EMBL-EBI

Kinetic models
[in [Systems] Neurobiology]
What, why and how

Nicolas Le Novère, EMBL-EBI

What is Systems Biology

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- *“[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems*" Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

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- « *Je tiens impossible de connaître les parties sans connaître le tout, non plus que de connaître le tout sans connaître particulièrement les parties* » Blaise Pascal, Pensées, 1660.

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For us and for today ...

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- **Systems Biology** is the study of a biological systems taking into account all its constituents, *their relationships,* and *their evolution*

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- **Systems Biology** is the study of a biological systems taking into account all its constituents, *their relationships,* and *their evolution*

- **Computational Systems Biology** is the construction of quantitative models that describe the behaviour of a system, on its own, or in response to its environment

What is a model

- A model is a mathematical description of the components of a system, their relationships, and the evolution of both.
  - ordinary differential equations (system evolution) $dX/dt = f(X)$
  - partial differential equation (system description) $\nabla X = g(X)$
  - algebraic equations (conservation laws) $h(X) = 0$
  - probability distributions $PX = i(X)$
  - master equation $dPX/dt = j(PX)$
  - cell automata/finite elements
  - ...

Computer simulations Vs. mathematical models

One would like to be able to follow this more general process mathematically also. The difficulties are, however, such that one cannot hope to have any very embracing theory *of such processes, beyond the statement of the equations. It might be possible, however, to treat a few particular cases in detail* ***with the aid of a digital computer****. This method has the advantage that it is not so necessary to make simplifying assumptions as it is when doing a more theoretical type of analysis.*

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A.M. Turing (1952). The chemical basis of morphogenesis. *Phyl Trans Roy Soc Lond* B237: 37-72

[About the development from one developmental pattern to another, a non-linear process]

What is a simulation

- A simulation is the instantiation of a model over time, using a given algorithmic approach, and a particular software: A model can beget simulations giving different results!
  - Logical (boolean or discrete) approach
  - Deterministic approach
  - Stochastic approach
  - Fixed timesteps
  - Adaptative timesteps
  - ...
- Plus ... range of simulations
  - parameter scan
  - parameter search/optimisation
  - phase-plane analysis
  - bifurcation analysis
  - ...

Simulation in Neurobiology: electrical

- Hodgkin and Huxley
  "A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve". *J Physiol* 1952, 117: 500-544
- Rall
  “Branching dendritic trees and motoneuron membrane resistivity". *Exp Neurol* 1959, 1: 491-527
- Shepherd and Brayton
  “Computer simulation of a dendrodendritic synaptic circuit for self- and lateral-inhibition in the olfactory bulb”. *Brain Res* 1979, 175: 377–382
- Traub and Wong
  “Cellular mechanism of neuronal synchronisation in epilepsy”. *Science* 1982, 216: 745–747
- De Schutter and Bower
  “An Active Membrane Model of the Cerebellar Purkinje Cell”. *J Neurophysiol* 1994, 71: 375-419
  (1 neuron, 1600 compartments)
- Traub et al
  “Single-Column Thalamocortical Network Model Exhibiting Gamma Oscillations, Sleep Spindles, and Epileptogenic Bursts”. *J Neurophysiol* 2005, 93: 2194-2232.
  (3650 neurons, ~100 compartments)

Simulation in Neurobiology: chemical

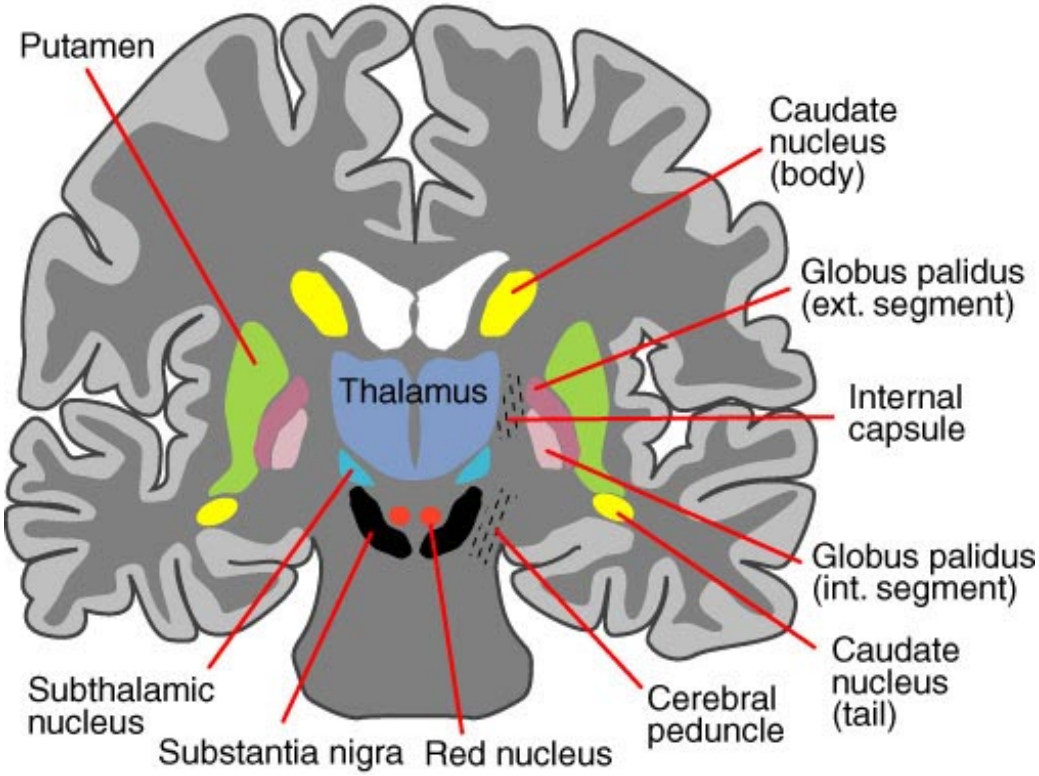
chemical kinetics (population-based)

- Justice, Nicolaysen, Michael
  "Modeling the dopaminergic nerve terminal". *J Neurosci Meth* 1988, 22: 239-252
- Kötter
  "Postsynaptic integration of glutamatergic and dopaminergic signals in the striatum". *Prog Neurobiol* 1994, 44: 163-196.
- Bhalla, Iyengar
  "Emergent properties of networks of biological signaling pathways". *Science* 1999, 283: 381-3

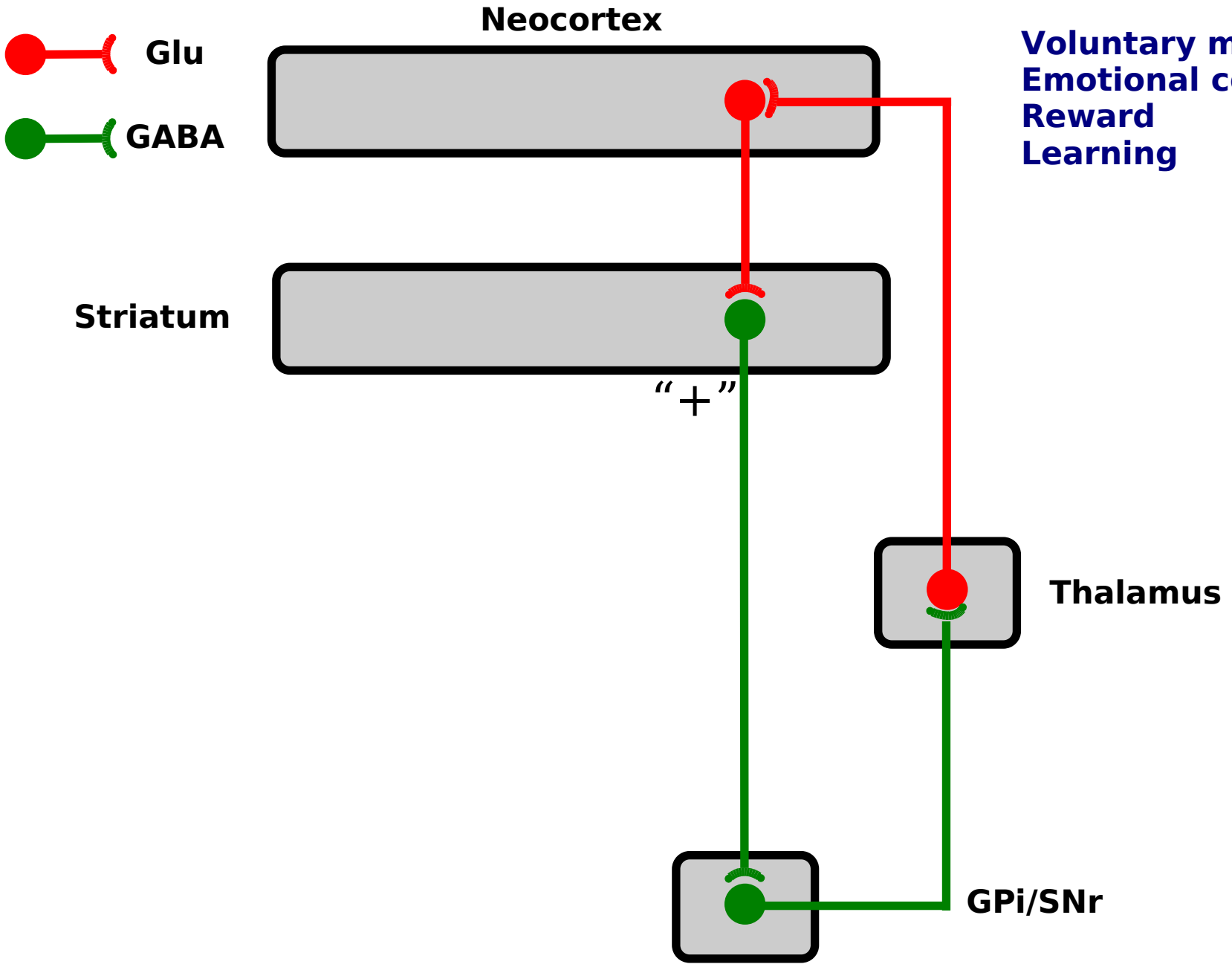
mesoscopic (agent-based)

- Land, Salpeter, Salpeter
  "Kinetic parameters for acetylcholine interaction in intact neuromuscular junction". *Proc Natl Acad Sci USA* 1981, 78:7200-7204
- Bartol, Land, Salpeter, Salpeter
  "Monte Carlo simulation of miniature endplate current generation in the vertebrate neuromuscular junction". *Biophys J* 1991, 59: 1290-1307
- Coggan et al
  "Evidence for Ectopic Neurotransmission at a Neuronal Synapse". *Science* 2005, 309: 446–451

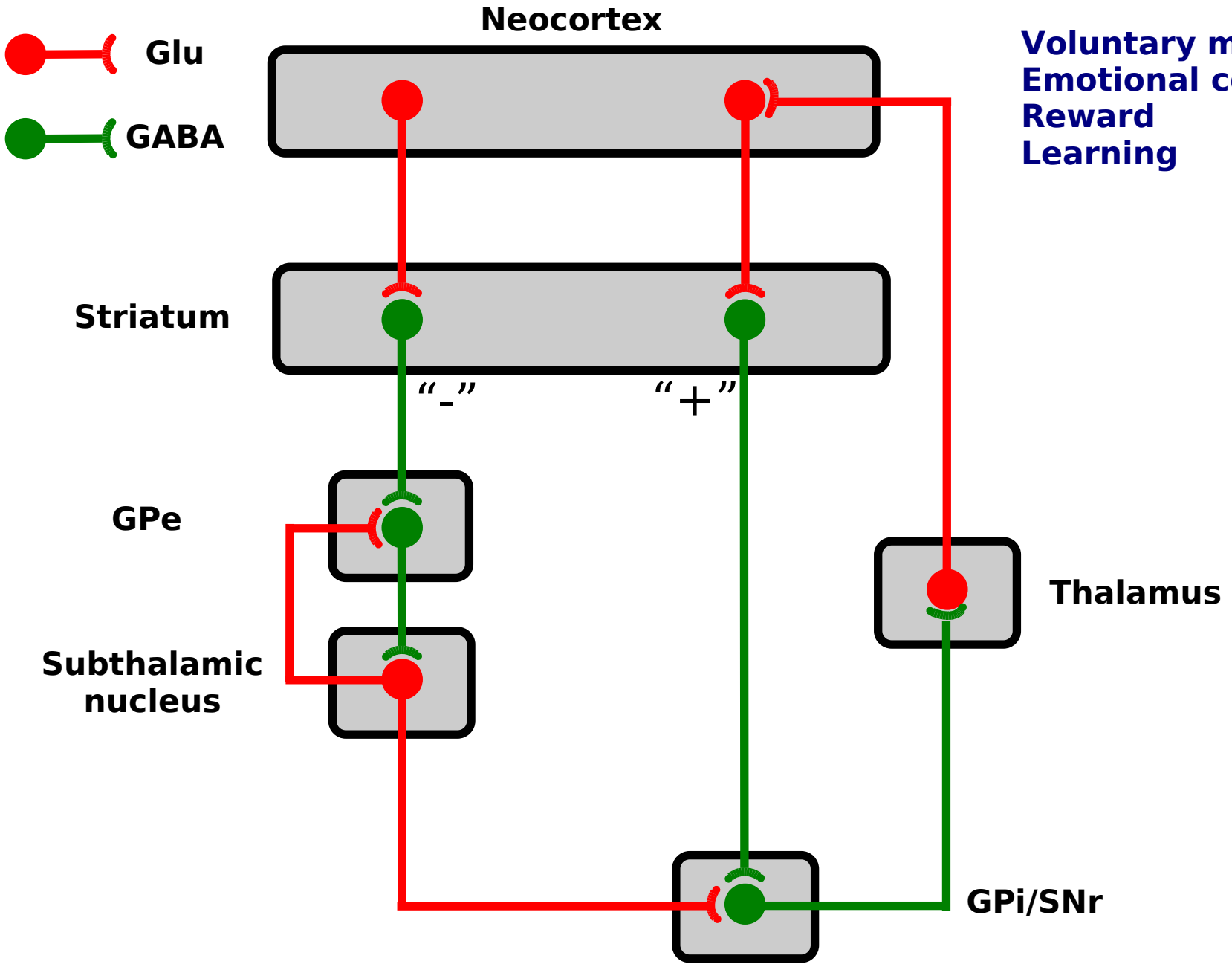
Basal ganglia



Cortico-striato thalamic loop



Cortico-striato thalamic loop



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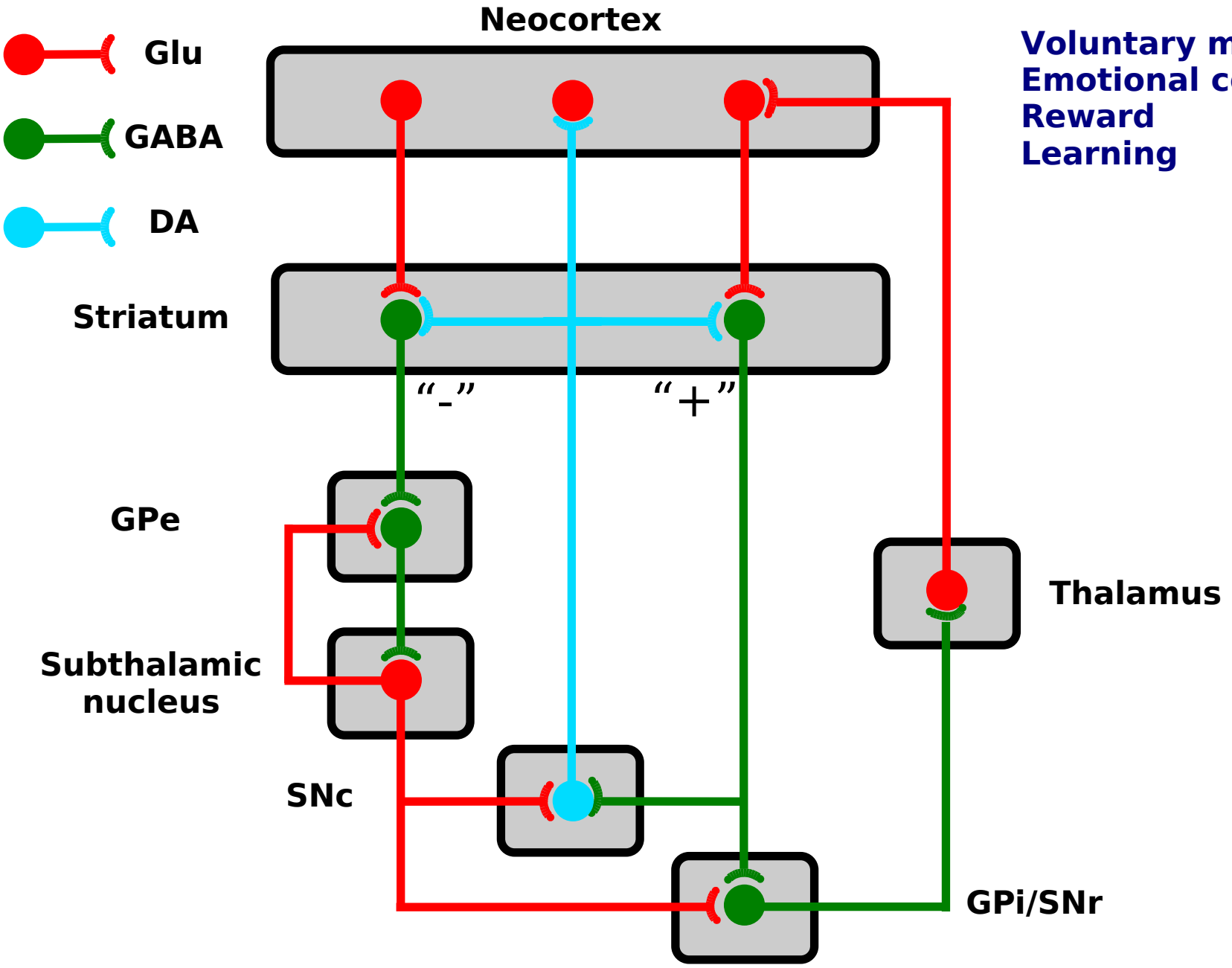

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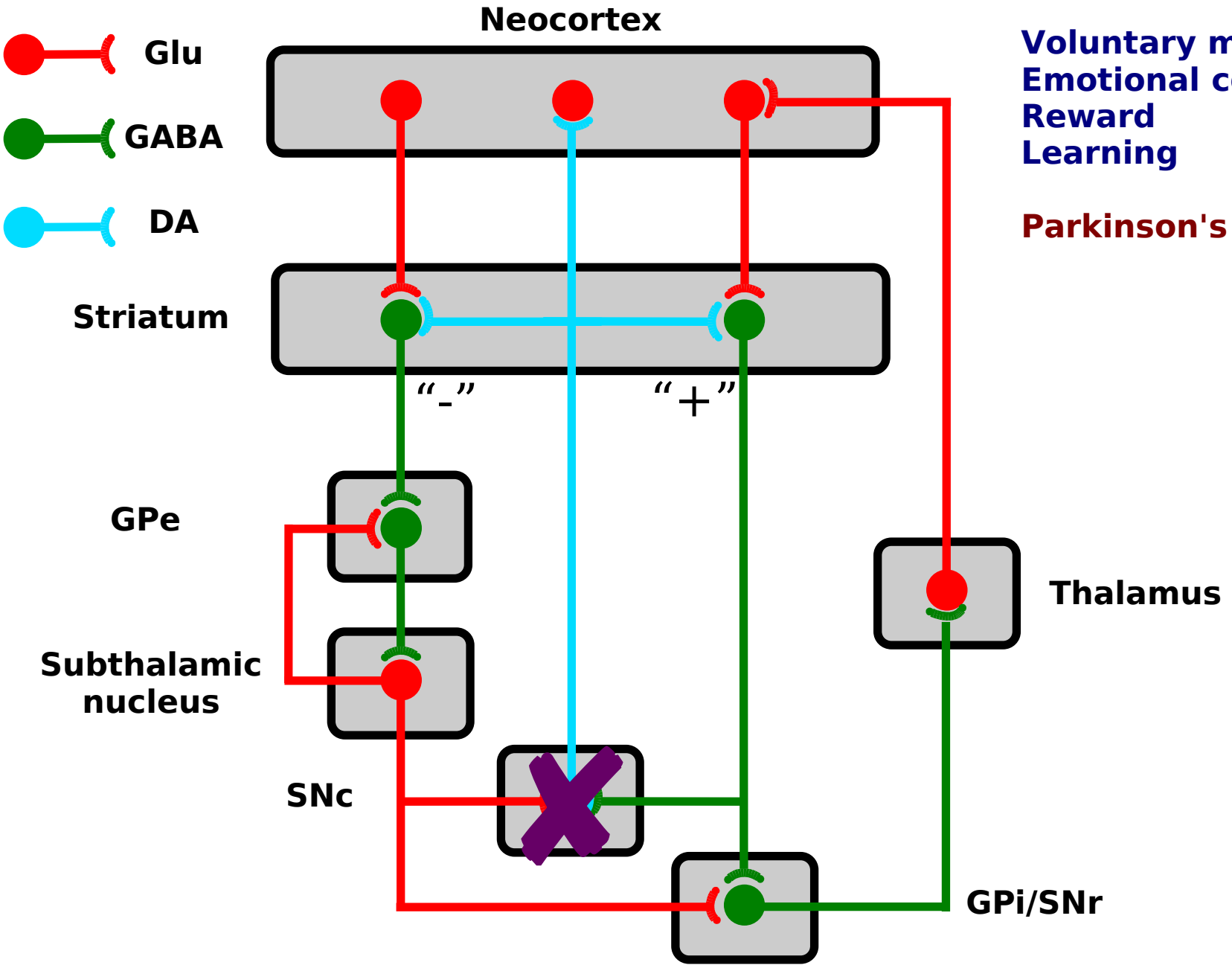
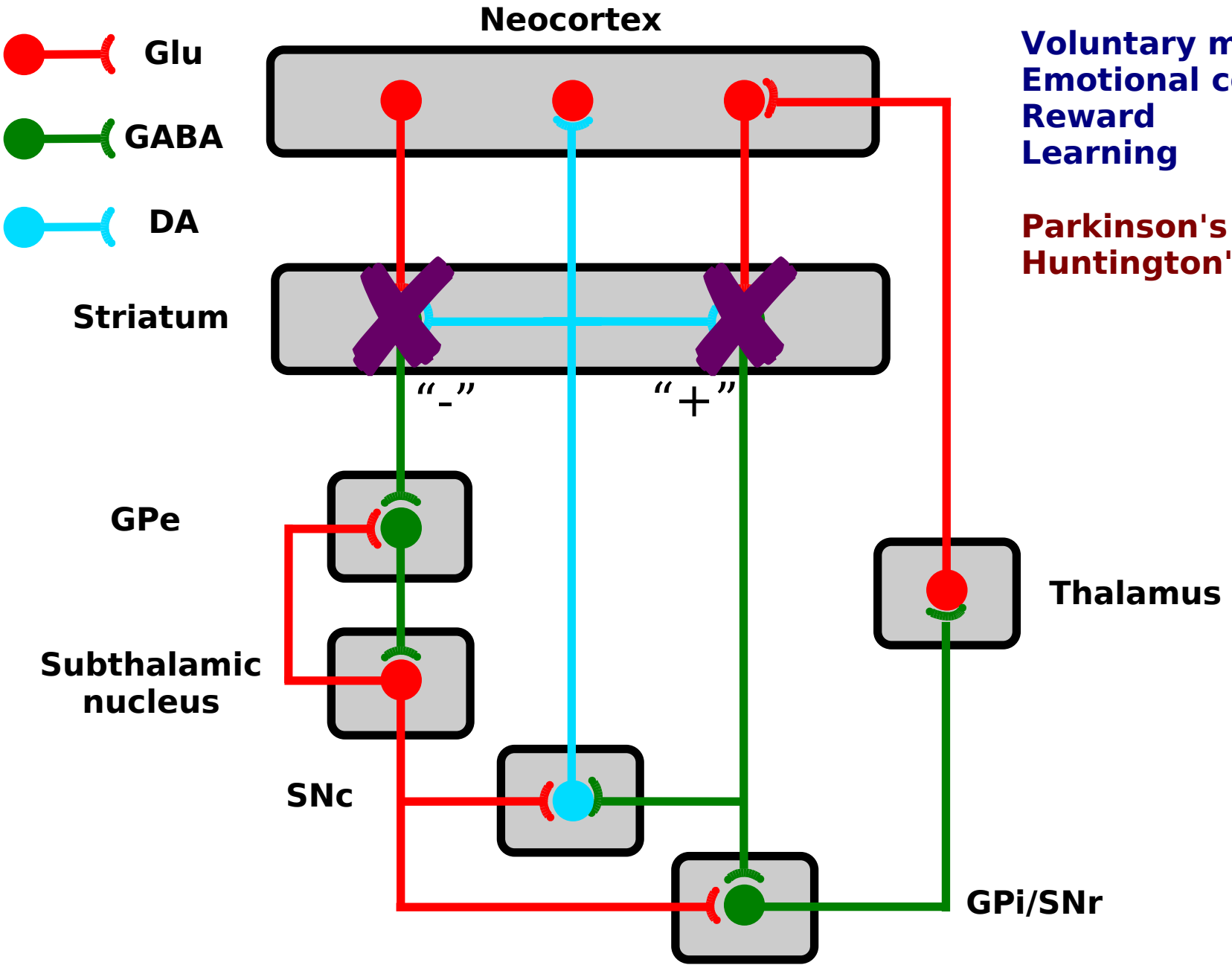


Voluntary motion
Emotional control
Reward
Learning

Parkinson's disease

Cortico-striato thalamic loop



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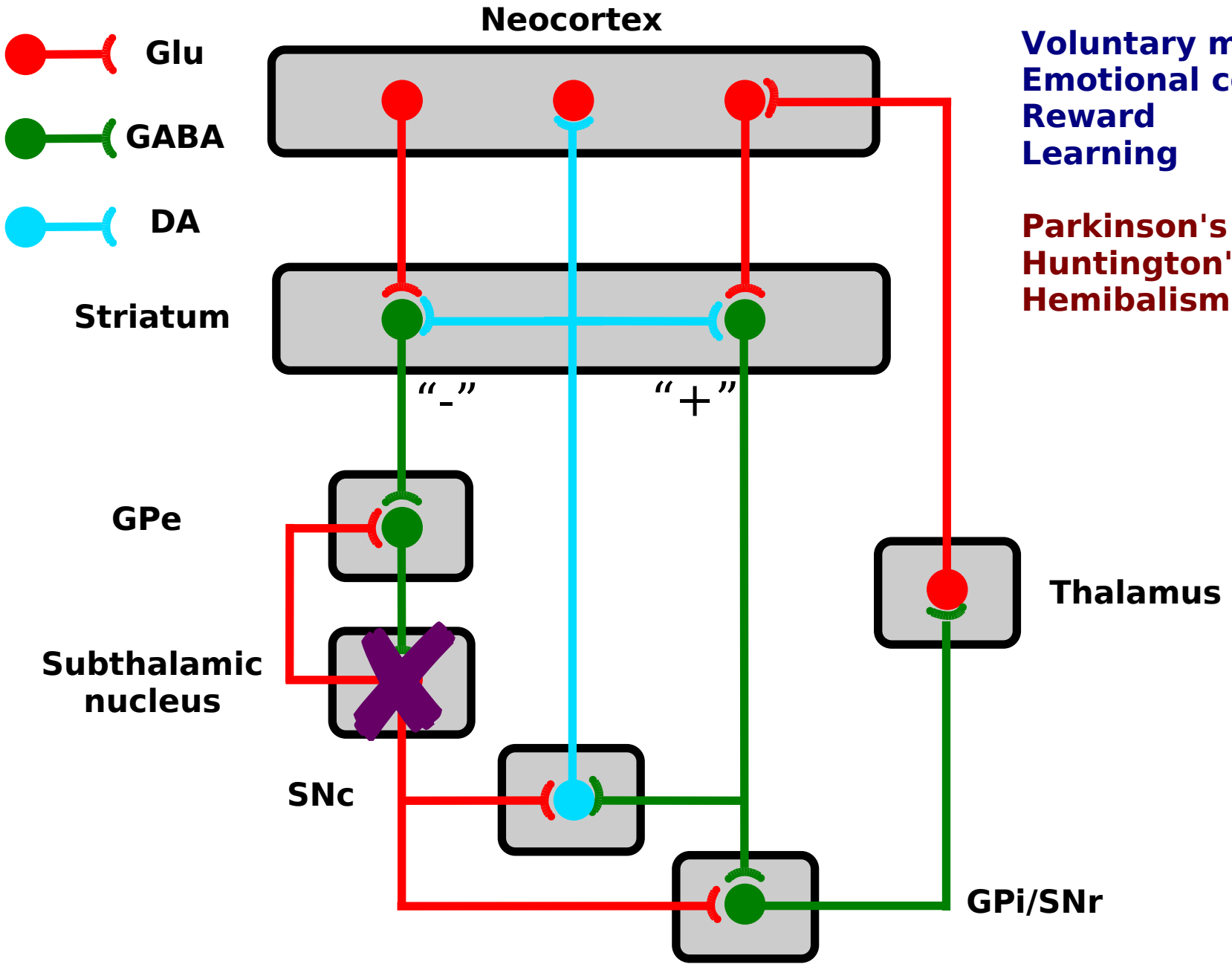

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Hemibalism

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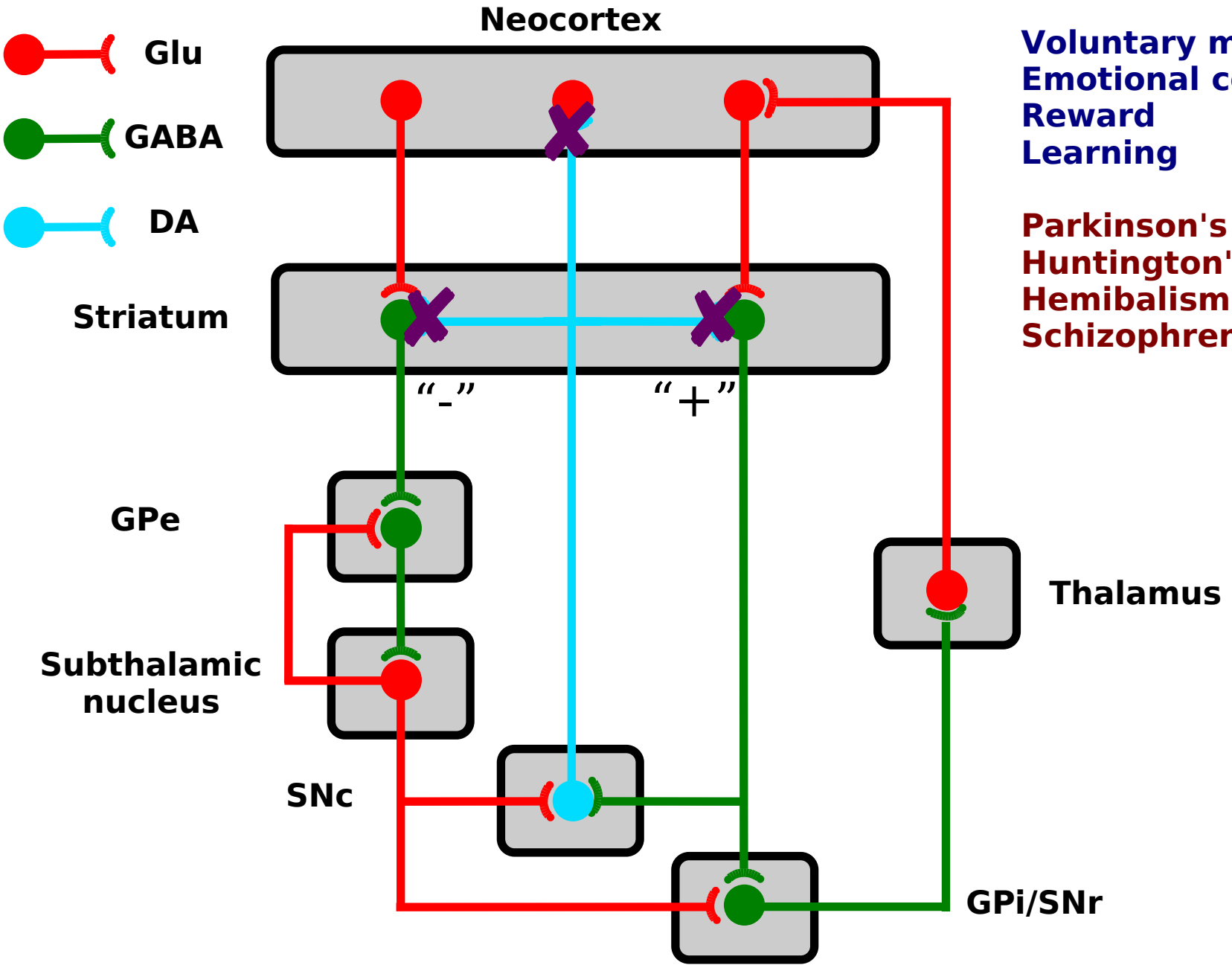

