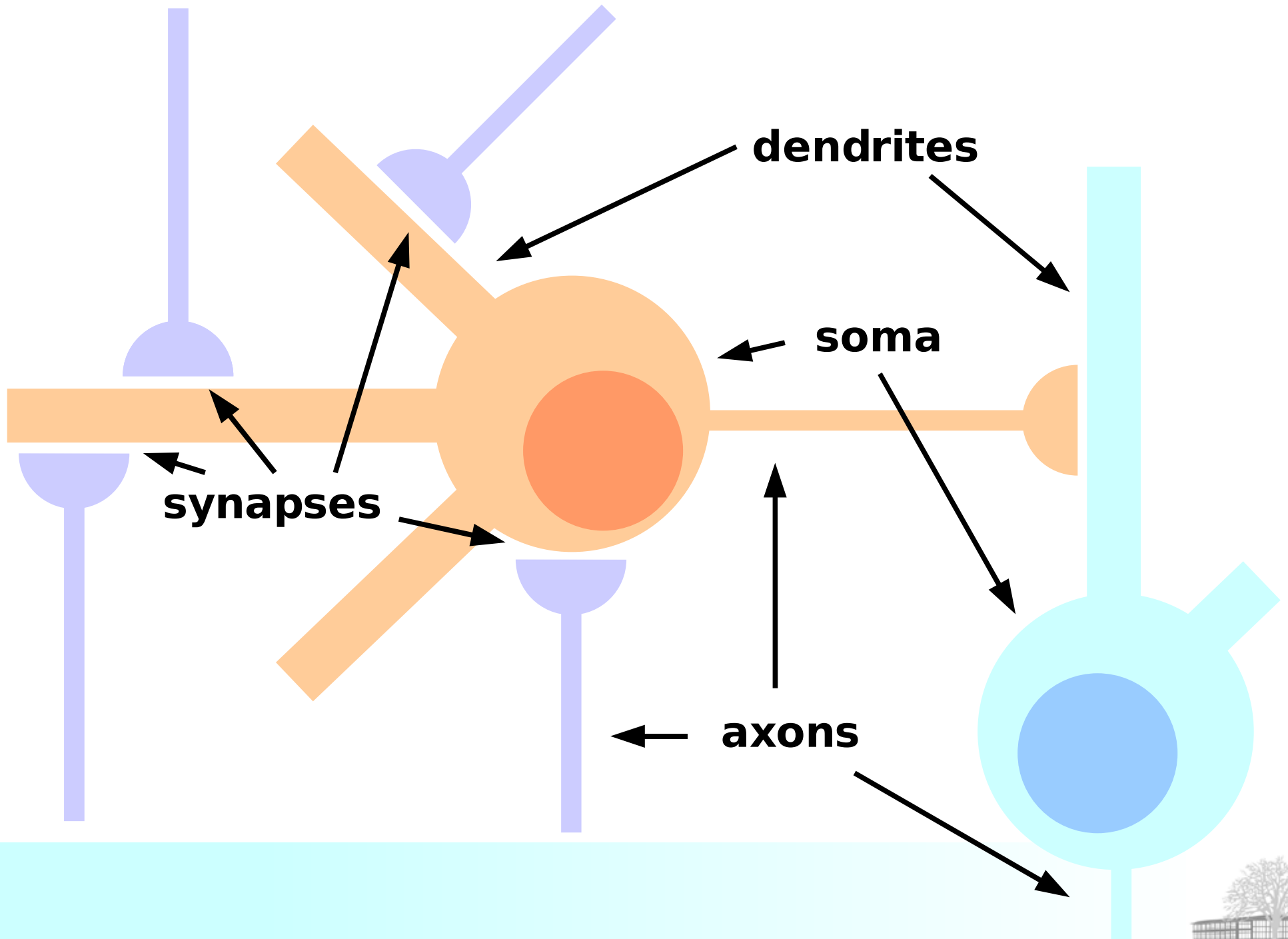
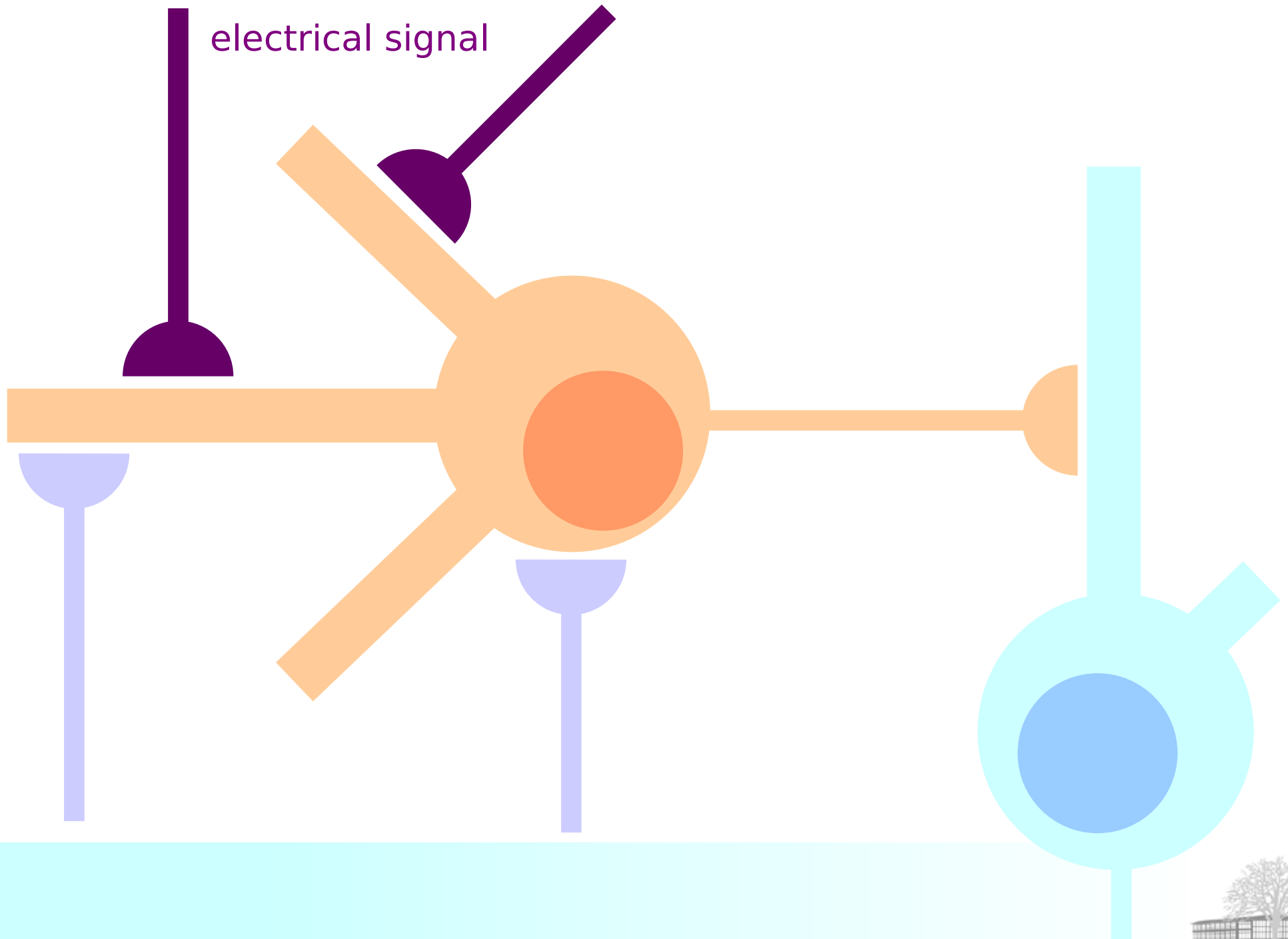


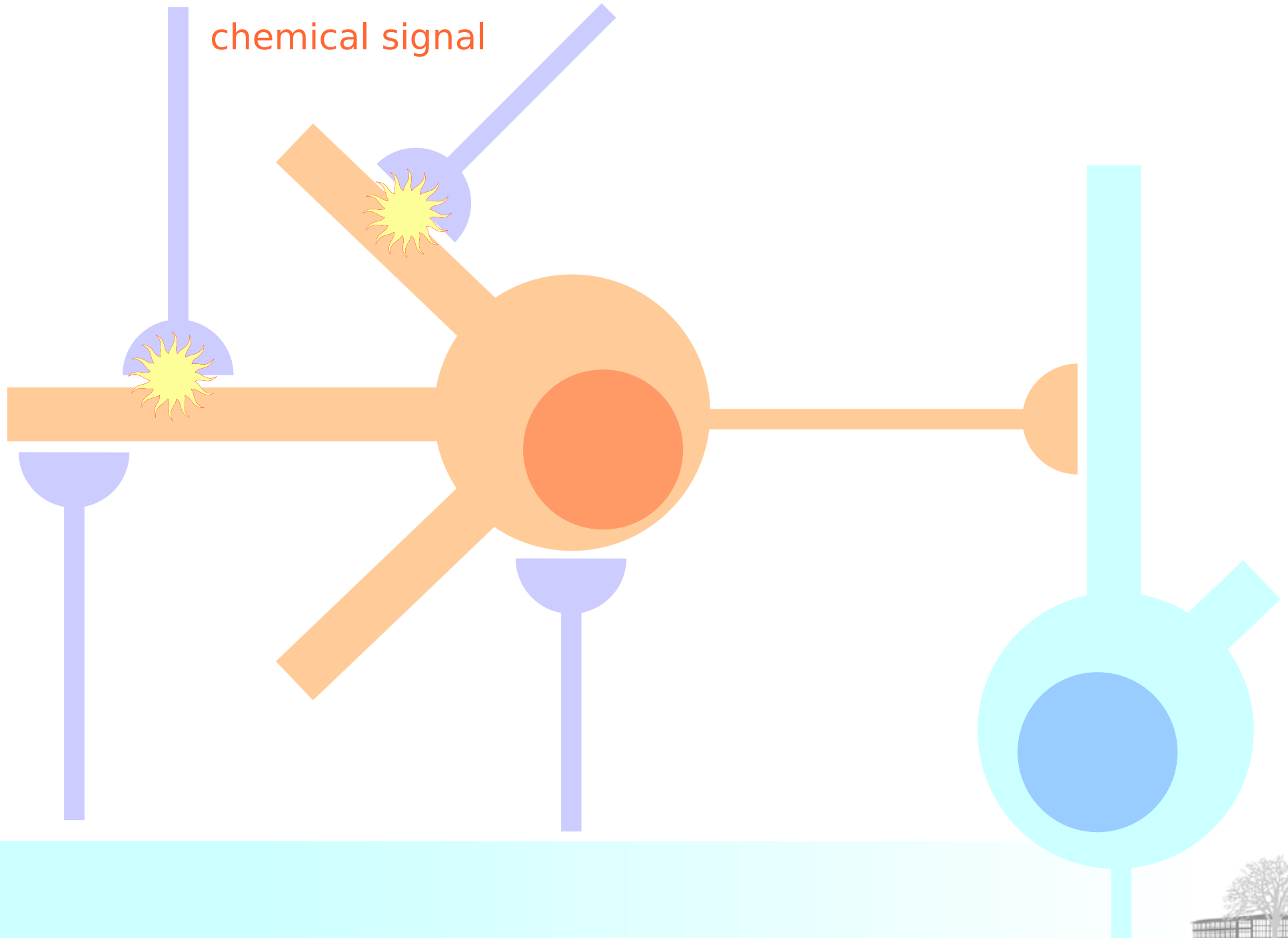
Systems Biology of Neuronal signalling

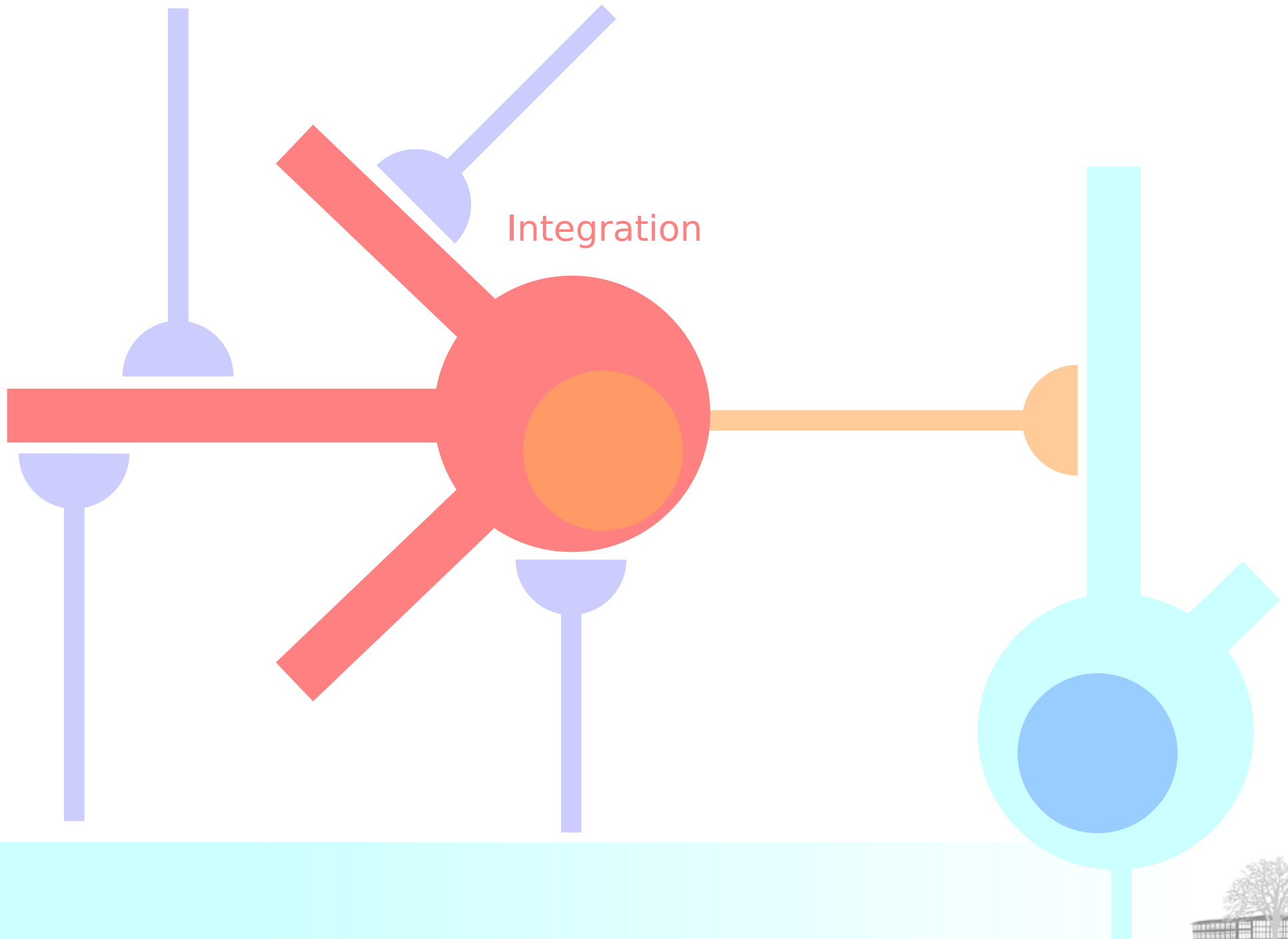
Nicolas Le Novère, EMBL-EBI, Hinxton (Cambridge), UK

