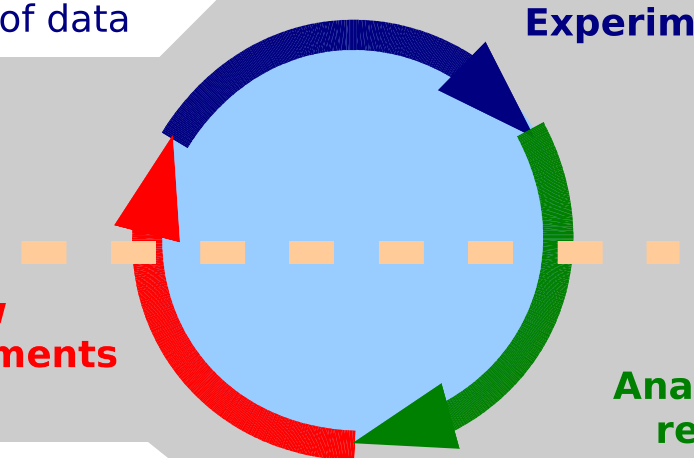
Computational Systems Neurobiology

Nicolas Le Novère, EMBL-EBI

Why computer simulations in Biology

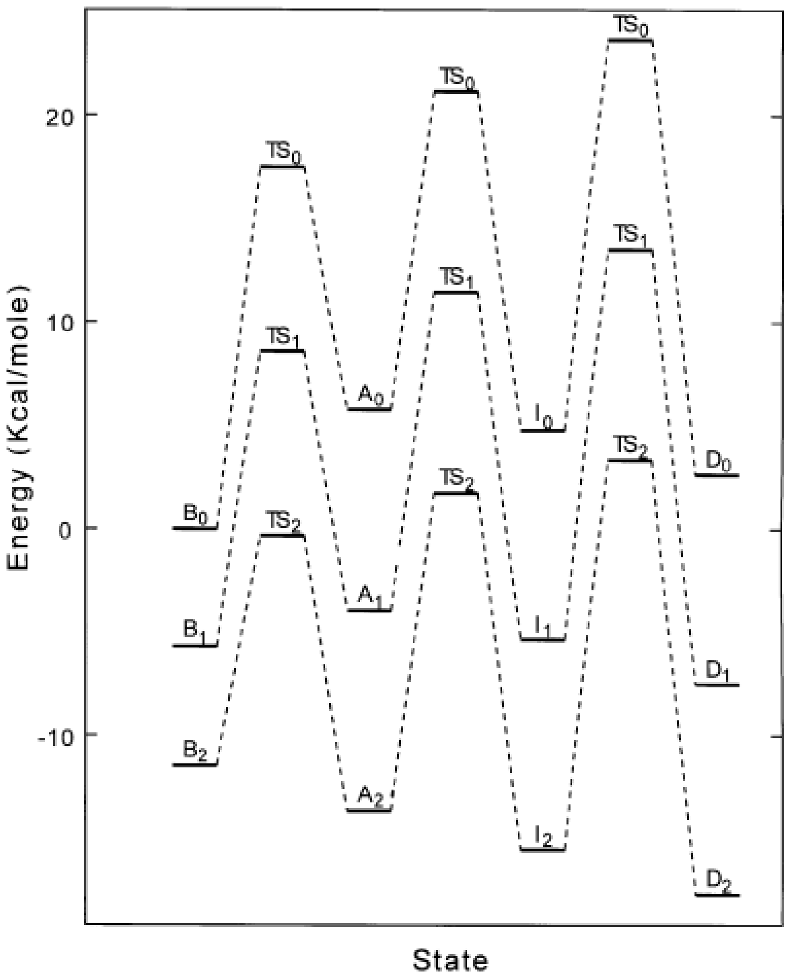
- Complexity of biological systems
  - Structural complexity: molecular and cellular levels
  - Functional complexity: network of relations, non-boolean relations
- Limitations of analytical approaches
  - Intractable system of equations
  - Existence of chaotic behaviours
  - Experiments often provides snapshots of processes
- Faster and cheaper computers
- Computing can complement experimental investigations by:
  - Storage, retrieval and analysis of data
  - Making predictions about future experiments
  - Virtual experiments, not feasible in reality

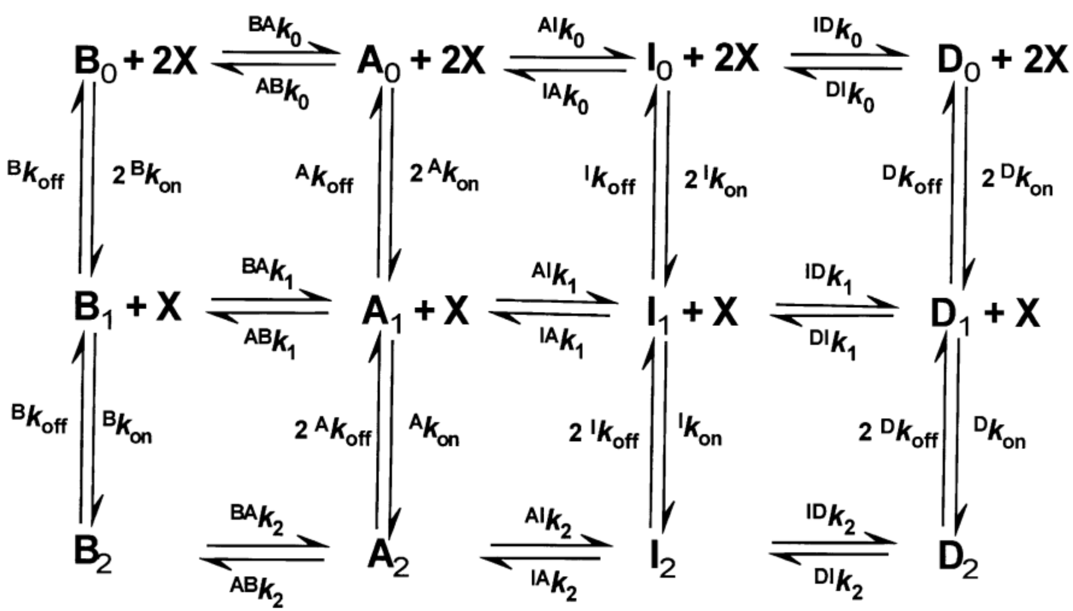


Simulation in Neurobiology

- 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
- [NEURON] Hines
  "A program for simulation of nerve equations with branching geometries". Int J Biomed Comput 1989, 24:55-68
- [GENESIS] Wilson, Bhalla, Uhley, Bower
  "GENESIS : A system for simulating neural networks." Advances in neural information processing systems. Touretzky, D. ed, 1989, pp. 485-492
- Land, Salpeter, Salpeter
  "Kinetic parameters for acetylcholine interaction in intact neuromuscular junction". Proc Natl Acad Sci USA 1981, 78:7200-7204
- [MCell] Bartol, Land, Salpeter, Salpeter
  "Monte Carlo simulation of miniature endplate current generation in the vertebrate neuromuscular junction". Biophy J 1991, 59: 1290-1307
- Bhalla US, Iyengar R.
  "Emergent properties of networks of biological signaling pathways. Science 1999 283: 381-387"
- Kotter R, Schirok D
  "Towards an integration of biochemical and biophysical models of neuronal information processing: a case study in the nigro-striatal system." Rev Neurosci 1999, 10: 247-266

