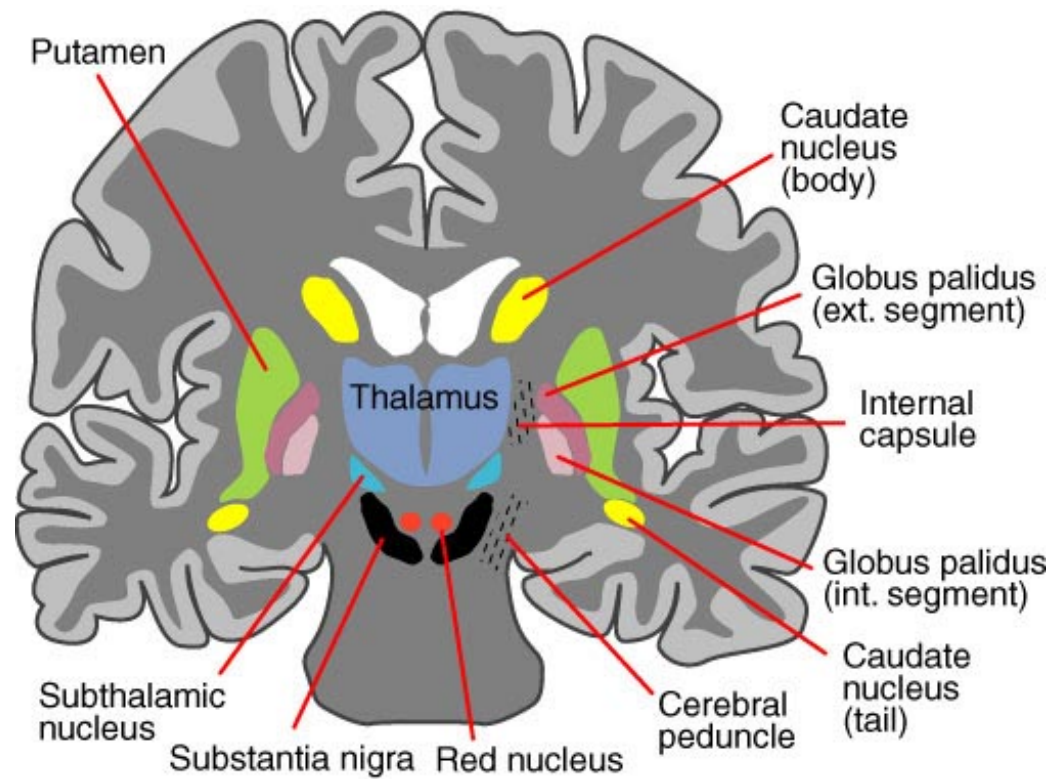
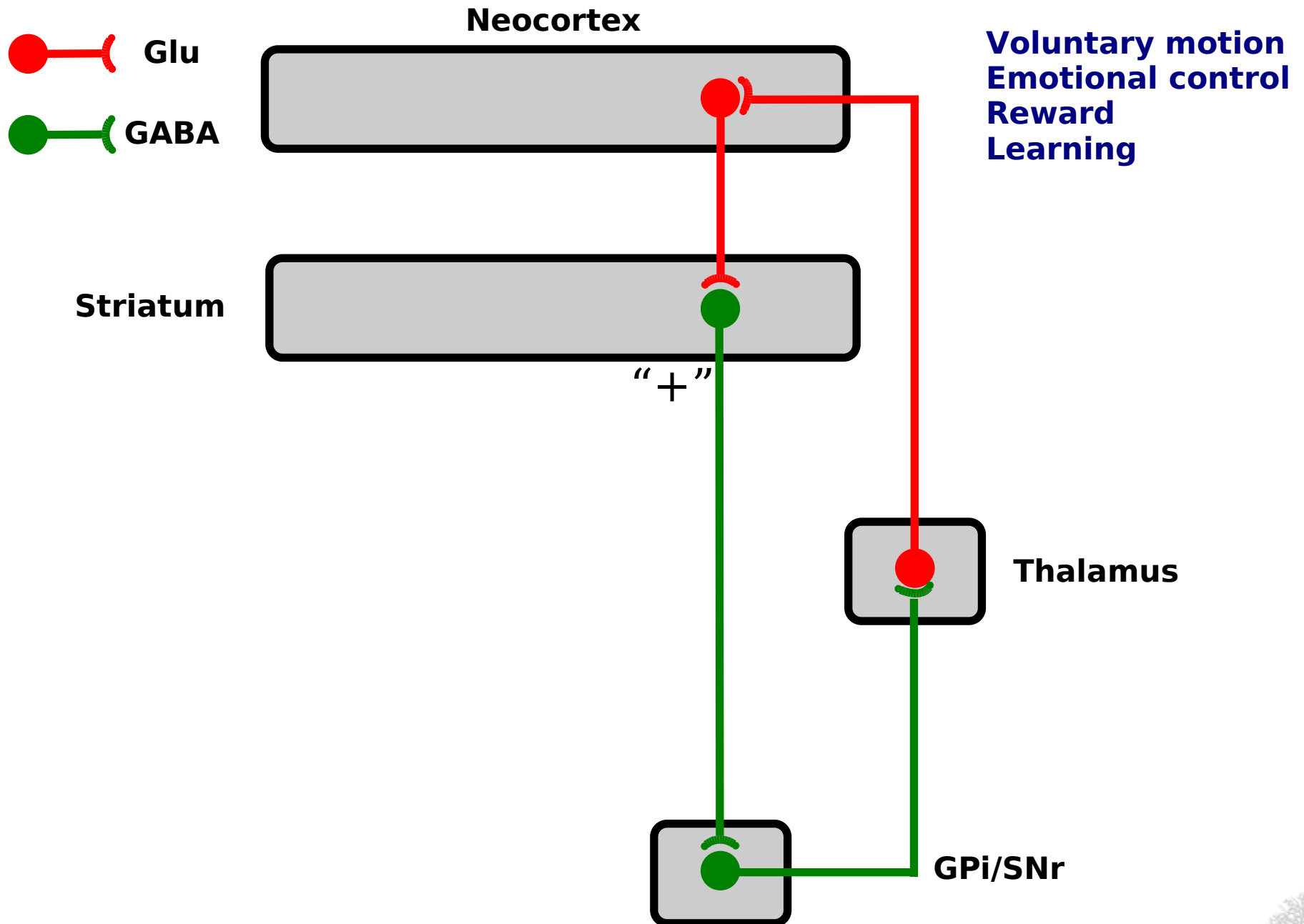


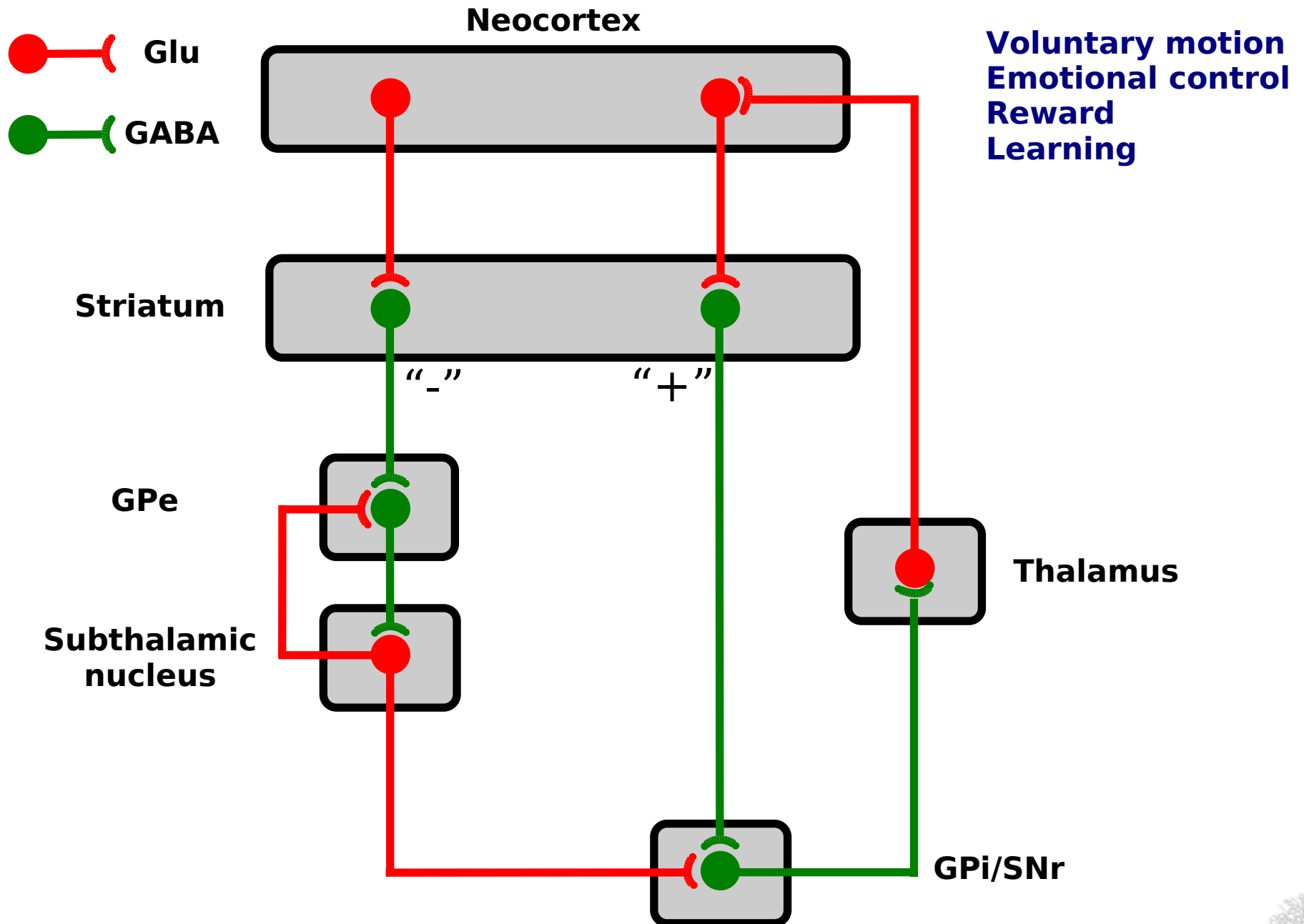
Computational Models of Synaptic Plasticity