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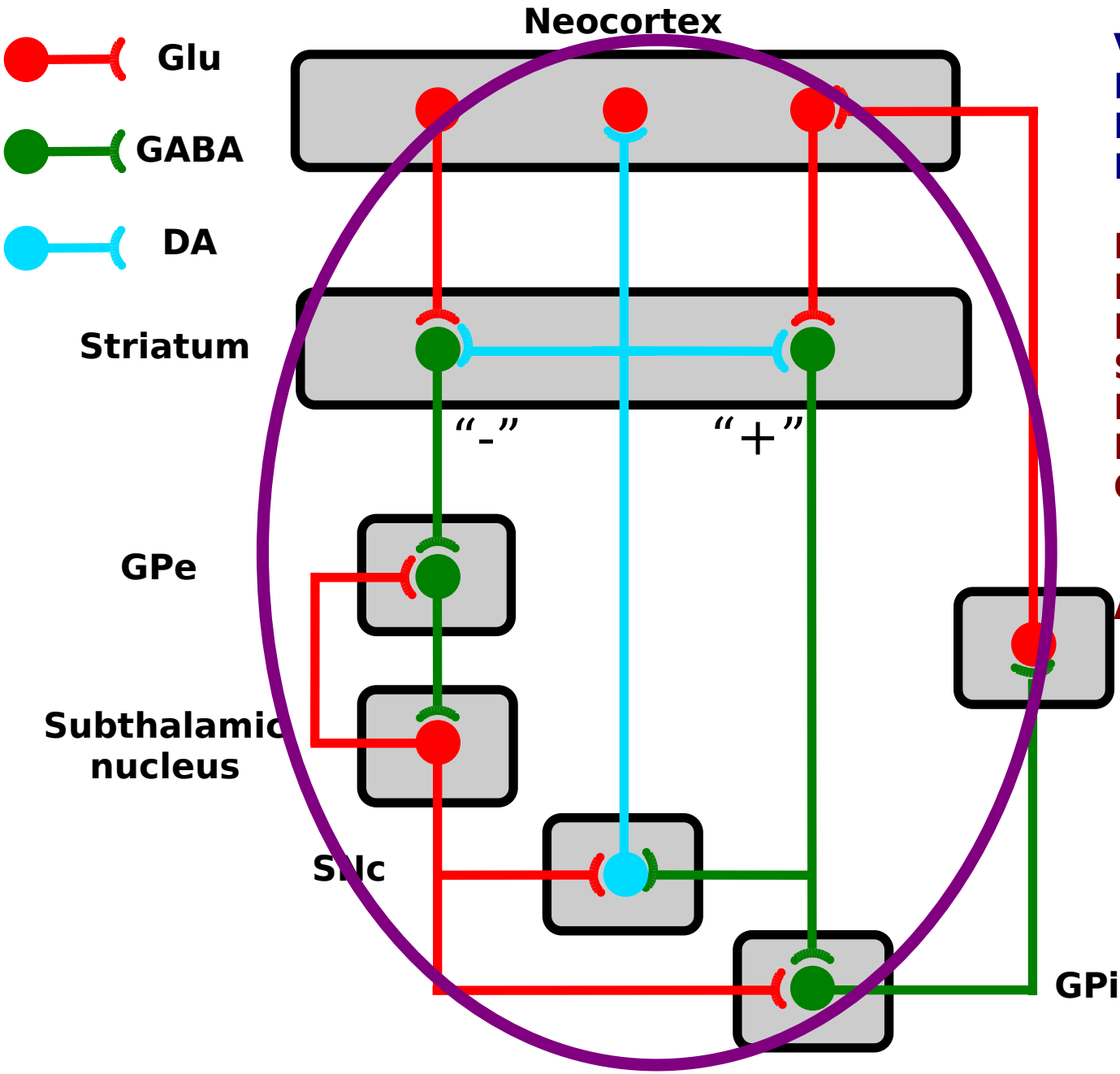
Parkinson's disease
Huntington's chorea
Hemibalism
Schizophrenia

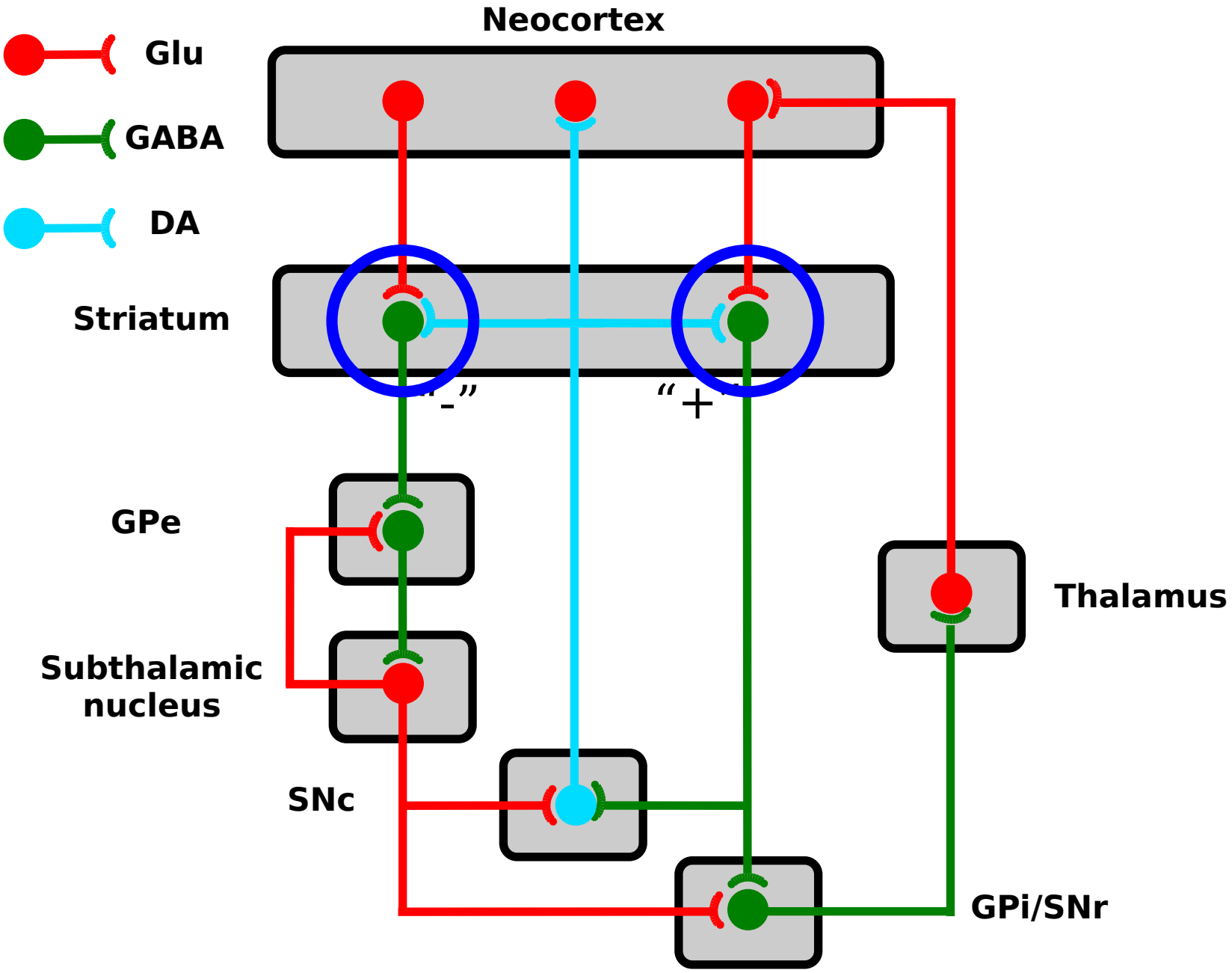
Cortico-striato thalamic loop



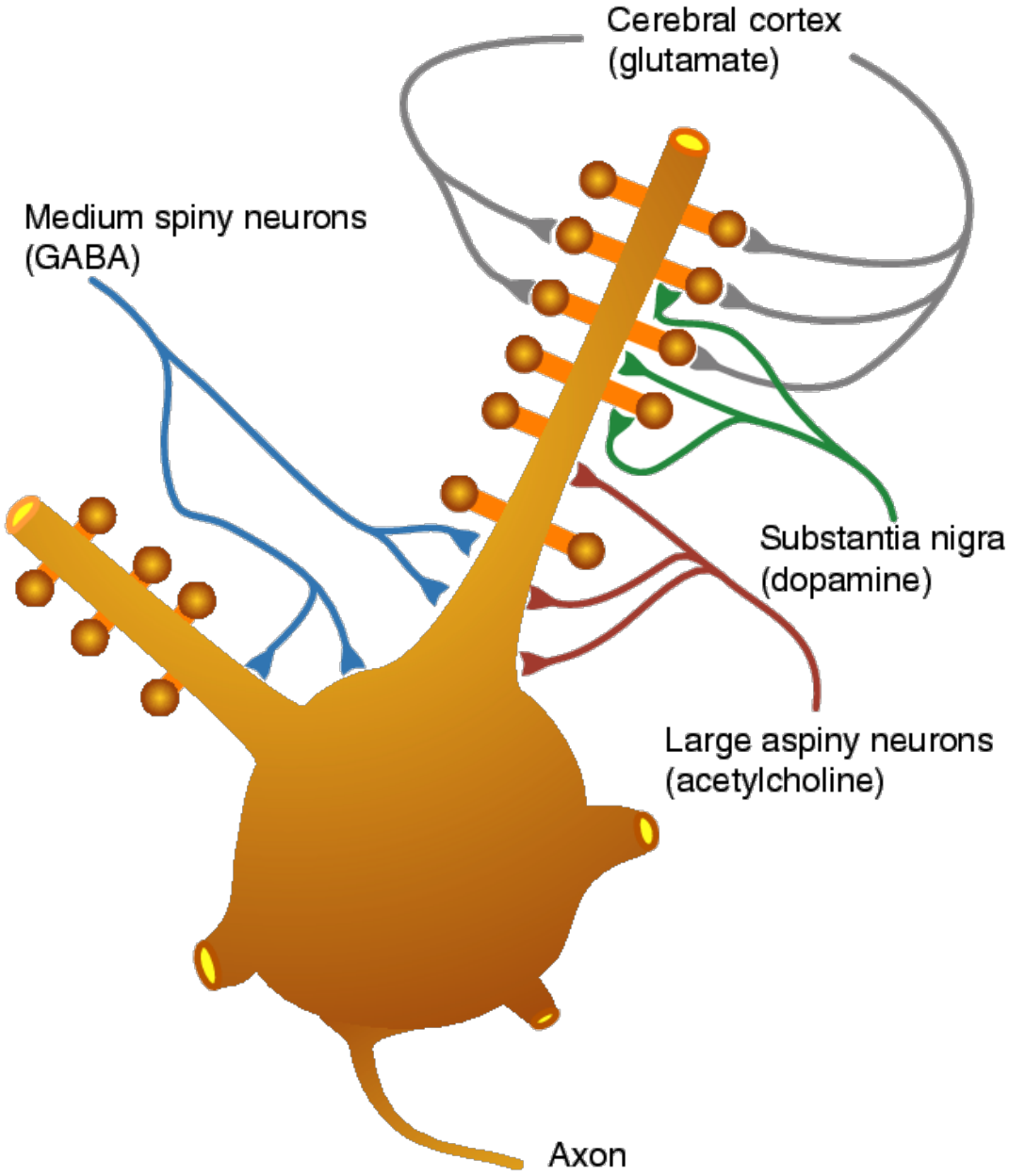
Voluntary motion
Emotional control
Reward
Learning

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

Cortico-striato thalamic loop



Multiple afferent signals



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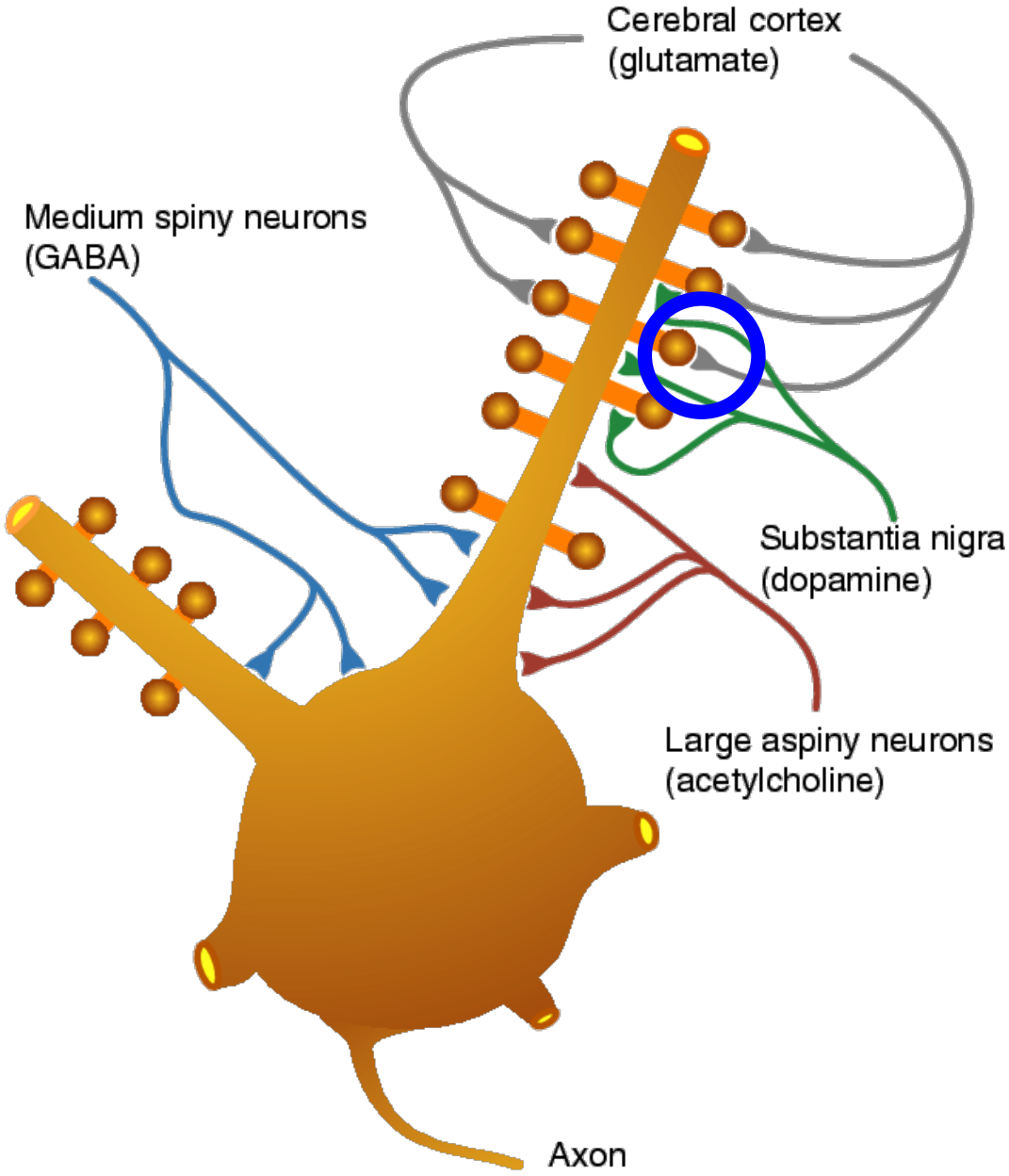
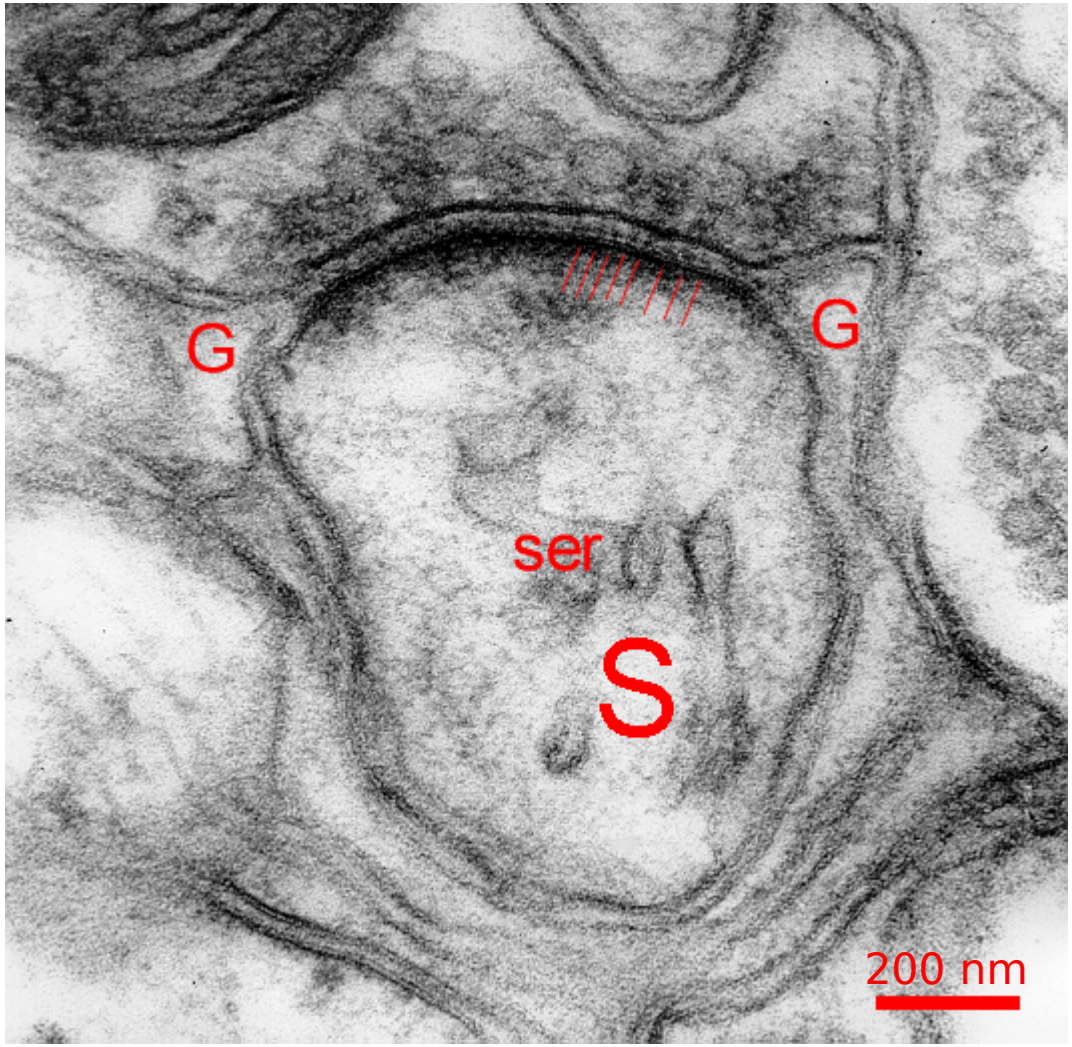


The spine as a “mini-cell”



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

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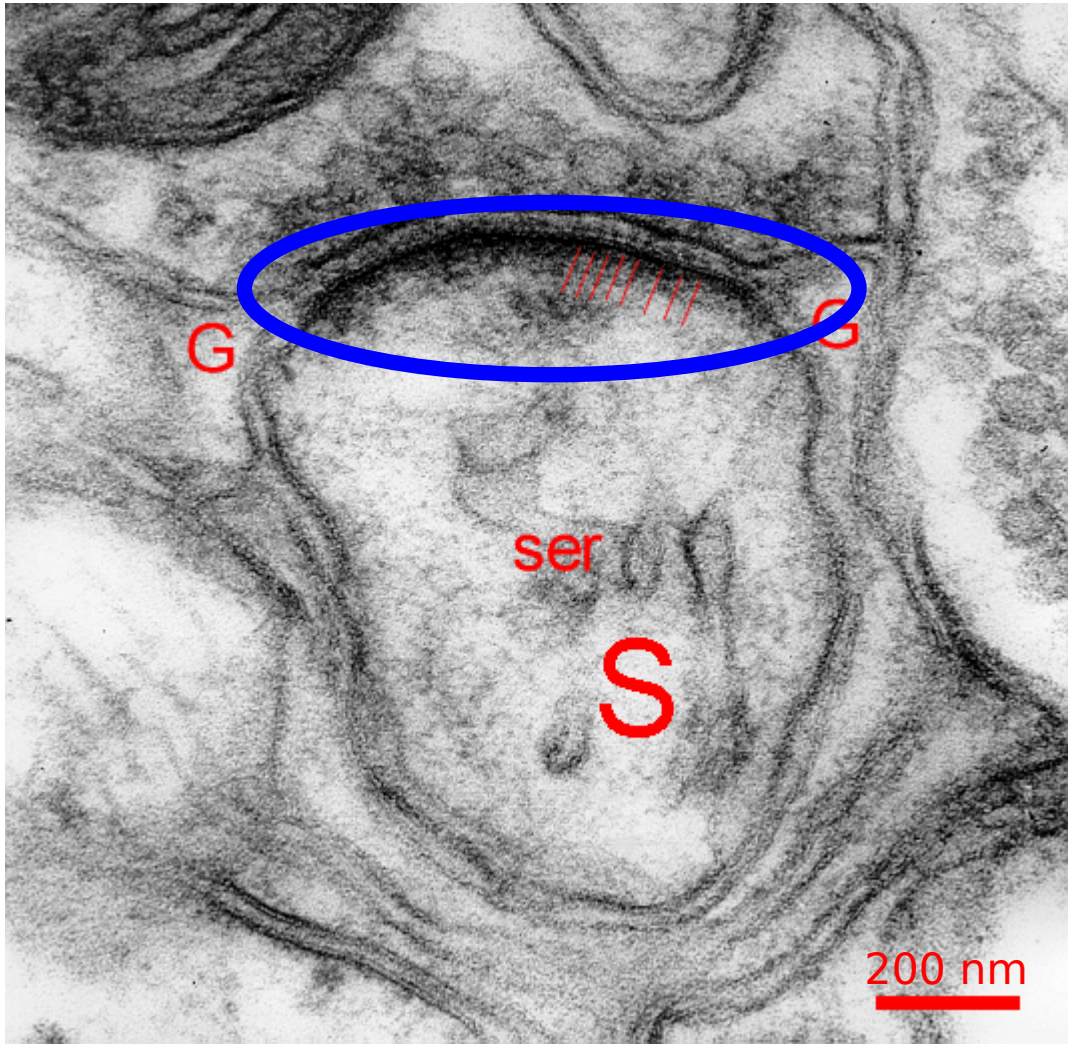

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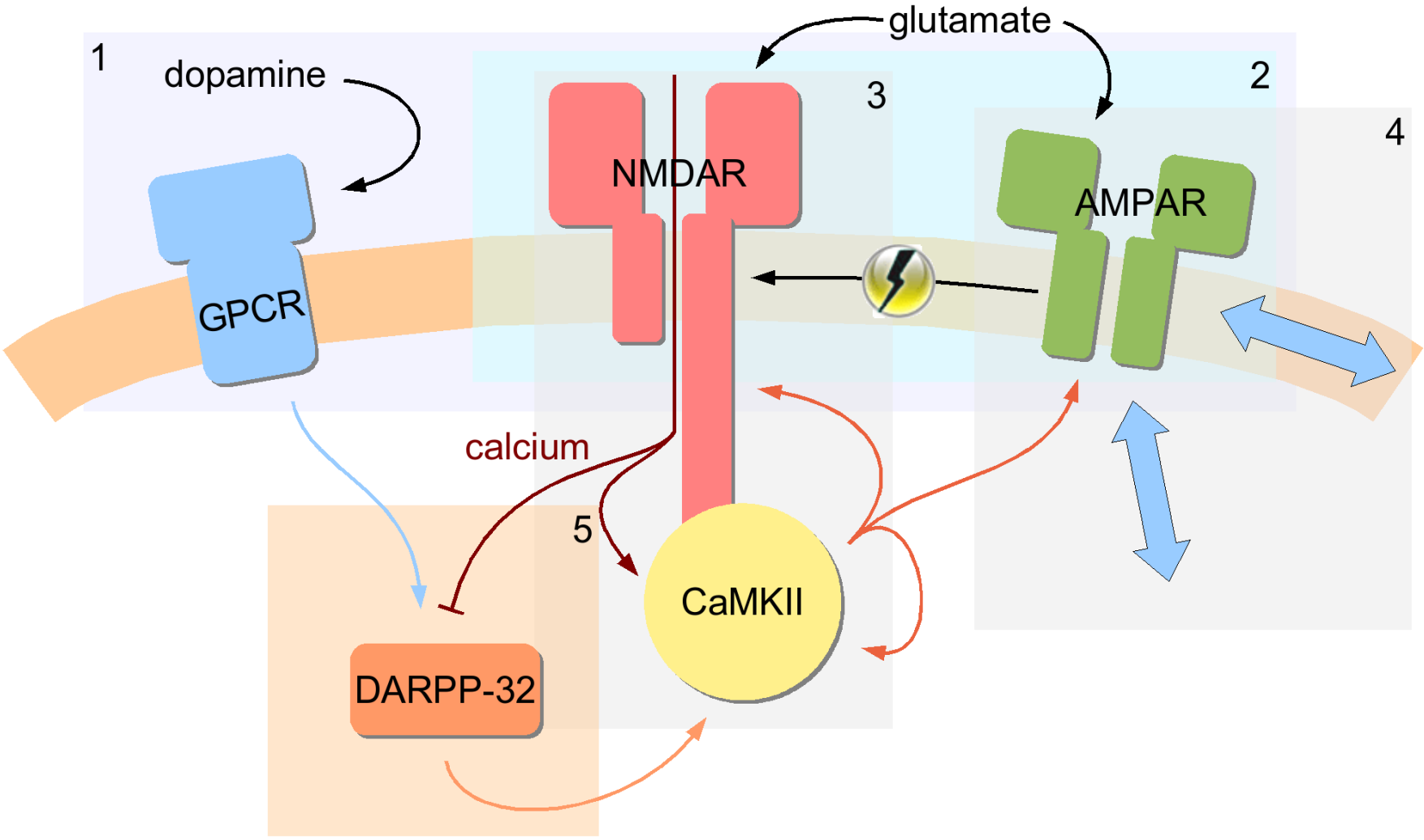
The research of the “compneur” group



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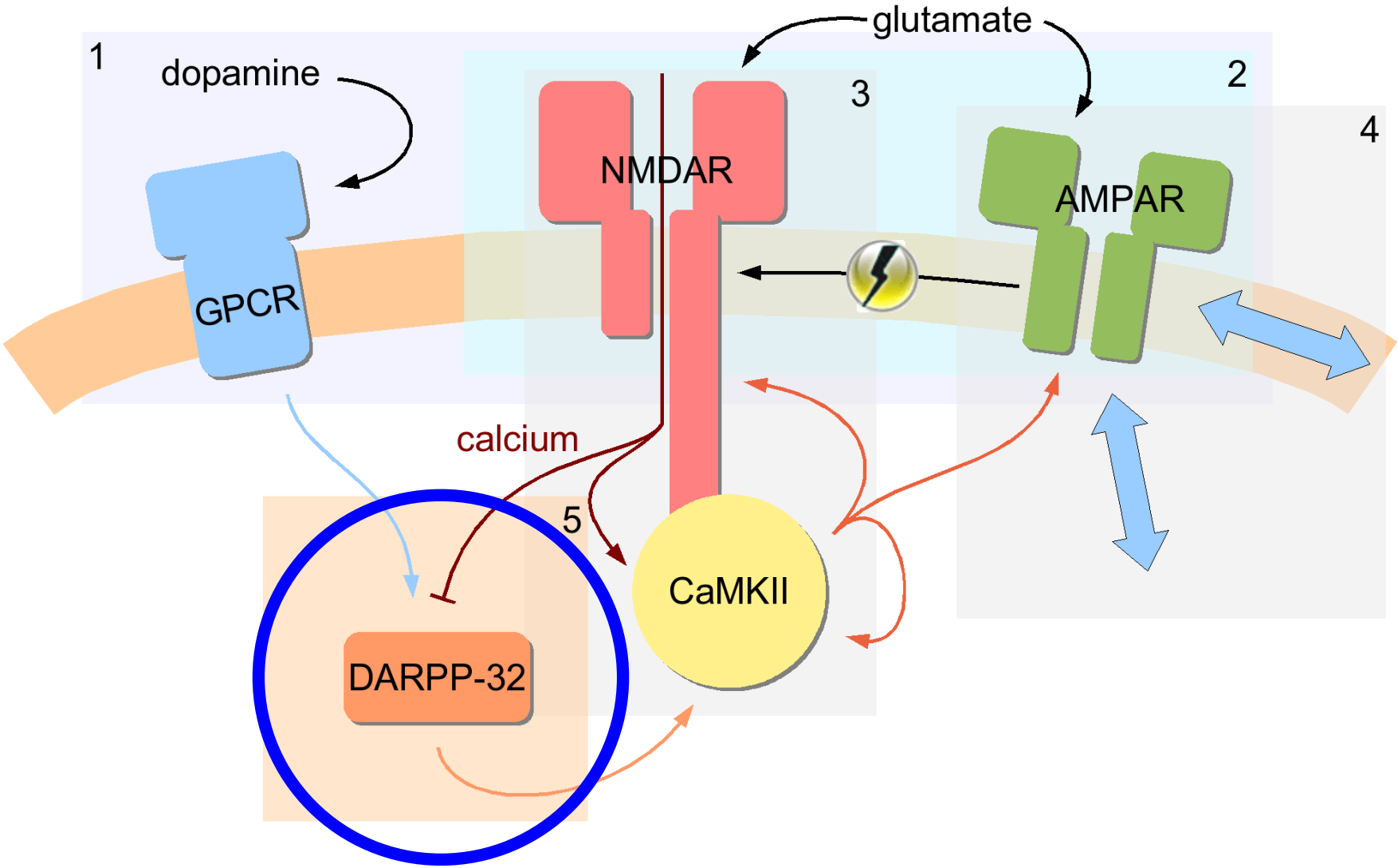

Fernandez E, Schiappa R, Girault JA, Le Novère N (2006)
DARPP-32 is a robust integrator of dopamine and glutamate signals.
PLoS Computational Biology, 2(12): e176.