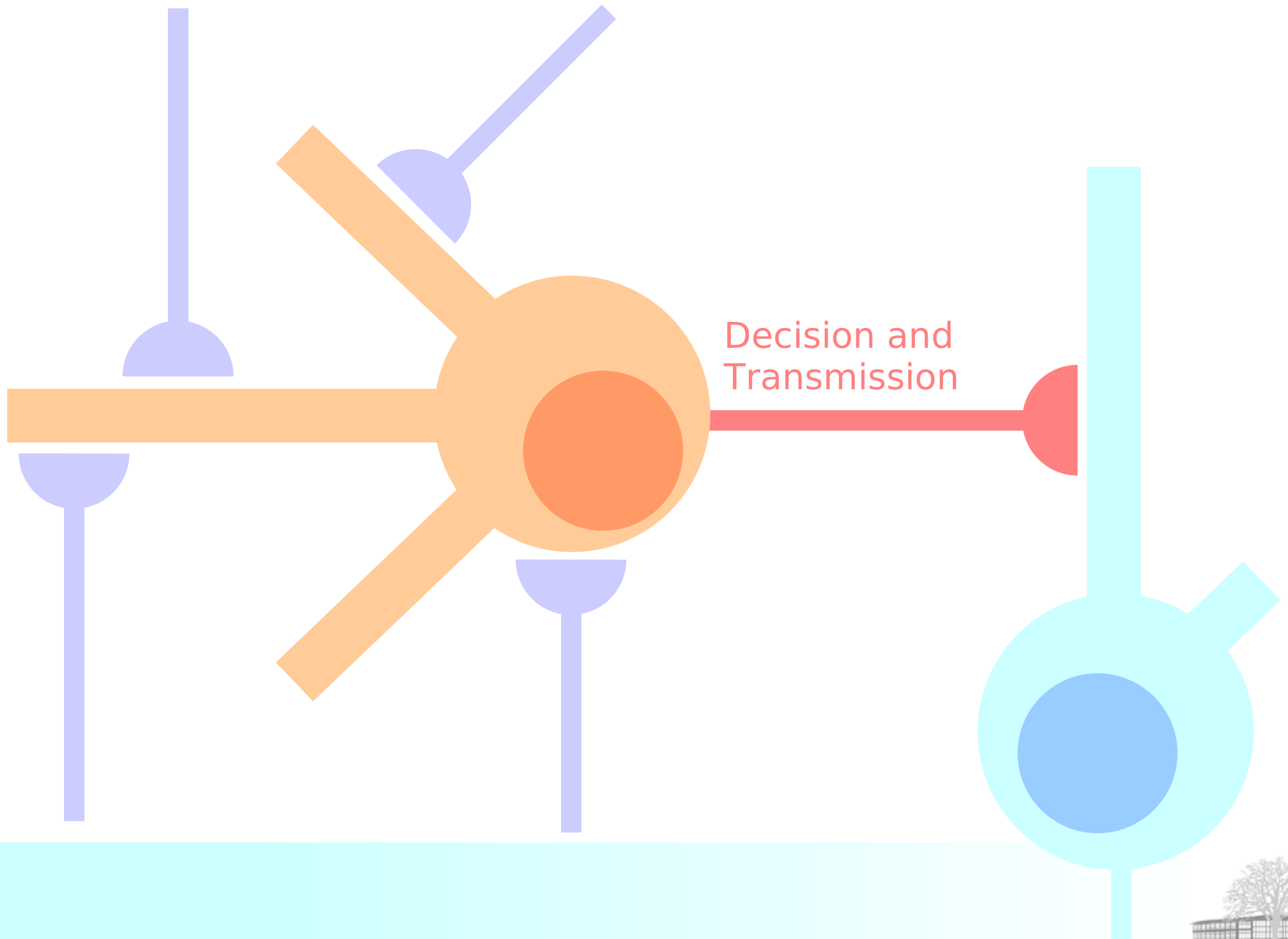


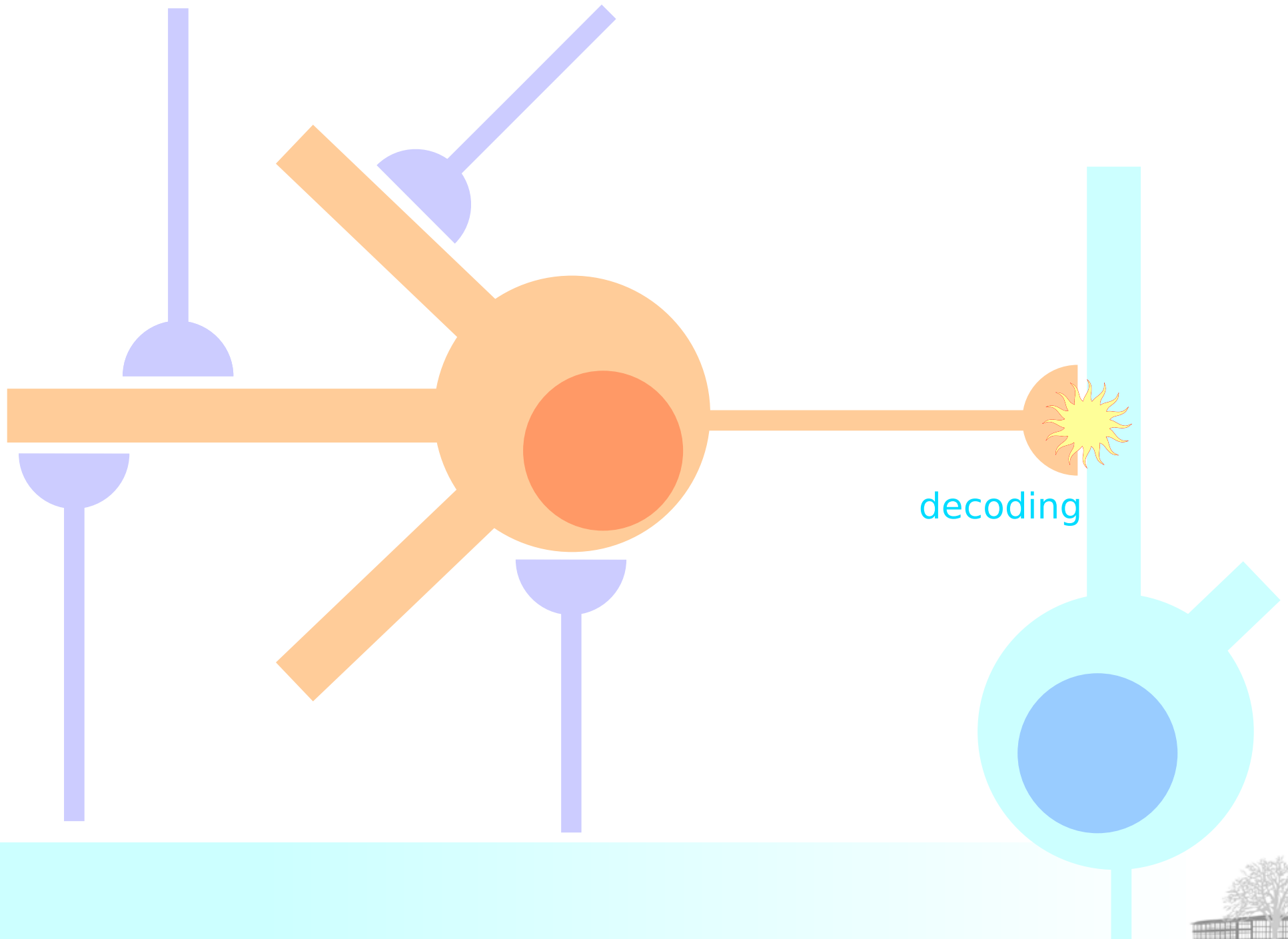




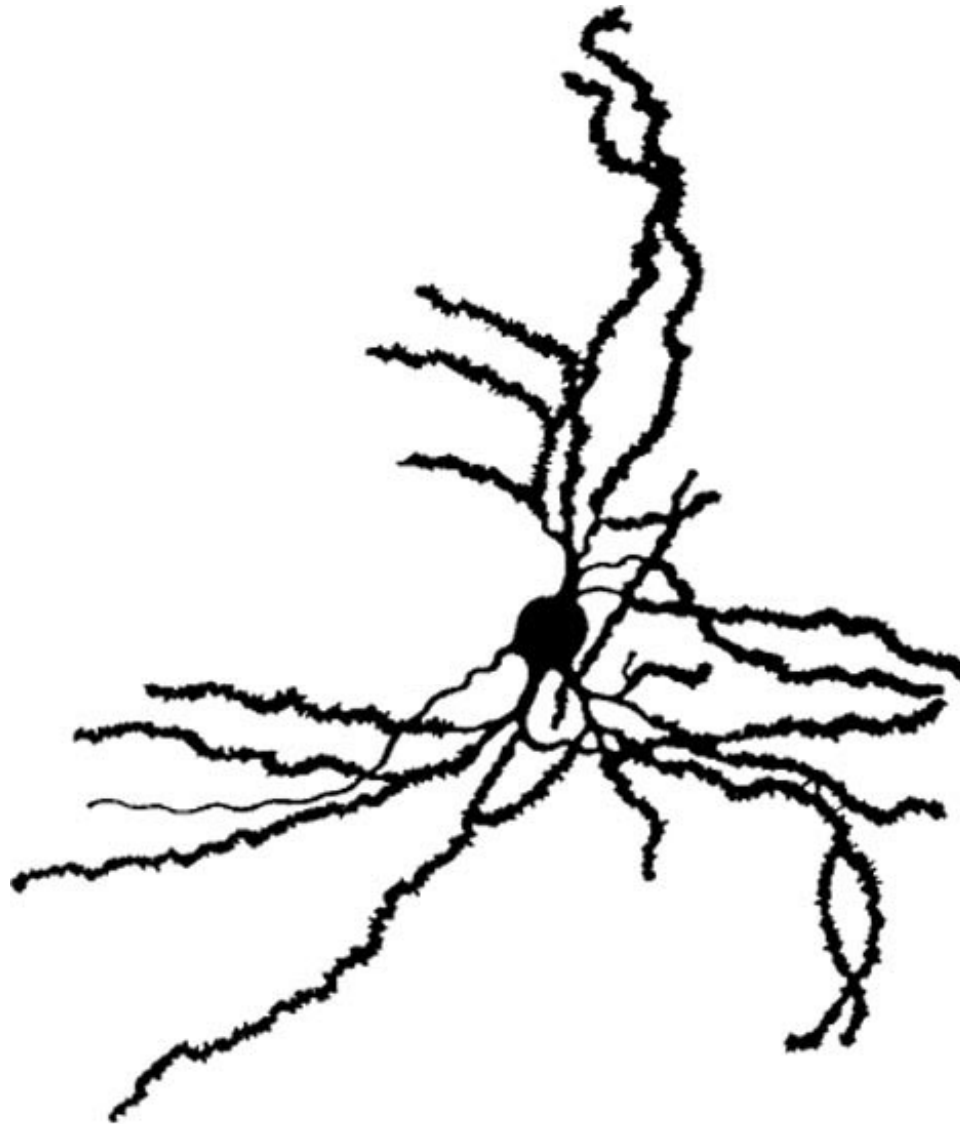


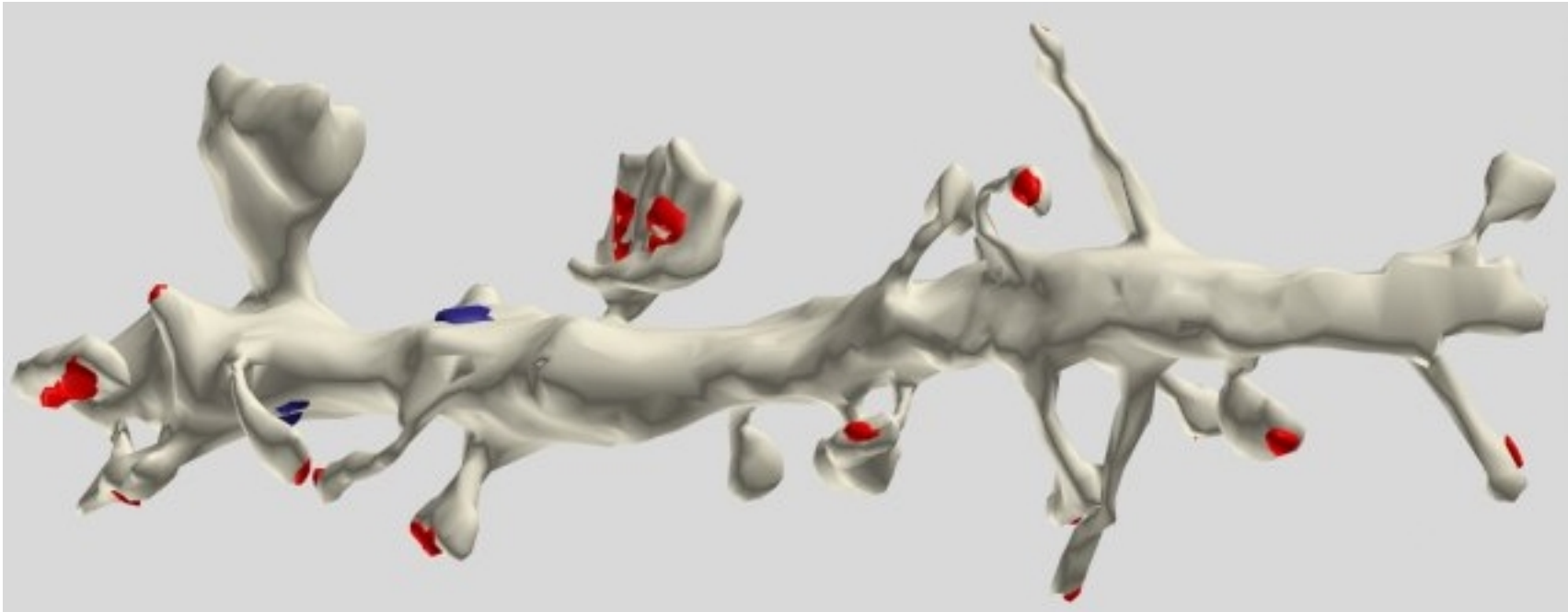


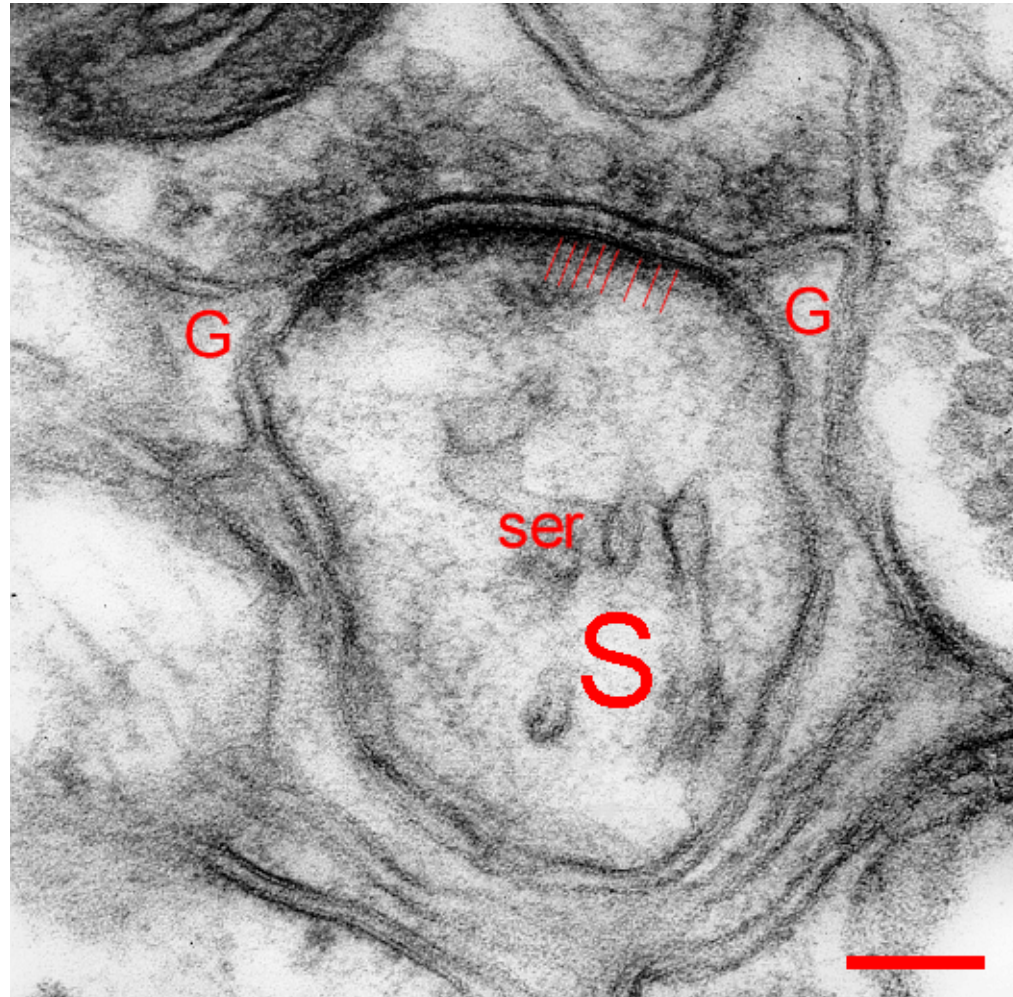


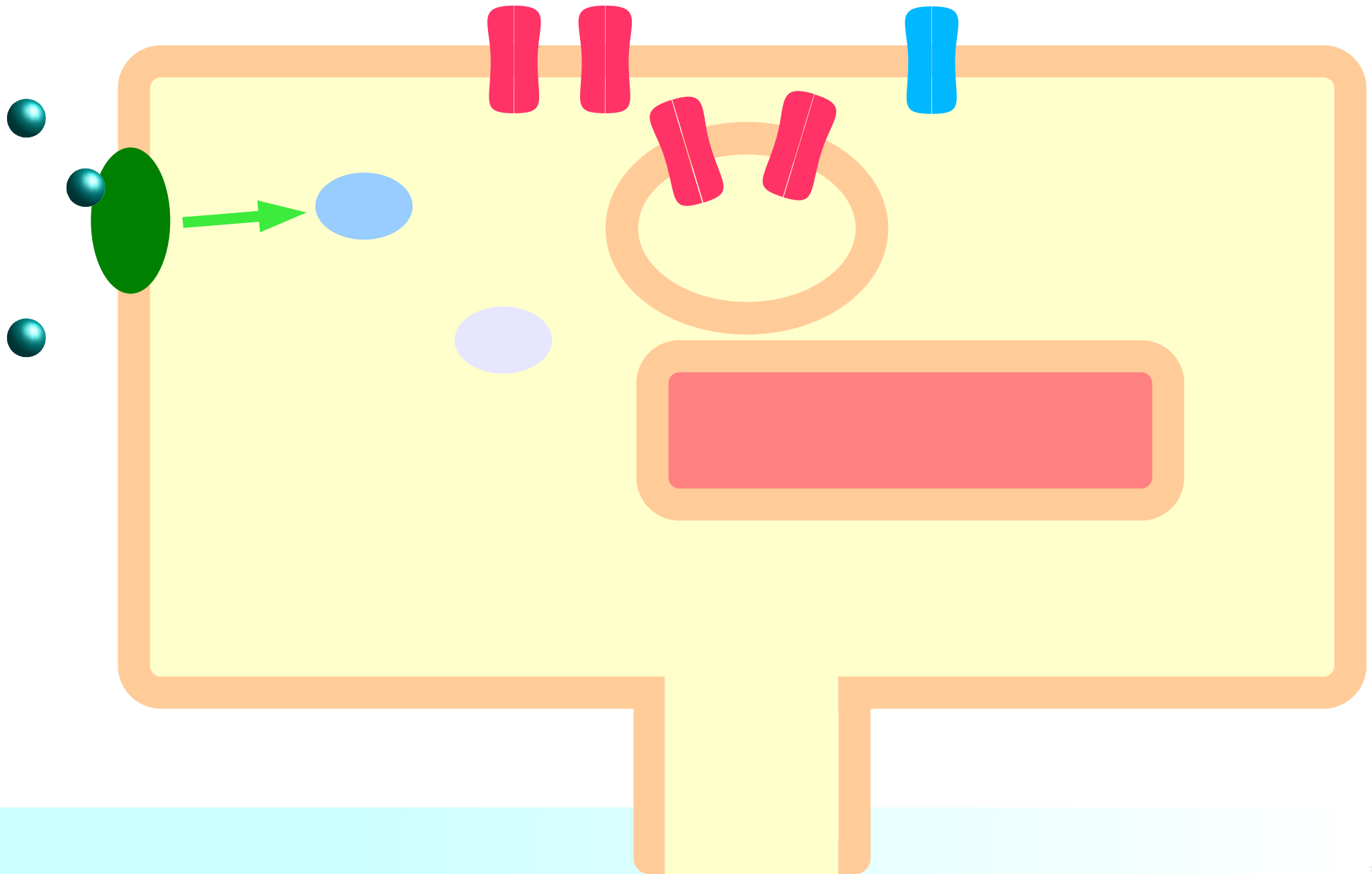


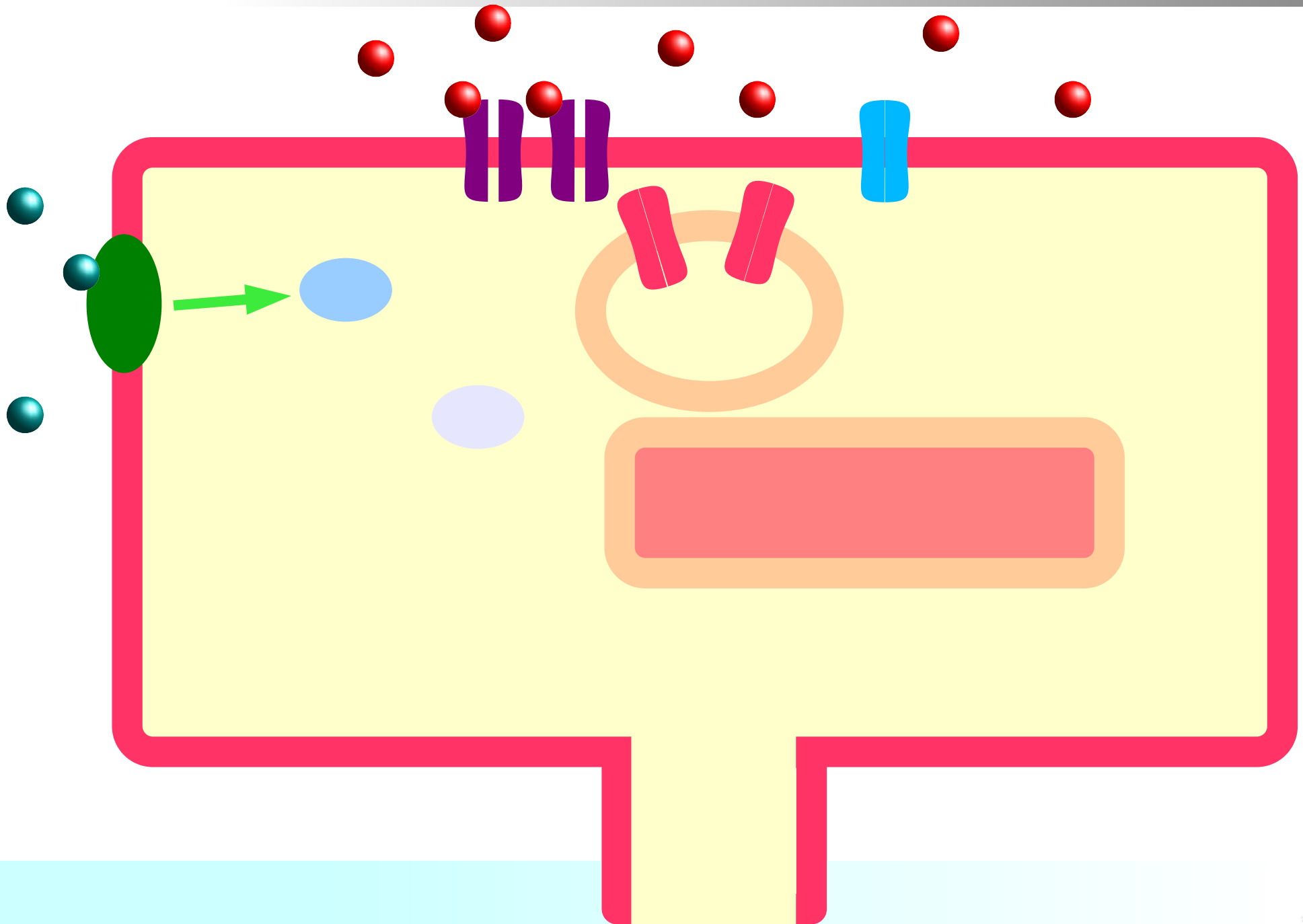
the Medium Spiny Neuron of the striatum

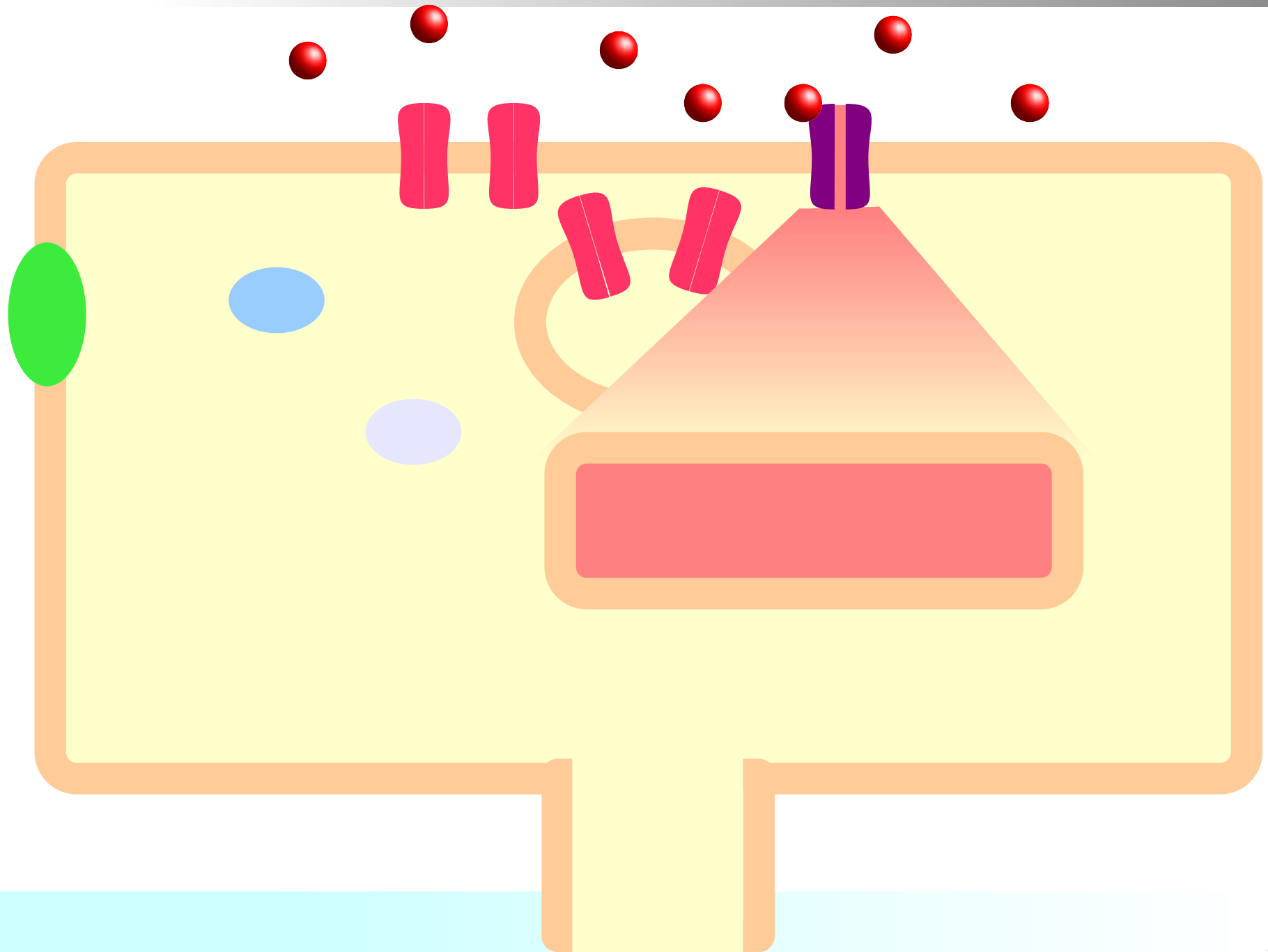


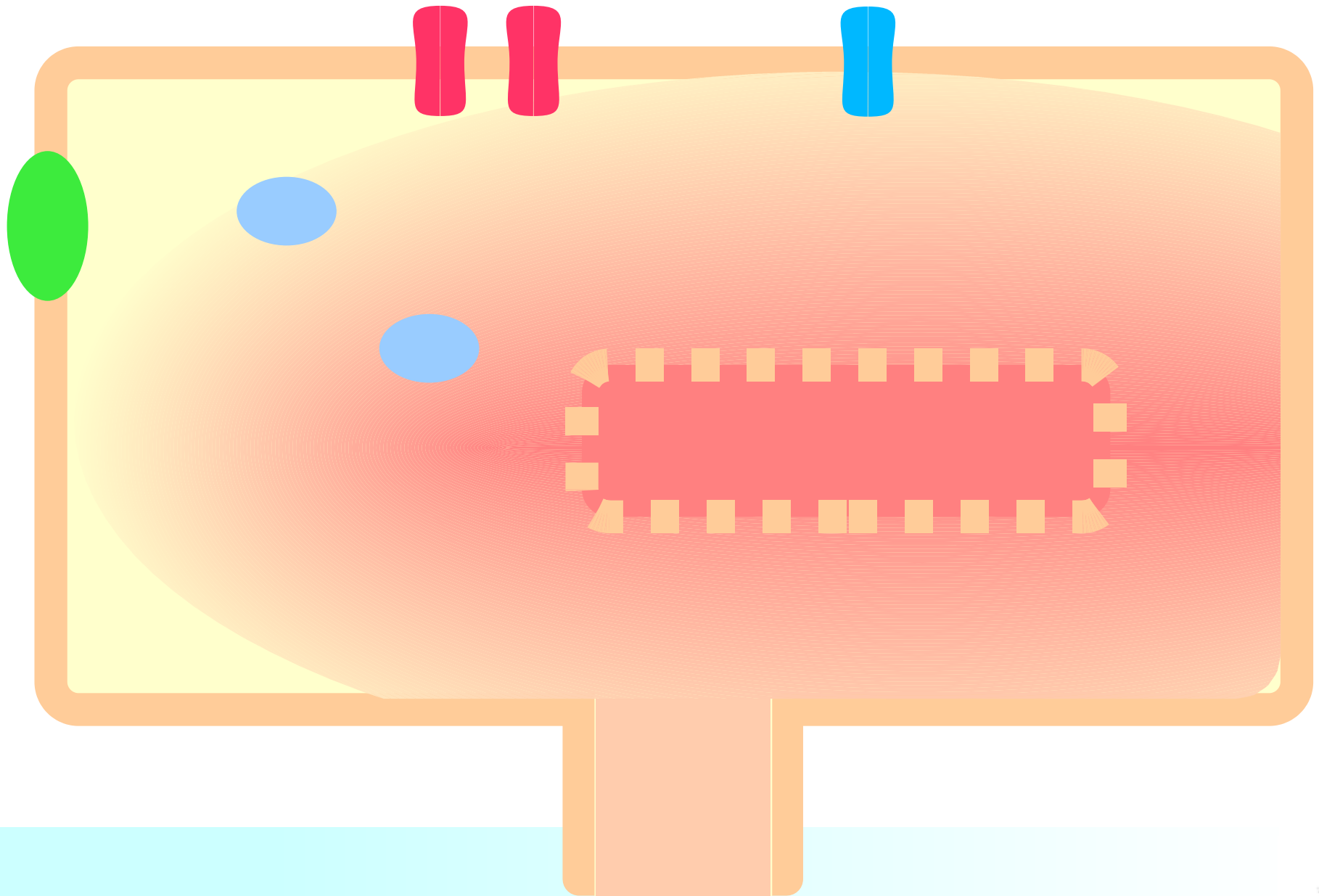


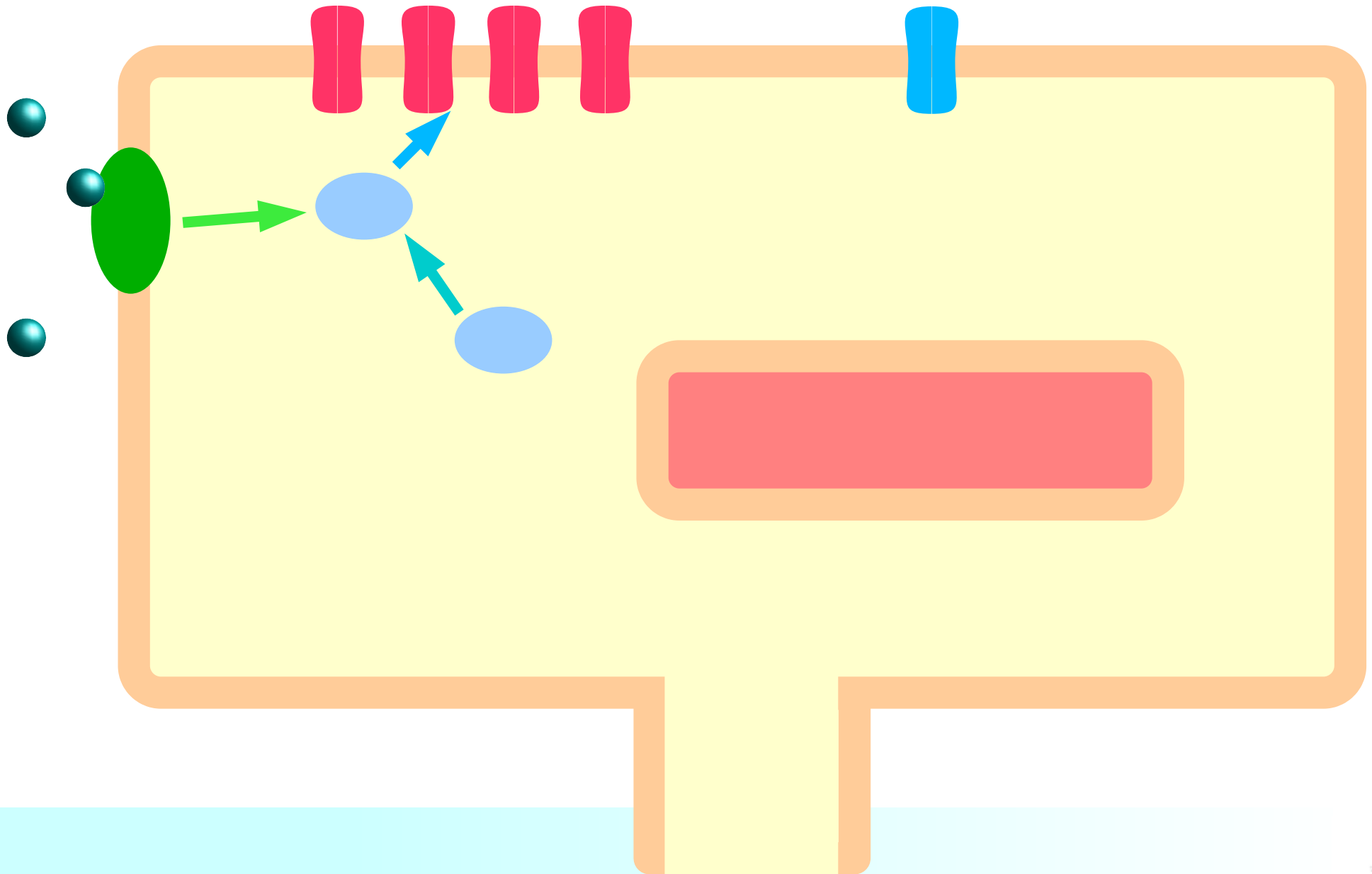










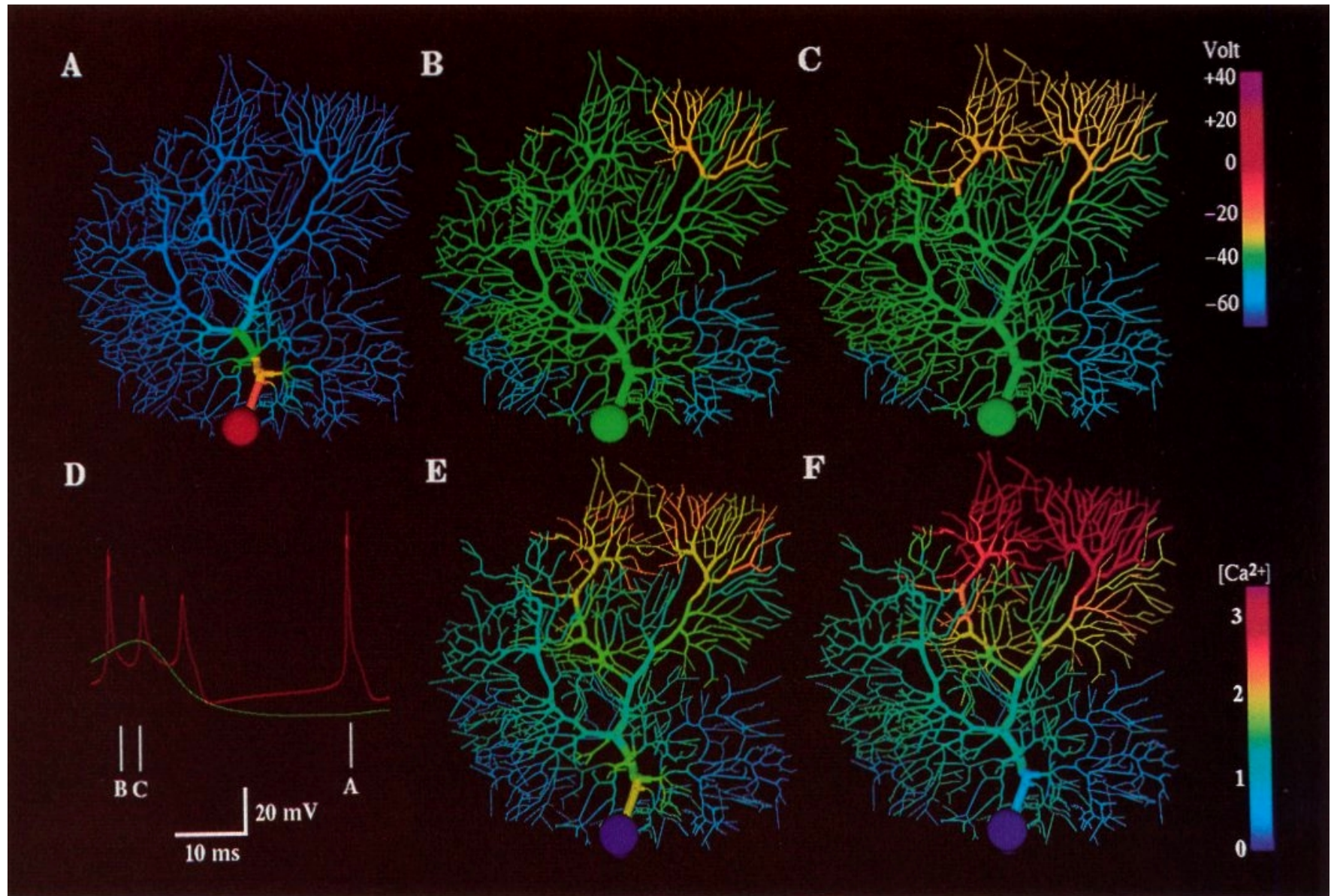


- Three types of information conveyed:
 - Propagation of electrical signals (leave the spine)
 - Diffusion of chemical signals (leave the spine)
 - Transitions between “states” (conformation, covalent modifications, density etc.)
- Diversity of modelling approaches:
 - electrical modelling
 - chemical kinetics
 - reaction-diffusion
 - single particle dynamics
 - etc.



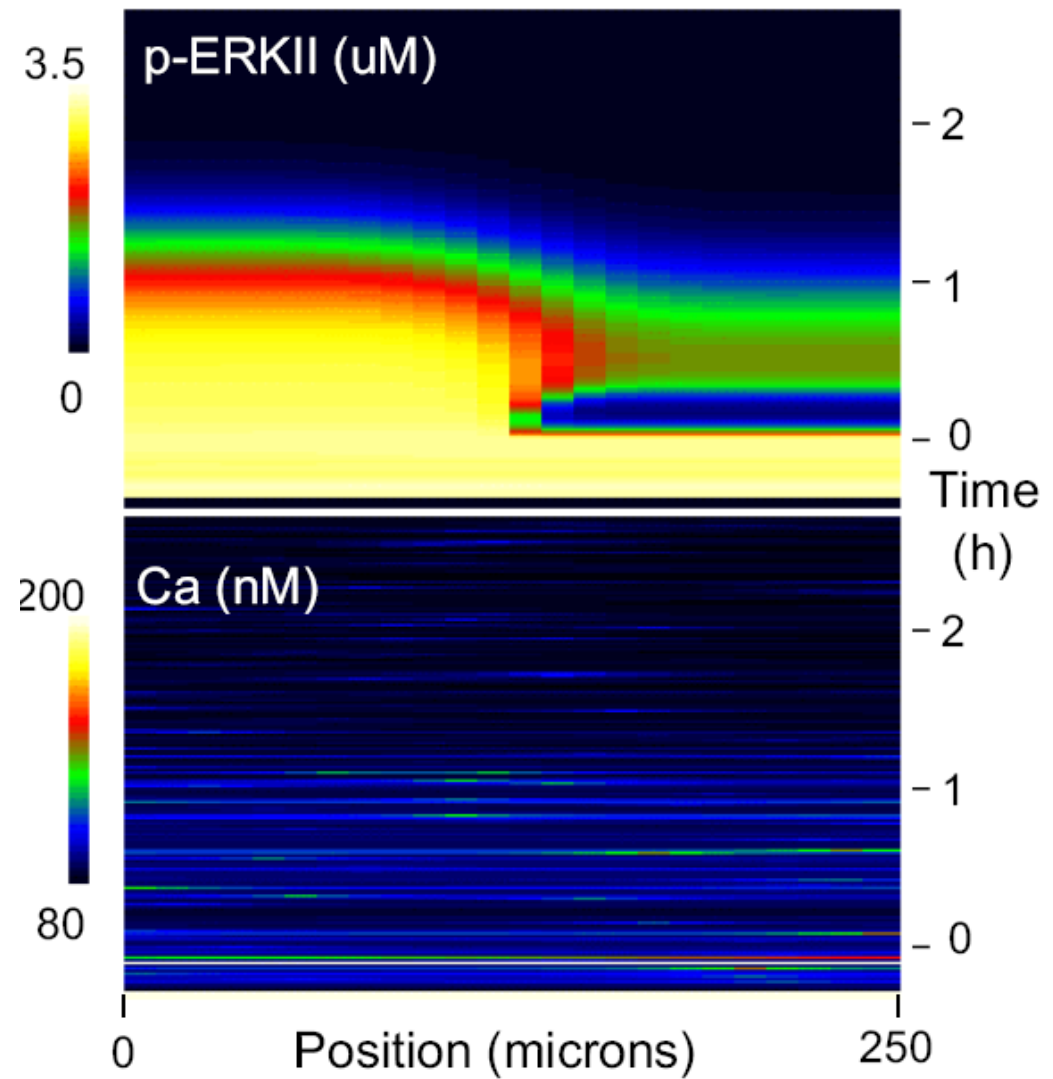
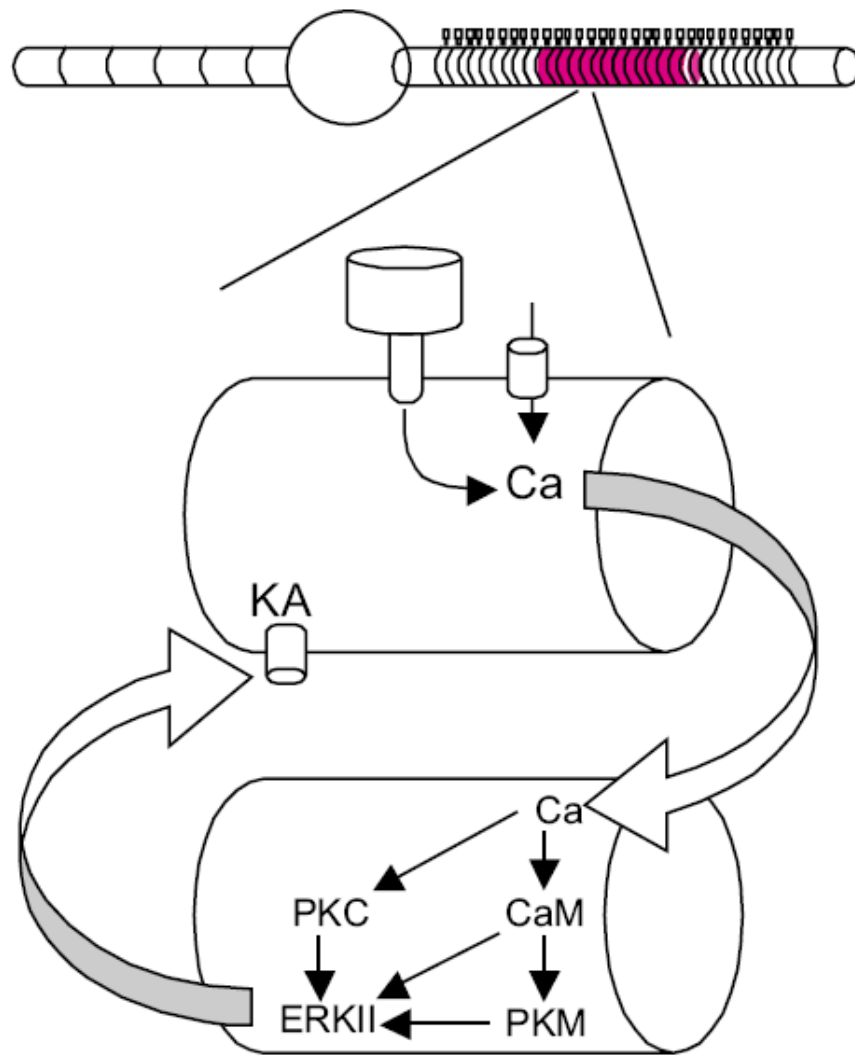
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"A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve". *J Physiol* 1952, 117: 500-544
- Rall
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"Towards an integration of biochemical and biophysical models of neuronal information processing: a case study in the nigro-striatal system." *Rev Neurosci* 1999, 10: 247-266





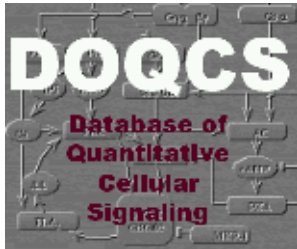
De Schutter and Bower (1994) *J Neurophysio*, 71: 375-419



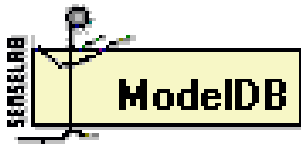


Upinder Bhalla (personal communication)





Bangalore, IN [**GENESIS**]

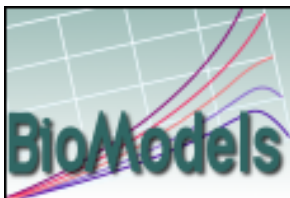


of SenseLab, USA [**NEURON**, **GENESIS** ...]



models repository, NZ [**CellML**]

JWS online ZA/NL/UK [**SBML**, **Pysces**]



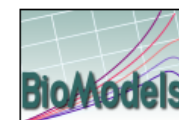
BioModels Database, EU/USA [**CellML**, **SBML**]

For more -> Jacky Snoep, Friday 9:00-10:00



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.

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👉 4th December 2006 - BioModels Database and DOQCS join forces [\[More\]](#)

👉 July 2006 - PLoS Computational Biology supports BioModels Database [\[more\]](#)

[Acknowledgements](#)

BioModels Database is developed in collaboration by the teams of [Nicolas Le Novère](#) (EMBL-EBI, United-Kingdom), [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 Stellenbosch 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) and the [National Institute of General Medical Sciences](#) (SBML team).

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

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

External contributors: BioModels Database would not exist 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 keep track and 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](#), [Xalan](#), [Xerces](#), [Jena](#) and [MySQL](#).

Main software used to curate models: [CellDesigner](#), [COPASI](#), [Jarnac](#), [MathSBML](#), [XPP-Aut](#), [SBMLdeSolver](#), [SBMLEditor](#) and [SBMLmerge](#).

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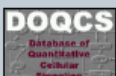
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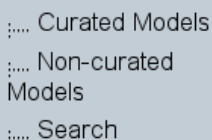
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Reference Publication

Publication ID: <u>12991237</u>	J Physiol 1952 Aug;117(4):500-44. A quantitative description of membrane current and its application to conduction and excitation in nerve. HODGKIN AL, HUXLEY AF. [more]
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Model

Original Model: <i>Unspecified</i>	bqbiol:is	set #1	<u>Taxonomy</u> <u>Loligo forbesi</u>
Submitter: <u>Nicolas Le Novere</u>			<u>Gene Ontology</u> <u>voltage-gated potassium channel activity</u>
Submission Date: 2005-09-13T14:22:40	bqbiol:isVersionOf	set #1	<u>Gene Ontology</u> <u>voltage-gated sodium channel activity</u>
Last Modification Date: 2006-09-24T00:55:29			<u>Gene Ontology</u> <u>action potential propagation</u>
Creation Date: 2005-03-31T14:09:21			
Creators: Maria Schilstra			

Compartments (1)

Species (0)

Rules (16)

Reactions (0)

Events (0)

– + ++

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- **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

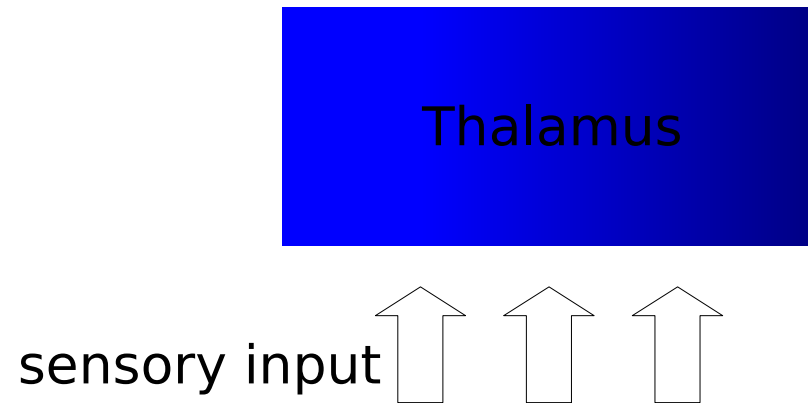
→ Systems Biology is scale-independent!

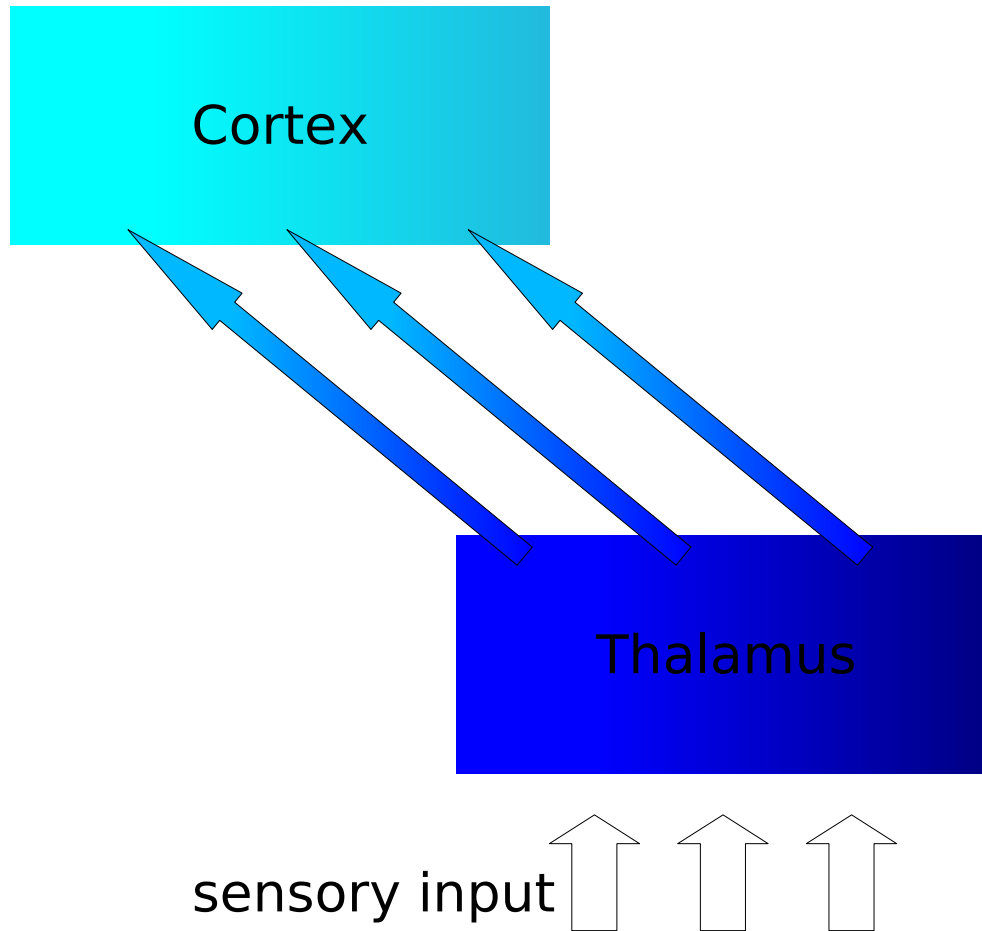


Integration of Dopamine and Glutamate signals by DARPP-32

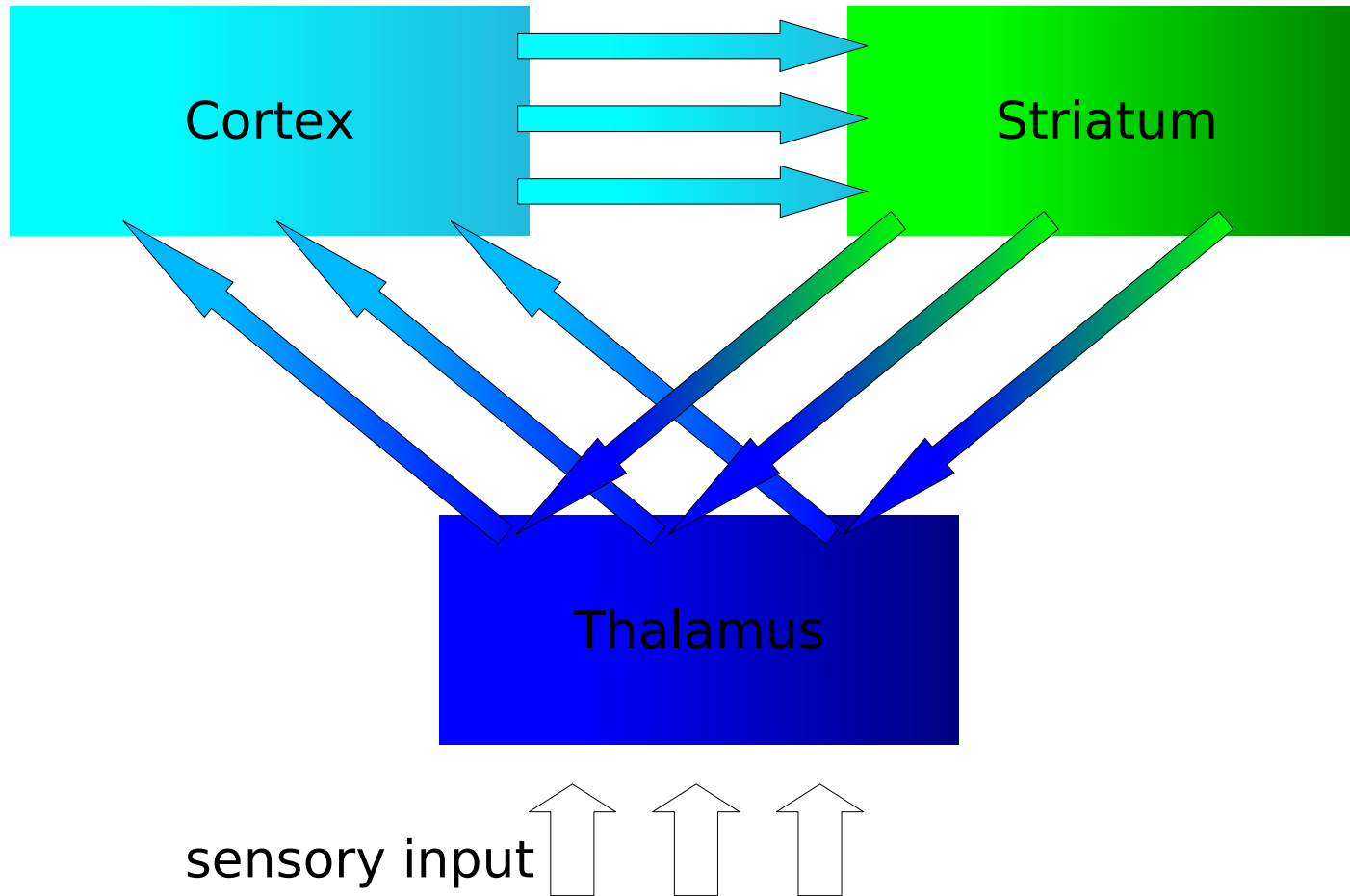
Fernandez E, Schiappa R, Girault JA, Le Novère N (2006) DARPP-32 is a robust integrator of dopamine and glutamate signals. *PLoS Computational Biology*, 2(12): e176.

