

Computational Models of Synaptic Plasticity

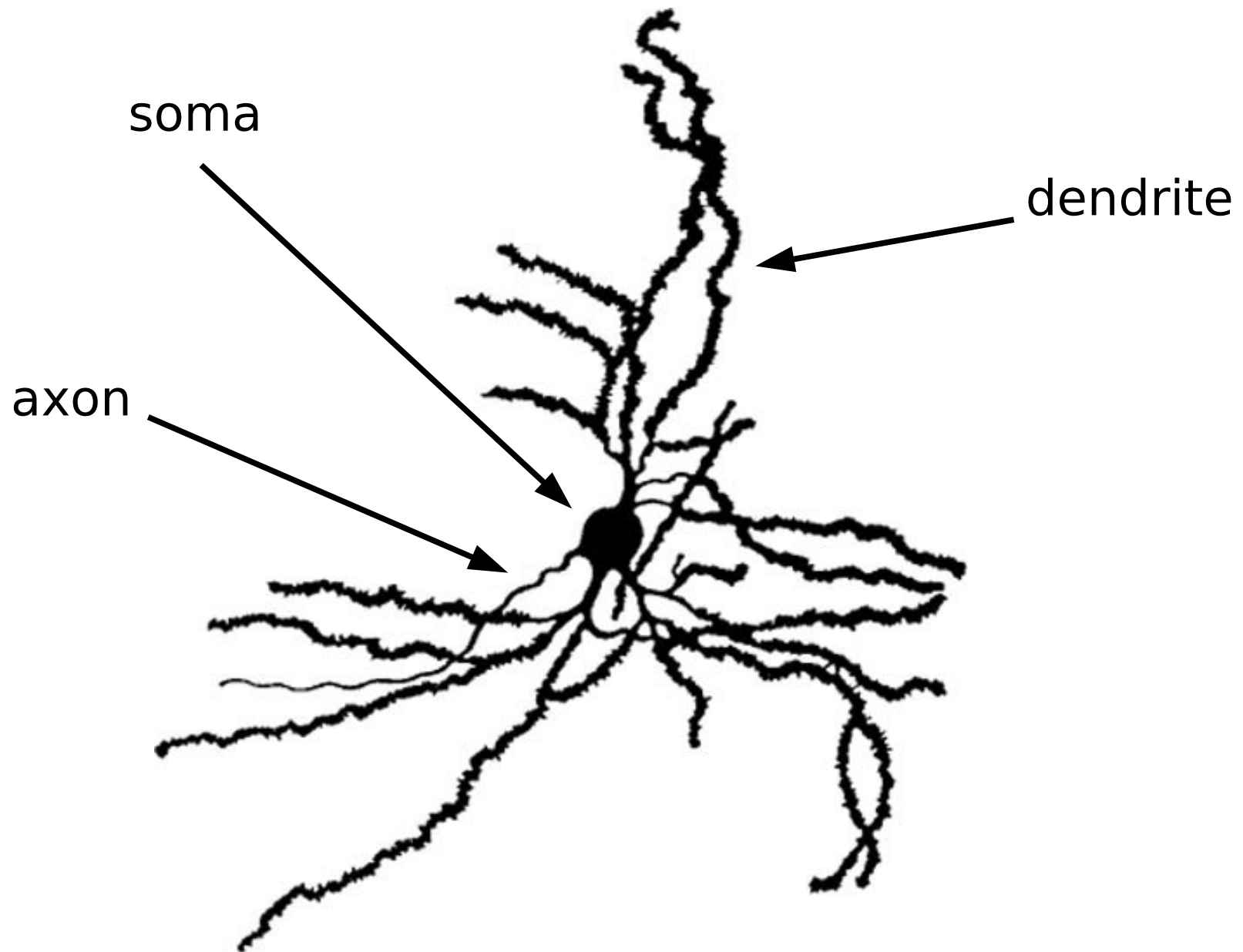
Nicolas Le Novère, EMBL-EBI

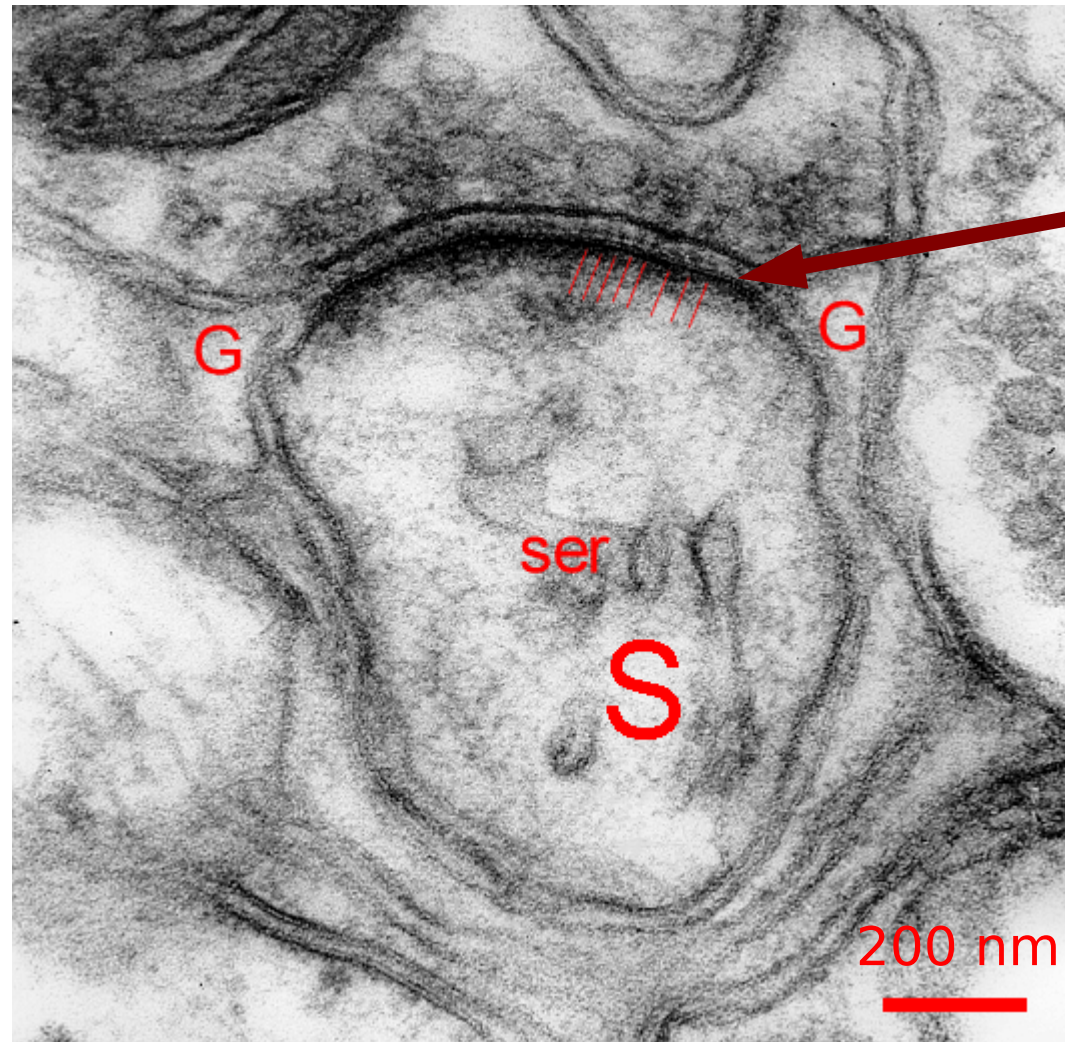


Linking biophysics and chemical kinetics to improve realism of models: calmodulin and synaptic plasticity