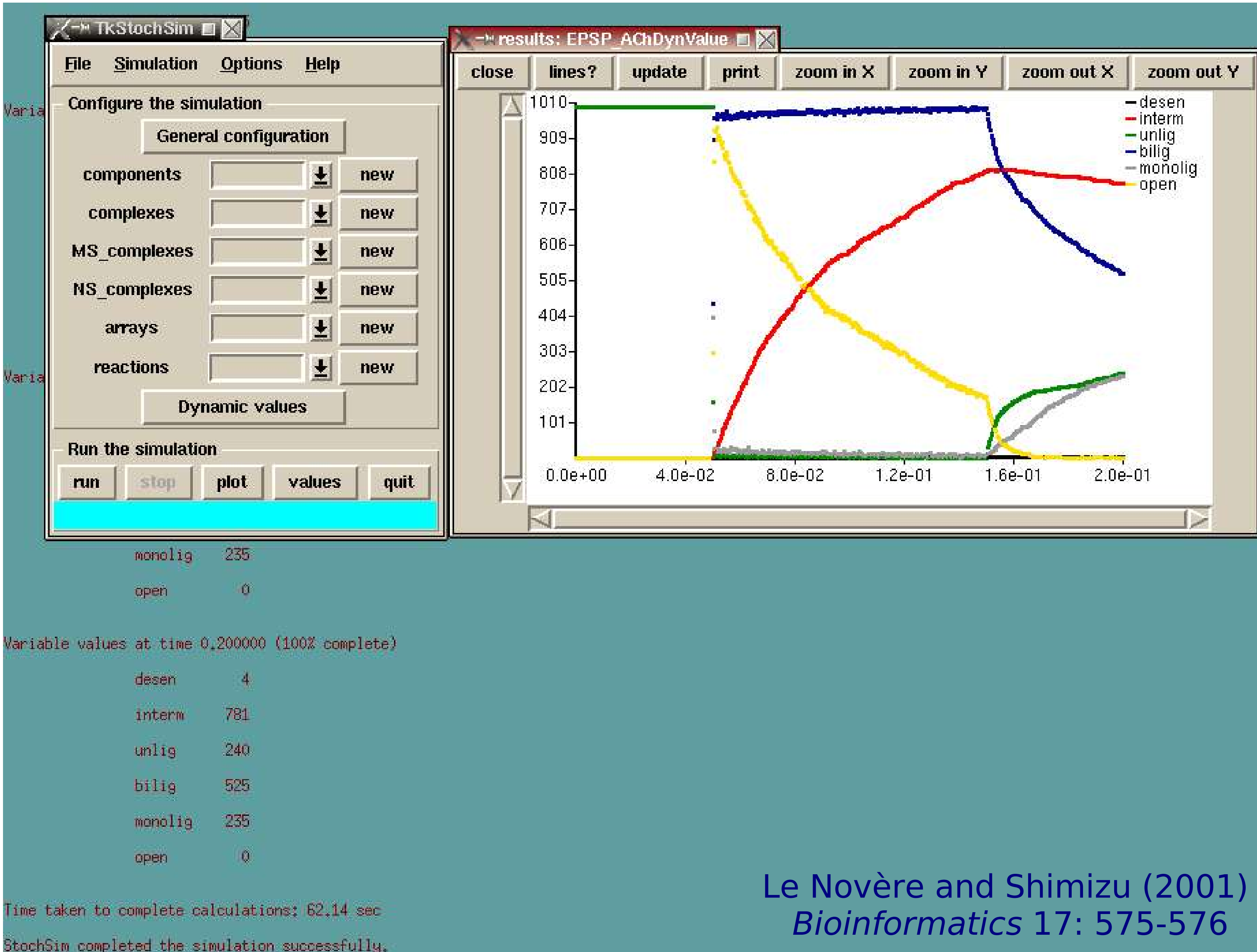
Kinetic model of receptor function





Edelstein et al. (1996) *Biol Cybern*, 75: 361-379

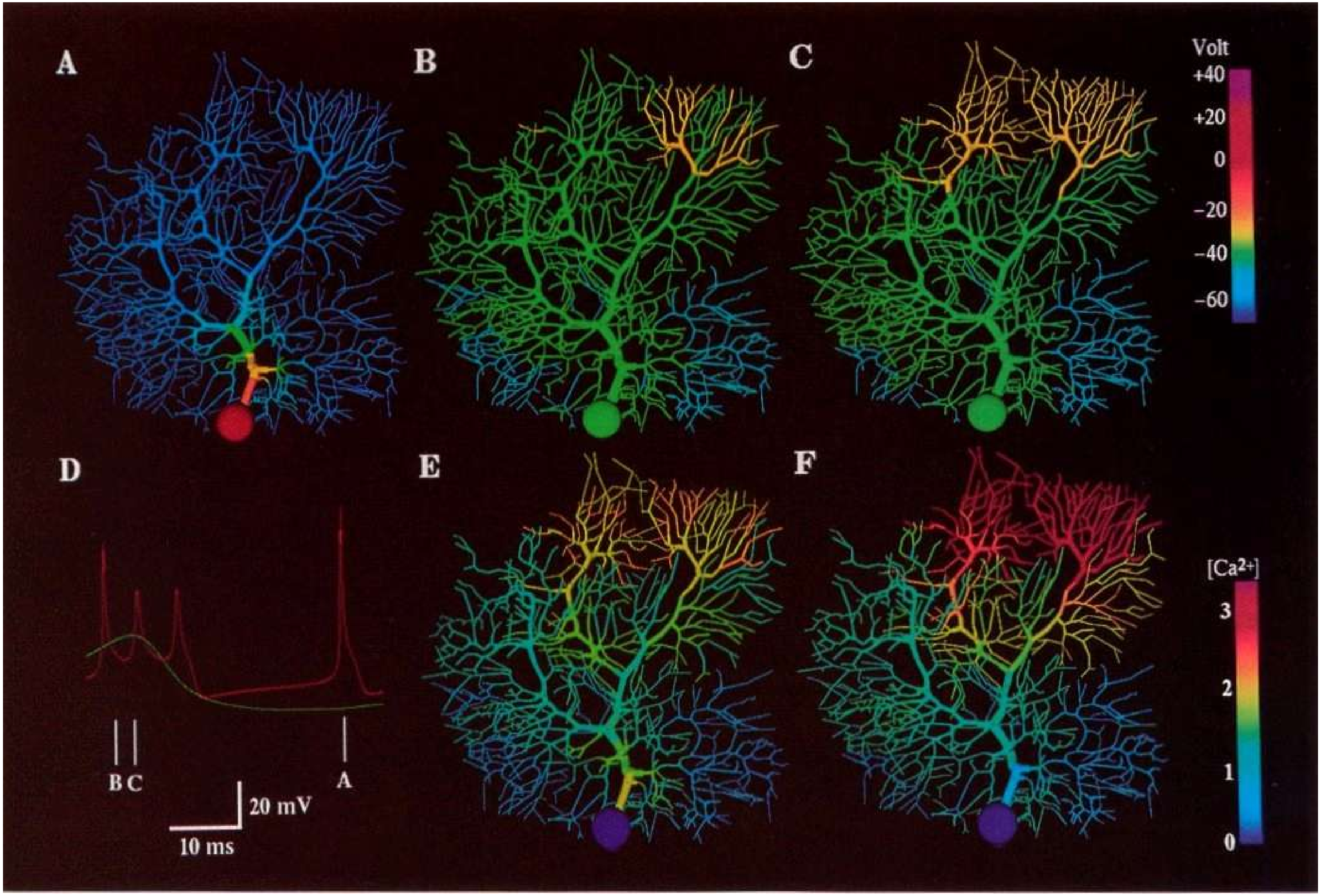
Excitatory post-synaptic potential



Le Novère and Shimizu (2001)
Bioinformatics 17: 575-576

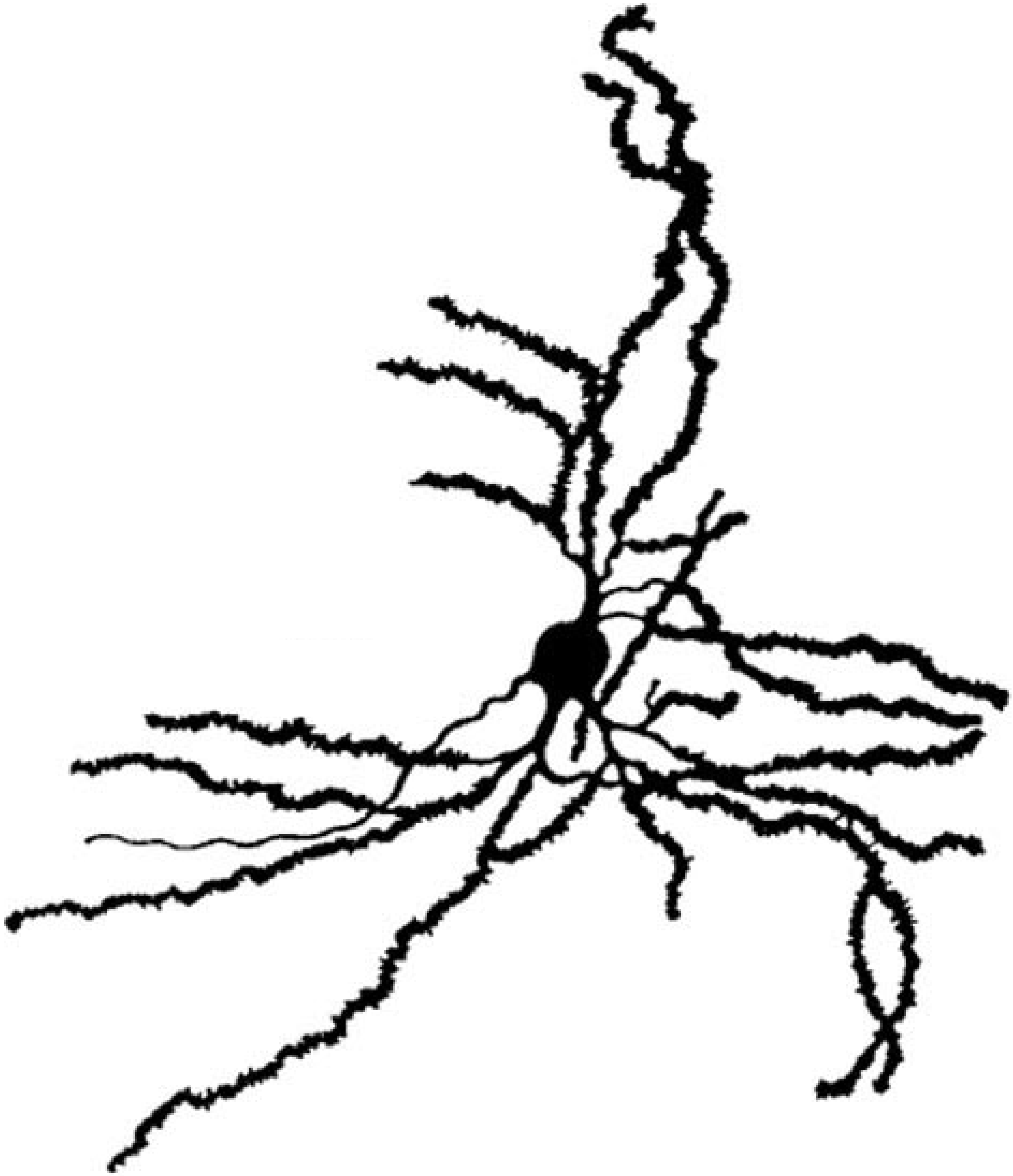
Computational Neurobiology

Compartmental models

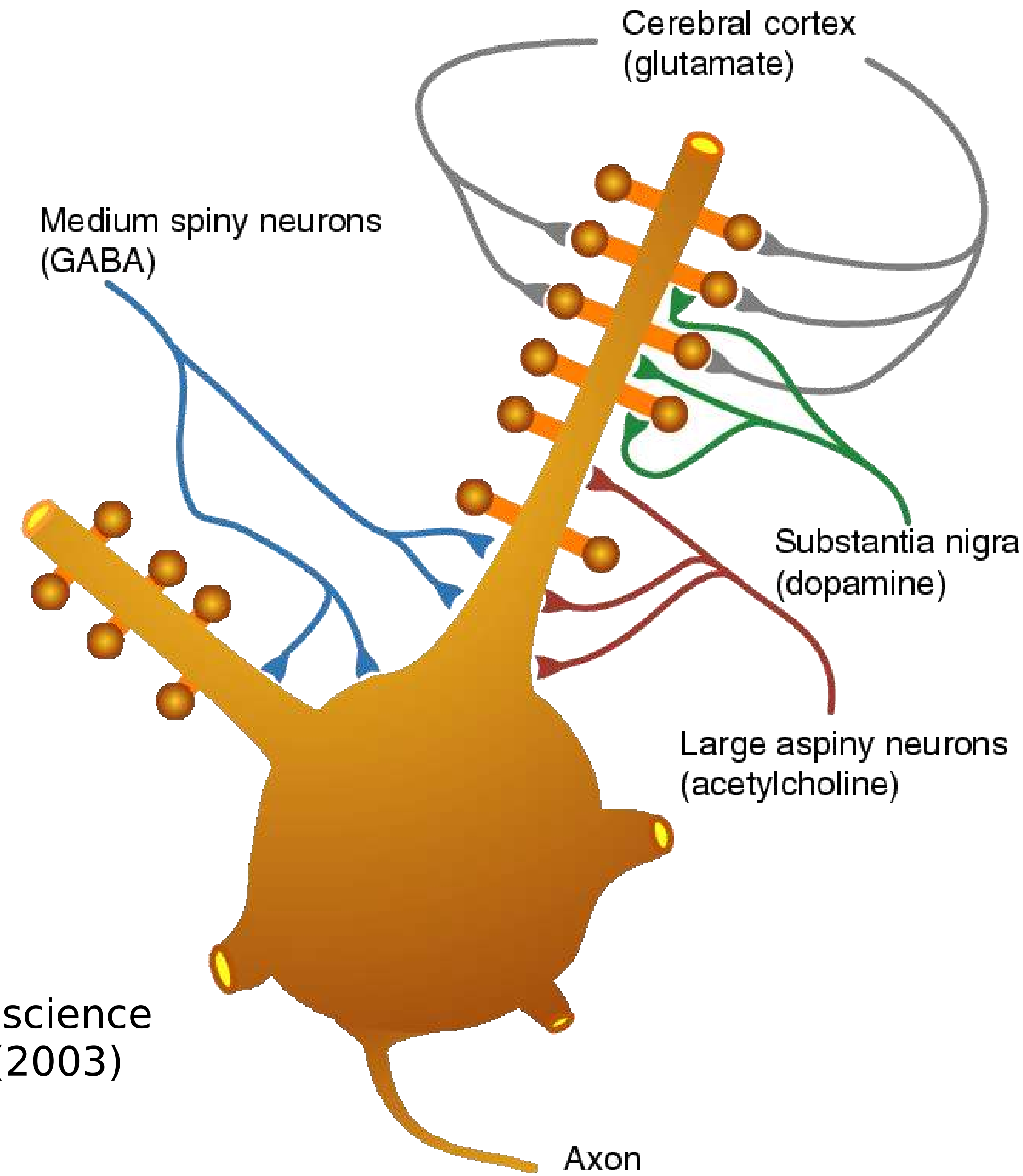


De Schuter and Bower (1994) *J Neurophysio*, 71: 375-419

the Medium Spiny Neuron of the striatum

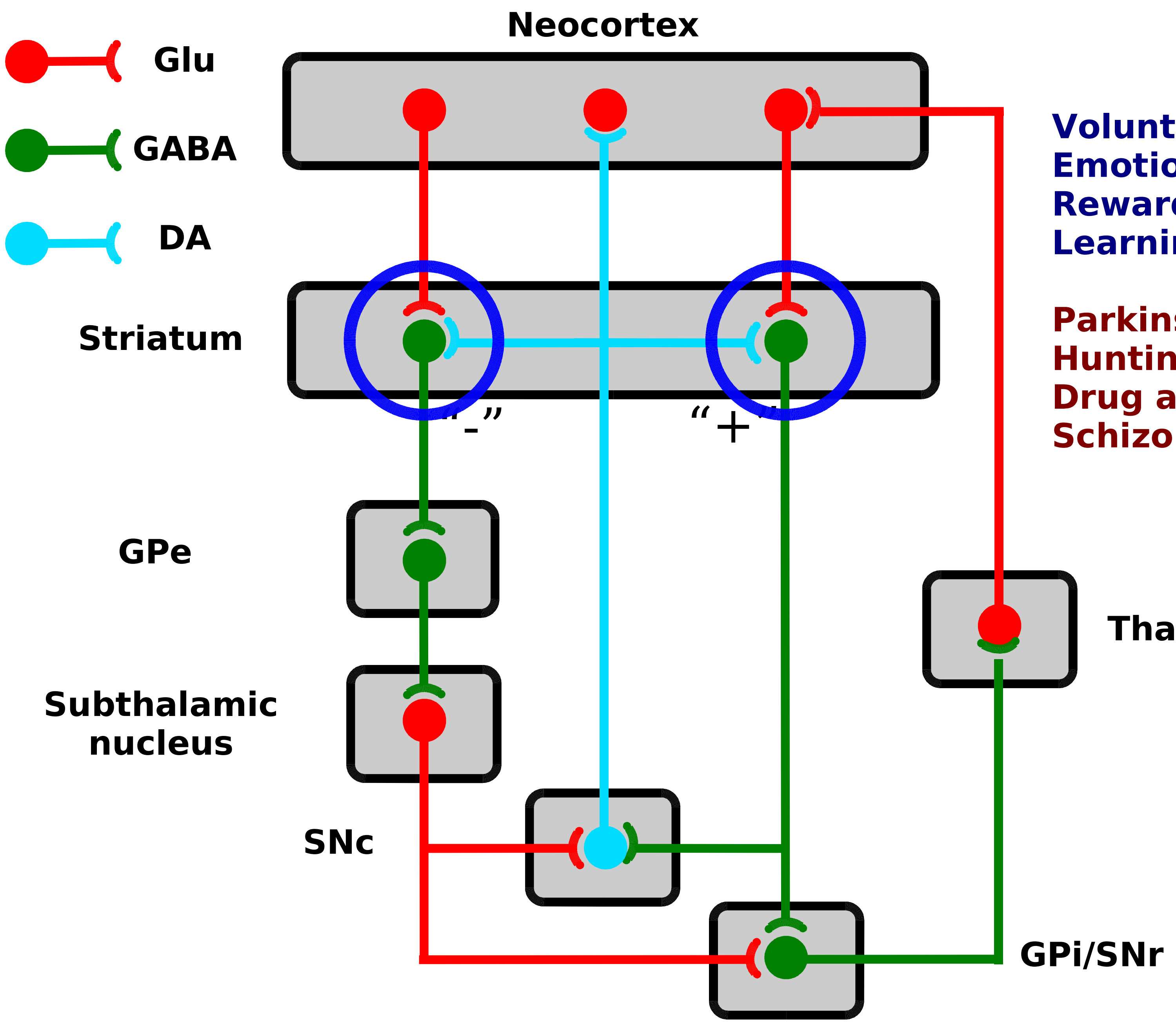


Multiple afferent signals



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

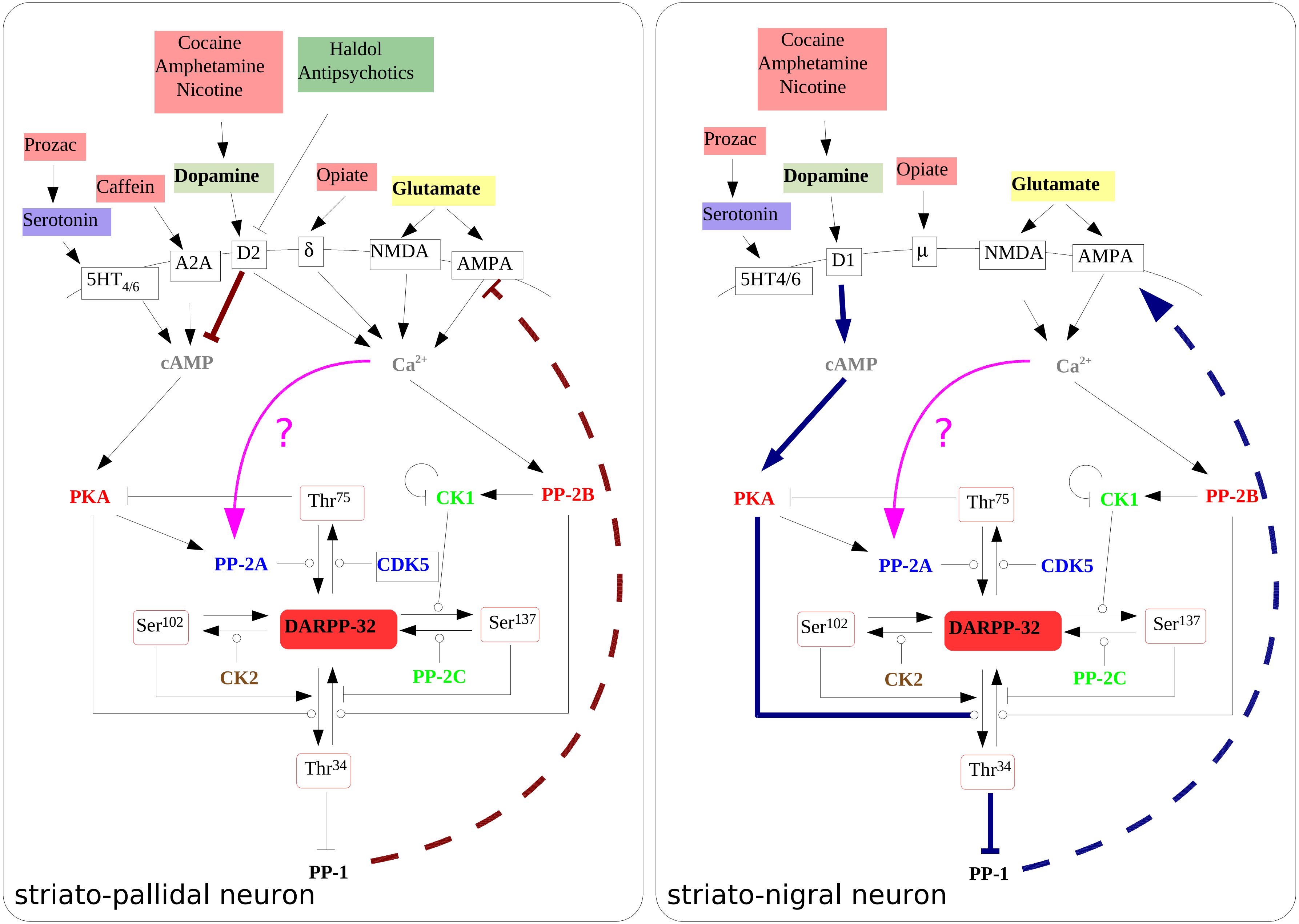
Dopamine mesotelencephalic pathway



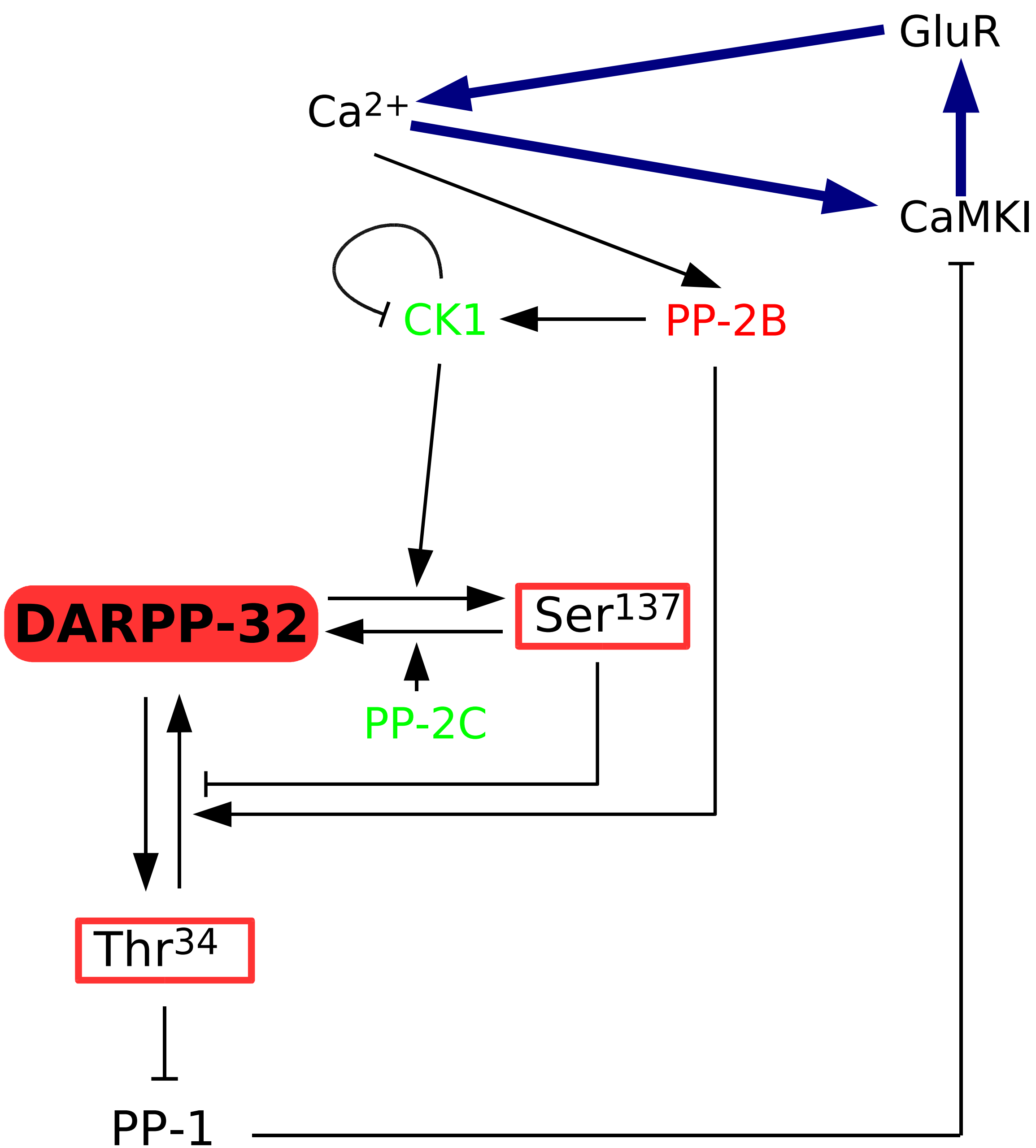
Voluntary motion
Emotional control
Reward
Learning

