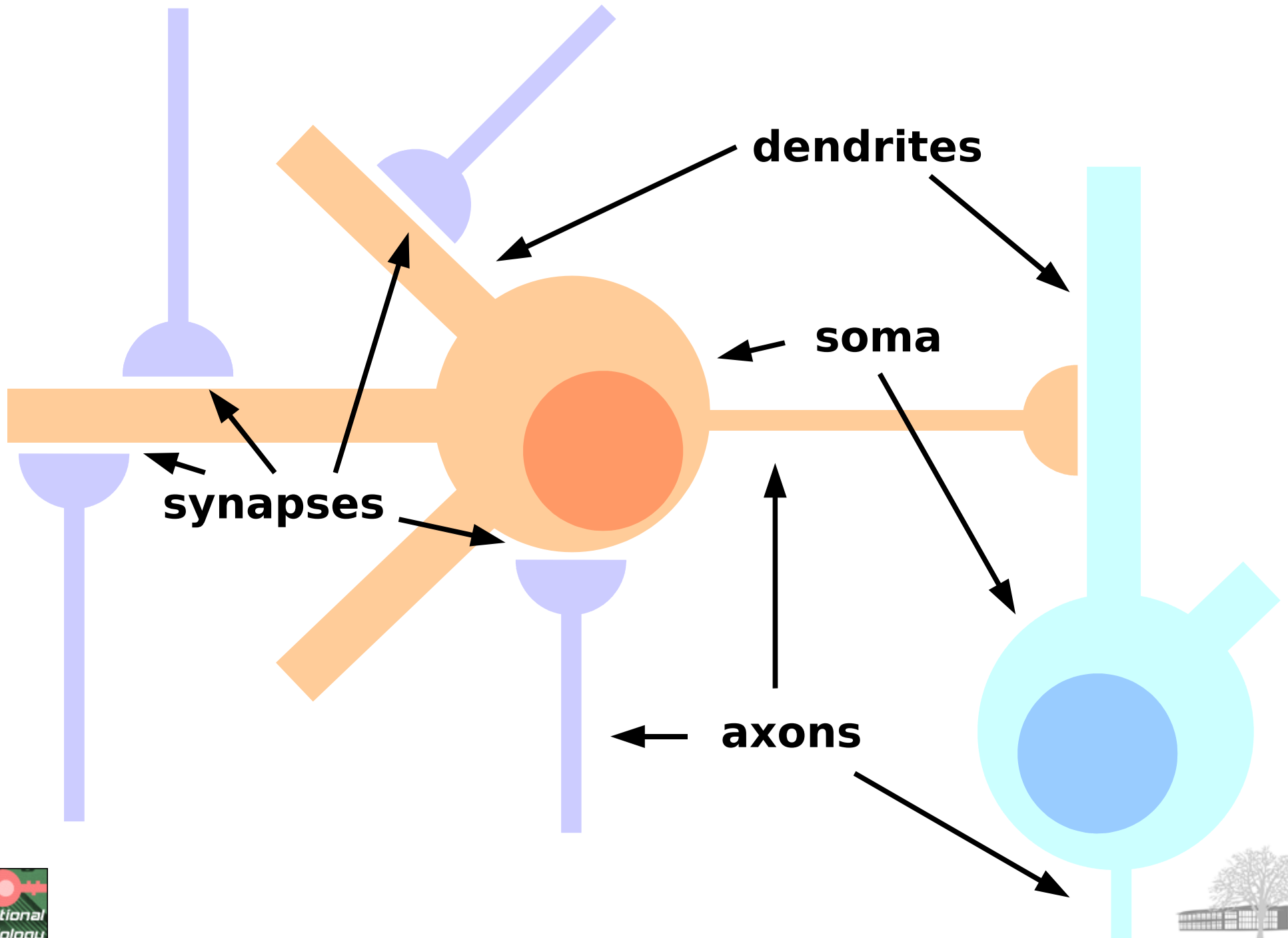
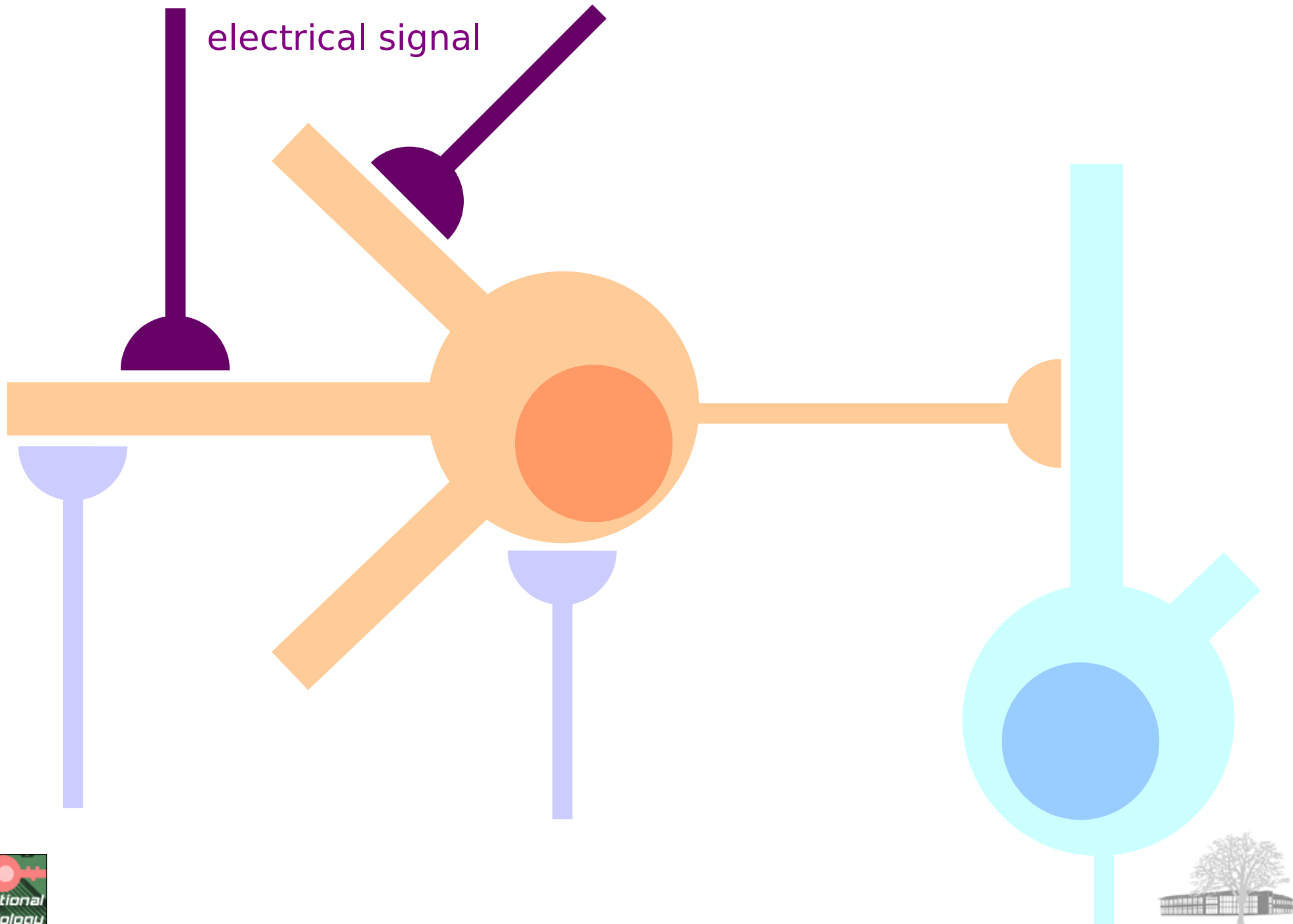
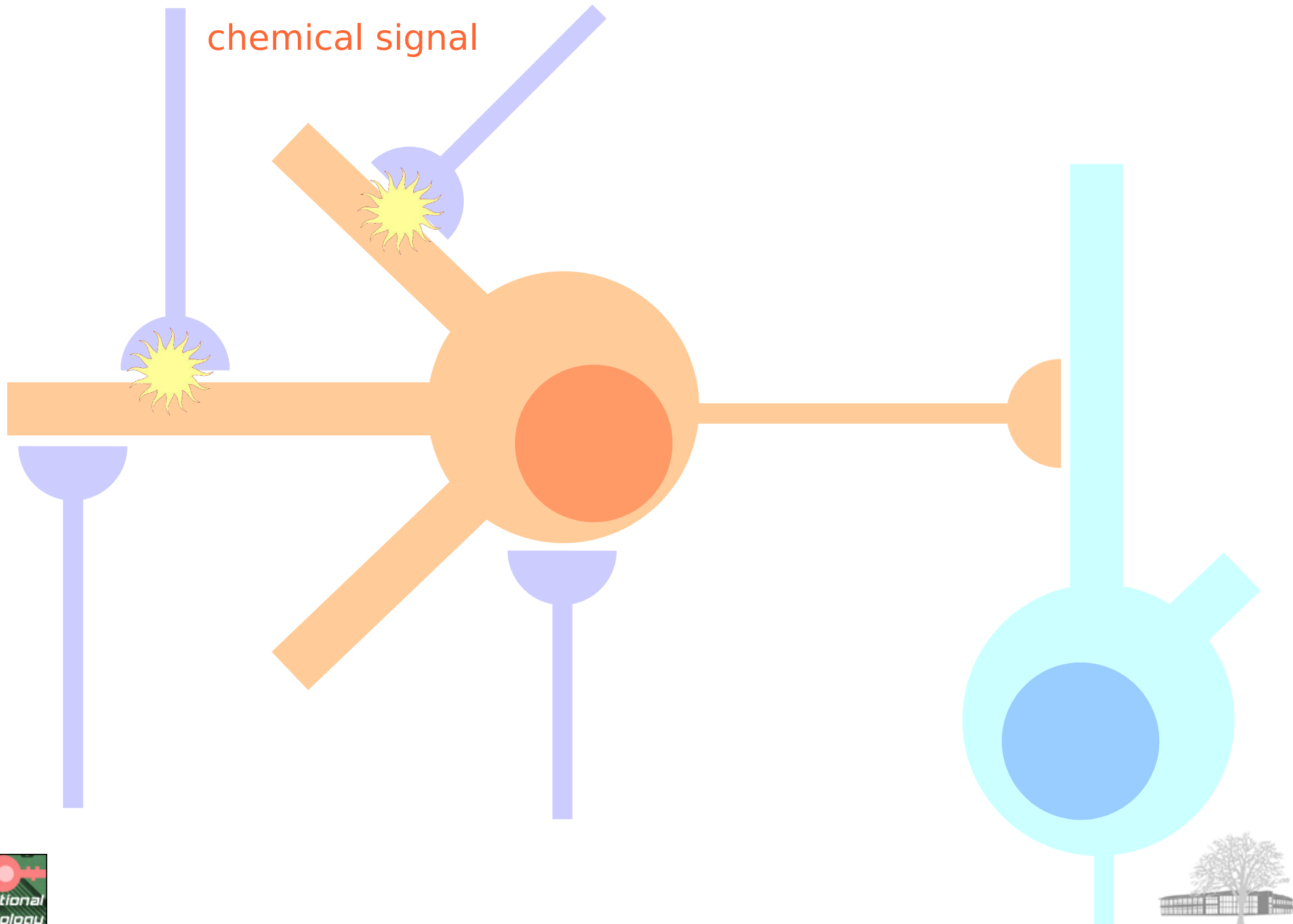


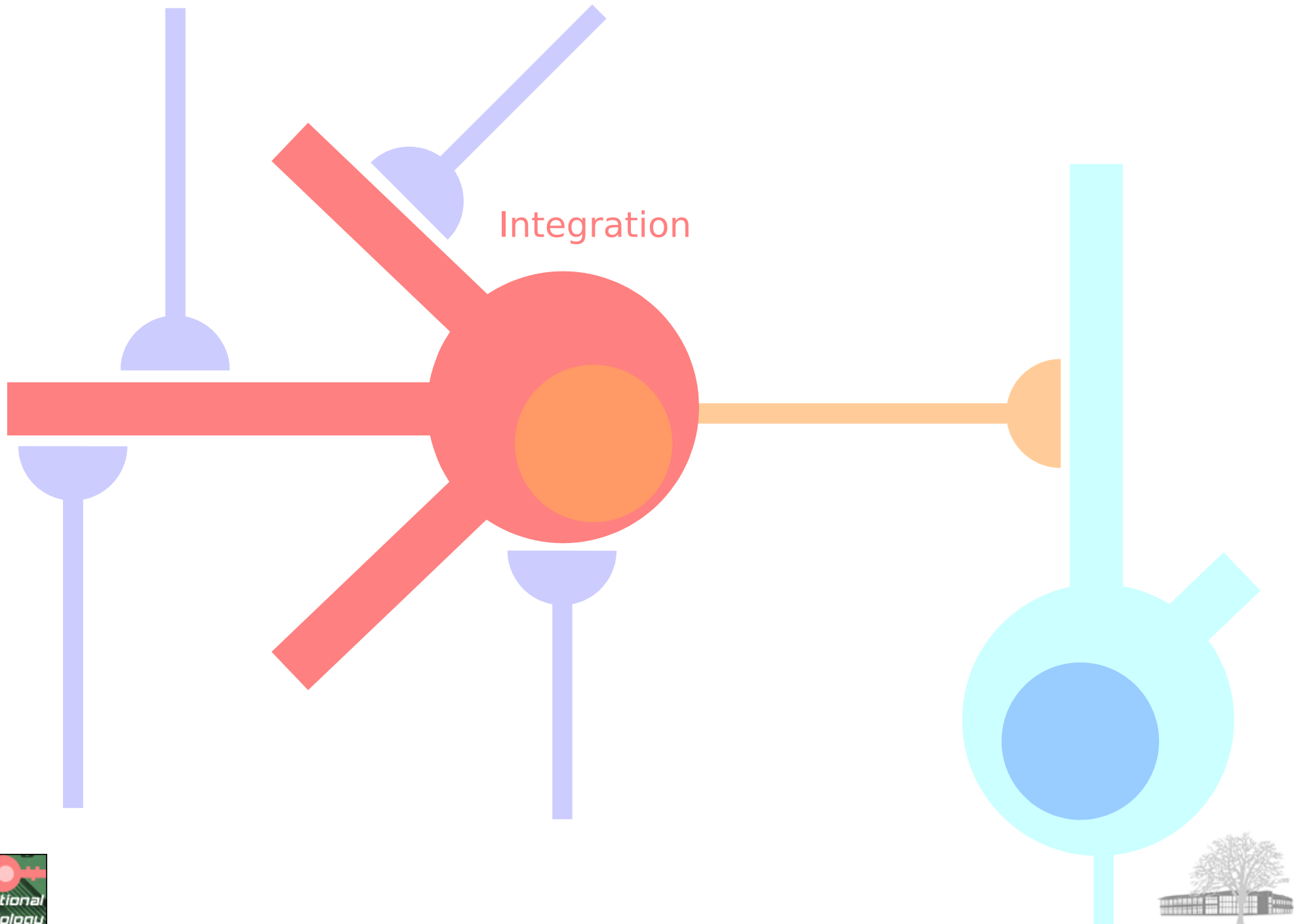
Simulation of neuronal signalling at the molecular and subcellular levels

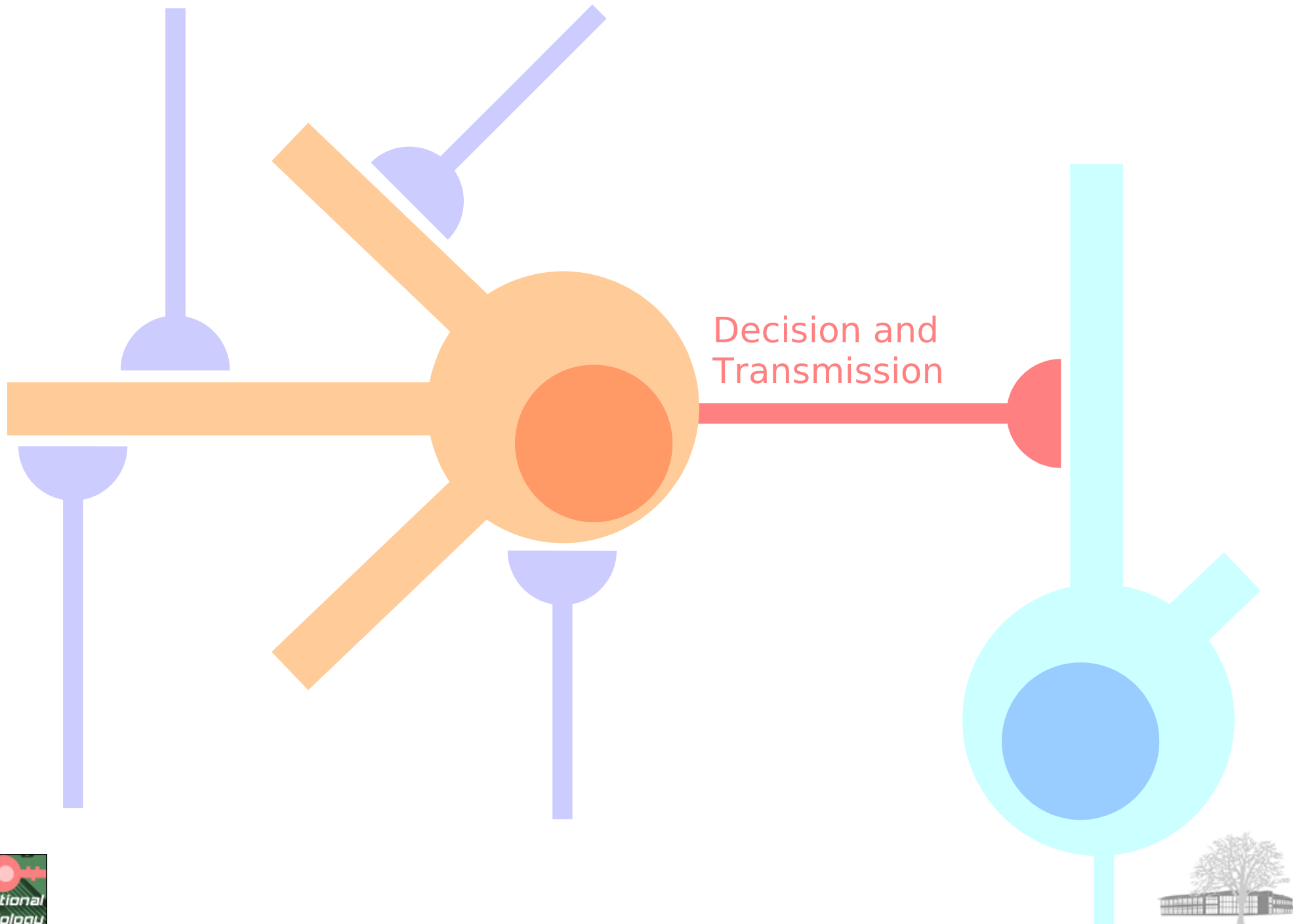
Nicolas Le Novère
Computational Neurobiology
EMBL-EBI



