Modélisation de l'intégration des signaux dans le neurone

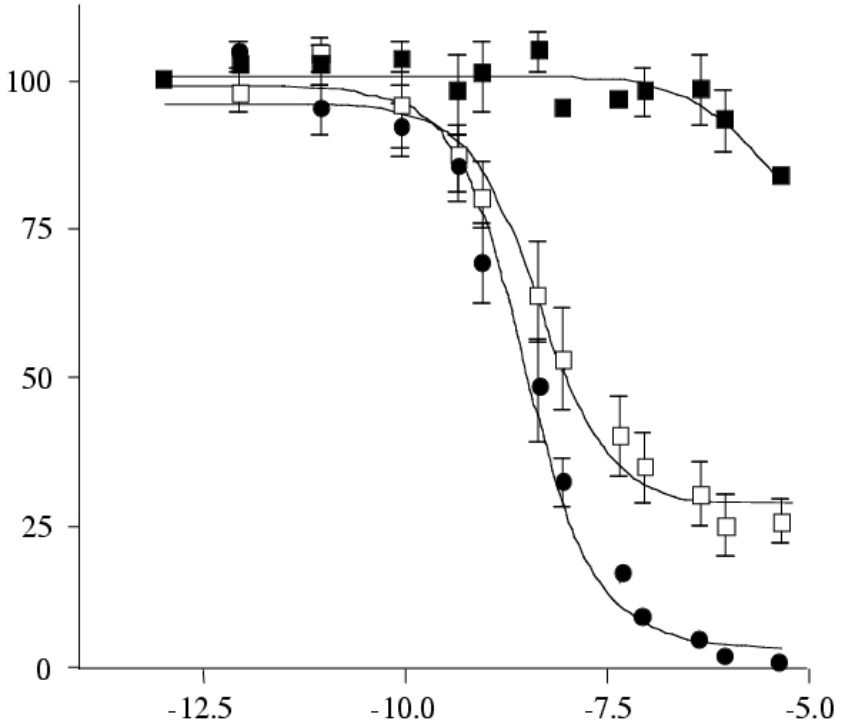
(Computational Systems Neurobiology)

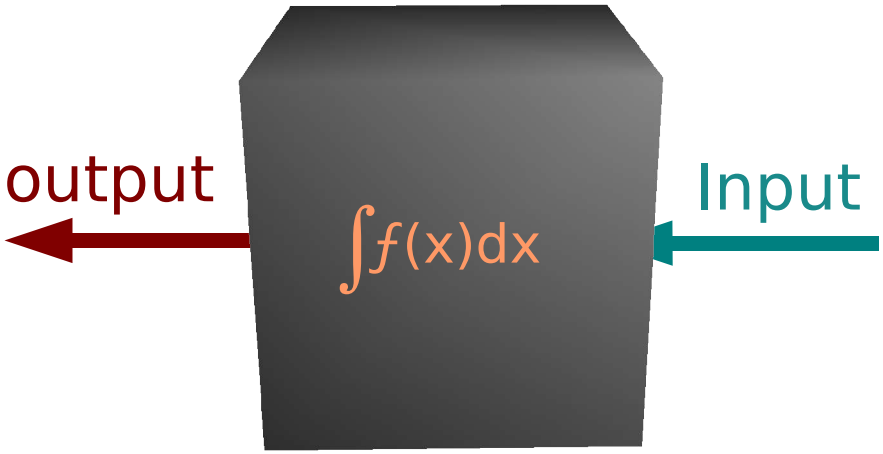
Nicolas Le Novère, EMBL-EBI

Classical approaches in theoretical biology

(1)-The phenomenology

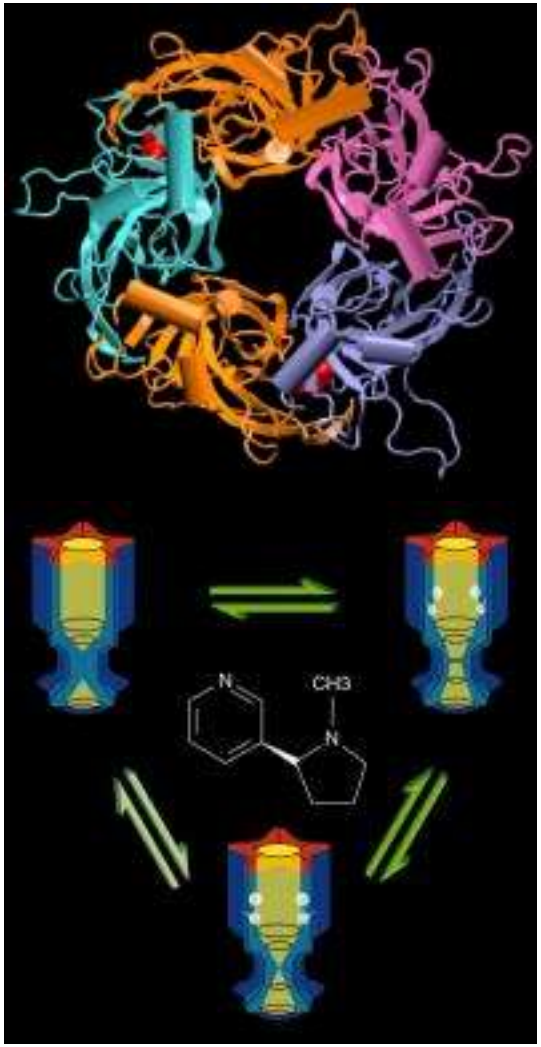
Snapshot of the system ⇒ Abstraction

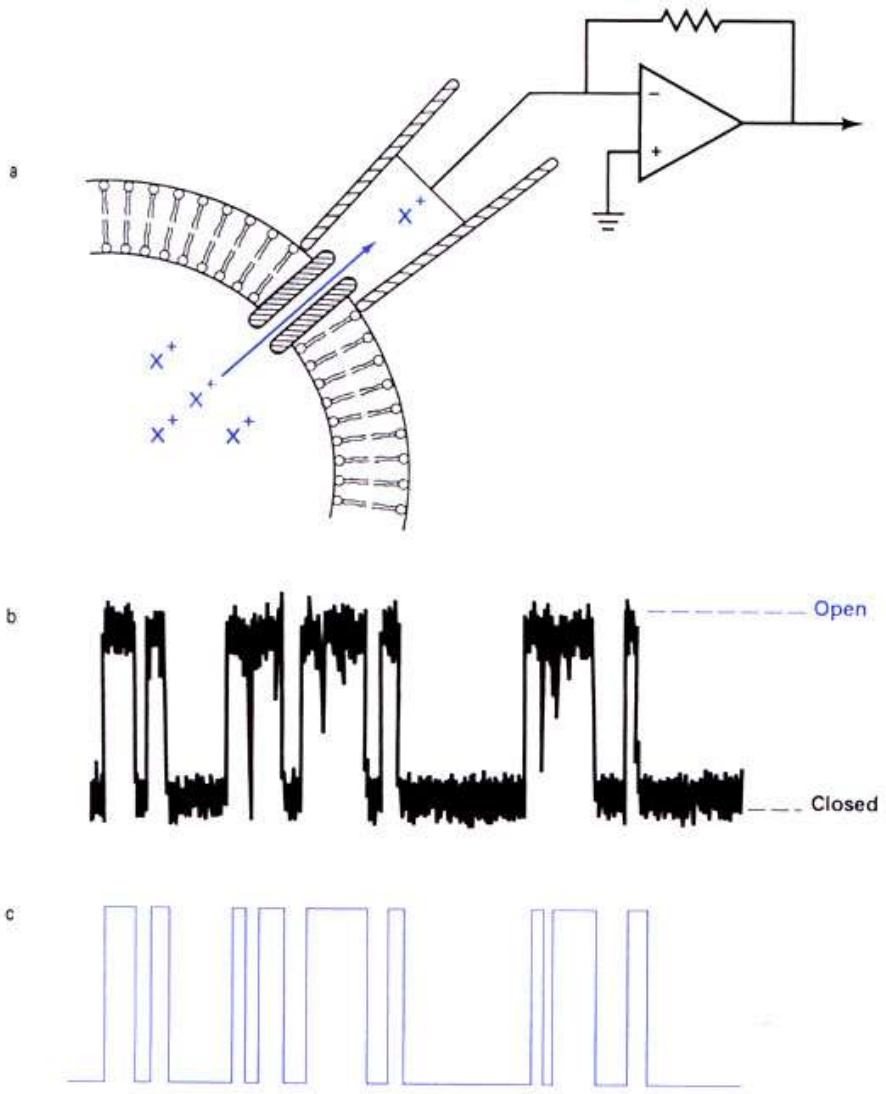




Classical approaches in theoretical biology

(2)-The reductionism





Systems Biology

- Reconstruction of dynamic systems from the properties of their elementary building blocks

- Made possible by large-scale data production
  & improvements of computing power and technologies

- Cybernetics properties are conserved across systems
  (control theory: feedback, feedforward, robustness...)
  Relationships between building blocks are more important than their elementary properties.
  The theoretical treatment is already available.

- A New Era:
  Pre-molecular Biology was *descriptive*
  Molecular Biology made Biology *explicative*
  Systems Biology makes Biology *predictive*

Why computational modelling?

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.*

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

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

Why computer simulations in Biology

- Complexity of biological systems
  - Structural complexity: molecular and cellular levels
  - Functional complexity: network of relations, non-boolean relations

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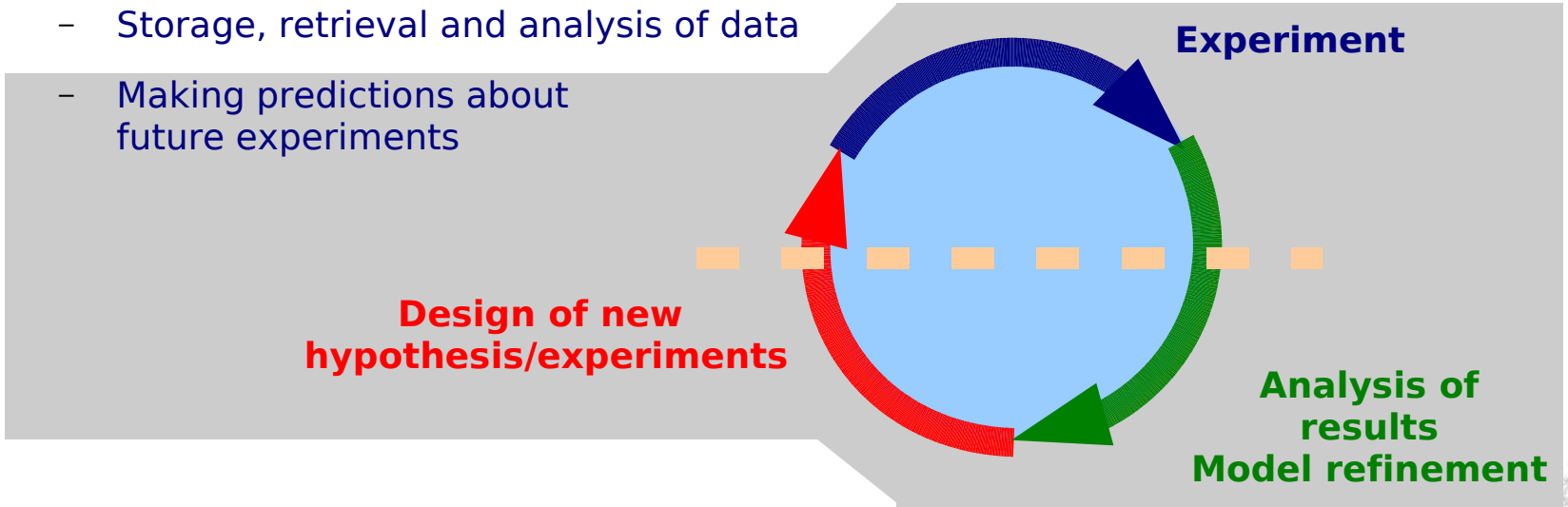

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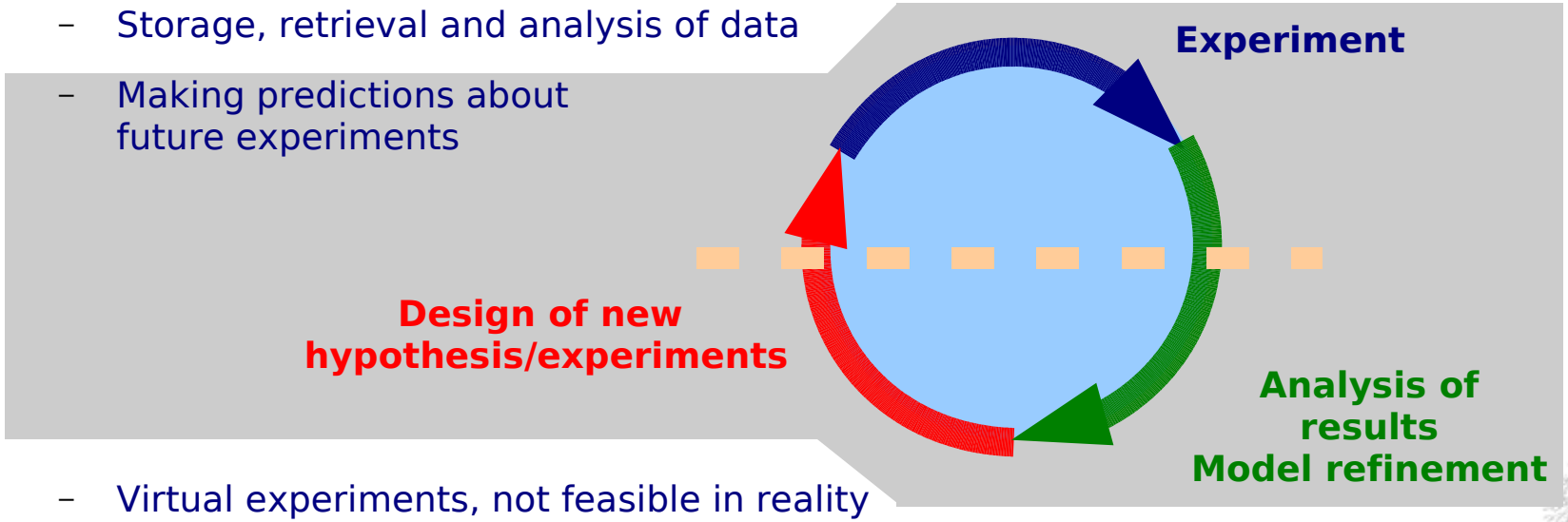


  - Virtual experiments, not feasible in reality

Modelling is at the core of biology

- Computational modelling in biology is a mature and complex field
  - Constellation of different approaches and algorithms signalling pathway:
    - graph/topology – flux analysis – kinetic simulation
    - discrete – continuous
    - ODE - PDE
  - Alternative models to describe the same phenomena Bacterial chemotaxis, Cell cycle, MAPK, EGFR signalling,
  - Being not omniscient, one has to leverage on each other expertise
- Computational modelling at the core of modern biology
  - Rise of functional genomics and systems biology Modern data are: high throughput, quantitative, quality-controlled
  - Number of models increasing exponentially
  - Size of the models is increasing with the data availability
  - “biologists” are more and more interested in challenging and using computer models

