

British outstation of the European Molecular Biology Laboratory

- Databases

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



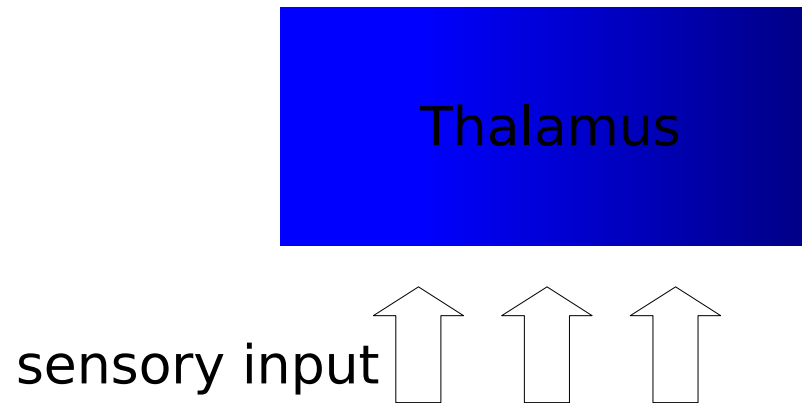
- Research groups

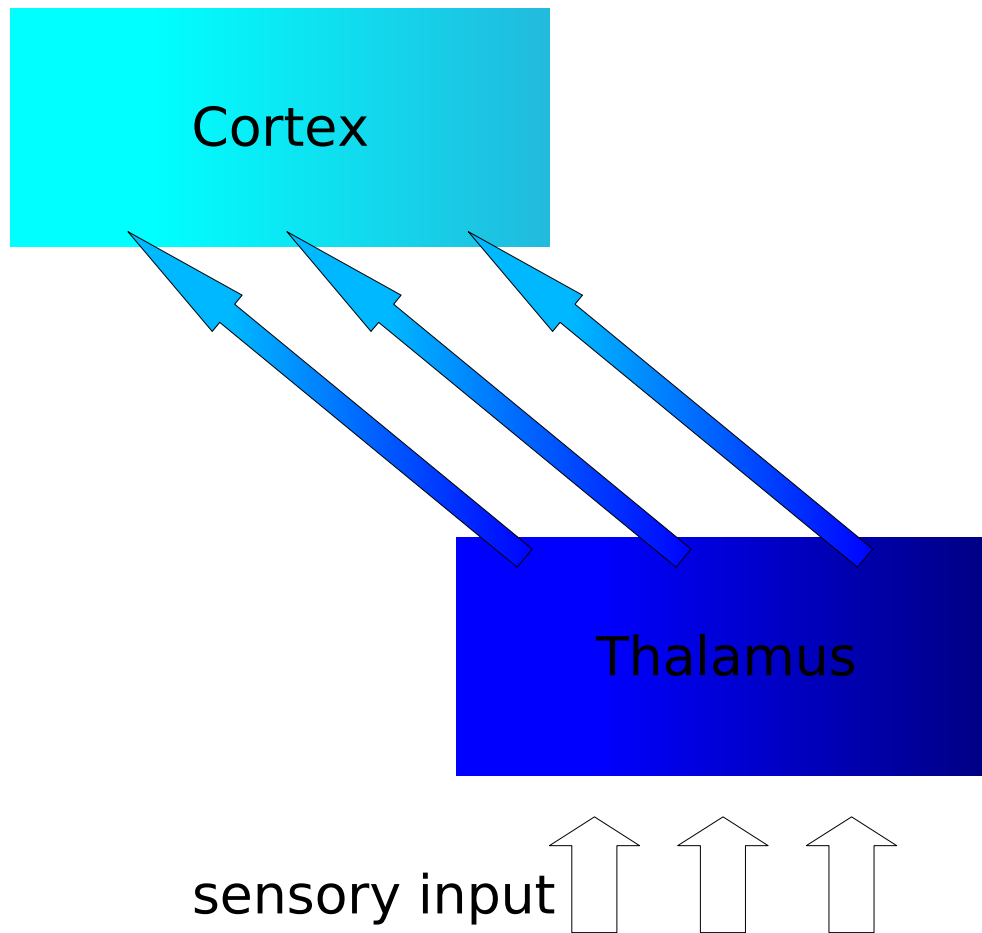
- Structural Genomics (Thornton)
- Molecular Evolution (Goldman)
- Text-Mining (Rebholz-Schumman)
- Computational Systems Biology (Le Novère)
- Statistical array analysis (Huber)
- Genomic analysis of regulatory systems (Luscombe)
- Functional genomics (Bertone)

> 2 500 000 hits per day

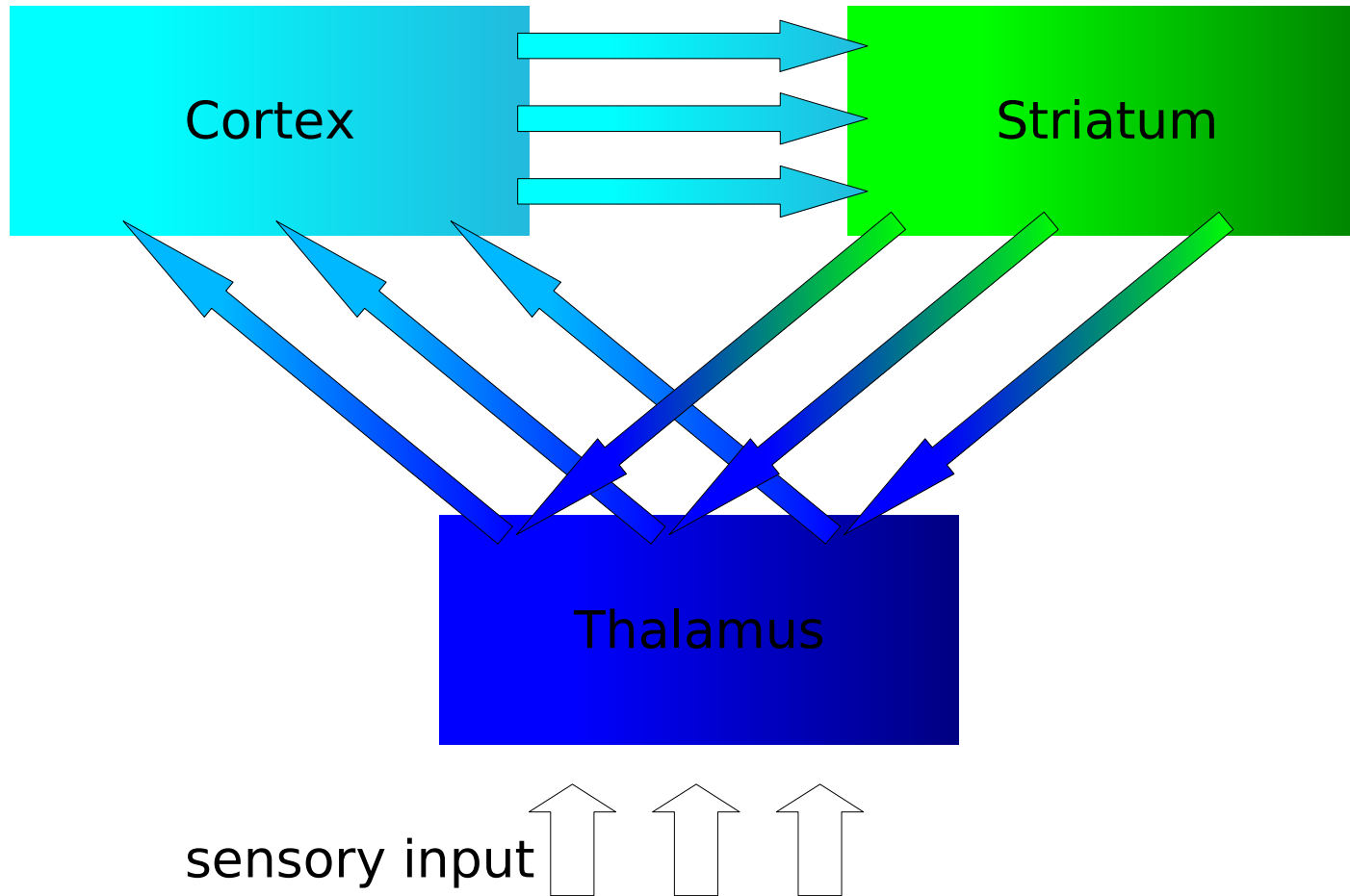
Integration of Dopamine and Glutamate signals by DARPP-32