Parkinson's
Huntington
Drug addiction
Schizophrenia

Biological model of DARPP-32 regulation



Negative loops: “russian dolls”



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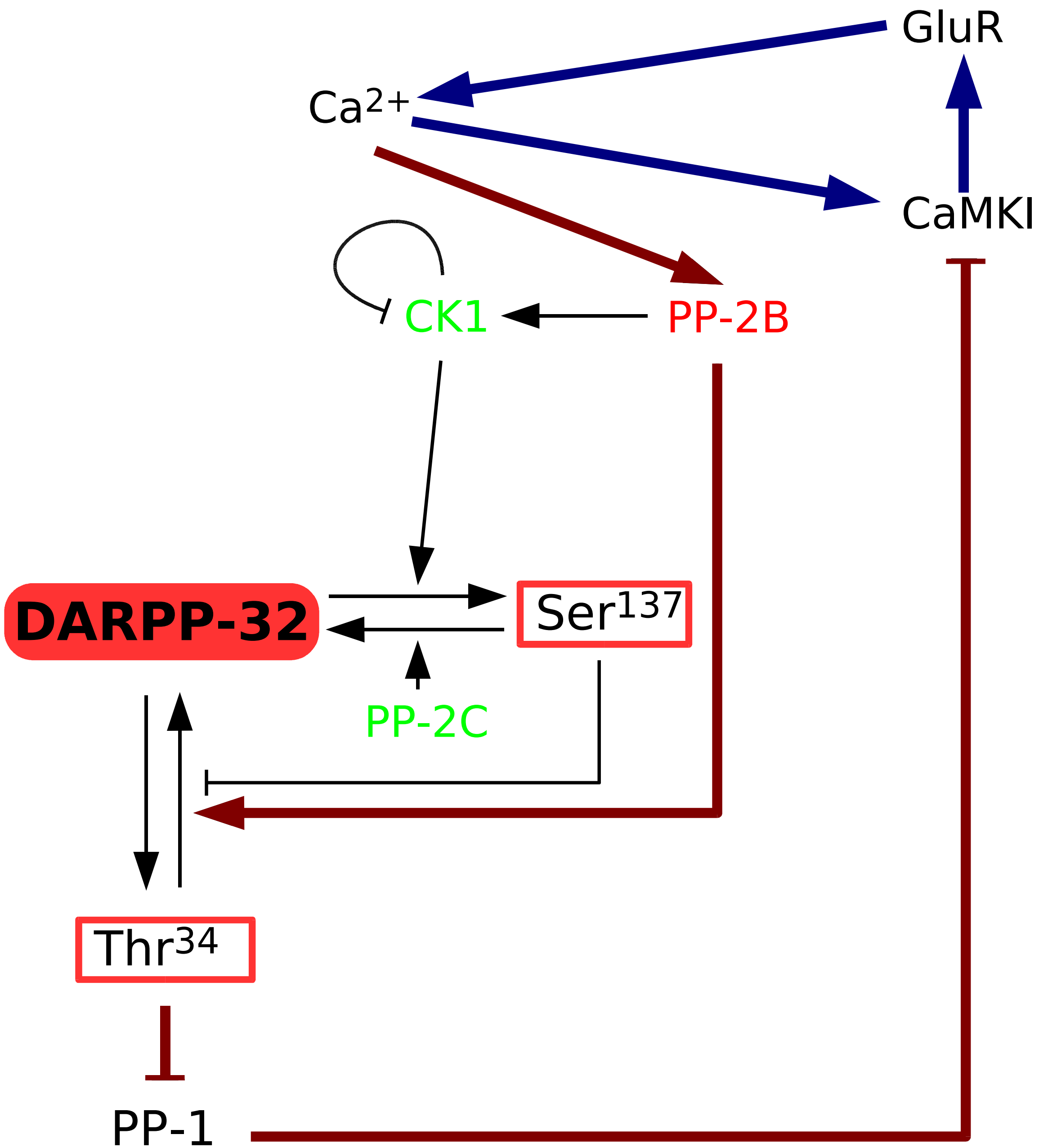
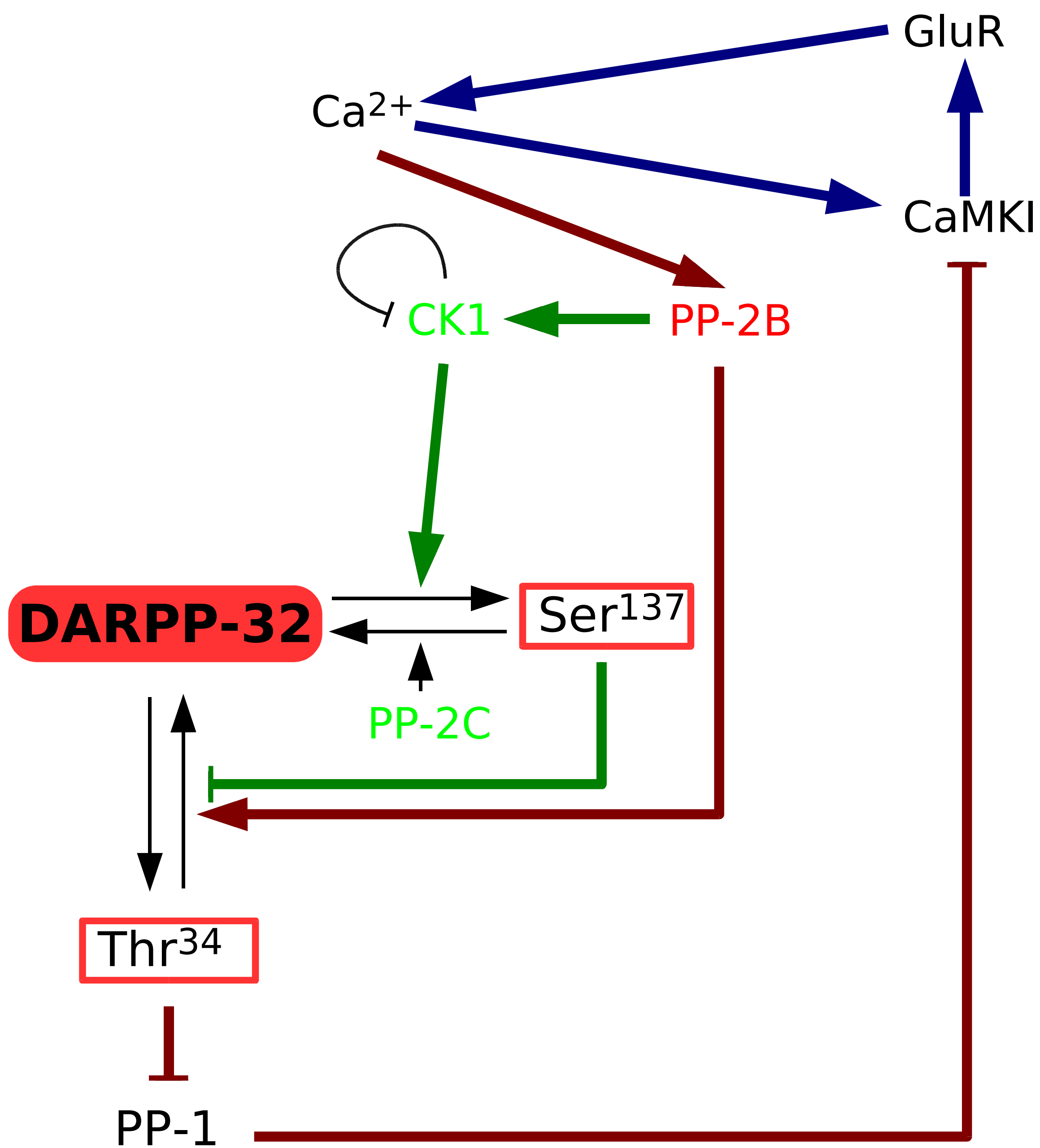
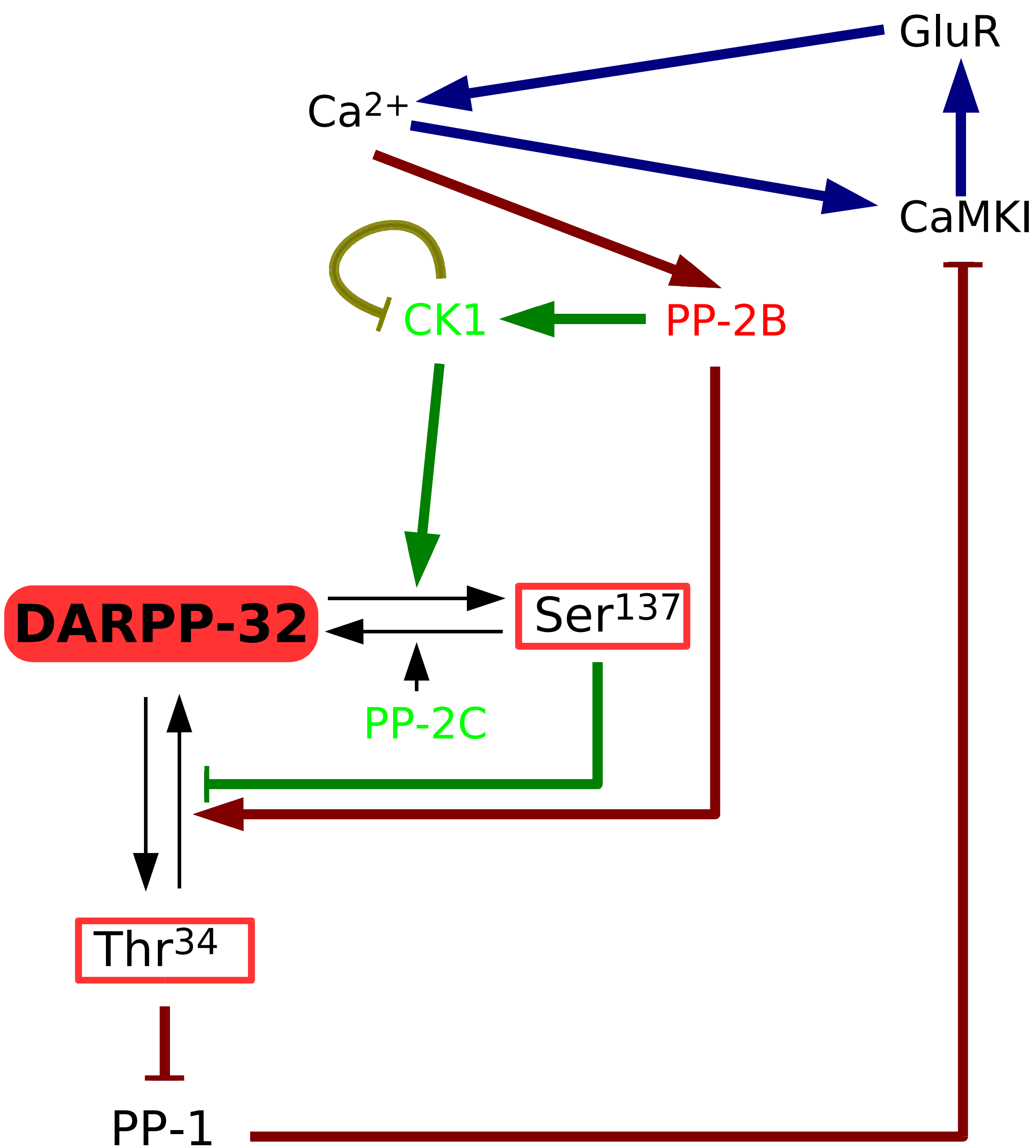


Negative loops: “russian dolls”

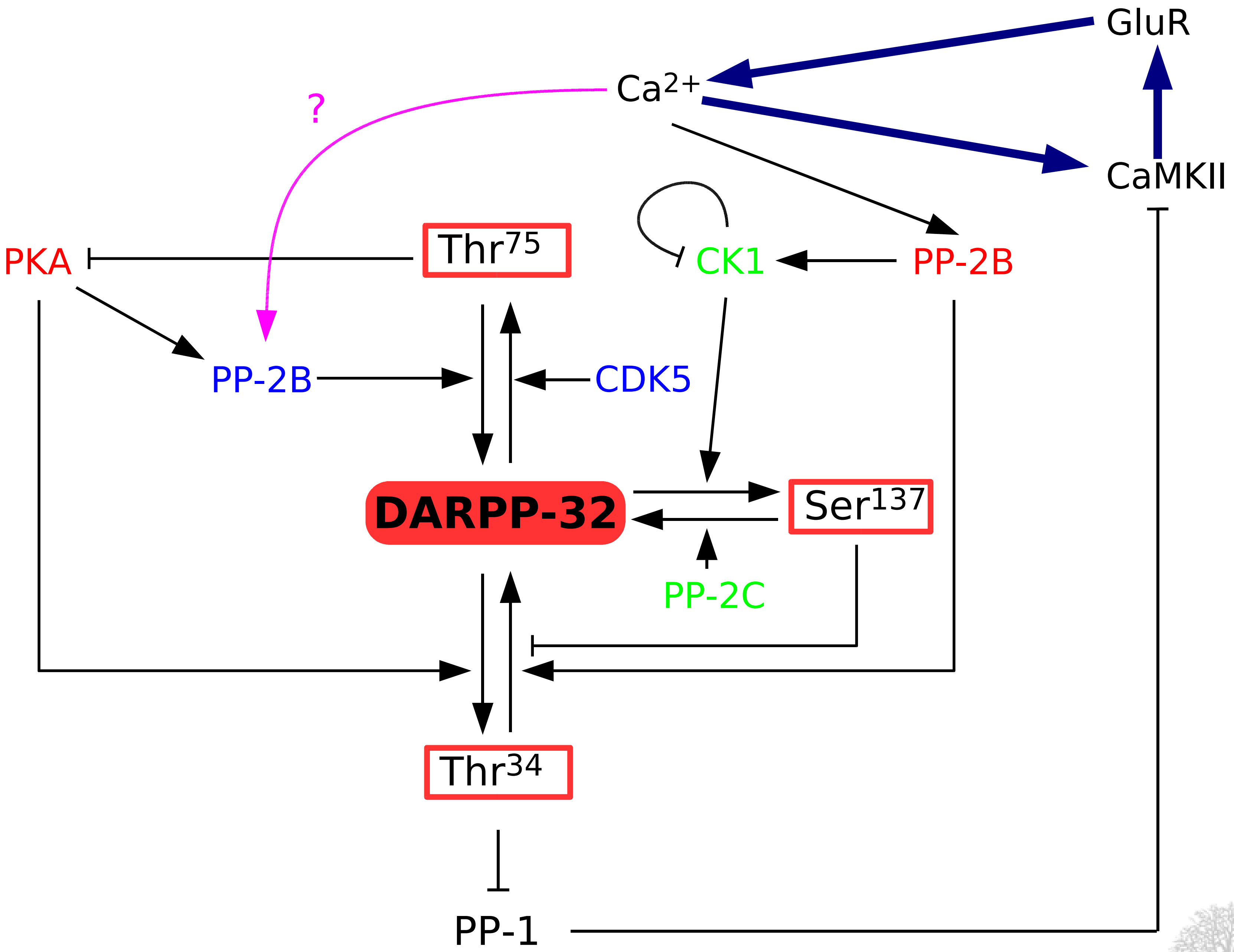


Negative loops: “russian dolls”



