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Modeling synaptic plasticity at molecular and sub-cellular levels

Nicolas Le Novère, EMBL-EBI

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European Bioinformatics Institute

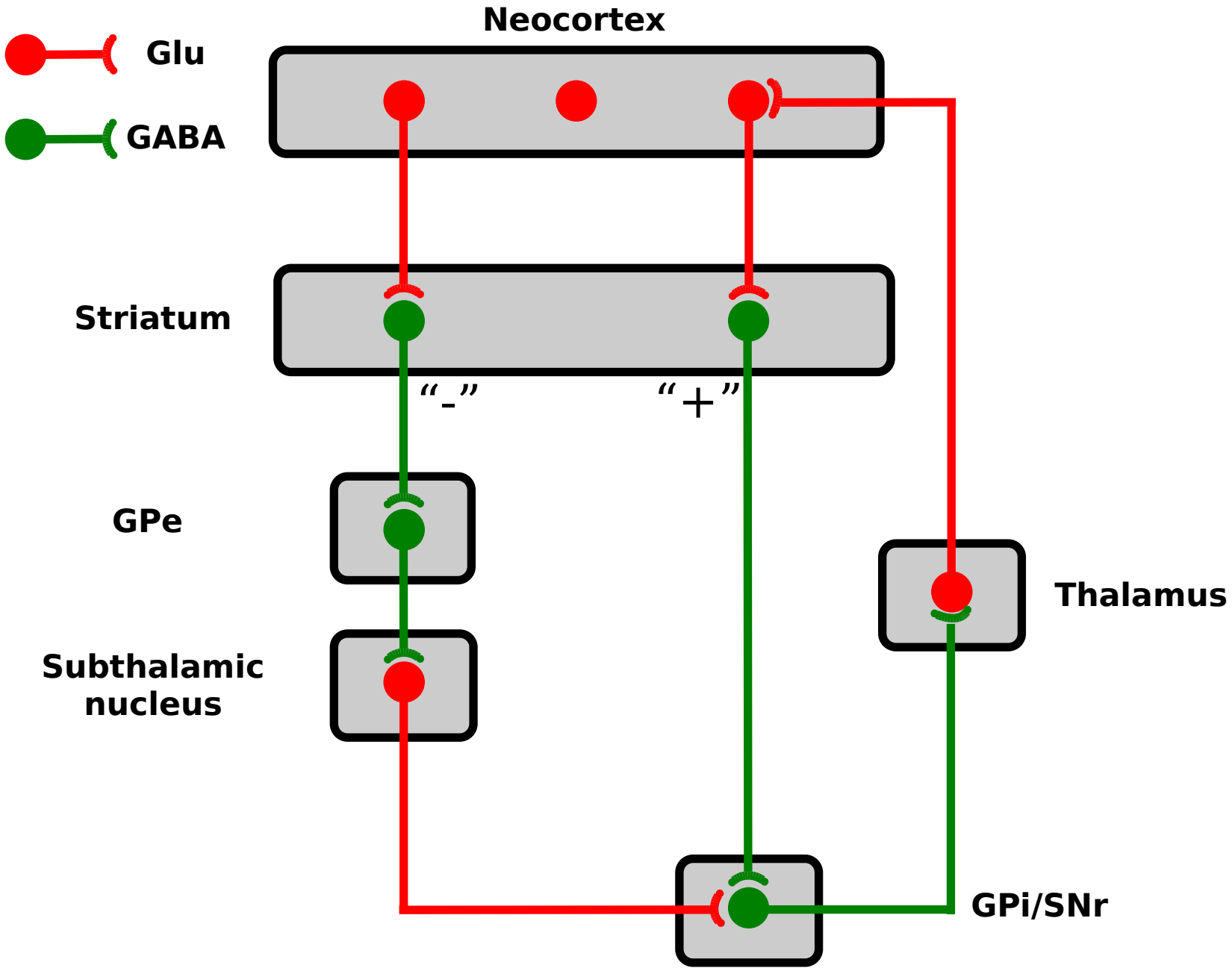
British outstation of the European Molecular Biology Laboratory

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

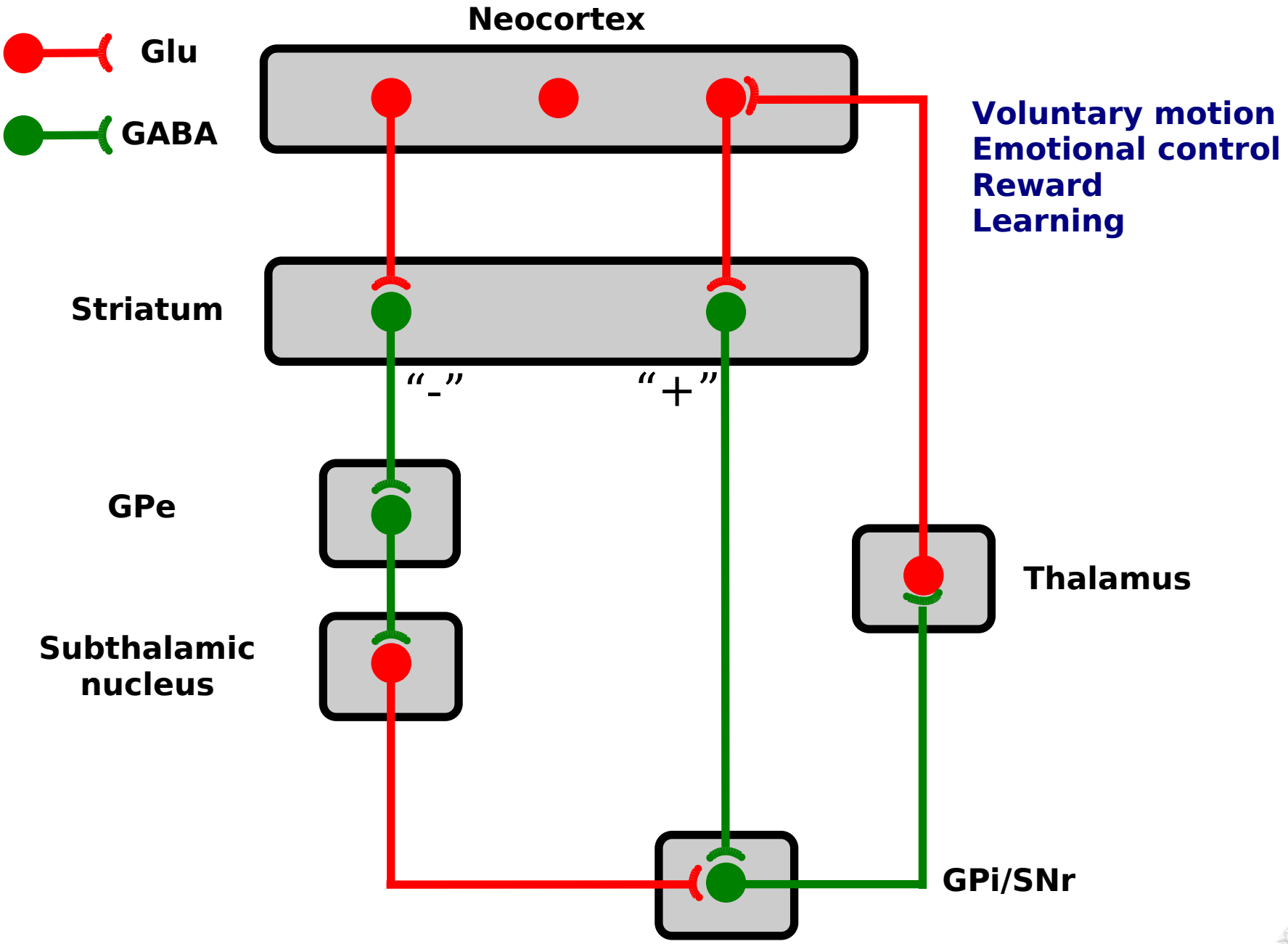
- Research groups
  - Structural Genomics (Thornton)
  - Molecular Evolution (Goldman)
  - Text-Mining (Rebholz-Schumman)
  - Computational Systems Biology (Le Novère)
  - Statistical array analysis (Huber)
  - Genomic analysis of regulatory systems (Luscombe)
  - Systems Biology of ES cells (Bertone)

Intl PhD programme, Marie-Curie PhD training, Master internships

Dopamine mesotelencephalic pathway



Dopamine mesotelencephalic pathway



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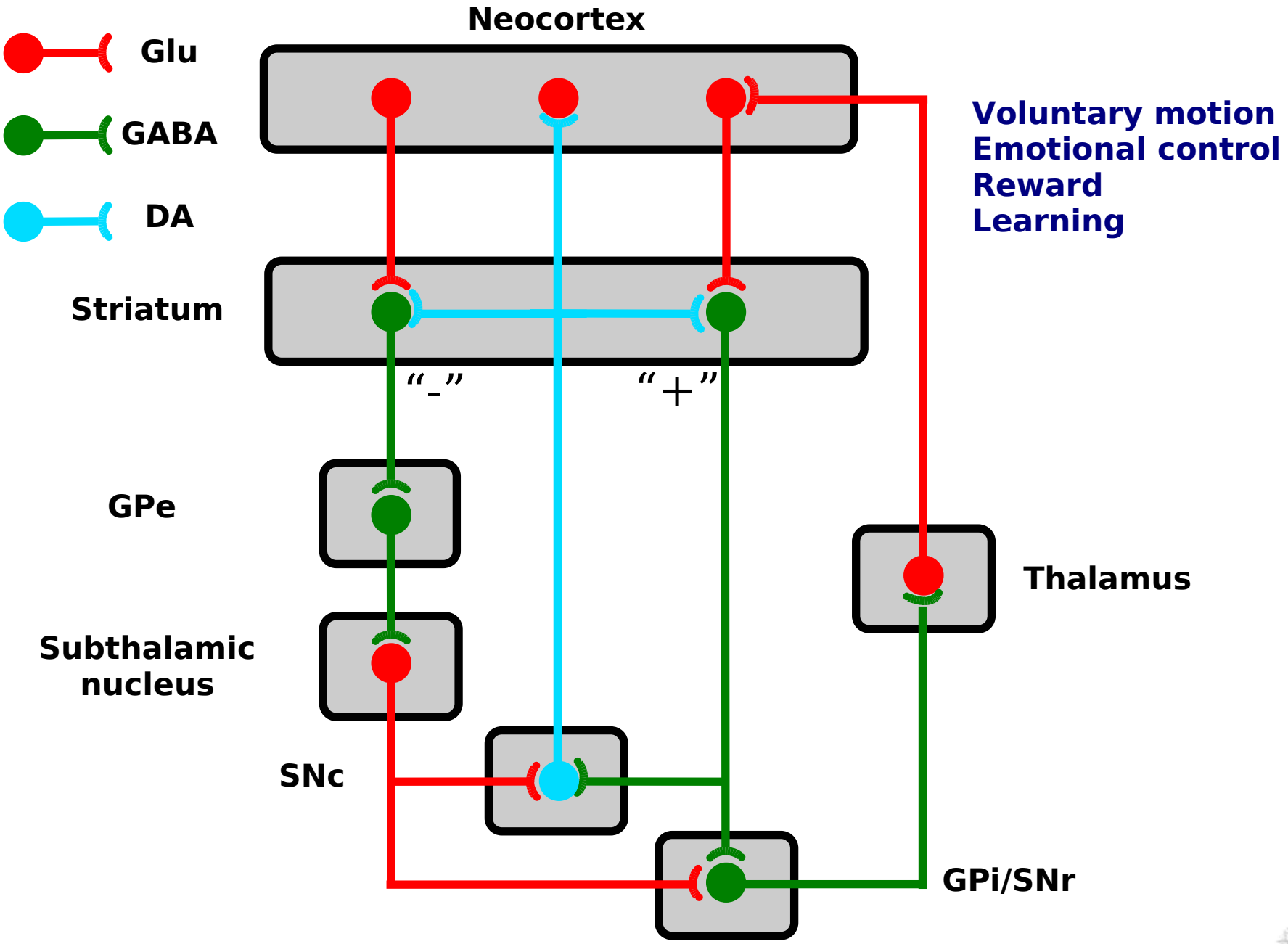

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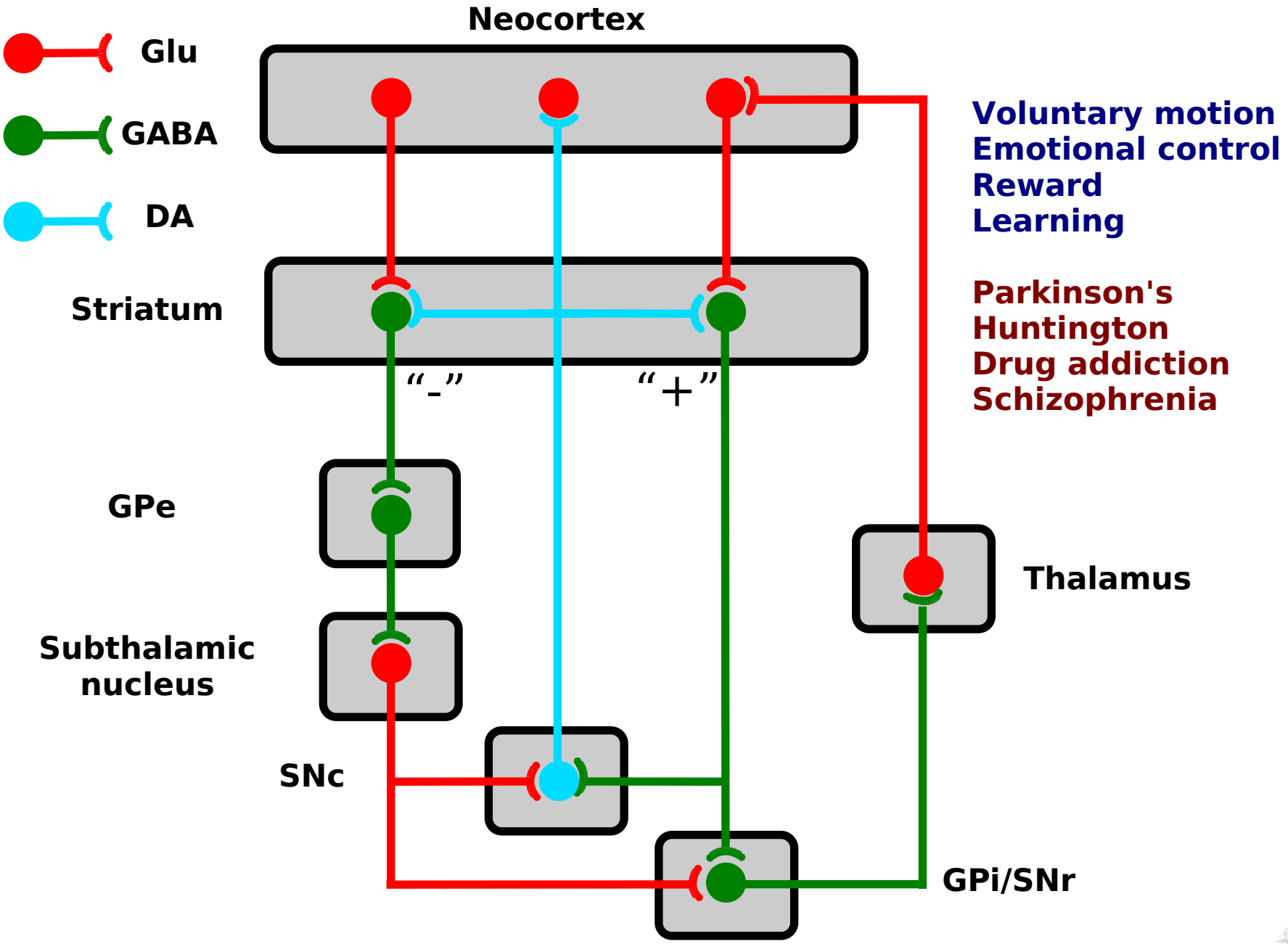

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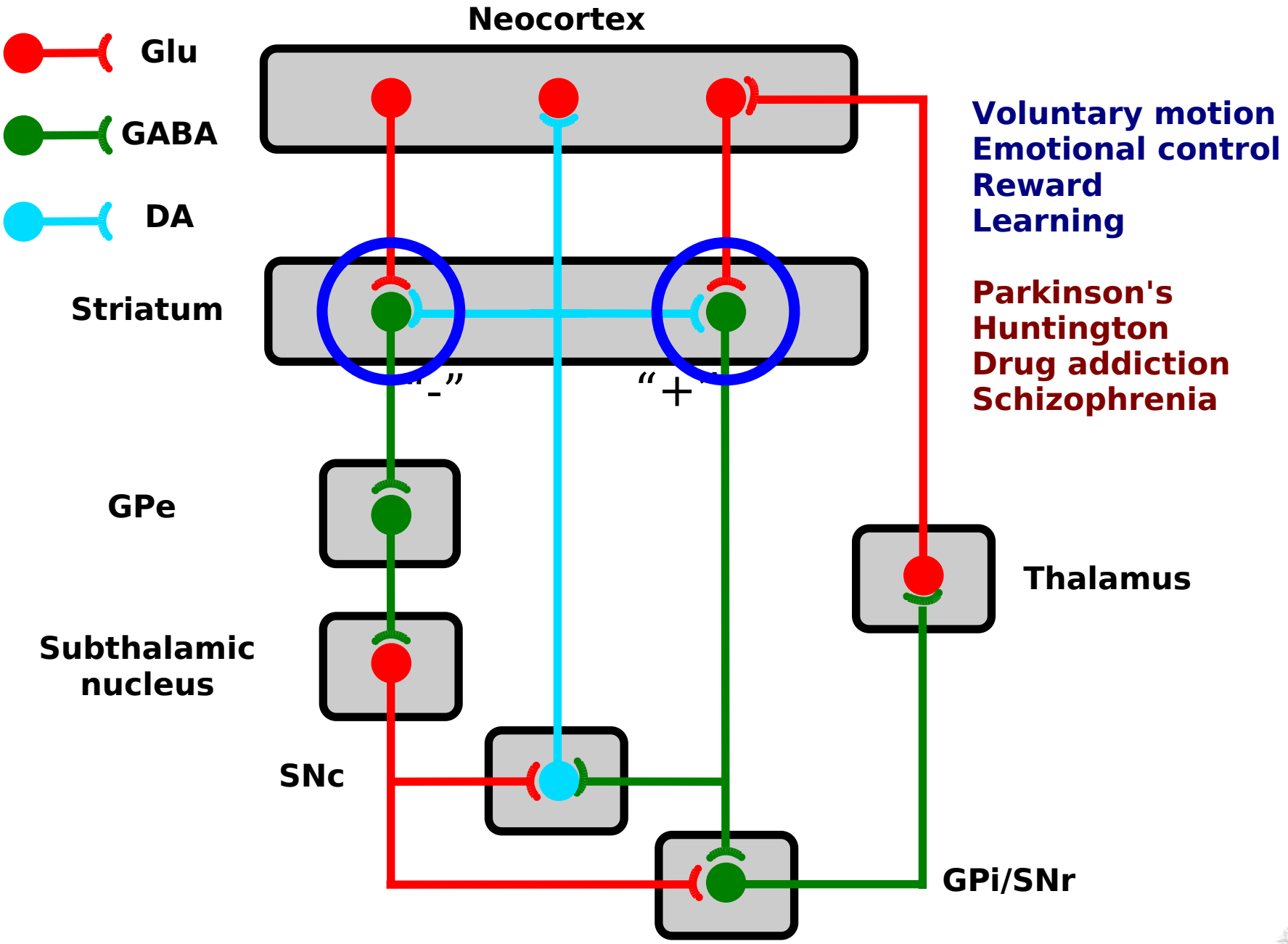
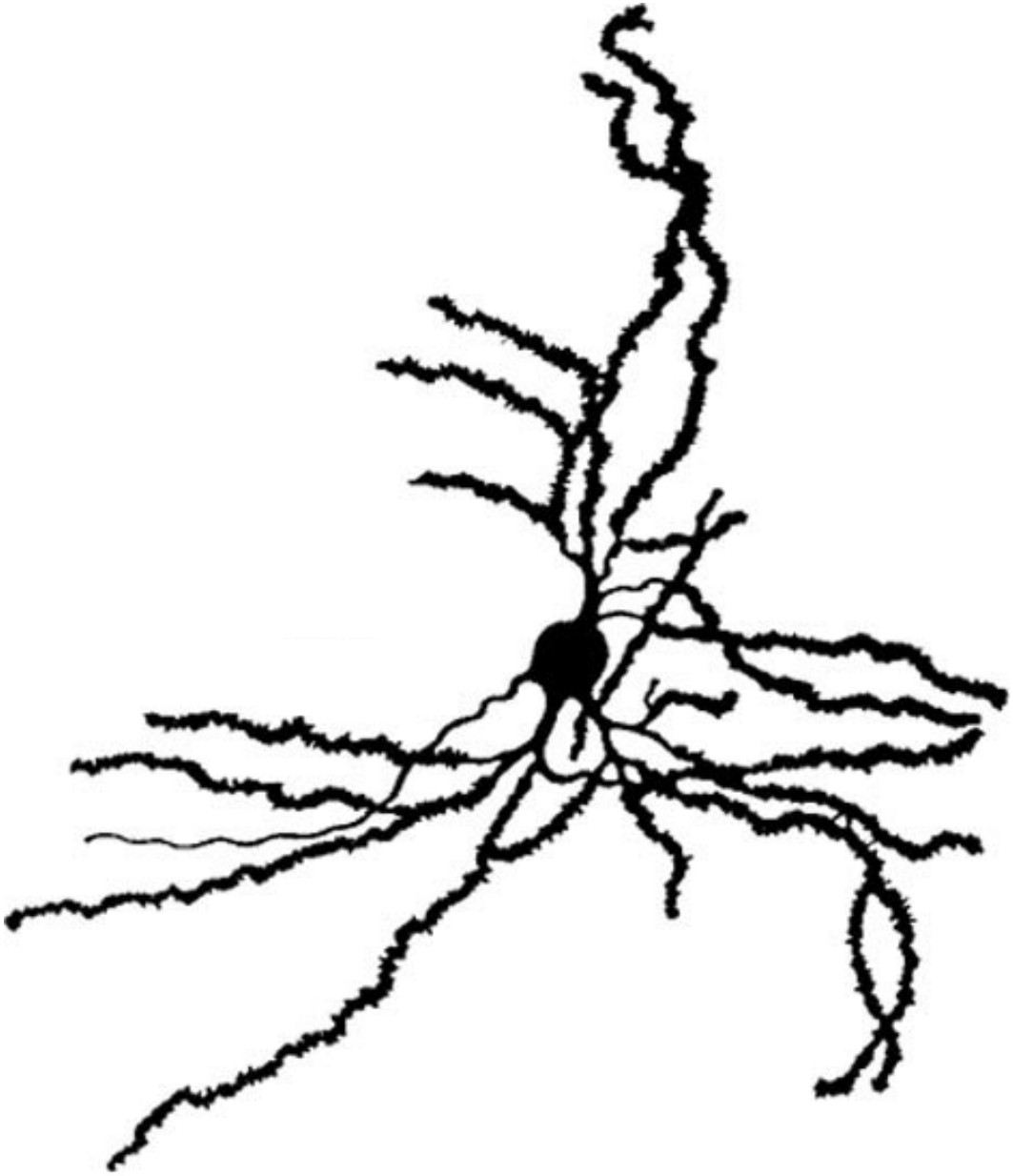
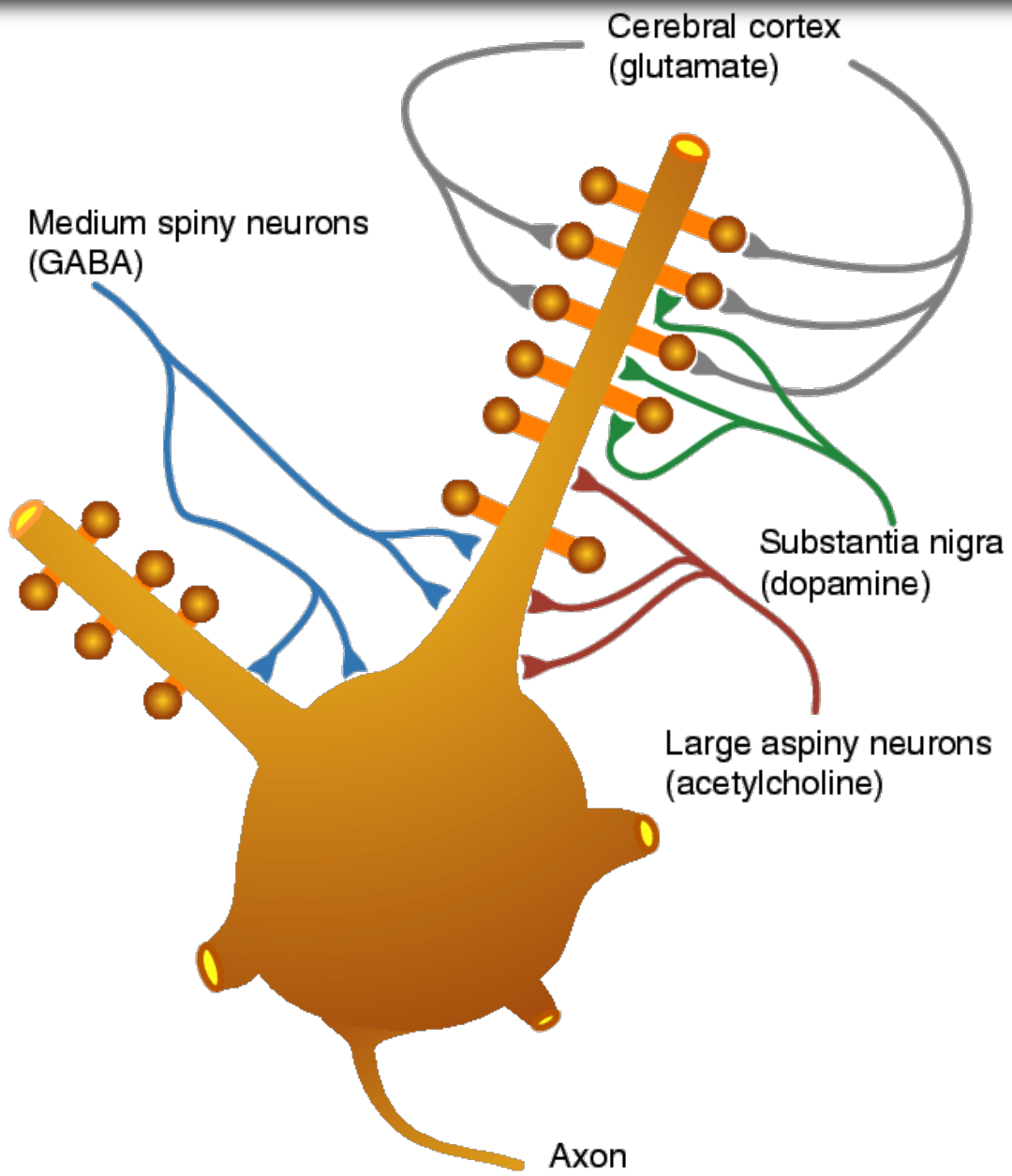


the Medium Spiny Neuron of the striatum



Multiple afferent signals



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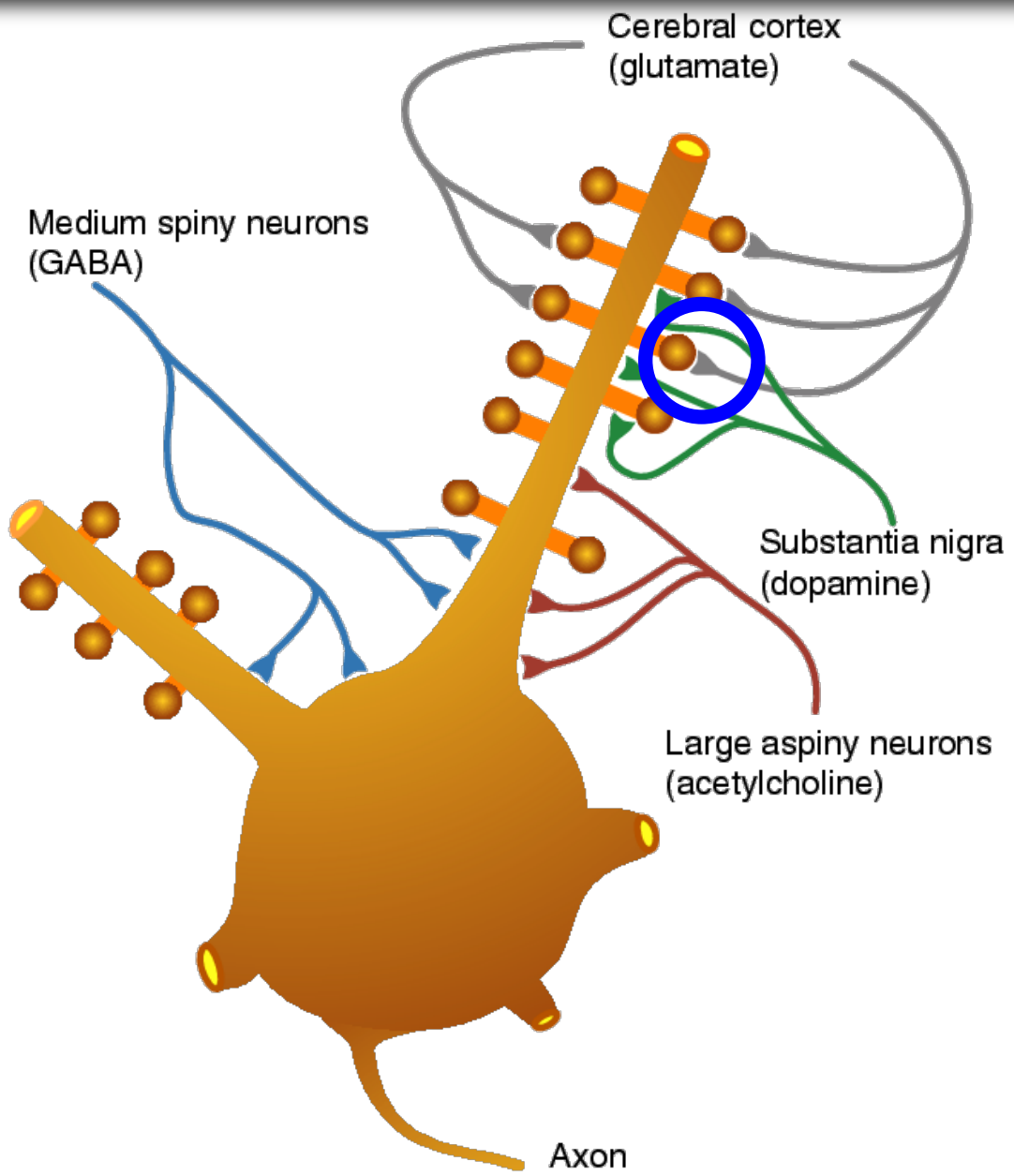
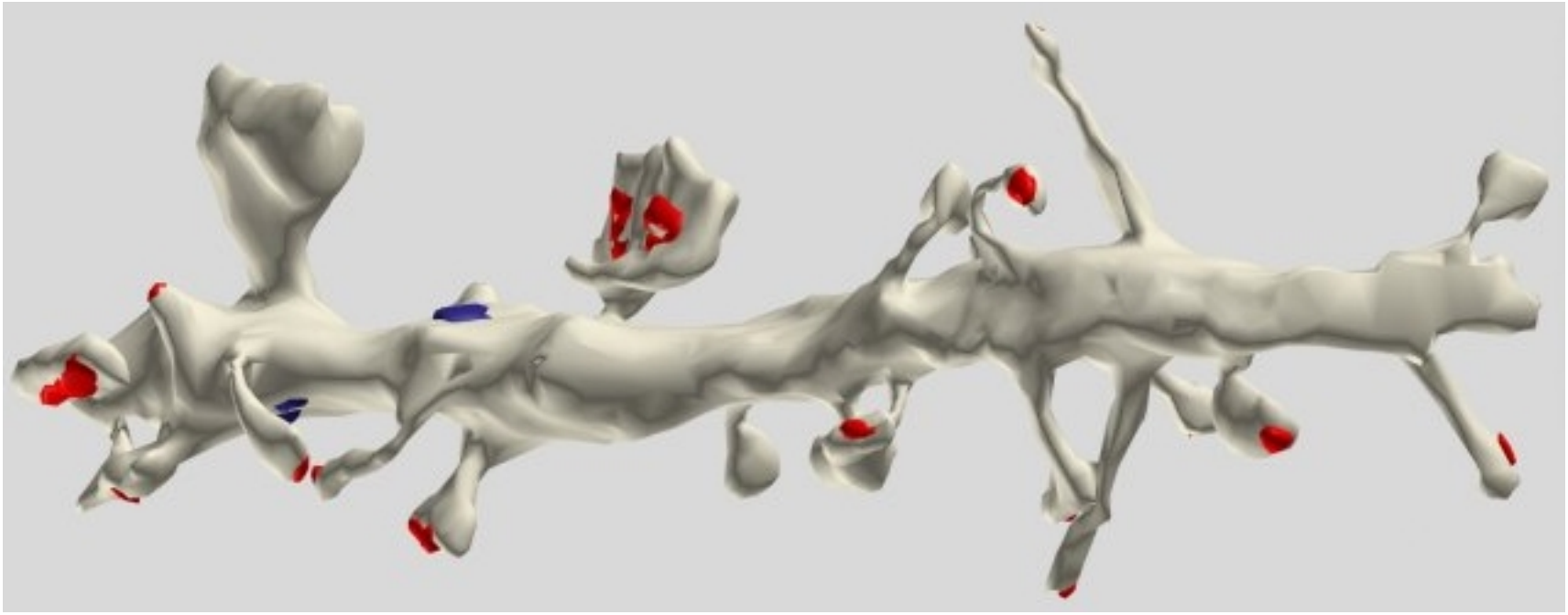
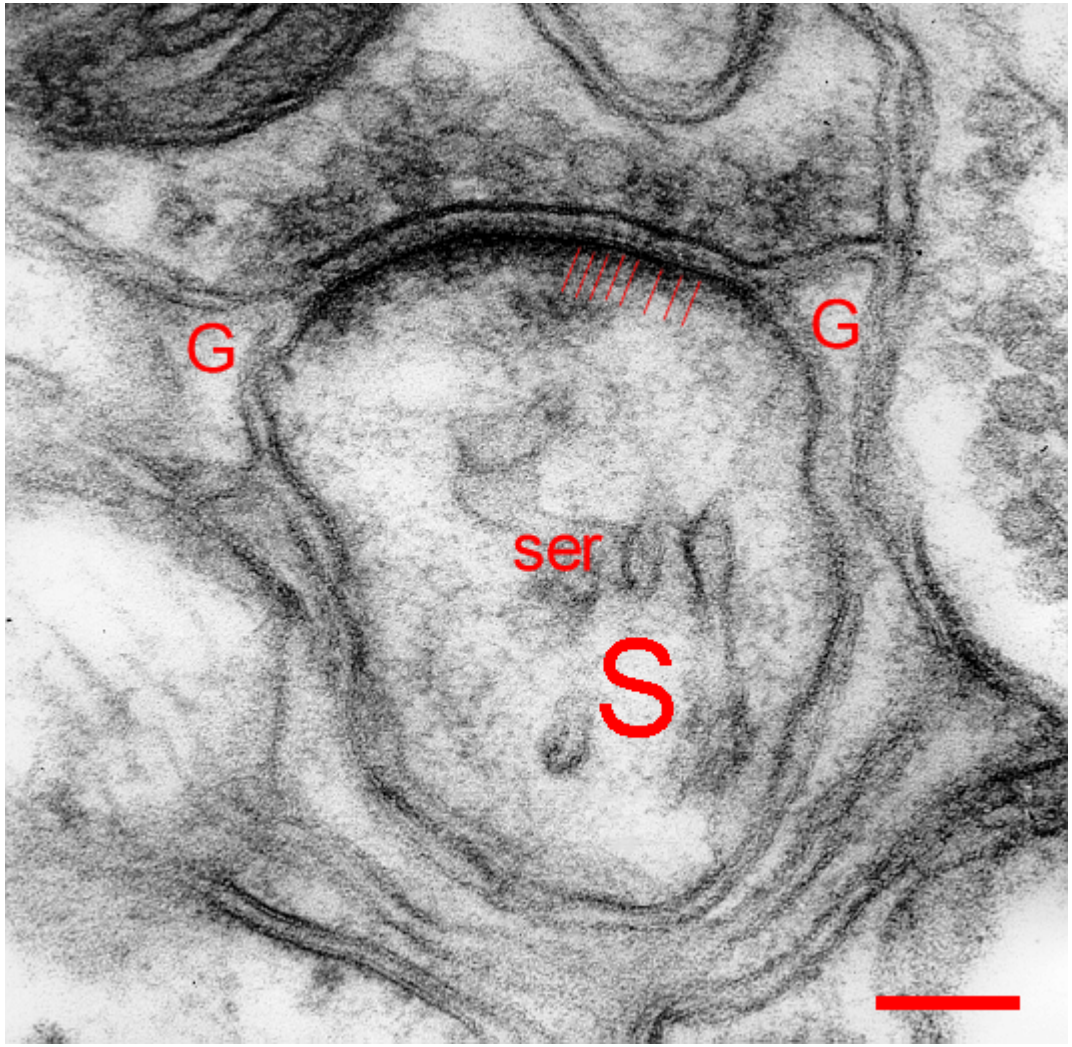


A spiny dendrite



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

The spine as a “mini-cell”



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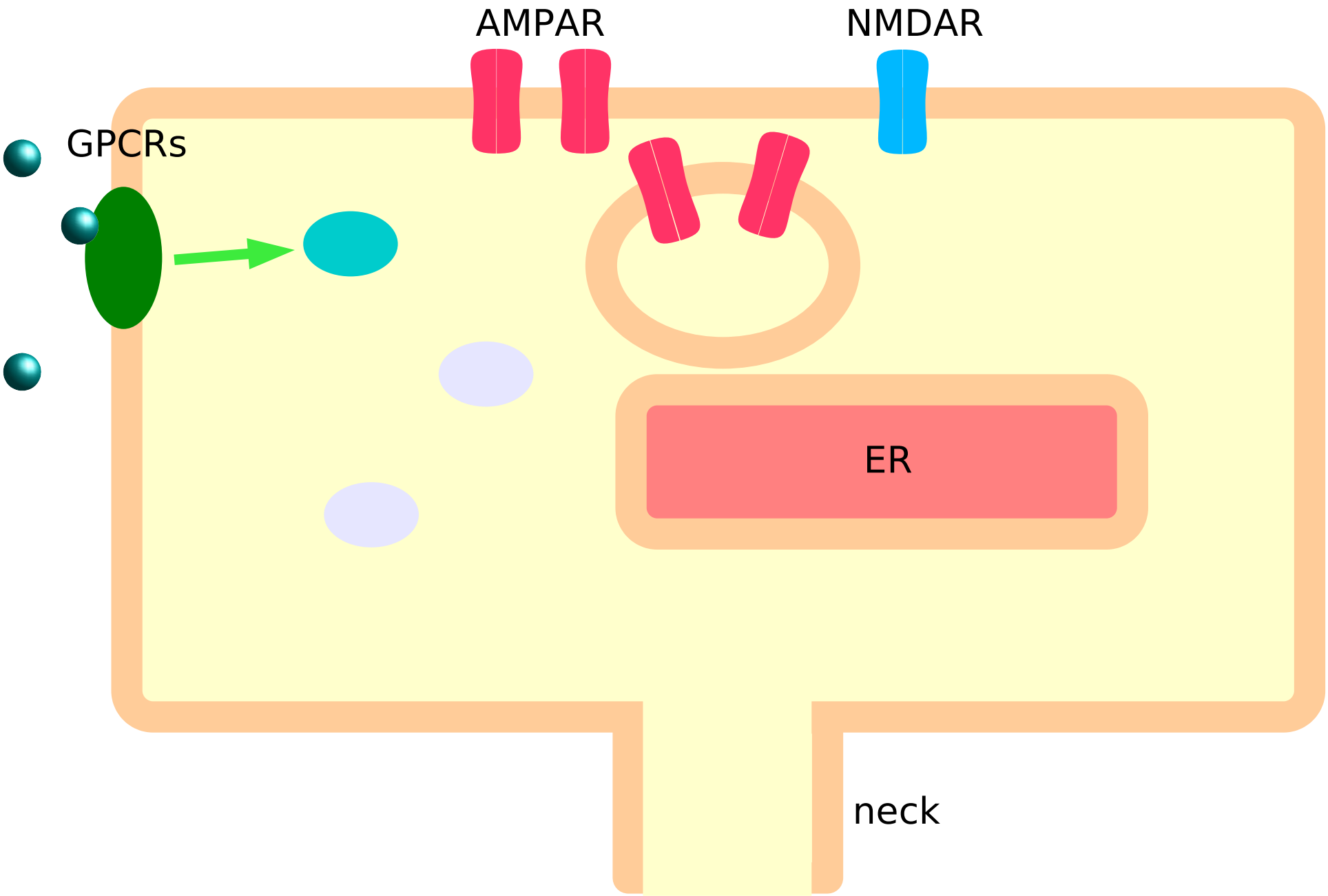
Signalling at the dendritic spine



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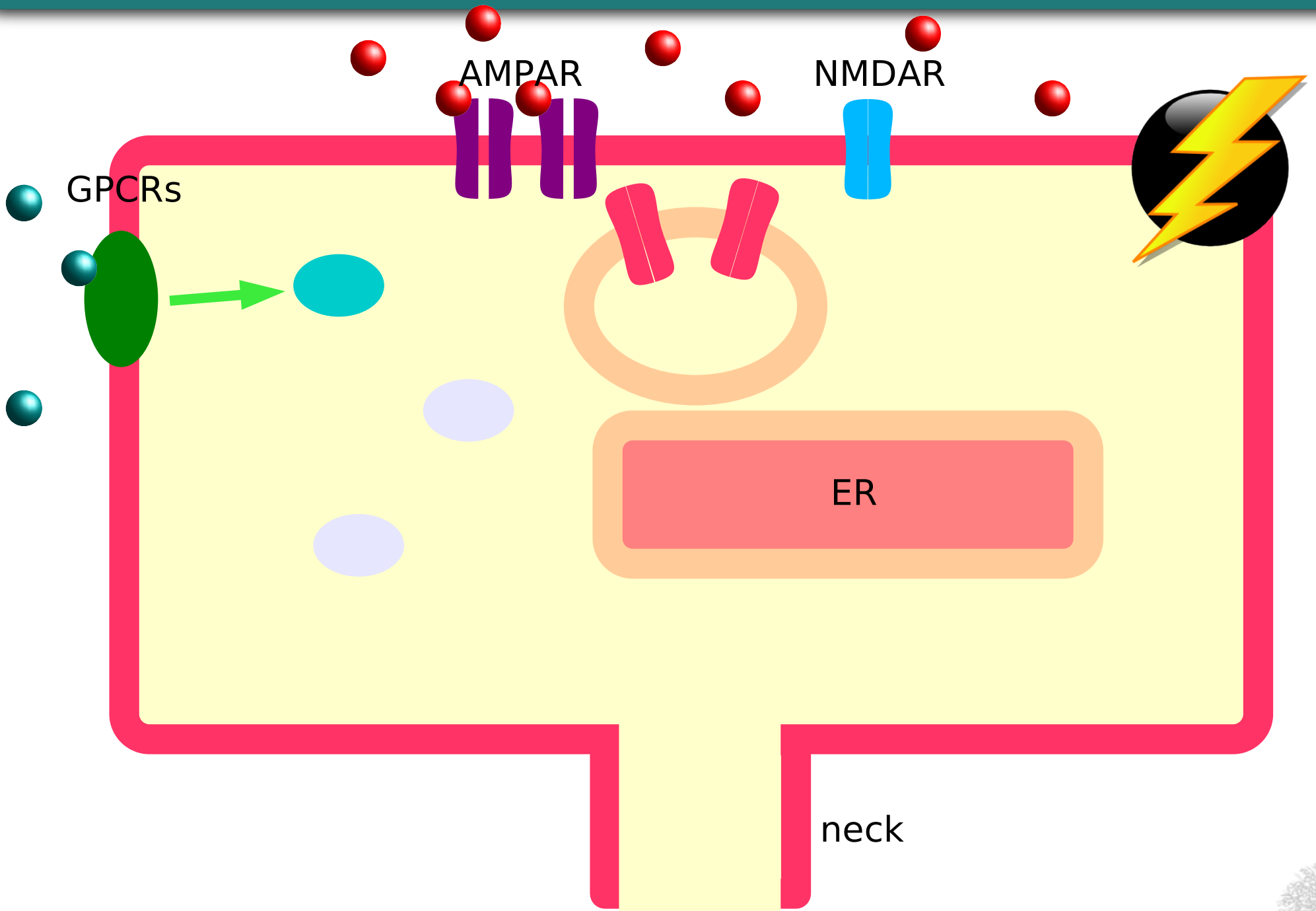