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

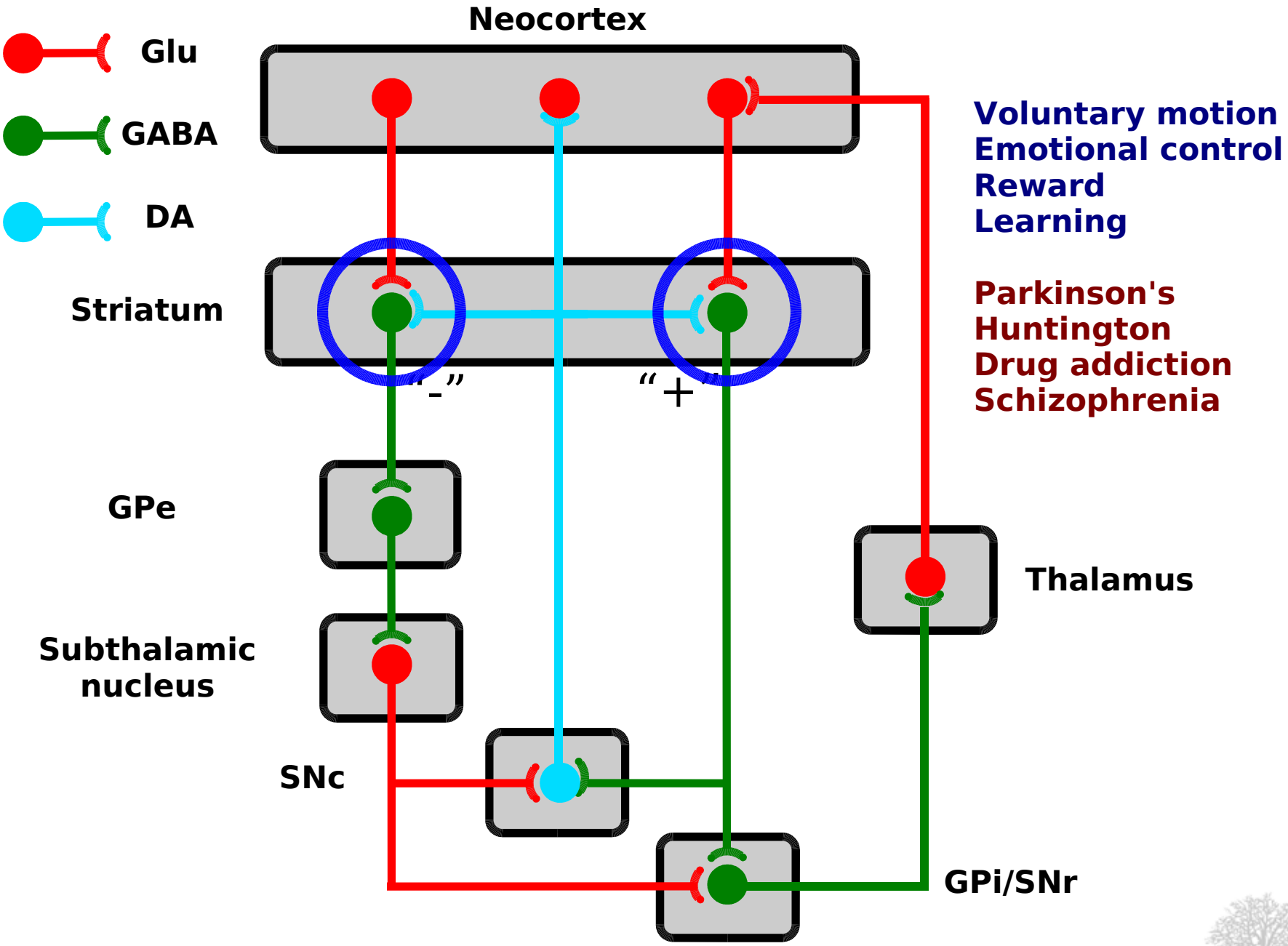
- Land, Salpeter, Salpeter
  "Kinetic parameters for acetylcholine interaction in intact neuromuscular junction". Proc Natl Acad Sci USA 1981, 78:7200-7204

- [MCell] Bartol, Land, Salpeter, Salpeter
  “Monte Carlo simulation of miniature endplate current generation in the vertebrate neuromuscular junction”. Biophy J 1991, 59: 1290-1307

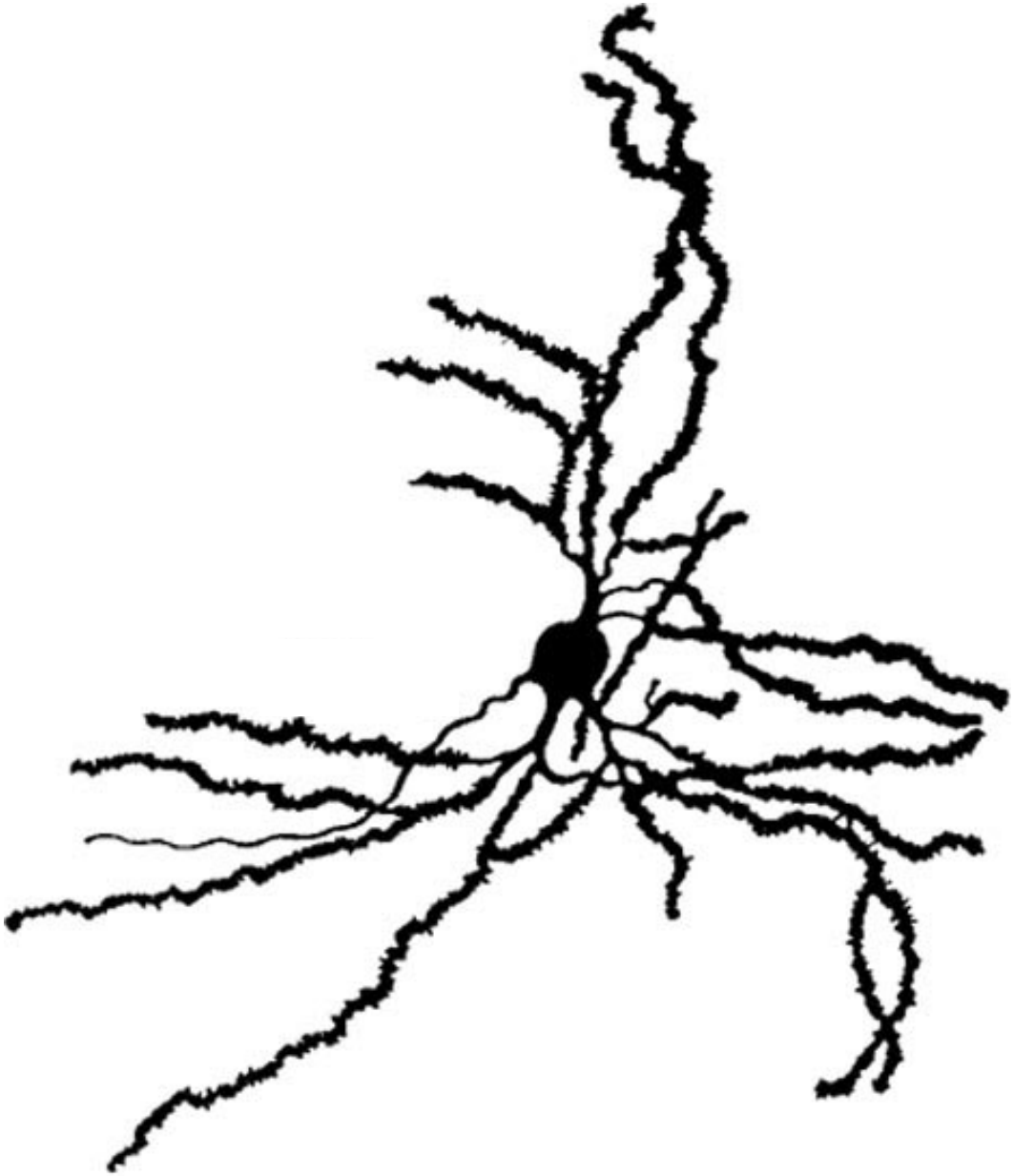
- Bhalla US, Iyengar R.
  “Emergent properties of networks of biological signaling pathways. Science 1999 283: 381-387”