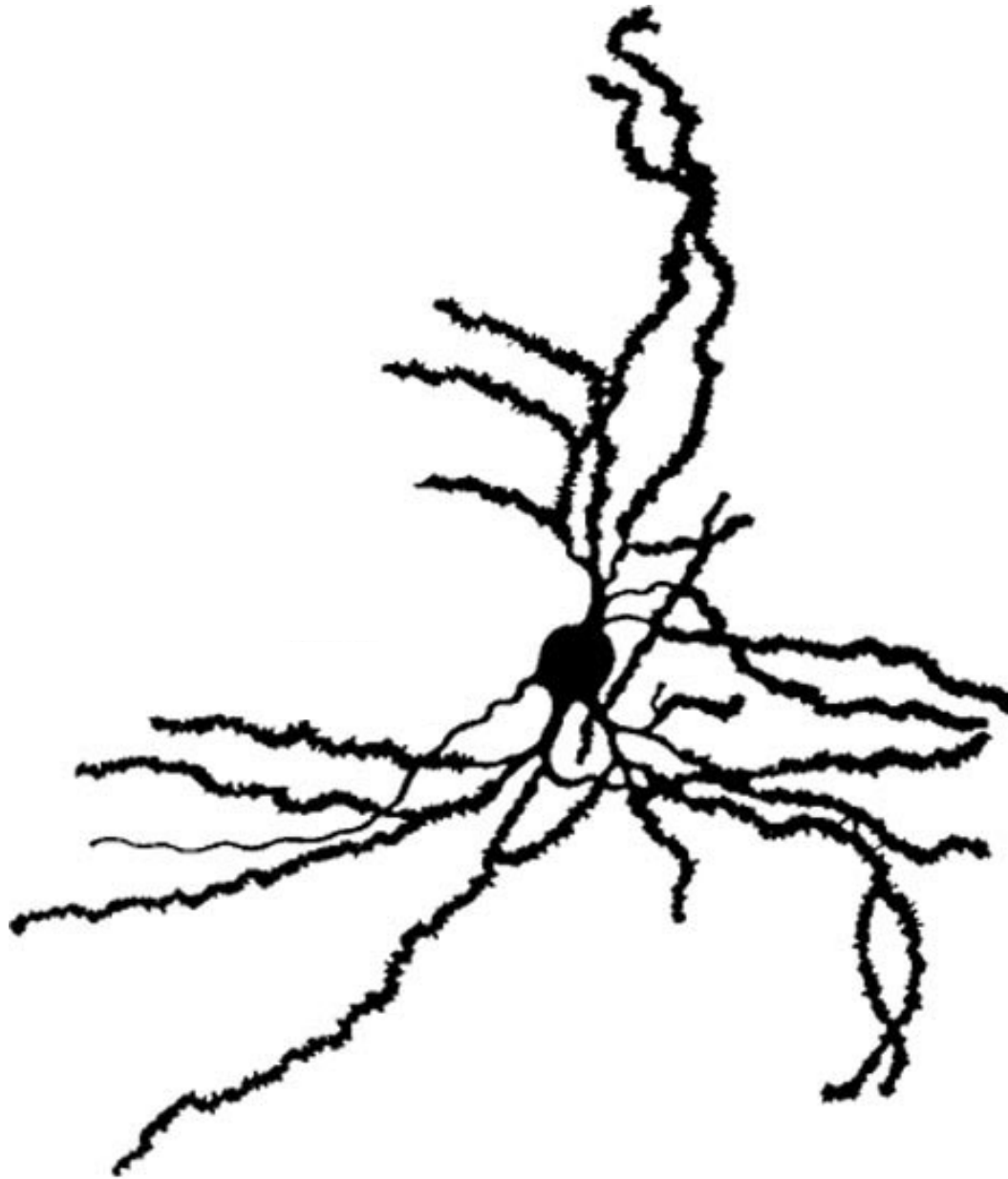


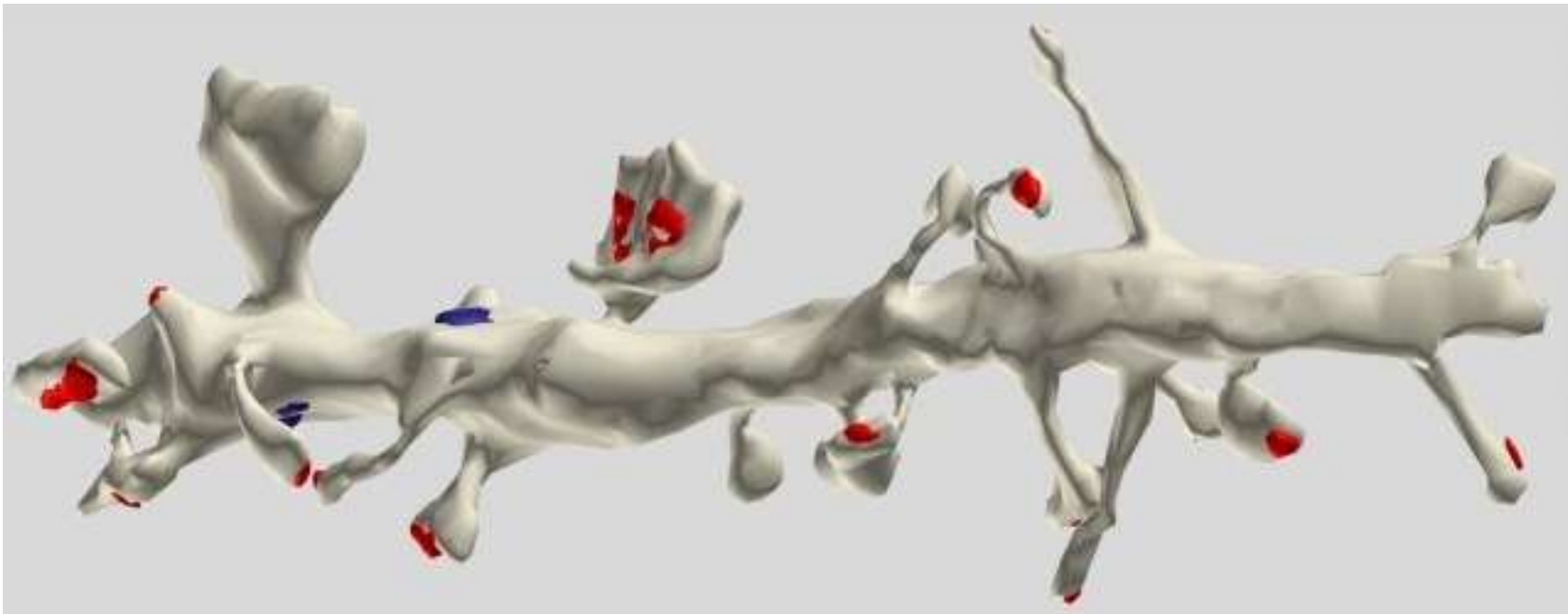


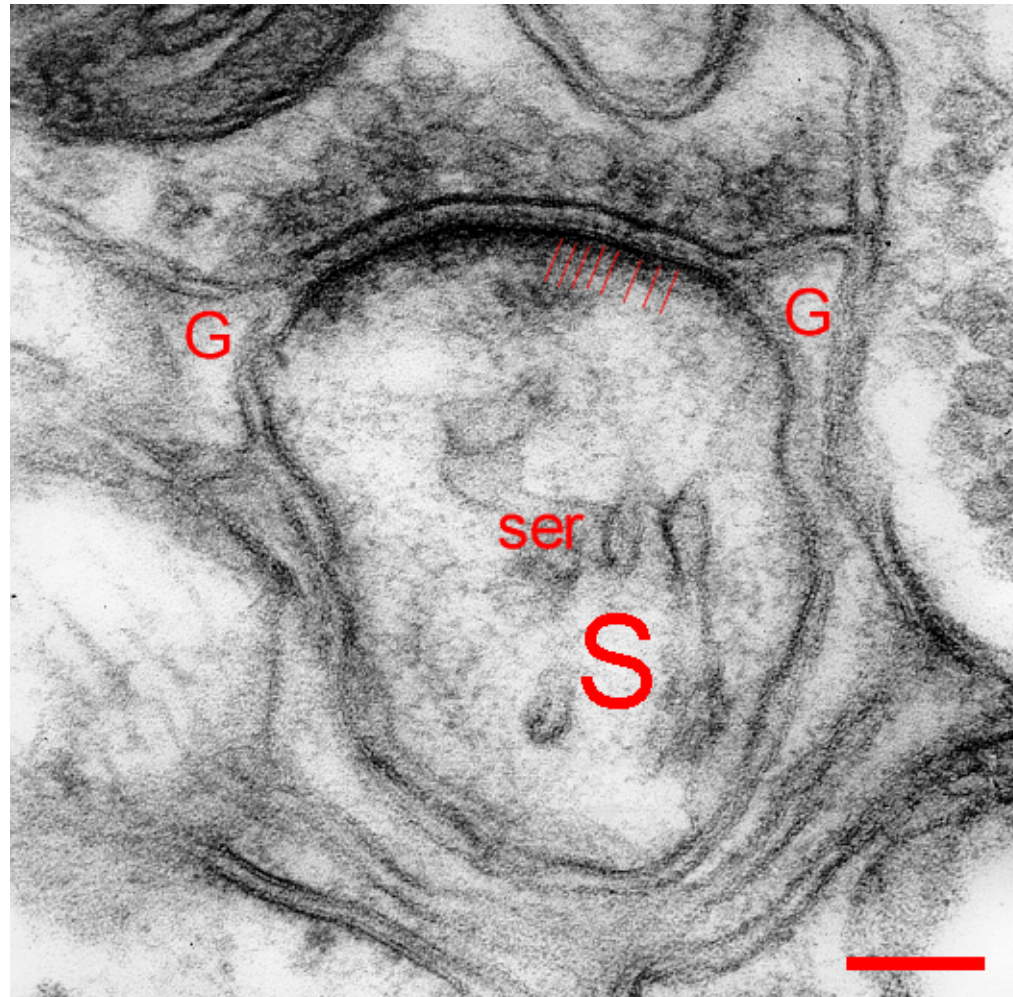


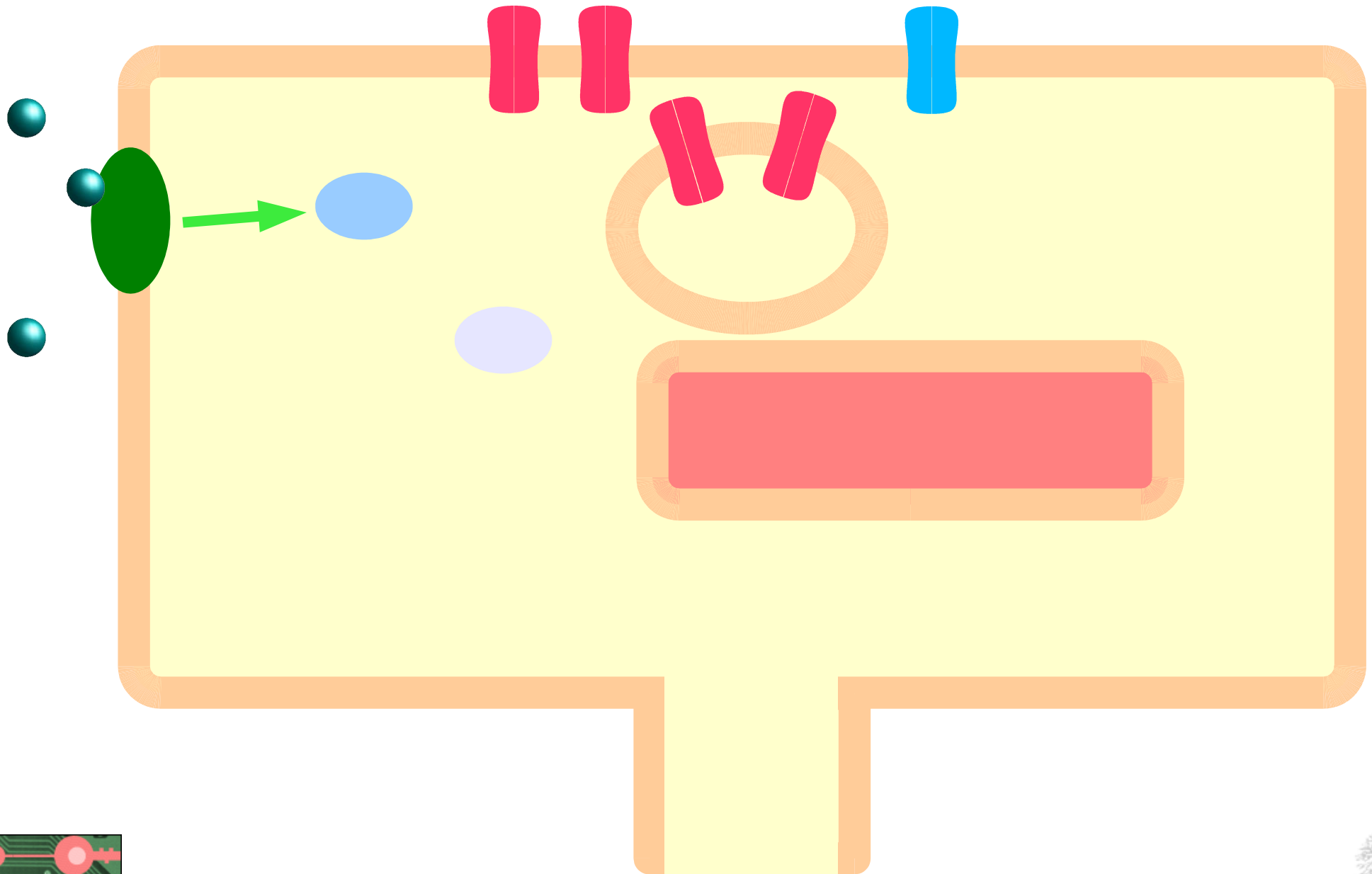


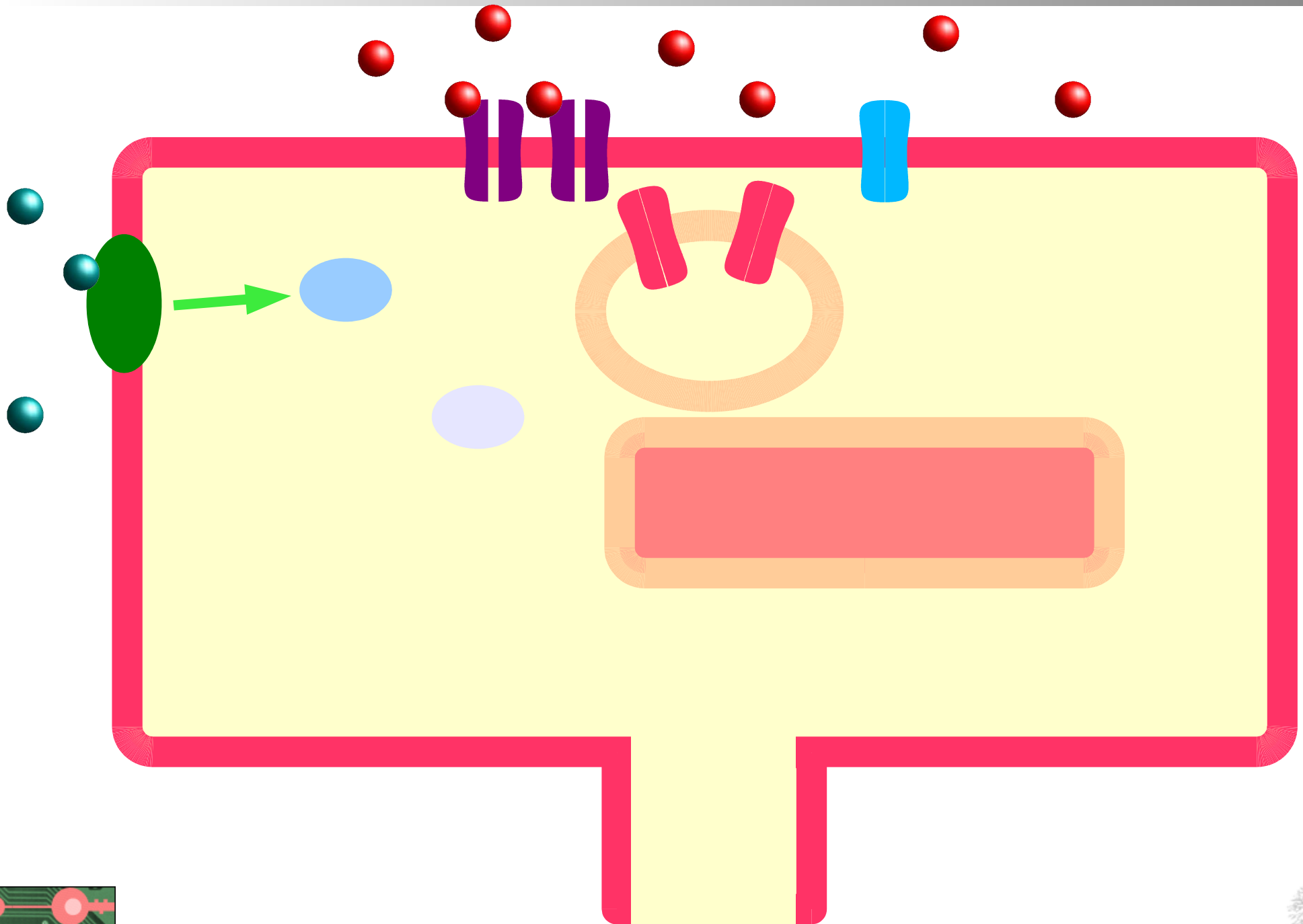
the Medium Spiny Neuron of the striatum

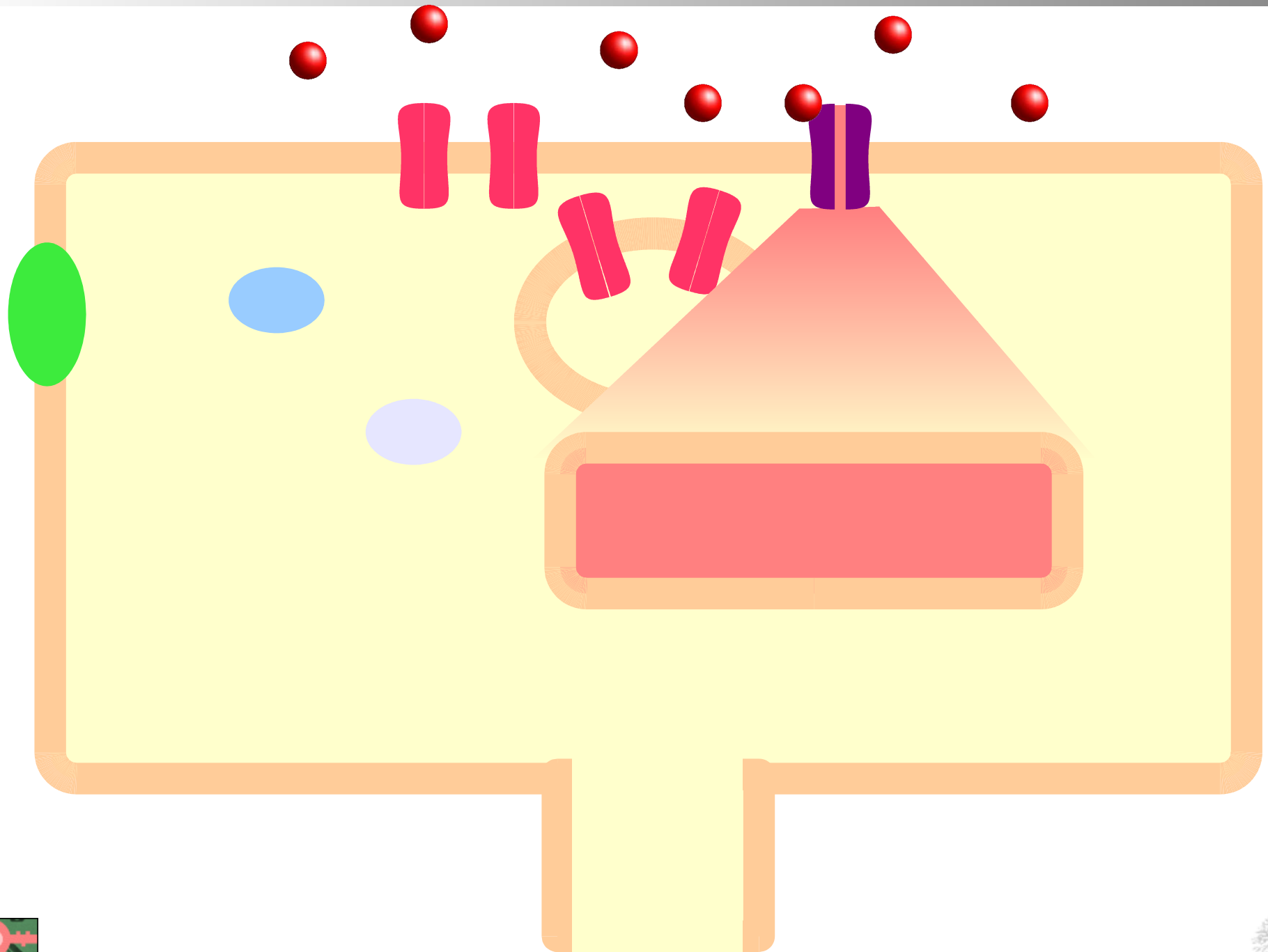


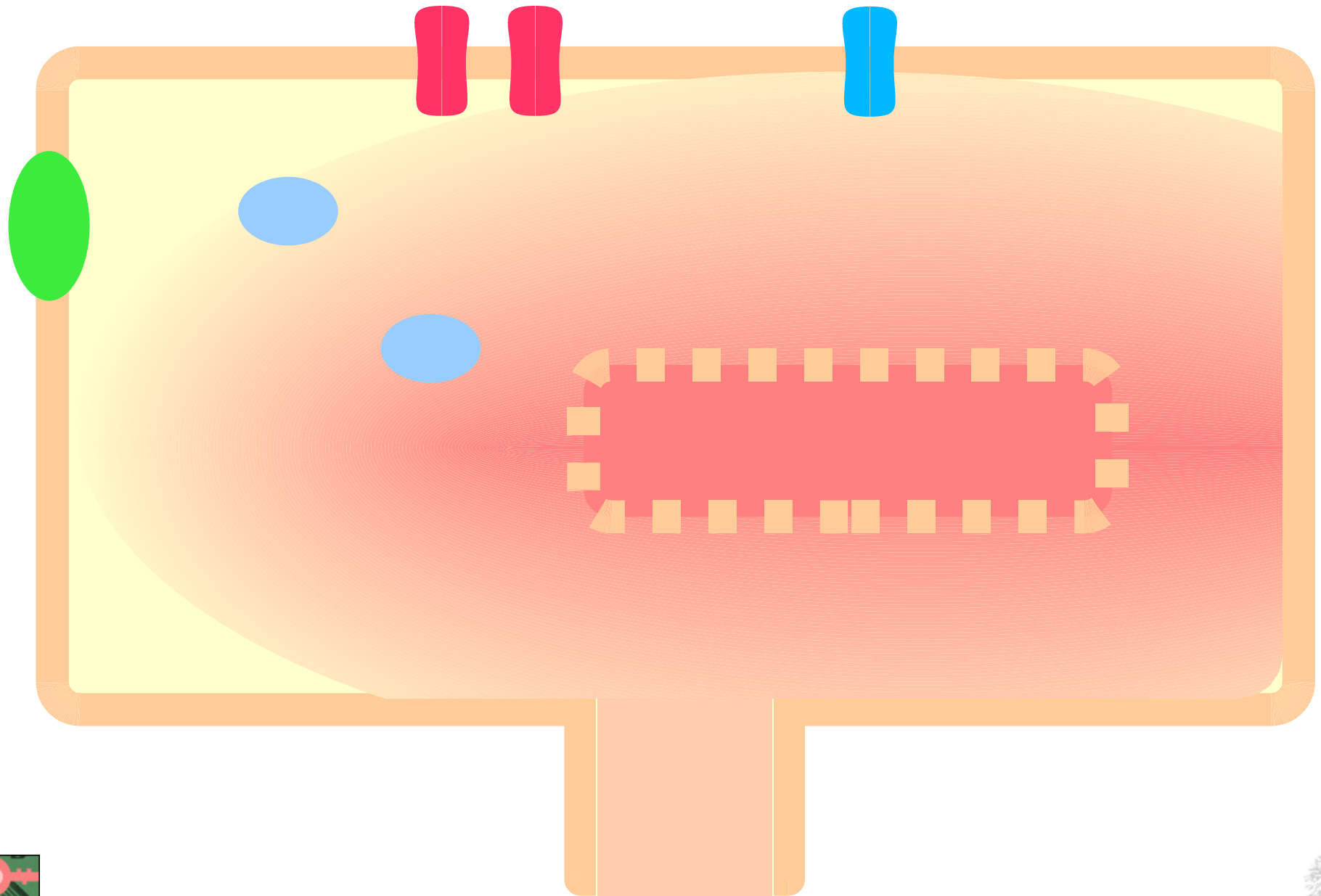


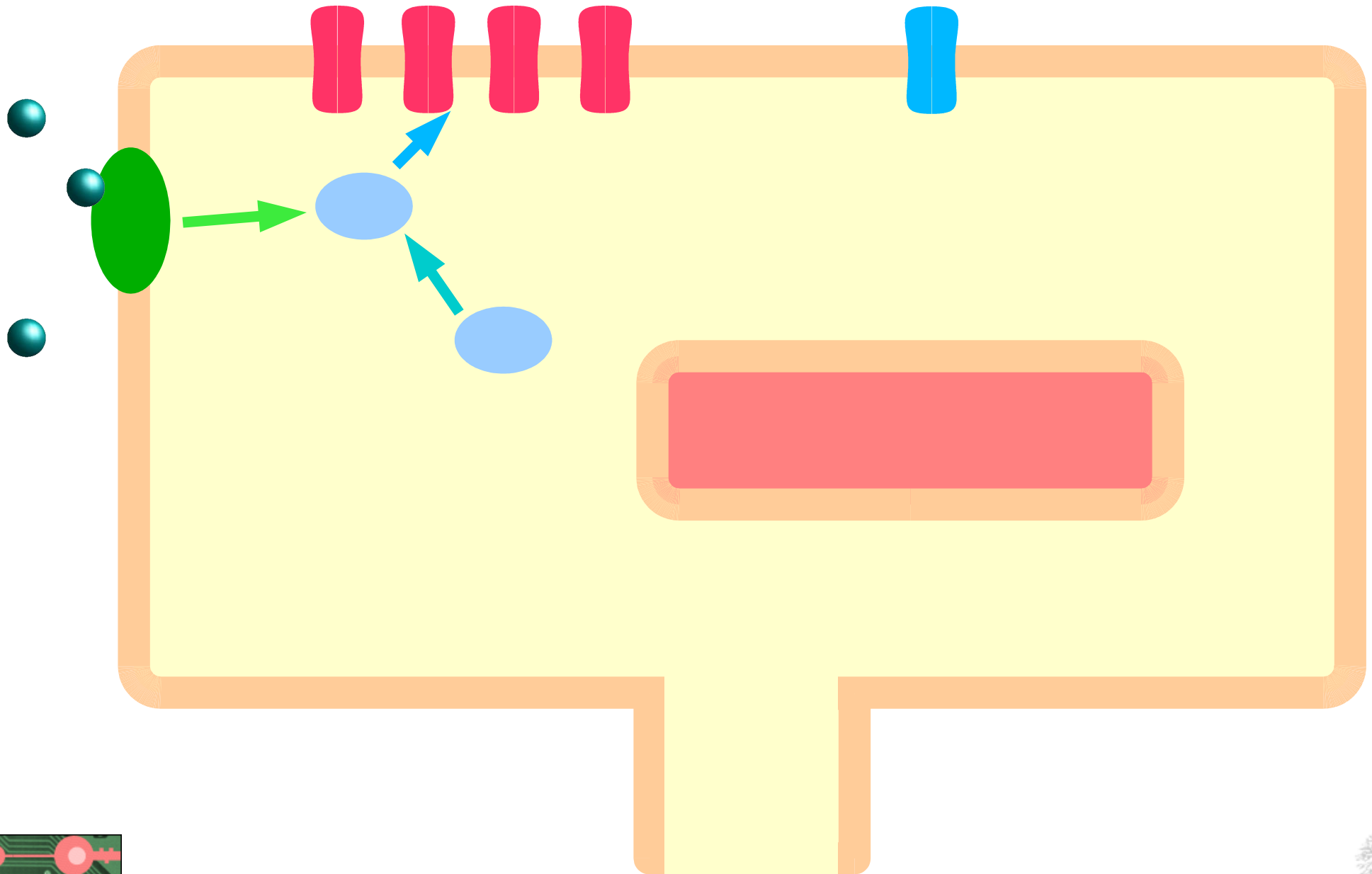






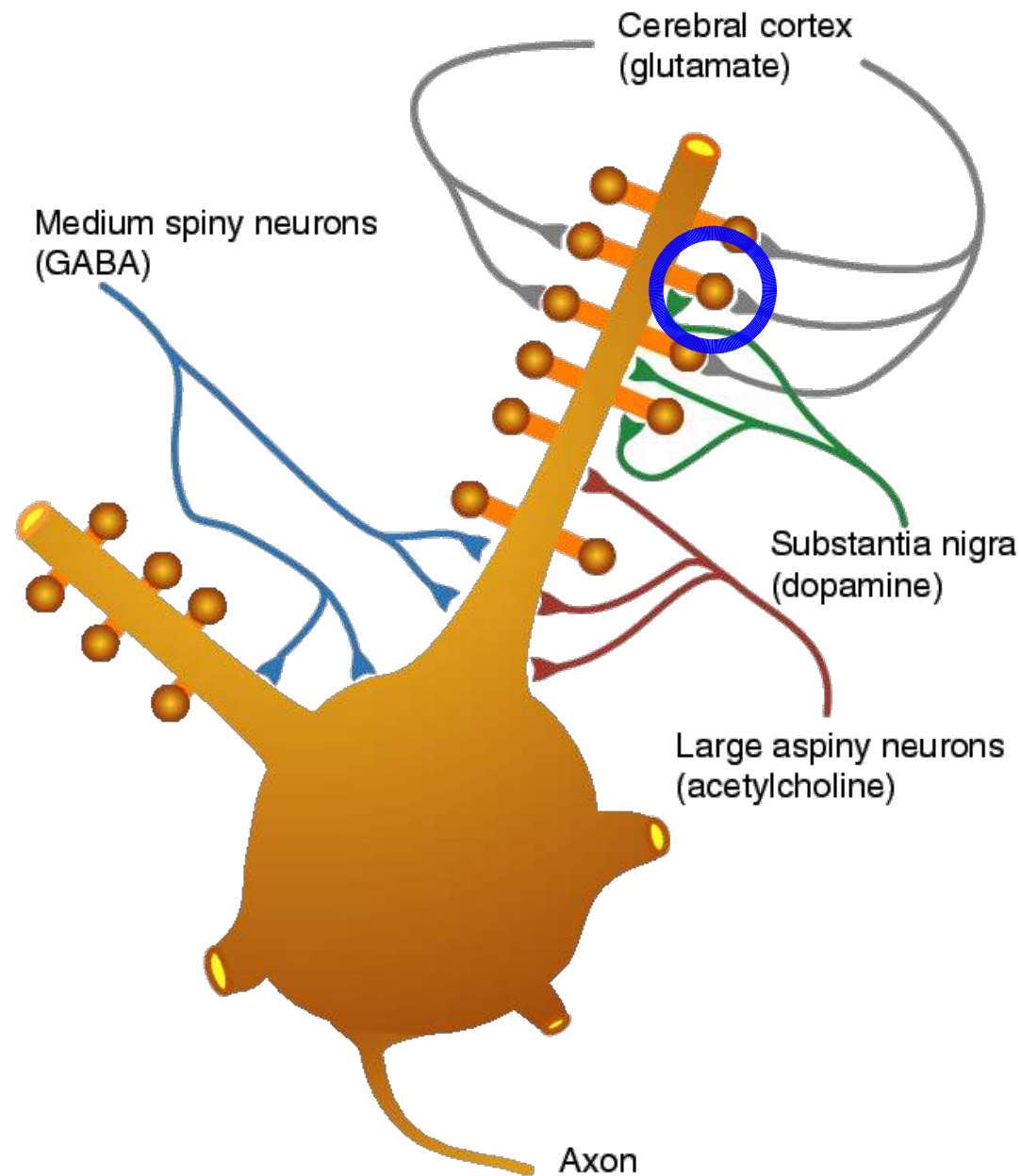




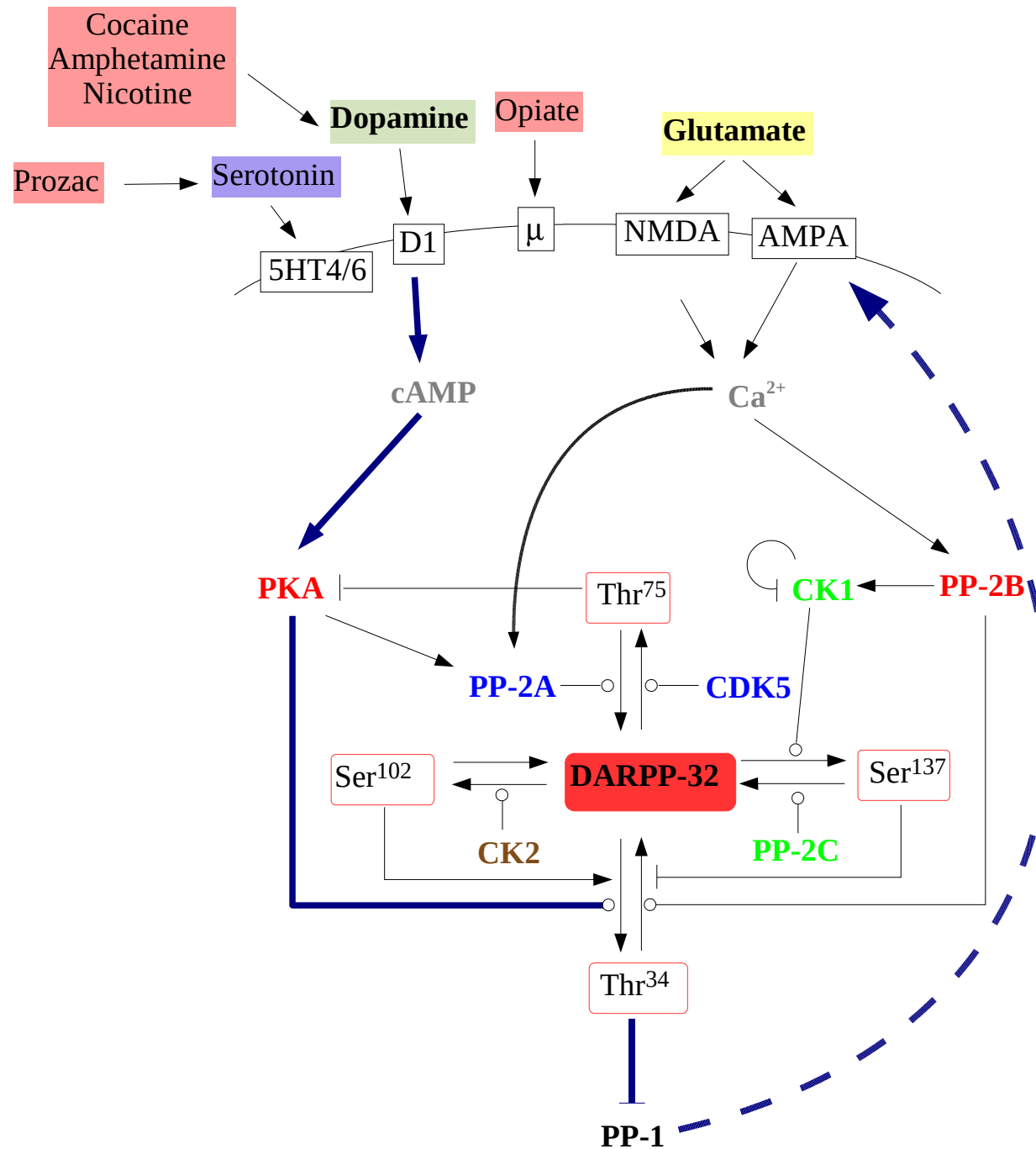


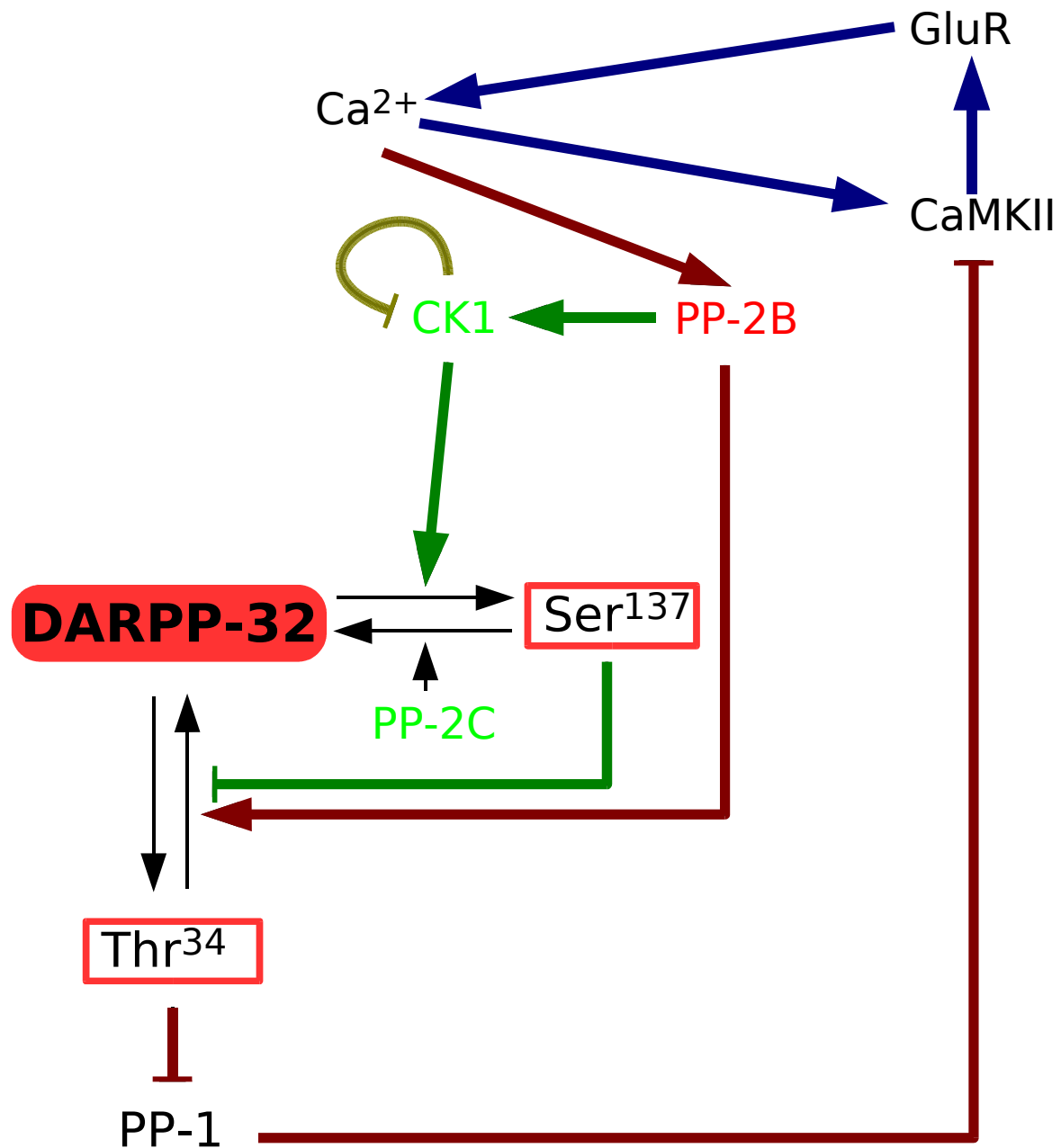
- Three types of information conveyed:
 - Propagation of electrical signals (leave the spine)
 - Diffusion of chemical signals (leave the spine)
 - Transitions between “states” (conformation, covalent modifications, density etc.)
- Diversity of modelling approaches:
 - electrical modelling
 - chemical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

- Three types of information conveyed:
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 - electrical modelling
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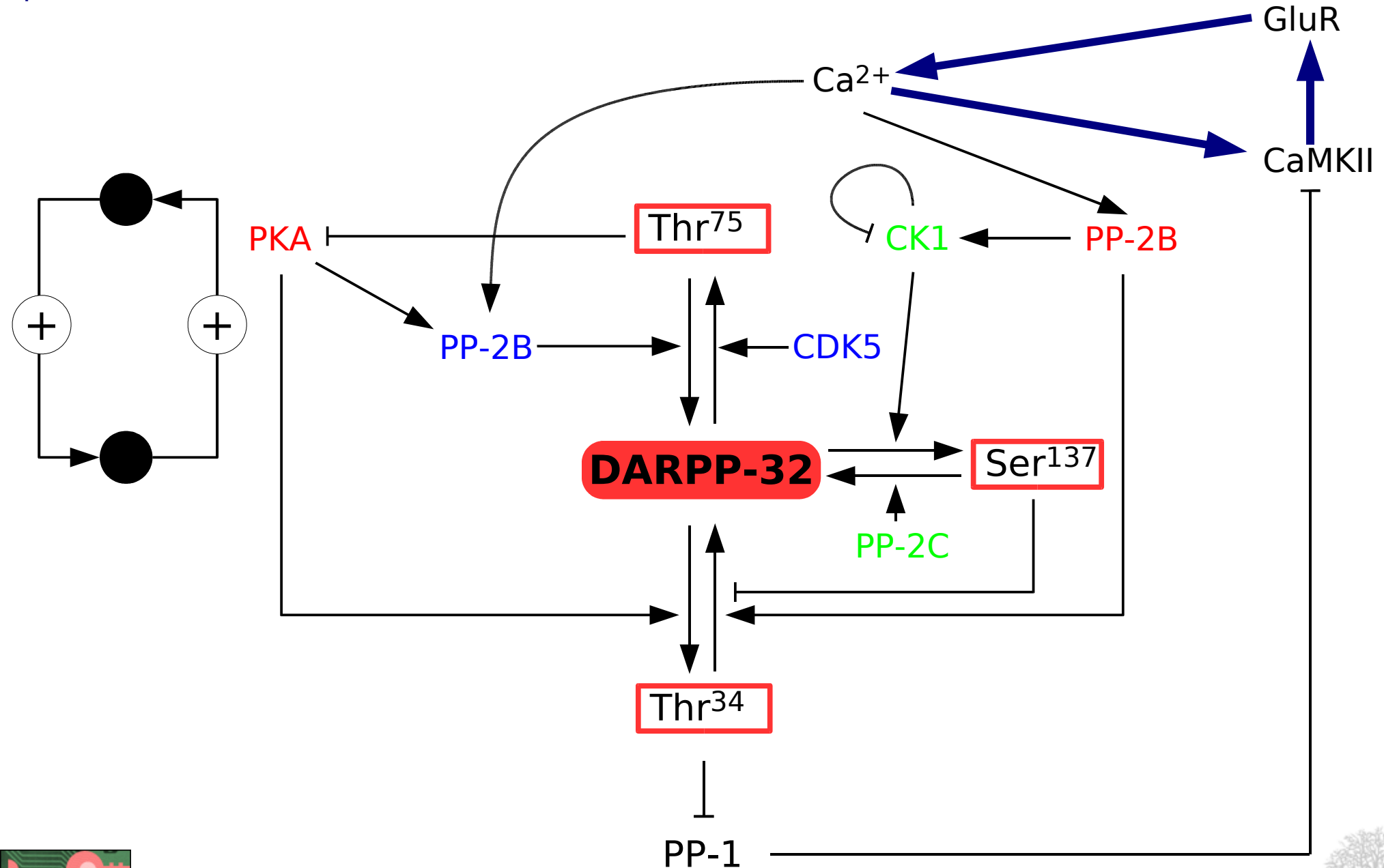