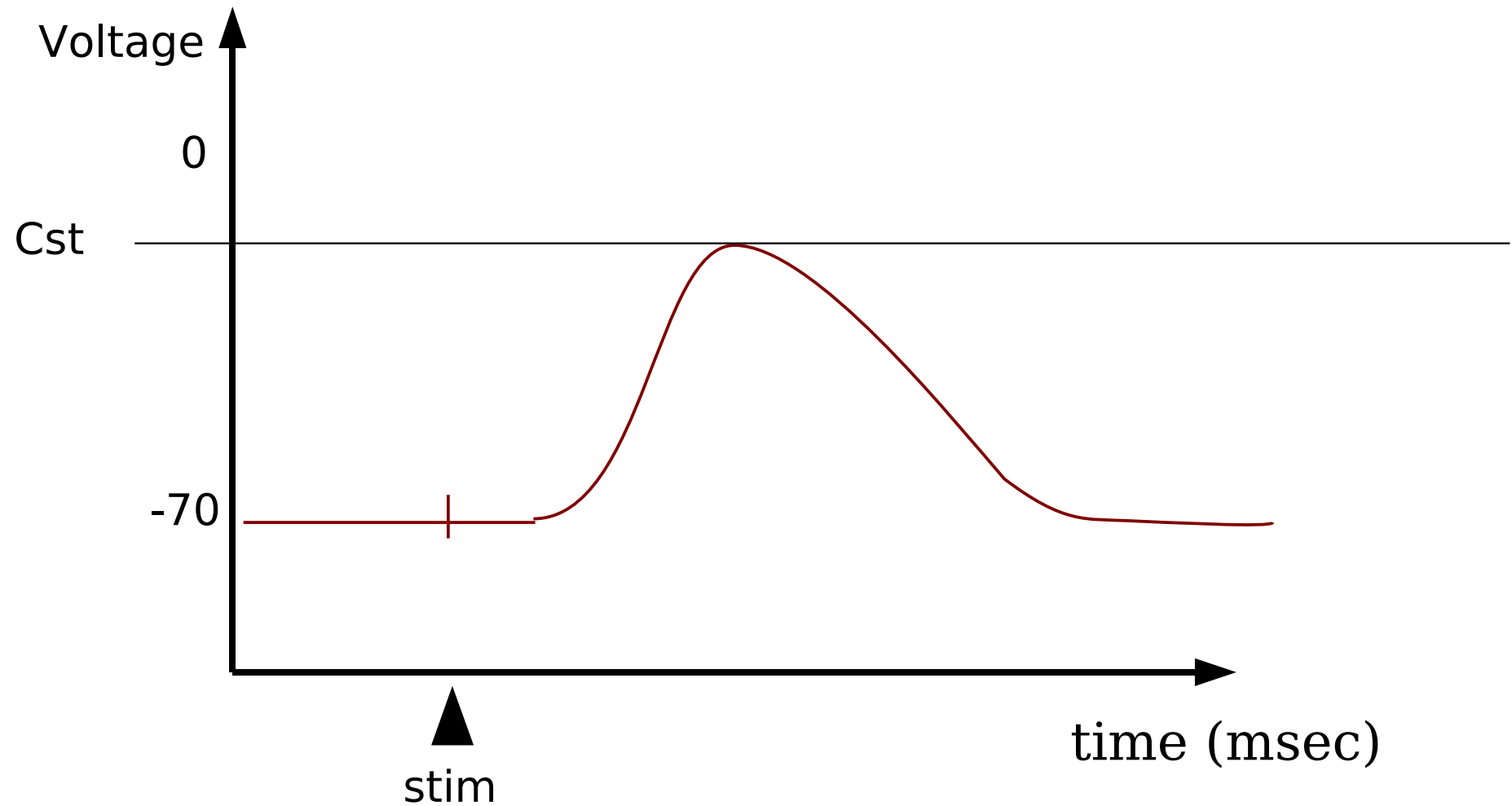
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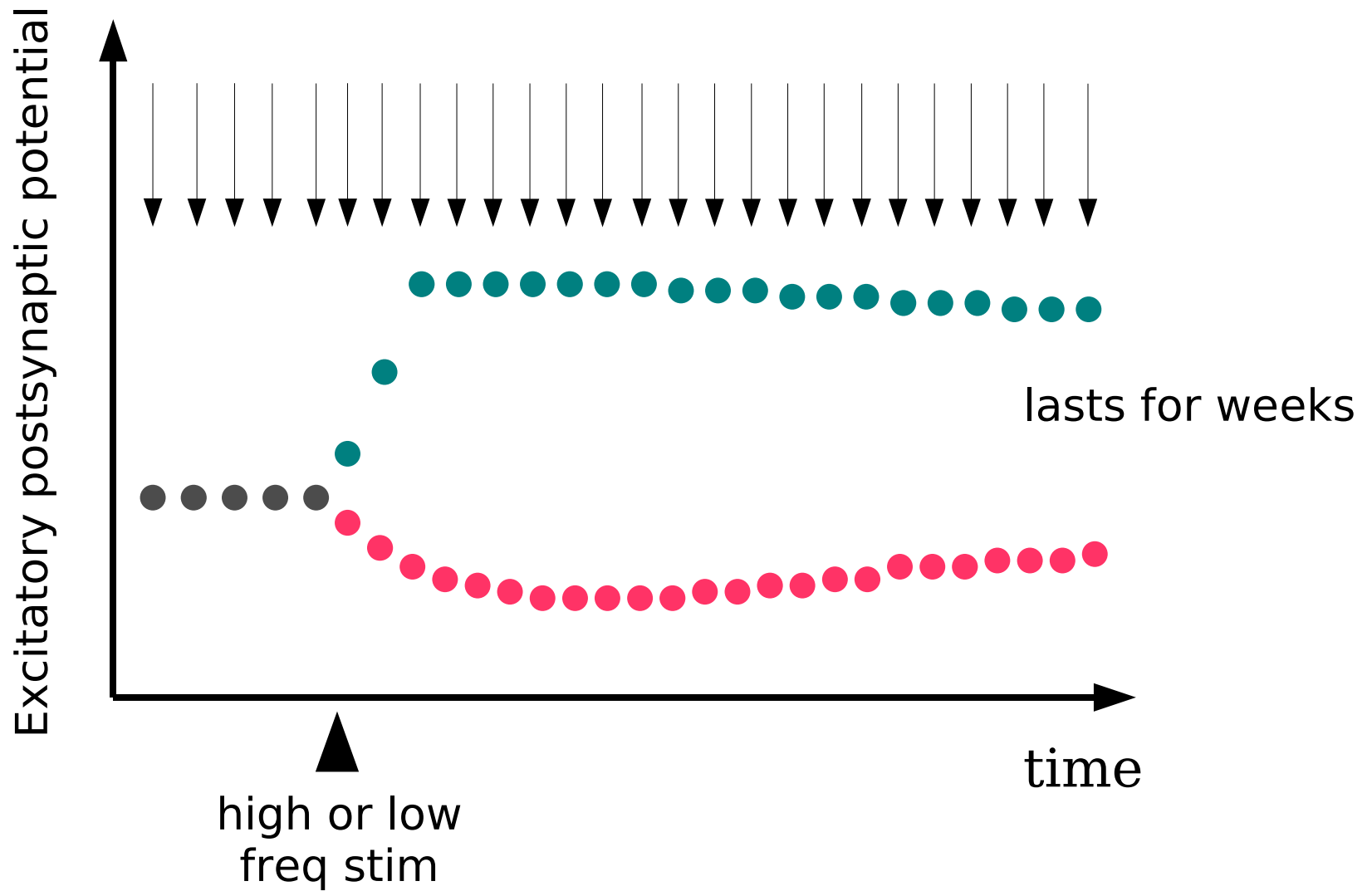