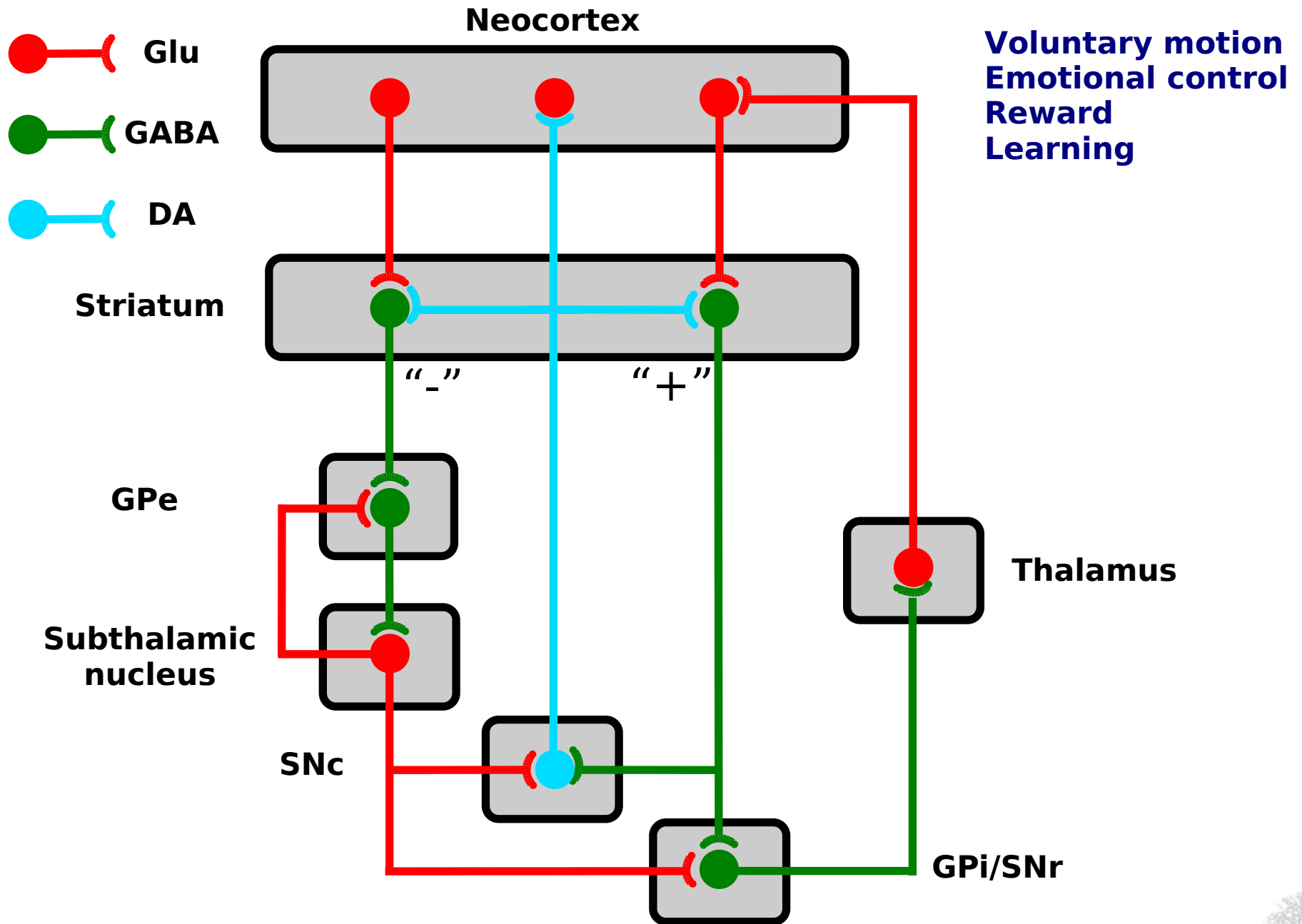
Nicolas Le Novère, EMBL-EBI

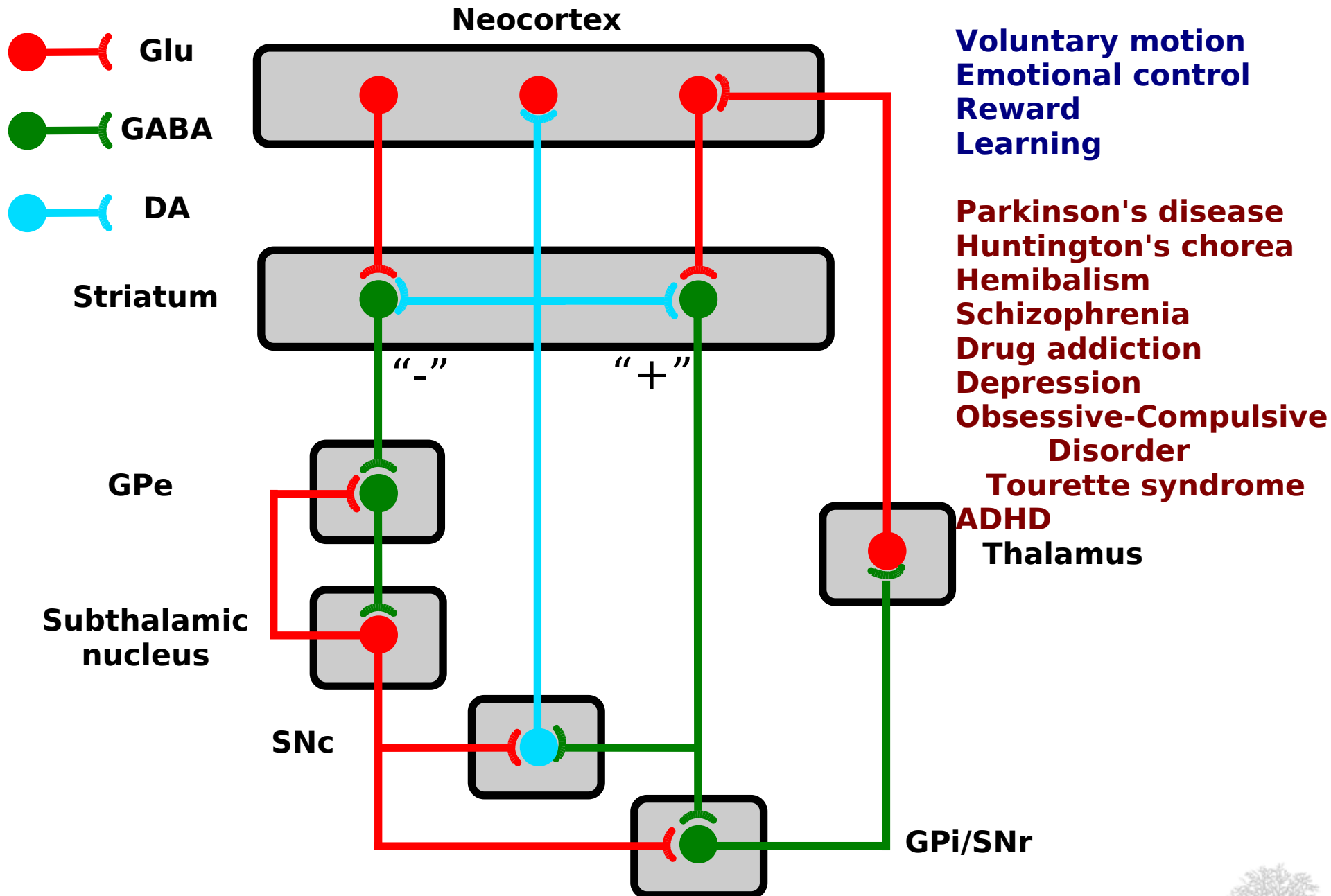


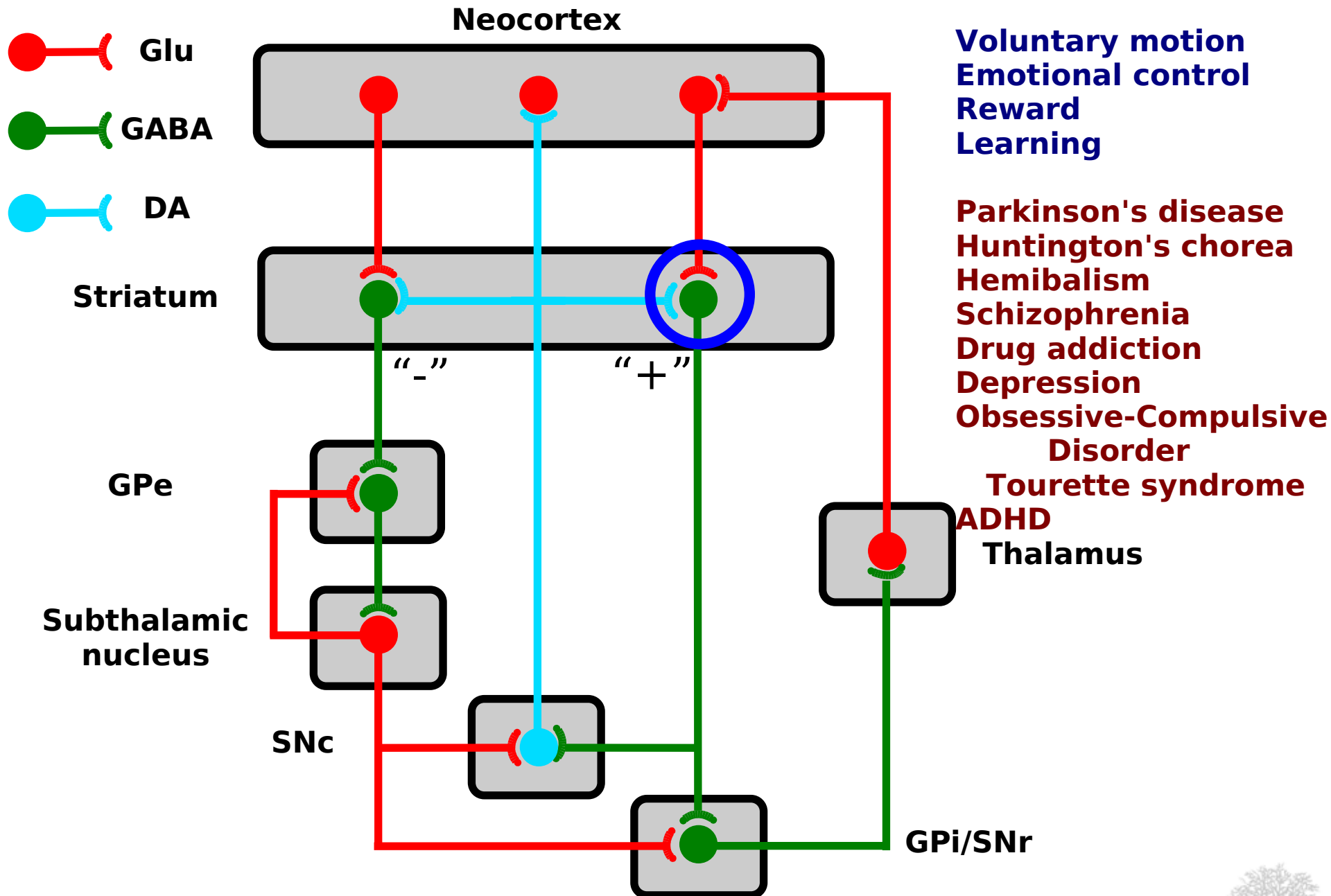


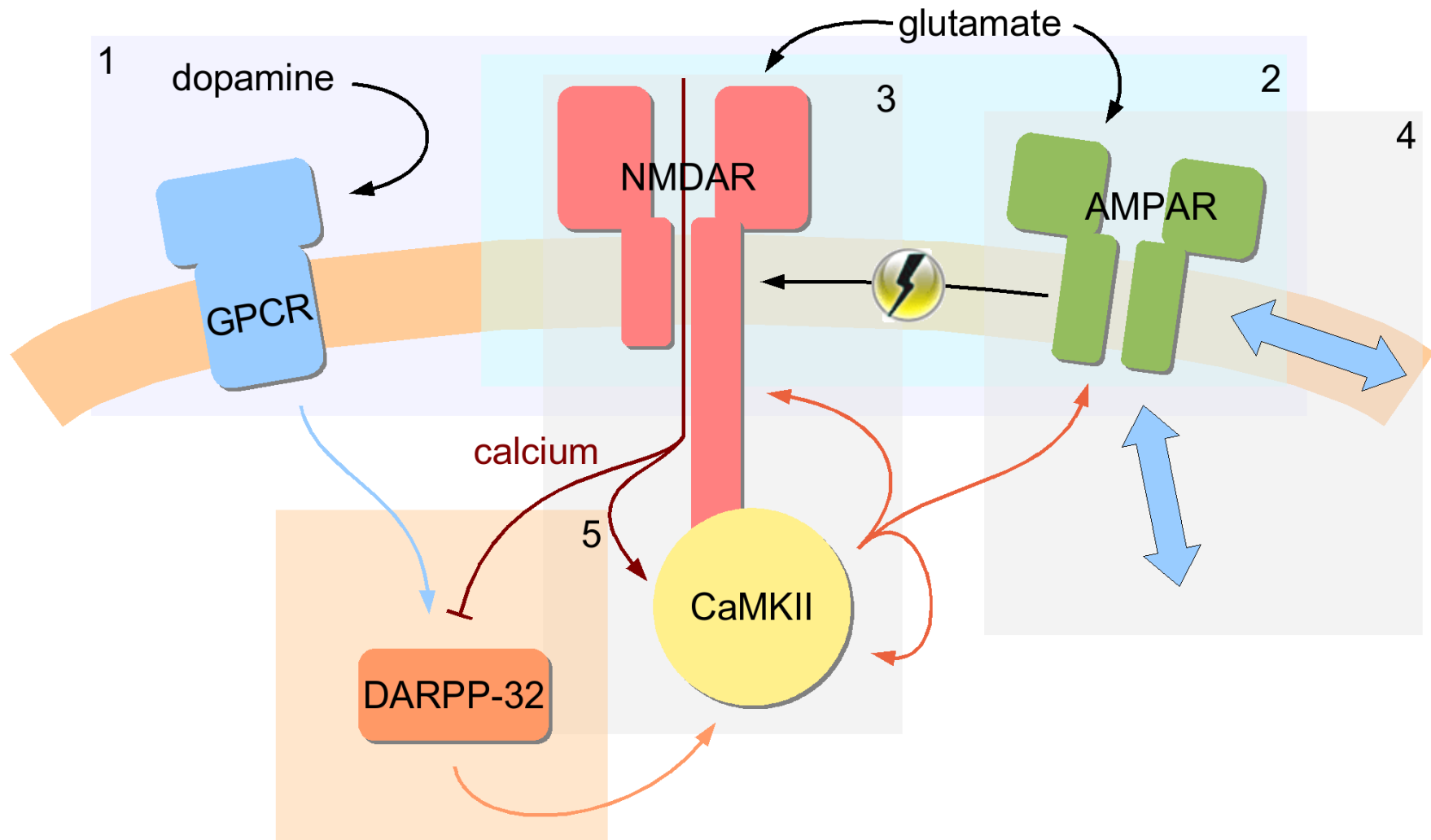


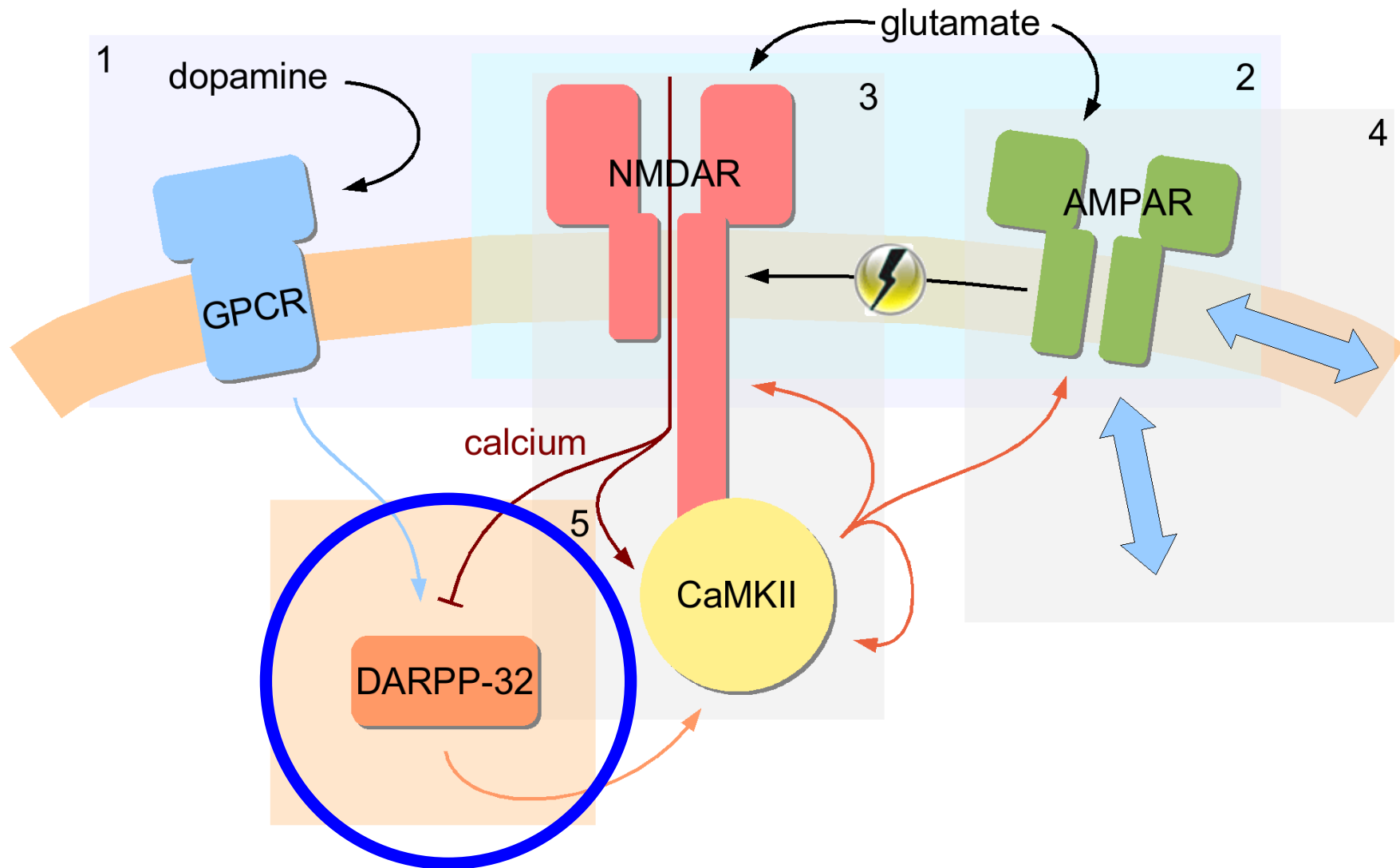






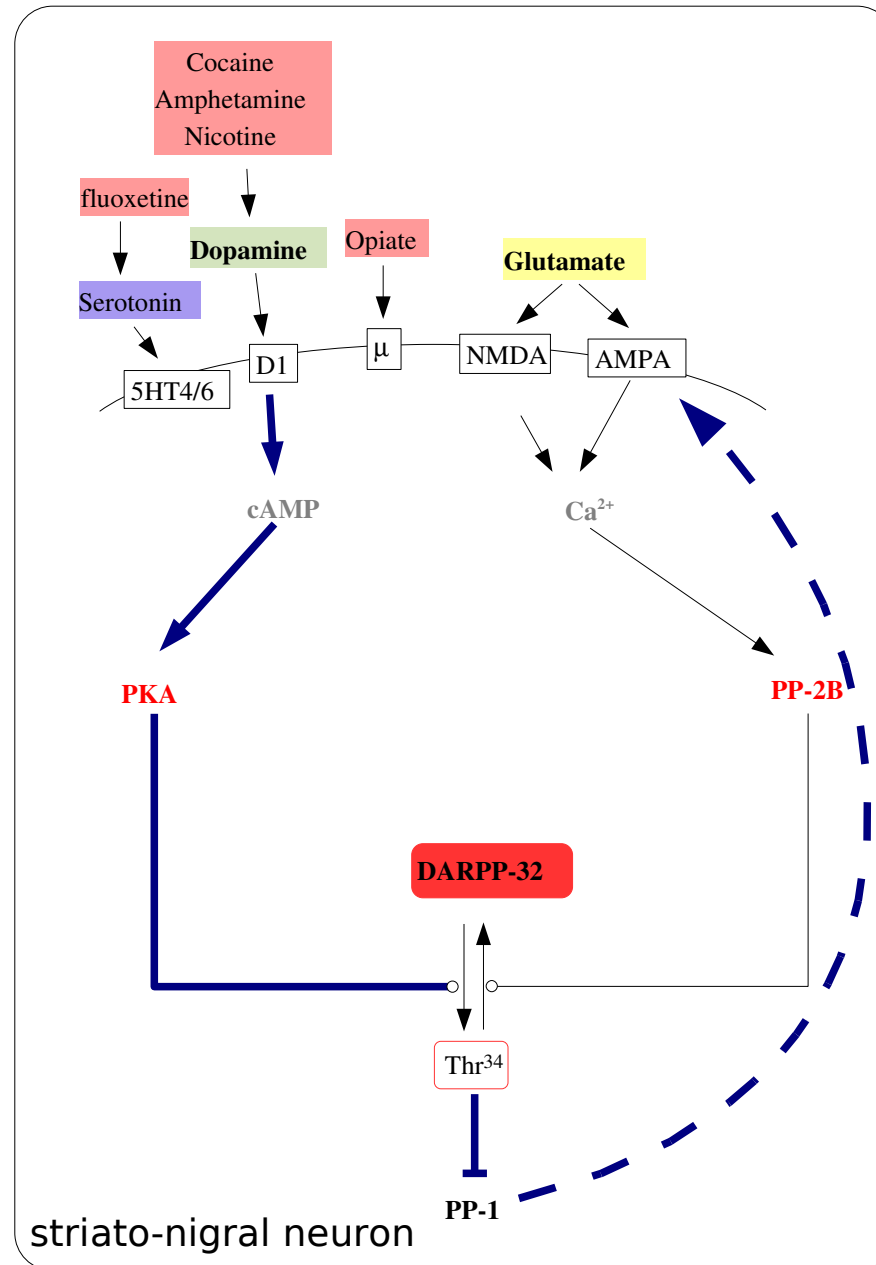