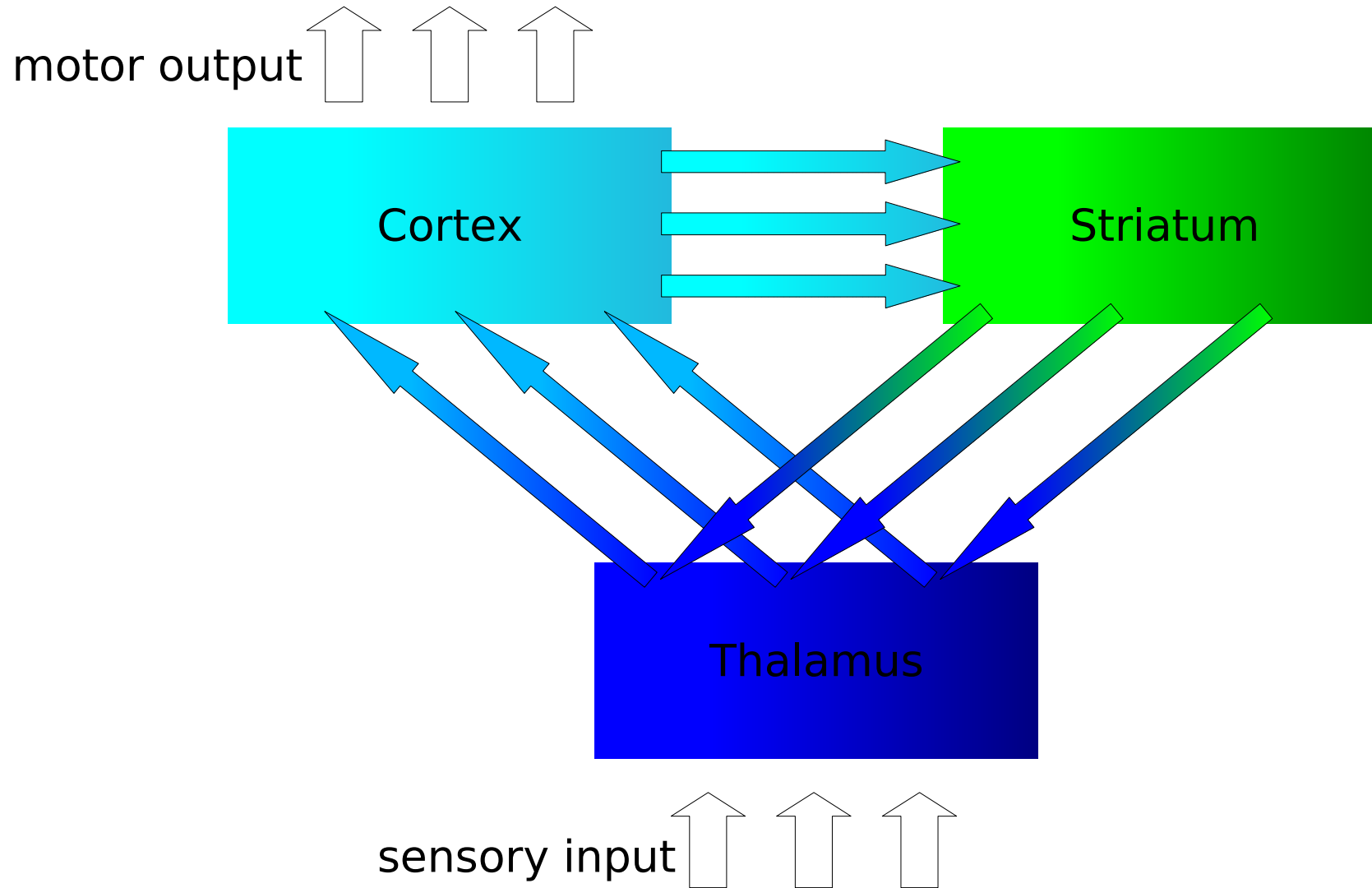


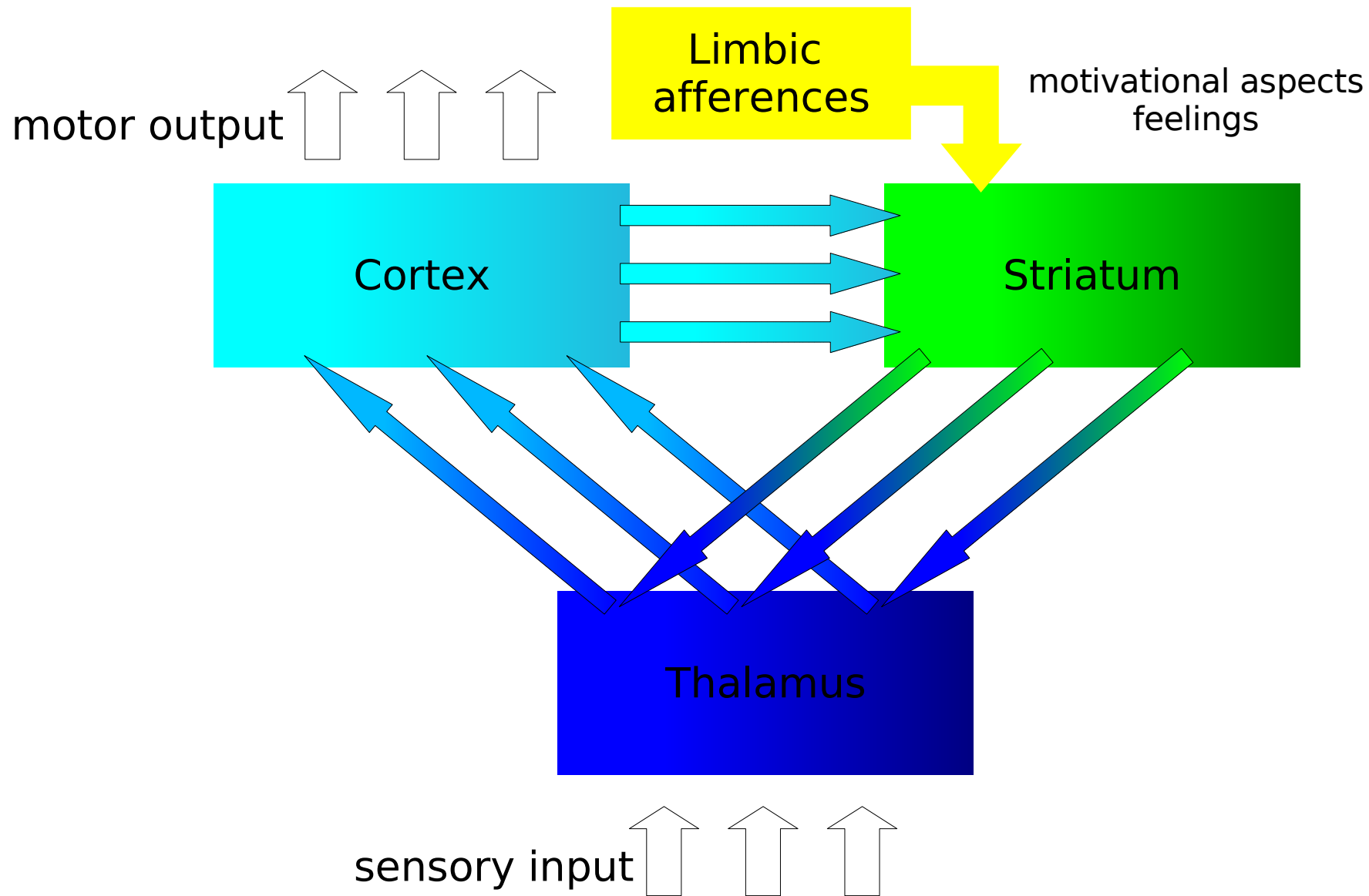


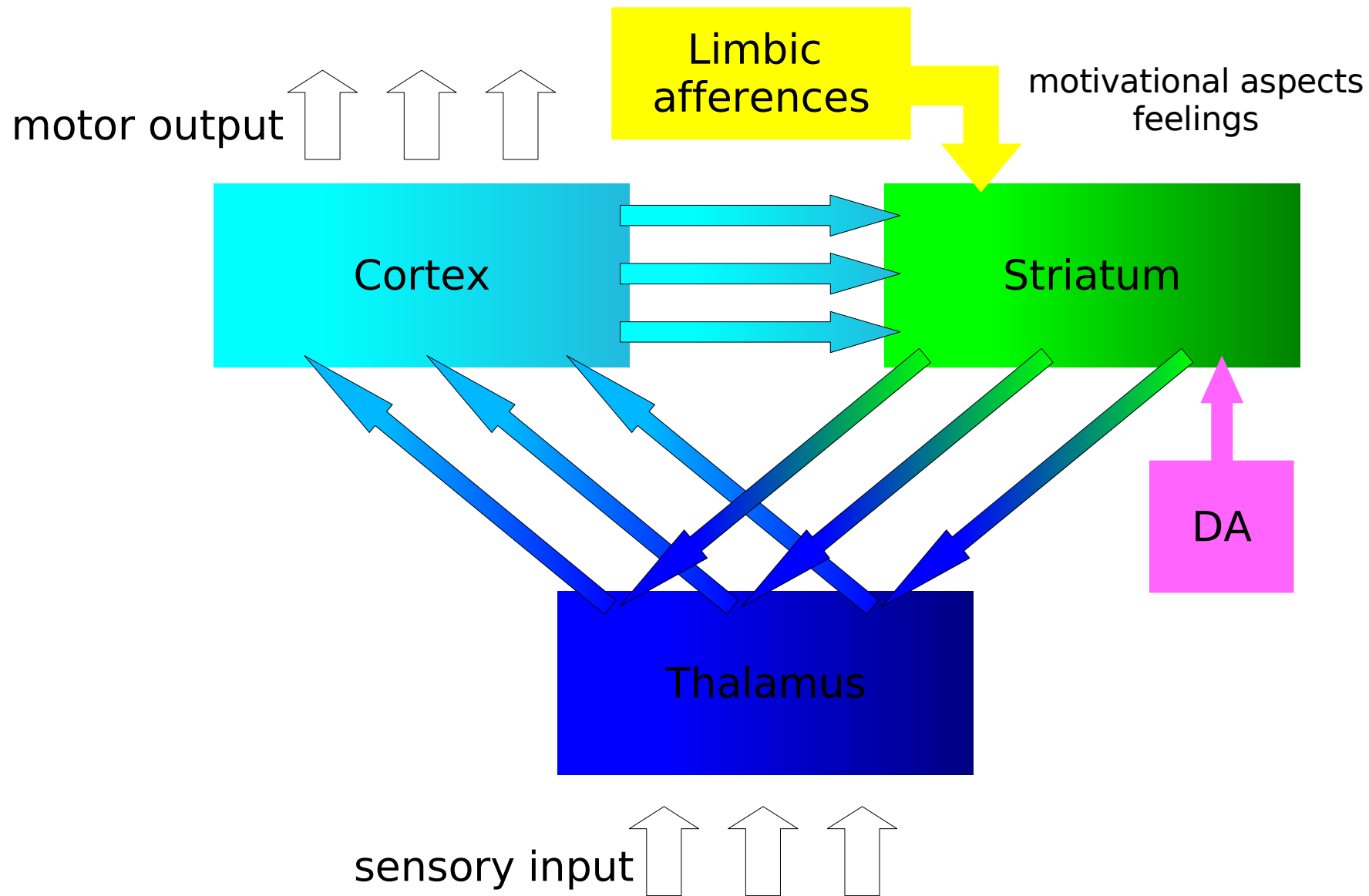


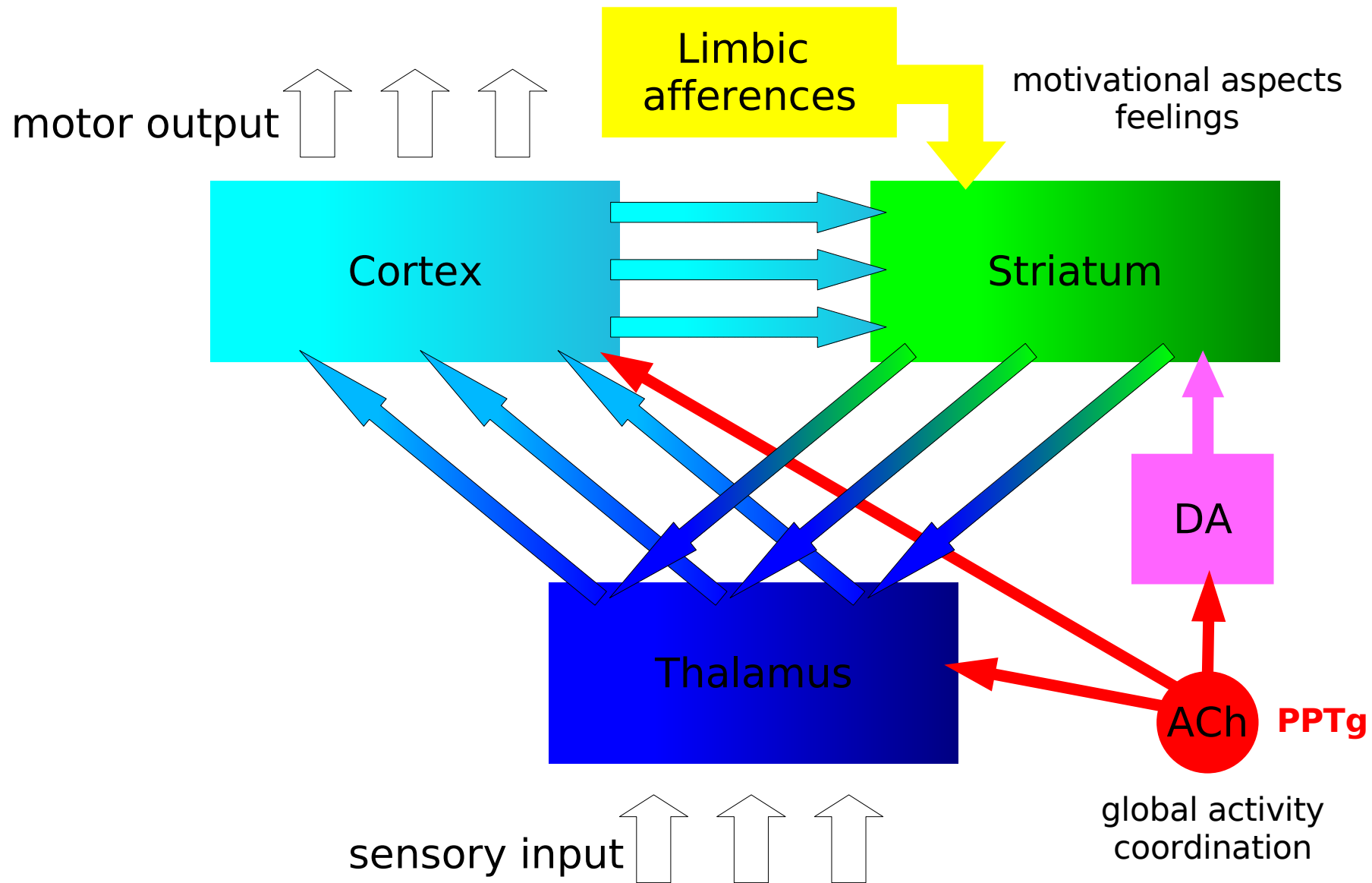
cortico-striato-thalamic loop





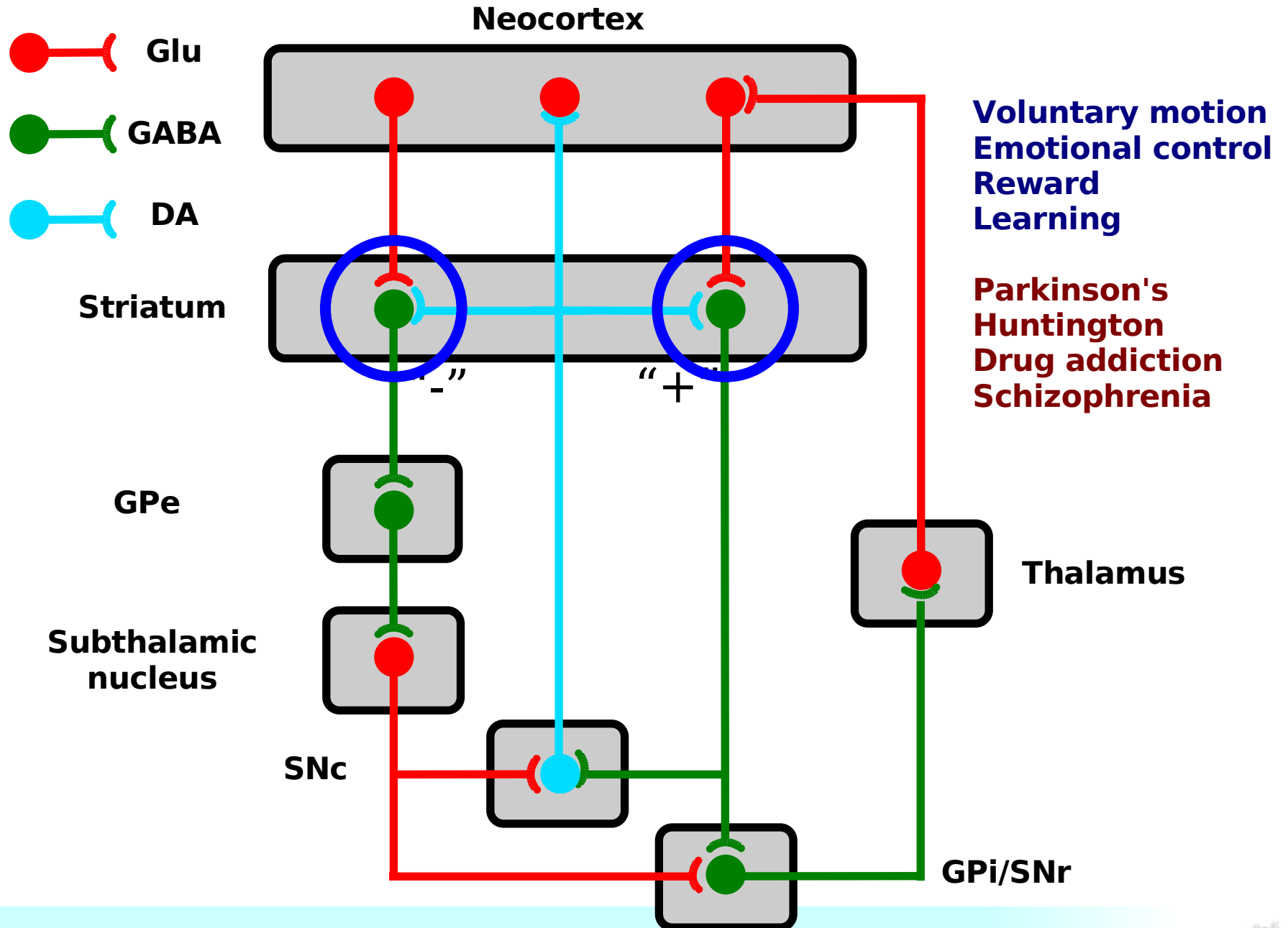


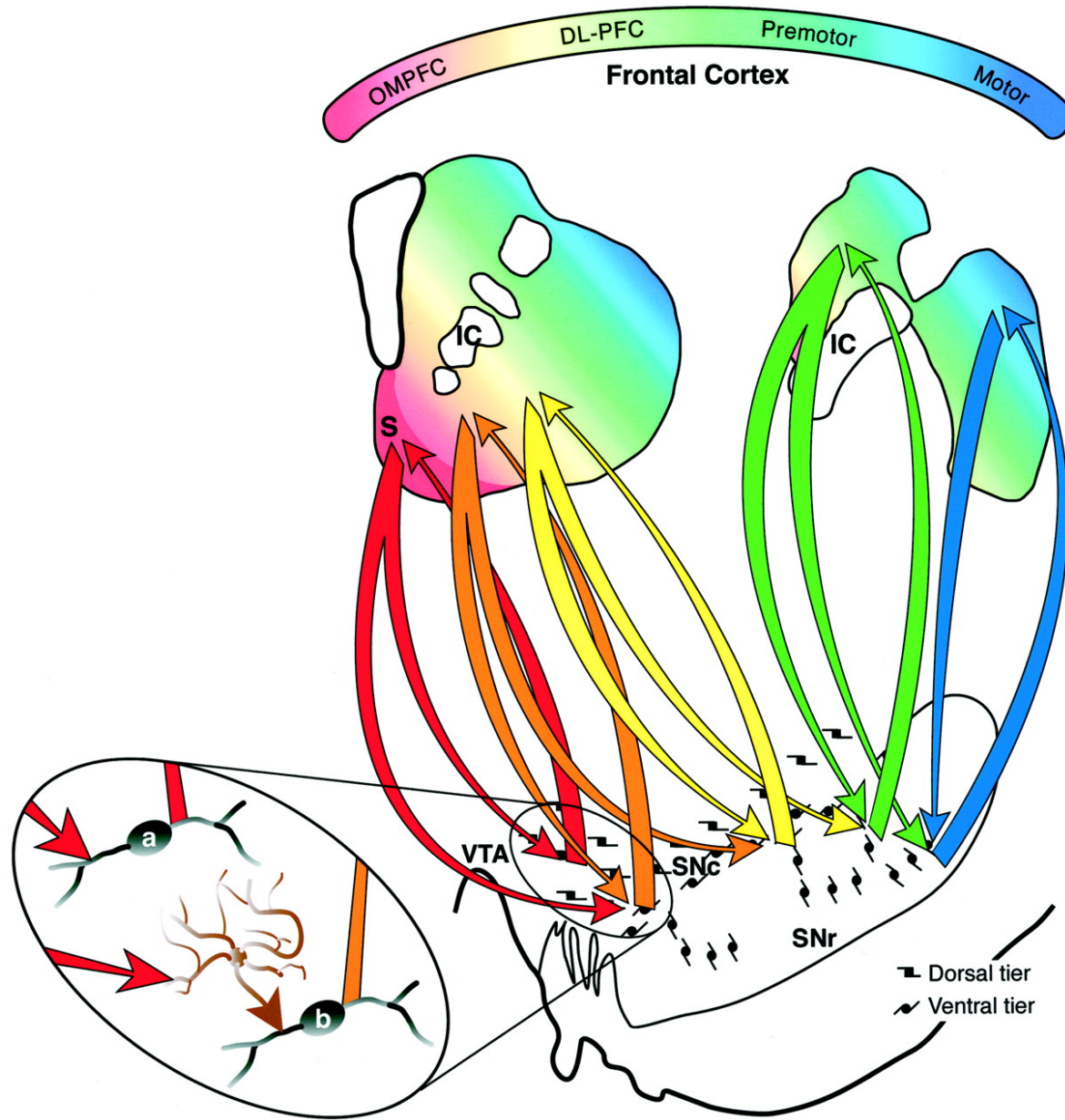


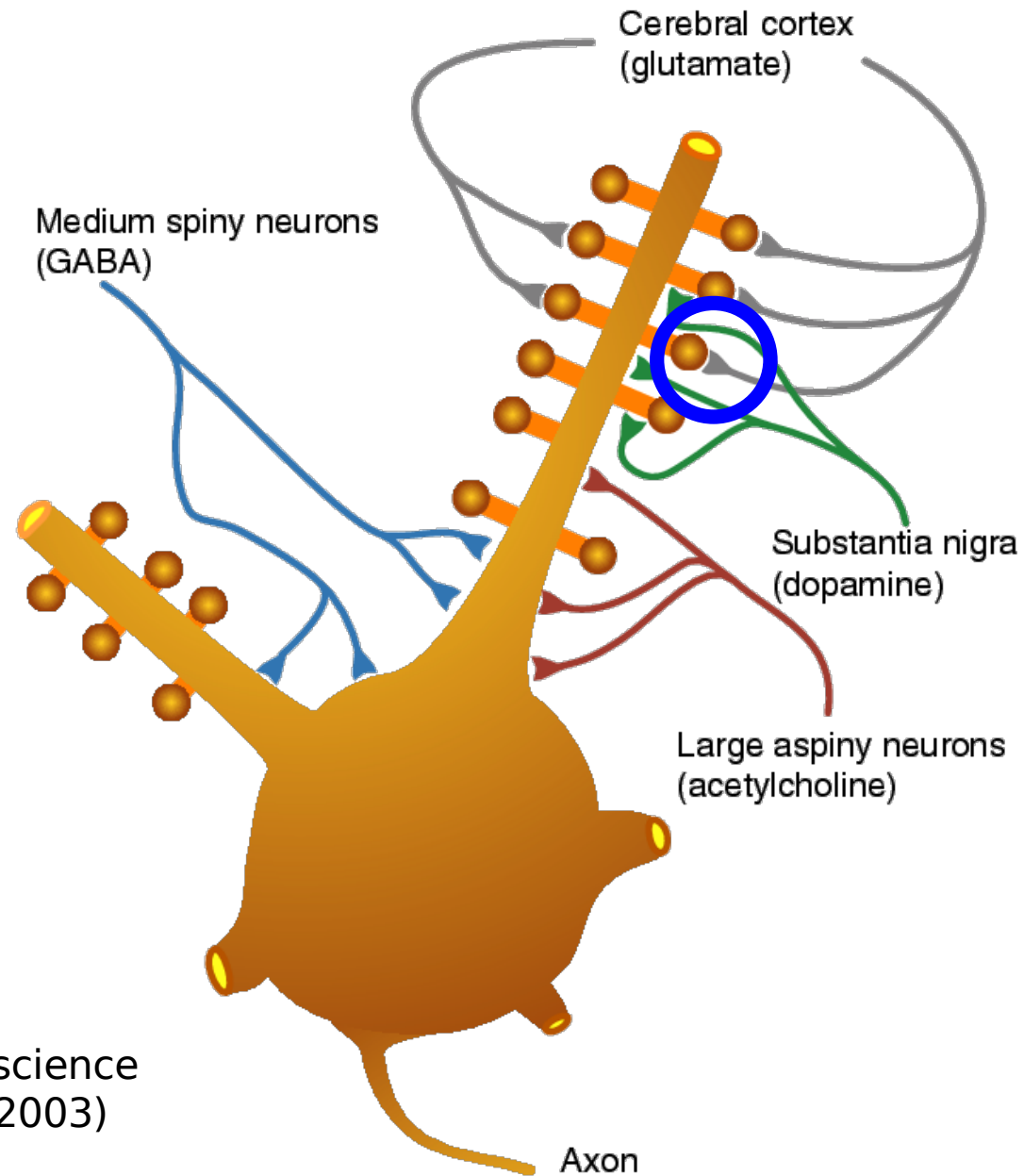




Dopamine mesotelencephalic pathway



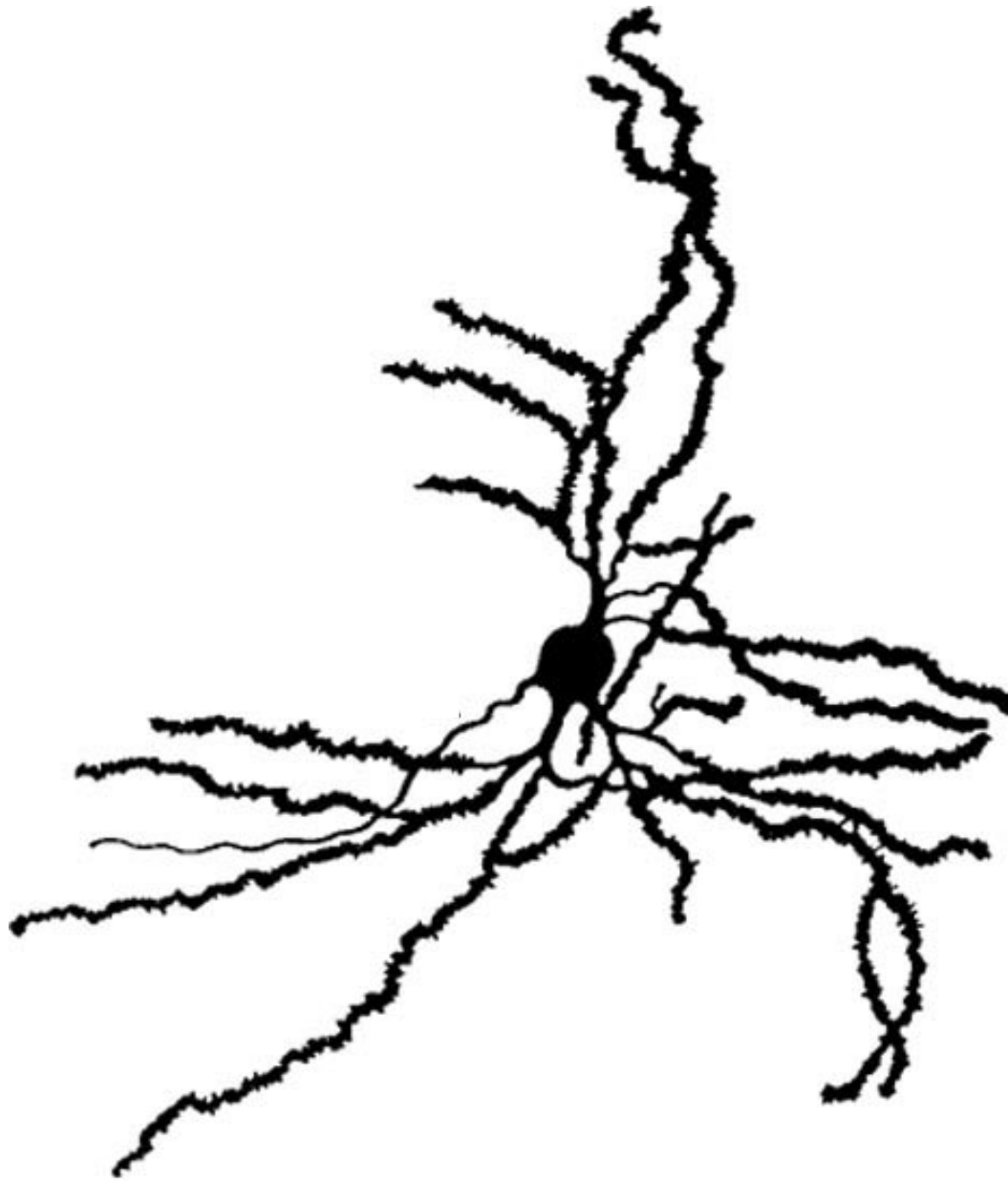


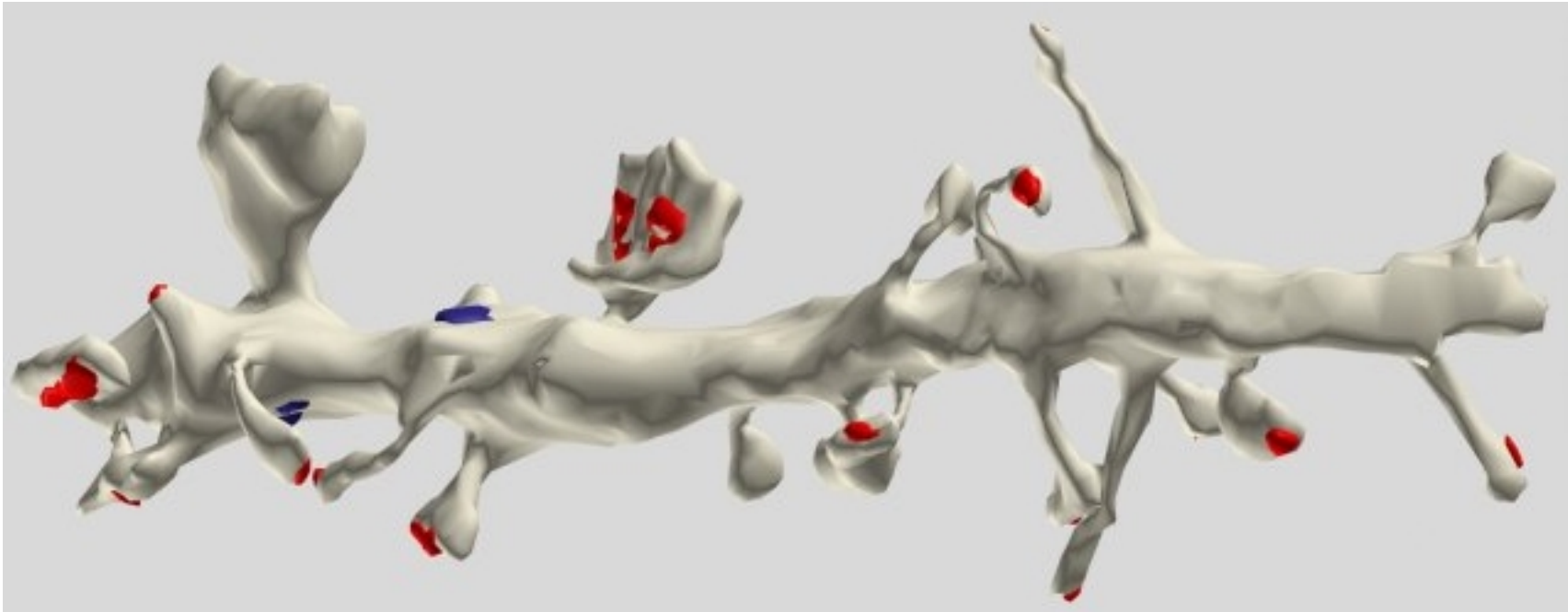


Fundamental Neuroscience
Squire et al. 2nd ed(2003)

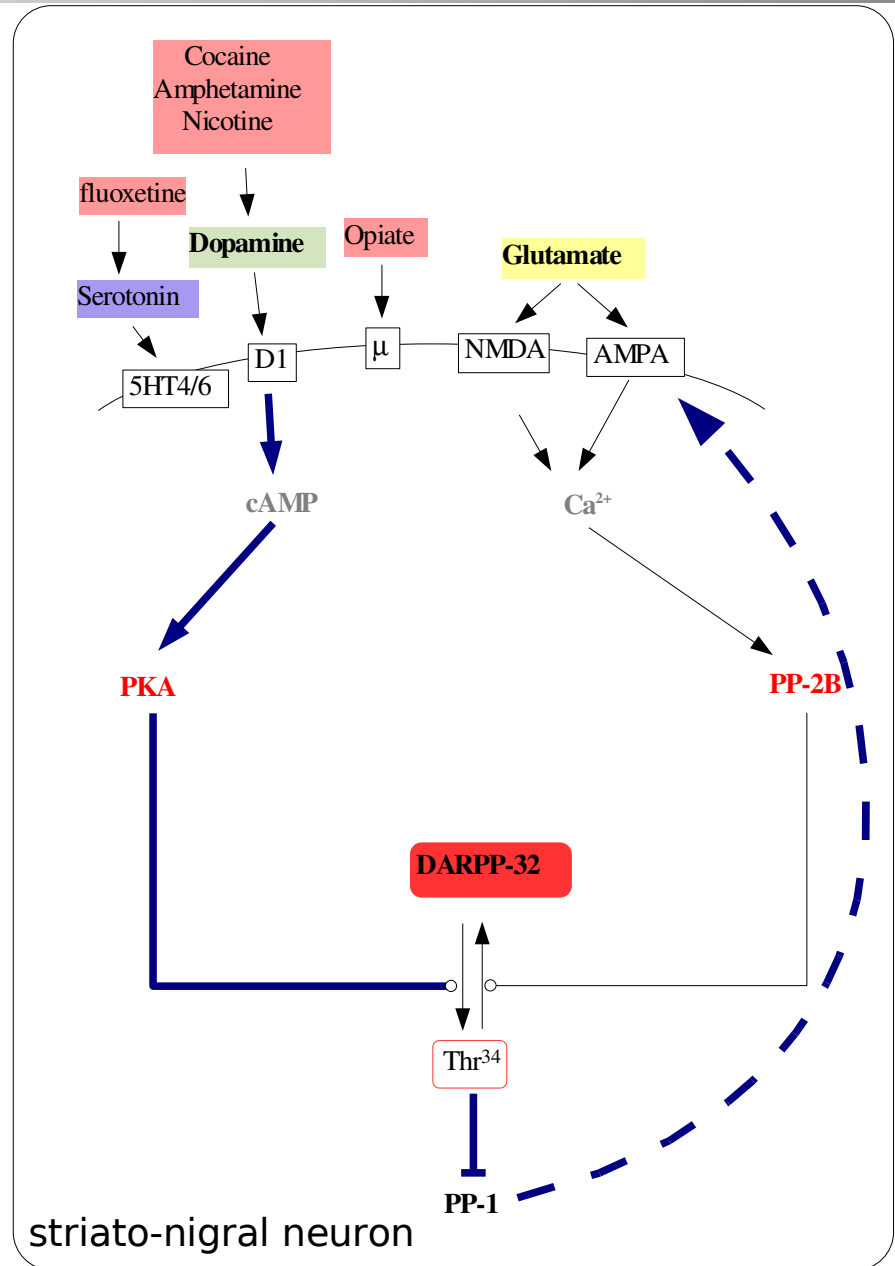
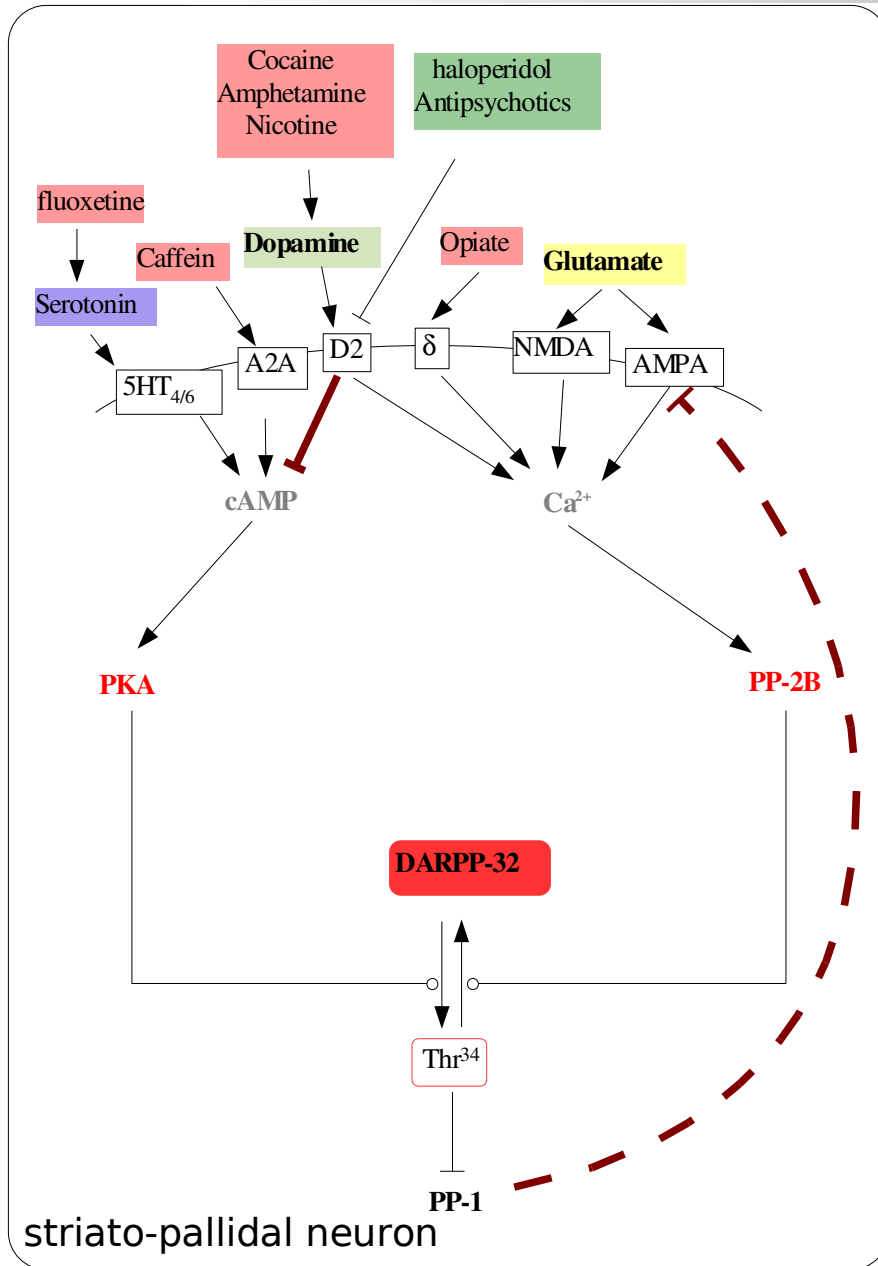