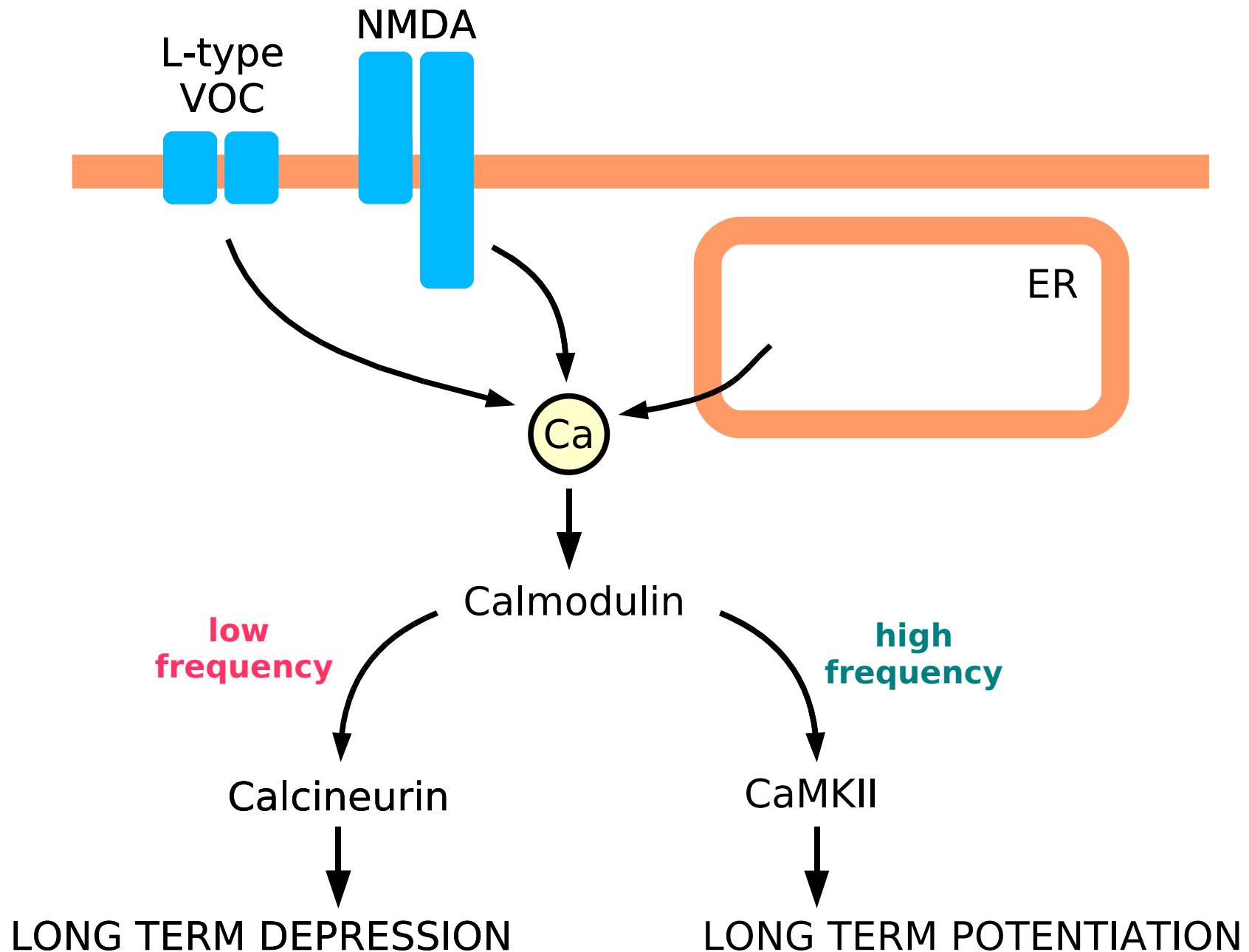


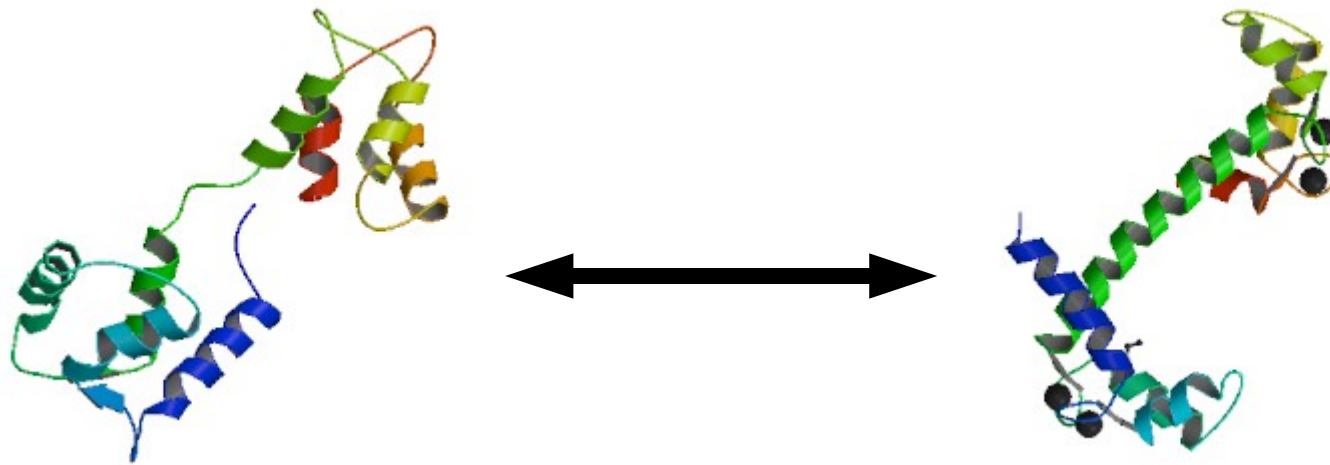


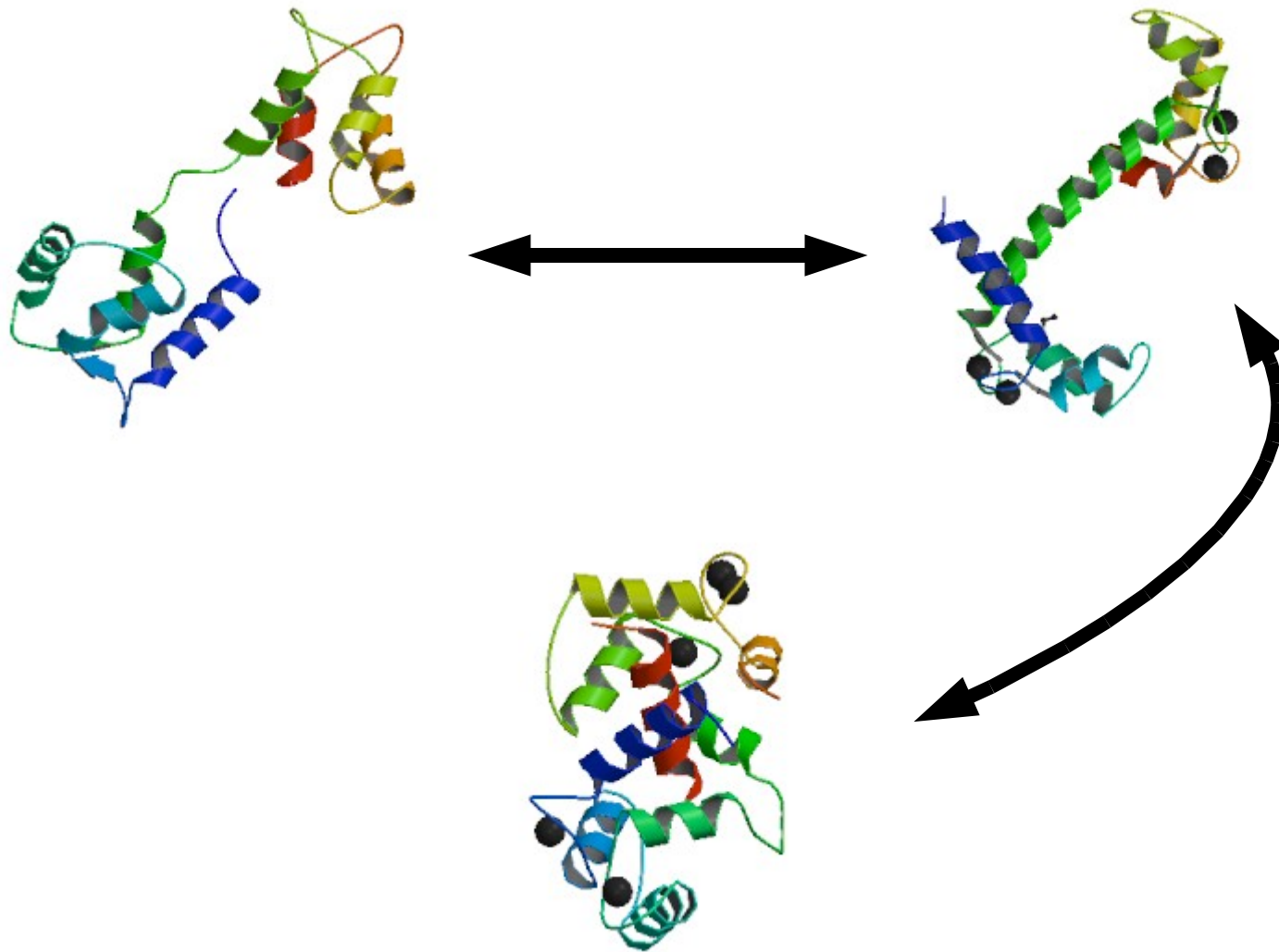
post-synaptic
density











- ASSUMPTION: 4 independent binding sites
- ASSUMPTION: Same affinity for all sites



Waage and Guldberg (1864).