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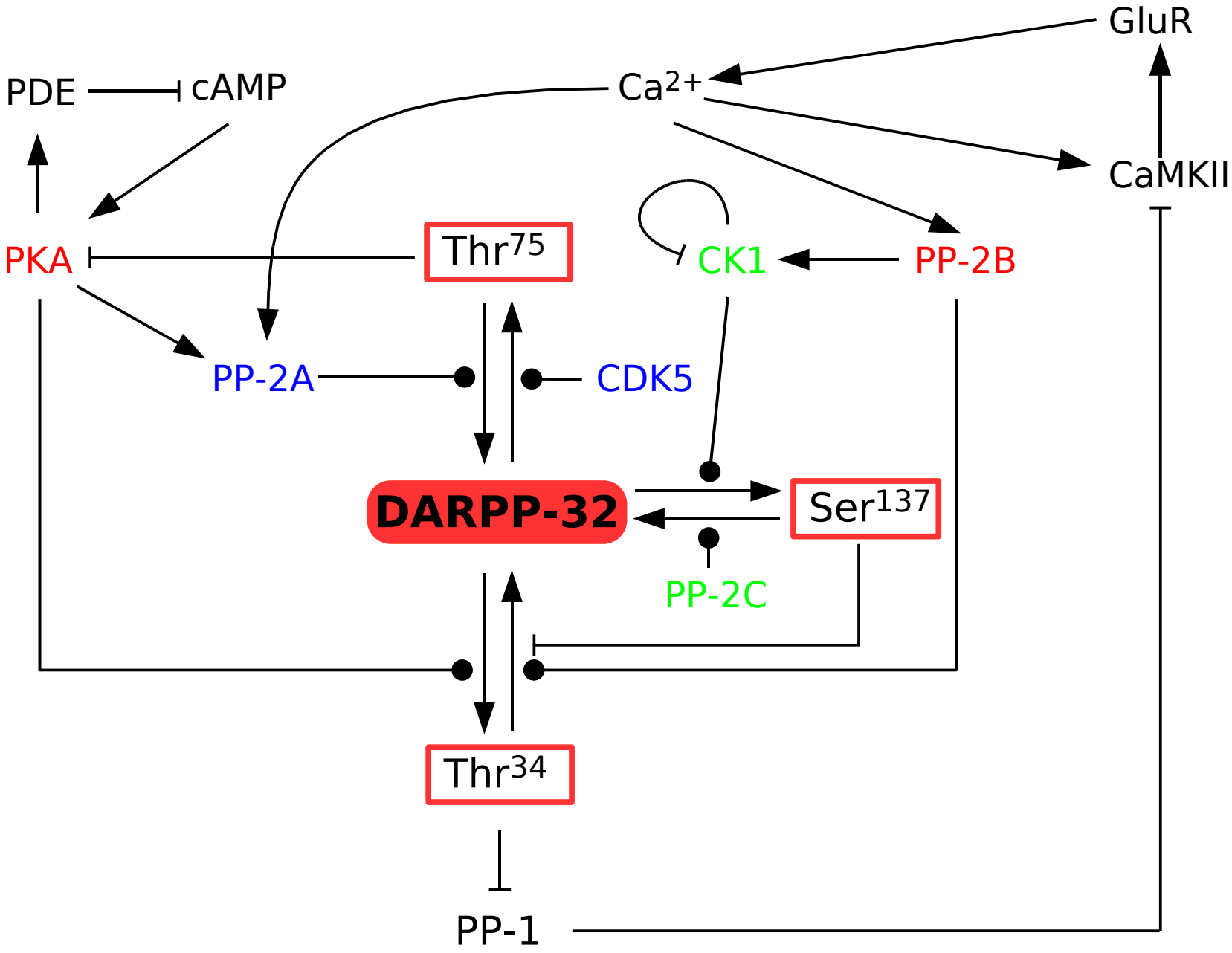
Biological model of DARPP-32



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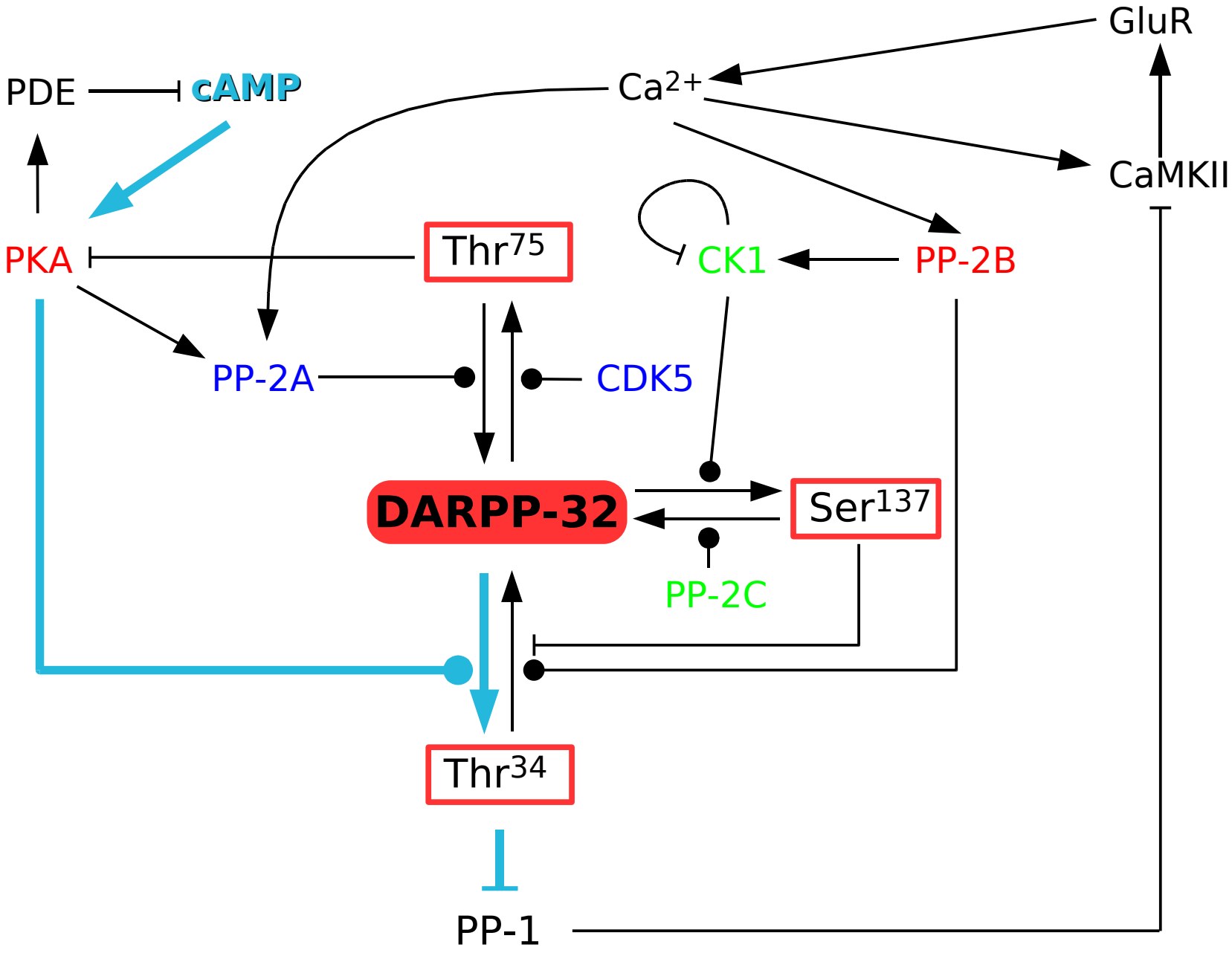

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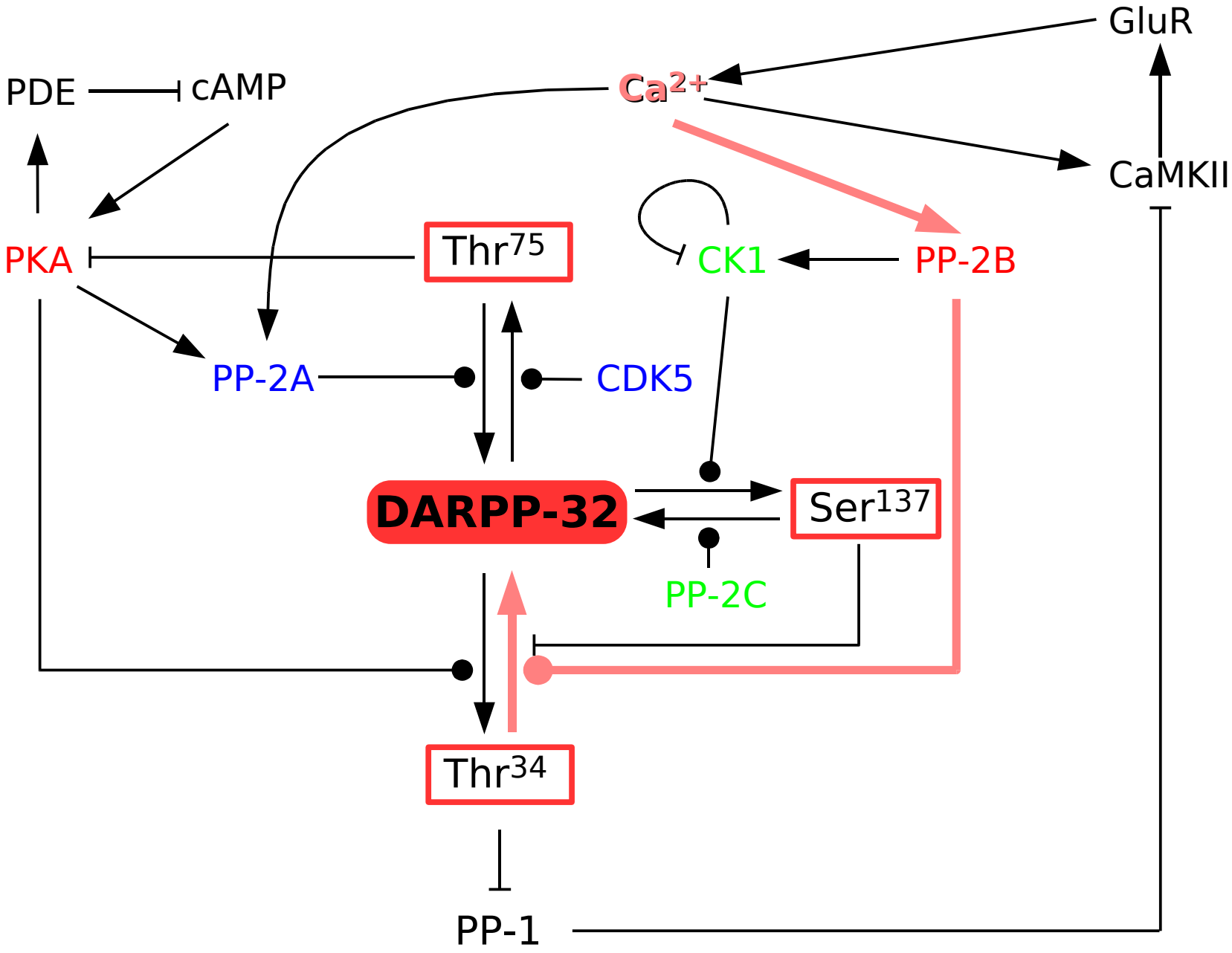
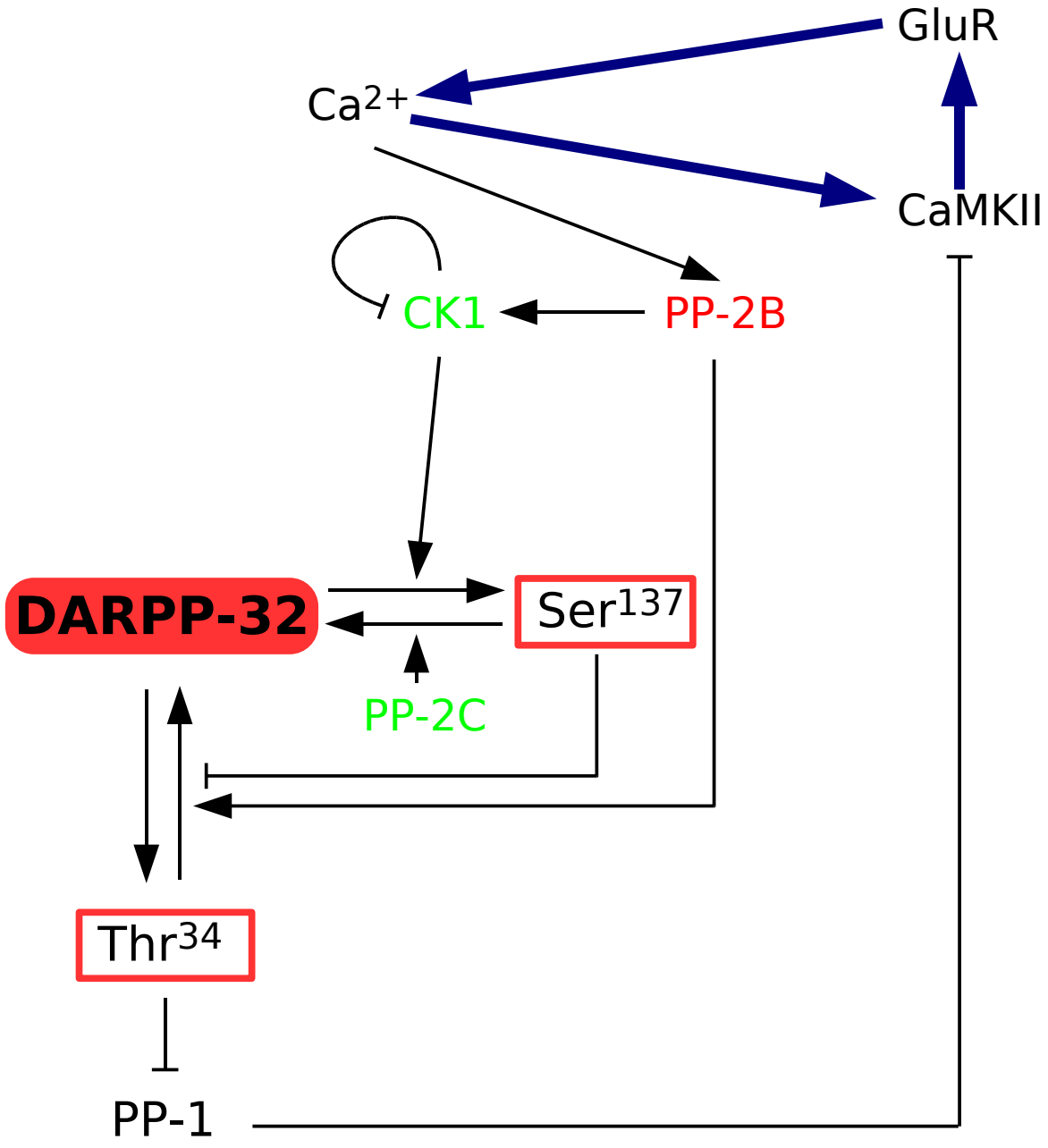


Why we do need kinetic simulations



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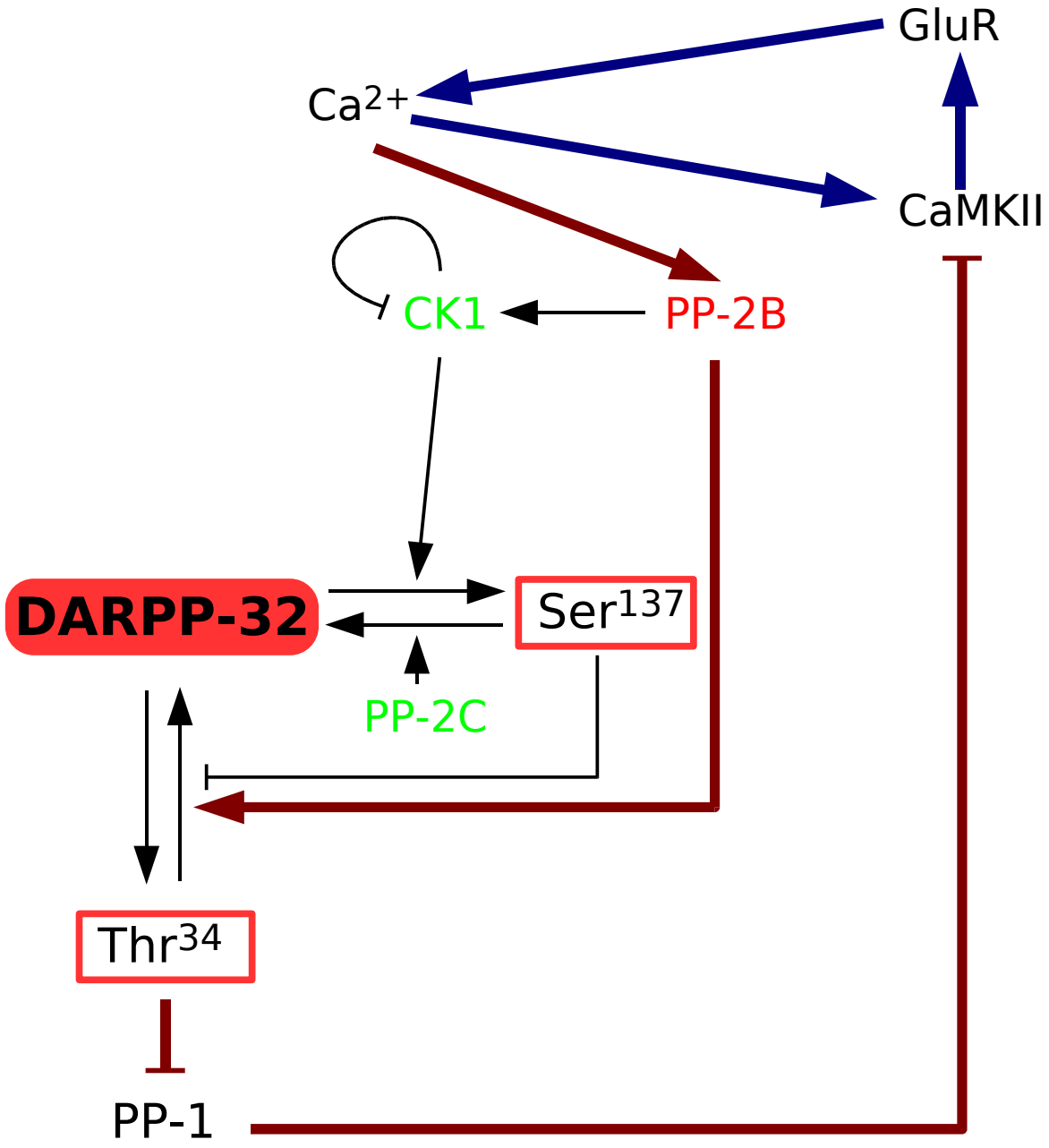

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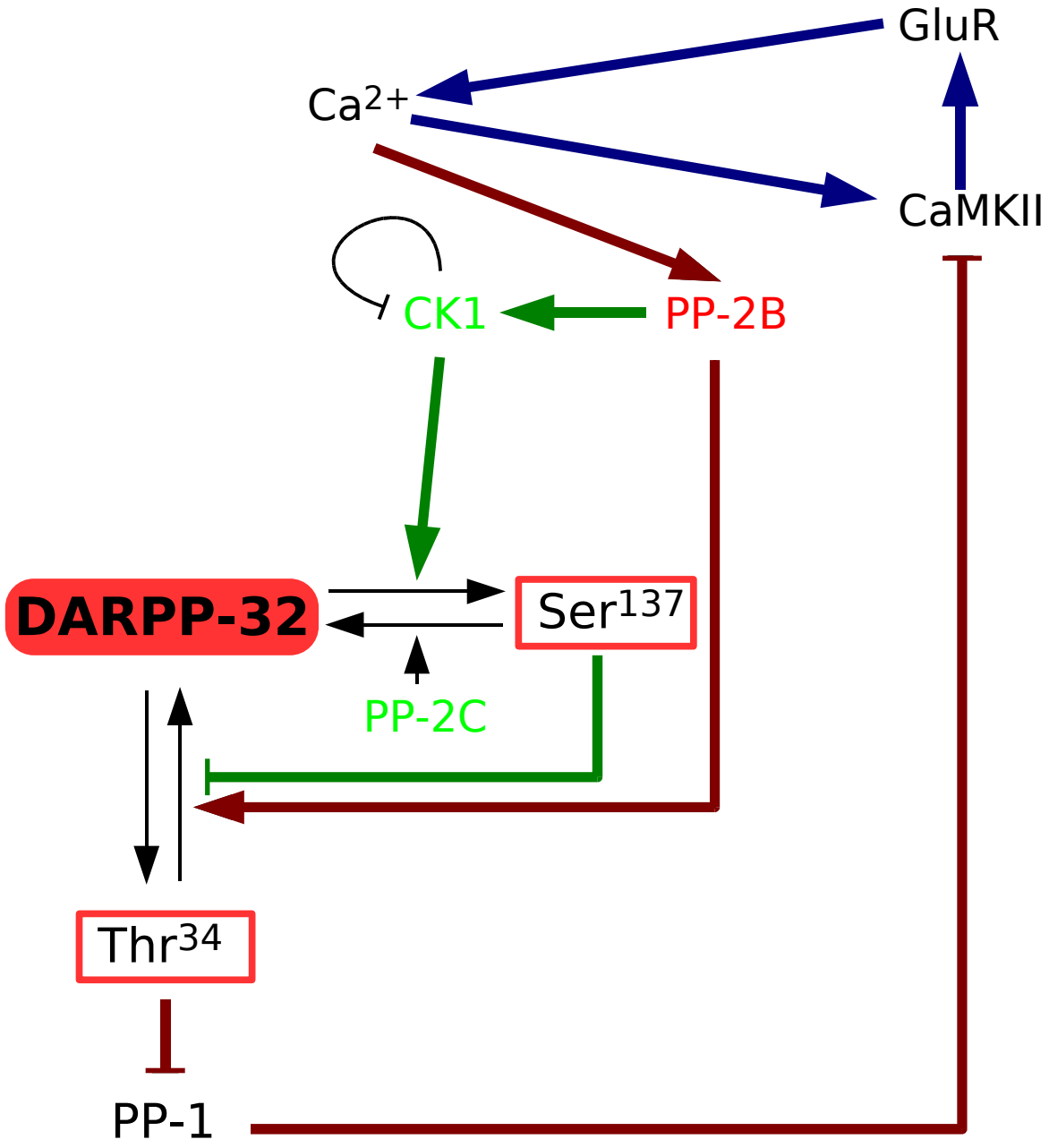

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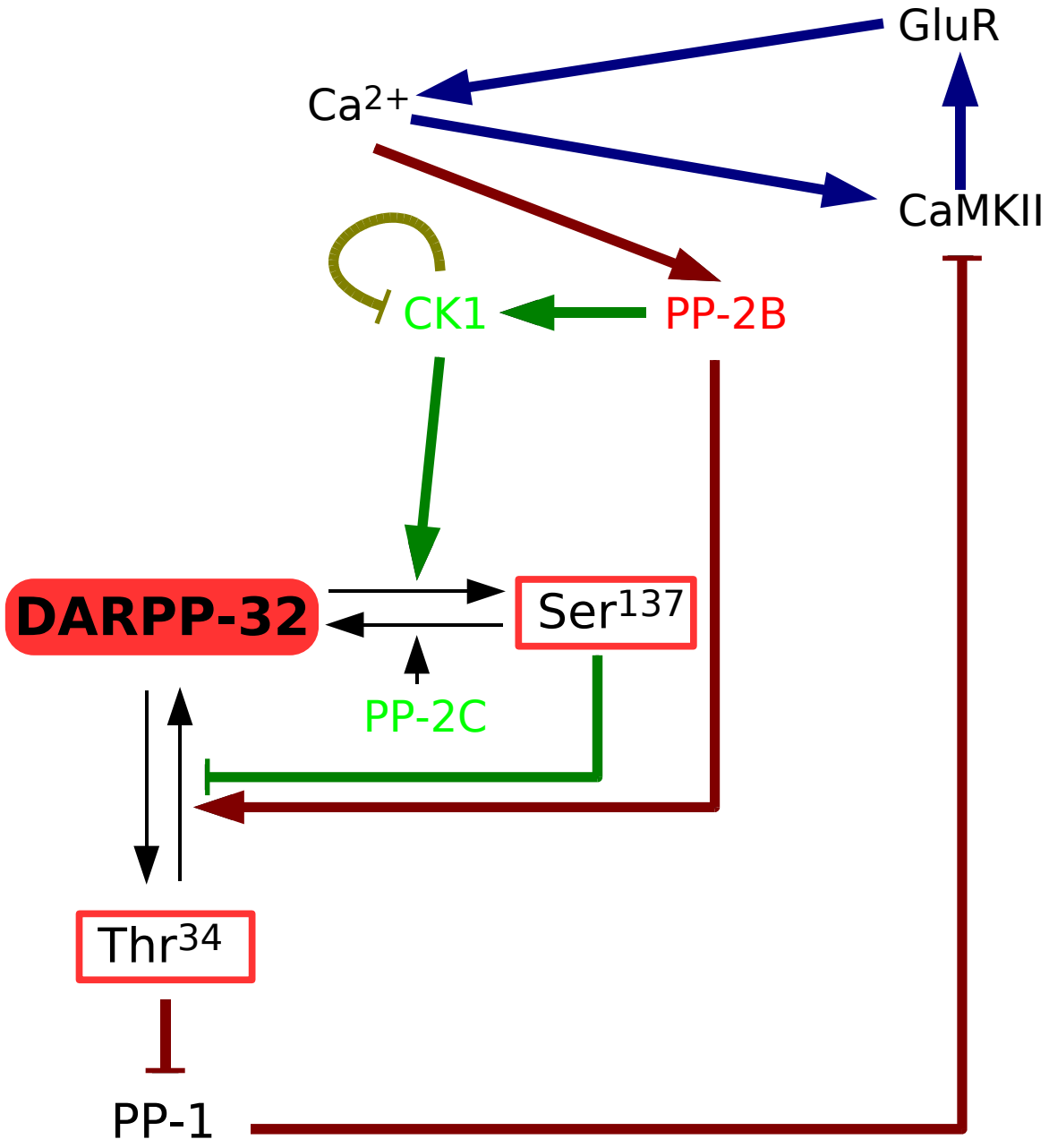
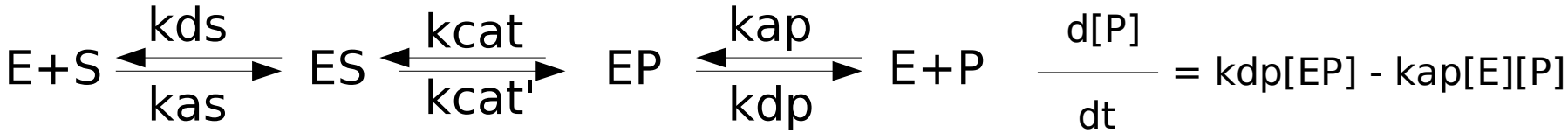
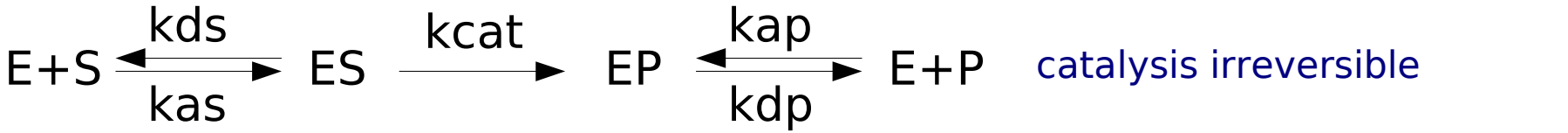


Choose the right formalism

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

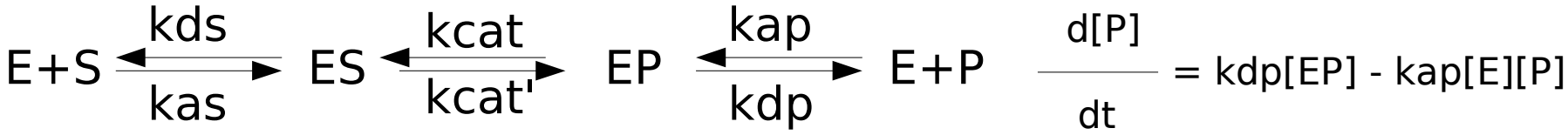
Choose the right formalism



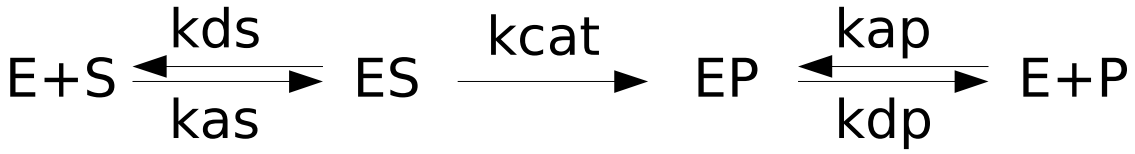


catalysis irreversible

Choose the right formalism



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



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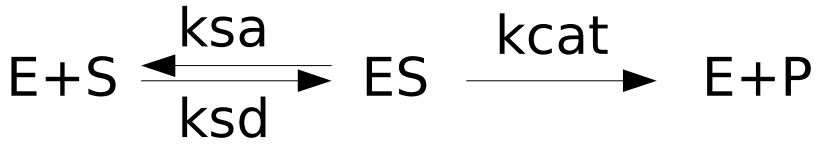
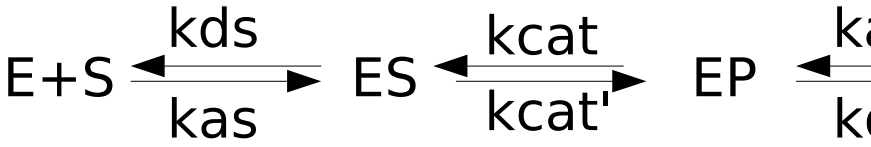


product is consumed before rebinding

Choose the right formalism



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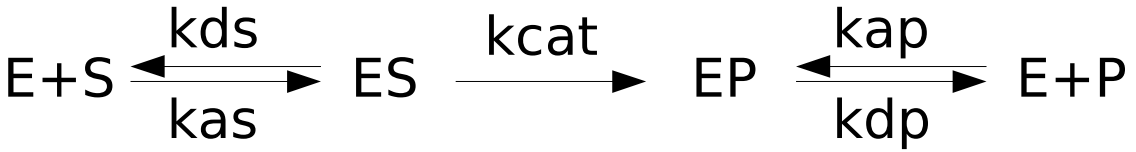

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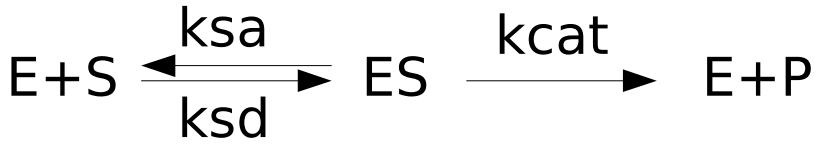

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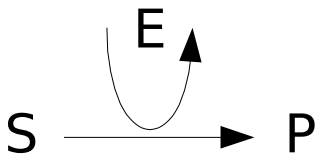


steady-state

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

Chemical model of DARPP-32 regulation

79 species, 151 reactions

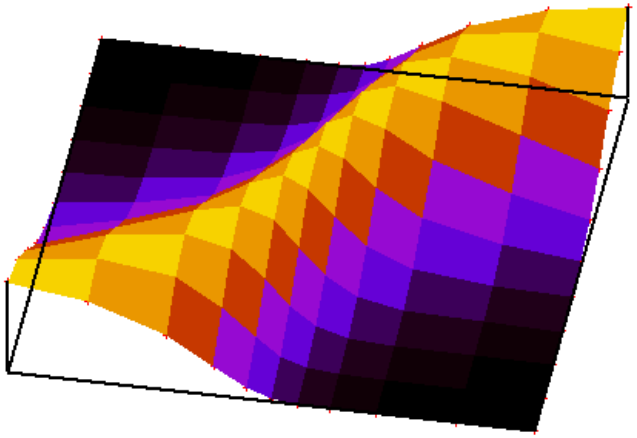
- D + CDK5 ⇔ D_CDK5 → D75 + CDK5
- D75 + PP2A ⇔ D75_PP2A → D + PP2A
- D75 + PP2ACa ⇔ D75_PP2ACa → D + PP2ACa
- D75 + PP2AP ⇔ D75_PP2AP → D + PP2AP
- D75 + PP2APCa ⇔ D75_PP2APCa → D + PP2APCa
- D137 + CDK5 ⇔ D137_CDK5 → D75-137 + CDK5
- D75-137 + PP2A ⇔ D75-137_PP2A → D137 + PP2A
- D75-137 + PP2ACa ⇔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