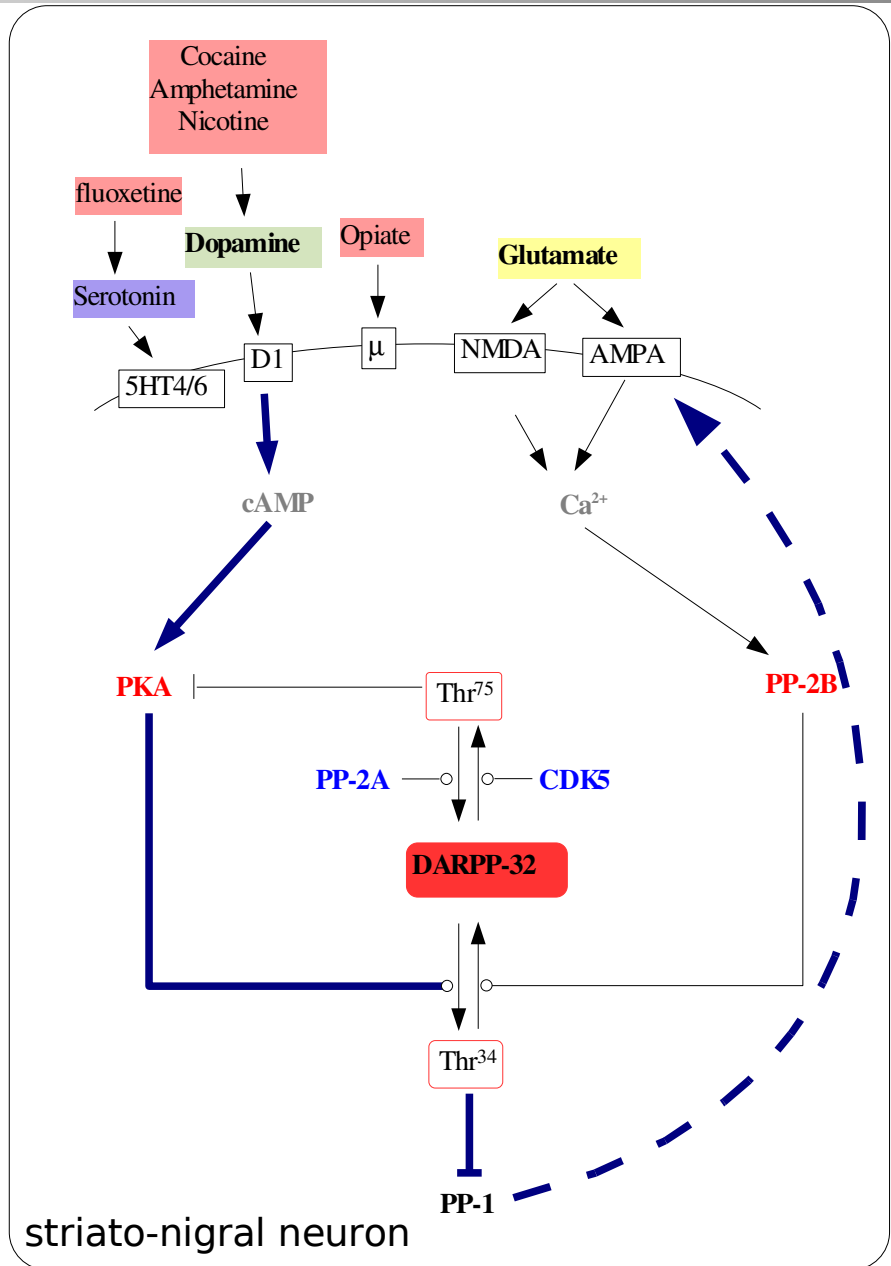
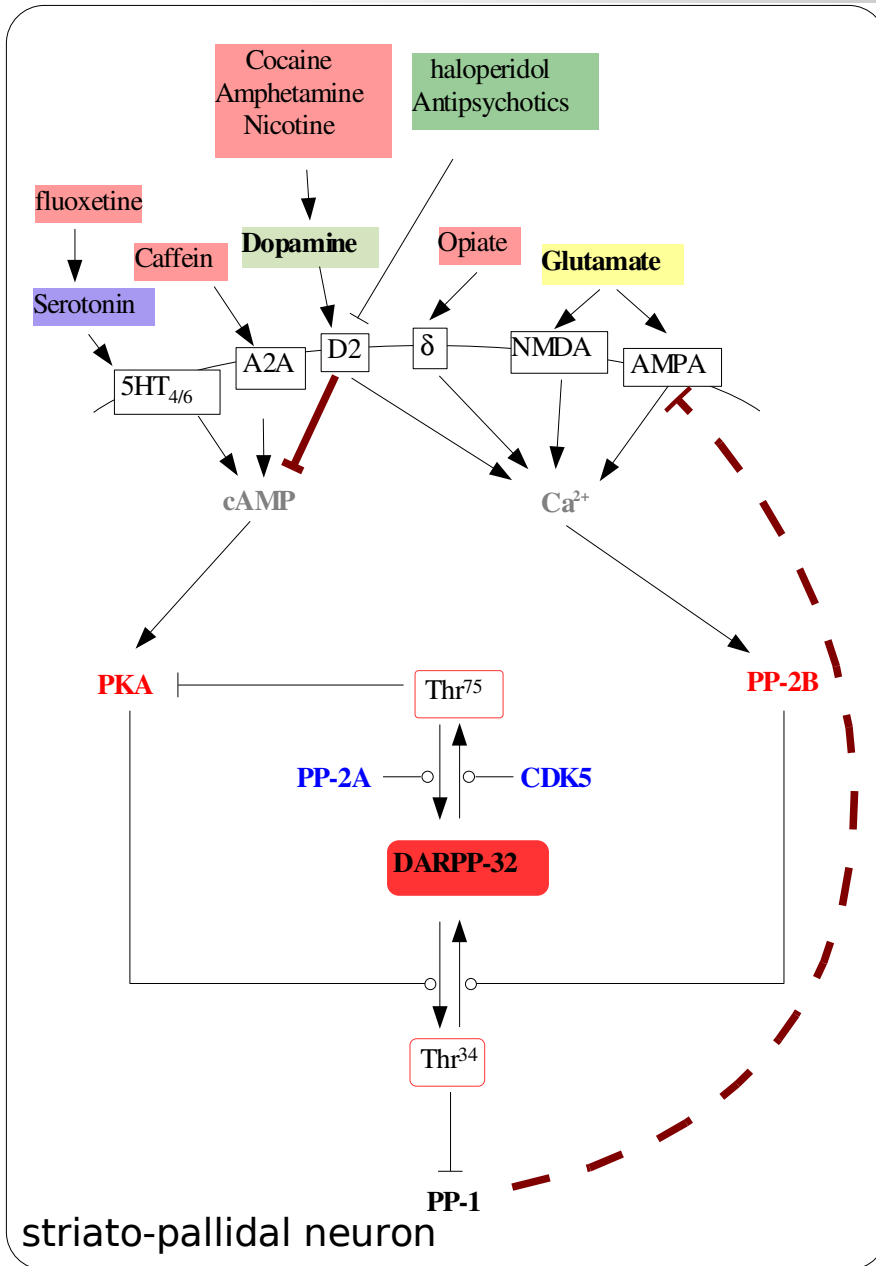
the Medium Spiny Neuron of the striatum

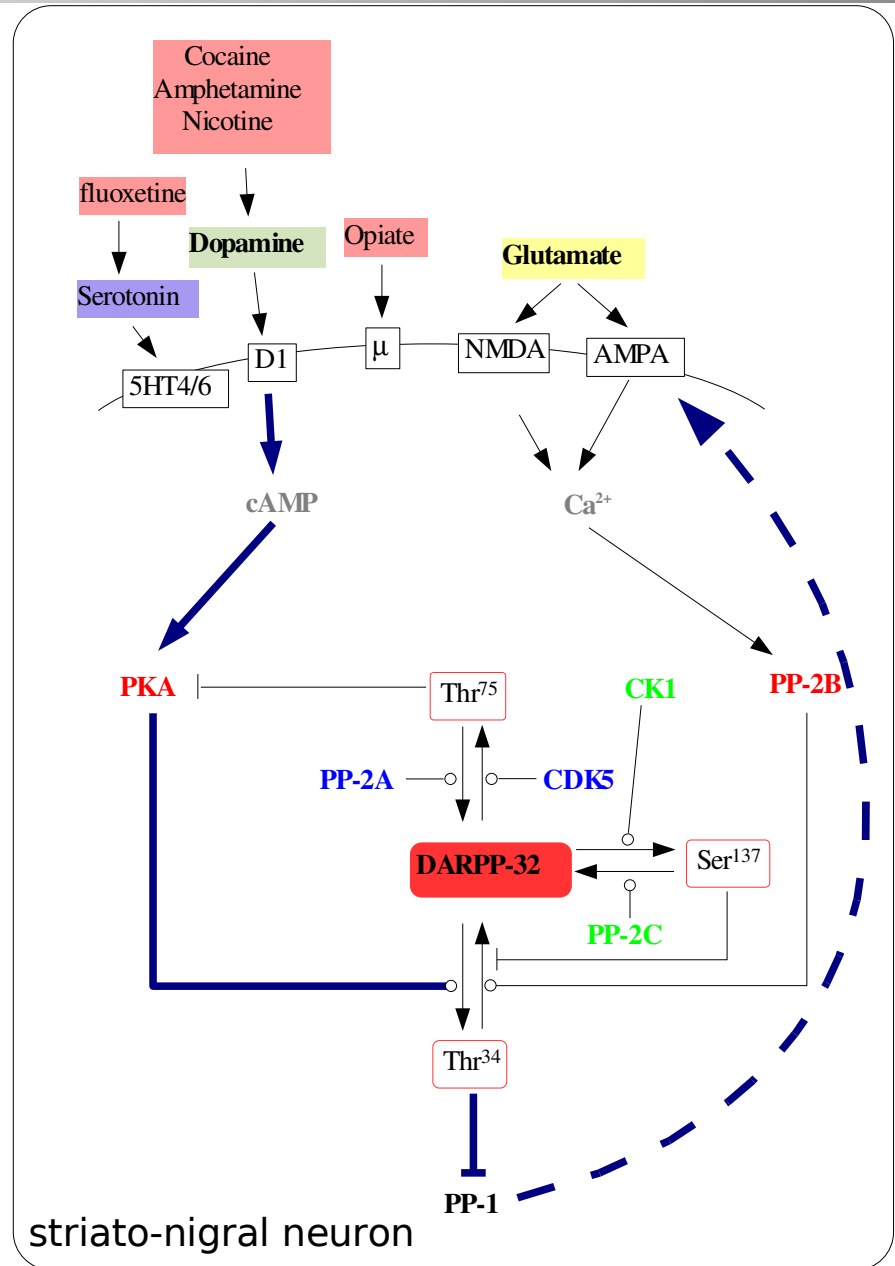
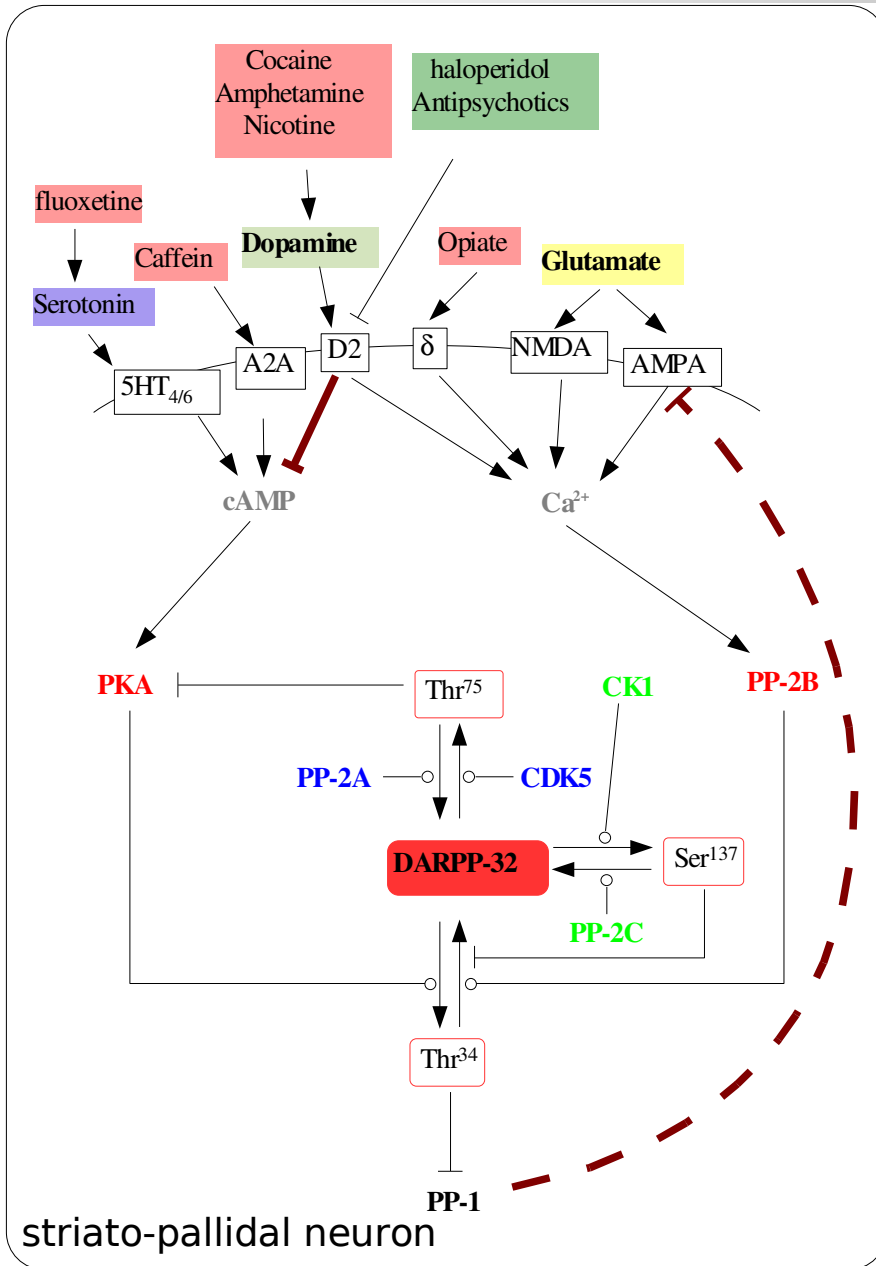


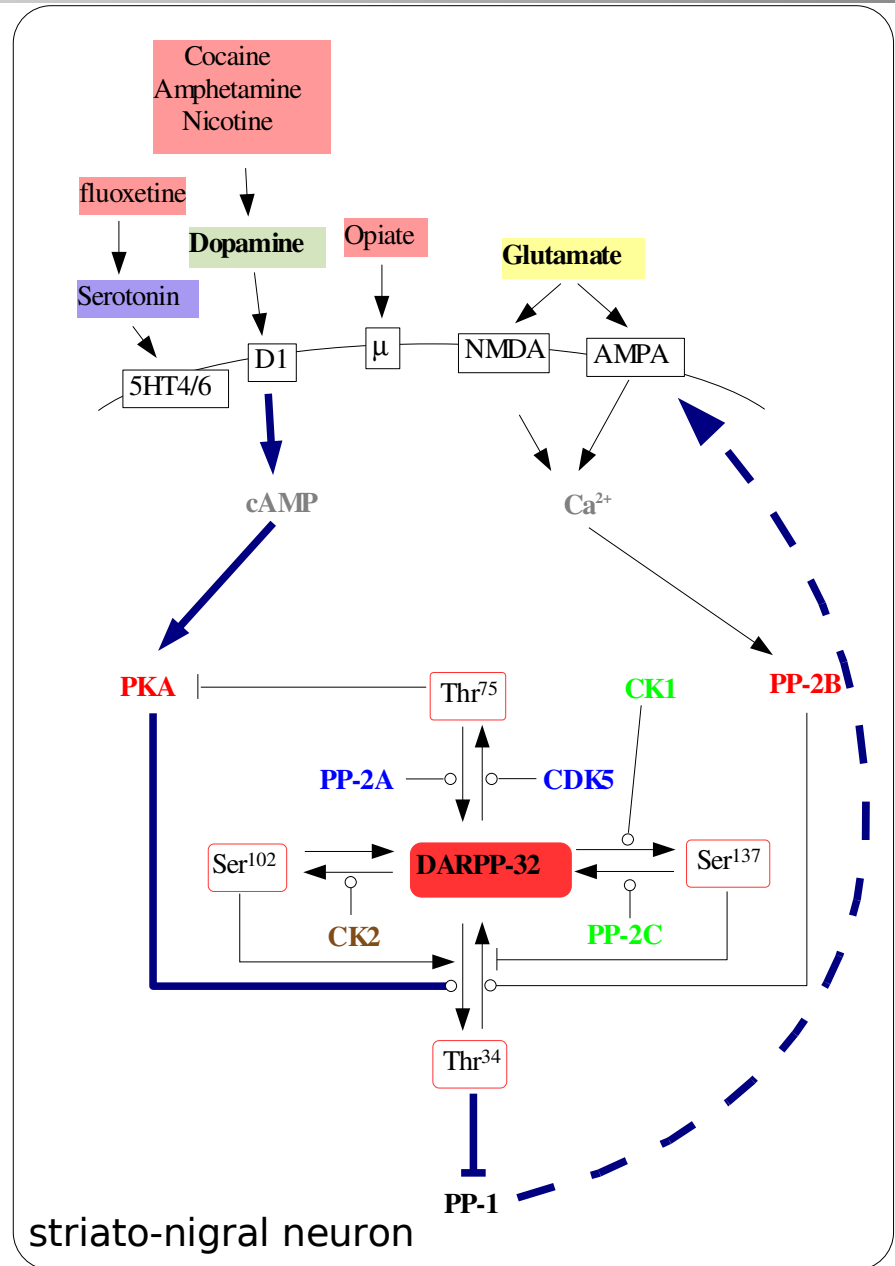
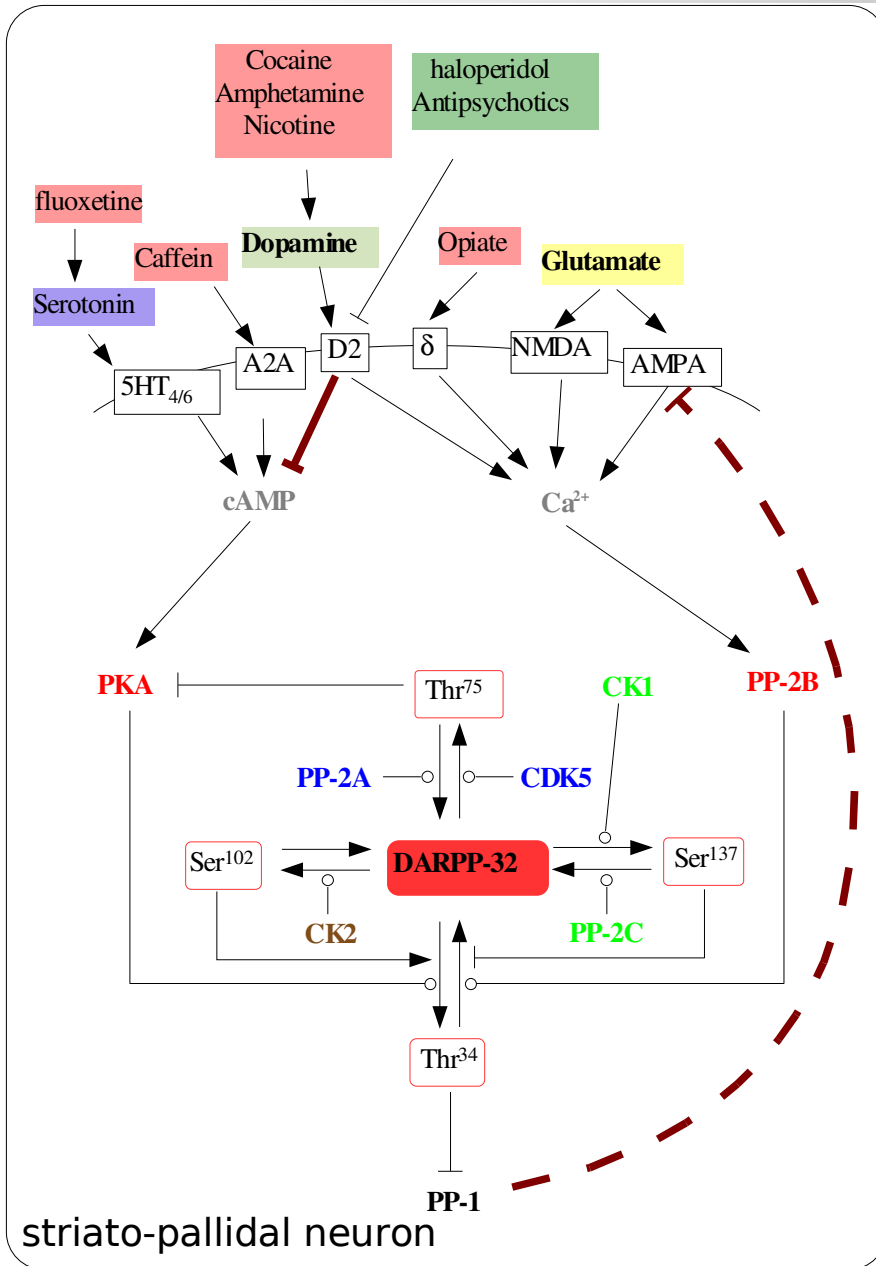


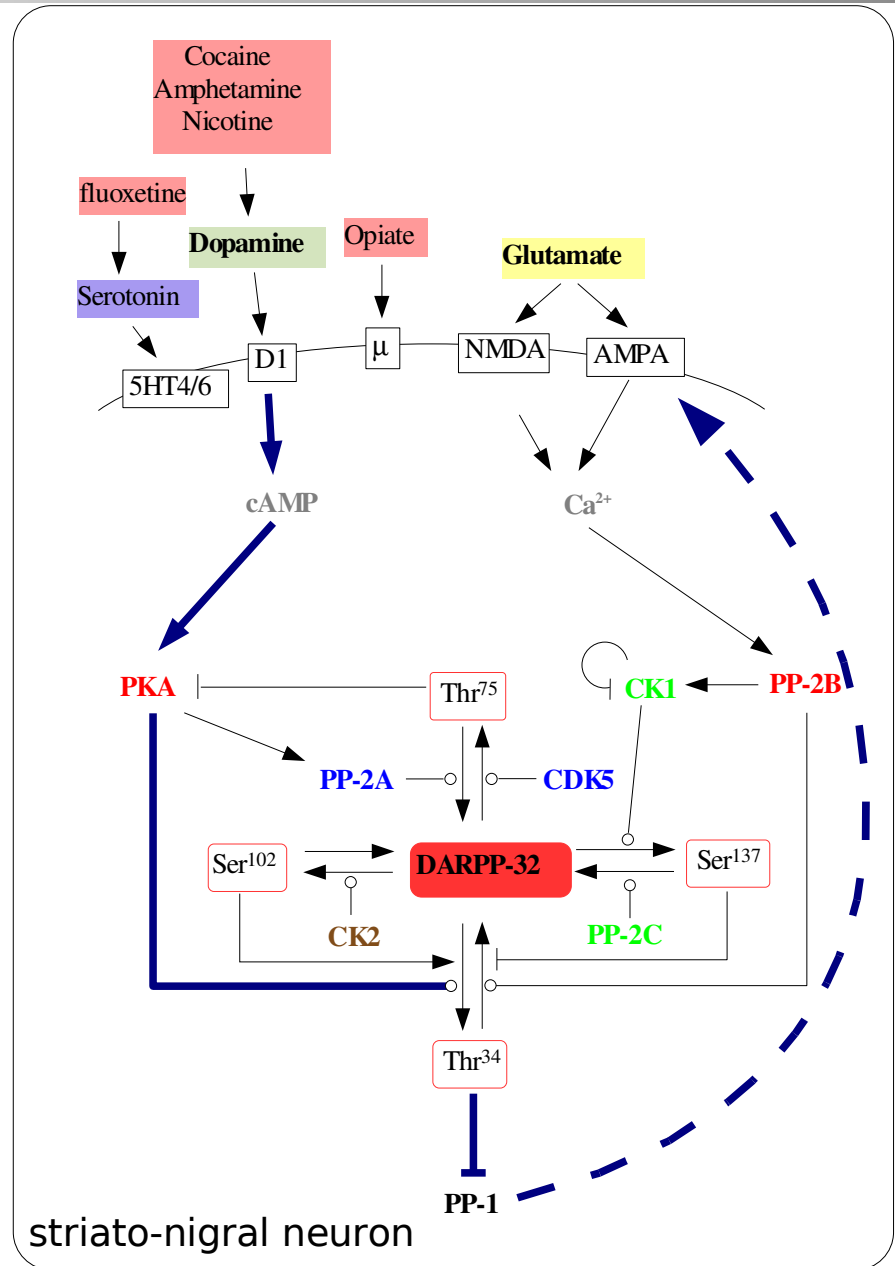
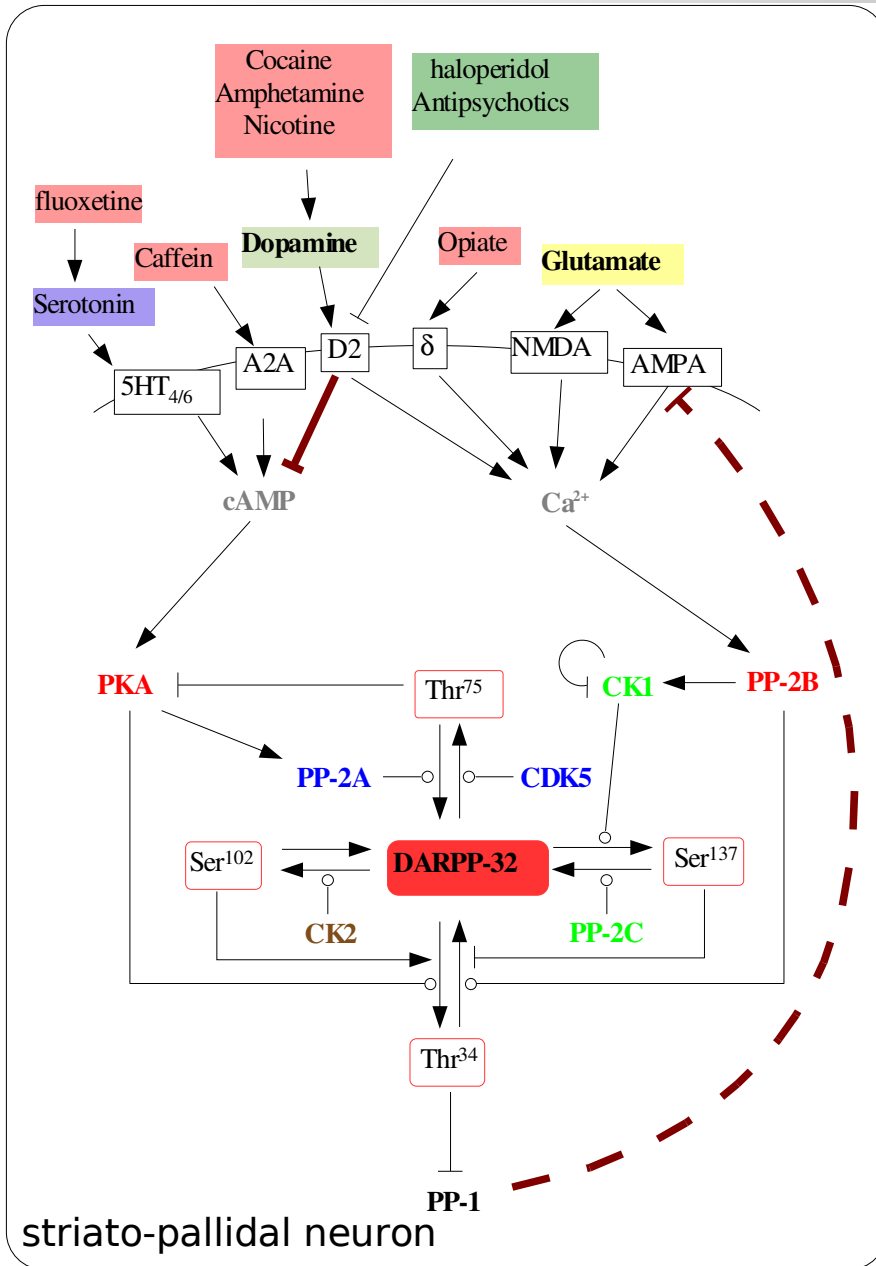
Biological model of DARPP-32 regulation