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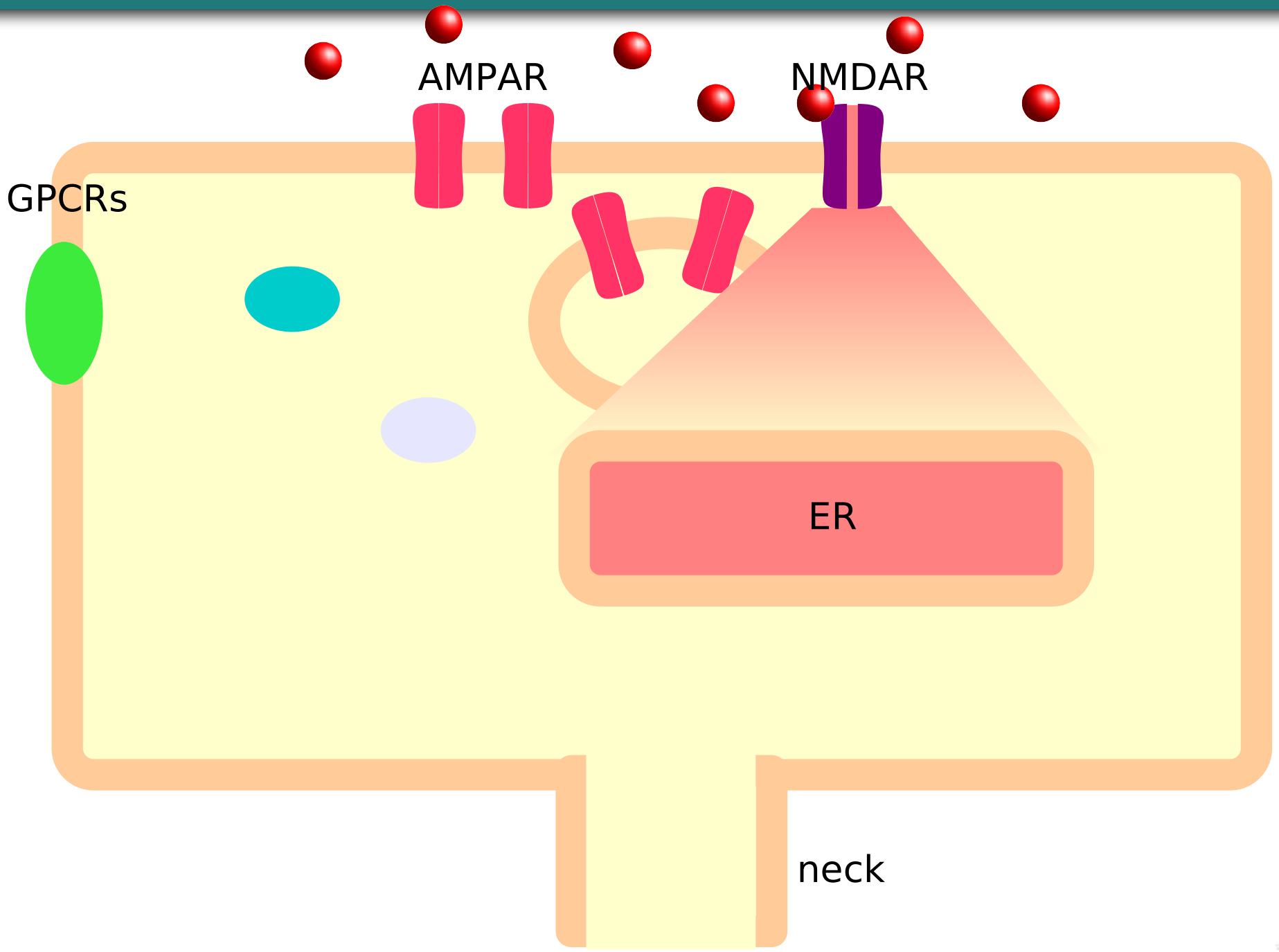

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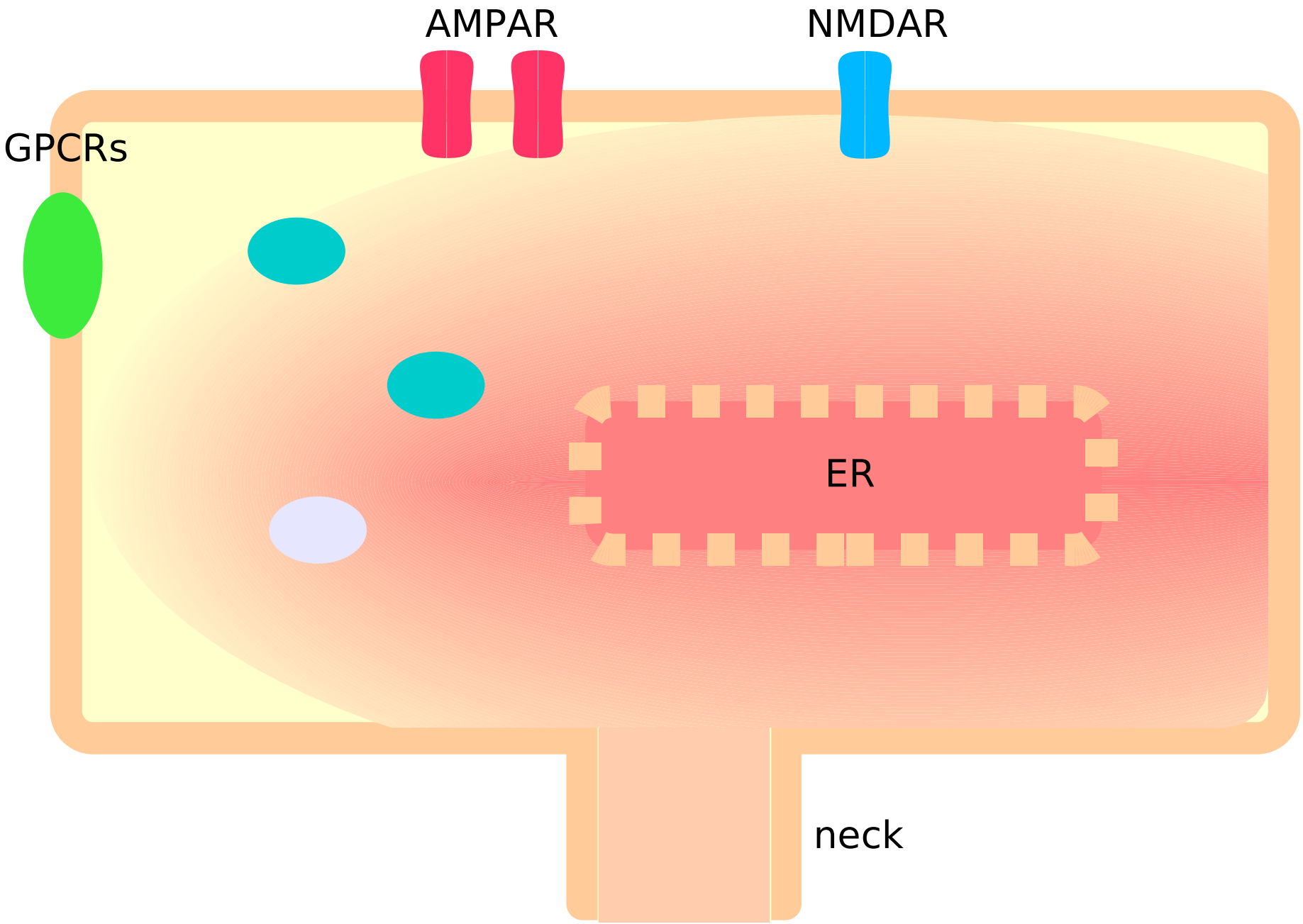
Signalling at the dendritic spine



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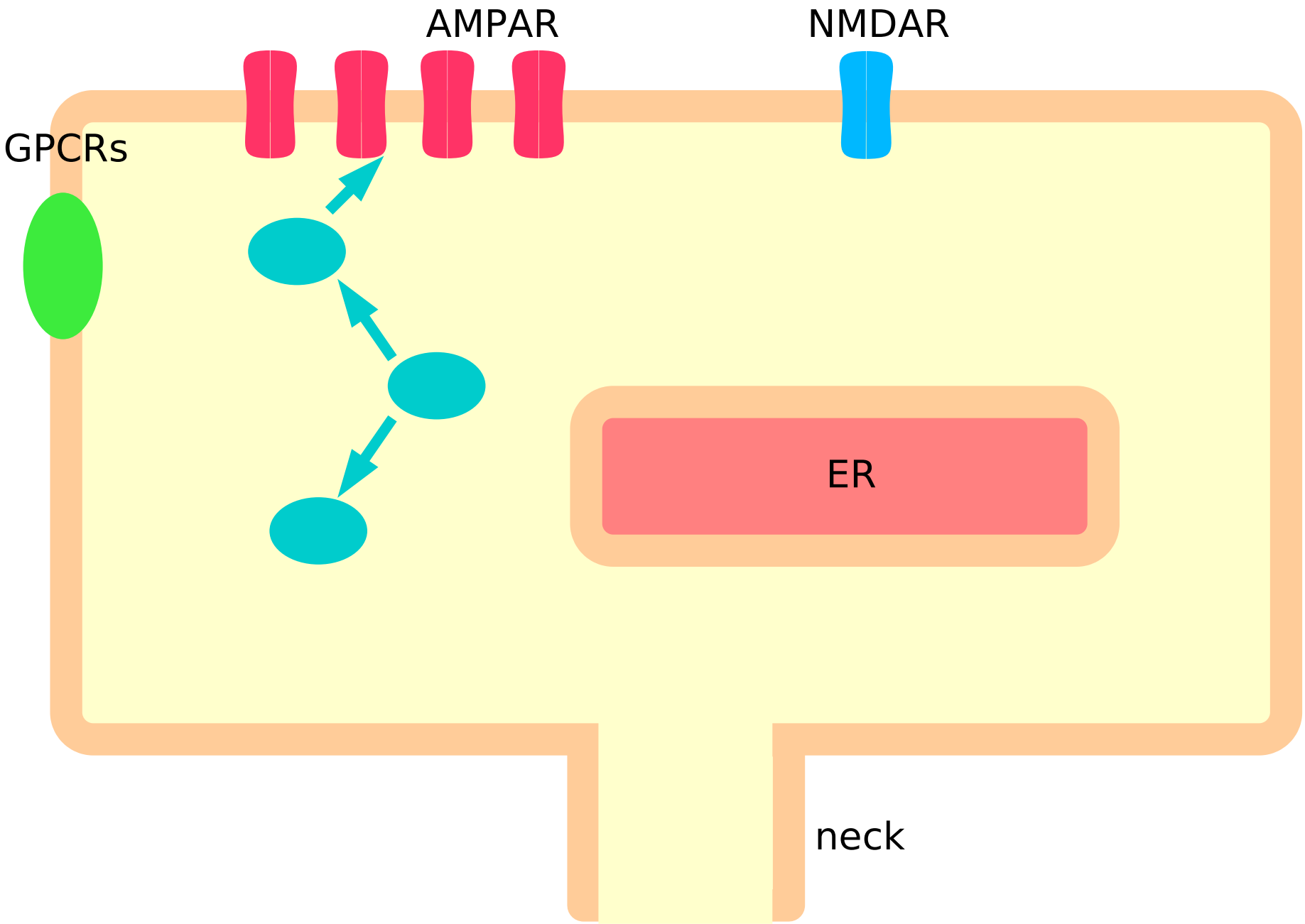
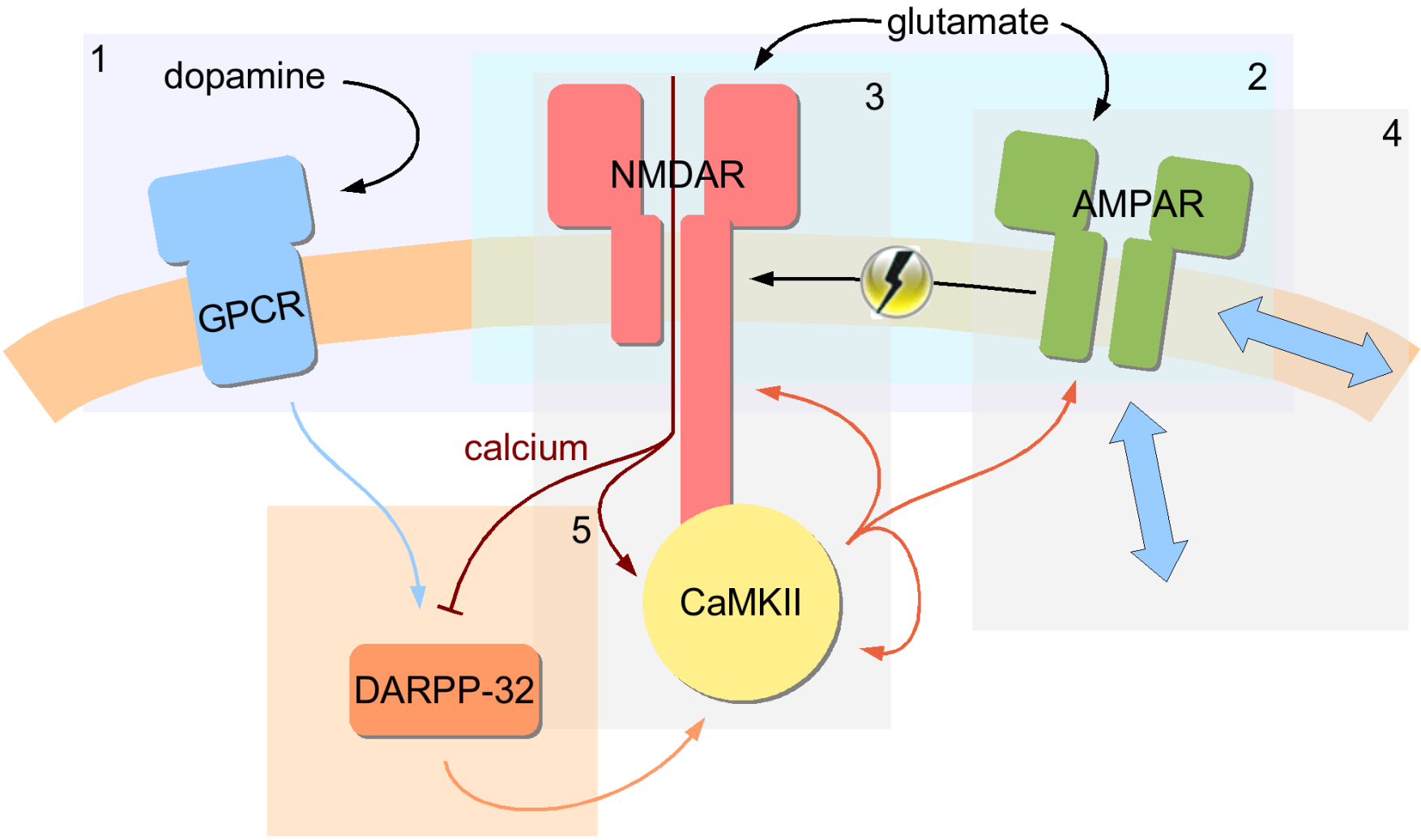


Diversity of questions and methods

- Three types of information conveyed:
  - Propagation of electrical signals (leave the spine)
  - Diffusion of chemical signals (leave the spine)
  - Transitions between “states” (conformation, covalent modifications, density etc.)

- Diversity of modelling approaches:
  - electrical modelling (neural-network, cable approximation)
  - chemical kinetics (deterministic, stochastic ...)
  - reaction-diffusion (PDE, finite elements ...)
  - single particle dynamics
  - etc.

The research of the group



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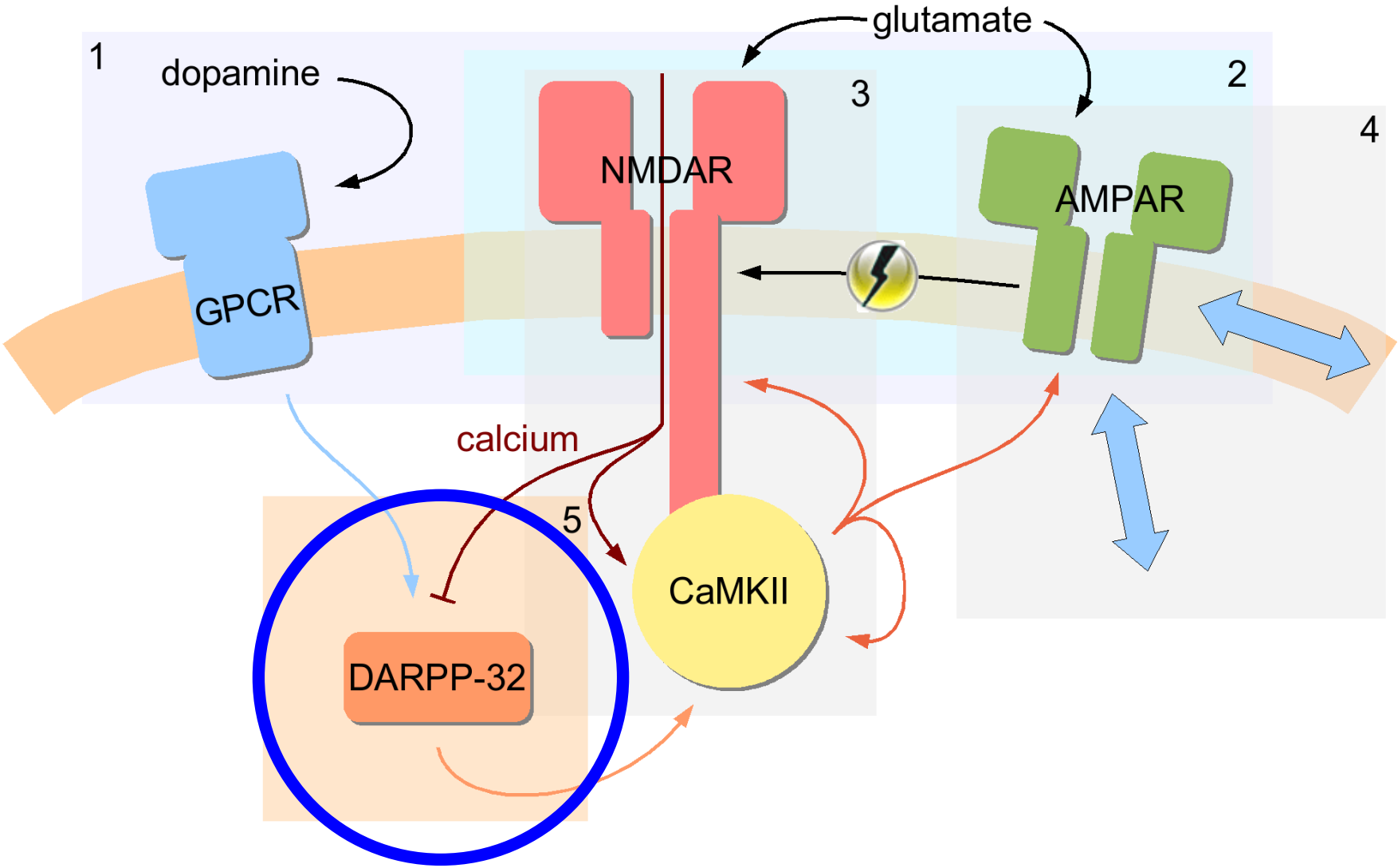

Fernandez E, Schiappa R, Girault JA, Le Novère N (2006)
DARPP-32 is a robust integrator of dopamine and glutamate signals.
PLoS Computational Biology, 2(12): e176.

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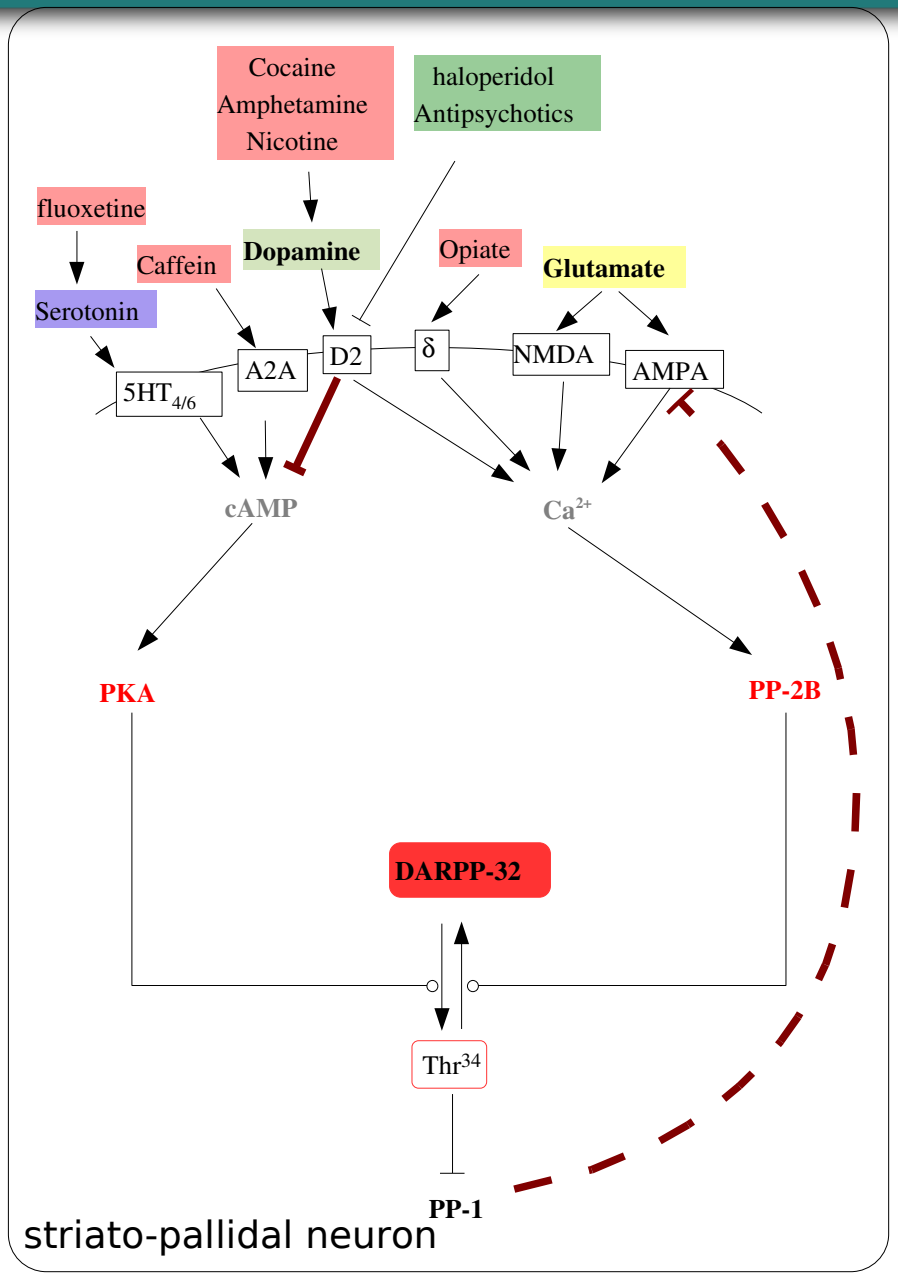
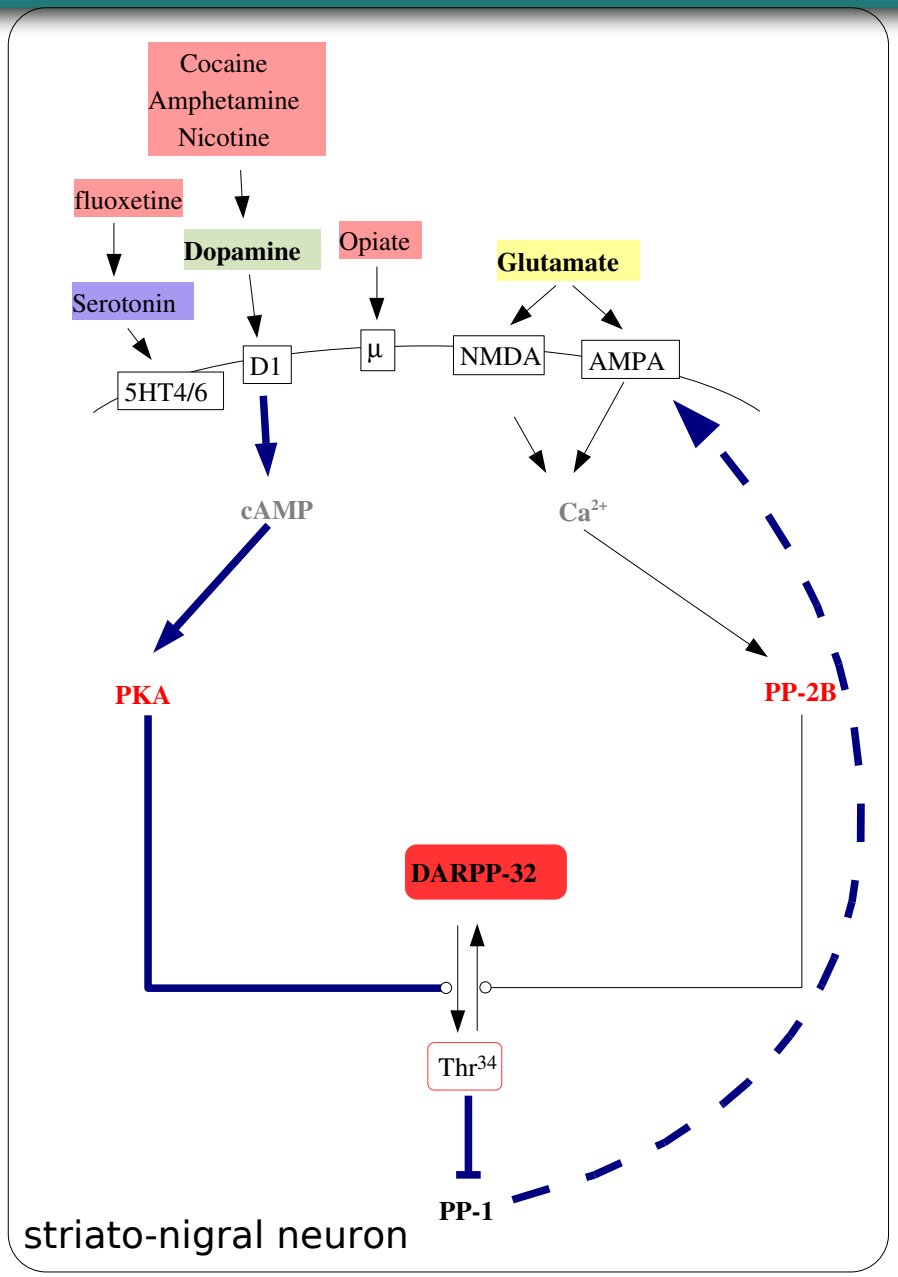
Biological model of DARPP-32 regulation





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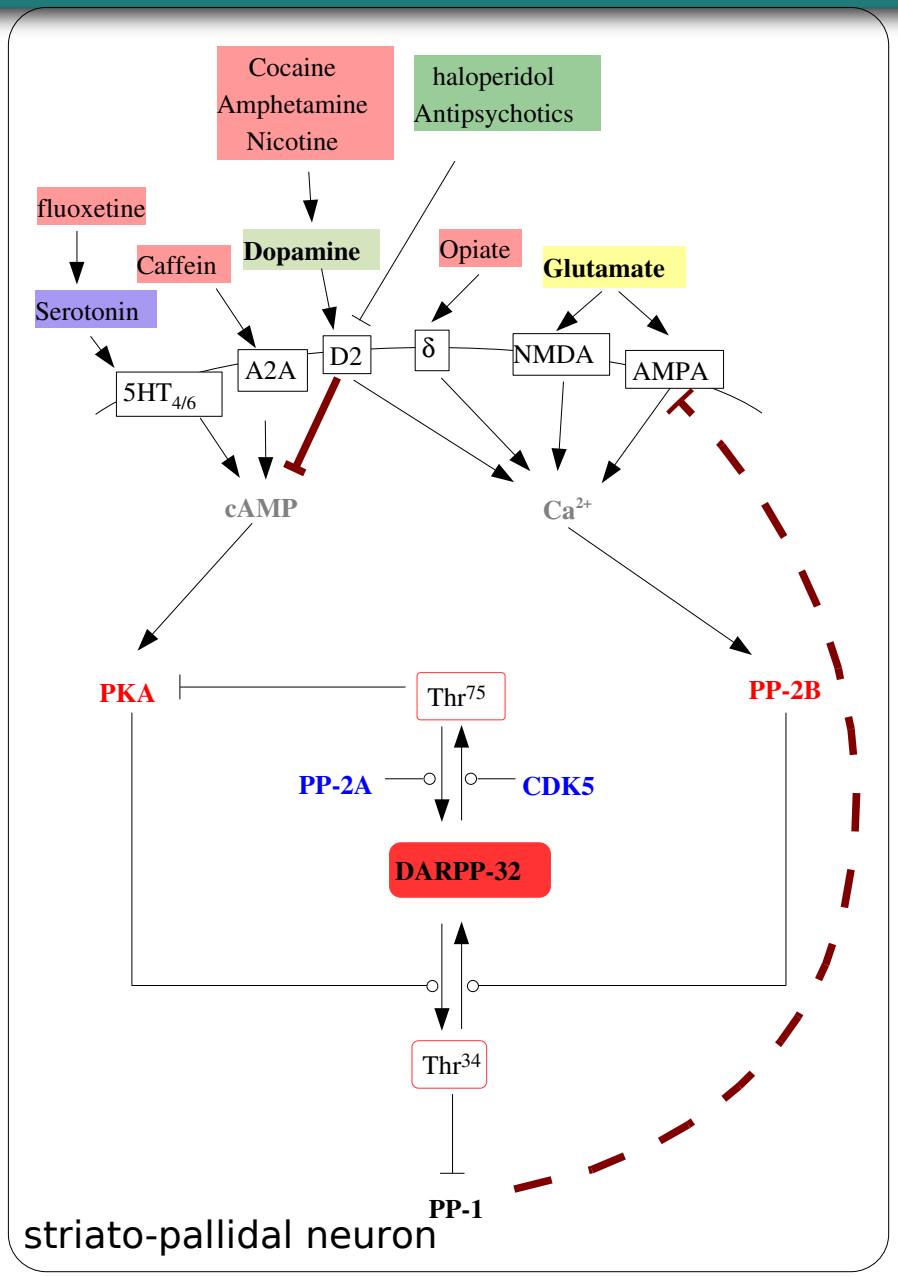

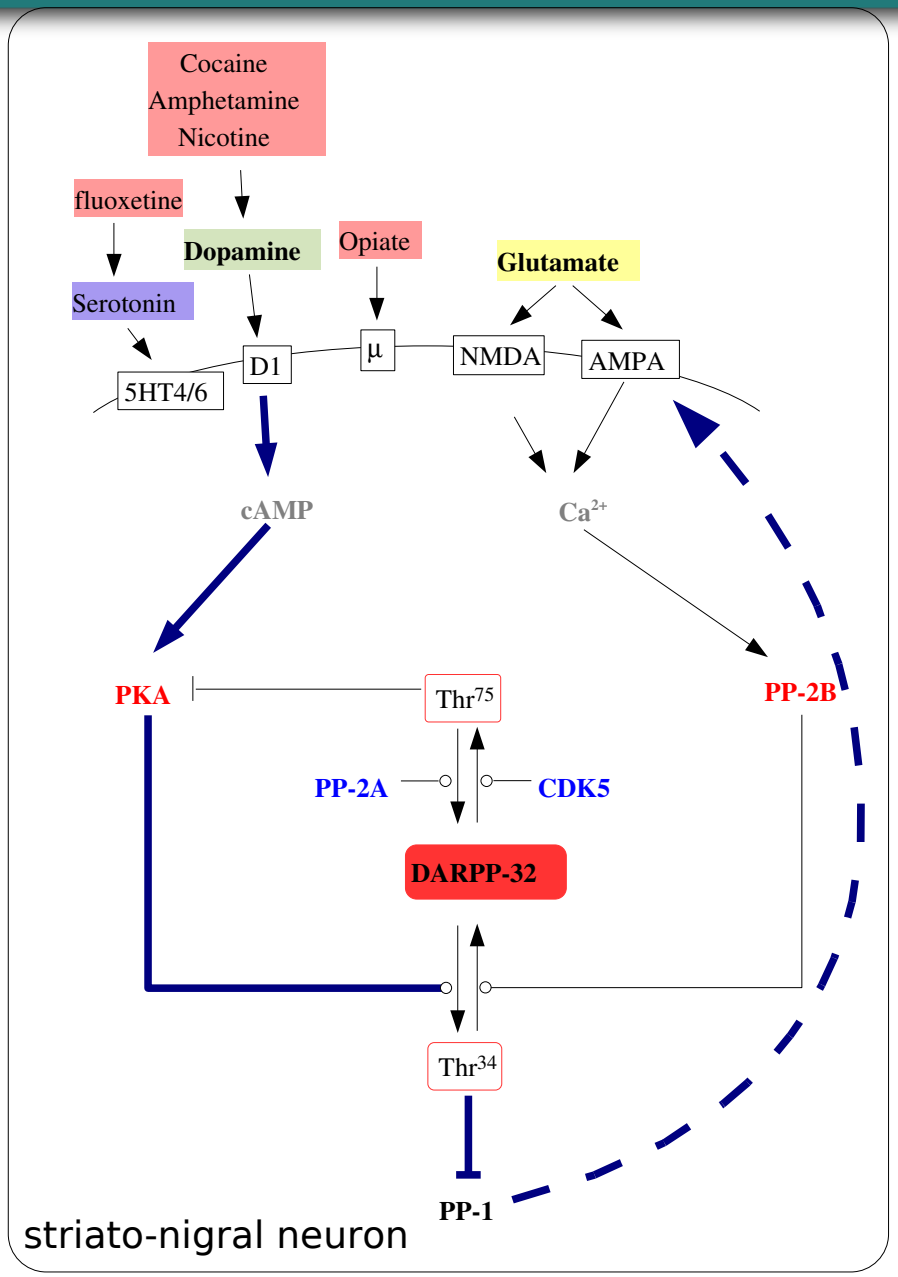

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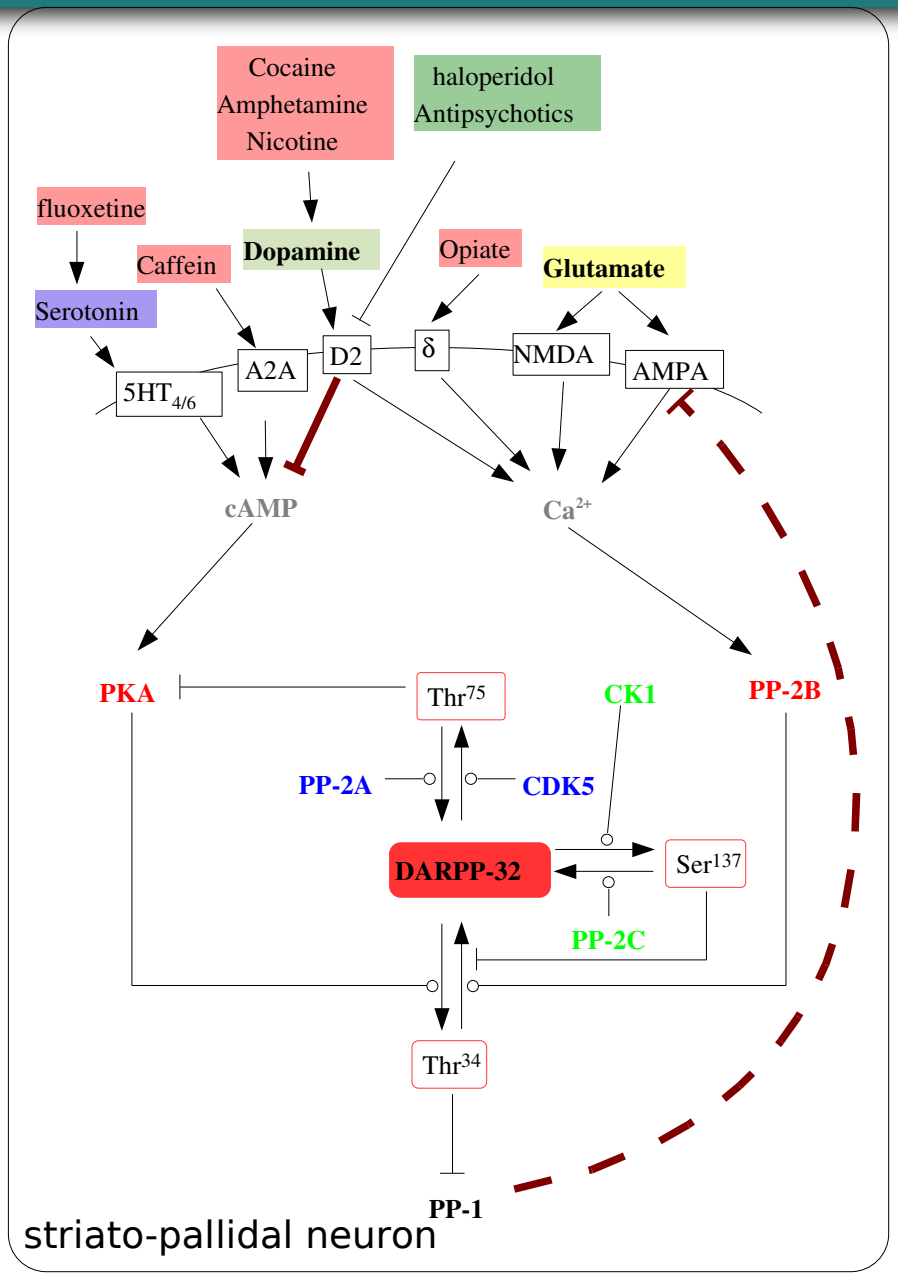

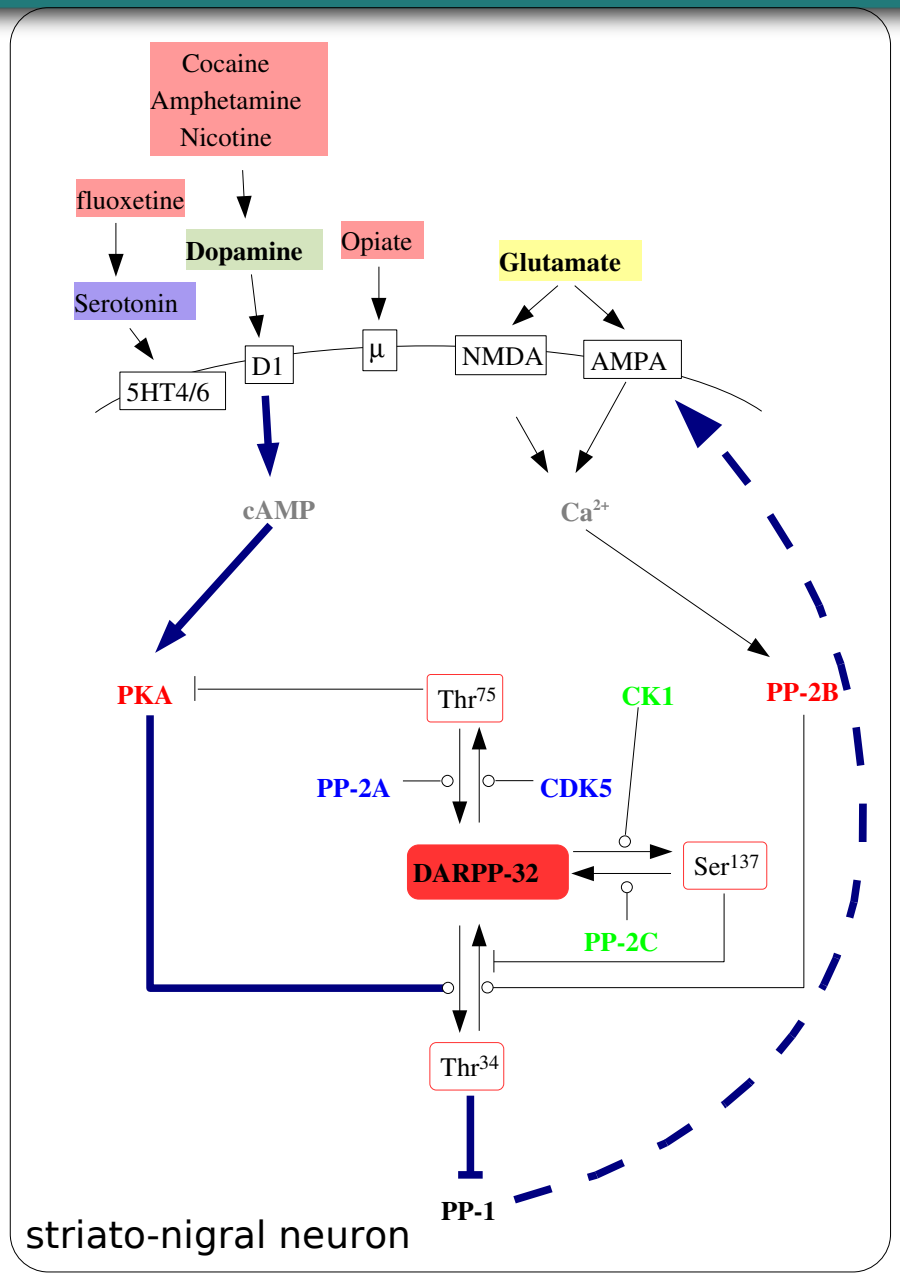

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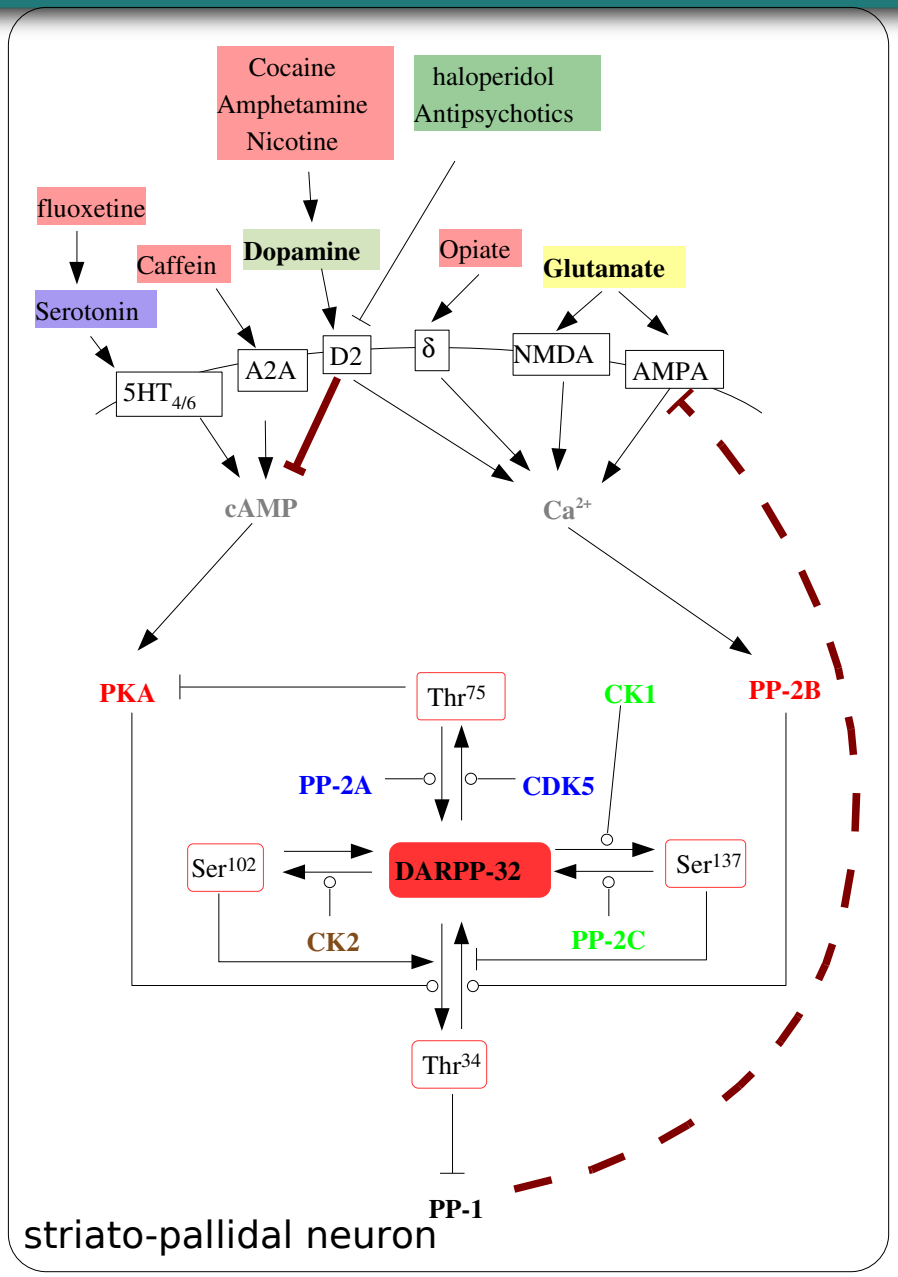