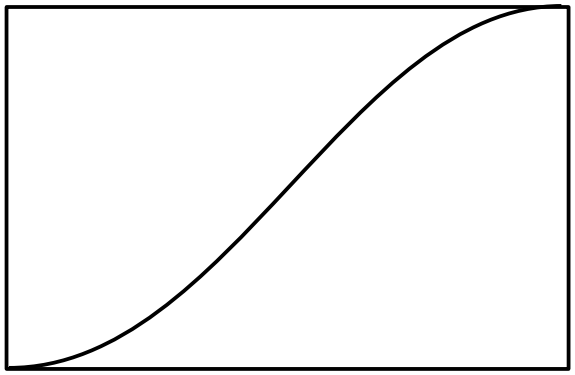
- D + PKA ⇔ D_PKA → D34 + PKA
- D34 + PP2B ⇔ D34_PP2B → D + PP2B
- D75 + PKA ⇔ D75_PKA → D34-75 + PKA
- D34-75 + PP2B ⇔ D34-75_PP2B → D75 + PP2B
- D137 + PKA ⇔ D137_PKA → D34-137 + PKA
- D34-137 + PP2B ⇔ D34-135_PP2B → D137 + PP2B
- D75-137 + PKA ⇔ D75-137_PKA → D34-75-137 + PKA
- D34-75-137 + PP2B ⇔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

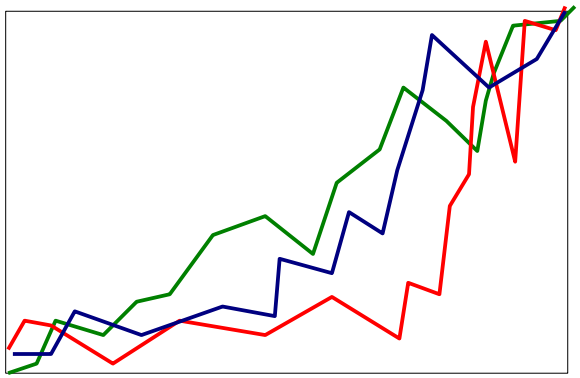
Different modelling approaches



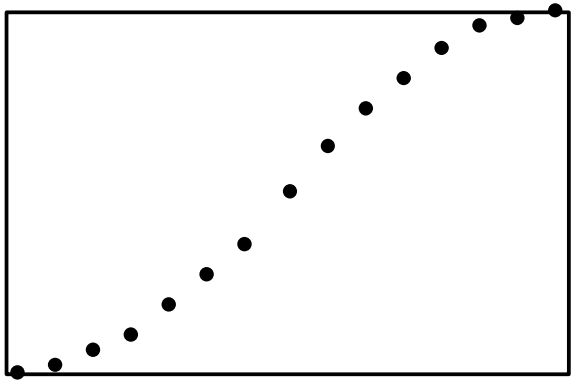
Grand Probability function: P(X,t)



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

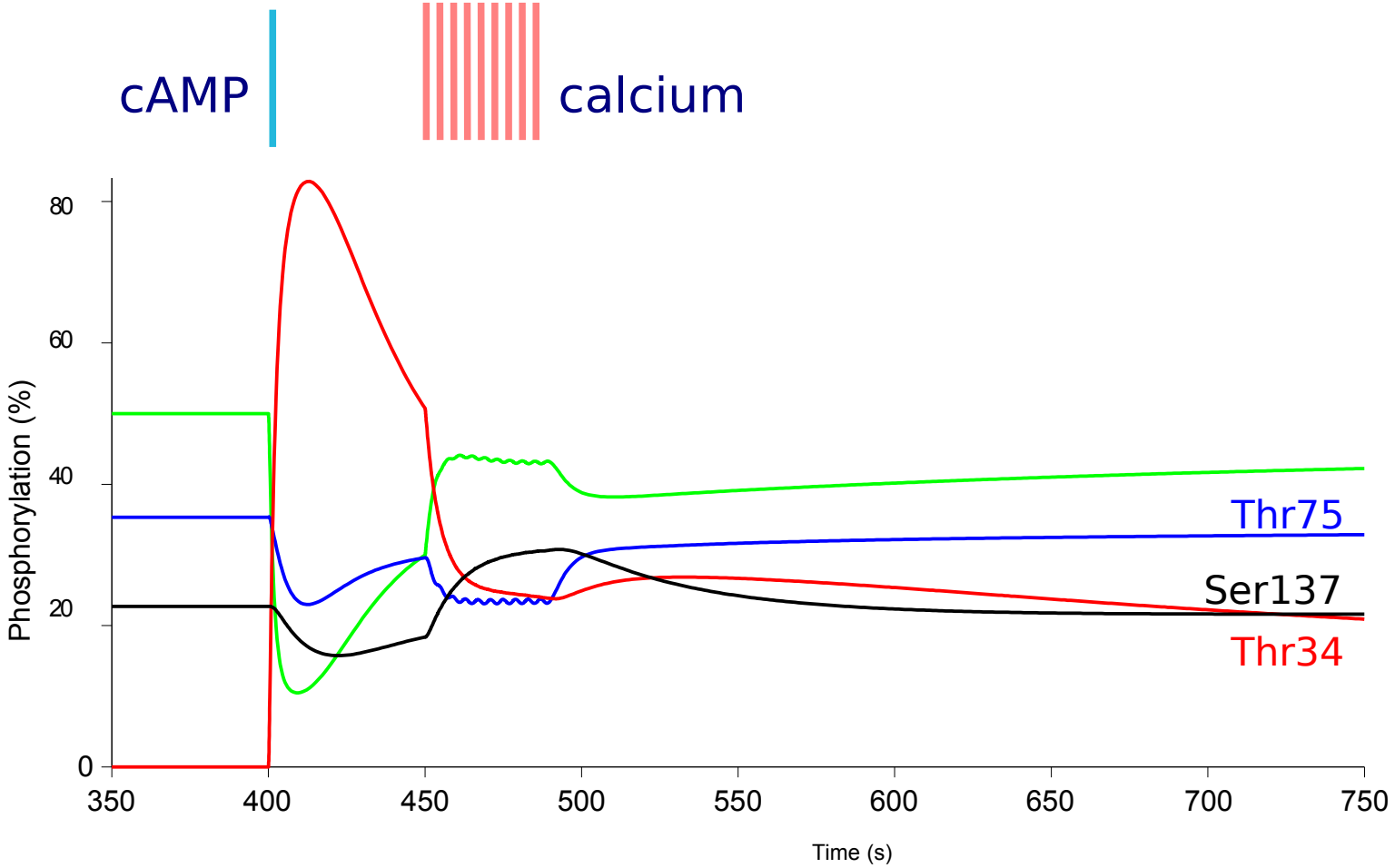


stochastic approach: P(X,t)/(X',t-1)

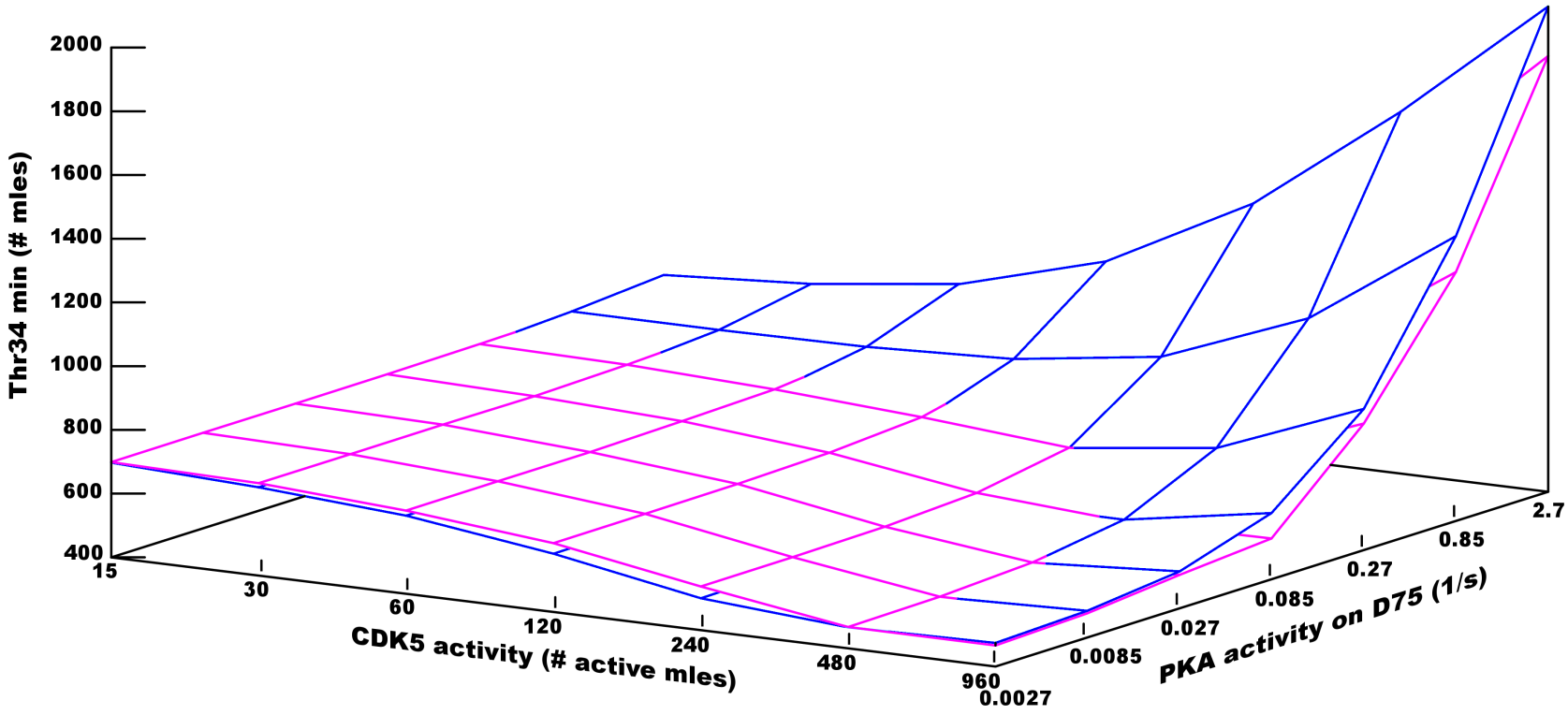


deterministic approach: (X,t)=f(X',t-1)

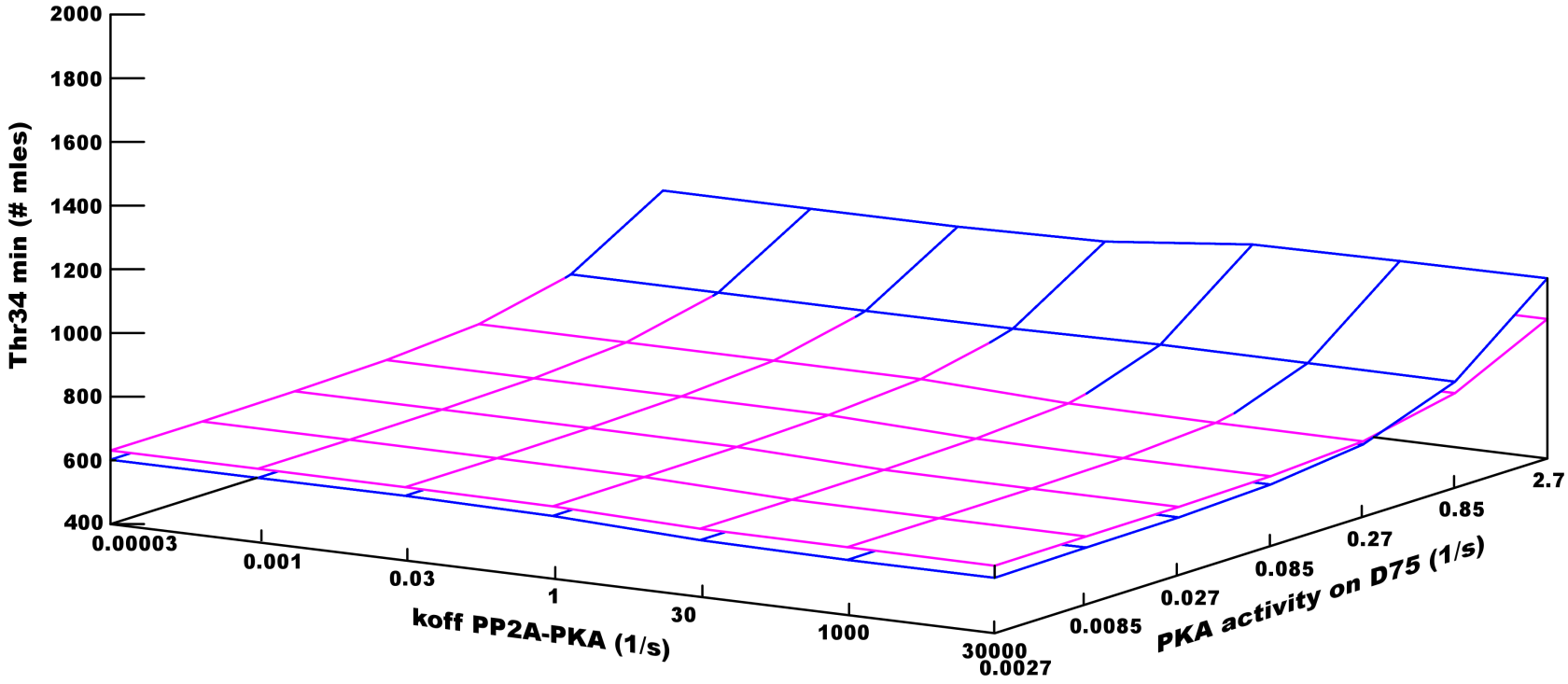
Dynamic simulations of DARPP-32 function