- 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

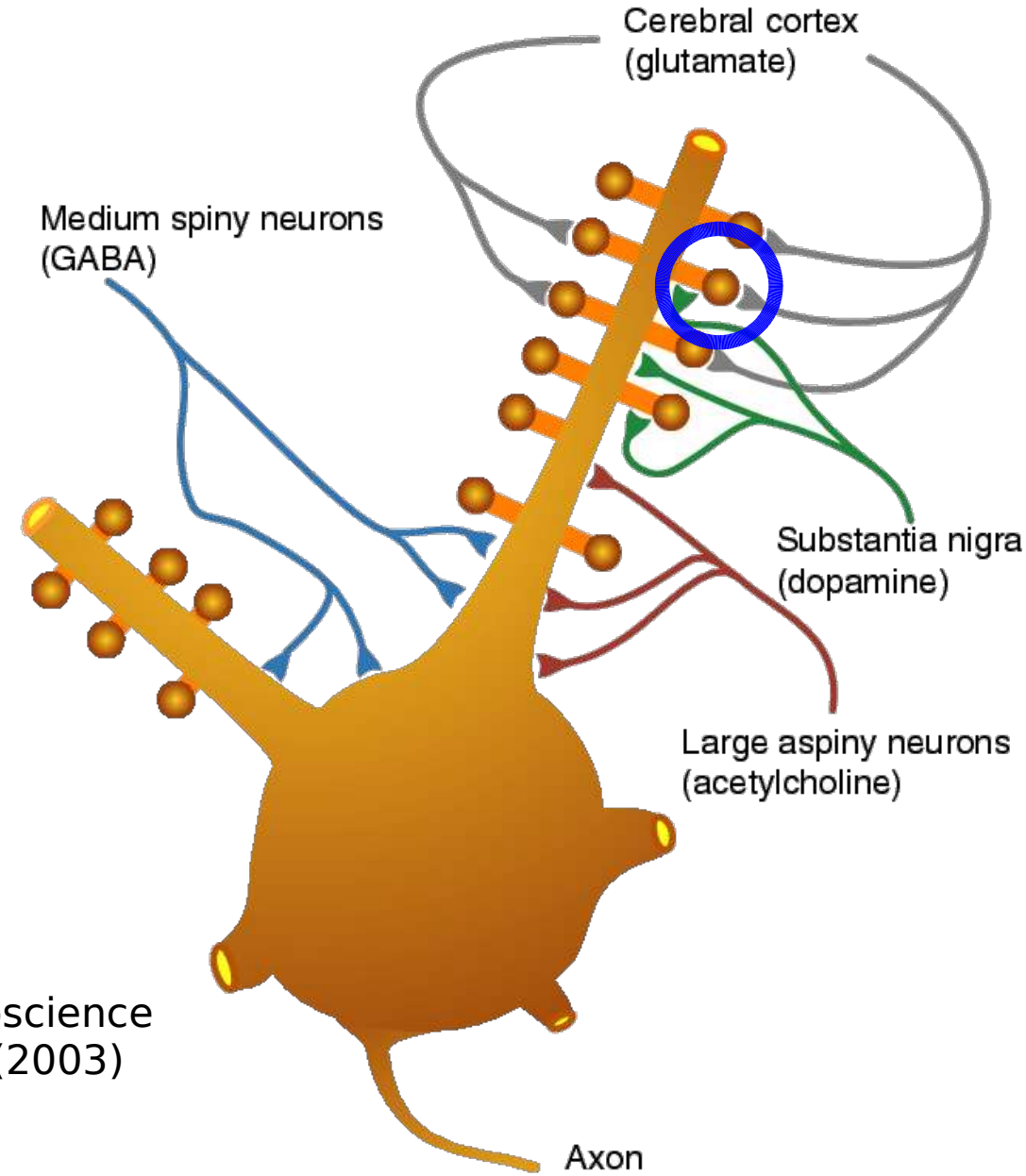
Dopamine mesotelencephalic pathway



the Medium Spiny Neuron of the striatum

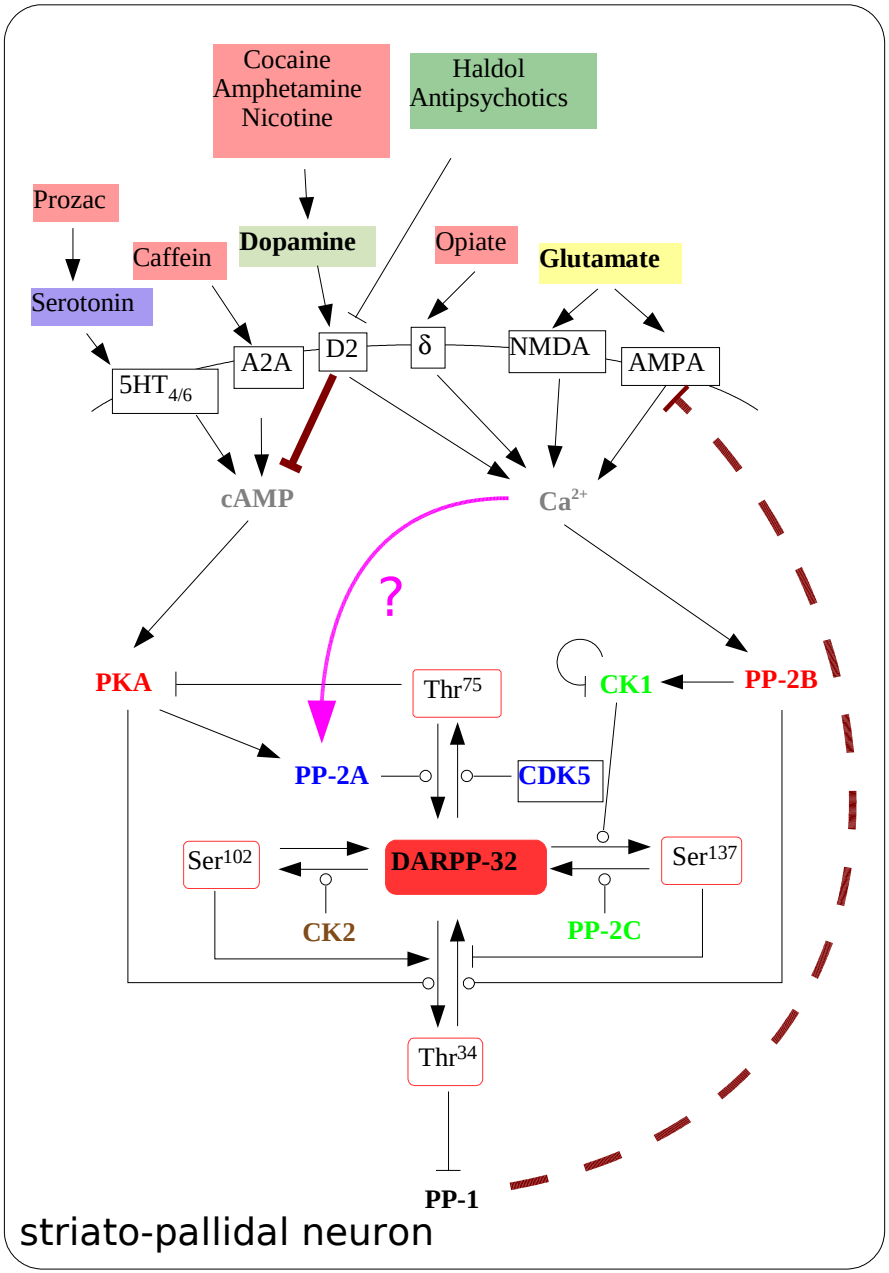


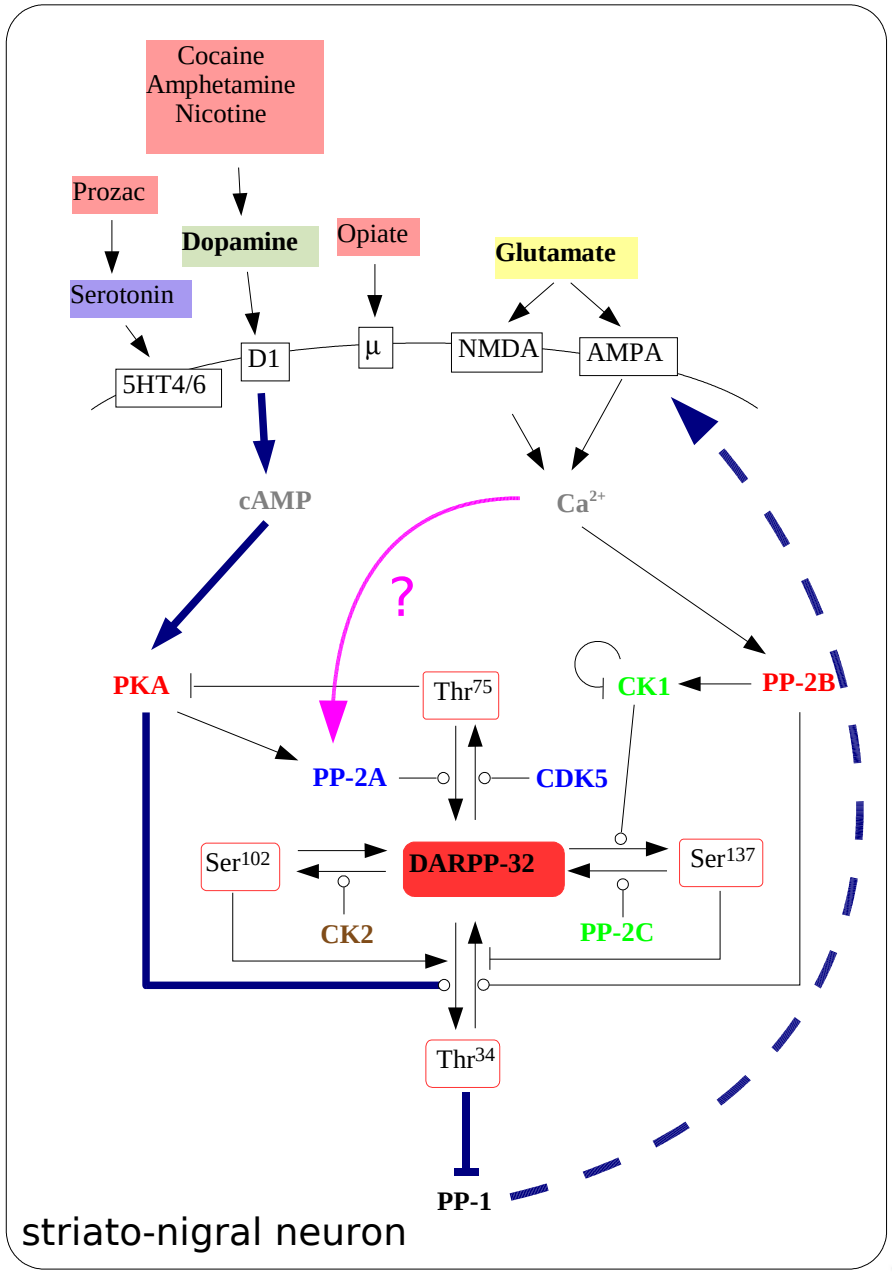
Multiple afferent signals



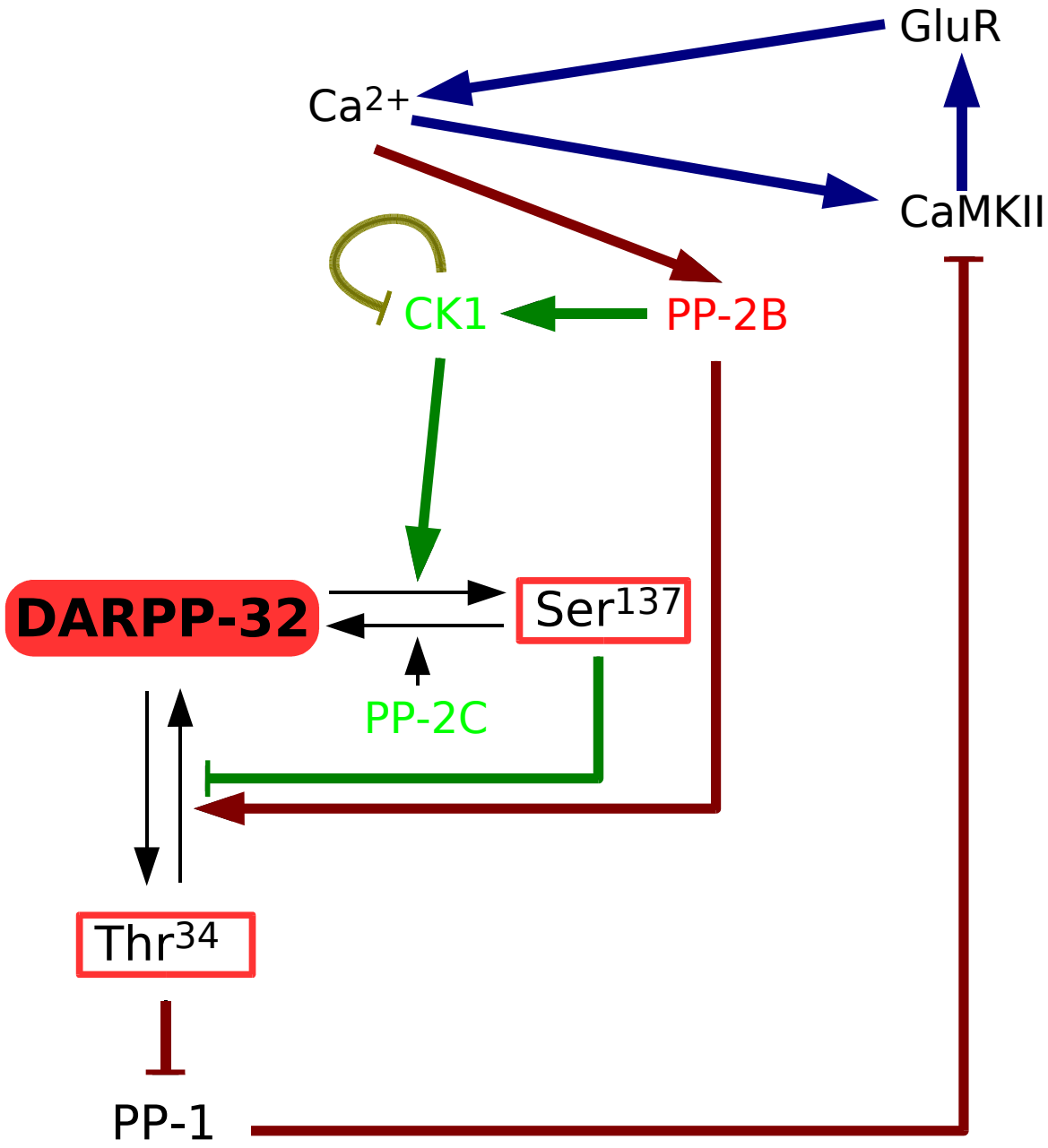
Fundamental Neuroscience
Squire et al. 2nd ed(2003)

Biological model of DARPP-32 regulation



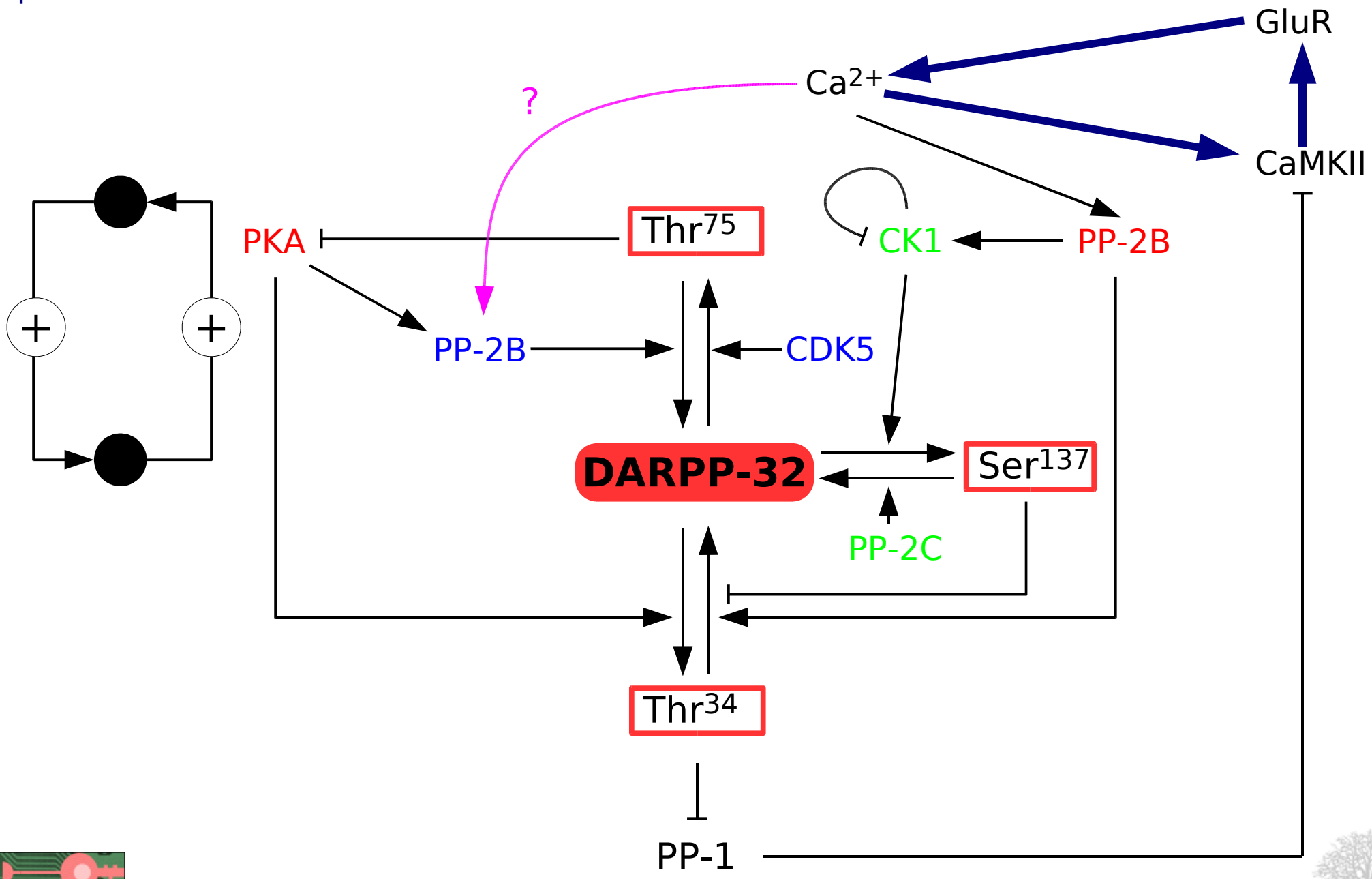


Negative loops: “russian dolls”



All the cybernetics in one system

positive feedback



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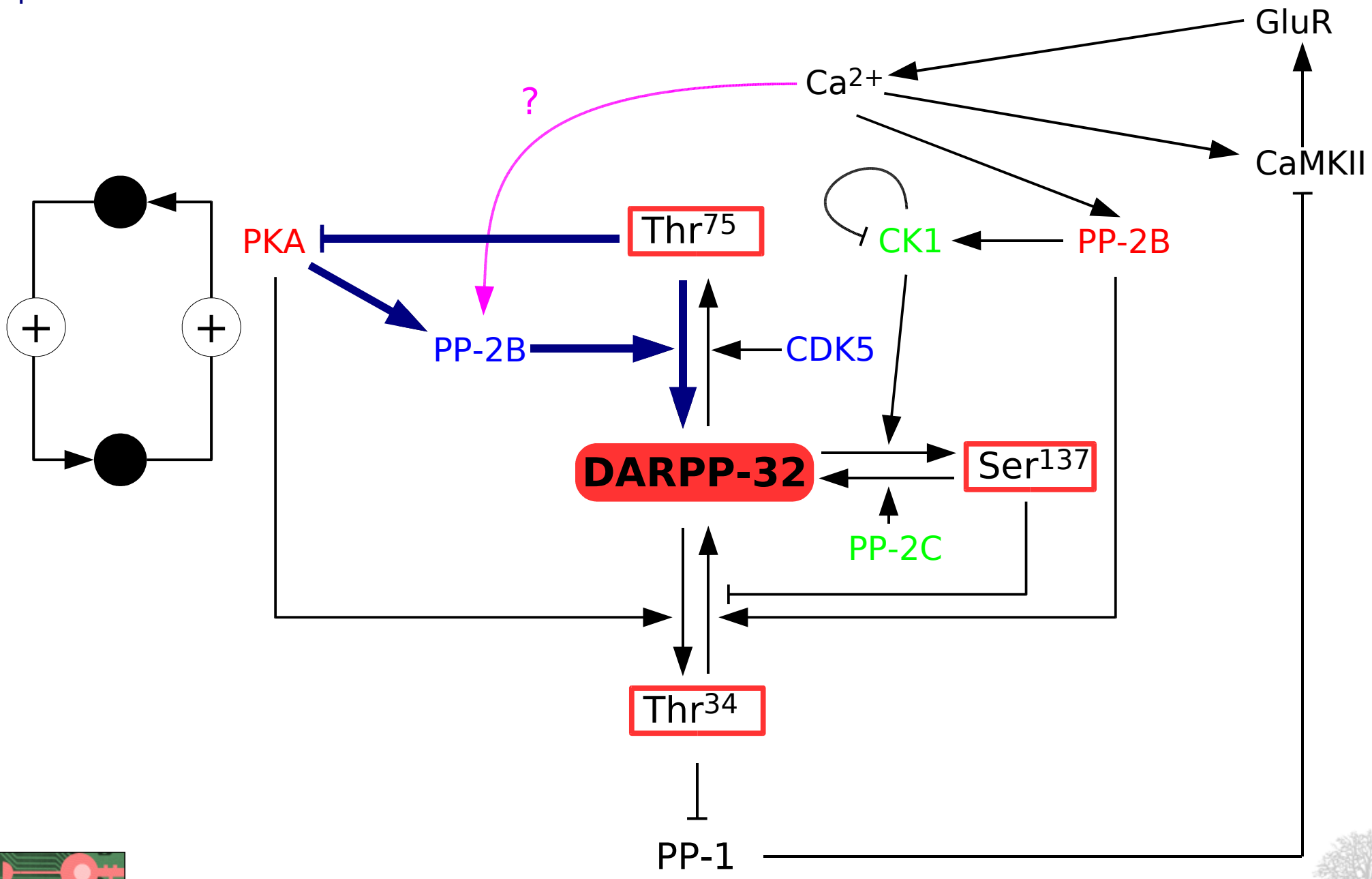

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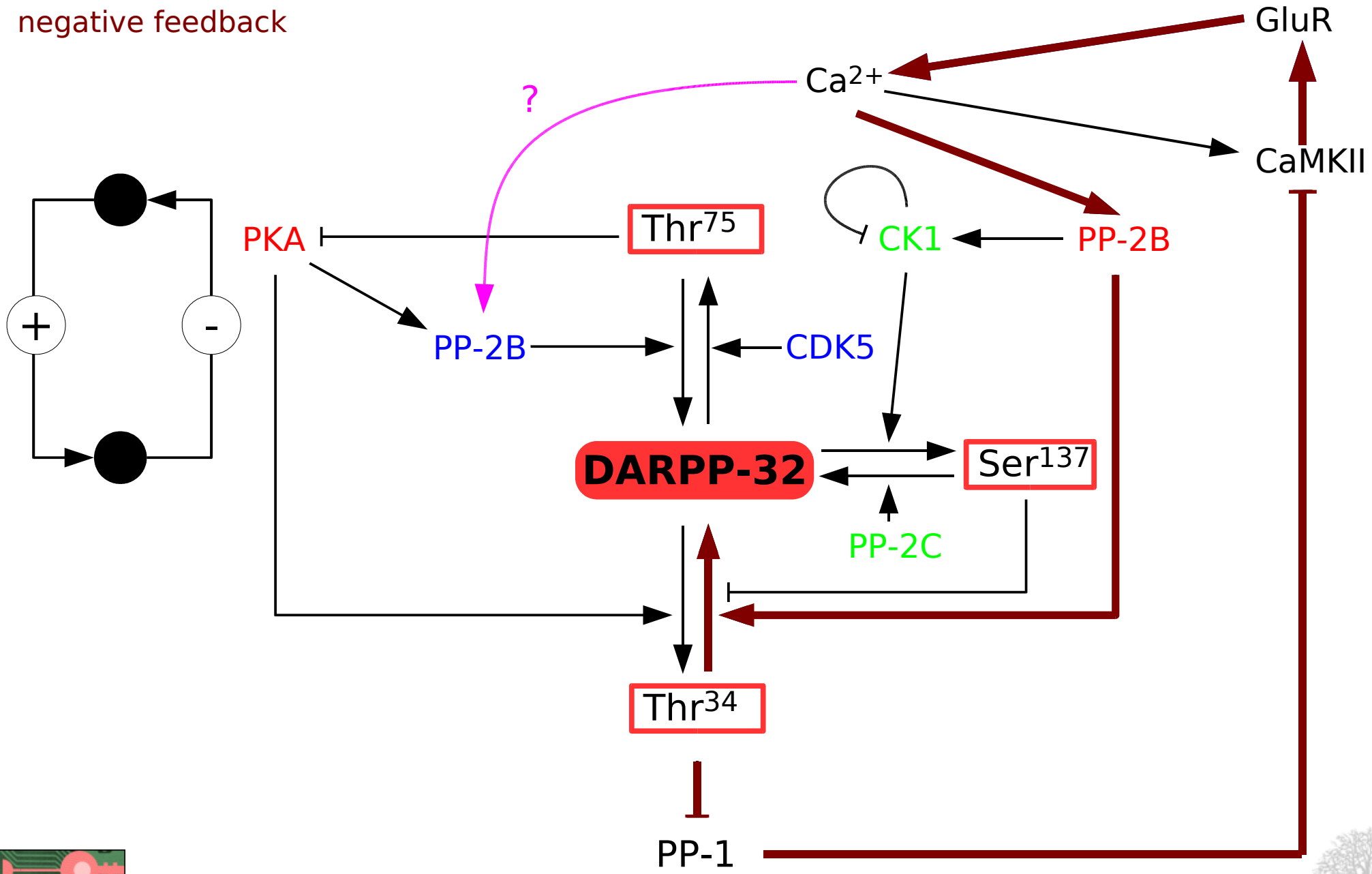