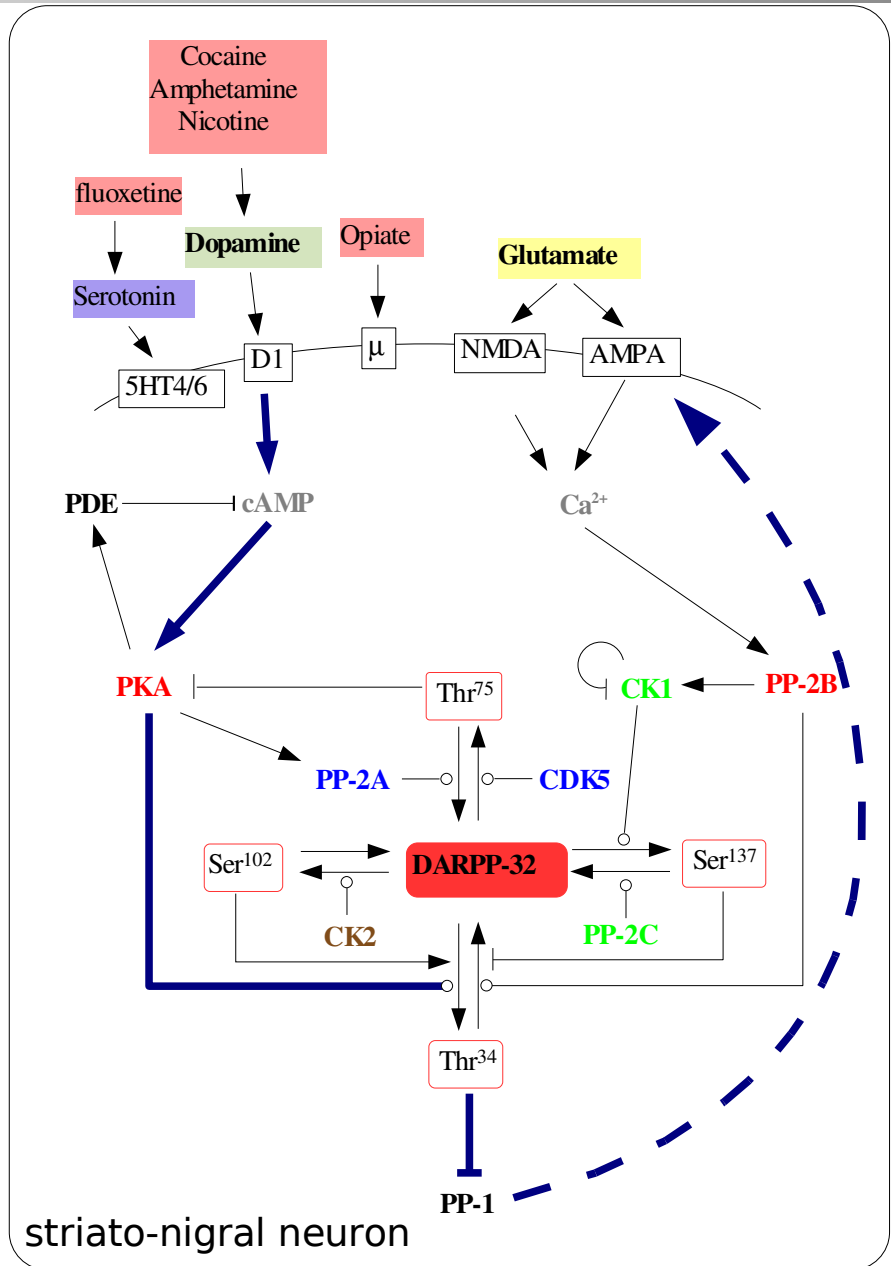
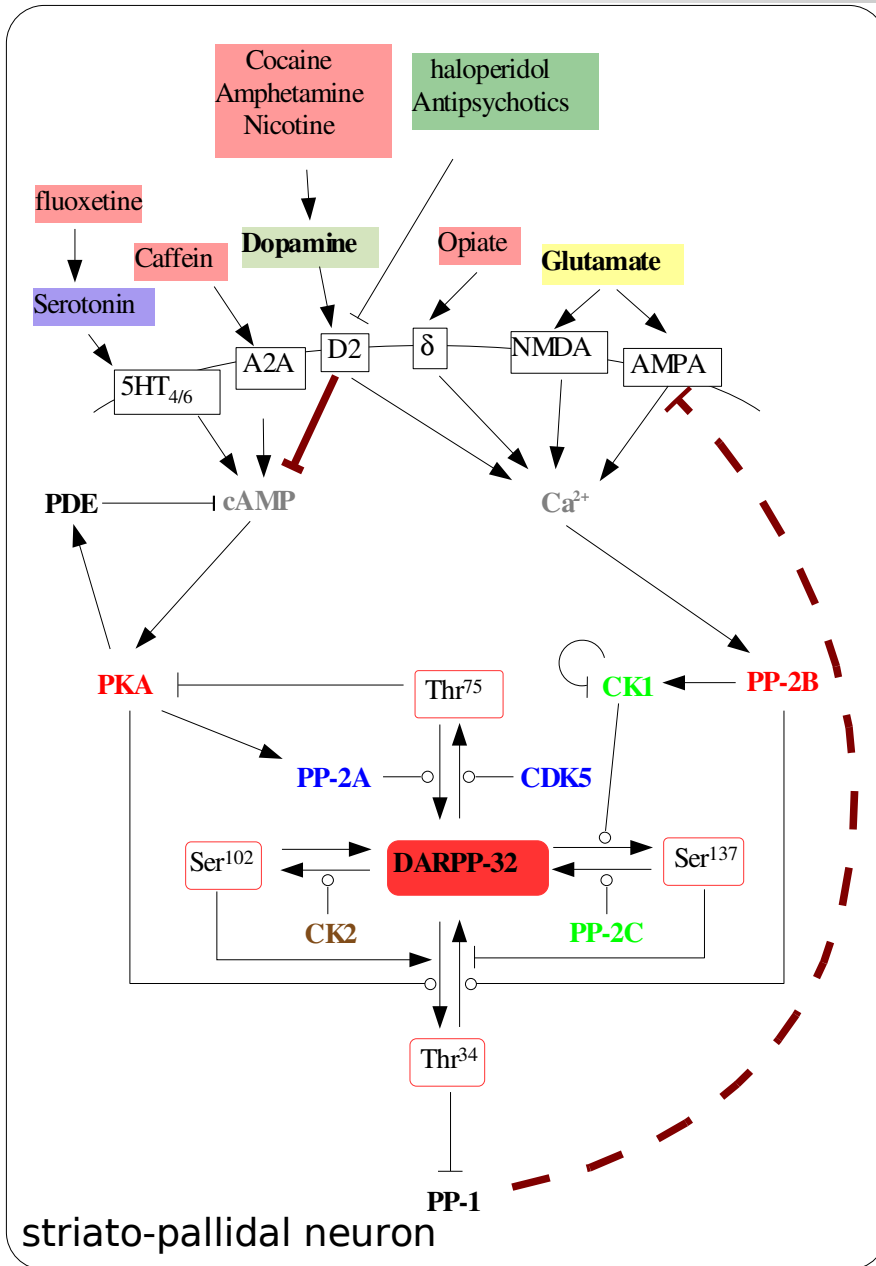




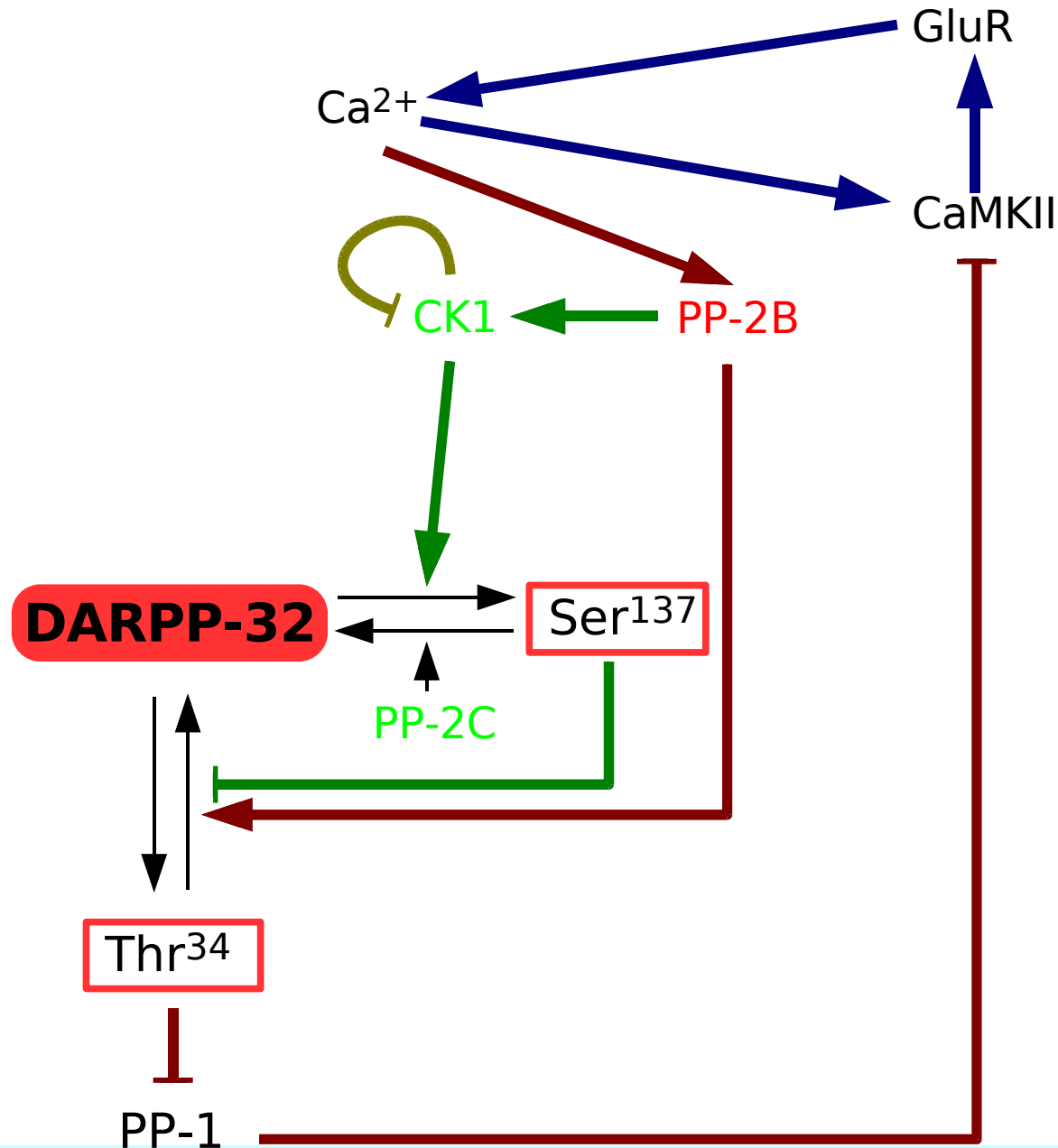


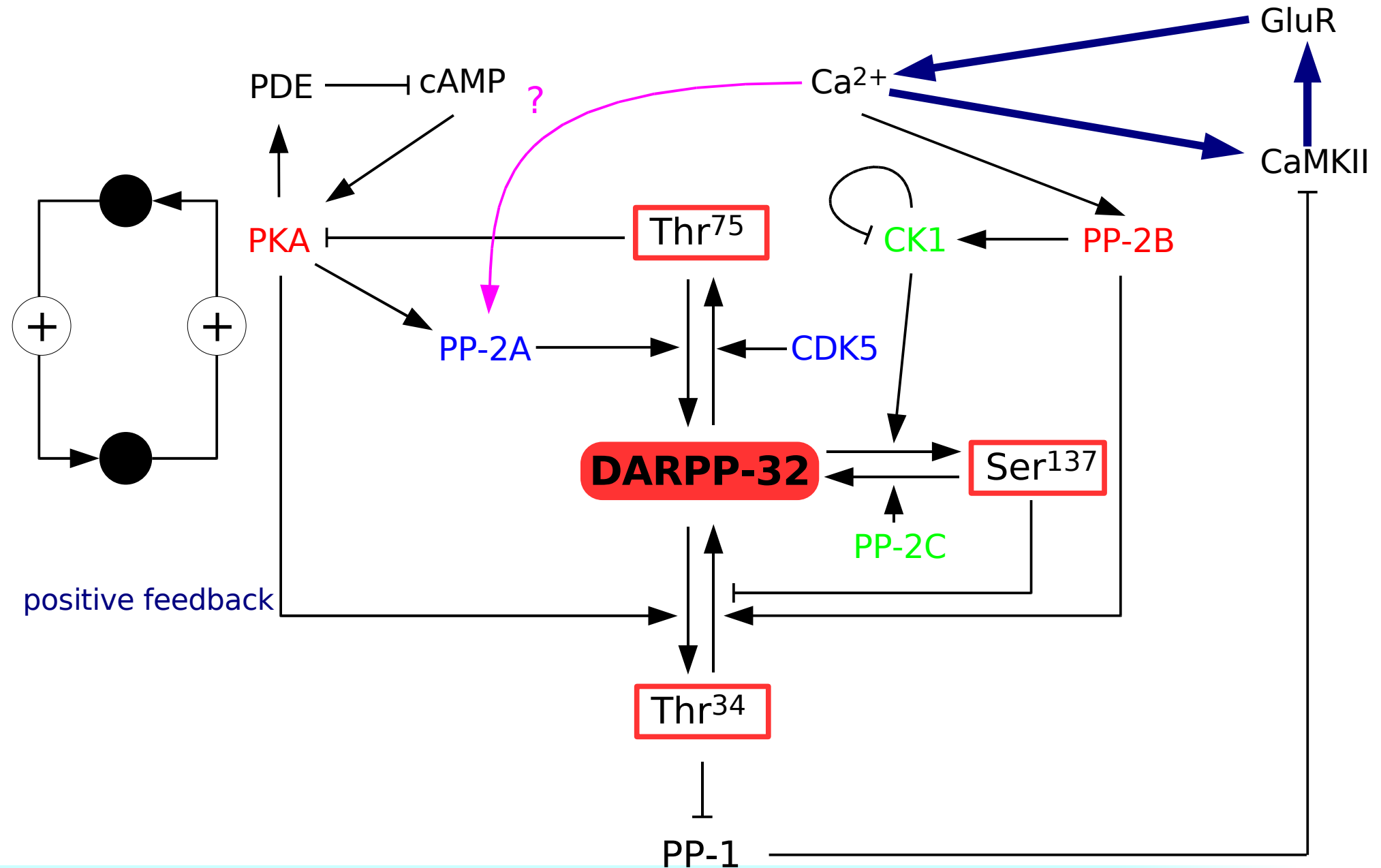


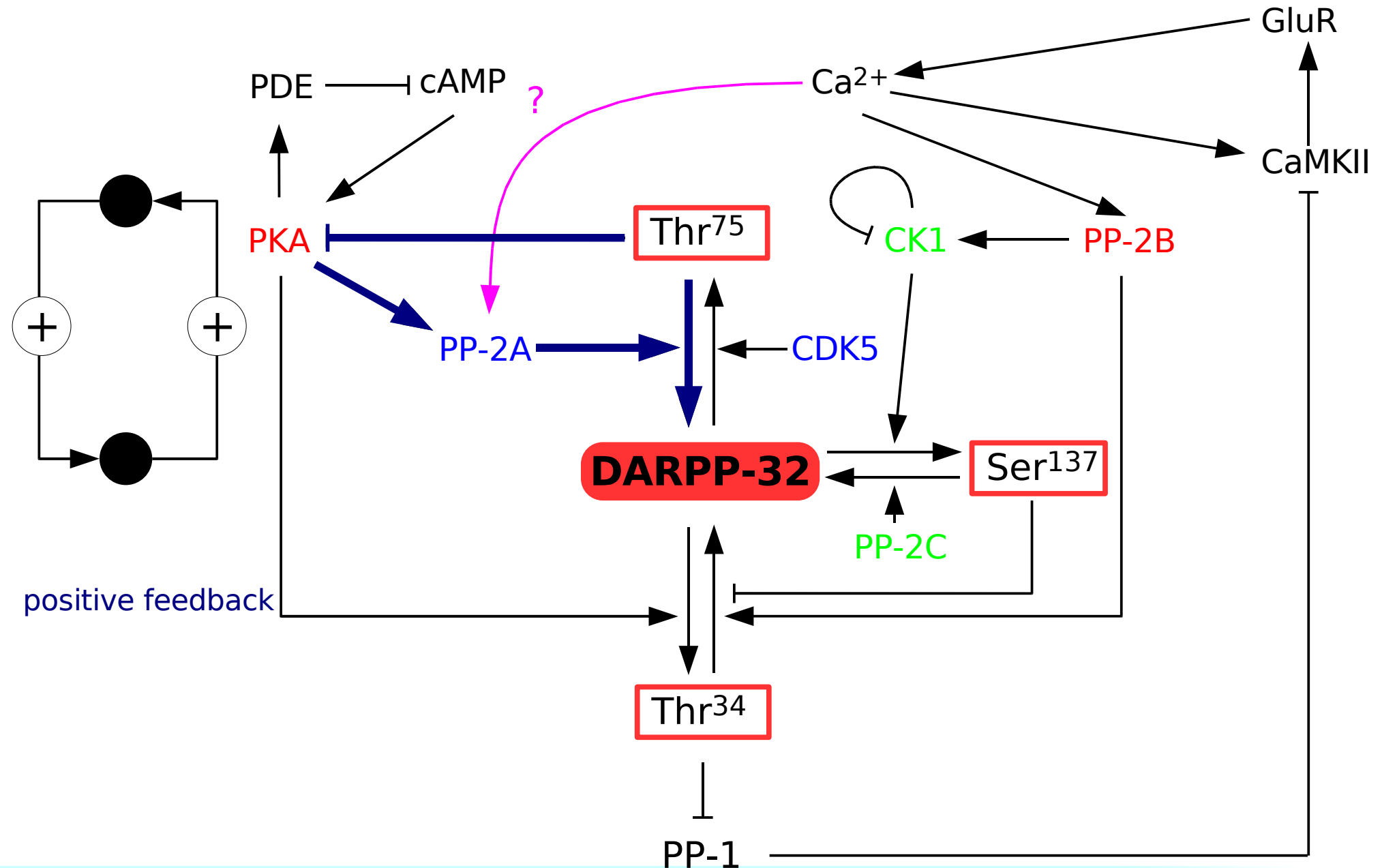
Biological model of DARPP-32 regulation

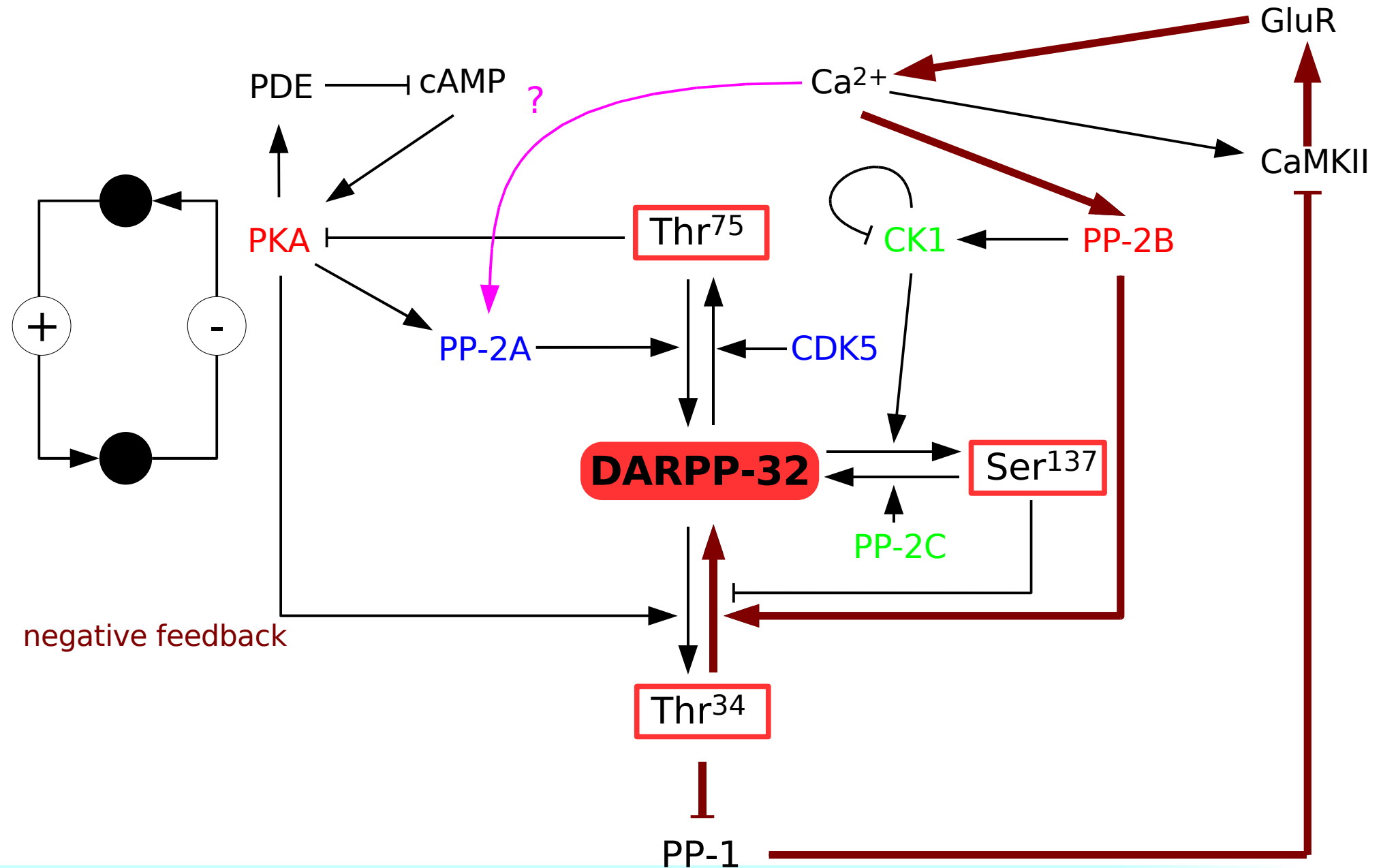


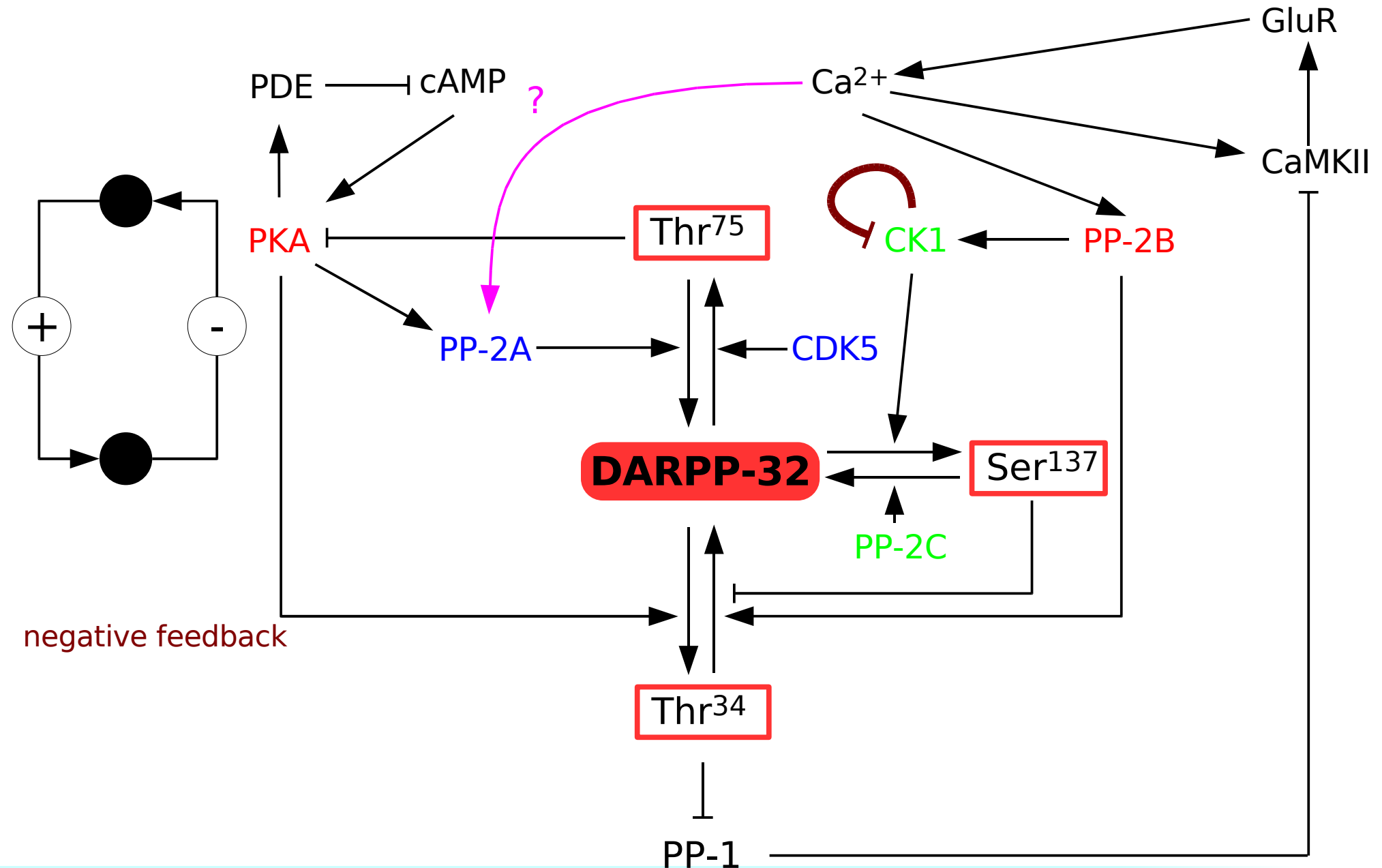
Negative loops: "russian dolls"