- ASSUMPTION: 4 independent binding sites
- ASSUMPTION: Same affinity for all sites



Waage and Guldberg (1964).

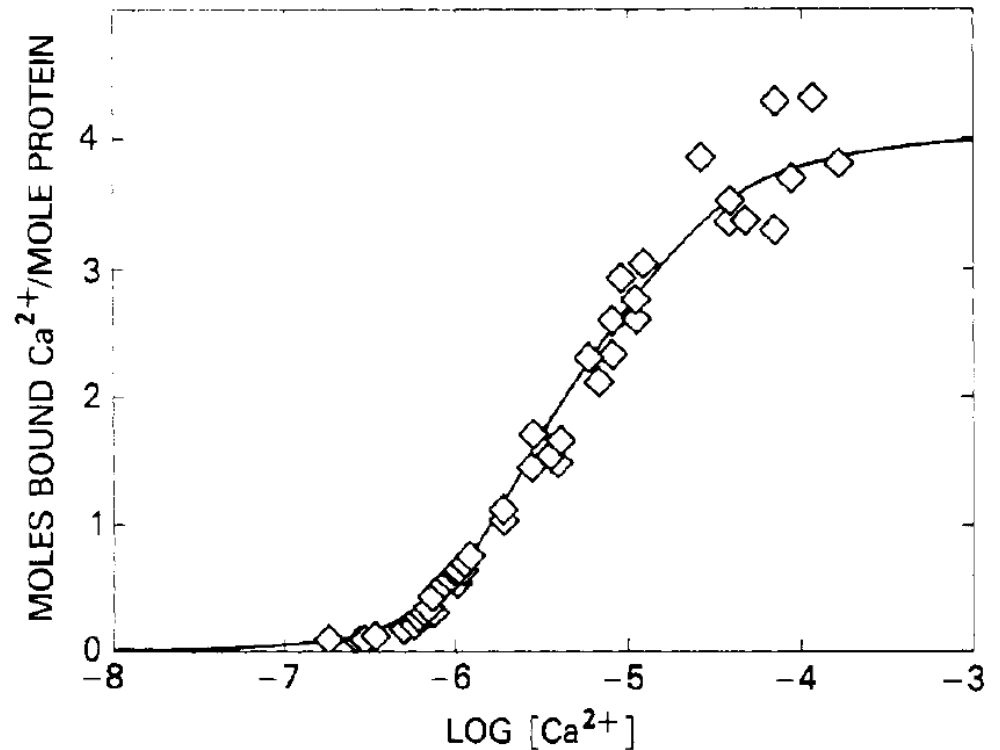
$$\frac{\overline{[\text{CaM}^*]}}{[\text{CaM}]} = \frac{[\text{Ca}]^4}{K^4 + [\text{Ca}]^4}$$

Hill (1910).



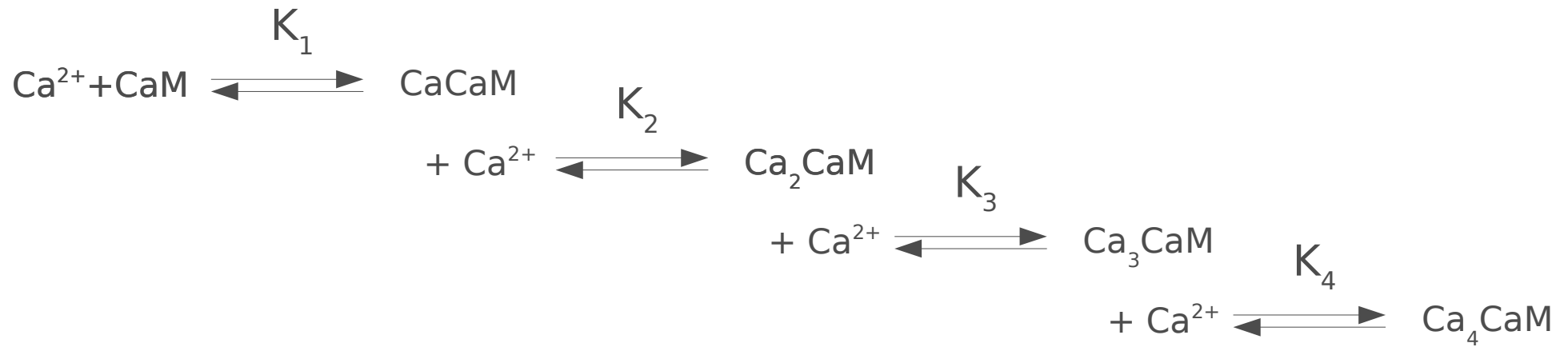
$$\bar{Y} = \frac{K_1[\text{Ca}] + 2K_1K_2[\text{Ca}]^2 + 3K_1K_2K_3[\text{Ca}]^3 + 4K_1K_2K_3K_4[\text{Ca}]^4}{1 + K_1[\text{Ca}] + K_1K_2[\text{Ca}]^2 + K_1K_2K_3[\text{Ca}]^3 + K_1K_2K_3K_4[\text{Ca}]^4}$$