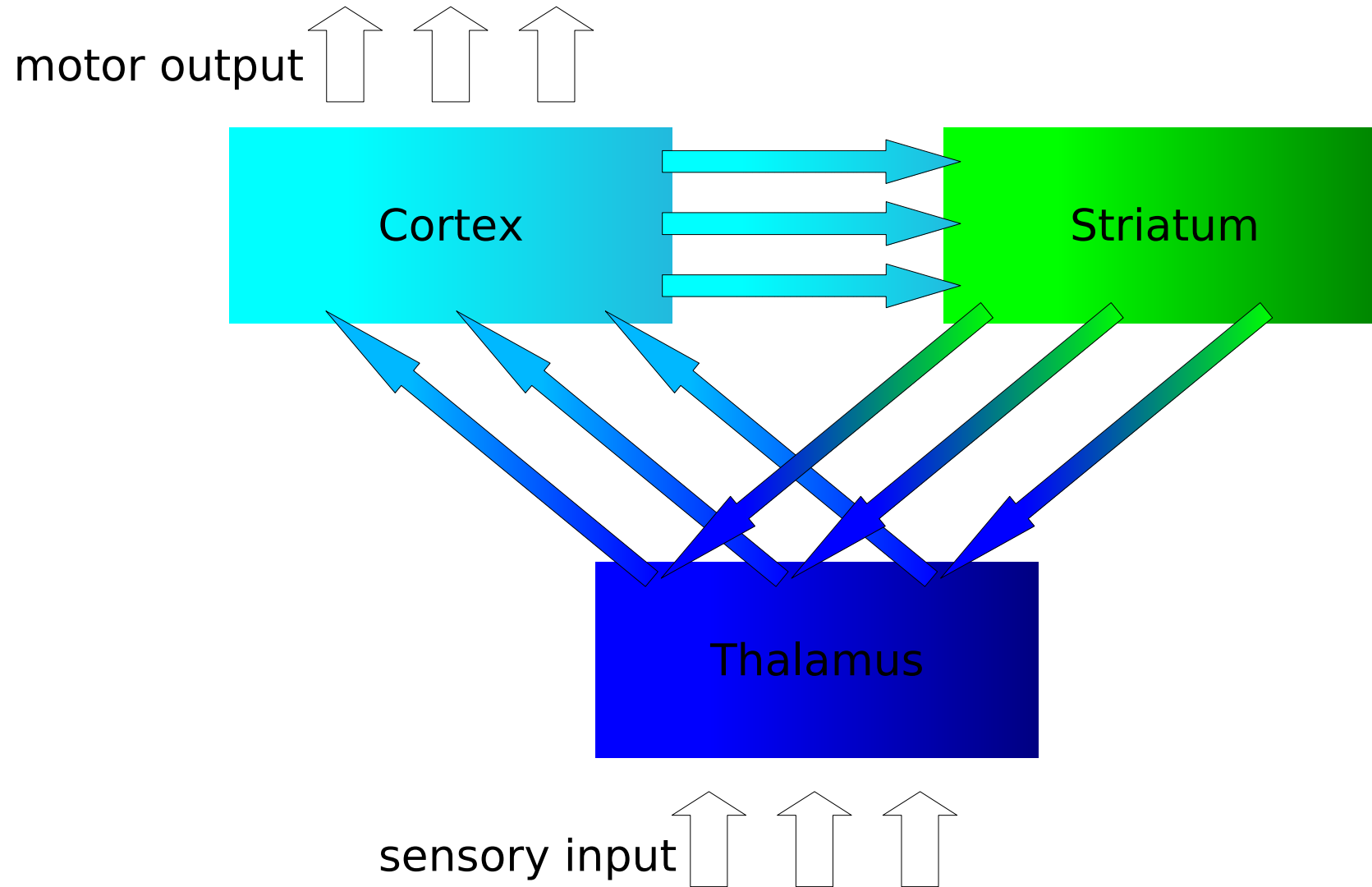


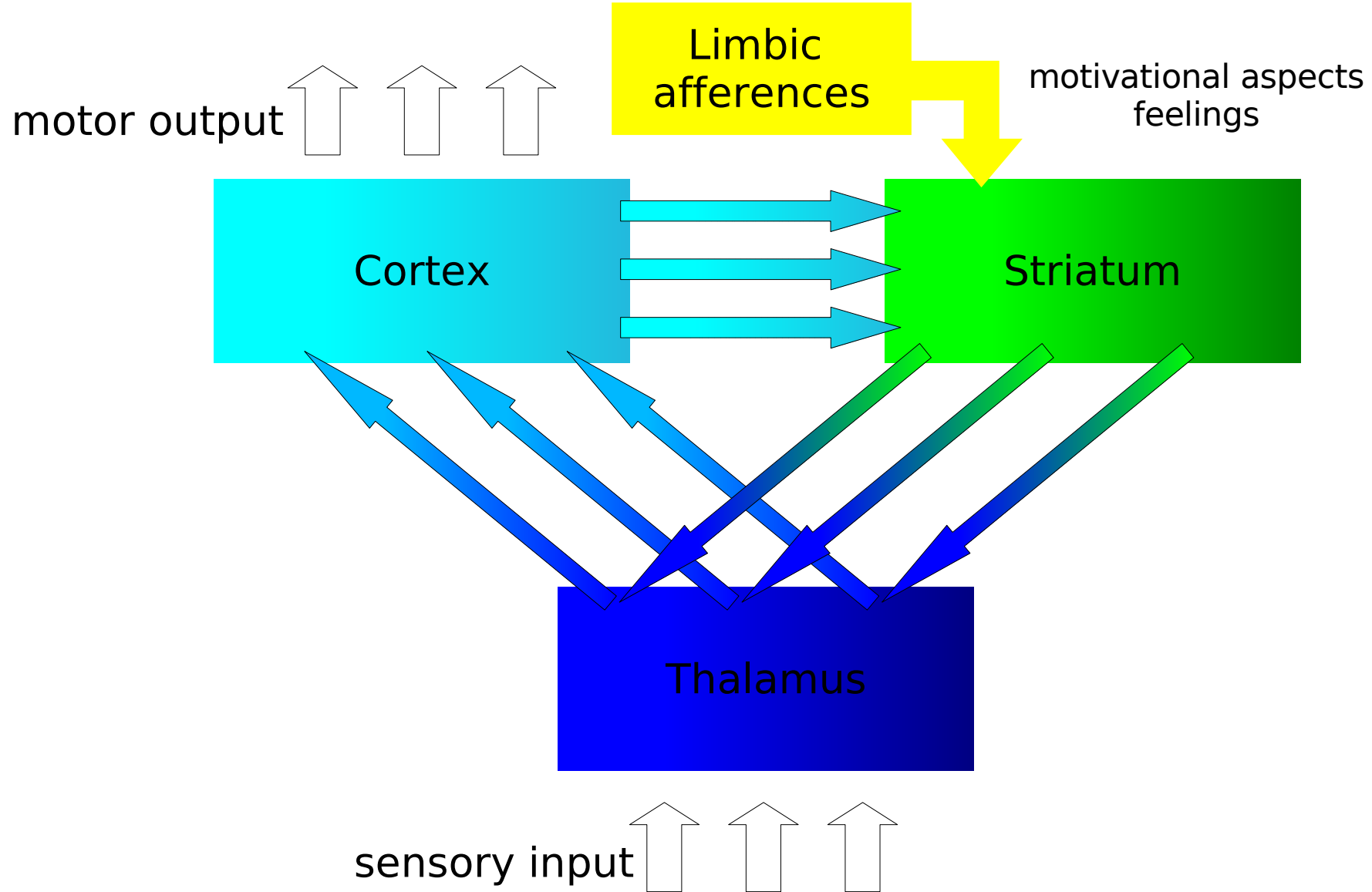


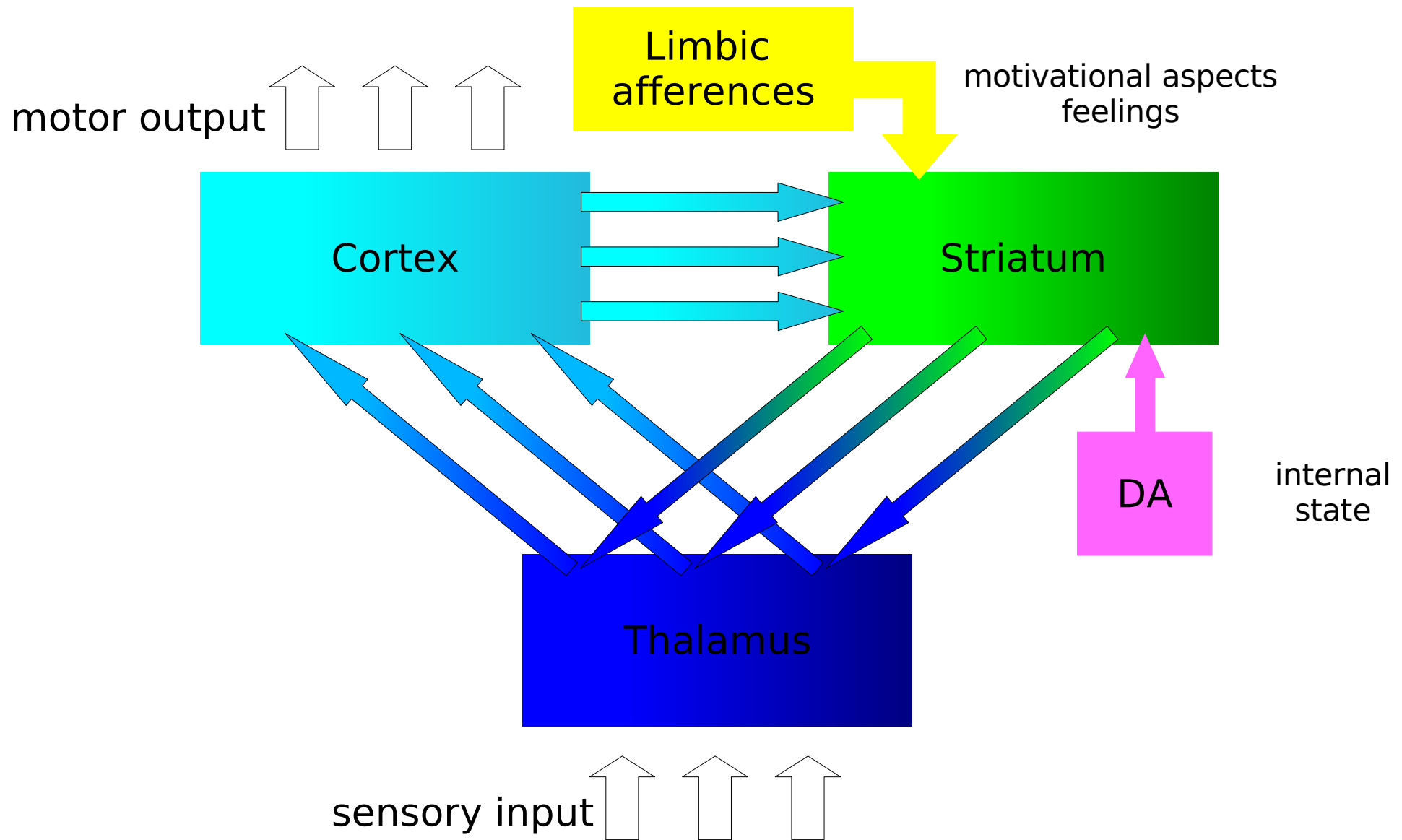


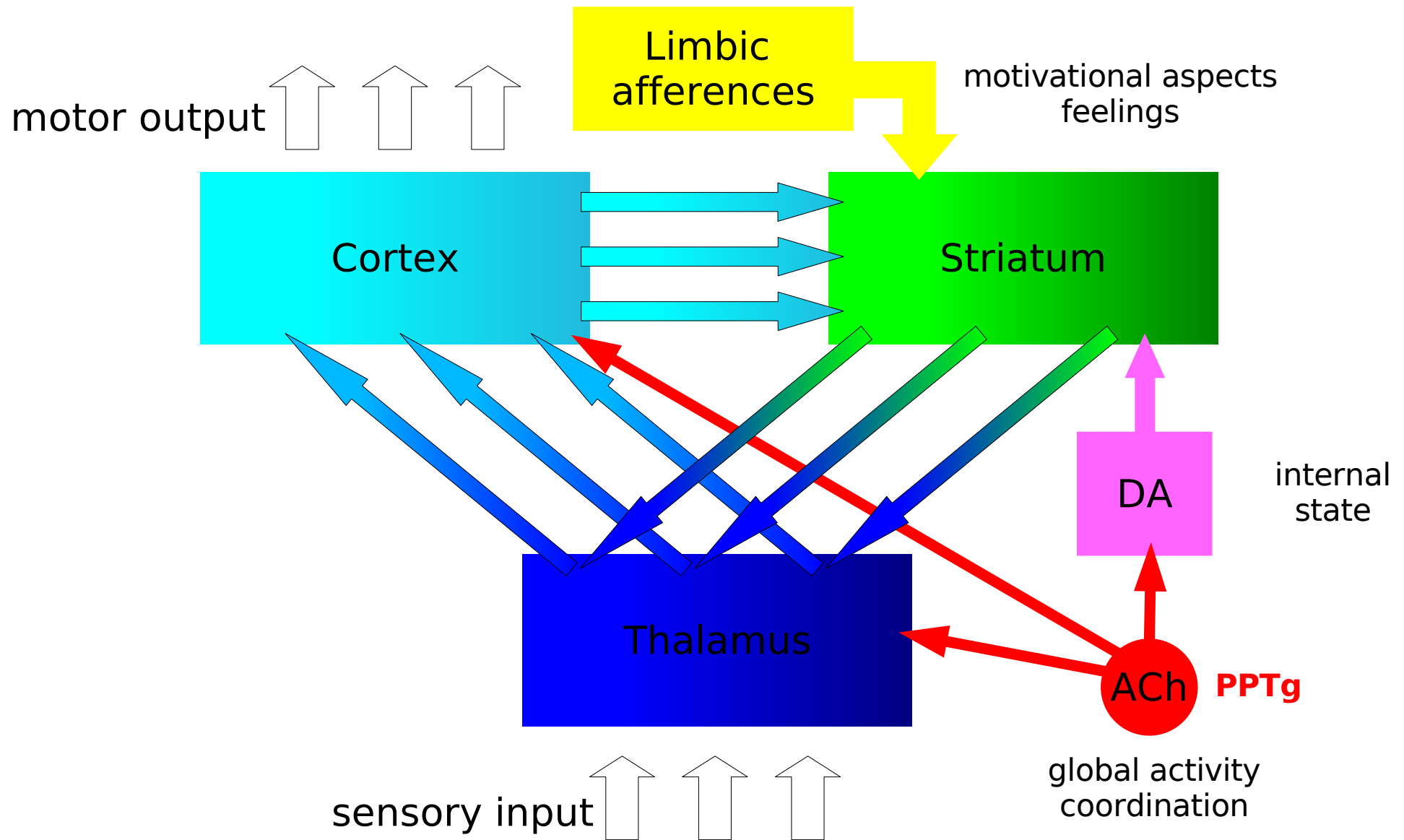
cortico-striato-thalamic loop



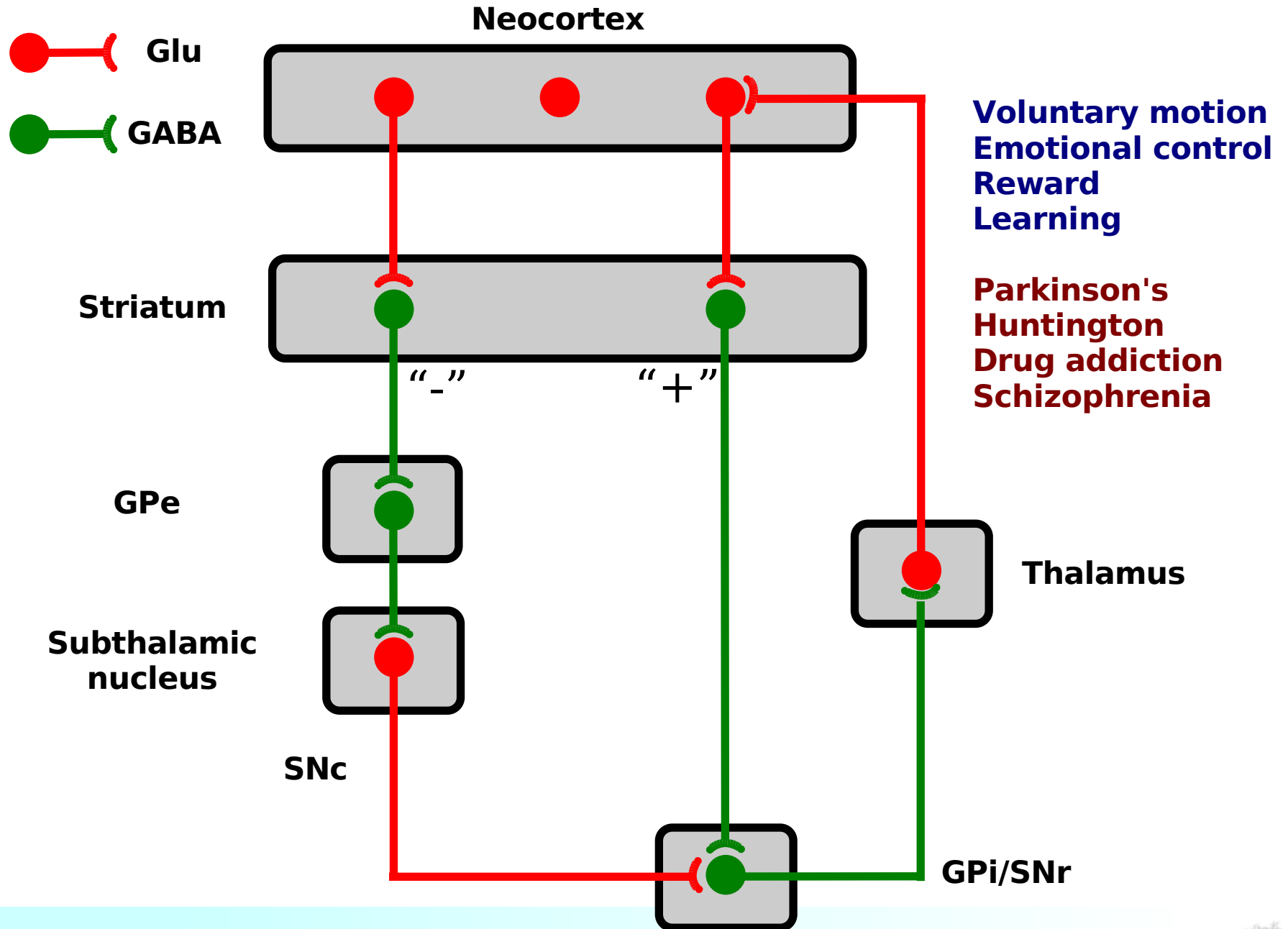




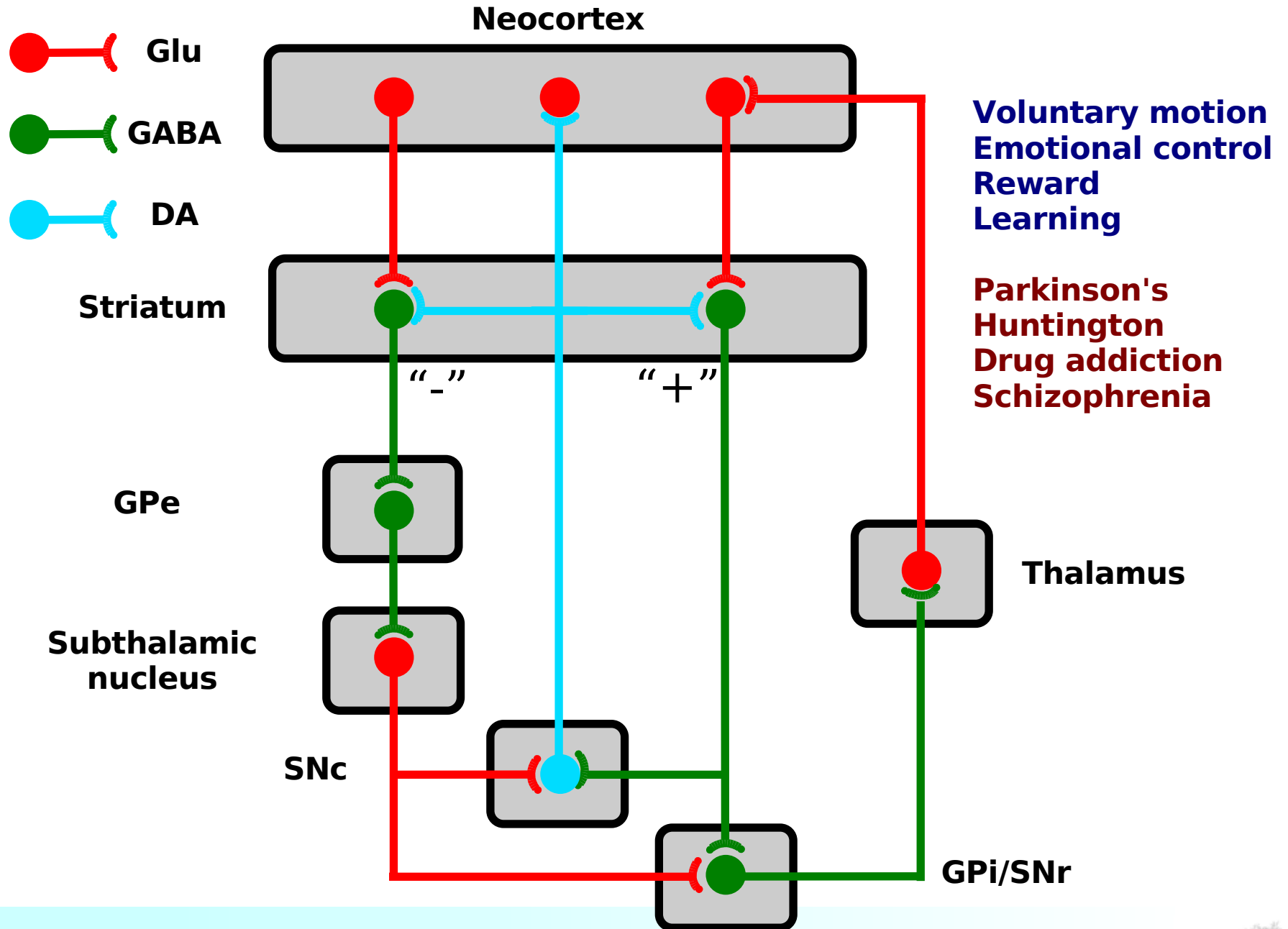




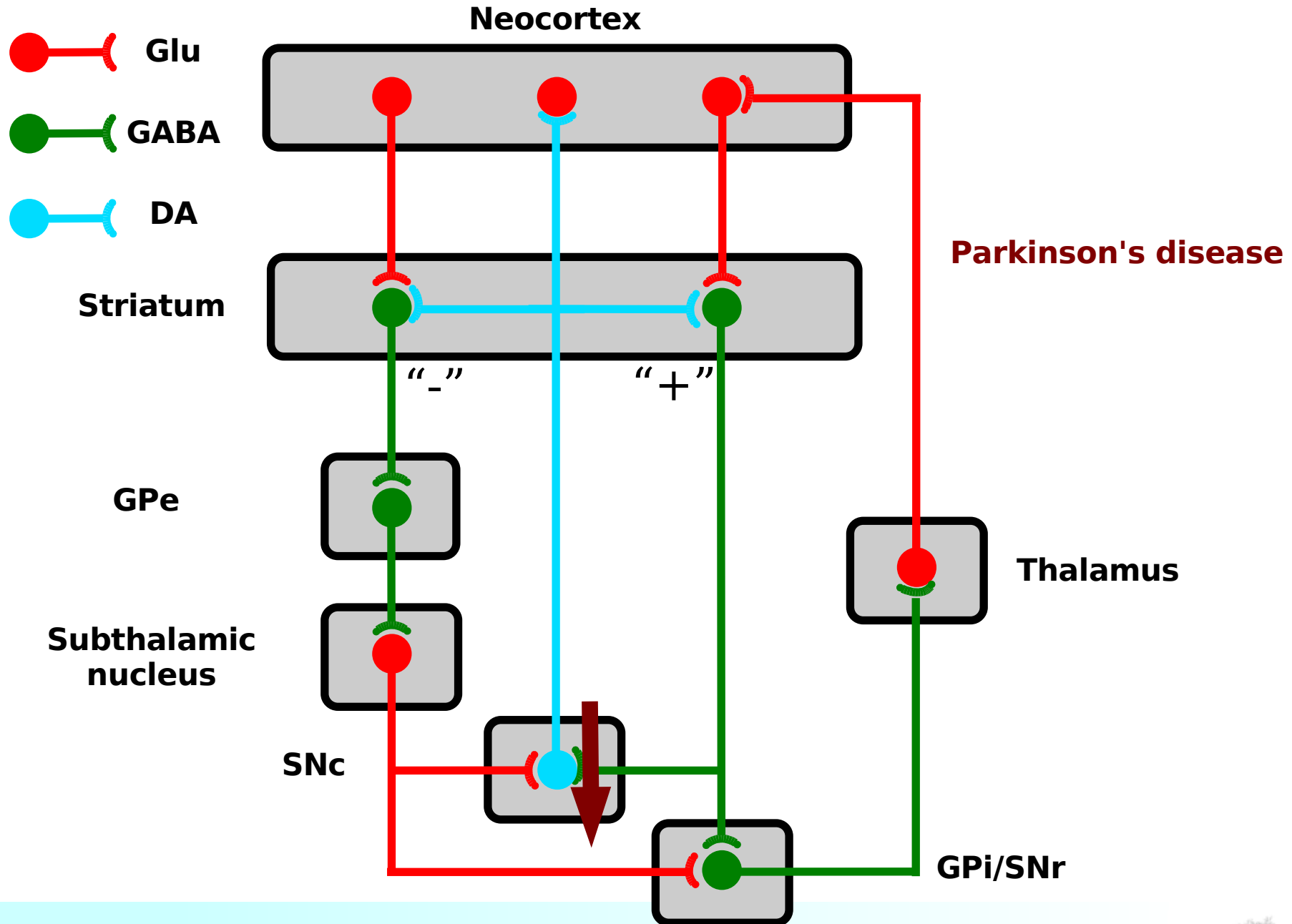
Dopamine mesotelencephalic pathway



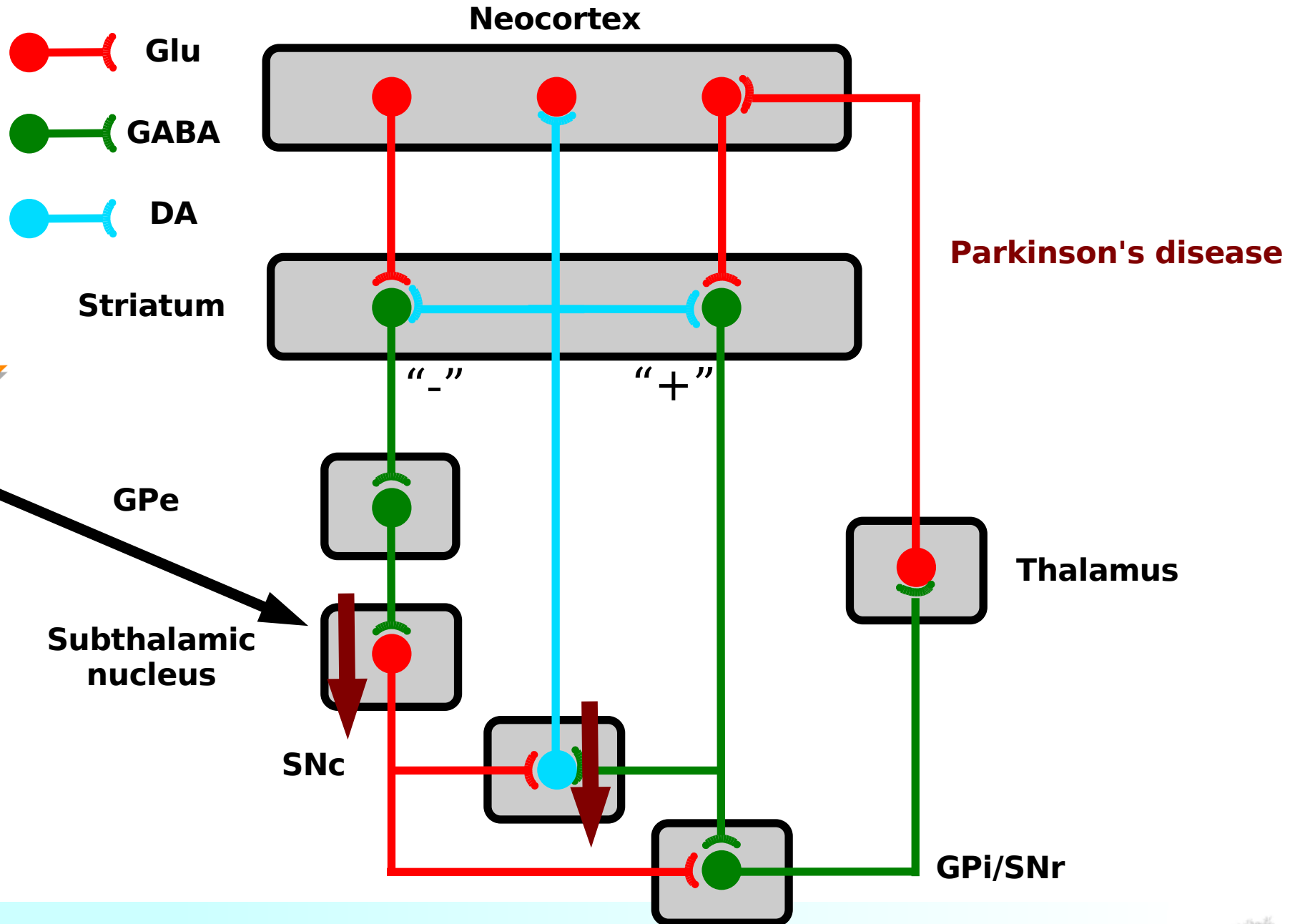
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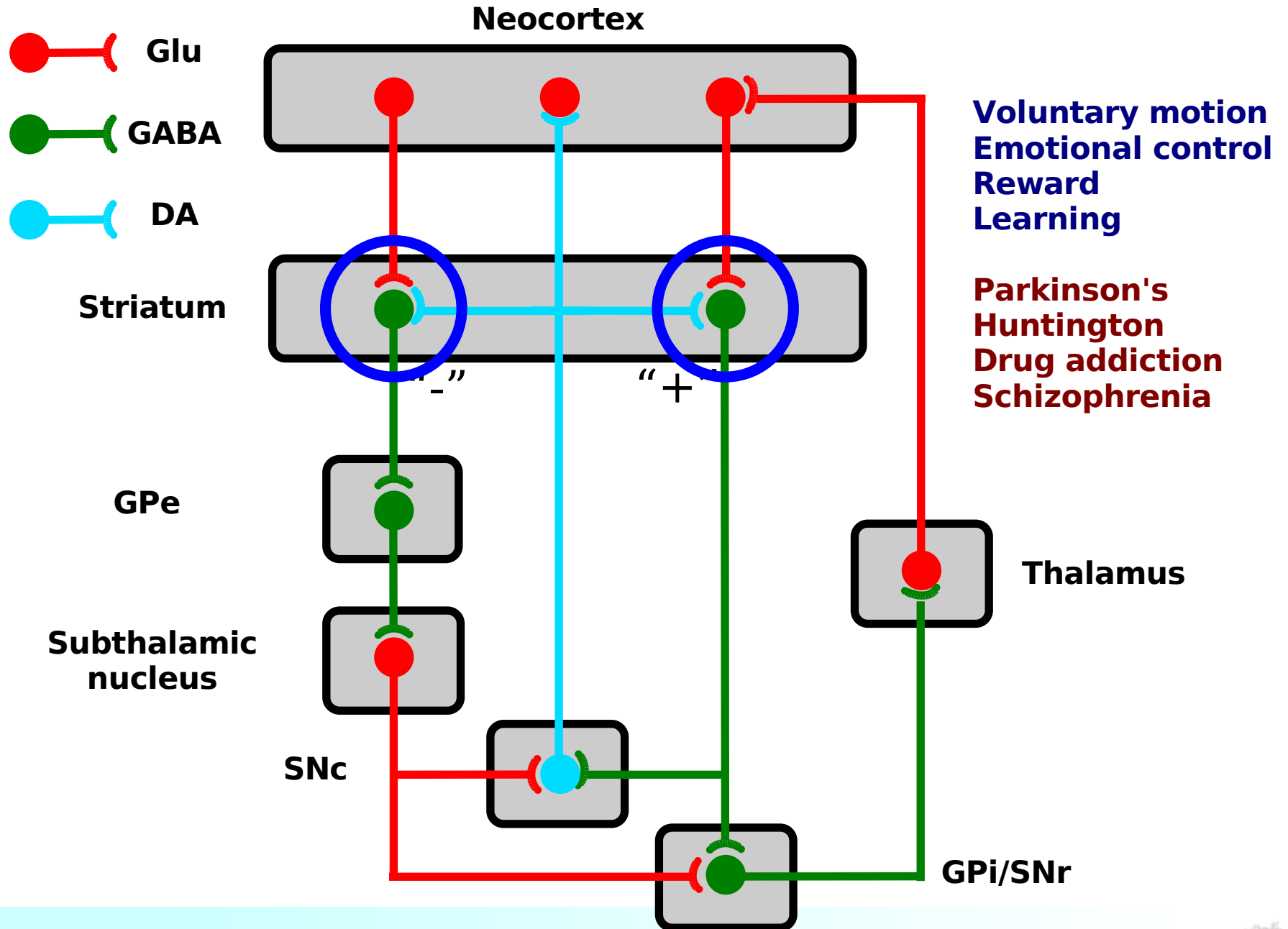
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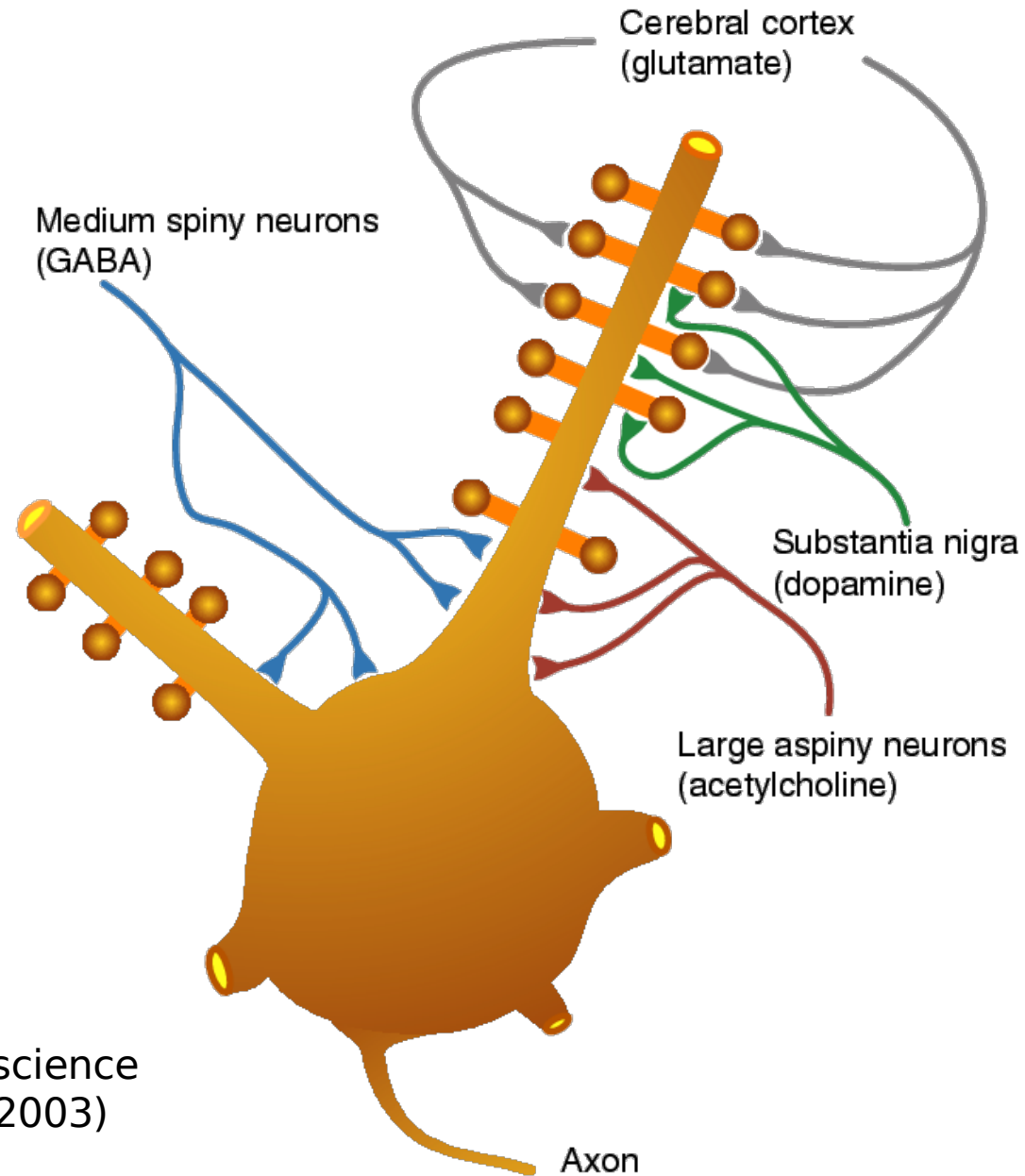


Dopamine mesotelencephalic pathway



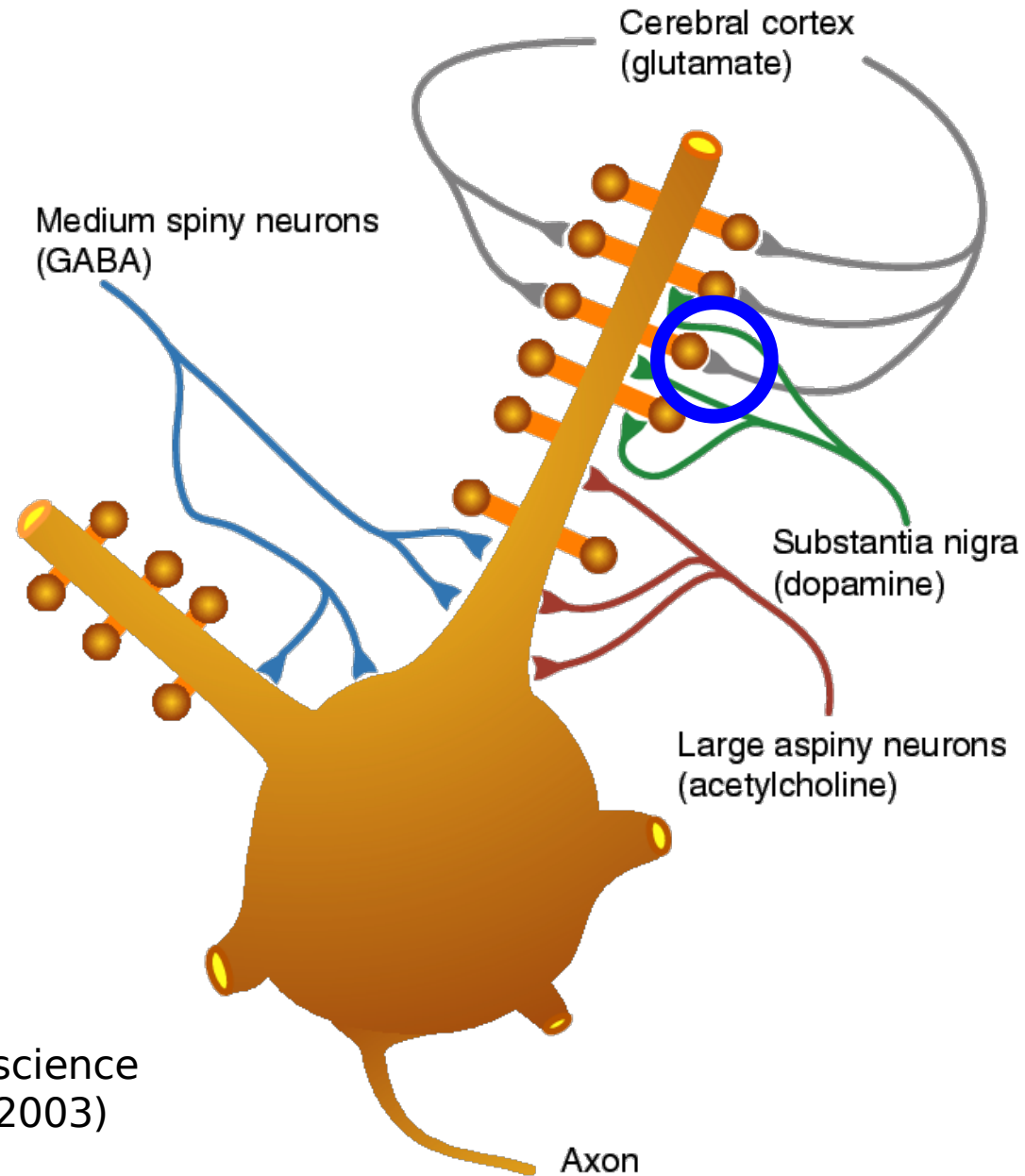
Dopamine mesotelencephalic pathway





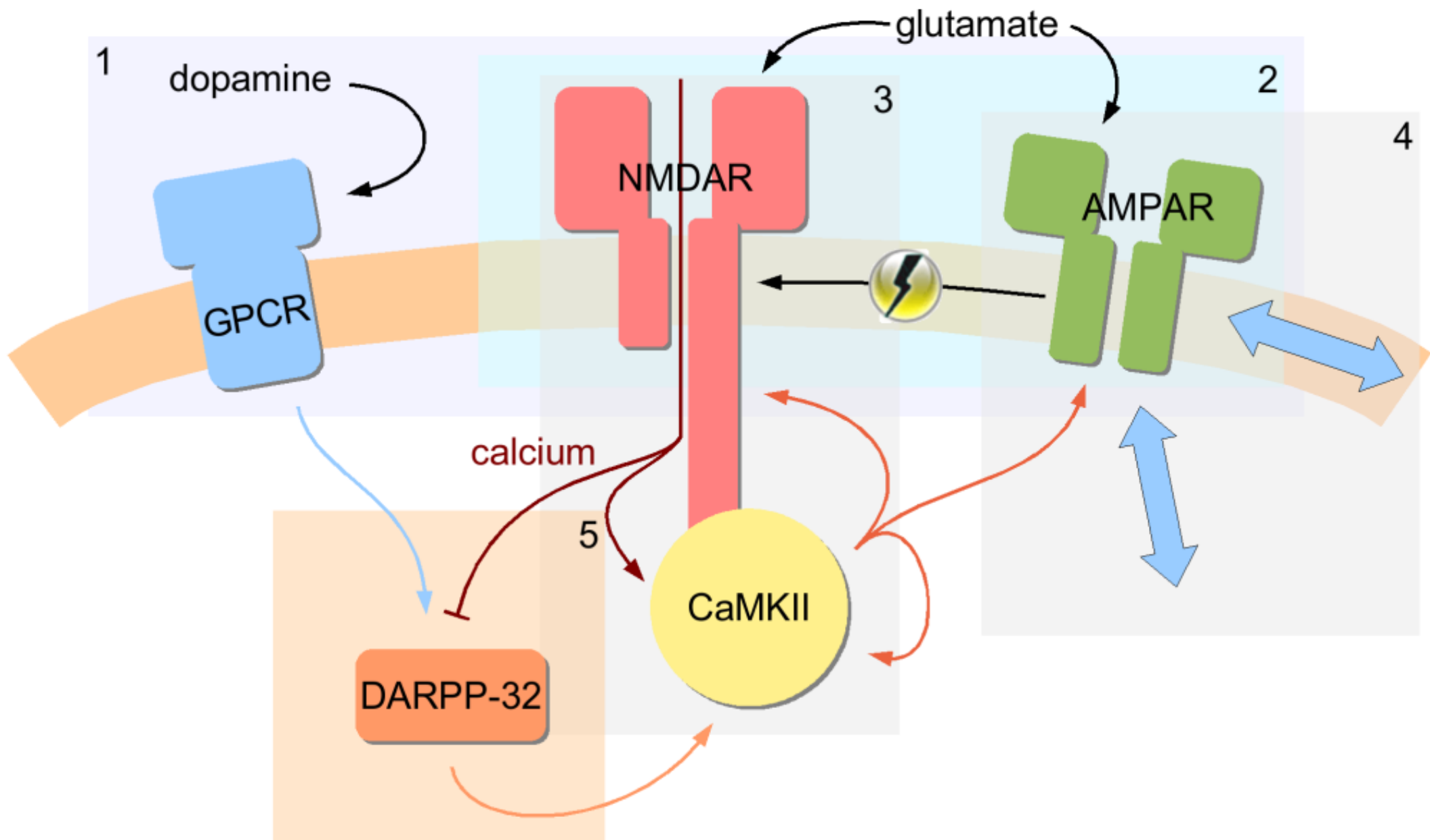
Fundamental Neuroscience
Squire et al. 2nd ed(2003)



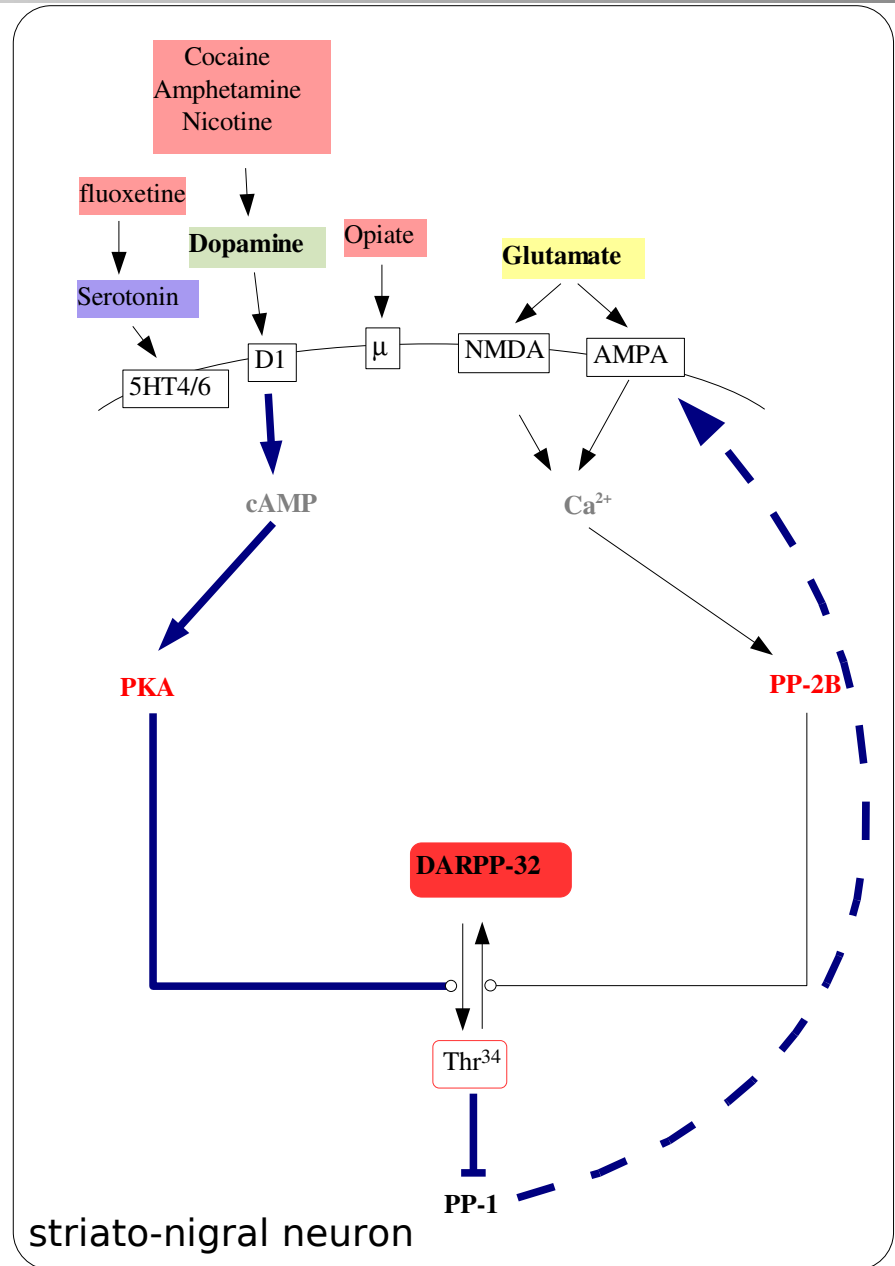
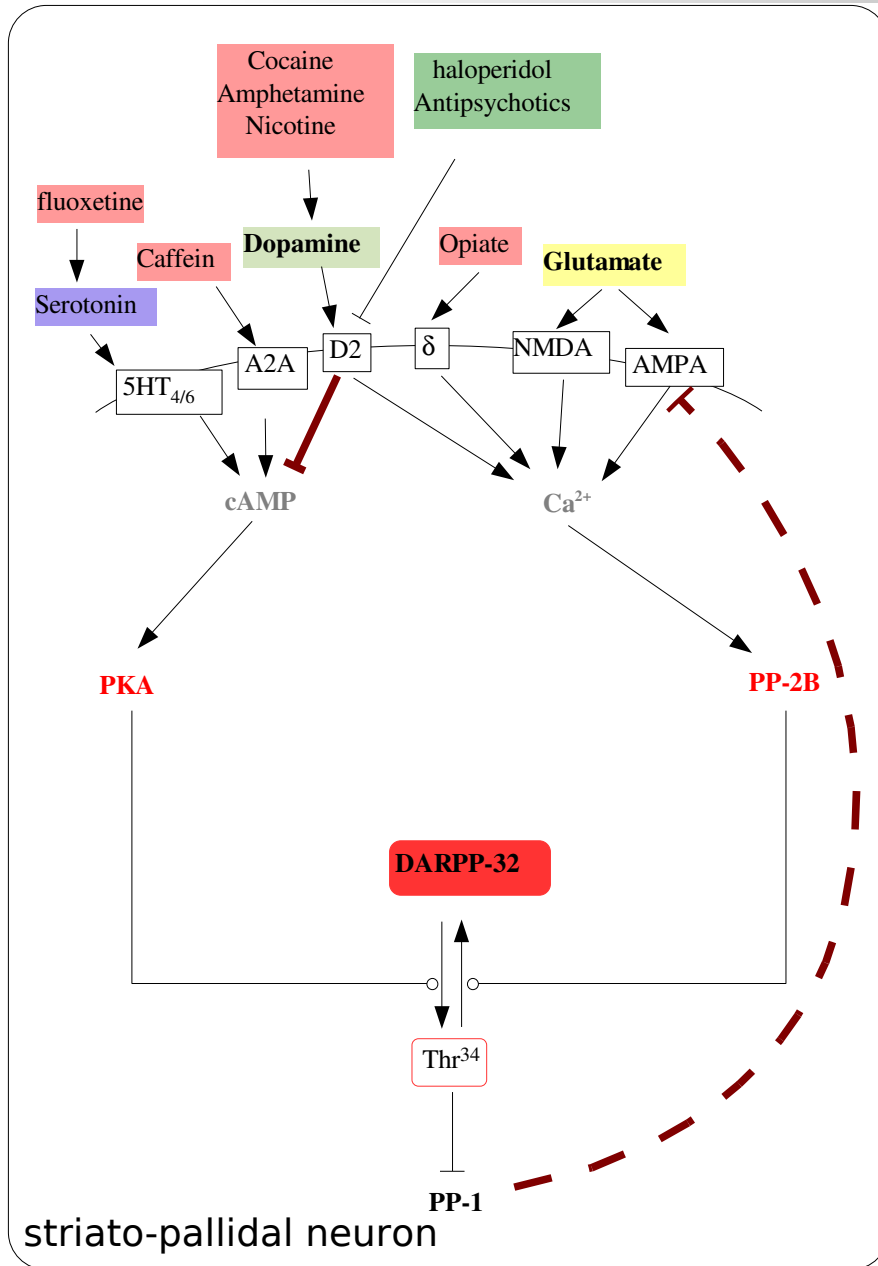


Fundamental Neuroscience
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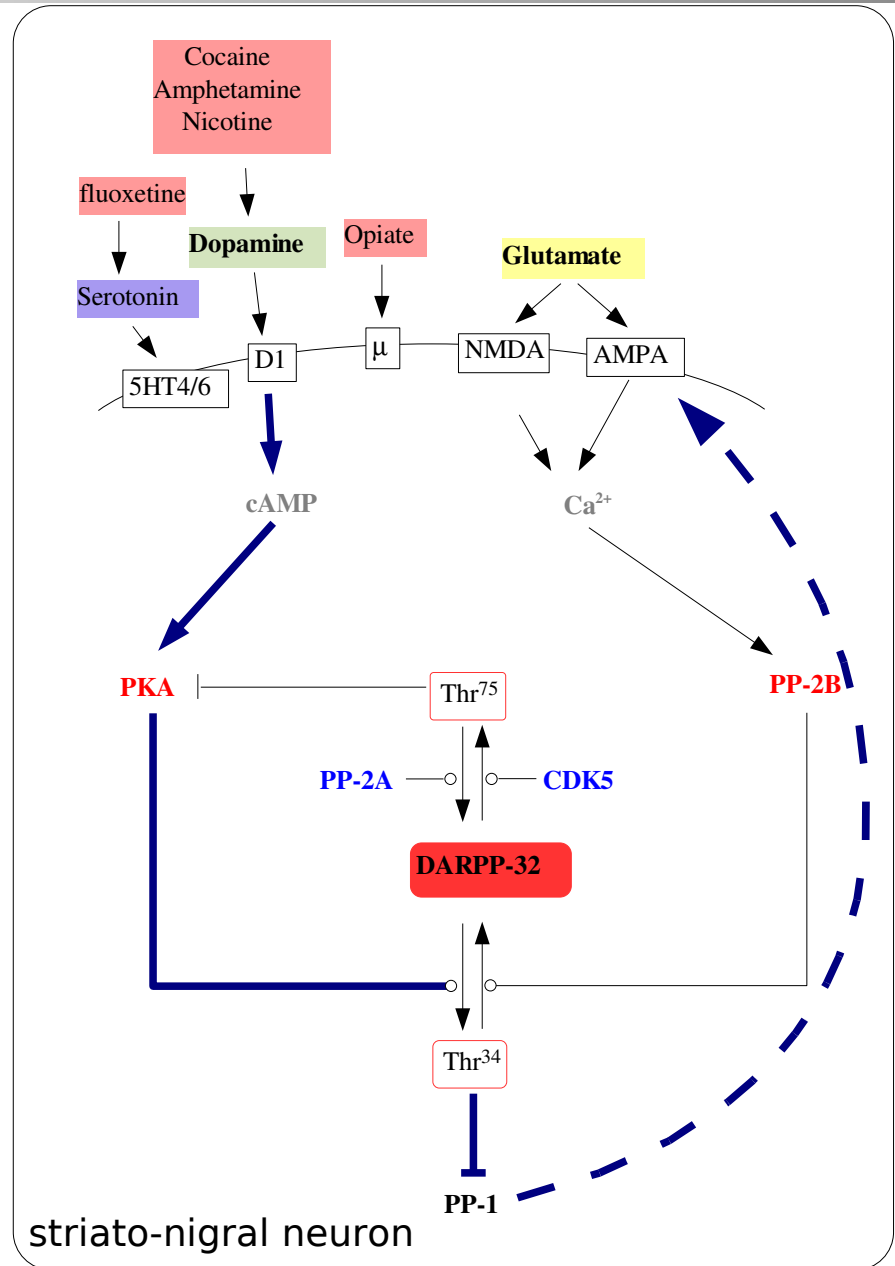
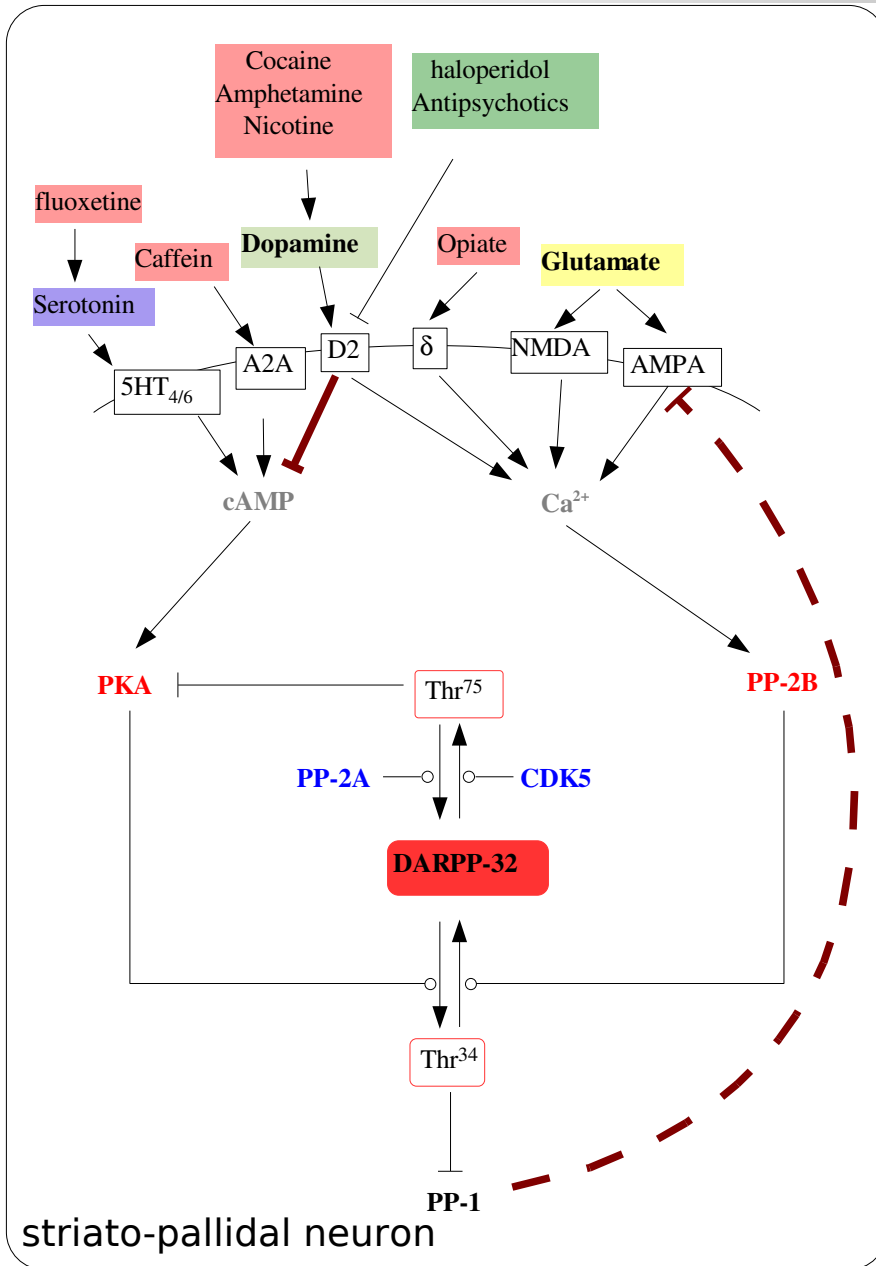




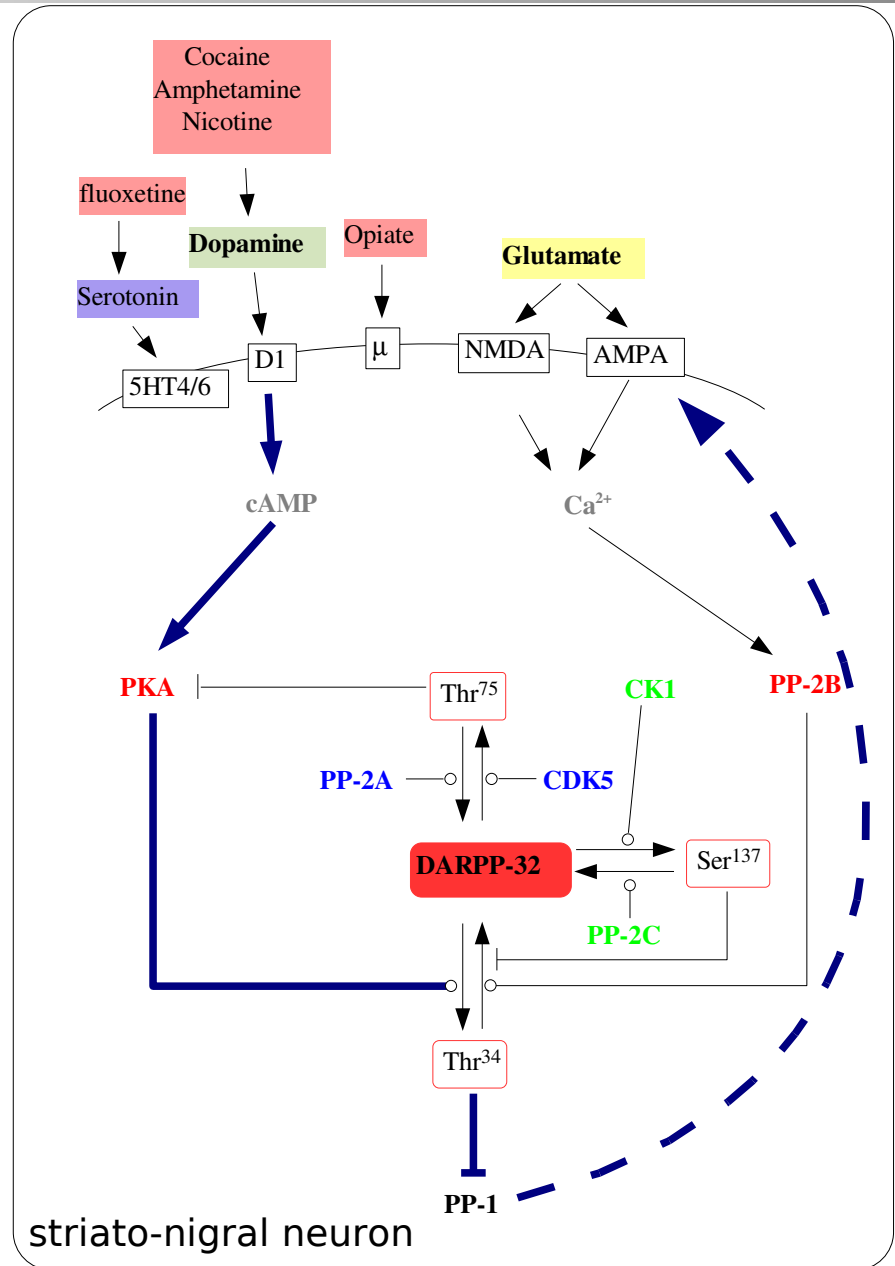
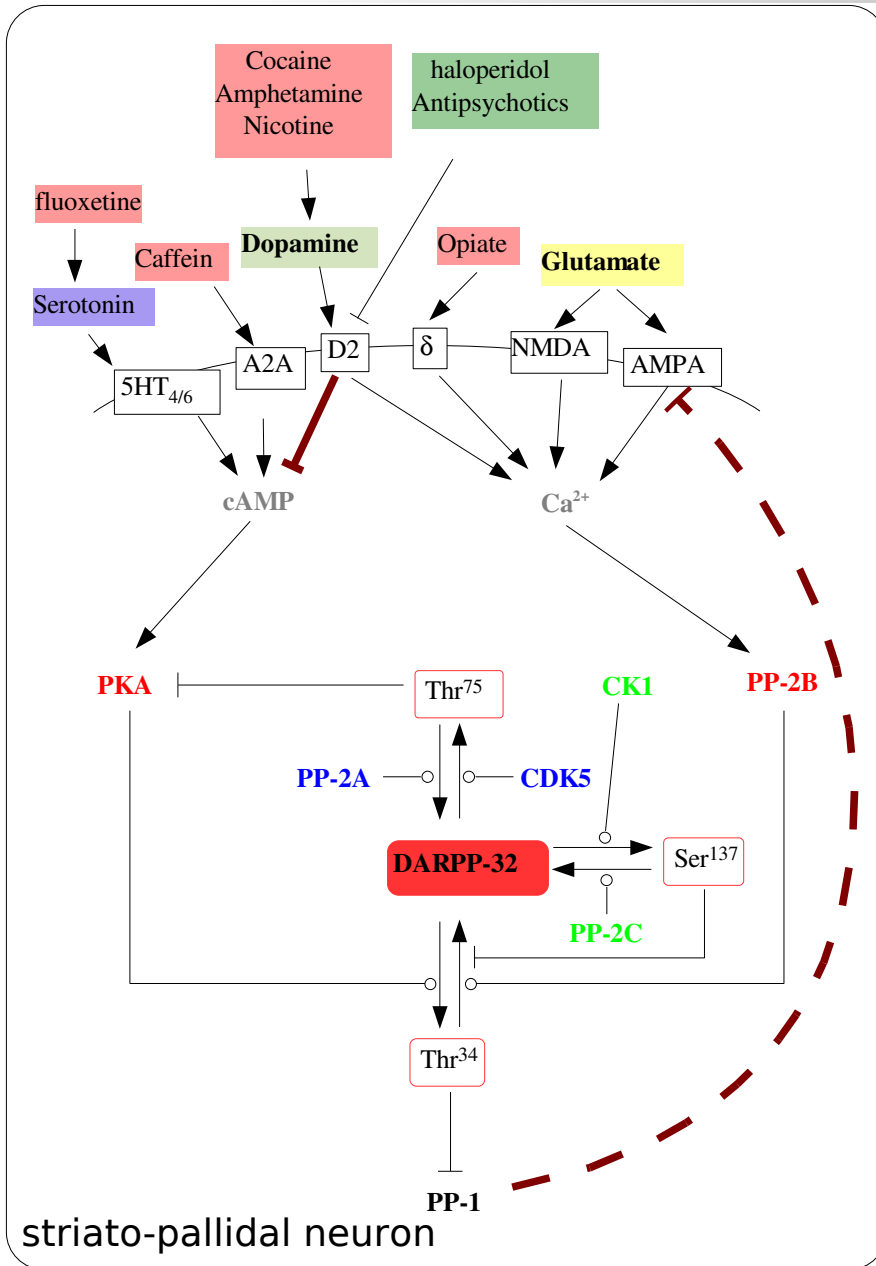
Biological model of DARPP-32 regulation