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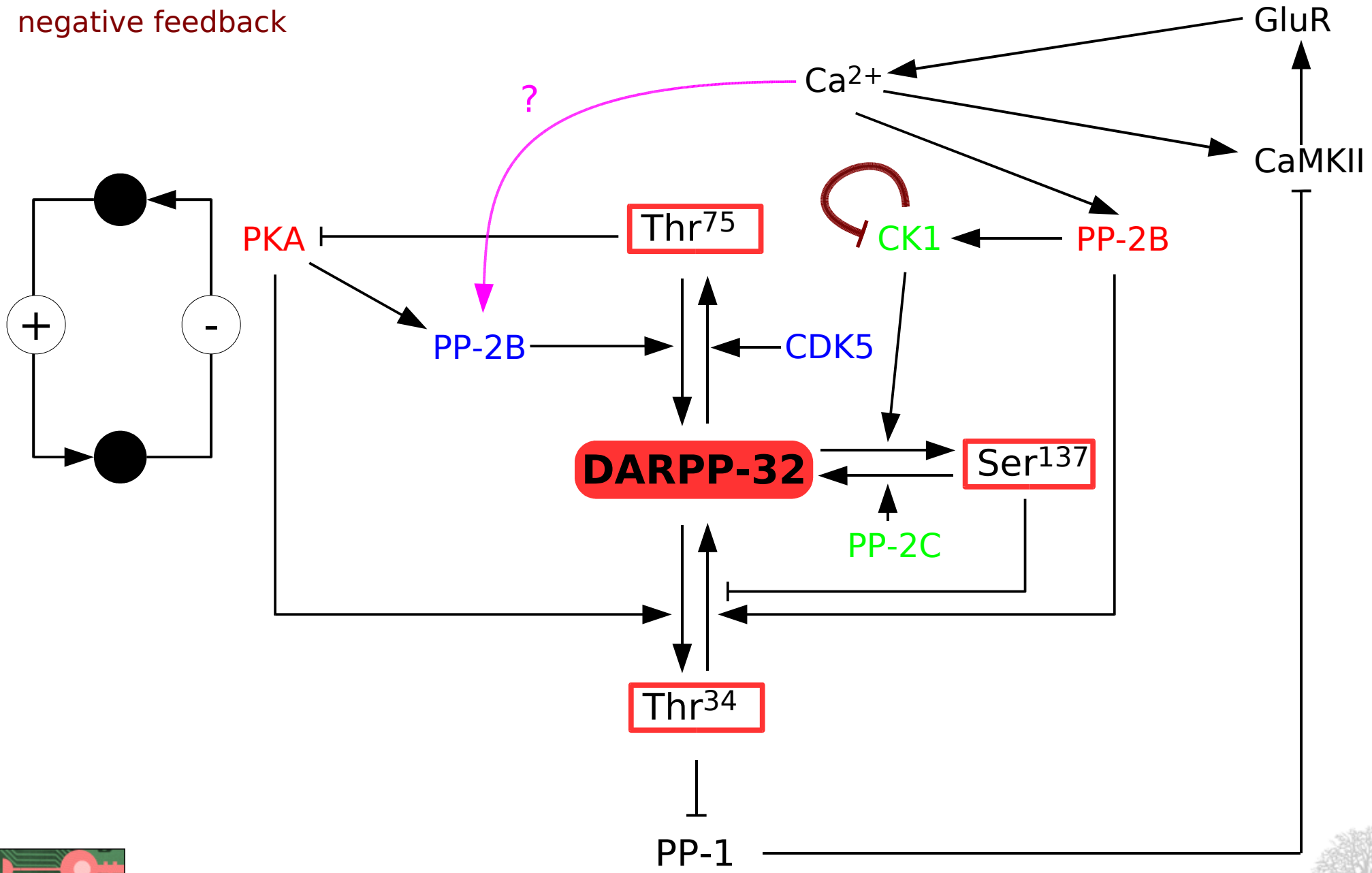

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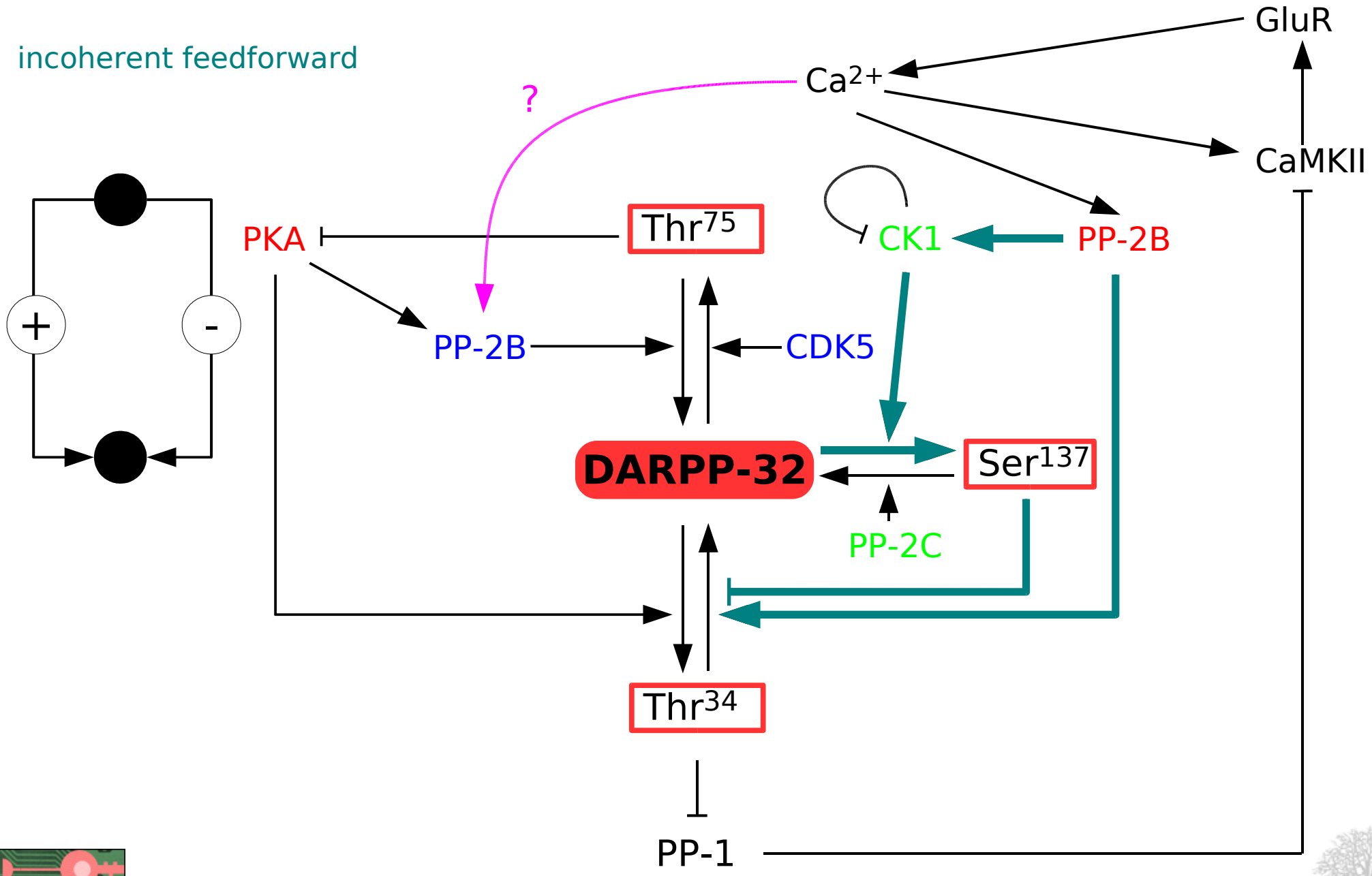
incoherent feedforward



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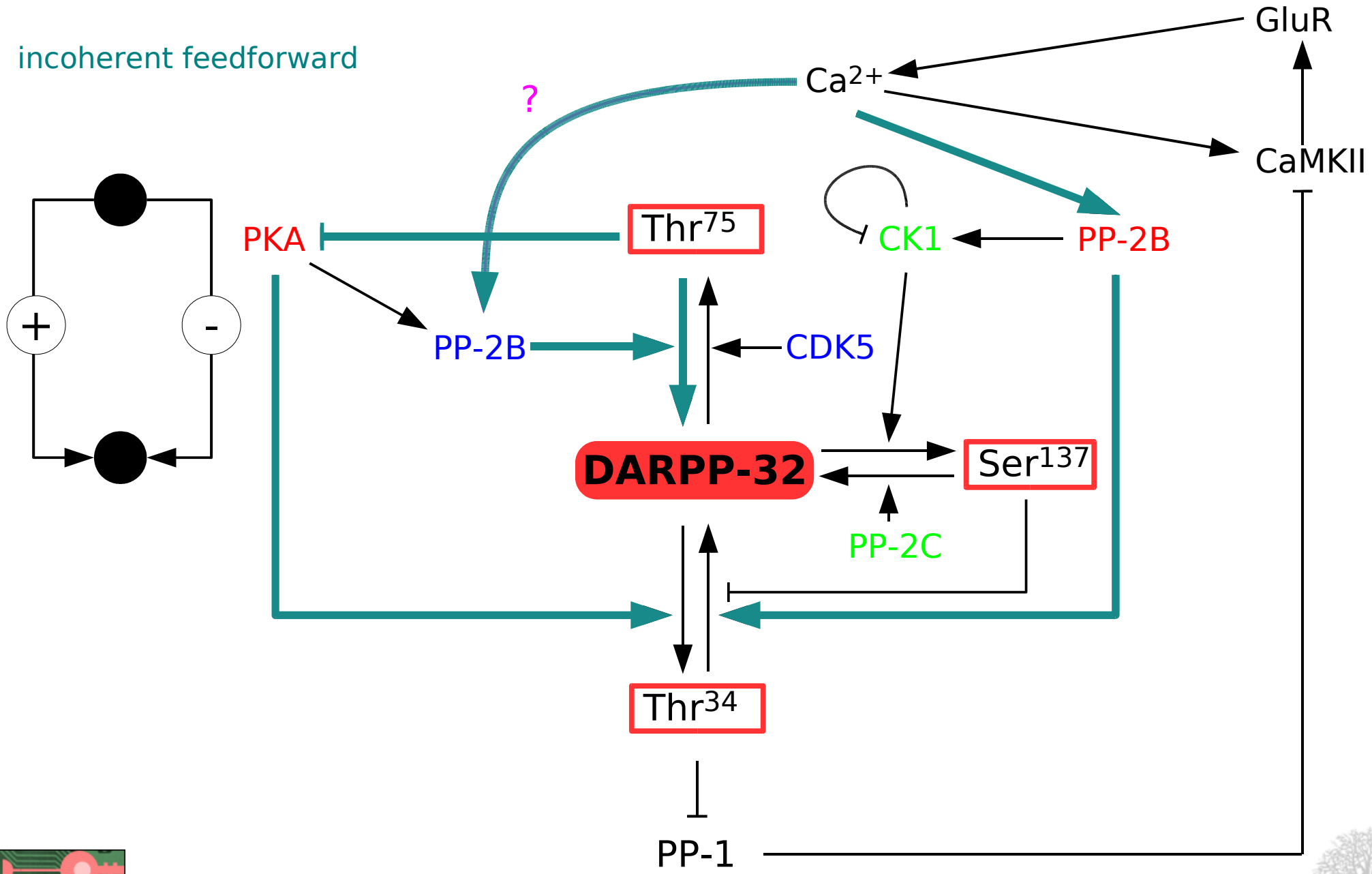

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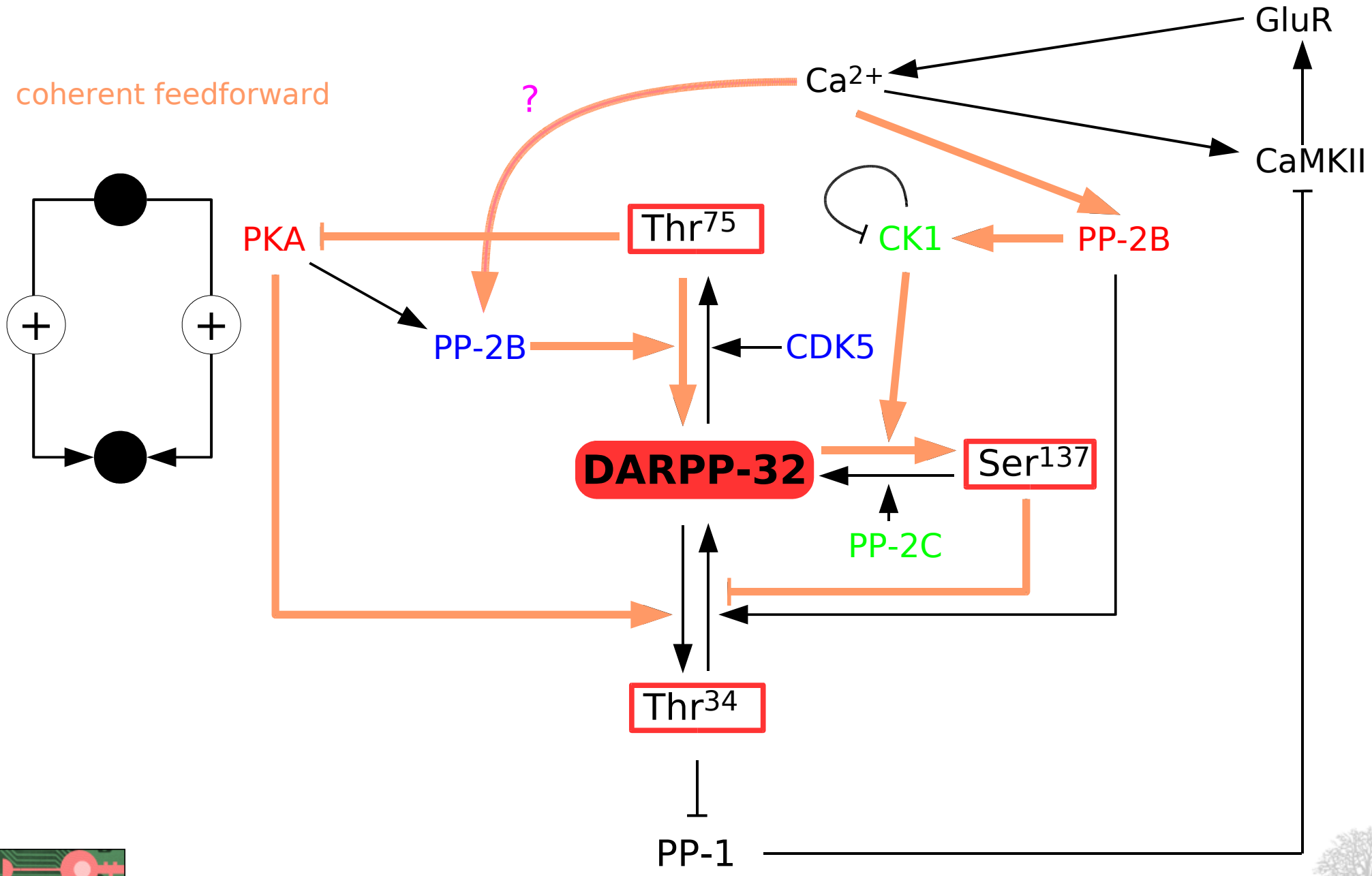
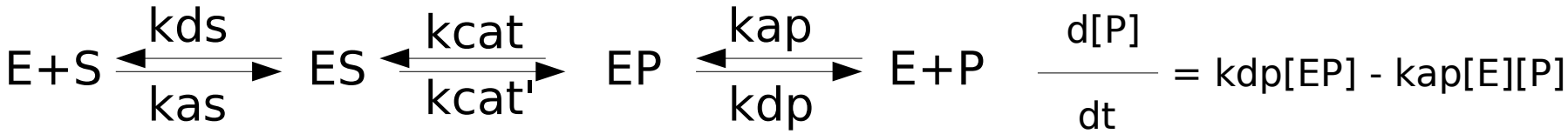
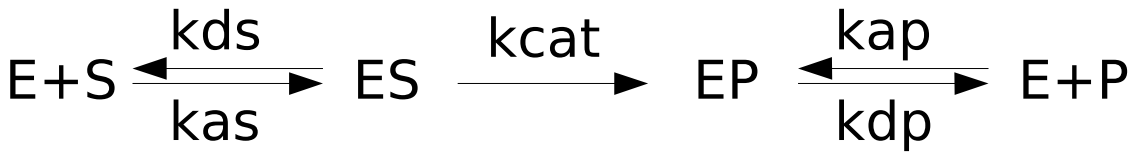