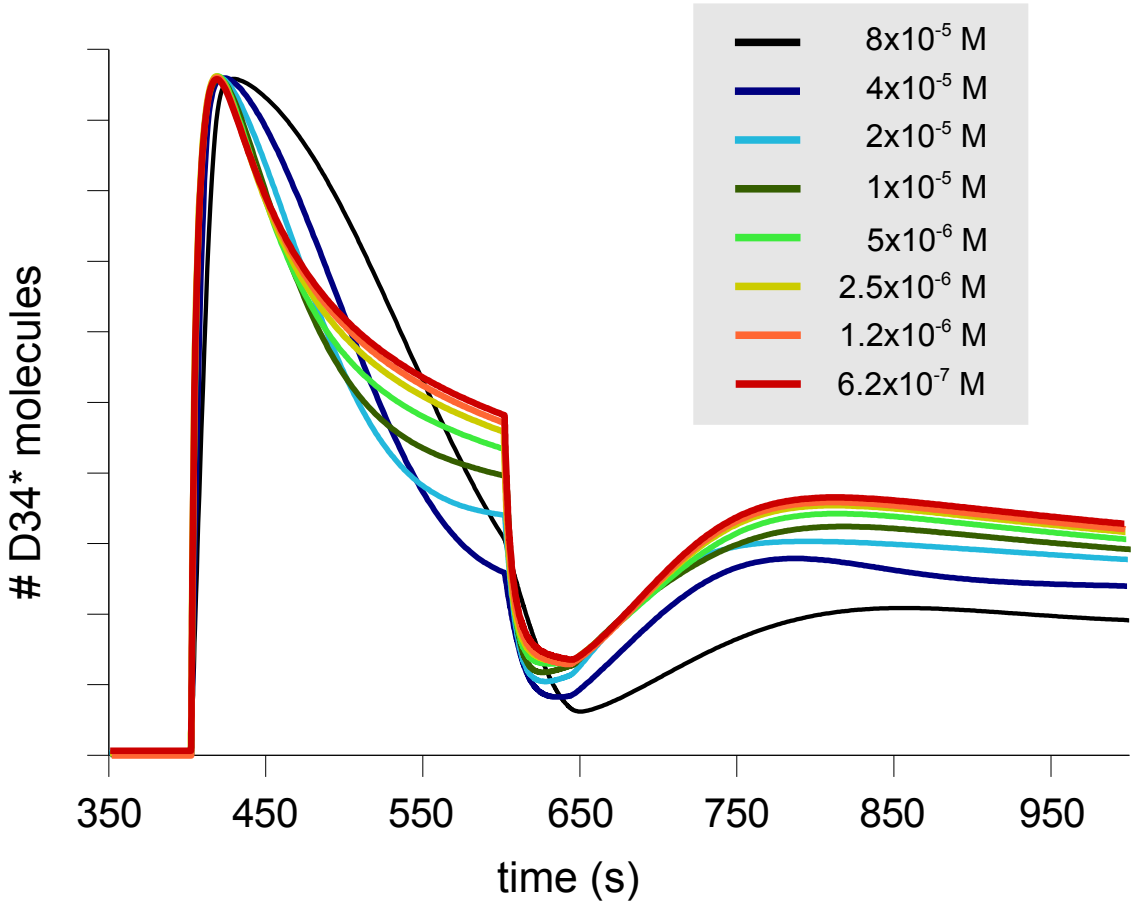
Some parameters are sensitive



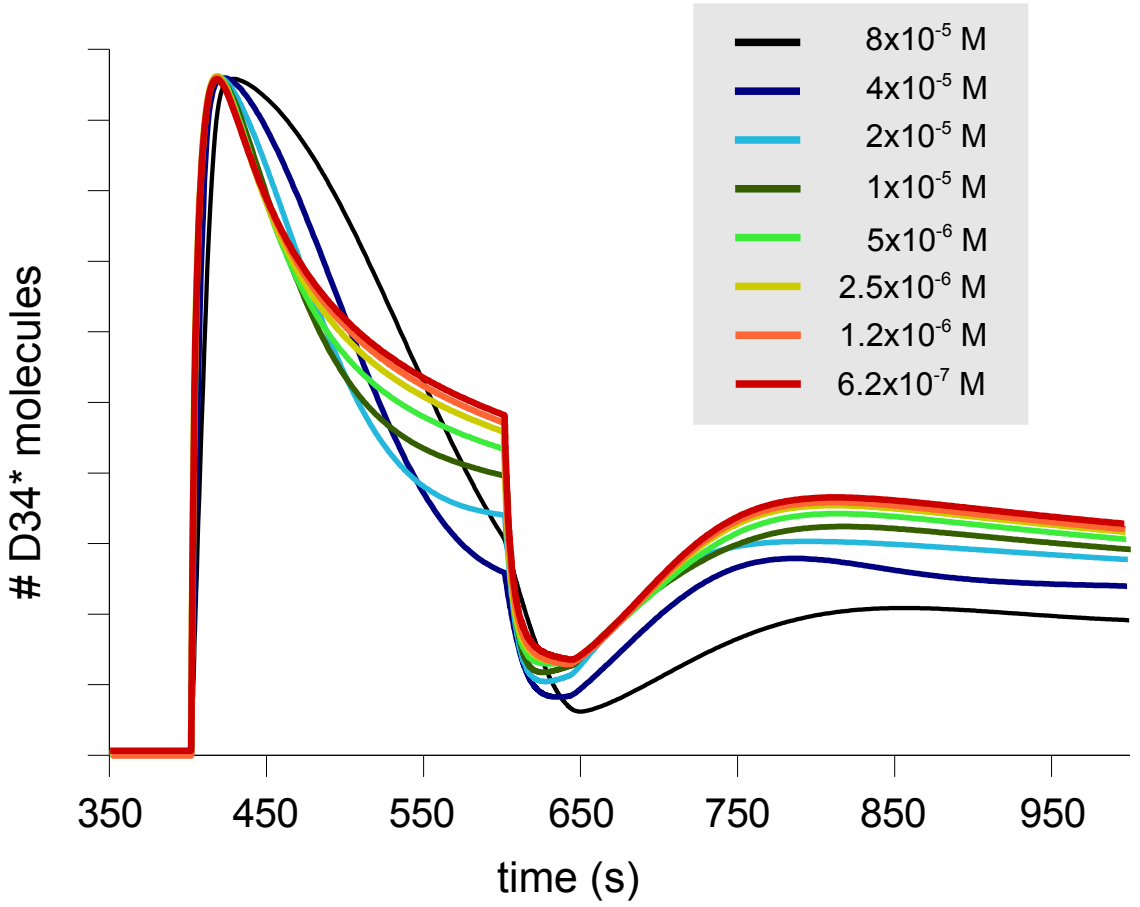
Some parameters are robust



DARPP-32 as a robust integrator

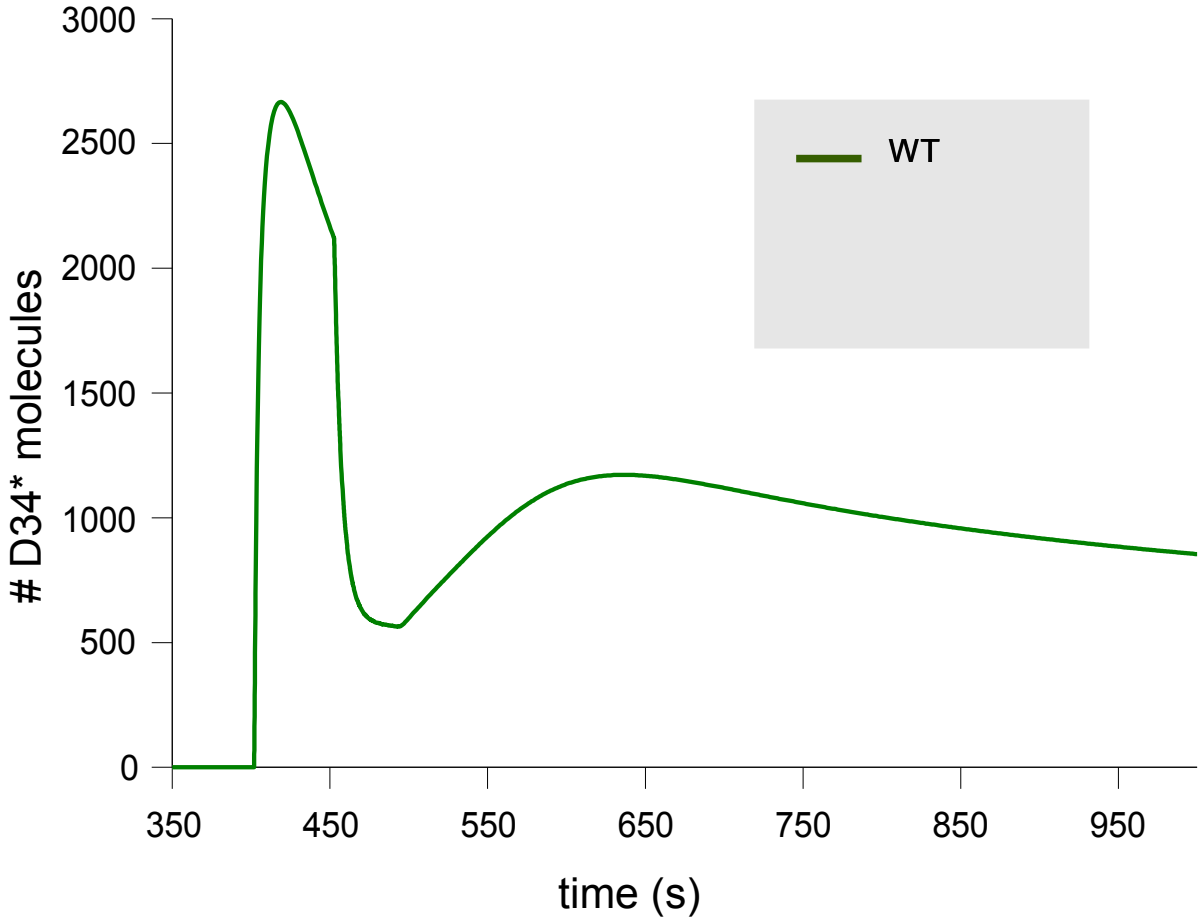


DARPP-32 as a robust integrator

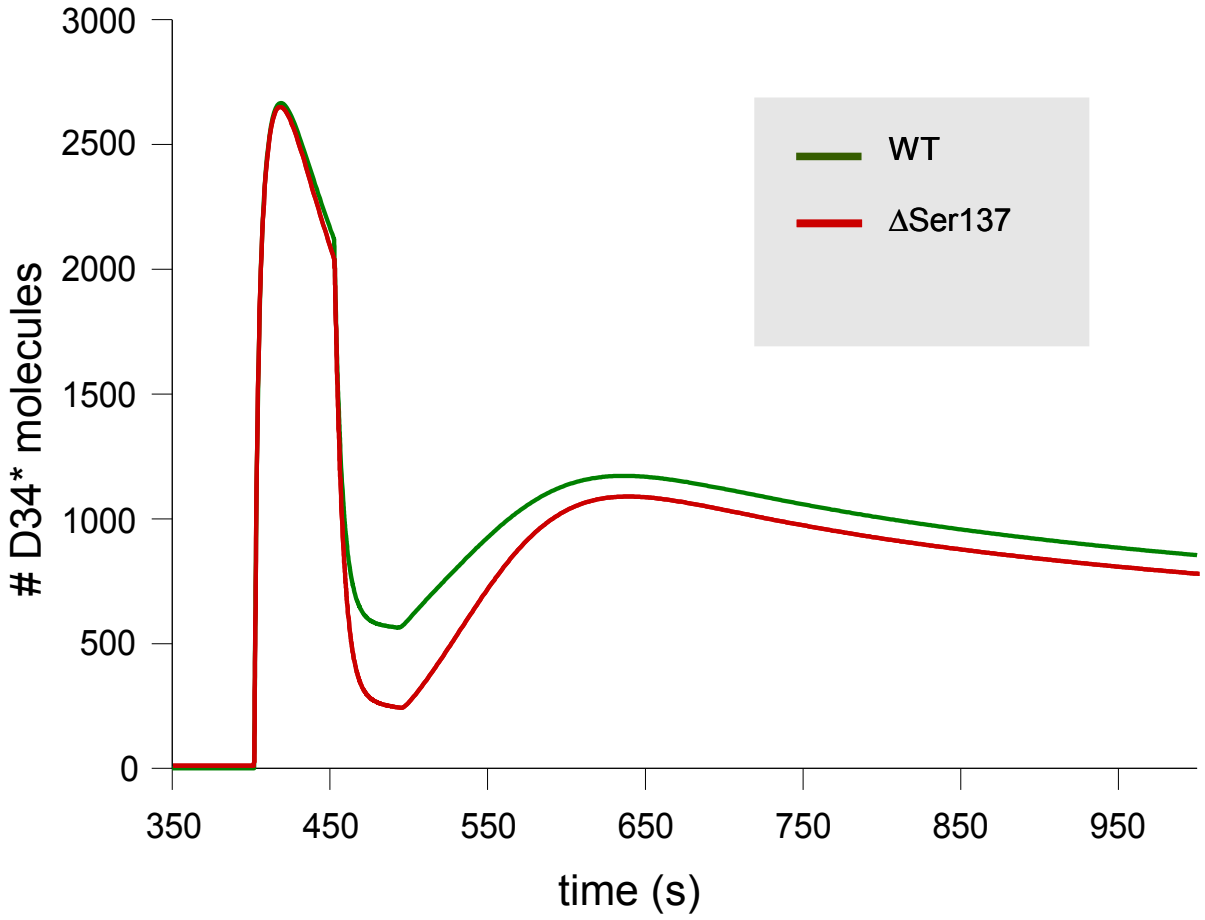


Heterozygous DARPP-32 +/- do not display phenotypes

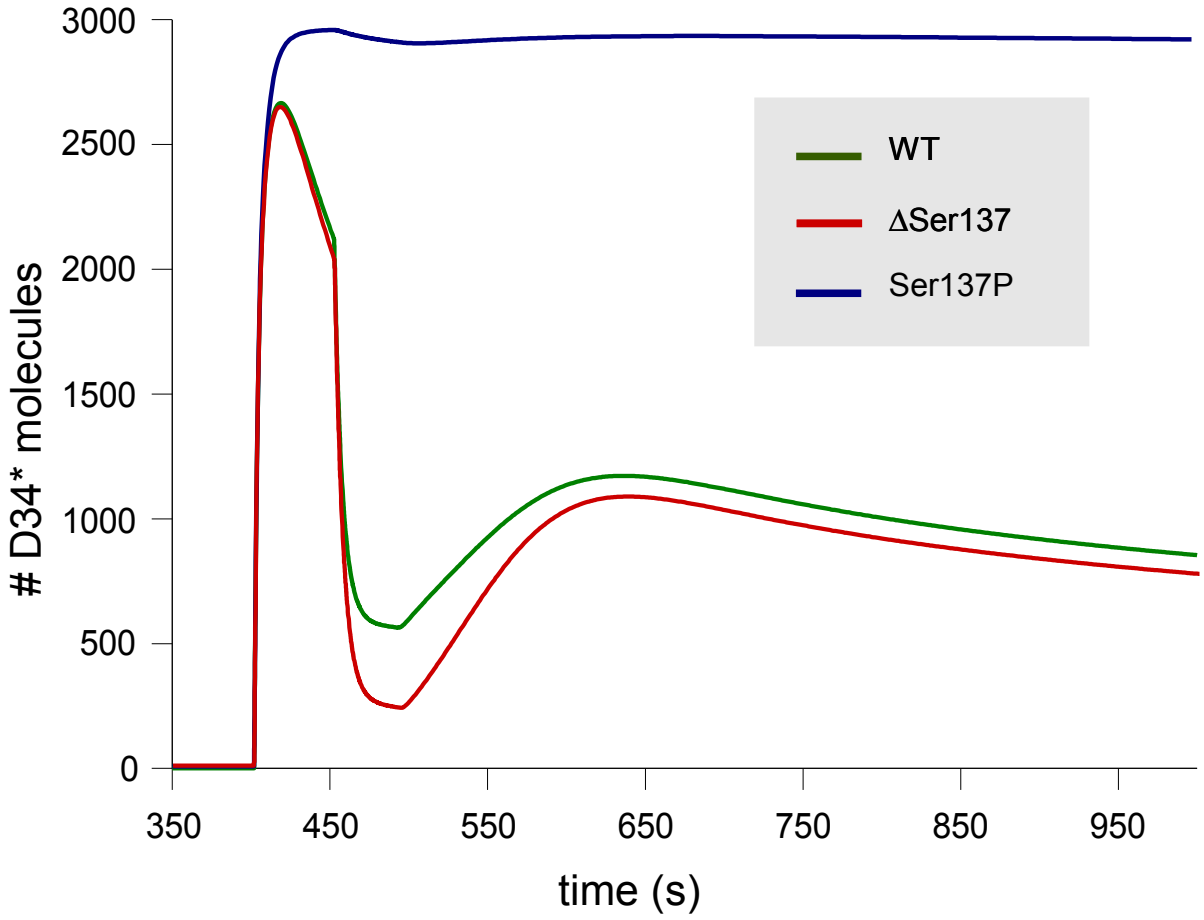
Mutation *in silico*

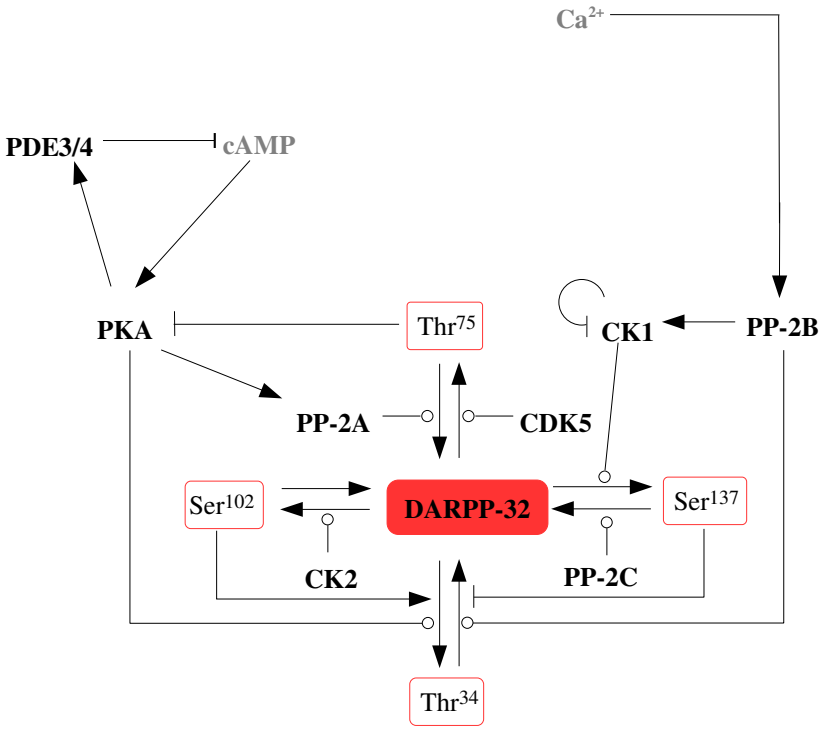


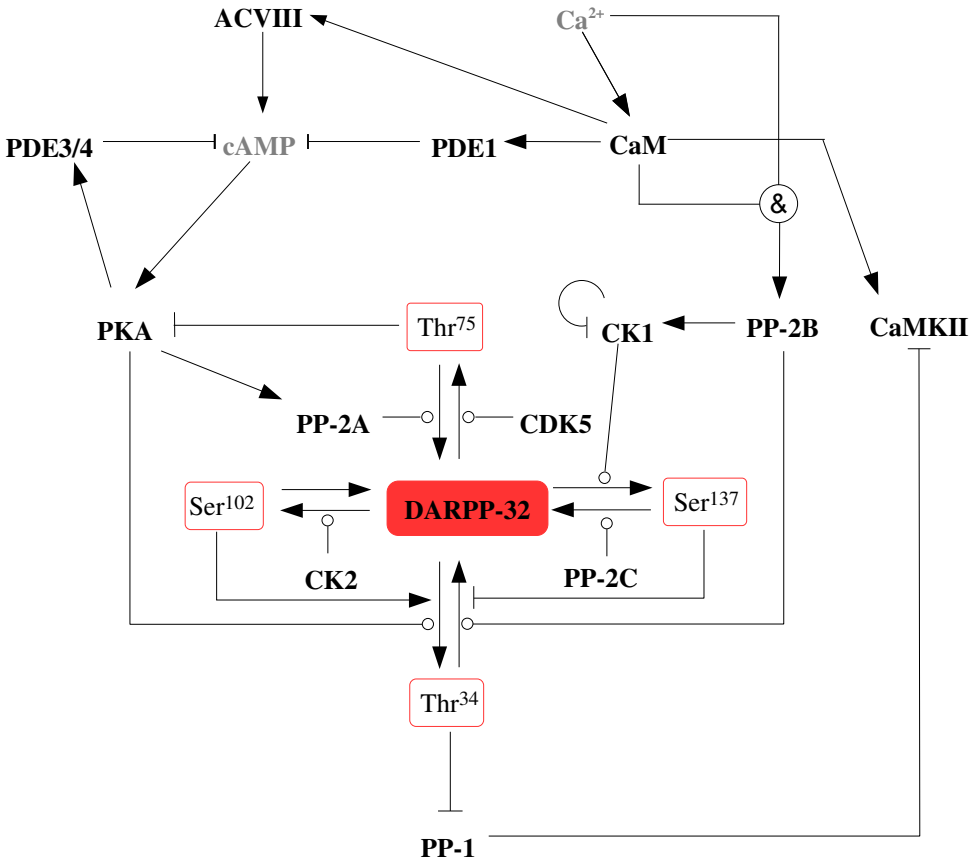
Mutation *in silico*



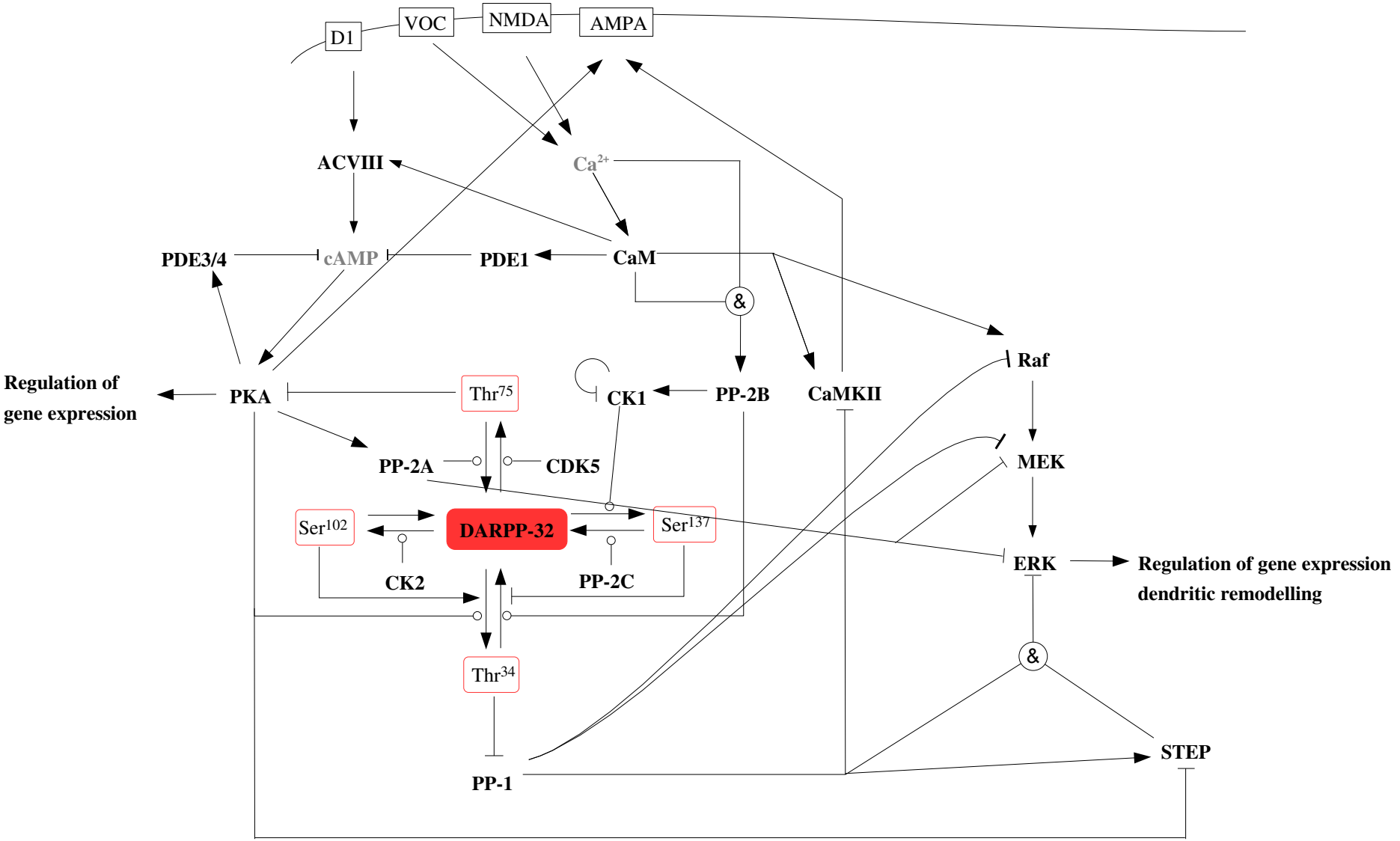
Mutation *in silico*




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


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

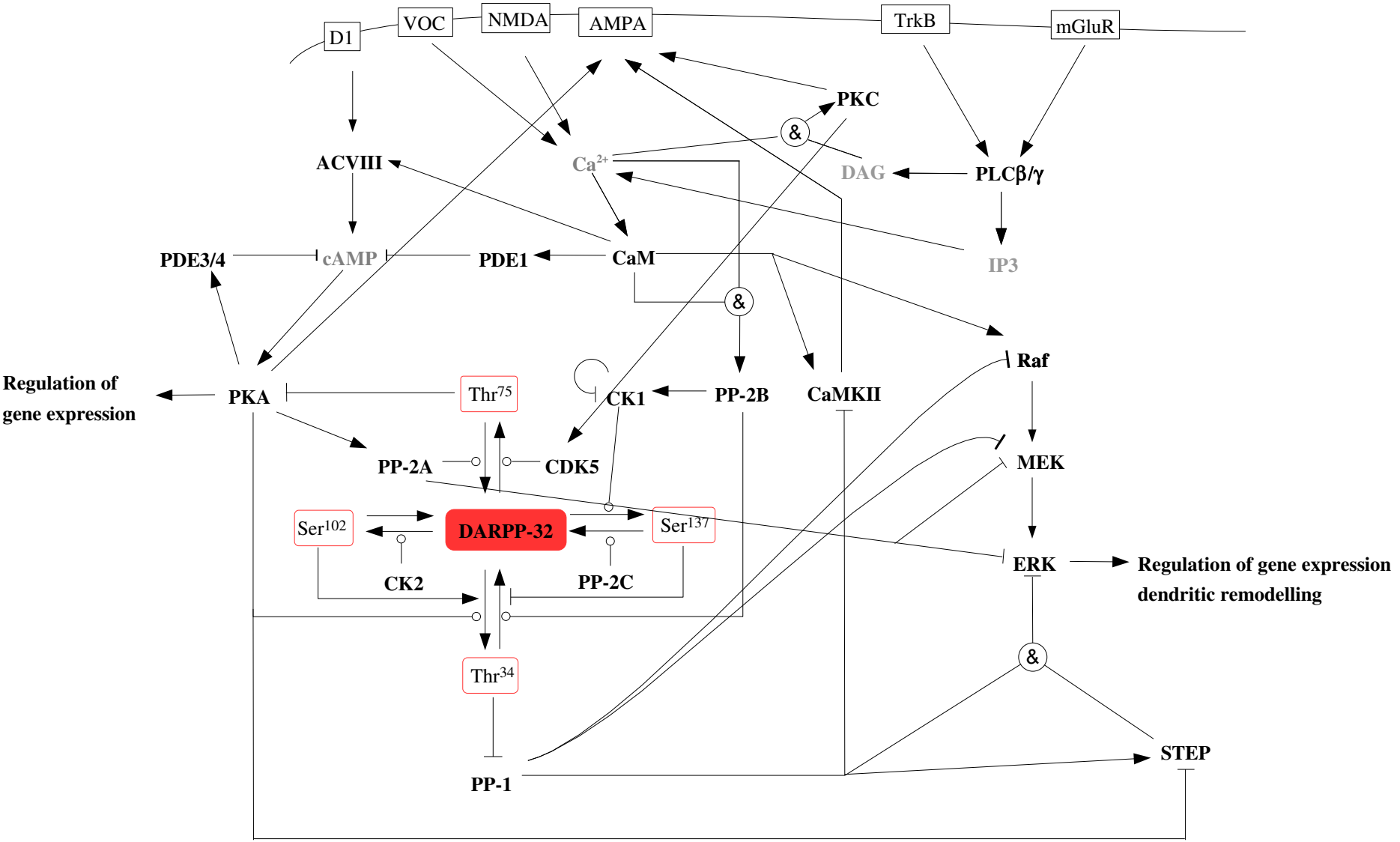
Future



Collaboration

Jean-Antoine Girault, Paris

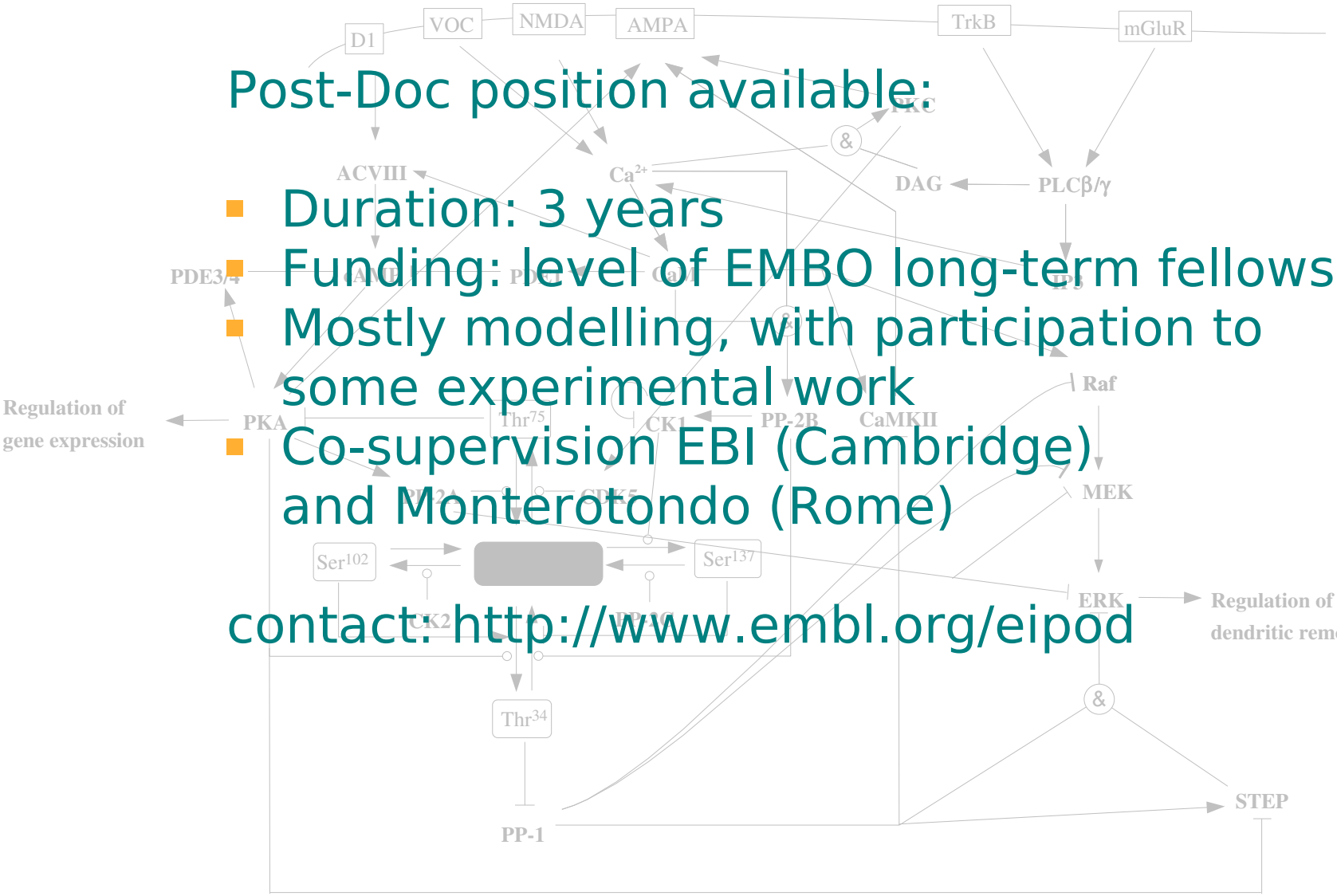
Future



Collaboration

Liliana Minichiello, Monterotondo

Future



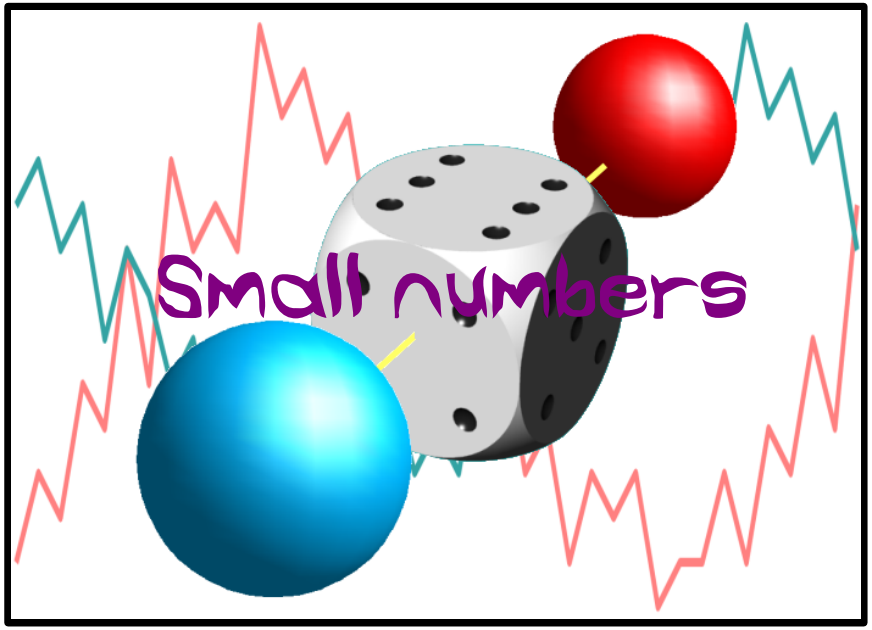
Post-Doc position available:

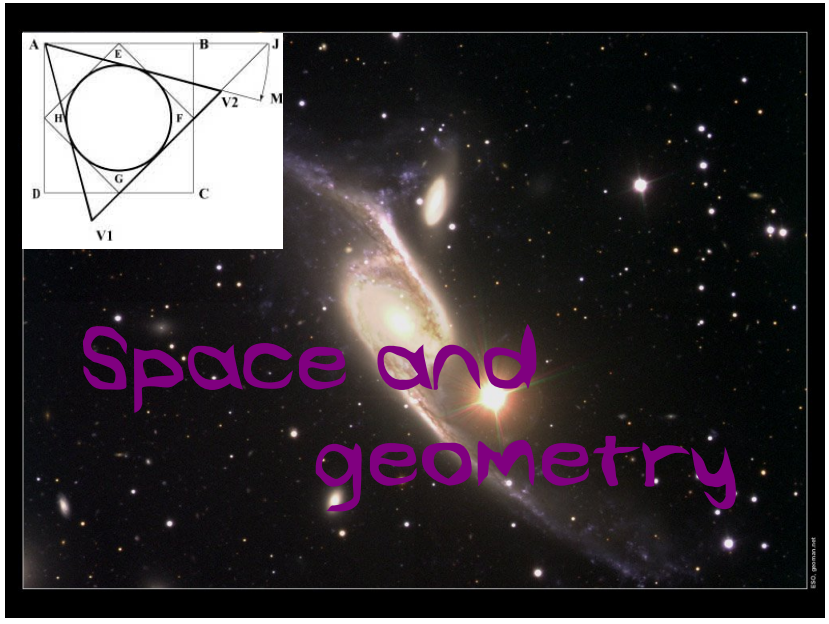
- Duration: 3 years
- Funding: level of EMBO long-term fellowship
- Mostly modelling, with participation to some experimental work
- Co-supervision EBI (Cambridge) and Monterotondo (Rome)

contact: http://www.embl.org/eipod

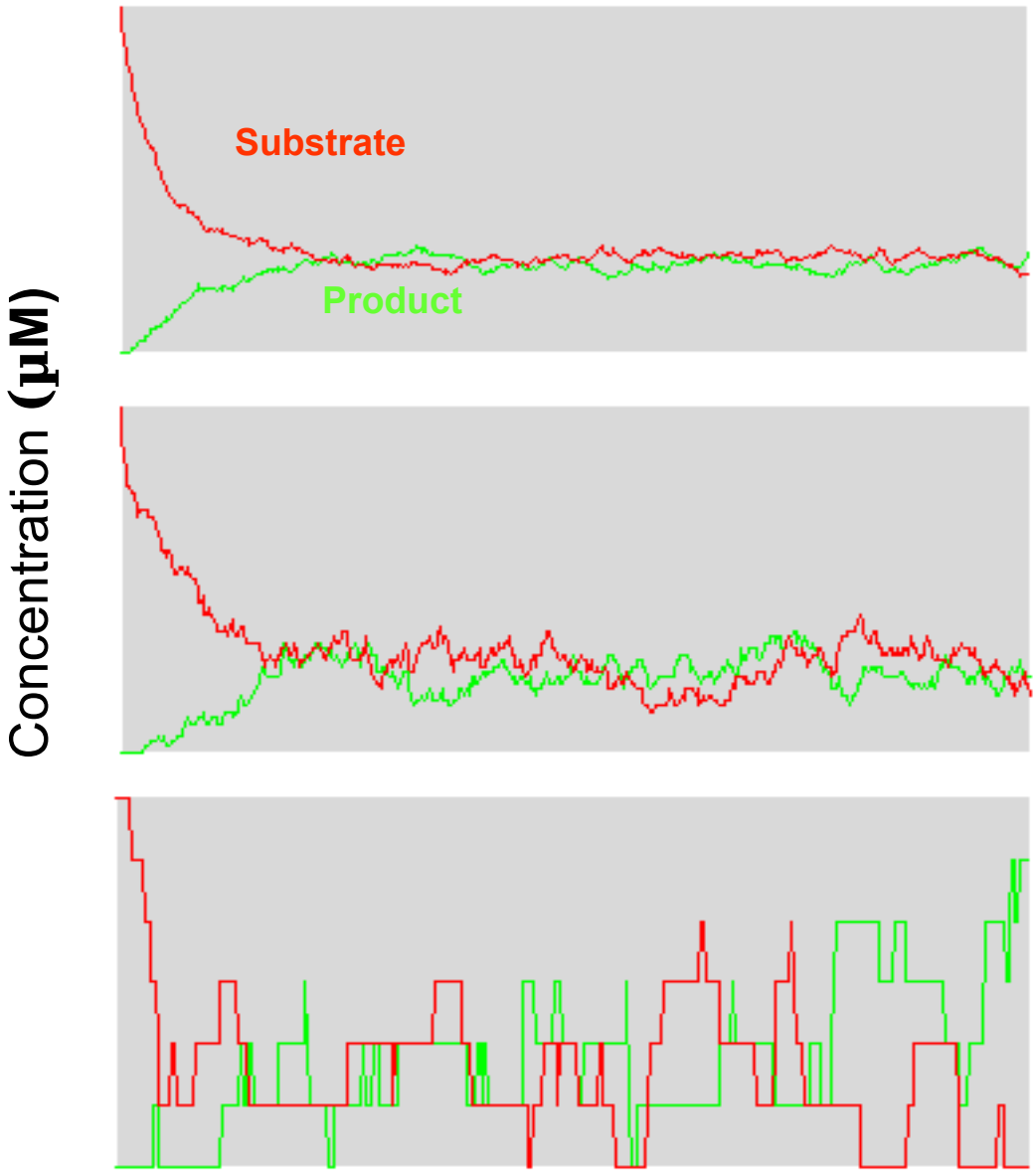
Collaboration
Liliana Minichiello, Monterotondo

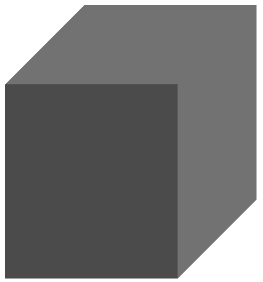
The three curses of modelling signalling





On small numbers





10^{-15} litres

10^{-16} litres

10^{-17} litres

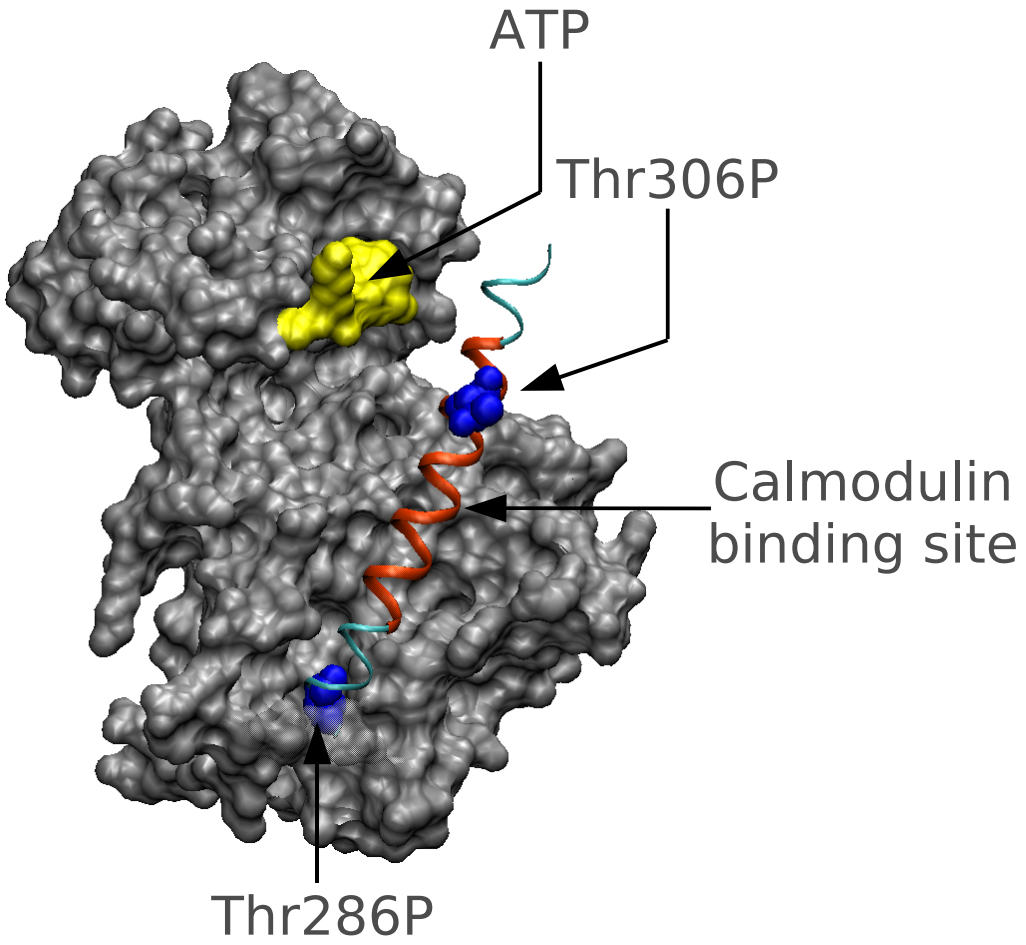
Small numbers in the dendritic spine

In a system with n components, the noise increases according to $\sqrt{n}$

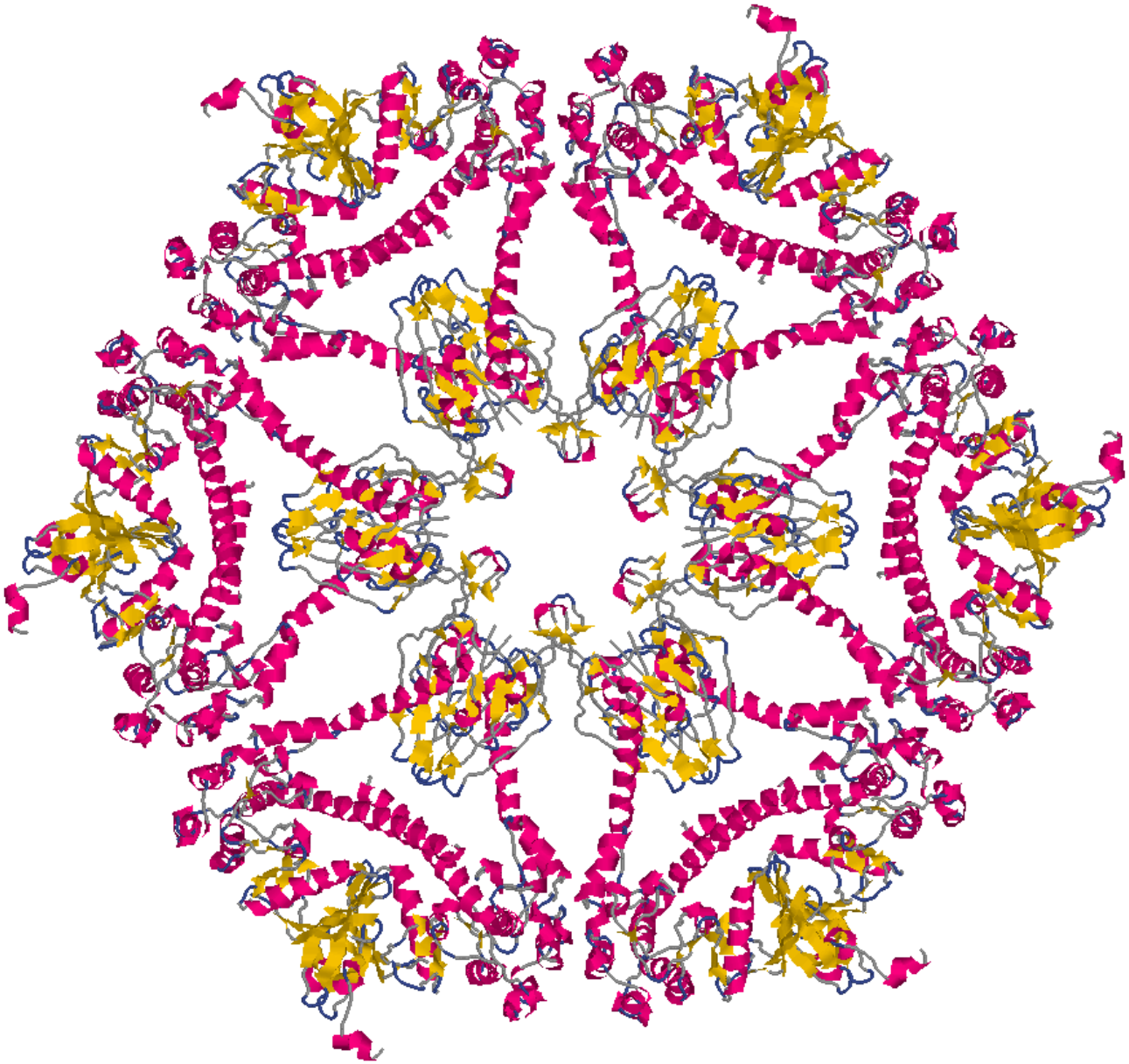
- number of AMPA receptors in a PSD: 50-100
- most kinases and phosphatases $\propto$ 100
- number of free calcium ions per spine at resting state: 5-50

$\Rightarrow$ Impact of the noise (random fluctuations) is significant!