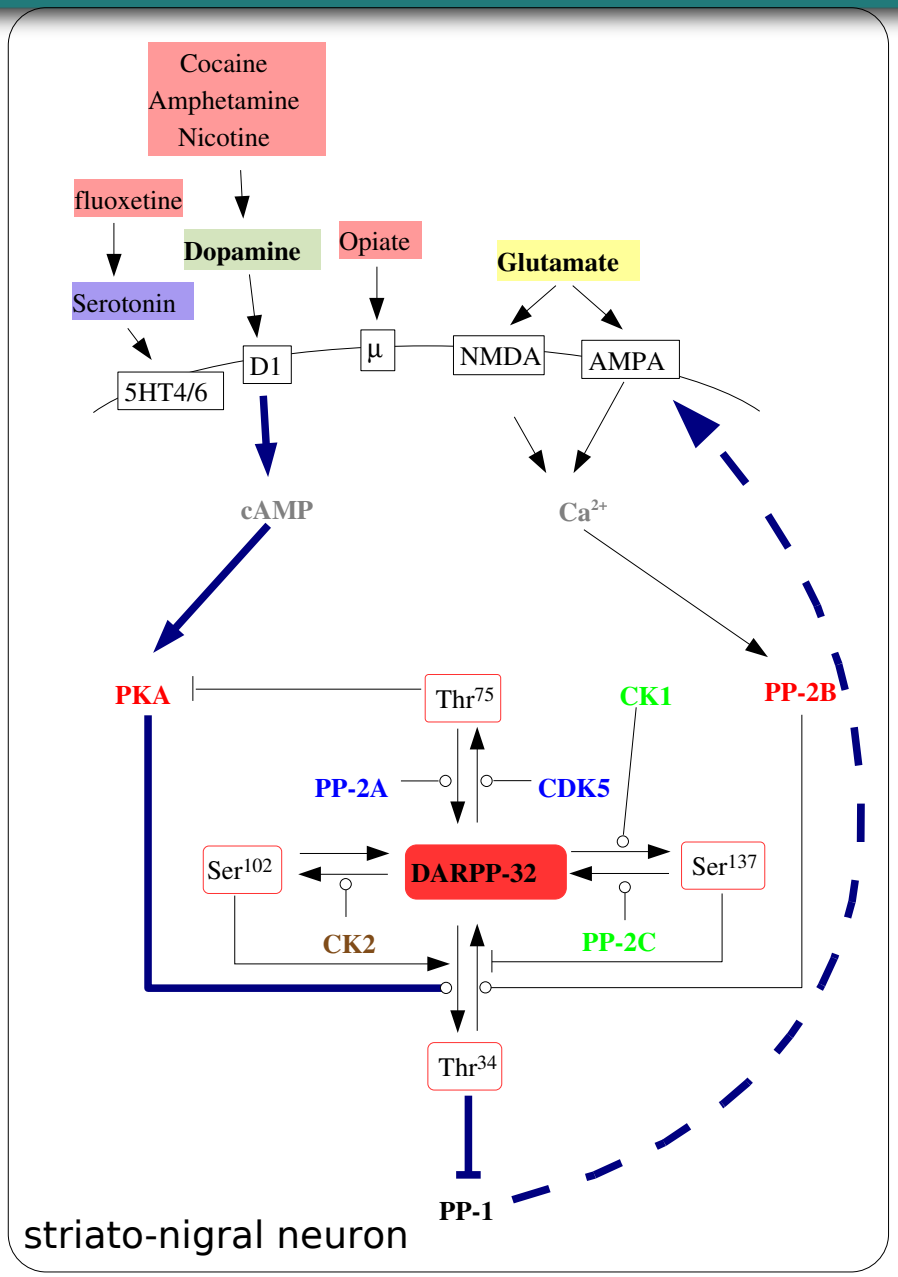

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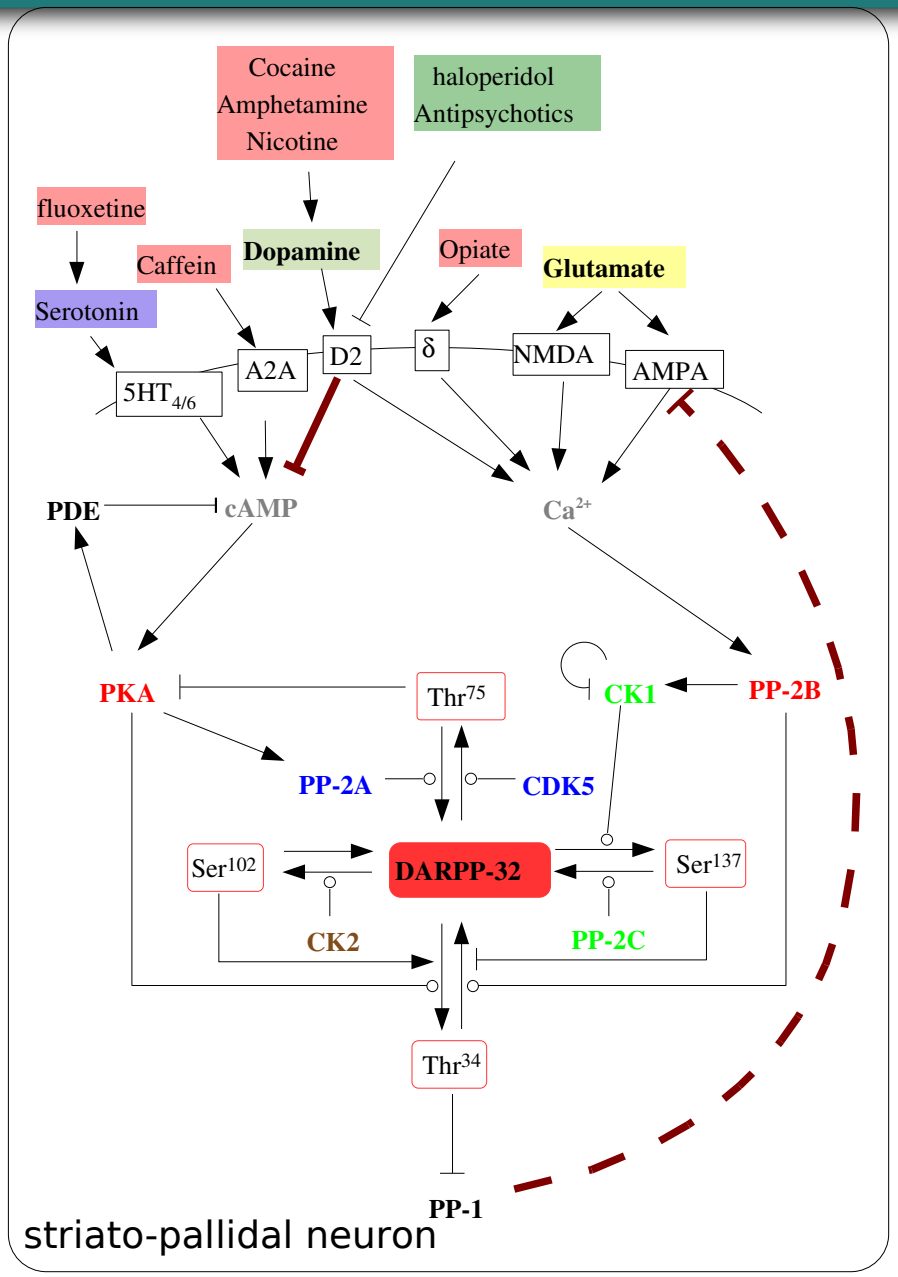

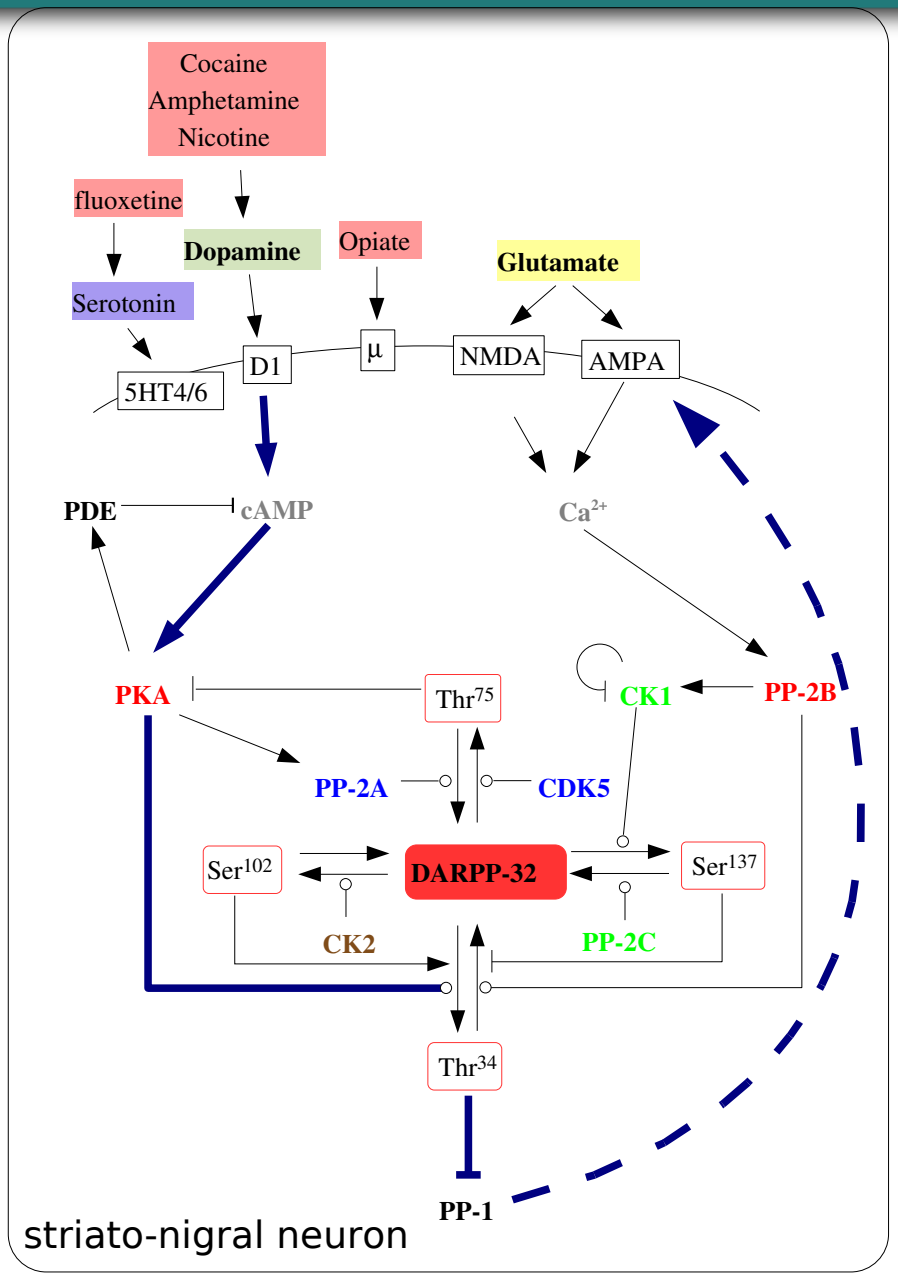

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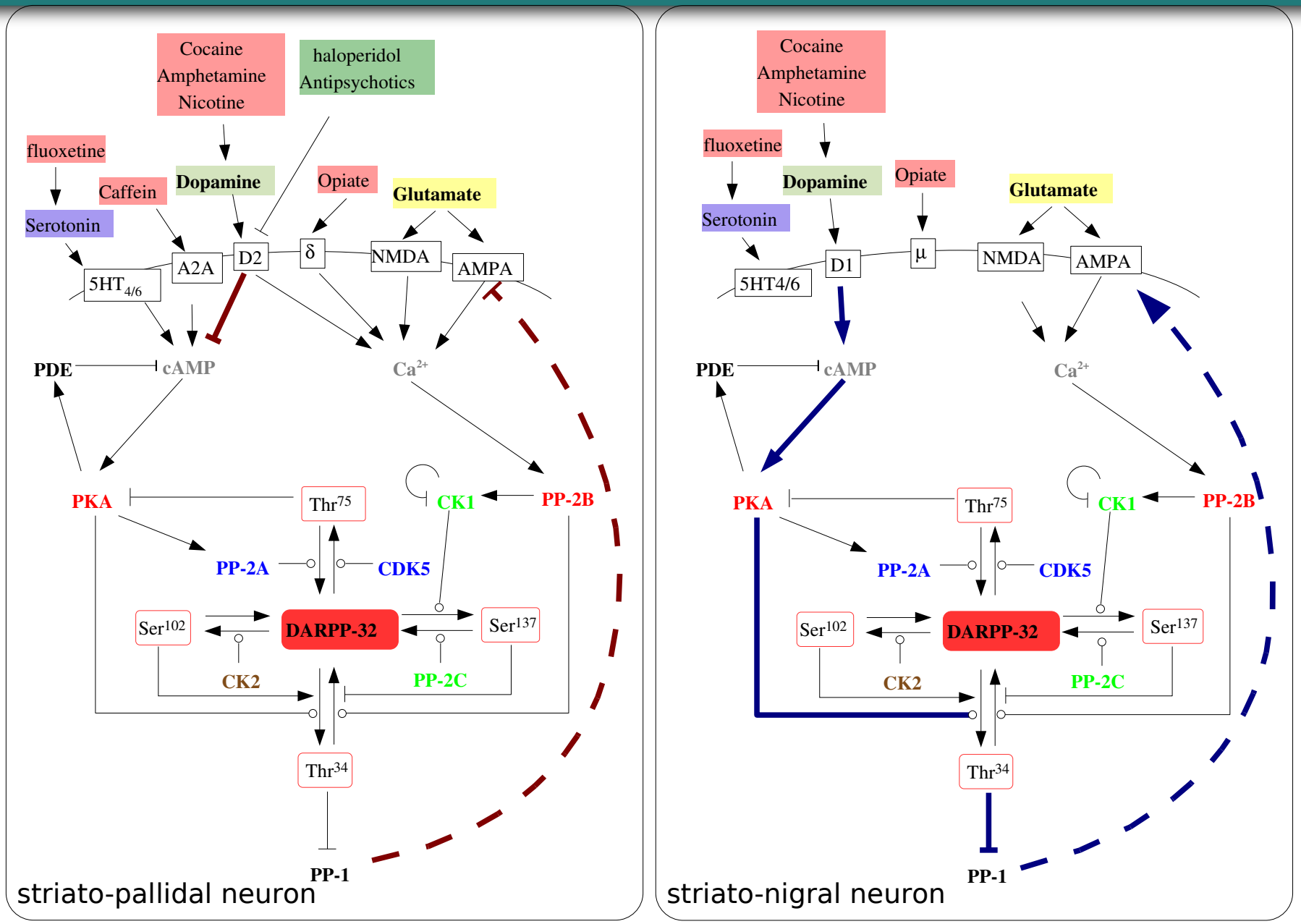
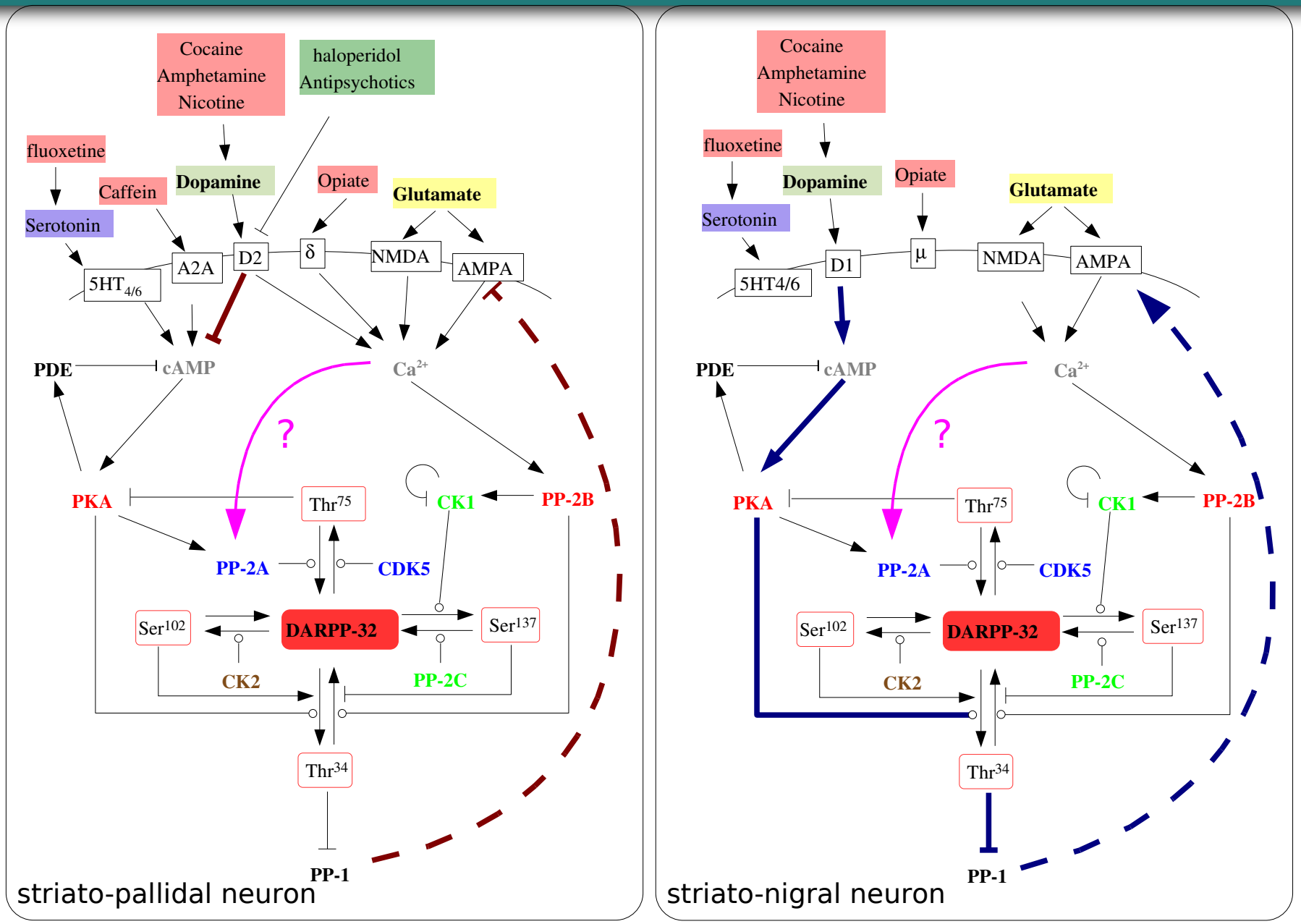


DARPP-32 is a “hub” for phosphatases and kinase in the post-synaptic compartment

Biological model of DARPP-32 regulation



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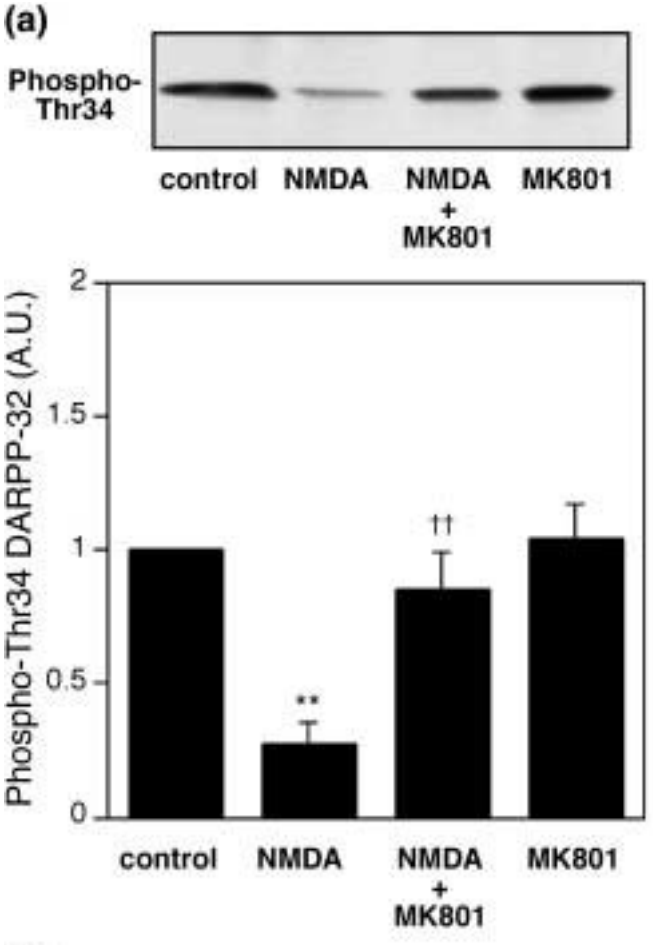
What is the questionmark?



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

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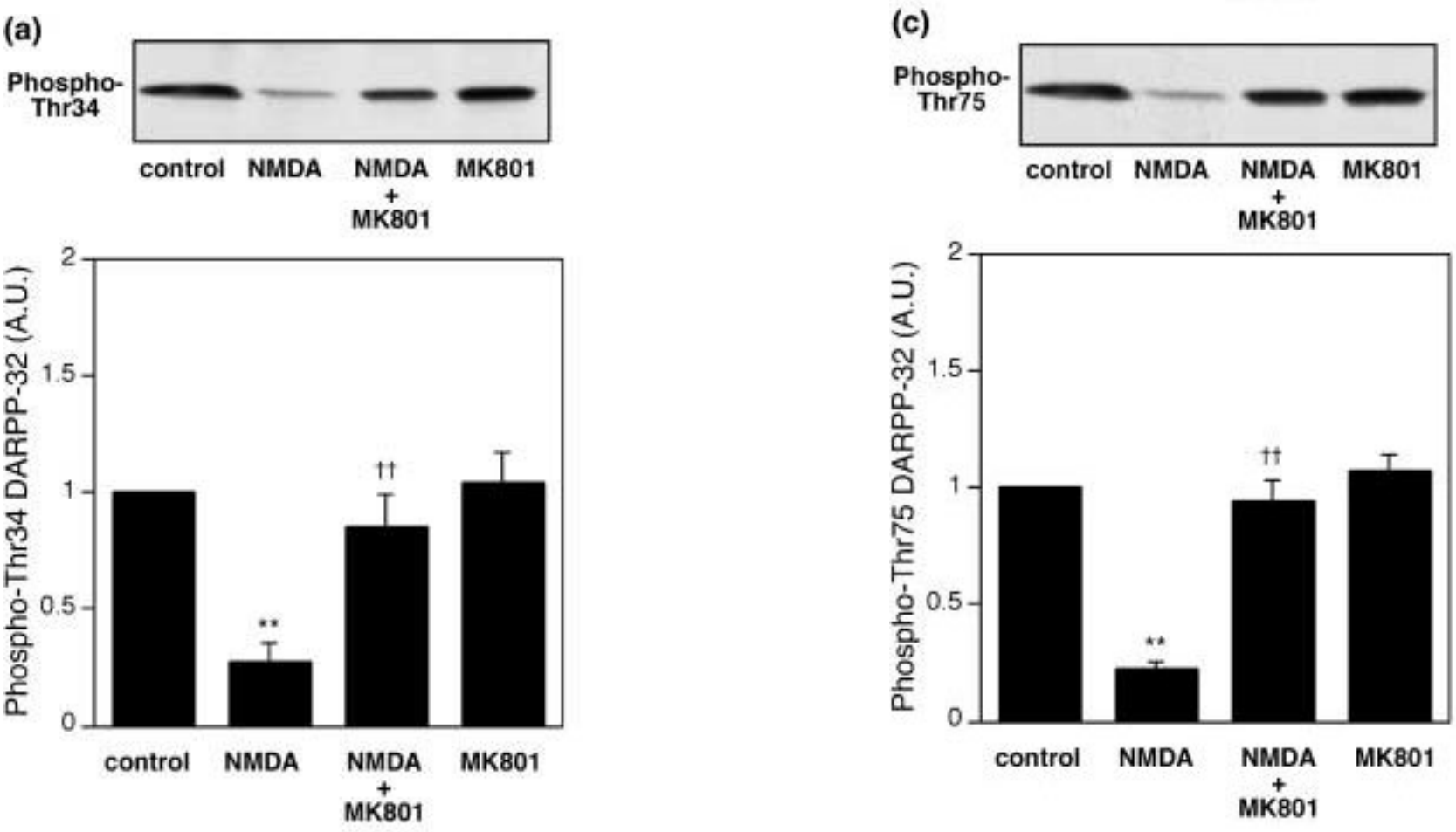

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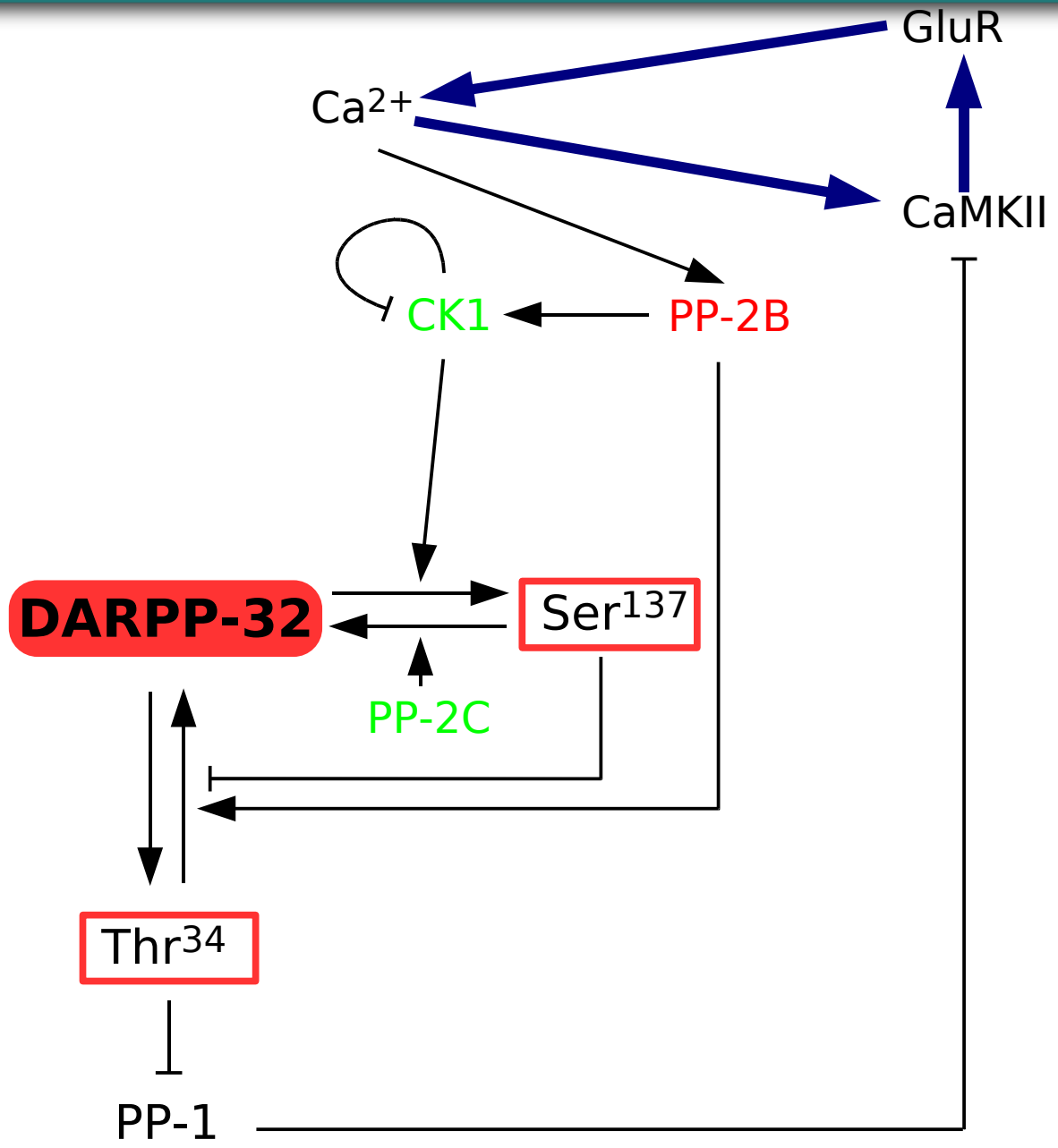
Negative loops: “russian dolls”



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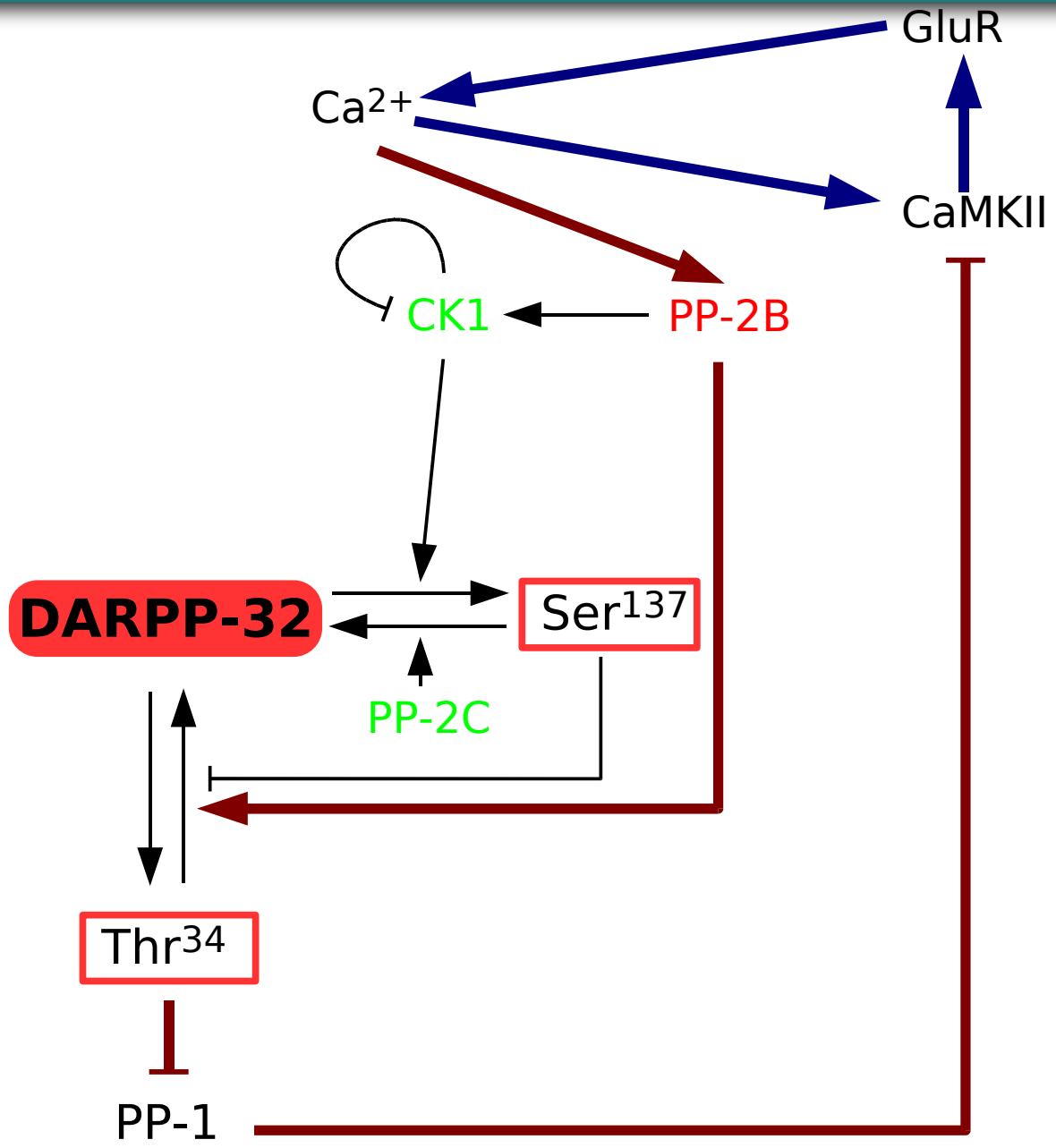

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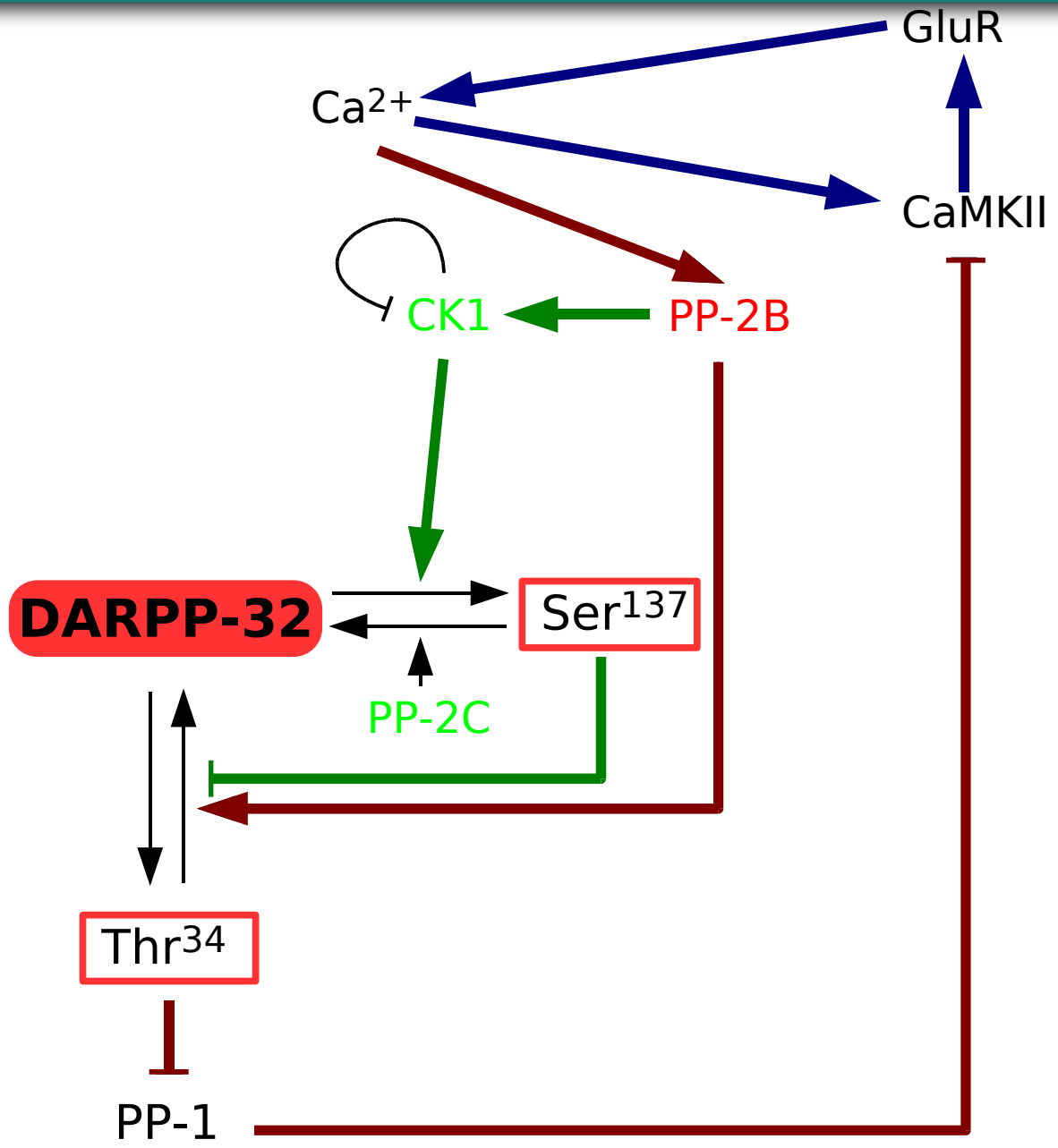

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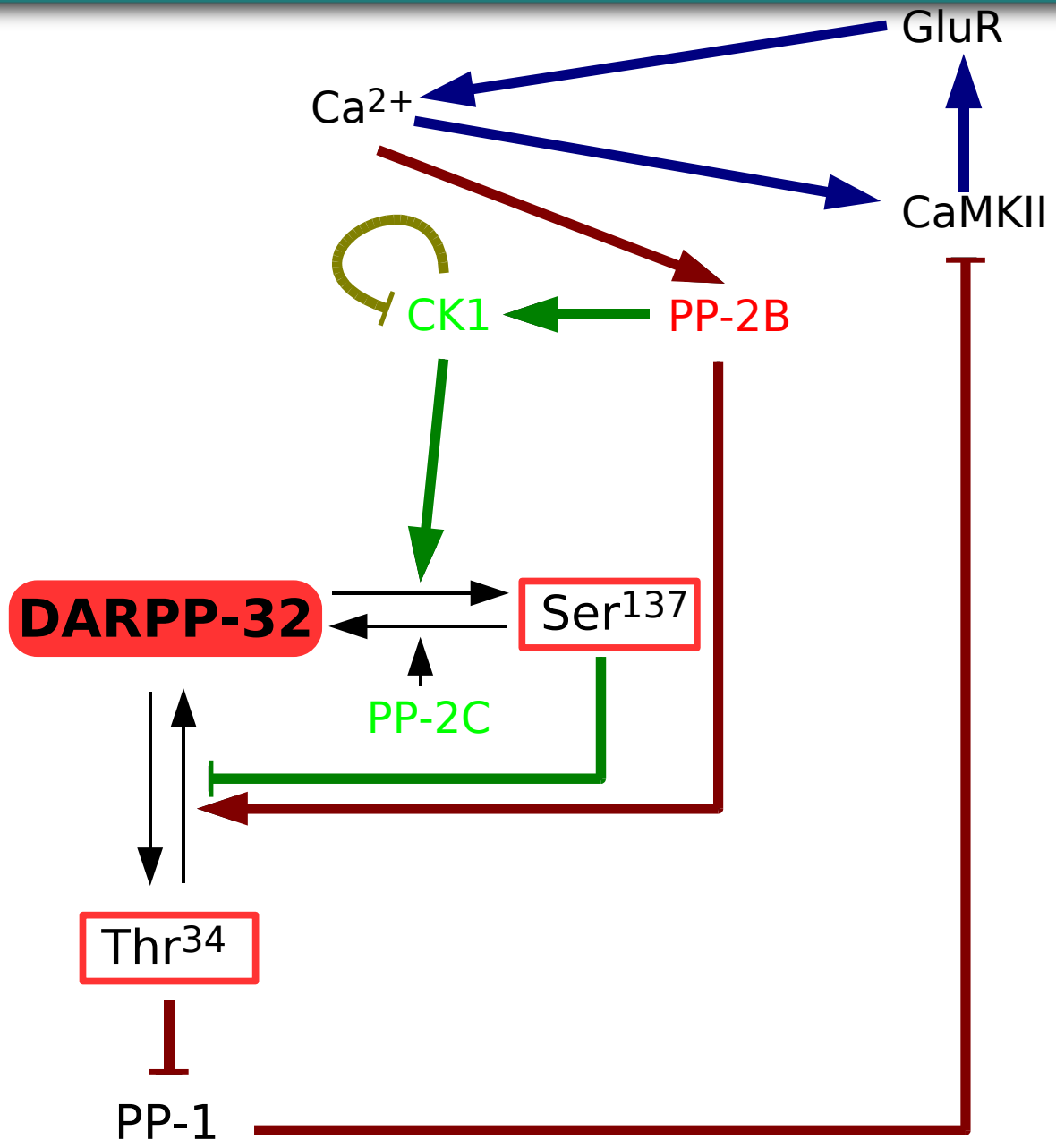
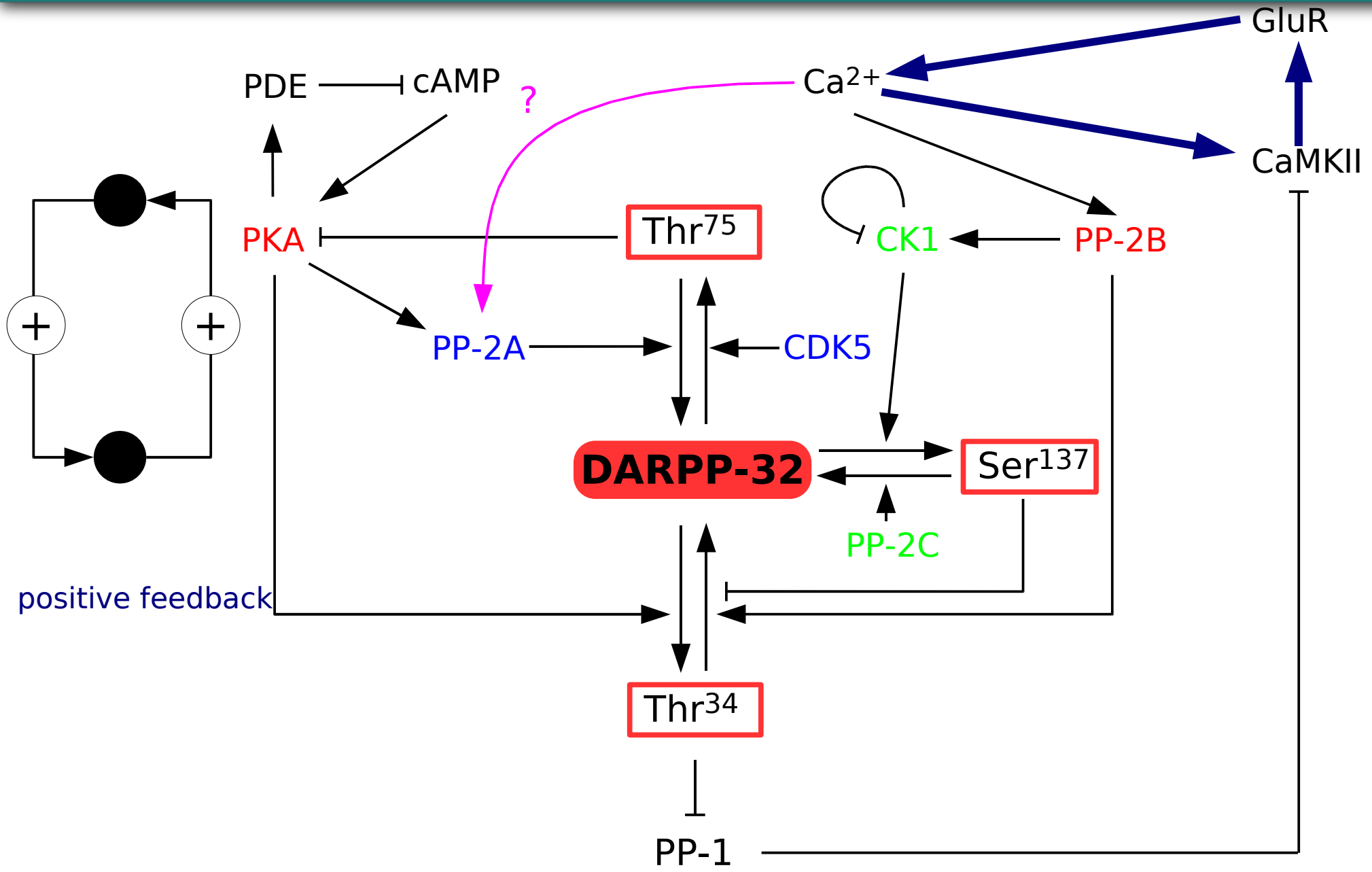


All the cybernetics in one system



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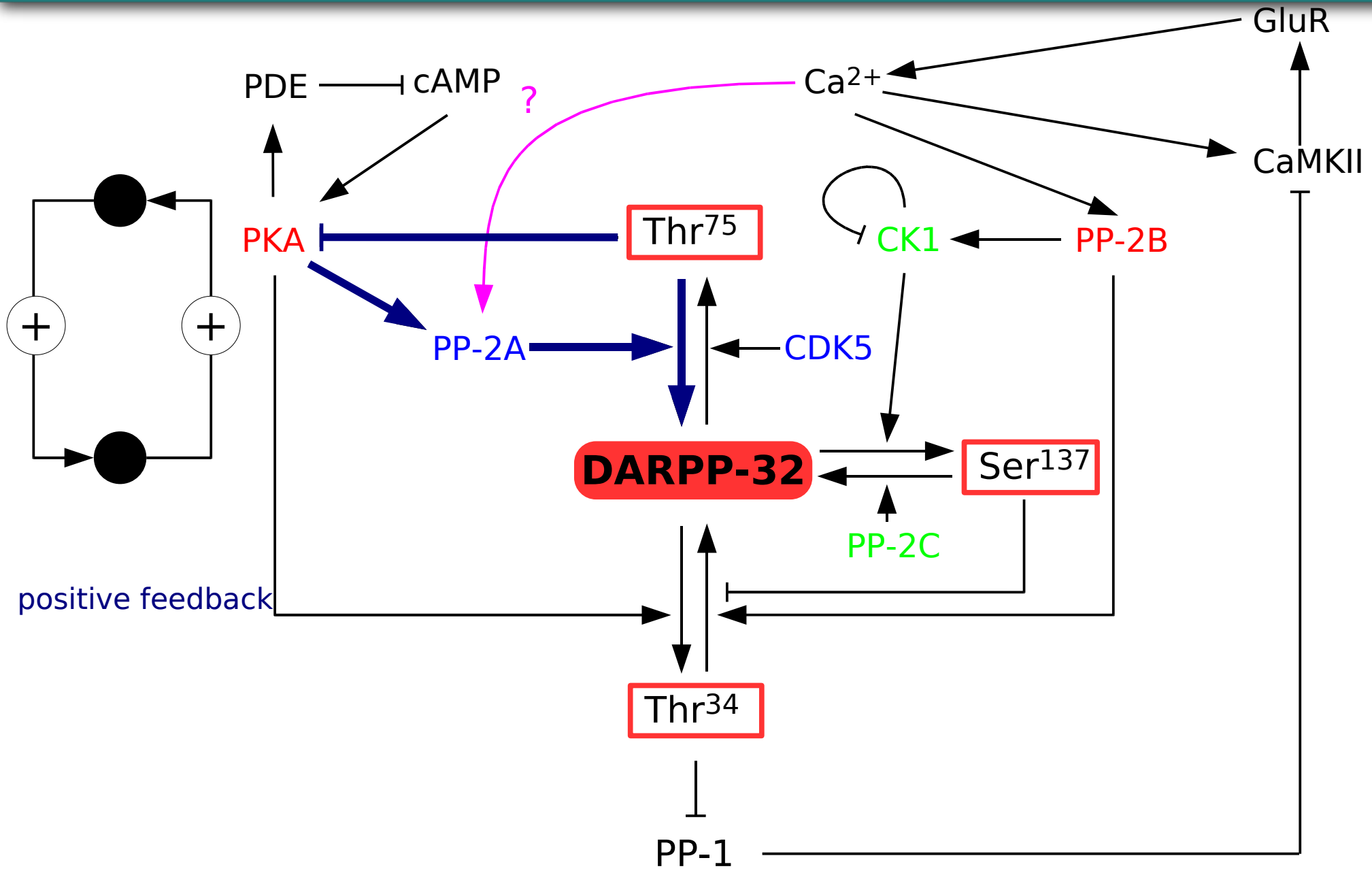

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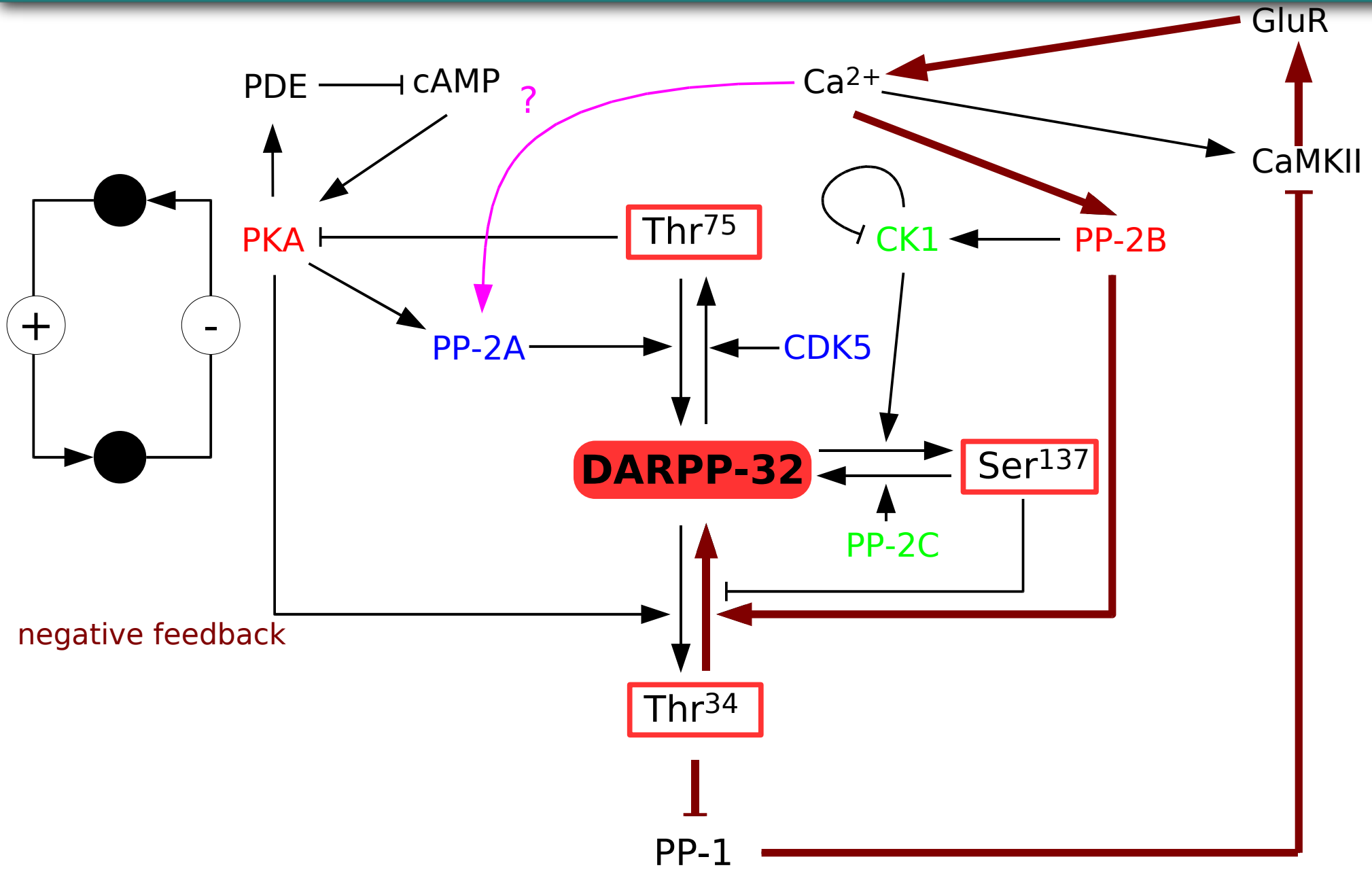