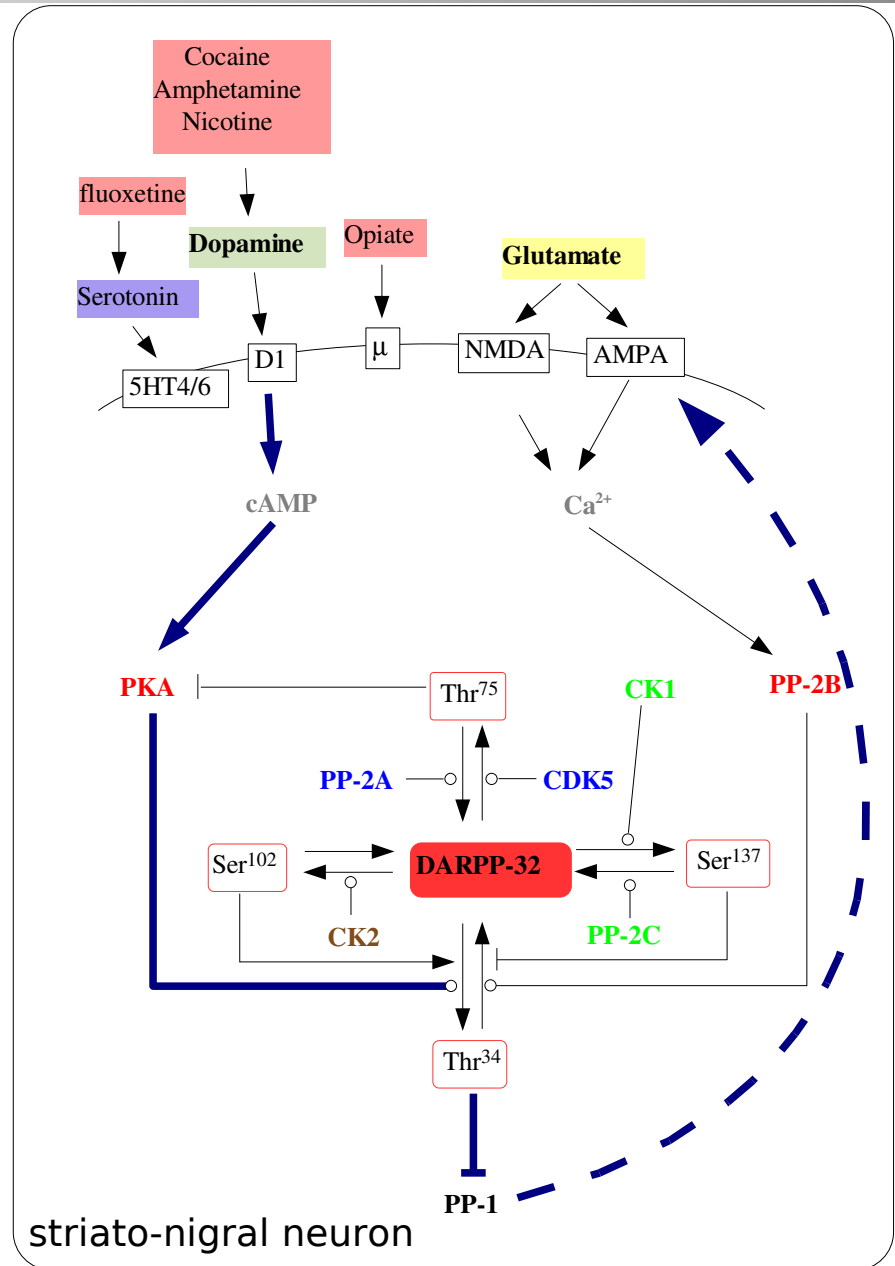
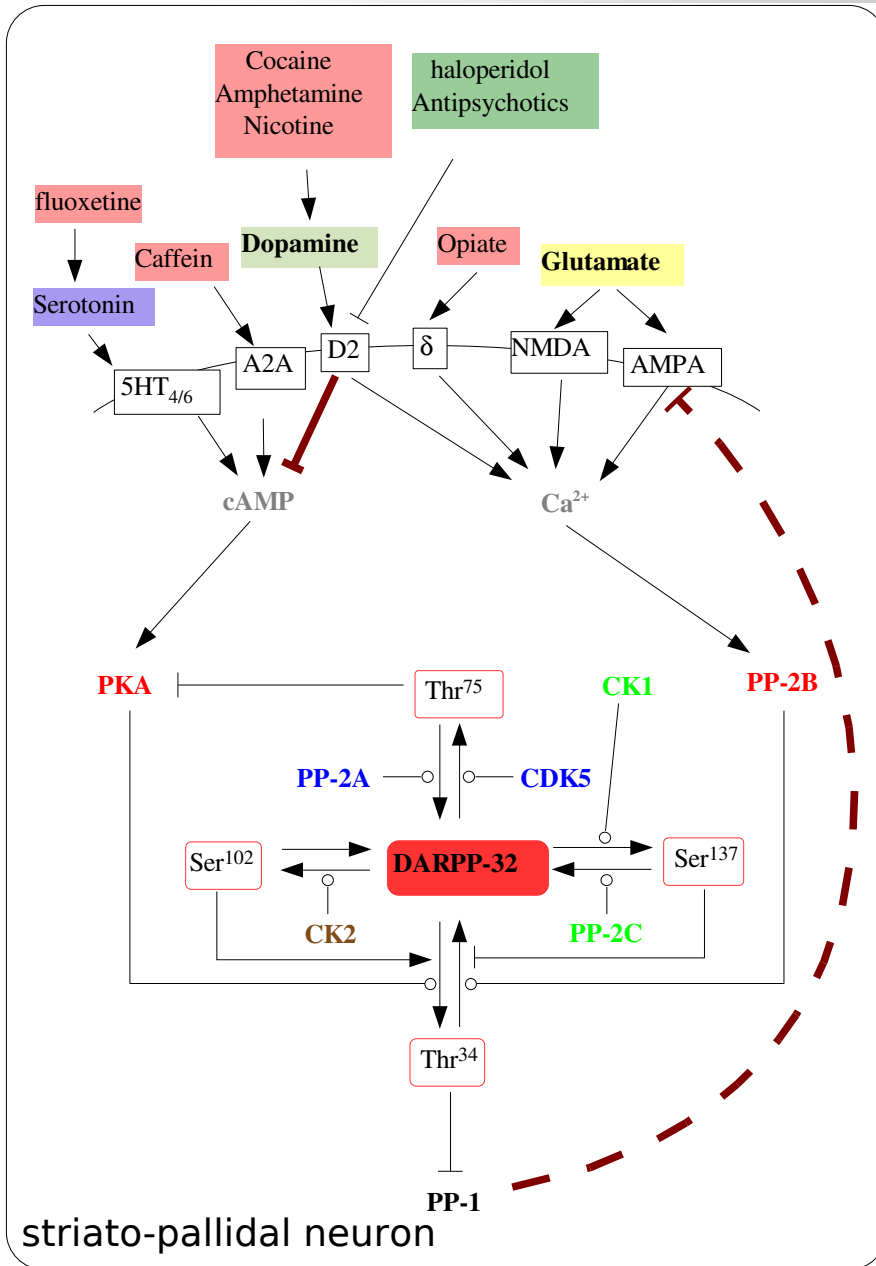
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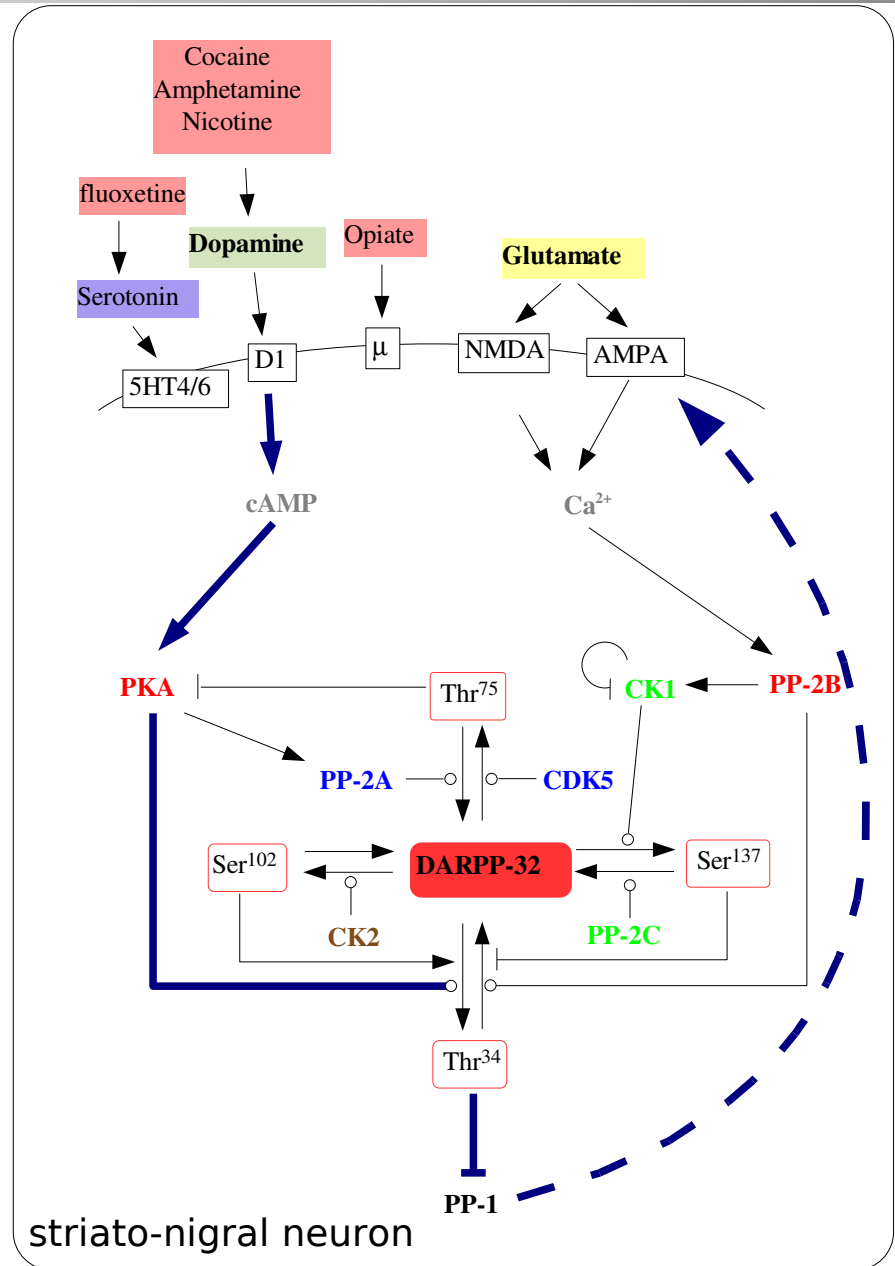
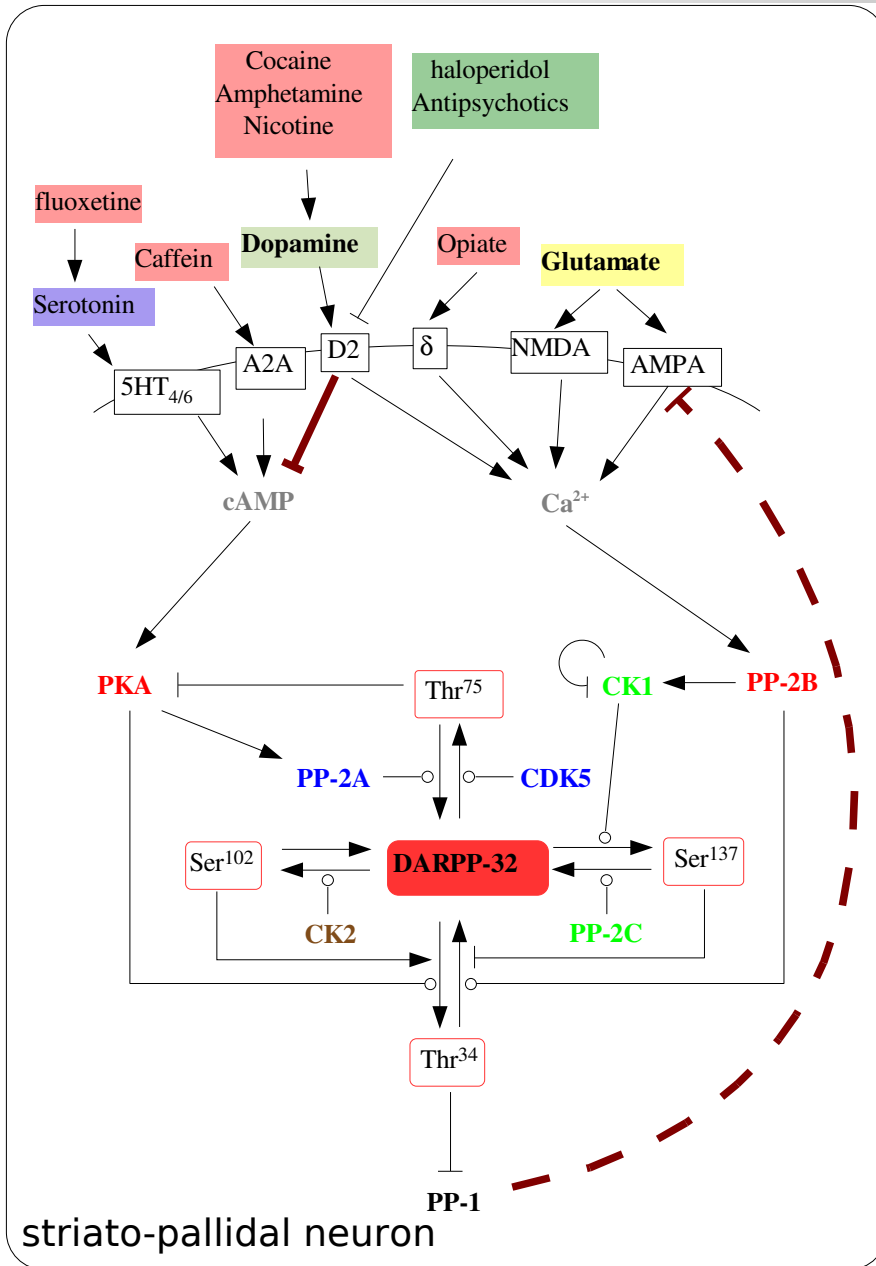
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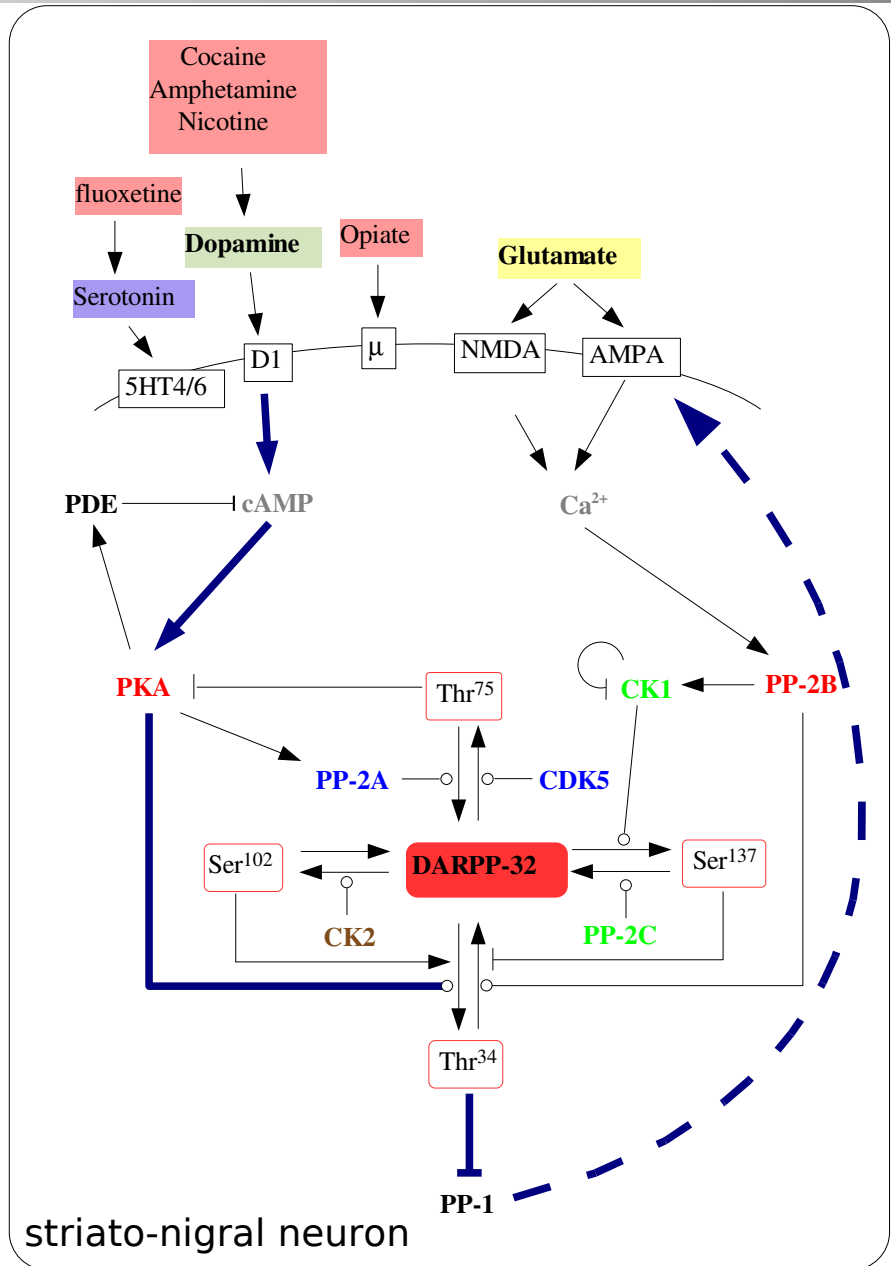
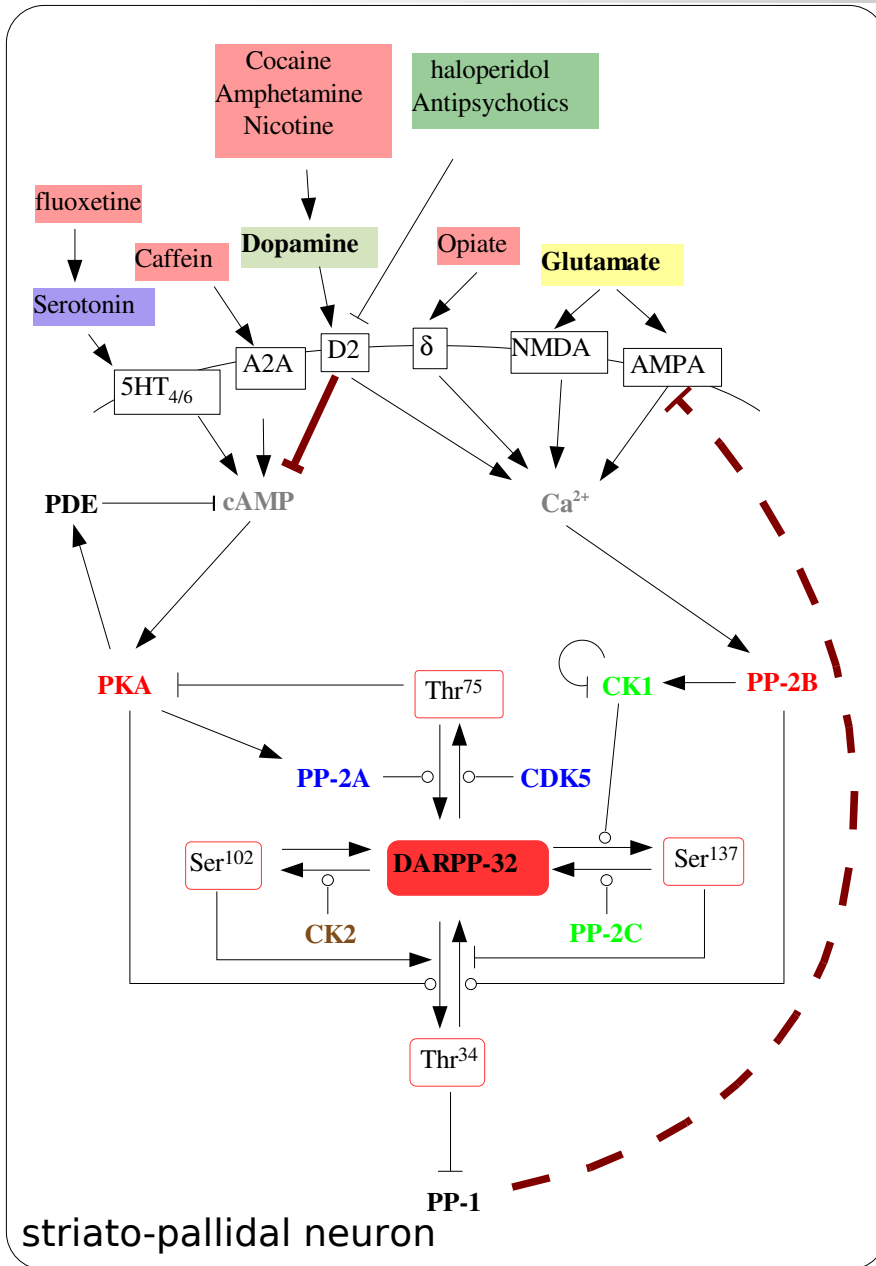
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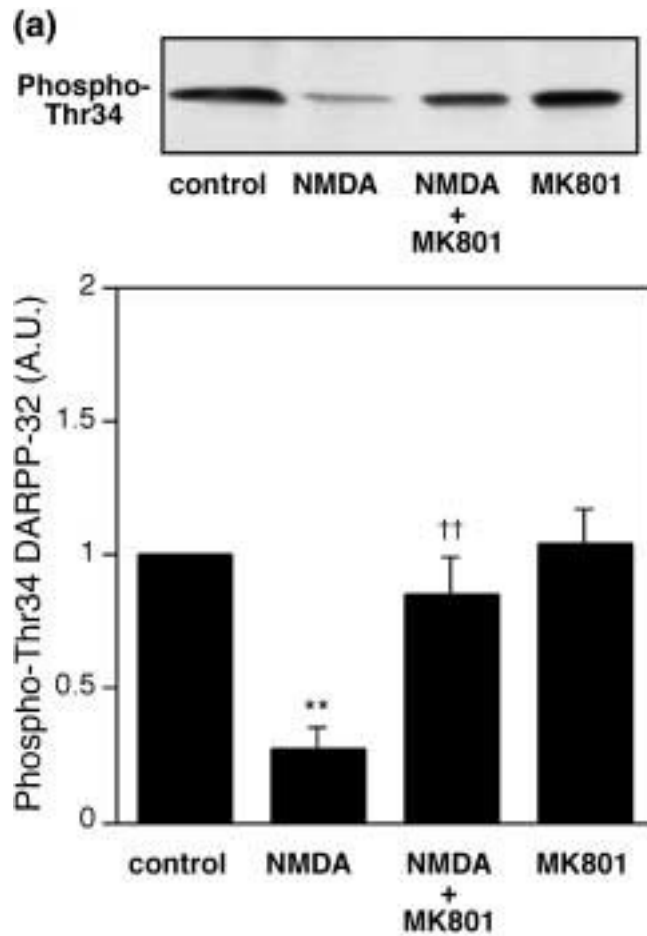


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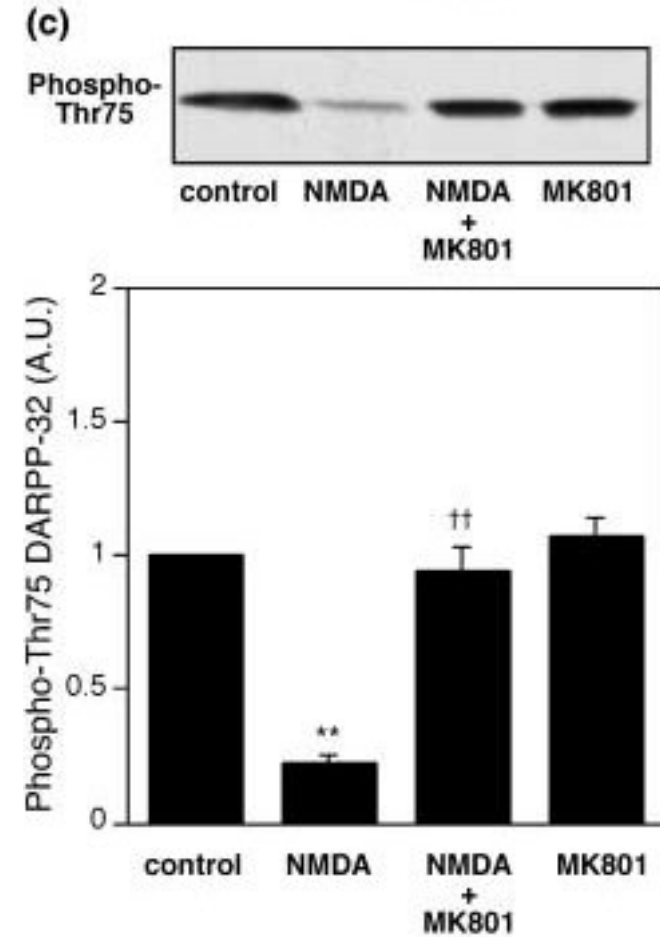
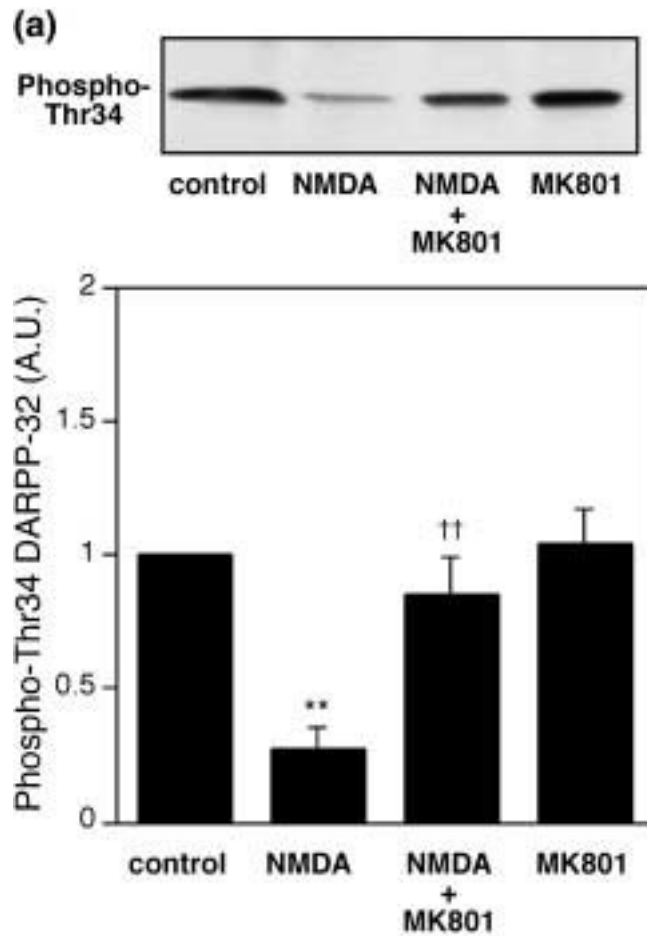
Biological model of DARPP-32 regulation





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

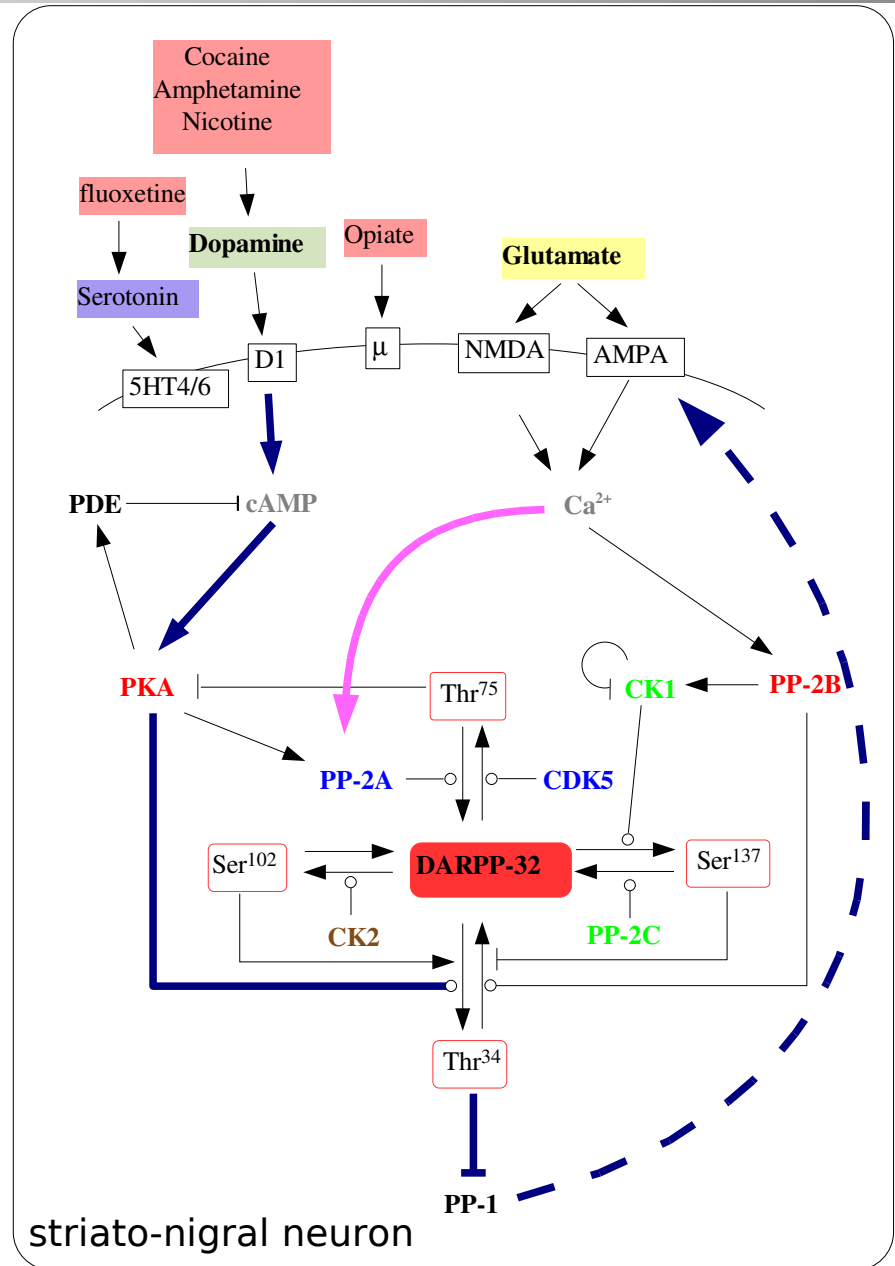
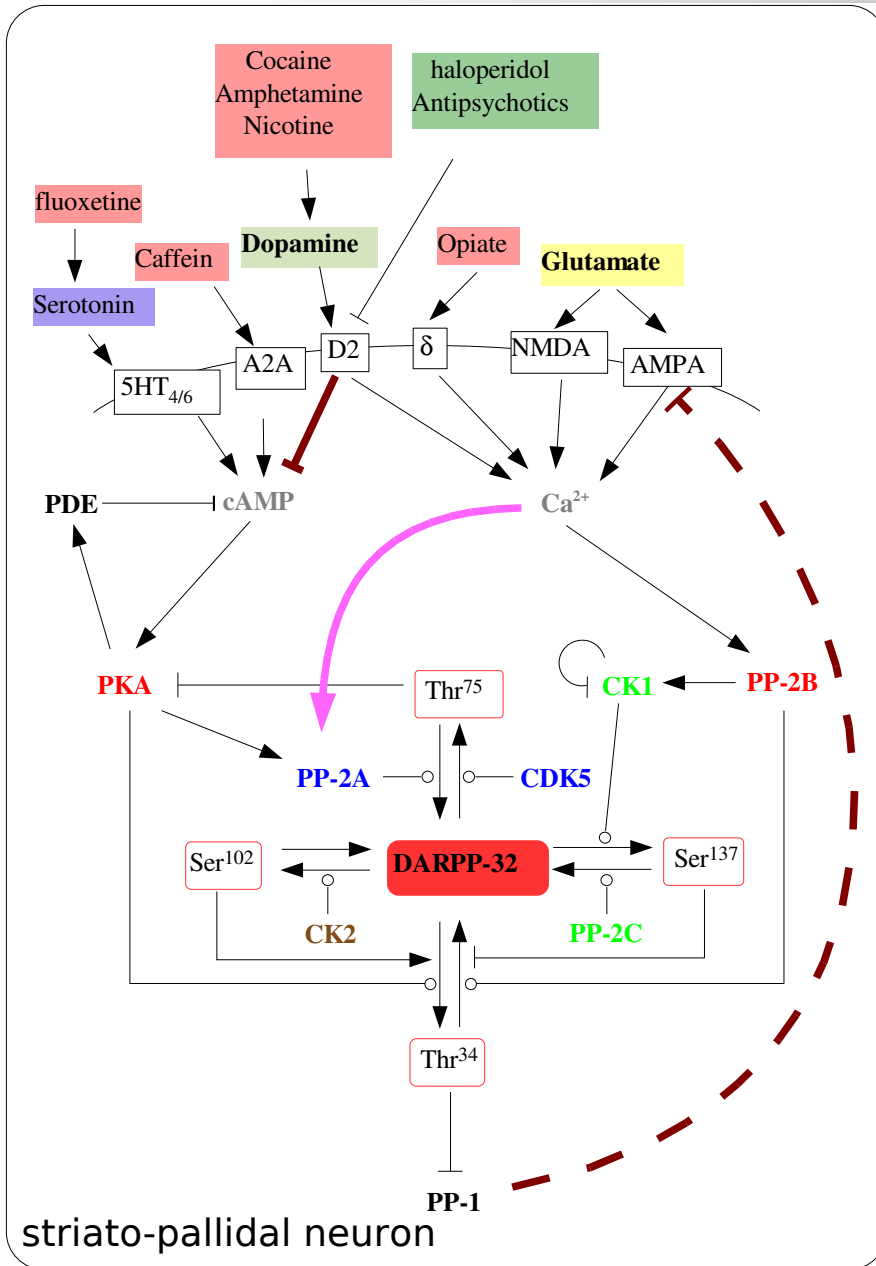


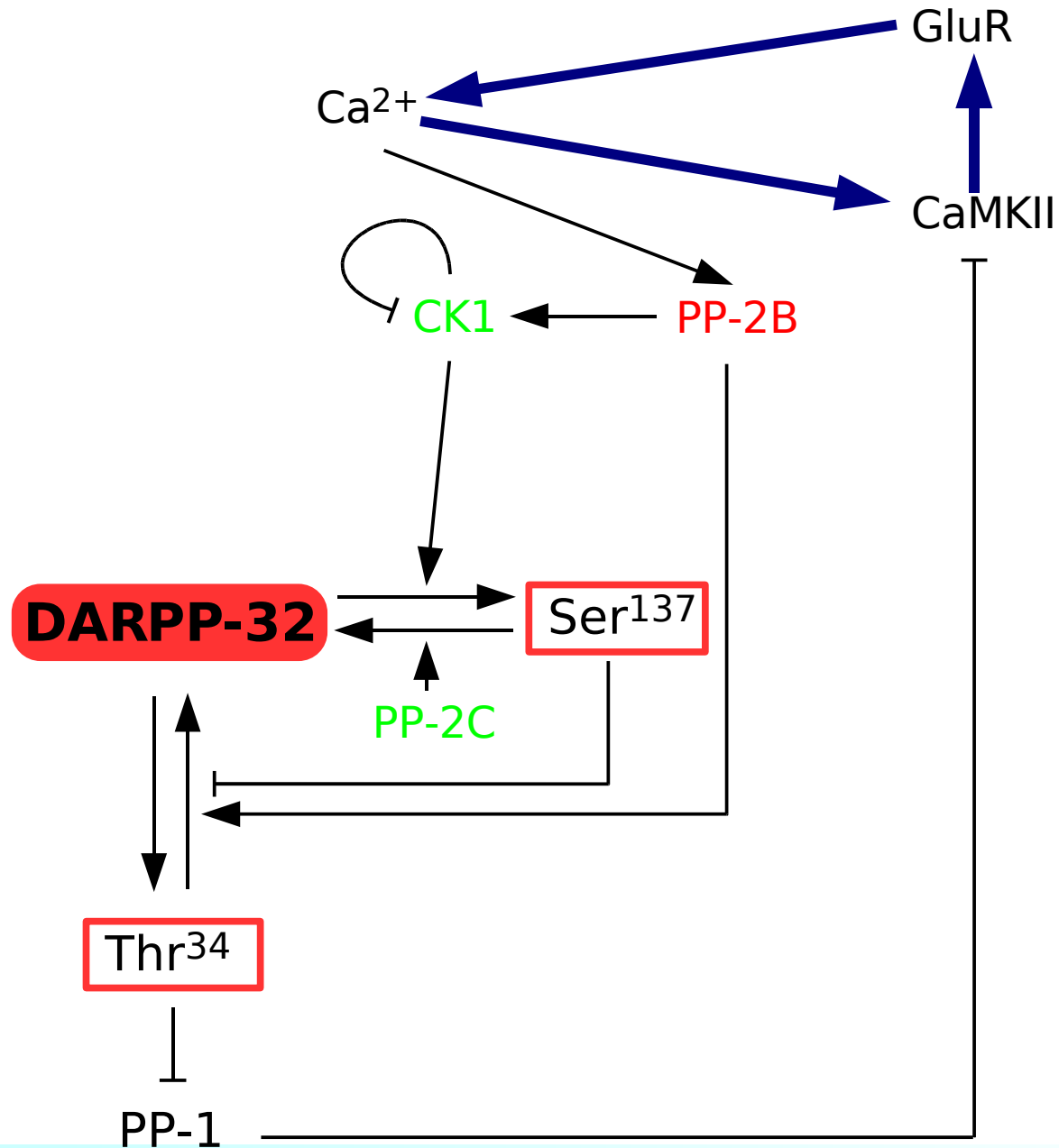


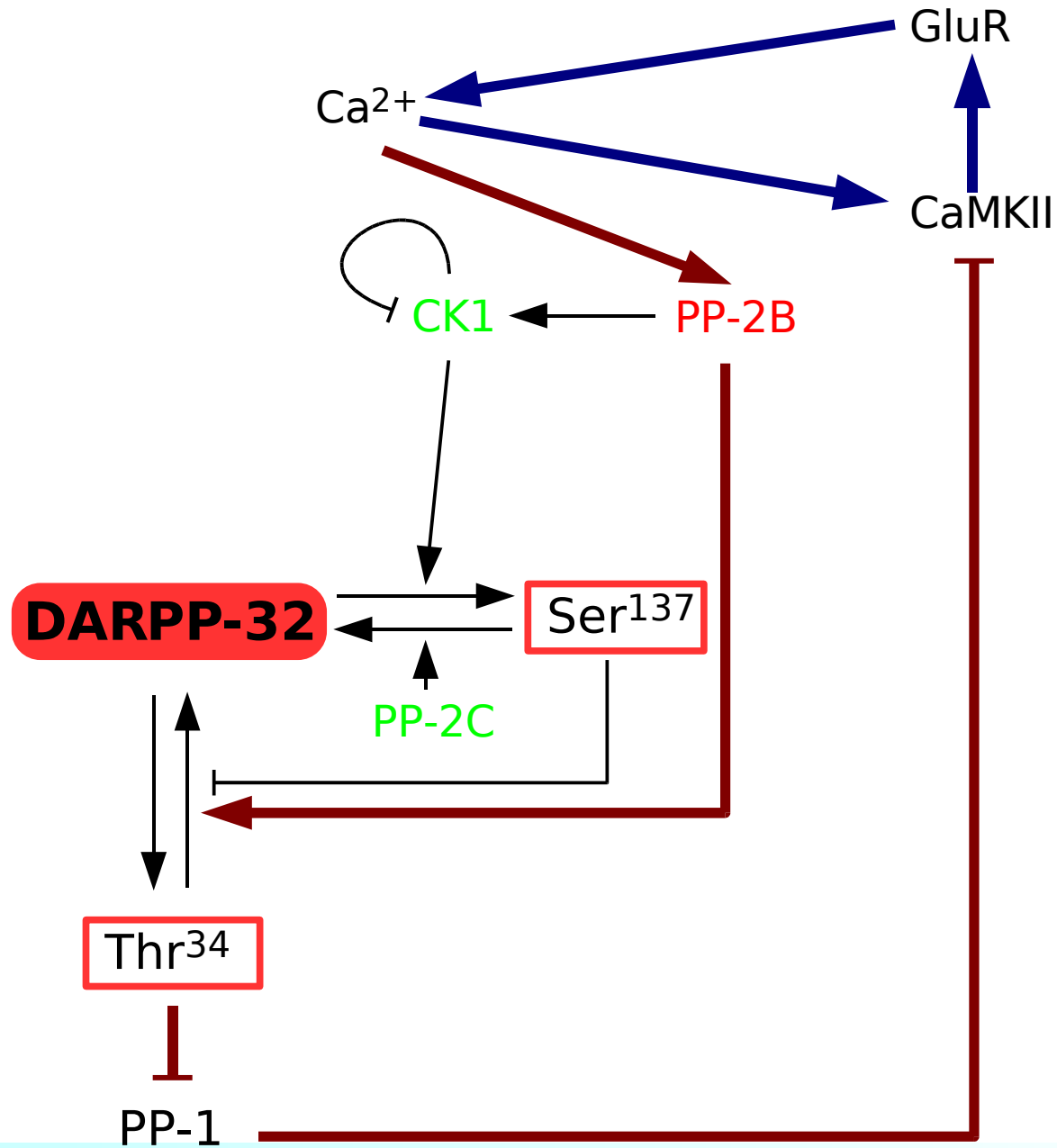
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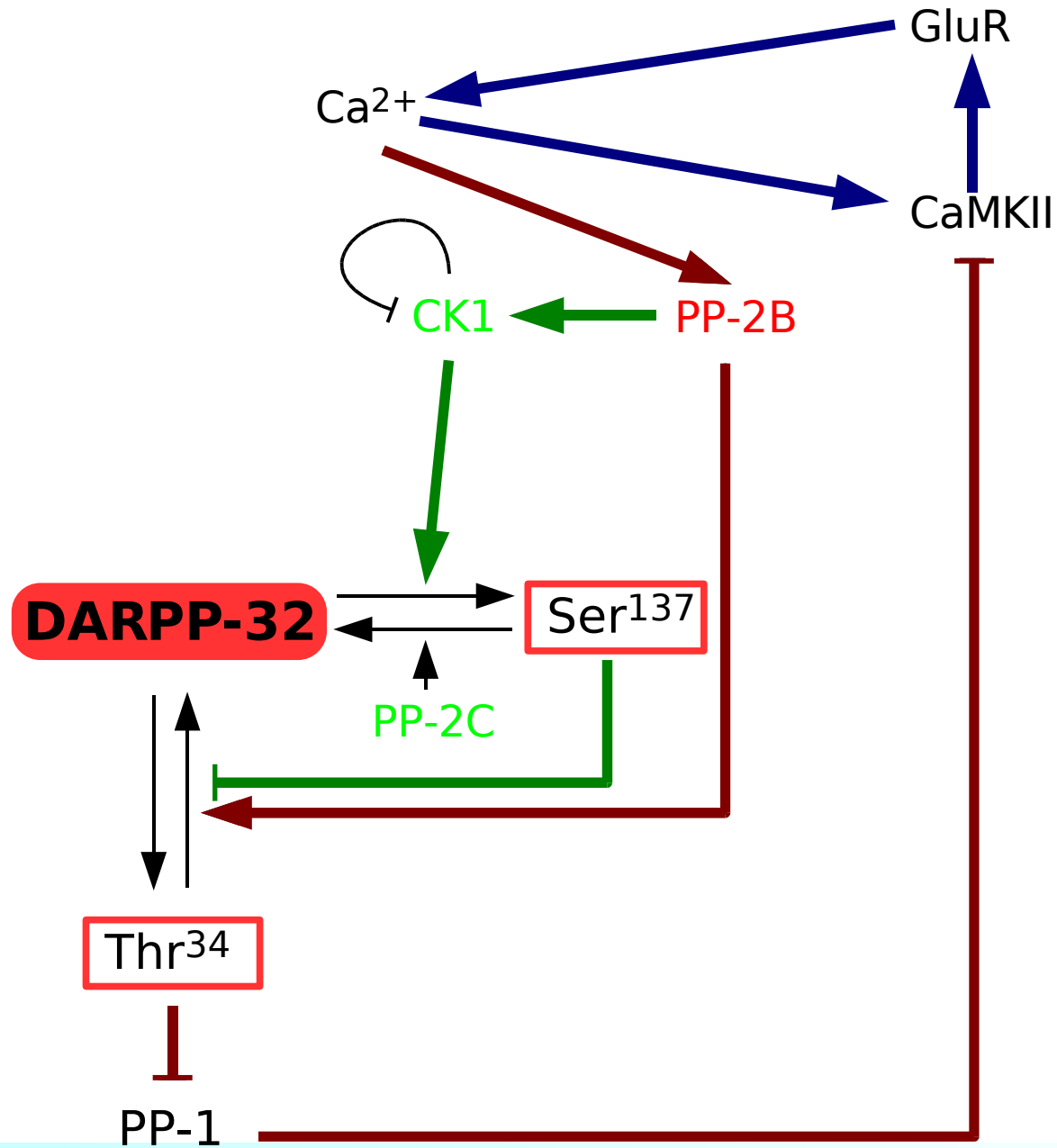