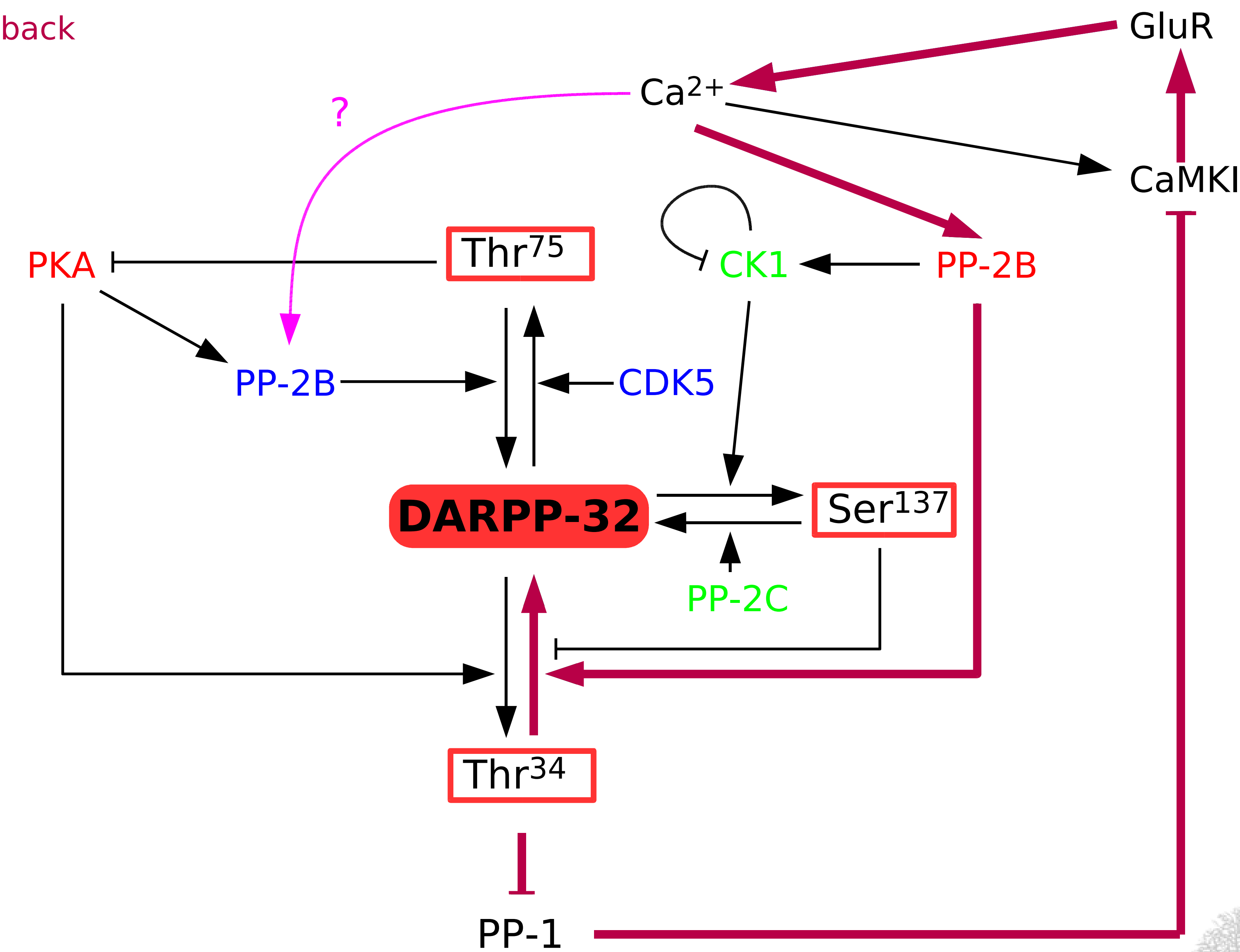
All the cybernetics in one system

positive feedback



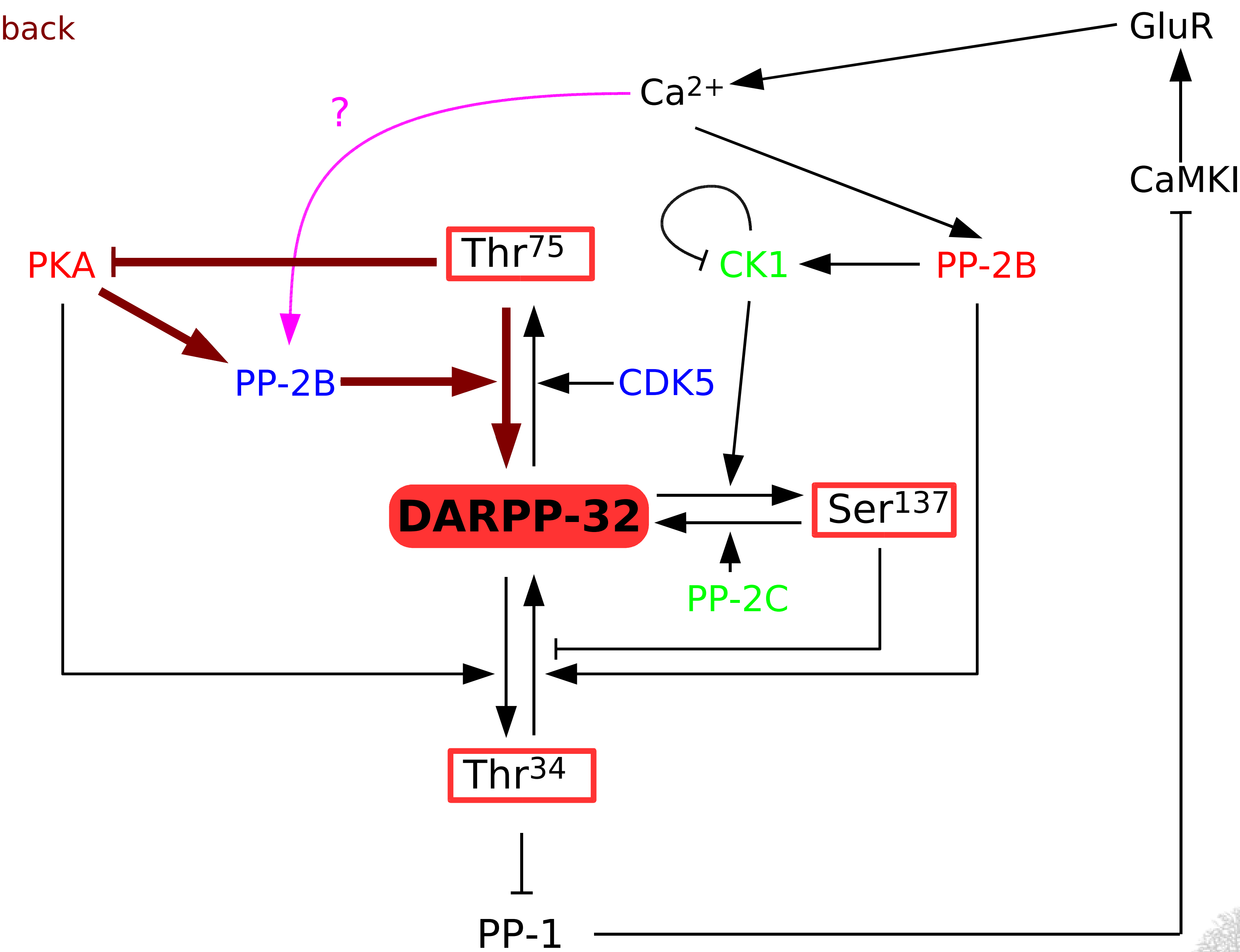
All the cybernetics in one system

negative feedback



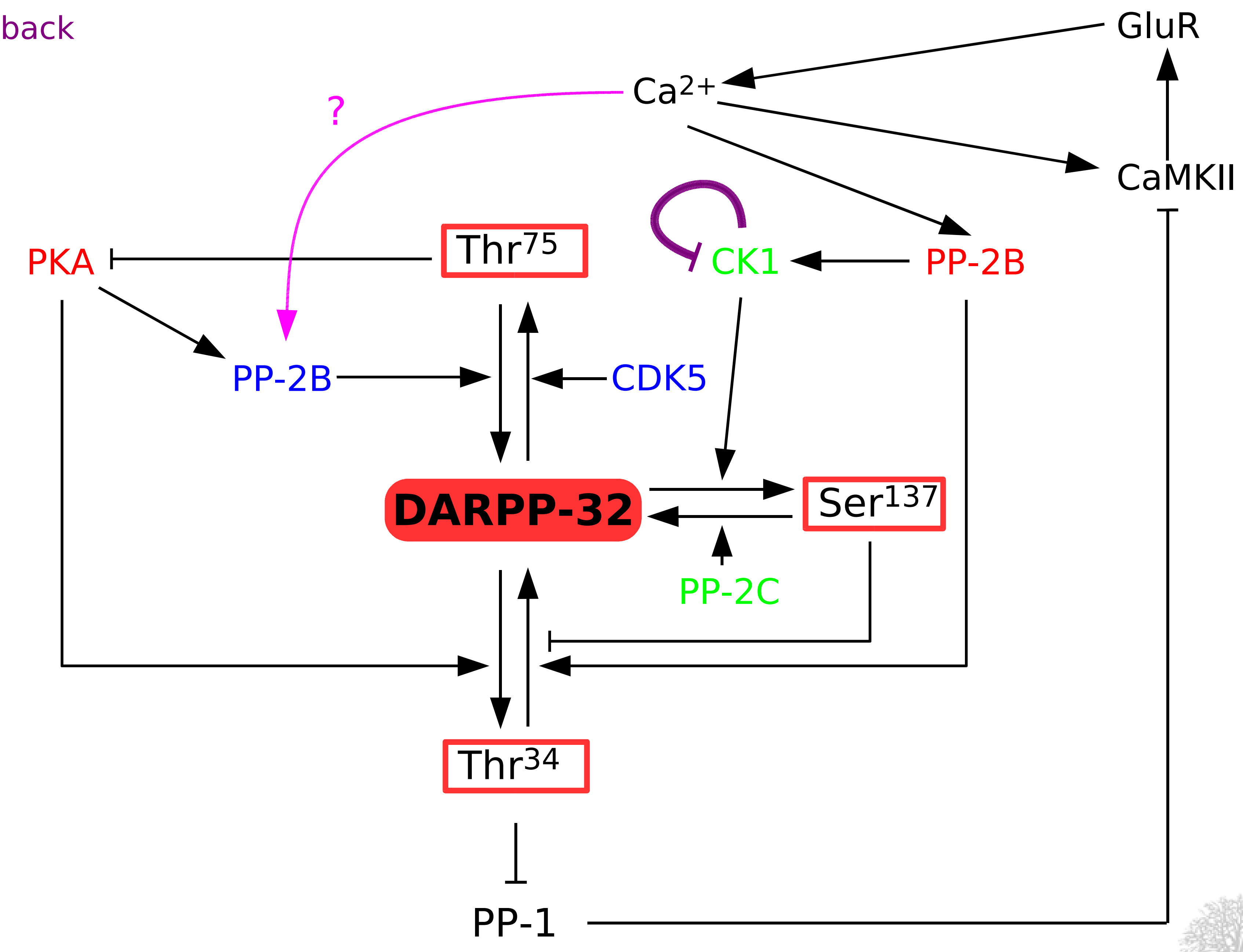
All the cybernetics in one system

negative feedback



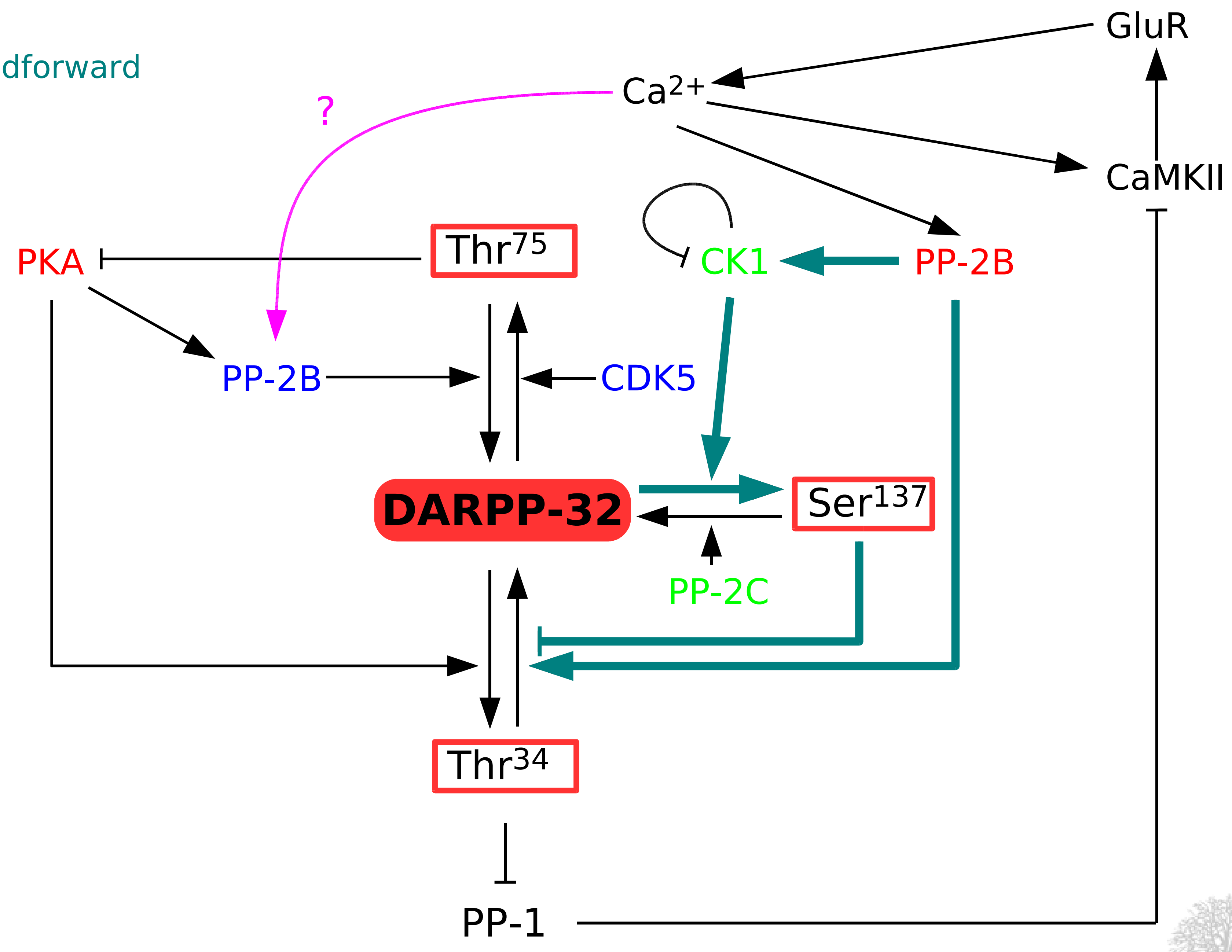
All the cybernetics in one system

negative feedback

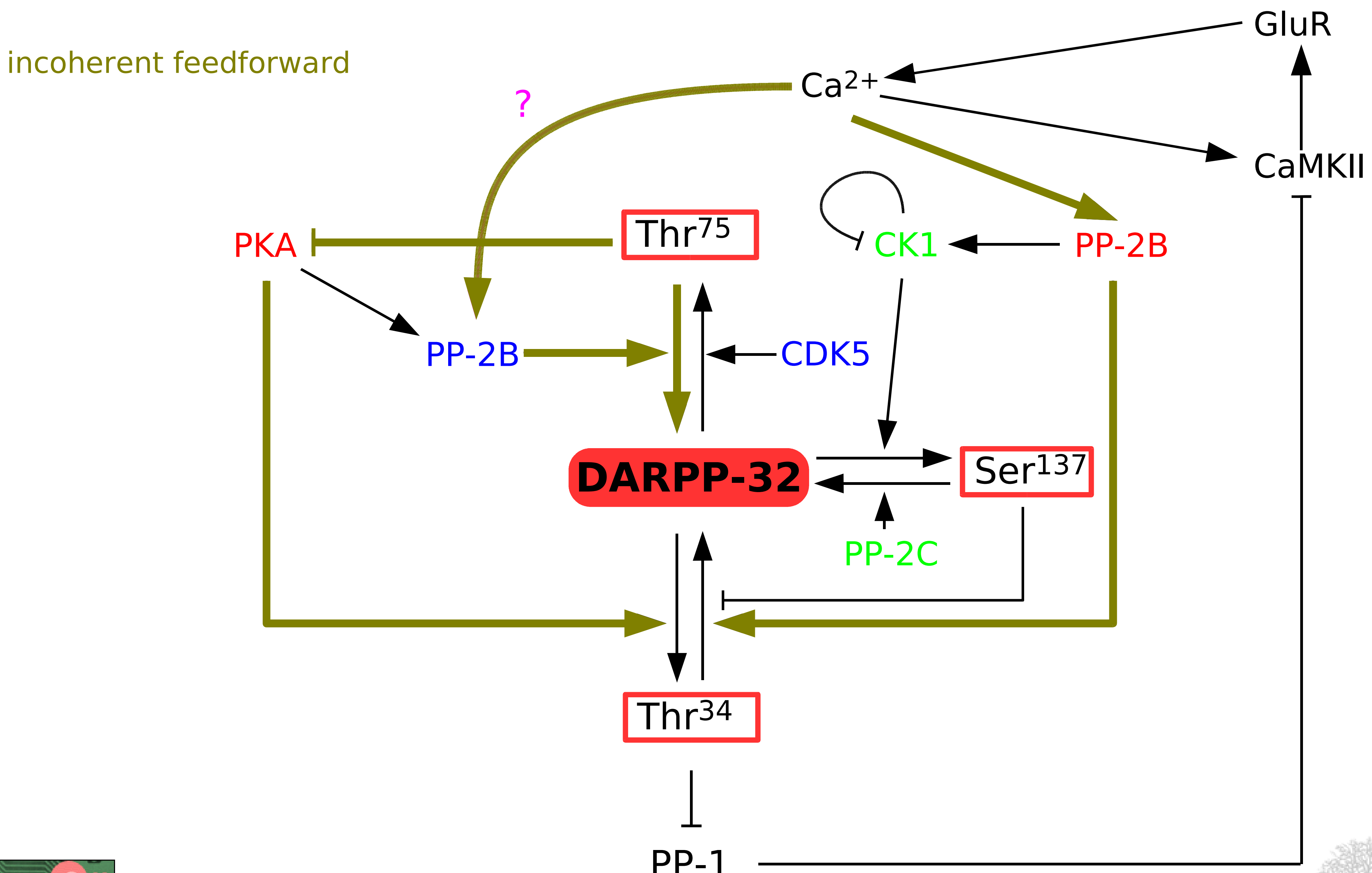


All the cybernetics in one system

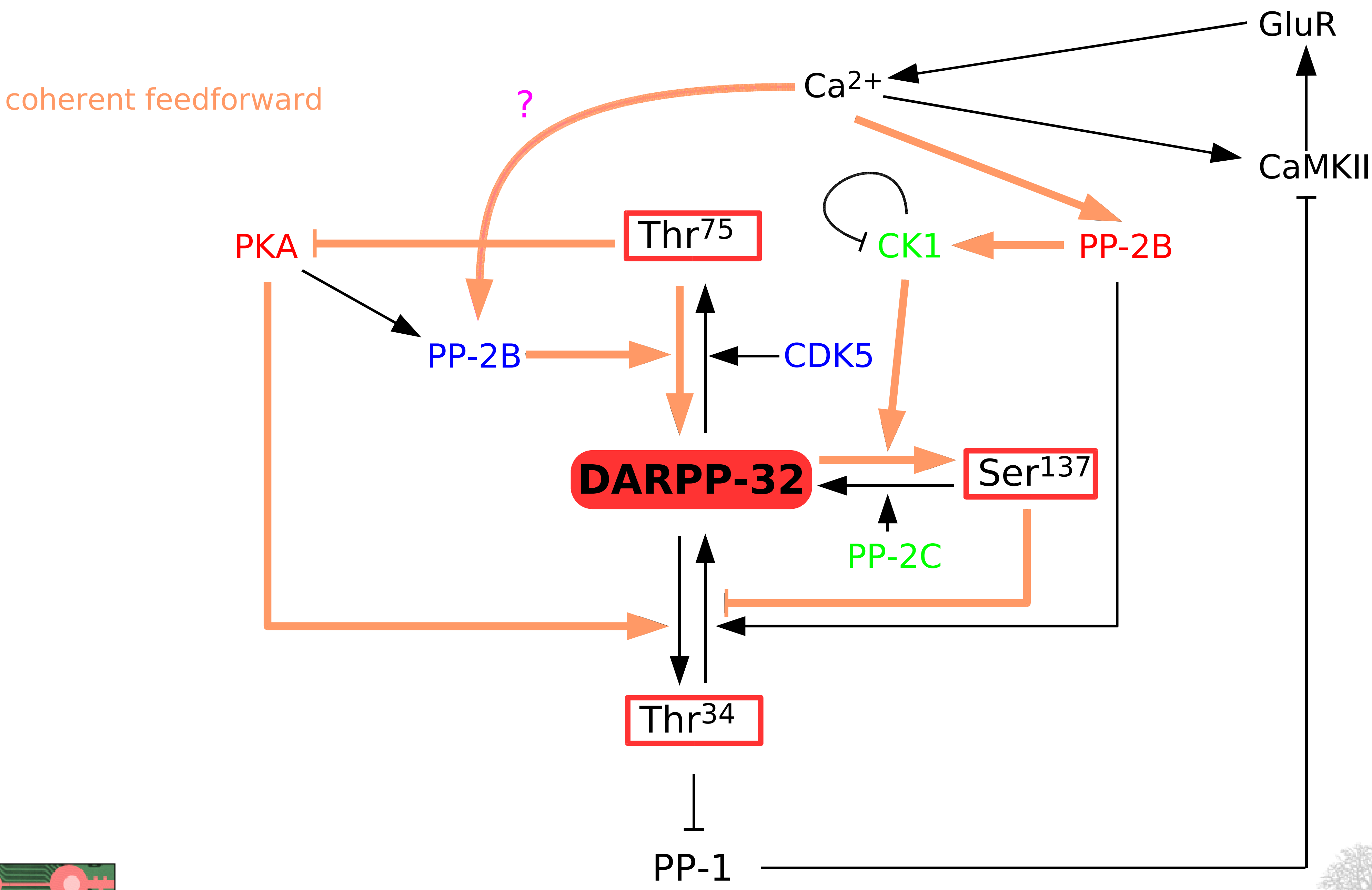
incoherent feedforward



All the cybernetics in one system



All the cybernetics in one system



Choose the right formalism

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

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

catalysis irreversible

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

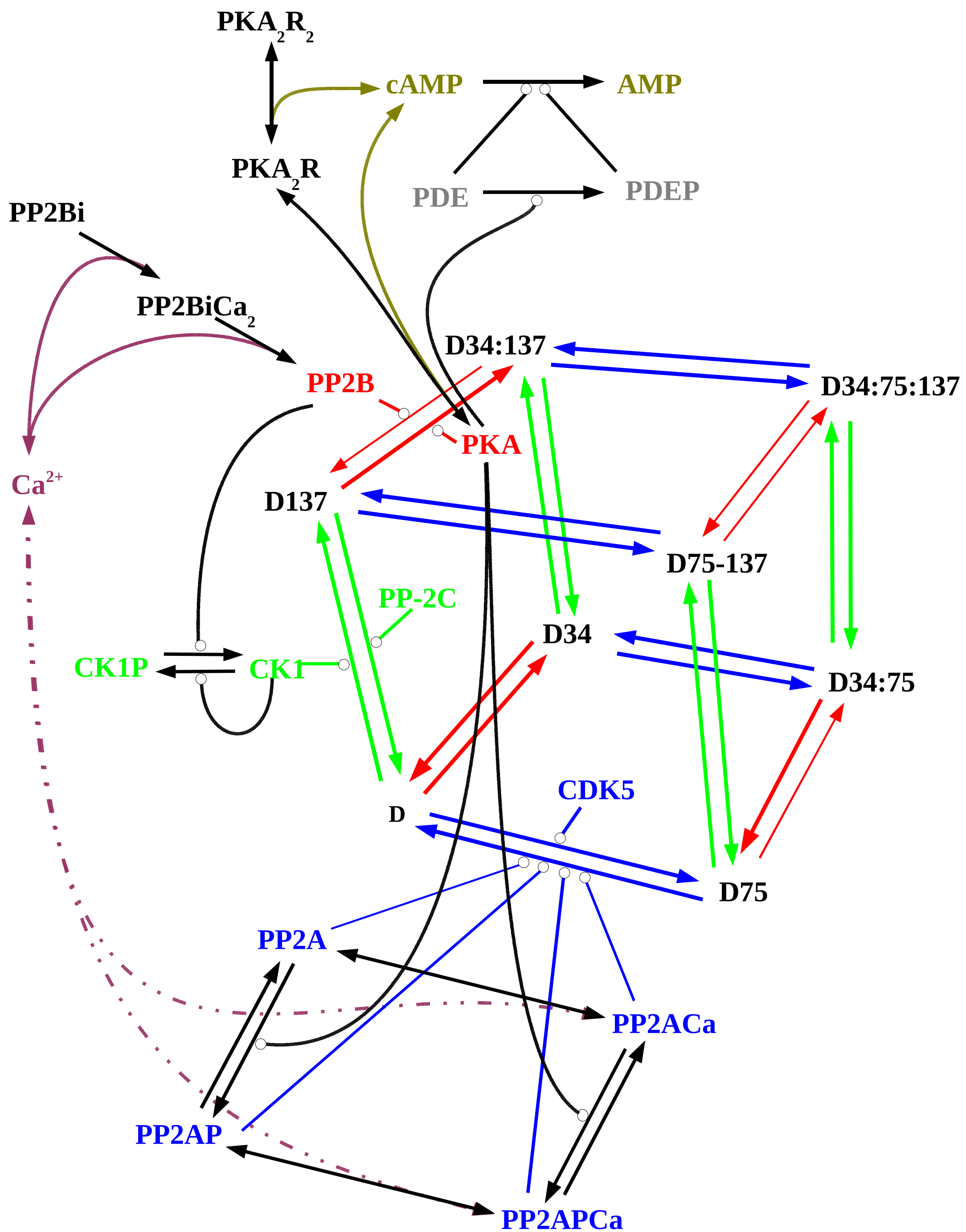
product is consumed before rebinding

$$\mathrm{S} \xrightarrow{E} \mathrm{P}$$

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

68 species, 124 reactions

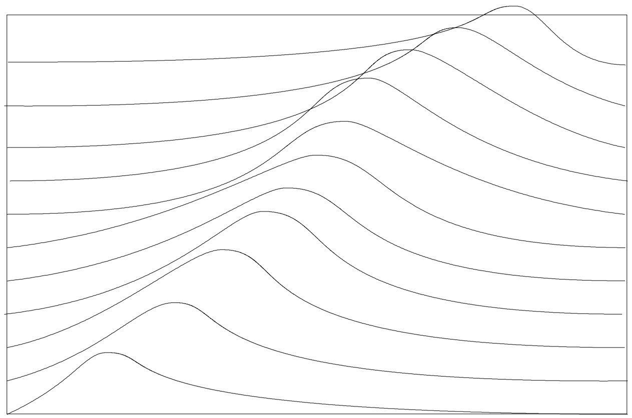
- D + CDK5 ⇔ D_CDK5 → D75 + CDK5
- D75 + PP2A ⇔ D75_PP2A → D + PP2A
- D75 + PP2AP ⇔ D75_PP2AP → D + PP2AP
- D137 + CDK5 ⇔ D137_CDK5 → D75-137 + CDK5
- D75-137 + PP2A ⇔ D75-137_PP2A → D137 + PP2A
- D75-137 + PP2AP ⇔ D75-137_PP2AP → D137 + PP2AP
- D34 + CDK5 ⇔ D34_CDK5 → D34-75 + CDK5