Biological model of DARPP-32 regulation

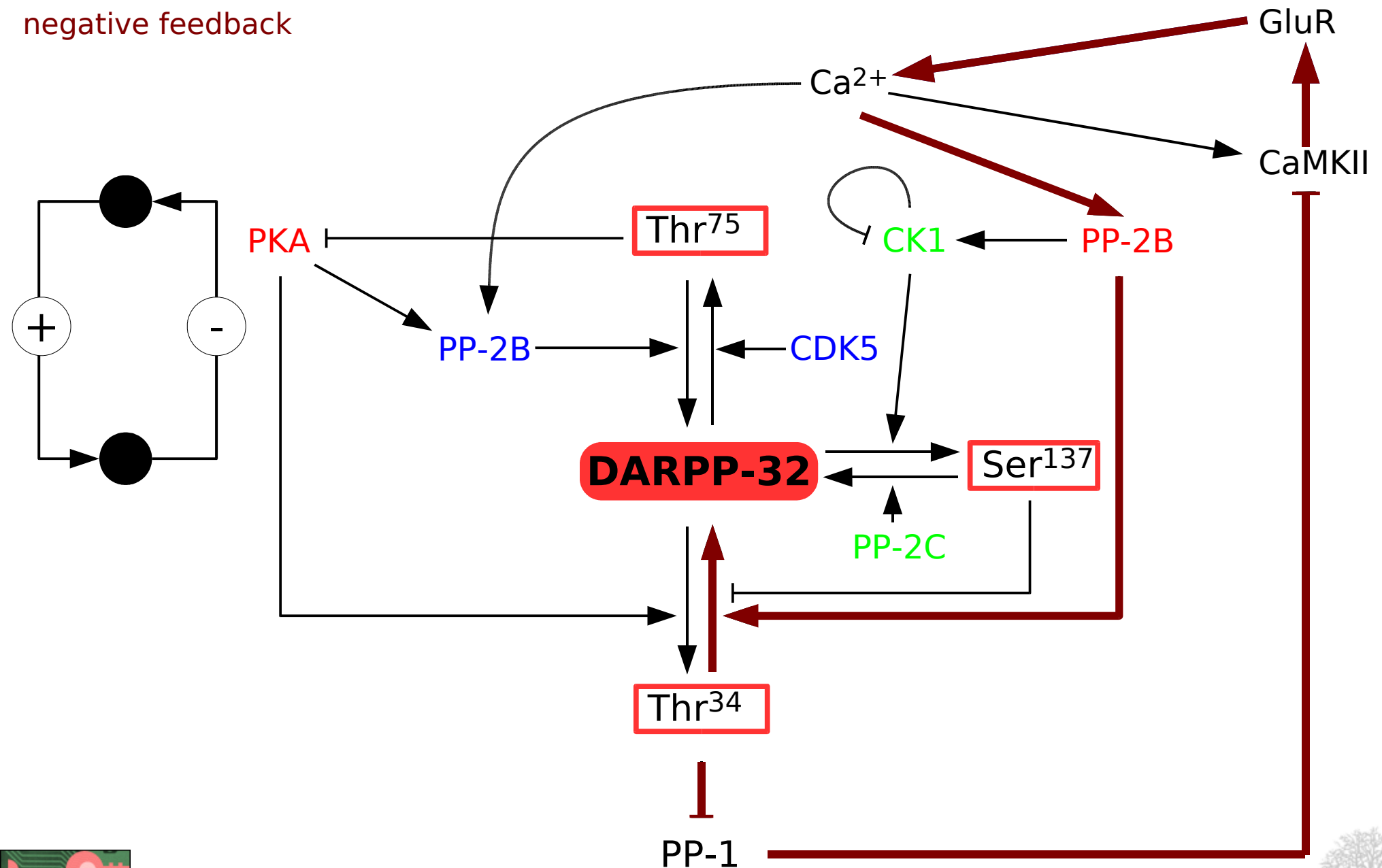




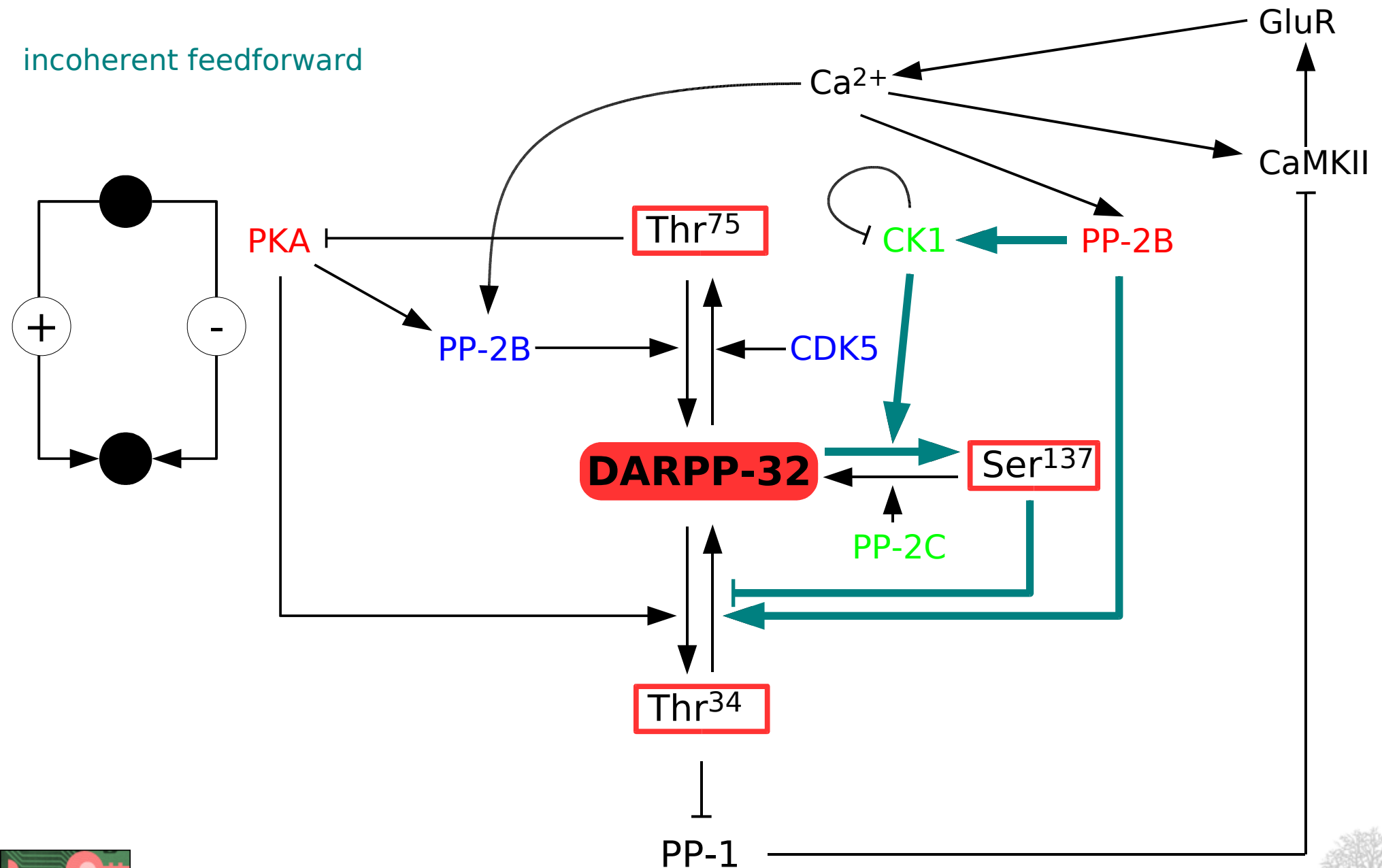
positive feedback



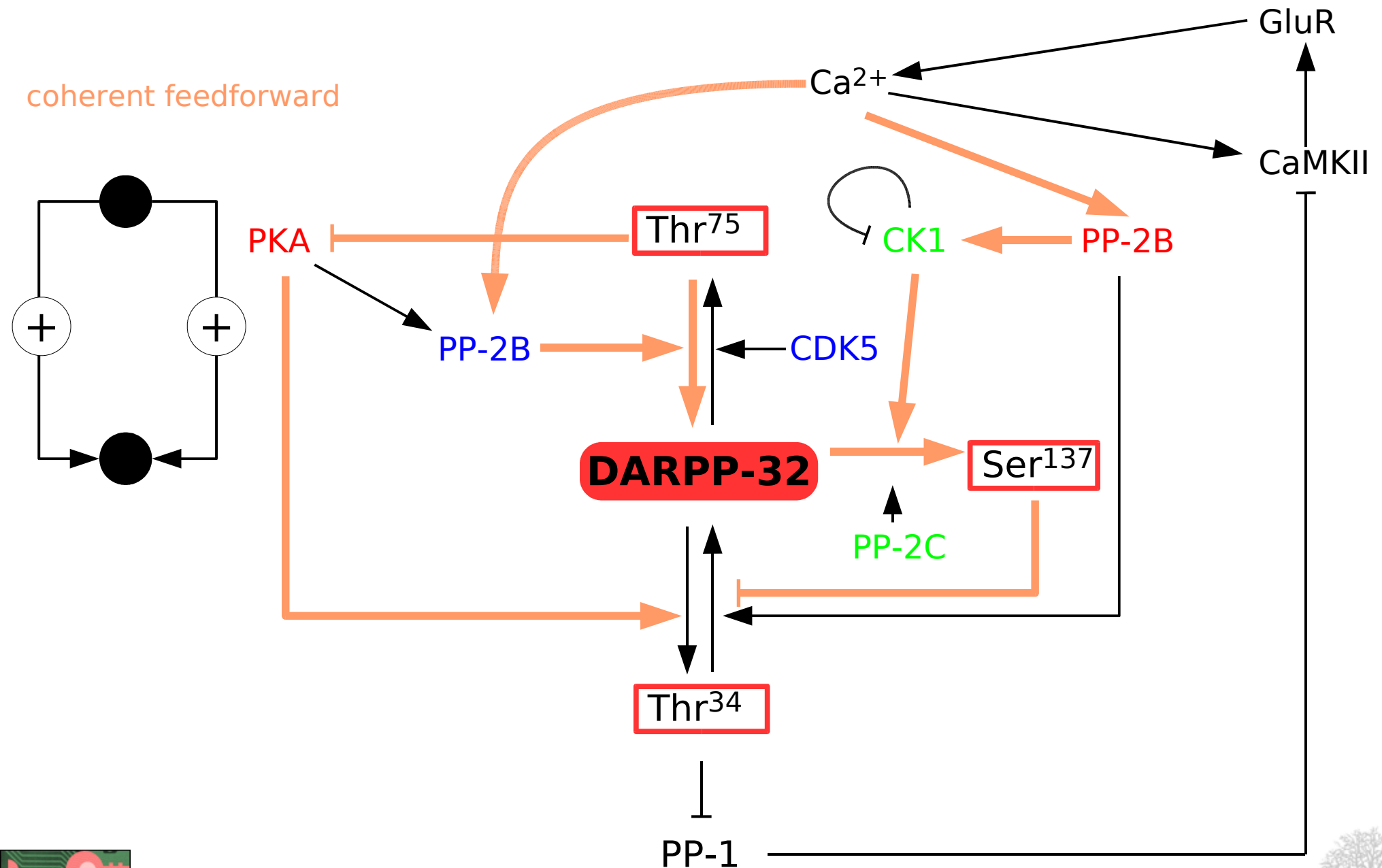
negative feedback



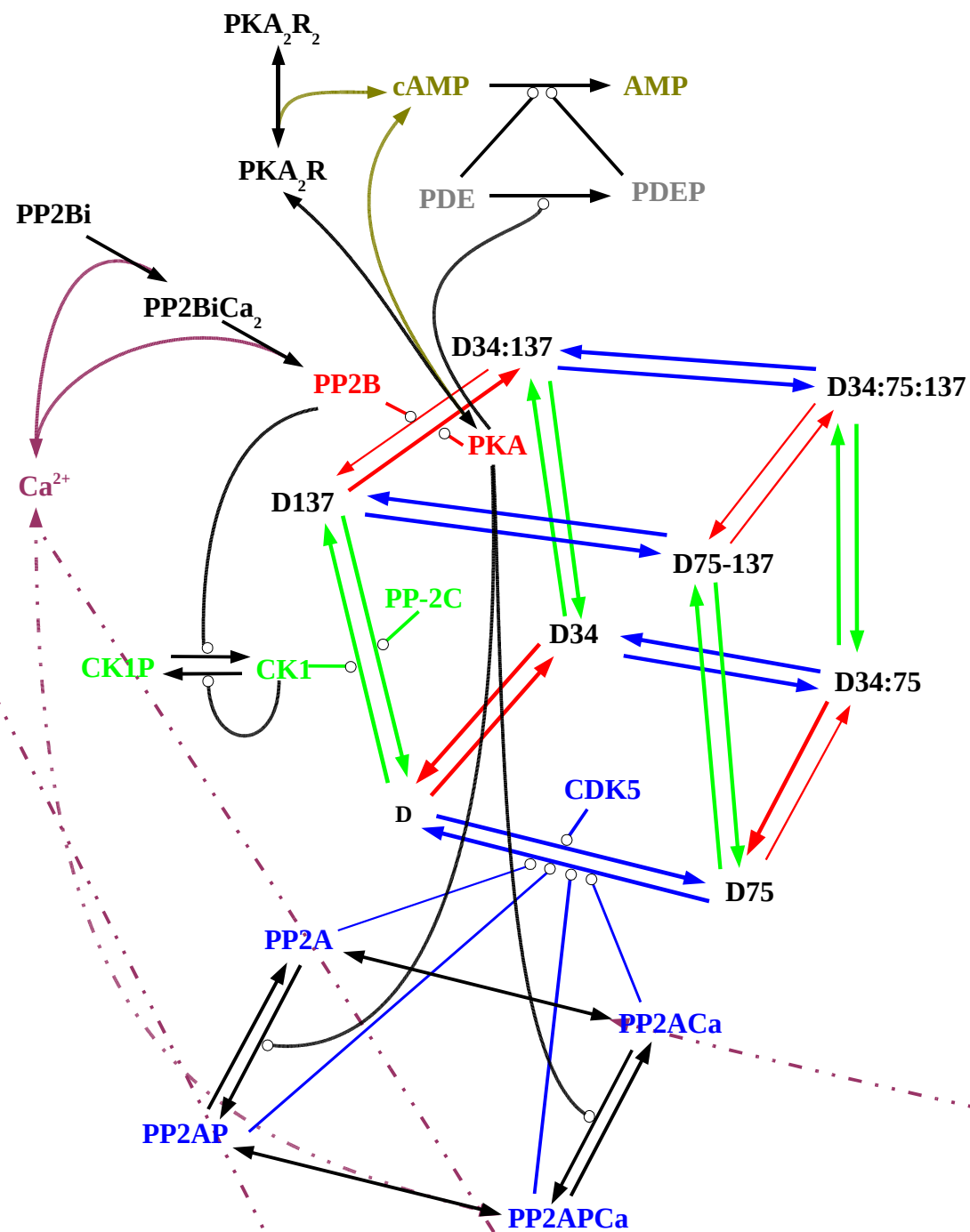
incoherent feedforward



coherent feedforward



Chemical model of DARPP-32 regulation



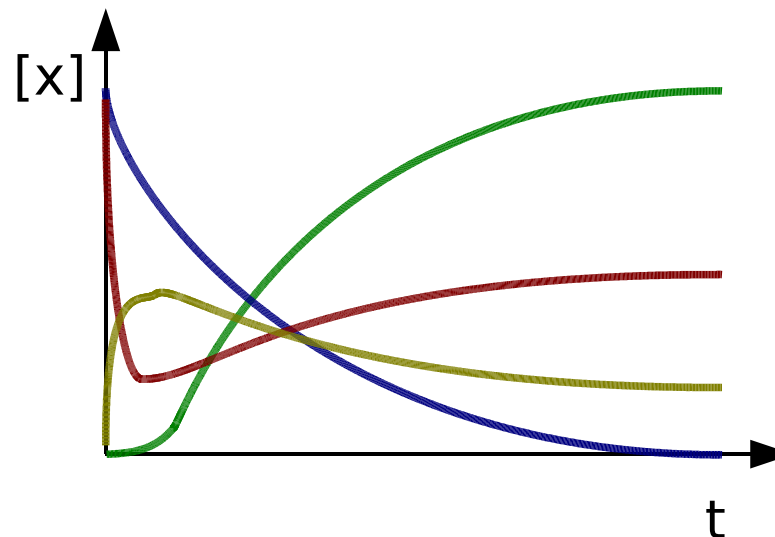
- $D + CDK5 \rightleftharpoons D_CDK5 \rightarrow D75 + CDK5$
- $D75 + PP2A \rightleftharpoons D75_PP2A \rightarrow D + PP2A$
- $D75 + PP2ACa \rightleftharpoons D75_PP2ACa \rightarrow D + PP2ACa$
- $D75 + PP2AP \rightleftharpoons D75_PP2AP \rightarrow D + PP2AP$
- $D75 + PP2APCa \rightleftharpoons D75_PP2APCa \rightarrow D + PP2APCa$
- $D137 + CDK5 \rightleftharpoons D137_CDK5 \rightarrow D75-137 + CDK5$
- $D75-137 + PP2A \rightleftharpoons D75-137_PP2A \rightarrow D137 + PP2A$
- $D75-137 + PP2ACa \rightleftharpoons D75-137_PP2ACa \rightarrow D137 + PP2ACa$
- $D75-137 + PP2AP \rightleftharpoons D75-137_PP2AP \rightarrow D137 + PP2AP$
- $D75-137 + PP2APCa \rightleftharpoons D75-137_PP2APCa \rightarrow D137 + PP2APCa$
- $D34 + CDK5 \rightleftharpoons D34_CDK5 \rightarrow D34-75 + CDK5$
- $D34-75 + PP2A \rightleftharpoons D34-75_PP2A \rightarrow D34 + PP2A$
- $D34-75 + PP2ACa \rightleftharpoons D34-75_PP2ACa \rightarrow D34 + PP2ACa$
- $D34-75 + PP2AP \rightleftharpoons D34-75_PP2AP \rightarrow D34 + PP2AP$
- $D34-75 + PP2APCa \rightleftharpoons D34-75_PP2APCa \rightarrow D34 + PP2APCa$
- $D34-137 + CDK5 \rightleftharpoons D34-137_CDK5 \rightarrow D34-75-137 + CDK5$