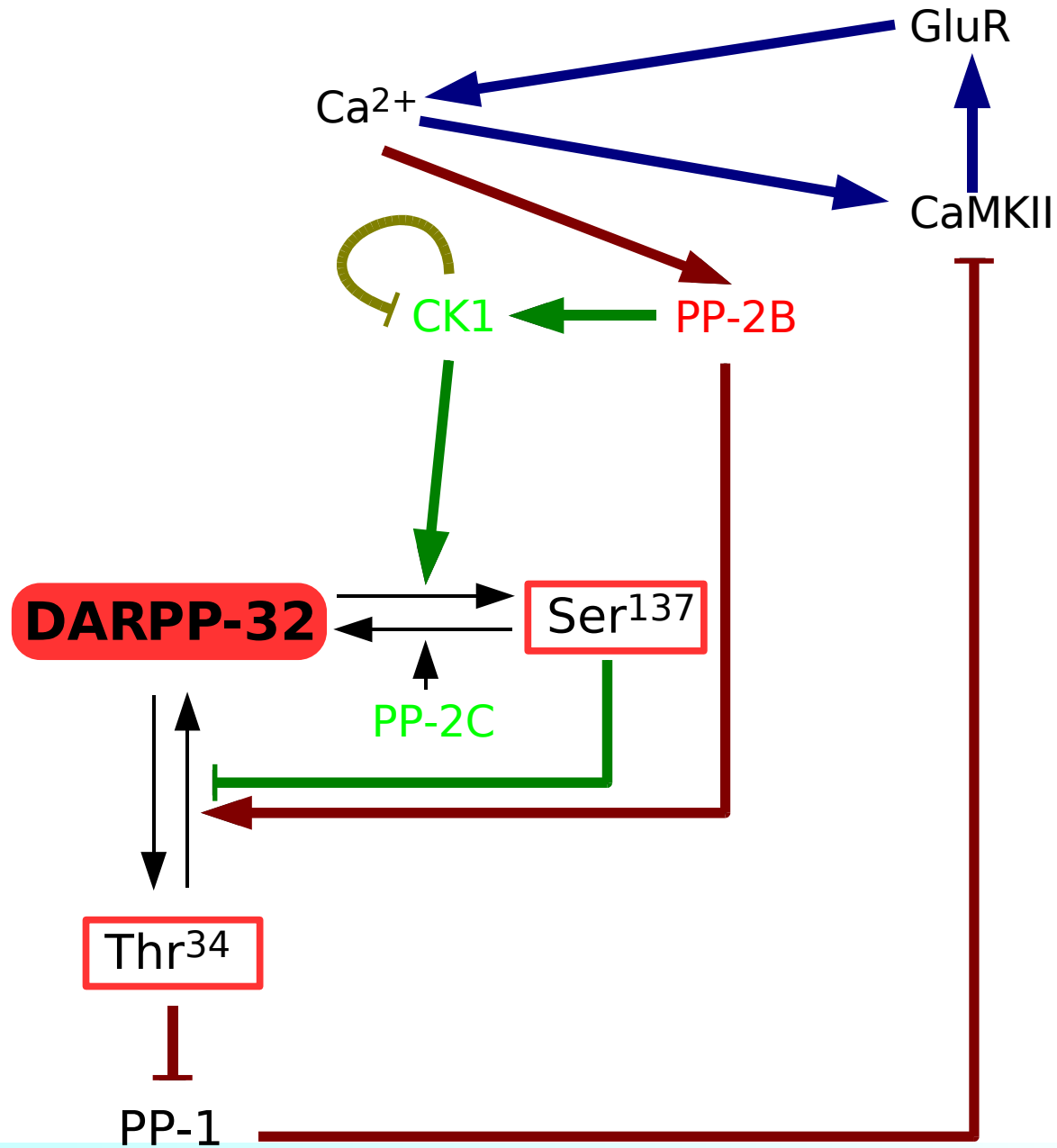
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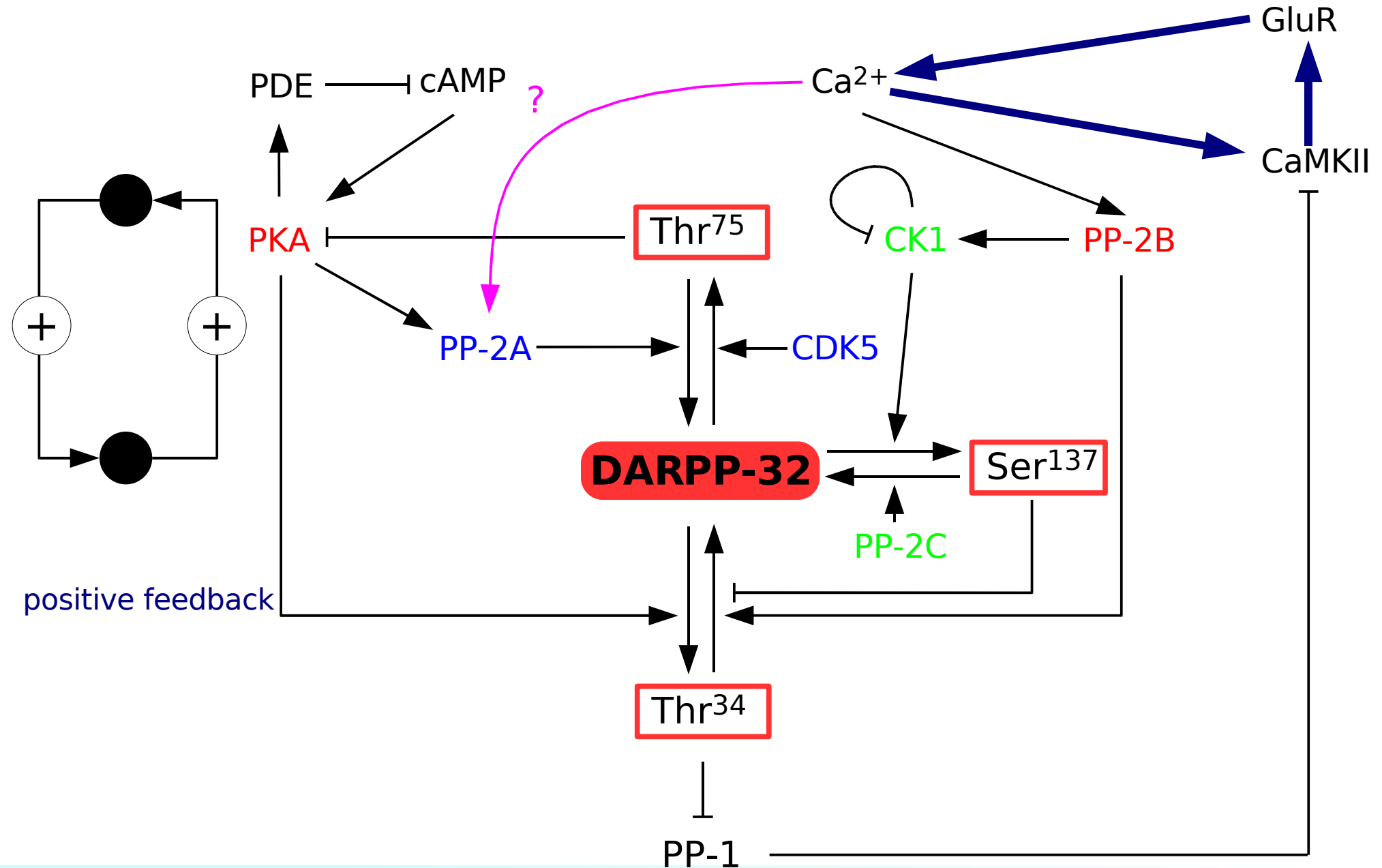


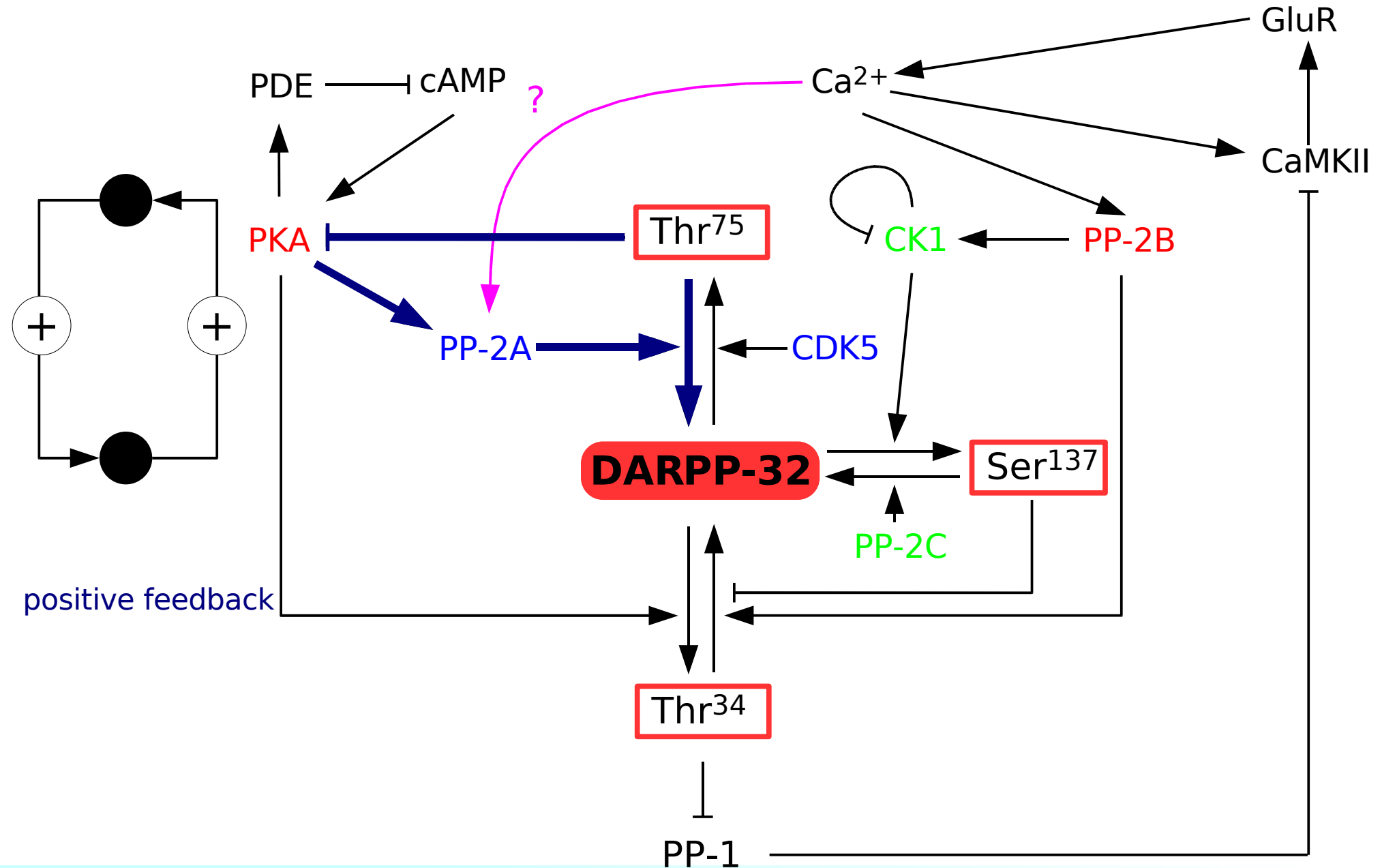




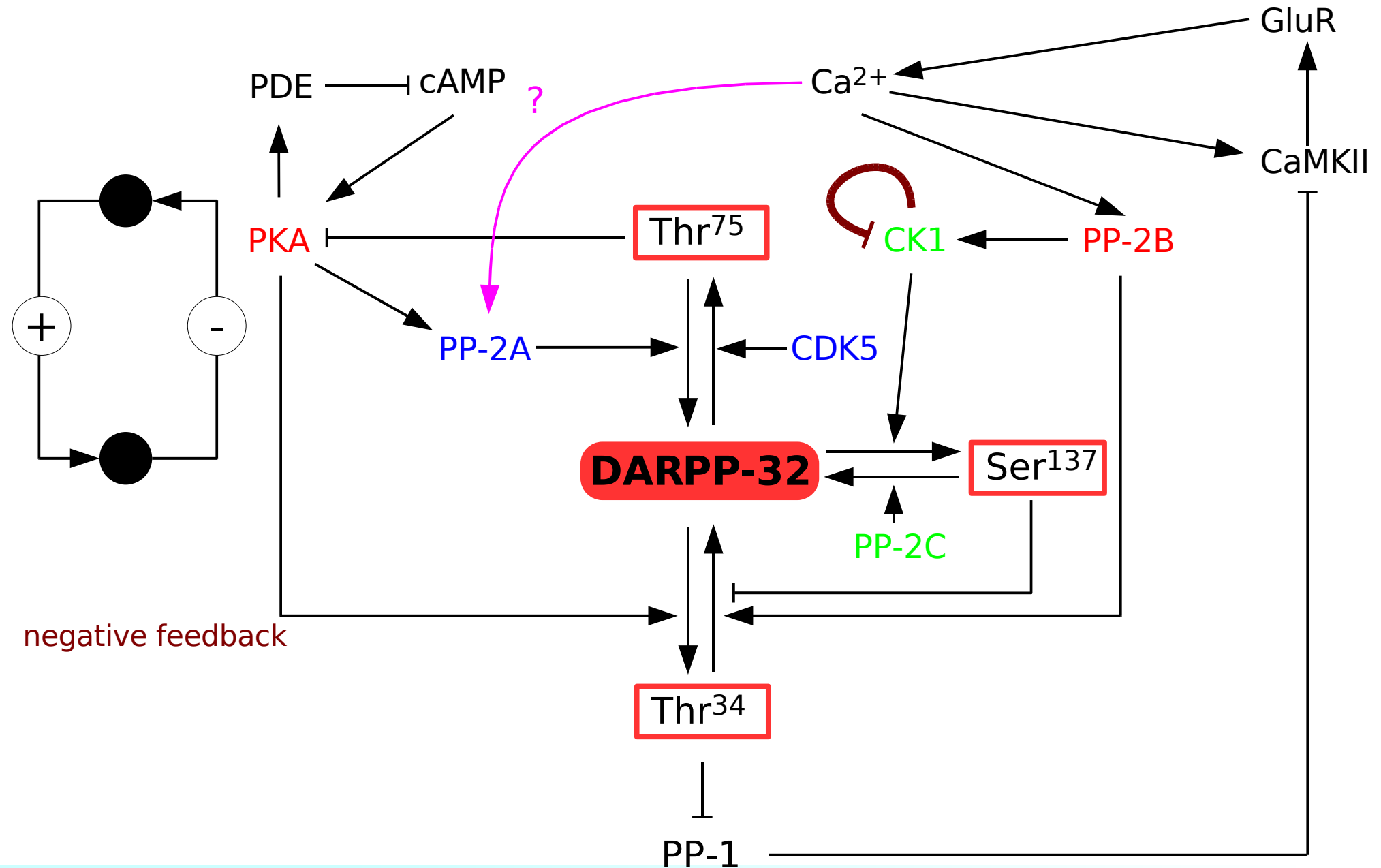


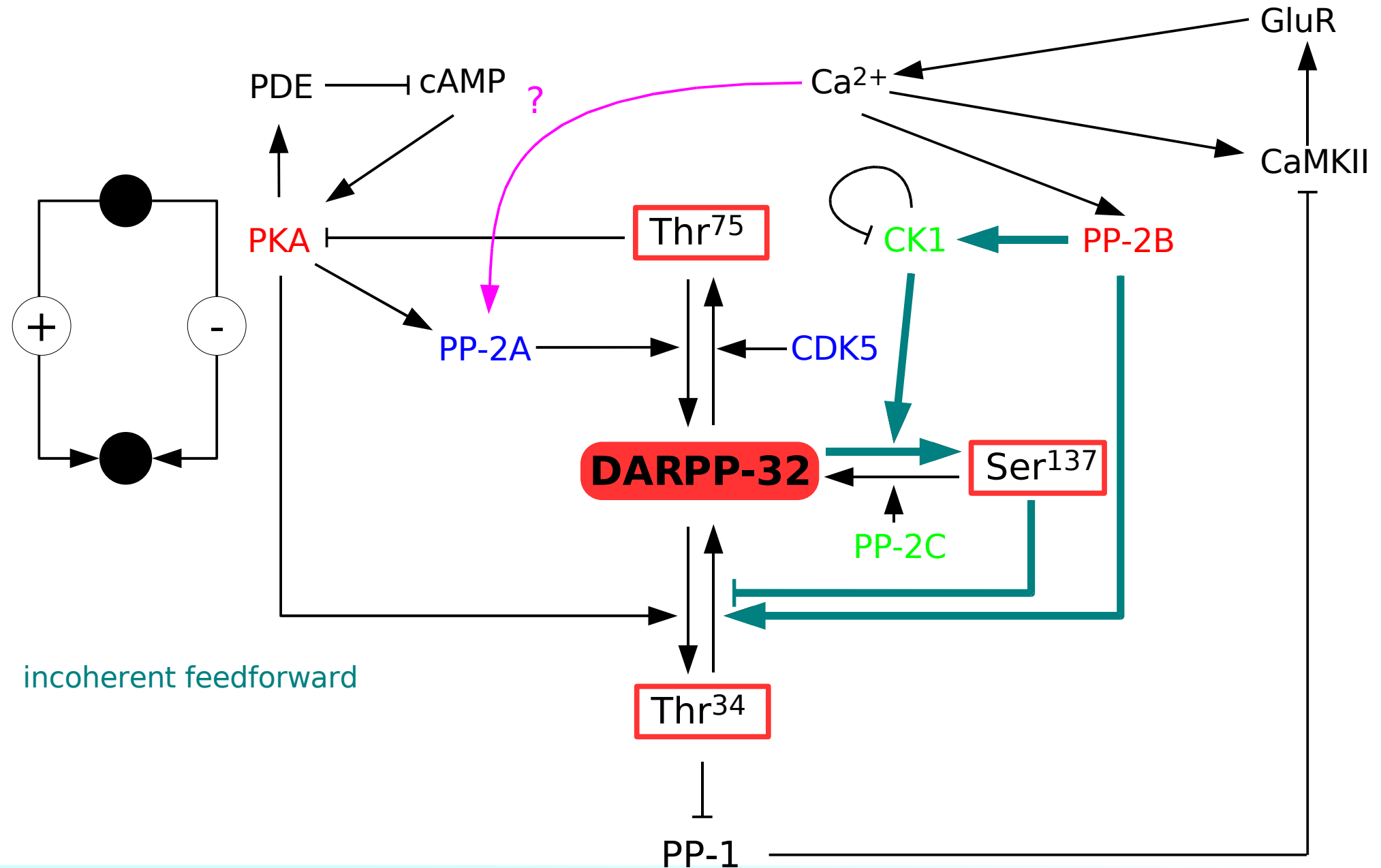


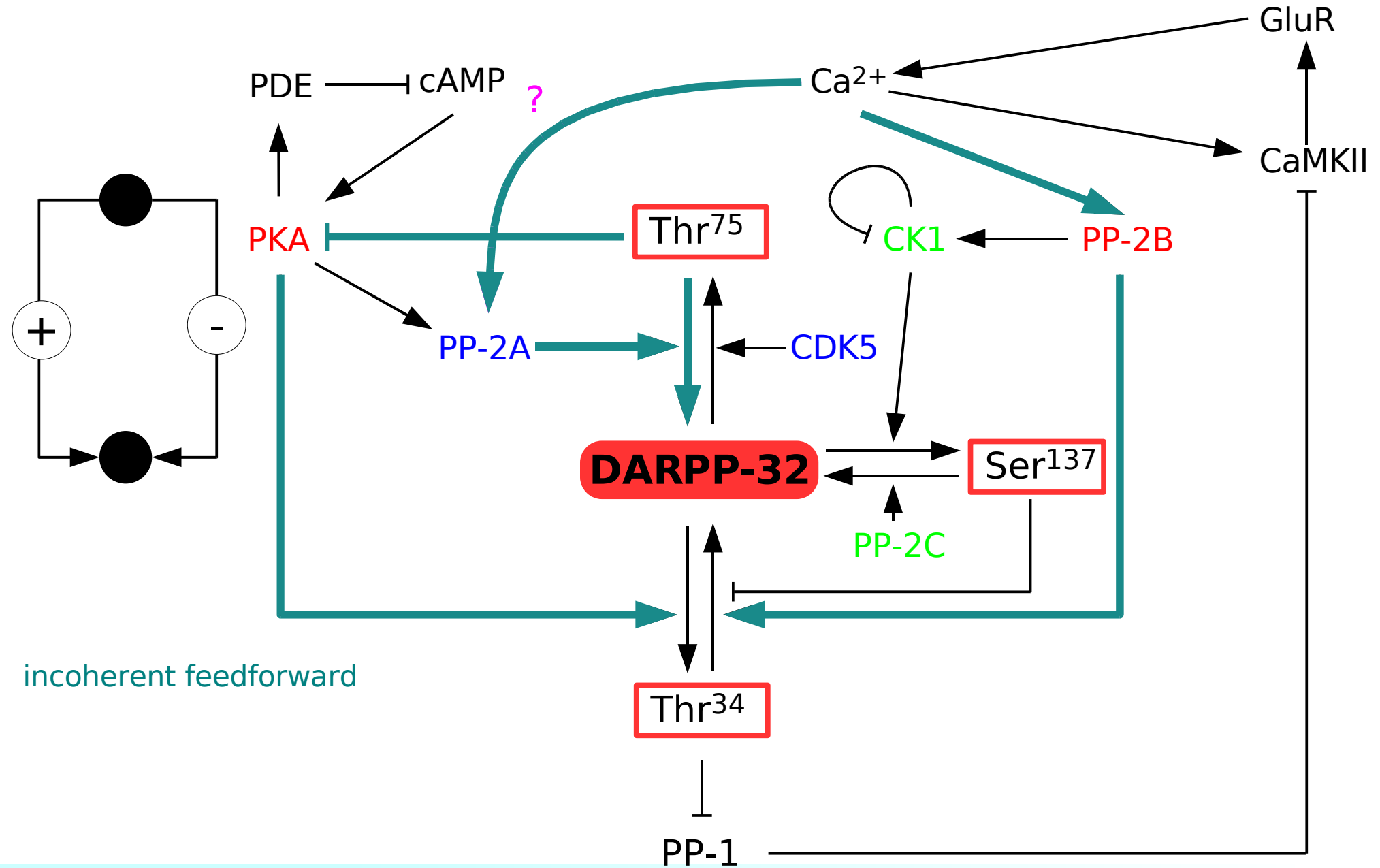


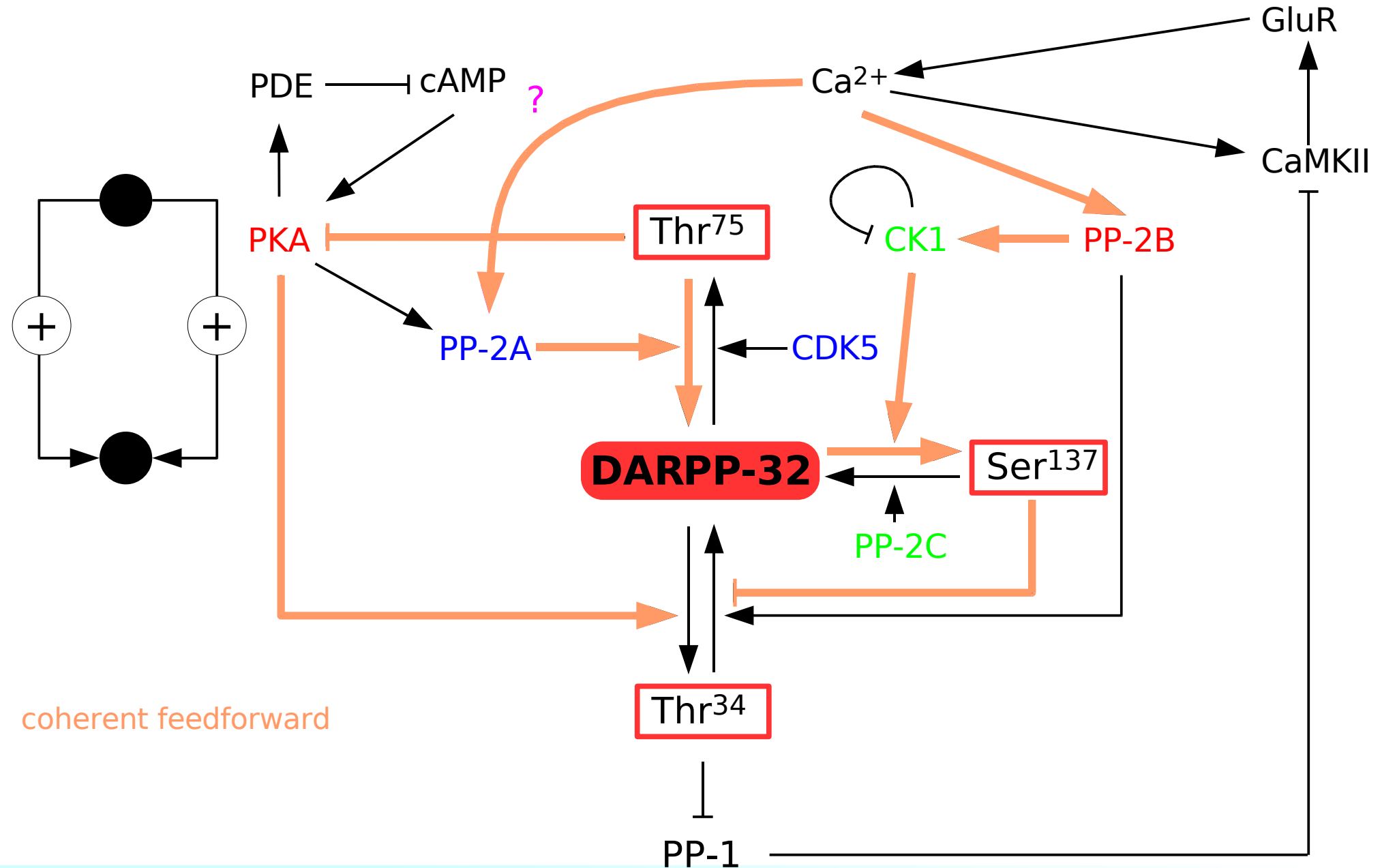










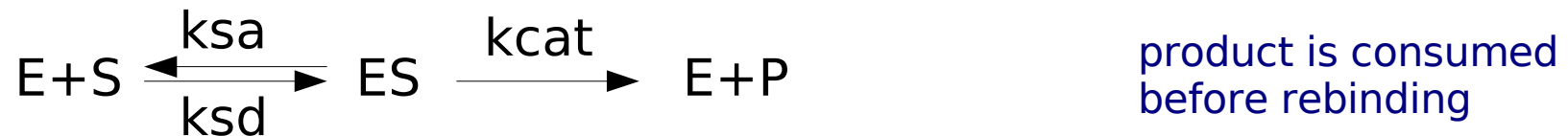
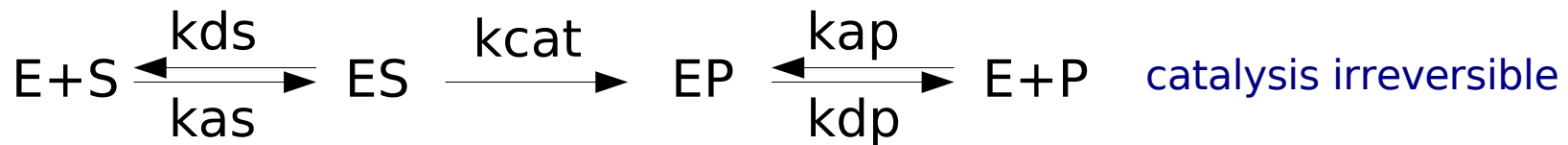
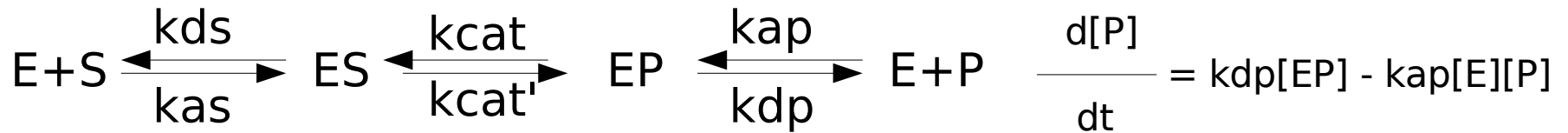


- $D + CDK5 \rightleftharpoons D_CDK5 \rightarrow D75 + CDK5$
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- $D75 + PP2AP \rightleftharpoons D75_PP2AP \rightarrow D + PP2AP$
- $D75 + PP2APCa \rightleftharpoons D75_PP2APCa \rightarrow D + PP2APCa$
- $D137 + CDK5 \rightleftharpoons D137_CDK5 \rightarrow D75-137 + CDK5$
- $D75-137 + PP2A \rightleftharpoons D75-137_PP2A \rightarrow D137 + PP2A$
- $D75-137 + PP2ACa \rightleftharpoons D75-137_PP2ACa \rightarrow D137 + PP2ACa$
- $D75-137 + PP2AP \rightleftharpoons D75-137_PP2AP \rightarrow D137 + PP2AP$
- $D75-137 + PP2APCa \rightleftharpoons D75-137_PP2APCa \rightarrow D137 + PP2APCa$
- $D34 + CDK5 \rightleftharpoons D34_CDK5 \rightarrow D34-75 + CDK5$
- $D34-75 + PP2A \rightleftharpoons D34-75_PP2A \rightarrow D34 + PP2A$
- $D34-75 + PP2ACa \rightleftharpoons D34-75_PP2ACa \rightarrow D34 + PP2ACa$
- $D34-75 + PP2AP \rightleftharpoons D34-75_PP2AP \rightarrow D34 + PP2AP$
- $D34-75 + PP2APCa \rightleftharpoons D34-75_PP2APCa \rightarrow D34 + PP2APCa$
- $D34-137 + CDK5 \rightleftharpoons D34-137_CDK5 \rightarrow D34-75-137 + CDK5$
- $D34-75-137 + PP2A \rightleftharpoons D34-75-137_PP2A \rightarrow D34-137 + PP2A$
- $D34-75-137 + PP2ACa \rightleftharpoons D34-75-137_PP2ACa \rightarrow D34-137 + PP2ACa$
- $D34-75-137 + PP2AP \rightleftharpoons D34-75-137_PP2AP \rightarrow D34-137 + PP2AP$
- $D34-75-137 + PP2APCa \rightleftharpoons D34-75-137_PP2APCa \rightarrow D34-137 + PP2APCa$
- $D + CK1 \rightleftharpoons D_CK1 \rightarrow D137 + CK1$
- $D137 + PP2C \rightleftharpoons D137_PP2C \rightarrow D + PP2C$
- $D75 + CK1 \rightleftharpoons D75_CK1 \rightarrow D75-137 + CK1$
- $D75-137 + PP2C \rightleftharpoons D75-137_PP2C \rightarrow D75 + PP2C$
- $D34 + CK1 \rightleftharpoons D34_CK1 \rightarrow D34-137 + CK1$
- $D34-75 + PP2C \rightleftharpoons D34-75_PP2C \rightarrow D75 + PP2C$
- $D34-75 + CK1 \rightleftharpoons D34-75_CK1 \rightarrow D34-75-137 + CK1$
- $D34-75-137 + PP2C \rightleftharpoons D34-75-137_PP2C \rightarrow D34-75 + PP2C$
- $CK1 + CK1 \rightleftharpoons CK1_CK1 \rightarrow CK1P + CK1$
- $CK1P + PP2B \rightleftharpoons CK1P_PP2B \rightarrow CK1 + PP2B$

79 species, 151 reactions

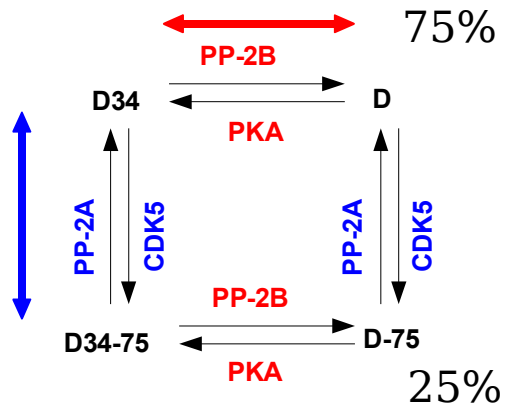
- $D + PKA \rightleftharpoons D_PKA \rightarrow D34 + PKA$
- $D34 + PP2B \rightleftharpoons D34_PP2B \rightarrow D + PP2B$
- $D75 + PKA \rightleftharpoons D75_PKA \rightarrow D34-75 + PKA$
- $D34-75 + PP2B \rightleftharpoons D34-75_PP2B \rightarrow D75 + PP2B$
- $D137 + PKA \rightleftharpoons D137_PKA \rightarrow D34-137 + PKA$
- $D34-137 + PP2B \rightleftharpoons D34-135_PP2B \rightarrow D137 + PP2B$
- $D75-137 + PKA \rightleftharpoons D75-137_PKA \rightarrow D34-75-137 + PKA$
- $D34-75-137 + PP2B \rightleftharpoons D34-75-135_PP2B \rightarrow D75-137 + PP2B$
- $PP2A + PKA \rightleftharpoons PP2A_PKA \rightarrow PP2AP + PKA$
- $PP2ACa + PKA \rightleftharpoons PP2ACa_PKA \rightarrow PP2APCa + PKA$
- $\emptyset \rightarrow Ca^{2+}$
- $Ca^{2+} \rightarrow \emptyset$
- $PP2Bi + 2Ca \rightleftharpoons PP2Bi_Ca2$
- $PP2Bi_Ca + 2Ca \rightleftharpoons PP2B$
- $PP2A + Ca \rightleftharpoons PP2ACa$
- $PP2AP + Ca \rightleftharpoons PP2APCa$
- $R2_PKA2 + cAMP \rightleftharpoons cAMP_R2_PKA2$
- $cAMP_R2_PKA2 + cAMP \rightleftharpoons cAMP2_R2_PKA2$
- $cAMP2_R2_PKA2 + cAMP \rightleftharpoons cAMP3_R2_PKA2$
- $cAMP3_R2_PKA2 + cAMP \rightleftharpoons cAMP4_R2_PKA2$
- $cAMP4_R2_PKA2 \rightleftharpoons cAMP4_R2_PKA + PKA$
- $cAMP4_R2_PKA \rightleftharpoons cAMP4_R2 + PKA$
- $PKA + PDE \rightleftharpoons PKA_PDE \rightarrow PKA + PDEP$
- $cAMP + PDE \rightleftharpoons cAMP_PDE \rightarrow AMP + PDE$
- $cAMP + PDEP \rightleftharpoons cAMP_PDEP \rightarrow AMP + PDEP$

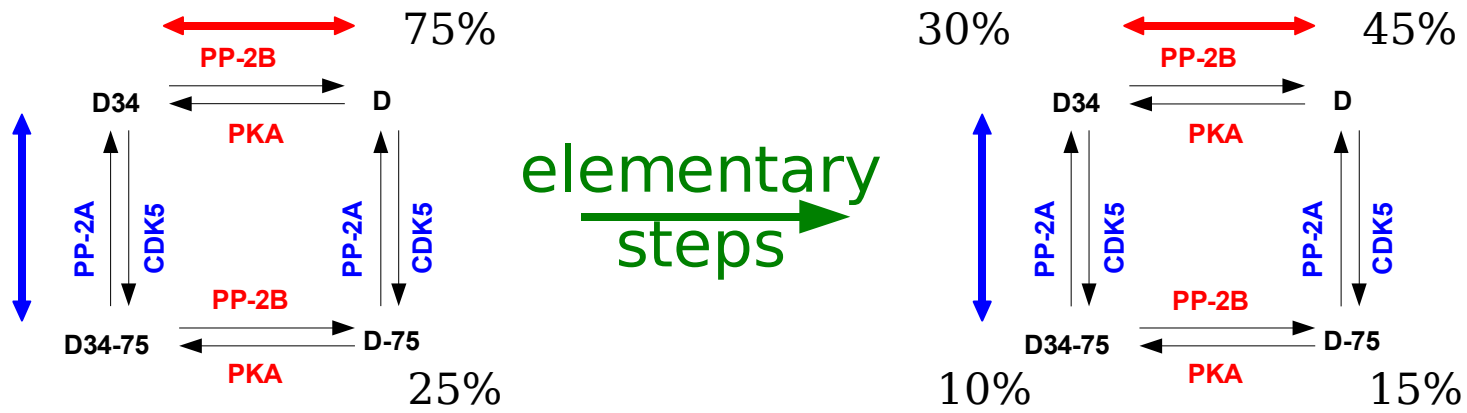


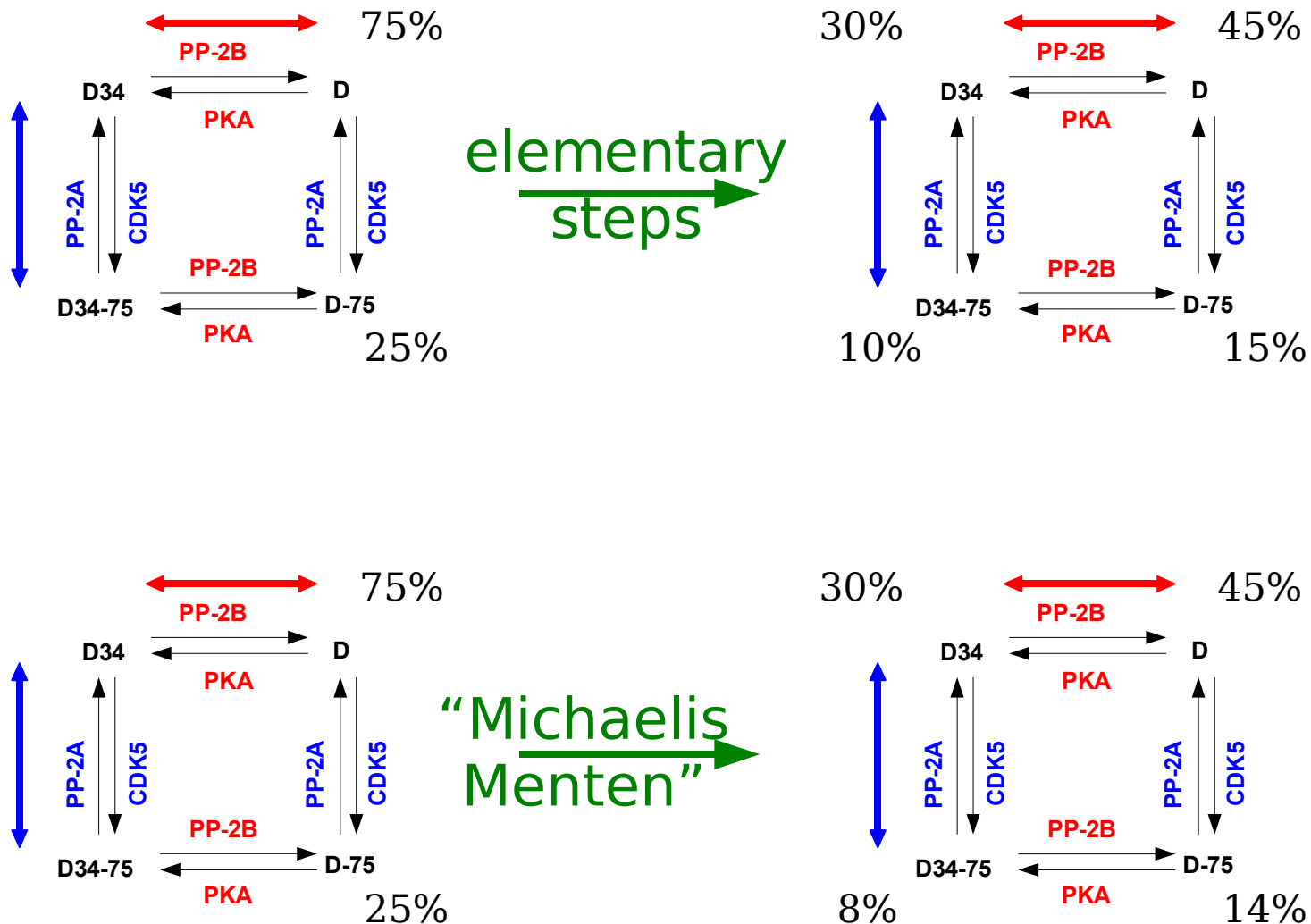


$$\frac{d[P]}{dt} = \frac{[E] k_{cat}}{1 + \frac{K_m}{[S]}}$$



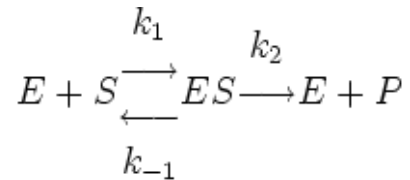






1) unbalance; 2) $\Sigma \neq 100\%!!!$





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

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

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

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

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

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

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

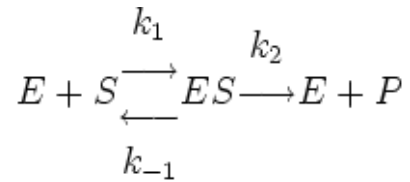
$$K_m = \frac{k_{-1} + k_2}{k_1}$$

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

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

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





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

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

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

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

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

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

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

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

steady-state!!!