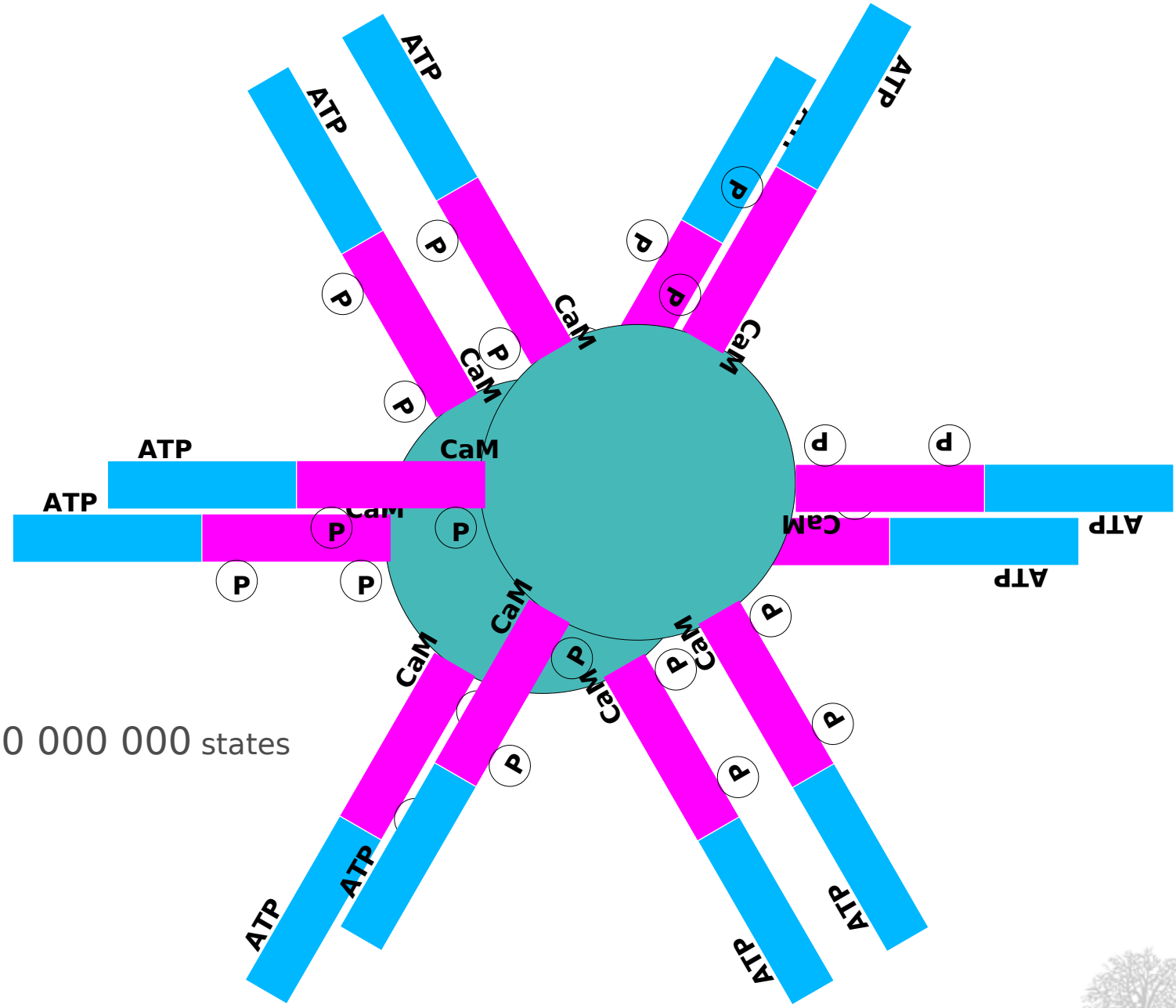
Multiple state-variables



Polymeric assemblies



Combinatorial explosion

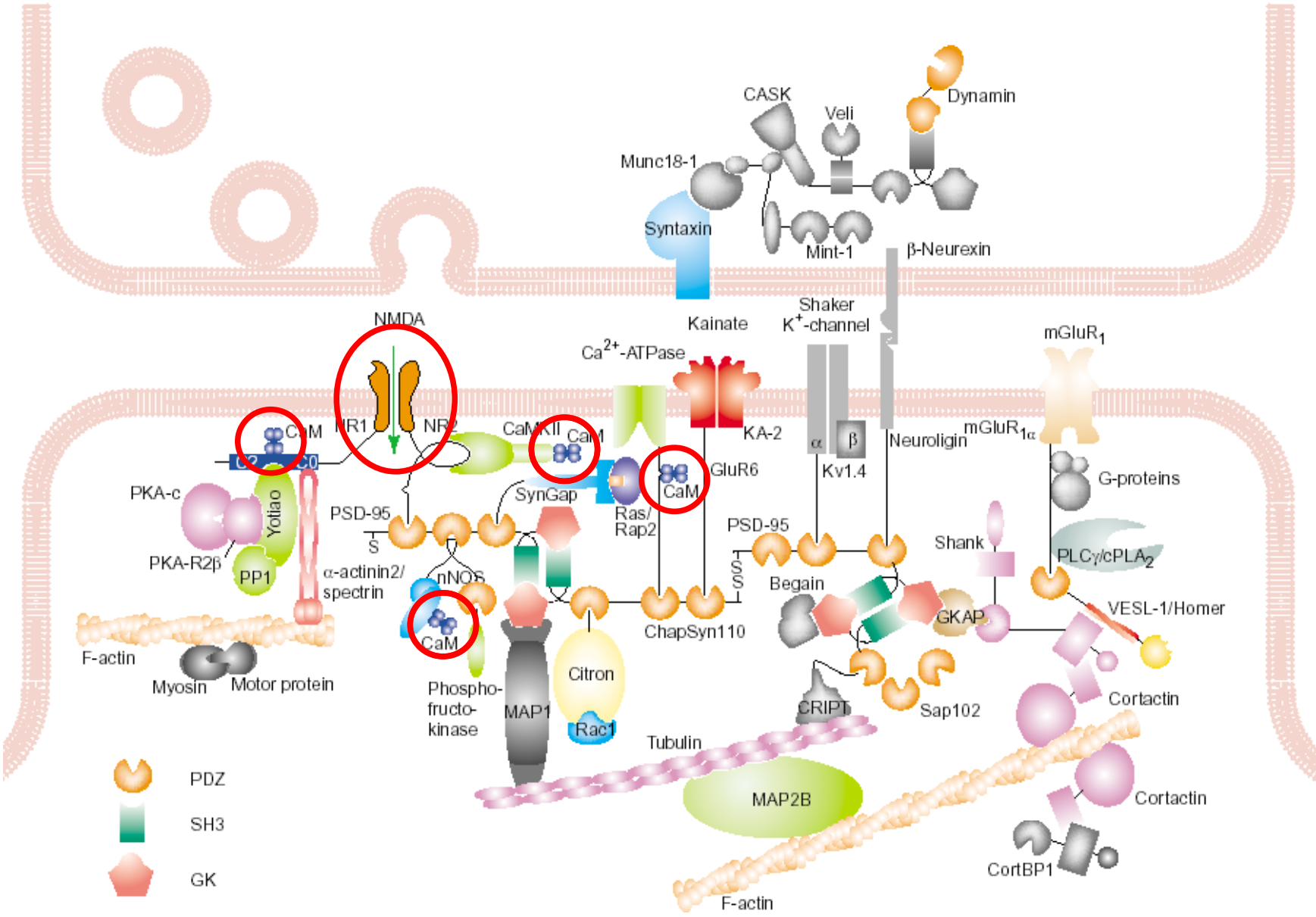


5x12 state variables=

1 152 900 000 000 000 000 states

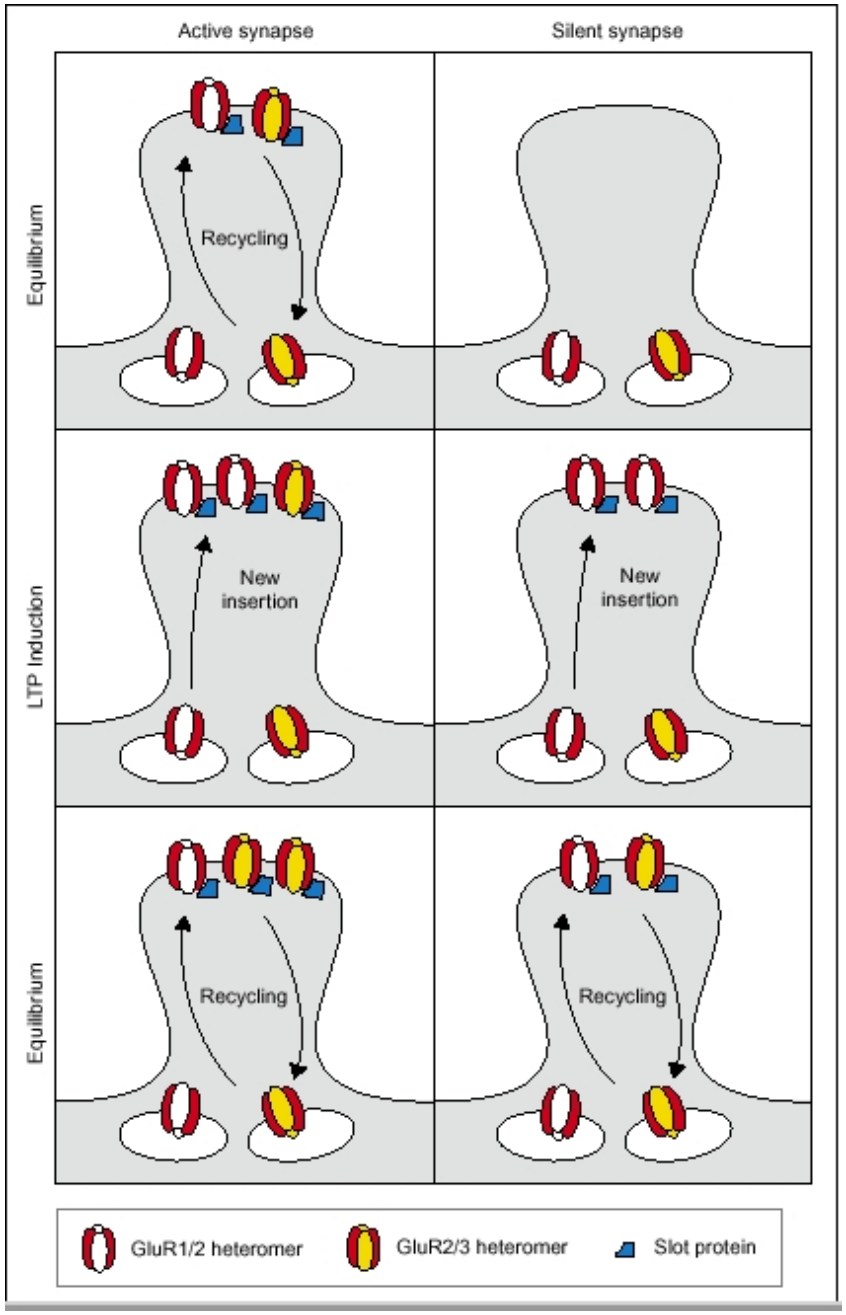
(1 billion of billion)

Complex post-synaptic machinery

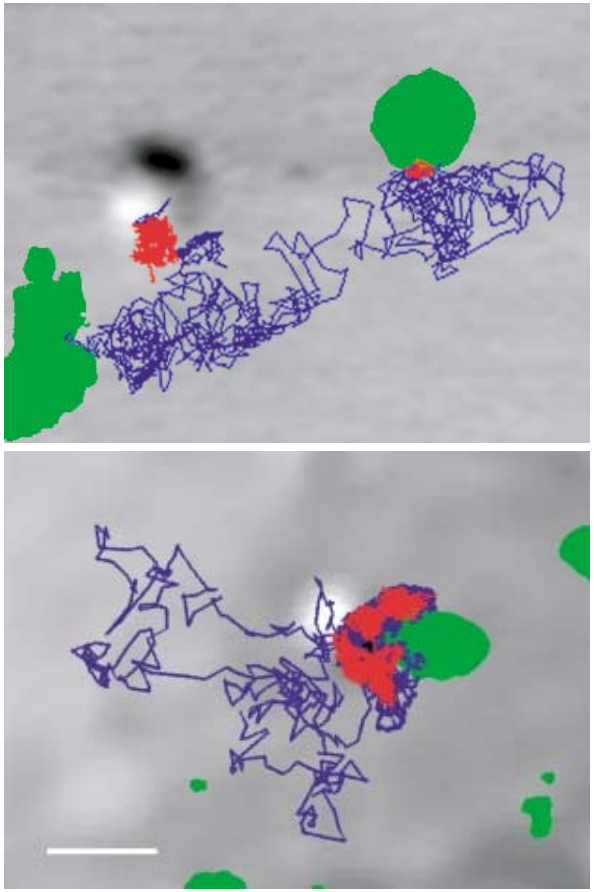


Husi & Grant (2001) *TINS, 24*: 259-266

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 for 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

Agent-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, Bray. Predicting temporal fluctuations in an intracellular signalling pathway. *J Theor Biol* 1998, 192: 117–128.
- Le Novère, Shimizu. StochSim: modelling of stochastic biomolecular processes. *Bioinformatics* 2001, 17: 575-576

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

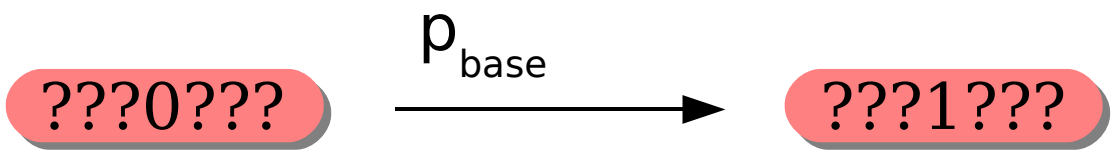
Kinetic constant to probability

$$d[A]/dt = -k[A][B] \qquad P = \frac{k\, n(n+n_0)\Delta t}{2VN_A}$$

$$d[A]/dt = -k[A] \qquad P = \frac{k\, n(n+n_0)\Delta t}{n_0}$$

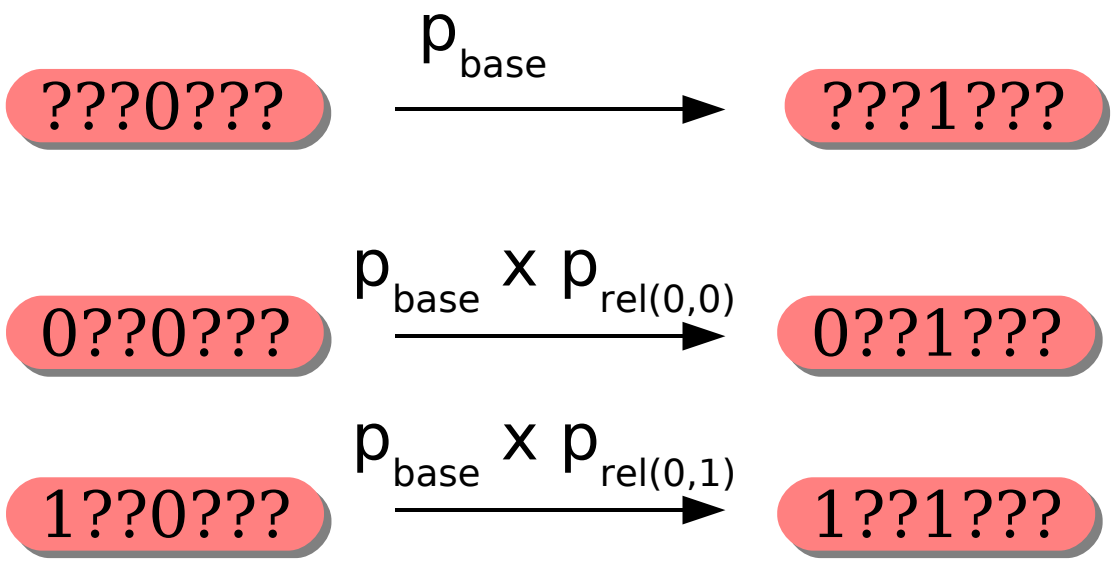
n: # molecules in the system
n_0: # pseudomolecules in the system
V: volume of the system
N_A: Avogadro constant

Multistate reactions



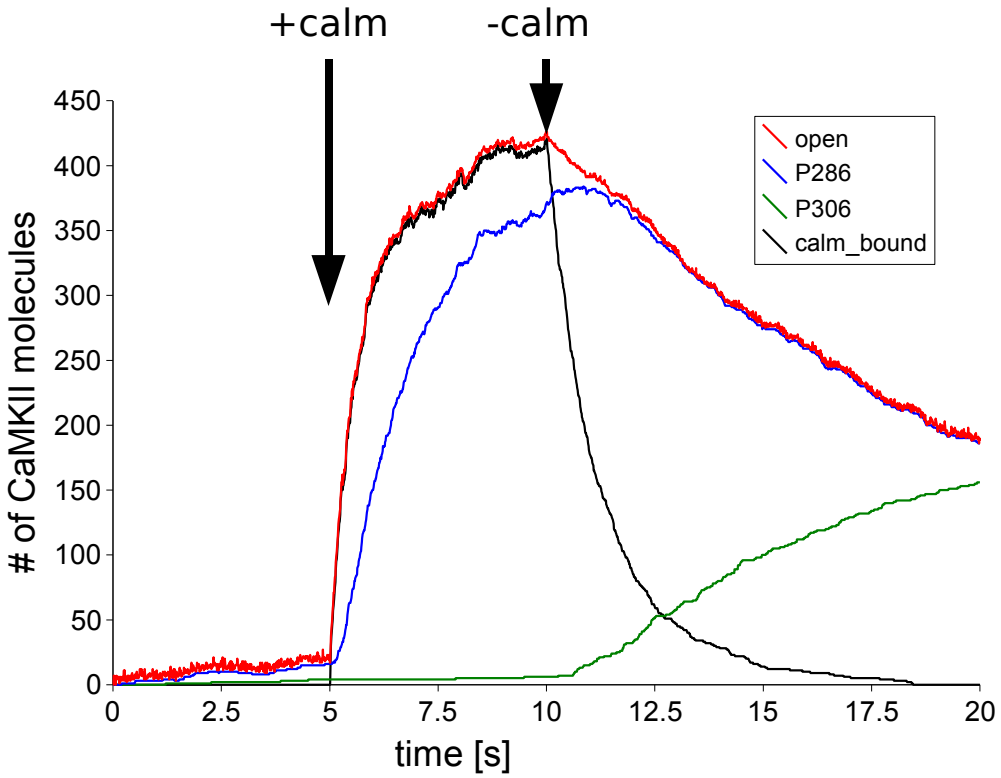
- '?' Flags do not affect the reaction

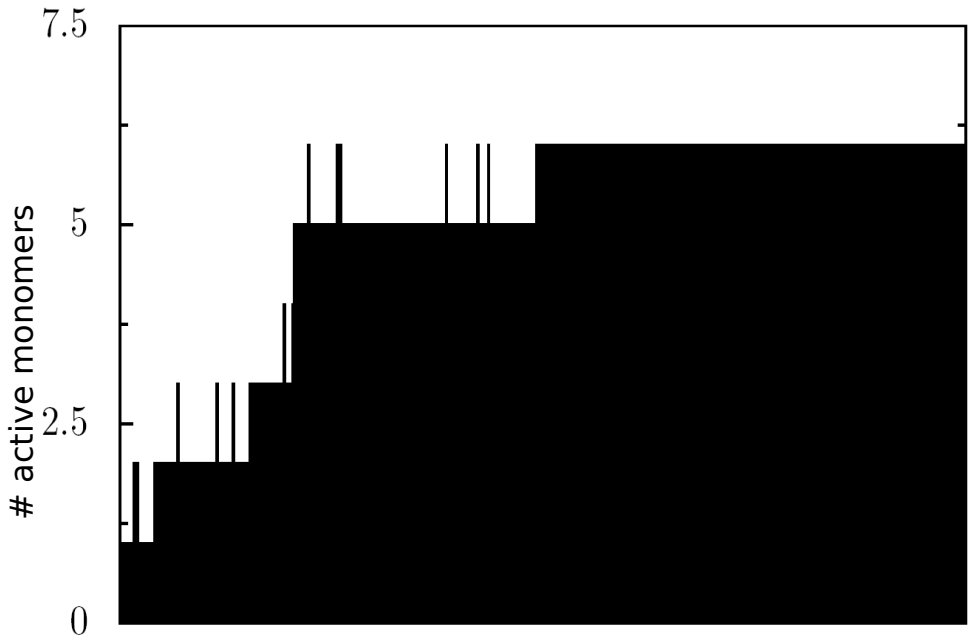
Multistate reactions



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

Simulation of ca/calmoduline kinase II



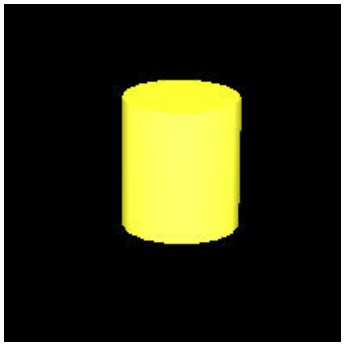


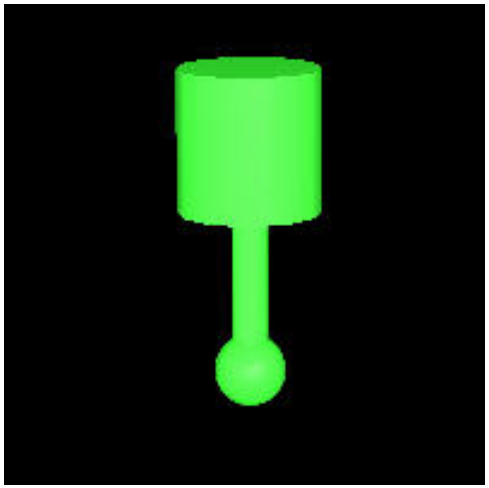
Meredys: Mesoscopic reaction-diffusion

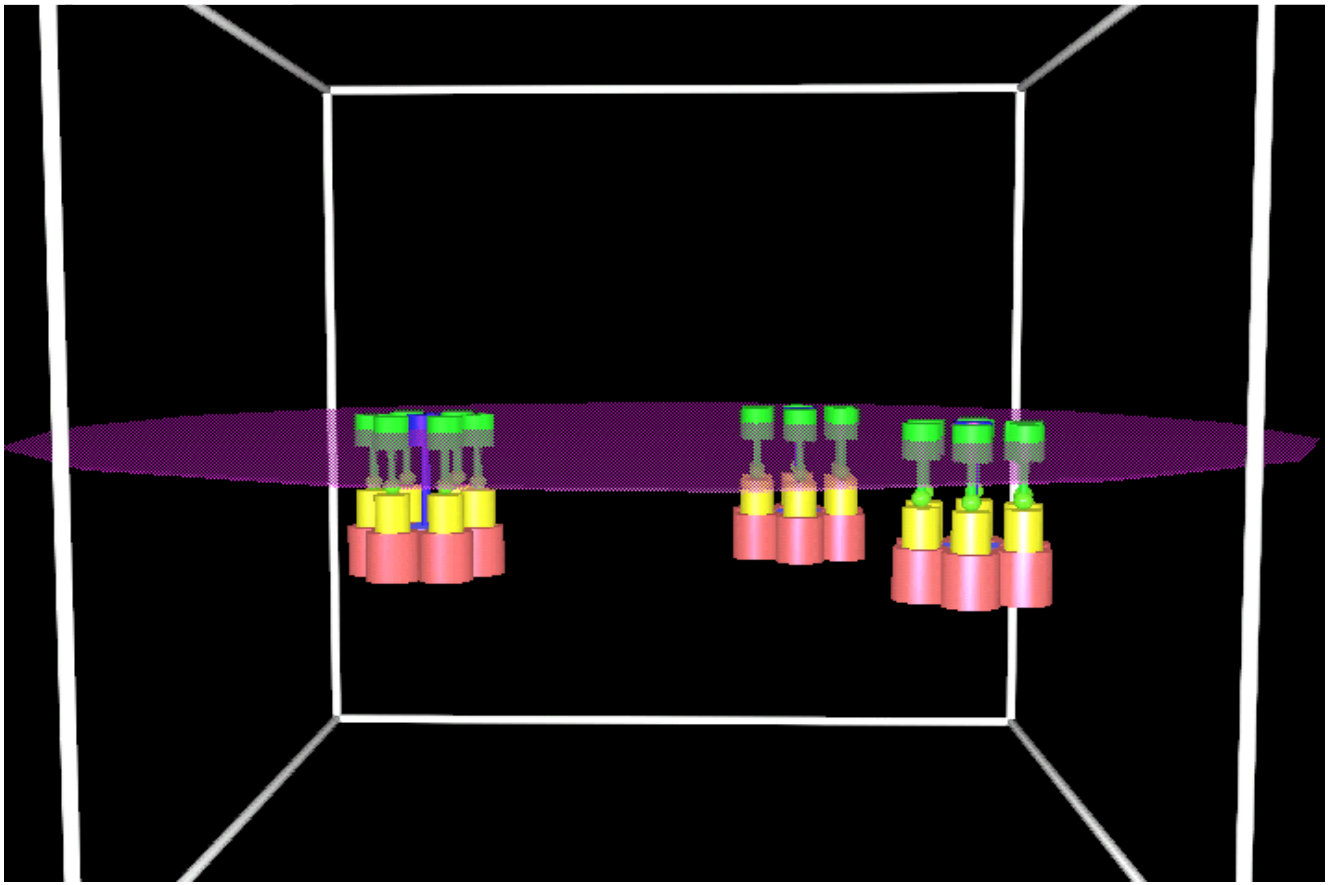
- Tolle and Le Novère (2006) Particle-based Stochastic Simulation in Systems Biology. *Current Bioinformatics, 1: 315-320*

- Agent-based stochastic simulations
- Possibility of transient complexes
- Multistate entities
- Diffusion in real space

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

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 $\bar{\theta}^2 = 2D_R t = 2\mathrm{kb}_R t$
- 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

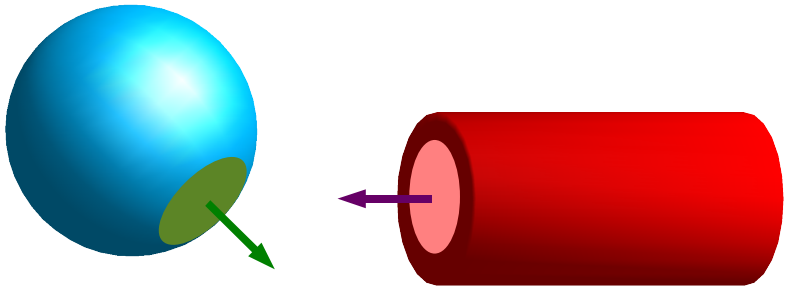
- Unrestricted brownian motion – Low Translation/Rotational

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

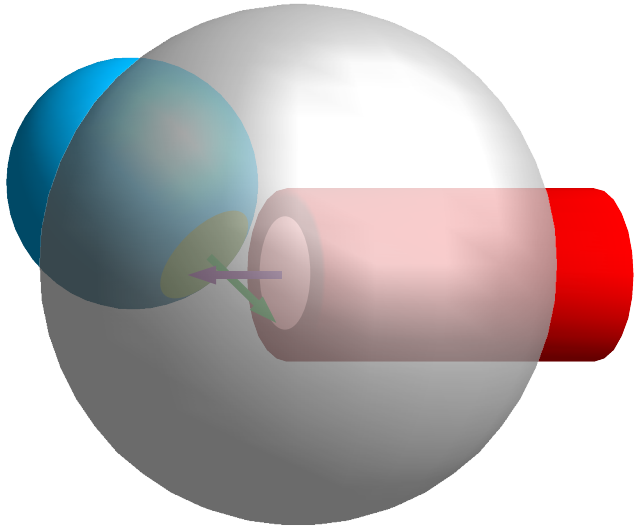
- Intra-membrane diffusion (Saffman and Delbrück 1975)
  High Translational/Rotational

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

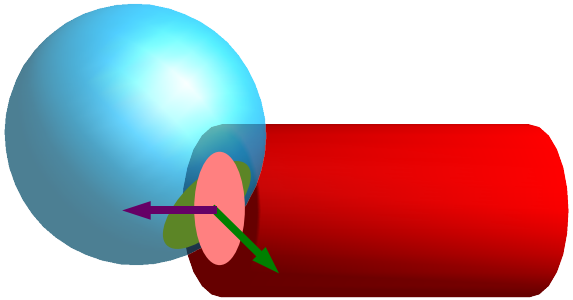
Reactions and complex formation



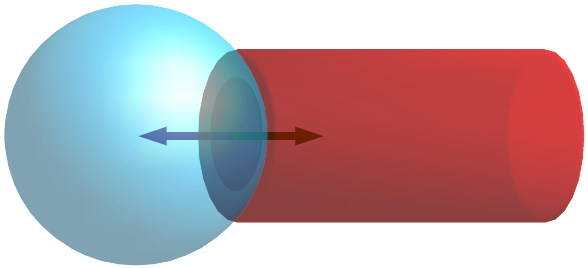
Reactions and complex formation



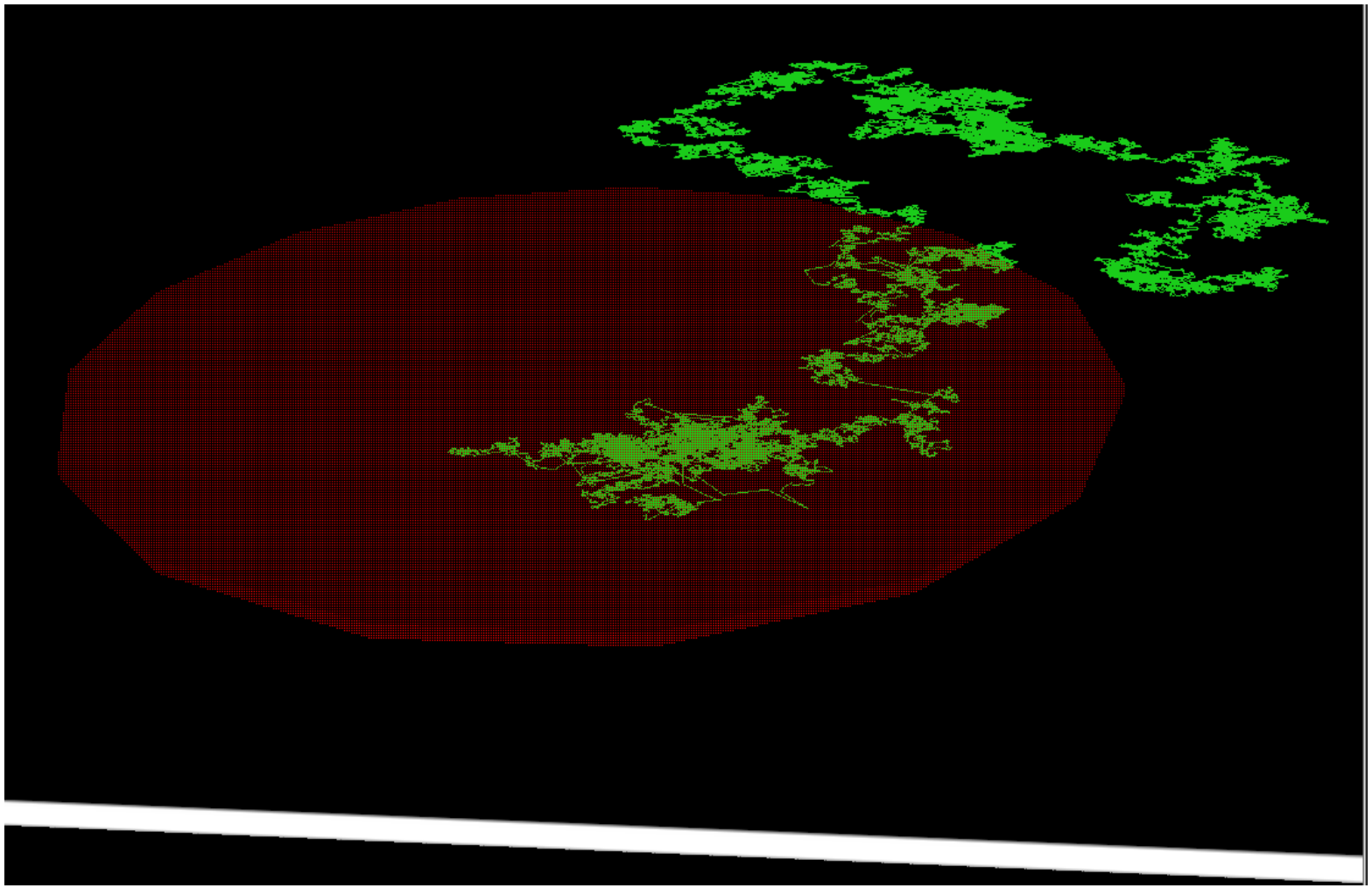
Reactions and complex formation

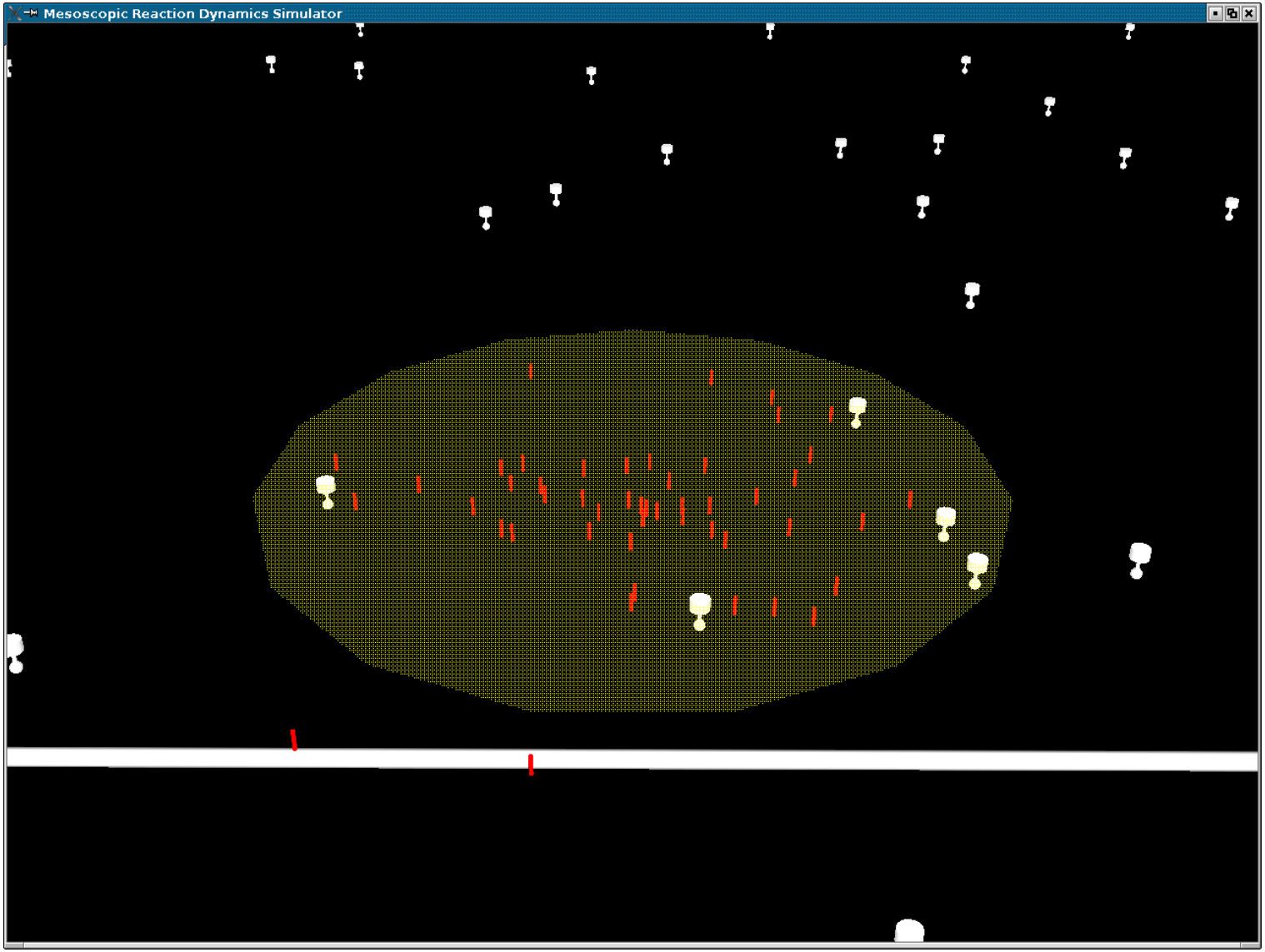


Reactions and complex formation



Mesoscopic simulations of receptor diffusion




Mesoscopic Reaction Dynamics Simulator

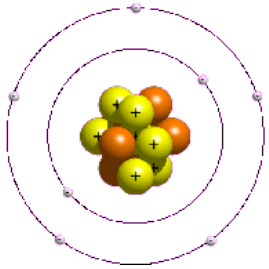
EMBL-EBI

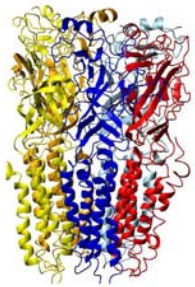
What does CSB aim to achieve?