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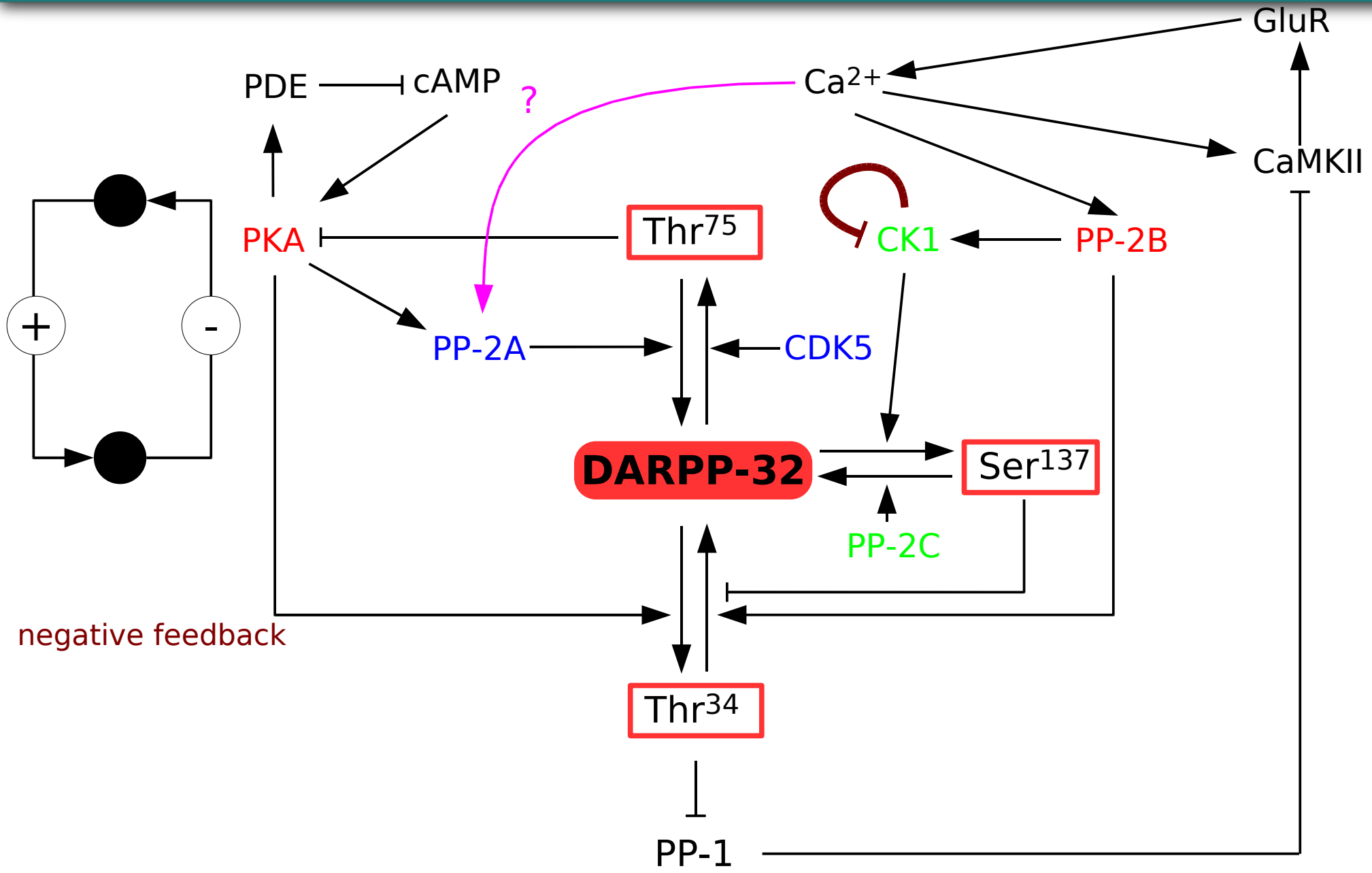

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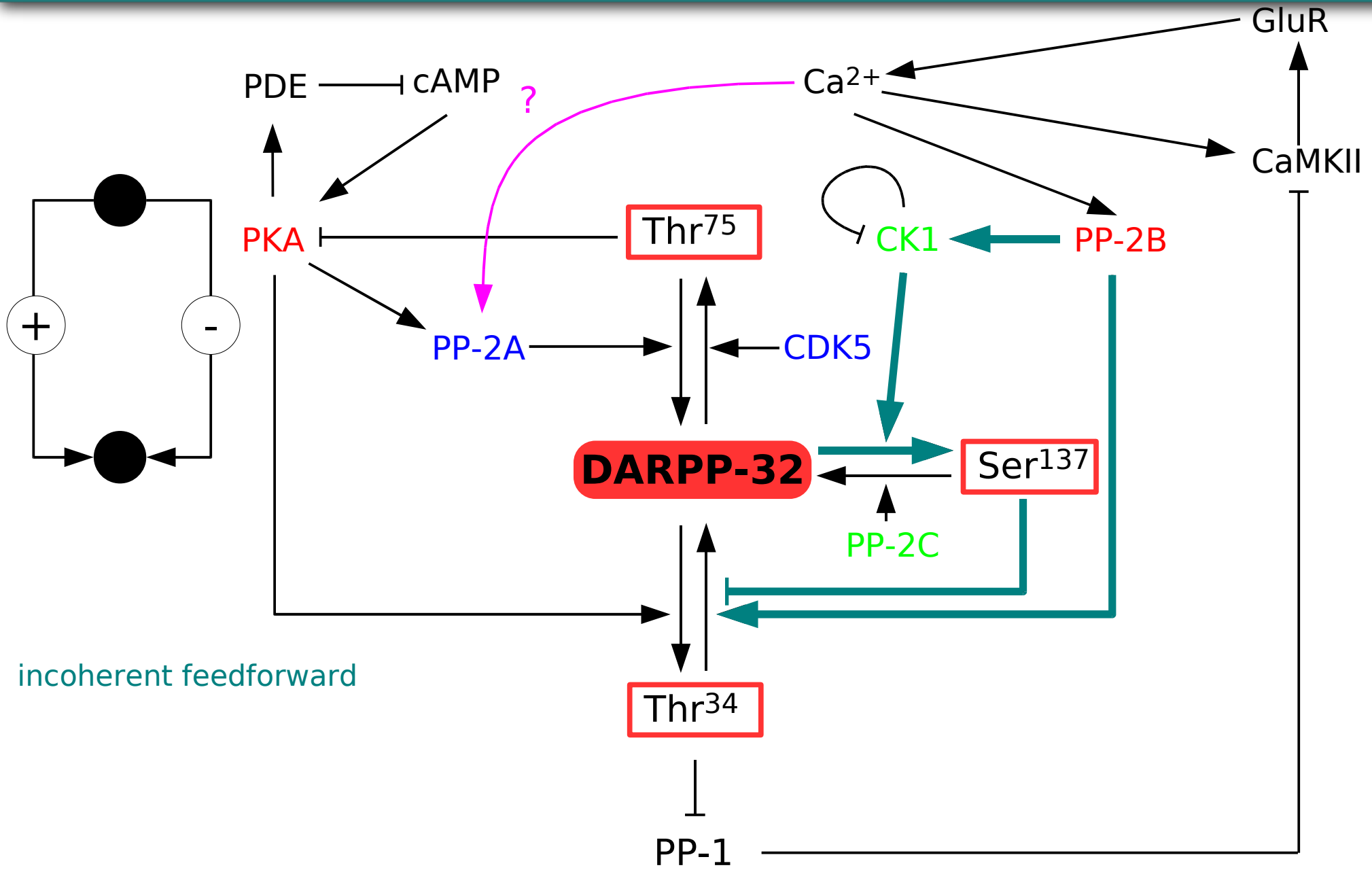

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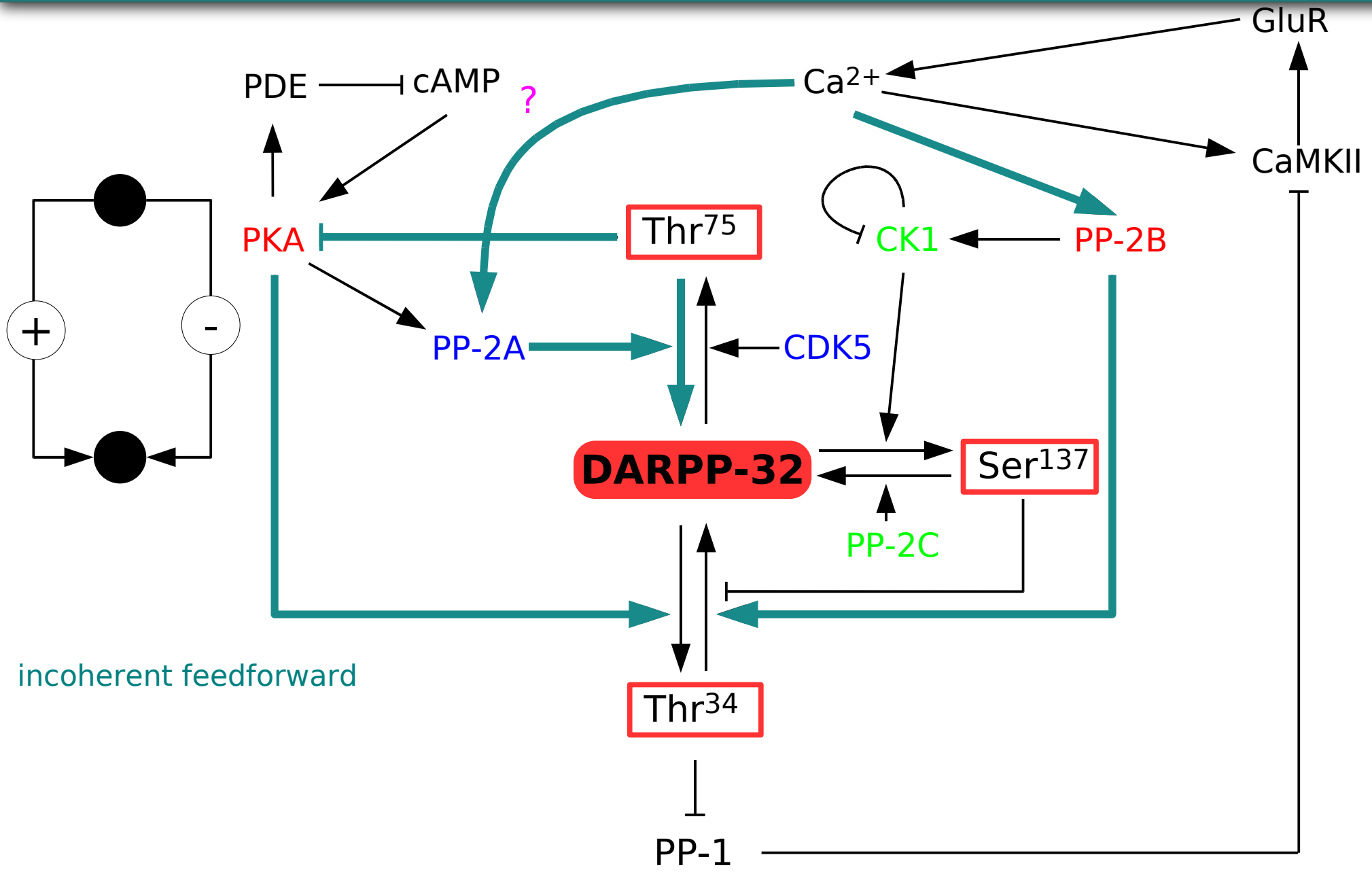

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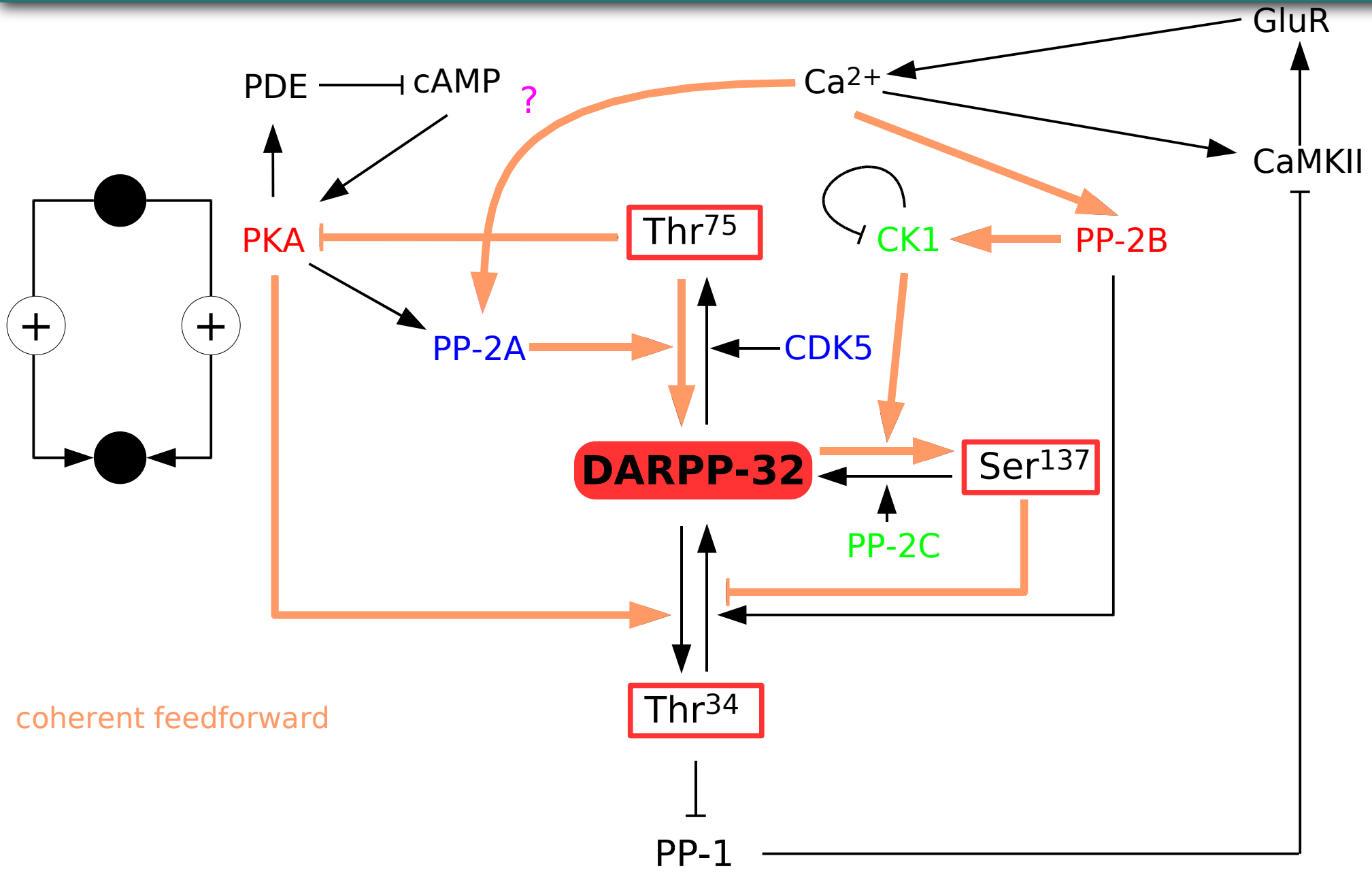
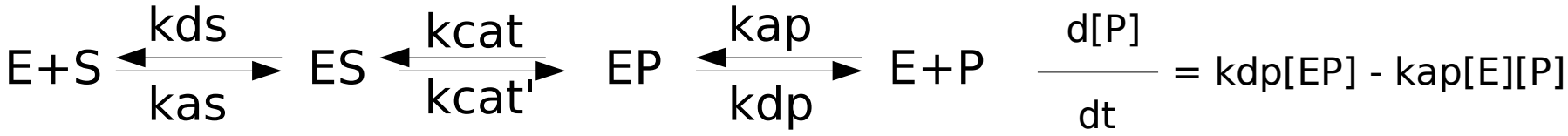


coherent feedforward

Choose the right formalism



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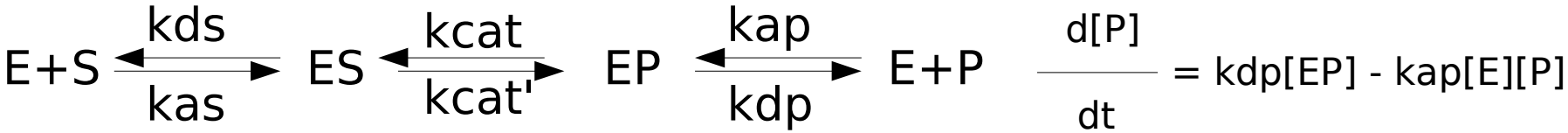
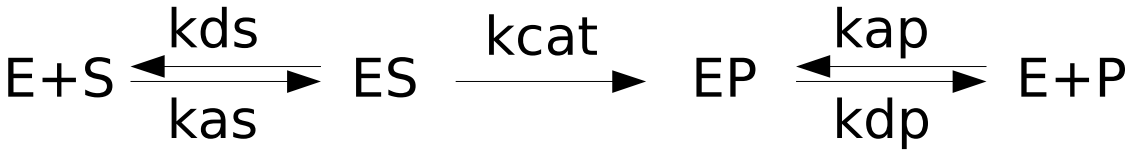




catalysis irreversible

Choose the right formalism

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

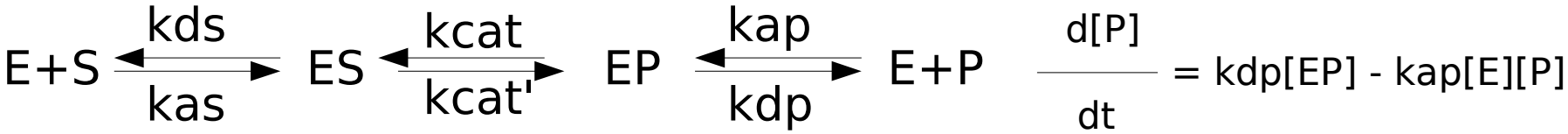
$$E+S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \xrightarrow{kcat} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E+P$$

catalysis irreversible

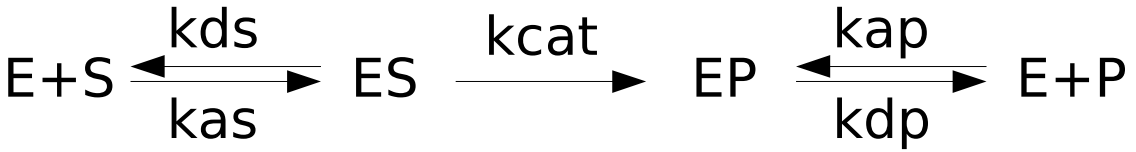
$$E+S \underset{ksd}{\overset{ksa}{\rightleftharpoons}} ES \xrightarrow{kcat} E+P$$

product is consumed before rebinding

Choose the right formalism



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



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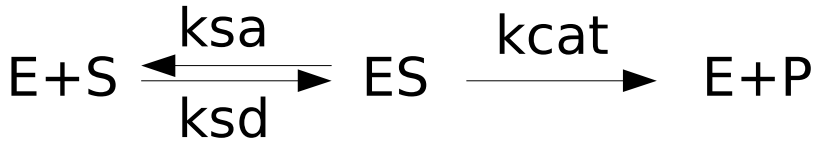

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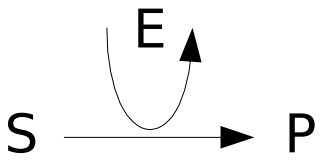
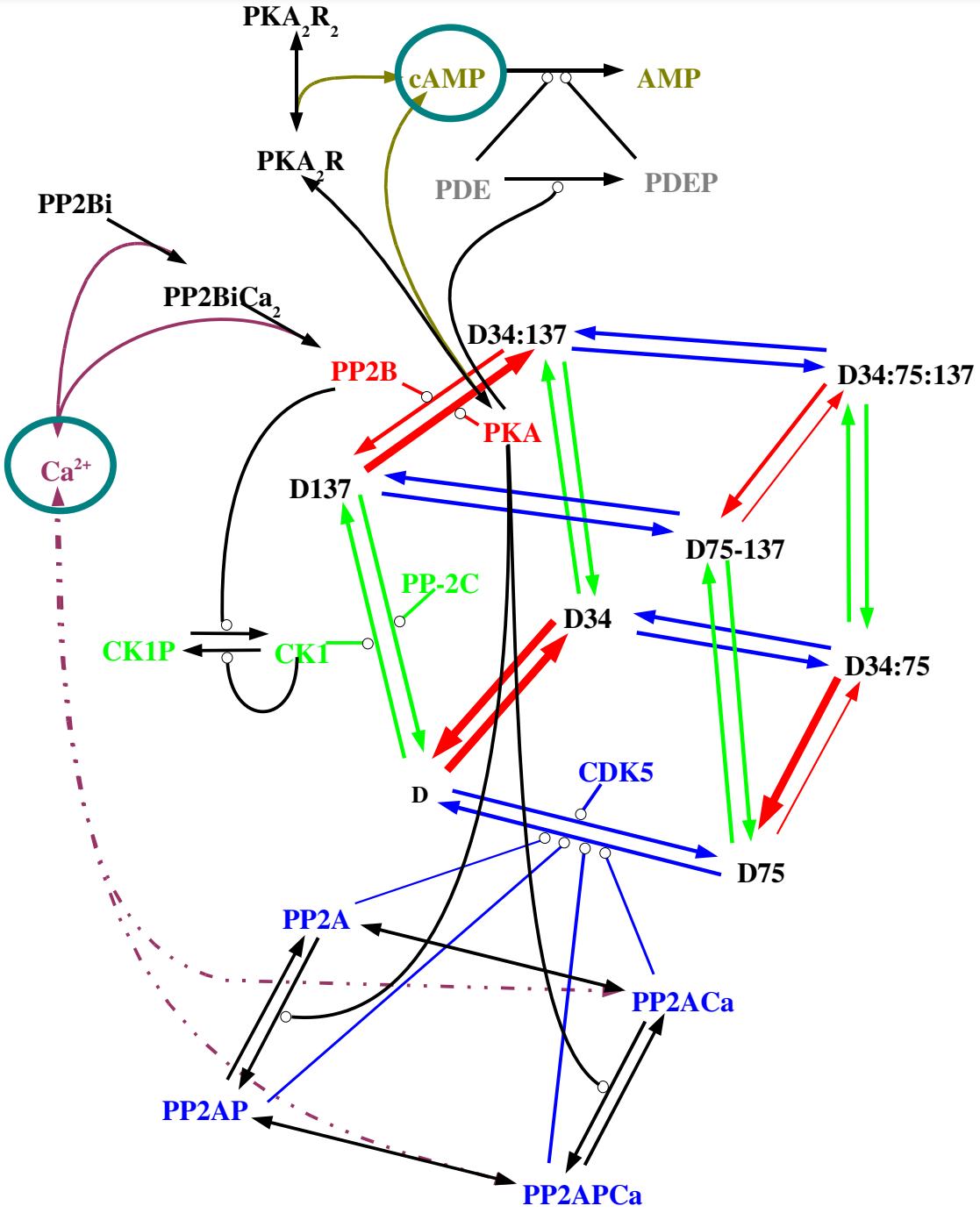


steady-state

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

Chemical model of DARPP-32 regulation



Chemical model of DARPP-32 regulation

79 species, 151 reactions

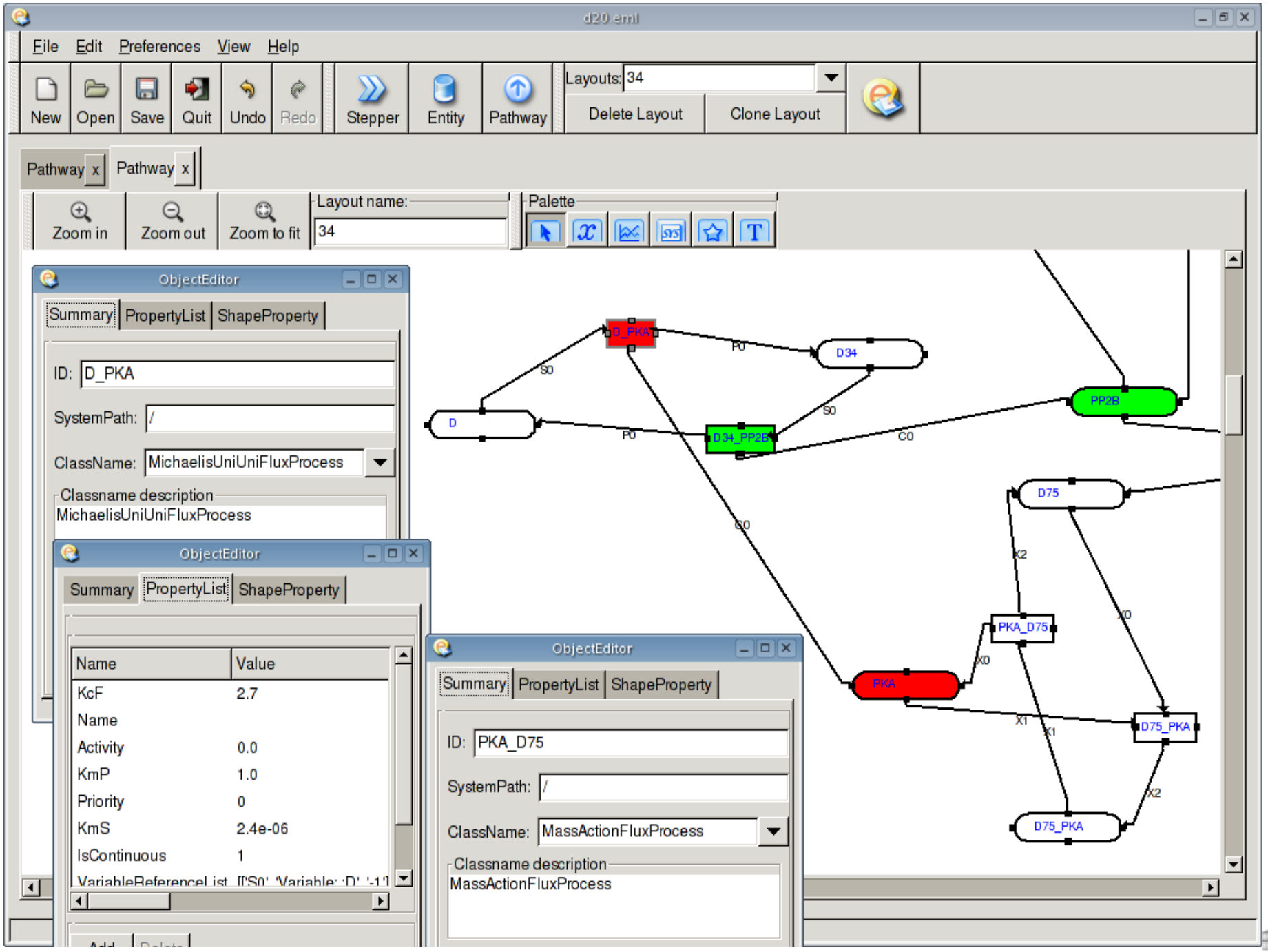
- D + CDK5 ⇔ D_CDK5 → D75 + CDK5
- D75 + PP2A ⇔ D75_PP2A → D + PP2A
- D75 + PP2ACa ⇔ D75_PP2ACa → D + PP2ACa
- D75 + PP2AP ⇔ D75_PP2AP → D + PP2AP
- D75 + PP2APCa ⇔ D75_PP2APCa → D + PP2APCa
- D137 + CDK5 ⇔ D137_CDK5 → D75-137 + CDK5
- D75-137 + PP2A ⇔ D75-137_PP2A → D137 + PP2A
- D75-137 + PP2ACa ⇔ 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

- 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



Mathematical model

Mathematical model

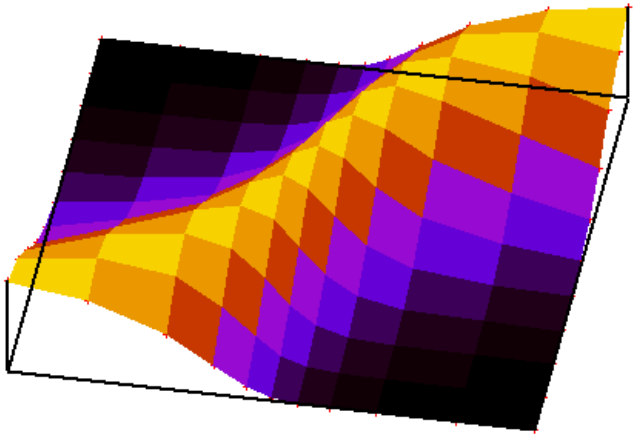
$$d[D]/dt = -k_1[CDK5][D] + k_2[D\_CDK5]$$

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

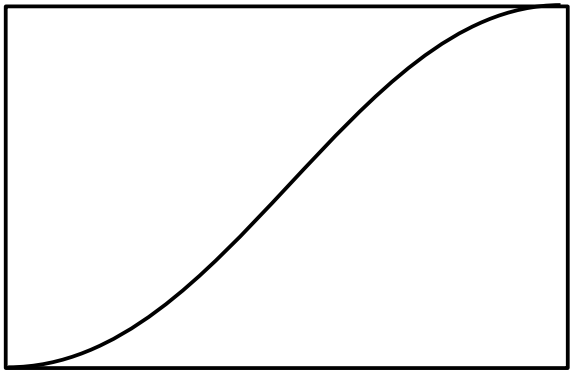
$$d[CDK5]/dt = -k_1[CDK5][D] + k_2[D\_CDK5] + k_3[D\_CDK5]$$

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

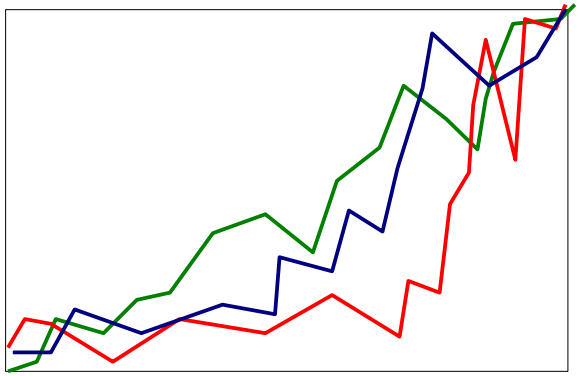
Different modelling approaches



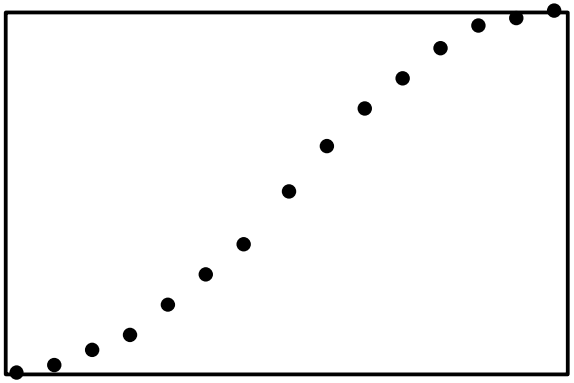
Grand Probability function: P(X,t)



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



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

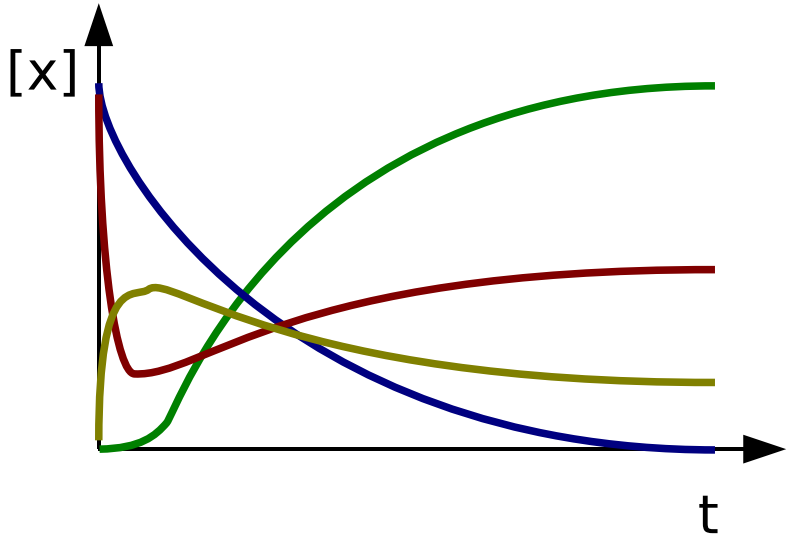


deterministic approach: (X,t)=f(X',t-1)

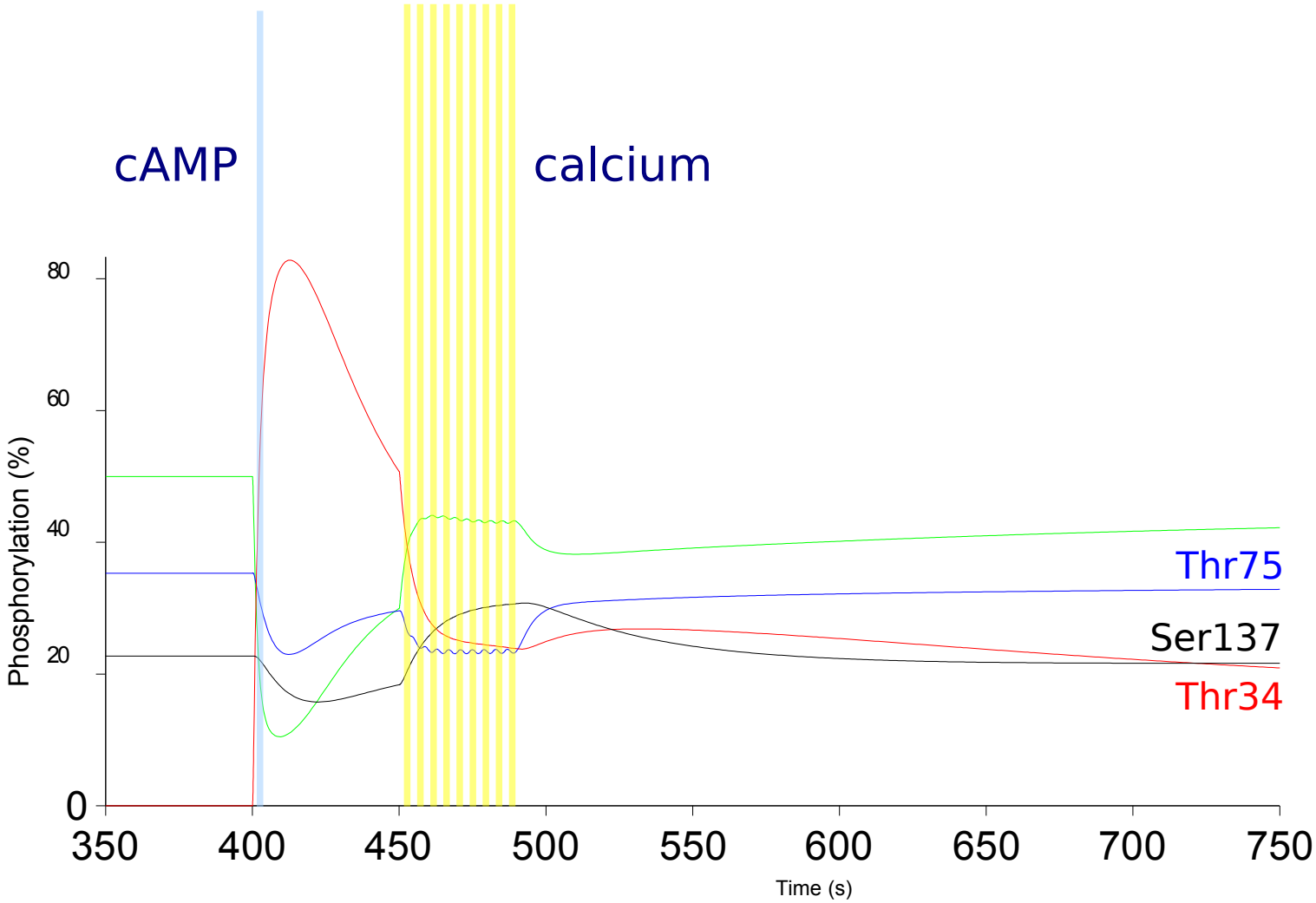
Mathematical model

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

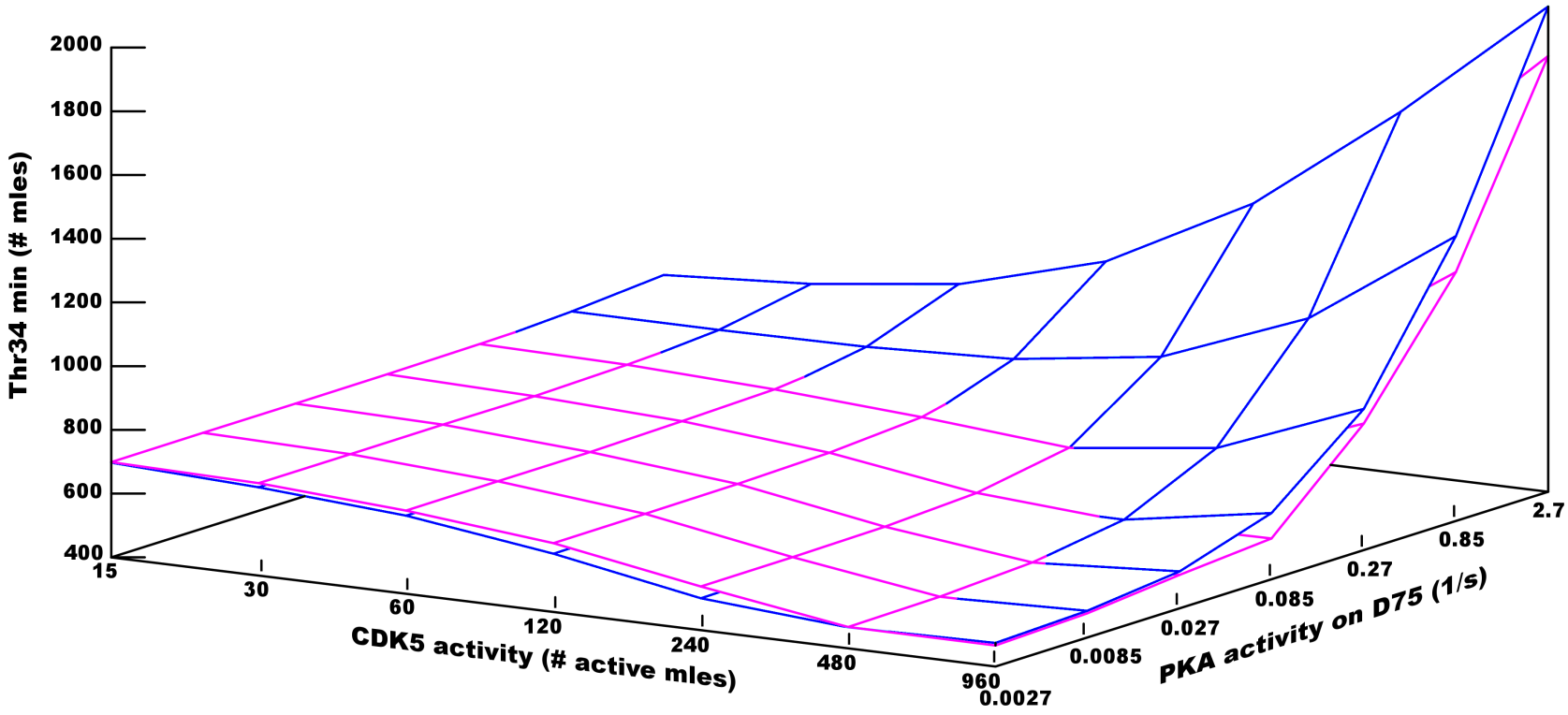
$$\begin{aligned}
d[D]/dt &= -k_1[CDK5][D] + k_2[D_CDK5] \\
d[D\text{-}75P]/dt &= + k_3[D_CDK5] \\
d[CDK5]/dt &= -k_1[CDK5][D] + k_2[D_CDK5] + k_3[D_CDK5] \\
d[D_CDK5]/dt &= +k_1[CDK5][S] - k_2[D_CDK5] - k_3[D_CDK5]
\end{aligned}$$



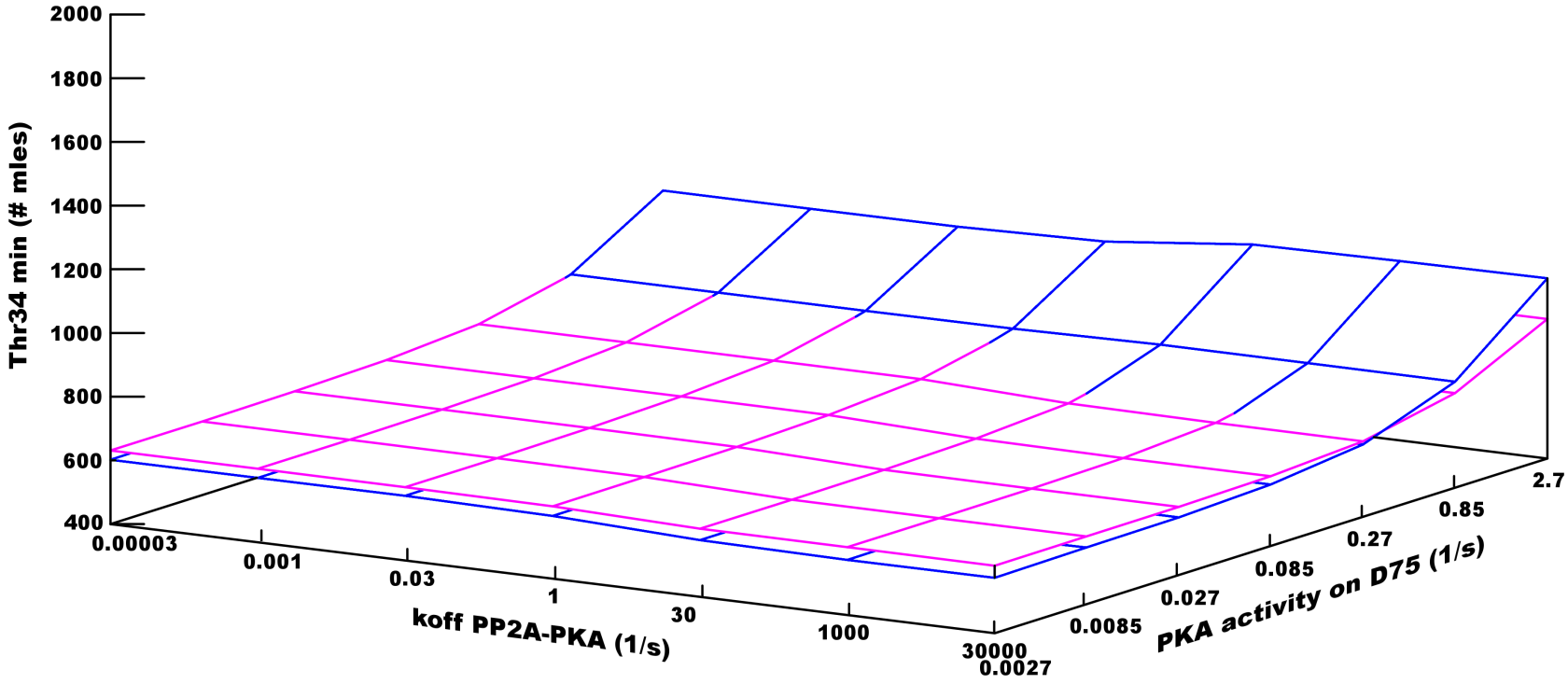
Dynamic simulations of DARPP-32 function