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

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

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



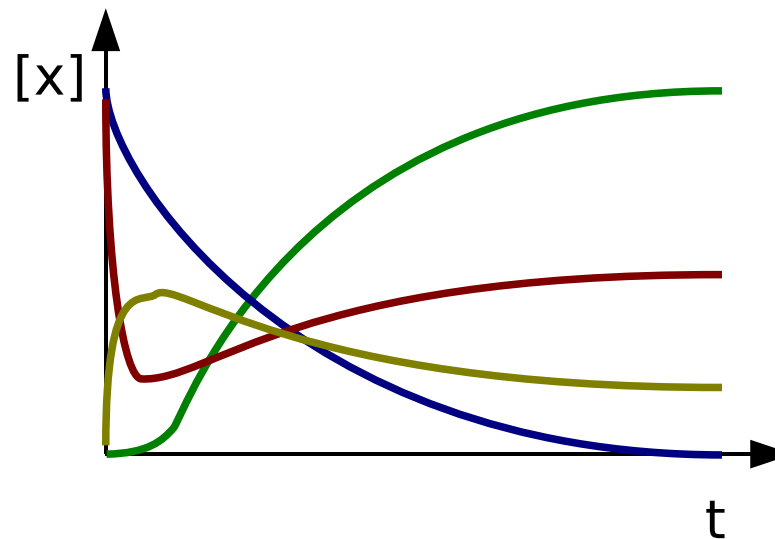


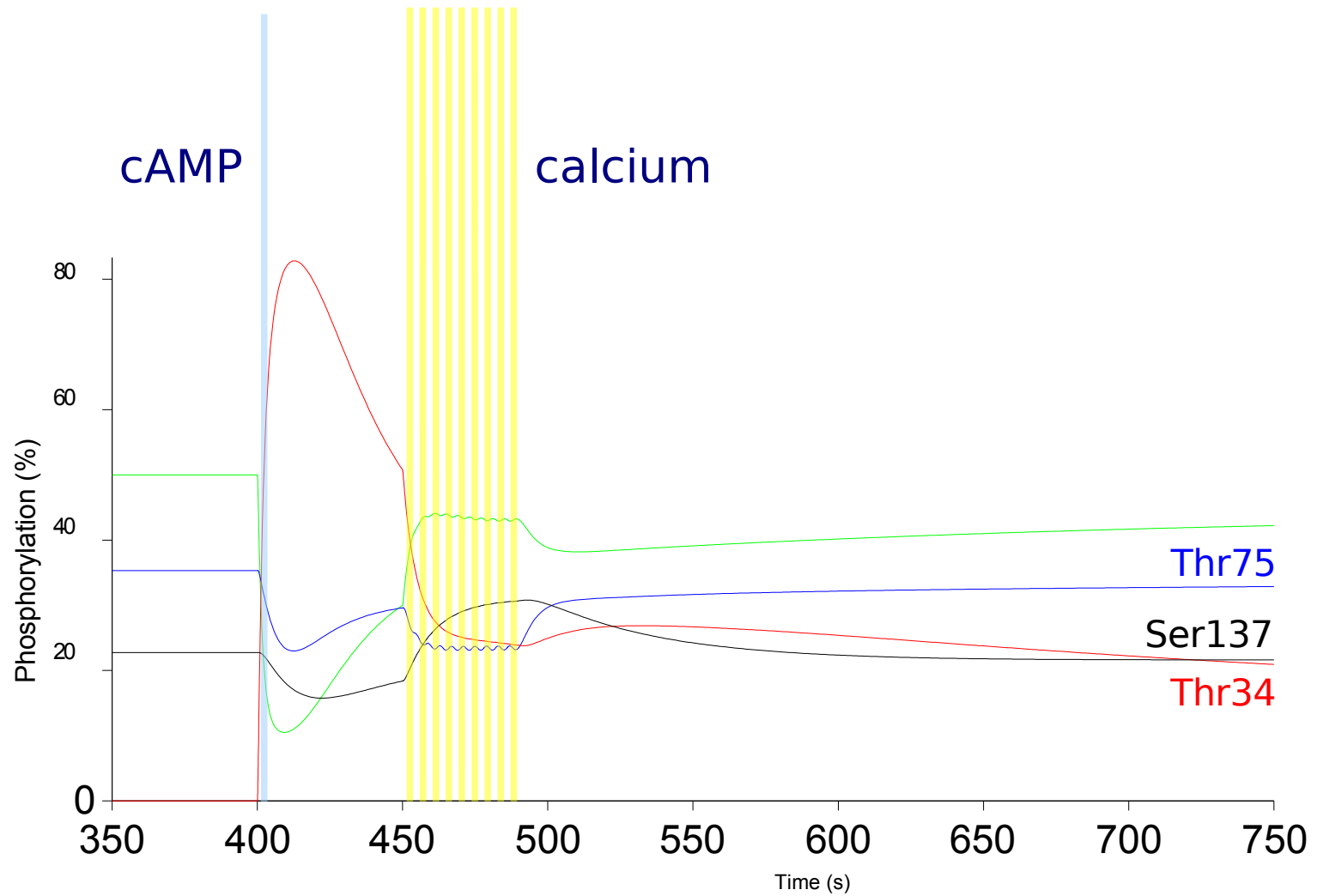
$$\frac{d[\text{D}]}{dt} = -k_1[\text{CDK5}][\text{D}] + k_2[\text{D_CDK5}]$$

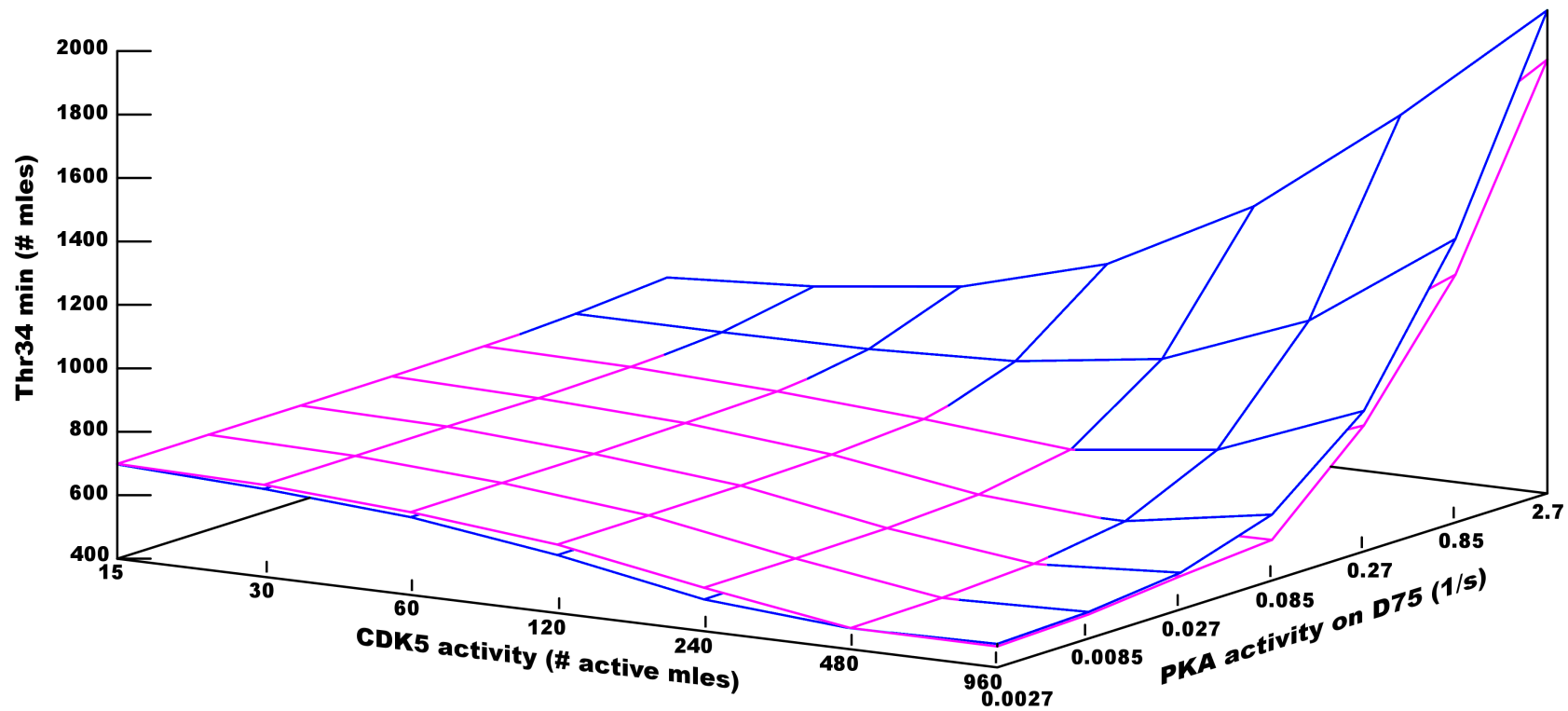
$$\frac{d[\text{D-75P}]}{dt} = +k_3[\text{D_CDK5}]$$

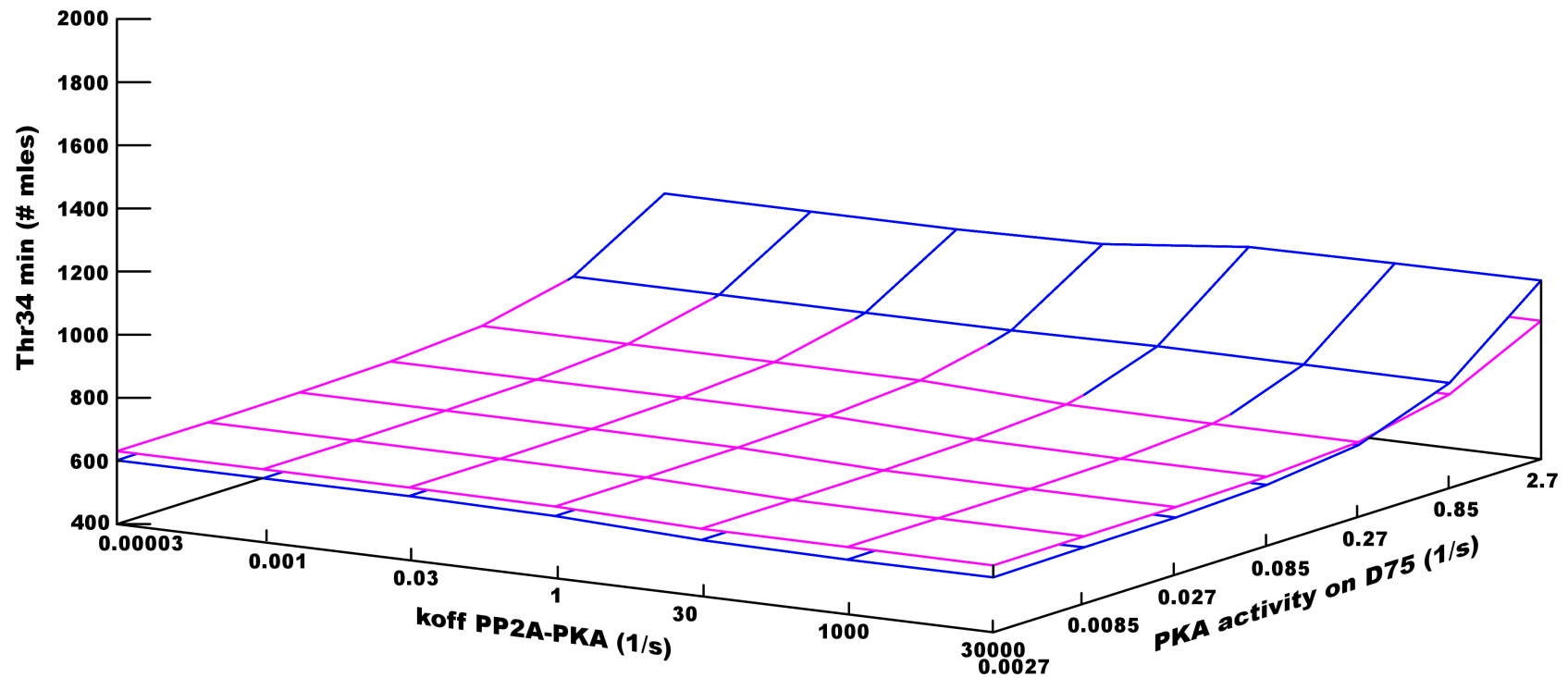
$$\frac{d[\text{CDK5}]}{dt} = -k_1[\text{CDK5}][\text{D}] + k_2[\text{D_CDK5}] + k_3[\text{D_CDK5}]$$

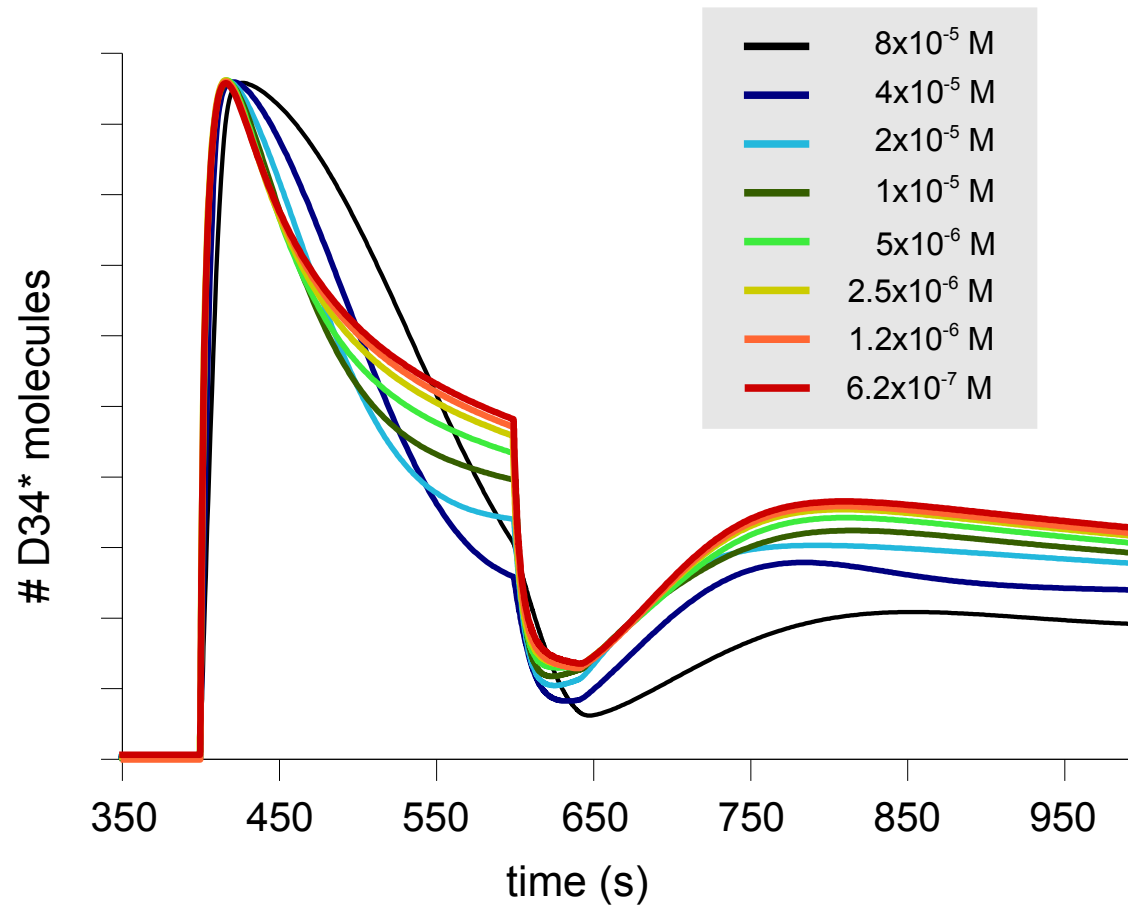
$$\frac{d[\text{D_CDK5}]}{dt} = +k_1[\text{CDK5}][\text{D}] - k_2[\text{D_CDK5}] - k_3[\text{D_CDK5}]$$

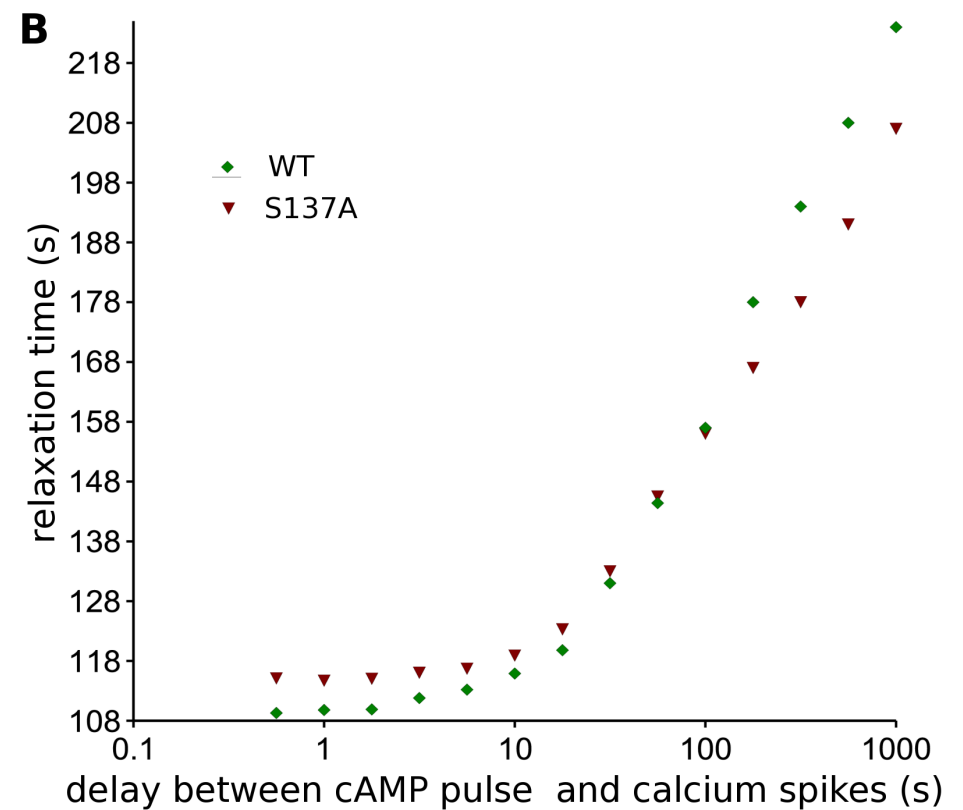
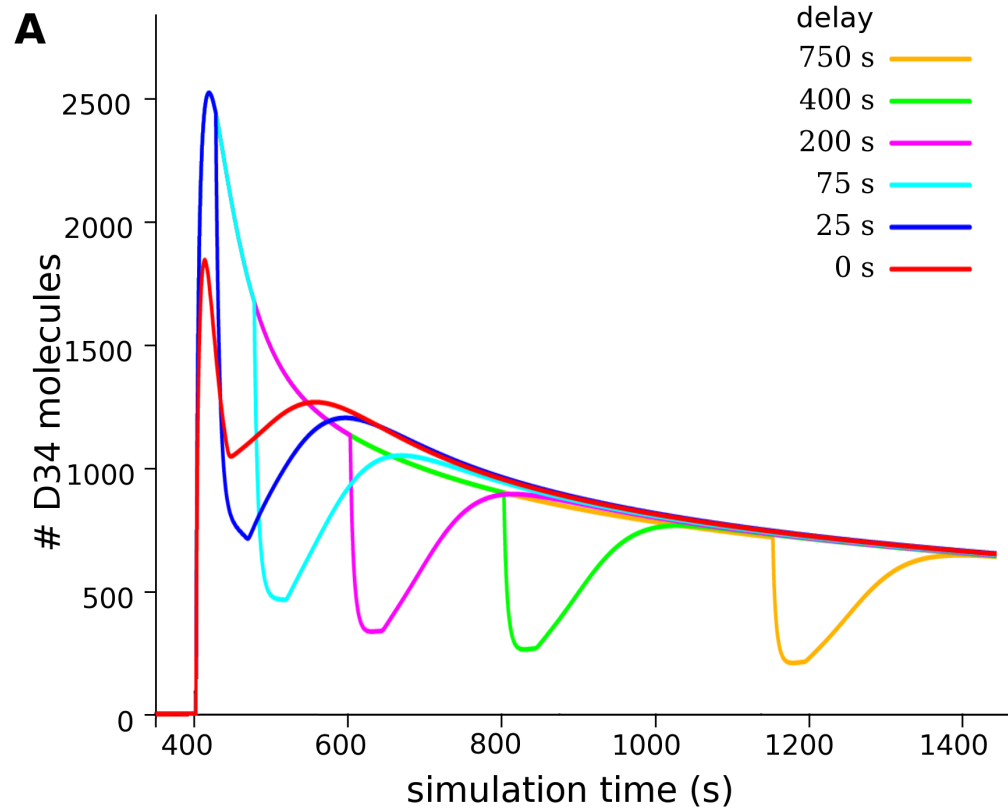


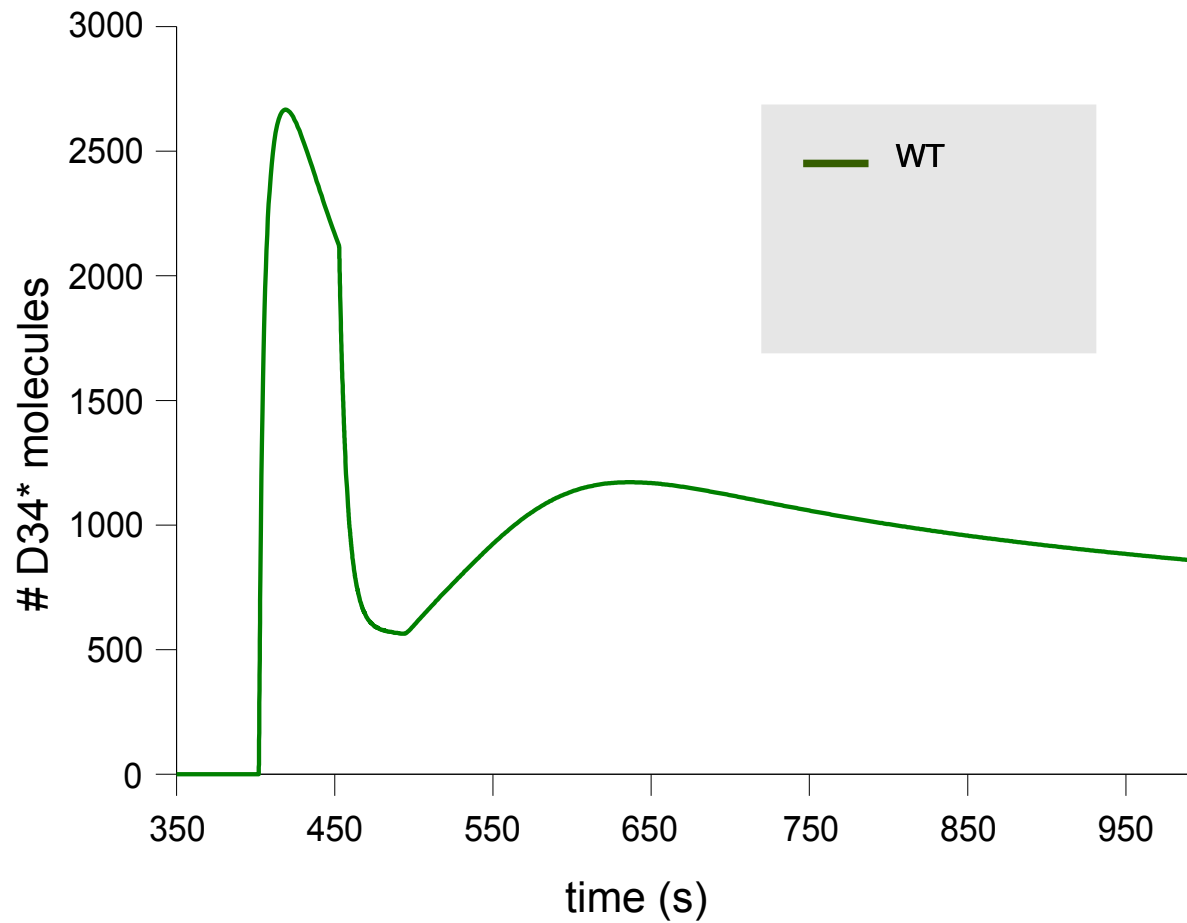


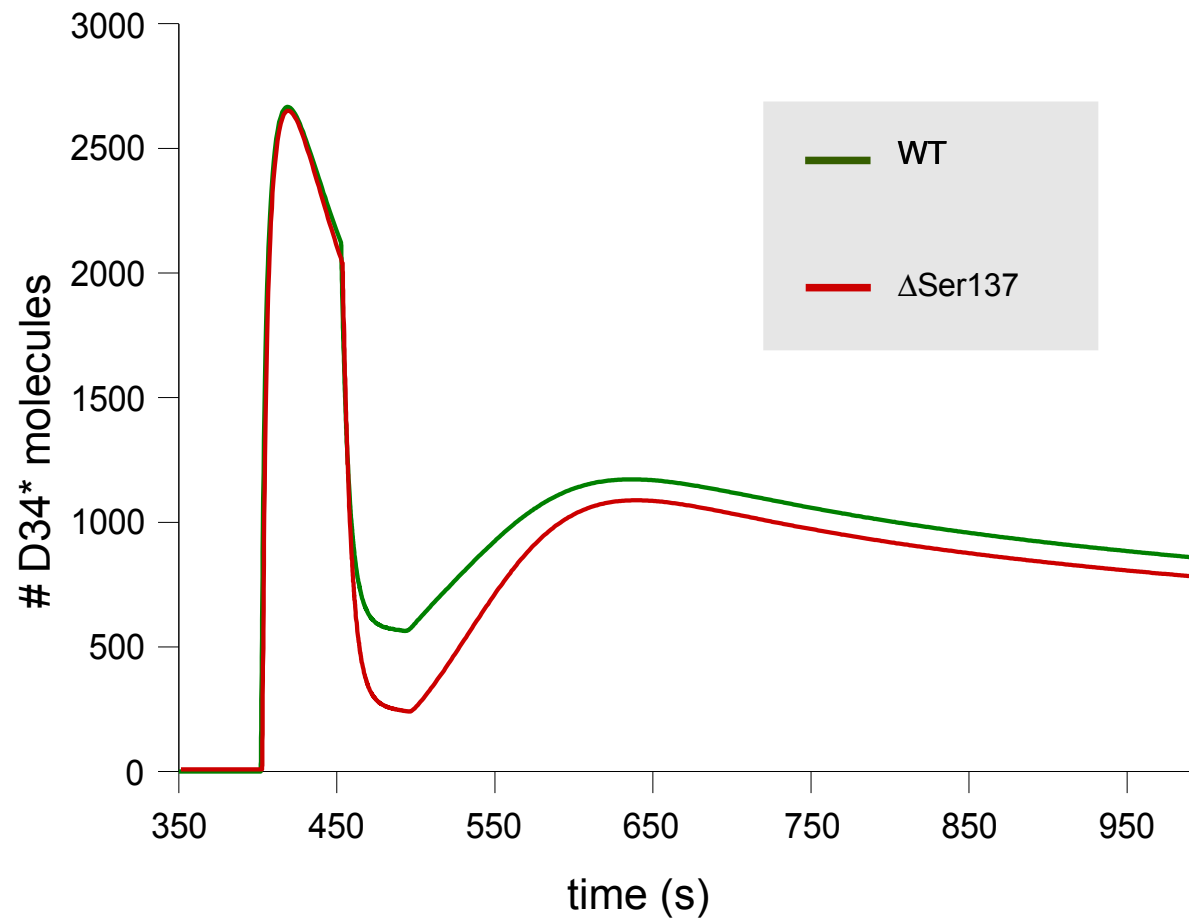


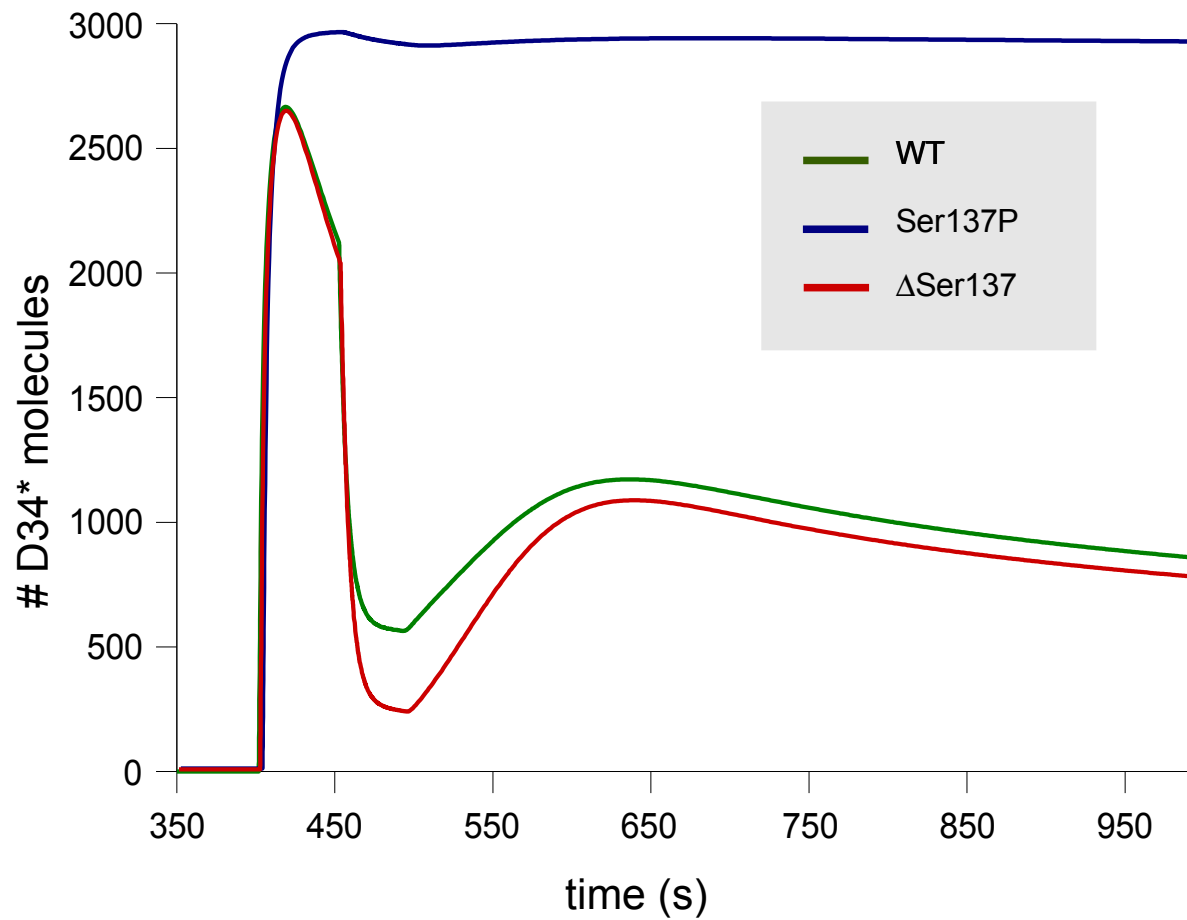






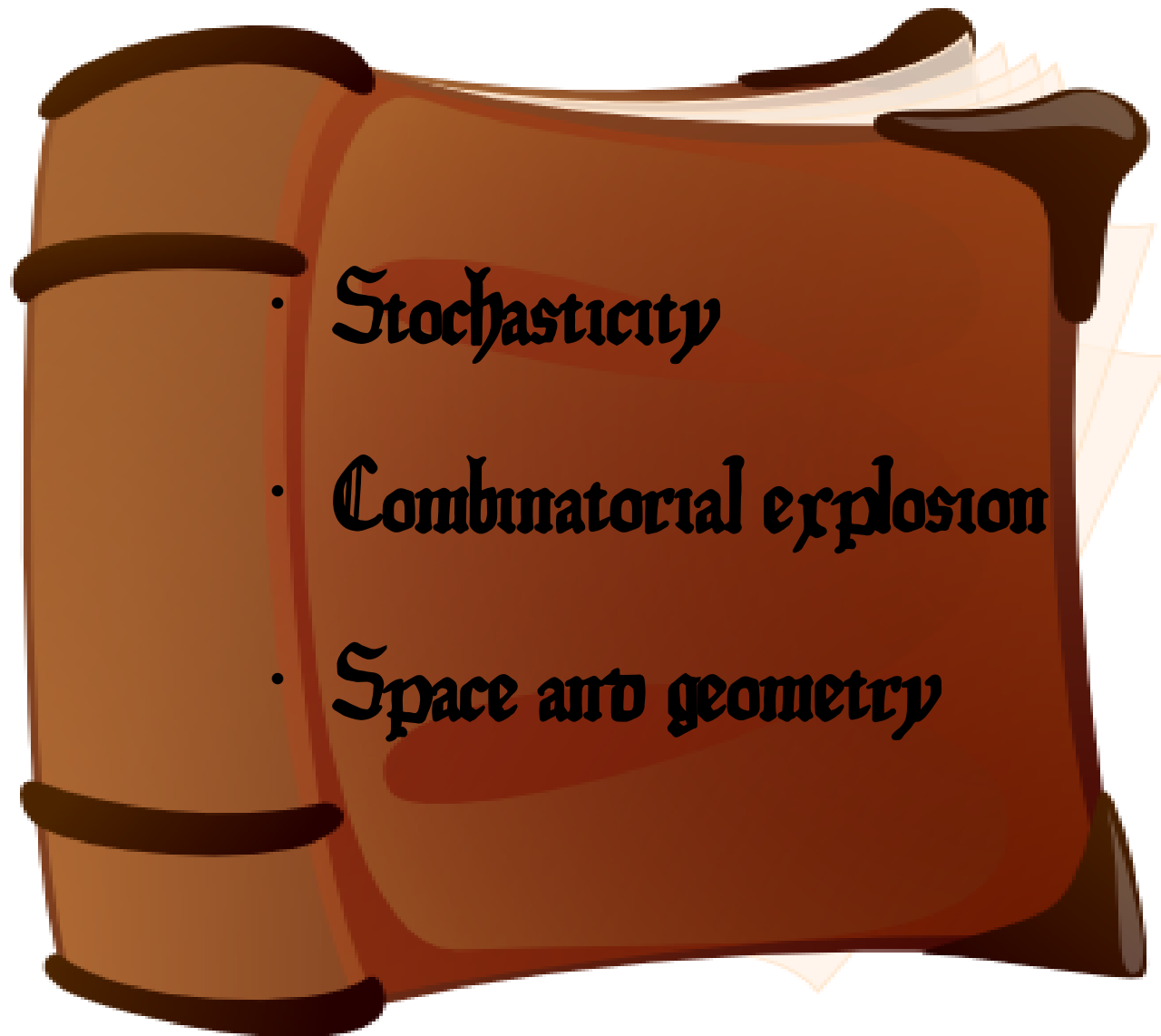


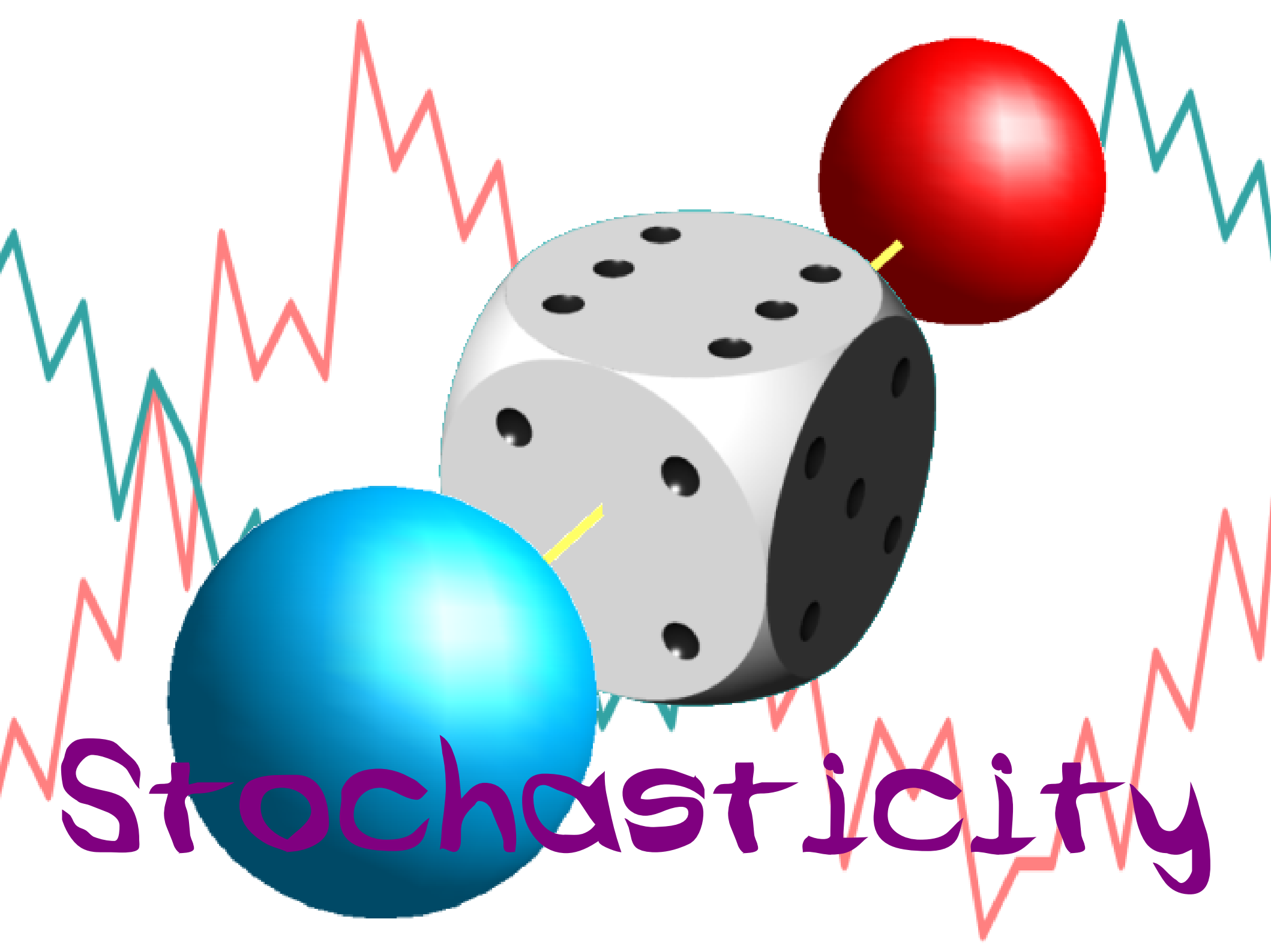




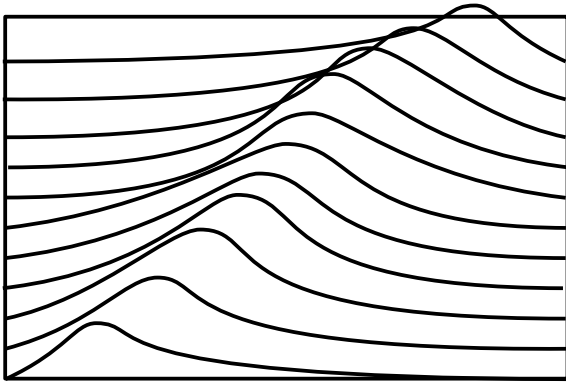






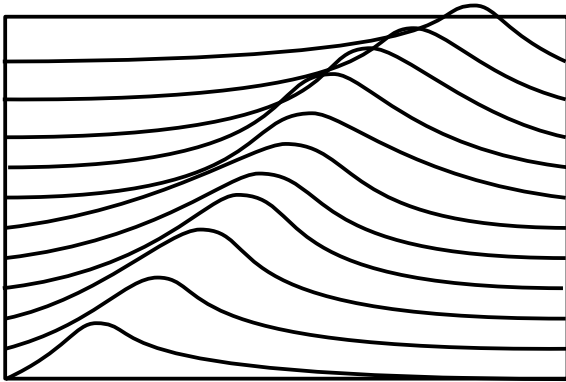


Stochasticity

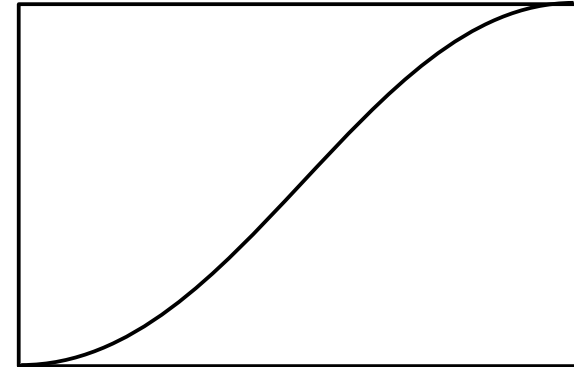


Grand Probability function: $P(X,t)$

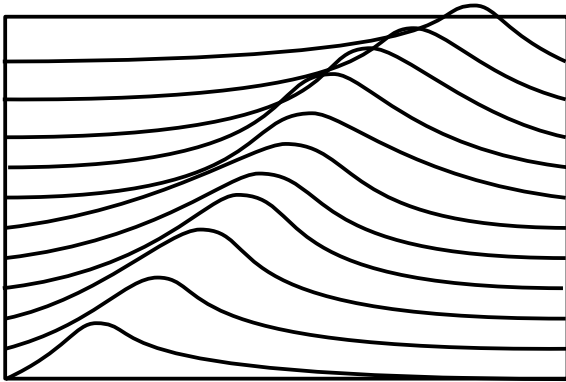




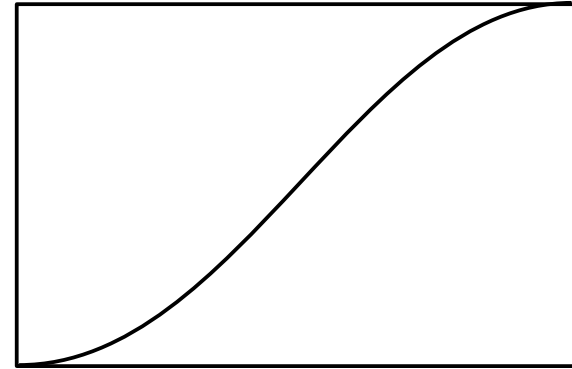
Grand Probability function: $P(X,t)$



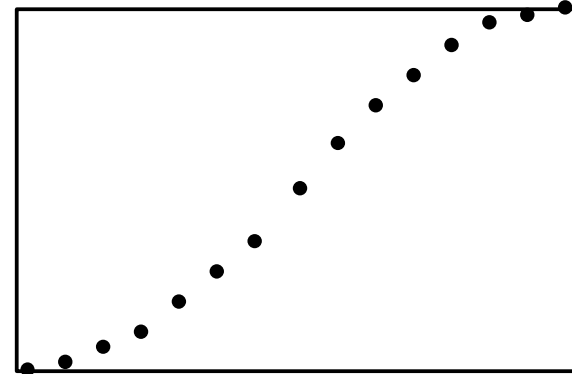
typologic view of the world: $(X)=f(t)$



Grand Probability function: $P(X,t)$

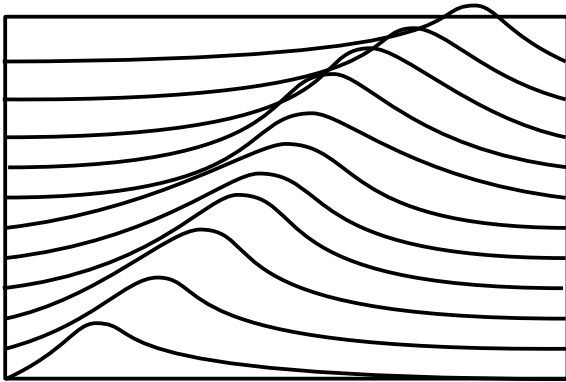


typologic view of the world: $(X)=f(t)$

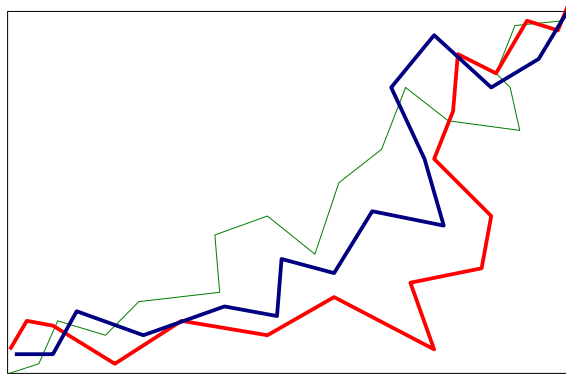


deterministic approach: $(X,t)=f(X',t-1)$

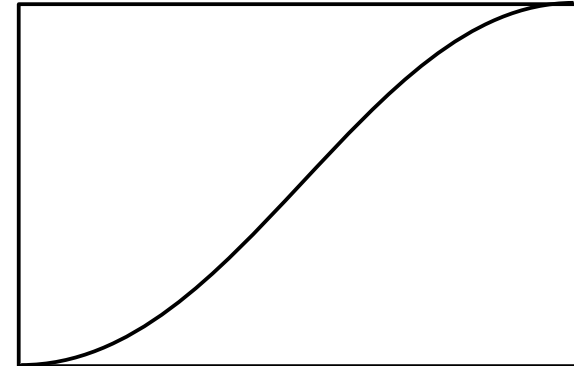




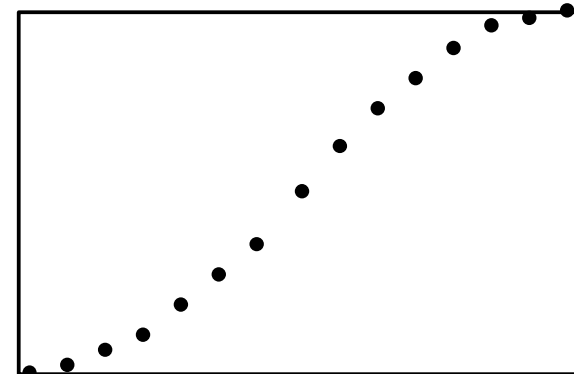
Grand Probability function: $P(X,t)$



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



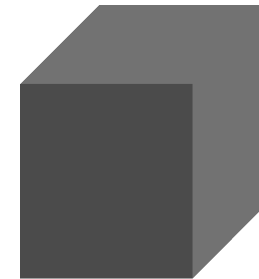
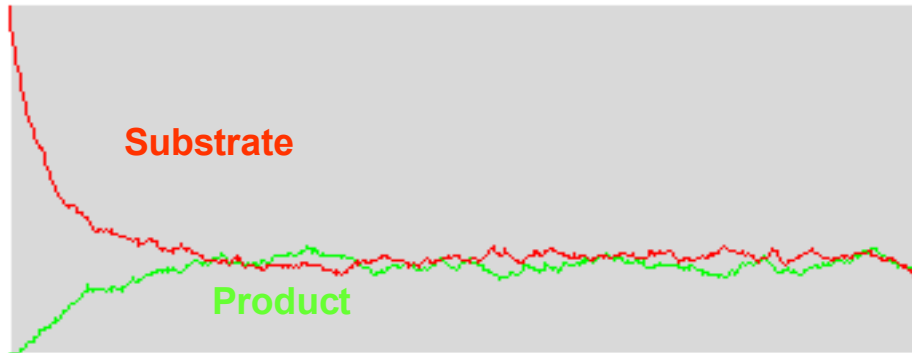
typologic view of the world: $(X)=f(t)$