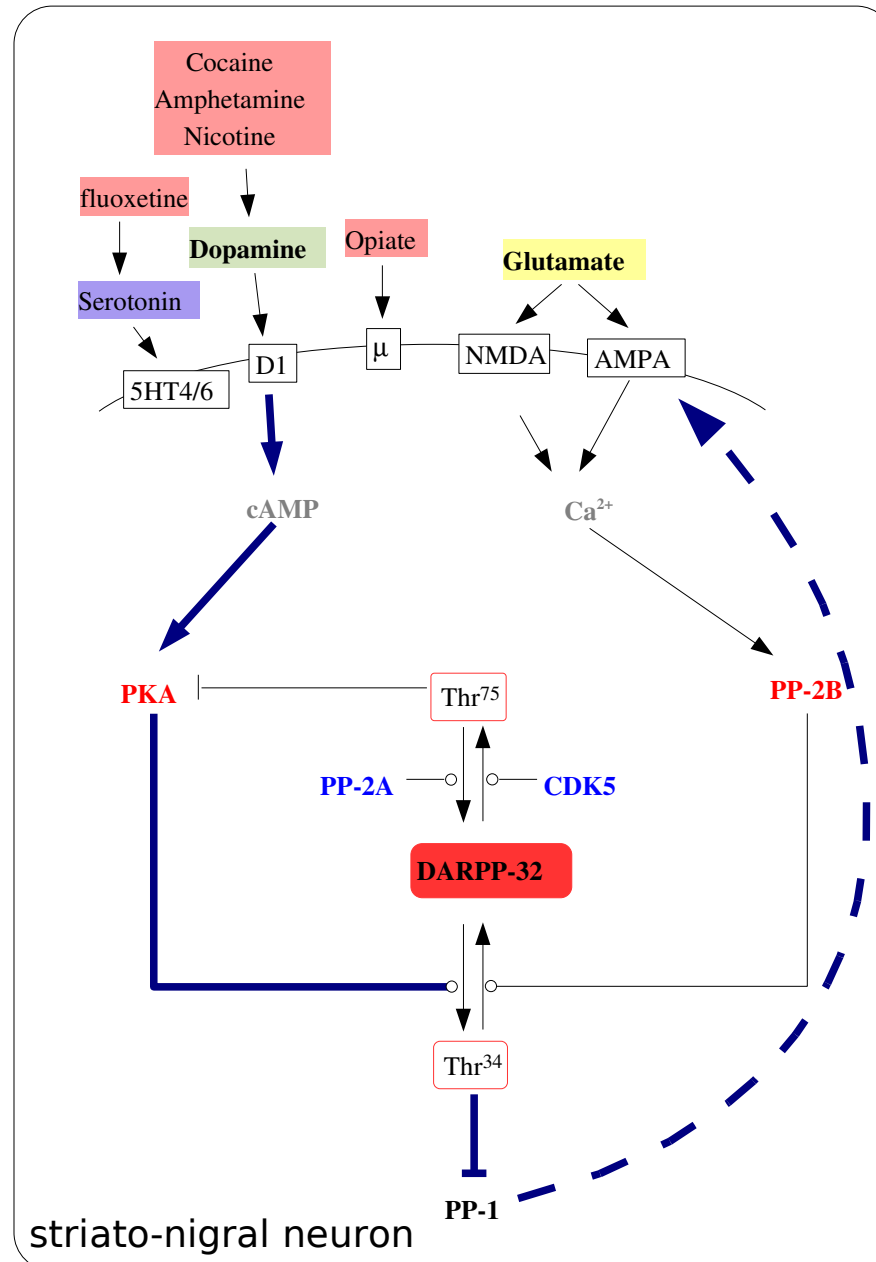


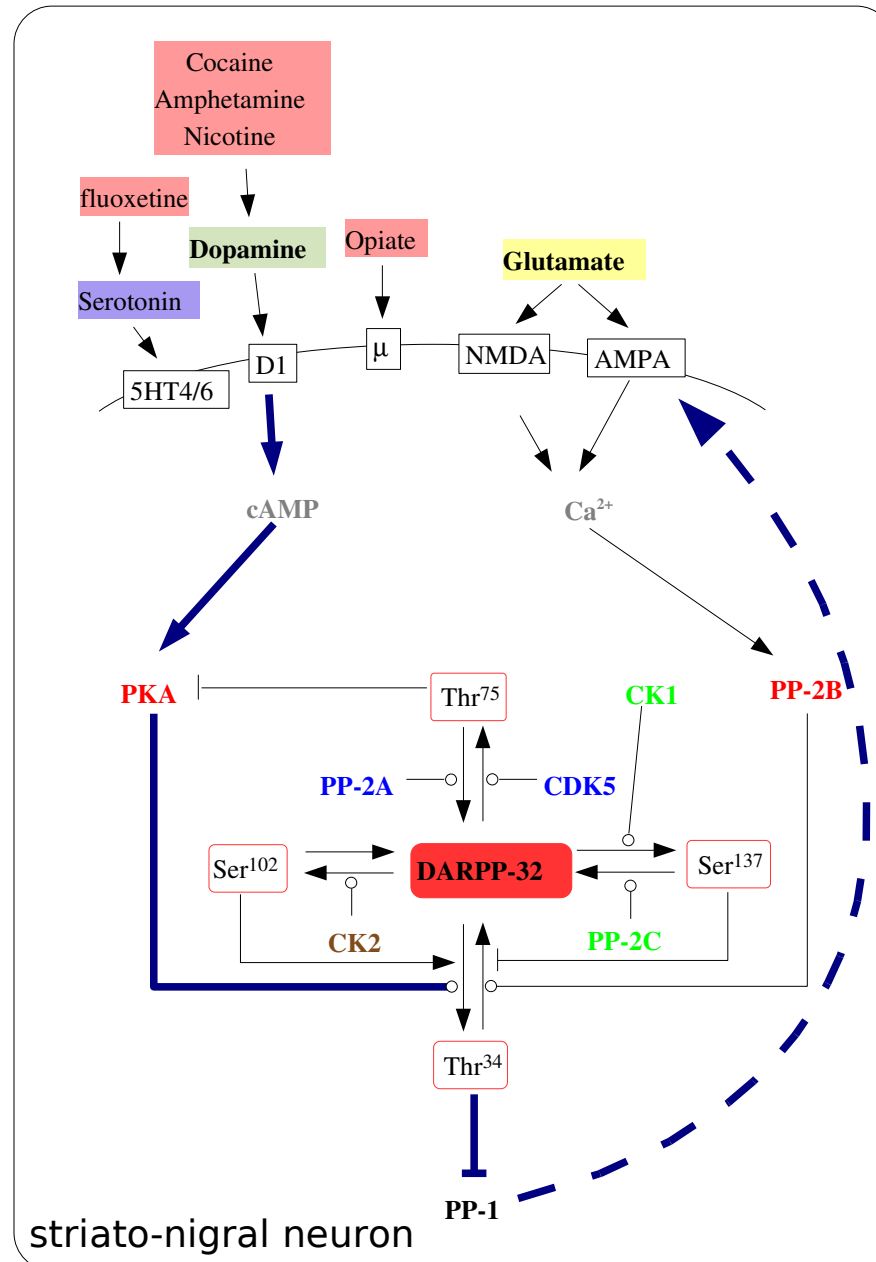


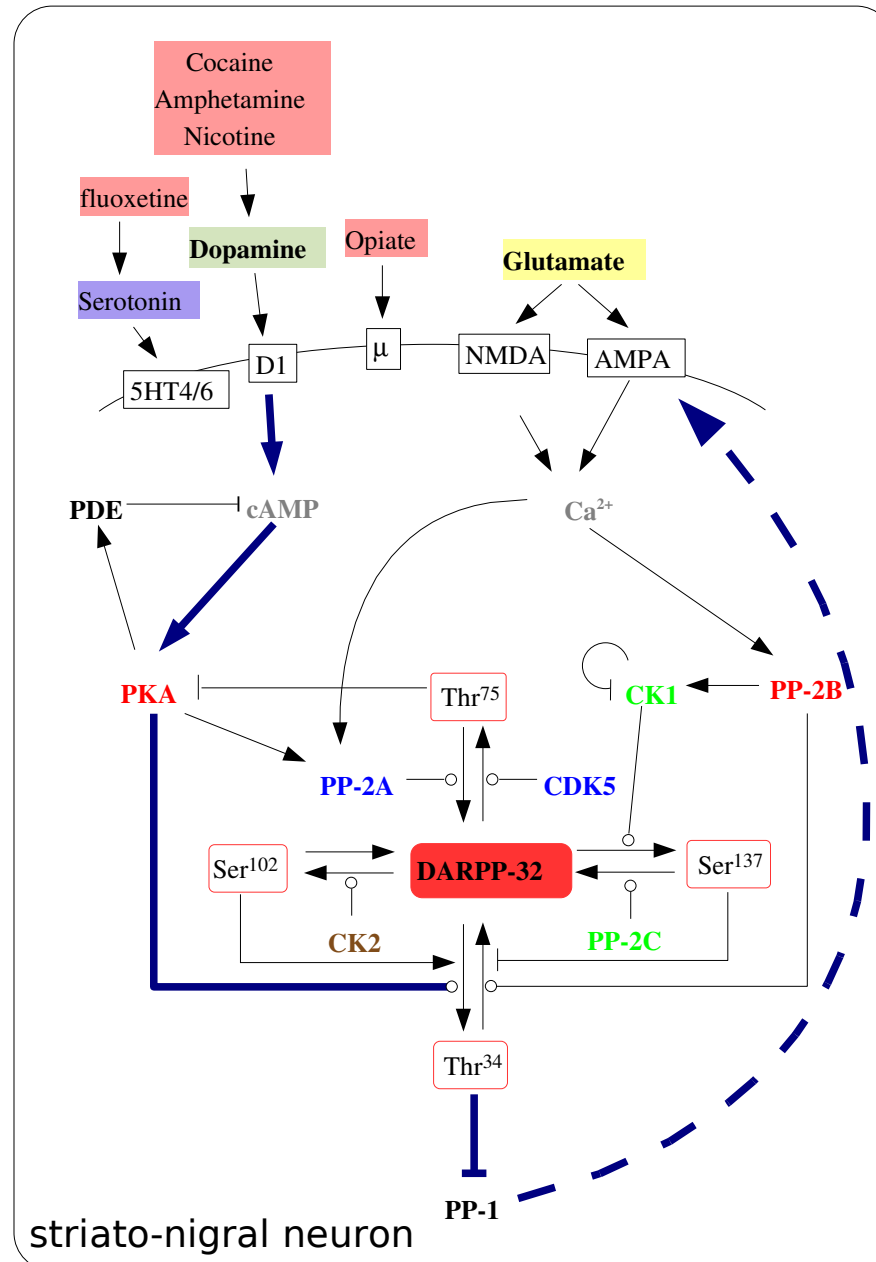
Fernandez E, Schiappa R, Girault JA, Le Novère N (2006)
DARPP-32 is a robust integrator of dopamine and glutamate signals.
PLoS Computational Biology, 2(12): e176.