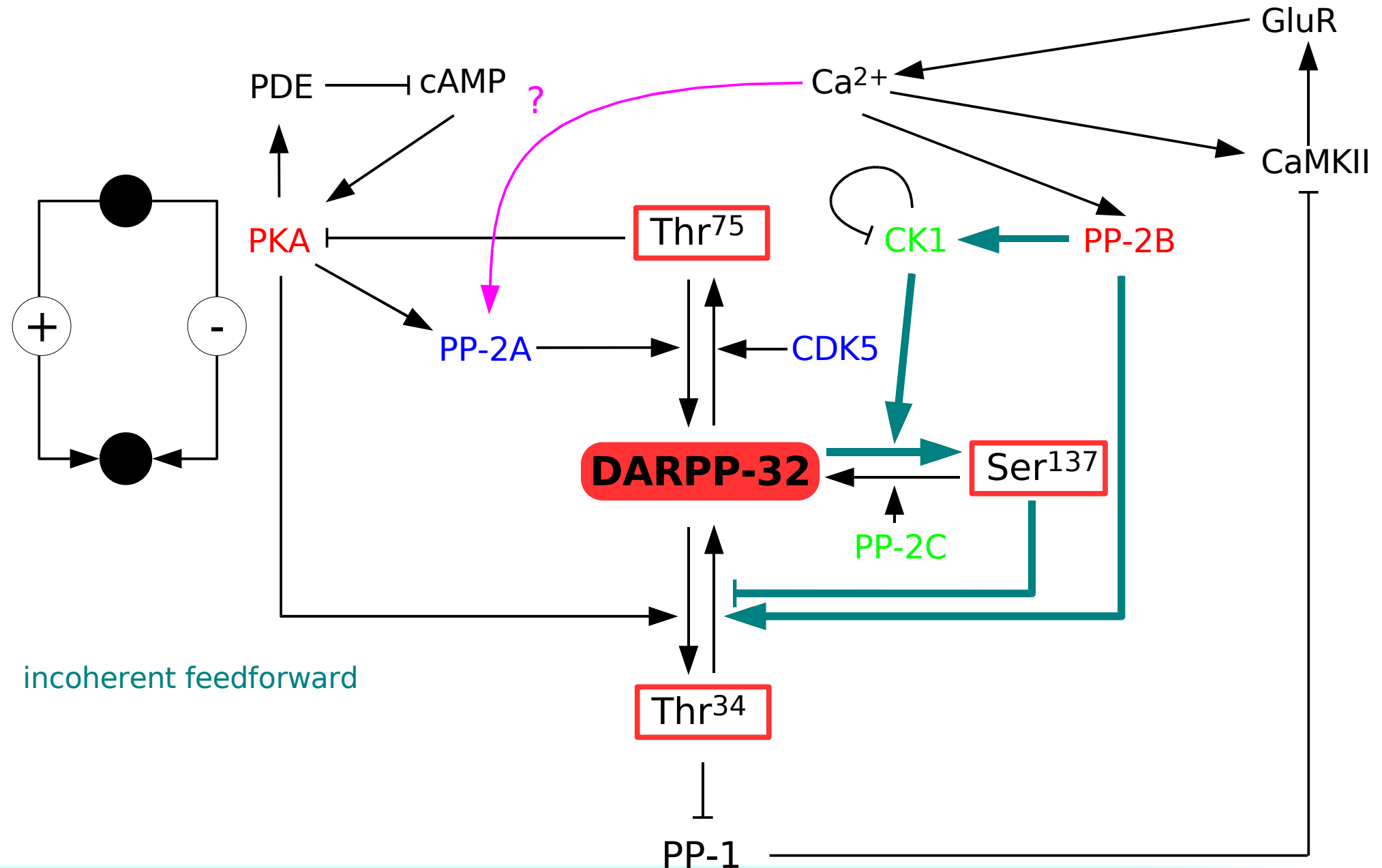






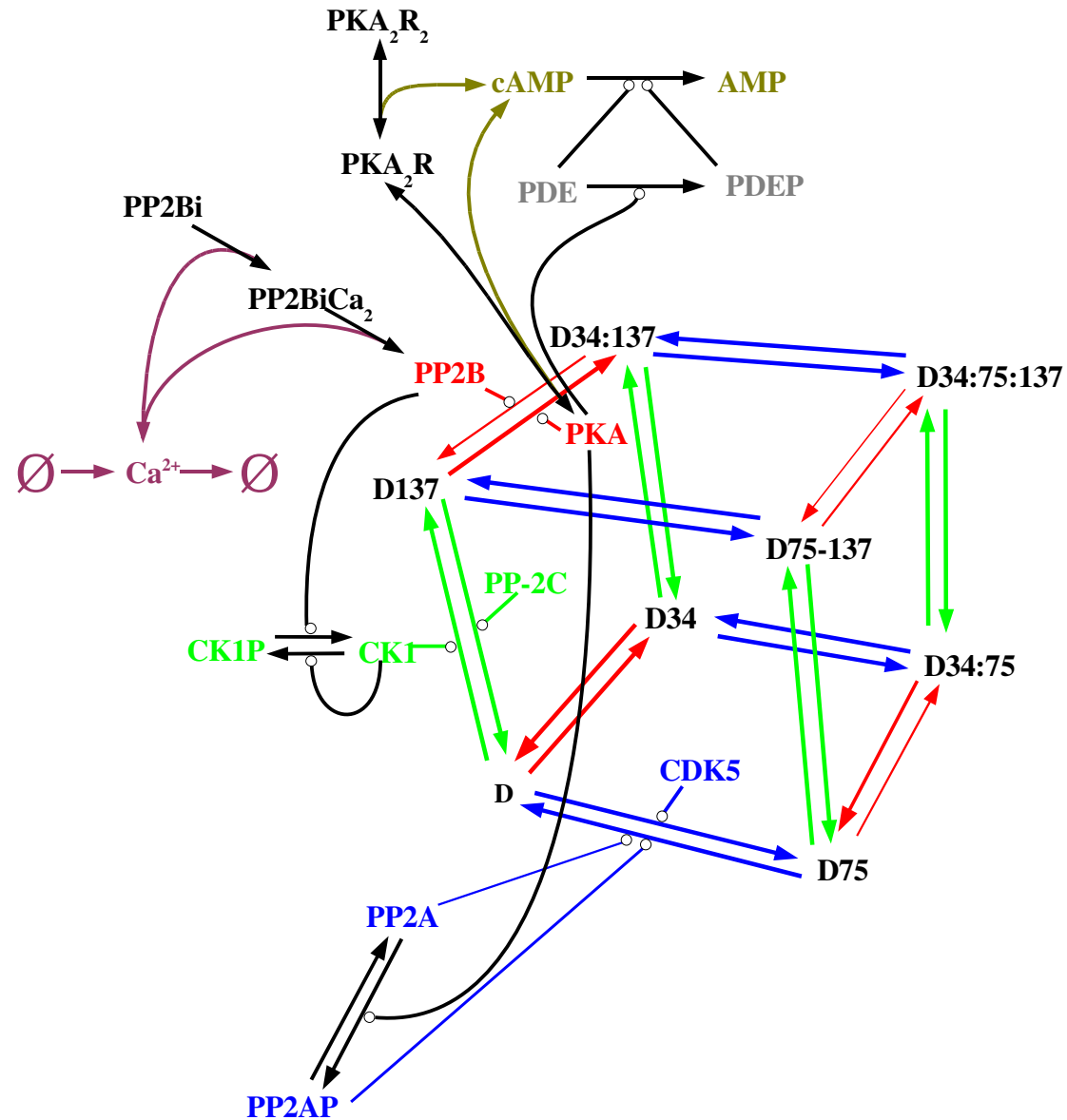




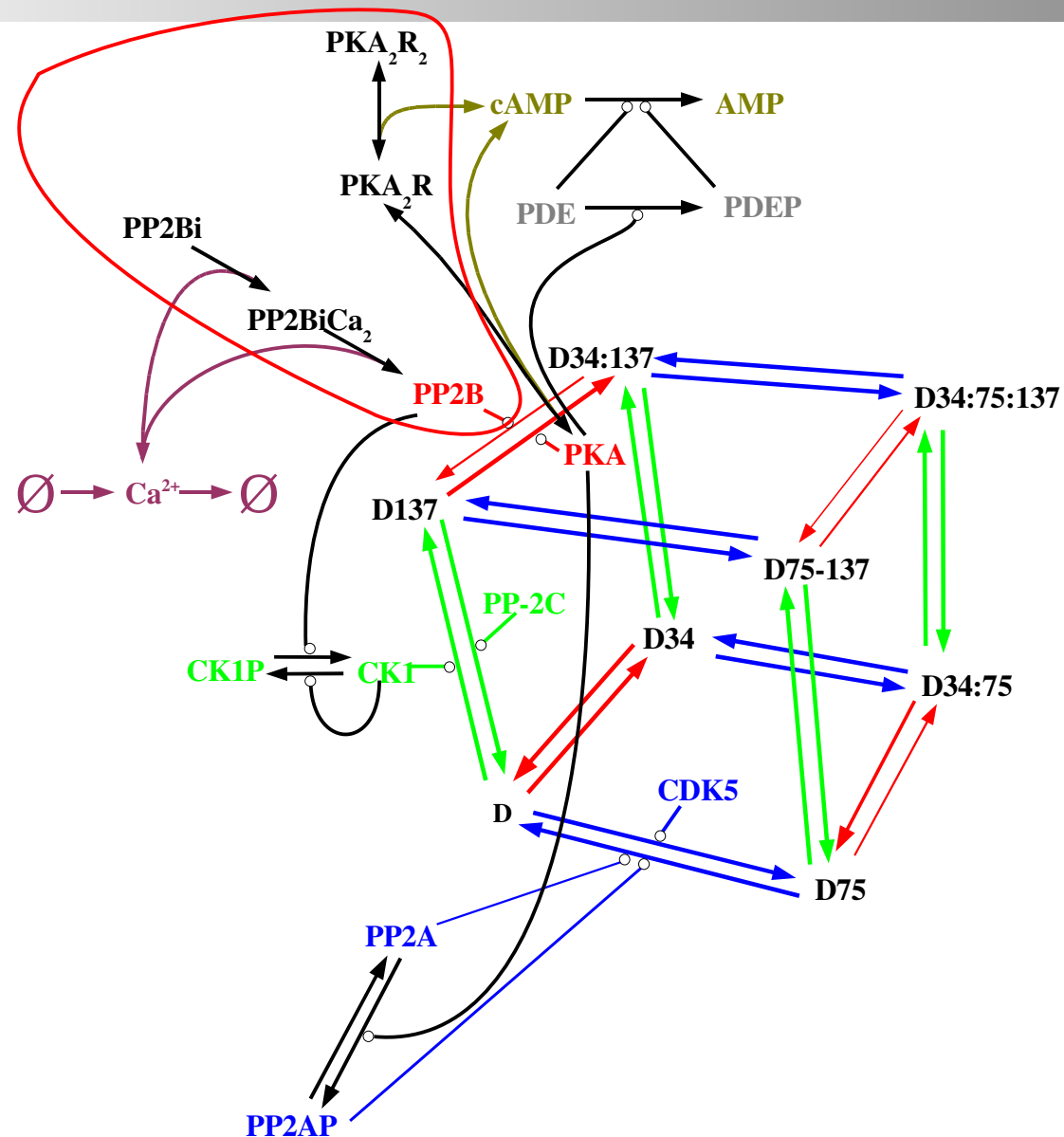


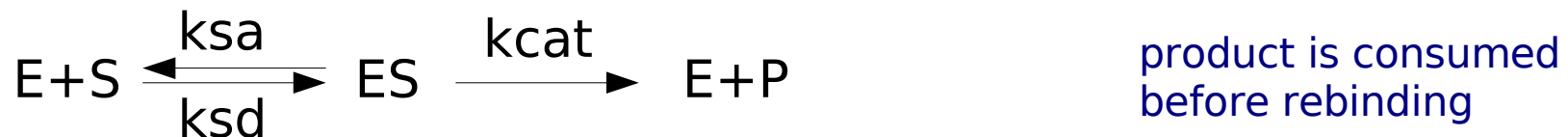
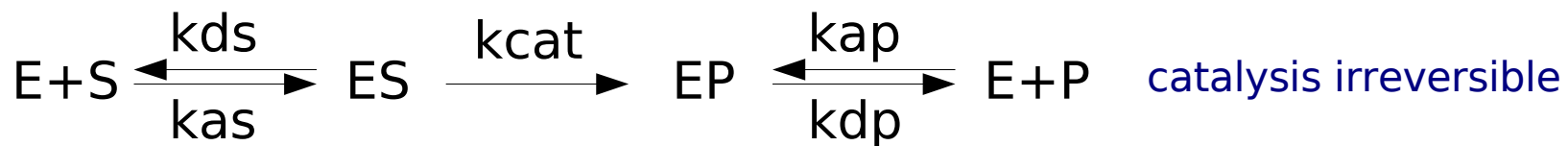
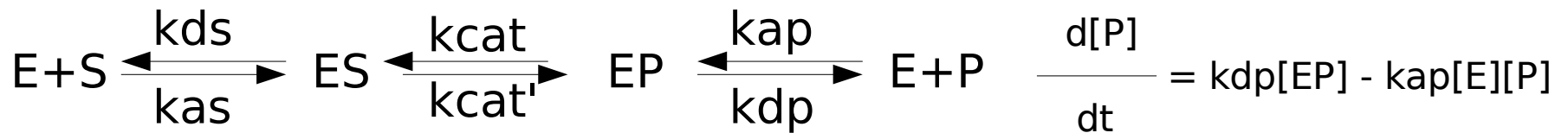
incoherent feedforward





stolen from DQCS

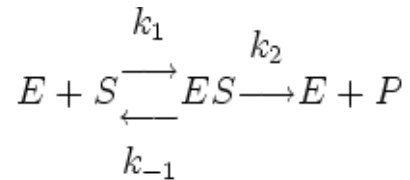




$$\frac{d[P]}{dt} = \frac{[E] k_{cat}}{1 + \frac{K_m}{[S]}}$$







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

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

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

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

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

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

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

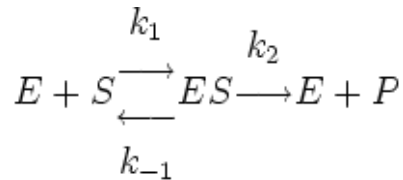
$$K_m = \frac{k_{-1} + k_2}{k_1}$$

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

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

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





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

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

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

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

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

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

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

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

steady-state!!!

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

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

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



77 species, 145 reactions

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

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



Euler method:

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

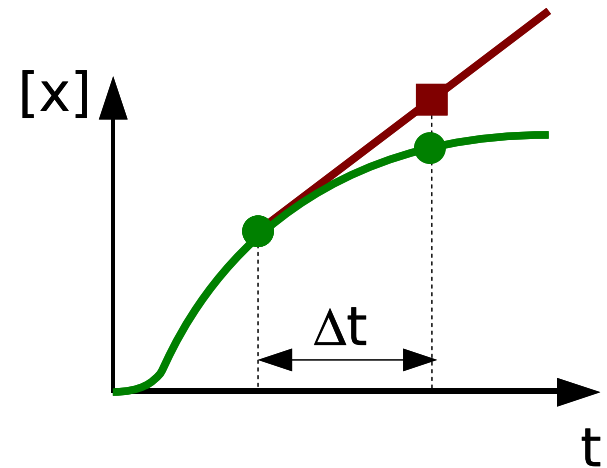
$$[x]_{t+\Delta t} \approx [x]_t + d[x]/dt \cdot \Delta t$$

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

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

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

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



4th order Runge-Kutta:

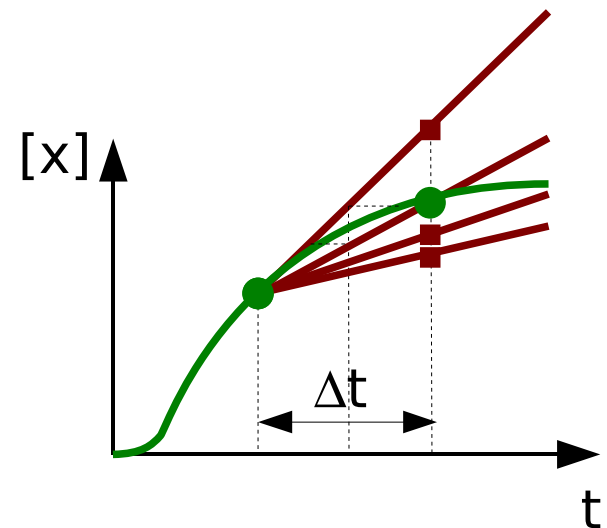
$$[x]_{t+\Delta t} = [x]_t + (F_1 + 2F_2 + 2F_3 + F_4)/6 \cdot \Delta t$$

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

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

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

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



- <http://www.e-cell.org/>
- Takahashi *et al.* (2005). A multi-algorithm, multi-timescale method for cell simulation. *Bioinformatics*, 20: 538-546



d20 eml

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

Icons: Selection, Link, Diagram, System, Star, Text

ObjectEditor

Summary PropertyList ShapeProperty

ID: D_PKA

SystemPath: /

ClassName: MichaelisUniUniFluxProcess

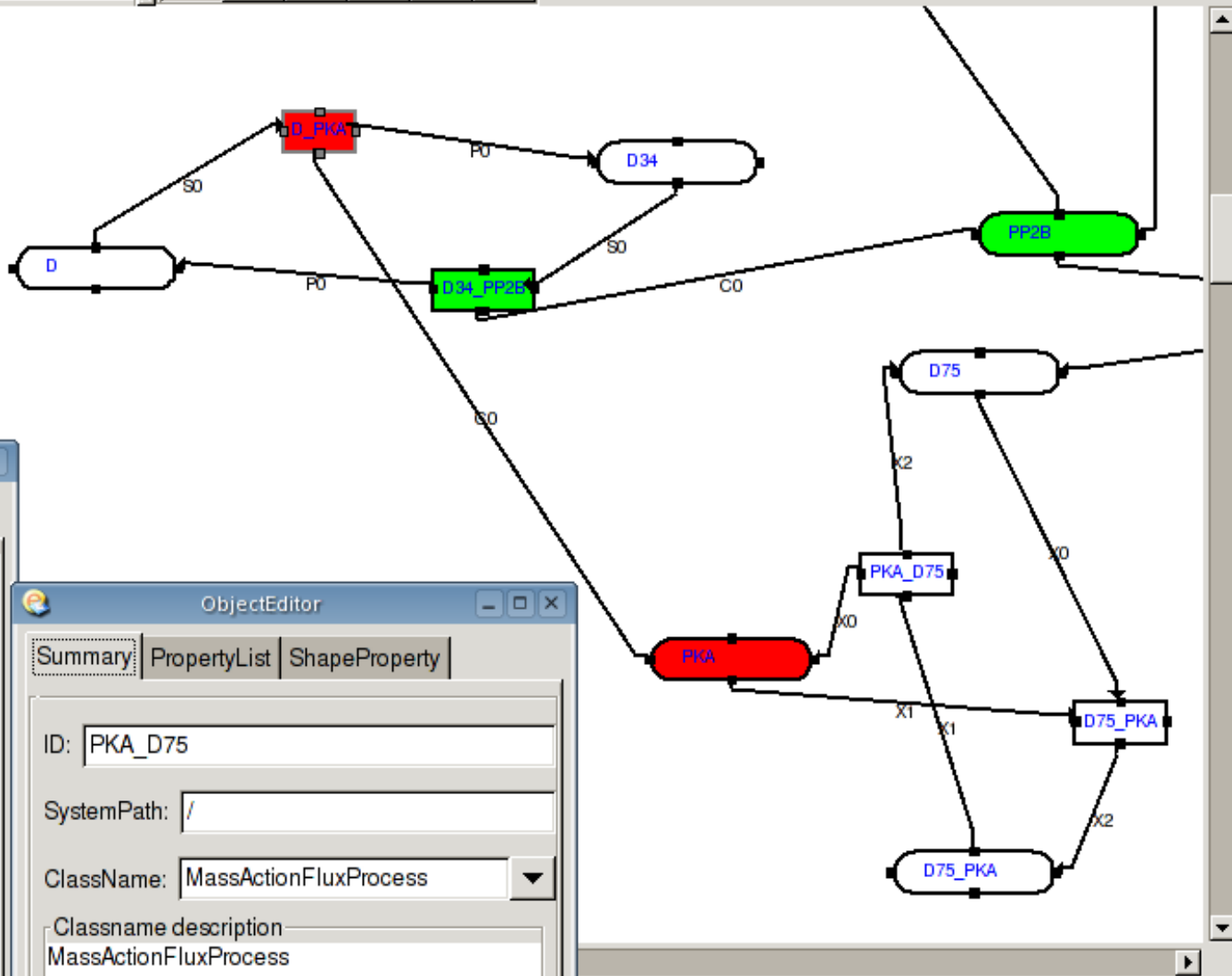
Classname description
MichaelisUniUniFluxProcess

ObjectEditor

Summary PropertyList ShapeProperty

Name	Value
KcF	2.7
Name	
Activity	0.0
KmP	1.0
Priority	0
KmS	2.4e-06
IsContinuous	1
VariableReferenceList	['S0', 'Variable: 'D' '1']

Add Delete



ObjectEditor

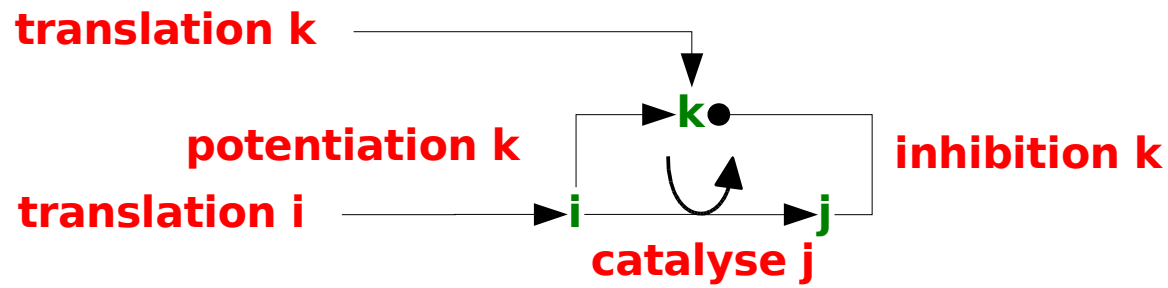
Summary PropertyList ShapeProperty

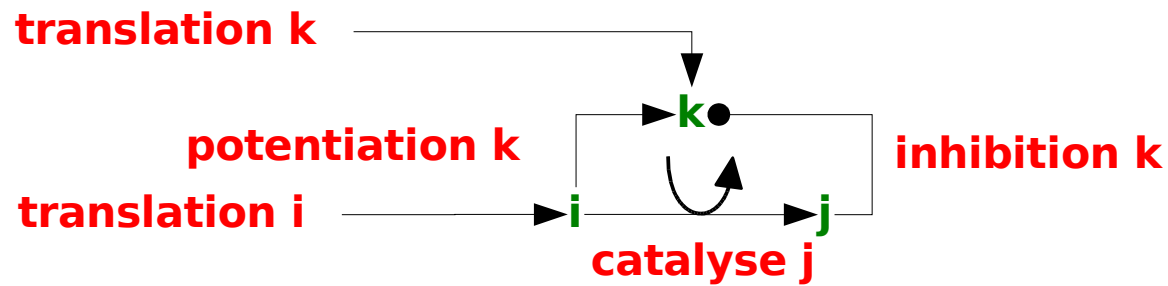
ID: PKA_D75

SystemPath: /

ClassName: MassActionFluxProcess

Classname description
MassActionFluxProcess



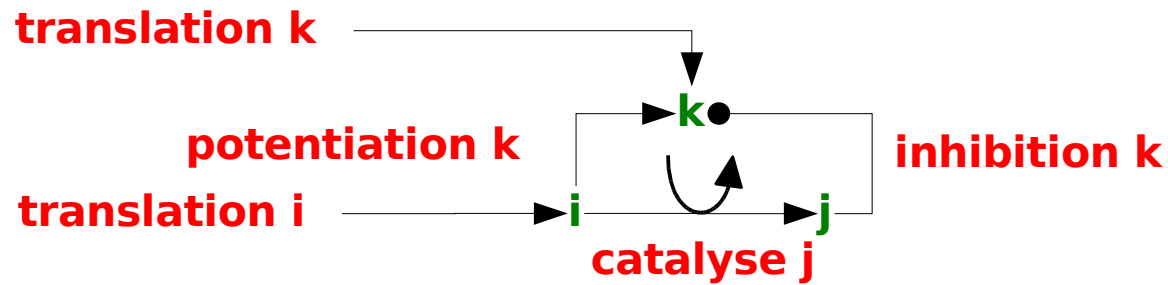


variable j

variable i

variable k





catalyse j
(ExpressionFluxProcess)

inhibition k
(MassActionFluxProcess)

potentiation k
(MassActionFluxProcess)

translation i
(GillespieProcess)