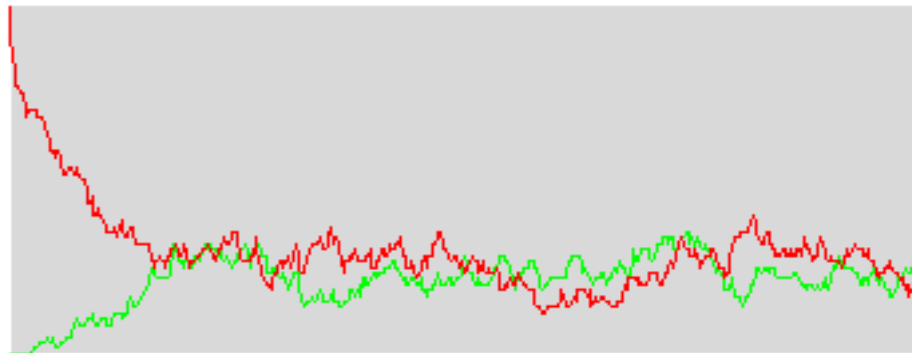
deterministic approach: $(X,t)=f(X',t-1)$



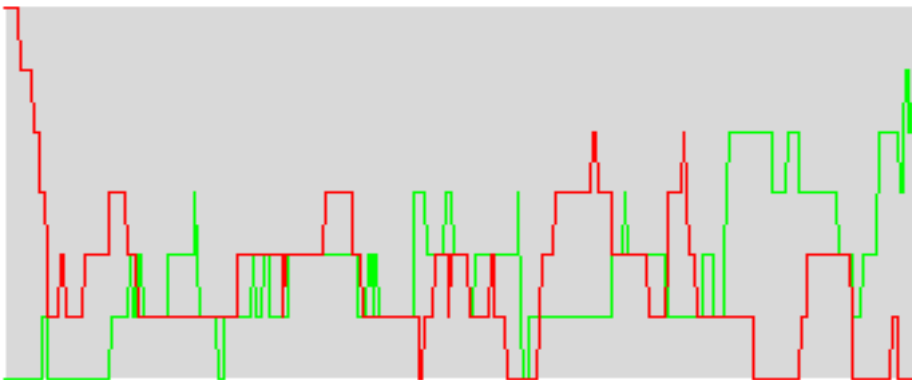
Concentration (μM)



10^{-15} litres

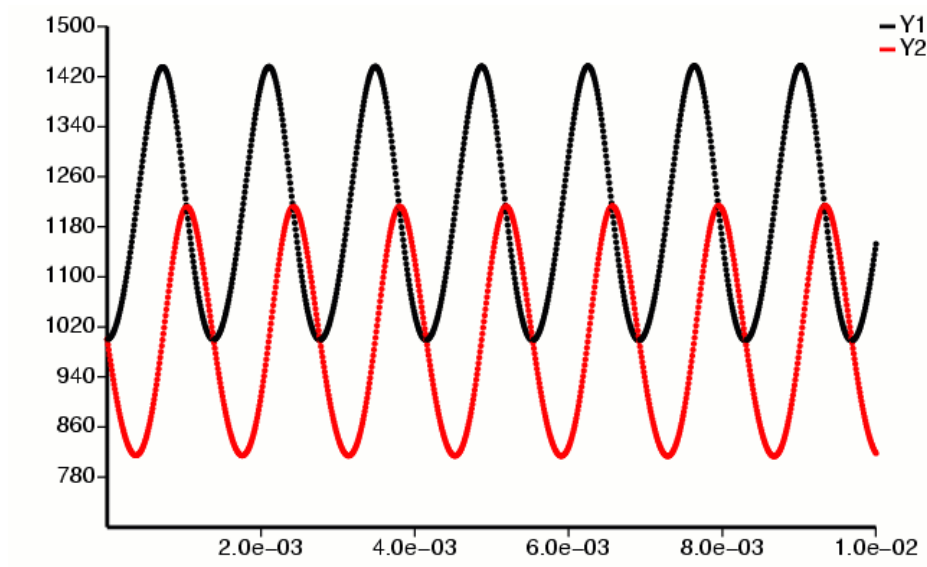


10^{-16} litres

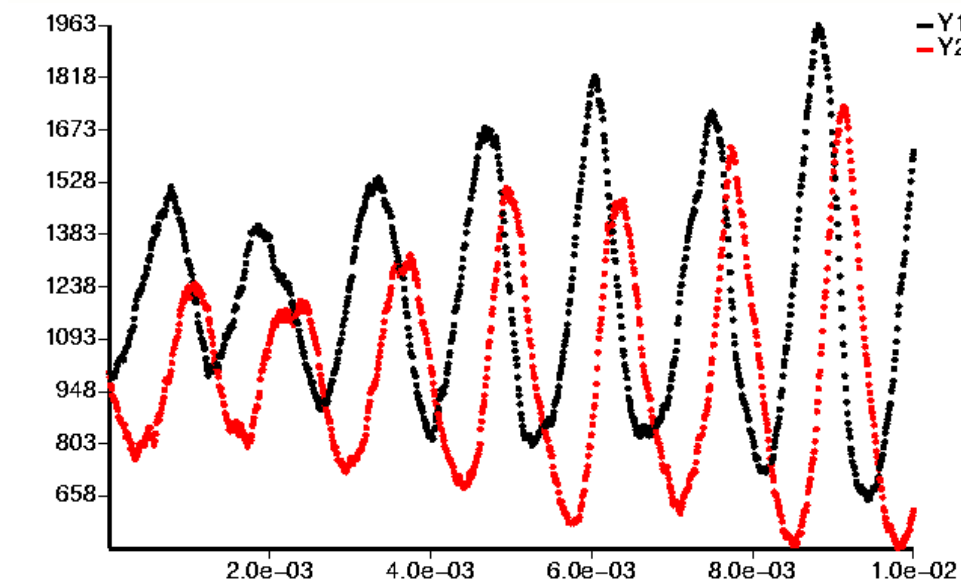


10^{-17} litres



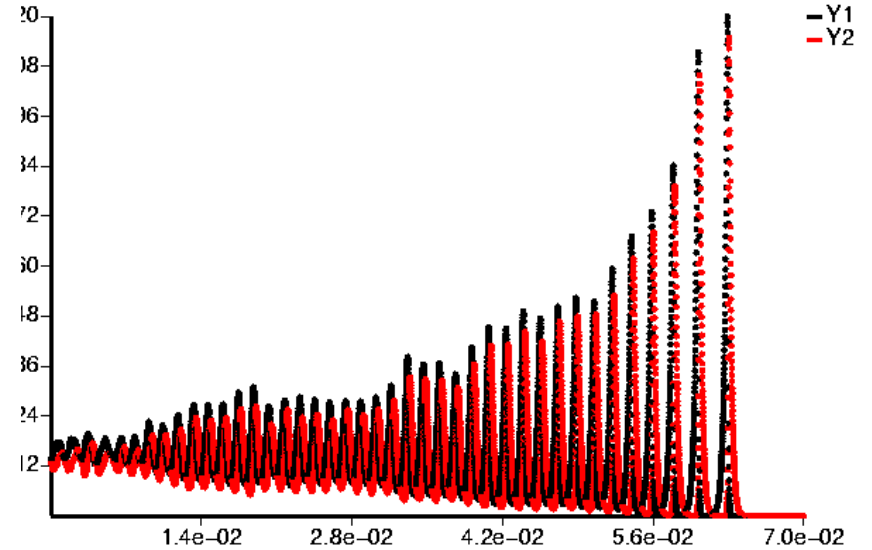
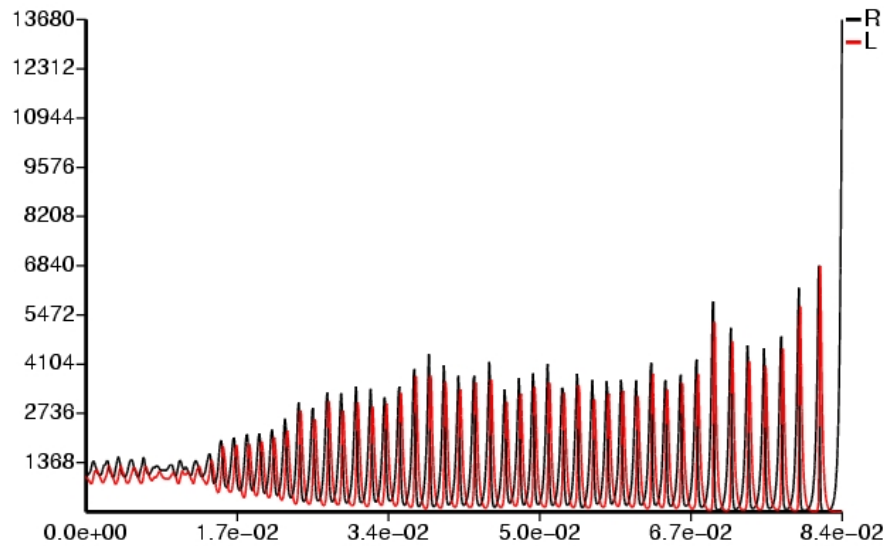
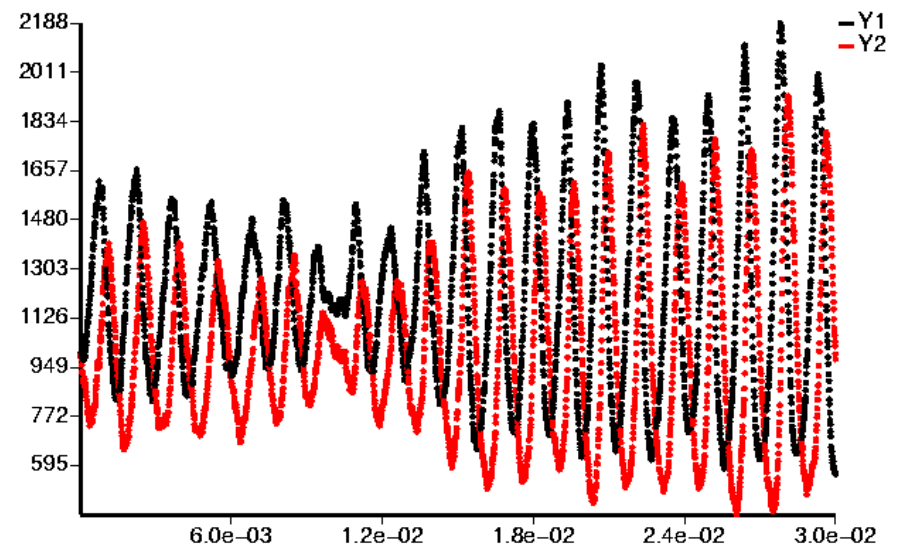
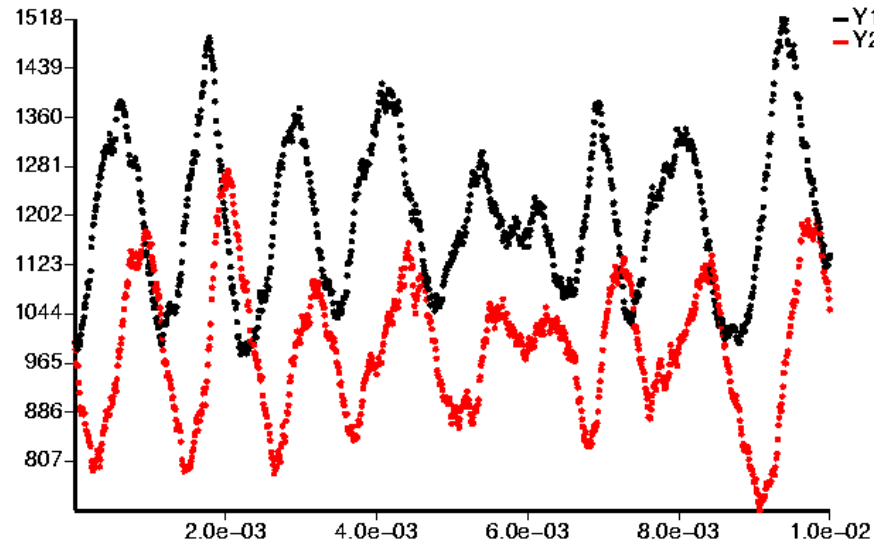


deterministic result



stochastic result





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



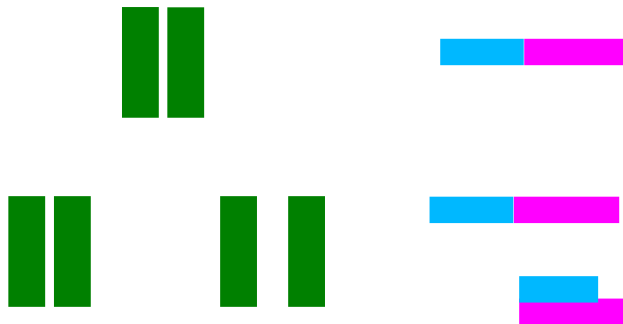


Combinatorial Explosion



NMDA + CaMKII $\rightleftharpoons$ NMDA-CaMKII





NMDA + CaMKII $\rightleftharpoons$ NMDA-CaMKII

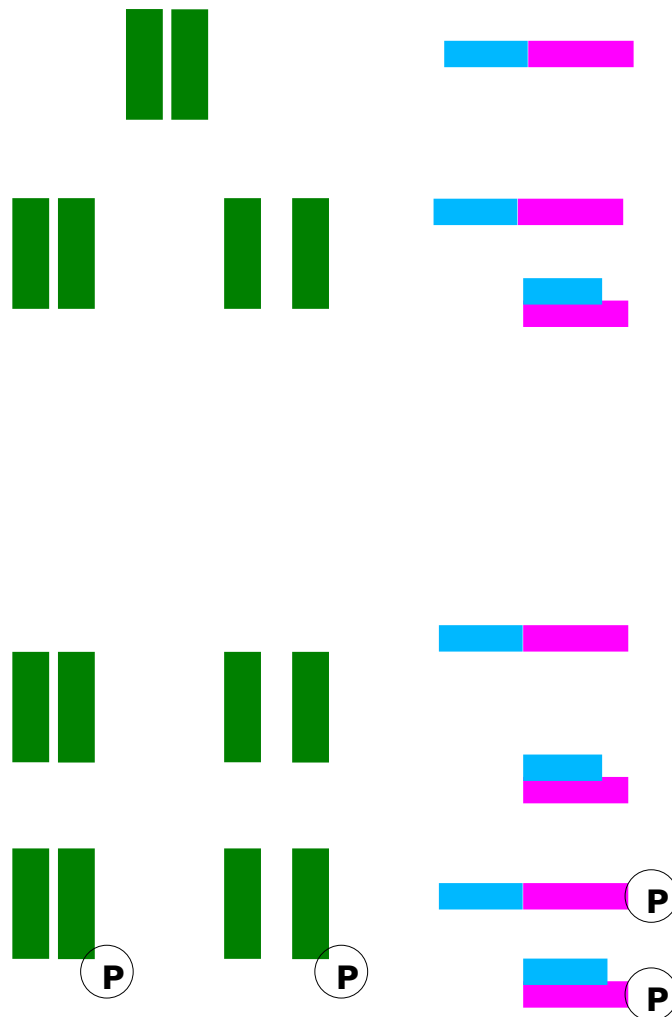
NMDAc + CaMKIIC $\rightleftharpoons$ NMDAc-CaMKIIC

NMDAo + CaMKIIC $\rightleftharpoons$ NMDAc-CaMKIIC

NMDAc + CaMKIIO $\rightleftharpoons$ NMDAc-CaMKIIO

NMDAo + CaMKIIO $\rightleftharpoons$ NMDAc-CaMKIIO





NMDA + CaMKII $\rightleftharpoons$ NMDA-CaMKII

NMDAc + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAo + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAc + CaMKIIo $\rightleftharpoons$ NMDAc-CaMKIIo

NMDAo + CaMKIIo $\rightleftharpoons$ NMDAc-CaMKIIo

NMDAc + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAo + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAc + CaMKIIo $\rightleftharpoons$ NMDAc-CaMKIIo

NMDAo + CaMKIIo $\rightleftharpoons$ NMDAc-CaMKIIo

pNMDAc + CaMKIIc $\rightleftharpoons$ pNMDAc-CaMKIIc

pNMDAo + CaMKIIc $\rightleftharpoons$ pNMDAc-CaMKIIc

pNMDAc + CaMKIIo $\rightleftharpoons$ pNMDAc-CaMKIIo

pNMDAo + CaMKIIo $\rightleftharpoons$ pNMDAc-CaMKIIo

NMDAc + pCaMKIIc $\rightleftharpoons$ NMDAc-pCaMKIIc

NMDAo + pCaMKIIc $\rightleftharpoons$ NMDAc-pCaMKIIc

NMDAc + pCaMKIIo $\rightleftharpoons$ NMDAc-pCaMKIIo

NMDAo + pCaMKIIo $\rightleftharpoons$ NMDAc-pCaMKIIo

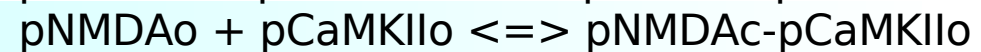
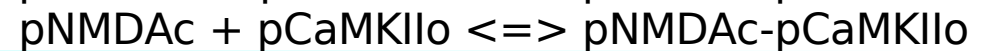
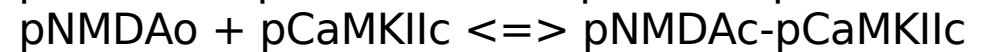
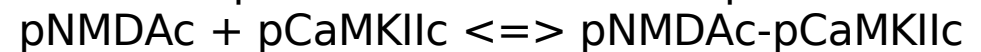
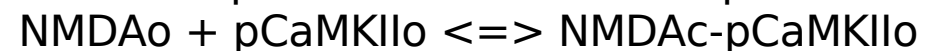
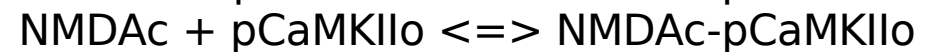
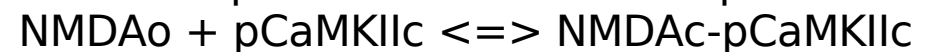
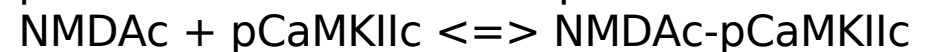
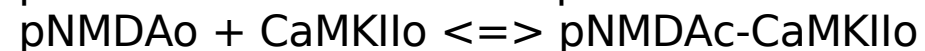
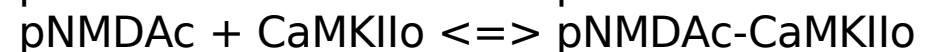
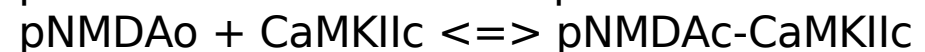
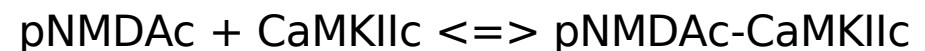
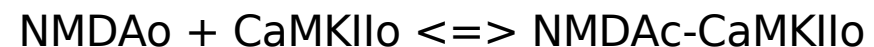
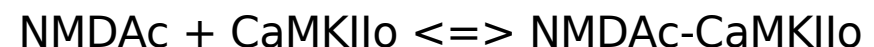
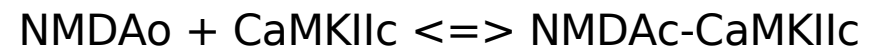
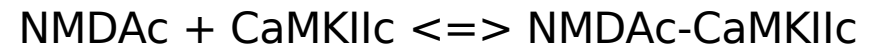
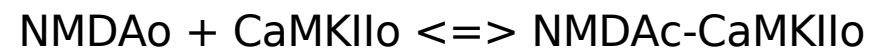
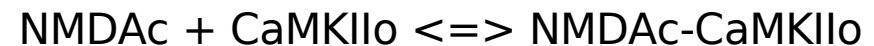
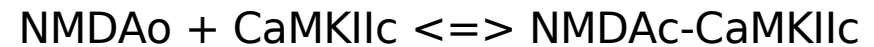
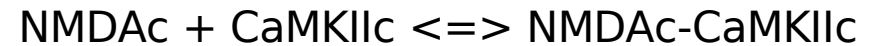
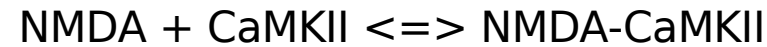
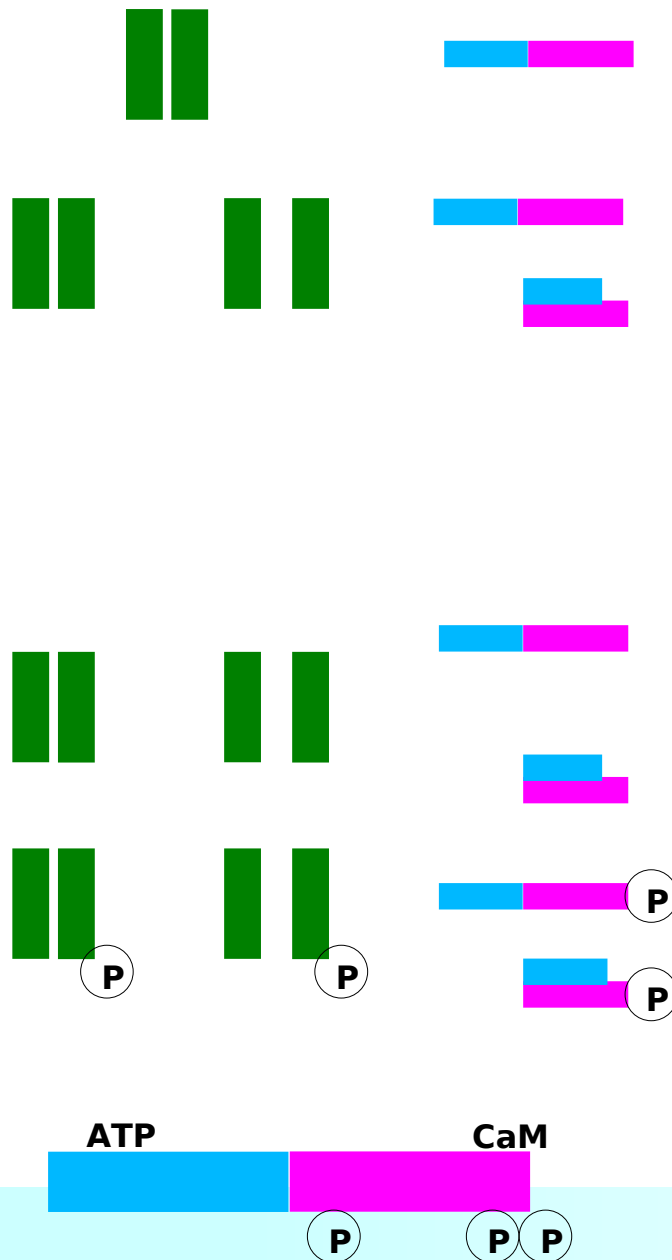
pNMDAc + pCaMKIIc $\rightleftharpoons$ pNMDAc-pCaMKIIc

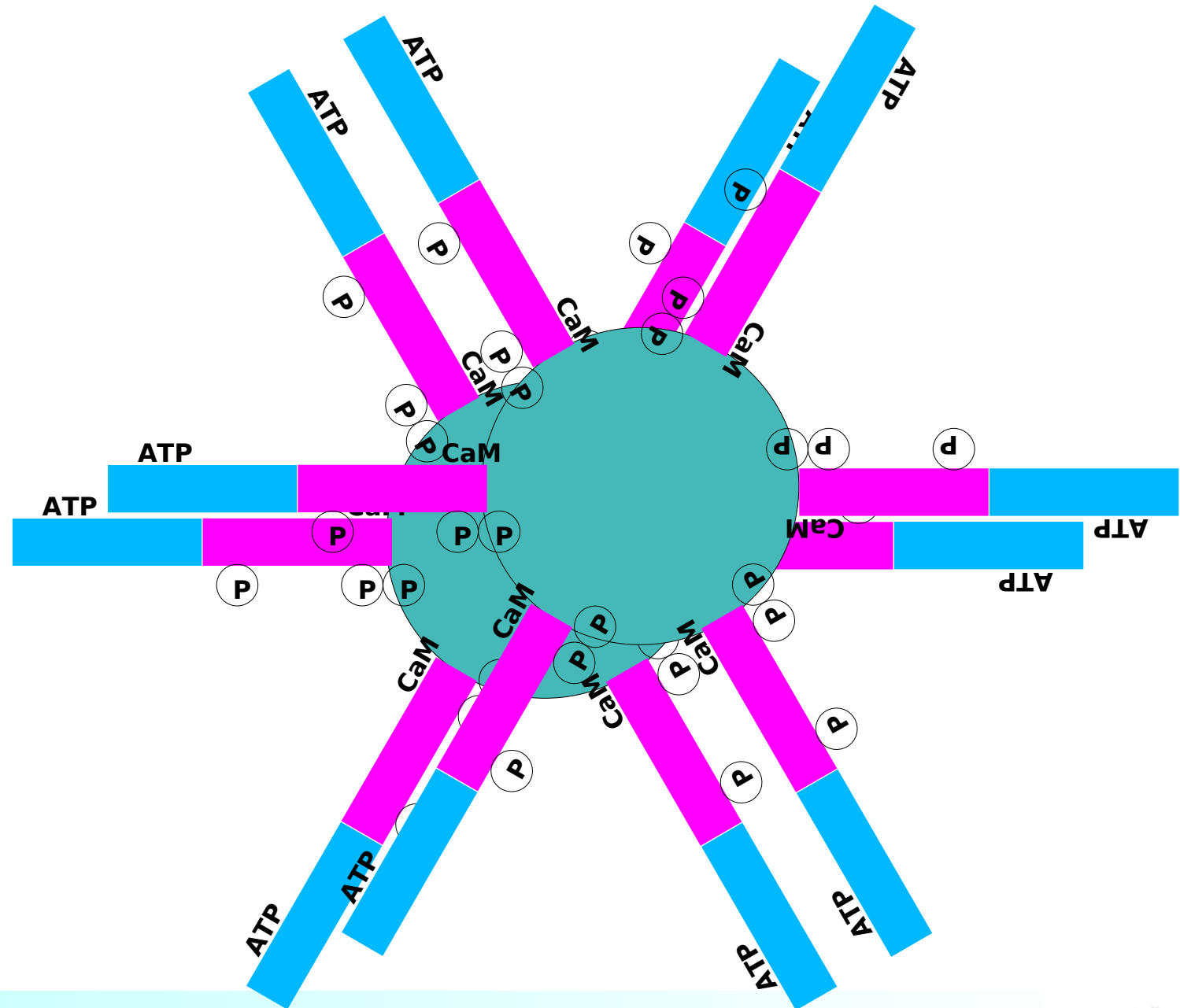
pNMDAo + pCaMKIIc $\rightleftharpoons$ pNMDAc-pCaMKIIc

pNMDAc + pCaMKIIo $\rightleftharpoons$ pNMDAc-pCaMKIIo

pNMDAo + pCaMKIIo $\rightleftharpoons$ pNMDAc-pCaMKIIo

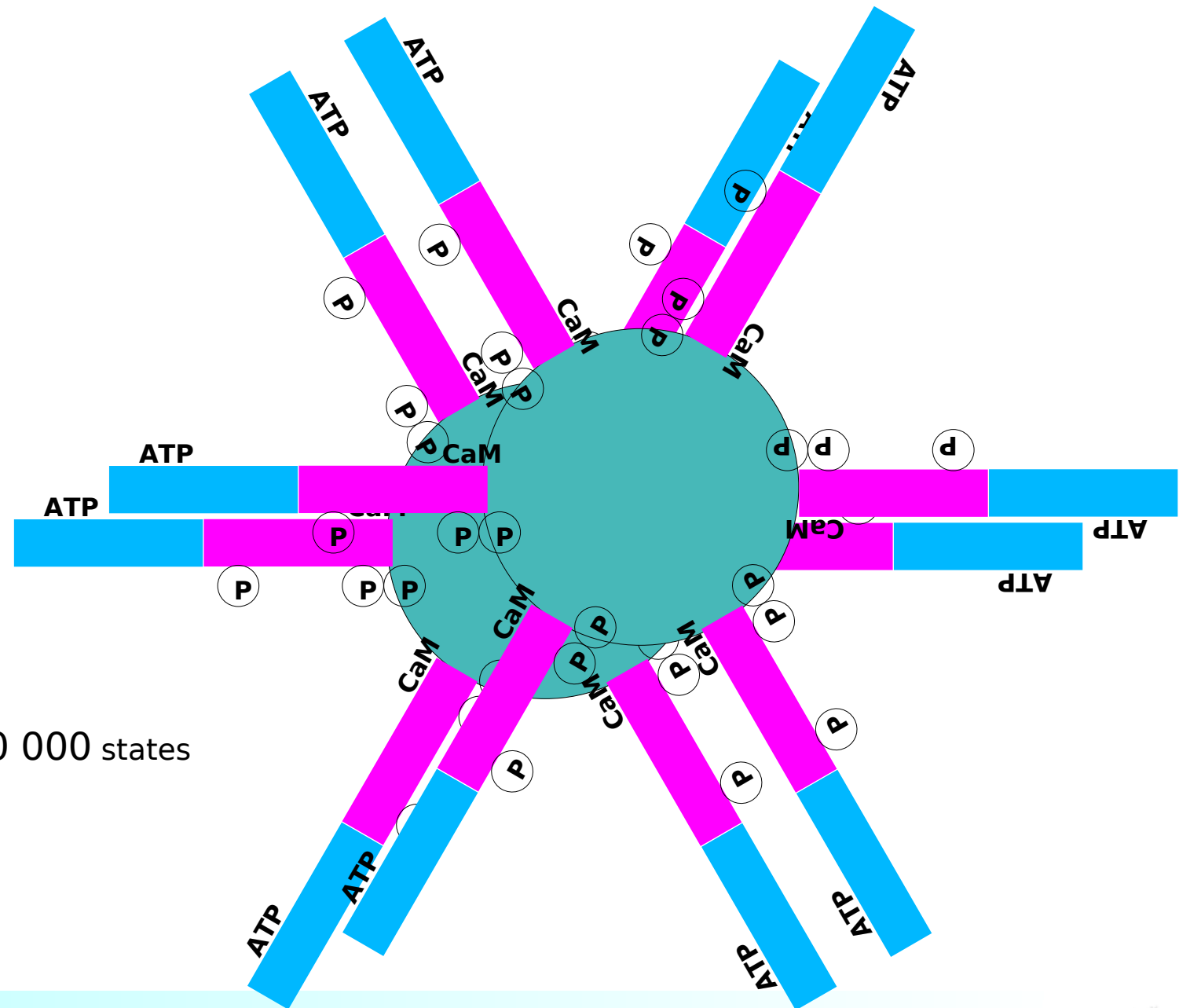






5x12 state variables=



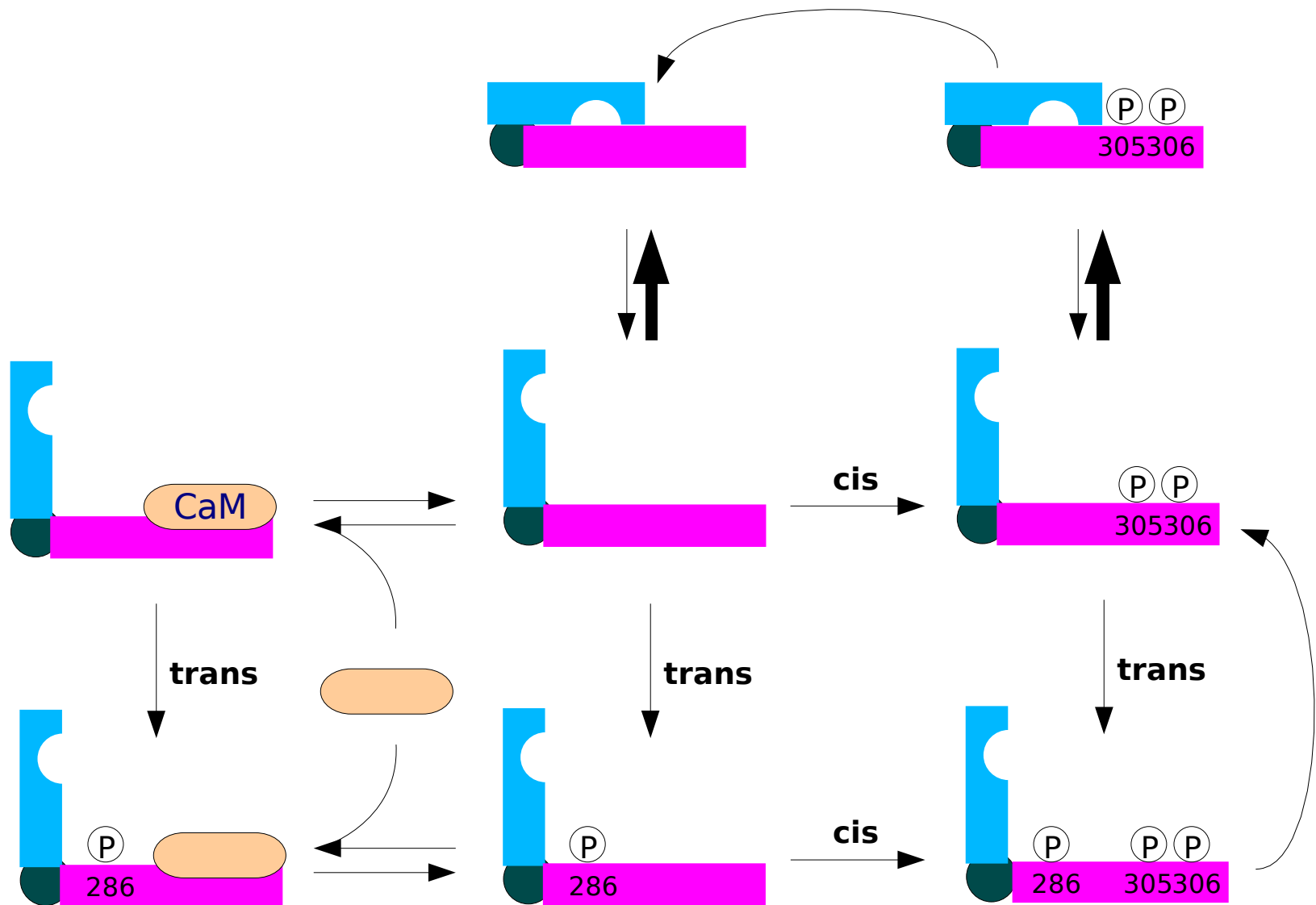


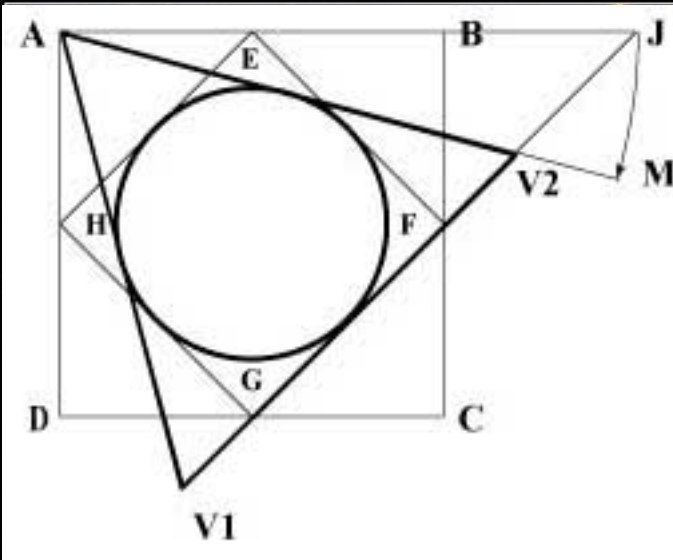
5x12 state variables=

1 152 900 000 000 000 000 states

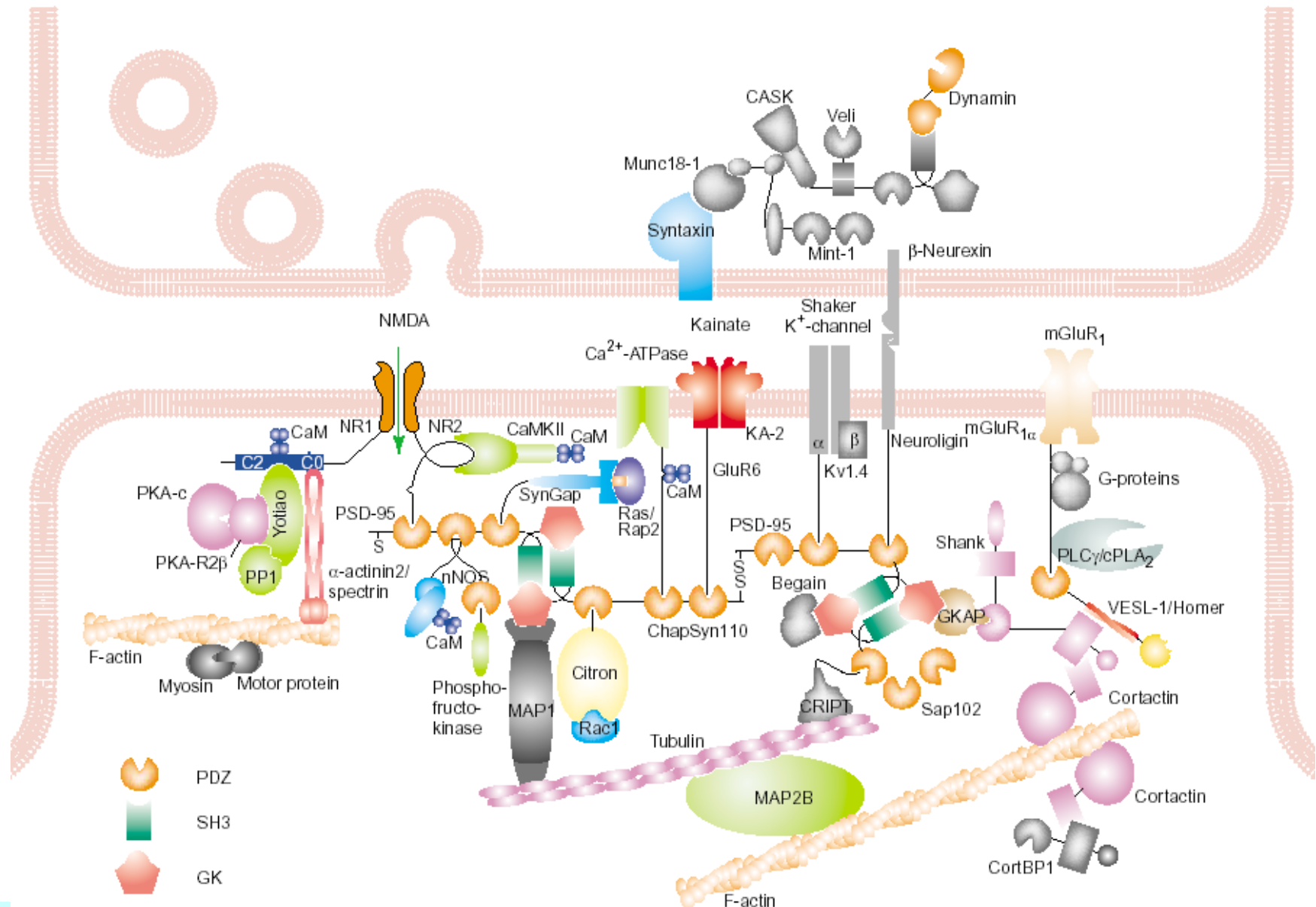
(1 billion of billion)

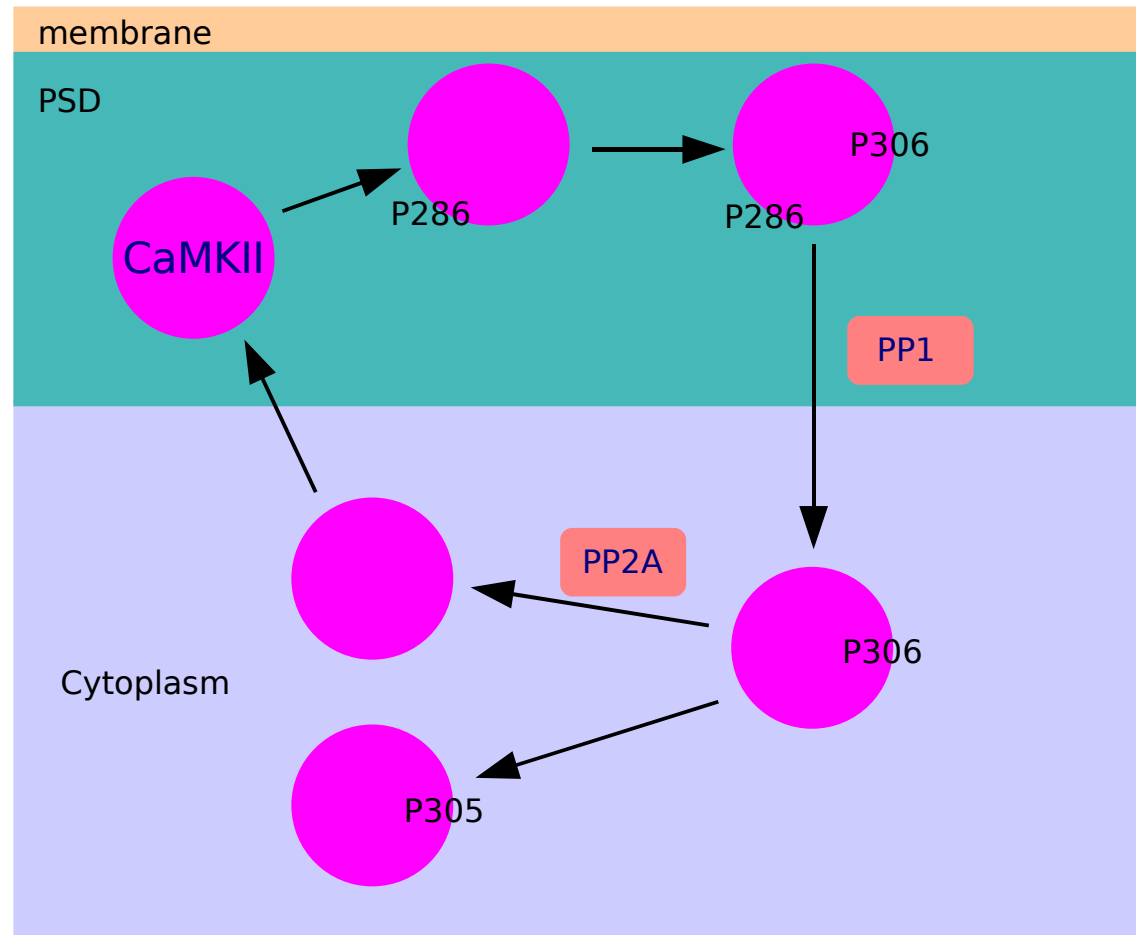




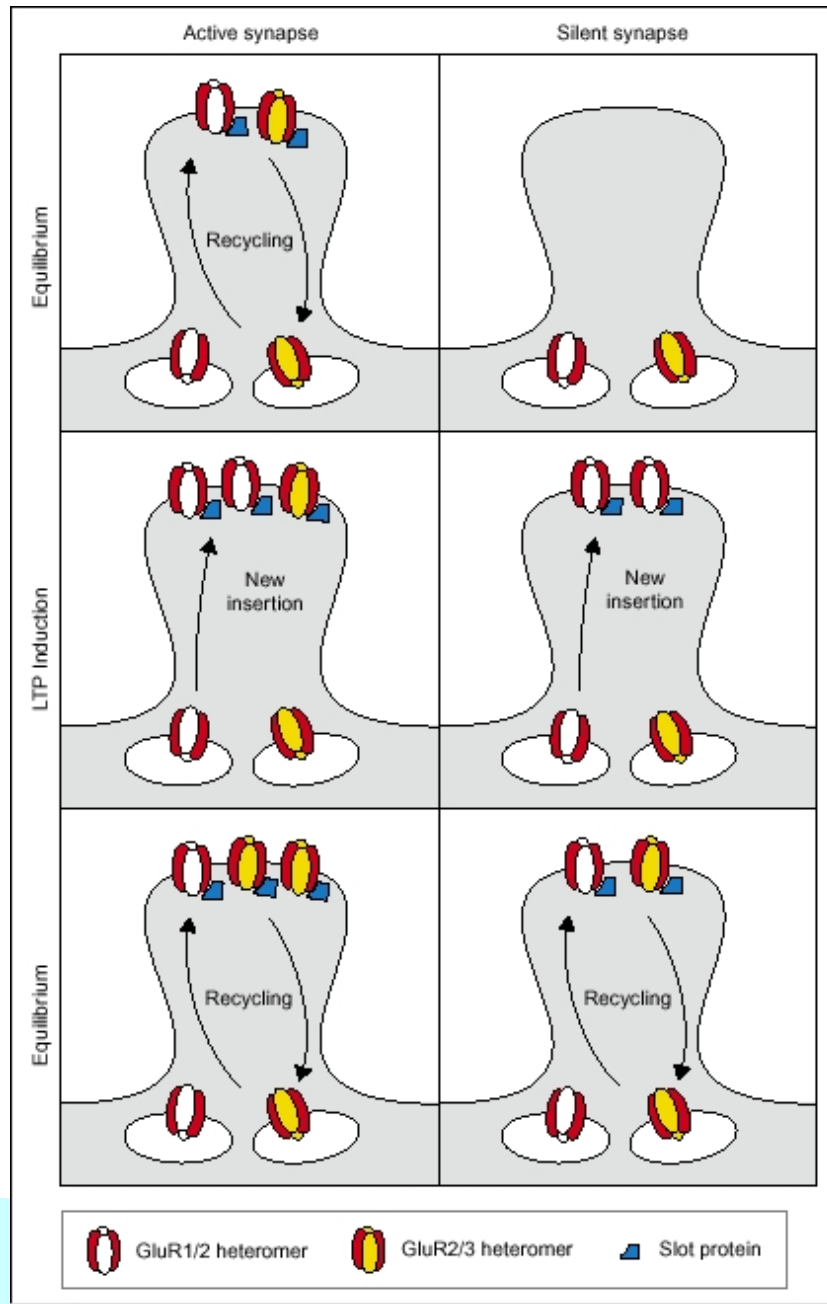


Space and
geometry

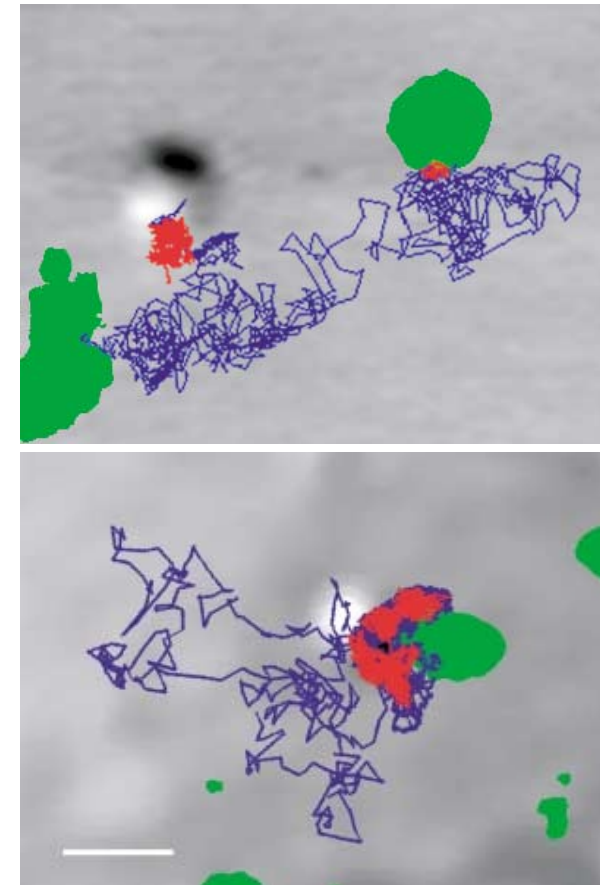




Receptors for neurotransmitters are moving



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



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



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-diffusion)
- Molecules under different states are represented by different pools