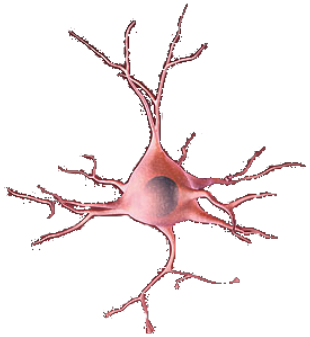
What does CSB aim to achieve?

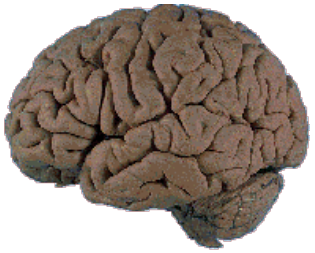
10^{-10} 10^{-8} 10^{-7} 10^{-5} 10^{-2} 10^{-0} m

spatial scale problem





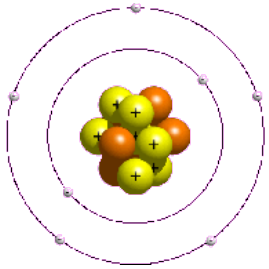
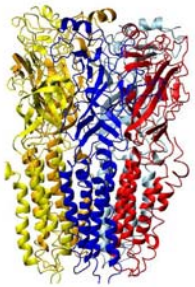
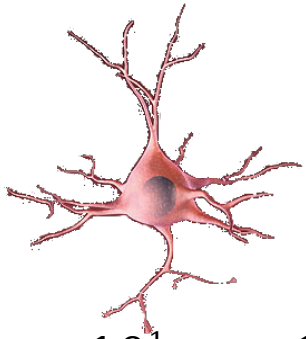
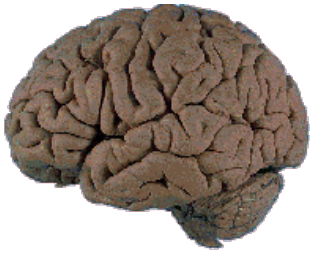




What does CSB aim to achieve?

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

spatial scale problem

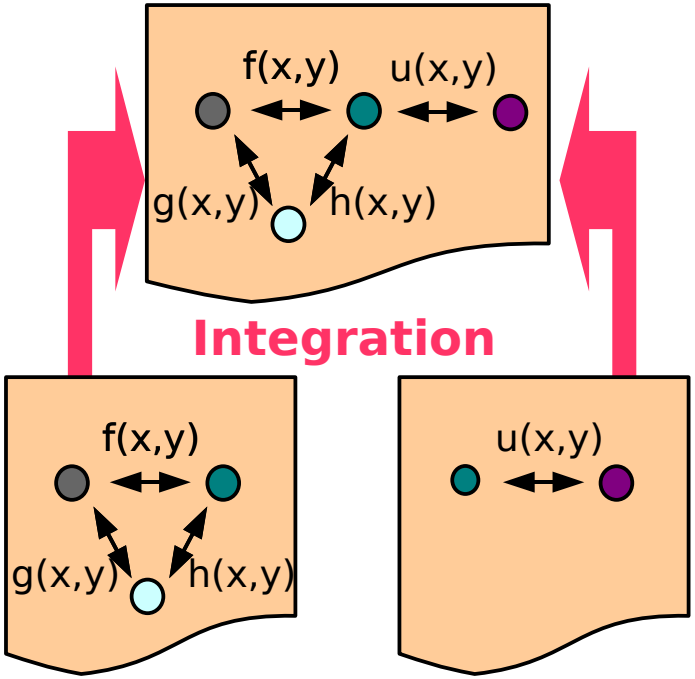

10^{-12} 10^{-6} 10^{-1} 10^{1} 10^{3} 10^{5} 10^{7} 10^{9} s

time scale problem

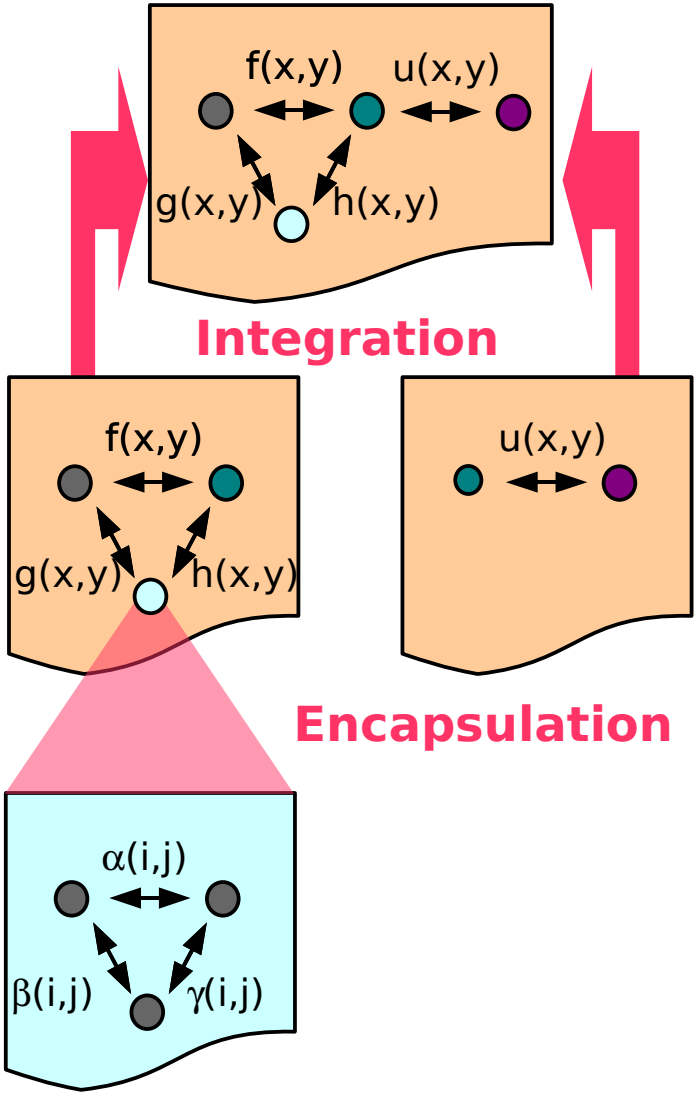
molecular dynamics
conformational transition
molecule diffusion
nerve signal
signalling cascade
gene regulation
circadian rhythm
cell cycle
reproduction
life cycle

Technical bottlenecks

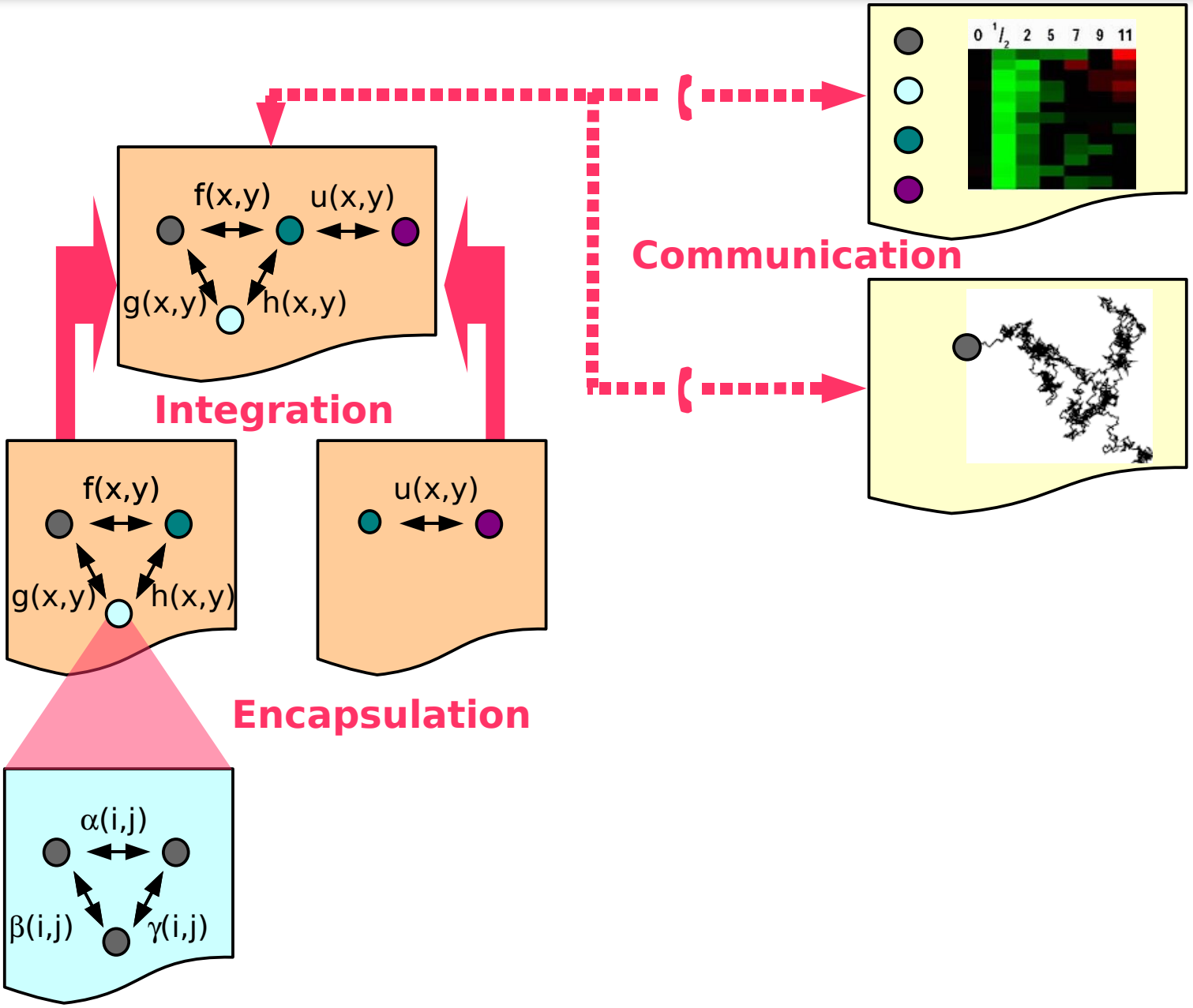
Technical bottlenecks



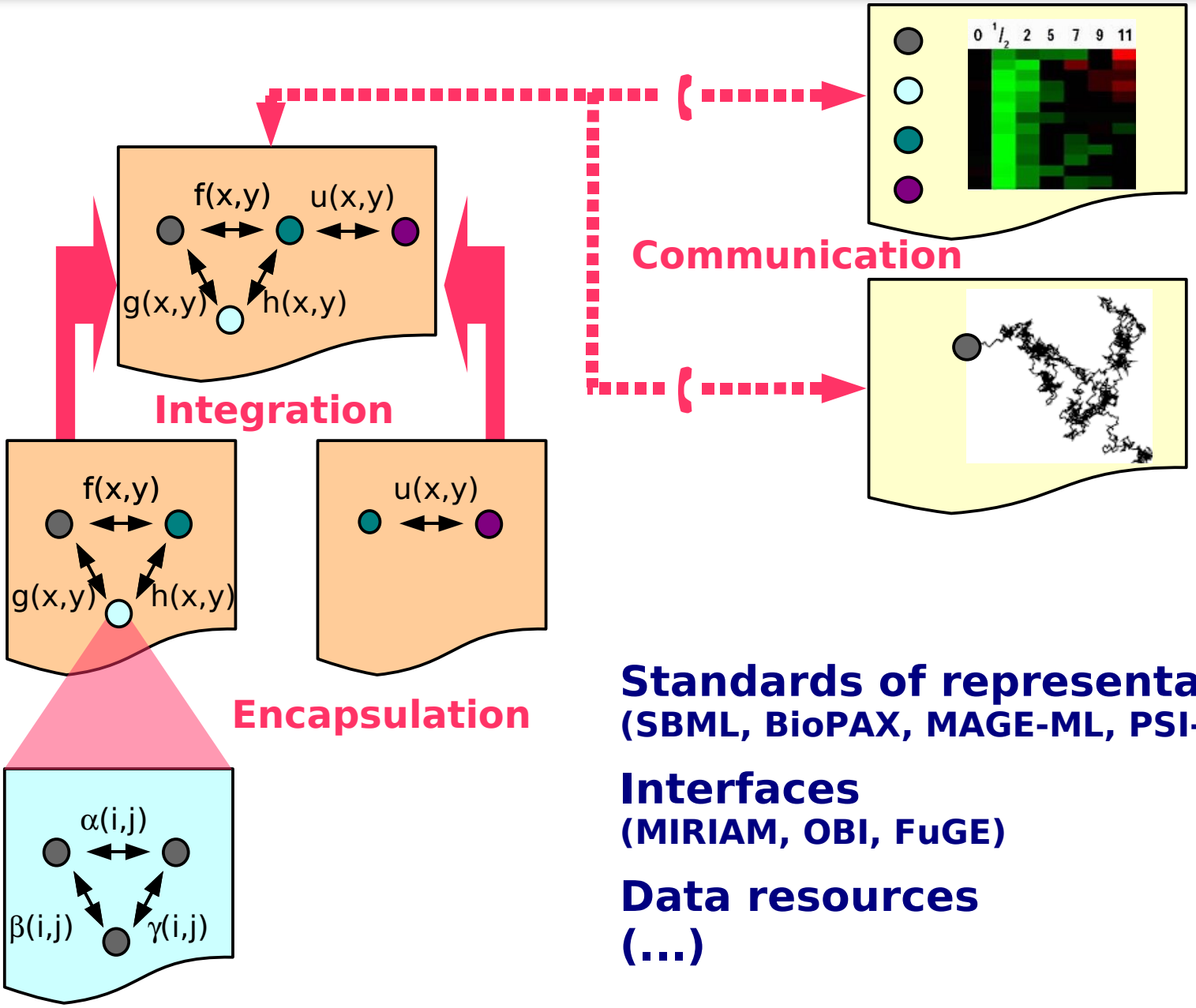
Technical bottlenecks



Technical bottlenecks



How to address them



Standards of representation
(SBML, BioPAX, MAGE-ML, PSI-MI etc.)

Interfaces
(MIRIAM, OBI, FuGE)

Data resources
(...)

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.

What is SBML?

"*The goal of SBML is to help people to disagree as precisely as possible*". Ed Franck, Argonne National Laboratory

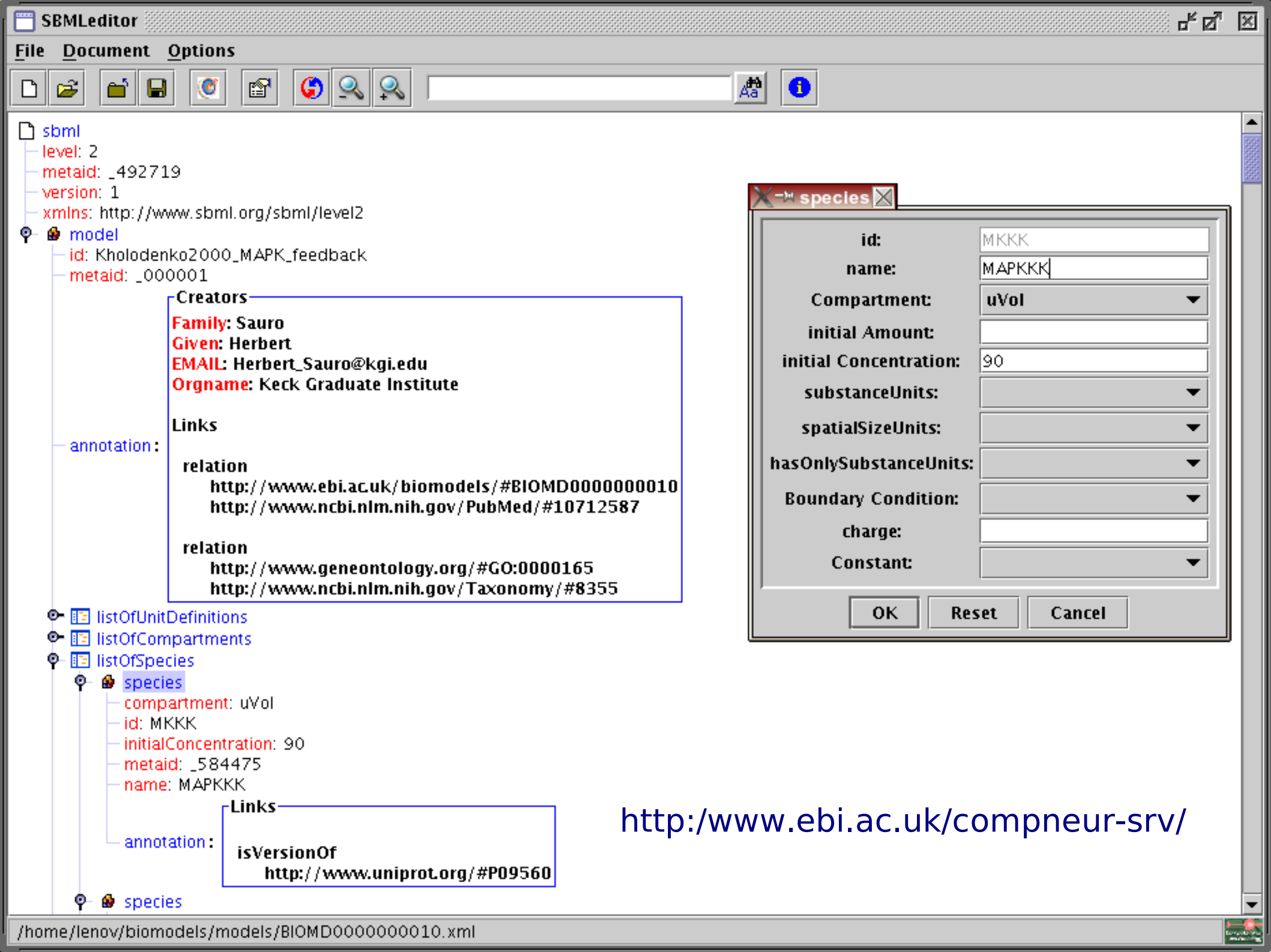
What is SBML?

SBML is a computer readable format for representing models describing the dynamical behaviour of biological entities