- $D34-75-137 + PP2A \rightleftharpoons D34-75-137_PP2A \rightarrow D34-137 + PP2A$
- $D34-75-137 + PP2ACa \rightleftharpoons D34-75-137_PP2ACa \rightarrow D34-137 + PP2ACa$
- $D34-75-137 + PP2AP \rightleftharpoons D34-75-137_PP2AP \rightarrow D34-137 + PP2AP$
- $D34-75-137 + PP2APCa \rightleftharpoons D34-75-137_PP2APCa \rightarrow D34-137 + PP2APCa$
- $D + CK1 \rightleftharpoons D_CK1 \rightarrow D137 + CK1$
- $D137 + PP2C \rightleftharpoons D137_PP2C \rightarrow D + PP2C$
- $D75 + CK1 \rightleftharpoons D75_CK1 \rightarrow D75-137 + CK1$
- $D75-137 + PP2C \rightleftharpoons D75-137_PP2C \rightarrow D75 + PP2C$
- $D34 + CK1 \rightleftharpoons D34_CK1 \rightarrow D34-137 + CK1$
- $D34-75 + PP2C \rightleftharpoons D34-75_PP2C \rightarrow D75 + PP2C$
- $D34-75 + CK1 \rightleftharpoons D34-75_CK1 \rightarrow D34-75-137 + CK1$
- $D34-75-137 + PP2C \rightleftharpoons D34-75-137_PP2C \rightarrow D34-75 + PP2C$
- $CK1 + CK1 \rightleftharpoons CK1_CK1 \rightarrow CK1P + CK1$
- $CK1P + PP2B \rightleftharpoons CK1P_PP2B \rightarrow CK1 + PP2B$

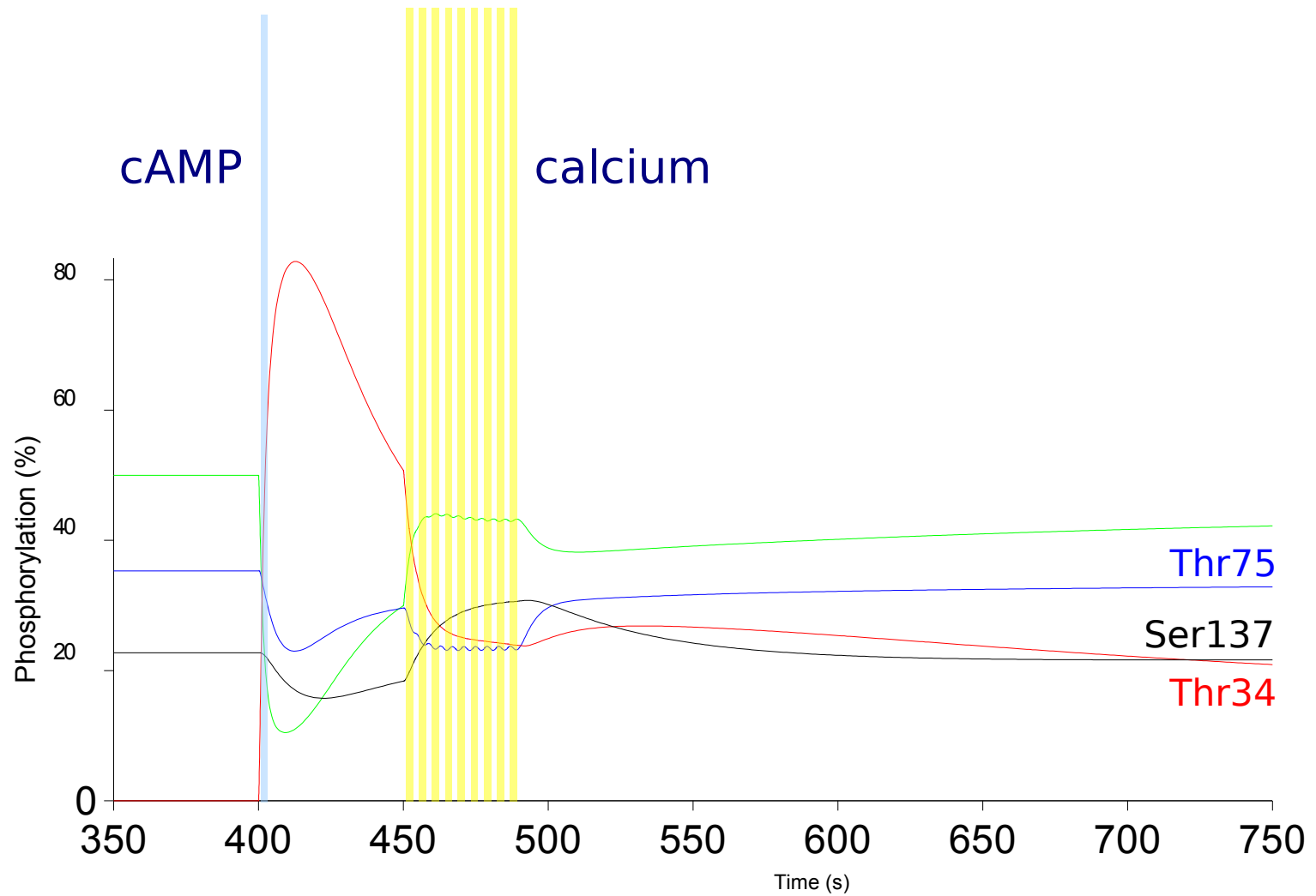
79 species, 156 reactions

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

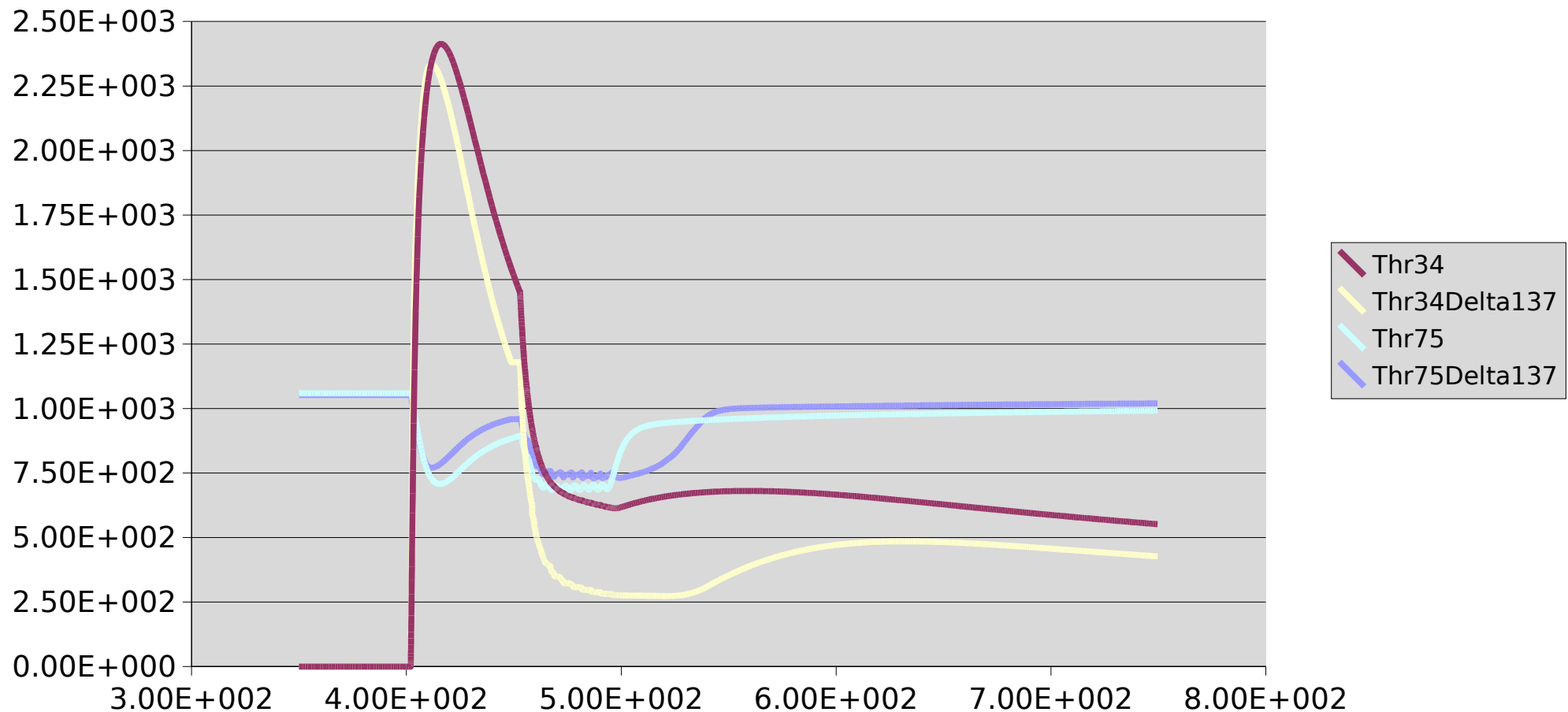


$$\begin{aligned} \frac{d[\text{D}]}{dt} &= -k_1[\text{CDK5}][\text{D}] + k_2[\text{D_CDK5}] \\ \frac{d[\text{D-75P}]}{dt} &= +k_3[\text{D_CDK5}] \\ \frac{d[\text{CDK5}]}{dt} &= -k_1[\text{CDK5}][\text{D}] + k_2[\text{D_CDK5}] + k_3[\text{D_CDK5}] \\ \frac{d[\text{D_CDK5}]}{dt} &= +k_1[\text{CDK5}][\text{D}]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



