [R_B] + [R_C] + [R_D]) + ([T_A] + [T_B] + [T_C] + [T_D])}$$

Derivation of Adair's constants

$$K_1 = 4\frac{([R_0] + L[R_0])[X]}{\left(\frac{[R_0][X]}{K_A^R} + \frac{[R_0][X]}{K_B^R} + \frac{[R_0][X]}{K_C^R} + \frac{[R_0][X]}{K_D^R}\right) + \left(\frac{[T_0][X]}{K_A^T} + \frac{[T_0][X]}{K_B^T} + \frac{[T_0][X]}{K_C^T} + \frac{[T_0][X]}{K_D^T}\right)}$$

$$= 4\frac{[R_0][X](1+L)}{[R_0][X]\left(\frac{1}{K_A^R} + \frac{1}{K_B^R} + \frac{1}{K_C^R} + \frac{1}{K_D^R}\right) + [T_0][X]\left(\frac{1}{K_A^T} + \frac{1}{K_B^T} + \frac{1}{K_C^T} + \frac{1}{K_D^T}\right)} =$$

$$= 4\frac{[R_0][X](1+L)}{[R_0][X]\left(\frac{1}{K_A^R} + \frac{1}{K_B^R} + \frac{1}{K_C^R} + \frac{1}{K_D^R}\right) + L[R_0][X]\left(\frac{1}{K_A^T} + \frac{1}{K_B^T} + \frac{1}{K_C^T} + \frac{1}{K_D^T}\right)}$$

EMBL-EBI

Chemical model of DARPP-32 regulation