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

A more realistic example ...

```
<species
    id="A"
    name="α-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="http://www.uniprot.org/#P68370"/>
            <rdf:li rdf:resource="http://www.geneontology.org/#GO:0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```


SBMLeditor
File Document Options
sbml
level: 2
metaid: _492719
version: 1
xmlns: http://www.sbml.org/sbml/level2
model
id: Kholodenko2000_MAPK_feedback
metaid: _000001
Creators
Family: Sauro
Given: Herbert
EMAIL: Herbert_Sauro@kgi.edu
Orgname: Keck Graduate Institute
Links
annotation:
relation
http://www.ebi.ac.uk/biomodels/#BIOMD0000000010
http://www.ncbi.nlm.nih.gov/PubMed/#10712587
relation
http://www.geneontology.org/#GO:0000165
http://www.ncbi.nlm.nih.gov/Taxonomy/#8355
listOfUnitDefinitions
listOfCompartments
listOfSpecies
species
compartment: uVol
id: MKKK
initialConcentration: 90
metaid: _584475
name: MAPKKK
Links
annotation:
isVersionOf
http://www.uniprot.org/#P09560
species
species
id: MKKK
name: MAPKKK
Compartment: uVol
initial Amount:
initial Concentration: 90
substanceUnits:
spatialSizeUnits:
hasOnlySubstanceUnits:
Boundary Condition:
charge:
Constant:
OK
Reset
Cancel
http:/www.ebi.ac.uk/compneur-srv/
/home/lenov/biomodels/models/BIOMD0000000010.xml

SBML is not limited to biochemistry!

- Rate Rules can describe the temporal evolution of any quantitative parameter, e.g. transmembrane voltage;
- Events can describe any discontinuous change, e.g. neurotransmitter release;
- A species is an entity participating to a reaction, **not always** a **chemical** entity:
  - It can be a molecule
  - It can be a cell
  - It can be an organ
  - It can be an organism

➔ Remember, Systems Biology is scale-free!

New: SBML Level 2 Version 3

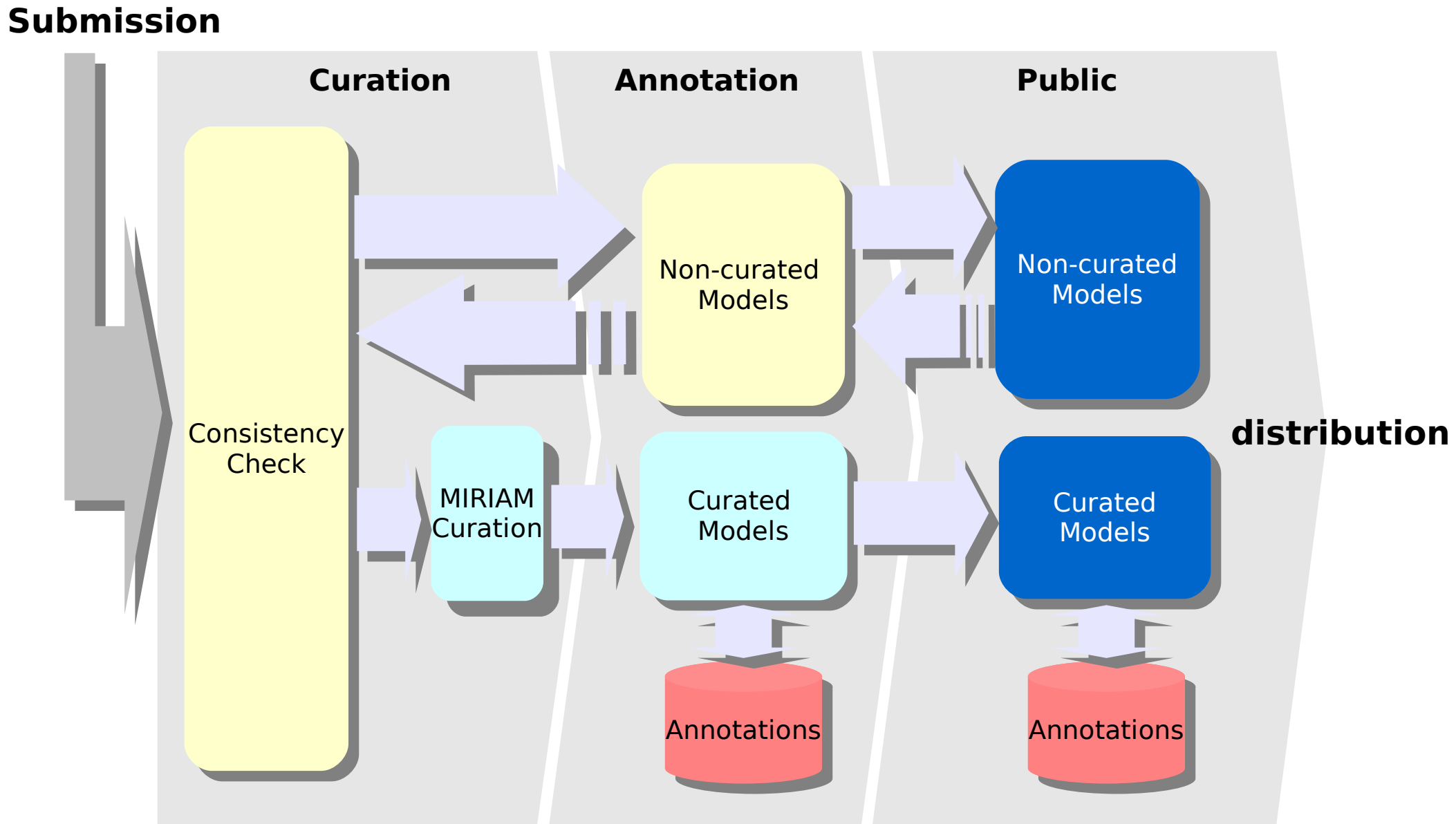
Hucka M, Finney AM, Hoops S, Keating SM, Le Novère N (2007)
Systems Biology Markup Language (SBML) Level 2:
Structures and Facilities for Model Definitions.

- Released on June 16th 2007
- Simpler and cleaner (units ...)
- Generic entities (compartmentType, speciesType)
  ➔ path to generalised reactions
- Constraints and initialAssignments
- Controlled annotations (MIRIAM + SBO)
- Backward compatible with Level 2 Version 1
- More detailed and bug-free specification ... 164 pages, 10pt, small margin!

BioModels Database

- Store and serve quantitative models of biomedical interest
- Only models described in the peer-reviewed scientific literature.
- Models are curated: computer software check the syntax, while human curators check the semantics.
- Models are simulated to check the reference correspondence
- Model components are annotated, to improve identification and retrieval.
- Models are accepted in several formats, and served in several others.
- Aims to be the “UniProt” of quantitative modelling.

Production pipeline



BioModels

- Curated Models
- Non-curated Models
- Search
- Simulate in JWS

- Submit Your Model

- Sign-in

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- Model of the Month
- Meetings
- Support
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BIOMODELS.NET

Computational Neurobiology | SBML | DOQCS Database of Quantitative Cellular Signaling | SBW | SBI | JWS online

BioModels Database

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

A Database of Annotated Published Models

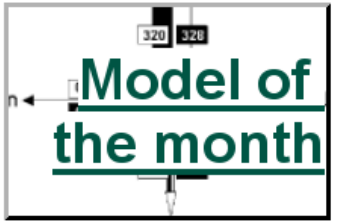
BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways, controlled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



Acknowledgements

BioModels Database is developed by the teams of Nicolas Le Novère (EMBL-EBI, United-Kingdom) and Michael Hucka (SBML Team, Caltech, USA) in collaboration with Upinder Bhalla (DOQCS, National Center for Biological Sciences, India), Herbert Sauro (Keck Graduate Institute, USA), Hiroaki Kitano (Systems Biology Institute, Japan), Hans Westerhoff and Jacky Snoep (JWS Online, Stellenbosch (ZA) and Manchester (UK) Universities and Stellenbosh University, ZA), as part of the BioModels.net initiative. BioModels Database development has benefitted from funds of the European Molecular Biology Laboratory (Le Novère team), the National Institute of General Medical Sciences (SBML team), and the DARPA (Sauro team)

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)

External contributors: BioModels Database would not exists without the continuous support of many people, whether by their contribution of models, of software, or by their constructive comments and criticisms. It is unfortunately impossible to acknowledge all of them here, without risking to be unfair. Therefore, a big collective thank-you all.

BioModels Database is built thanks to many third-party free software such as libSBML, Jakarta Tomcat, Xindice, Lucene, Xalan, Xerces, Axis, Jena and MySQL, plus all the free software coming with the GNU/Linux systems.

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

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BIOMODELS.NET

JWS online

Search - Models

Text Search

You can search BioModels Database for models using one or more of the following criteria:

- *BioModels ID* → Search BioModels Database for *exact* BioModels identifiers (for example *BIOMD0000000001* or *BIOMD0000000022*).
- *Person* → Search BioModels Database for model submitter and/or creator(s) names, or model reference publication author(s) names (for example *Nicolas Le Novère*, *Nicolas*, *Bruce Shapiro* or *Shapiro*, *Edelstein* or *Novak*).
- *SBML Elements* → Search BioModels Database using the content of either "name" or "*notes*" SBML elements (for example *Edelstein* or *nicotinic*). Select the checkbox behind, if you want to find documents which matches the exact phrase; otherwise, all words will be searched as default.
- *Resource* → Search BioModels Database for related information found in the models reference publication or third-party resources, by either publication/resource identifier or text (for example *9256450* or *cyclin* for publication, *GO:0007049* or *cell cycle* for Gene Ontology, *P04551* or *cell division* for UniProt).
- *Resource ID* → Search BioModels Database for annotations, by third-party resource identifiers (for example *IPR002394* for InterPro, *hsa04080* for KEGG Pathway, *68910* for Reactome).

A part from the *BioModels ID* -based search, for every other criteria the search operates on a *contains the entered string basis*, case-insensitive. That is, searching *Person* for *Shapi* or *shapi* will return the same results as searching for *Shapiro* or *shapiro*. In addition, since search strings are treated as words, do not enter regular expressions.

Multiple criteria can be combined with either *and* or *or*. If *and* is selected, only those models satisfying all the criteria will be returned. If instead *or* is selected, all the models satisfying at least one of the criteria will be returned.

BioModels ID:

Person:

SBML Elements: ☐ match the **exact phrase**

Resource: Gene Ontology — map kinase

Resource:

Resource:

Publication
ChEBI
Gene Ontology
Taxonomy
UniProt

Resource ID:

Resource ID: BIND

Resource ID: BIND

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BIOMODELS.NET

Computational Neurobiology

SBML

DOQCS Database of Quantitative Cellular Signaling

SBW

SBI

JWS online

Search - Models

The search totally returned **15** models.

New Search

Show 10 Only

15 Curated Models returned.

BioModels ID	Name	Publication ID	Last Modified
BIOMD0000000009	Huang1996_MAPK_ultrasens	8816754	2006-12-29T00:54:48
BIOMD0000000010	Kholodenko2000_MAPK_feedback	10712587	2007-01-10T10:35:07
BIOMD0000000011	Levchenko2000_MAPK_noScaffold	10823939	2007-01-10T10:22:40
BIOMD0000000014	Levchenko2000_MAPK_Scaffold	10823939	2007-01-26T22:30:39
BIOMD0000000026	Markevich2004_MAPK_orderedElementary	14744999	2006-12-29T00:28:06
BIOMD0000000027	Markevich2004_MAPK_orderedMM	14744999	2006-12-29T00:28:55
BIOMD0000000028	Markevich2004_MAPK_phosphoRandomElementary	14744999	2006-12-29T00:39:36
BIOMD0000000029	Markevich2004_MAPK_phosphoRandomMM	14744999	2006-12-29T00:43:12
BIOMD0000000030	Markevich2005_MAPK_AllRandomElementary	14744999	2006-12-29T01:03:25
BIOMD0000000031	Markevich2004_MAPK_orderedMM2kinases	14744999	2006-12-29T21:41:12
BIOMD0000000032	Kofahl2004_pheromone	15300679	2007-06-08T11:42:52
BIOMD0000000033	Brown2004_NGF_EGF_signaling	14525003	2006-12-29T23:16:17
BIOMD0000000049	Sasagawa2005_MAPK	15793571	2007-03-02T23:37:04
BIOMD0000000084	Hornberg2005_ERKcascade	15634347	2007-01-03T05:59:37
BIOMD0000000099	Laub1998_SpontaneousOscillations	9843585	2007-04-30T21:59:10

New Search

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BIOMODELS.NET

BIOMD0000000010 - Kholodenko2000_MAPK_feedback

SBML L2 V1 | CellML | SciLab | XPP | BioPAX

Simulation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Graph | JWS Online

Submit Model Comment/Bug

Reference Publication

Publication ID: 10712587

Eur J Biochem 2000 Mar;267(6):1583-8.
Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades.
Kholodenko BN.
Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu [more]

Model

Original Model: *Unspecified*
Submitter: Nicolas Le Novere
Submission Date: 2005-09-13T13:39:02
Last Modification Date: 2007-01-10T10:35:07
Creation Date: 2005-02-12T00:18:12
Creators: Herbert Sauro

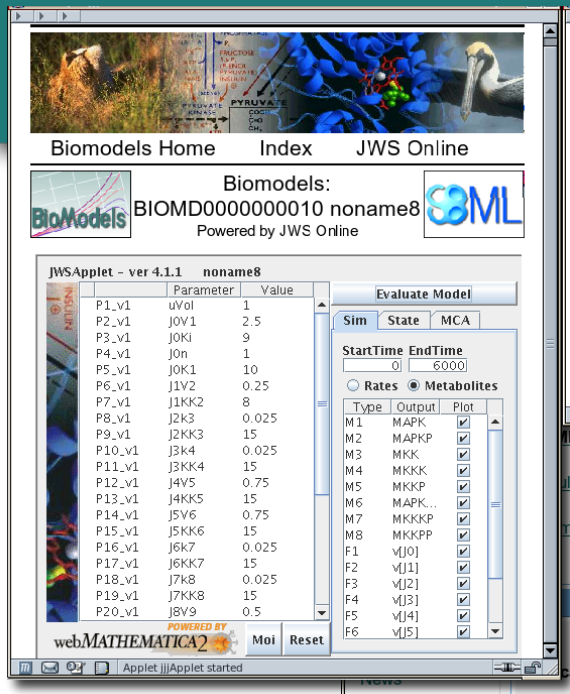
bqbiol:is	set #1	**Taxonomy**	Xenopus laevis
bqbiol:isVersionOf	set #1	**Gene Ontology**	MAPKKK cascade
bqbiol:isHomologTo	set #1	**Reactome**	REACT_634

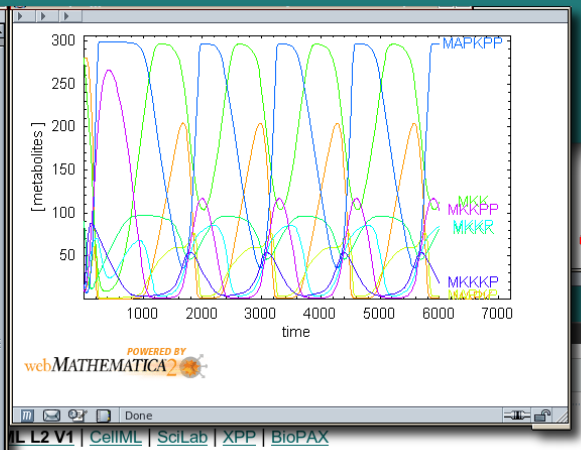
Compartments (1)

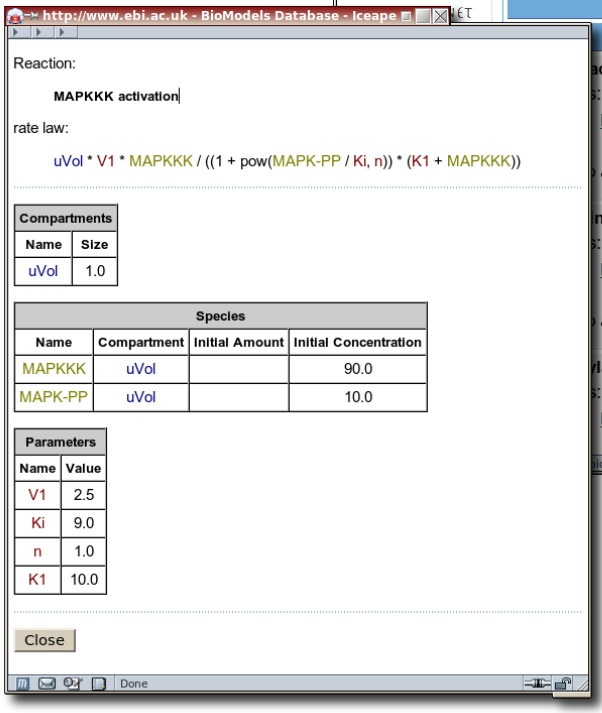
Species (8)

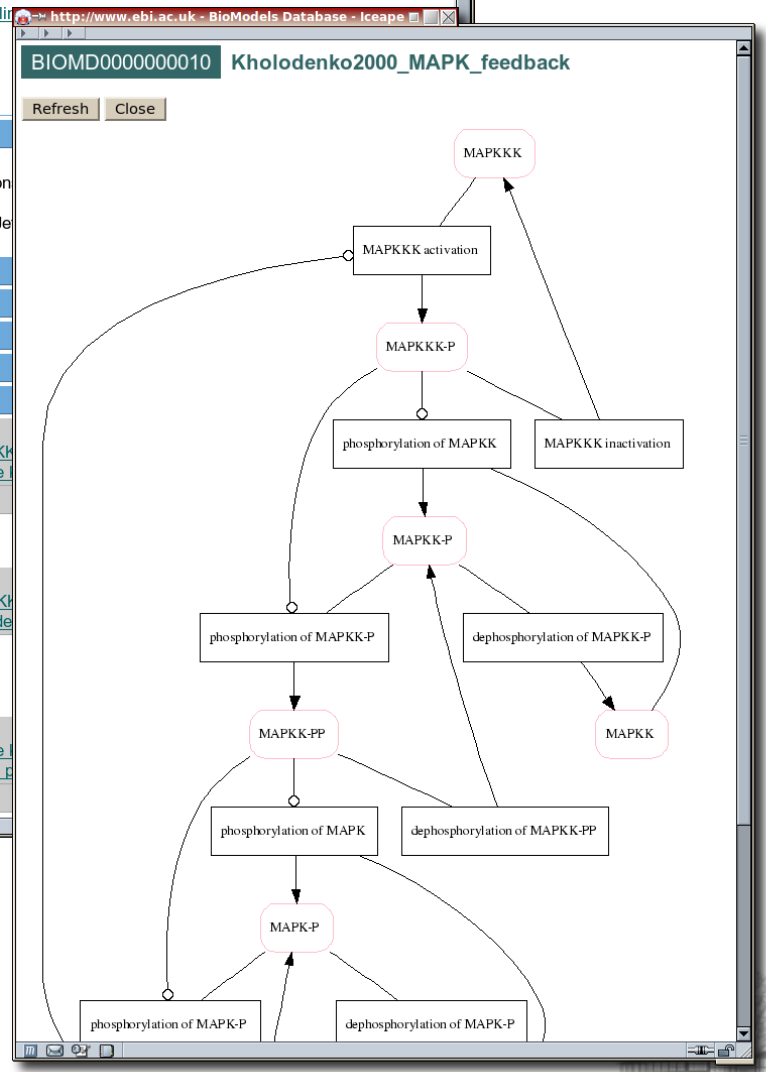
MAPKKK Compartment: uVol *Referred to as: MKKK*	bqbiol:isVersionOf	set #1	**UniProt**	RAF1_XENLA
MAPKKK-P Compartment: uVol *Referred to as: MKKK_P*	bqbiol:isVersionOf	set #1	**UniProt**	RAF1_XENLA
MAPKK Compartment: uVol *Referred to as: MKK*	bqbiol:isVersionOf	set #1	**UniProt**	MP2K1_XENLA
MAPKK-P	bqbiol:isVersionOf	set #1	**UniProt**	MP2K1_XENLA

Different views of a model









ML L2 V1 | CellML | SciLab | XPP | BioPAX

lation Result | GIF Reaction Graph | SVG Reaction Graph | Dynamic Reaction Graph | JWS Onlin

mit Model Comment/Bug

Reference Publication

cation ID: 10712587

Eur J Biochem 2000 Mar;267(6):1583-8.
Negative feedback and ultrasensitivity can bring about oscillation
Kholodenko BN.
Department of Pathology, Anatomy and Cell Biology, Thomas Je
Boris.Kholodenko@mail.tju.edu [more]

Model

Compartments (1)

Species (8)

Rules (0)

Reactions (10)

activation
MAPKKK
MAPKKK-P
MAPK-PP
as: J0

bqbiol:isVersionOf set #1 Enzyme Nomenclature 2.7.11.1
Gene Ontology activation of MAPKK
Gene Ontology MAP kinase kinase
bqbiol:isHomologTo set #1 Reactome REACT_525

inactivation
MAPKKK-P
MAPKKK
as: J1

bqbiol:isVersionOf set #1 Enzyme Nomenclature 3.1.3.16
Gene Ontology inactivation of MAPKK
Gene Ontology protein amino acid de

lation of MAPK
MAPKK
MAPKKK-P

bqbiol:isVersionOf set #1 Enzyme Nomenclature 2.7.11.25
Gene Ontology MAP kinase kinase
Gene Ontology protein amino acid p
bqbiol:isHomologTo set #1 Reactome REACT_614

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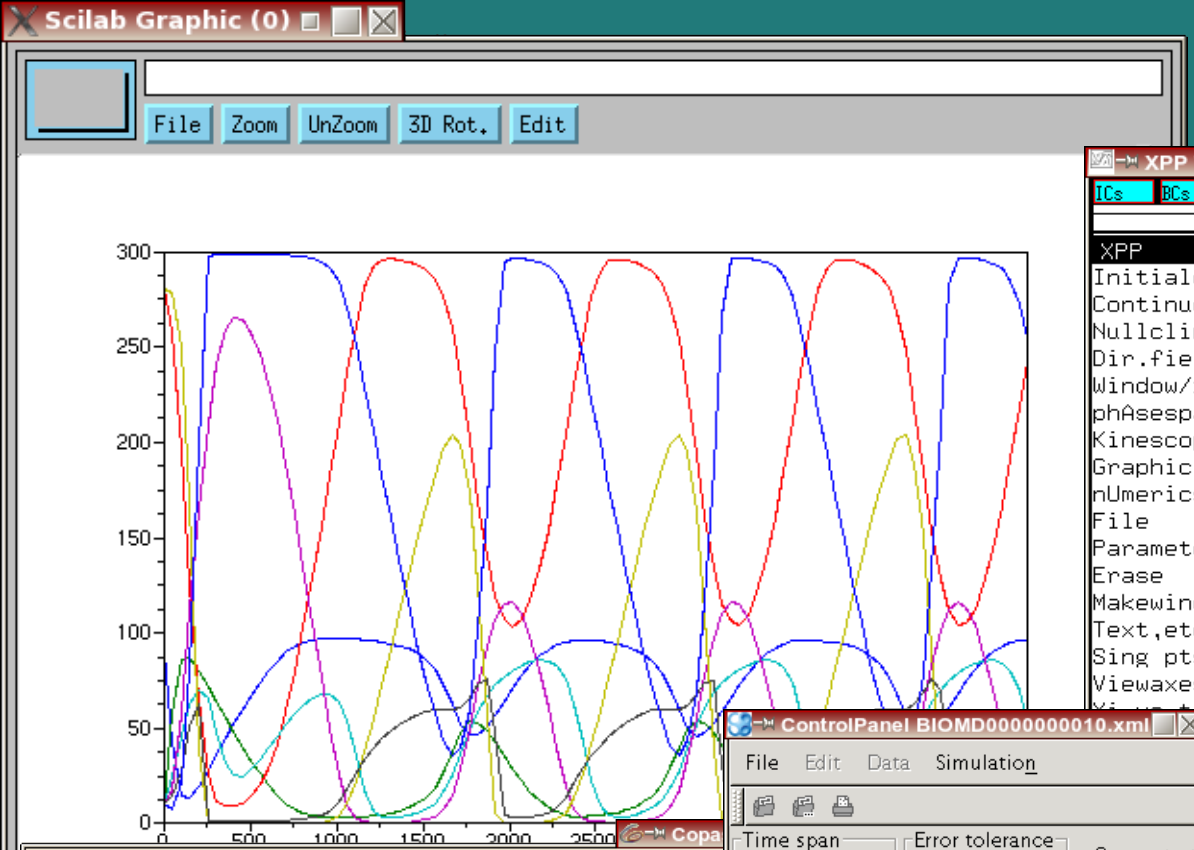
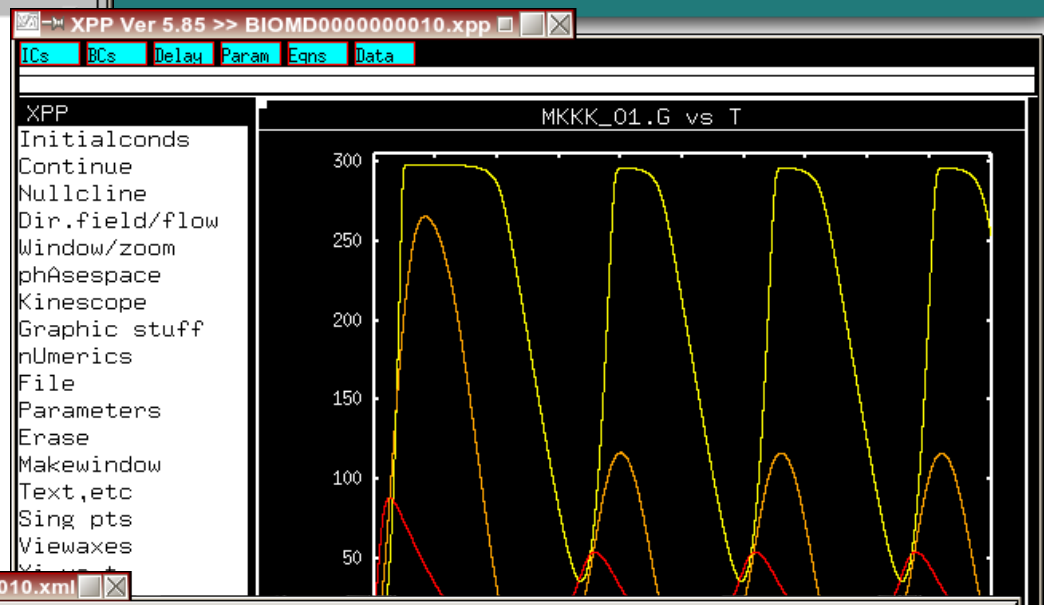
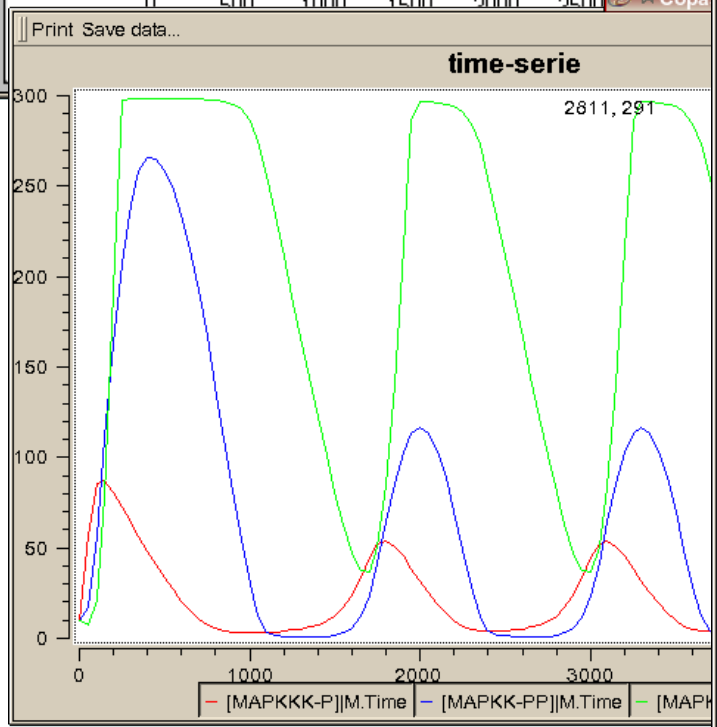
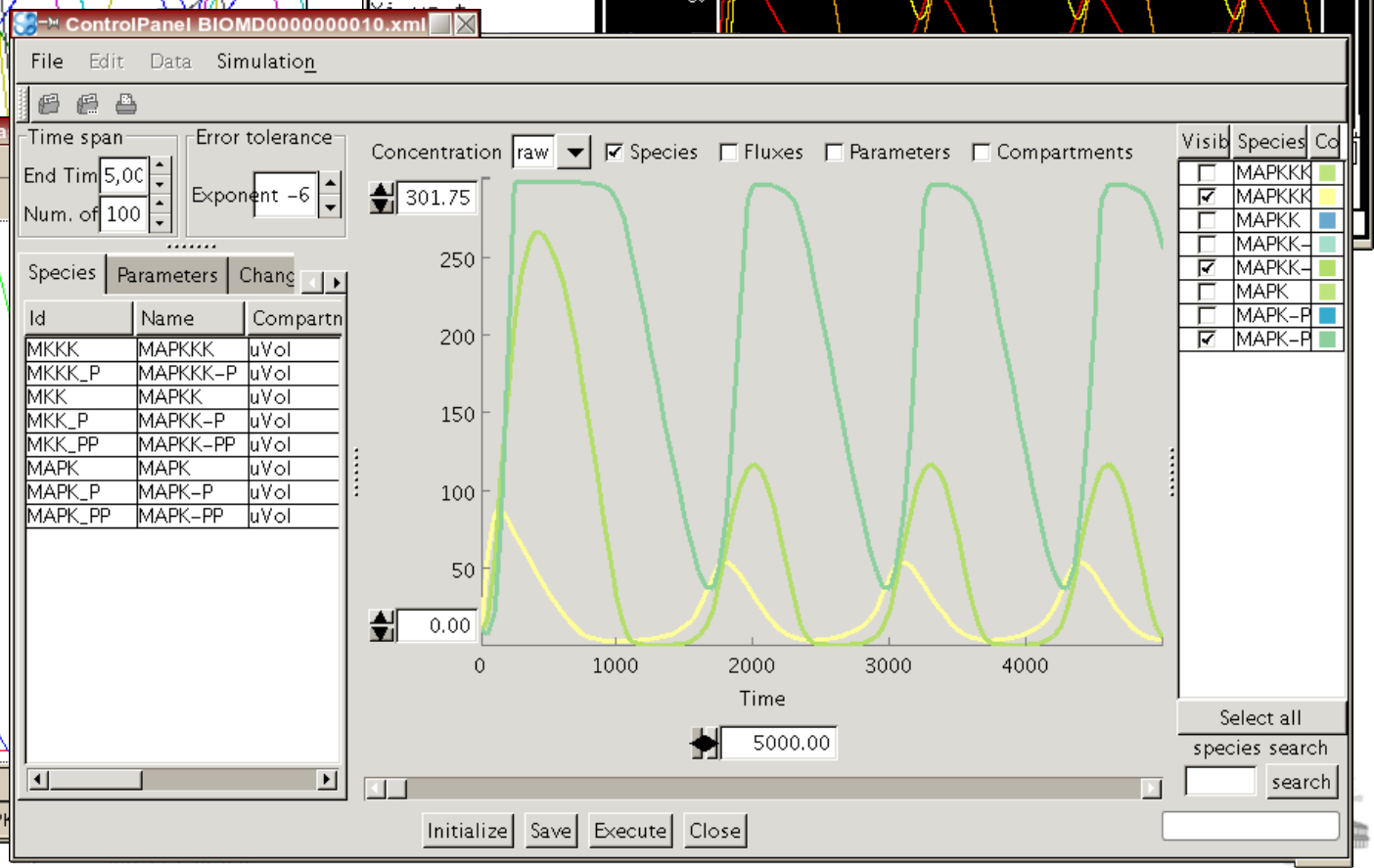
Kholodenko 2000

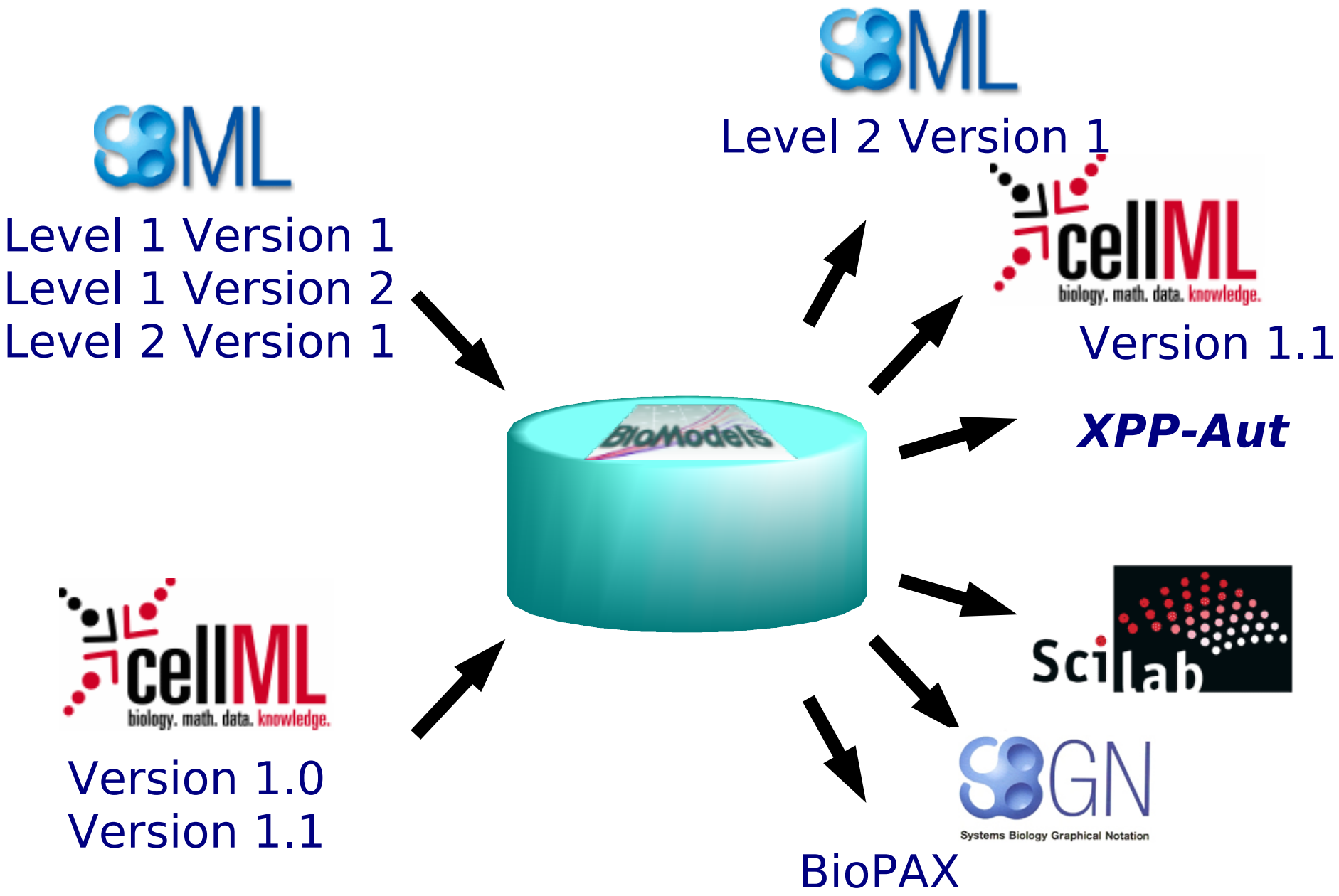




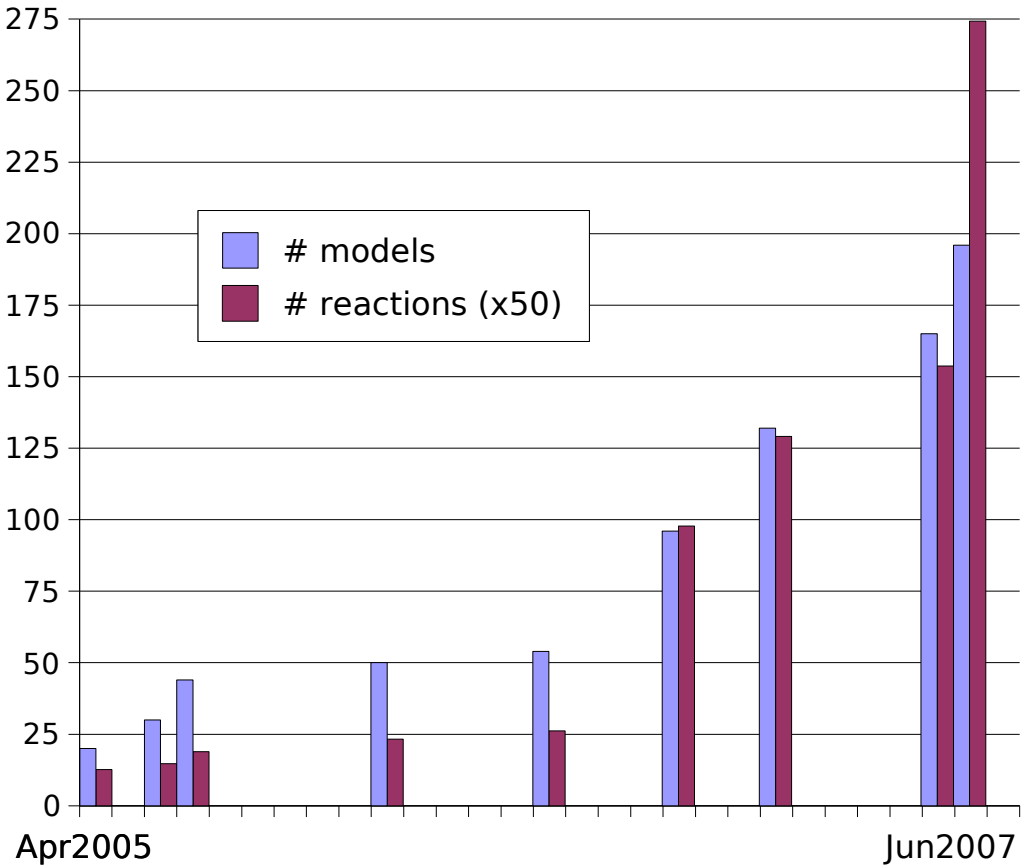


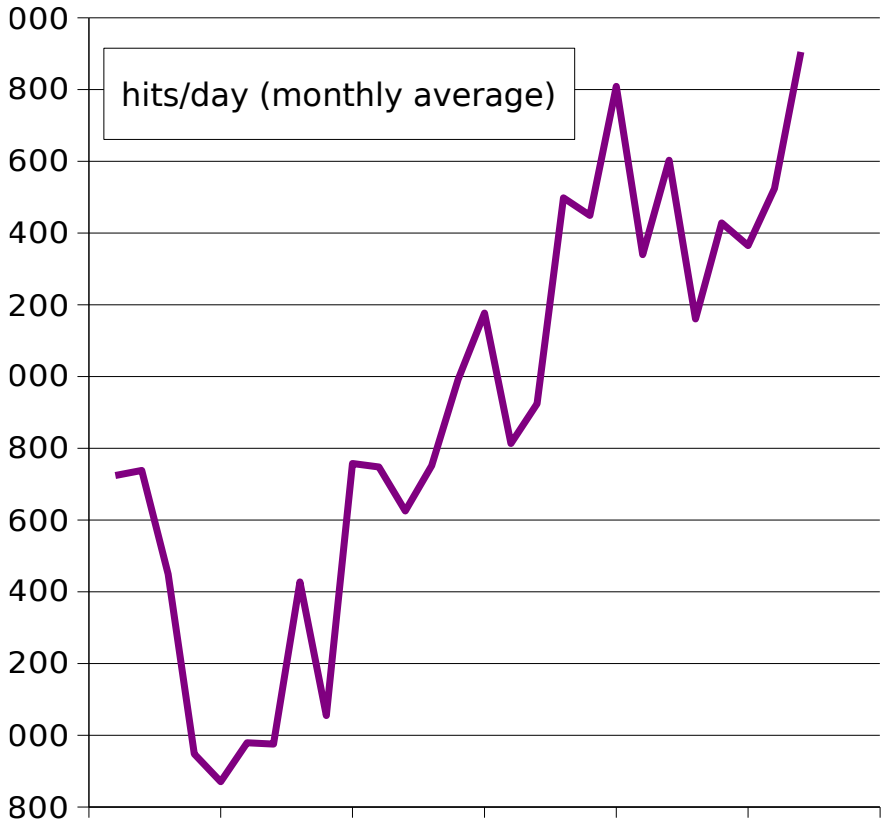


BioModels DB and interoperability in CSB



Steady-increase of BioModels DB





EMBL-EBI

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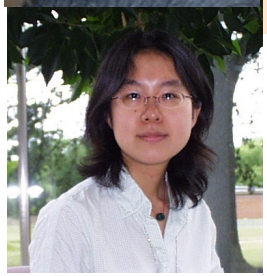

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Collaboration on standards and resources

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  - Hans Westerhoff
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  - Molecular Systems Biology
  - PLoS Journals
  - BioMedCentral Journals
- Programs used for curation
  - CellDesigner/SBMLodeSolver
  - COPASI
  - Jarnac/JDesigner
  - MathSBML
  - SBMLeditor
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The community of Systems Biology for their contributions of models and comments.