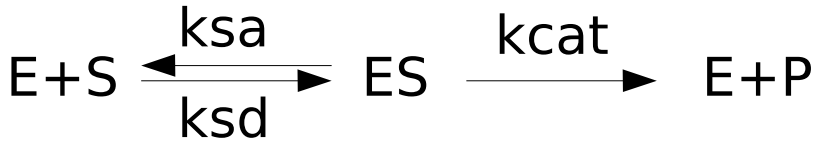
Choose the right formalism



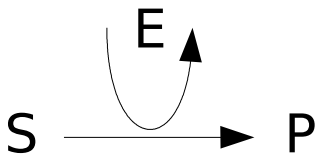
$$\frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$



catalysis irreversible



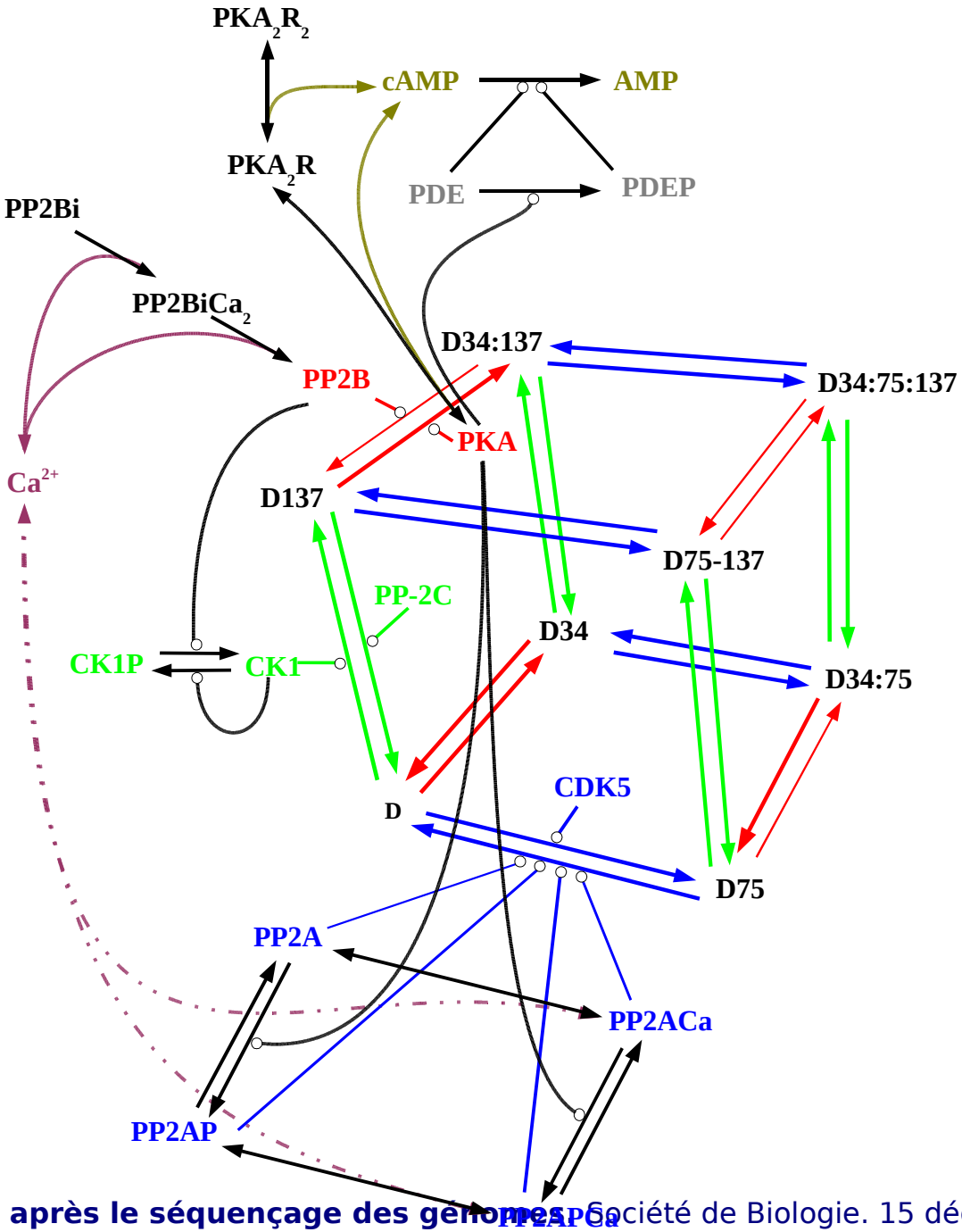
product is consumed before rebinding



steady-state

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

Chemical model of DARPP-32 regulation



Chemical model of DARPP-32 regulation

68 species, 124 reactions

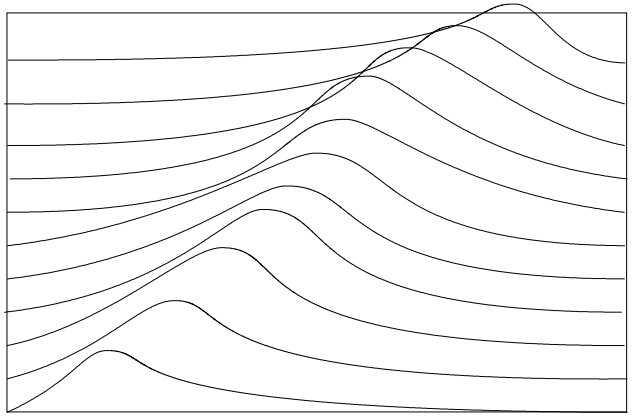
- D + CDK5 ⇔ D_CDK5 → D75 + CDK5
- D75 + PP2A ⇔ D75_PP2A → D + PP2A
- D75 + PP2AP ⇔ D75_PP2AP → D + PP2AP
- D137 + CDK5 ⇔ D137_CDK5 → D75-137 + CDK5
- D75-137 + PP2A ⇔ D75-137_PP2A → D137 + PP2A
- D75-137 + PP2AP ⇔ D75-137_PP2AP → D137 + PP2AP
- D34 + CDK5 ⇔ D34_CDK5 → D34-75 + CDK5
- D34-75 + PP2A ⇔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

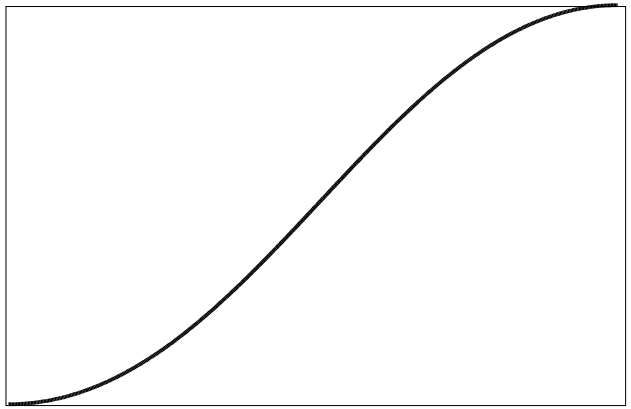
- D + PKA ⇔ D_PKA → D34 + PKA
- D34 + PP2B ⇔ D34_PP2B → D + PP2B
- D75 + PKA ⇔ D75_PKA → D34-75 + PKA
- D34-75 + PP2B ⇔ D34-75_PP2B → D75 + PP2B
- D137 + PKA ⇔ D137_PKA → D34-137 + PKA
- D34-137 + PP2B ⇔ D34-135_PP2B → D137 + PP2B
- D75-137 + PKA ⇔ D75-137_PKA → D34-75-137 + PKA
- D34-75-137 + PP2B ⇔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

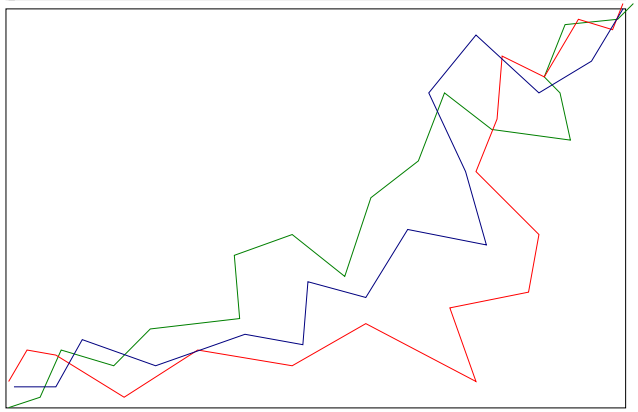
Mathematical model



Grand Probability function: P(X,t)

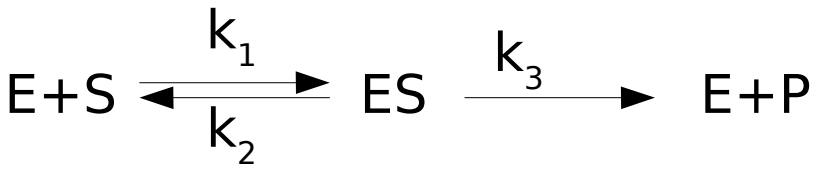


deterministic approach: $(X,t+\Delta t)=f(X',t)$



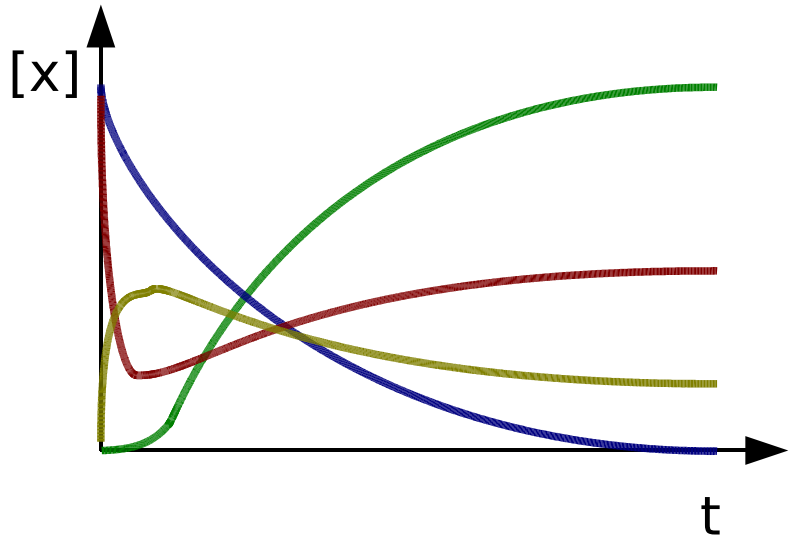
stochastic approach: $P(X,t+\Delta t)/(X',t)$

Mathematical model



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:

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

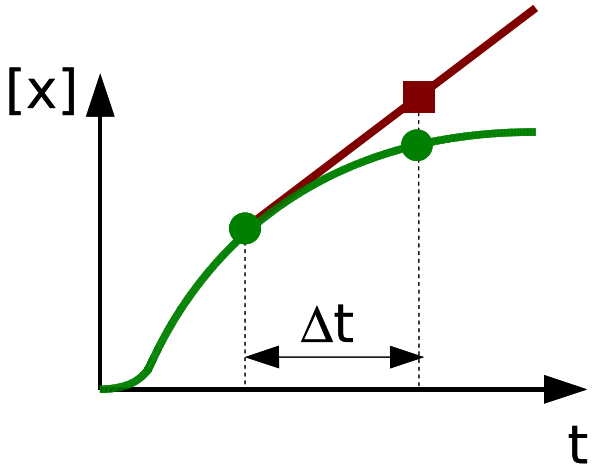
$$[x]_{t+\Delta t} \approx [x]_t + d[x]/dt \,.\, \Delta t$$

$$[P]_{t+\Delta t} = [P]_t + k_3[ES]_t \,.\, \Delta t$$

$$[E]_{t+\Delta t} = [E]_t + k_3[ES]_t \,.\, \Delta t$$

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

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



4^{th} order Runge-Kutta:

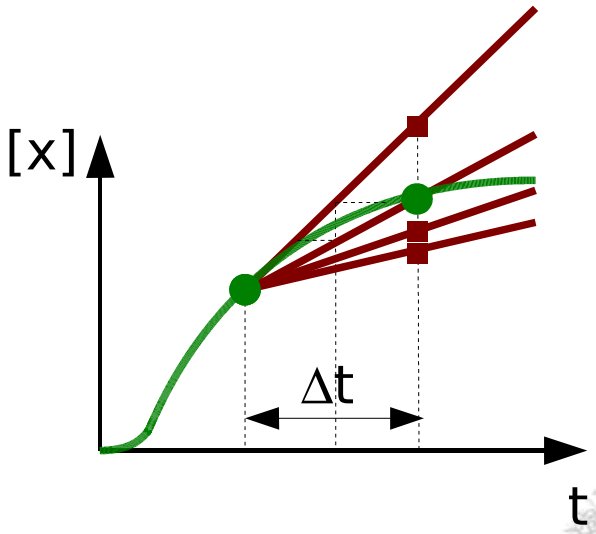
$$[x]_{t+\Delta t} = [x]_t + (F_1+2F_2+2F_3+F_4)/6 \,.\, \Delta t$$