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



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



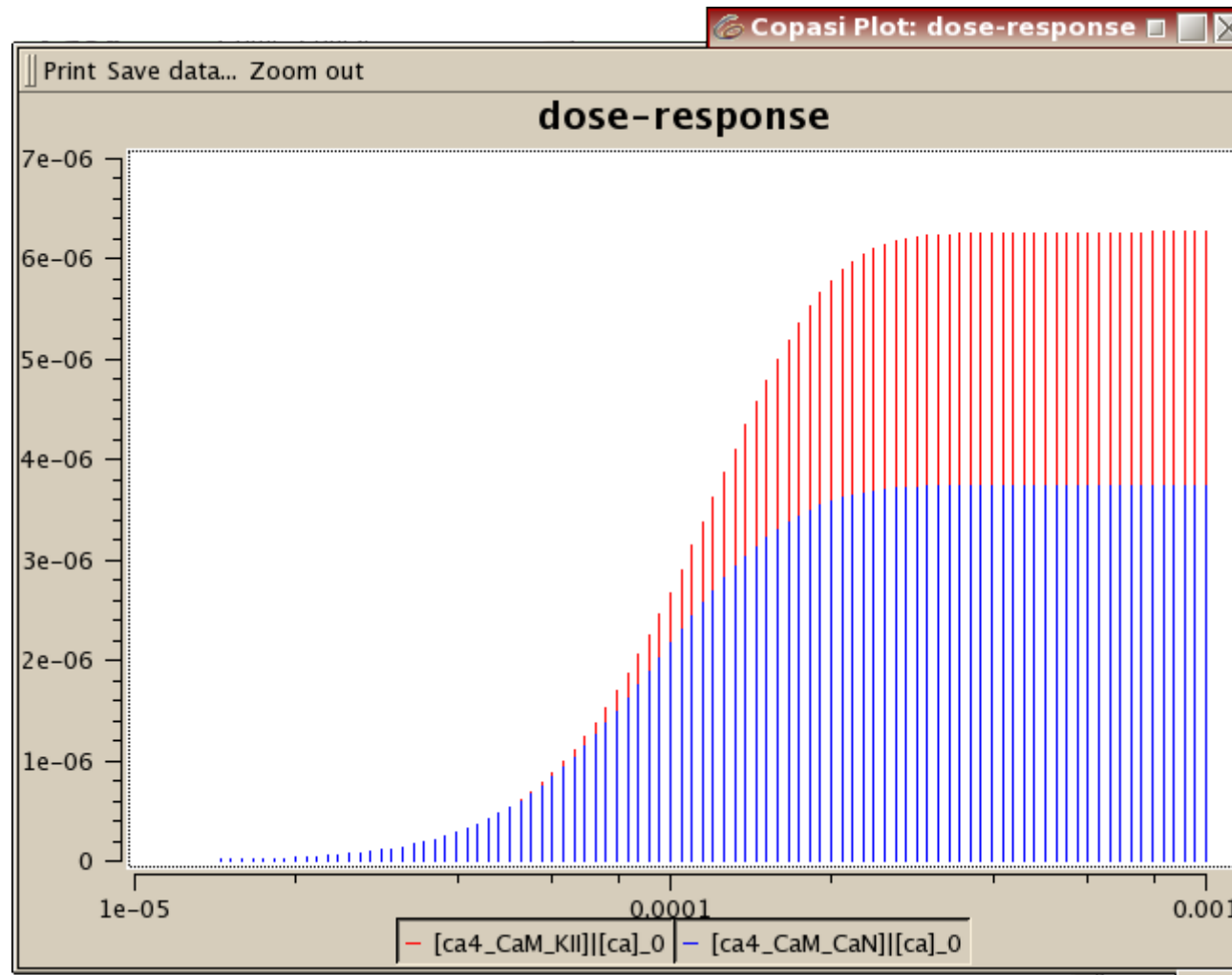


Binding to target



- 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) $\cong$ Calcineurin



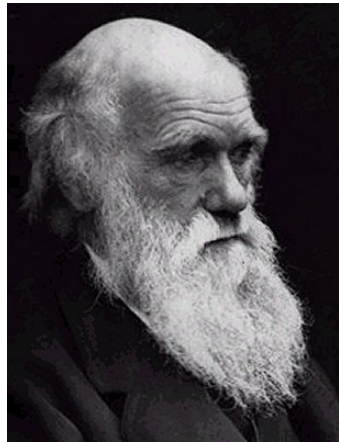




- Induction = BAD
(intelligent design, Lamarck's first law, antibody moulding, directed axonal growth, induced-fit ...)

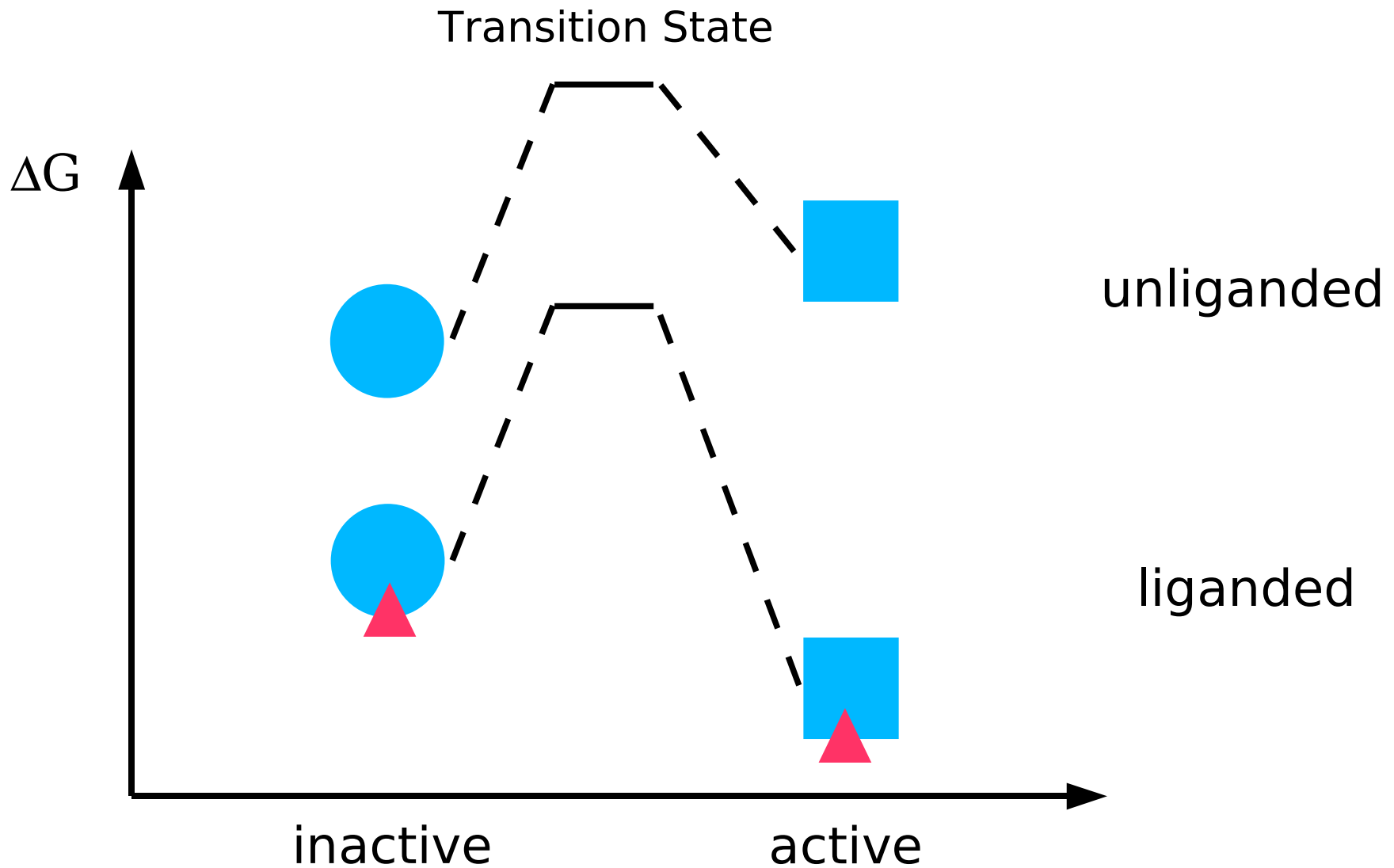


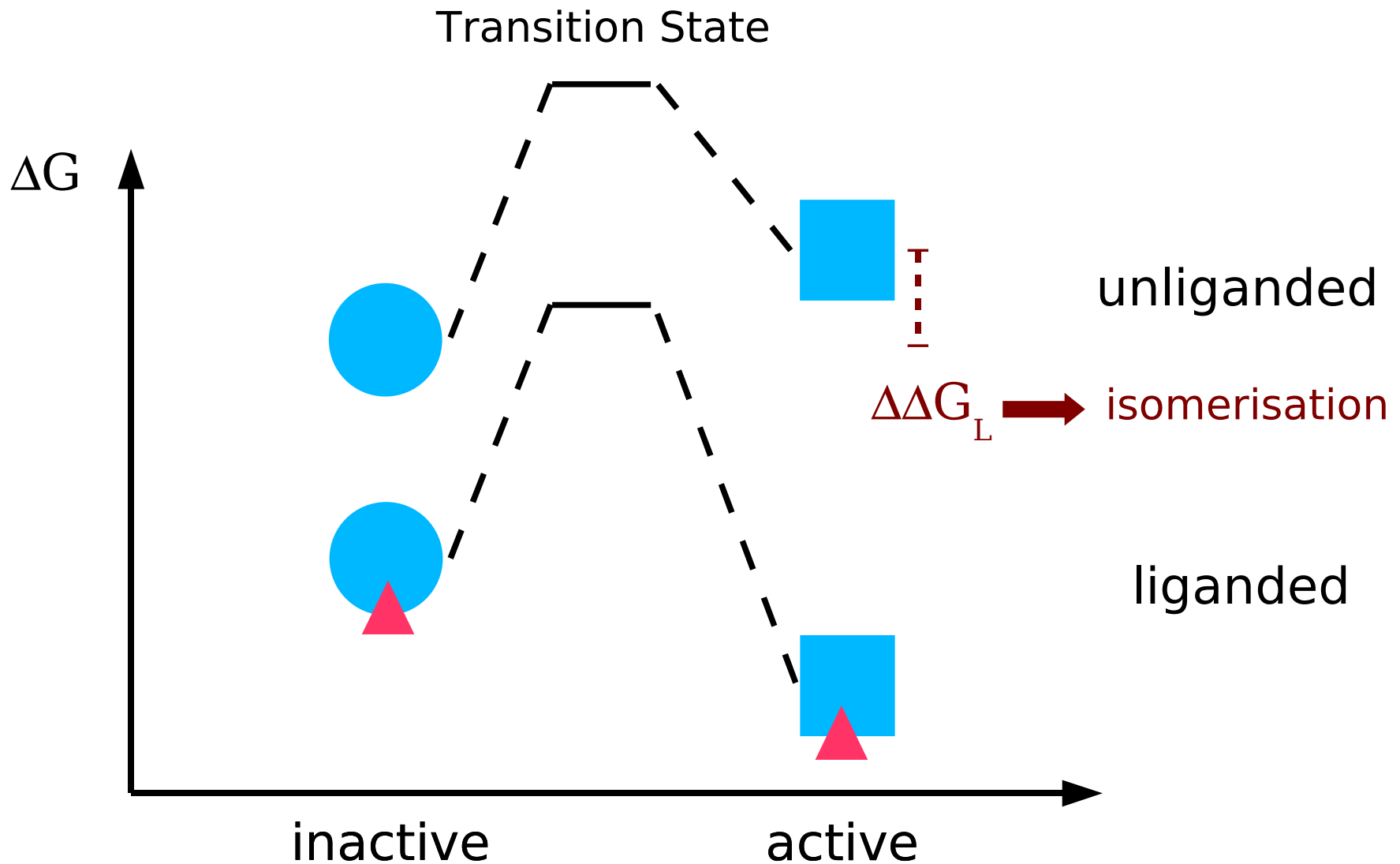
- Induction = BAD
(intelligent design, Lamarck's first law, antibody moulding, directed axonal growth, induced-fit ...)
- Selection = GOOD
(natural selection, clonal selection, synapse stabilisation, concerted transitions ...)