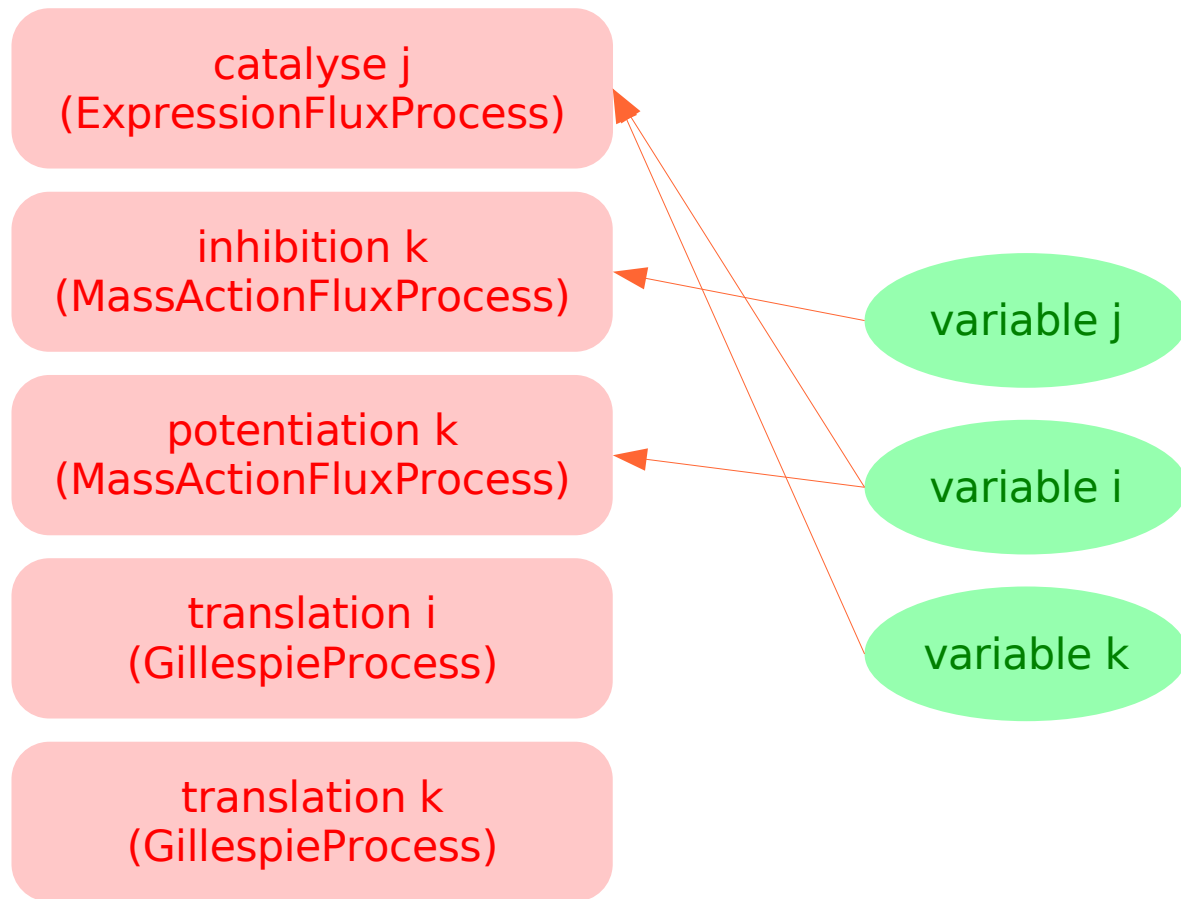
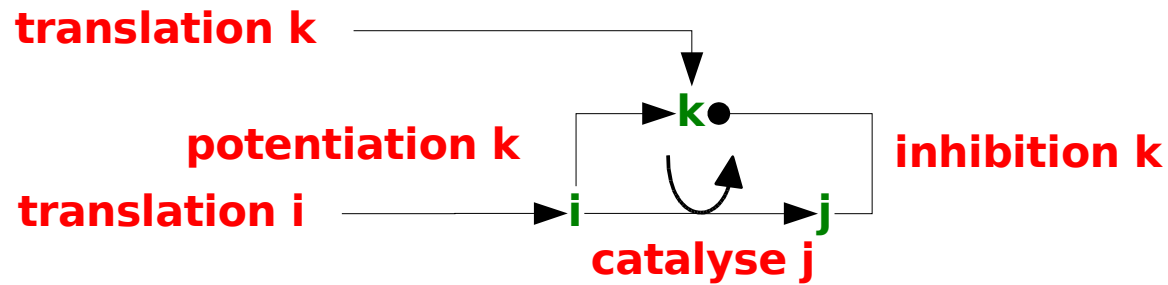
translation k
(GillespieProcess)

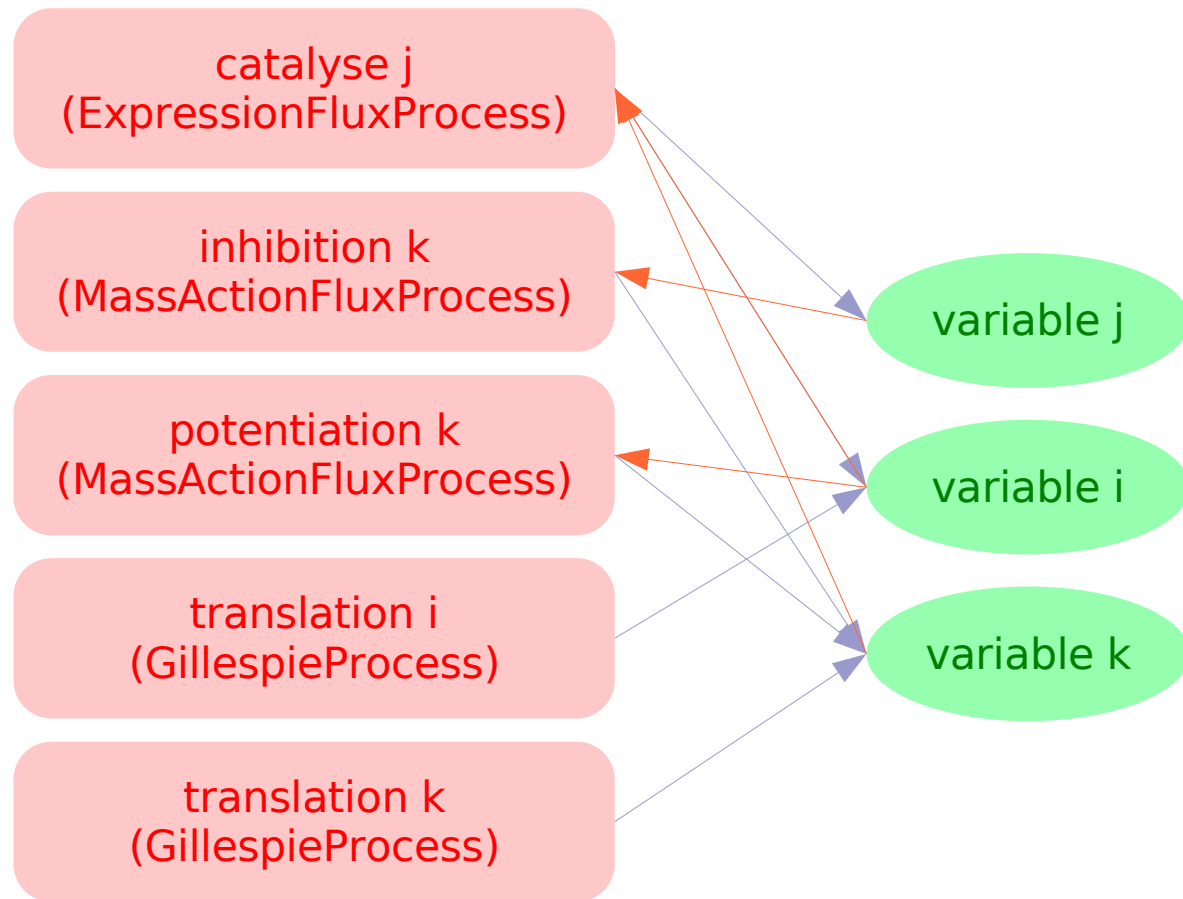
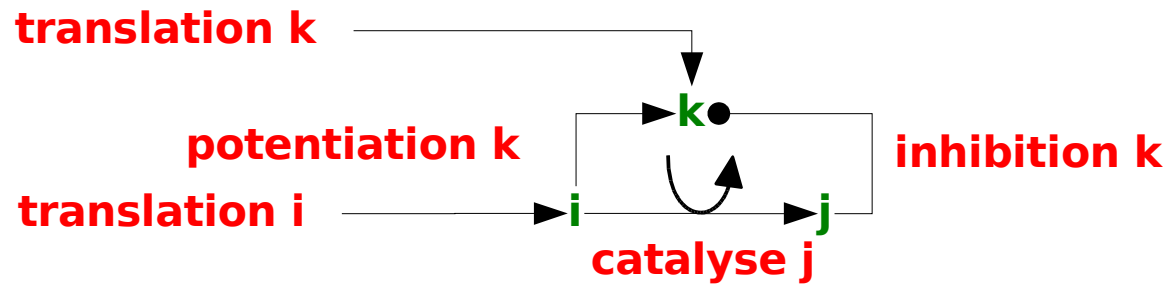
variable j

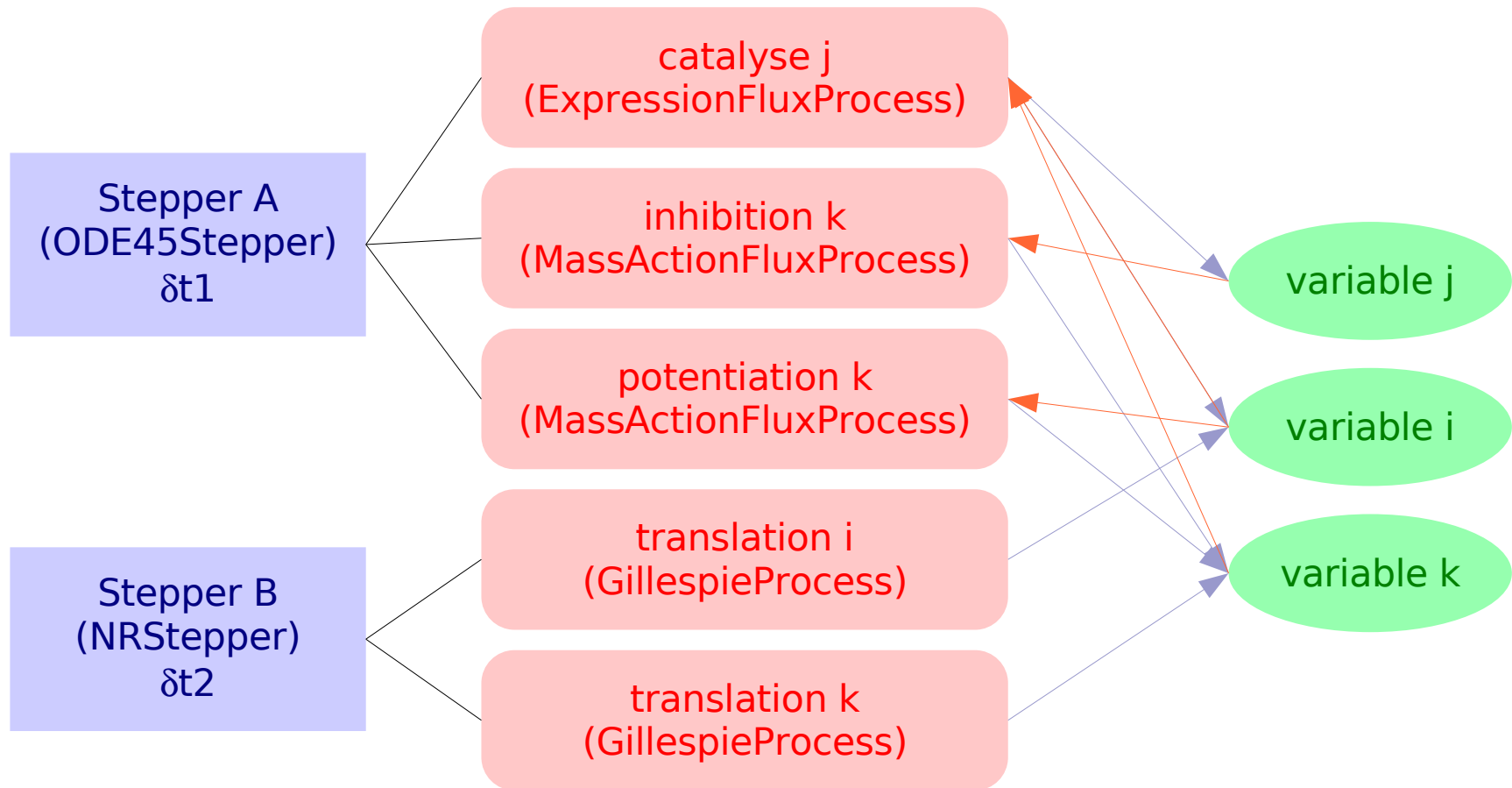
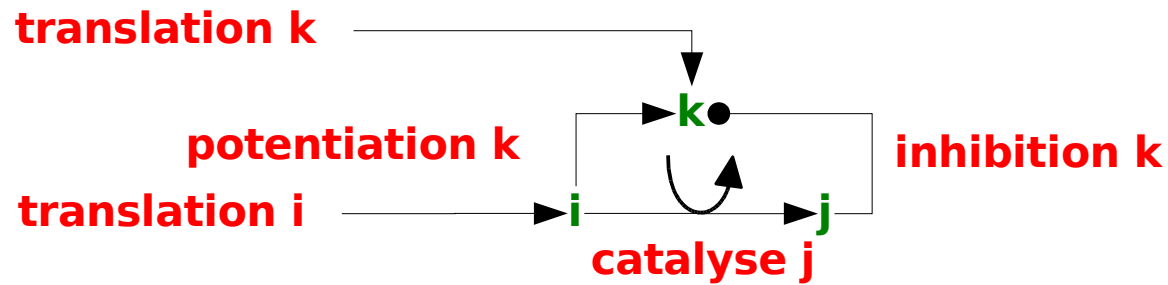
variable i

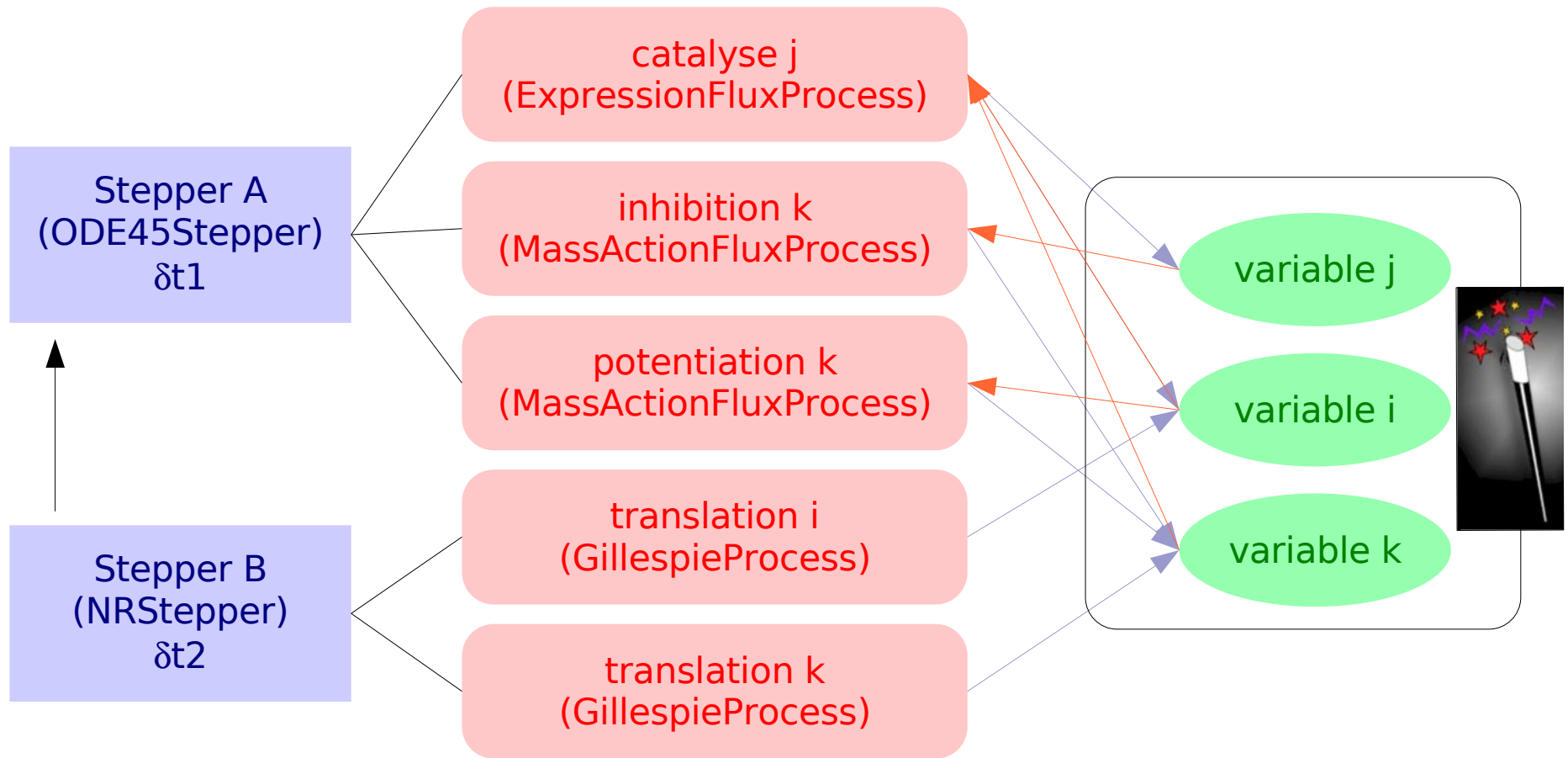
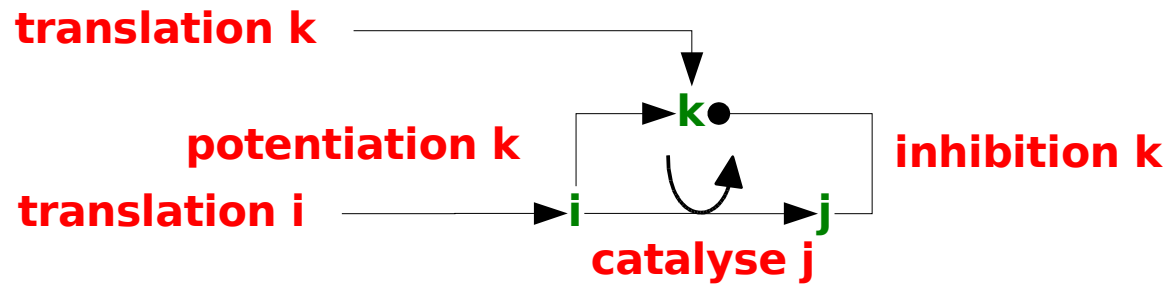
variable k