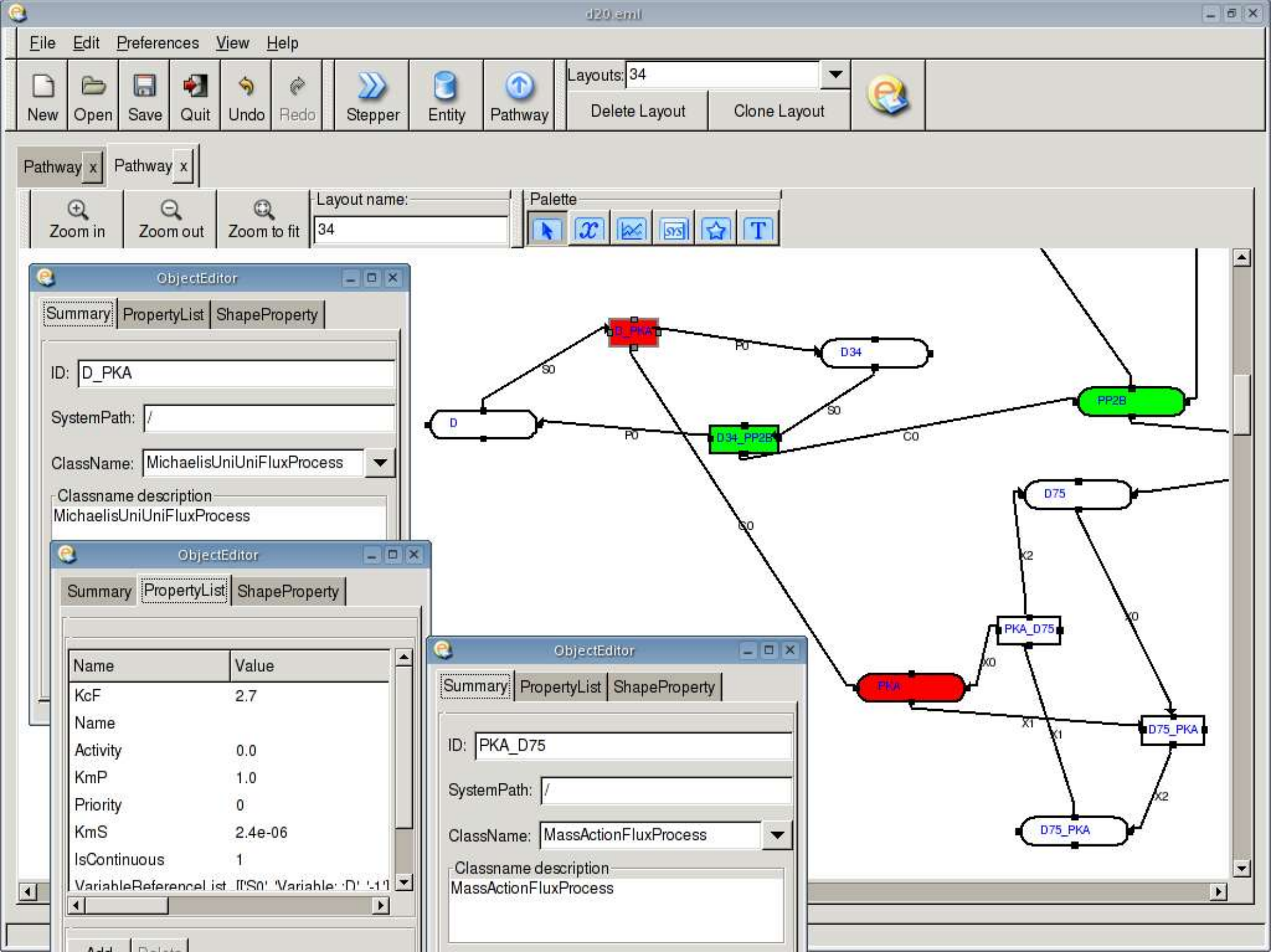
with $F_1 = d[x]/dt = f([x], t)$

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

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

$F_4 = f([x]_t + \Delta t \,.\, F_3, t+ \Delta t)$

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File Edit Preferences View Help
New Open Save Quit Undo Redo Stepper Entity Pathway
Layouts: 34
Delete Layout 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 Value
KcF 2.7
Name
Activity 0.0
KmP 1.0
Priority 0
KmS 2.4e-06
IsContinuous 1
ObjectEditor
Summary PropertyList ShapeProperty
ID: PKA_D75
SystemPath: /
ClassName: MassActionFluxProcess
Classname description
MassActionFluxProcess
D_PKA
D34
D
D34_PP2B
PP2B
D75
PKA_D75
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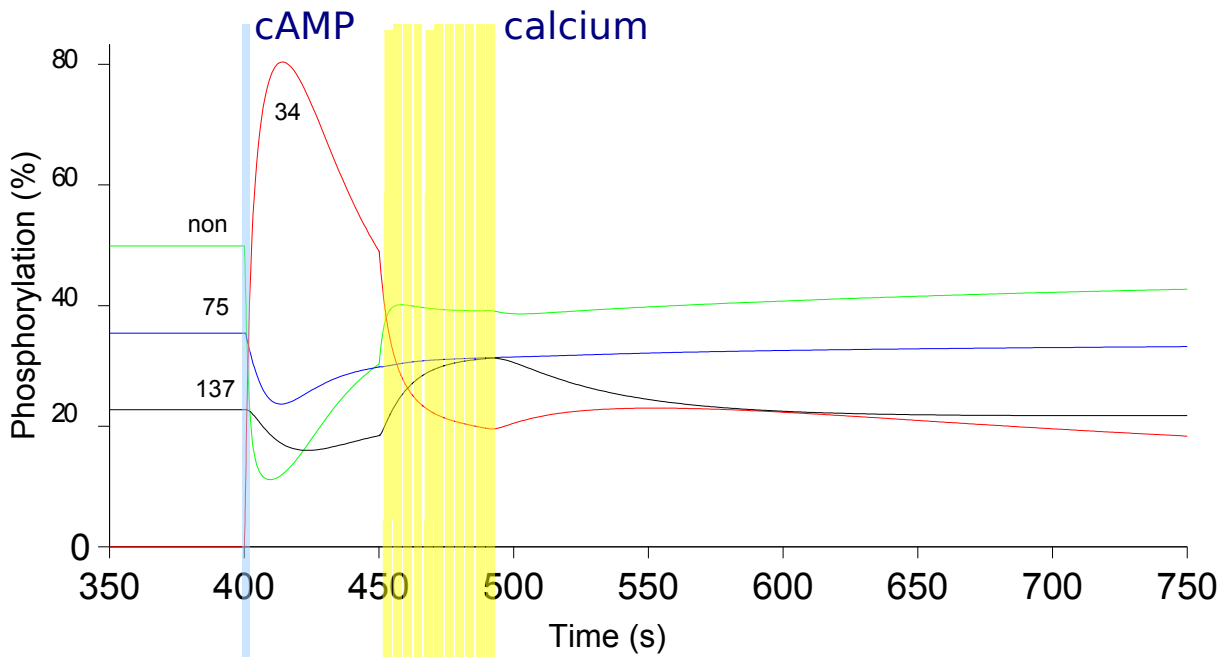
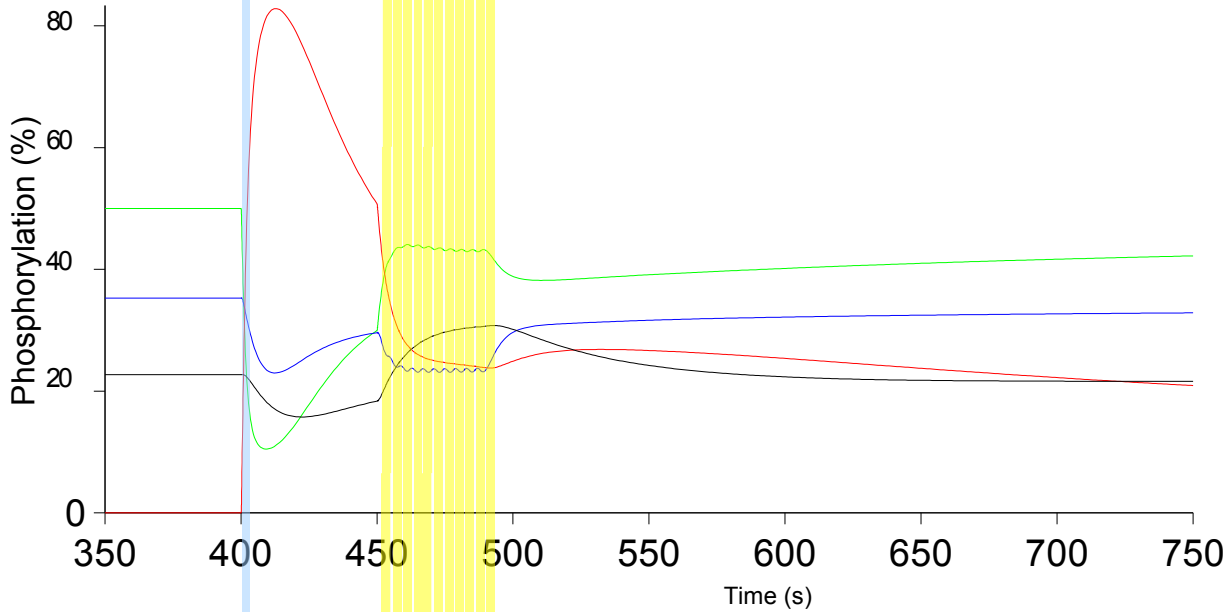
S0
C0
X0
X1
X2