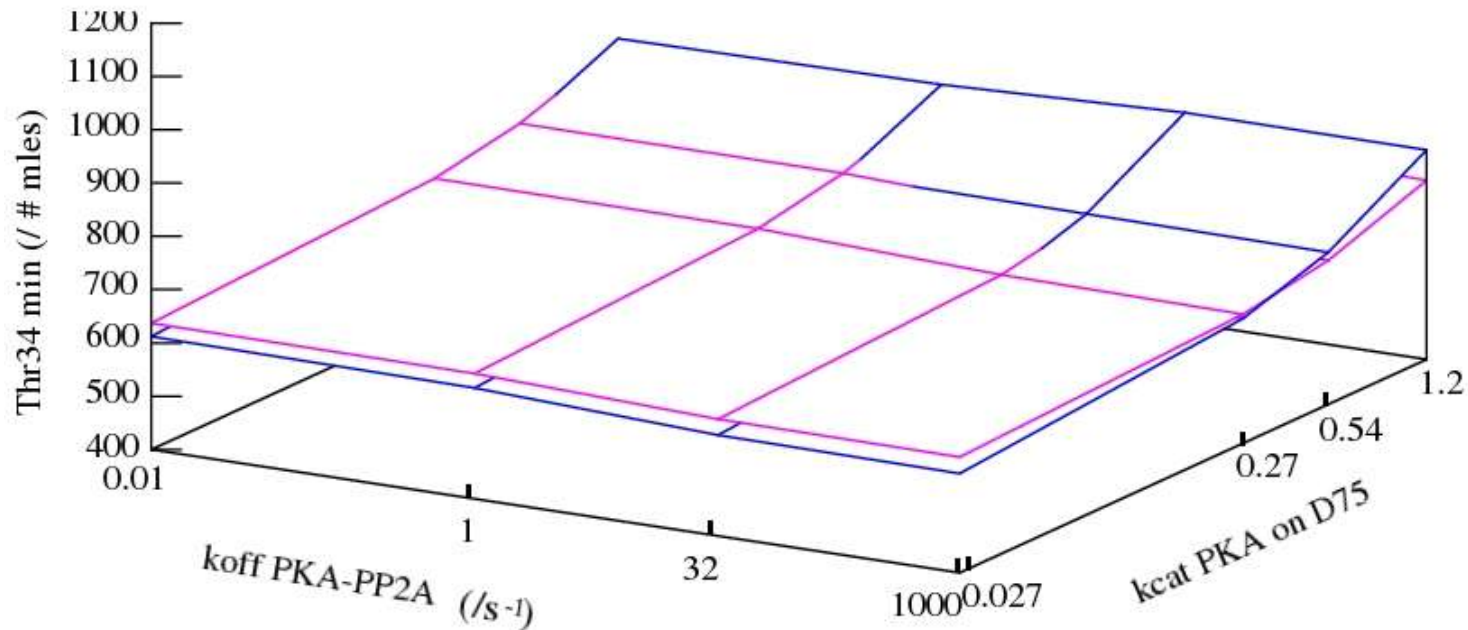
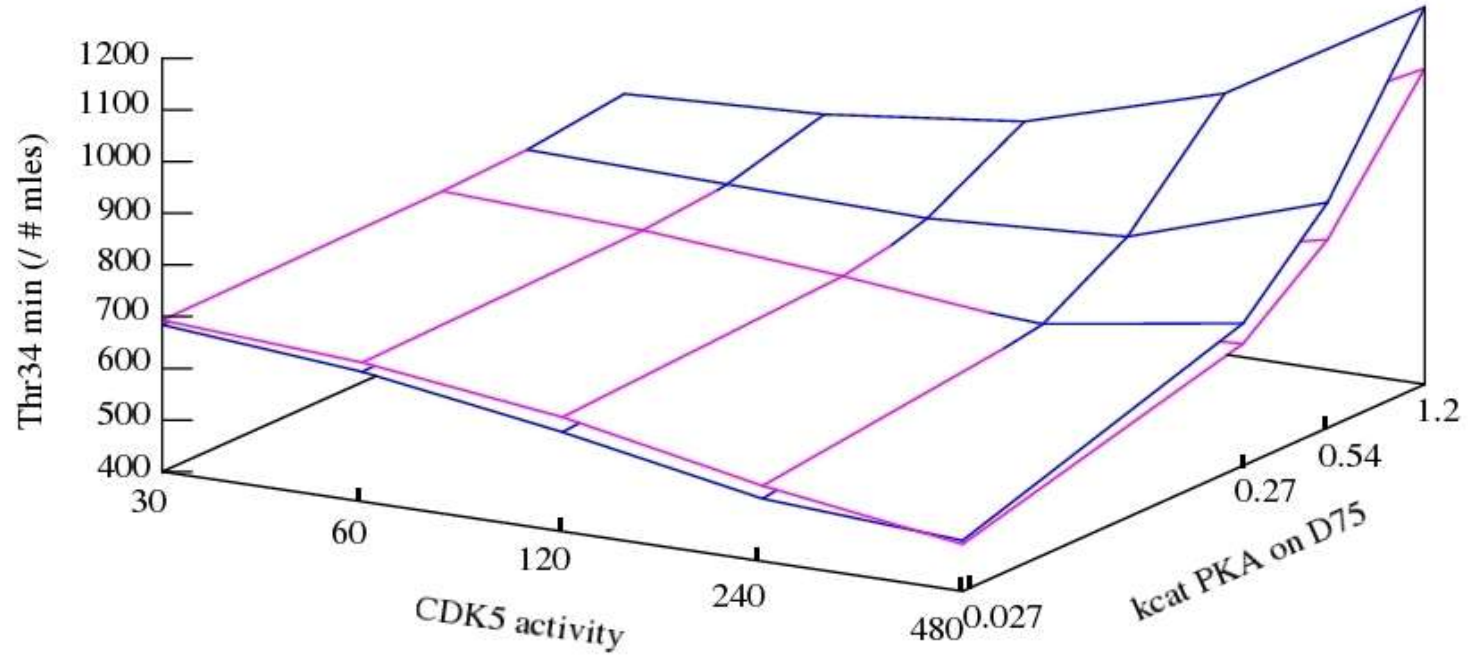


cAMP pulse then Ca²⁺ spikes



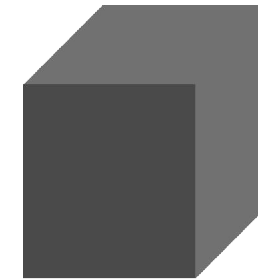
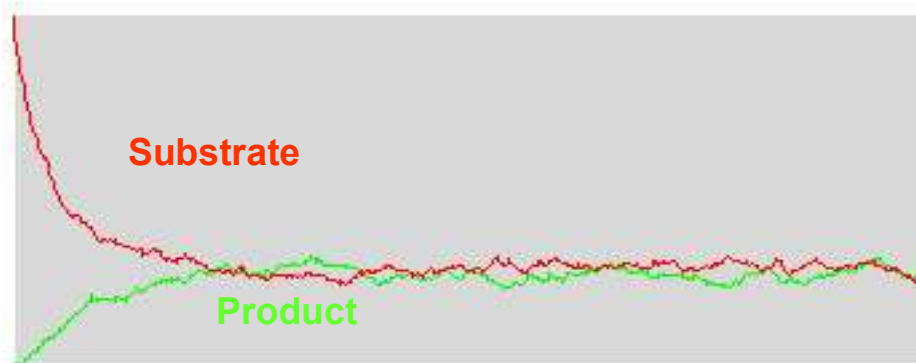
model A ———

model B ———

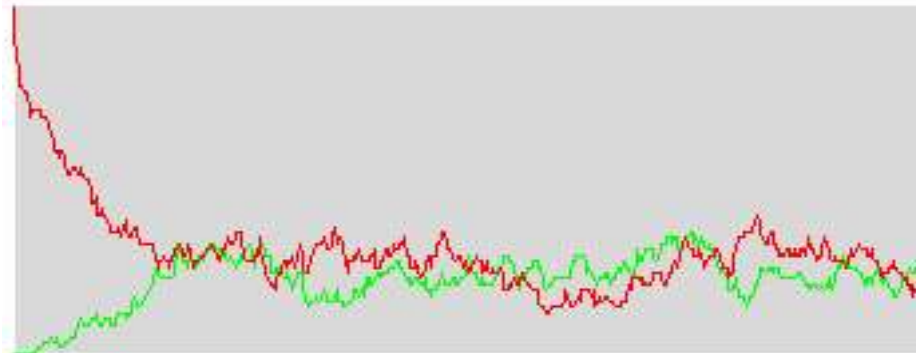




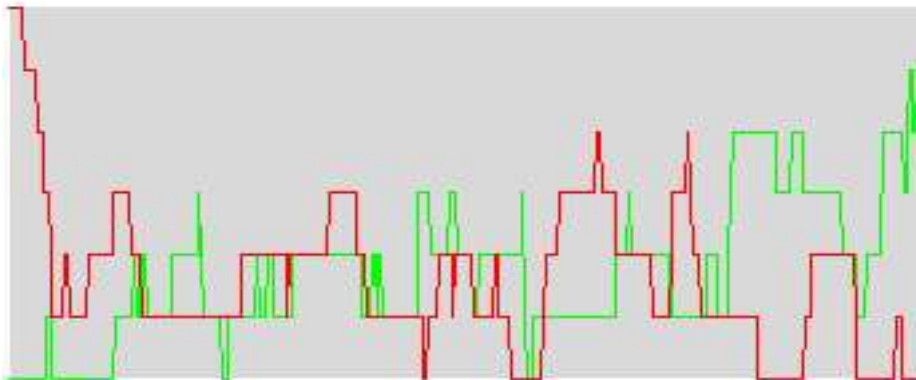
Concentration (μM)



10^{-15} litres



10^{-16} litres

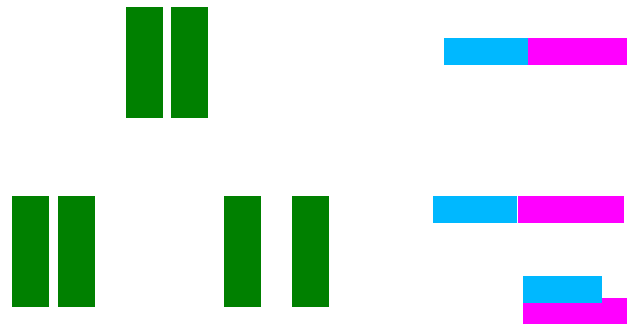


10^{-17} litres

Stochastic Simulation



NMDA + CaMKII $\rightleftharpoons$ NMDA-CaMKII



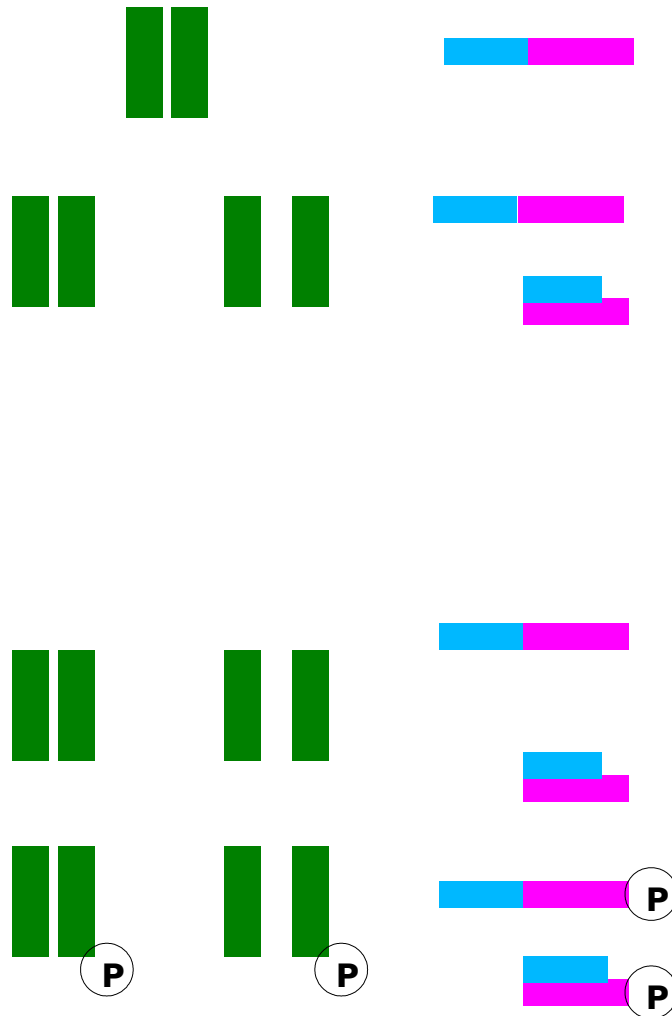
NMDA + CaMKII $\rightleftharpoons$ NMDA-CaMKII

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

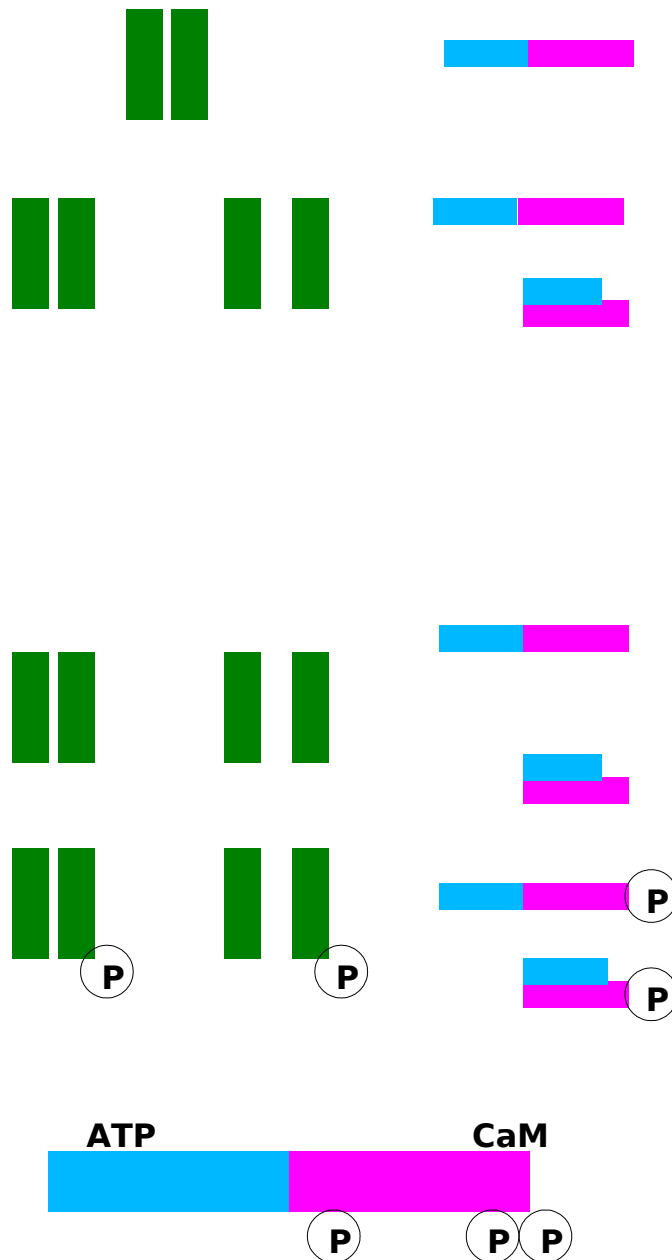
NMDAo + pCaMKIIo $\rightleftharpoons$ NMDAc-pCaMKIIo

pNMDAc + pCaMKIIc $\rightleftharpoons$ pNMDAc-pCaMKIIc

pNMDAo + pCaMKIIc $\rightleftharpoons$ pNMDAc-pCaMKIIc

pNMDAc + pCaMKIIo $\rightleftharpoons$ pNMDAc-pCaMKIIo

pNMDAo + pCaMKIIo $\rightleftharpoons$ pNMDAc-pCaMKIIo



NMDA + CaMKII $\rightleftharpoons$ NMDA-CaMKII

NMDAc + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAo + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAc + CaMKIlo $\rightleftharpoons$ NMDAc-CaMKIlo

NMDAo + CaMKIlo $\rightleftharpoons$ NMDAc-CaMKIlo

NMDAc + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAo + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAc + CaMKIlo $\rightleftharpoons$ NMDAc-CaMKIlo