- D34-75 + PP2A ⇔ D34-75_PP2A → D34 + PP2A
- D34-75 + PP2AP ⇔ D34-75_PP2AP → D34 + PP2AP
- D34-137 + CDK5 ⇔ D34-137_CDK5 → D34-75_137 + CDK5
- D34-75-137 + PP2A ⇔ D34-75-137_PP2A → D34-137 + PP2A
- D34-75-137 + PP2AP ⇔ D34-75-137_PP2AP → D34-137 + PP2AP

- 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

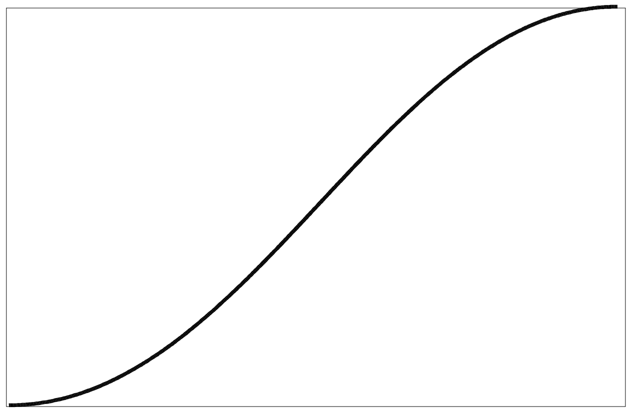
- D + PKA ⇔ D_PKA → D34 + PKA
- D34 + PP2B ⇔ D34_PP2B → D + PP2B
- D75 + PKA ⇔ D75_PKA → D34-75 + PKA
- D34-75 + PP2B ⇔ D34-75_PP2B → D75 + PP2B
- D137 + PKA ⇔ D137_PKA → D34-137 + PKA
- D34-137 + PP2B ⇔ D34-135_PP2B → D137 + PP2B
- D75-137 + PKA ⇔ D75-137_PKA → D34-75-137 + PKA
- D34-75-137 + PP2B ⇔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

- 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

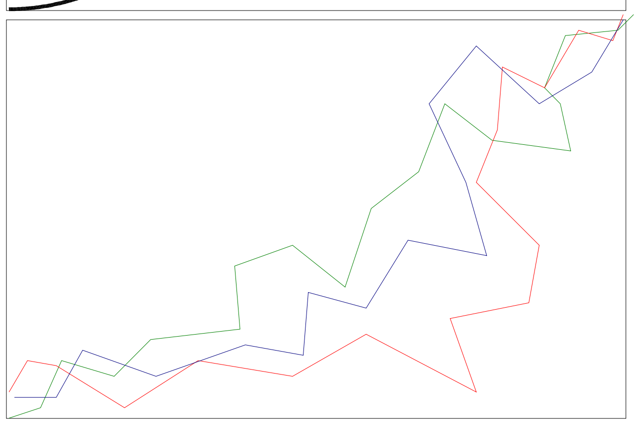
Mathematical model



Grand Probability function: P(X,t)



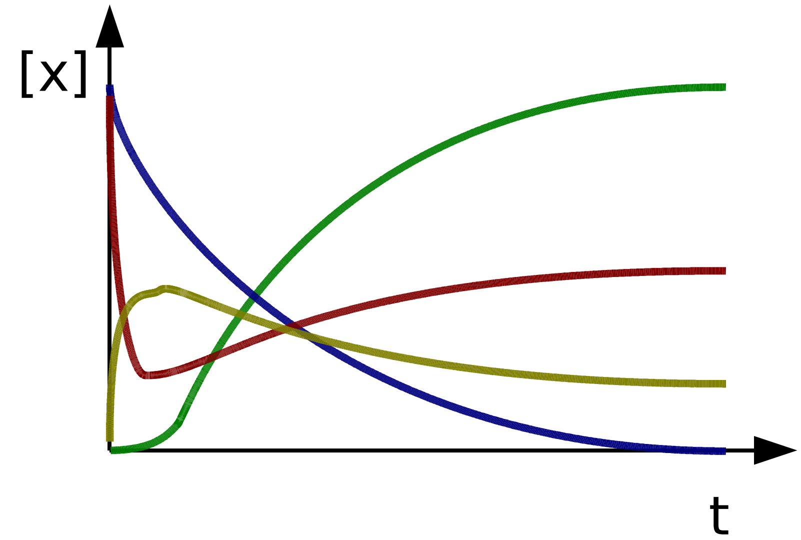
deterministic approach: (X,t)=f(X',t-1)



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

Mathematical model

$$E+S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E+P$$



Deterministic view: ODEs

$$d[S]/dt = k_2[ES]-k_1[E][S]$$
$$d[P]/dt = k_3[ES]$$
$$d[E]/dt = k_3[ES]$$
$$d[ES]/dt = k_1[E][S]-k_2[ES]-k_3[ES]$$

Stochastic view: probabilities

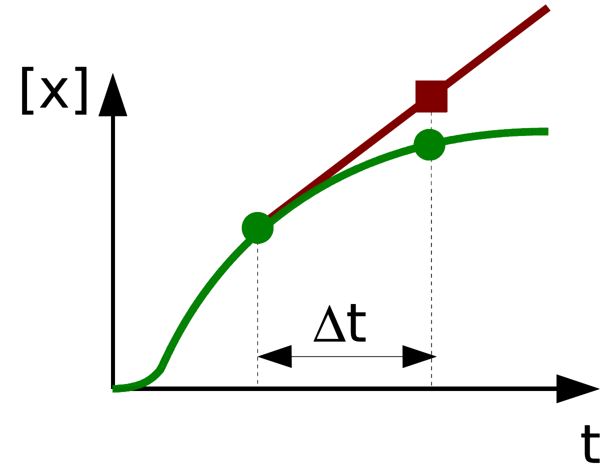
$$P_1/dt = k_1 n_E n_S/N_A V$$
$$P_2/dt = k_2 n_{ES}$$
$$P_3/dt = k_3 n_{ES}$$