Dynamic simulations of DARPP-32 function

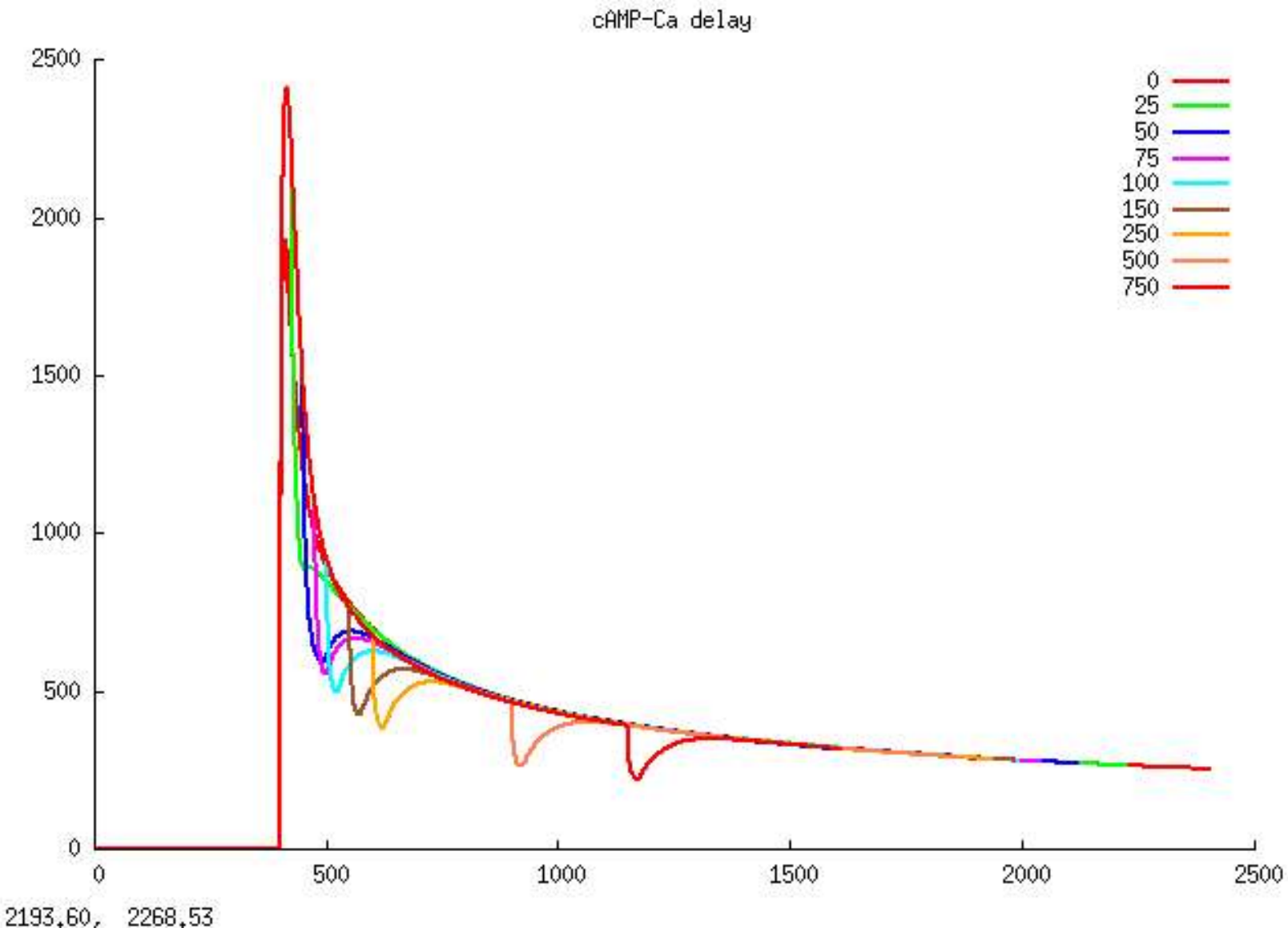
model A



model B



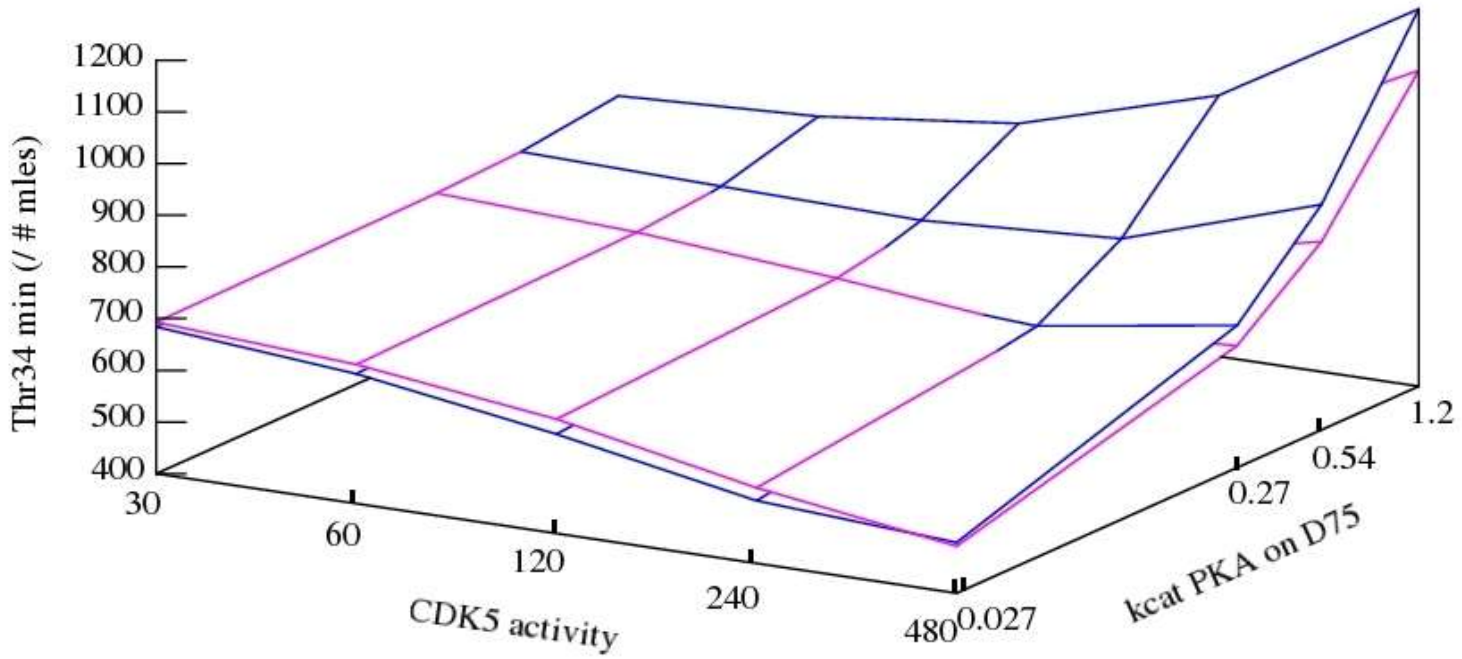
Varying parameters of the simulation

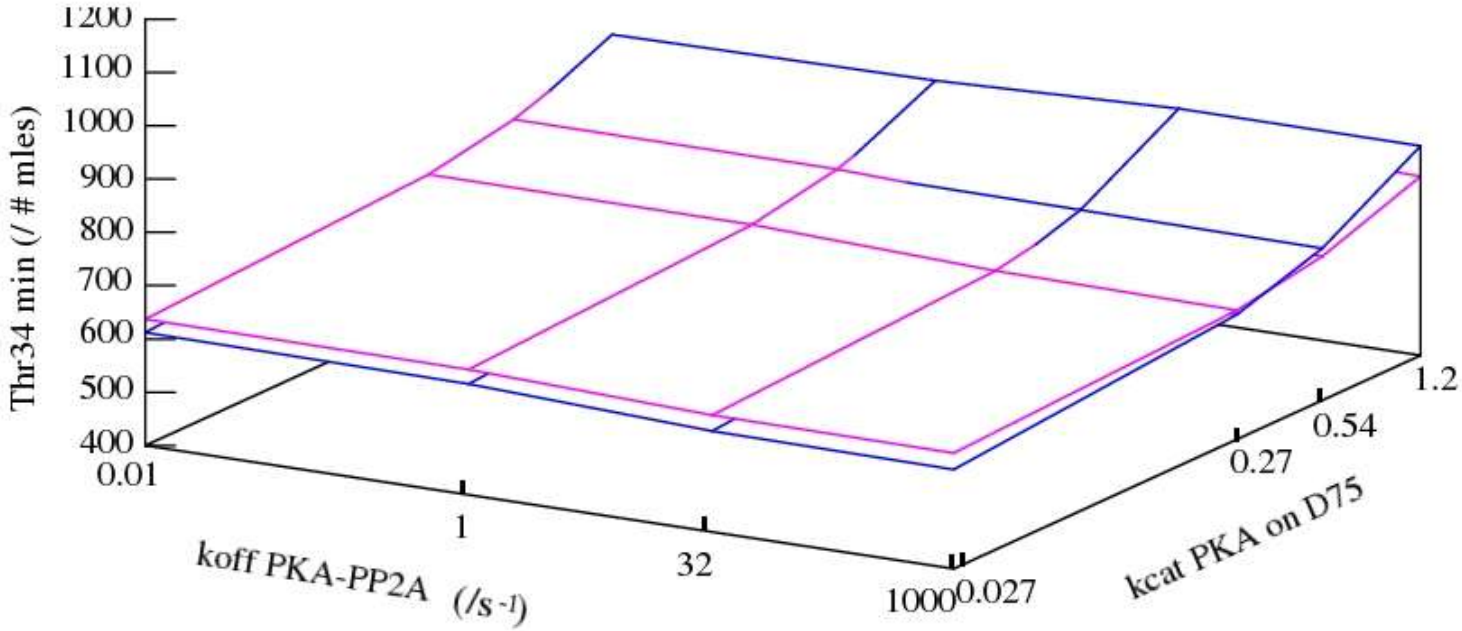


Sensitivity analysis

model A

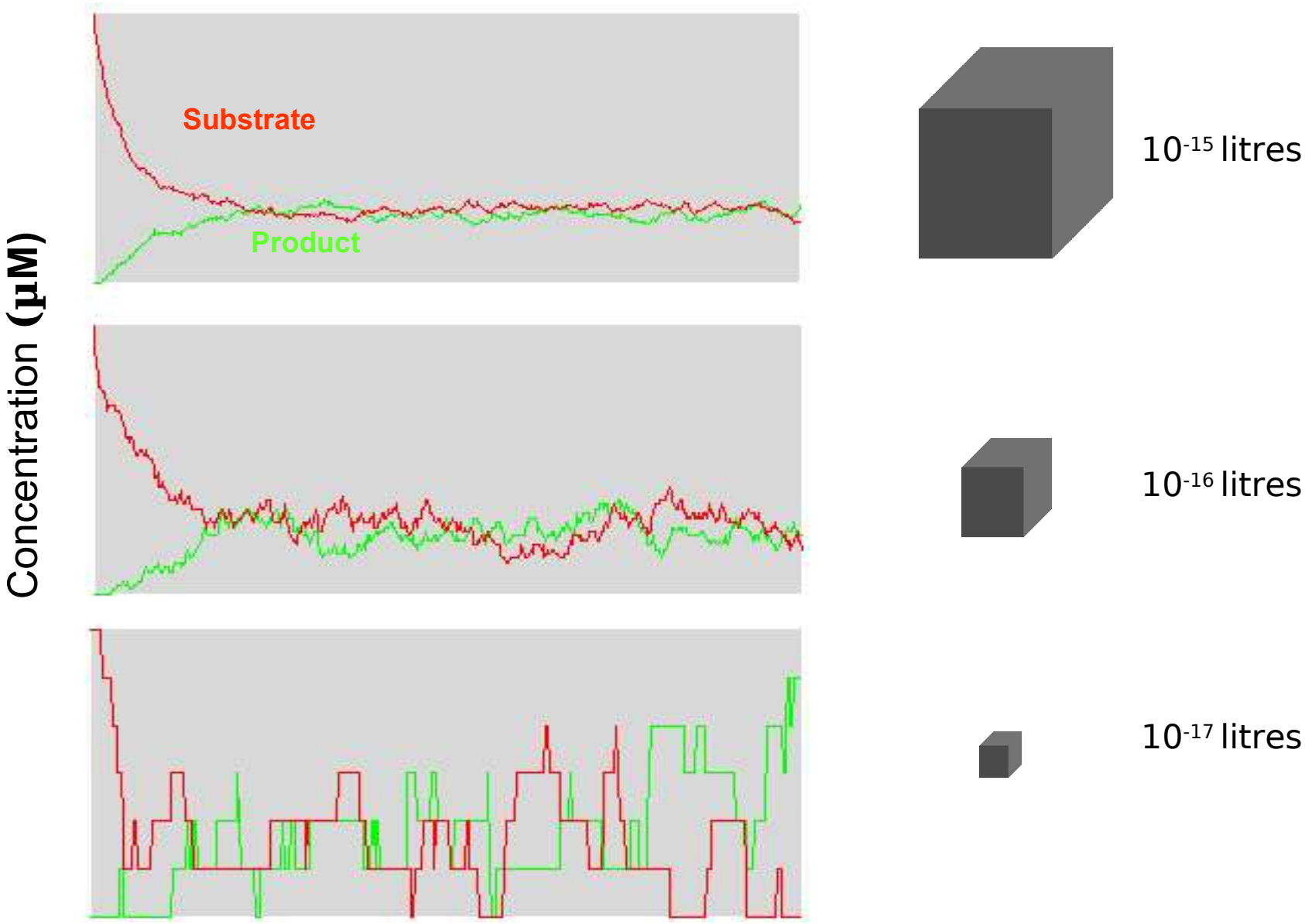
model B





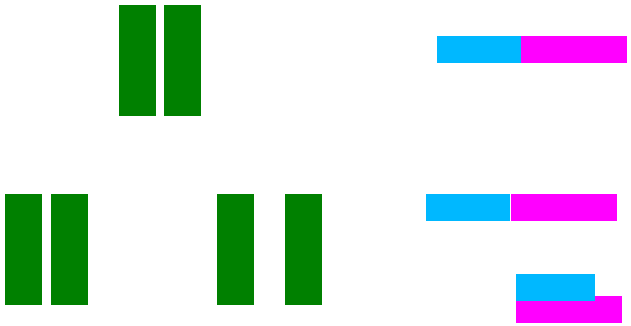
```
if (remaining_time > 10 min){
   next;
} else {
   skip(12);
   next;
}
```

On small numbers



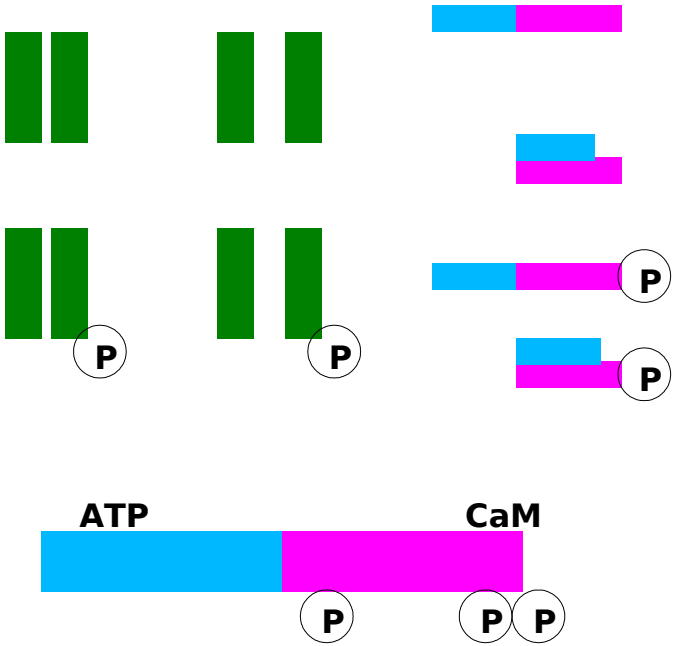
Number of calcium ions in a dendritic spine = 3-5 ...

Combinatorial explosion



NMDA + CaMKII <=> NMDA-CaMKII

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



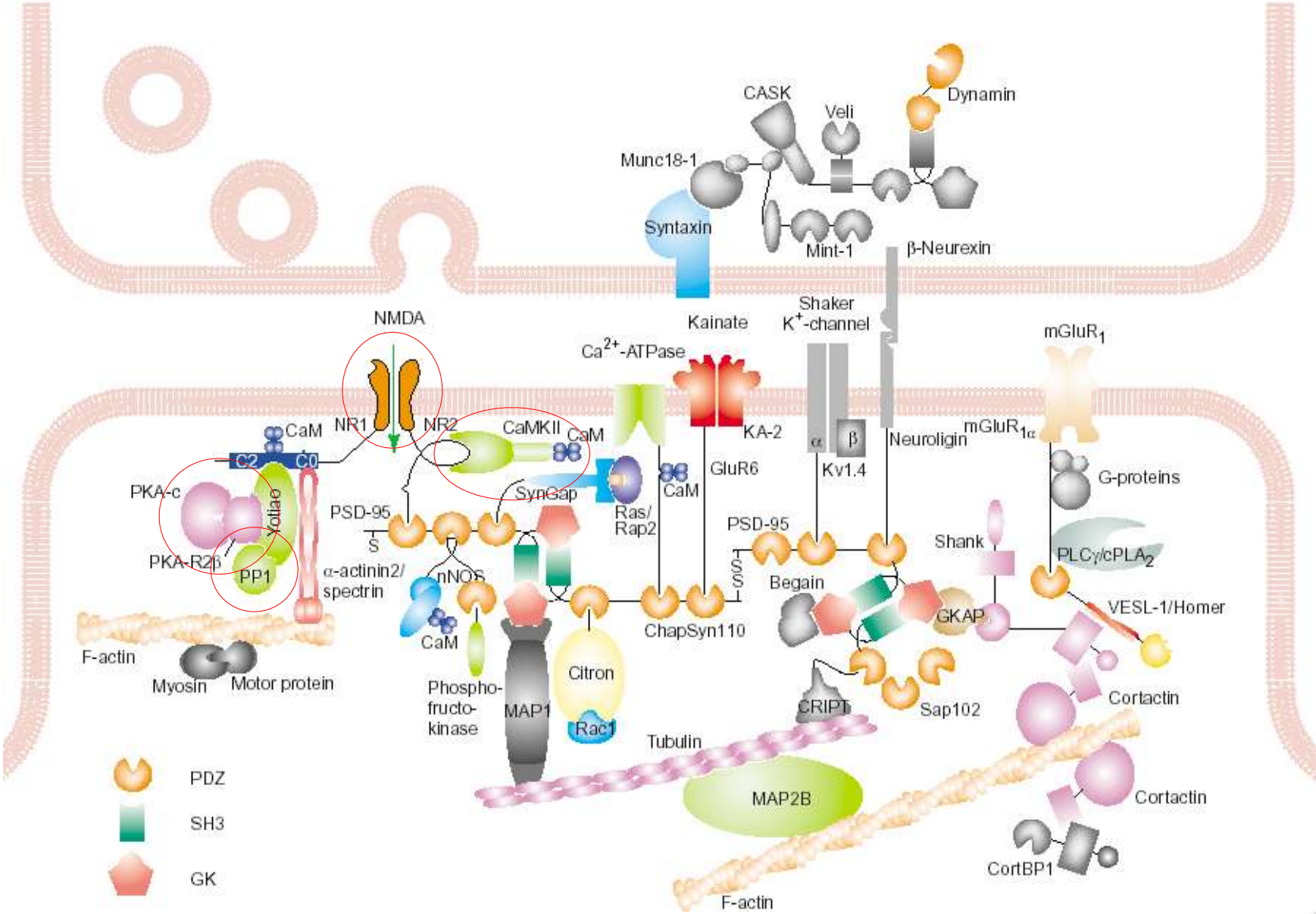
NMDAc + CaMKIIc <=> NMDAc-CaMKIIc
NMDAo + CaMKIIc <=> NMDAc-CaMKIIc
NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo
pNMDAc + CaMKIIc <=> pNMDAc-CaMKIIc
pNMDAo + CaMKIIc <=> pNMDAc-CaMKIIc
pNMDAc + CaMKIIo <=> pNMDAc-CaMKIIo
pNMDAo + CaMKIIo <=> pNMDAc-CaMKIIo
NMDAc + pCaMKIIc <=>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

Combinatorial explosion

- 10 states reacting with 10 states = 262144 reactions combinations. However, all the states do not affect all the reactions:
  - ☛ Useless computation

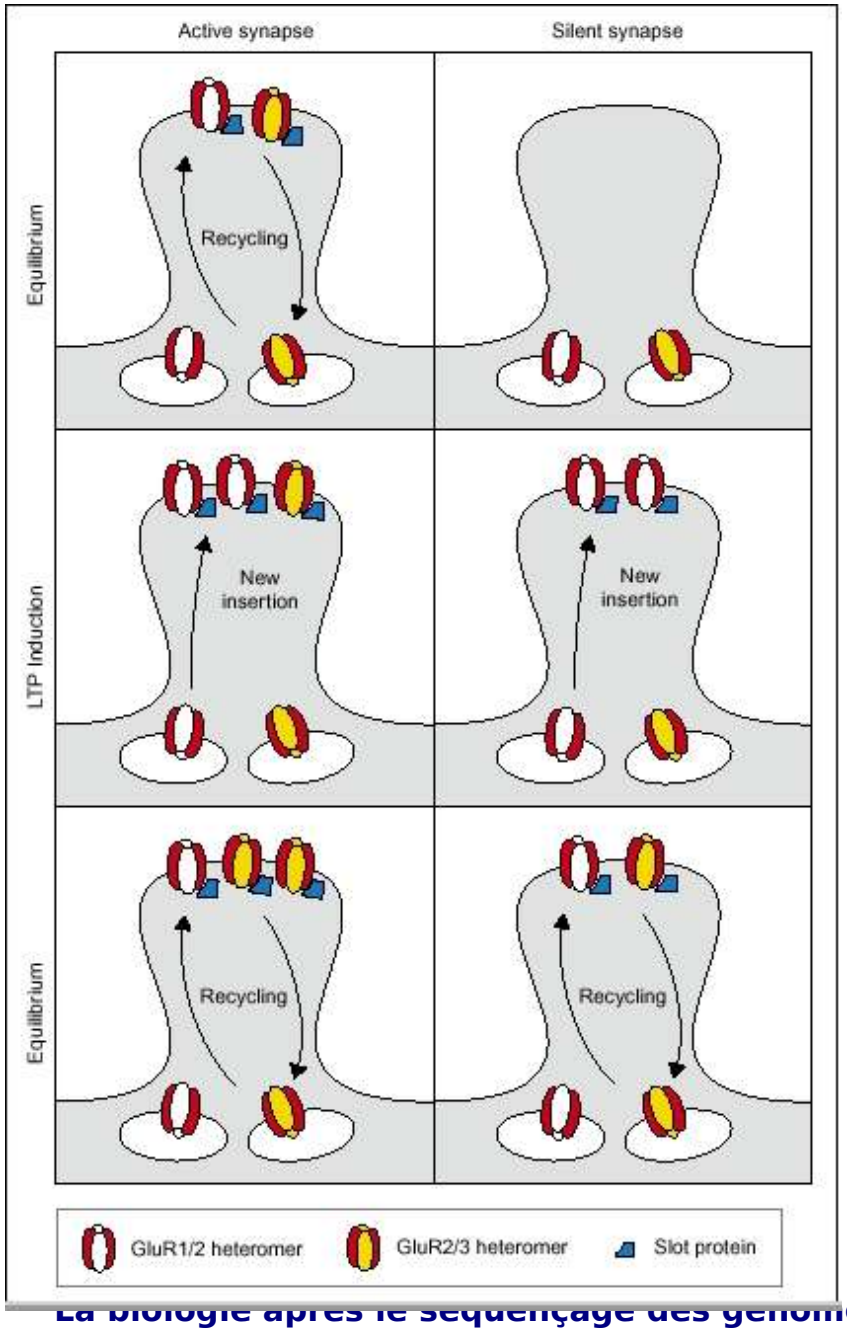
- 10 states reacting with 10 states = 1536 pools.
  One glutamatergique synapse ~ 60-100 receptors
  Often more pools than molecules
  - ☛ Useless computation

Complex post-synaptic machinery

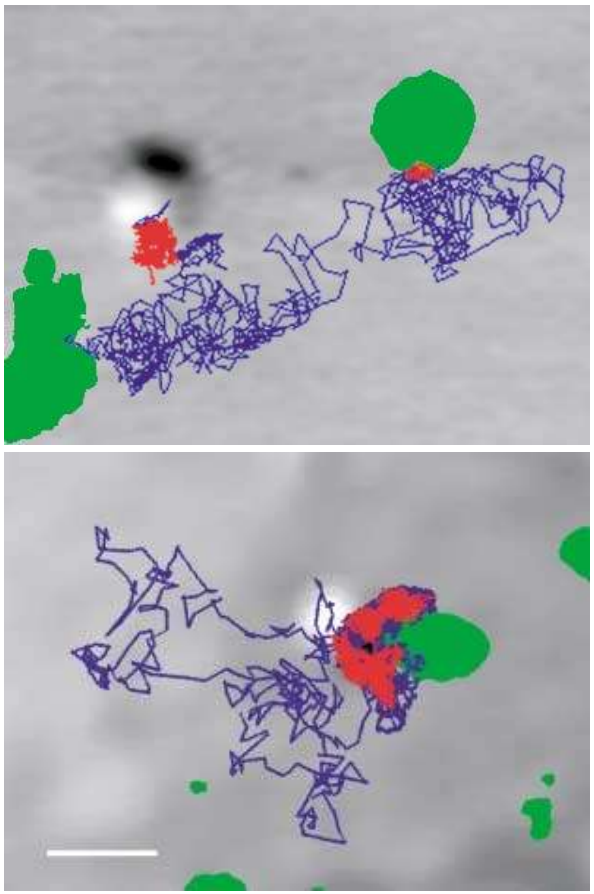


Husi & Grant (2001) *TINS, 24*: 259-266

Receptors for neurotransmitters are moving



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

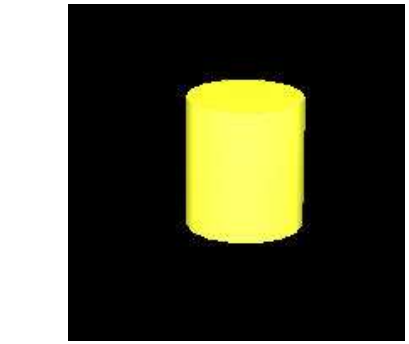


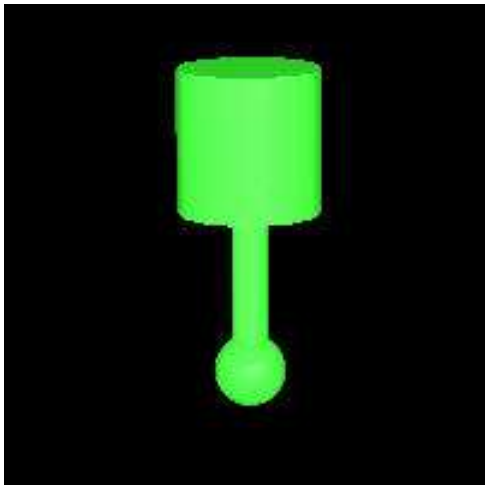
Choquet & Triller (2003)
Nat Rev Neurosci, 4: 251-265