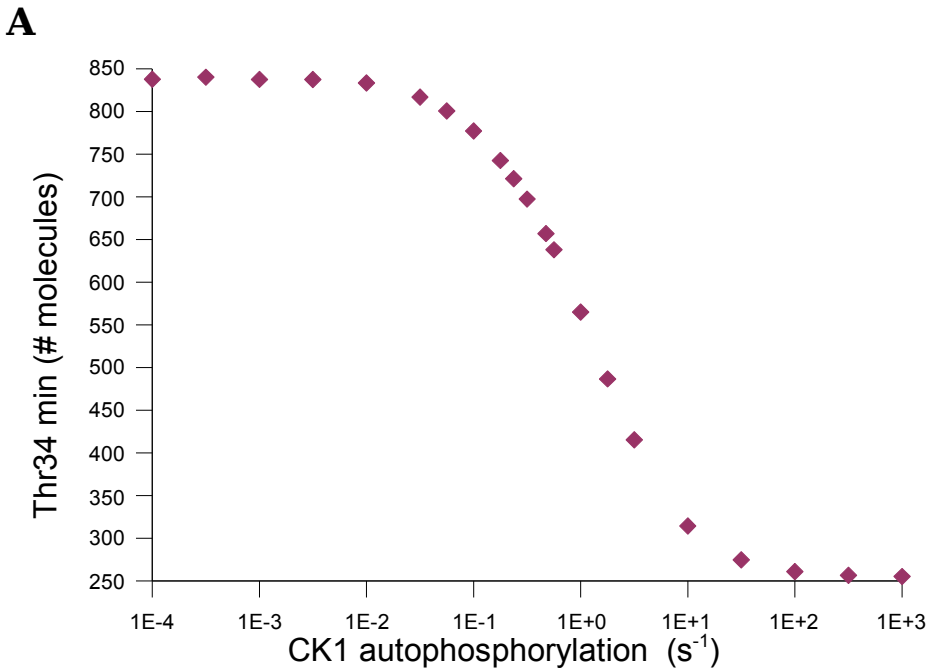
Some parameters are sensitive

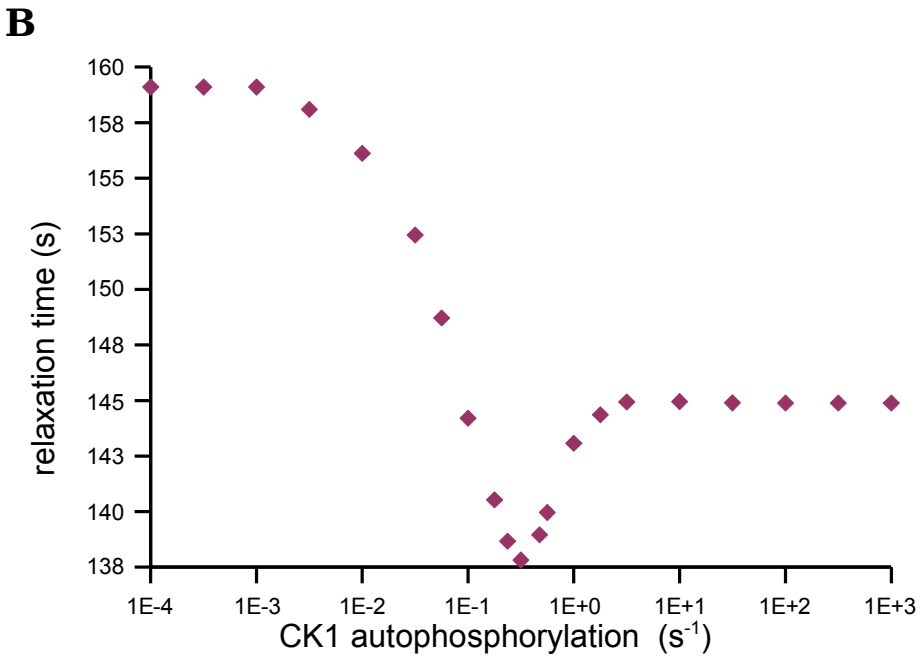


Some parameters are robust

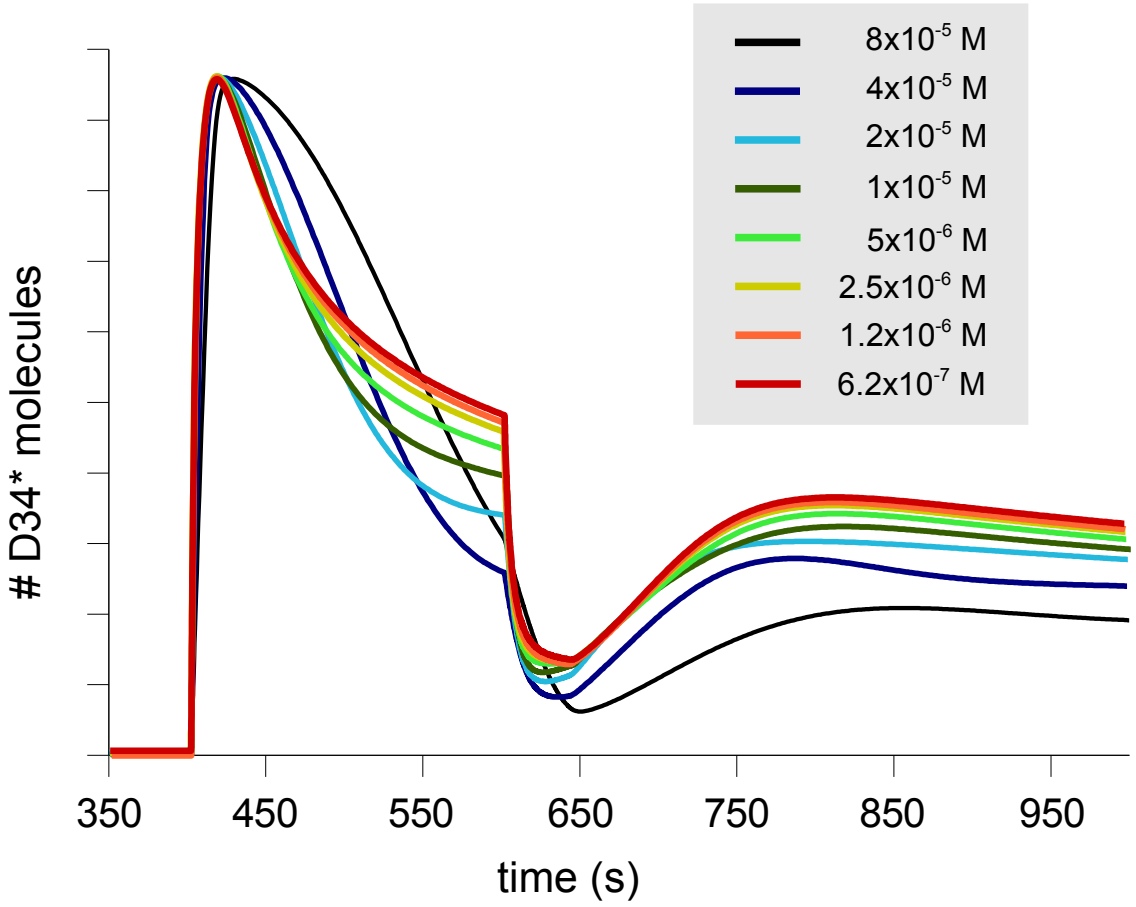


Optimality

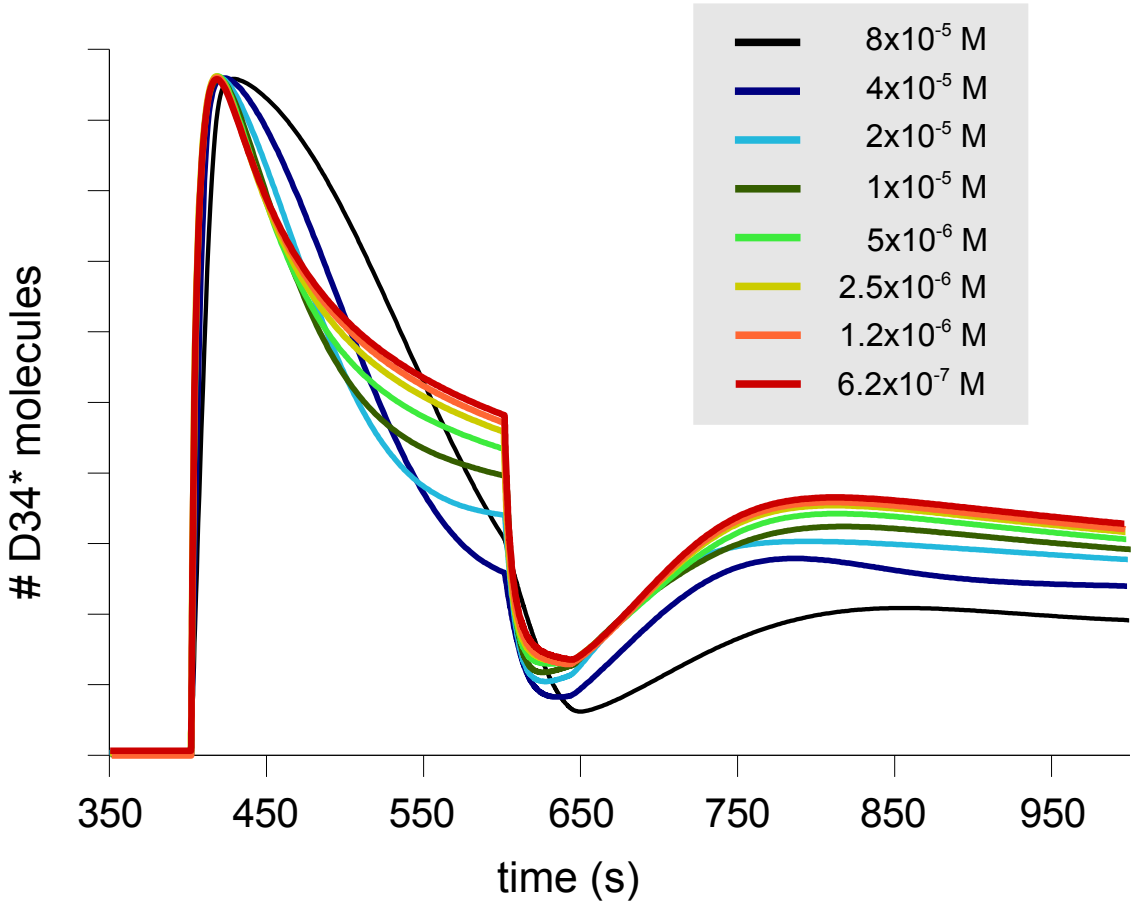

A
Thr34 min (# molecules)
850
800
750
700
650
600
550
500
450
400
350
300
250
1E-4
1E-3
1E-2
1E-1
1E+0
1E+1
1E+2
1E+3
CK1 autophosphorylation (s-1)


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

DARPP-32 as a robust integrator

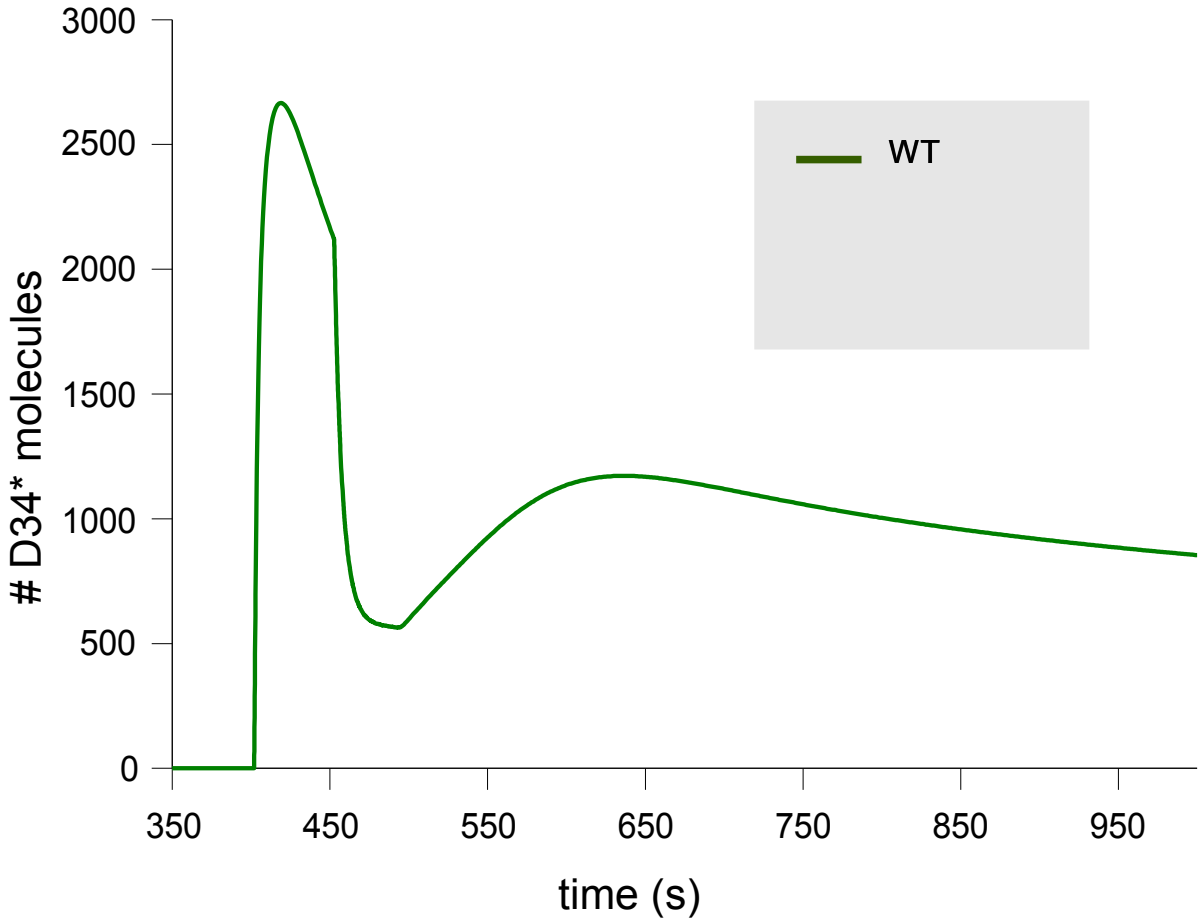


DARPP-32 as a robust integrator

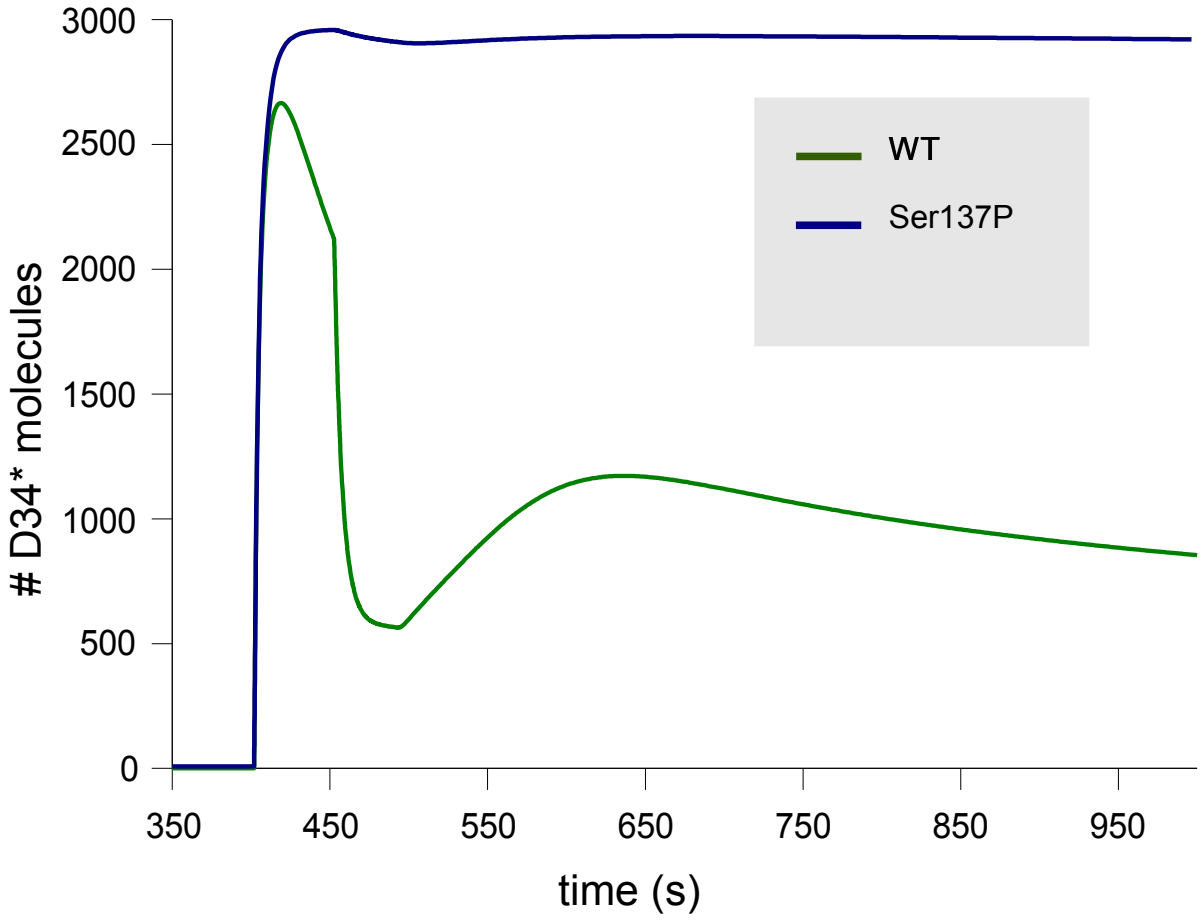


Heterozygous DARPP-32 +/- do not display phenotypes

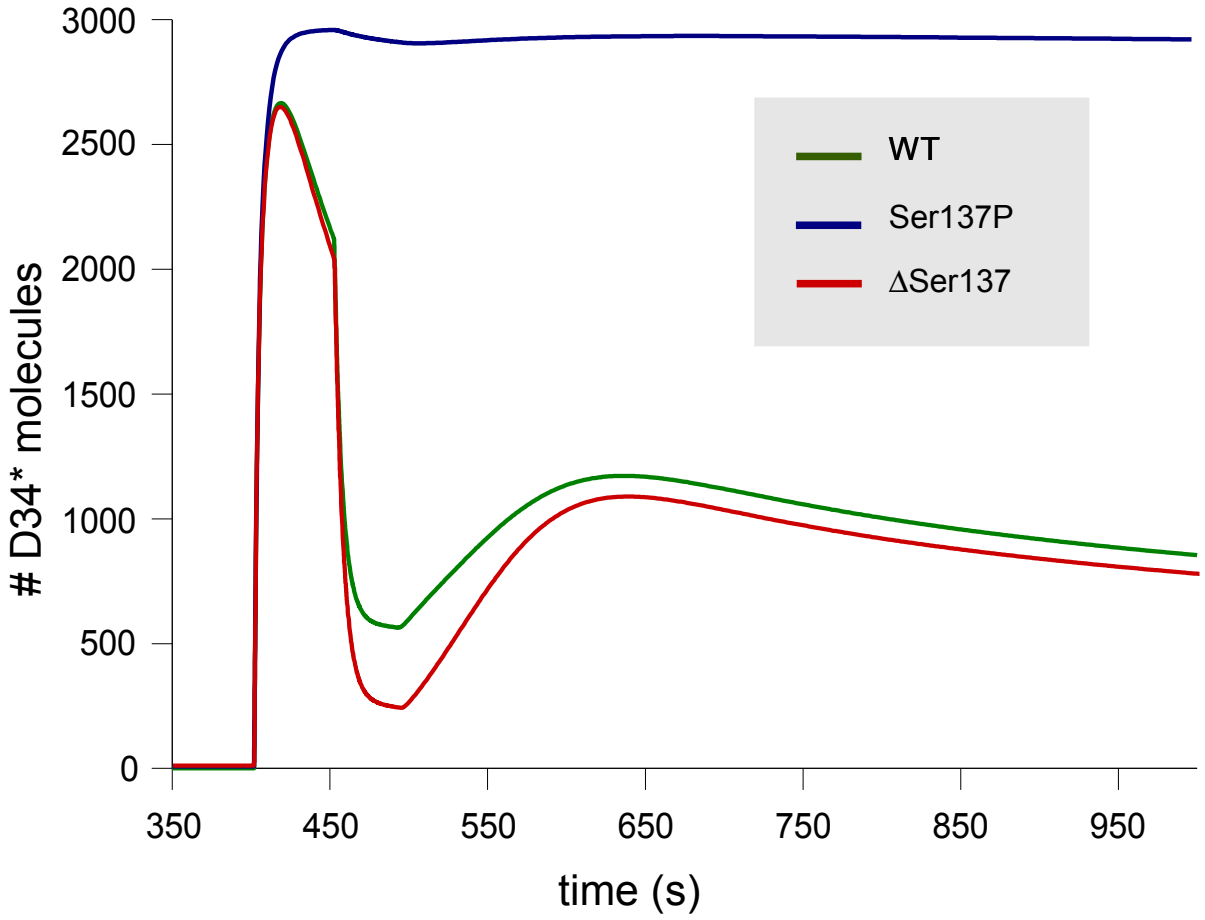
Mutation *in silico*



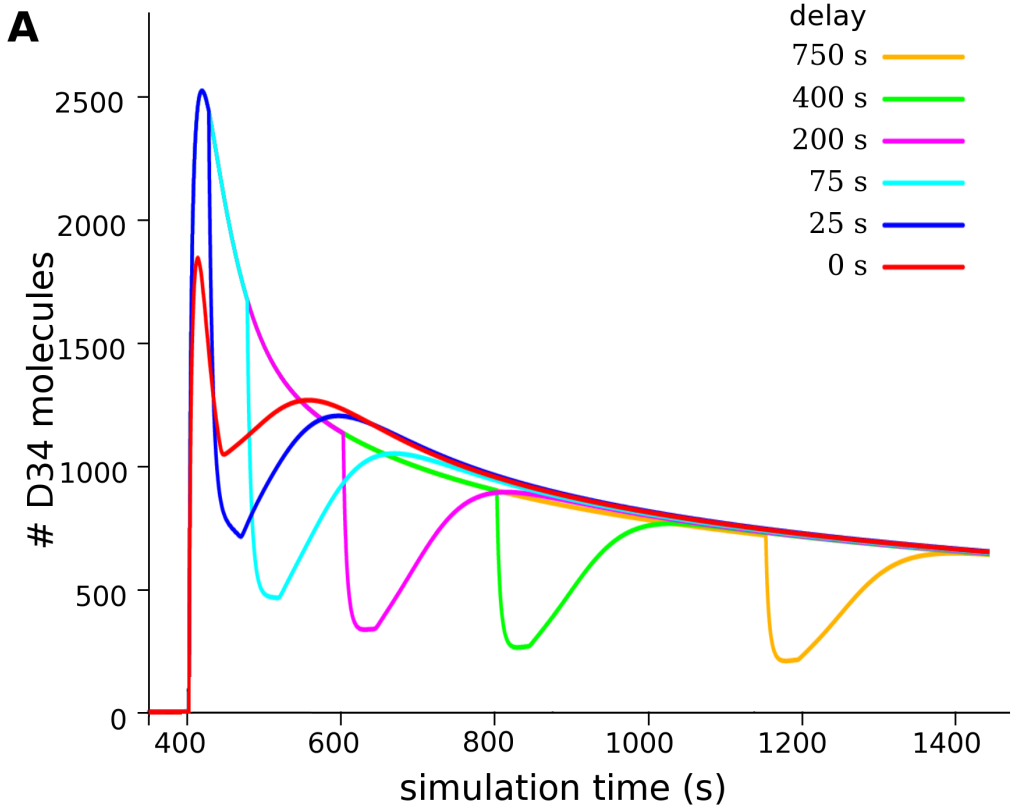
Mutation *in silico*

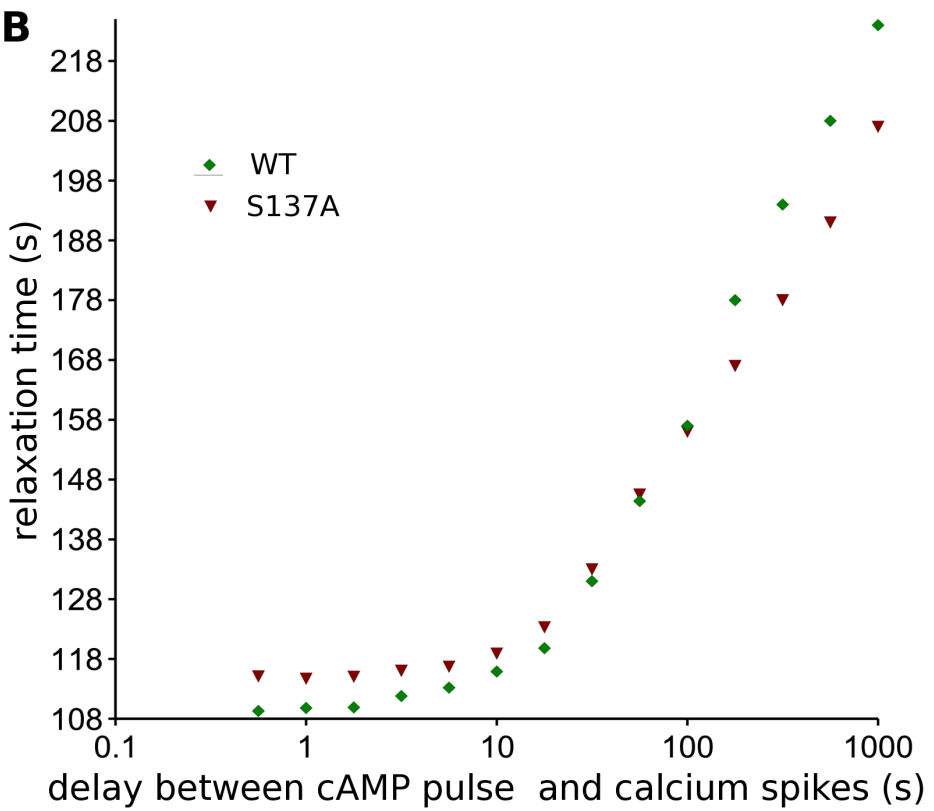


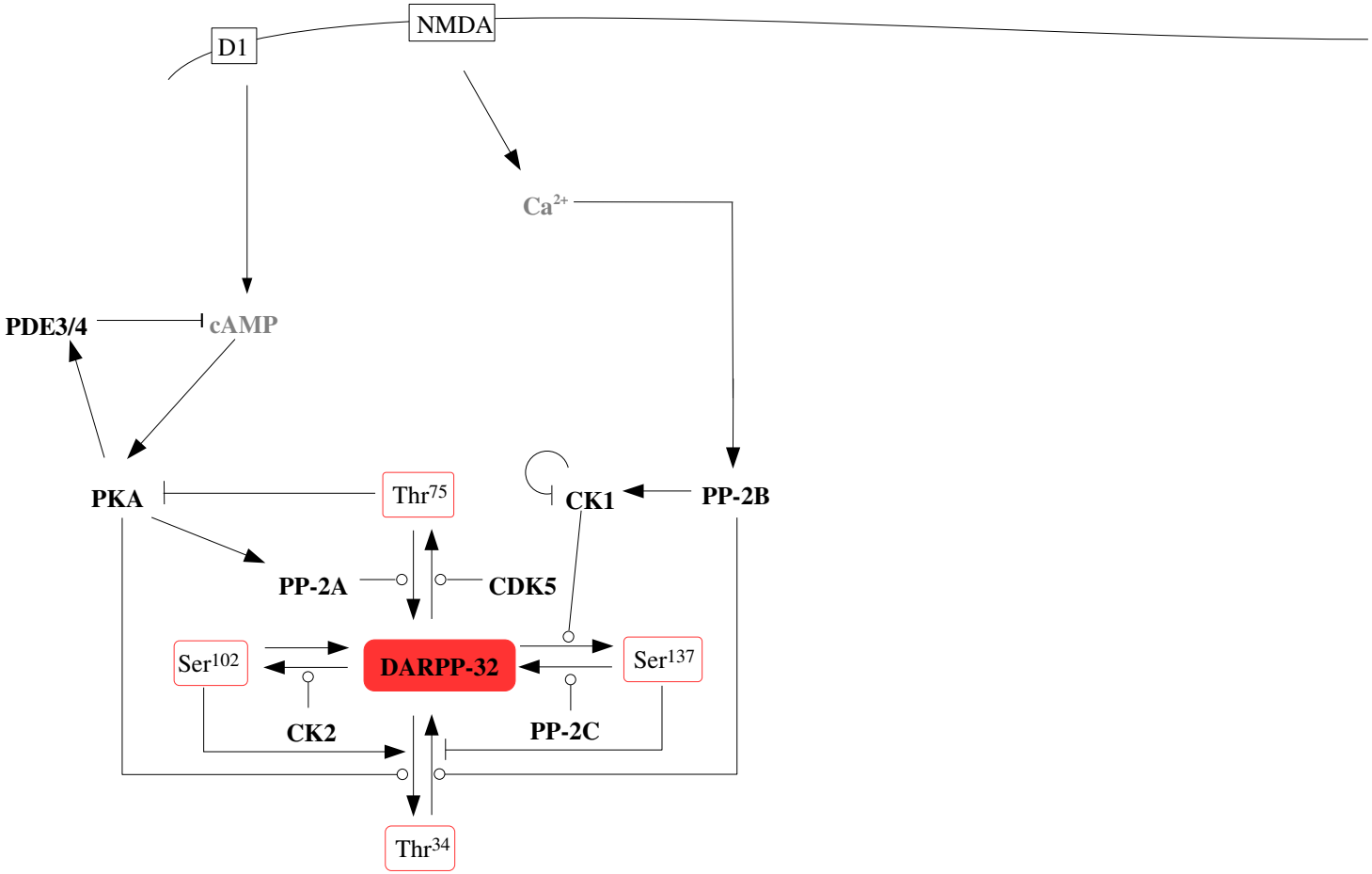
Mutation *in silico*



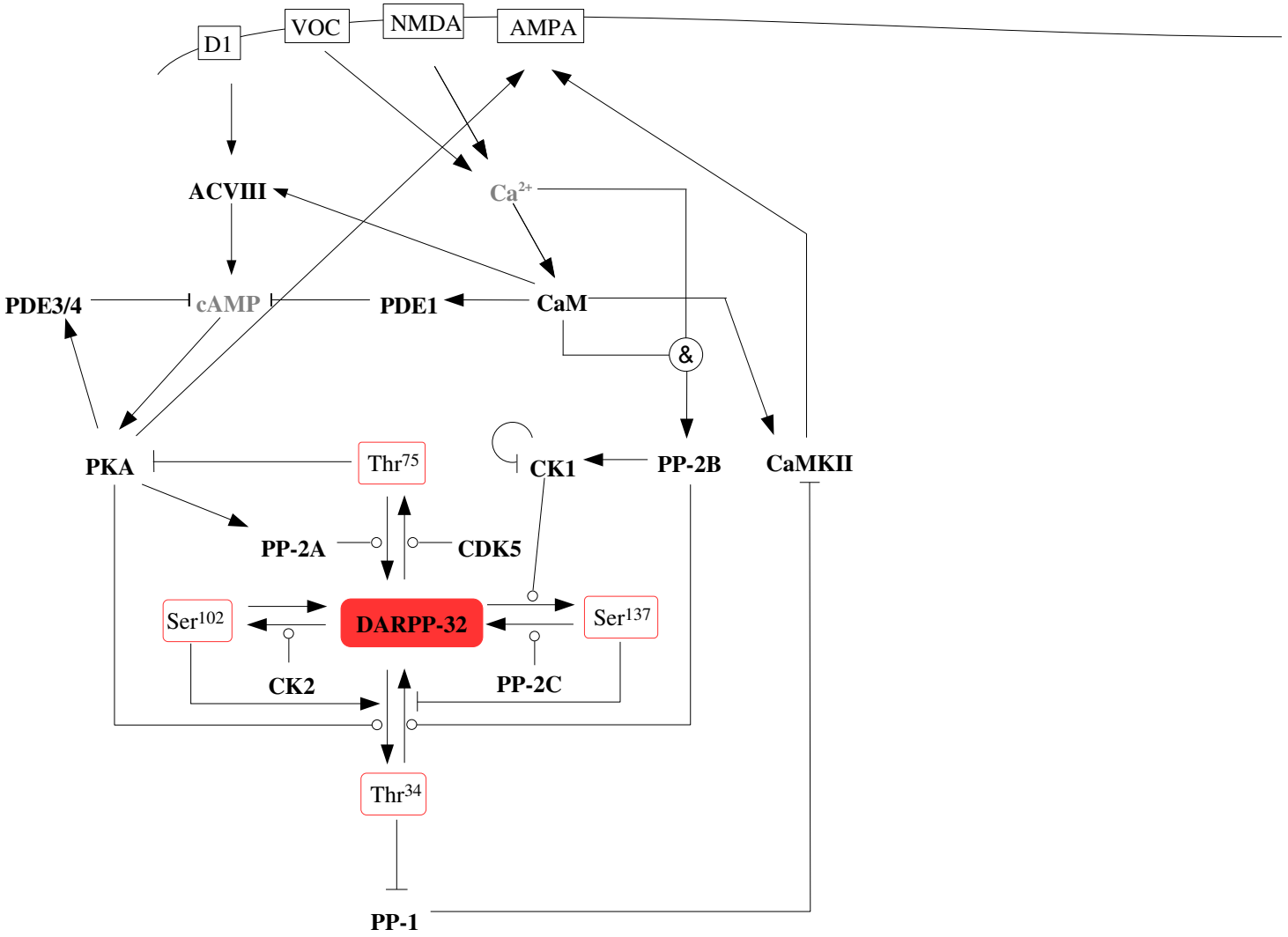
DARPP-32 as a coincidence detector

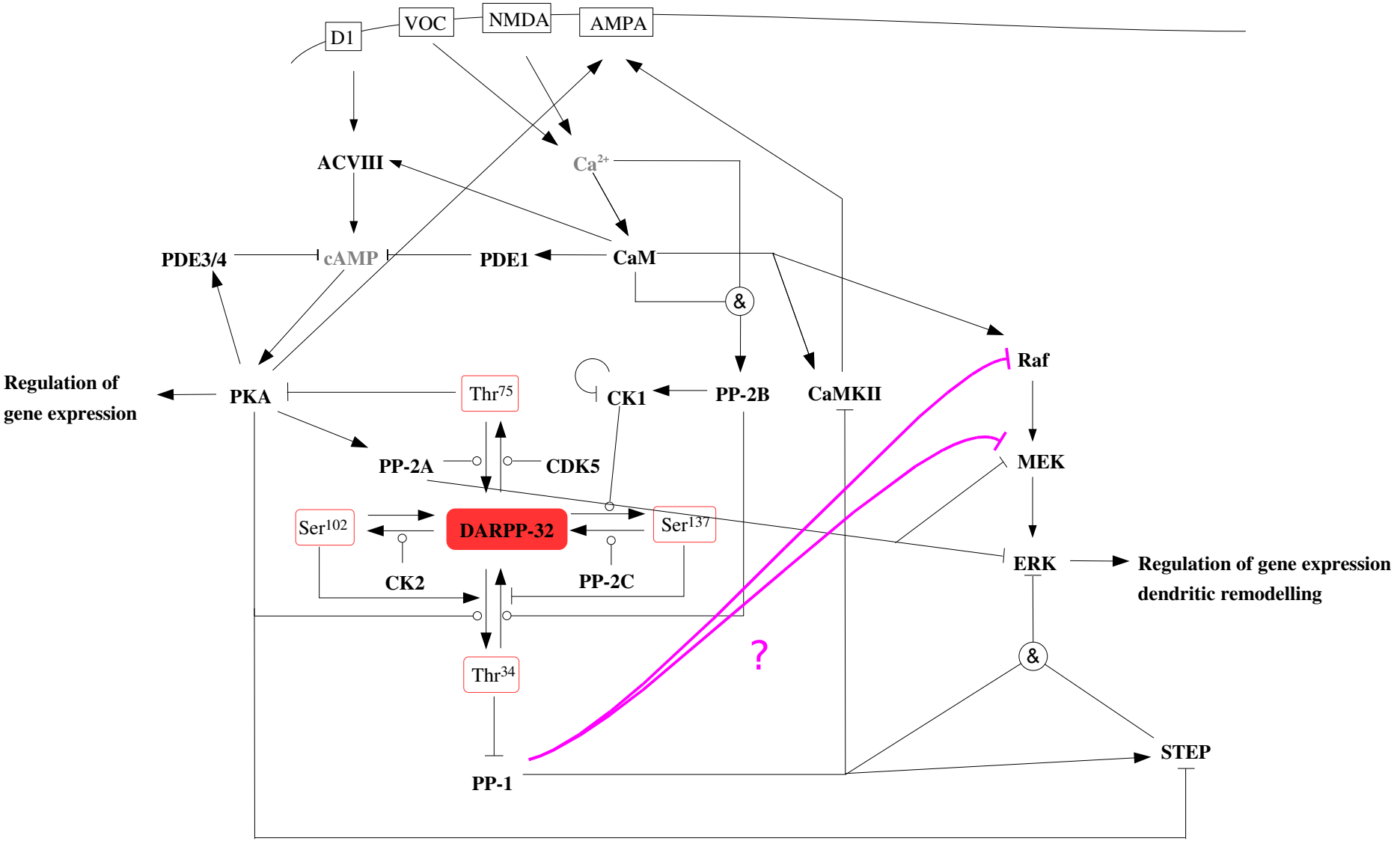





NMDA
D1
Ca2+
PDE3/4
cAMP
PKA
Thr75
CK1
PP-2B
PP-2A
CDK5
Ser102
DARPP-32
Ser137
CK2
PP-2C
Thr34

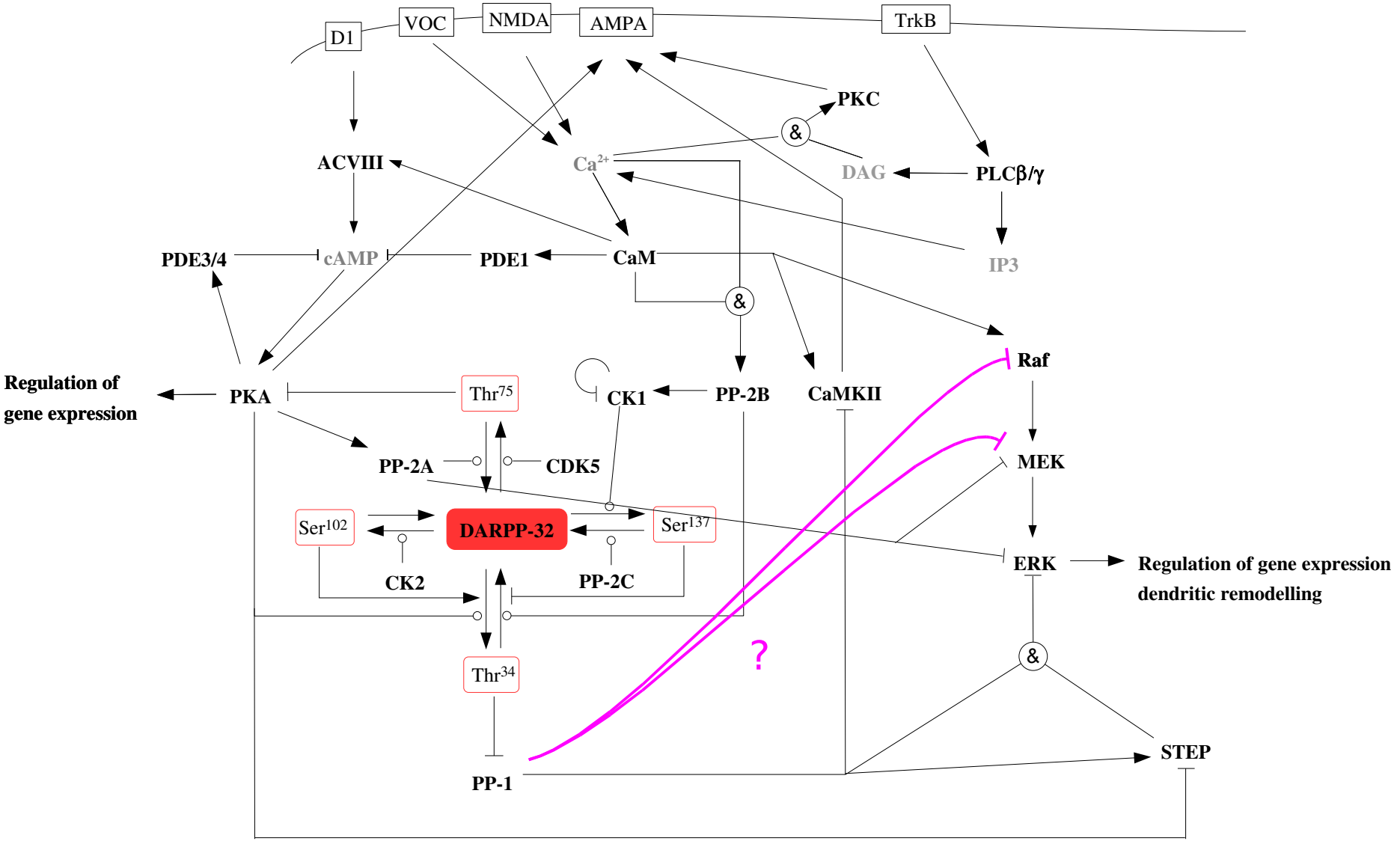
Present


D1
VOC
NMDA
AMPA
ACVIII
Ca2+
PDE3/4
cAMP
PDE1
CaM
&
PKA
Thr75
CK1
PP-2B
CaMKII
PP-2A
CDK5
Ser102
DARPP-32
Ser137
CK2
PP-2C
Thr34
PP-1



Collaboration

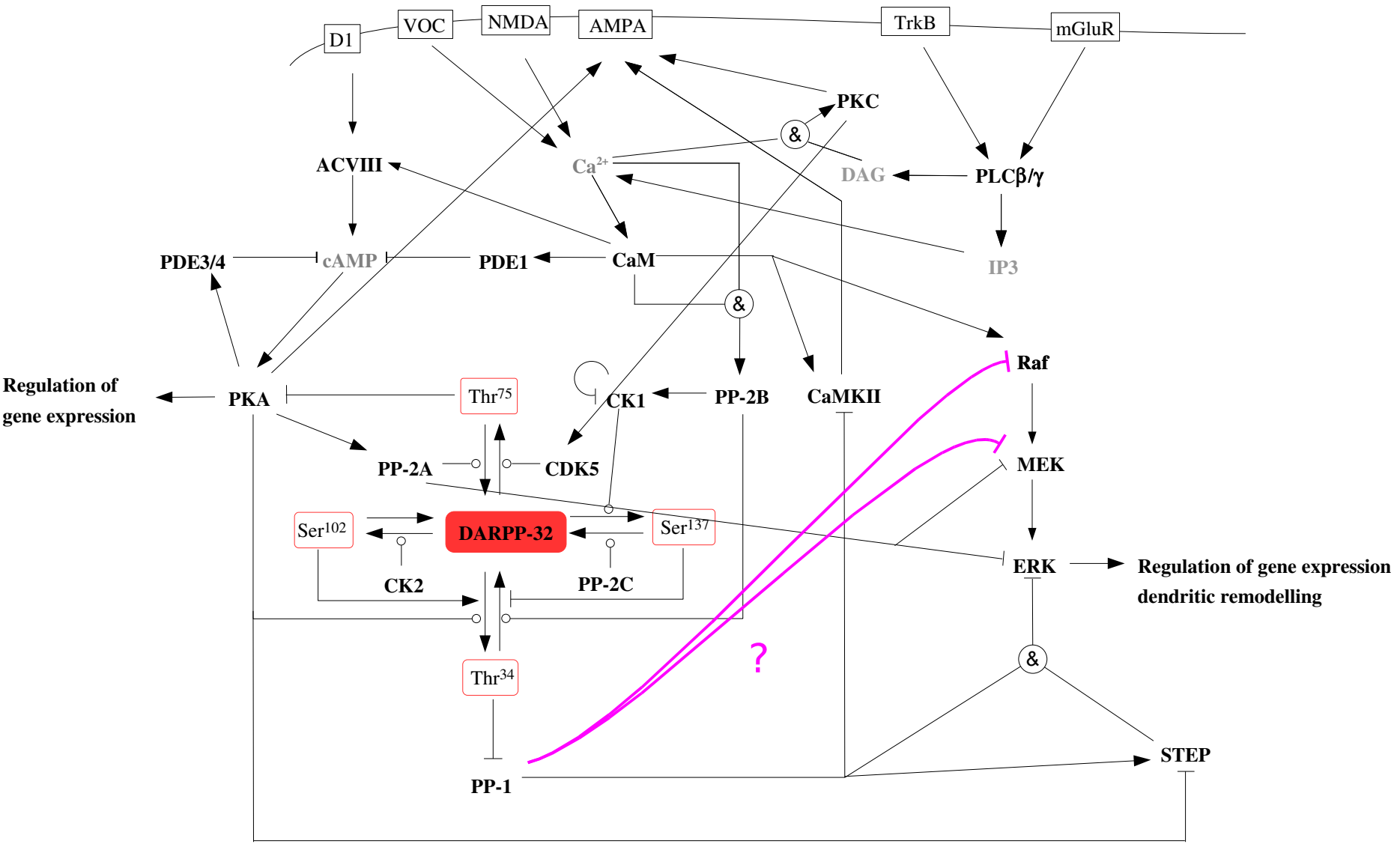
Jean-Antoine Girault, Paris



Collaboration

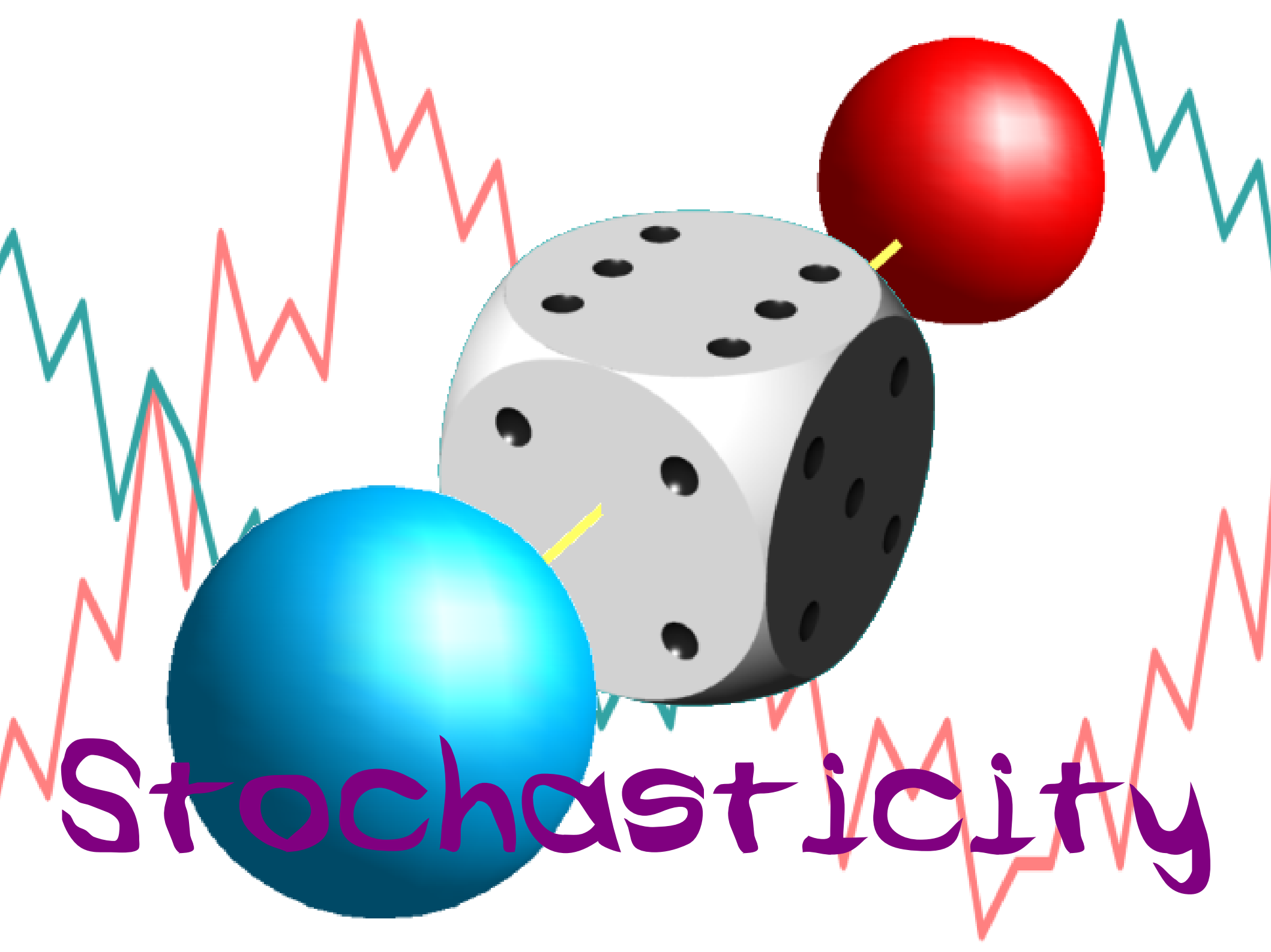
Liliana Minichiello, Monterotondo

What's next?