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

79 species, 151 reactions

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







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

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

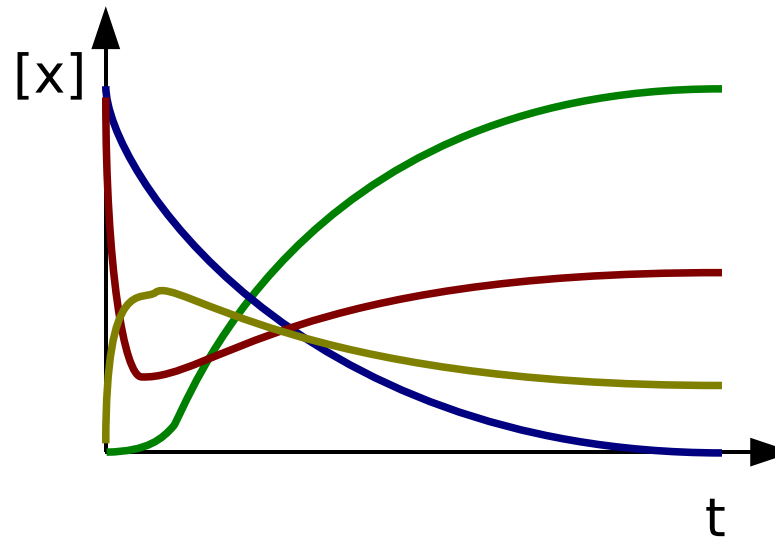
$$d[\text{CDK5}]/dt = -k_1[\text{CDK5}][\text{D}] + k_2[\text{D_CDK5}] + k_3[\text{D_CDK5}]$$

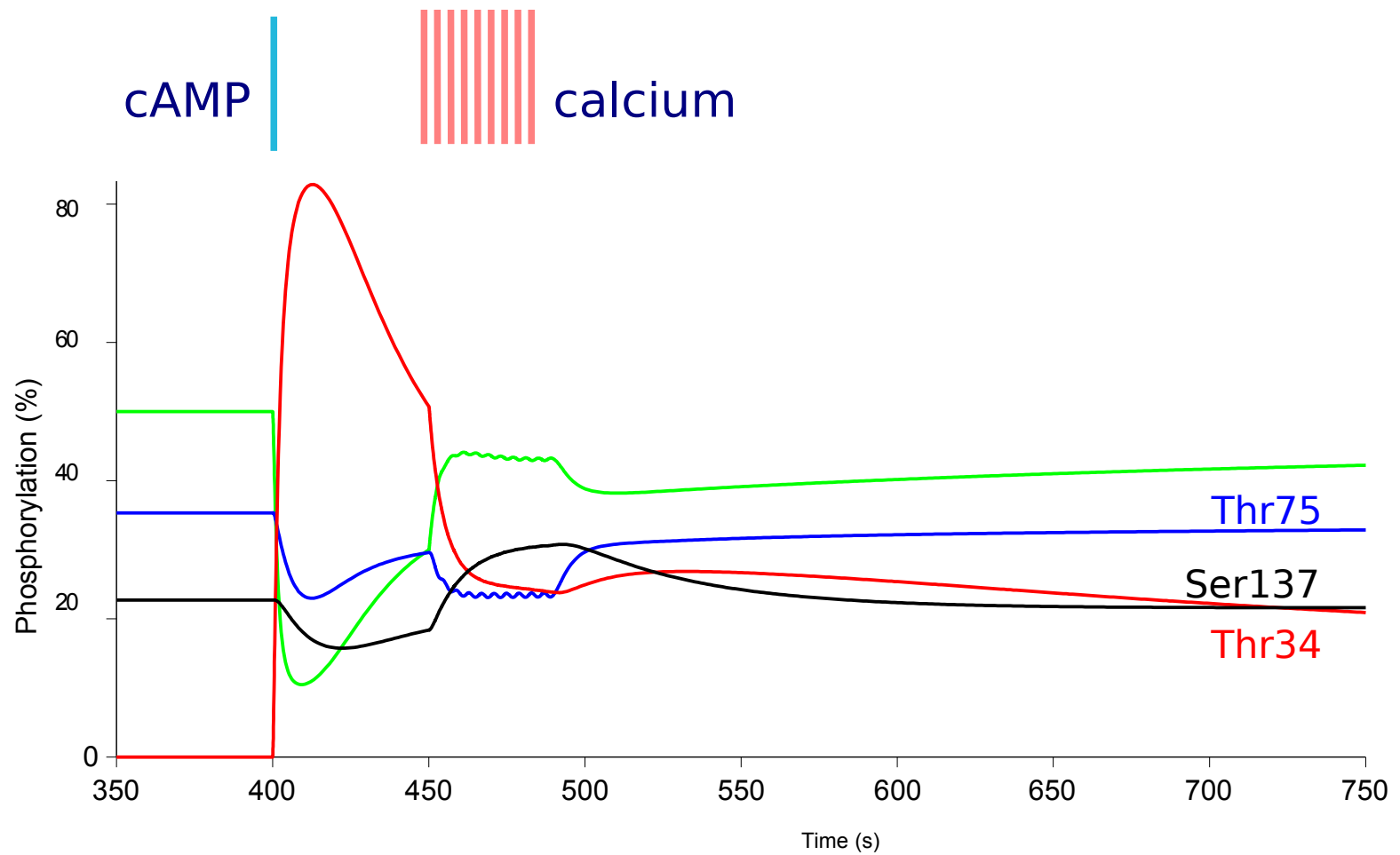
$$d[\text{D_CDK5}]/dt = +k_1[\text{CDK5}][\text{D}] - k_2[\text{D_CDK5}] - k_3[\text{D_CDK5}]$$

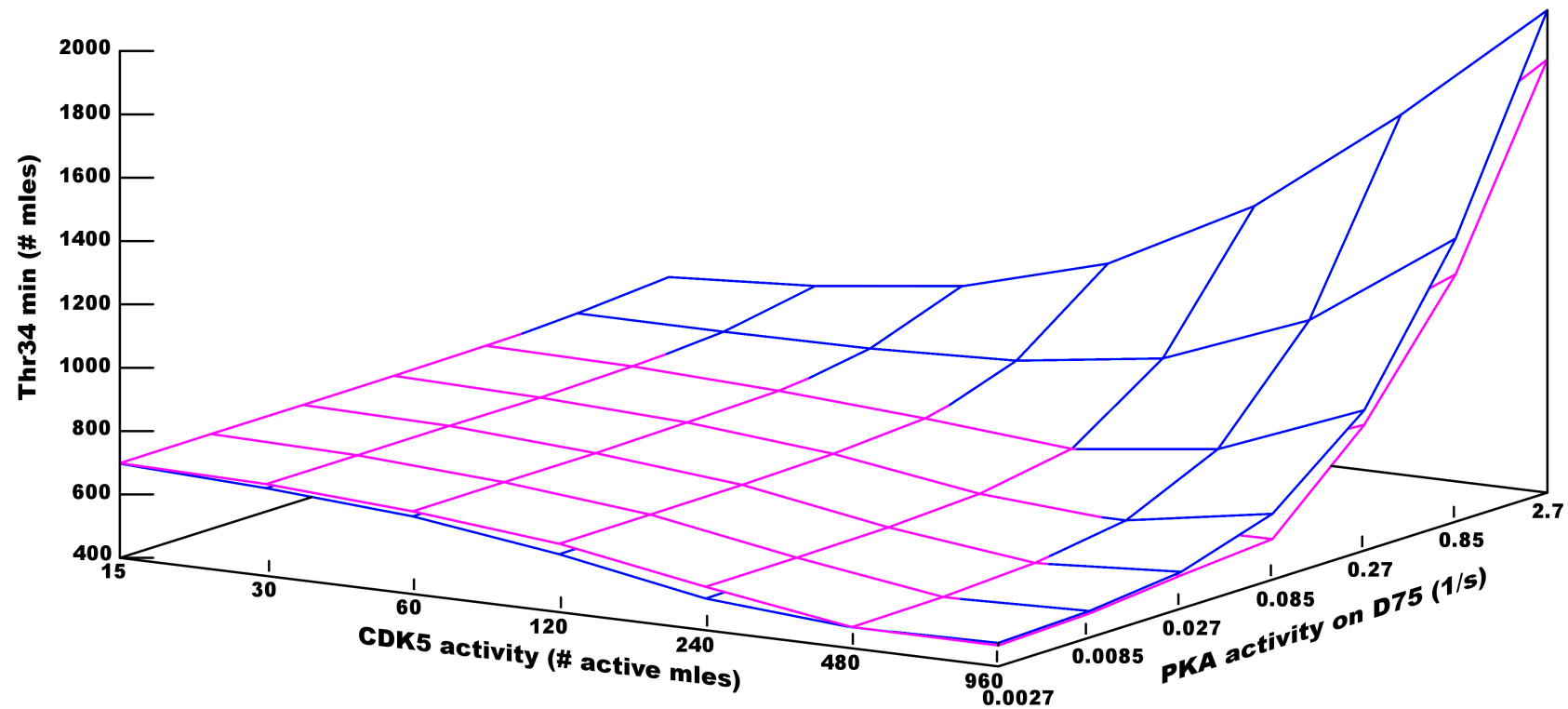


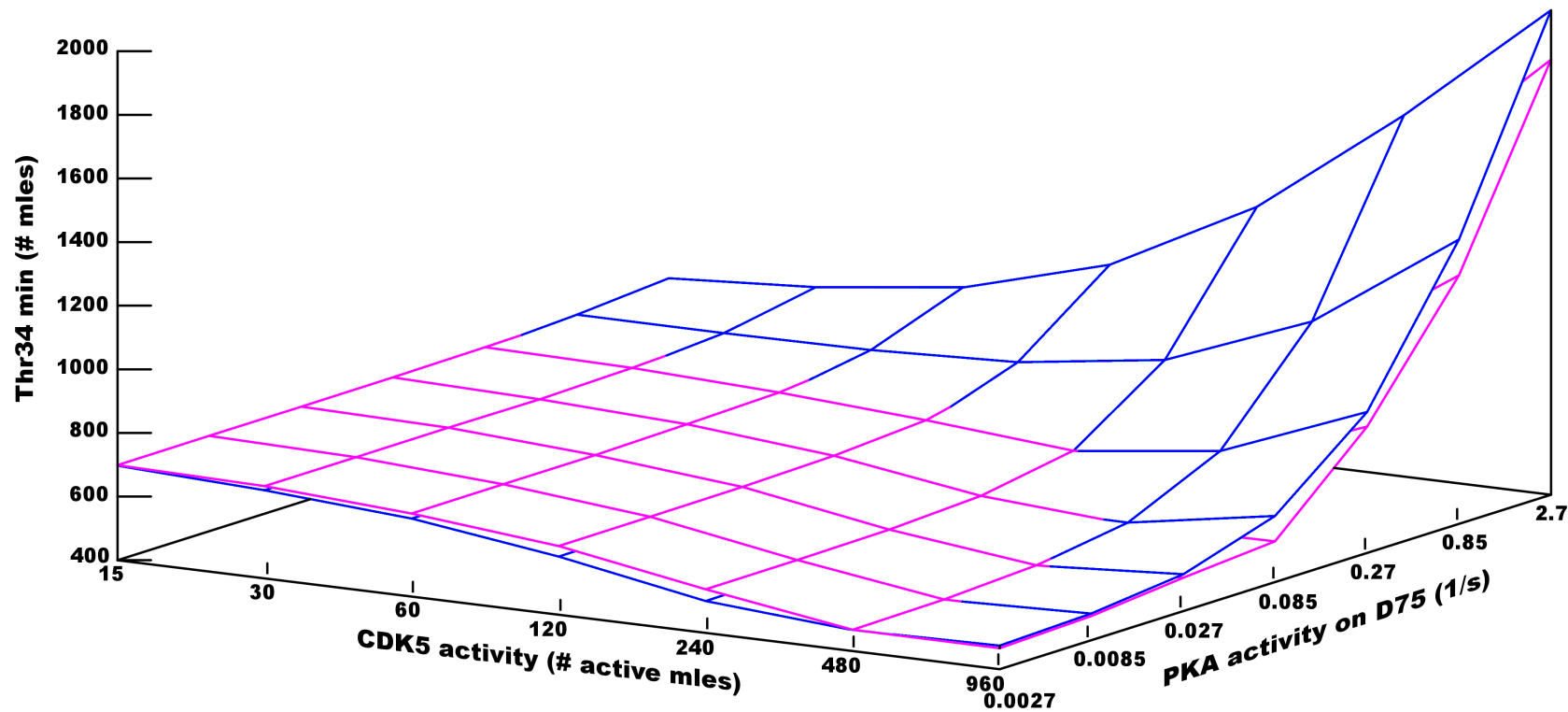


$$\begin{aligned} d[D]/dt &= -k_1[CDK5][D] + k_2[D_CDK5] \\ d[D-75P]/dt &= +k_3[D_CDK5] \\ d[CDK5]/dt &= -k_1[CDK5][D] + k_2[D_CDK5] + k_3[D_CDK5] \\ d[D_CDK5]/dt &= +k_1[CDK5][D] - k_2[D_CDK5] - k_3[D_CDK5] \end{aligned}$$