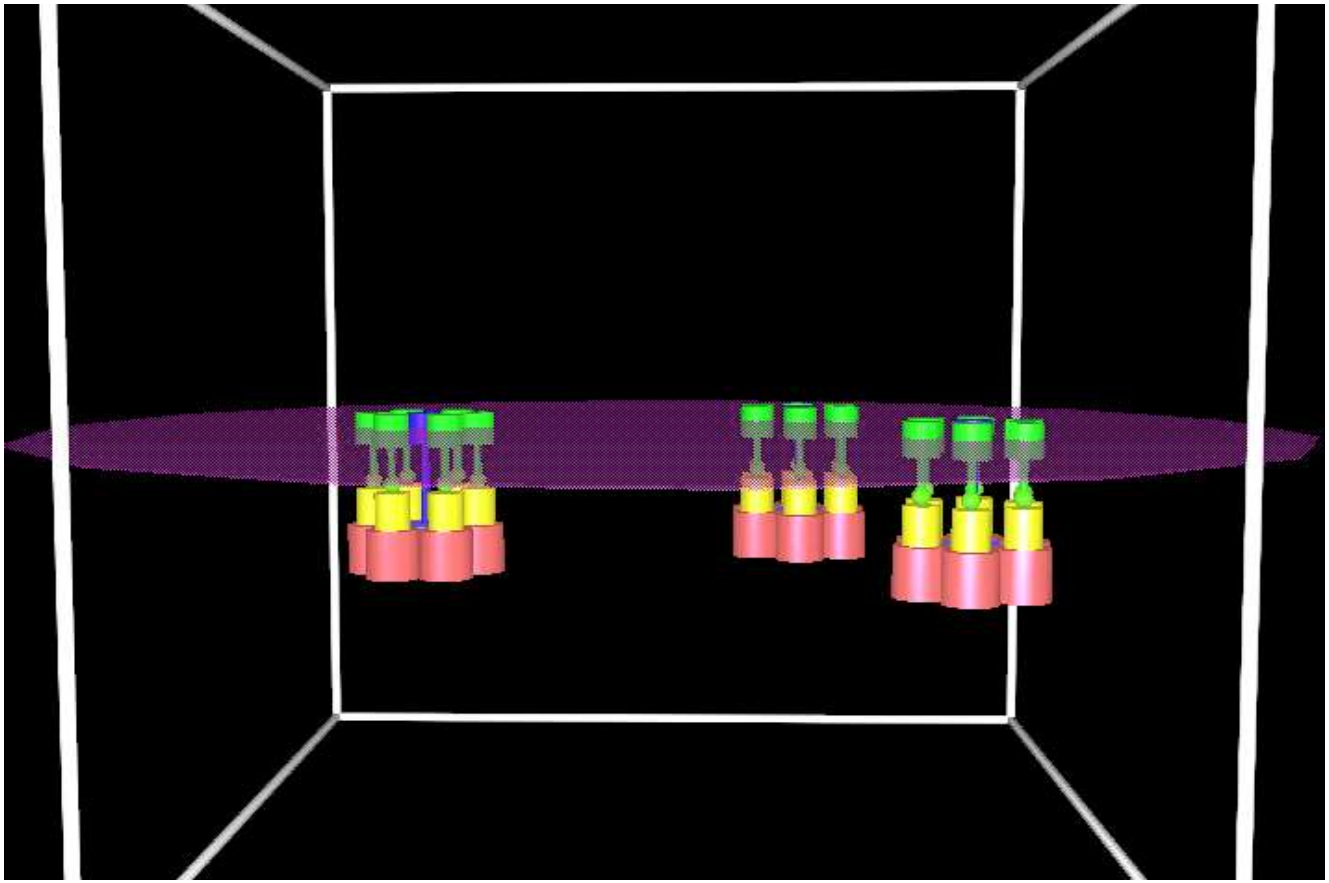
APS: the mesoscopic scale

- 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)

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

- Different diffusion spaces:
  - Static; Free diffusion; Membrane diffusion; Above membrane; Below membrane
- Two types of motion:
  - Translational $\bar{r}^2 = 2D_T t = 2kb_T t$
  - Rotational $\bar{\theta}^2 = 2D_R t = 2kb_R t$
- random walk algorithm

$$p(x,t) = \frac{1}{\sqrt{4\pi Dt}} \exp - \frac{x^2}{4Dt}$$ gaussian with $\sigma^2 = 2Dt$

  - Translational $\Delta(x,y,z) = \sqrt{2D_T t} \times gaussRand$
  - Rotational $\Delta\theta = \frac{\sqrt{2D_R t}}{r} \times gaussRand$
- Two types of diffusion equations:
  - unrestricted brownian motion – Low Trans/Rot
  - intra-membrane diffusion (Saffman and Delbrück 1975) – High Trans/Rot

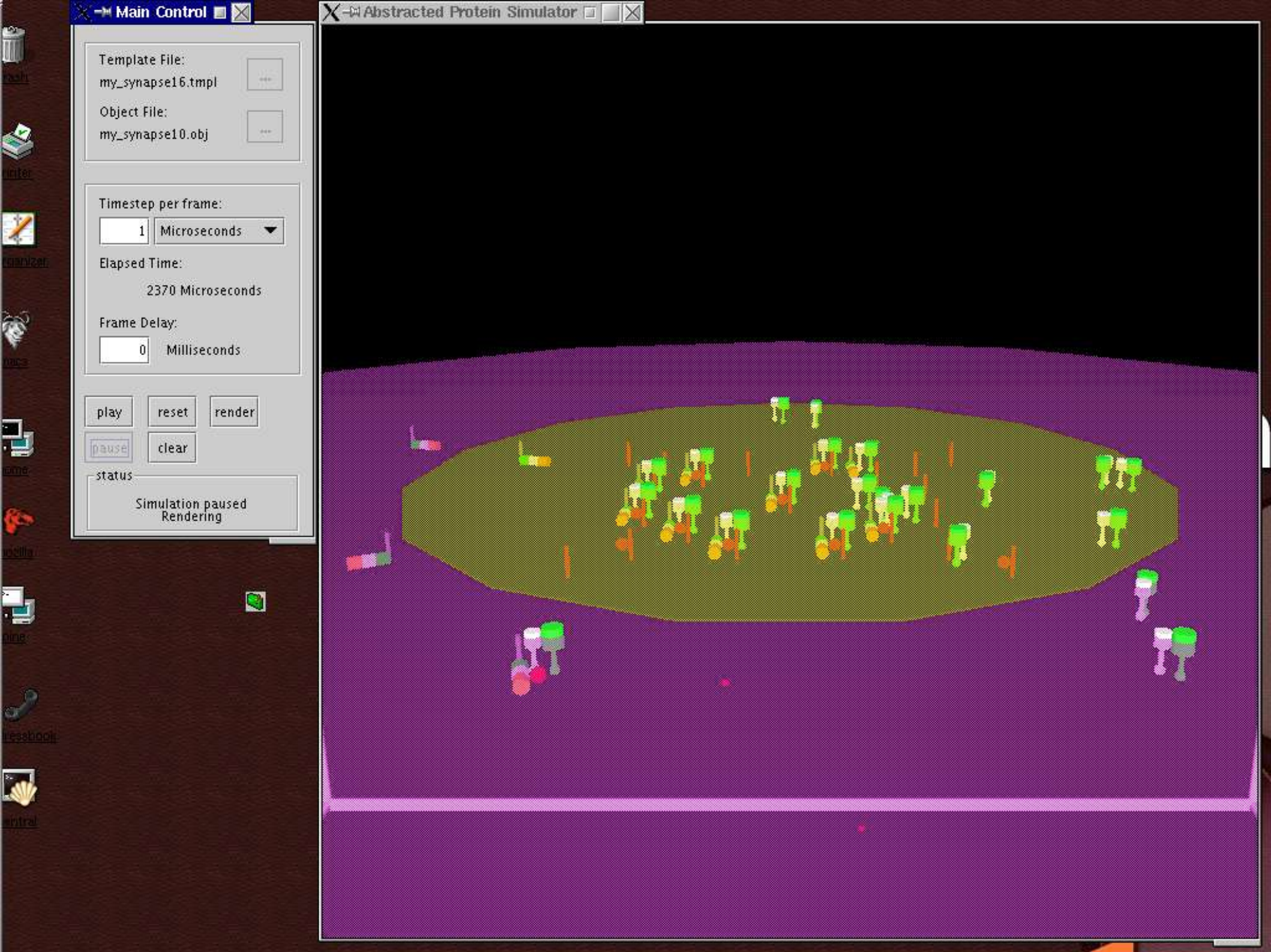
Molecule diffusion

- 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

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


Main Control
Template File:
my_synapse16.tmpl
Object File:
my_synapse10.obj
Timestep per frame:
1
Microseconds
Elapsed Time:
2370 Microseconds
Frame Delay:
0
Milliseconds
play
reset
render
pause
clear
status
Simulation paused
Rendering
Abstracted Protein Simulator

The limited factor in kinetic modelling is the experimental quantitative data

This is particularly true in Neurobiology

Hypothesis-driven Vs. systematic

- Most of the quantitative data available in Neurobiology was generated by hypothesis-driven experiments:
  - Tailored to answer a particular question
  - Valid in very specific experimental conditions
  - Minimum degrees of freedom: parameter set incomplete
  - Relative values rather than absolute (normalised data; mutant Vs. wild-type etc.)
- We need comprehensive data-set
  - Quantitative
  - Atomic
  - Statistically supported

SBML Systems Biology Markup Language

Google Search this site

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 90 software systems**, including the following (where '*' indicates SBML support in development):

BALSA	Cytoscape	MMT2	SBMLR
BASIS	DBsolve	Modesto	SBMLSim
BIOCHAM	Dizzy	Moleculizer	SBML Toolbox
BioCharon	E-CELL	Monod	SBSI Toolbox
biocyc2SBML	ecellJ	Narrator	SBW
BioGrid	ESS	NetBuilder	SCIpath
BioModels	FluxAnalyzer	PANTHER Pathway	Sigmoid*
BioNetGen	Fluxor	PathArt	SigPath
BioPathway Explorer	Gepasi	PathScout	SigTran
Bio Sketch Pad	INSILICO discovery	PathwayLab	SIMBA
BioSens	JACOBIAN	Pathway Tools	SimBiology
BioSPICE Dashboard	Jarnac	PathwayBuilder	Simpathica
BioSpreadsheet	JDesigner	PaVESy	SimWiz
BioTapestry	JigCell	PNK	SmartCell
BioUML	JWS Online	Reactome	SRS Pathway Editor
BSTLab	Karyote*	ProcessDB	StochSim
CADLIVE	KEGG2SBML	PROTON	STOCKS
CellDesigner	Kinsolver*	pysbml	TERANODE Suite
Cellerator	libSBML	PySCeS	Trelis
CellML2SBML	MathSBML	runSBML	Virtual Cell
Cellware	MesoRD	SBML ODE Solver	WinSCAMP
CL-SBML	MetaboLogica	SBMLeditor	XPPAUT
COPASI	MetaFluxNet	SBMLmerge	

SYNTAXE

MathWorks SimBiology Released

(November 12, 2005) **SimBiology**, the systems biology toolkit from the makers of MATLAB, is now available.

read more

Database Curator Sought

(November 11, 2005) The Caltech group is looking for a full-time postdoc to perform database curation for BioModels Database.

read more

Narrator supports SBML

(November 9, 2005) **Narrator** is a graphical modeling tool for biological processes, integrating an intuitive overview of the system being modeled with an underlying ODE interpretation.

read more

SBToolbox v1.5

(November 7, 2005) Version 1.5 of the **Systems Biology Toolbox** for MATLAB, by Henning Schmidt, features many enhancements, fixes, and new detailed tutorials.

read more

JACOBIAN Supports SBML

(October 25, 2005) Numerica Technology's **JACOBIAN** is a dynamic modeling and optimization software with support for model

Minimum Information Requested In the Annotation of biochemical Models (MIRIAM)

SÉMANTIQUE

Le Novère N., Finney A., Hucka M., Bhalla U., Campagne F., Collado-Vides J., Crampin E., Halstead M., Klipp E., Mendes P., Nielsen P., Sauro H., Shapiro B., Snoep J.L., Spence H.D., Wanner B.L.

Nature Biotechnology **(2005), 23: 1509-1515**

BioModels Database: A Free, Centralized Database of Curated, Published, Quantitative Kinetic Models of Biochemical and Cellular Systems

Le Novère N., Bornstein B., Broicher A., Courtot M., Donizelli M., Dharuri H., Li L., Sauro H., Schilstra M., Shapiro B., Snoep J.L., Hucka M.

***Nucleic Acids Research*, (2006), 34: in the press**

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- APS
  - Fred Howell
  - Dan Mossop
- DARPP-32
  - Jean-Antoine Girault
  - Denis Hervé

The EBI team

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<compneur>
  <member name="Nicolas Le Novère" role="leader"/>
  <member name="Mélanie Courtot" role="developer"/>
  <member name="Éric Fernandez" role="post-doc"/>
  <member name="Chen Li" role="developer">
  <member name="Lu Li" role="developer"/>
  <member name="Nicolas Rodriguez" role="developer"/>
  <member name="Melanie Stefan" role="PhD student"/>
  <member name="Dominic Tölle" role="PhD student"/>
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Computational Neurobiology Group

The interests of the group Computational Neurobiology revolve around signal transduction in neurons, ranging from the molecular structure of membrane proteins involved in neurotransmission to modelling signalling pathways. A strong focus is the molecular and cellular basis of neuroadaptation in neurons of the basal ganglia. We also provide services that facilitate our research, including database production and software development.

Modelling requires various types of software, including design environments and simulators. The Systems Biology Markup Language (SBML) is designed to facilitate the exchange of biological models between different types of software. Involved in the development of SBML since the origin of the project, we are working on the language extensions=20 and developing software that supports SBML. Moving from the form to the content, we are also developing standards for model curation and annotation, and controlled vocabularies to increase the information content of models.

However well a model is designed, it is useful only if potential users can access it. The BioModels Database is an effort to develop a data resource that allows biologists to store, search and retrieve published mathematical models of biological interest.

A significant proportion of the proteins involved in neuronal signalling are embedded in biological membranes. Their three-dimensional structures are seldom known and this precludes a clear understanding of their function. E-MeP, the European Membrane Protein Consortium focusses on solving the bottlenecks that prevent the high-throughput determination of their structures.

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

Setting the standard for computer models of life

December 7th 2005 Scientists from 14 different organisations including the EMBL-European Bioinformatics Institute annouce MIRIAM, a new quality standard for biochemical models, in the 6 December issue of *Nature Biotechnology*. MIRIAM will help researchers to reuse, modify and combine computer models of biochemical processes to gain a fuller understanding of life at the molecular and cellular level ...more

A new way to share models of biological systems

Apr 11th 2005 - BioModels, the world's first database of annotated

European Bioinformatics Institute

British outstation of the European Molecular Biology Laboratory

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

    + ~200 other resources

- Research groups
  - Comparative genomics (Ouzounis)
    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)

Marie Curie Training site Fellowships: 3-6 months. Fully funded.