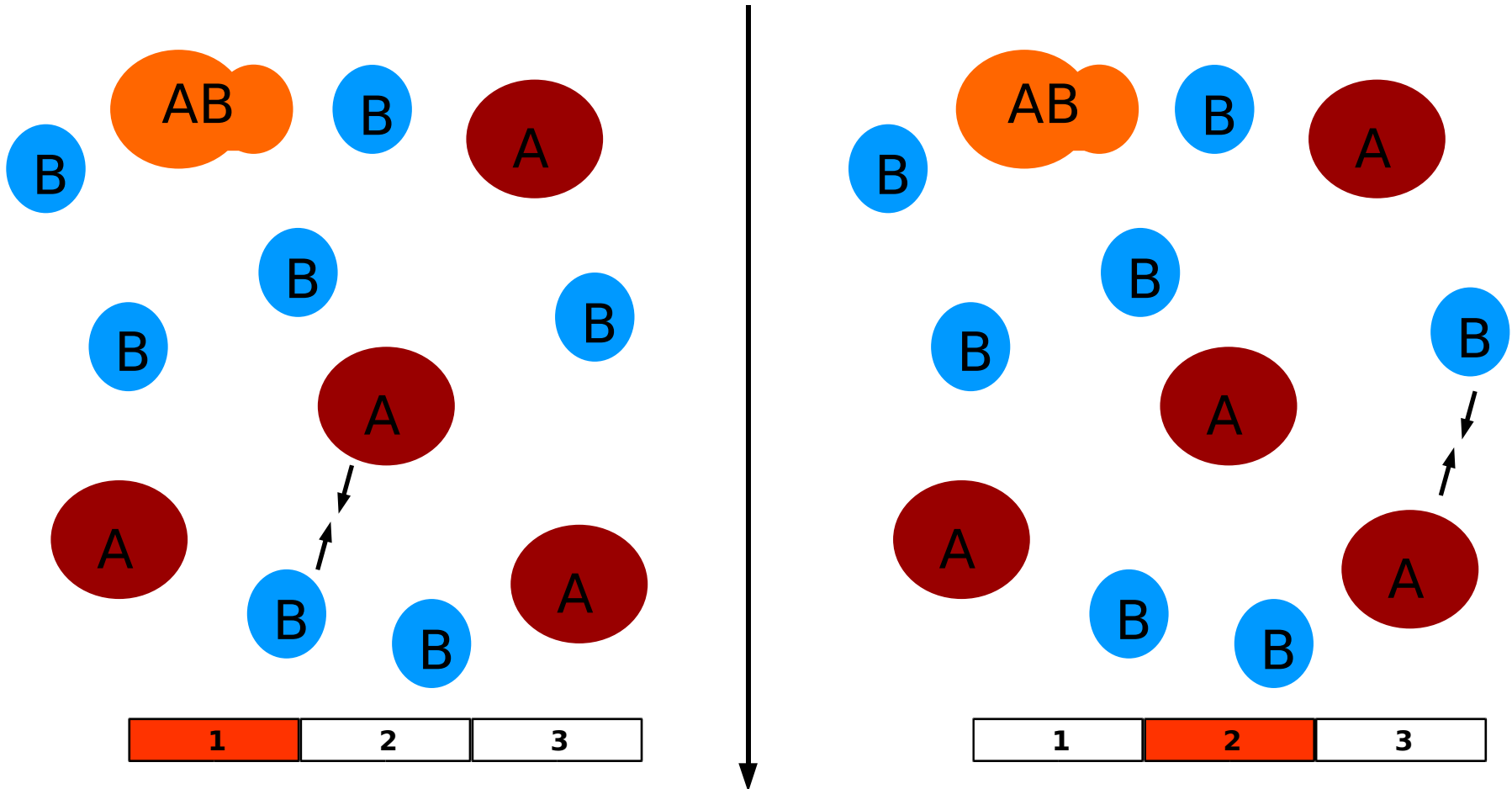
Particle-based simulation

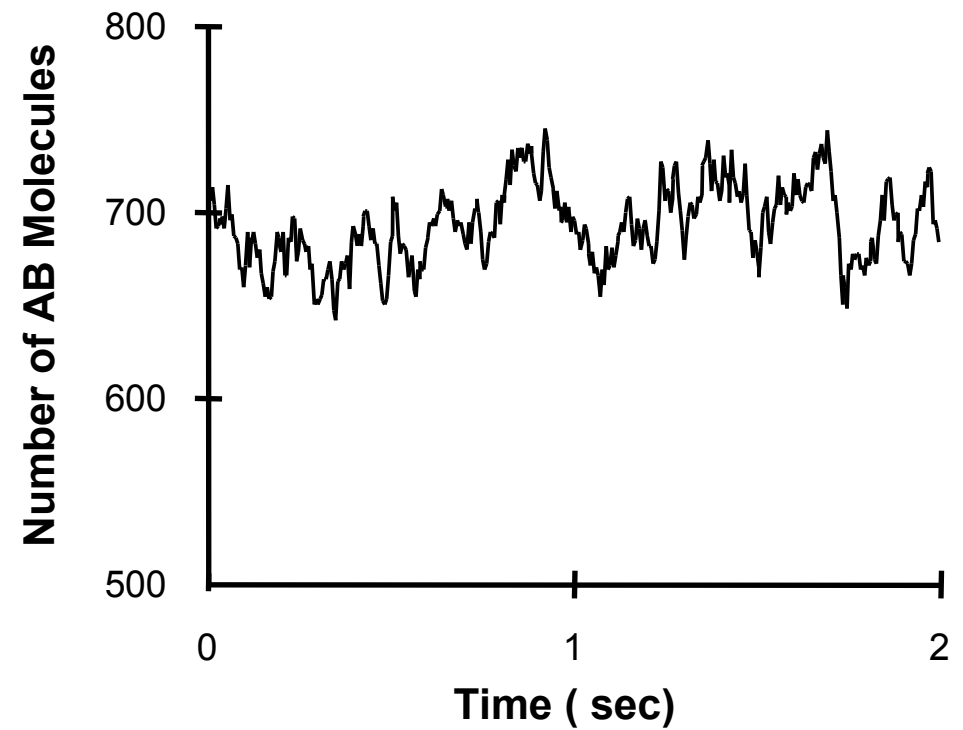
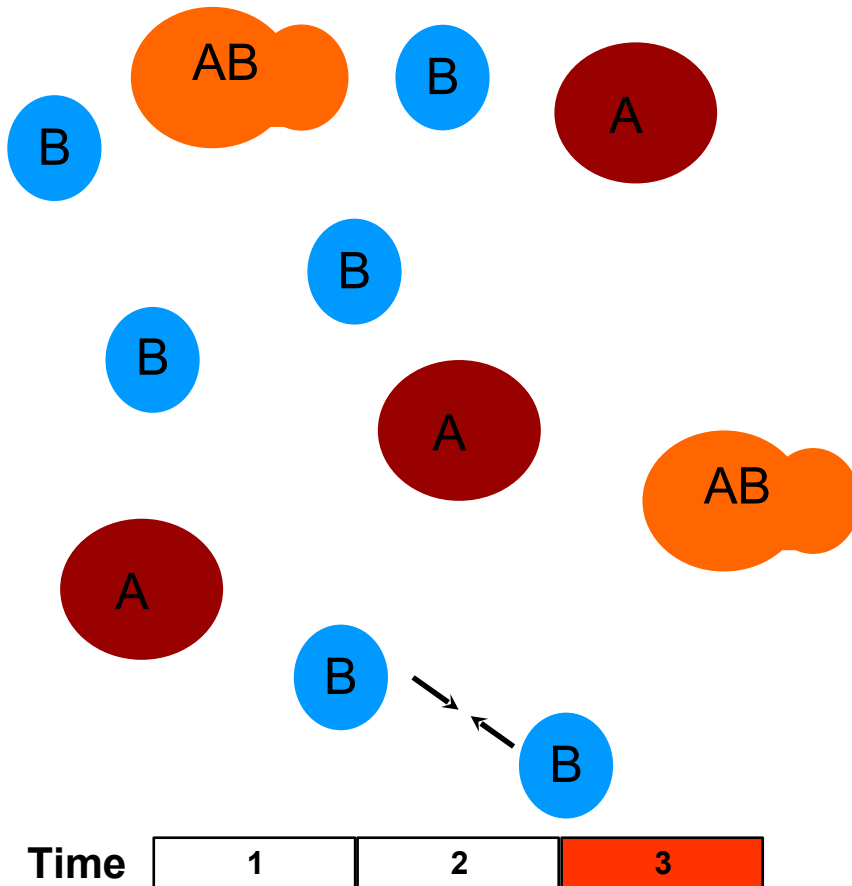
- Discrete representation of molecules
- Generally stochastic algorithms (but not always: deterministic automata)
- Generally location of molecules (but not always: StochSim v1)
- Representation of the movements of (some) molecules
- Possibility of multistates molecules

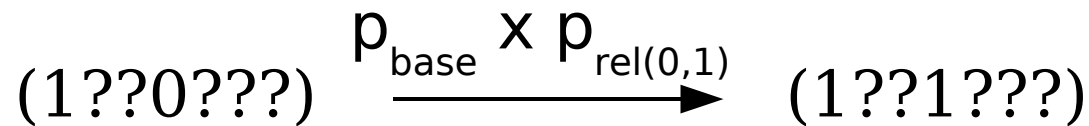
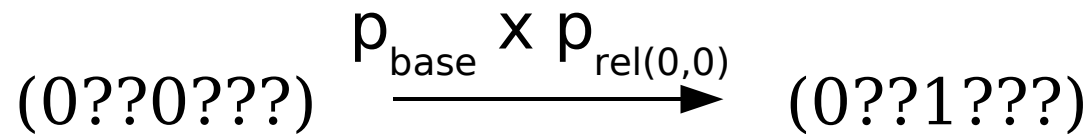
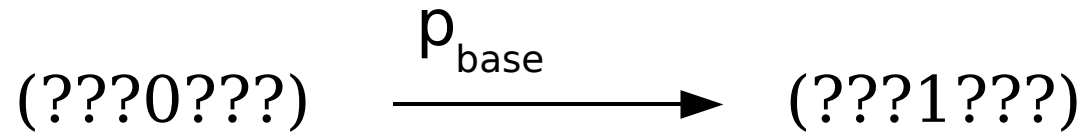


- Morton-Firth CJ, Bray D (1998) *J. Theor. Biol.* 192: 117–128.
- Le Novère N, Shimizu TS (2001) *Bioinformatics* 17: 575-576
- Particle-based stochastic simulations
- Possibility of multistate complexes
- Rapid equilibria to reduce stiffness problems
- 2D lattices of various geometry



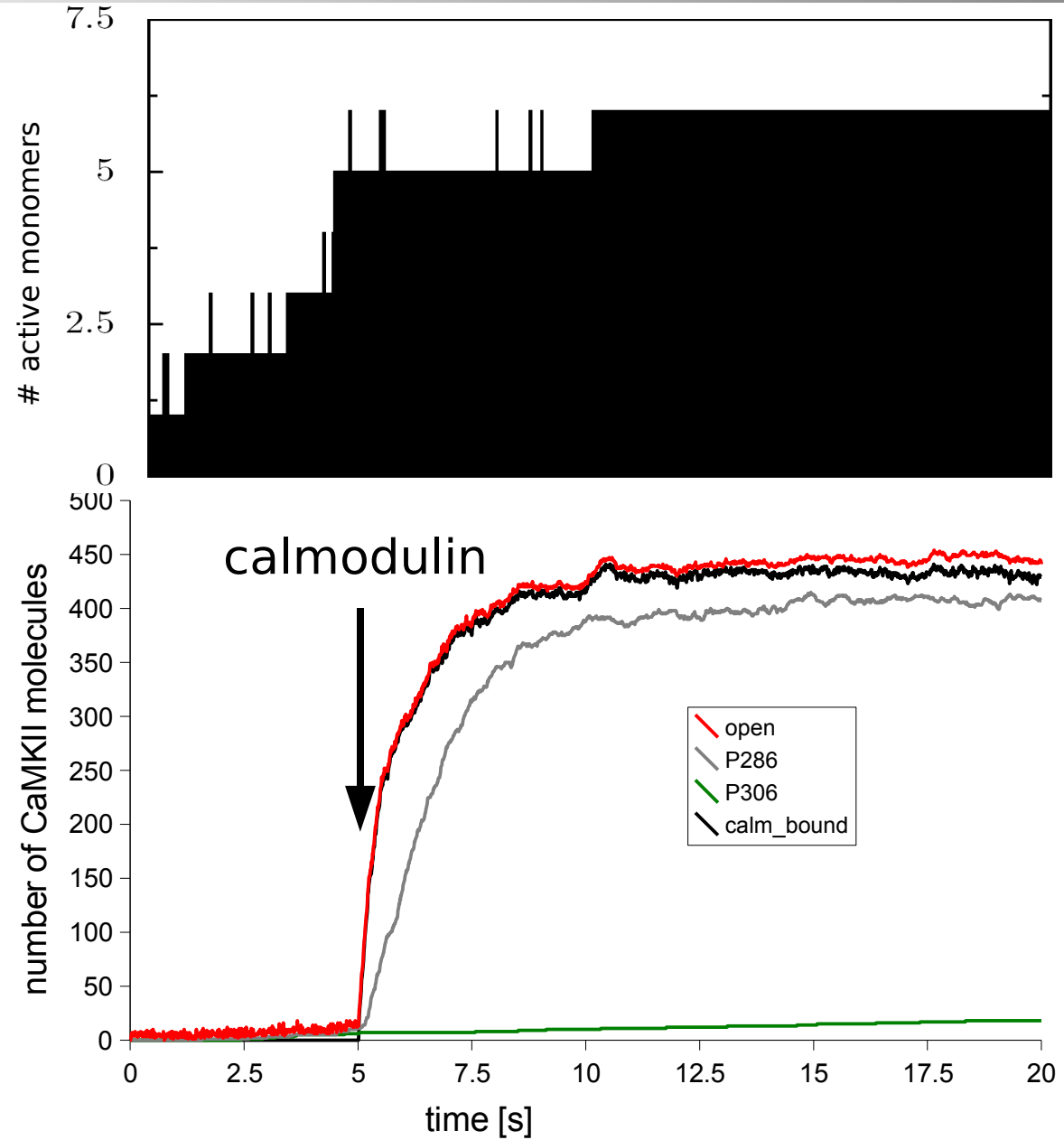
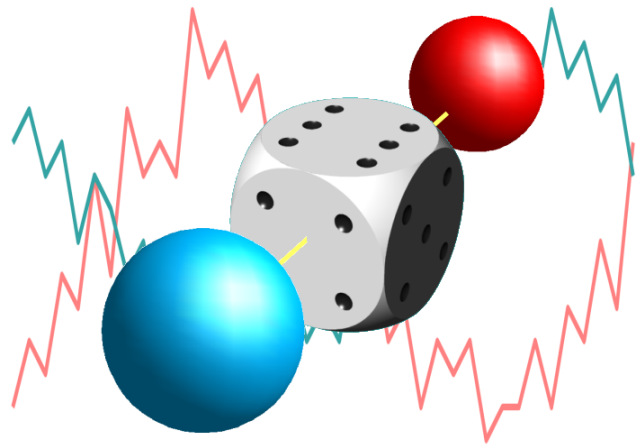






- '?' Flags do not affect the reaction
- only 4 species are needed instead of 128

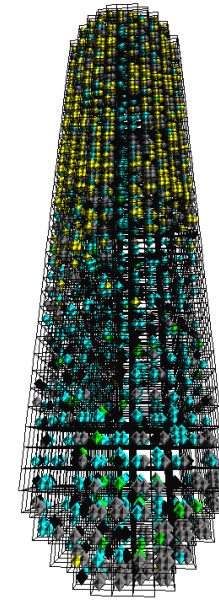




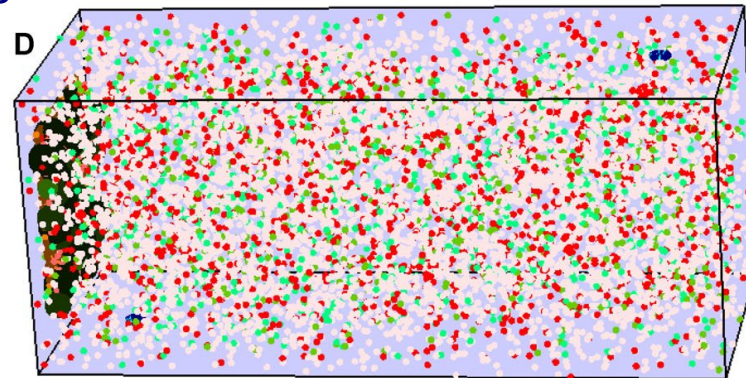
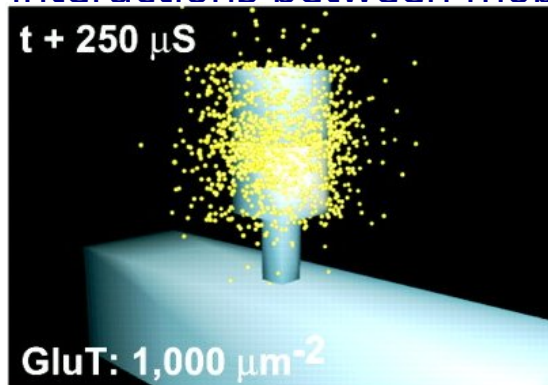
- molecule abstracted $\Rightarrow$ macroscopic scale
- atomic details $\Rightarrow$ microscopic scale
- Abstracted but realistic geometry $\Rightarrow$ mesoscopic scale
- Relative size of object respected
- Differential location of binding sites
- realistic movements (velocity and topology)



- Population based (“spatial Gillespie”)
 - SmartCell, Mesord
 - finite elements (voxels), no individual molecules



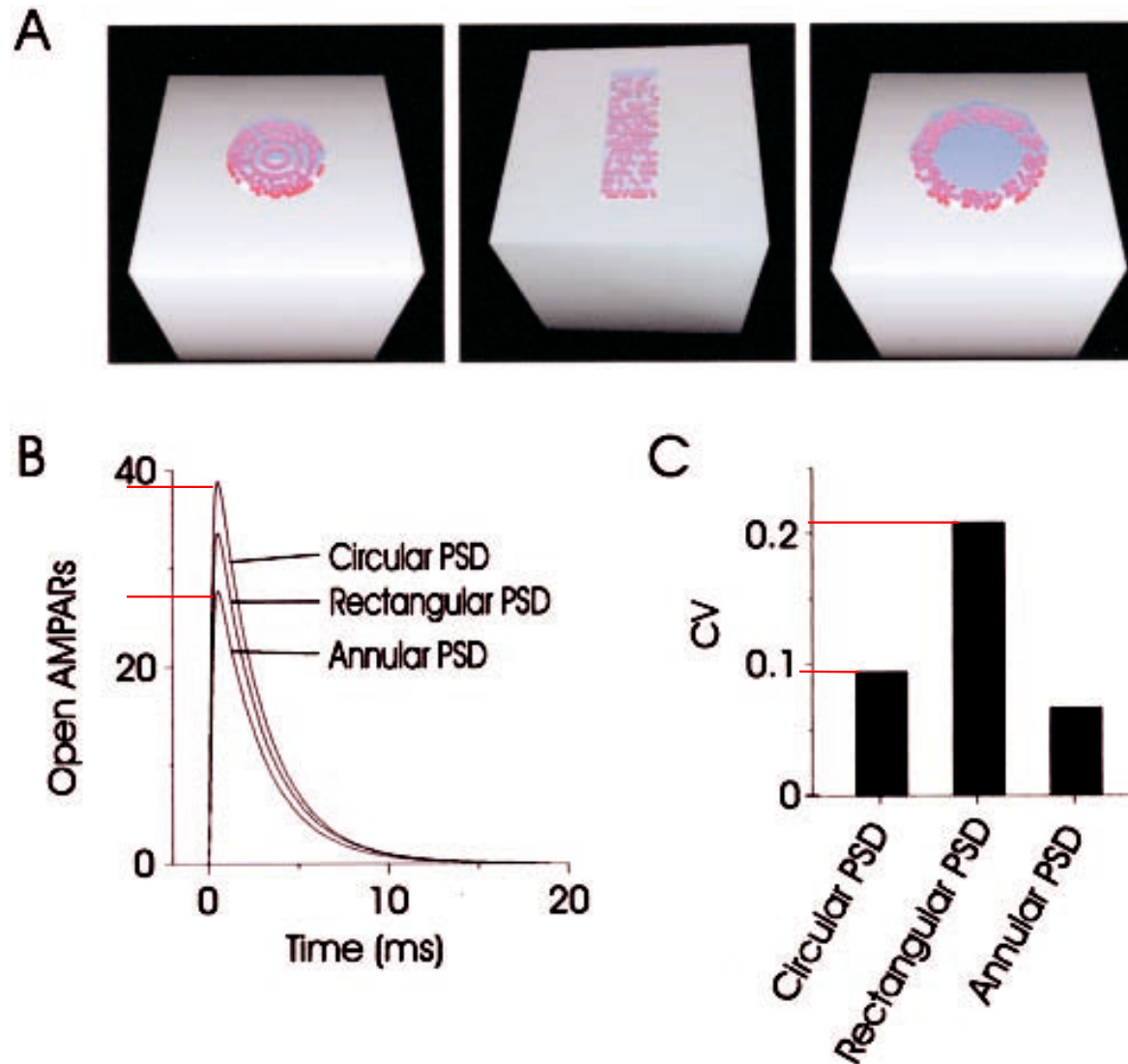
- Single-particle based
 - MCell: individual small molecules, ray-tracing. Immobile reactive surfaces. no interactions between mobile molecules



- Smoldyn: individual small molecules, reactions between them
- Meredys: Everything plus topology of molecules

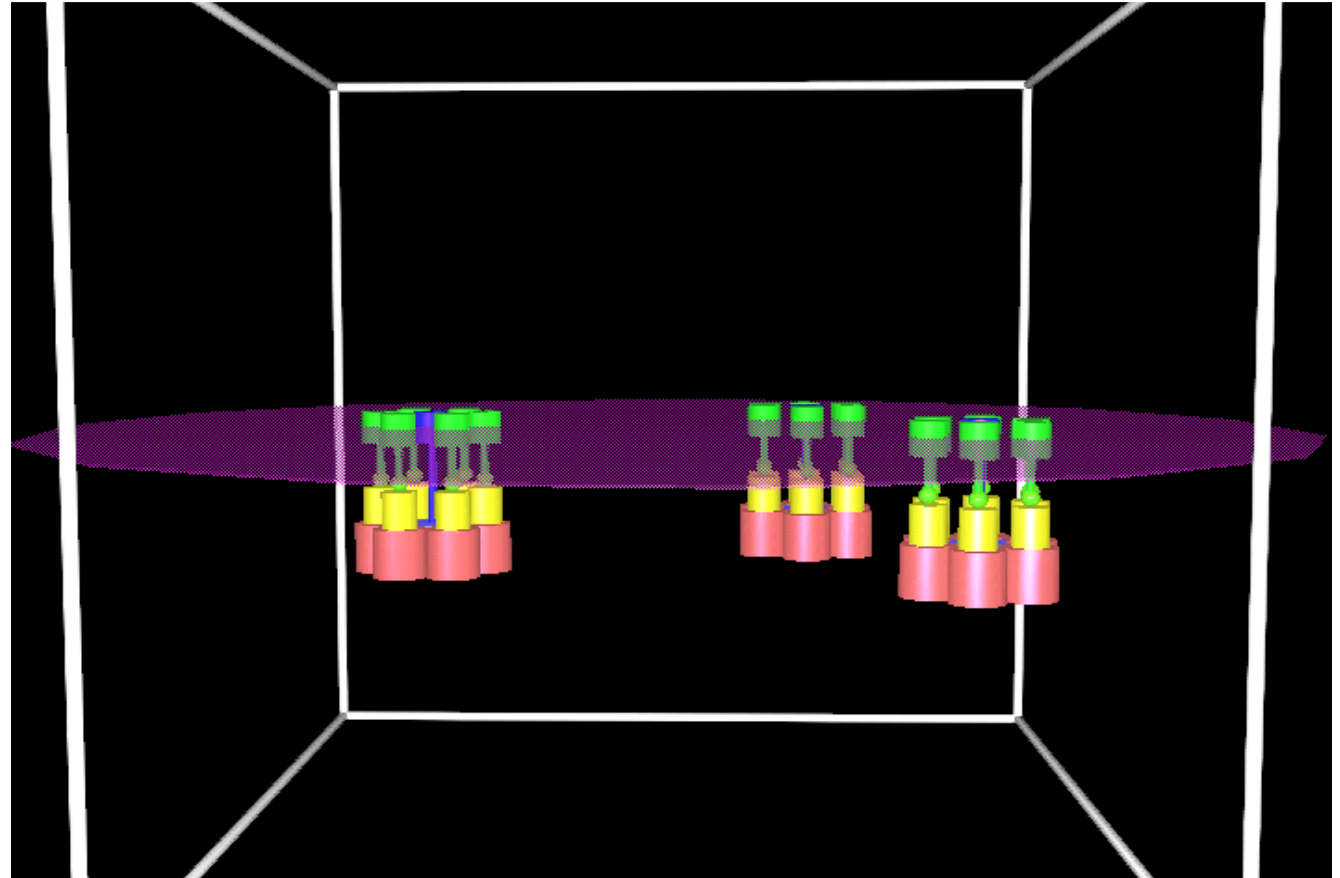
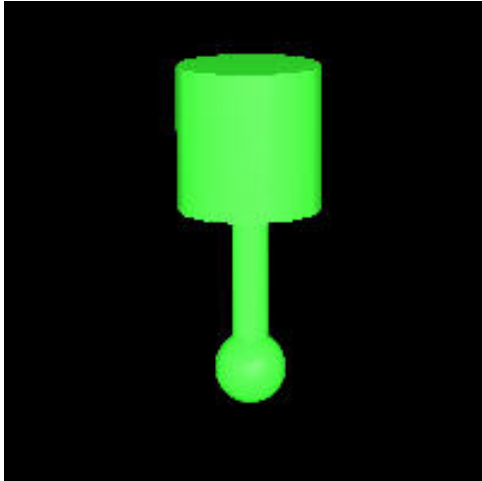
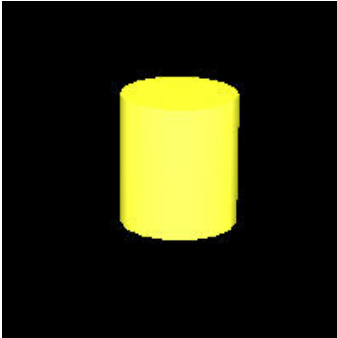


The position of receptors affects the signal



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





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.



- 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

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

- Translational $\Delta(x, y, z) = \sqrt{2D_T t} \times \text{gaussRand}$
- Rotational $\Delta\theta = \frac{\sqrt{2D_R t}}{r} \times \text{gaussRand}$

- Two types of diffusion equations:
 - unrestricted brownian motion – Low Trans/Rot
 - intra-membrane diffusion (Saffman and Delbrück 1975) – High Trans/Rot



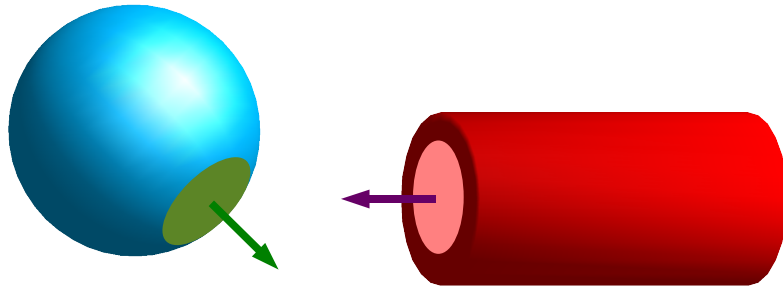
- Unrestricted brownian motion – Low Translation/Rotational

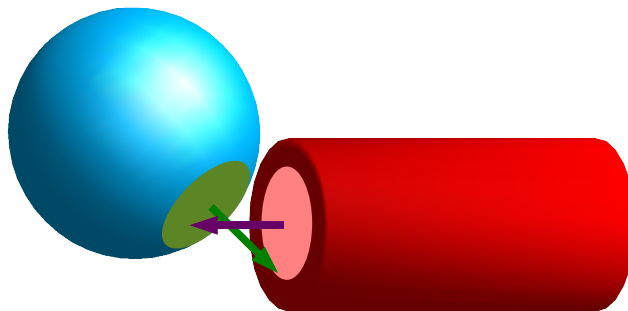
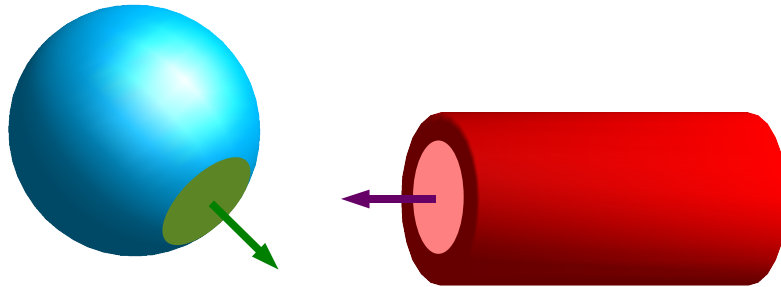
$$b_T = \frac{1}{6\pi\mu r} \quad b_R = \frac{1}{8\pi\mu r^3} \quad \frac{b_T}{b_R} = \frac{4}{3}r^2$$

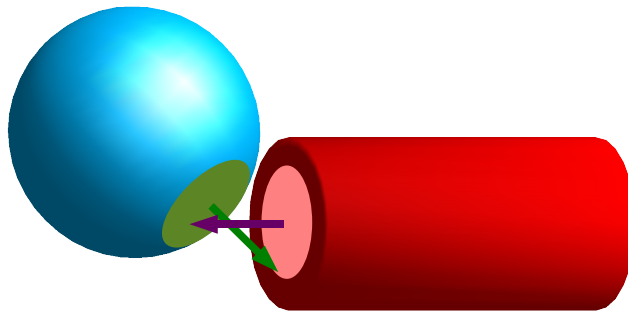
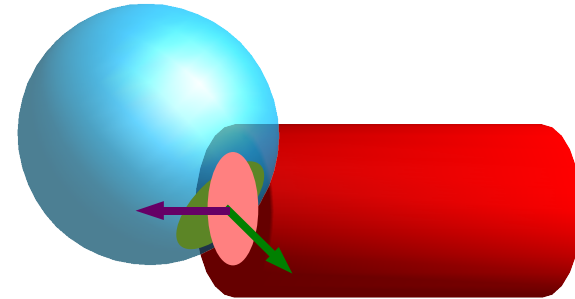
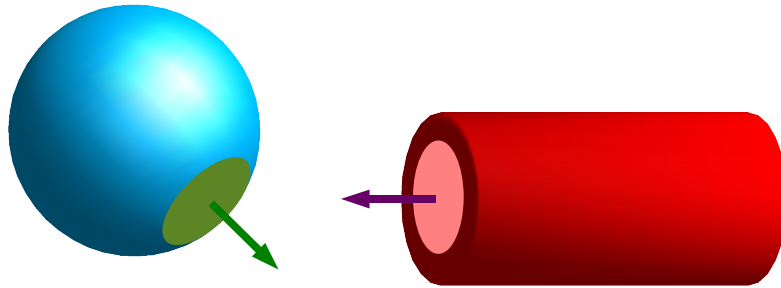
- Intra-membrane diffusion (Saffman and Delbrück 1975)
High Translational/Rotational

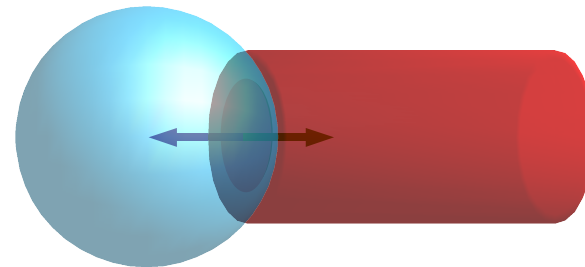
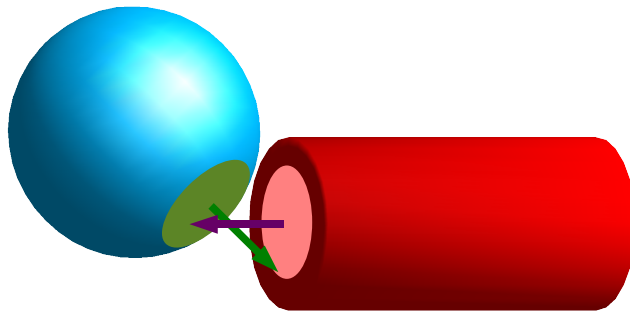
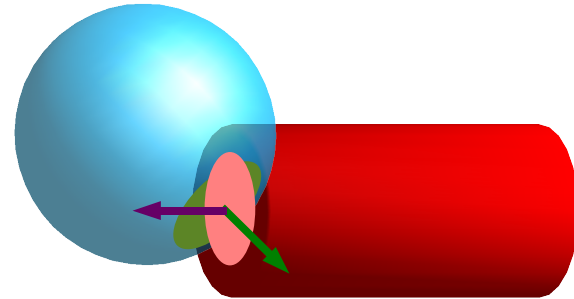
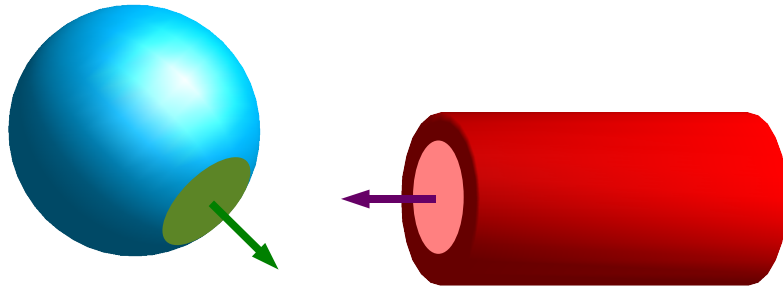
$$b_T = \frac{1}{4\pi\mu h} \left(\log\left(\frac{\mu h}{\mu' r}\right) - \gamma \right) \quad b_R = \frac{1}{4\pi\mu r^2 h} \quad \frac{b_T}{b_R} = \left(\log\left(\frac{\mu h}{\mu' r}\right) - \gamma \right) \times r^2$$

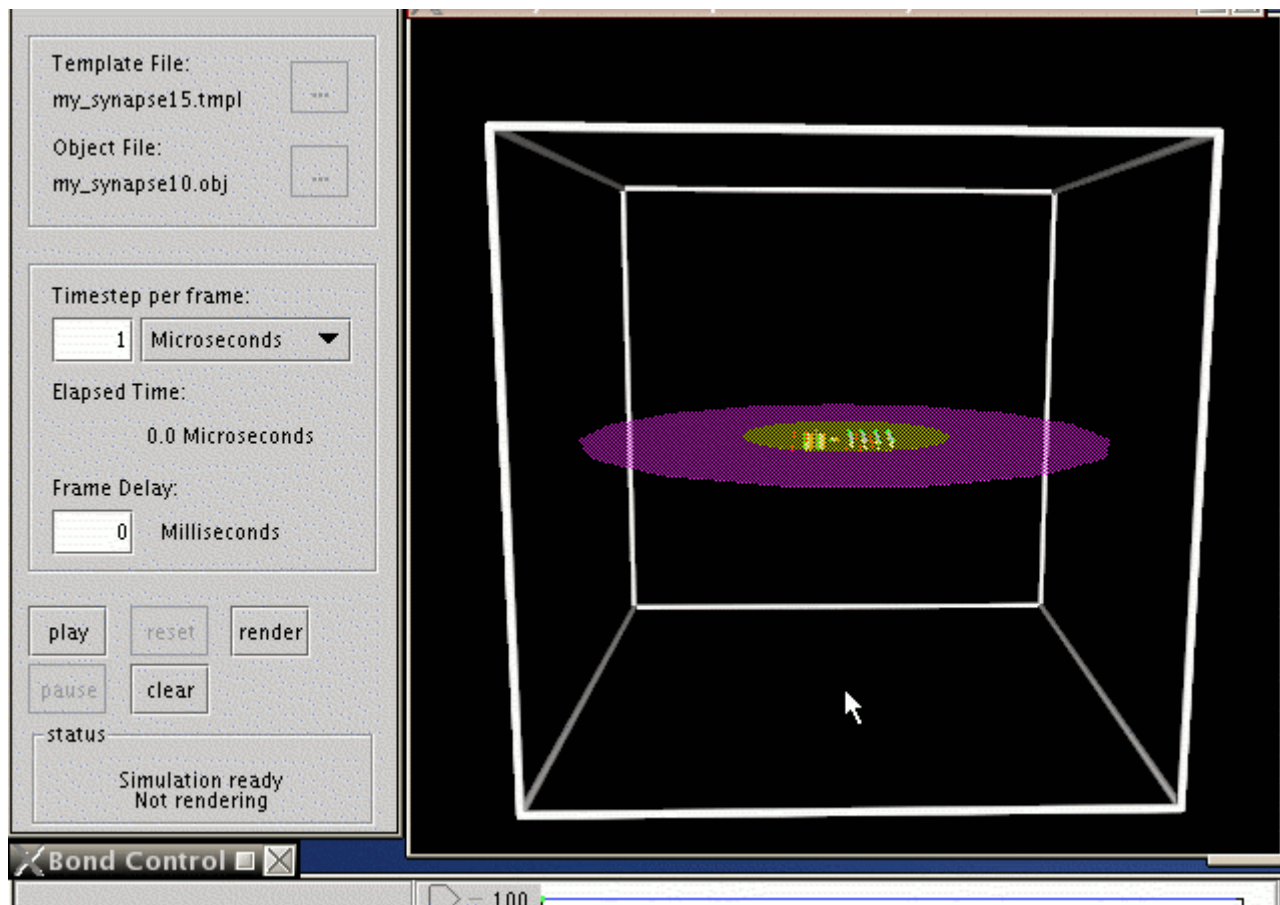




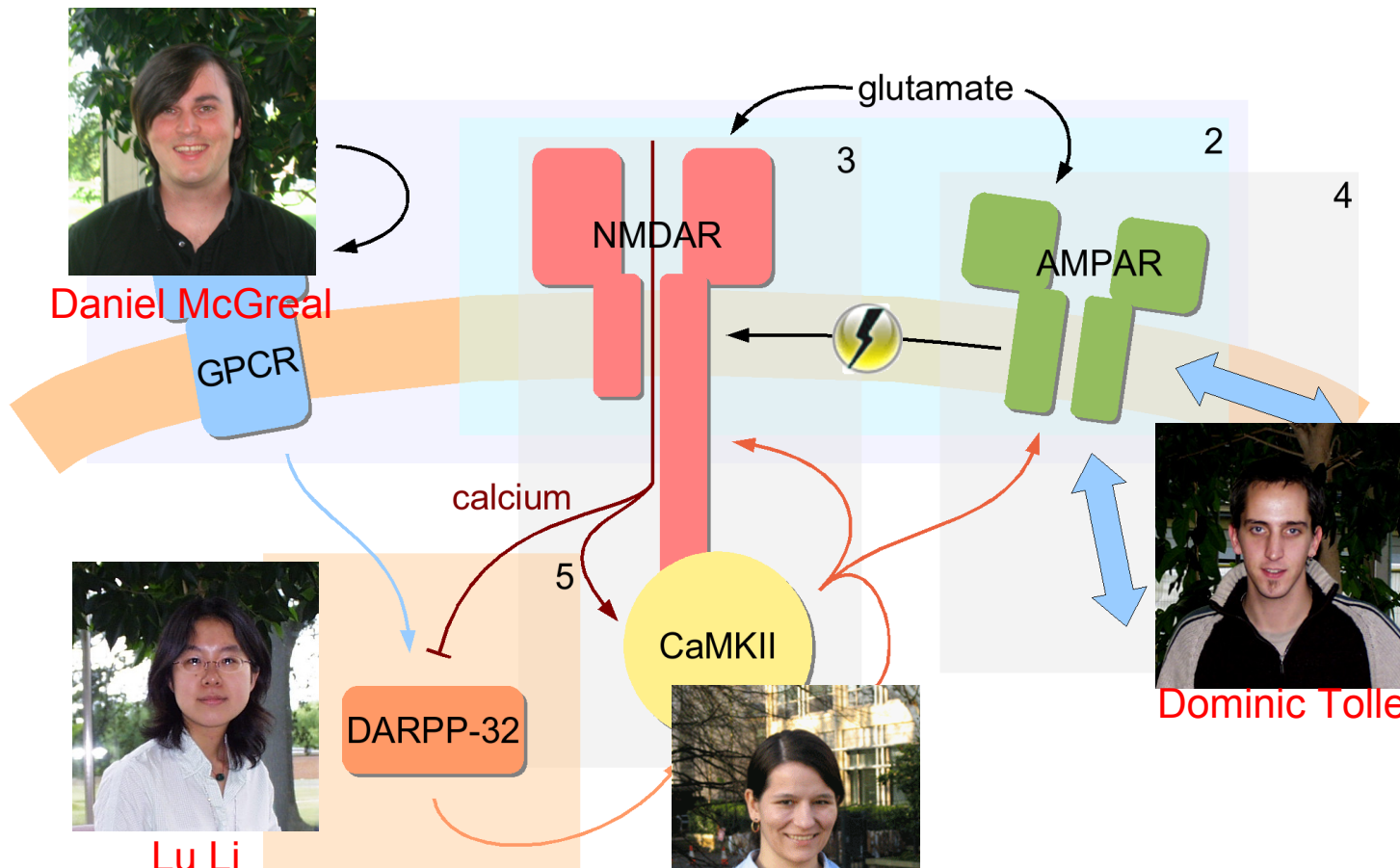












Daniel McGreal



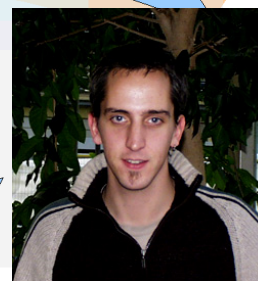
Lu Li



Melanie Stefan



Stuart Edelstein



Dominic Tolle

Melanie Courtot



Nicolas Rodriguez



Chen Li



Camille Laibe



Enuo He



- E-cell

Kouichi Takahashi
Kazunari Kaizu
Gabor Bereczki

- COPASI

Stefan Hoops
Sven Sahle
Ralf Gauges

- SBMLodeSolver

Rainer Machne

- XPP-aut

Bard Ermentrout

- Experimental Collaborators
(INSERM U536, Paris)

Jean-Antoine Girault

Denis Herve



British outstation of the European Molecular Biology Laboratory

- Databases

- Sequences, structures



- Transcriptomics, Proteomics pathways, models



- Controlled vocabularies and dictionaries



- Research groups

- Structural Genomics (Thornton)

- Molecular Evolution (Goldman)

- Text-Mining (Rebholz-Schumman)

- Computational Systems Biology (Le Novère)

- Statistical array analysis (Huber)

- Genomic analysis of regulatory systems (Luscombe)

- Systems Biology of ES cells (Bertone)

**Marie Curie Training site Fellowships: PhD 3-6 months. Fully funded.
Undergraduate trainees: 5-6 months.**