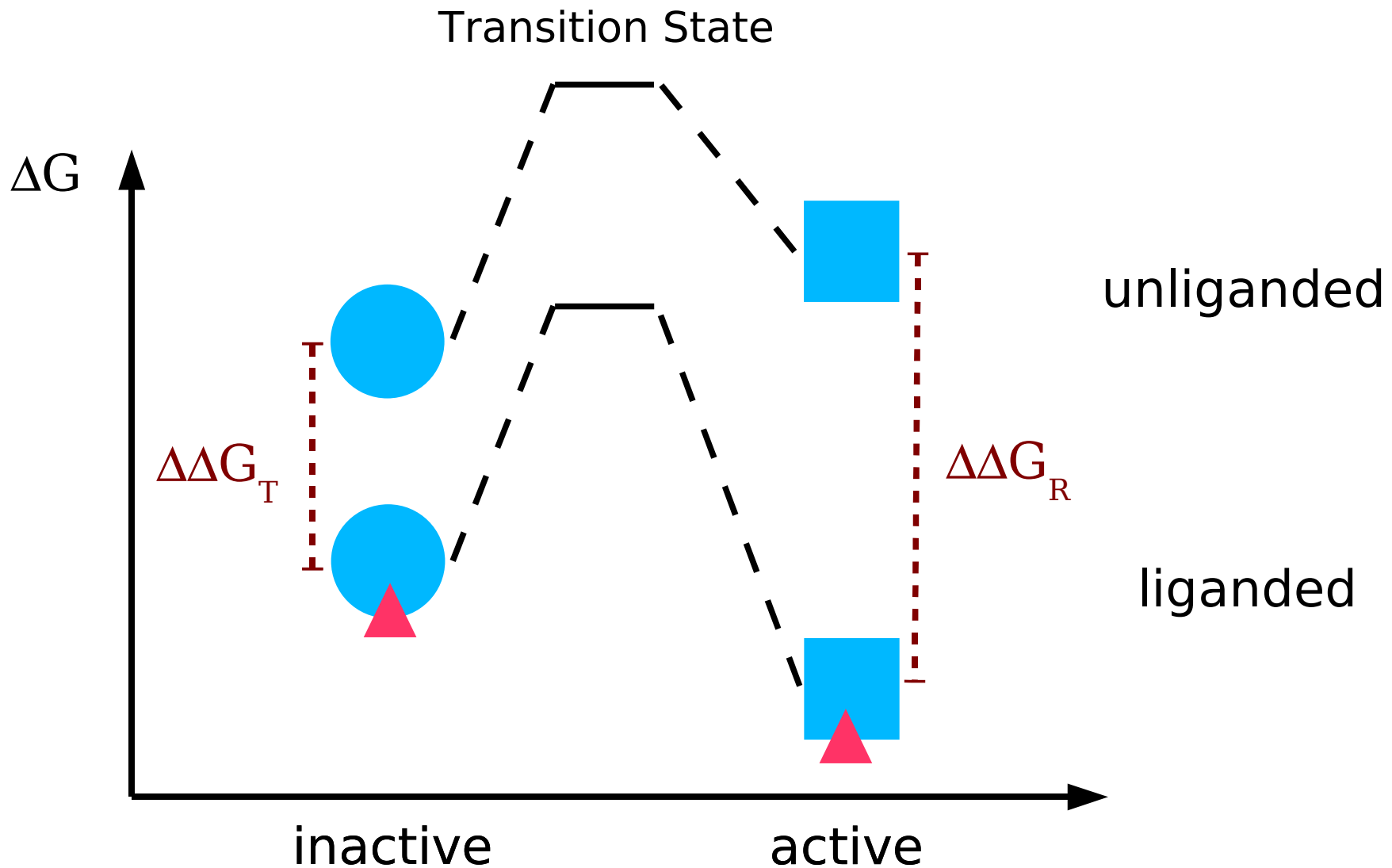


➡ Monod, Wyman, Changeux (1965). *J Mol Biol*, 12: 88-118



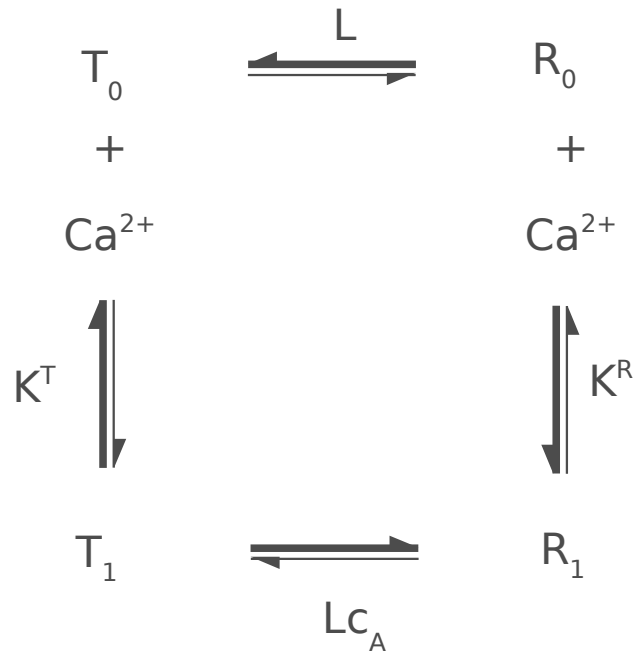






$$K \propto e^{-(\Delta\Delta G/RT)}$$

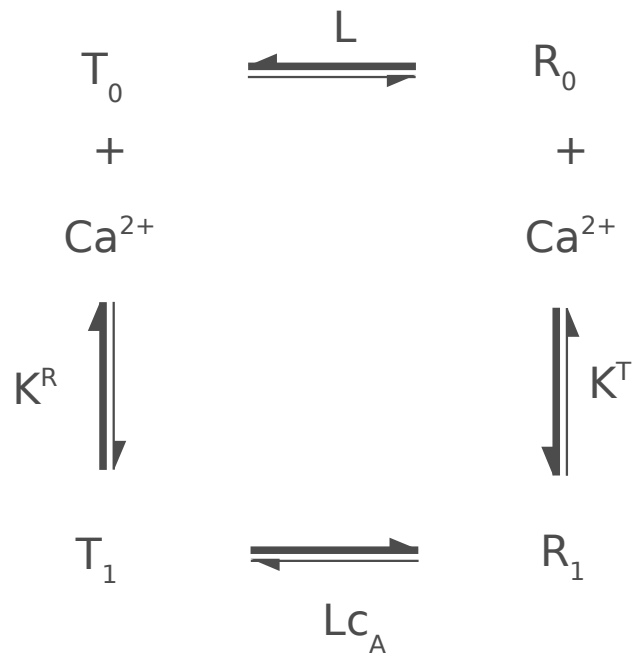




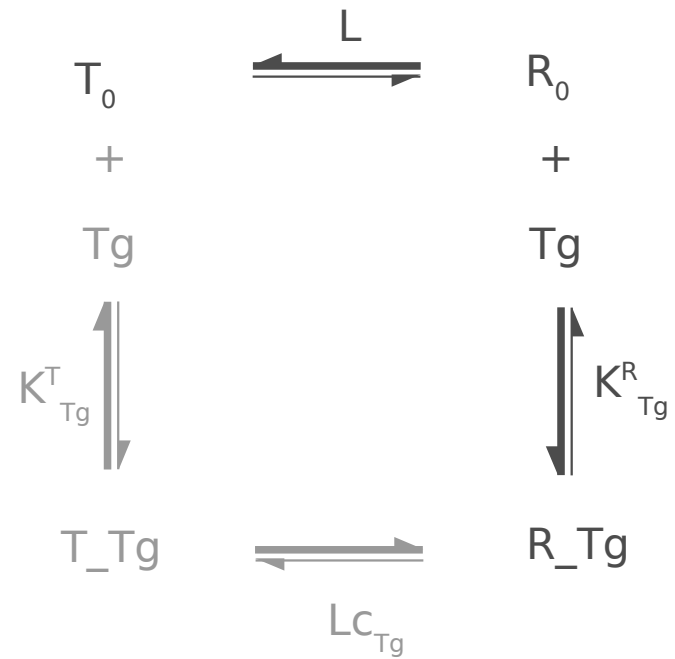
$$L = \frac{[T_0]}{[R_0]}$$

$$C_I = \frac{K_I^R}{K_I^T}$$



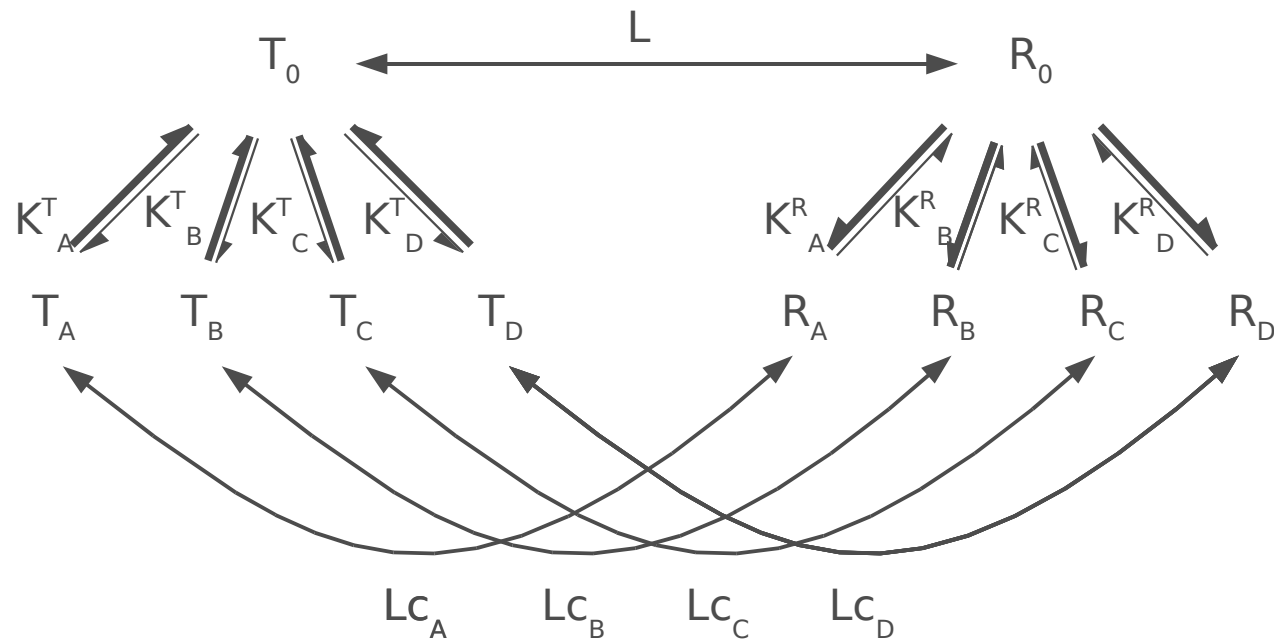


$$L = \frac{[T_0]}{[R_0]}$$



$$C_I = \frac{K^R_I}{K^T_I}$$

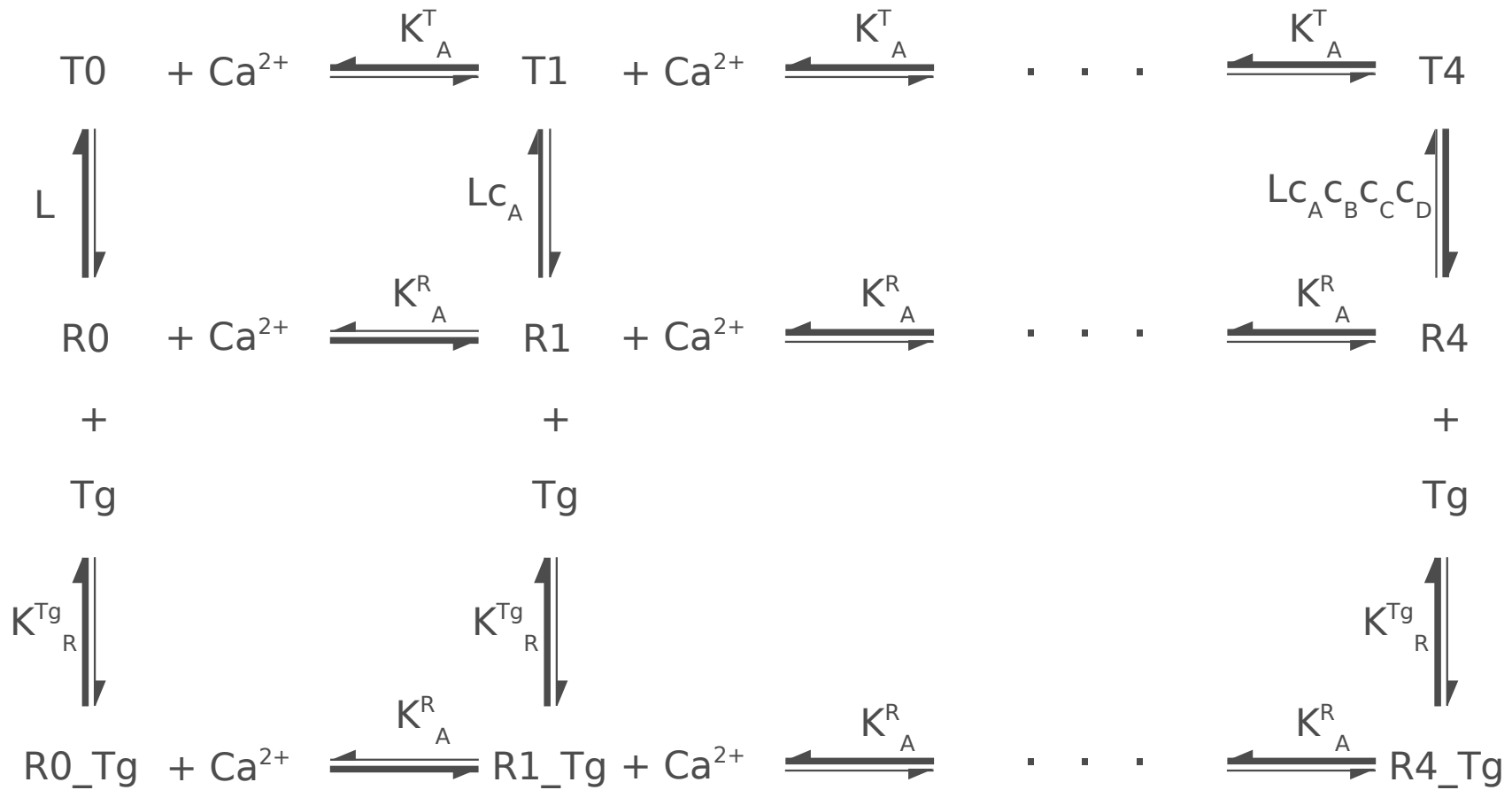




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$$L = \frac{[T0]}{[R0]}$$

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



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

- CaN affinity for CaM R state $\gg$ CaMKII one
- $[CaMKII] \gg [CaN]$



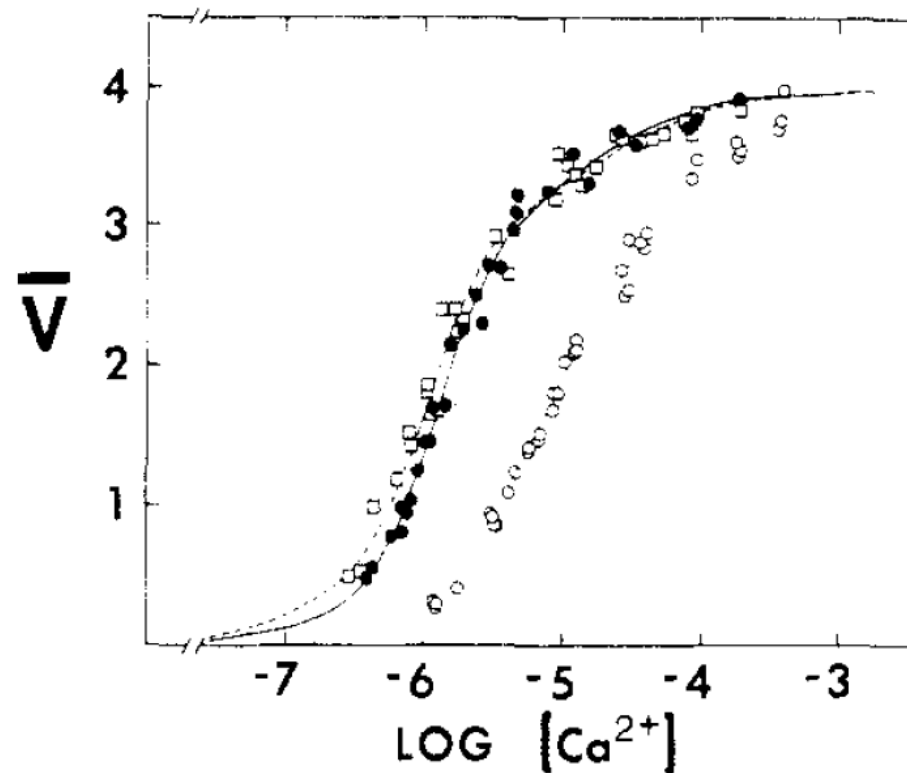