Computational model

Euler method:

$$d[x]/dt \approx ([x]_{t+\Delta t} - [x]_t\,) \,/\, \Delta t$$

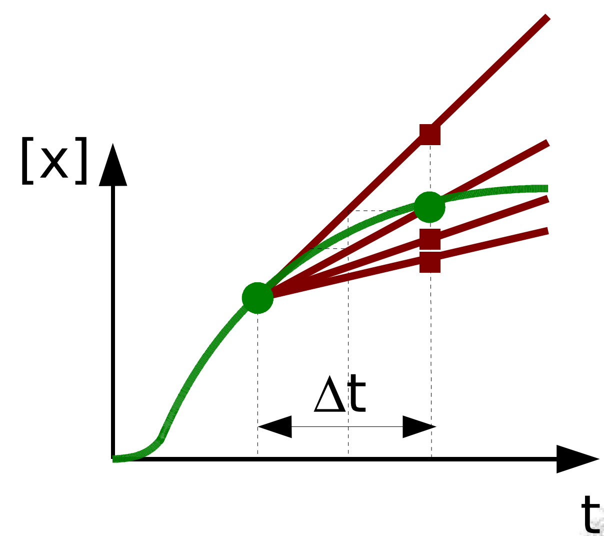
$$[x]_{t+\Delta t} \approx [x]_t + d[x]/dt \,.\, \Delta t$$



$$[P]_{t+\Delta t} = [P]_t + k_3[ES]_t \,.\, \Delta t$$
$$[E]_{t+\Delta t} = [E]_t + k_3[ES]_t \,.\, \Delta t$$
$$[S]_{t+\Delta t} = [S]_t + (k_2[ES]_t - k_1[E]_t[S]_t) \,.\, \Delta t$$
$$[ES]_{t+\Delta t} = [S]_t + (k_1[ES]_t - (k_1+k_3)[E]_t[S]_t) \,.\, \Delta t$$

4^{th} order Runge-kutta:

$$[x]_{t+\Delta t} = [x]_t + (F_1+2F_2+2F_3+F_4)/6 \,.\, \Delta t$$

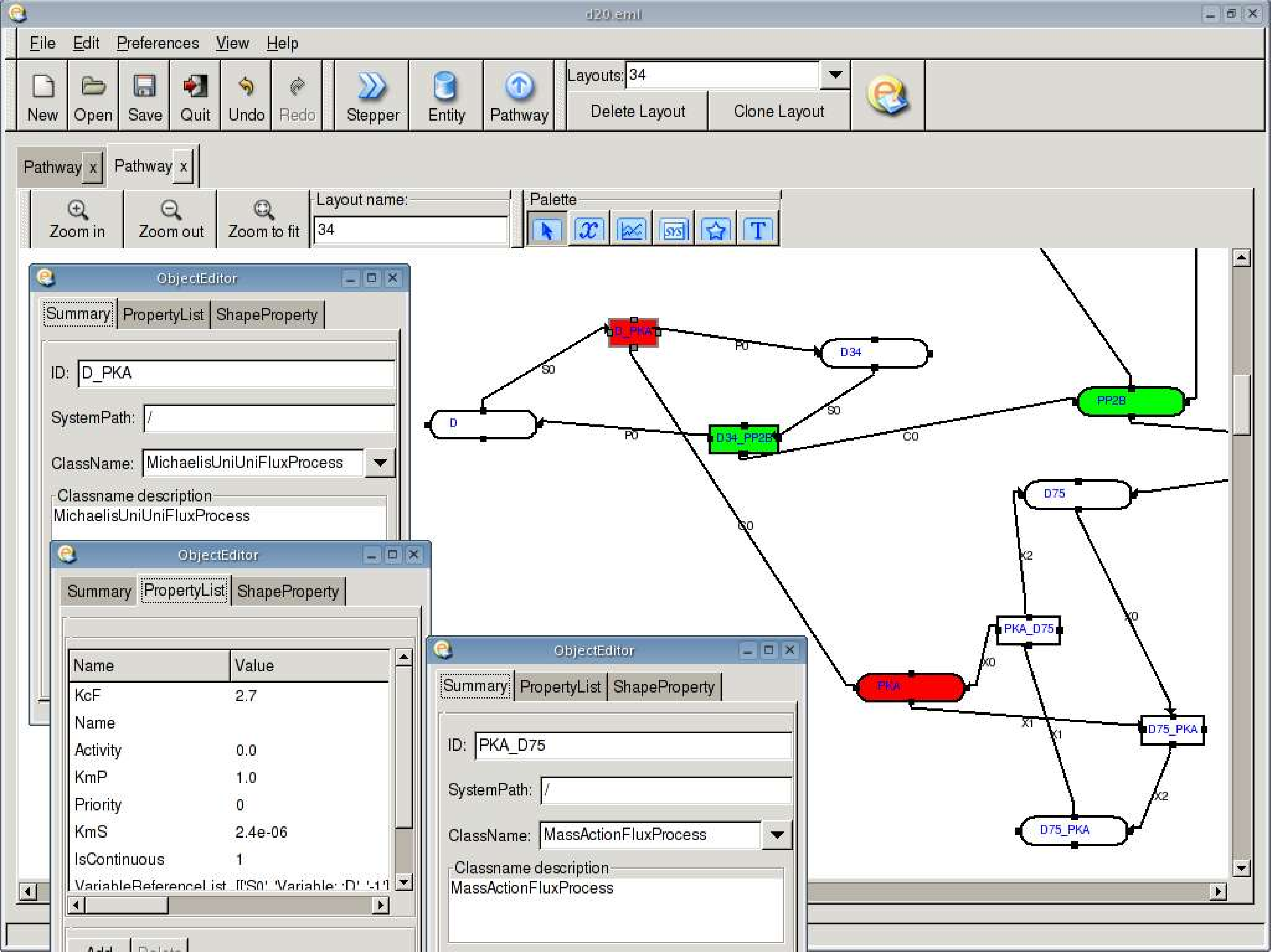


with $F_1 = d[x]/dt = f([x], t)$

$F_2 = f([x]_t + \Delta t/2 \,.\, F_1, t+ \Delta t/2)$

$F_3 = f([x]_t + \Delta t/2 \,.\, F_2, t+ \Delta t/2)$

$F_4 = f([x]_t + \Delta t \,.\, F_3, t+ \Delta t)$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Clone Layout
Pathway x
Pathway x
Zoom in
Zoom out
Zoom to fit
Layout name:
34
Palette
ObjectEditor
Summary
PropertyList
ShapeProperty
ID: D_PKA
SystemPath: /
ClassName: MichaelisUniUniFluxProcess
Classname description
MichaelisUniUniFluxProcess
ObjectEditor
Summary
PropertyList
ShapeProperty
Name
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2.7
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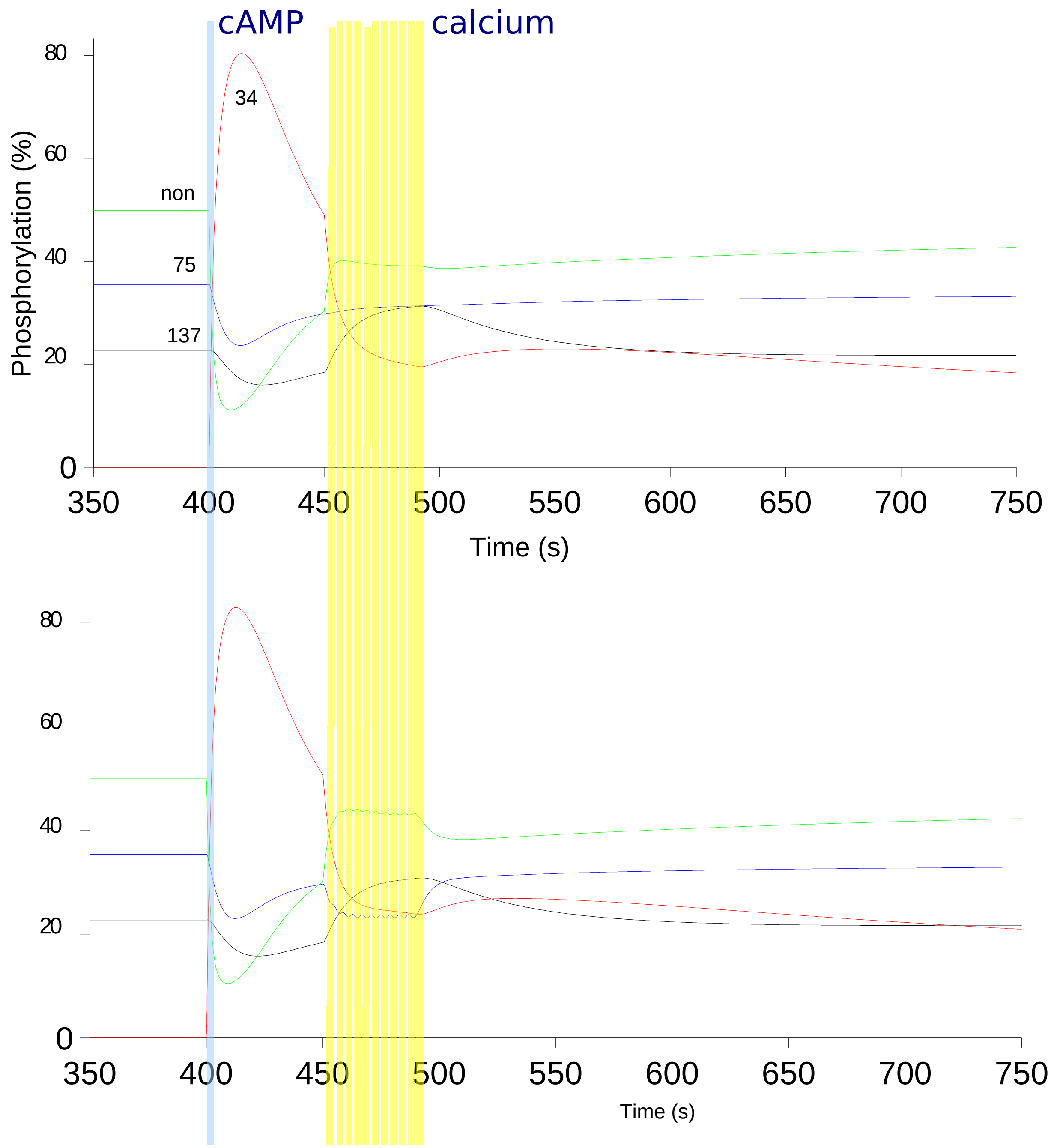
MassActionFluxProcess
D_PKA
P0
D34
S0
S0
D
P0
D34_PP2B
C0
PP2B
C0
D75
X2
PKA_D75
X0
X0
PKA
X1
X1
D75_PKA
X2
D75_PKA

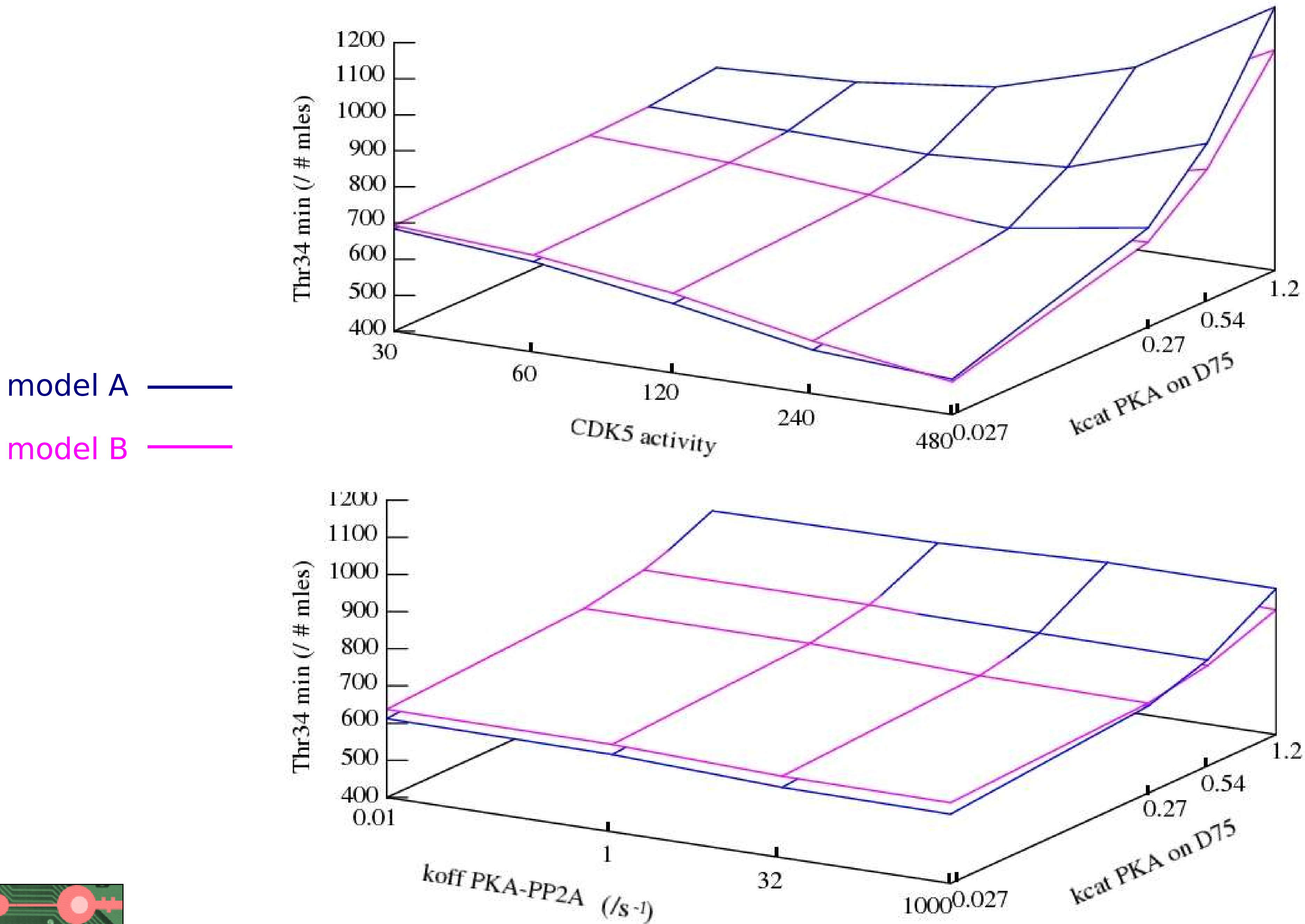
Dynamic simulations of DARPP-32 function