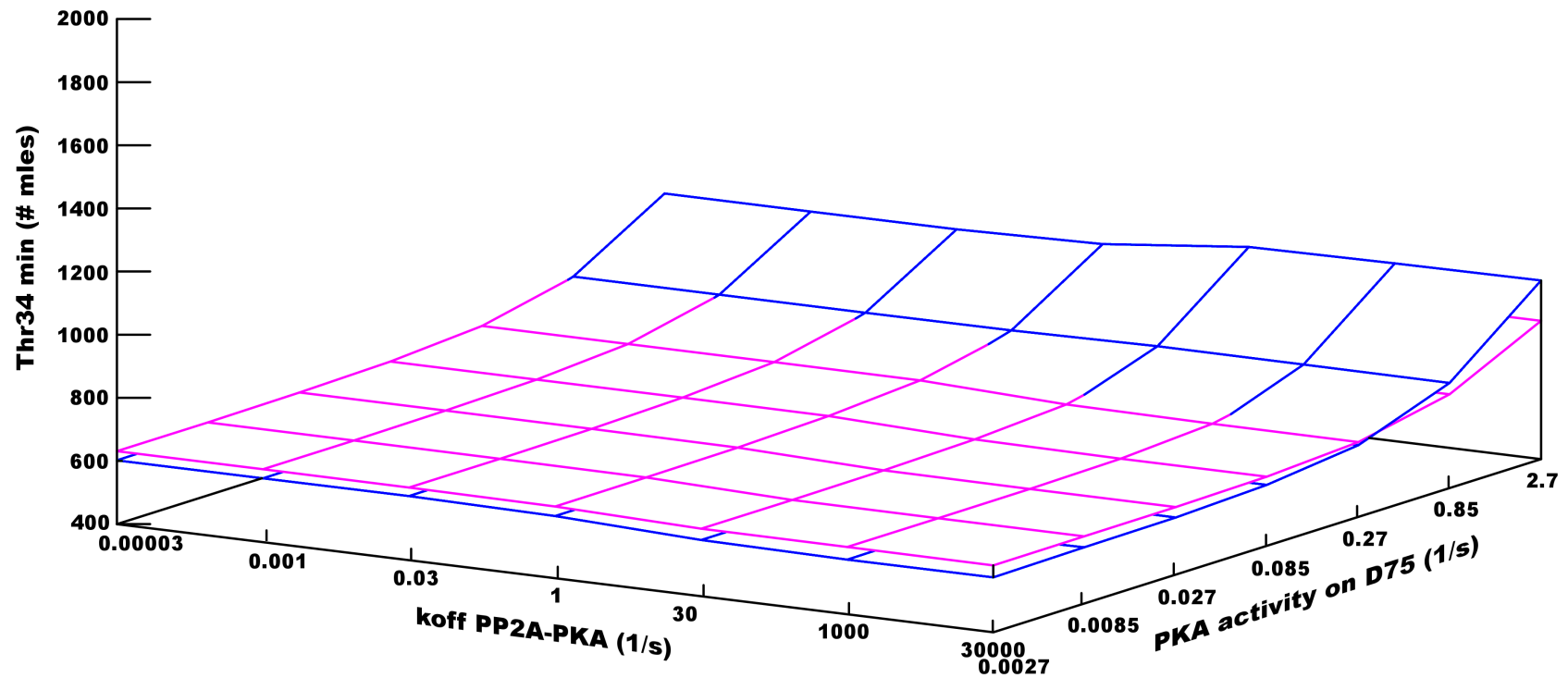


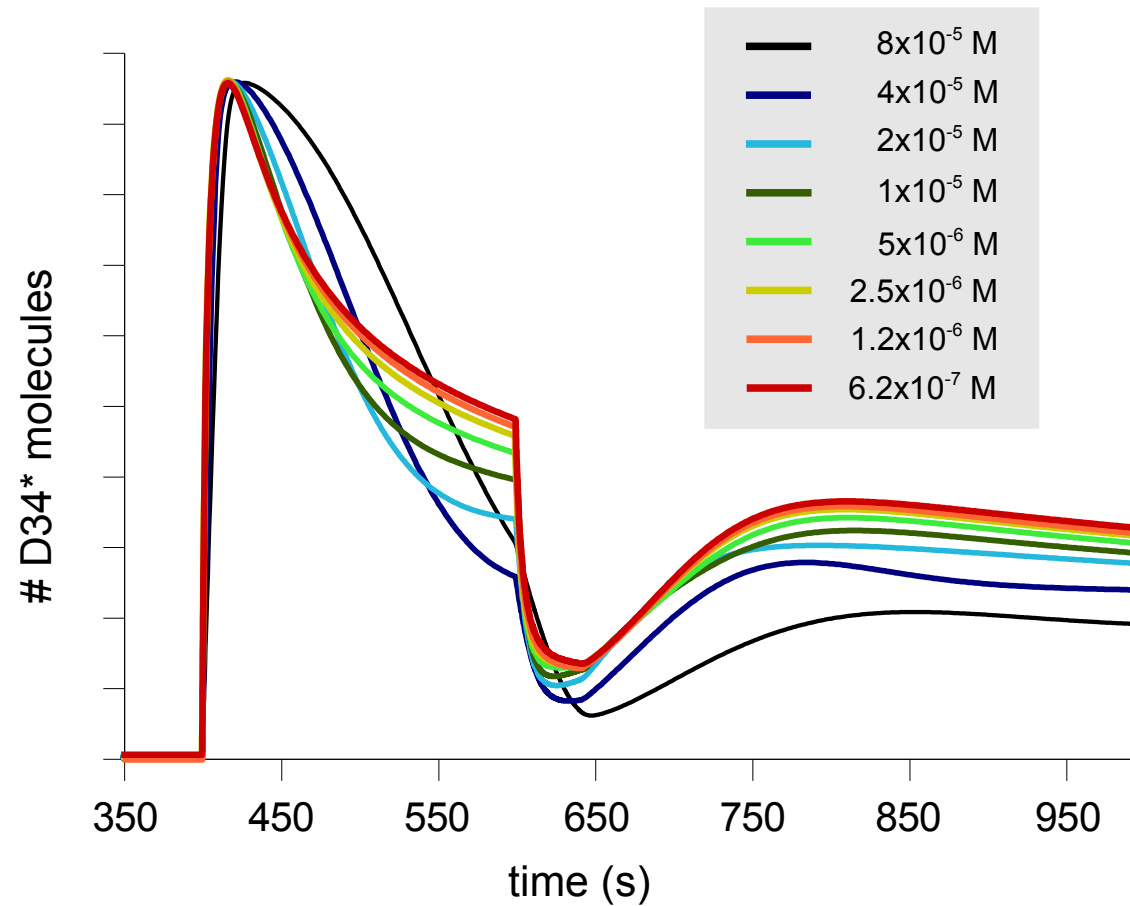


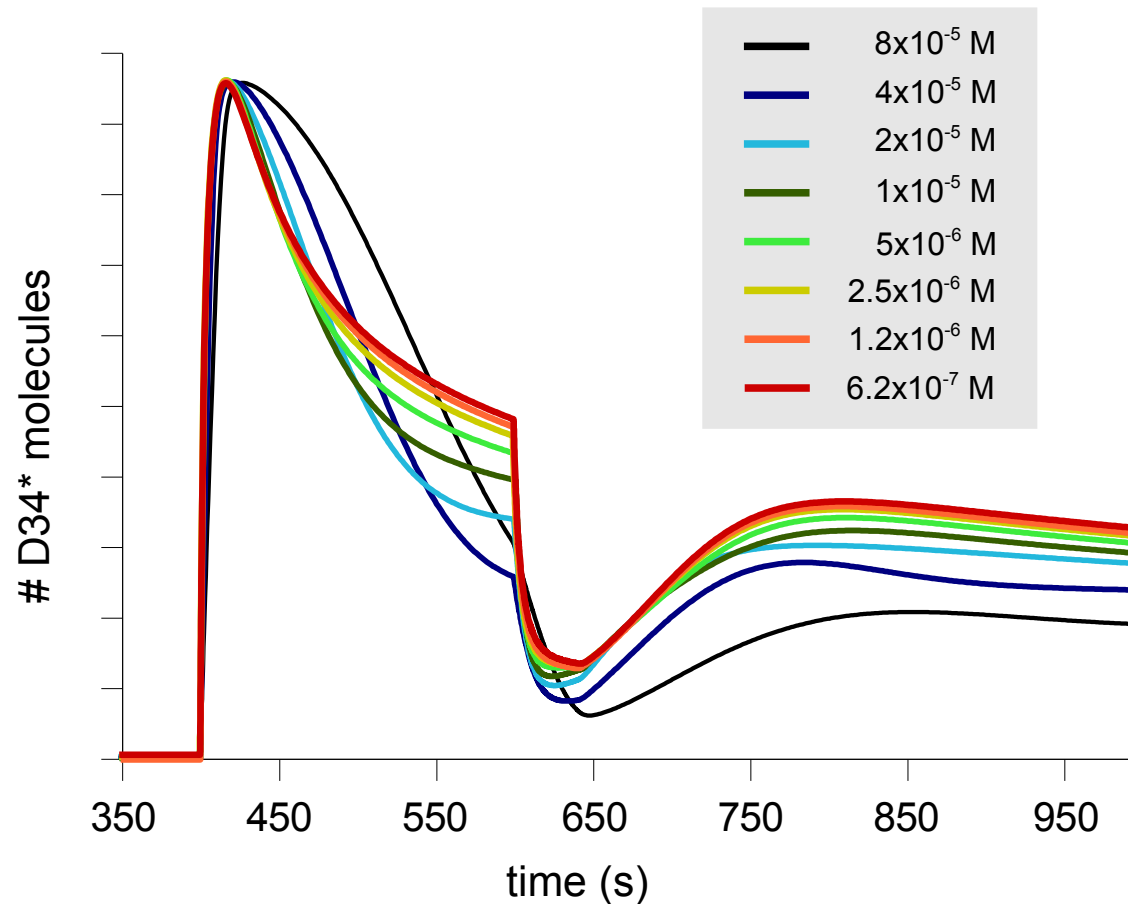


Takahashi *et al.* (2005). Increased activity of cyclin-dependent kinase 5 leads to attenuation of cocaine-mediated dopamine signaling. *Proc Natl Acad Sci USA*, 102:1737-1742.