NMDAo + CaMKIlo $\rightleftharpoons$ NMDAc-CaMKIlo

pNMDAc + CaMKIIc $\rightleftharpoons$ pNMDAc-CaMKIIc

pNMDAo + CaMKIIc $\rightleftharpoons$ pNMDAc-CaMKIIc

pNMDAc + CaMKIlo $\rightleftharpoons$ pNMDAc-CaMKIlo

pNMDAo + CaMKIlo $\rightleftharpoons$ pNMDAc-CaMKIlo

NMDAc + pCaMKIIc $\rightleftharpoons$ NMDAc-pCaMKIIc

NMDAo + pCaMKIIc $\rightleftharpoons$ NMDAc-pCaMKIIc

NMDAc + pCaMKIlo $\rightleftharpoons$ NMDAc-pCaMKIlo

NMDAo + pCaMKIlo $\rightleftharpoons$ NMDAc-pCaMKIlo

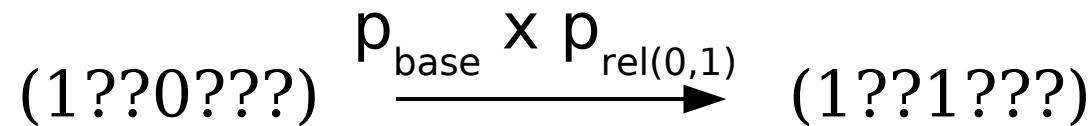
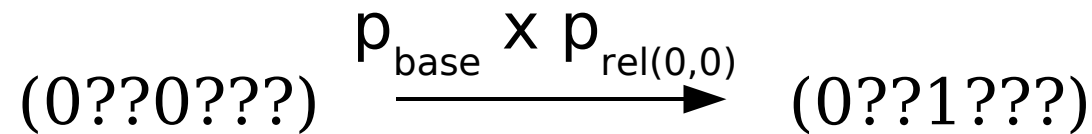
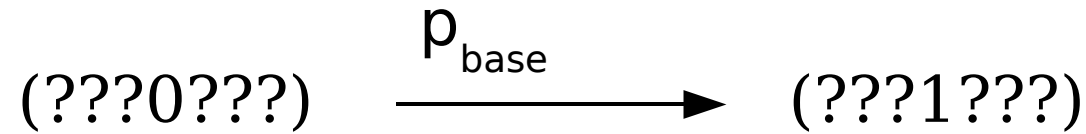
pNMDAc + pCaMKIIc $\rightleftharpoons$ pNMDAc-pCaMKIIc

pNMDAo + pCaMKIIc $\rightleftharpoons$ pNMDAc-pCaMKIIc

pNMDAc + pCaMKIlo $\rightleftharpoons$ pNMDAc-pCaMKIlo

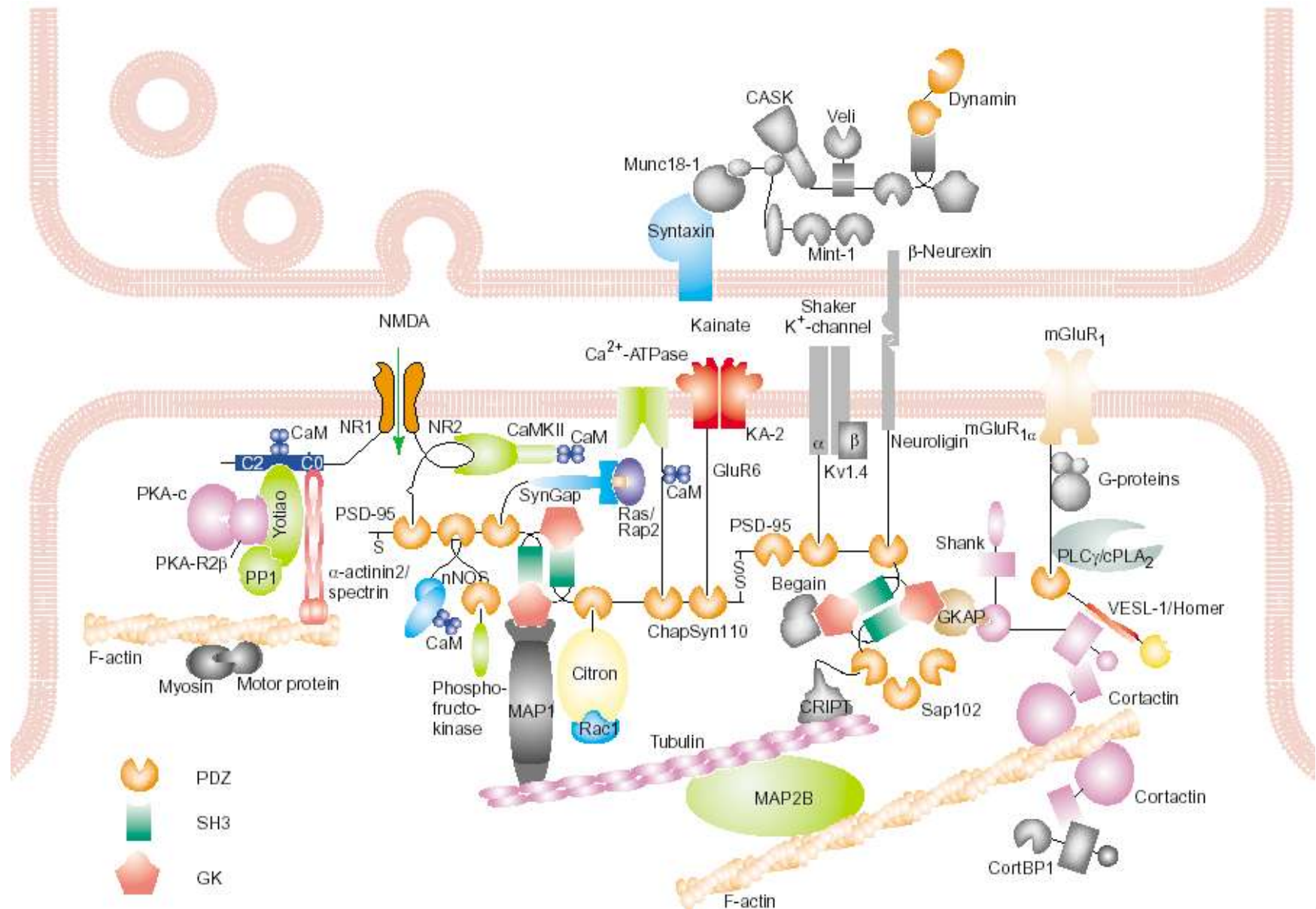
pNMDAo + pCaMKIlo $\rightleftharpoons$ pNMDAc-pCaMKIlo

- 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 glutamatergic synapse ~ 60-100 receptors
Often more pools than molecules
 - ☛ Useless computation

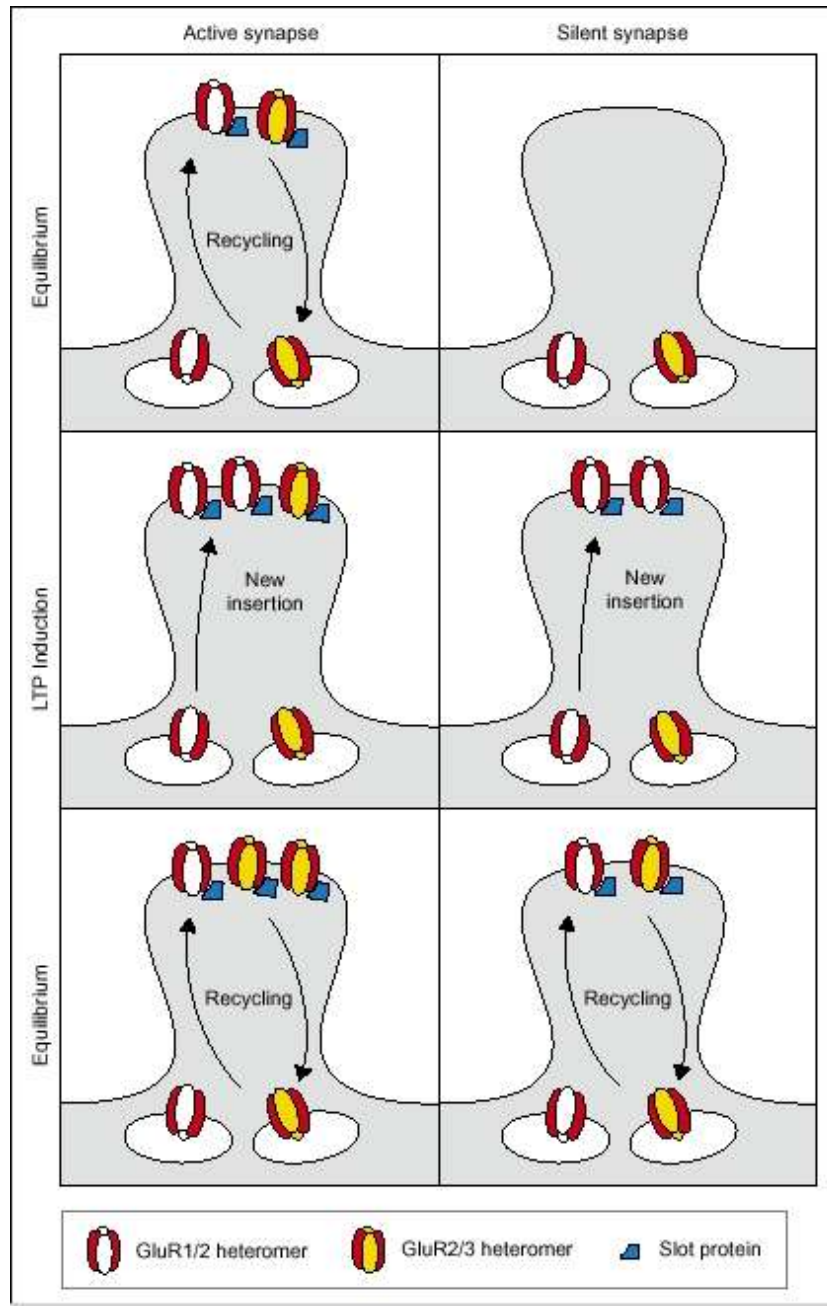


- '?' Flags do not affect the reaction
- only 4 species are needed instead of 128

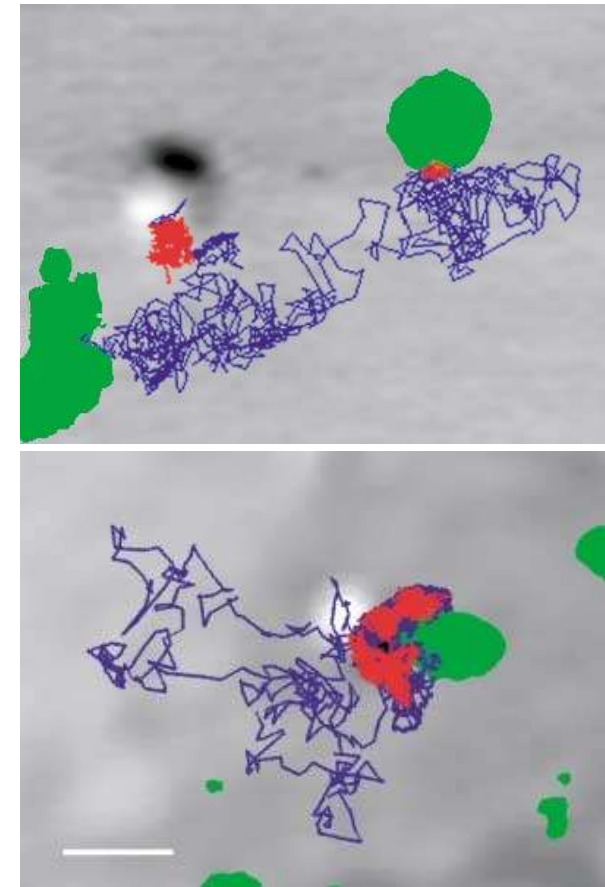
Single-particle simulation



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



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



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

Accurate representation of space

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

- 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)

- 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 $\Delta\theta = \frac{\sqrt{2D_R t}}{r} \times \text{gaussRand}$

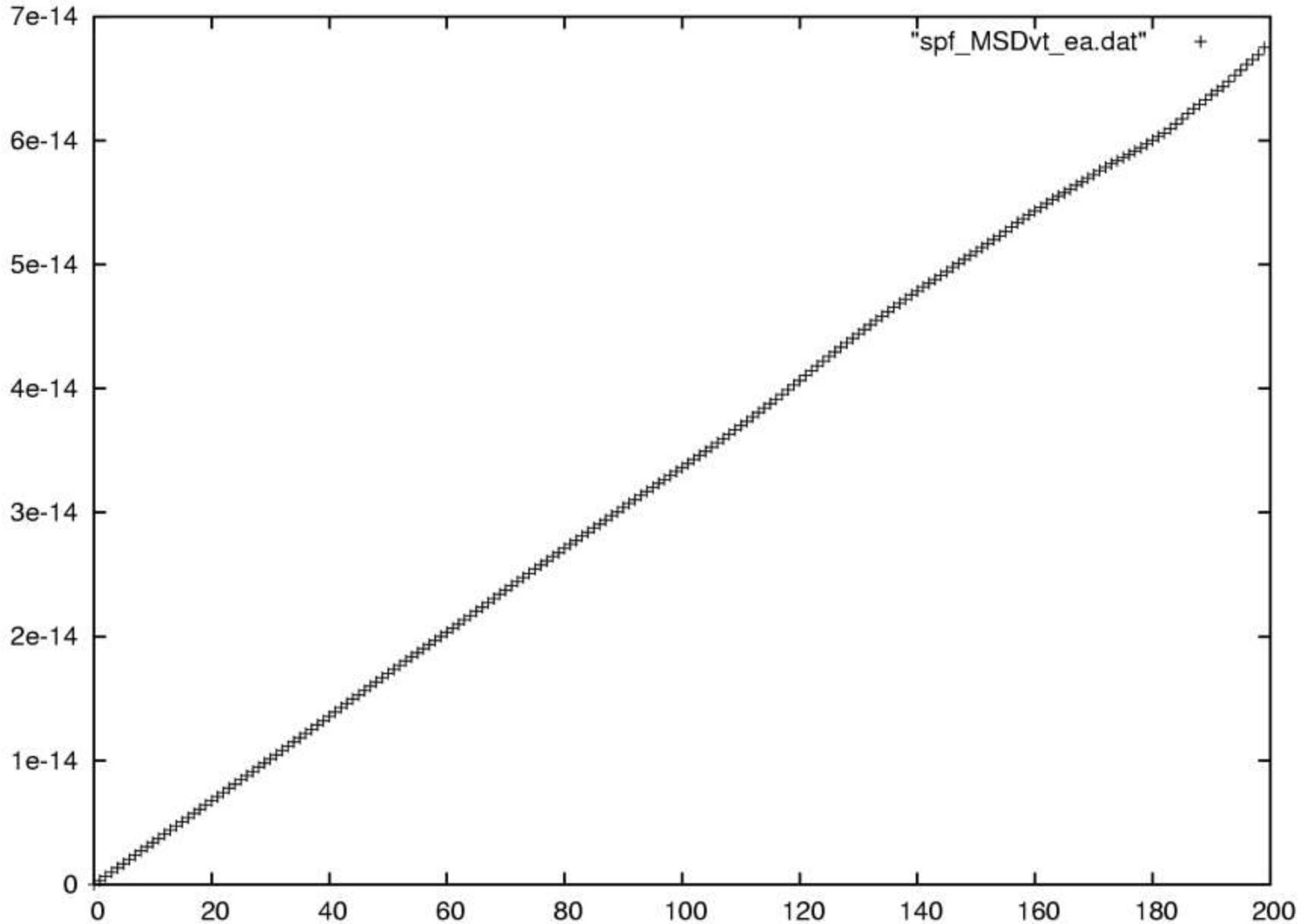
- Two types of diffusion equations:
 - unrestricted brownian motion – Low Trans/Rot
 - intra-membrane diffusion (Saffman and Delbrück 1975) – High Trans/Rot

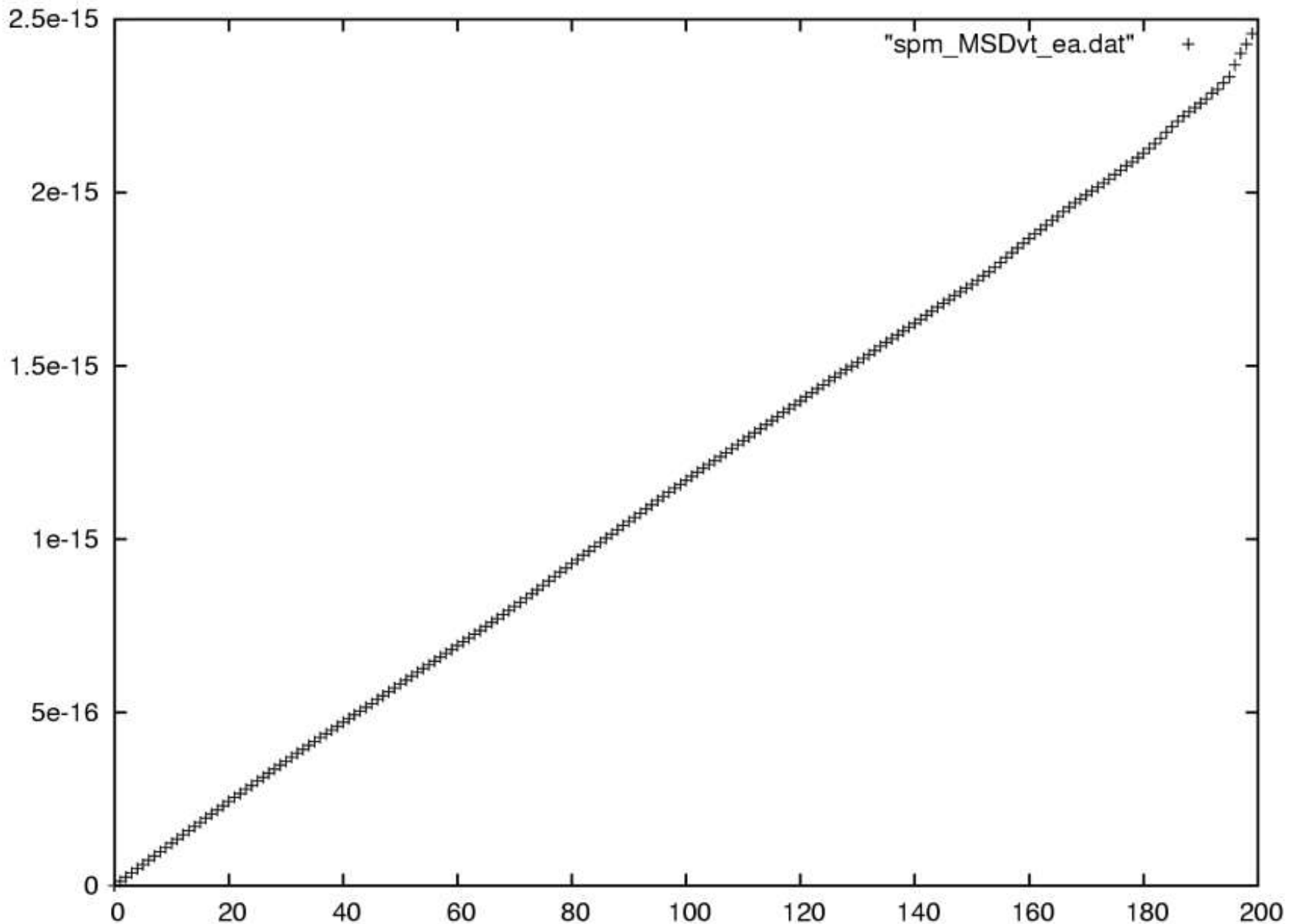
- Unrestricted brownian motion – Low Translation/Rotational