model A

model B



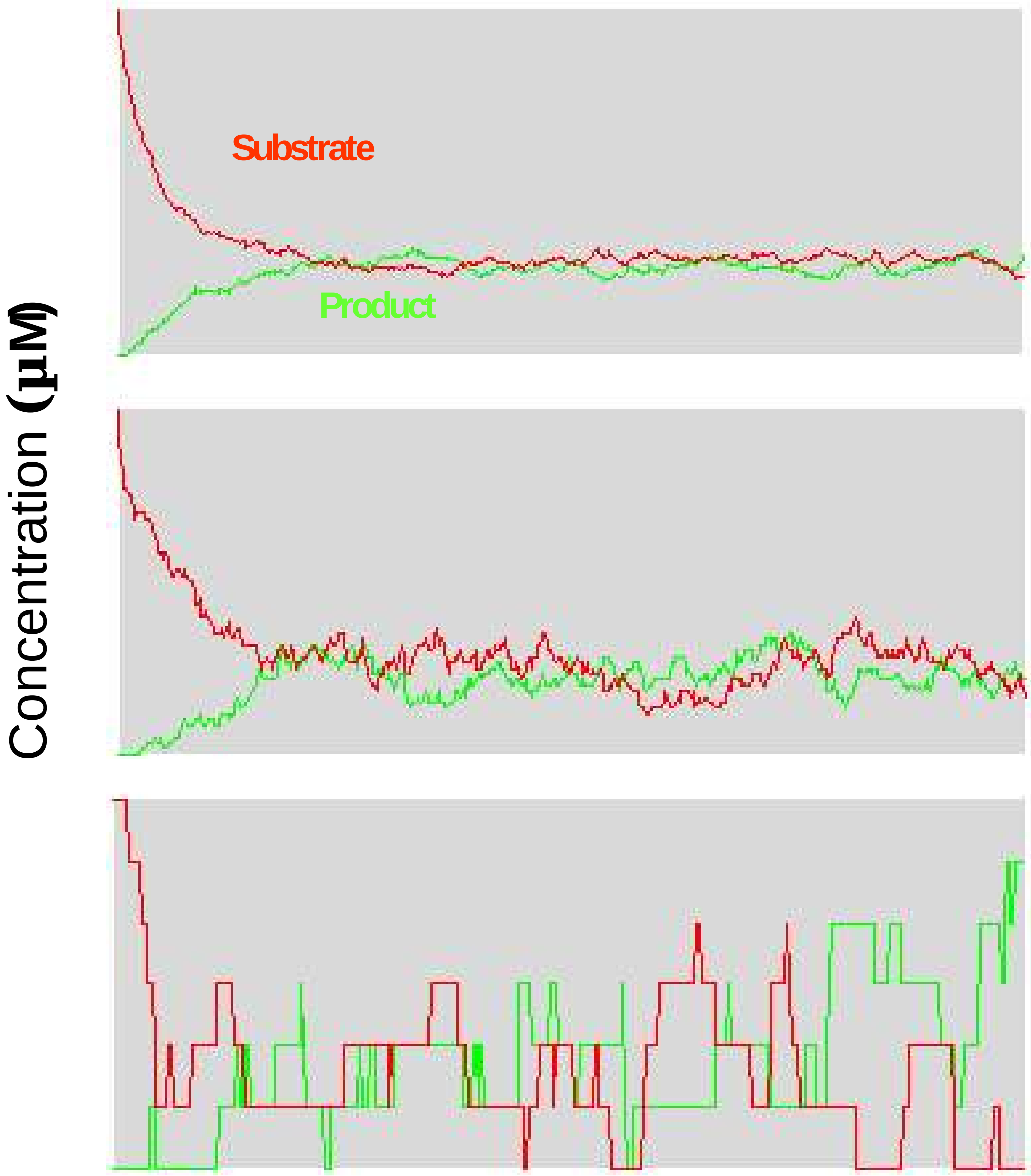
Perturbation and sensitivity analysis

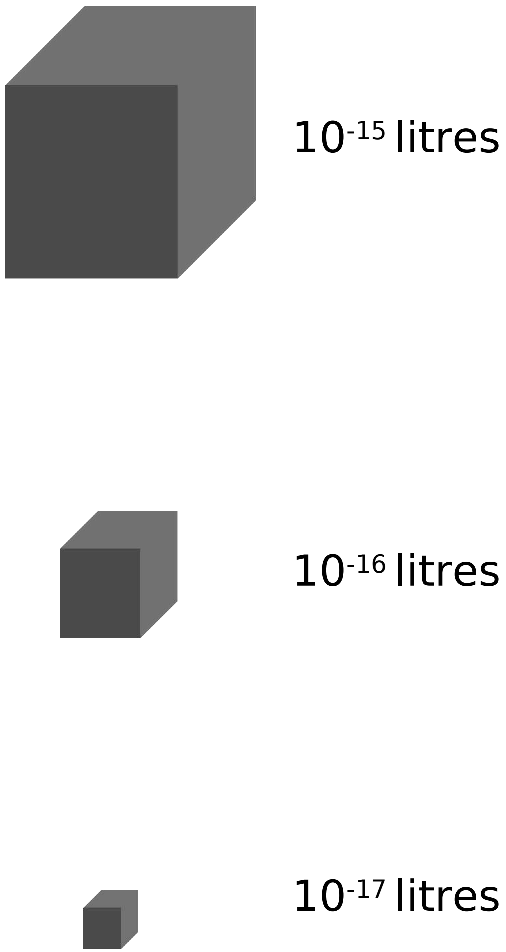


More info see

- Marta Cascante – Today 11:00
- Thomas Millat – Friday. 9:00
- Shankar Subramaniam – Saturday 11:50

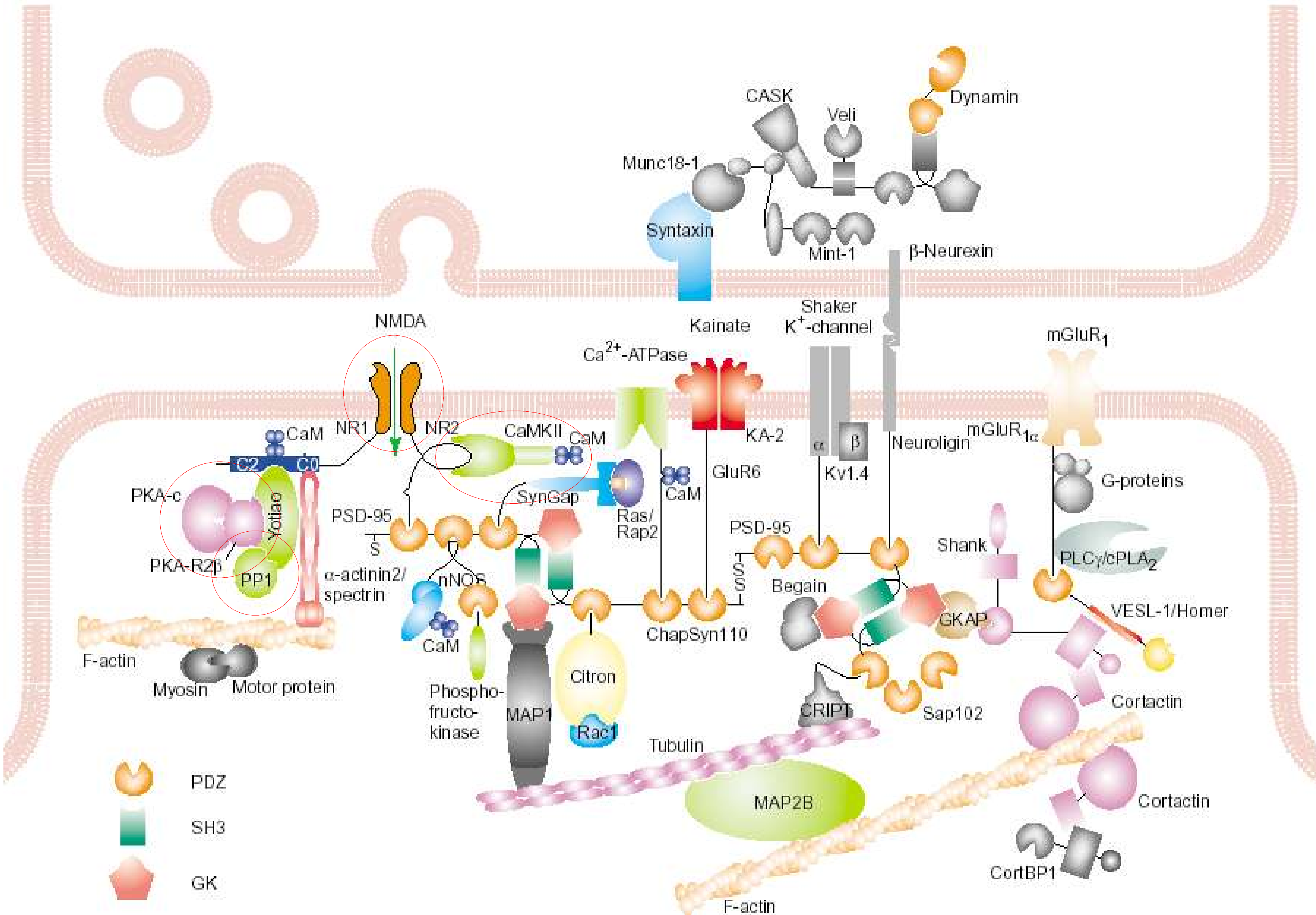
On small numbers





Number of calcium ions in a dendritic spine = 3-5 ...

Complex post-synaptic machinery



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

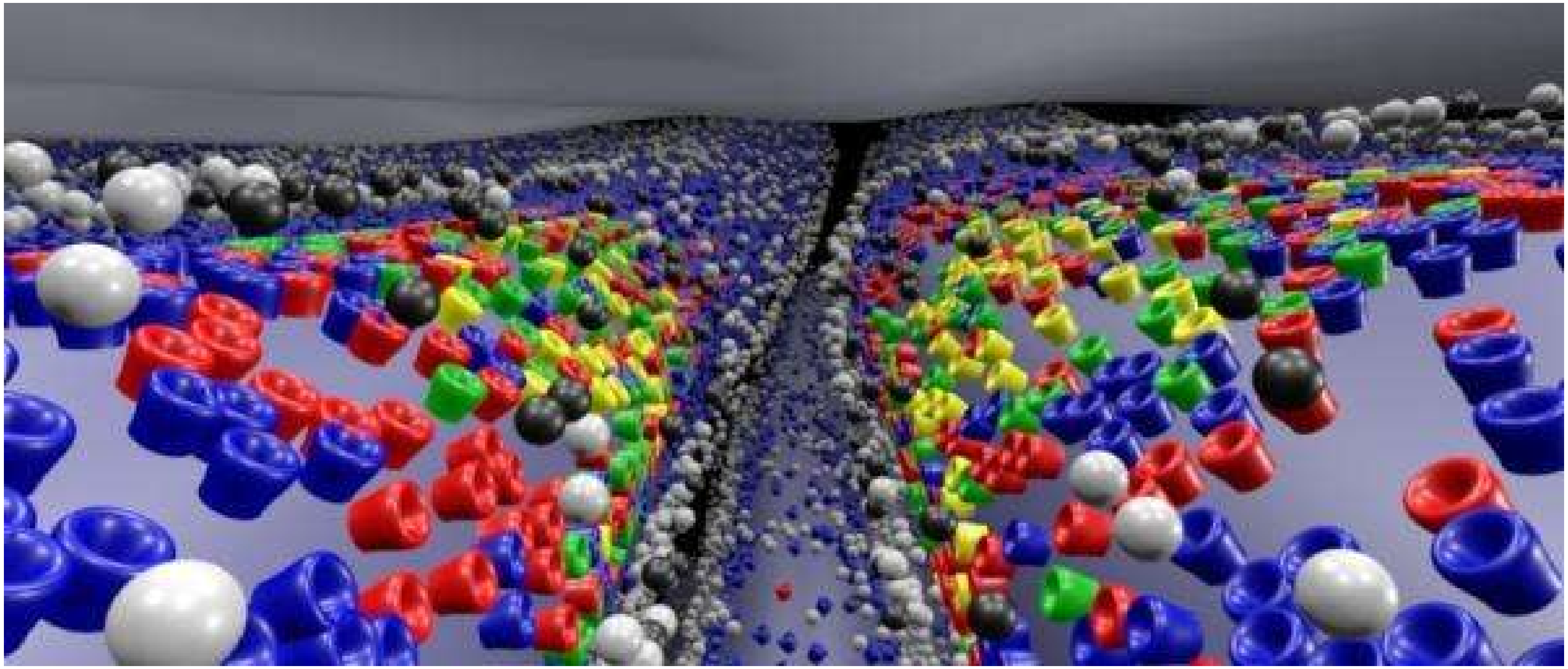
Need another paradigm of simulation

Population-based simulation

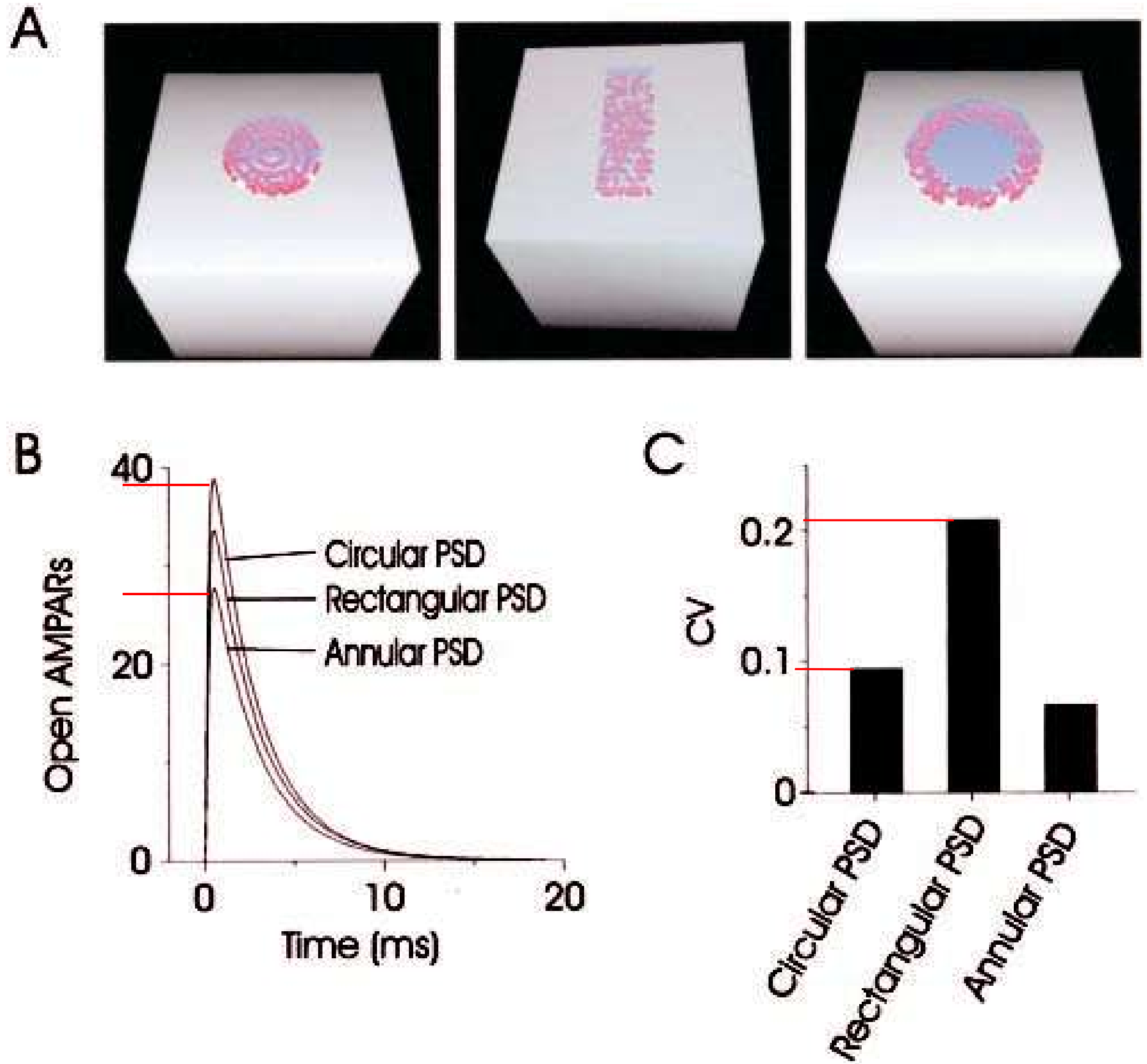
- Continuous representation of populations
- Generally deterministic algorithms to simulate the evolution of populations (but not always: Gillespie)
- Generally no representation of space (but not always: finite elements)
- No movements (but not always: PDE or reaction-diffussion)
- Molecules under different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