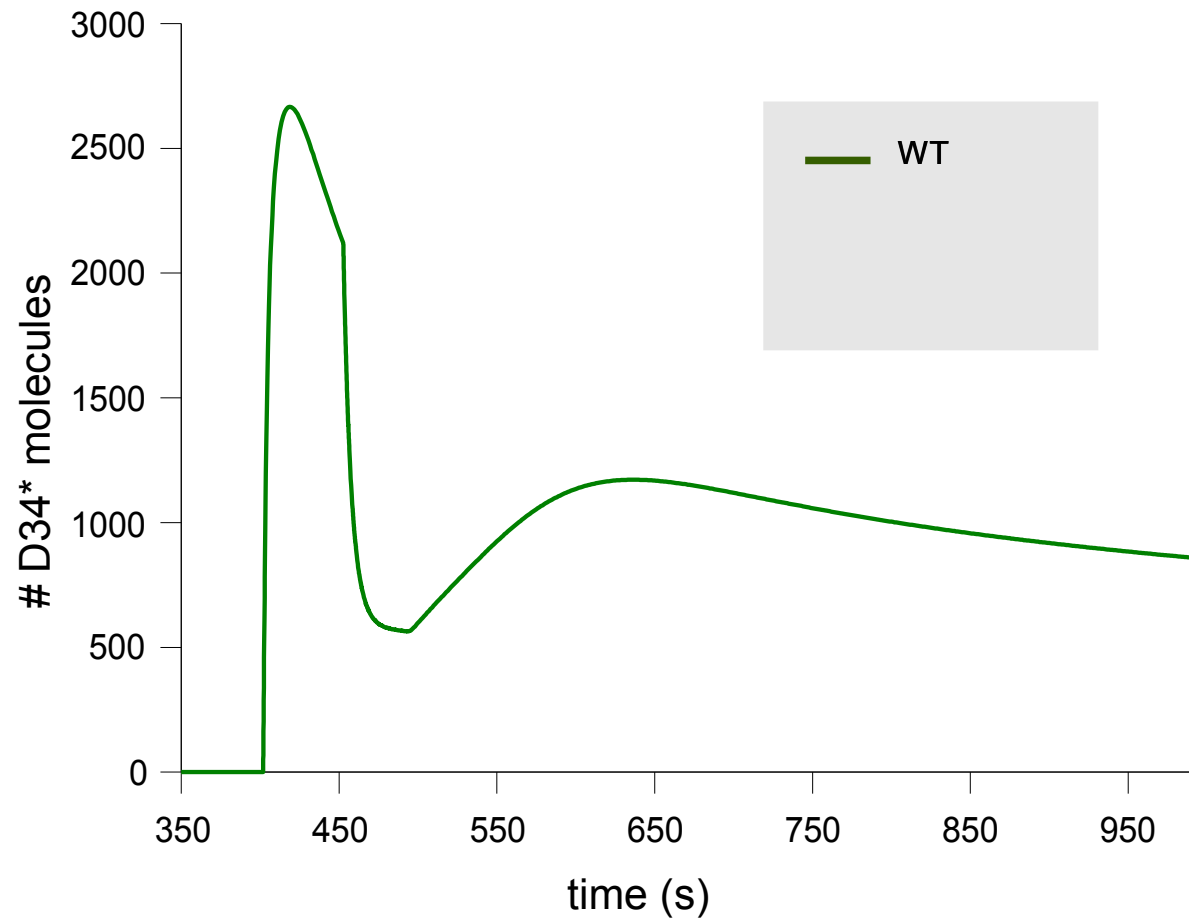


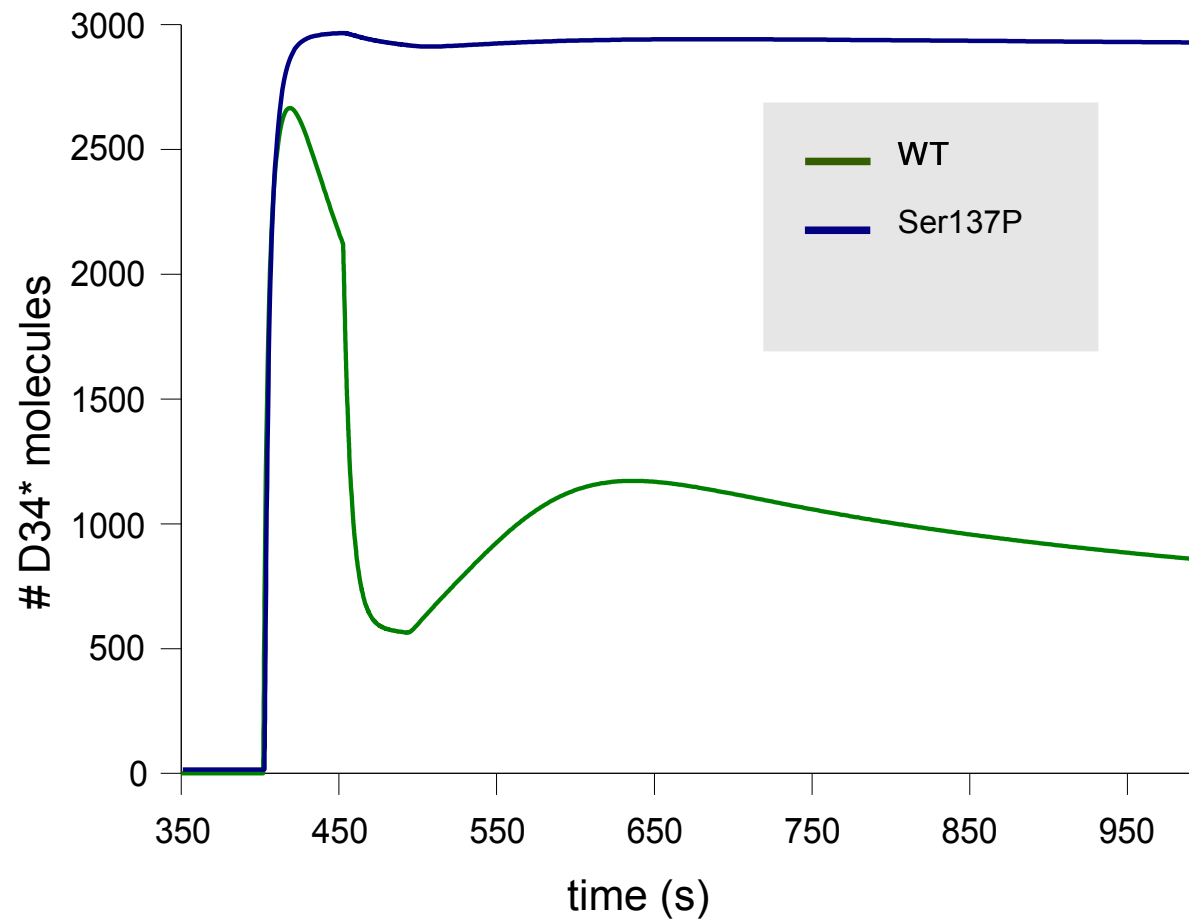


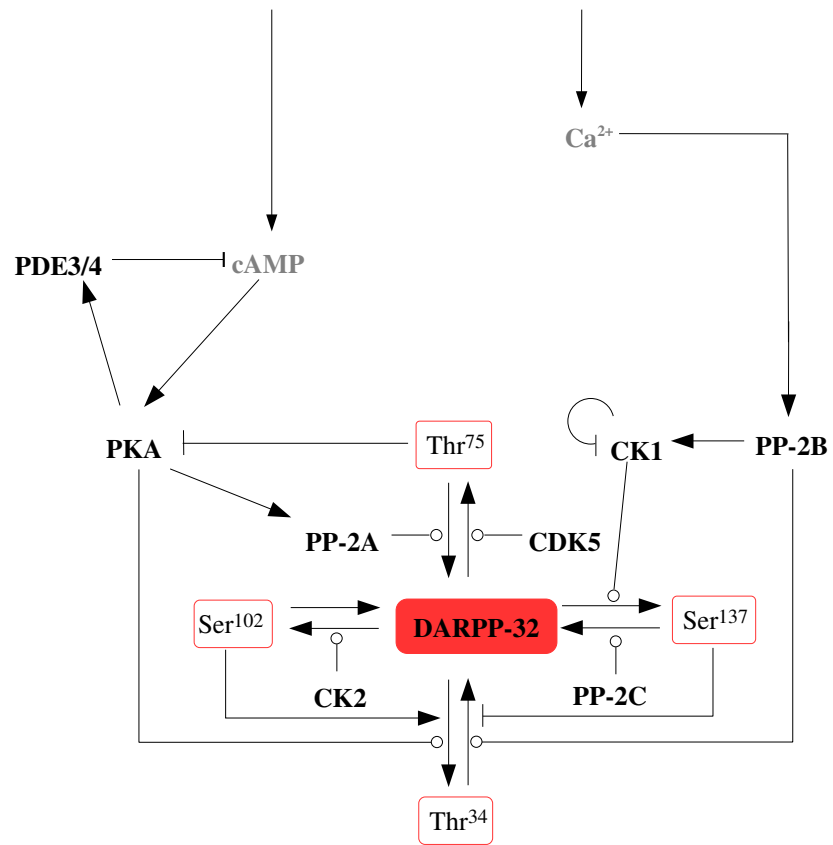


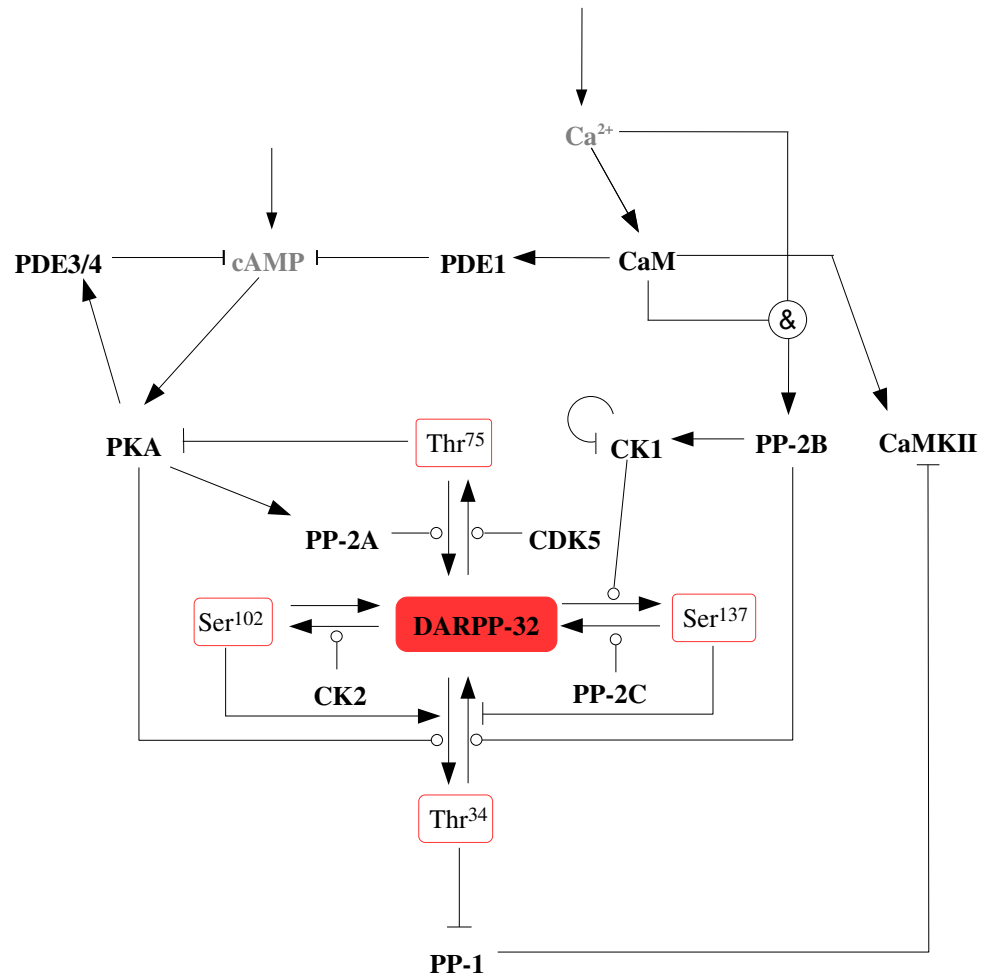
Heterozygous DARPP-32 +/- do not display phenotypes