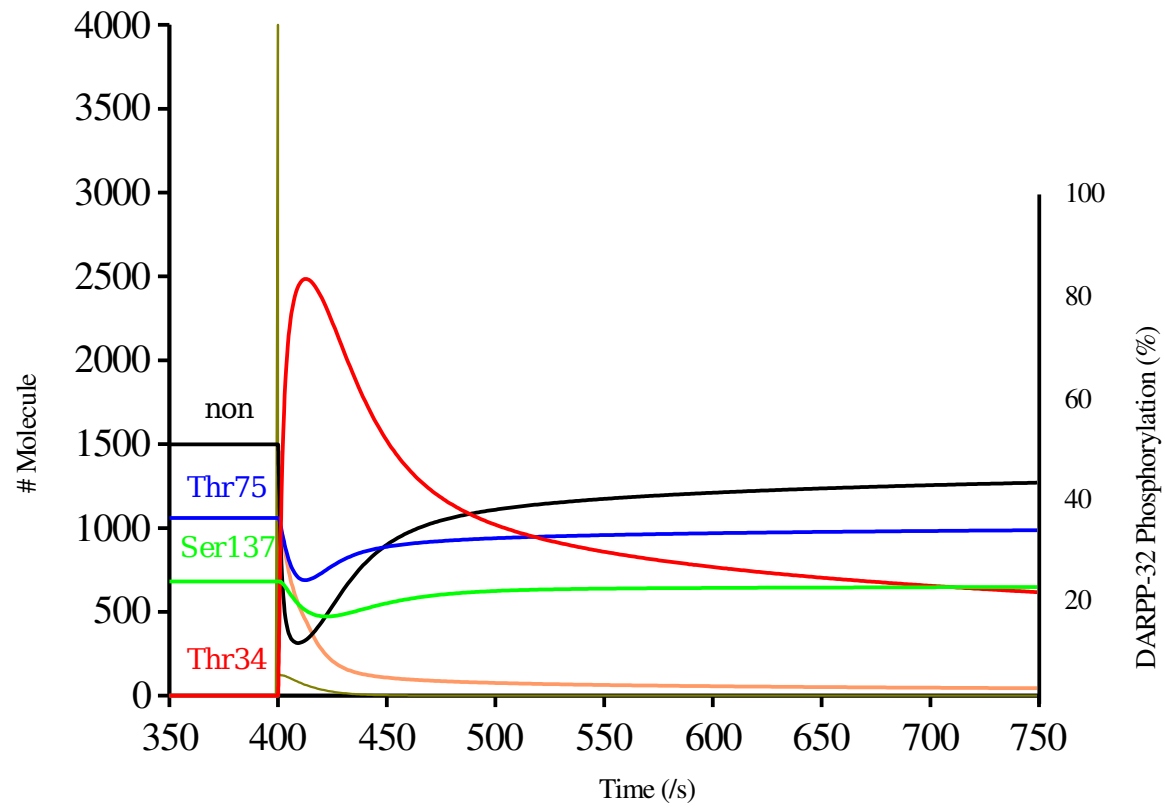




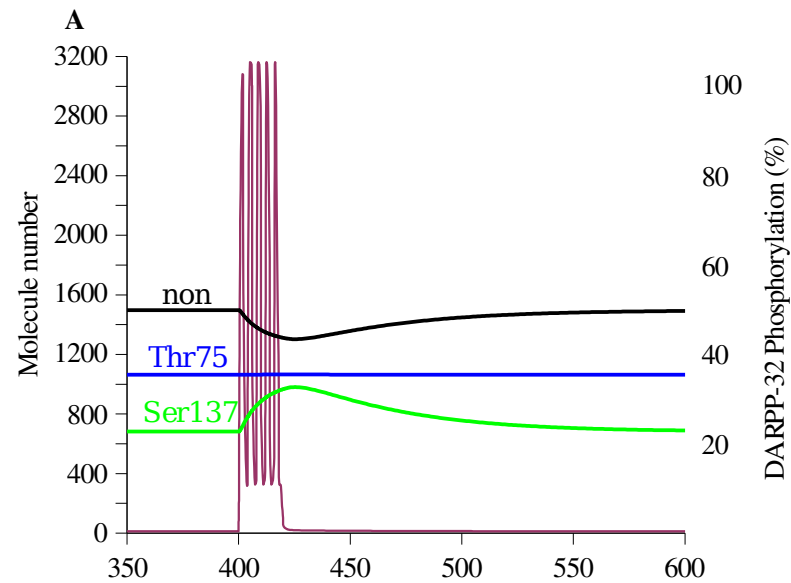


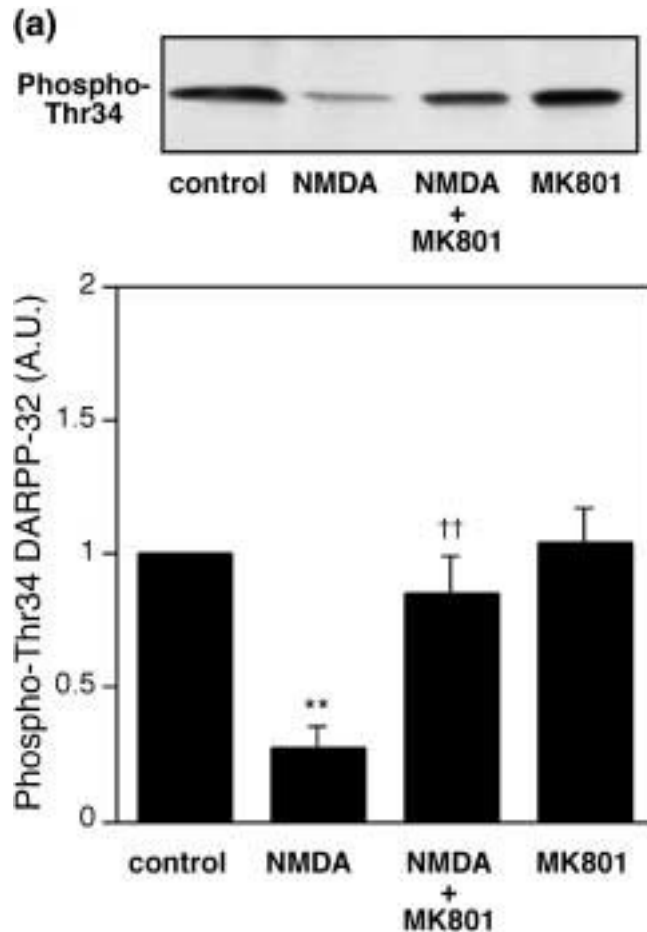






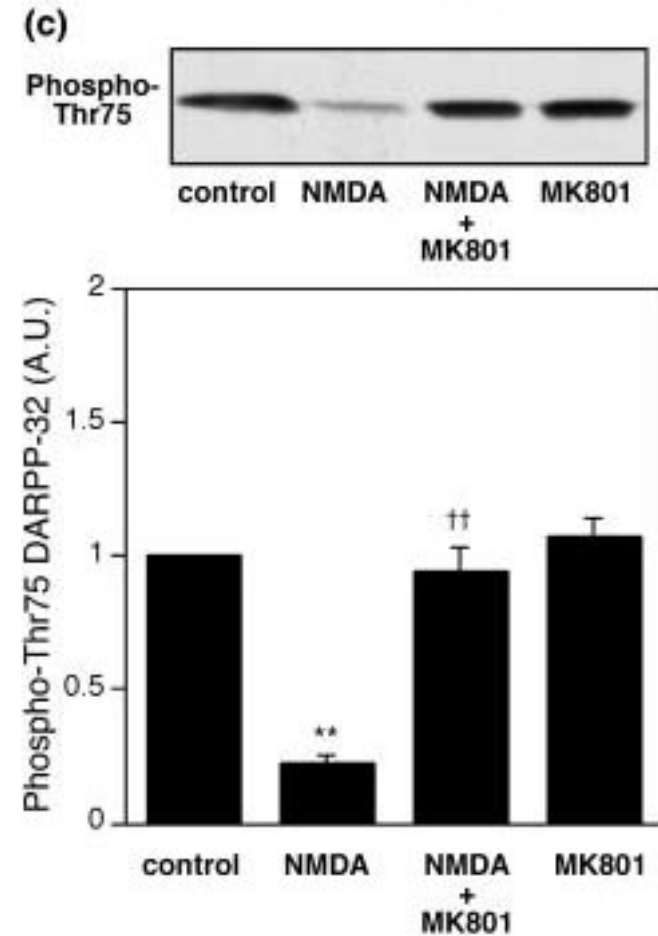
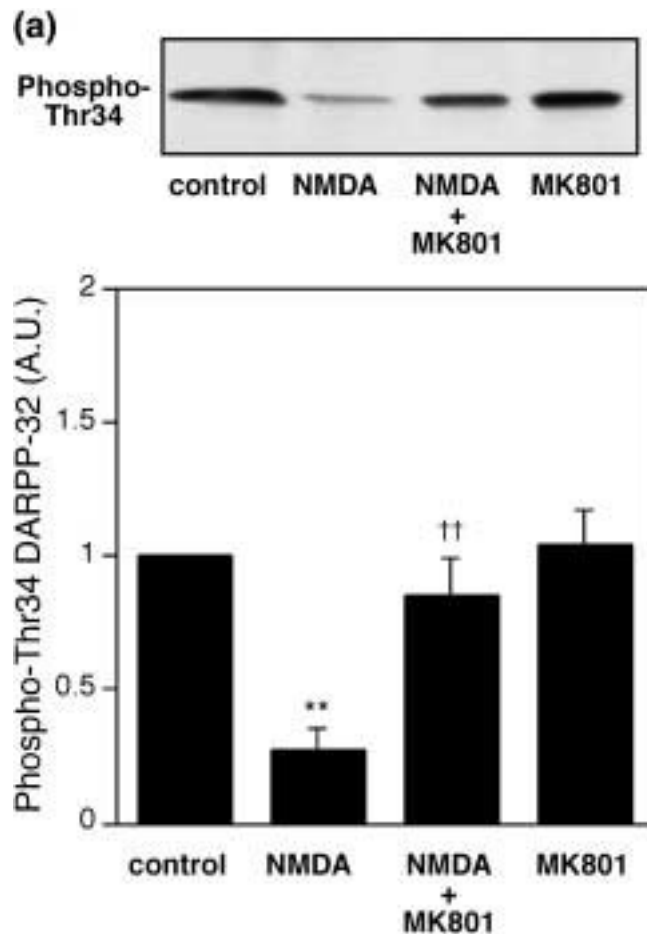
model A





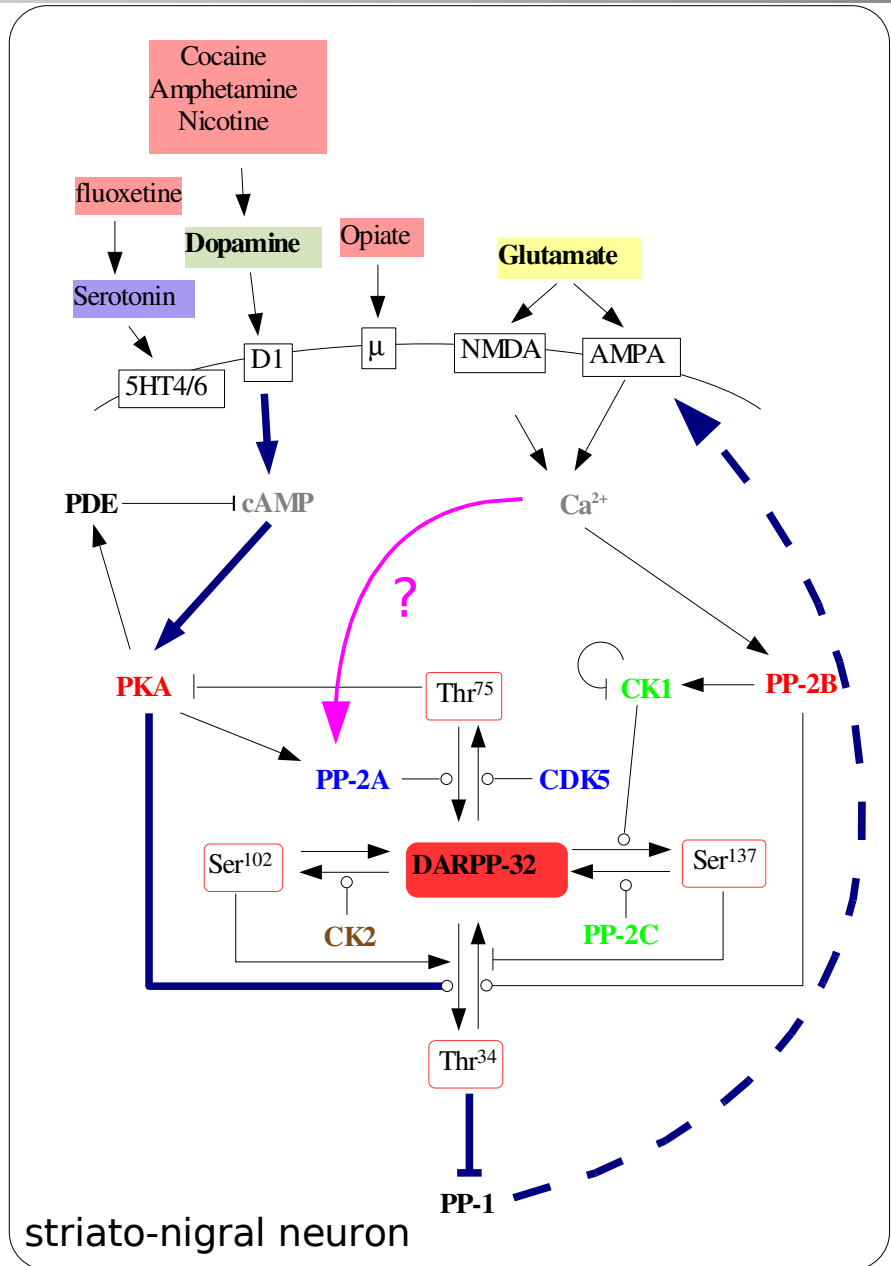
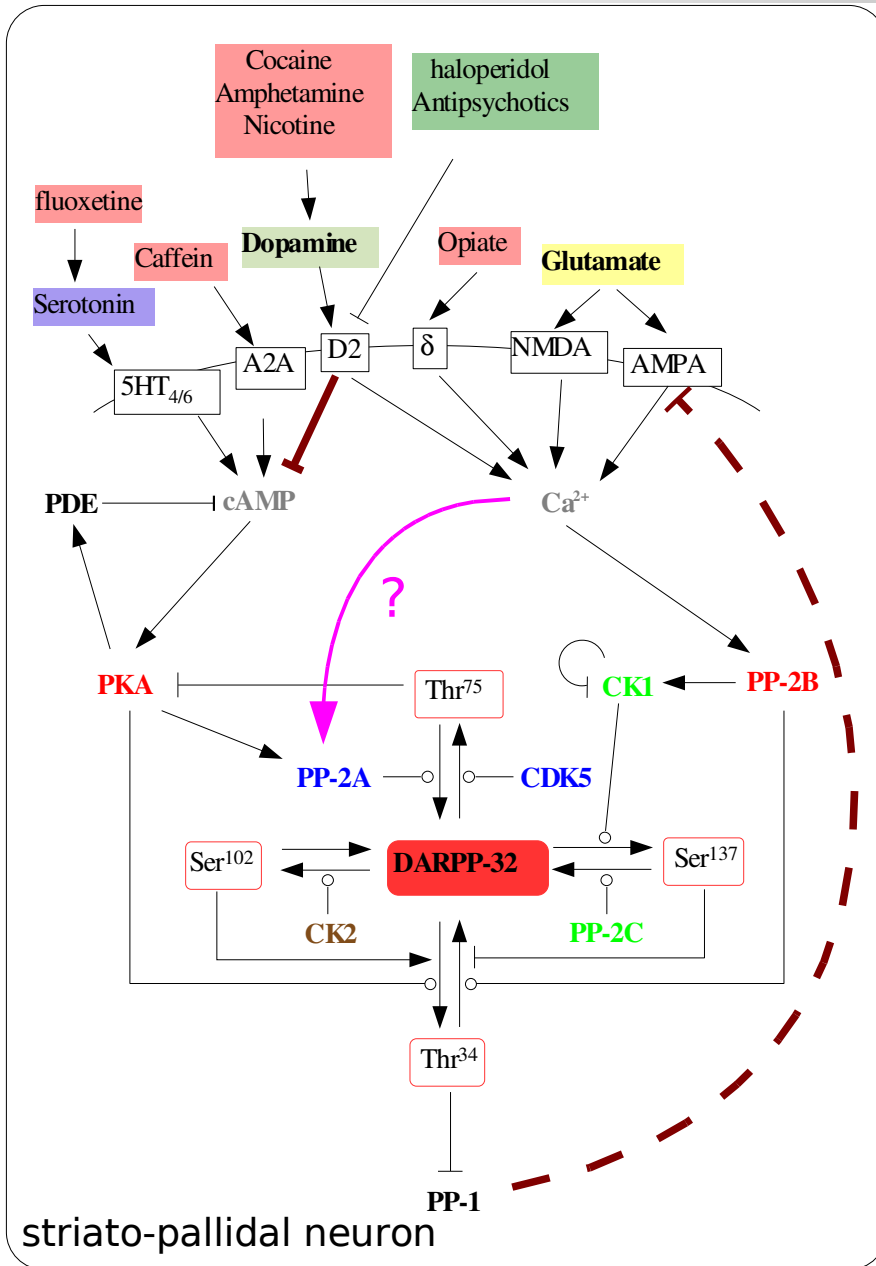
Nishi *et al.* (2002). *J Neurochem*, 82: 832-841

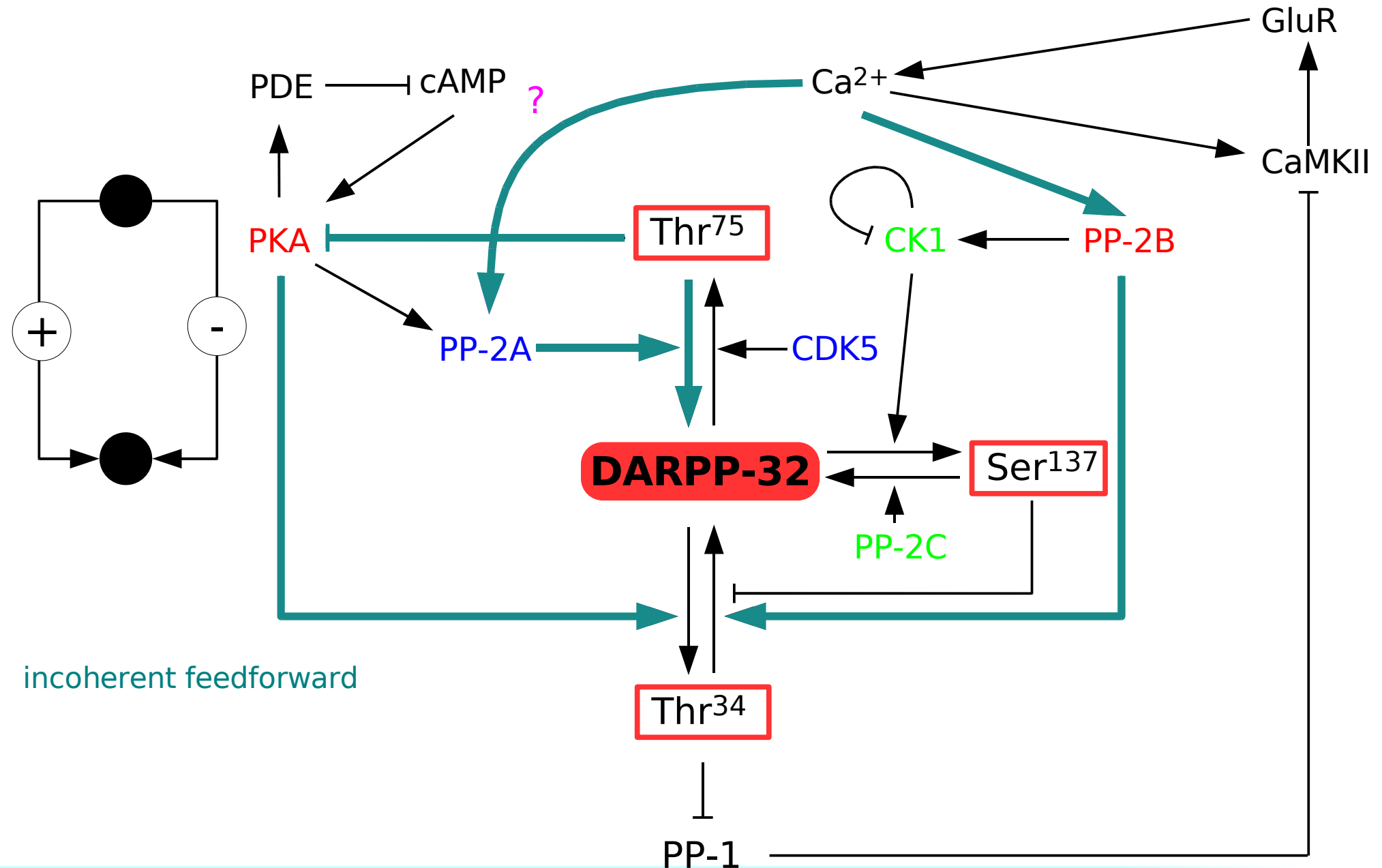


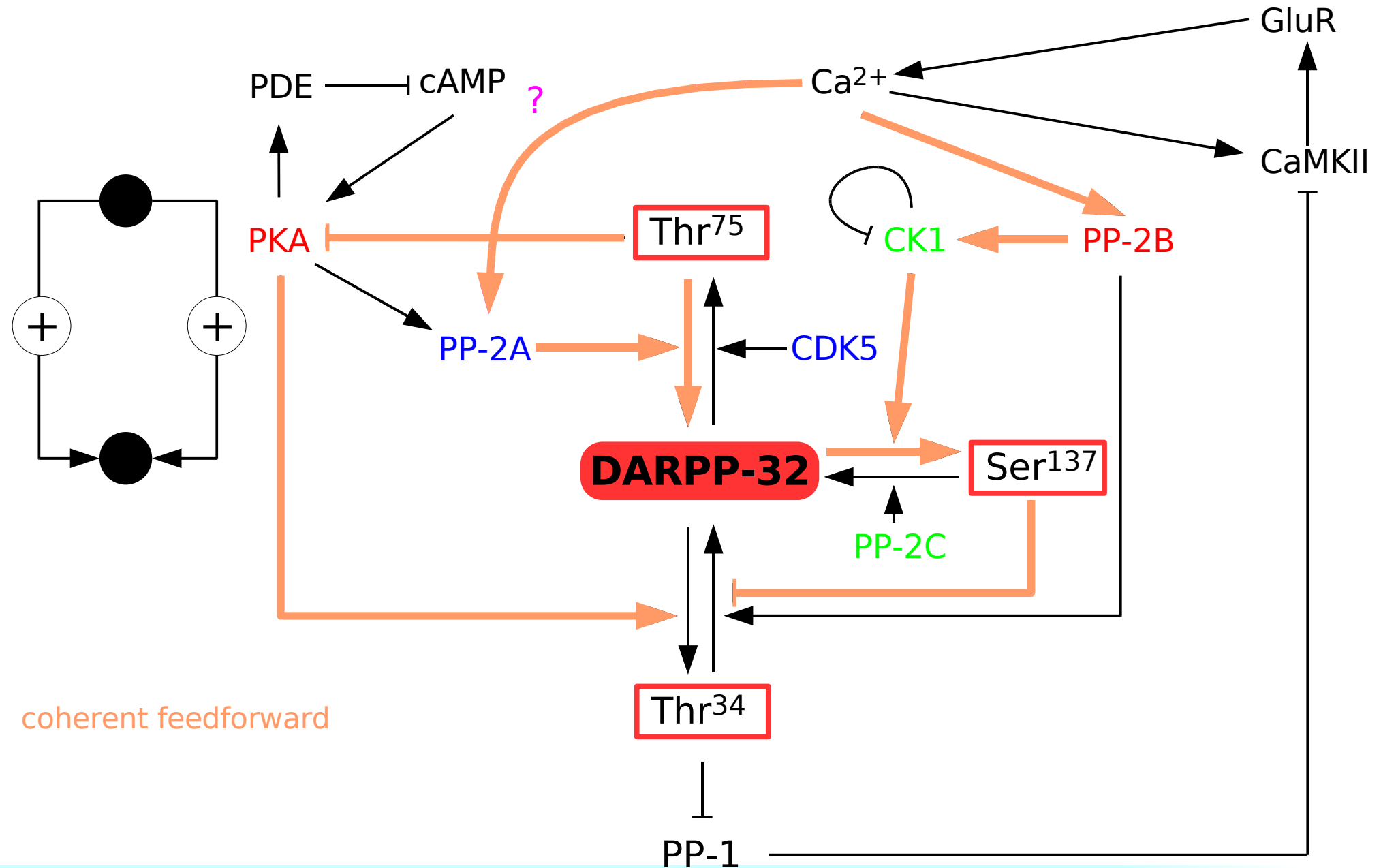


Nishi *et al.* (2002). *J Neurochem*, 82: 832-841

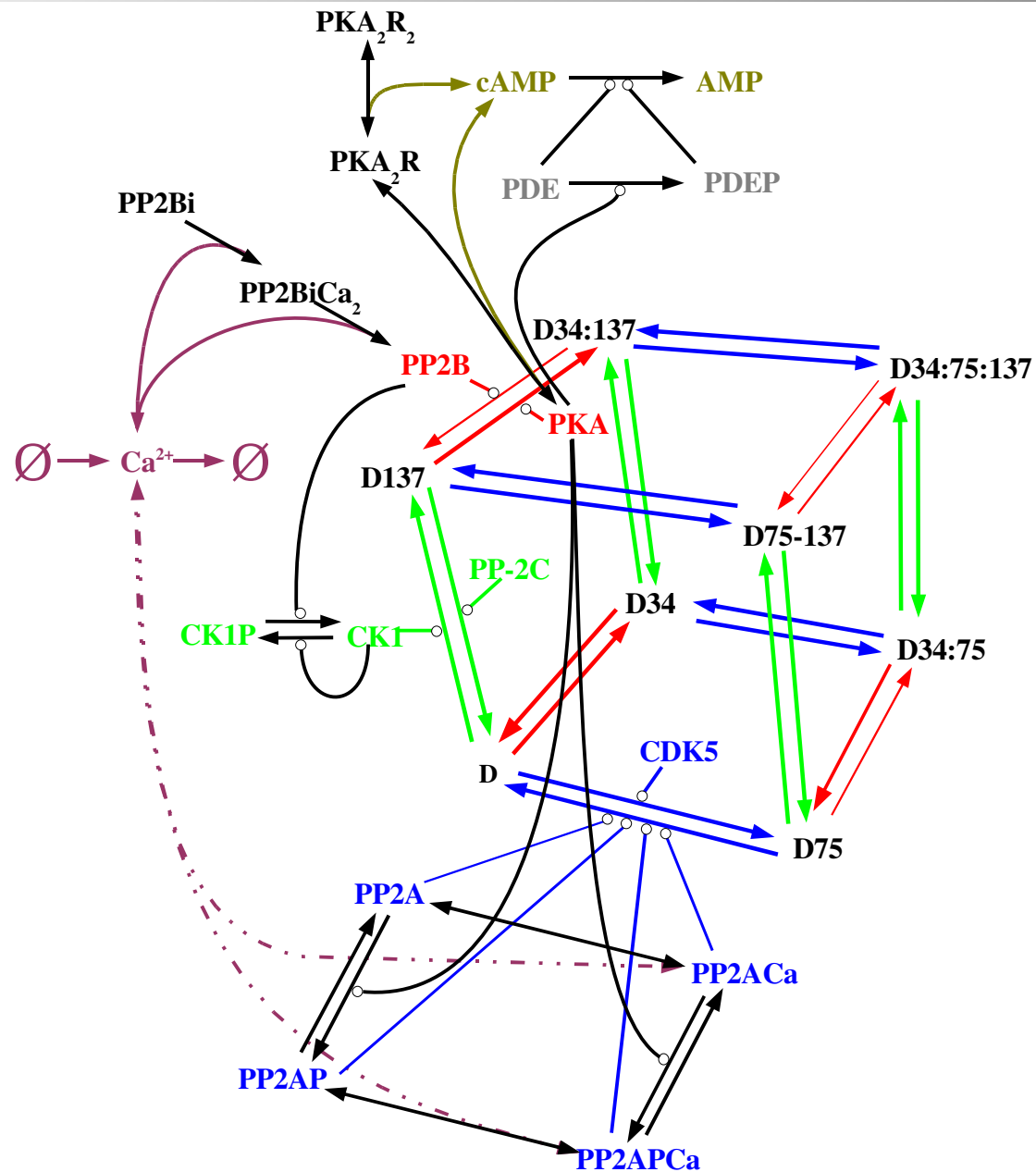








Chemical model of DARPP-32 regulation



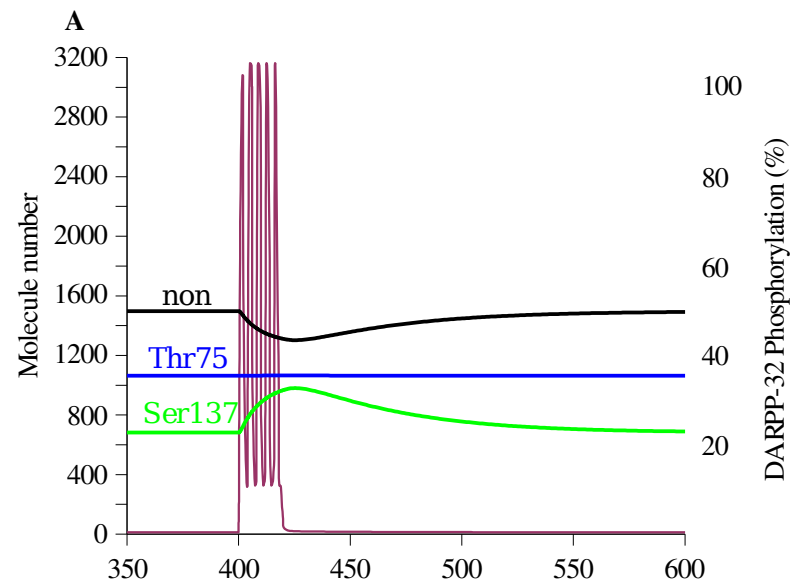
- $D + CDK5 \rightleftharpoons D_CDK5 \rightarrow D75 + CDK5$
- $D75 + PP2A \rightleftharpoons D75_PP2A \rightarrow D + PP2A$
- $D75 + PP2ACa \rightleftharpoons D75_PP2ACa \rightarrow D + PP2ACa$
- $D75 + PP2AP \rightleftharpoons D75_PP2AP \rightarrow D + PP2AP$
- $D75 + PP2APCa \rightleftharpoons D75_PP2APCa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