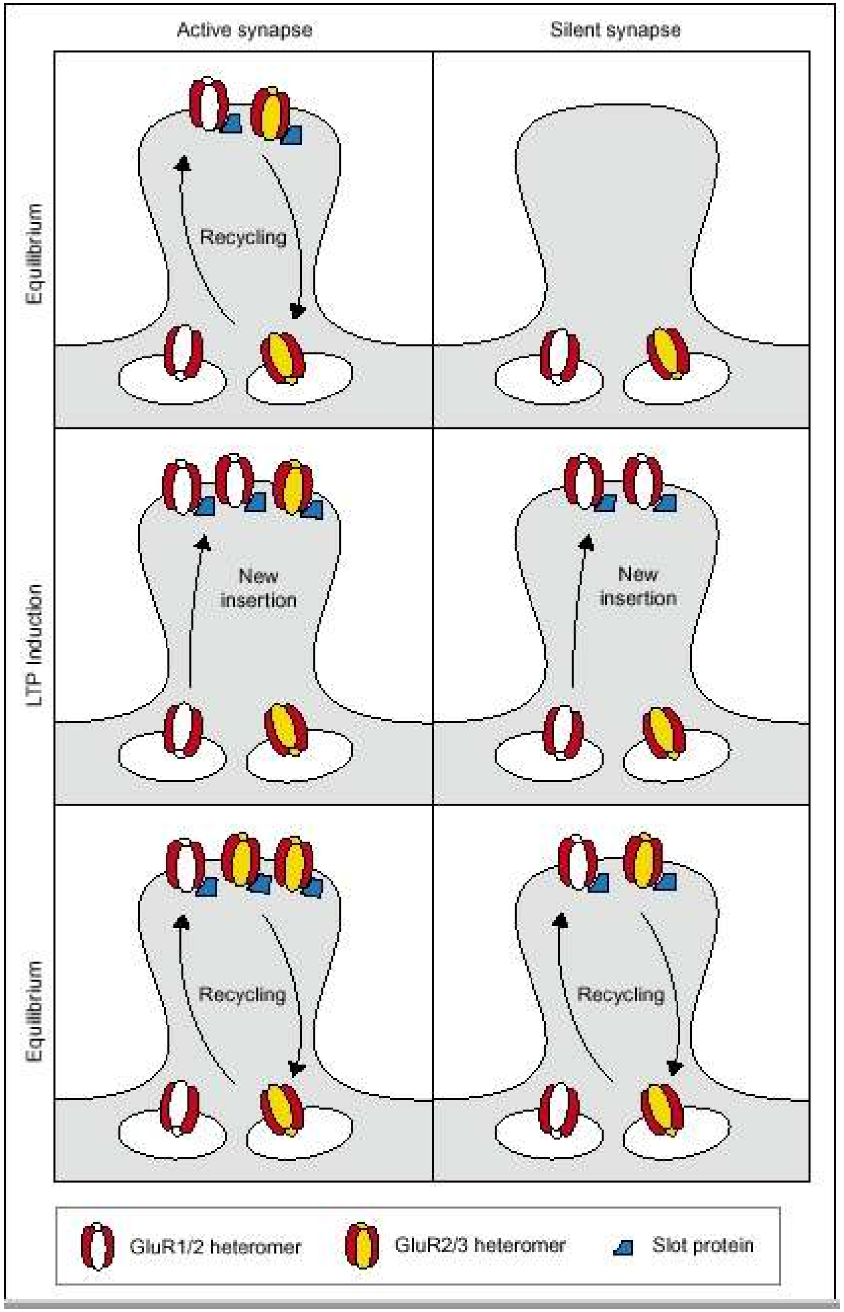


The position of receptors affects the signal

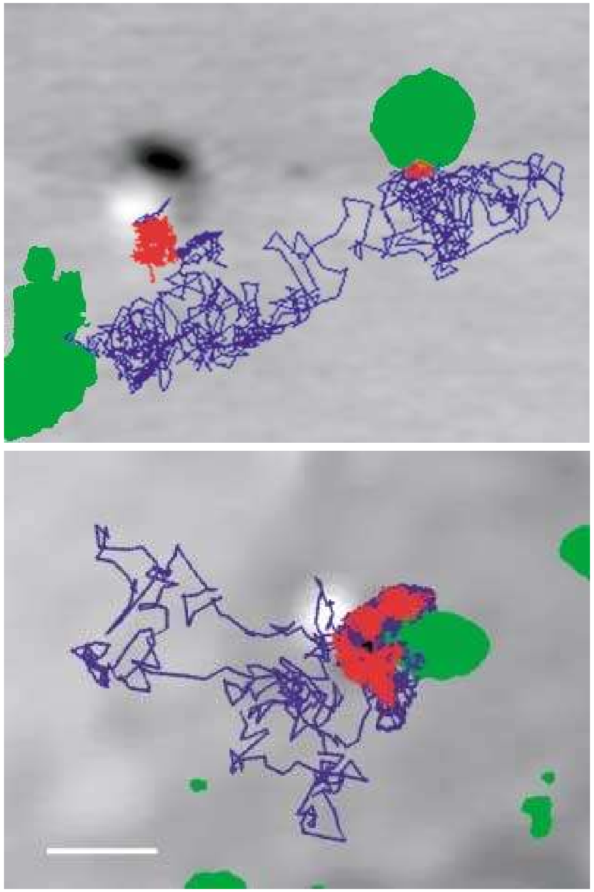


Franks et al. (2003) *J Neurosci*, 23: 3186-3195

Receptors for neurotransmitters are moving



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



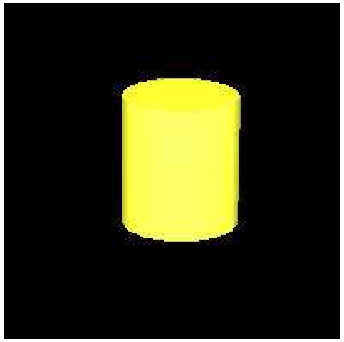
Choquet & Triller (2003)
Nat Rev Neurosci, 4: 251-265

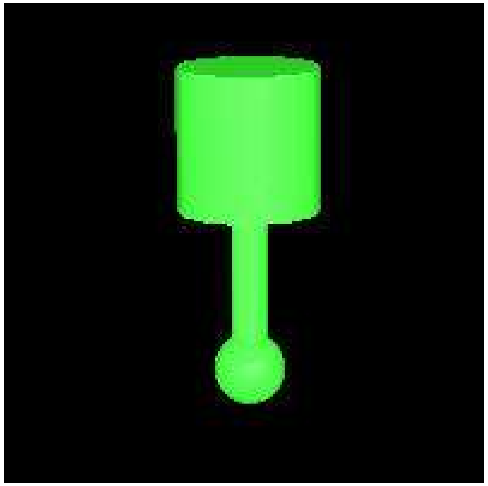
APS: the mesoscopic scale

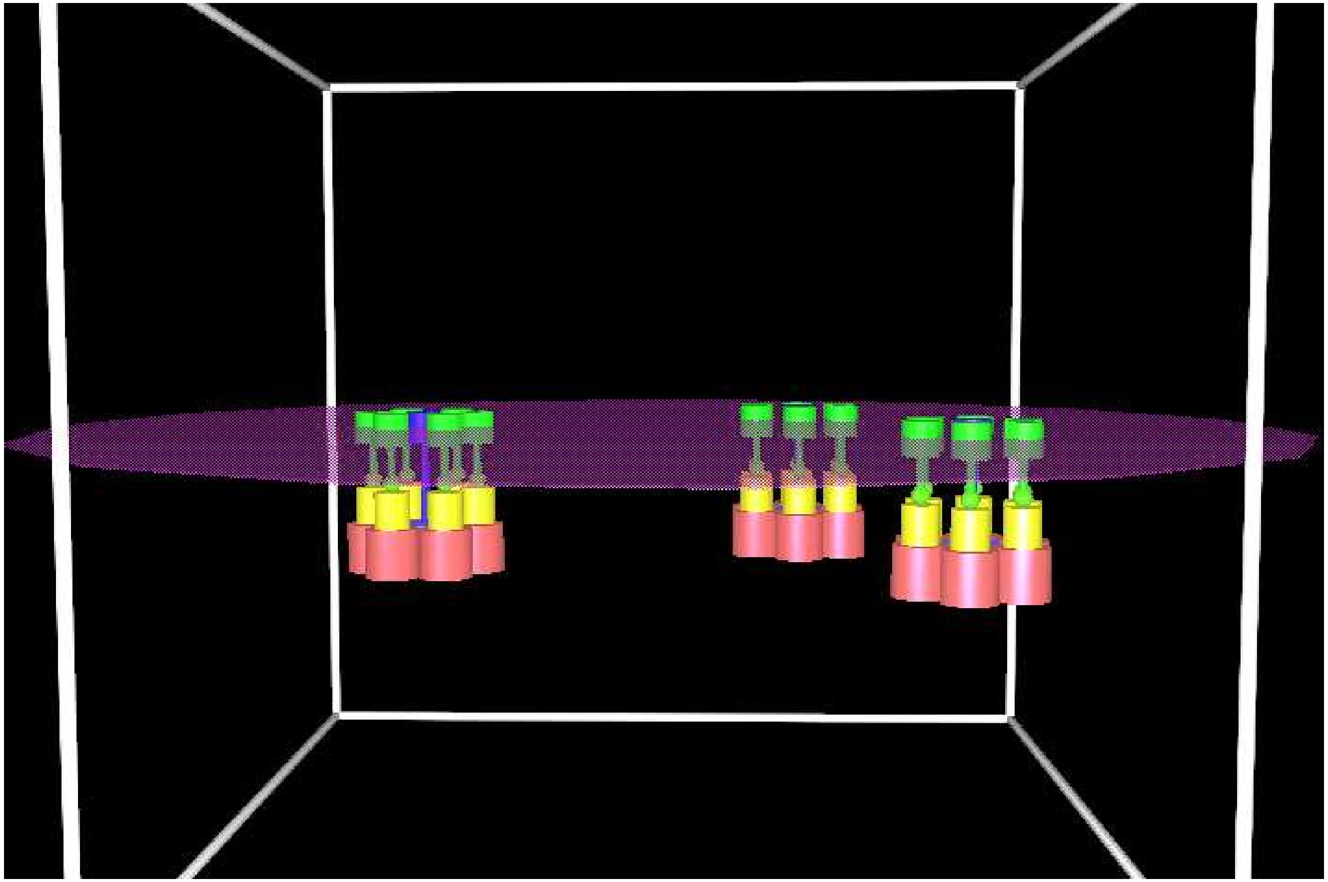
- molecule abstracted ⇒ macroscopic scale
- atomic details ⇒ microscopic scale
- Abstracted but realistic geometry ⇒ mesoscopic scale
- Relative size of object respected
- Differential location of binding sites
- realistic movements (speed and topology)

Computational Neurobiology

Particles, Objects and Clusters







Particles carry binding sites

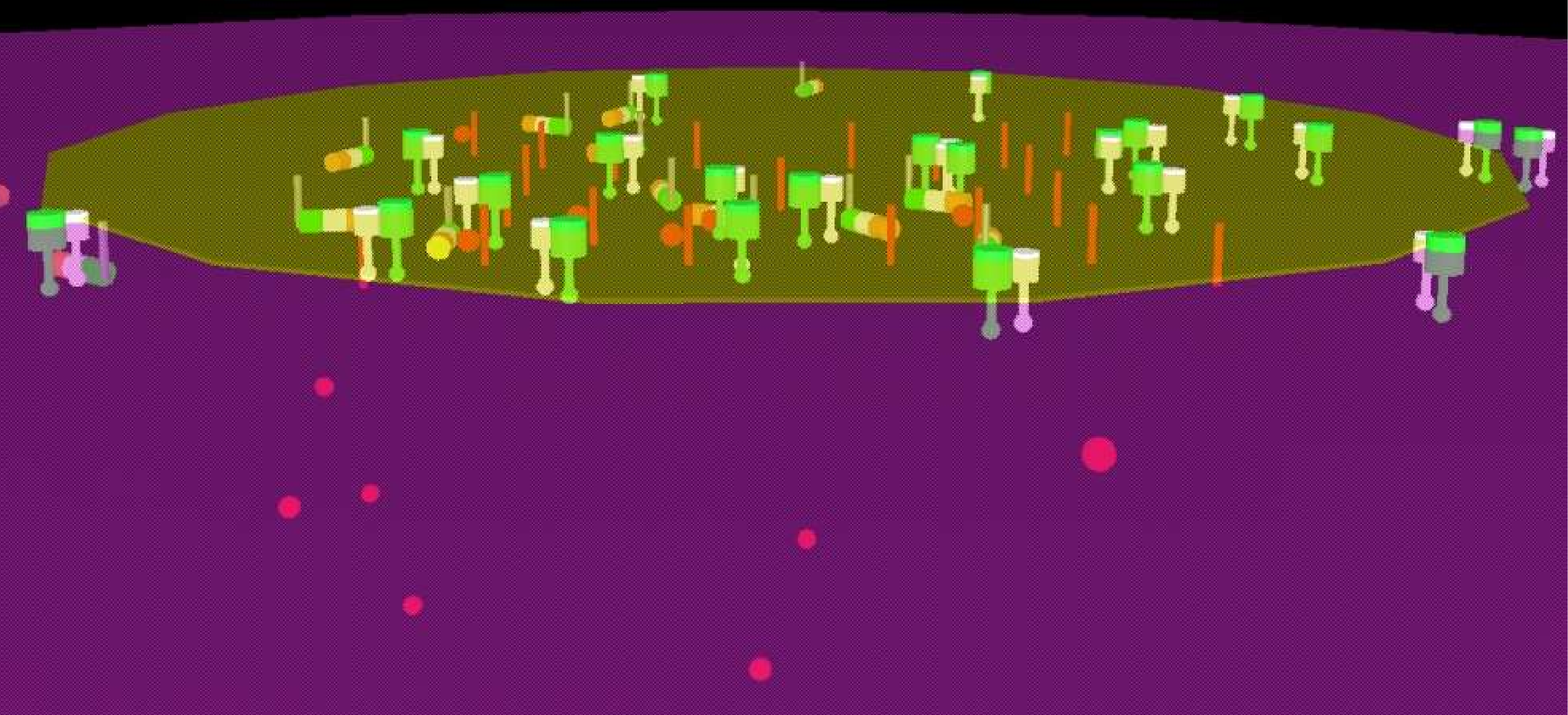
Cluster class allows recording of Center Of Mass, radius, RMS displacement; possibility of cluster state

Clusters are dynamically created and destroyed – transient.

Molecule diffusion

- 2D or 3D random walk algorithm.
- Different diffusion spaces:
  - Static; Free diffusion; Membrane diffusion; Above membrane; Below membrane
- Two types of motion:
  - Translational
  - Rotational
- Two types of diffusion equations:
  - unrestricted brownian motion, either in 3D or 2D – Low Trans/Rot
  - intra-membrane diffusion (Saffman and Delbrück 1975) – High Trans/Rot

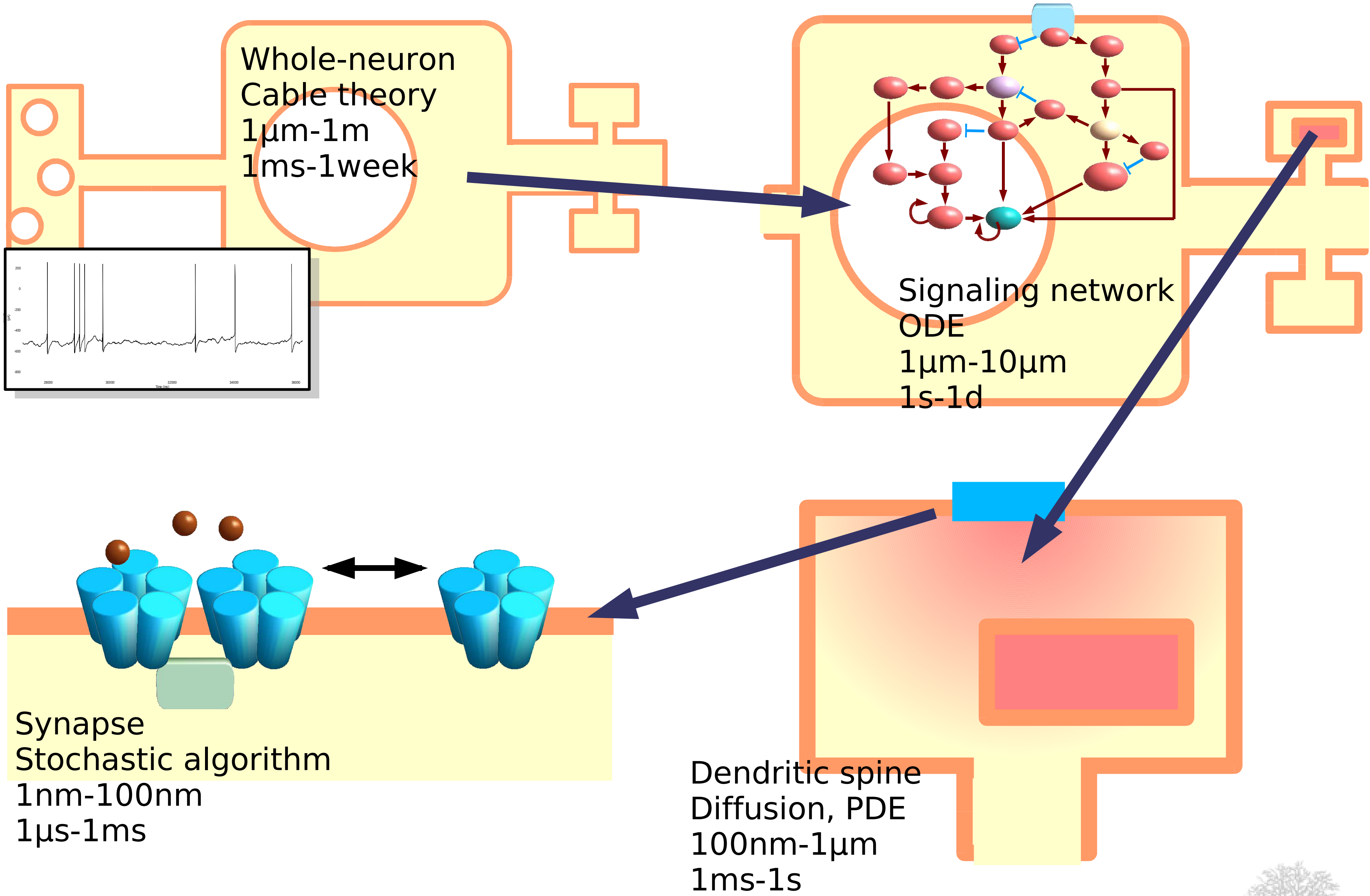
$$P(r + \Delta r, t + \Delta t) = \left(\frac{4kT\Delta t}{3\mu a}\right)^{-\frac{1}{2}} \times \mathrm{e}^{-\left(\frac{4kT}{3\pi\mu a}\right)^{-1} \times \frac{\Delta r^2}{\Delta t}}$$



More info see

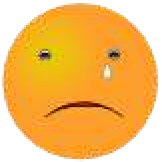
- Misha Linial – Friday 18:10

Multi-scale multi-algorithm problem



The limited factor in kinetic modelling is the experimental quantitative data

This is particularly true in Neurobiology



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