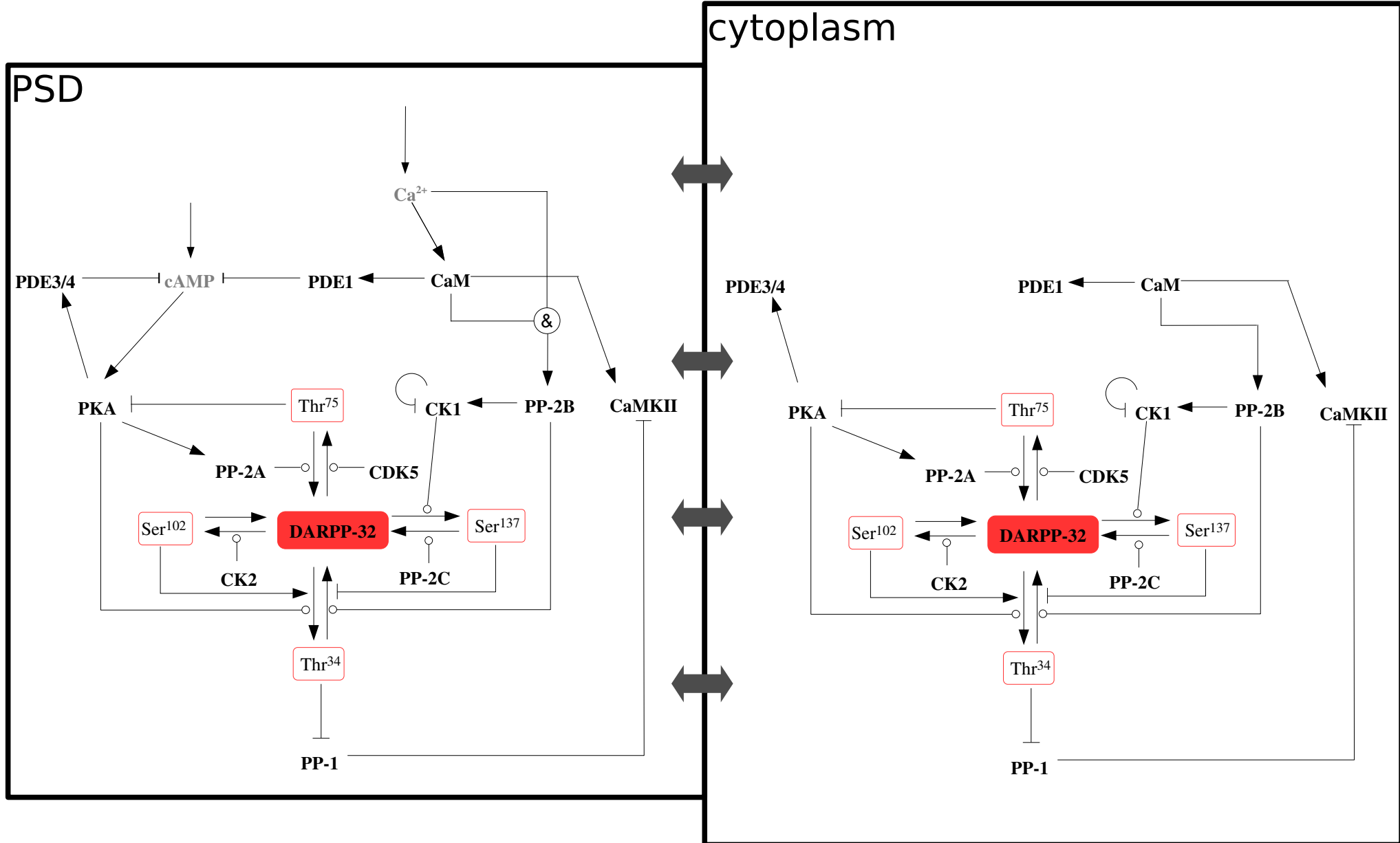


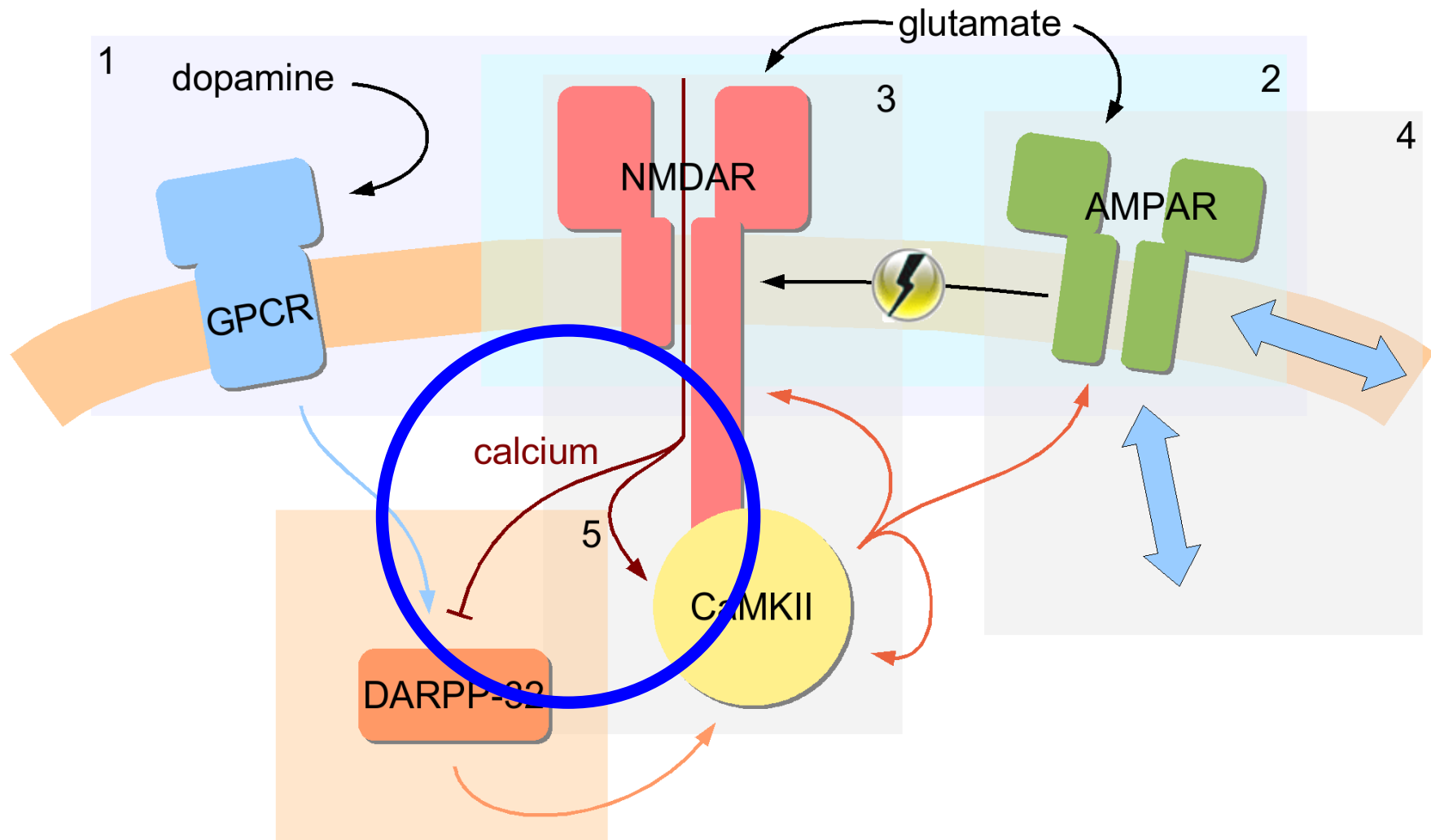


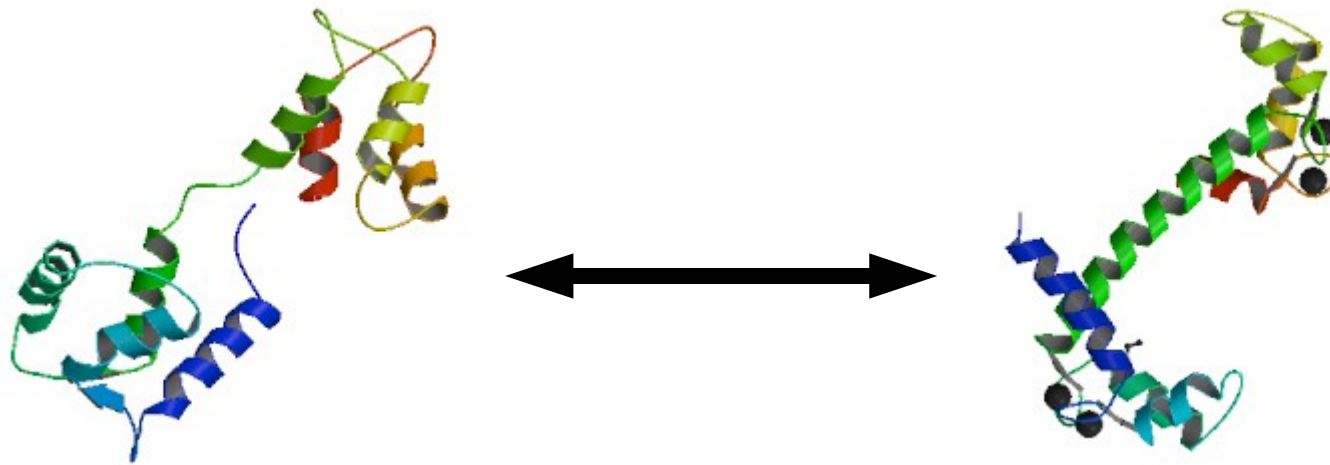


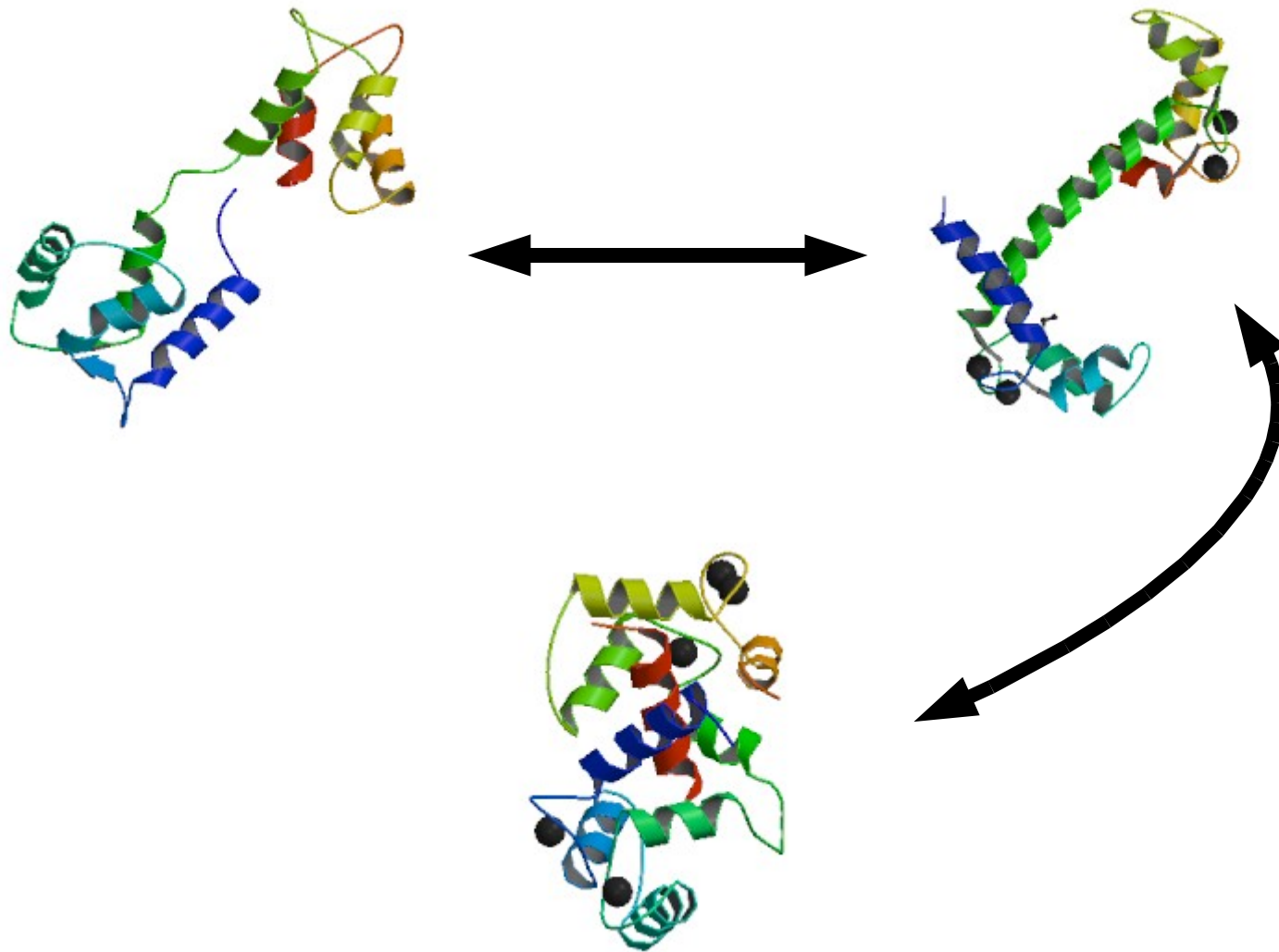












- 4 independent binding sites
- One affinity per site



Waage and Guldberg (1964).

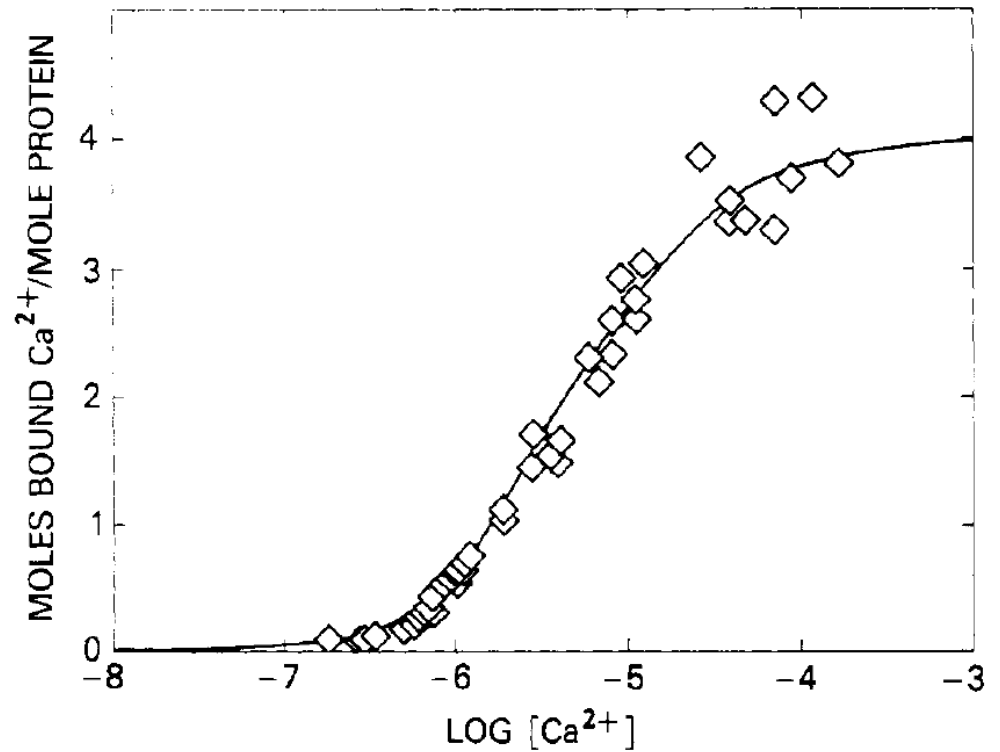
$$\overline{[\text{CaM}^*]} = \frac{[\text{Ca}]^4}{K^4 + [\text{Ca}]^4}$$

Hill (1910).



$$\bar{Y} = \frac{K_1[\text{Ca}] + 2K_1K_2[\text{Ca}]^2 + 3K_1K_2K_3[\text{Ca}]^3 + 4K_1K_2K_3K_4[\text{Ca}]^4}{1 + K_1[\text{Ca}] + K_1K_2[\text{Ca}]^2 + K_1K_2K_3[\text{Ca}]^3 + K_1K_2K_3K_4[\text{Ca}]^4}$$

Adair (1925)
J Biol Chem, 63: 529-545



Crouch and Klee (1980)
Biochemistry, 19: 3692-3698



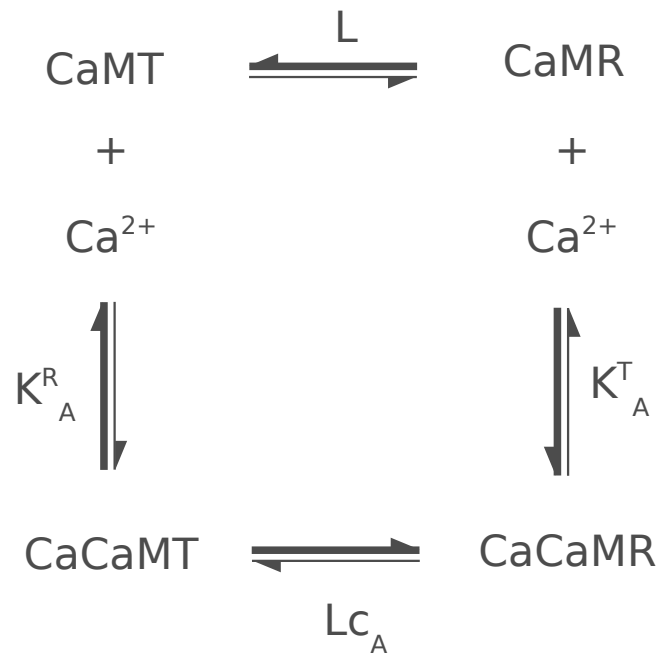


- Calmodulin bound to three calcium activates calcineurin
 - Kincaid and Vaughan (1986). *PNAS*, 83: 1193-1197
- Calmodulin bound to two calcium can bind CaMKII
 - Shifman et al (2006). *PNAS*, 103: 13968-13973
- Calmodulin affinity for calcium increases once bound to CaMKII
 - Shifman et al (2006) [but many previous reports on other targets: e.g. Burger et al (1983). *JBC*, 258: 14733-14739 ; Olwin et (1984). *JBC* 259: 10949-10955]
- Calcium activates both LTP and LTD through calmodulin
 - Lisman (1989) *PNAS*, 86: 9574-9578
 - High $[Ca^{2+}]$ (high freq) $\cong$ CaMKII ; Low $[Ca^{2+}]$ (low freq) $\cong$ PP2B

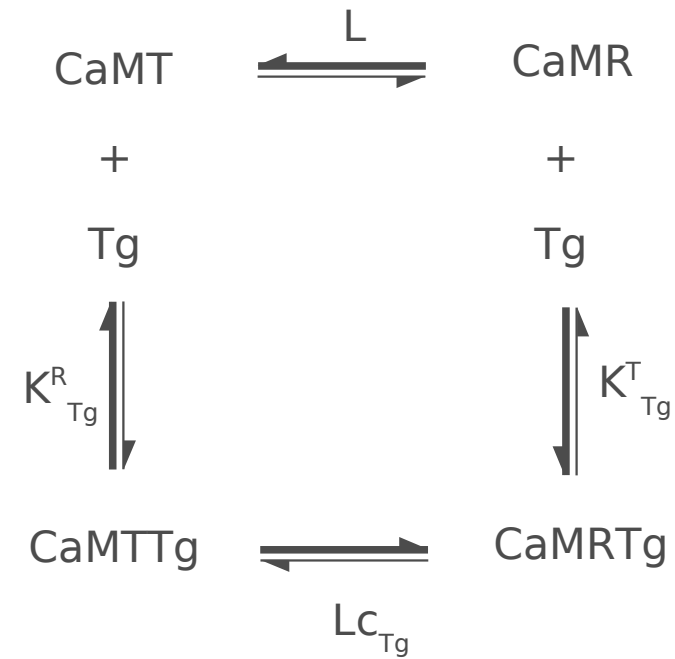


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- ➡ Monod, Wyman, Changeux (1965). *J Mol Biol*, 12: 88-118



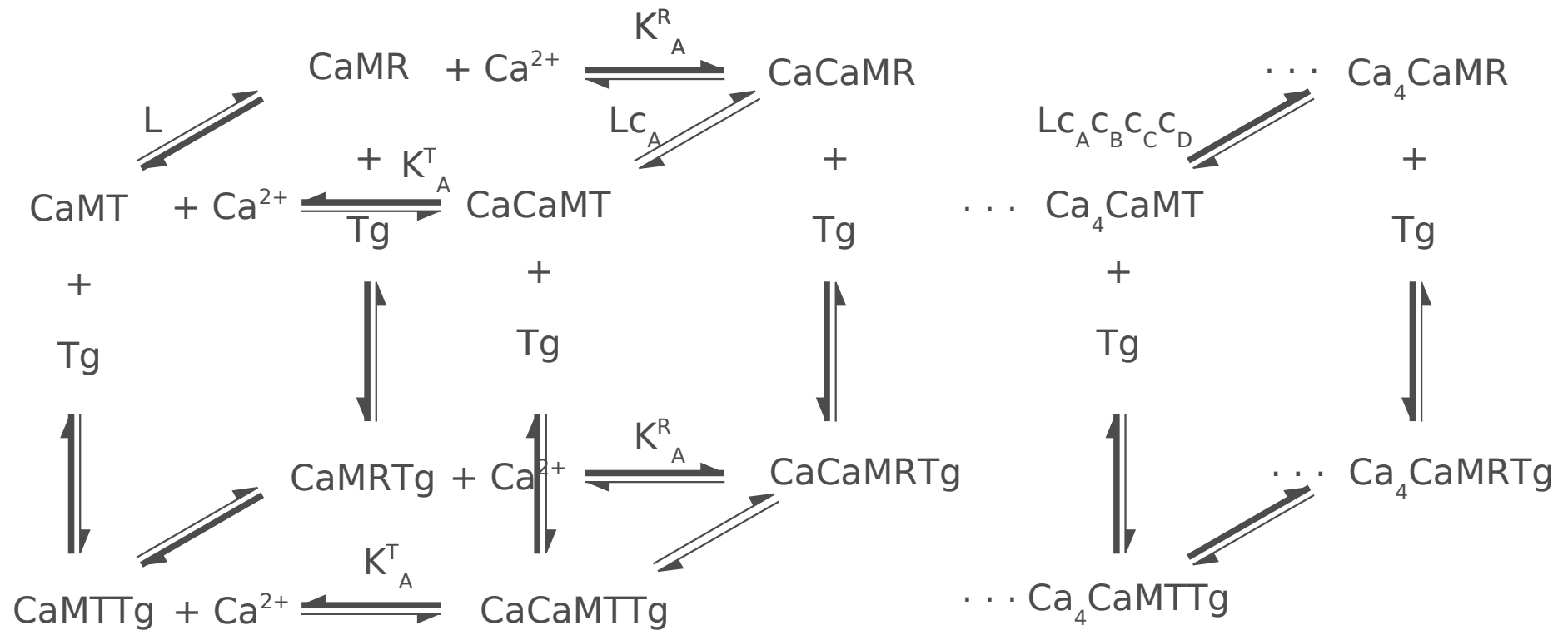


$$L = \frac{[\text{CaMT}]}{[\text{CaMR}]}$$



$$C_i = \frac{K_i^R}{K_i^T}$$





$$K_1 = 4 \frac{1 + L}{\frac{1}{K_A^R} + \frac{1}{K_B^R} + \frac{1}{K_C^R} + \frac{1}{K_D^R} + L \left(\frac{1}{K_A^T} + \frac{1}{K_B^T} + \frac{1}{K_C^T} + \frac{1}{K_D^T} \right)}$$



$$K_1 = 4 \frac{1 + L}{\frac{1}{K_A^R} + \frac{1}{K_B^R} + \frac{1}{K_C^R} + \frac{1}{K_D^R} + L \left(\frac{1}{K_A^T} + \frac{1}{K_B^T} + \frac{1}{K_C^T} + \frac{1}{K_D^T} \right)}$$

$$K_i = \frac{N - i + 1}{i} \frac{S_{i-1}^R + LS_{i-1}^T}{S_i^R + LS_i^T}$$

$$S_i^R := \sum_{K_j^R \in \{K_A^R, K_B^R, \dots\}, j_1 < j_2 < \dots < j_i} \frac{1}{K_{j_1}^R} \cdots \frac{1}{K_{j_i}^R}$$

$$S_i^T := \sum_{K_j^T \in \{K_A^T, K_B^T, \dots\}, j_1 < j_2 < \dots < j_i} \frac{1}{K_{j_1}^T} \cdots \frac{1}{K_{j_i}^T}$$