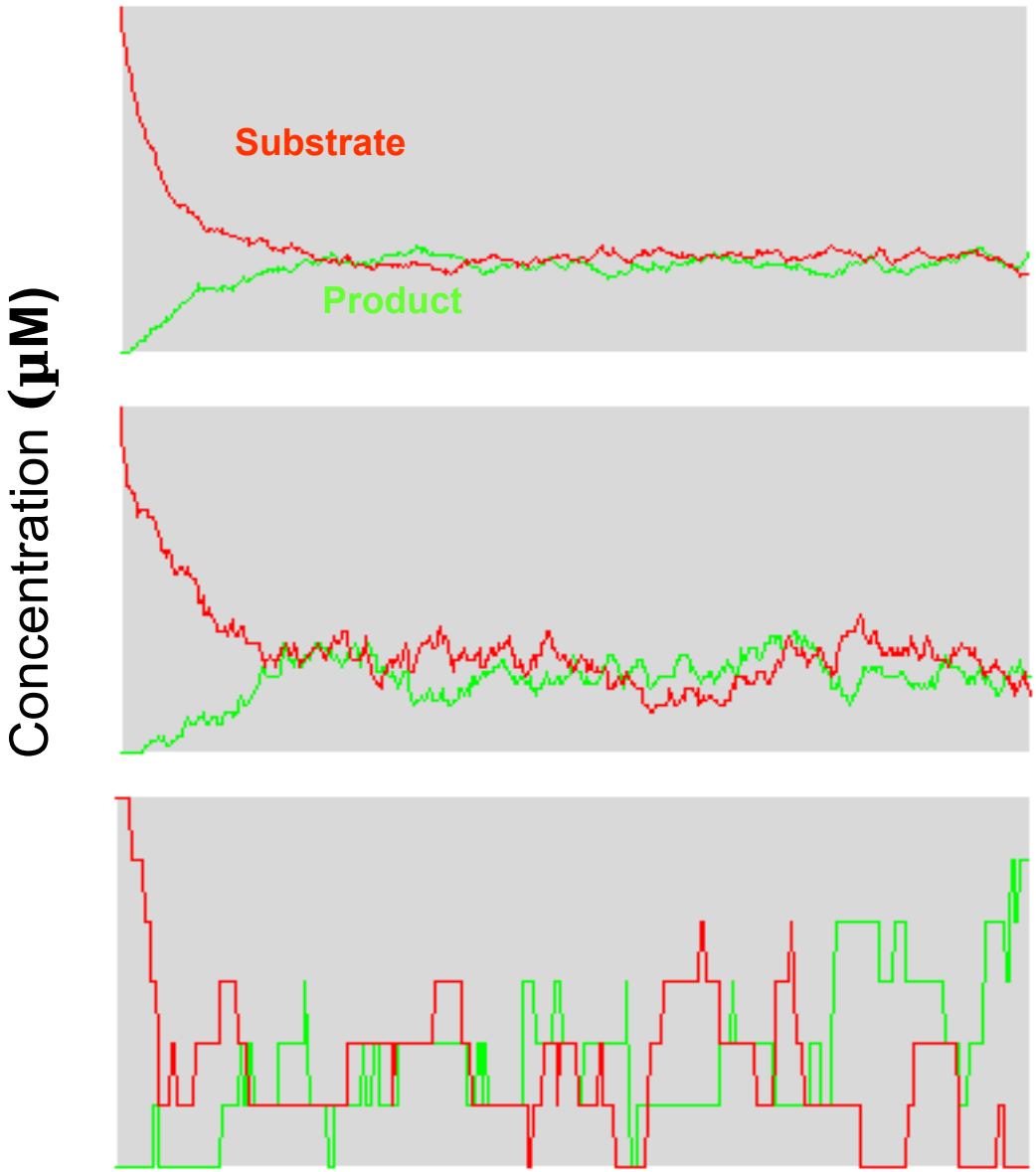

D1
VOC
NMDA
AMPA
TrkB
mGluR
PKC
&
ACVIII
Ca2+
DAG
PLCβ/γ
PDE3/4
cAMP
PDE1
CaM
IP3
&
Raf
Regulation of
gene expression
PKA
Thr75
CK1
PP-2B
CaMKII
PP-2A
CDK5
MEK
Ser102
DARPP-32
Ser137
ERK
Regulation of gene expression
dendritic remodelling
CK2
PP-2C
?
&
Thr34
STEP
PP-1

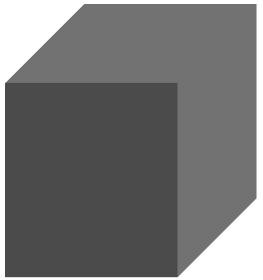
Am I happy?


NO


Stochasticity

On small numbers



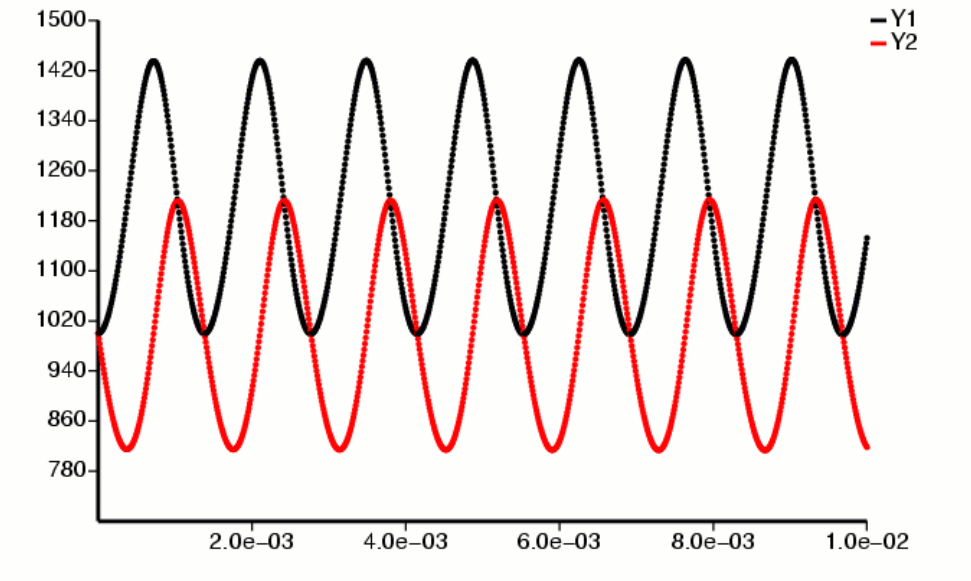


10^{-15} litres

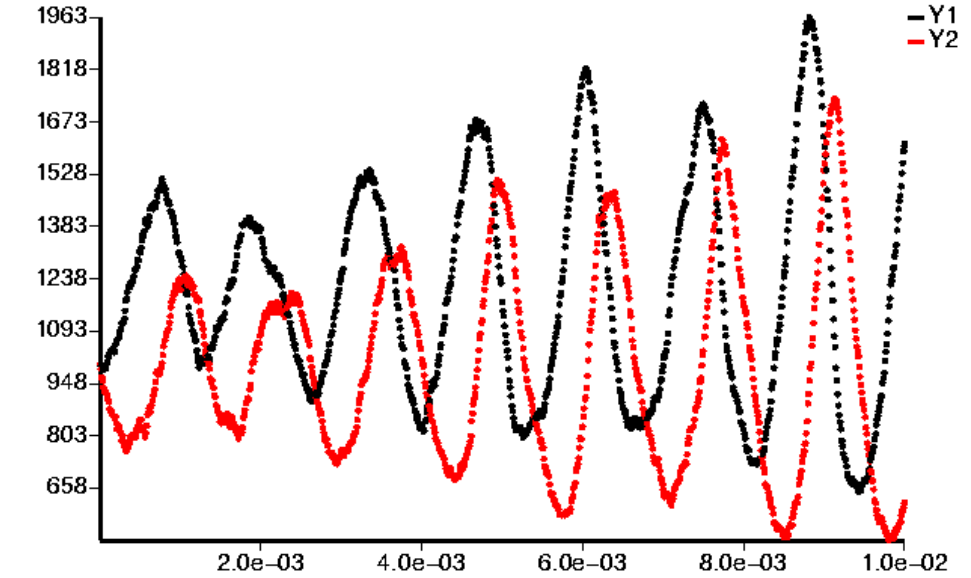
10^{-16} litres

10^{-17} litres

On determinism and reproducibility

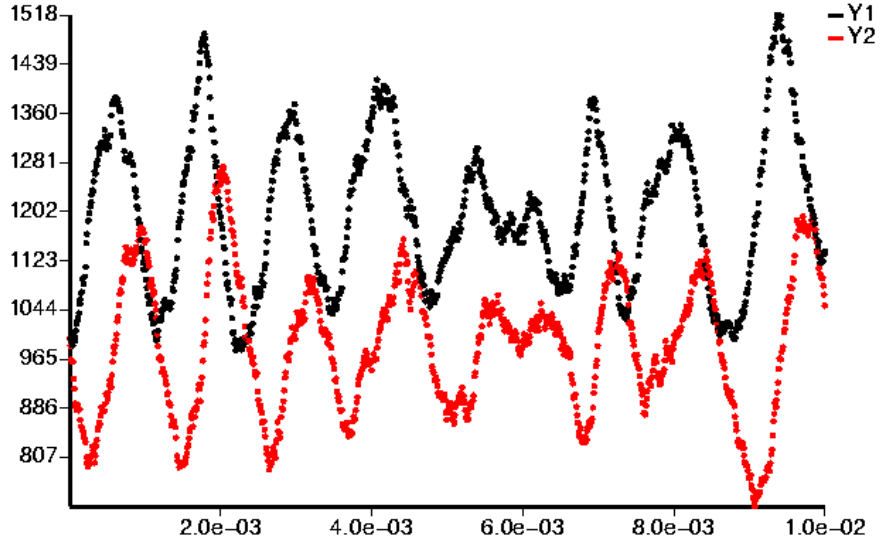


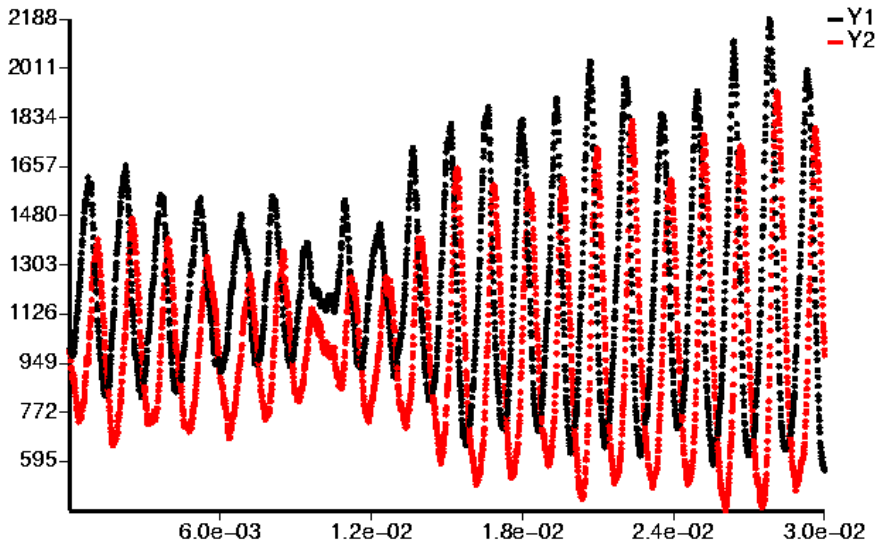
deterministic result

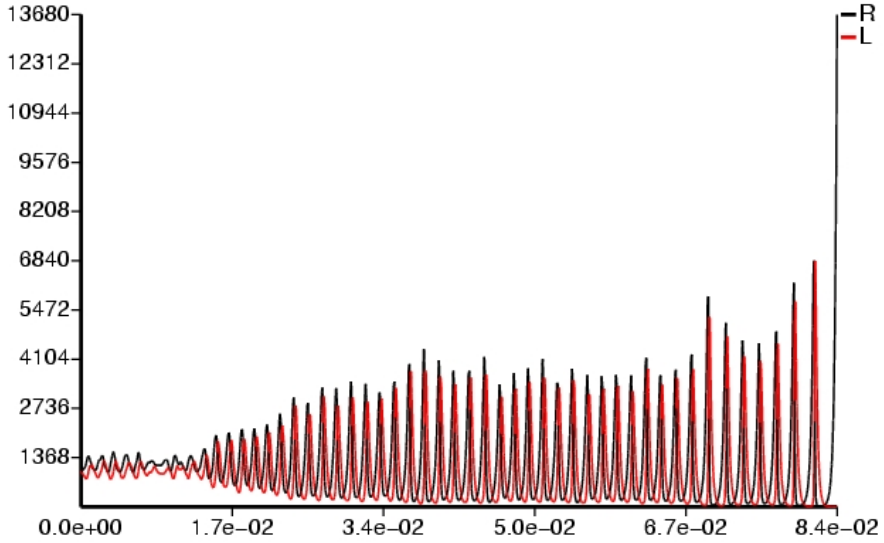


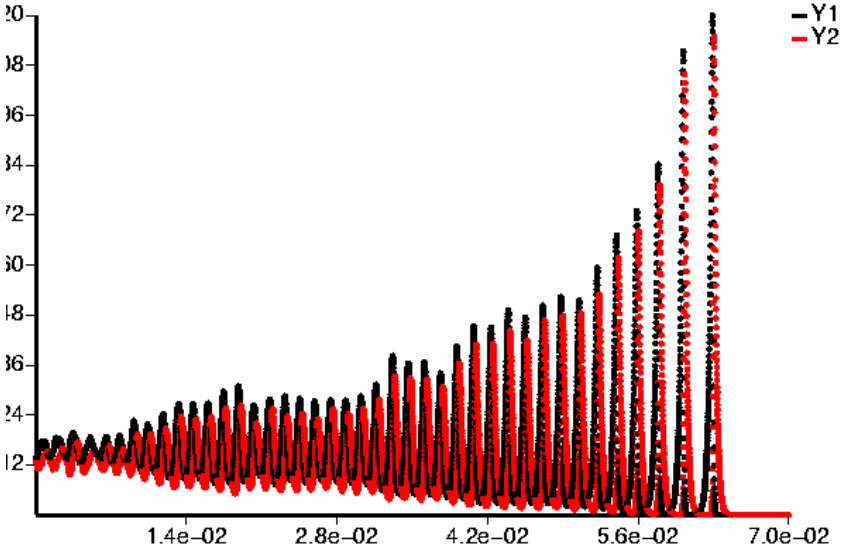
stochastic result

“Pathologic” behaviour









Small numbers in the dendritic spine

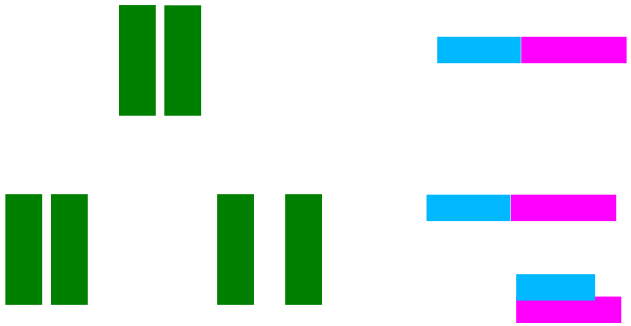
- number of AMPA receptors in a PSD: 50-100
- most kinases and phosphatases $\propto$ 100
- number of free calcium ions at rest state: 3-5


Combinatorial
Explosion

Combinatorial explosion

NMDA + CaMKII <=> NMDA-CaMKII

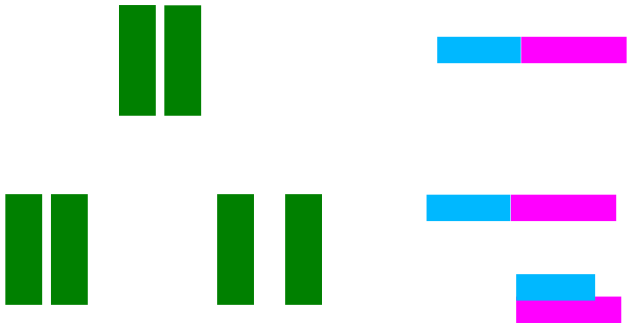
Combinatorial explosion



NMDA + CaMKII <=> NMDA-CaMKII

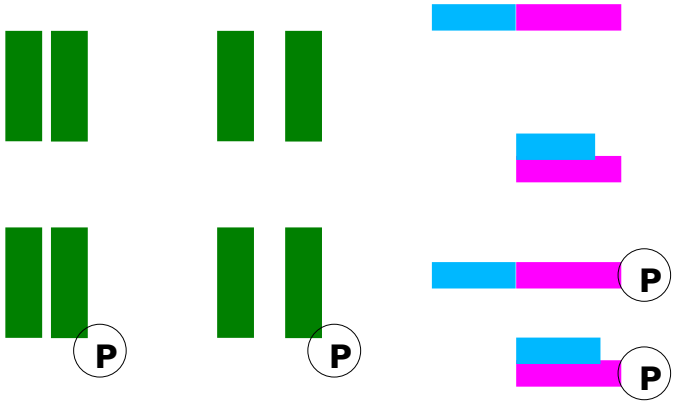
NMDAc + CaMKIIc <=> NMDAc-CaMKIIc
NMDAo + CaMKIIc <=> NMDAc-CaMKIIc
NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo

Combinatorial explosion

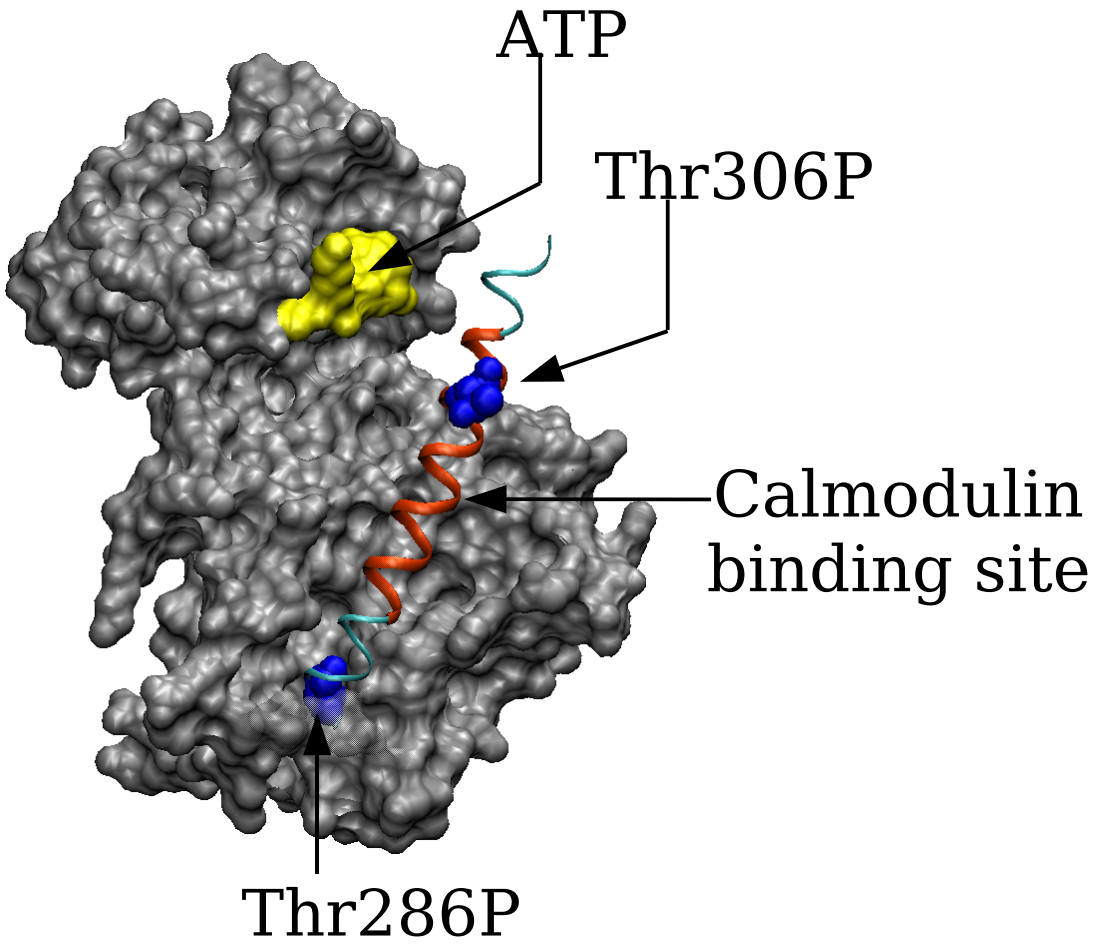


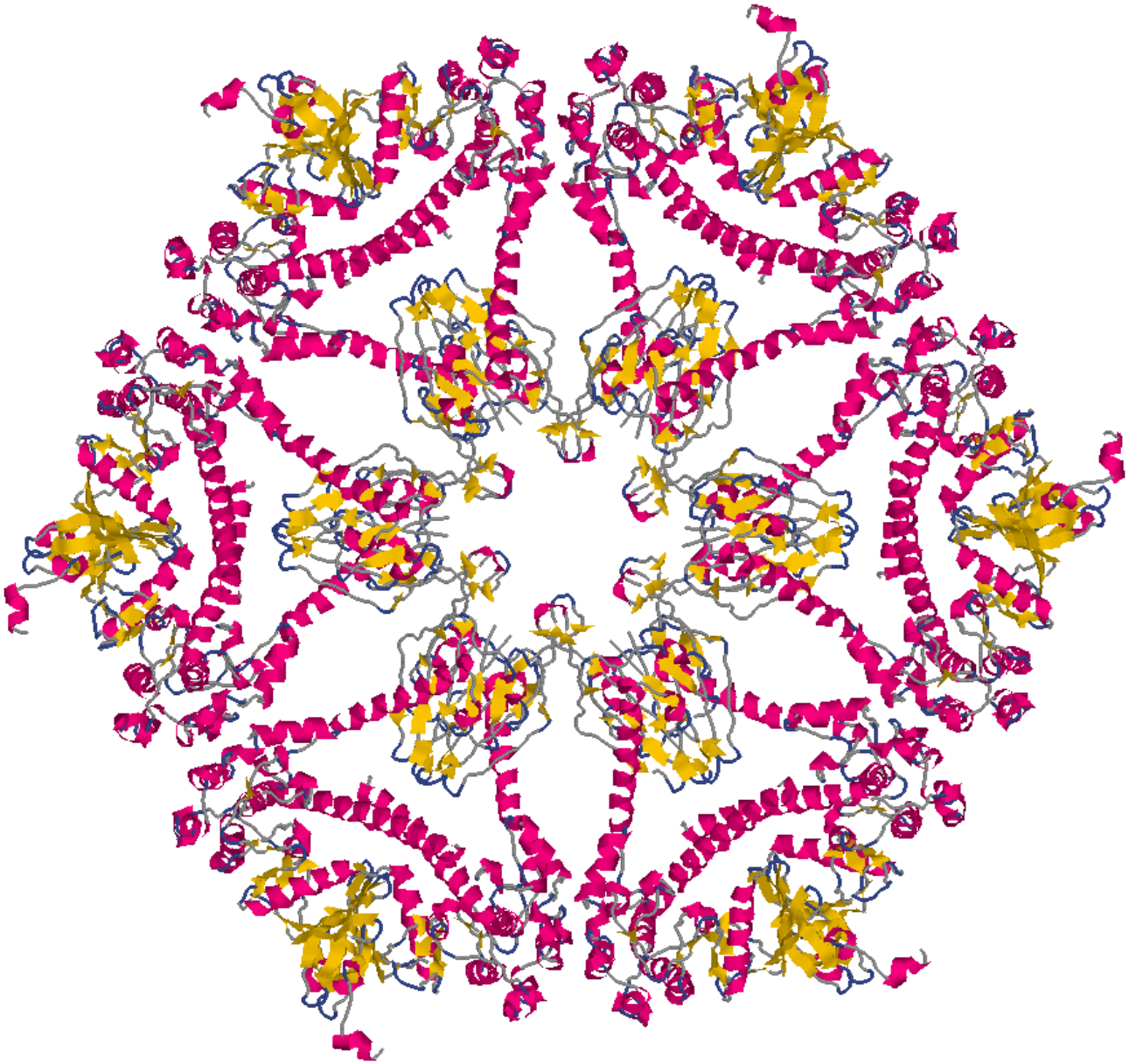
NMDA + CaMKII <=> NMDA-CaMKII

NMDAc + CaMKIIc <=> NMDAc-CaMKIIc
NMDAo + CaMKIIc <=> NMDAc-CaMKIIc
NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo



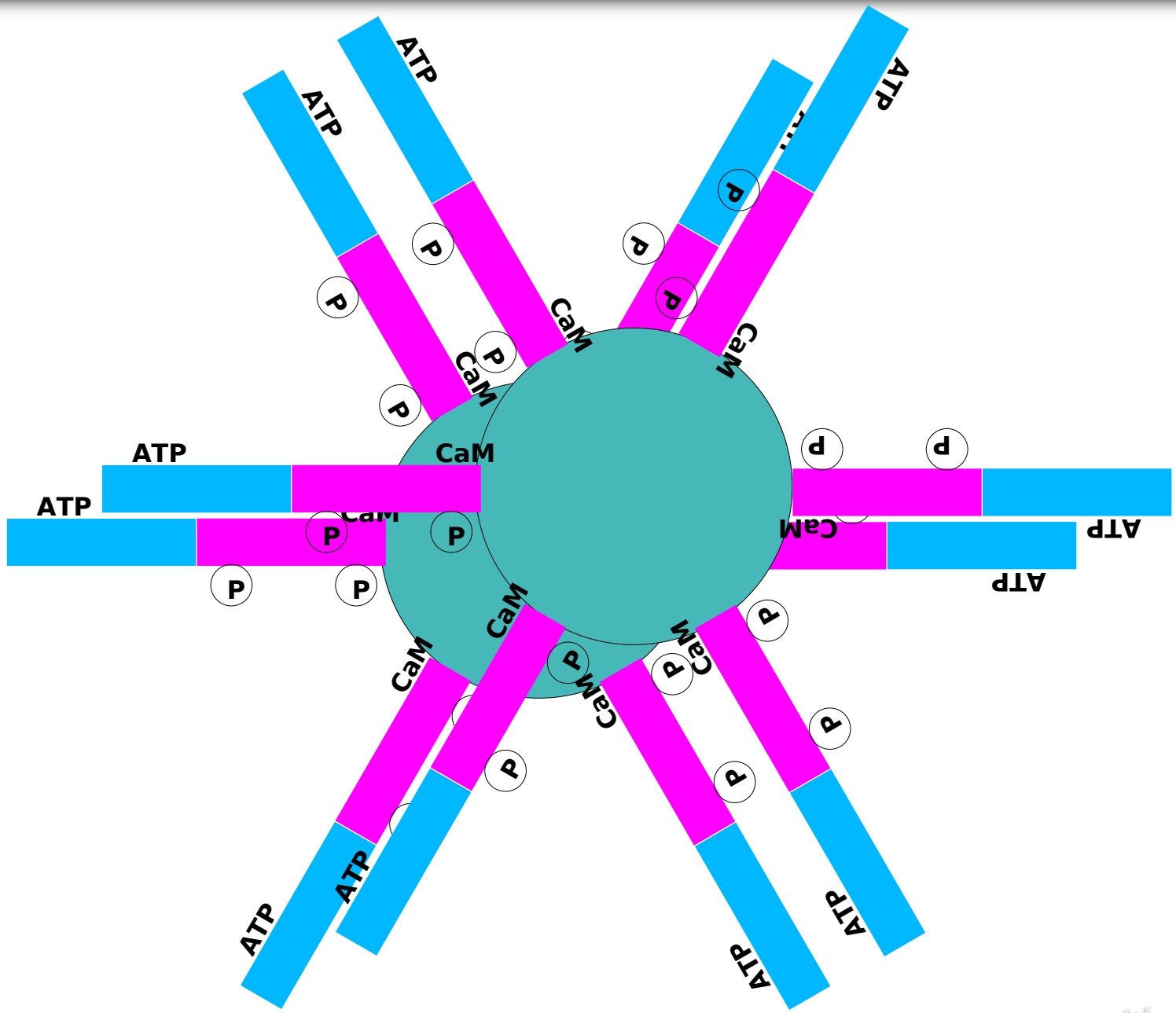
NMDAc + CaMKIIc <=> NMDAc-CaMKIIc
NMDAo + CaMKIIc <=> NMDAc-CaMKIIc
NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo
pNMDAc + CaMKIIc <=> pNMDAc-CaMKIIc
pNMDAo + CaMKIIc <=> pNMDAc-CaMKIIc
pNMDAc + CaMKIIo <=> pNMDAc-CaMKIIo
pNMDAo + CaMKIIo <=> pNMDAc-CaMKIIo
NMDAc + pCaMKIIc <=> NMDAc-pCaMKIIc
NMDAo + pCaMKIIc <=> NMDAc-pCaMKIIc
NMDAc + pCaMKIIo <=> NMDAc-pCaMKIIo
NMDAo + pCaMKIIo <=> NMDAc-pCaMKIIo
pNMDAc + pCaMKIIc <=> pNMDAc-pCaMKIIc
pNMDAo + pCaMKIIc <=> pNMDAc-pCaMKIIc
pNMDAc + pCaMKIIo <=> pNMDAc-pCaMKIIo
pNMDAo + pCaMKIIo <=> pNMDAc-pCaMKIIo


ATP
Thr306P
Calmodulin
binding site
Thr286P

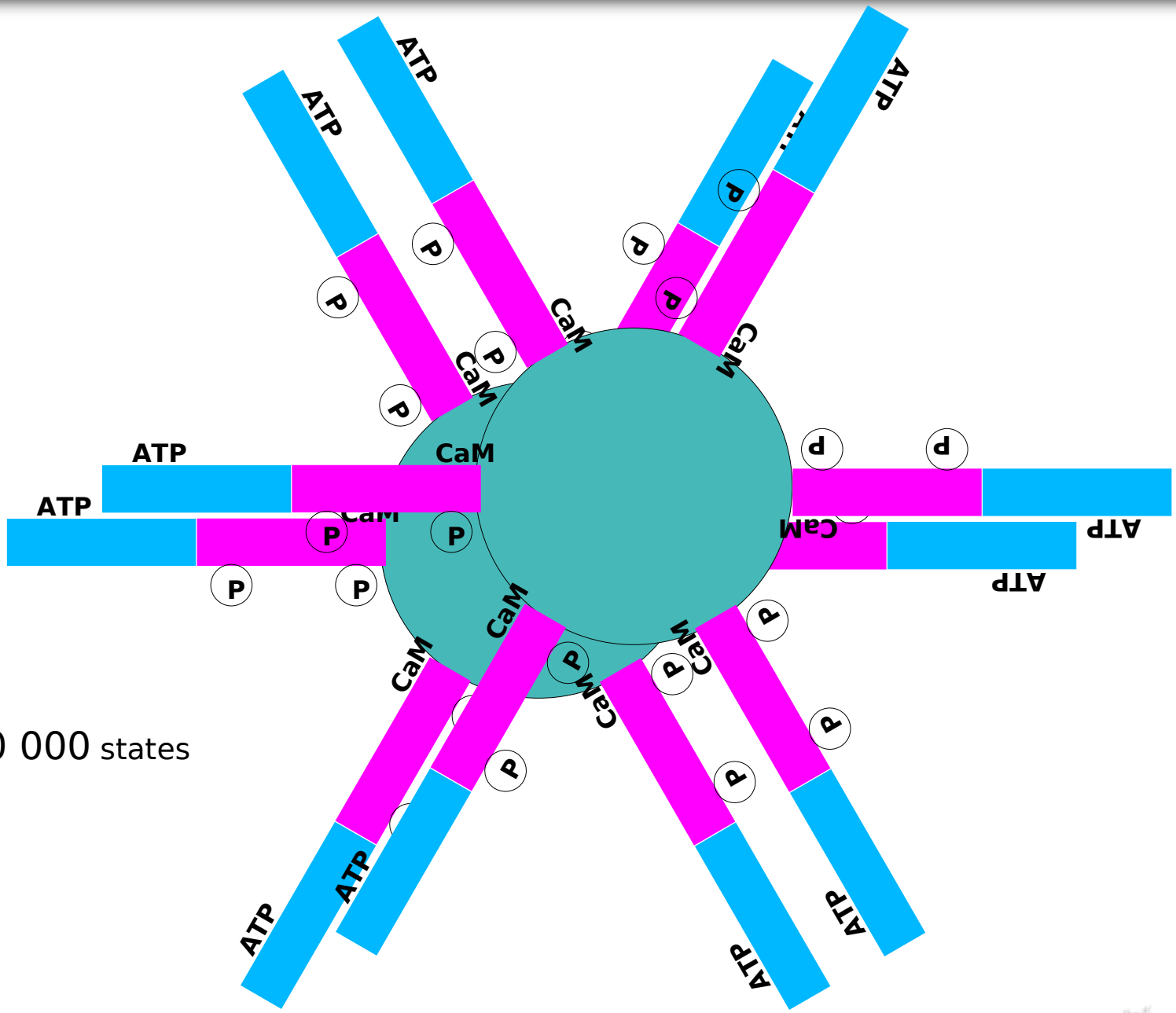


Combinatorial explosion

5x12 state variables=



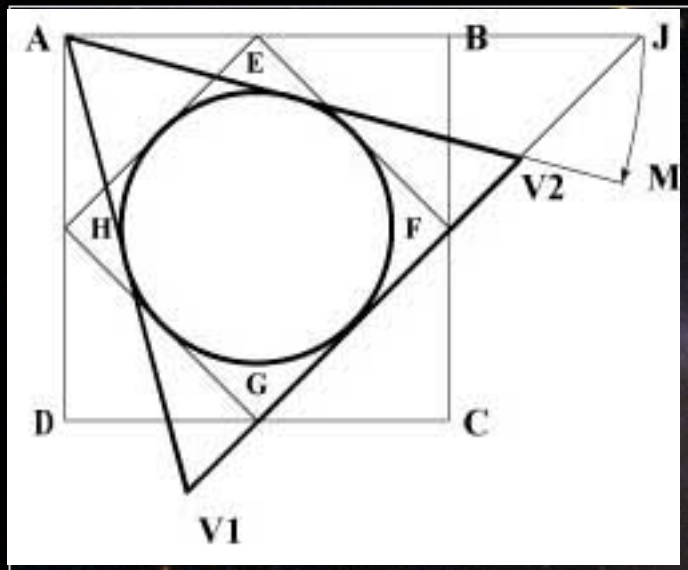
Combinatorial explosion



5x12 state variables=

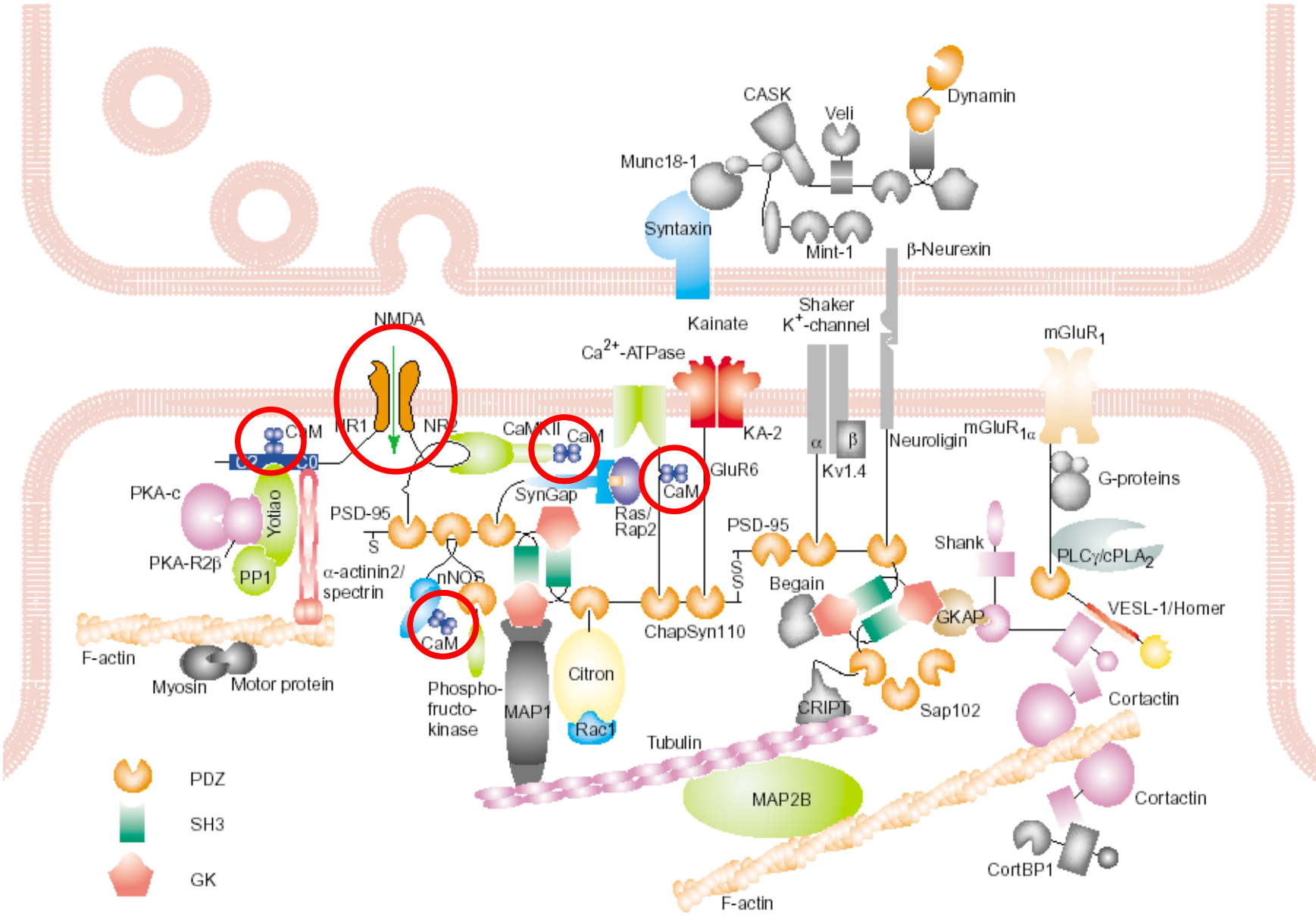
1 152 900 000 000 000 000 states

(1 billion of billion)



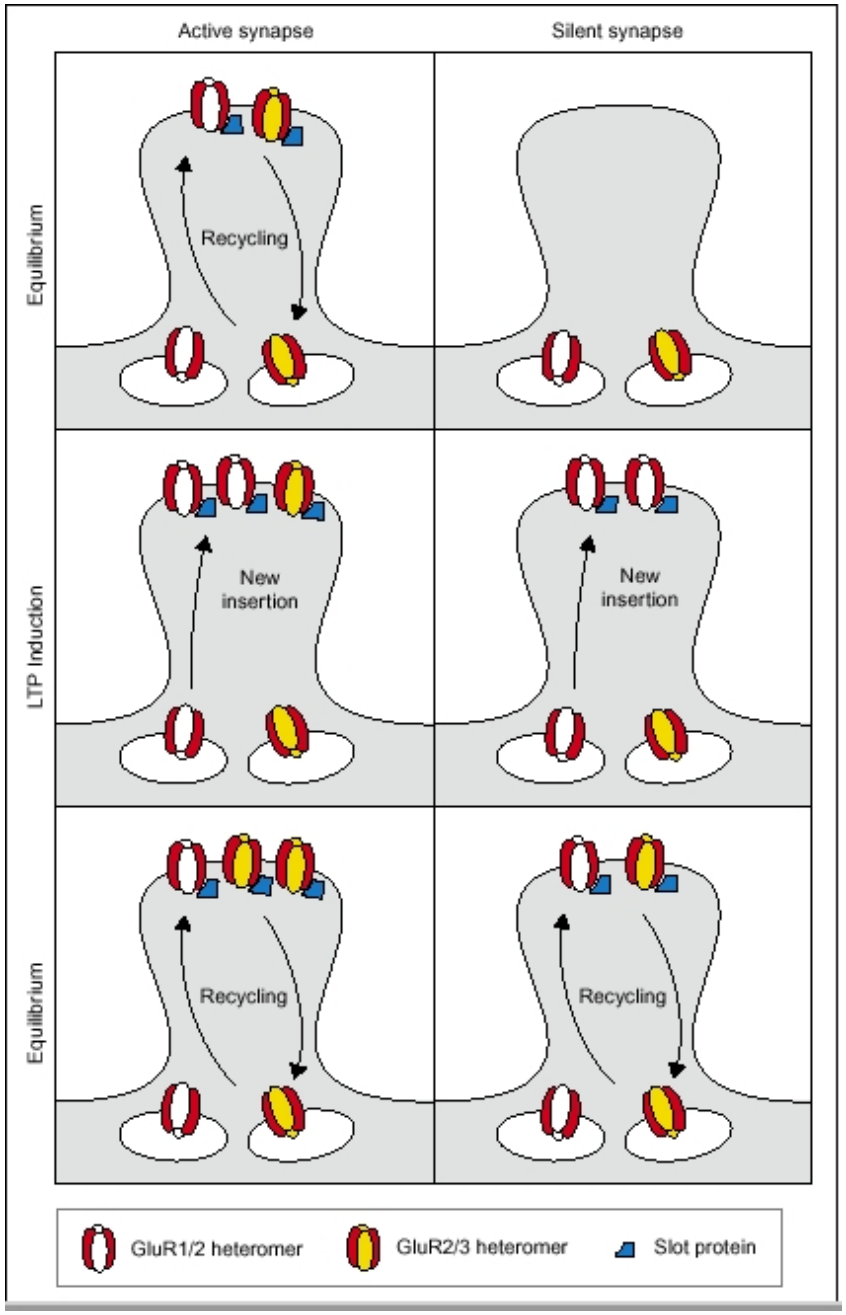
Space and geometry

Complex post-synaptic machinery

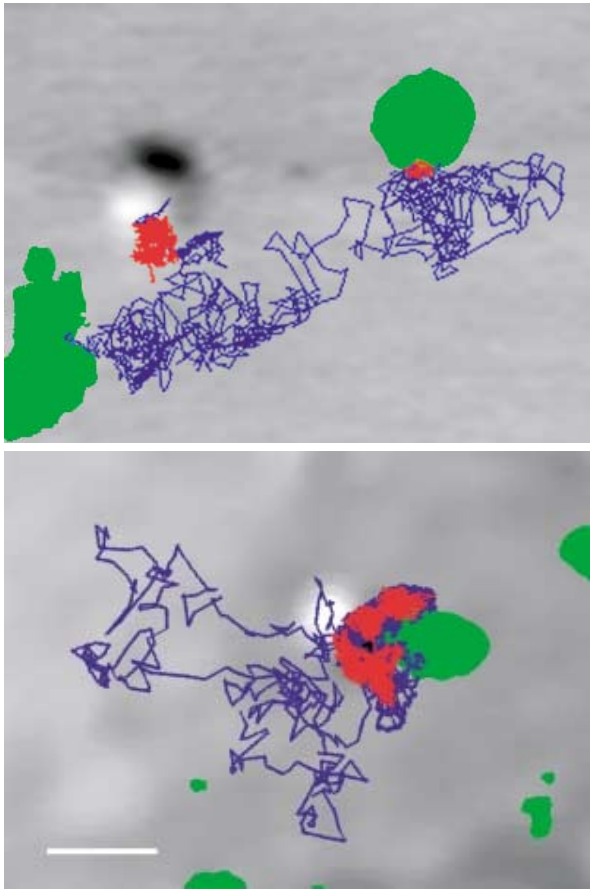


Husi & Grant (2001) *TINS, 24*: 259-266

Receptors for neurotransmitters are moving



Barry and Ziff. (2002)
Curr Opin Neurobiol, 12: 279-286



Choquet & Triller (2003)
Nat Rev Neurosci, 4: 251-265

Need another paradigm of simulation

Population-based simulation

- Continuous representation of populations
- Generally deterministic algorithms to simulate the evolution of populations (but not always: Gillespie)
- Generally no representation of space (but not always: finite elements)
- No movements (but not always: PDE or reaction-diffussion)
- Molecules under different states are represented by different pools