79 species, 151 reactions

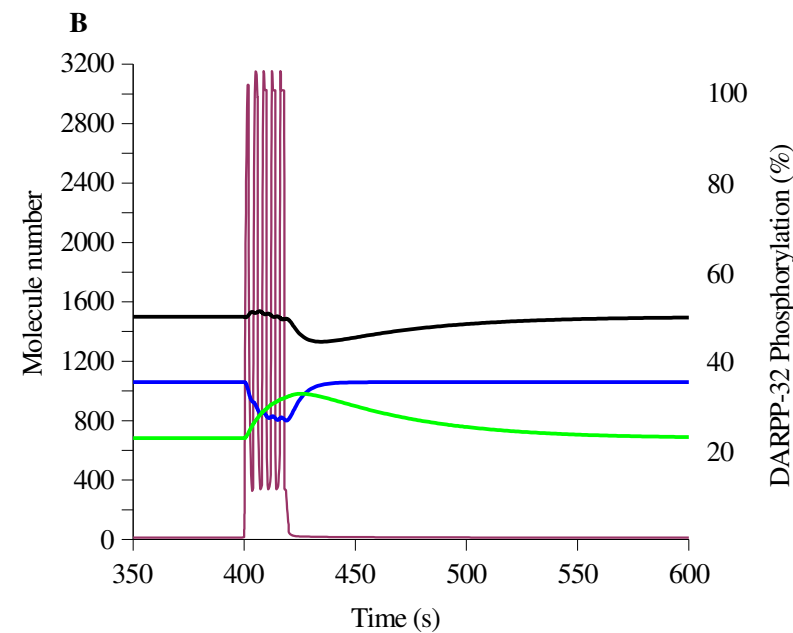
- $D + PKA \rightleftharpoons D_PKA \rightarrow D34 + PKA$
- $D34 + PP2B \rightleftharpoons D34_PP2B \rightarrow D + PP2B$
- $D75 + PKA \rightleftharpoons D75_PKA \rightarrow D34-75 + PKA$
- $D34-75 + PP2B \rightleftharpoons D34-75_PP2B \rightarrow D75 + PP2B$
- $D137 + PKA \rightleftharpoons D137_PKA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

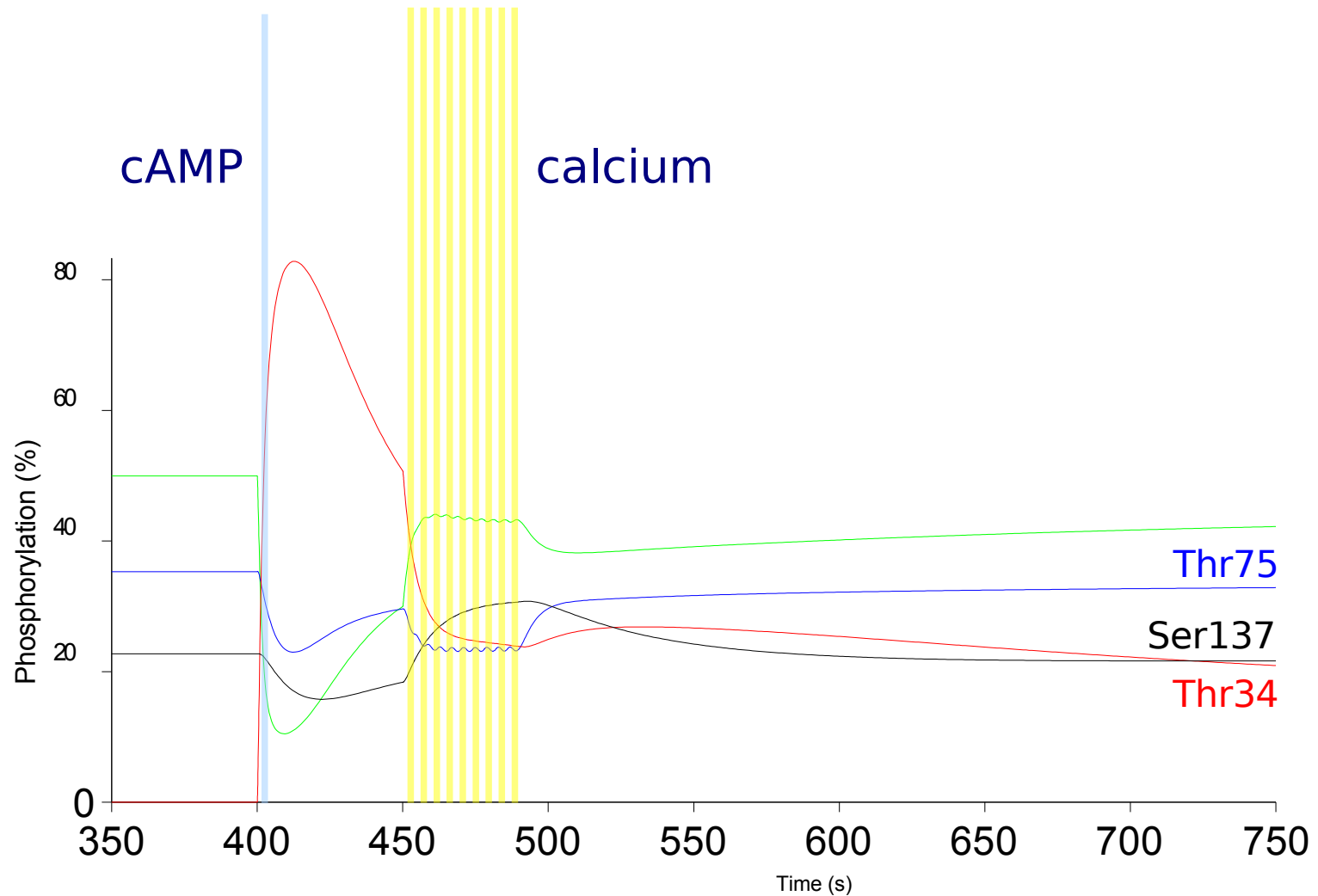


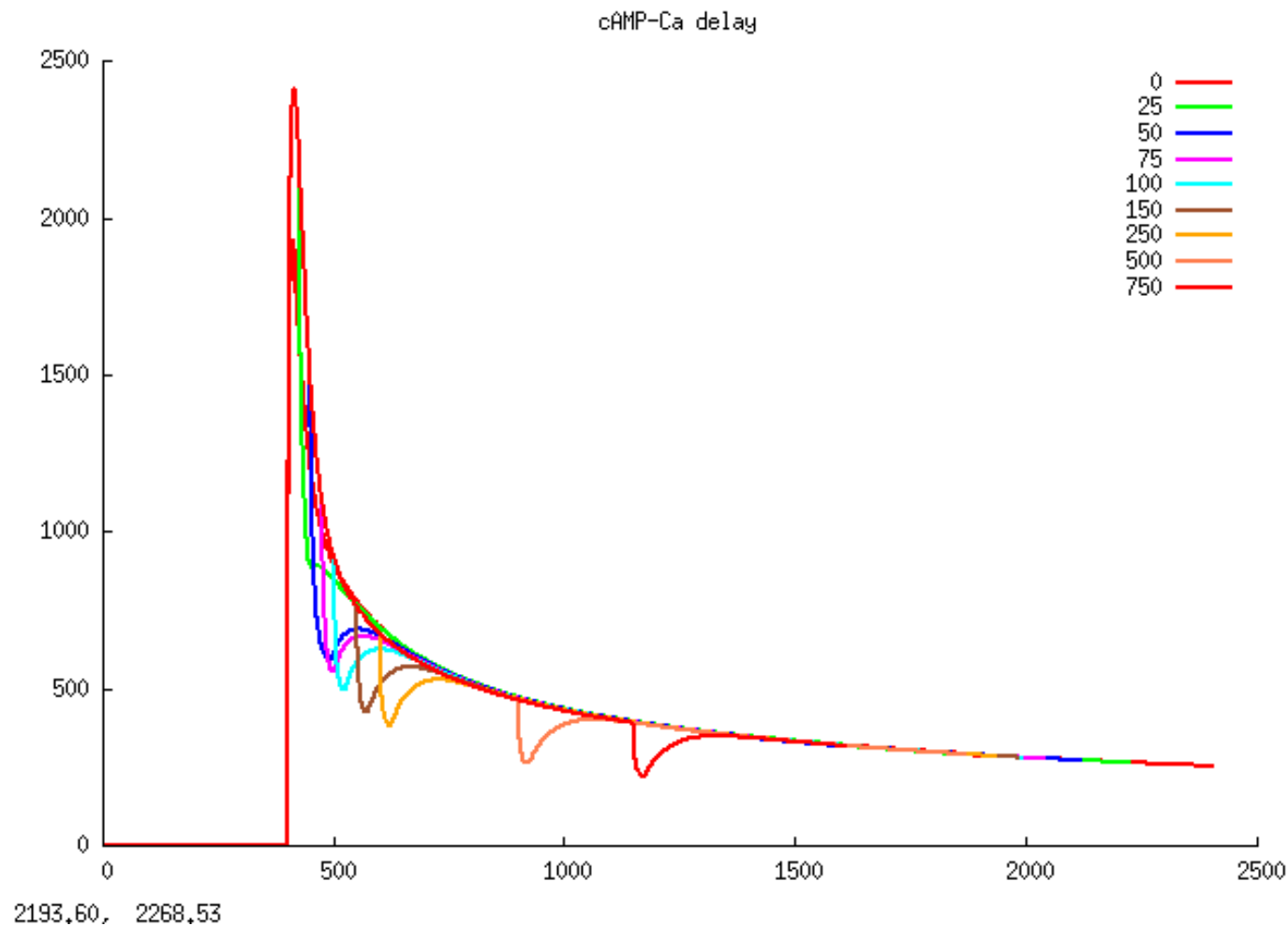
model A

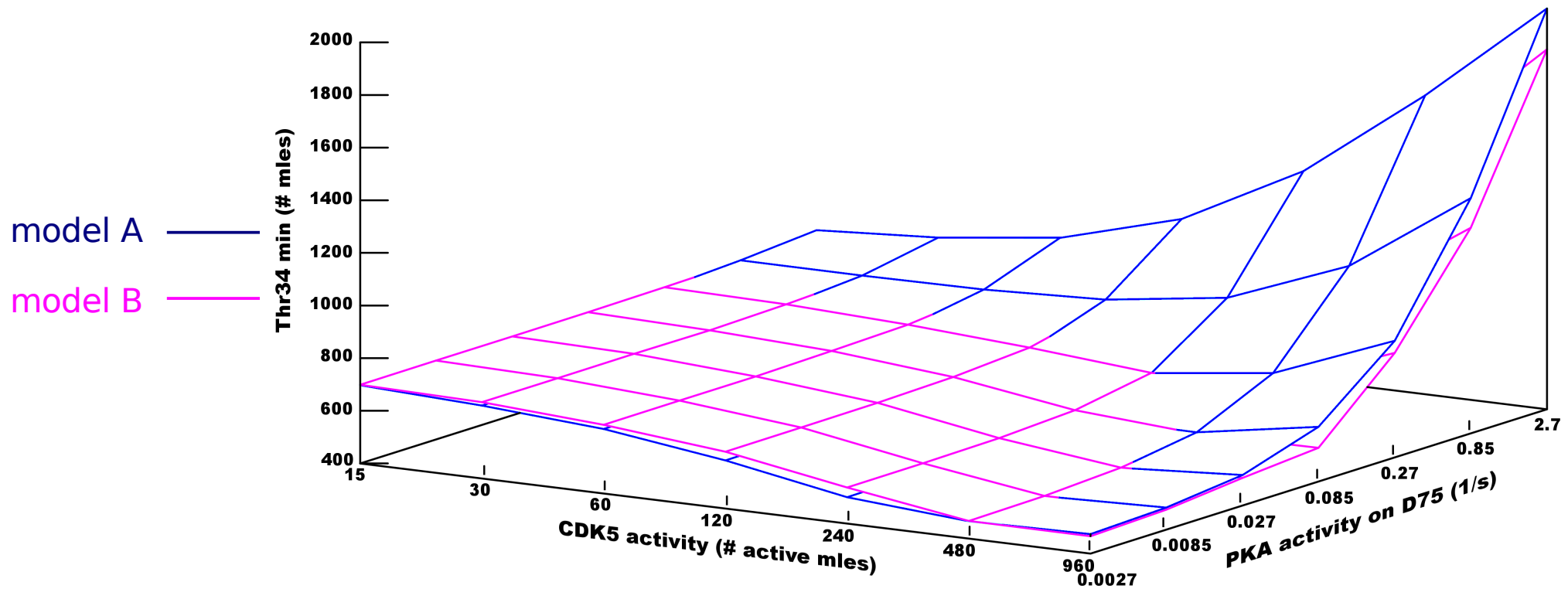


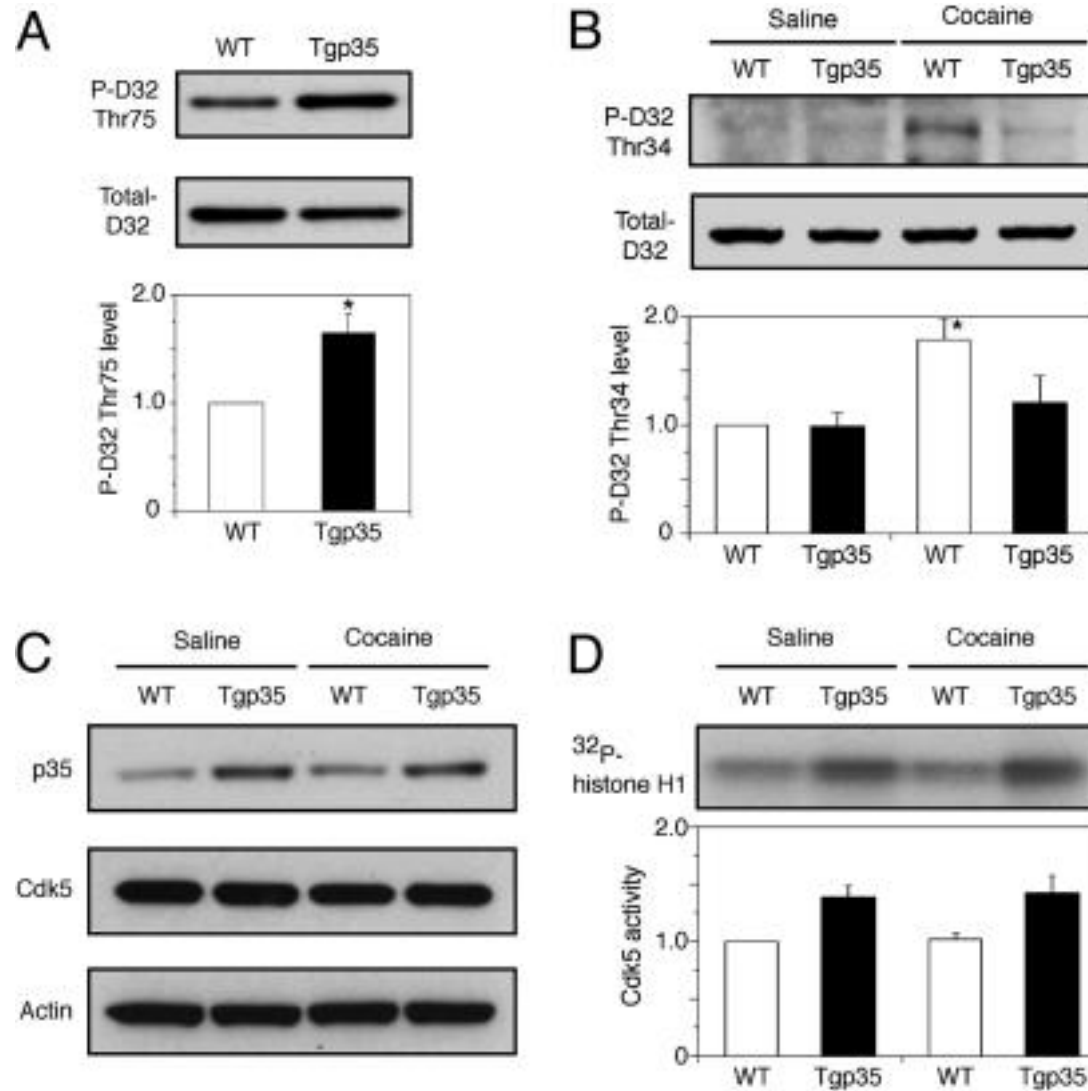
model B





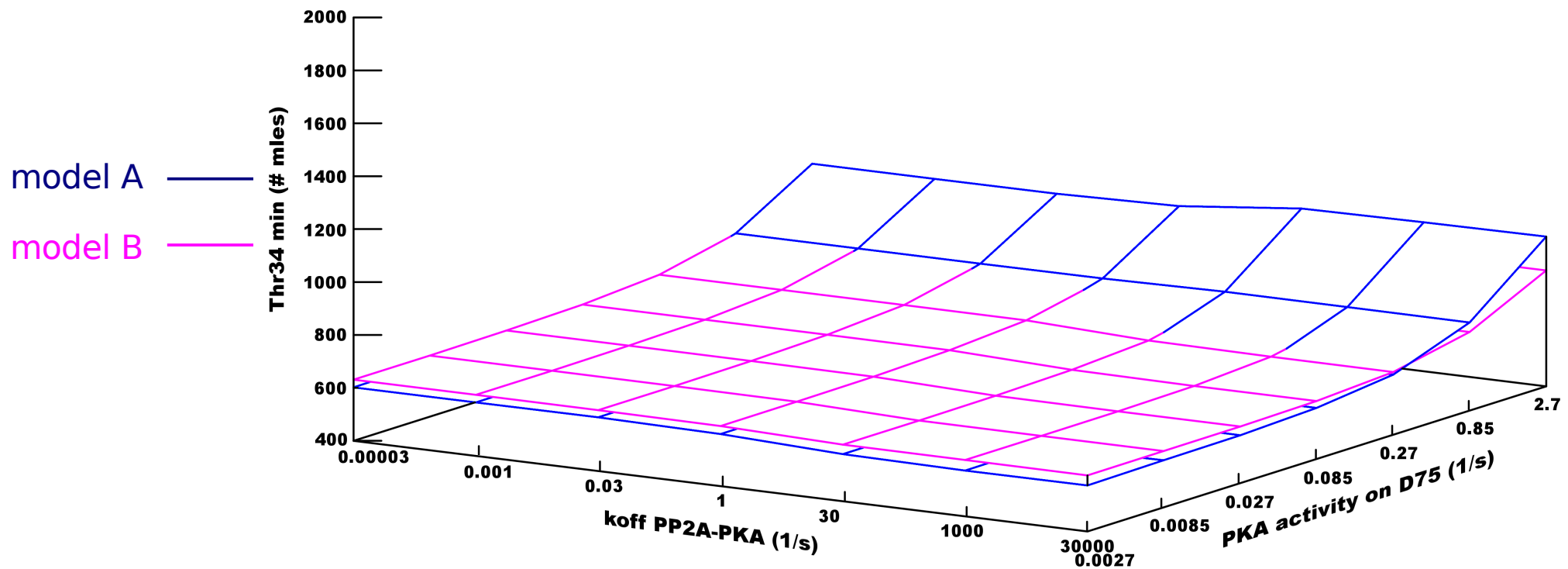






Takahahi *et al* (2005) *PNAS*, 102: 1737-1742

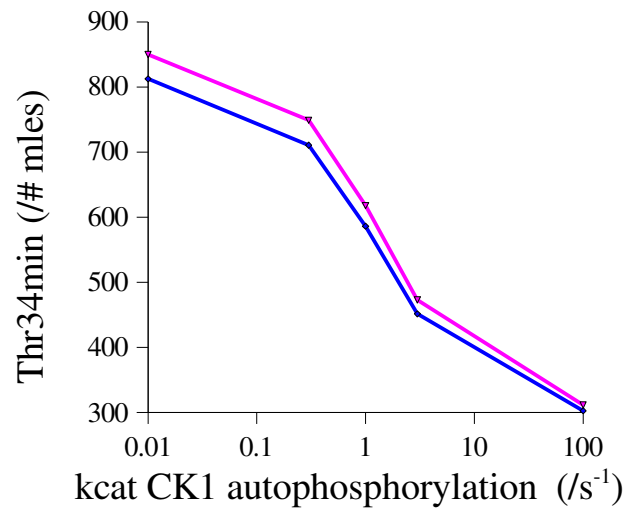




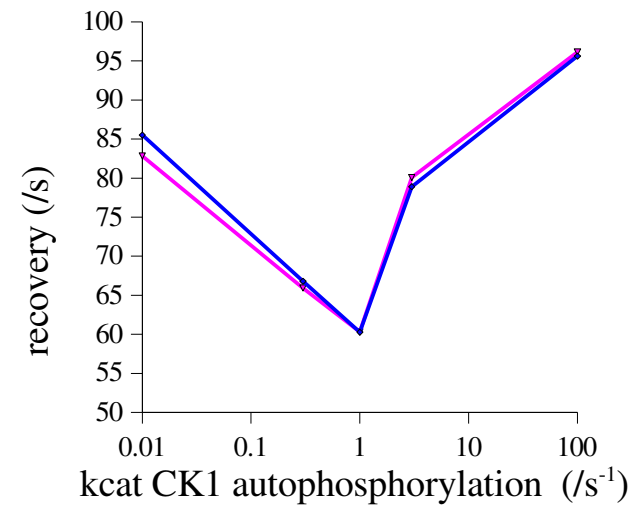
model A ———

model B ———

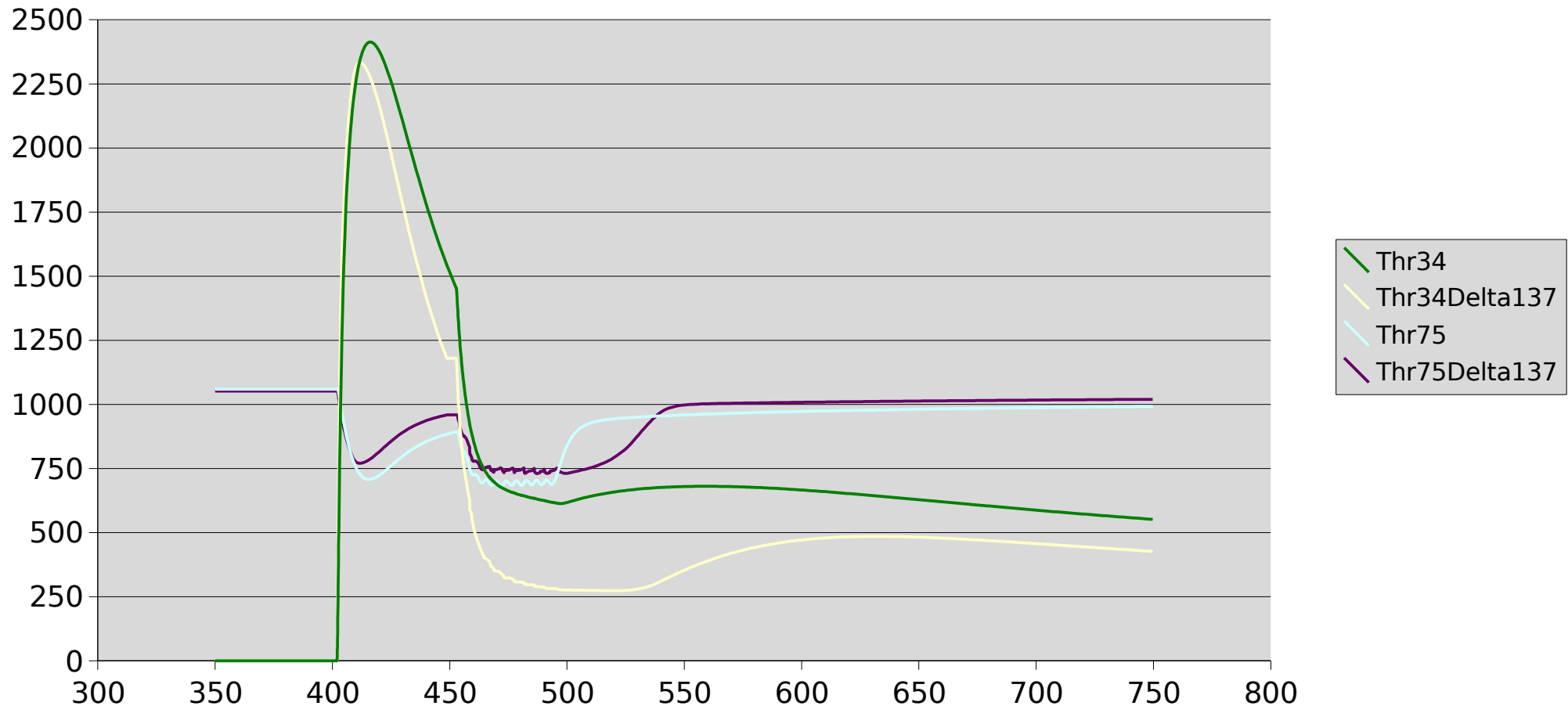
C



D



cAMP-50-Ca "Nishi"



- ODE systems are nice because easy to understand
- ODE systems can reproduce experimental observations
- ODE systems can produce some predictions

but ...



- ODE systems are nice because easy to understand
- ODE systems can reproduce experimental observations
- ODE systems can produce some predictions

but ...

- ODE systems are cumbersome; lead to large dimensionality.



- E-cell developers

Kouichi Takahashi

Kazunari Kaizu

Gabor Bereczki



- Eric Fernandez



Renaud Schiappa