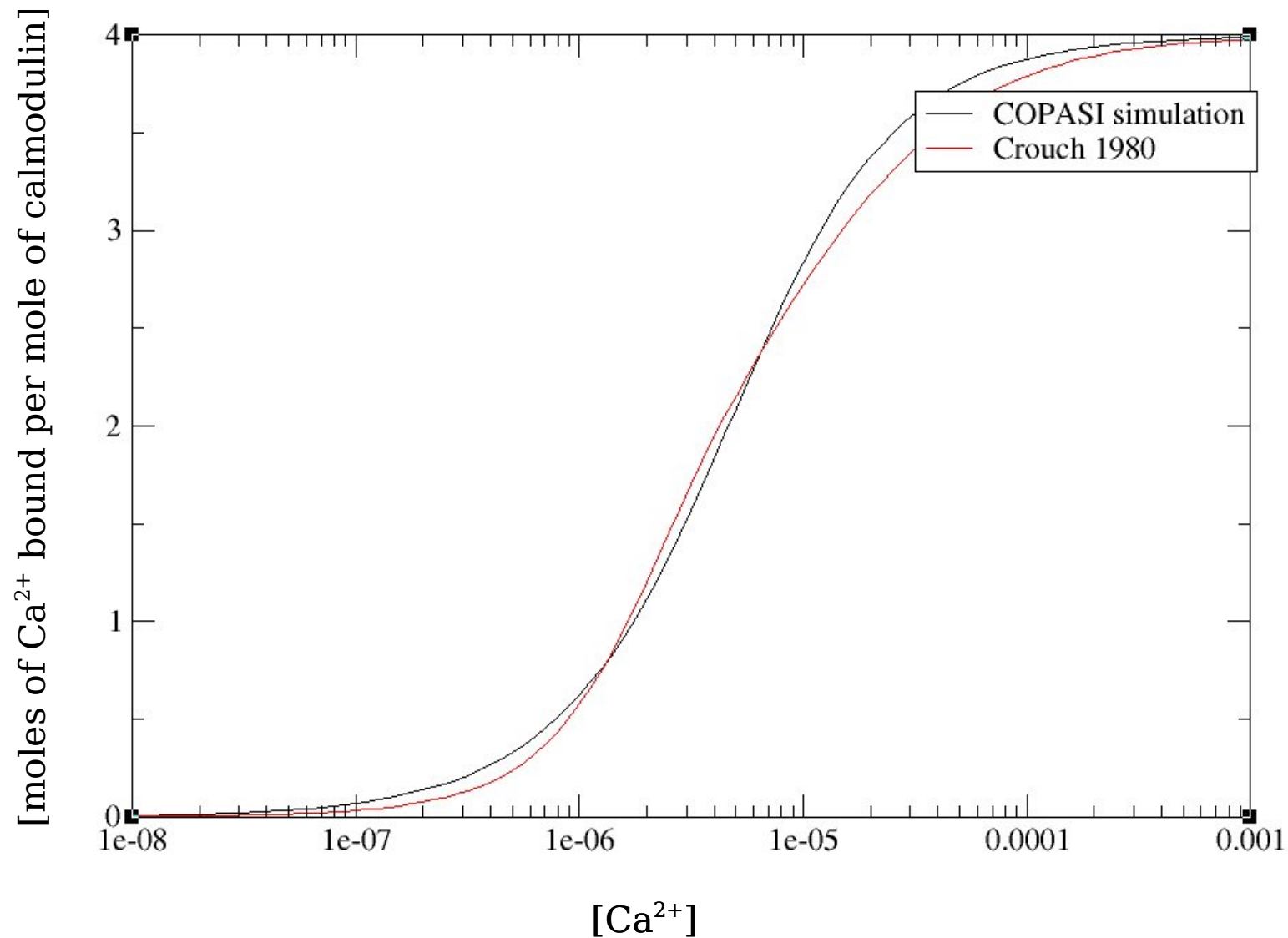


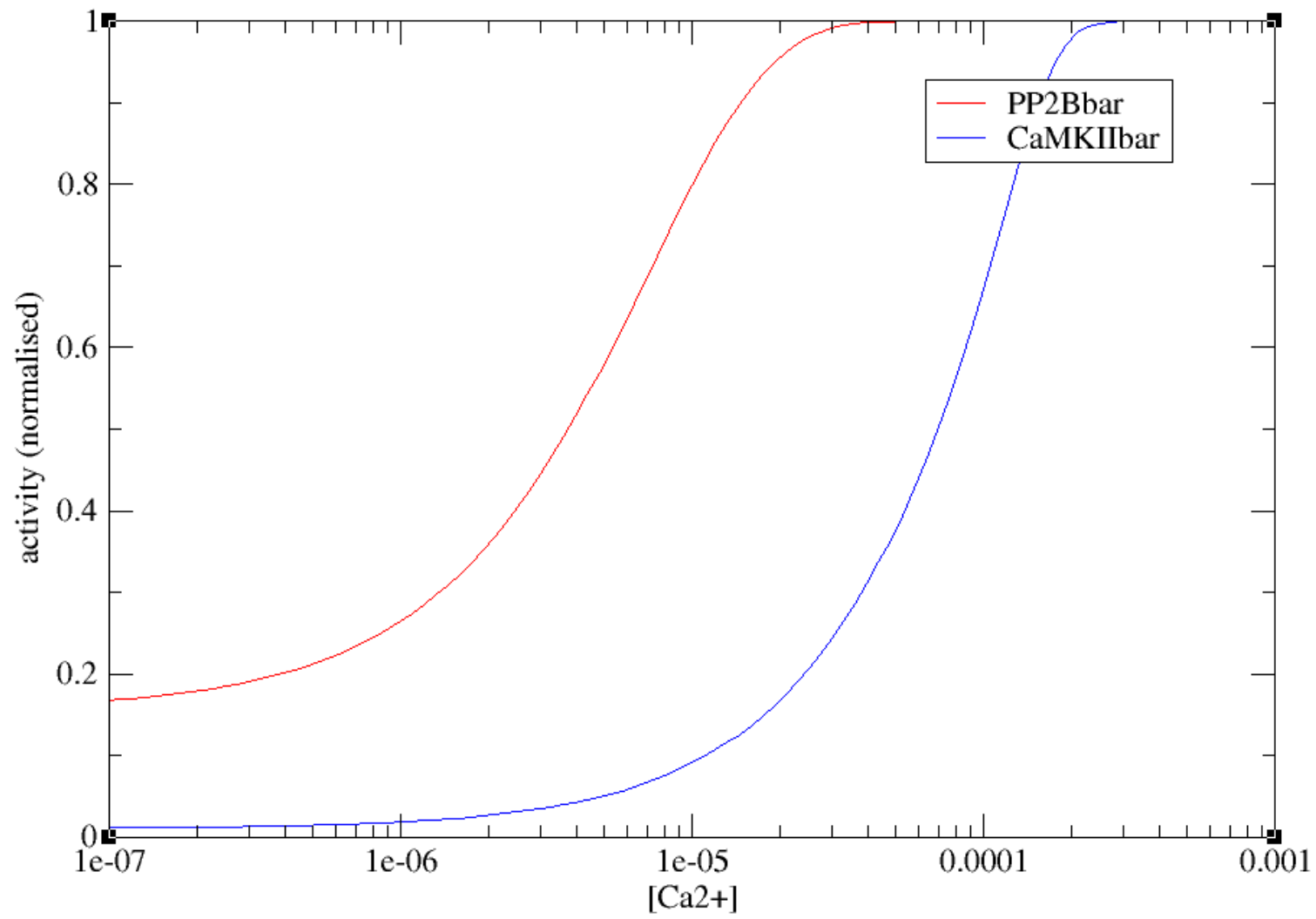
Parameter estimation constrained by:

- Calcium binding R and T states
 - Crouch and Klee (1980) *Biochemistry*, 19: 3692-3698
- Calcium binding R state only (locked by troponin) and isomerisation constant
 - Keller et al (1982). *Biochemistry*, 21: 156-162
- Calcium binding of N and C terminals
 - Shifman et al (2006) *PNAS*, 103: 13968-13973

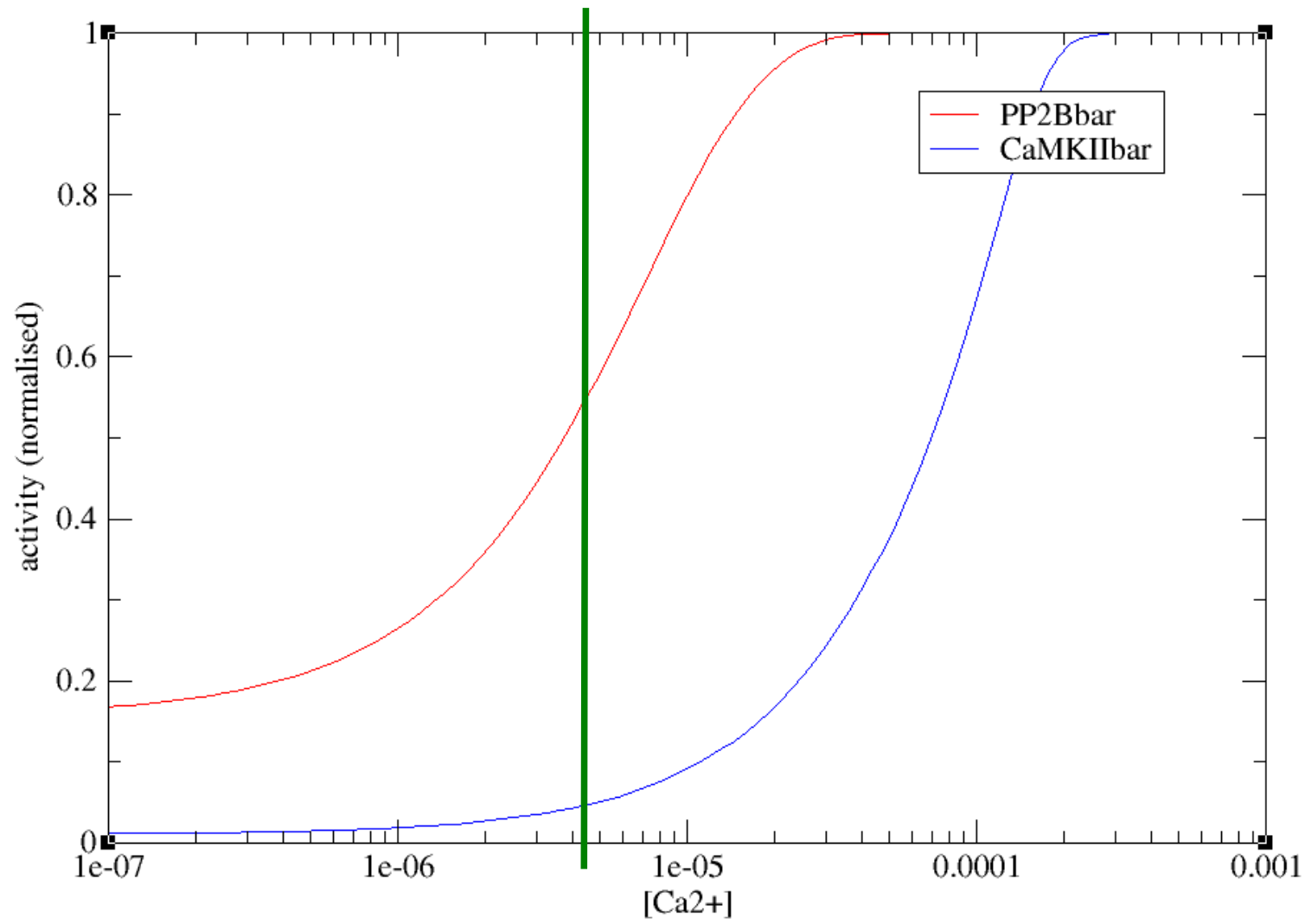
- PP2B affinity for CaM R state >> CaMKII one
- [CaMKII] >> [PP2B]

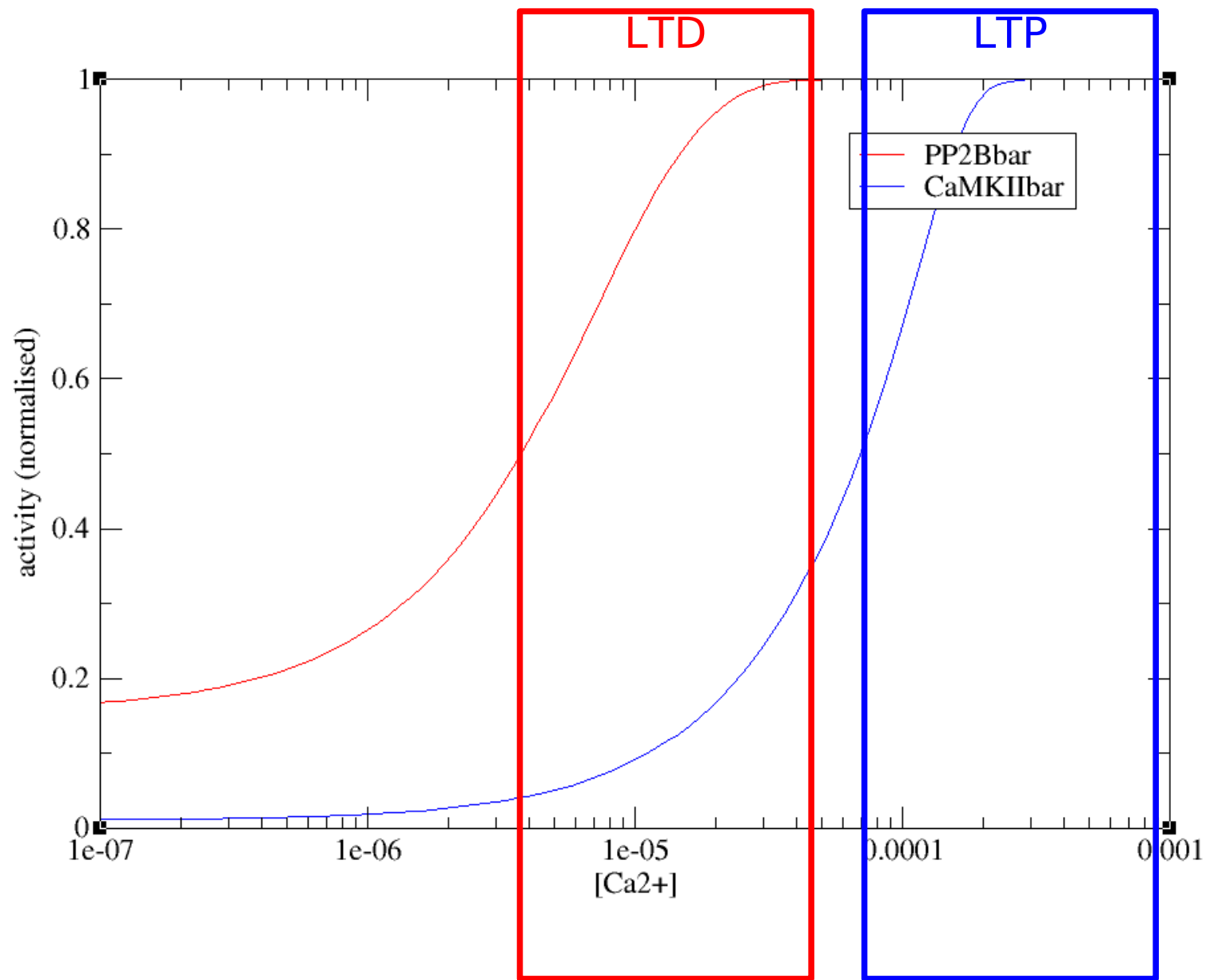






half saturation of calmodulin





- E-cell developers
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Kazunari Kaizu
Gabor Bereczki

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Ralf Gauges

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Christian Knuepfer, Marie-C student
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