Particle-based simulation

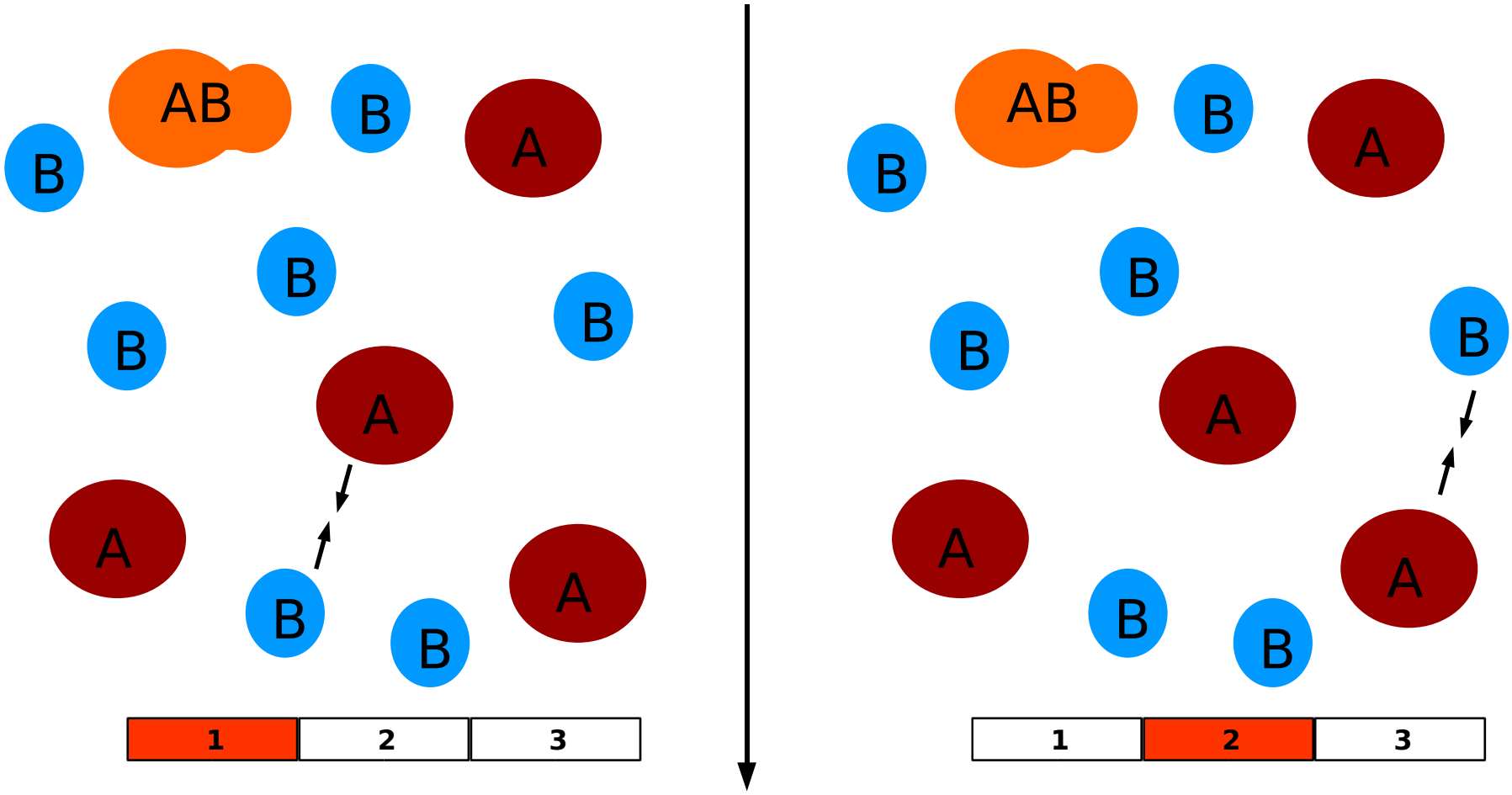
- Discrete representation of molecules
- Generally stochastic algorithms (but not always: deterministic automata)
- Generally location of molecules (but not always: StochSim v1)
- Representation of the movements of (some) molecules
- Possibility of multistates molecules

StochSim: Stochastic cellular automata

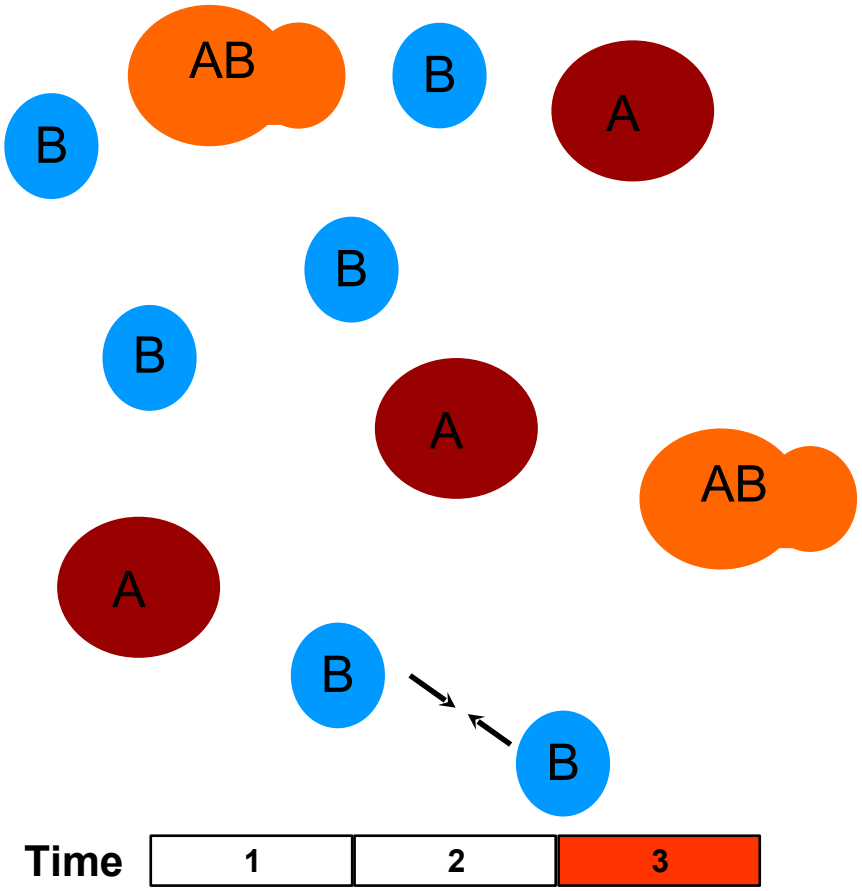
- Morton-Firth CJ, Bray D (1998) *J. Theor. Biol.* 192: 117–128.
- Le Novère N, Shimizu TS (2001) *Bioinformatics* 17: 575-576

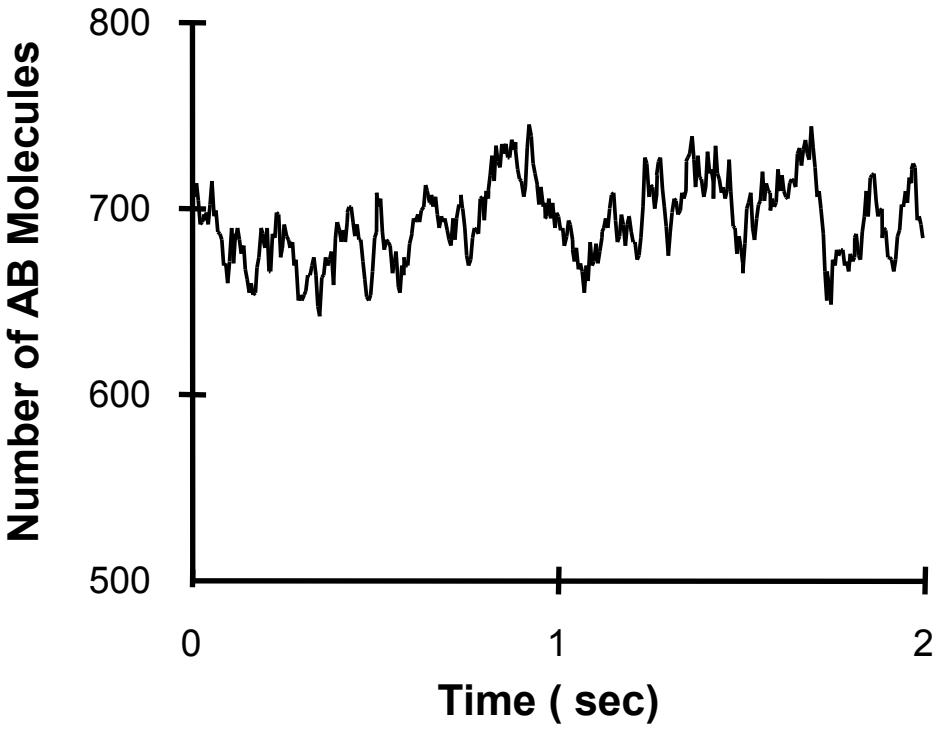
- Particle-based stochastic simulations
- Possibility of multistate complexes
- Rapid equilibria to reduce stiffness problems
- 2D lattices of various geometry

StochSim algorithm

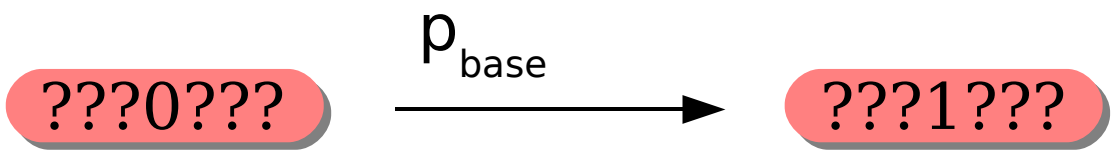


StochSim algorithm



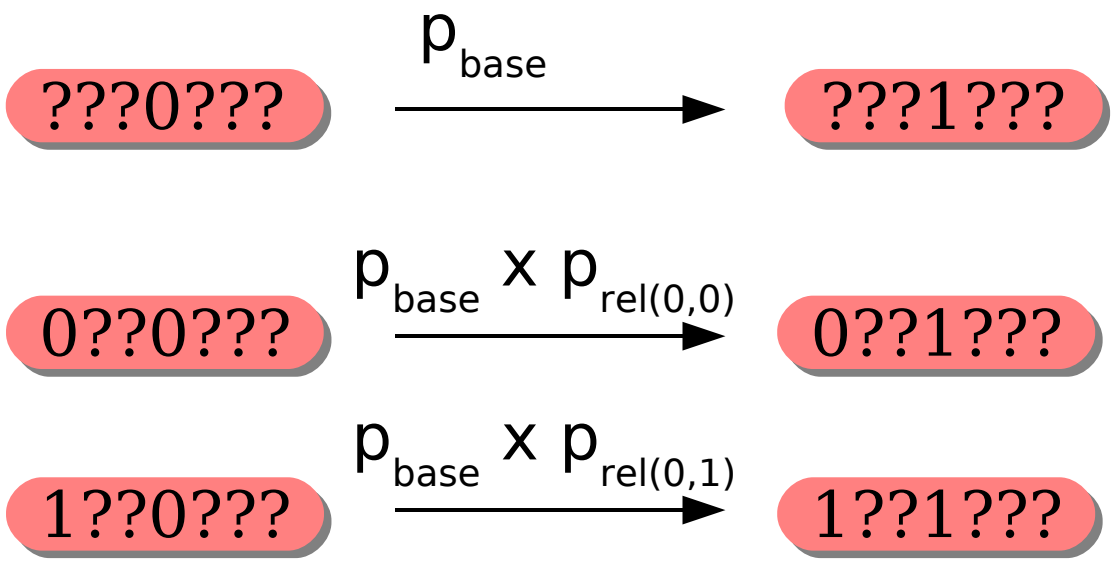


Multistate reactions



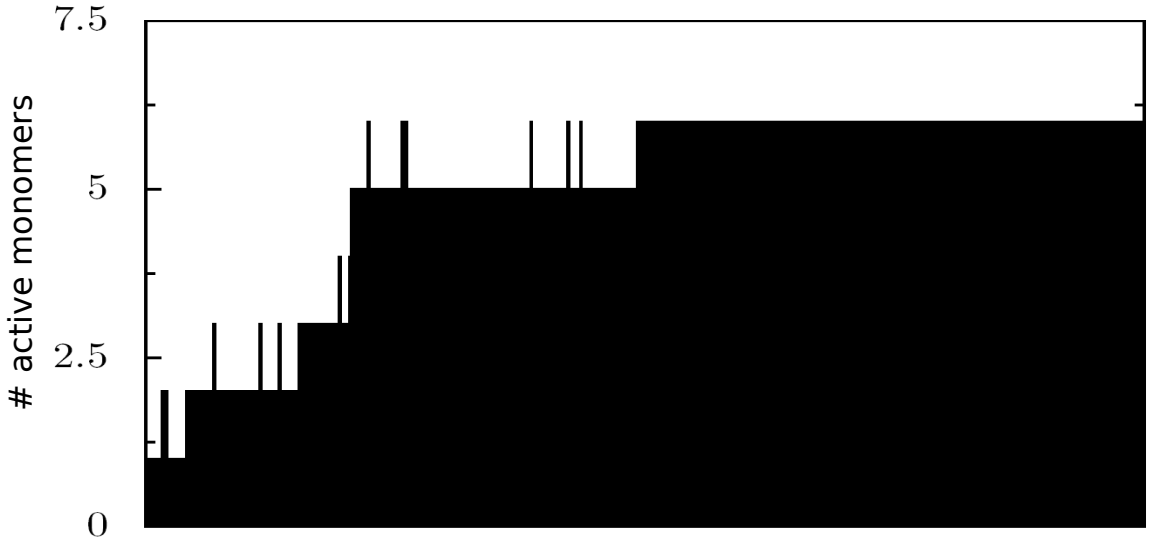
- '?' Flags do not affect the reaction

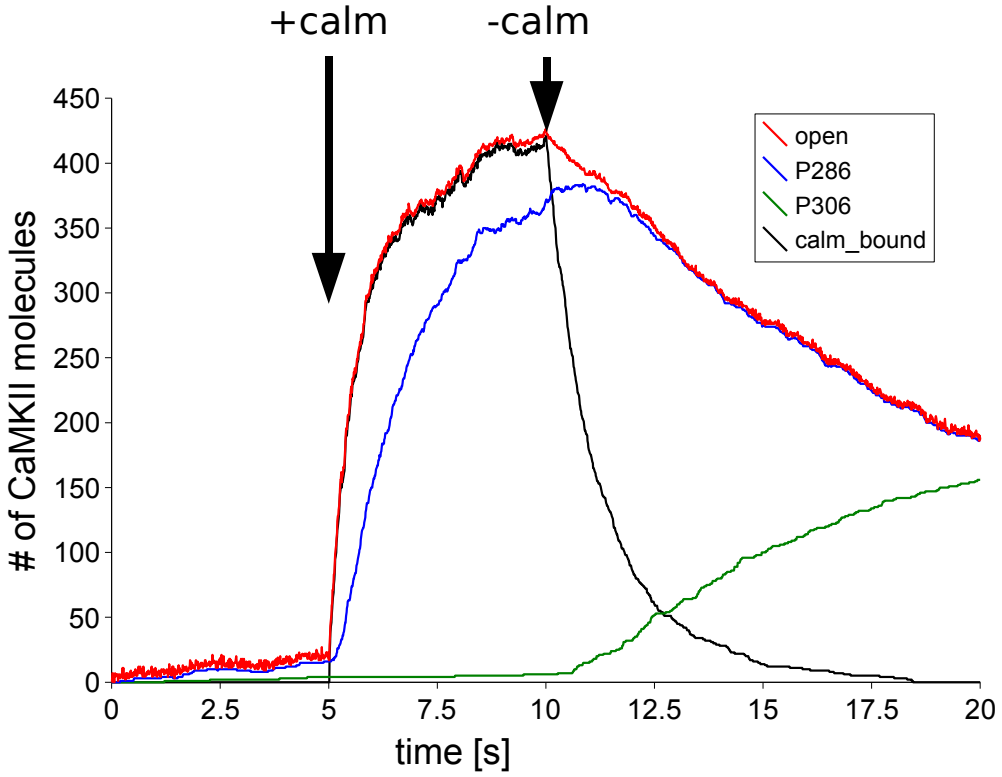
Multistate reactions



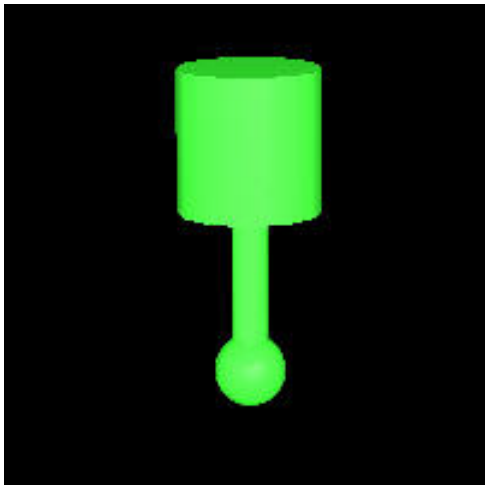
- '?' Flags do not affect the reaction
- only 4 species are needed instead of 128
- only 2 reactions are needed instead of 64

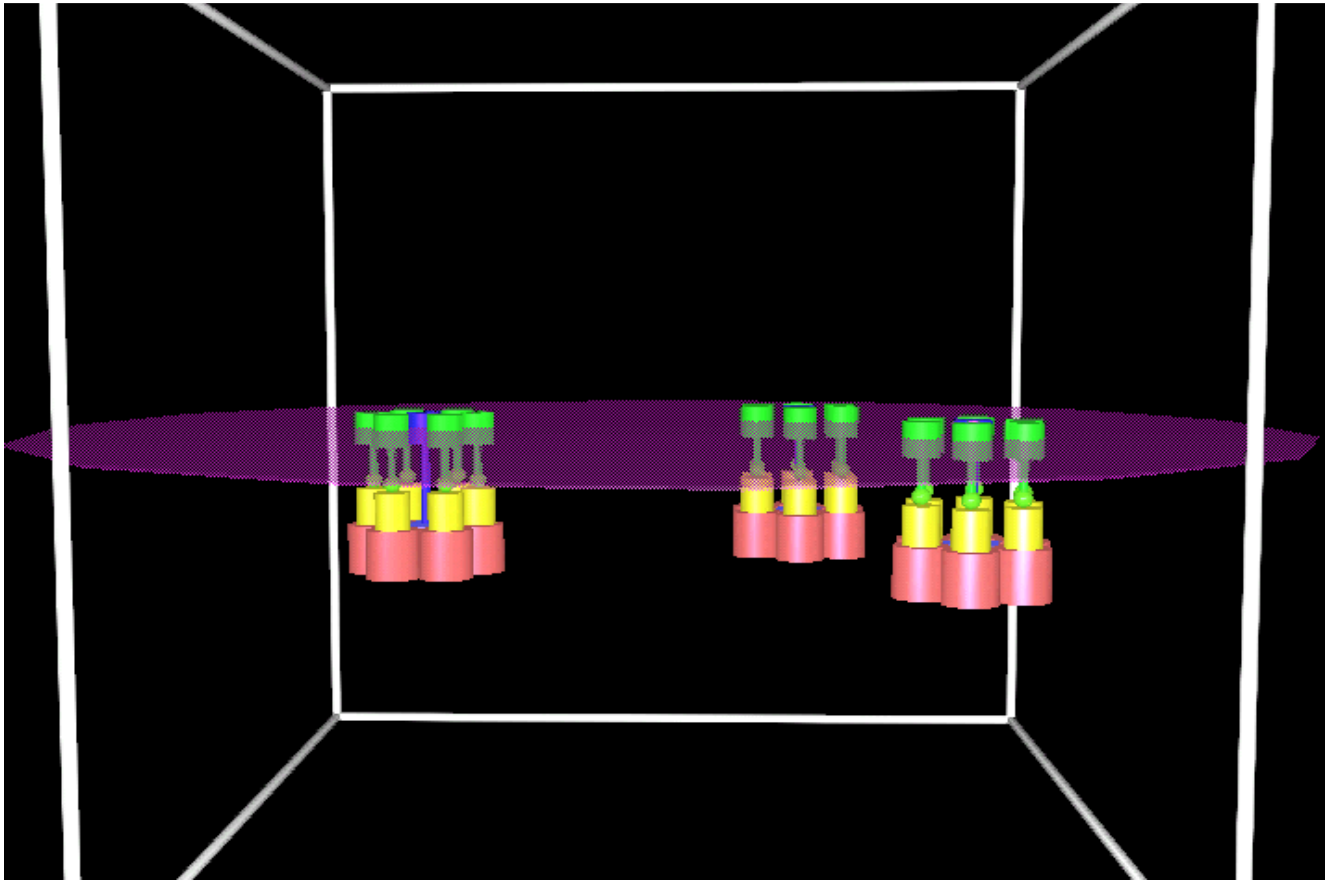
Stochastic simulation of multistate complexes





Meredys: Particles, Objects and Clusters





Particles carry binding surfaces
Cluster and object classes allows recording of Center Of Mass, radius, RMS displacement, state
Clusters are dynamically created and destroyed – transient

Tolle D, Le Novere N (2006)
Particle-based stochastic simulation in systems biology
Current Bioinformatics 1 (3): 315-320

Molecule diffusion

- Different diffusion spaces:
  - Static; Free diffusion; Membrane diffusion; Above membrane; Below membrane
- 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

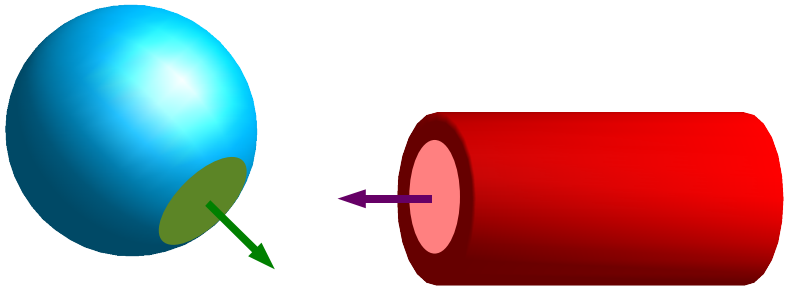
- Unrestricted brownian motion – Low Translation/Rotational

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

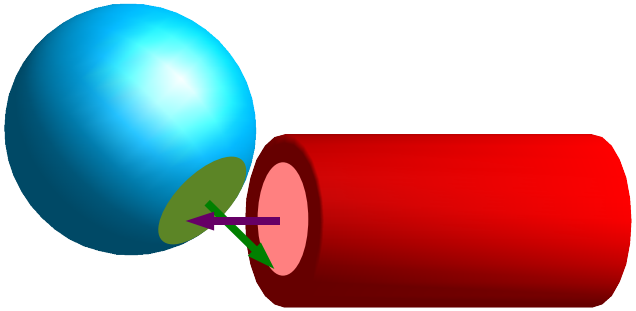
- Intra-membrane diffusion (Saffman and Delbrück 1975) High Translational/Rotational

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

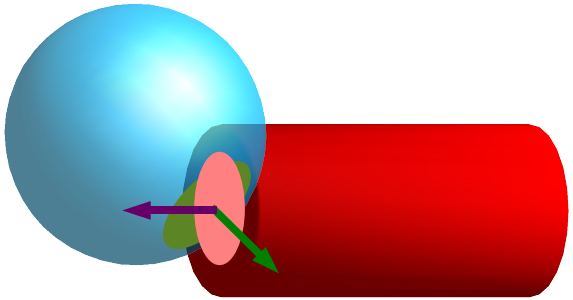
Reactions and complex formation



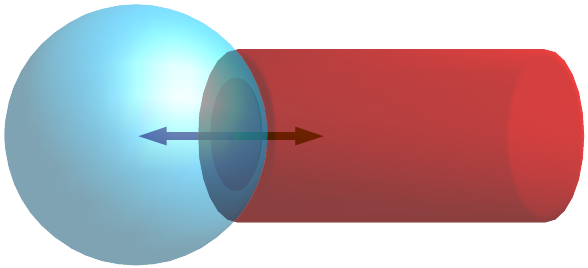
Reactions and complex formation



Reactions and complex formation

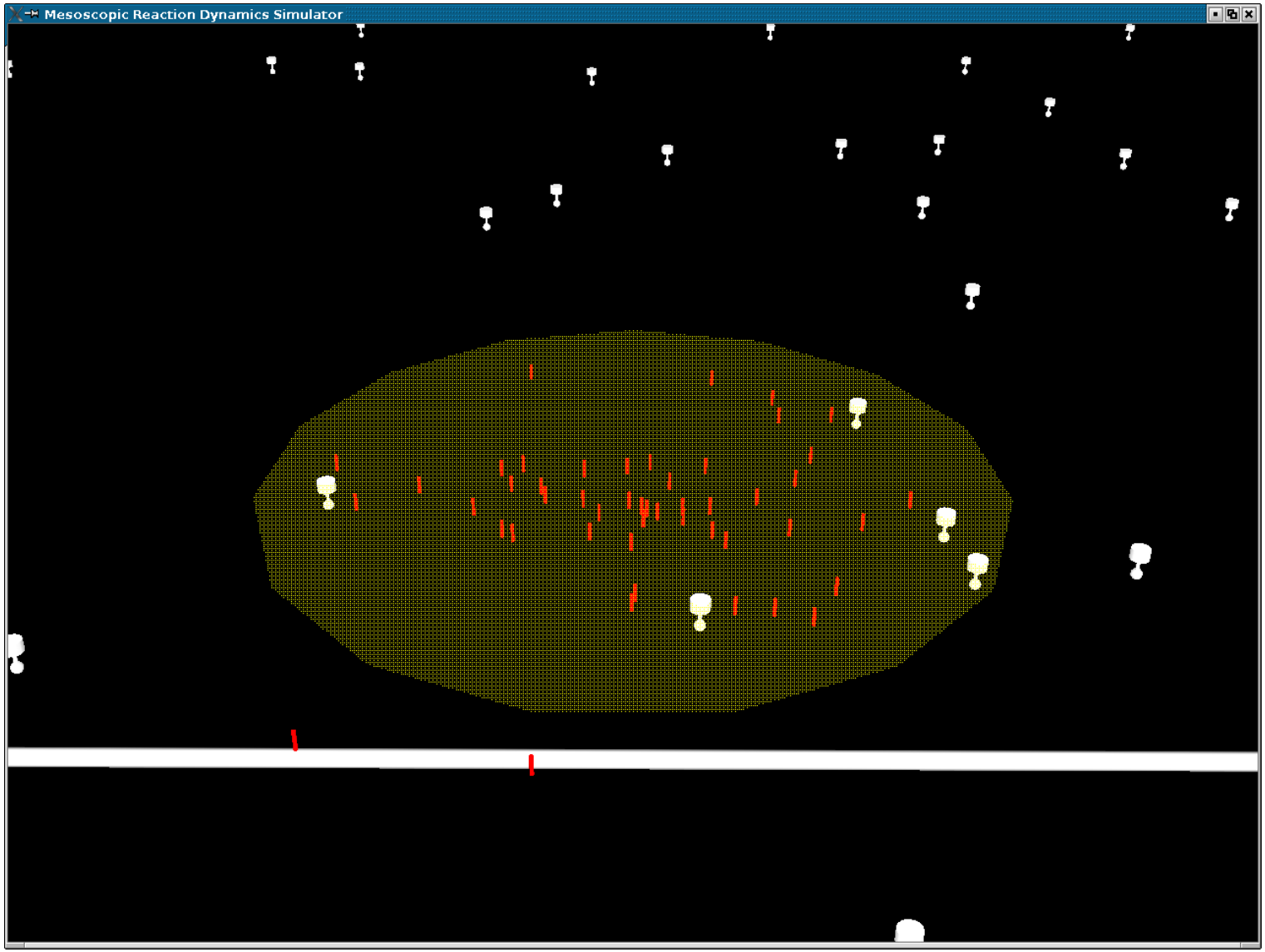


Reactions and complex formation



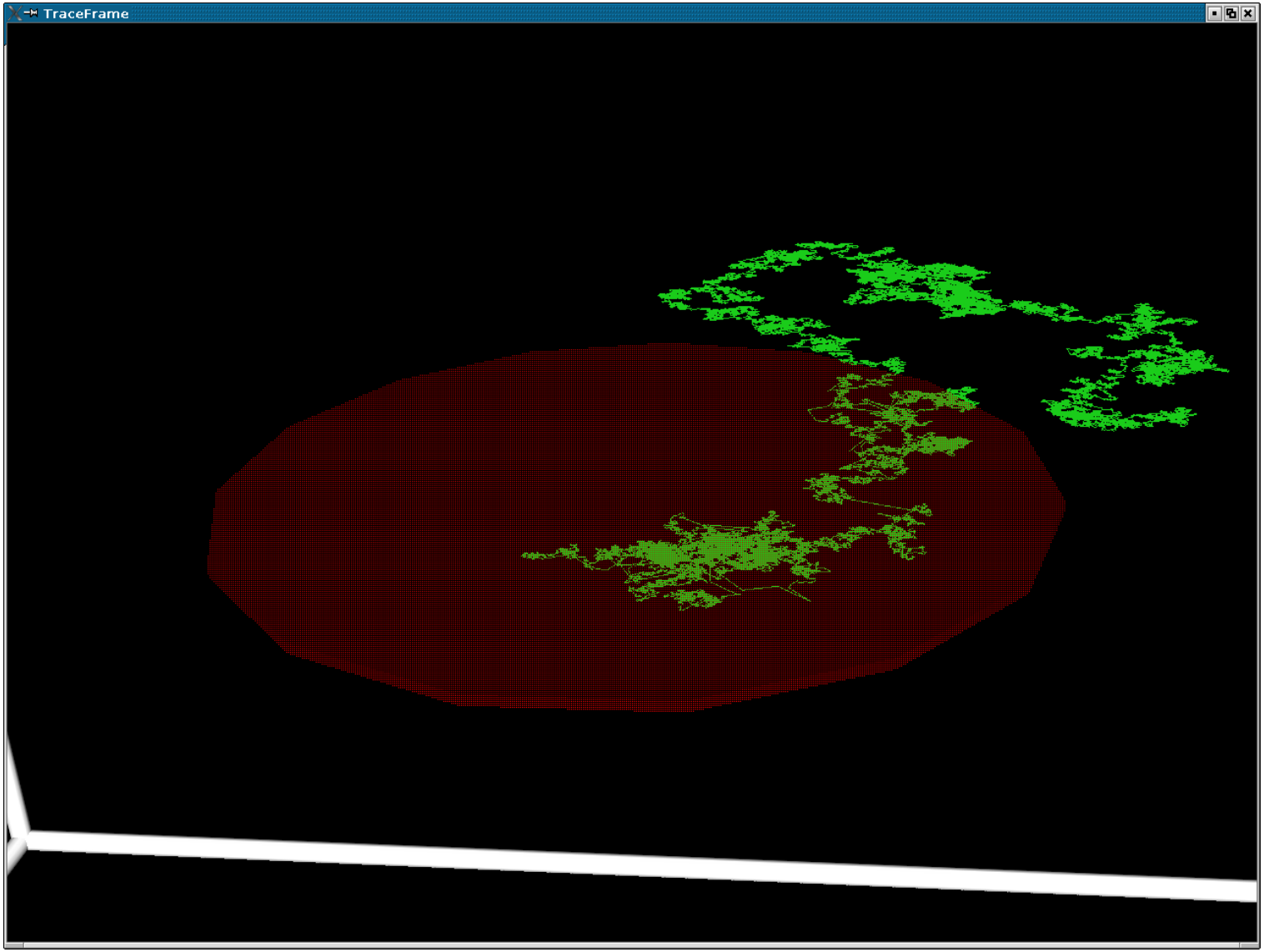
EMBL-EBI

Mesoscopic simulations of receptor diffusion

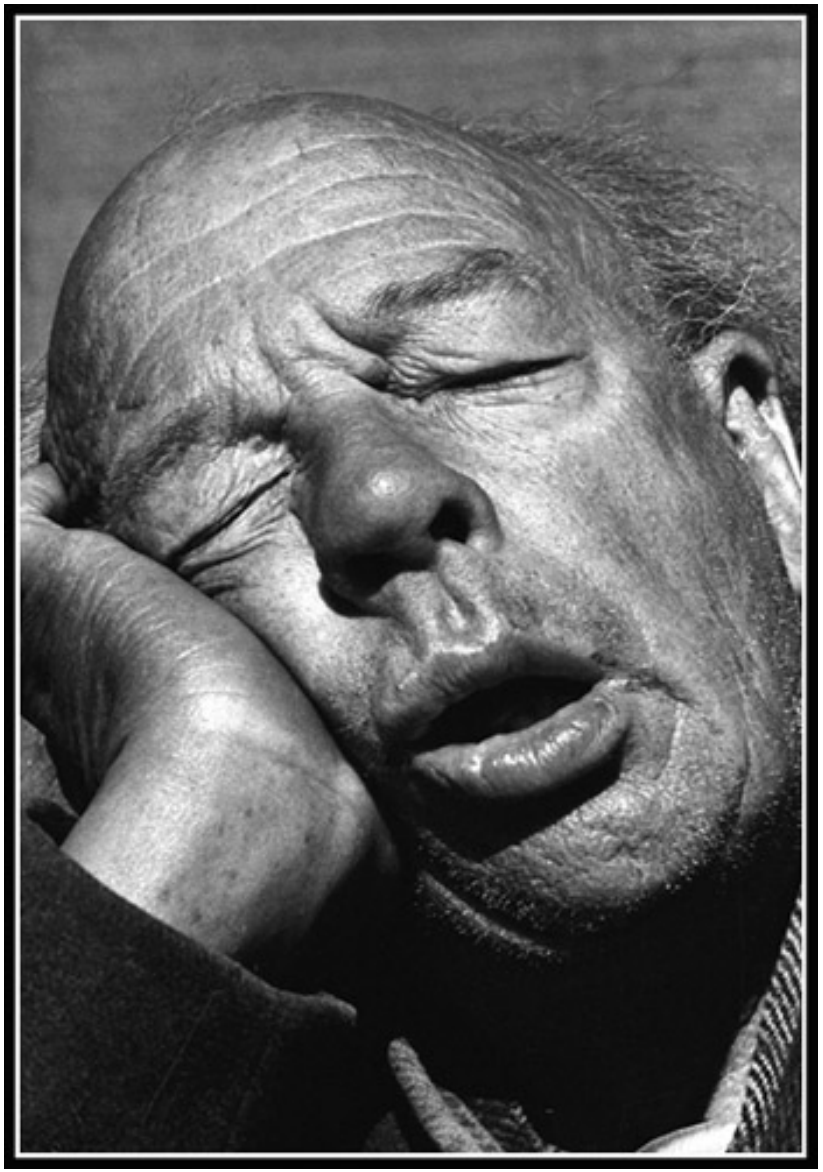


EMBL-EBI

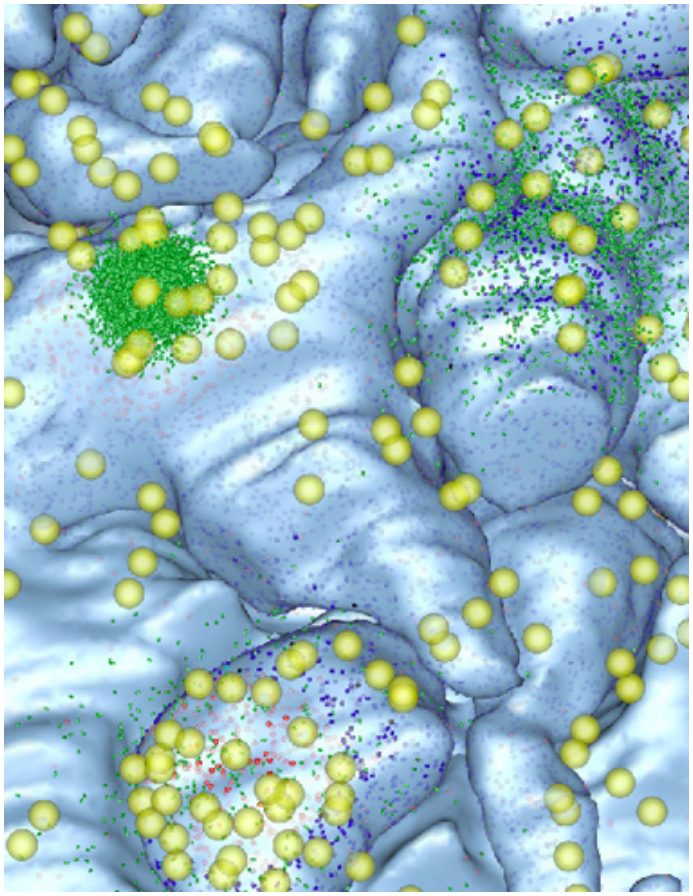
Mesoscopic simulations of receptor diffusion



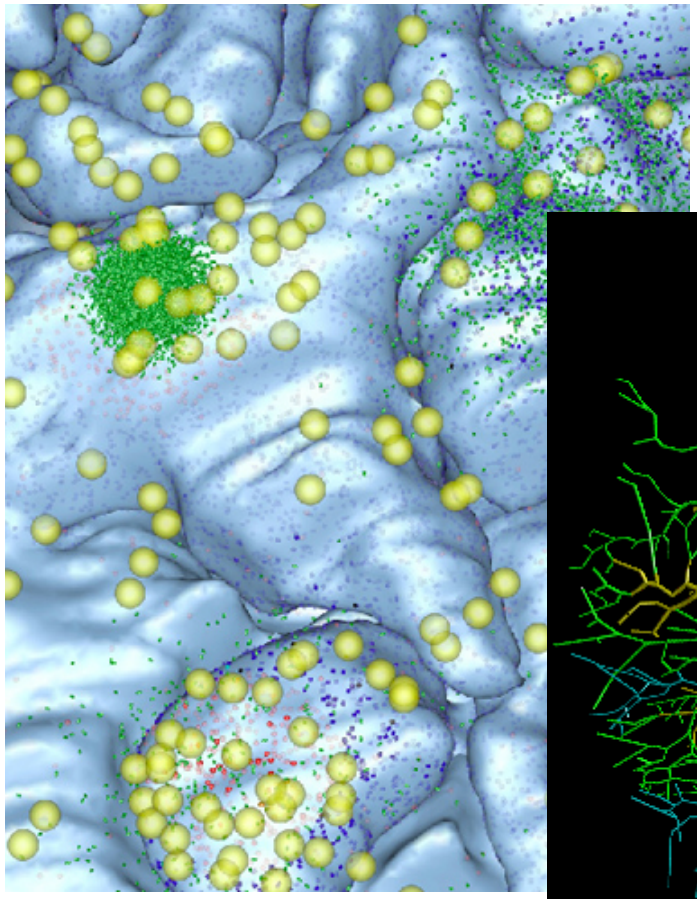
Had enough?