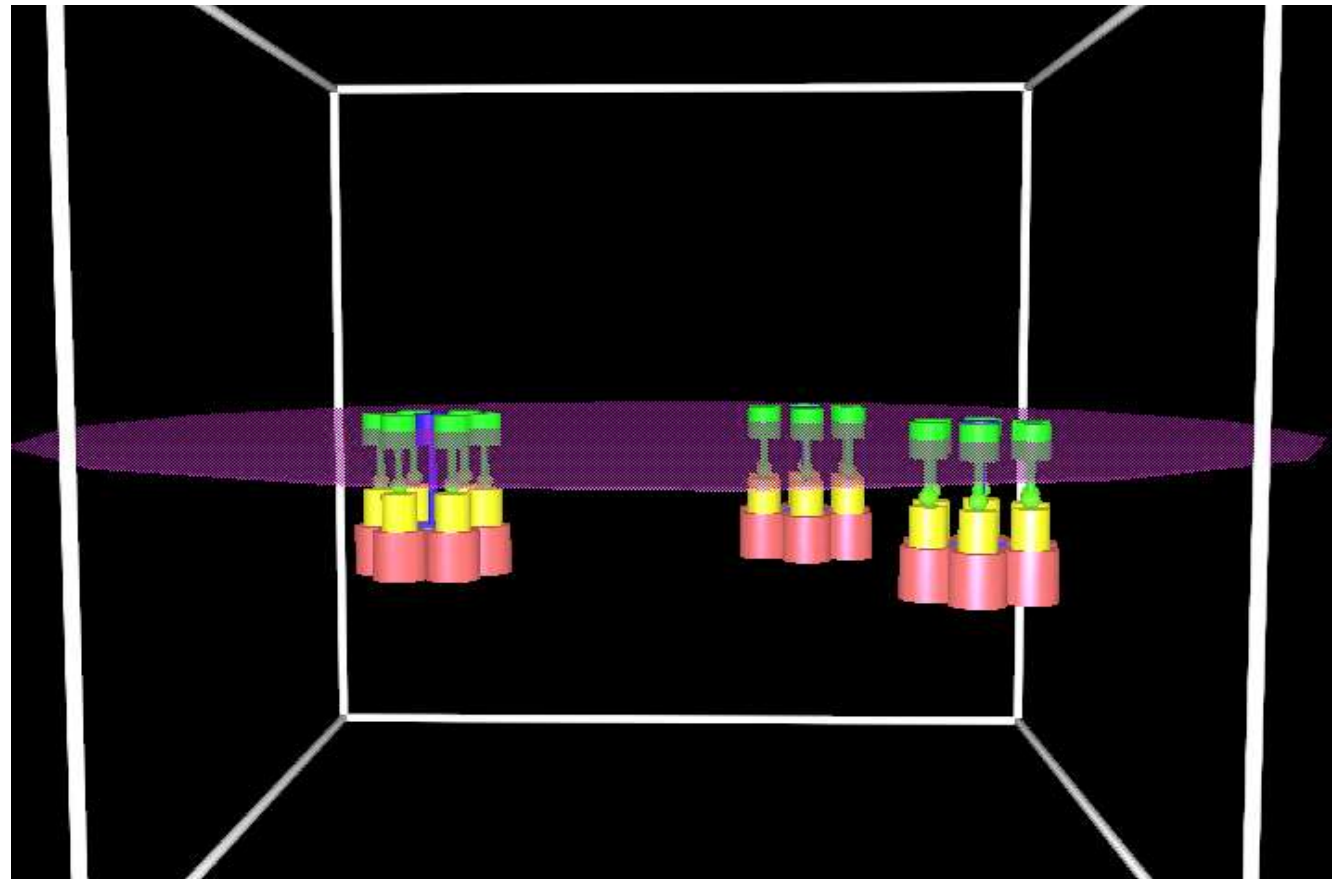
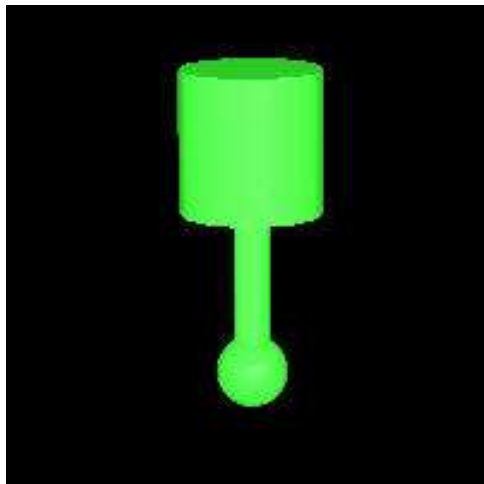
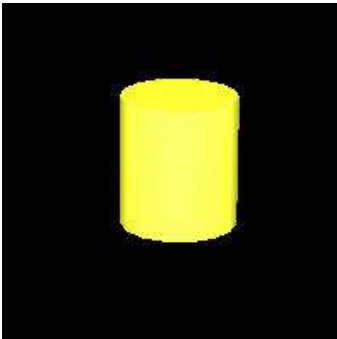
$$b_T = \frac{1}{6\pi\mu r} \quad b_R = \frac{1}{8\pi\mu r^3} \quad \frac{b_T}{b_R} = \frac{4}{3}r^2$$

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

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



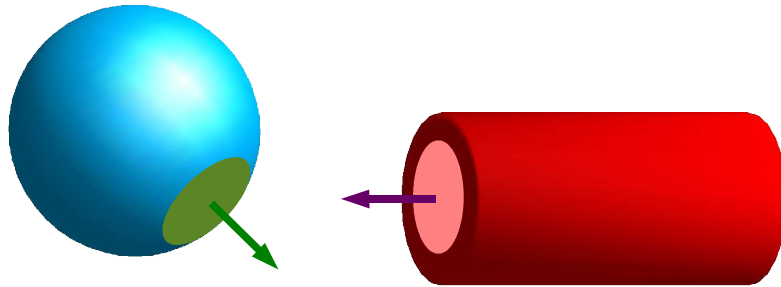


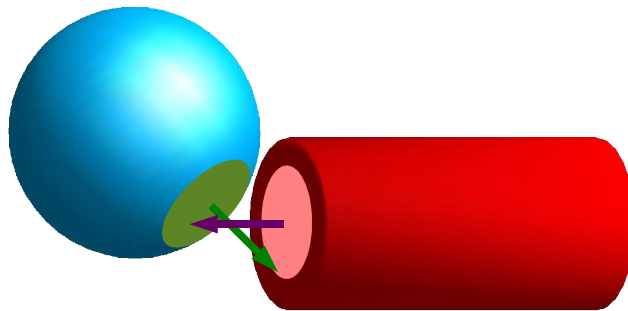
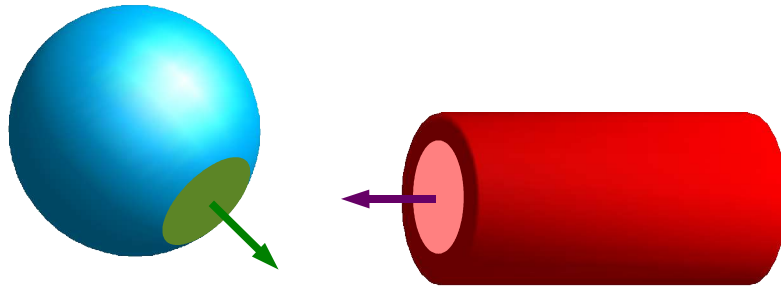


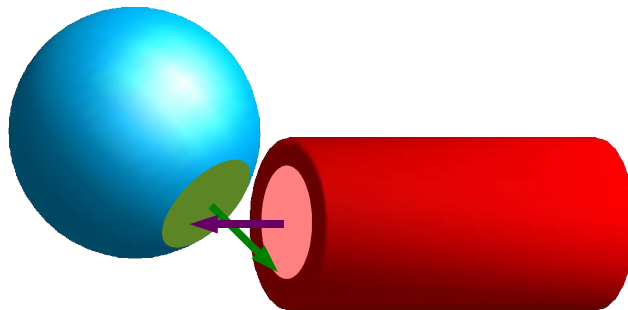
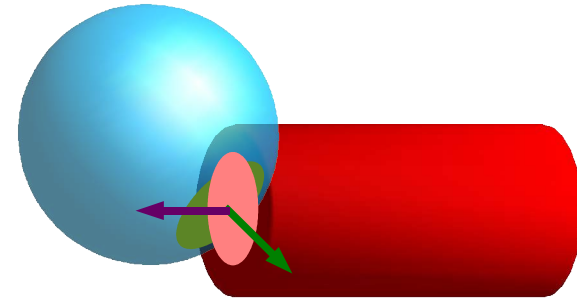
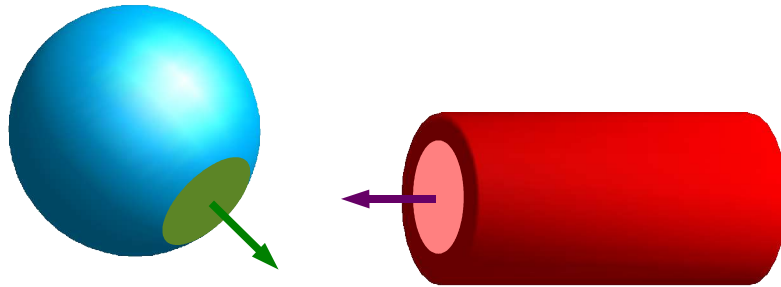
Particles carry binding sites

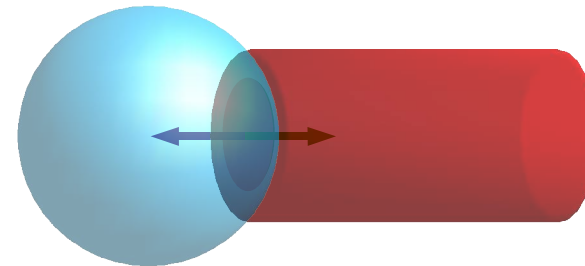
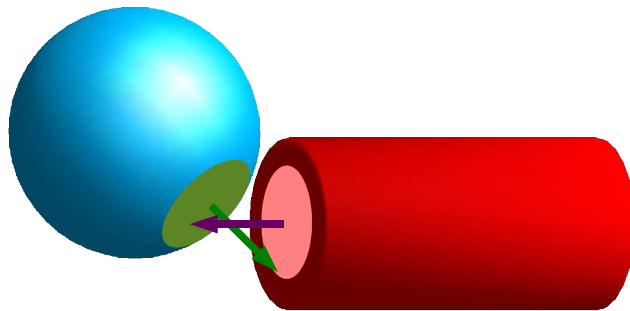
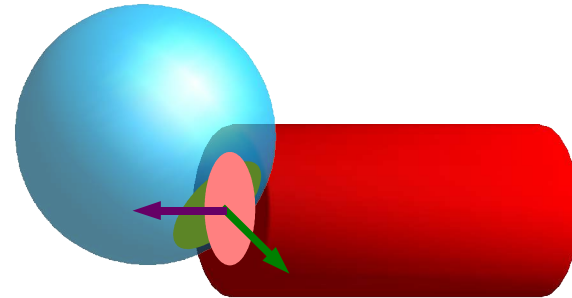
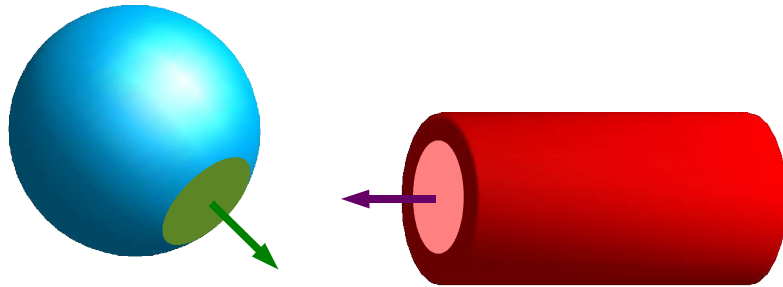
Cluster class allows recording of Center Of Mass, radius, RMS displacement;
possibility of cluster state

Clusters are dynamically created and destroyed – transient.









Main Control

Abstracted Protein Simulator

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

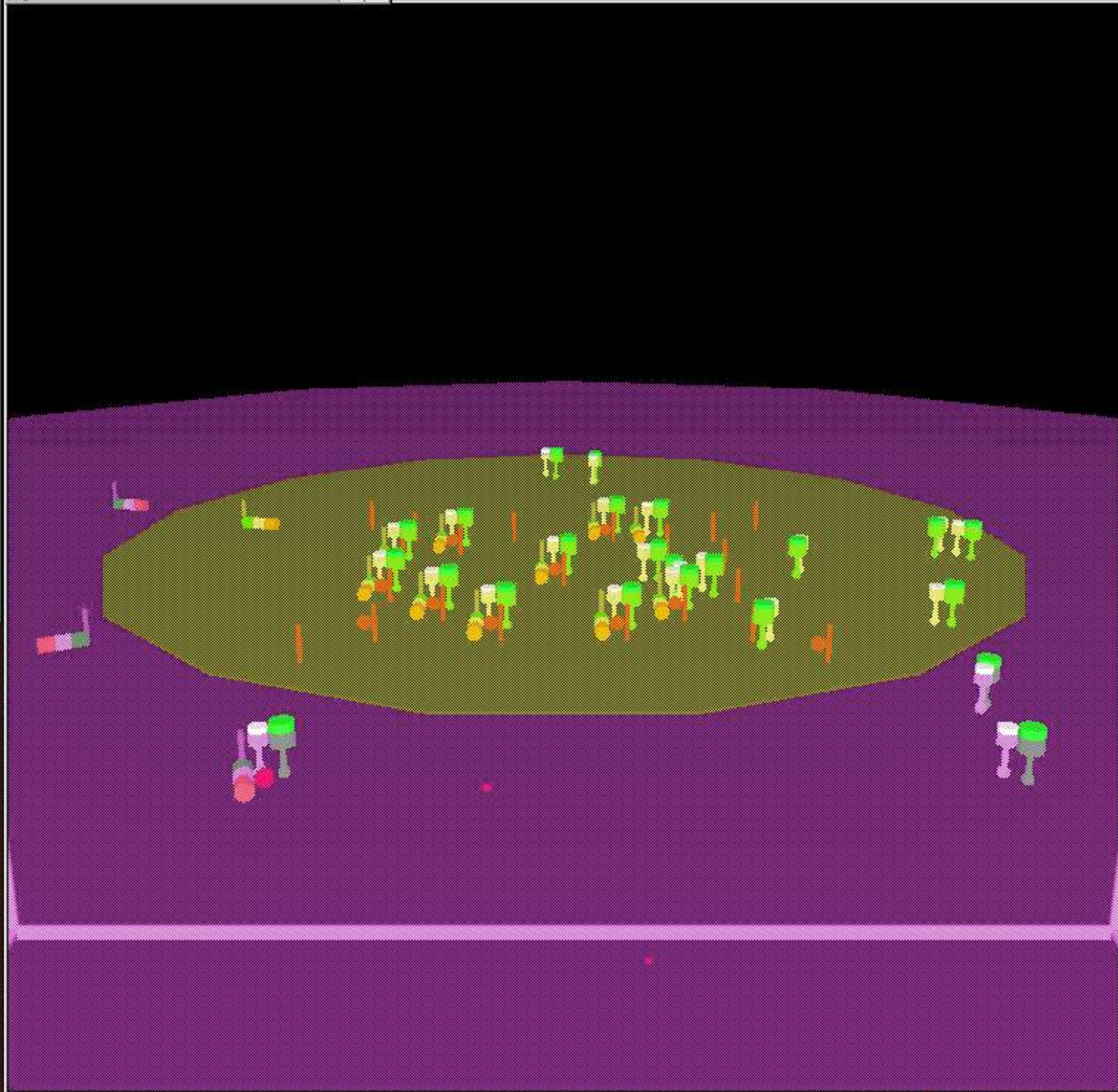
render

pause

clear

status

Simulation paused
Rendering







Nicolas Le Novère



Mélanie Courtot



Kathryn Hardwick



Chen Li

Lu Li

Nicolas Rodriguez

Melanie Stefan

Dominic Tölle

group leader

developer

administrative assistant

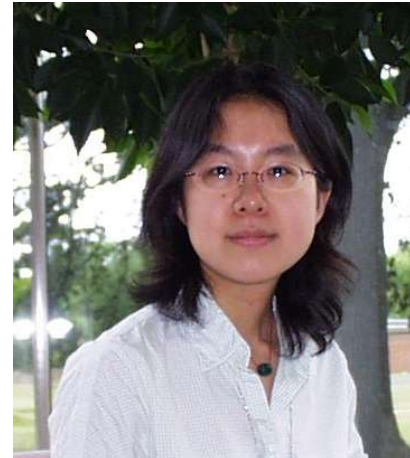
developer

developer

developer

PhD student

PhD student



Arnaud Henry



Renaud Schiappa

Trainee

Trainee

Eric Fernandez

Jean-Antoine Girault

former Post-doc

Experimental collaborator