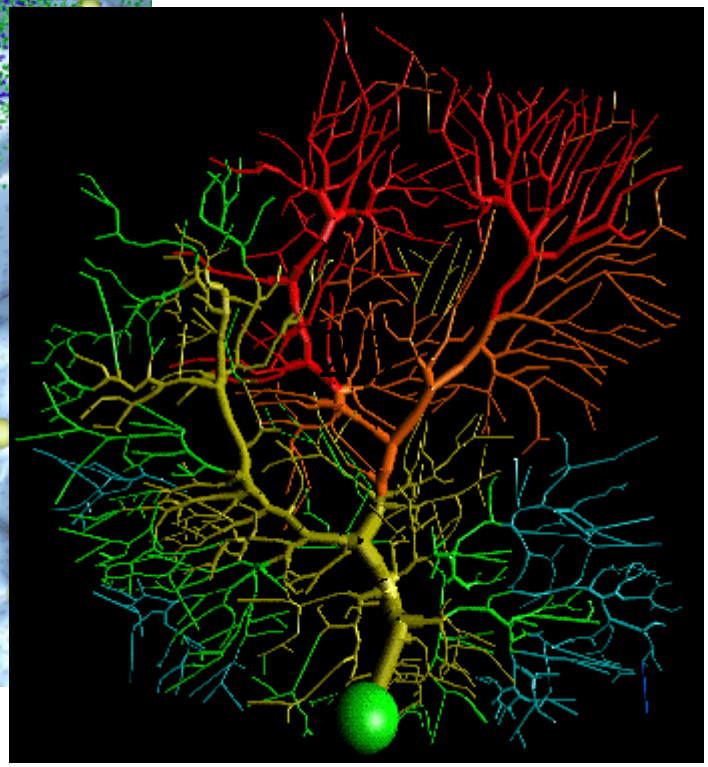


Single-particle model

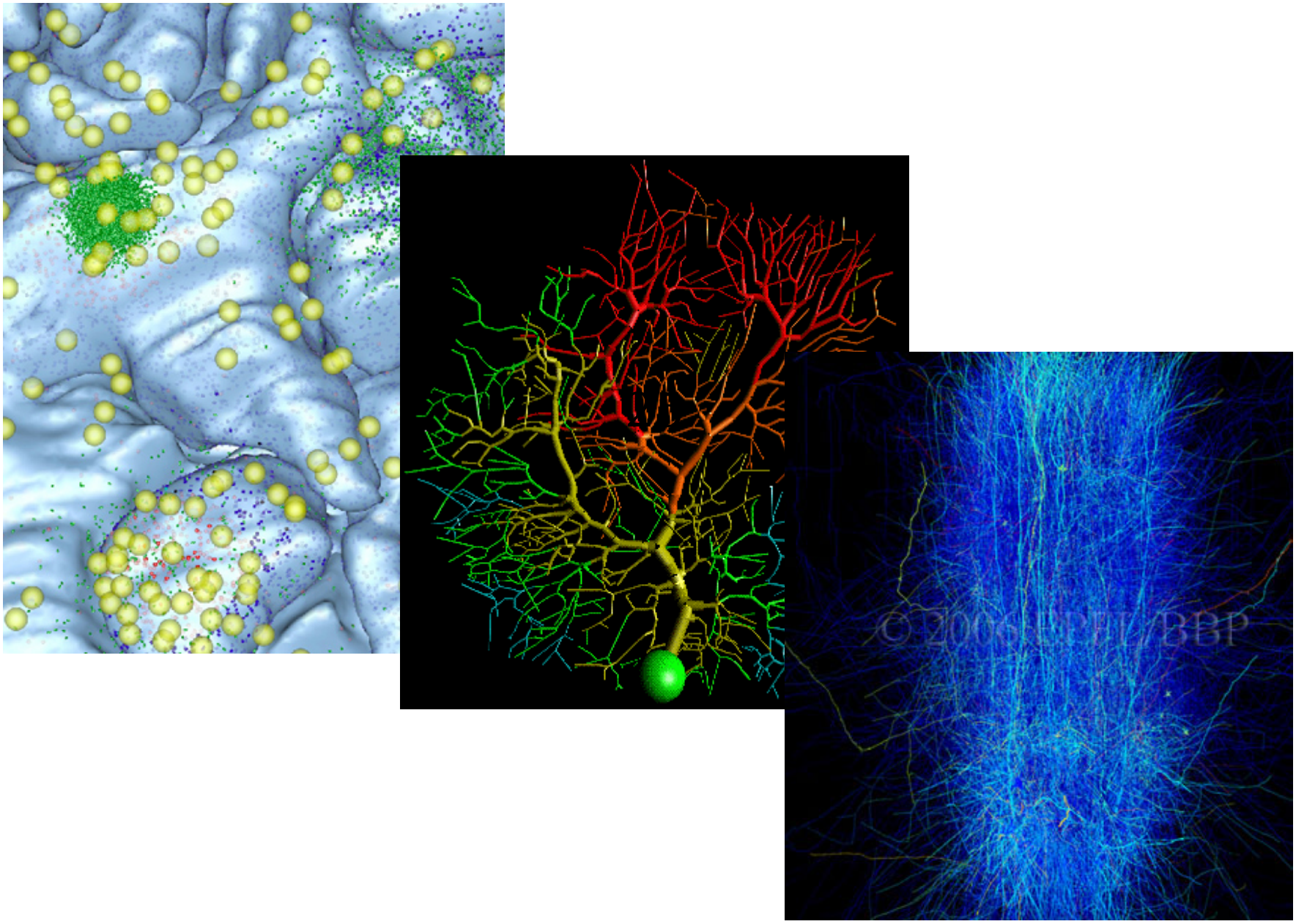


Whole-cell model



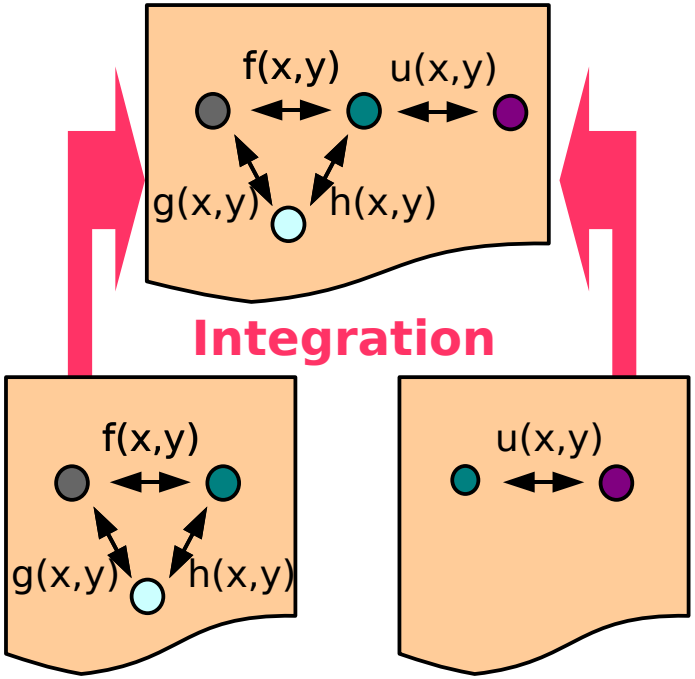


Tissue model

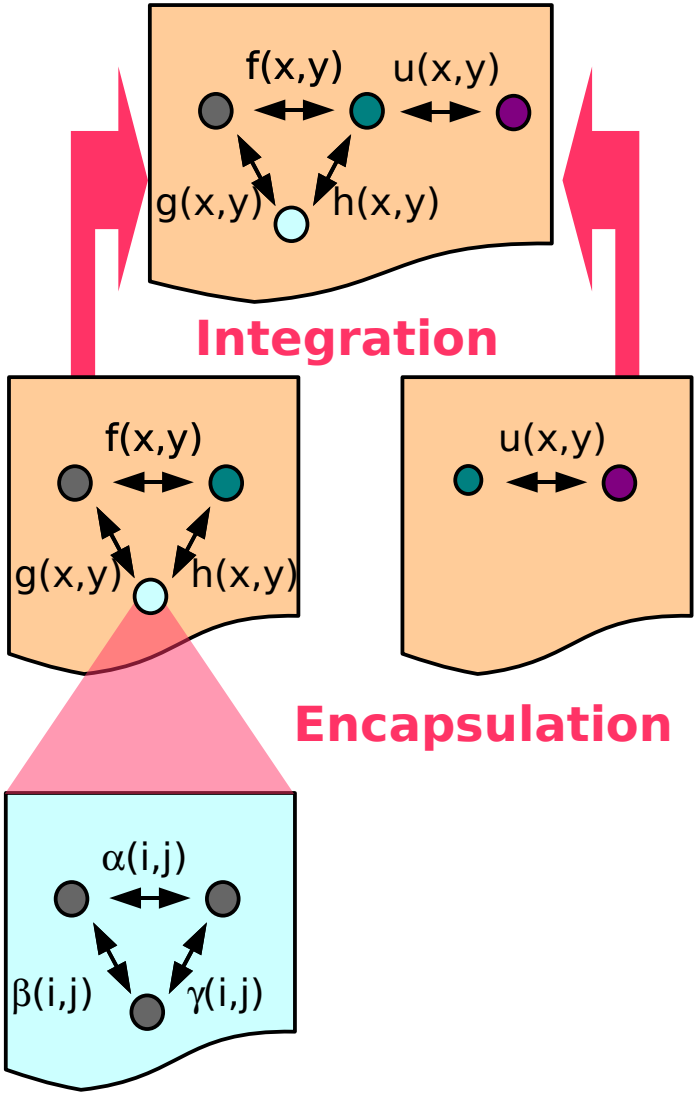


Technical bottlenecks

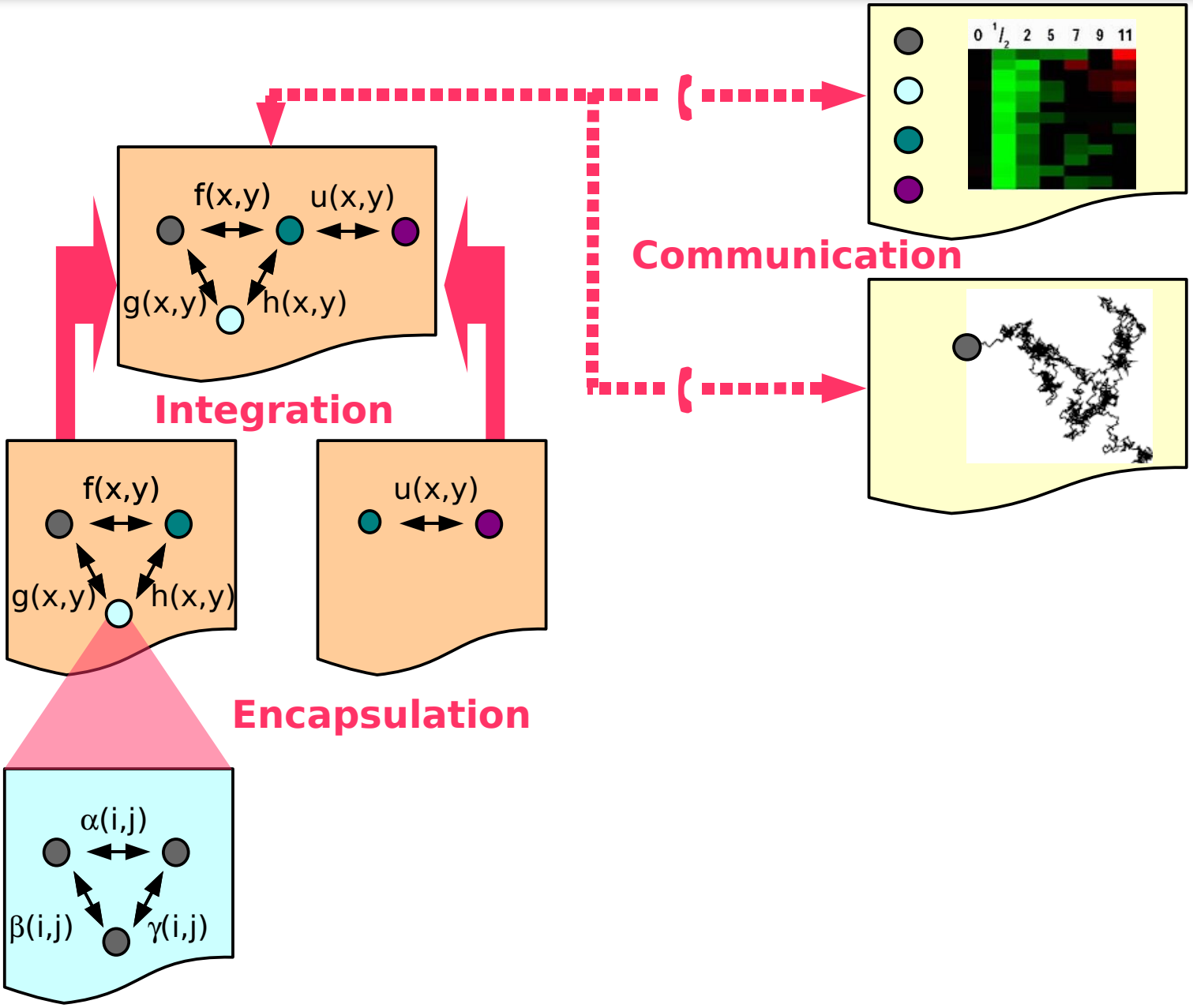
Technical bottlenecks



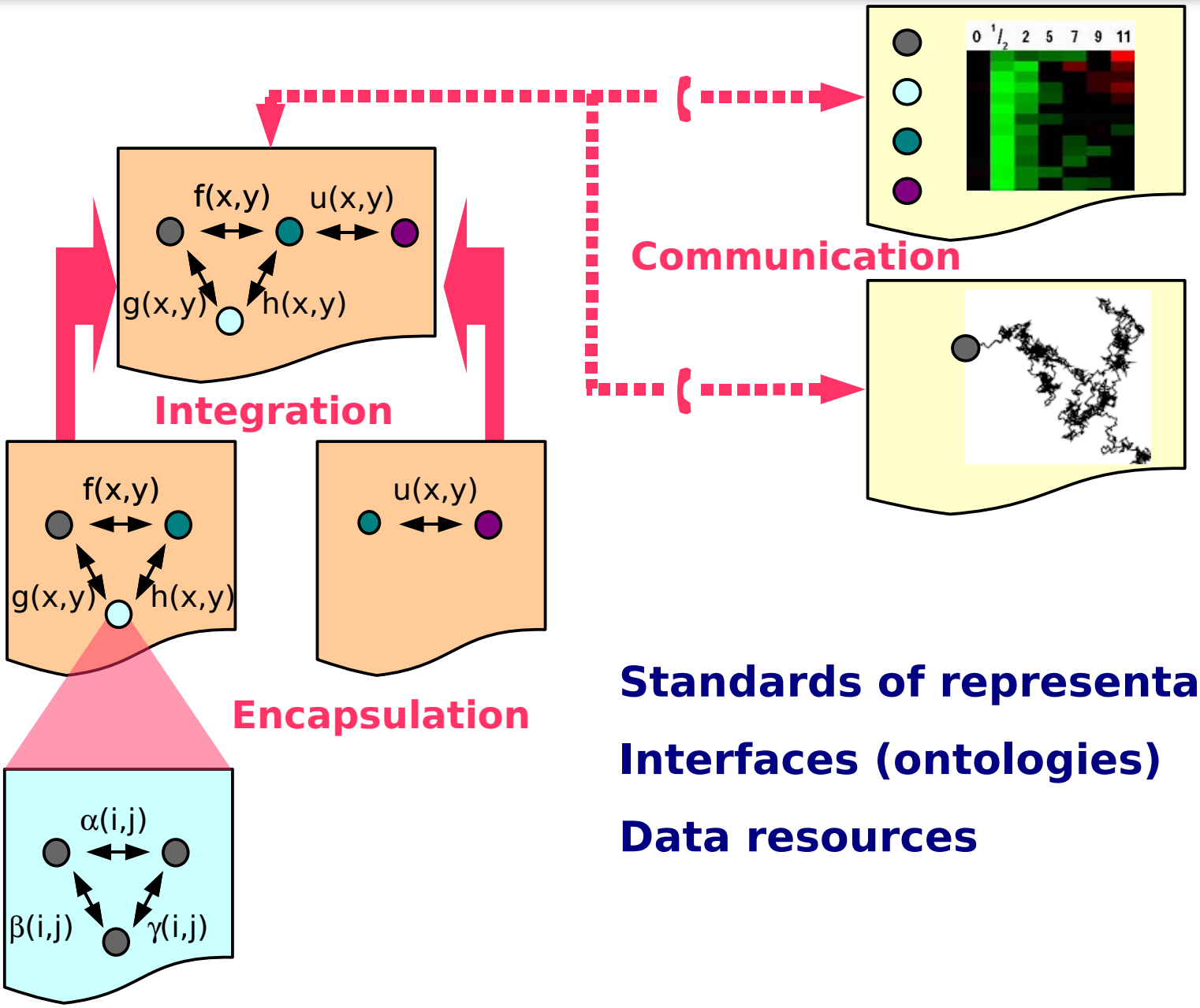
Technical bottlenecks



Technical bottlenecks



Technical bottlenecks



Standards of representation

Interfaces (ontologies)

Data resources

Community activities of compneur

- Systems Biology Markup Language (SBML) and associated tools (e.g. SBMLeditor)
  Hucka et al. (2003). The Systems Biology Markup Language (SBML): A Medium for Representation and Exchange of Biochemical Network Models. *Bioinformatics*, 19: 524-531.
  Rodriguez et al. (2007) SBMLeditor: effective creation of models in the Systems Biology Markup Language (SBML). BMC *Bioinformatics*, 8:79

- Systems Biology Graphical Notation (SBGN)

- Ontologies: the Systems Biology Ontology (SBO), the TErminology to Describe Dynamics (TEDDY)
  Le Novère N. (2006) Model storage, exchange and integration BMC Neuroscience, 7: S11.

- Minimal Information Requested In the Annotation of Models
  Le Novere et al (2005) Nature Biotechnology,
  Le Novère et al. (2005) Minimum Information Requested In the Annotation of biochemical Models (MIRIAM) *Nature Biotechnology*, 23: 1509-1515.

- BioModels Database
  Le Novère et al. (2006) BioModels Database: A Free, Centralized Database of Curated, Published, Quantitative Kinetic Models of Biochemical and Cellular Systems *Nucleic Acids Research*, 34: D689-D691.

SBML Systems Biology Markup Language

The Systems Biology Markup Language (SBML) is a computer-readable format for representing **models of biochemical reaction networks**. SBML is applicable to metabolic networks, cell-signaling pathways, regulatory networks, and many others.

Internationally Supported and Widely Used

SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is **supported by over 110 software systems**, including the following (where '*' indicates SBML support in development):

BALSA
BASIS
BIOCHAM
BioCharon
ByoDyn
BioCyc
BioGrid
BioModels
BioNetGen
BioPathwise
Bio Sketch Pad
BioSens
BioSPICE Dashboard
BioSpreadsheet
BioTapestry
BioUML
BSTLab
CADLIVE
CellDesigner
Cellerator
Cell Illustrator
CellML2SBML
Cellware
CL-SBML
CLEML
COPASI
Cyto-Sim
Cytoscape
DBsolve
Dizzy
E-CELL
ecellJ
ESS
FluxAnalyzer
Fluxor
Gepasi
Gillespie2
HSMB
HybridSBML
INSILICO discovery
JACOBIAN
Jarnac
JDesigner
JigCell
JSim
JWS Online
Karyote*
KEGG2SBML
Kineticon
Kinsolver*
libSBML
MathSBML
MesoRD
Meta-All
MetaFluxNet
MIRIAM
MMT2
Modesto
Moleculizer
Monod
Narrator
NetBuilder
Oscill8
PANTHER Pathway
PathArt
Pathway Analyser
PathwayLab
Pathway Tools
PathwayBuilder
PATIKAweb
PaVESy
PET
PNK
PottersWheel
ProcessDB
PROTON
pysbml
PySCeS
Reactome
RSBML
runSBML
SABIO-RK
SBML ODE Solver
SBML-PET
SBMLeditor
SBMLmerge
SBMLR
SBMLSim
SBMLToolbox
SBO
SBToolbox
SBW
SCIpath
Sigmoid*
SigPath
SigTran
SIMBA
SimBiology
Simpathica
SimPheny*
SimWiz
SloppyCell
SmartCell
SRS Pathway Editor
StochSim
StochKit
STOCKS
TERANODE Suite
Trelis
VANTED
Virtual Cell
WebCell
WinSCAMP
Xholon
XPPAUT

A Free and Open Language

Advances in biotechnology are leading to larger, more complex quantitative models. The systems biology

COPASI 4.1 Build 21 Released

(May 21, 2007) **COPASI** version 4.1 (build 21) has been released. COPASI is a free, general simulator for systems biology with a large number of features.

read more

SBML Hackathon 2007!

(April 3, 2007) This year's **SBML Hackathon** will be held at the University of Newcastle, UK. Please join us and don't forget to register ASAP!

read more

VANTED supports SBML

(April 3, 2007) **VANTED** is a network editing and visualization system with features for network-integrated visualization of data from experiments and simulations.

read more

RSBML, a package for R

(March 29, 2007) **RSBML** is a package that allows SBML to be imported into R either as an S4 object or a Bioconductor graph object.

read more

Xholon supports SBML

(March 27, 2007) **Xholon** is an open-source, general-purpose modeling and simulation tool. It can read models created using UML, among other things.

read more

See older news items.

```
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      <species id="B" compartment="cell" initialConcentration="0"/>
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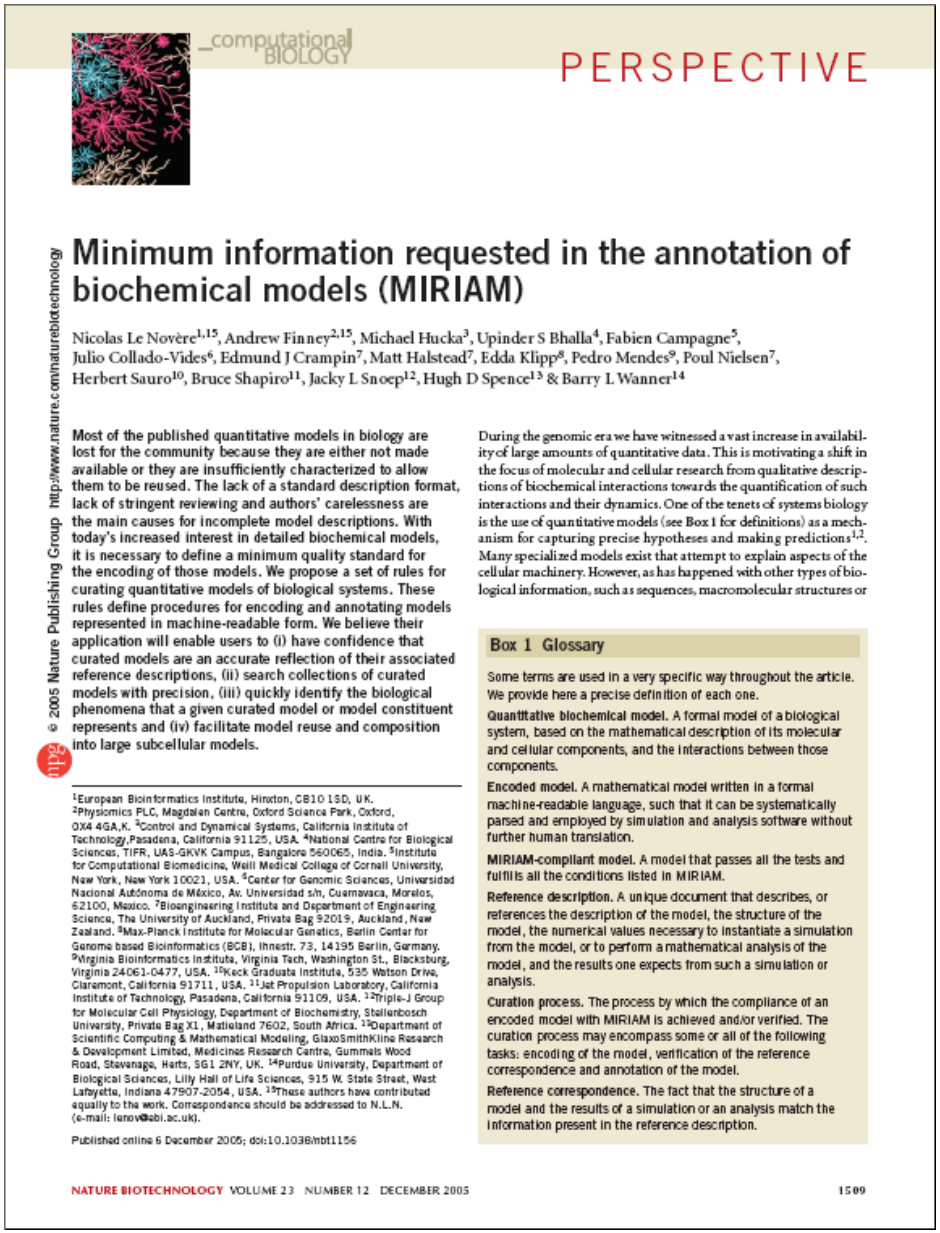
- Proposed guidelines for curation of quantitative models
  - Specifically about encoding & annotation
  - Limited to models that can be simulated
- Effort arose from a meeting organized by Andrew Finney during ICSB 2004
- Not specific to SBML; applicable to any structured model format



computational BIOLOGY

PERSPECTIVE

Minimum information requested in the annotation of biochemical models (MIRIAM)

Nicolas Le Novère[1,15], Andrew Finney[2,15], Michael Hucka[3], Upinder S Bhalla[4], Fabien Campagne[5], Julio Collado-Vides[6], Edmund J Crampin[7], Matt Halstead[7], Edda Klipp[8], Pedro Mendes[9], Poul Nielsen[7], Herbert Sauro[10], Bruce Shapiro[11], Jacky L Snoep[12], Hugh D Spence[13] & Barry L Wanner[14]

Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused. The lack of a standard description format, lack of stringent reviewing and authors' carelessness are the main causes for incomplete model descriptions. With today's increased interest in detailed biochemical models, it is necessary to define a minimum quality standard for the encoding of those models. We propose a set of rules for curating quantitative models of biological systems. These rules define procedures for encoding and annotating models represented in machine-readable form. We believe their application will enable users to (i) have confidence that curated models are an accurate reflection of their associated reference descriptions, (ii) search collections of curated models with precision, (iii) quickly identify the biological phenomena that a given curated model or model constituent represents and (iv) facilitate model reuse and composition into large subcellular models.

[1]European Bioinformatics Institute, Hinxton, CB10 1SD, UK. [2]Physiomics PLC, Magdalen Centre, Oxford Science Park, Oxford, OX4 4GA,K. [3]Control and Dynamical Systems, California Institute of Technology,Pasadena, California 91125, USA. [4]National Centre for Biological Sciences, TIFR, UAS-GKVK Campus, Bangalore 560065, India. [5]Institute for Computational Biomedicine, Weill Medical College of Cornell University, New York, New York 10021, USA. [6]Center for Genomic Sciences, Universidad Nacional Autónoma de México, Av. Universidad s/n, Cuernavaca, Morelos, 62100, Mexico. [7]Bioengineering Institute and Department of Engineering Science, The University of Auckland, Private Bag 92019, Auckland, New Zealand. [8]Max-Planck Institute for Molecular Genetics, Berlin Center for Genome based Bioinformatics (BCB), Ihnestr. 73, 14195 Berlin, Germany. [9]Virginia Bioinformatics Institute, Virginia Tech, Washington St., Blacksburg, Virginia 24061-0477, USA. [10]Keck Graduate Institute, 535 Watson Drive, Claramont, California 91711, USA. [11]Jet Propulsion Laboratory, California Institute of Technology, Pasadena, California 91109, USA. [12]Triple-J Group for Molecular Cell Physiology, Department of Biochemistry, Stellenbosch University, Private Bag X1, Matieland 7602, South Africa. [13]Department of Scientific Computing & Mathematical Modeling, GlaxoSmithKline Research & Development Limited, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, UK. [14]Purdue University, Department of Biological Sciences, Lilly Hall of Life Sciences, 915 W. State Street, West Lafayette, Indiana 47907-2054, USA. [15]These authors have contributed equally to the work. Correspondence should be addressed to N.L.N. (e-mail: lenov@ebi.ac.uk).

Published online 6 December 2005; doi:10.1038/nbt1156

During the genomic era we have witnessed a vast increase in availability of large amounts of quantitative data. This is motivating a shift in the focus of molecular and cellular research from qualitative descriptions of biochemical interactions towards the quantification of such interactions and their dynamics. One of the tenets of systems biology is the use of quantitative models (see Box 1 for definitions) as a mechanism for capturing precise hypotheses and making predictions[1,2]. Many specialized models exist that attempt to explain aspects of the cellular machinery. However, as has happened with other types of biological information, such as sequences, macromolecular structures or

Box 1 Glossary

Some terms are used in a very specific way throughout the article. We provide here a precise definition of each one.

Quantitative biochemical model. A formal model of a biological system, based on the mathematical description of its molecular and cellular components, and the interactions between those components.

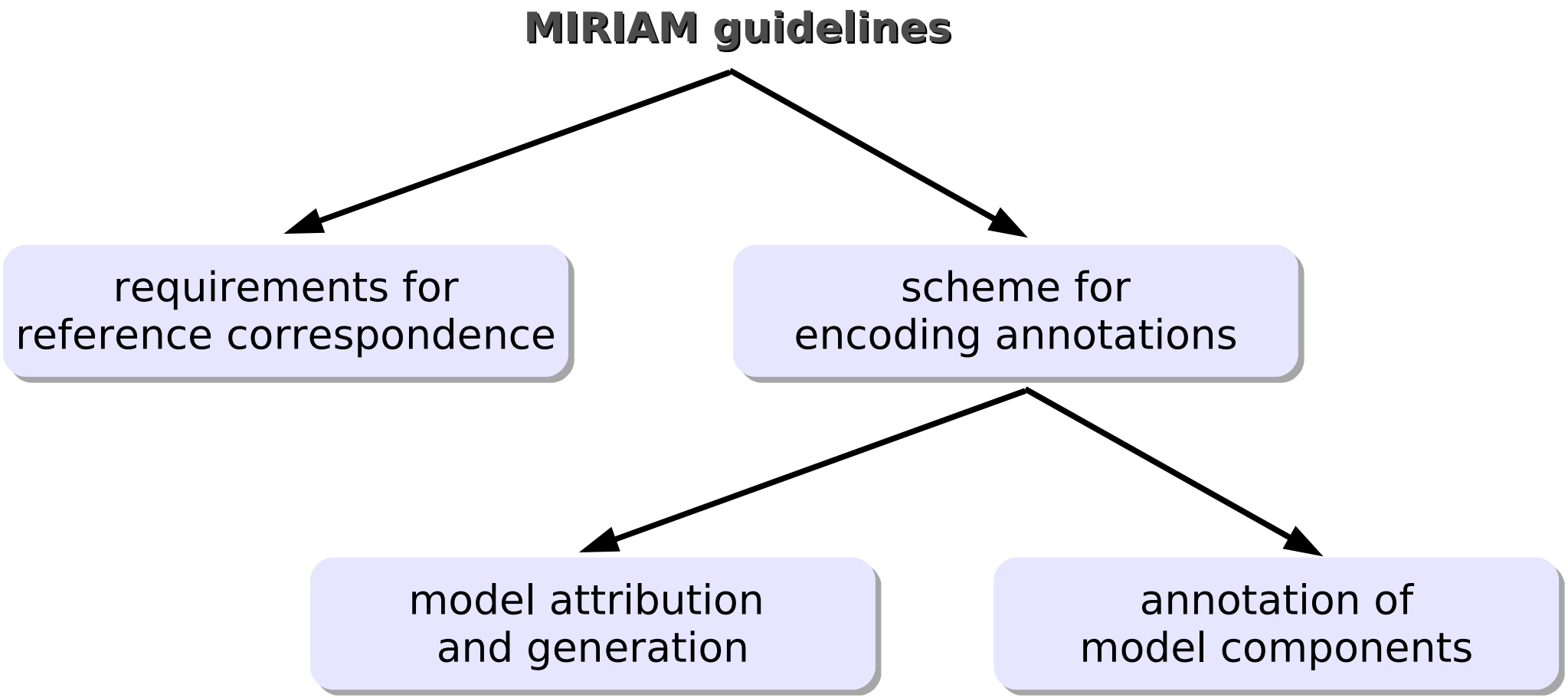
Encoded model. A mathematical model written in a formal machine-readable language, such that it can be systematically parsed and employed by simulation and analysis software without further human translation.

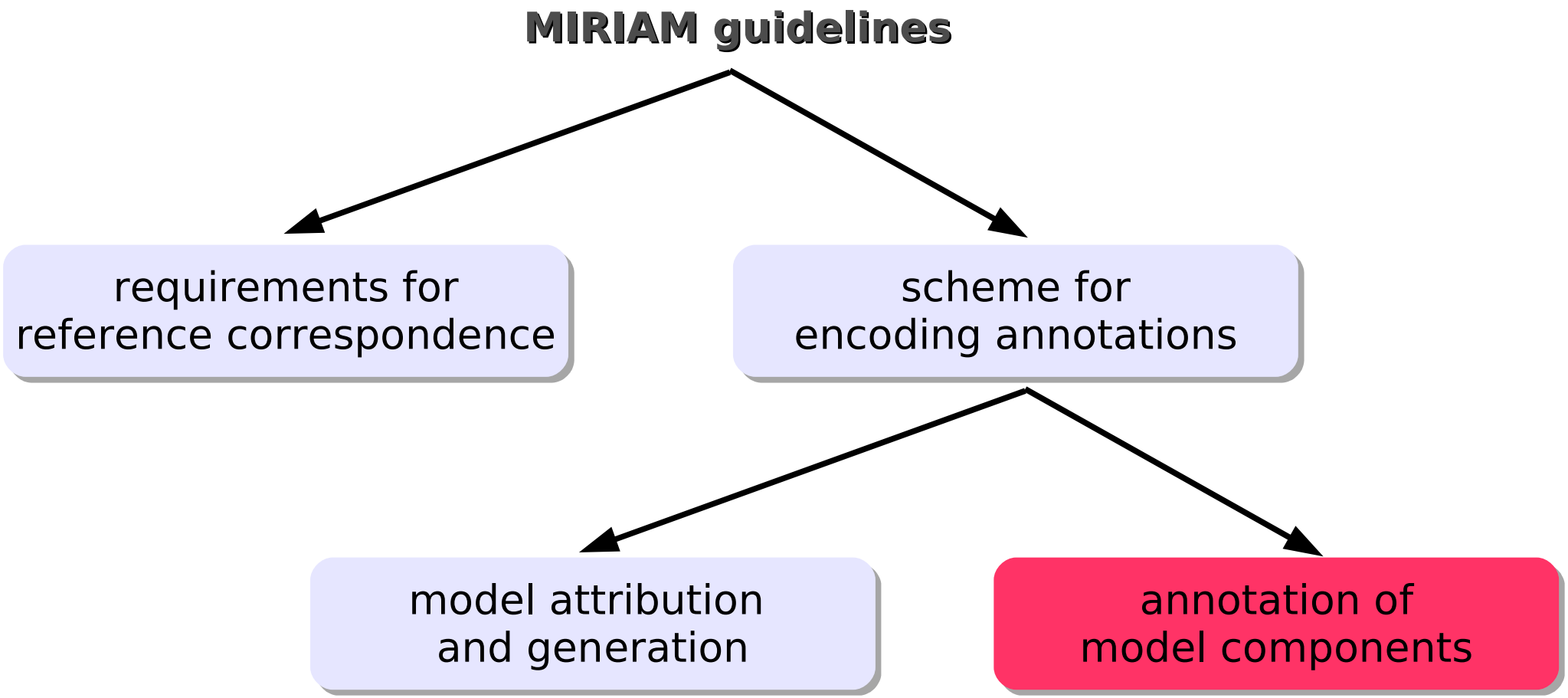
MIRIAM-compliant model. A model that passes all the tests and fulfills all the conditions listed in MIRIAM.

Reference description. A unique document that describes, or references the description of the model, the structure of the model, the numerical values necessary to instantiate a simulation from the model, or to perform a mathematical analysis of the model, and the results one expects from such a simulation or analysis.

Curation process. The process by which the compliance of an encoded model with MIRIAM is achieved and/or verified. The curation process may encompass some or all of the following tasks: encoding of the model, verification of the reference correspondence and annotation of the model.

Reference correspondence. The fact that the structure of a model and the results of a simulation or an analysis match the information present in the reference description.


MIRIAM guidelines
requirements for reference correspondence
scheme for encoding annotations
model attribution and generation
annotation of model components


MIRIAM guidelines
requirements for reference correspondence
scheme for encoding annotations
model attribution and generation
annotation of model components

MIRIAM annotation

```
<reaction id="r3b"
  name="phosphorylation of MAPKK"
  metaid="_506913">
  <annotation>
    <rdf:RDF
      xmlns:rdf="http://www.w3.org/1999/02/22-rd ...
      xmlns:bqbiol="http://biomodels.net/biology ...
      xmlns:bqmodel="http://biomodels.net/model- ...
      <rdf:Description rdf:about="#_506913">
        <bqbiol:isVersionOf>
          <rdf:Bag>
<rdf:li
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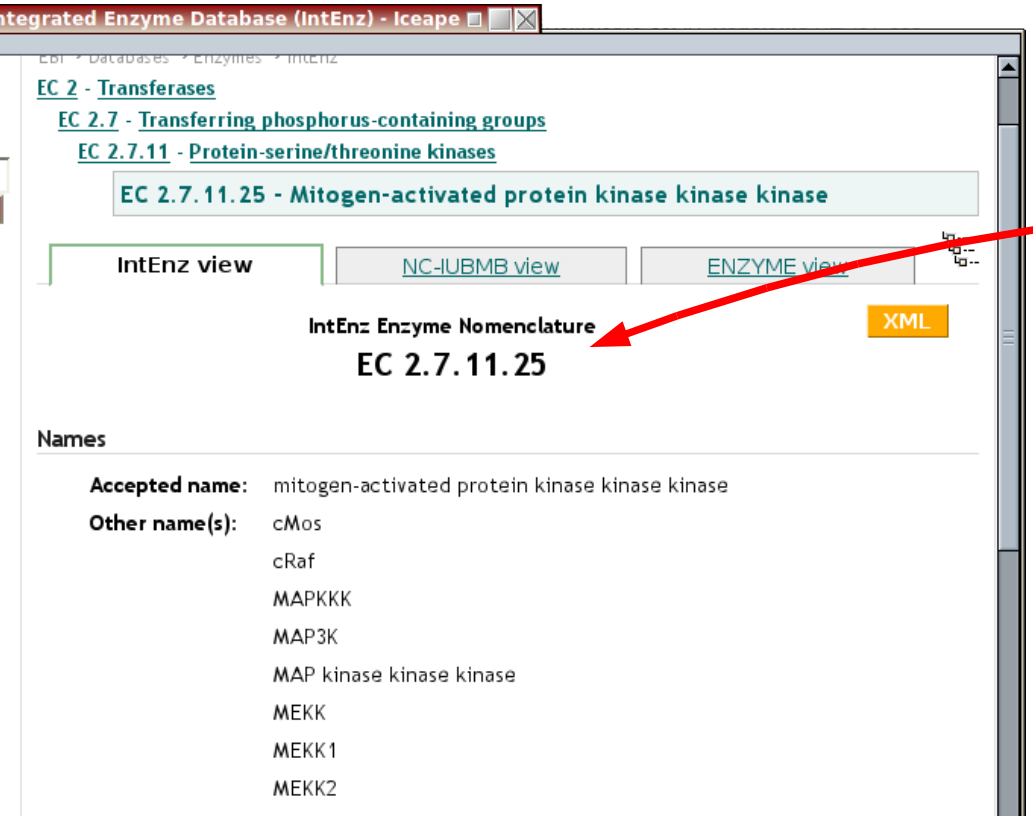
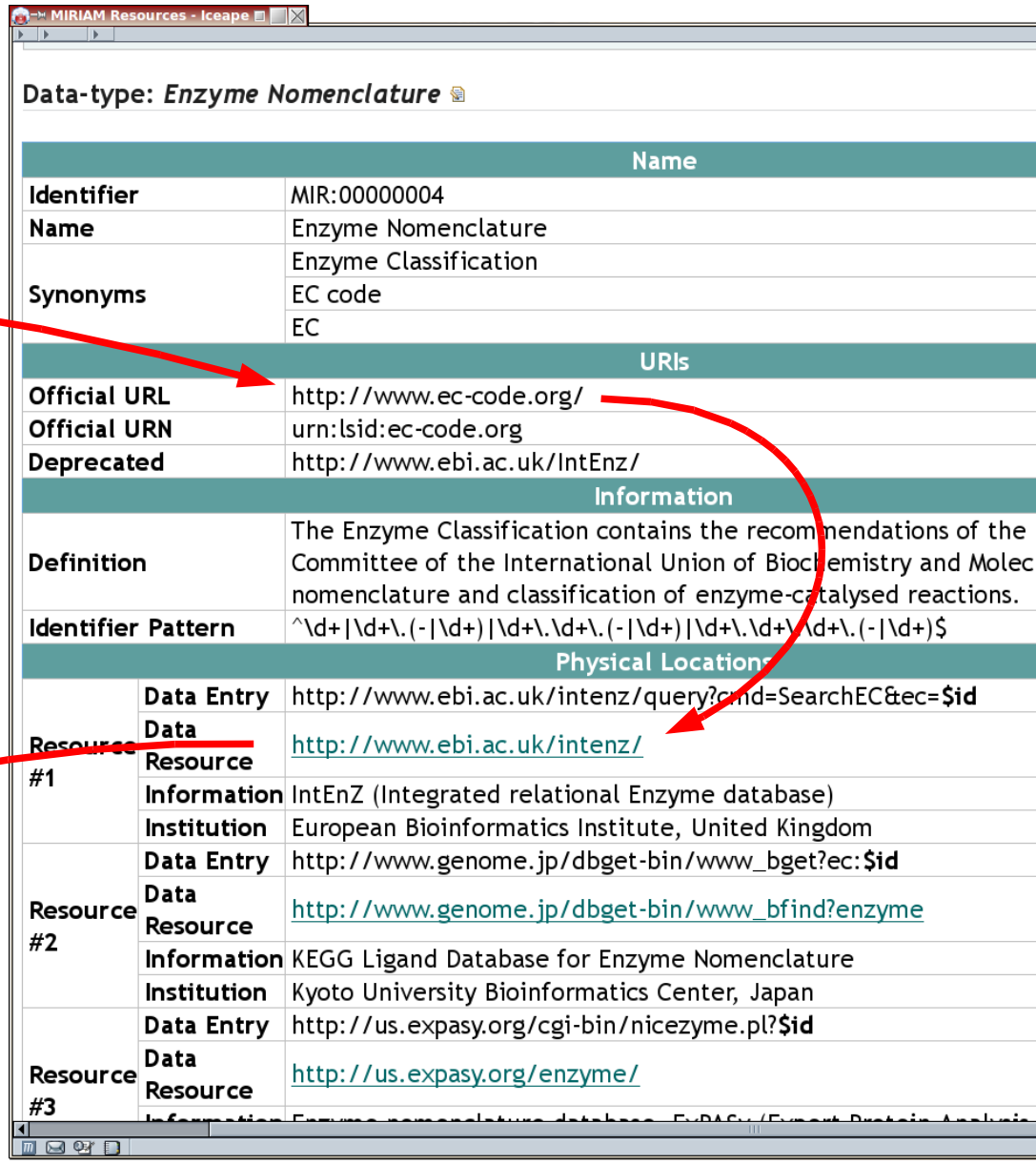
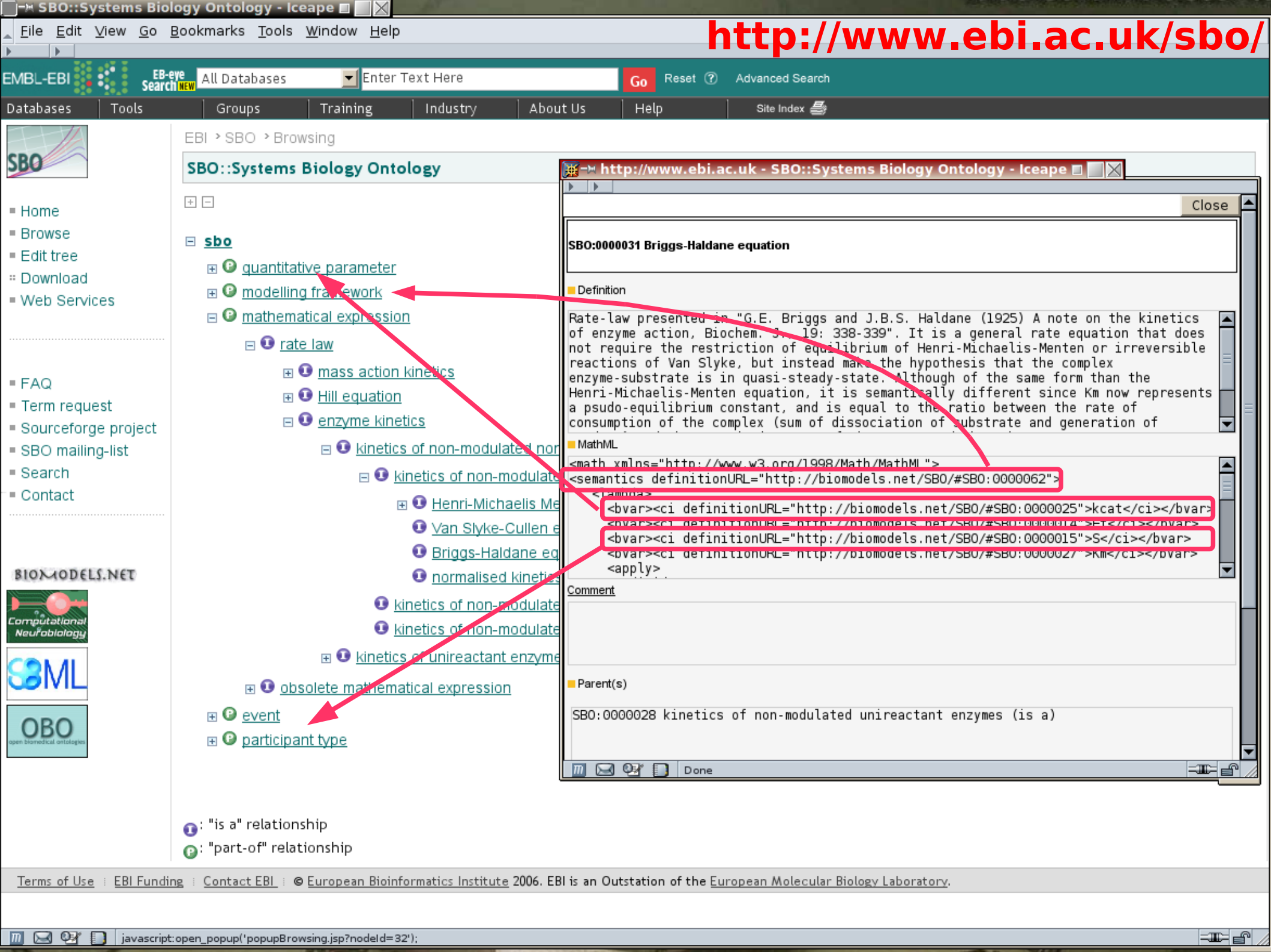
        </bqbiol:isVersionOf>
```






SBO::Systems Biology Ontology - Iceape
http://www.ebi.ac.uk/sbo/
File Edit View Go Bookmarks Tools Window Help
EMBL-EBI
EB-eye Search NEW
All Databases
Enter Text Here
Go
Reset
Advanced Search
Databases Tools Groups Training Industry About Us Help Site Index
EBI › SBO › Browsing
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quantitative parameter
modelling framework
mathematical expression
rate law
mass action kinetics
Hill equation
enzyme kinetics
kinetics of non-modulated nor
kinetics of non-modulate
Henri-Michaelis Me
Van Slyke-Cullen e
Briggs-Haldane eq
normalised kinetics
kinetics of non-modulate
kinetics of non-modulate
kinetics of unireactant enzyme
obsolete mathematical expression
event
participant type
: "is a" relationship
: "part-of" relationship
http://www.ebi.ac.uk - SBO::Systems Biology Ontology - Iceape
Close
SBO:0000031 Briggs-Haldane equation
Definition
Rate-law presented in "G.E. Briggs and J.B.S. Haldane (1925) A note on the kinetics of enzyme action, Biochem. J., 19: 338-339". It is a general rate equation that does not require the restriction of equilibrium of Henri-Michaelis-Menten or irreversible reactions of Van Slyke, but instead make the hypothesis that the complex enzyme-substrate is in quasi-steady-state. Although of the same form than the Henri-Michaelis-Menten equation, it is semantically different since Km now represents a psudo-equilibrium constant, and is equal to the ratio between the rate of consumption of the complex (sum of dissociation of substrate and generation of
MathML
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Comment
Parent(s)
SBO:0000028 kinetics of non-modulated unireactant enzymes (is a)
Done
Terms of Use | EBI Funding | Contact EBI | © European Bioinformatics Institute 2006. EBI is an Outstation of the European Molecular Biology Laboratory.
javascript:open_popup('popupBrowsing.jsp?nodeId=32');

http://www.ebi.ac.uk/biomodels/

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BIOMODELS.NET

A Database of Annotated Published Models

BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways, controlled vocabularies, etc.

[Browse curated models] [Browse non-curated models] [Search] [Simulate in JWS Online]

05th June 2007 - Eighth Release! [More] [Download All Models Under SBML L2 V1 Format]

17th April 2007 - BioModels Database ranked first data resource for Systems Biology [More] [Original article]

4th December 2006 - BioModels Database and DOQCS join forces [More]

Model of the month

Acknowledgements

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Model curators and annotators: Harish Dharuri, Enuo He, Nicolas Le Novère, Lu Li, Rainer Machne, Bruce Shapiro (Alumni: Maria Schilstra)

Developers: Mélanie Courtot, Camille Laibe, Chen Li (main developer), Lu Li, Nicolas Rodriguez (Alumni: Marco Donizelli, Arnaud Henry)

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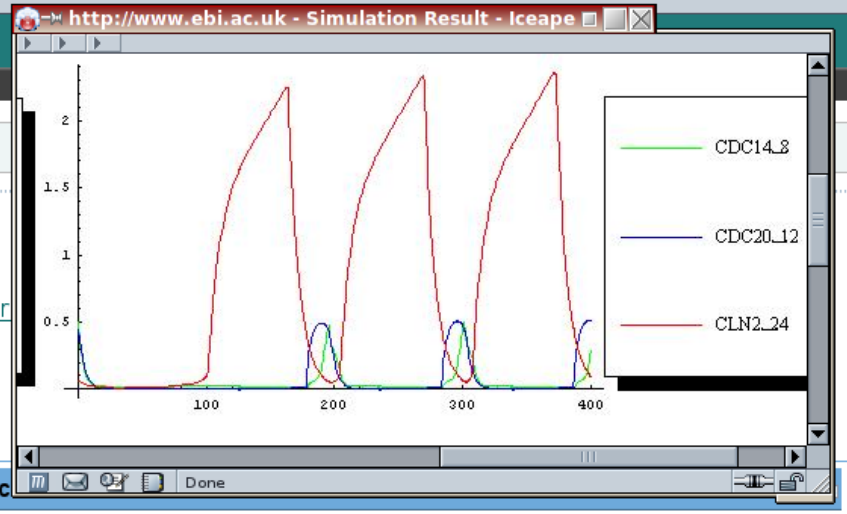
Main software used to curate models: CellDesigner, COPASI, Jarnac, MathSBML, RoadRunner, SBMLdeSolver, SBMLeditor, SBMLmerge and XPP-Aut.



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BIOMODELS.NET

BIOMD0000000056 - Chen2004_CellCycle

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

Simulation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Gr

Submit Model Comment/Bug

Reference Public

Publication ID: 15169868

Mol Biol Cell 2004 Aug;15(8):3841-62.
Integrative analysis of cell cycle control in budding yeast.
Chen KC, Calzone L, Csikasz-Nagy A, Cross FR, Novak B, Tyson JJ.
Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0406, USA.
kchen@vt.edu [more]

Model

Original Model: *Unspecified*
Submitter: Nicolas Le Novere
Submission Date: 2006-05-10T13:47:09
Last Modification Date: 2007-06-08T12:28:24
Creation Date: 2006-05-08T12:05:34
Creators: Harish Dharuri
Katherine C Chen

bqbiol:is	set #1	KEGG Pathway sce04111 Taxonomy Saccharomyces cerevisiae
bqbiol:isVersionOf	set #1	Gene Ontology mitotic cell cycle
bqbiol:isHomologTo	set #1	Reactome REACT_152

Compartments (1)

cell
Referred to as: cell_0

bqbiol:isVersionOf	set #1	Gene Ontology cell

Species (54)

BCK2
Compartment: cell
Referred to as: BCK2_1

bqbiol:is	set #1	UniProt BCK2_YEAST

BUB2

BUD

C2

C2P

EMBL-EBI

The “compneur” group

Daniel McGreal

Antonia Mayer

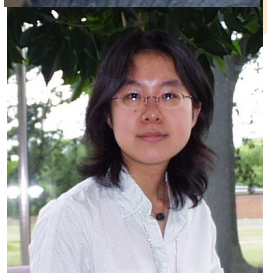
Christian Knuepfer

Melanie Courtot

Nicolas Rodriguez

Dominic Tolle

Eric Fernandez



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Melanie Stefan

Anika Oellrich

Stuart Edelstein

Chen Li

Enuo He

Camille Laibe

Collaboration on model development

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  Kazunari Kaizu

  Gabor Bereczki

- Collaborators
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  Denis Herve

- StochSim developers
  (Cambridge University)

  Karl Morton Firth

  Tom Shimizu

  (Yale University)

  Thierry Emonet

  (Argonne National Laboratory)

  Michael North

An international collaboration

- EBI
  - Nicolas Le Novère
  - Marco Donizelli
  - Chen Li
  - Mélanie Courtot
  - Lu Li
  - Camille Laibe
  - Arnaud Henry
  - Enuo He
  - Nicolas Rodriguez
  - Alexander Broicher
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  - Michael Hucka
  - Andrew Finney
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  - Sarah Keating
  - Harish Dharuri
- NCBS
  - Upinder Bhalla
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- Keck Graduate Institute
  - Herbert Sauro
- Vienna TBI
  - Rainer Machne
- Systems Biology Institute
  - Hiroaki Kitano
  - Akira Funahashi
- JWS Online
  - Jacky Snoep
  - Hans Westerhoff
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  - Molecular Systems Biology
  - PLoS Journals
  - BioMedCentral Journals
- Programs used for curation
  - CellDesigner/SBMLodeSolver
  - COPASI
  - Jarnac/JDesigner
  - MathSBML
  - SBMLeditor
  - XPP-Aut

The community of Systems Biology for their contributions of models and comments.