FIGURE 2: Ca^{2+} binding to CaM in the absence (O) and in the presence of stoichiometric ● and higher (□) concentrations of TnI.

Keller et al (1982) *Biochemistry*, 21: 156-162



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

$$\bar{Y} = \frac{\alpha(1 + \alpha)^{n-1}}{L \frac{1}{(1+\gamma)^m} + (1 + \alpha)^n}$$

- $\alpha = [\text{ligand}]/K_{\text{lig}}^R$
- $\gamma = [\text{activator}]/K_{\text{act}}^R$
- n : number of ligand binding sites
- m : number of activator binding sites

- Make $\bar{Y} = 0.5$ and replace α by $\alpha_{1/2}$ for both [troponin]



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

$$\bar{Y} = \frac{\alpha(1 + \alpha)^{n-1}}{L \frac{1}{(1+\gamma)^m} + (1 + \alpha)^n}$$

- $\alpha = [\text{ligand}]/K_{\text{lig}}^R$
 - $\gamma = [\text{activator}]/K_{\text{act}}^R$
 - n : number of ligand binding sites
 - m : number of activator binding sites
- $L \approx 20\,000$
- Make $\bar{Y} = 0.5$ and replace α by $\alpha_{1/2}$ for both [troponin]



$$\bar{Y} = \frac{\sum \alpha_i + 2 \sum \alpha_i \alpha_j + 3 \sum \alpha_i \alpha_j \alpha_k + 4 \alpha_A \alpha_B \alpha_C \alpha_D}{4 (\prod (1 + \alpha_i) + L \prod (1 + c_i \alpha_i))} + L \frac{(\sum c_i \alpha_i + 2 \sum c_i \alpha_i c_j \alpha_j + 3 \sum c_i \alpha_i c_j \alpha_j c_k \alpha_k + 4 c_A \alpha_A c_B \alpha_B c_C \alpha_C c_D \alpha_D)}{4 (\prod (1 + \alpha_i) + L \prod (1 + c_i \alpha_i))}$$

$$\alpha_i = [\text{Ca}]/K_i^R$$

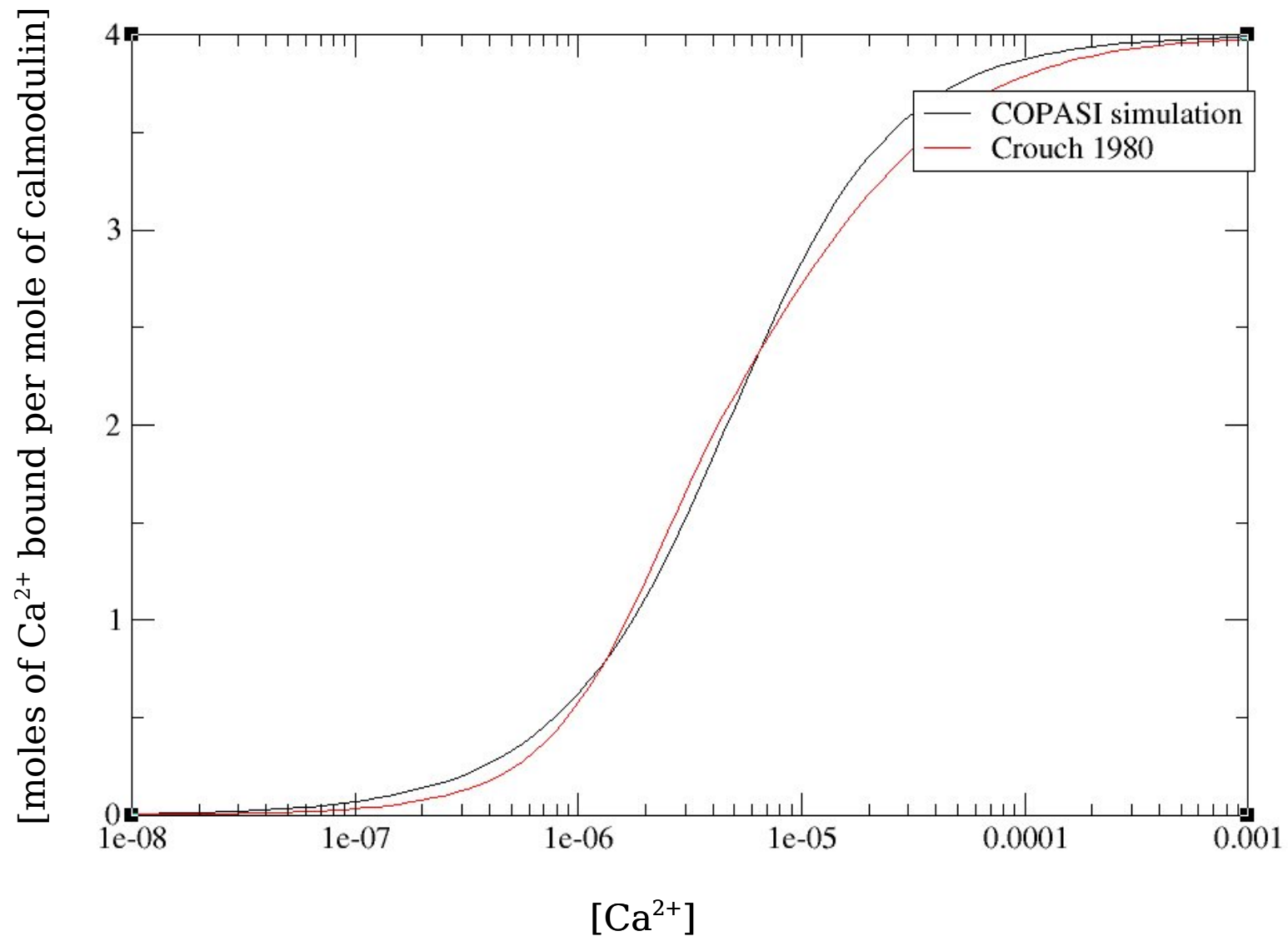
Use calmodulin with mutated Ca binding sites
(Shifman et al (2006) *PNAS*, 103: 13968-13973)

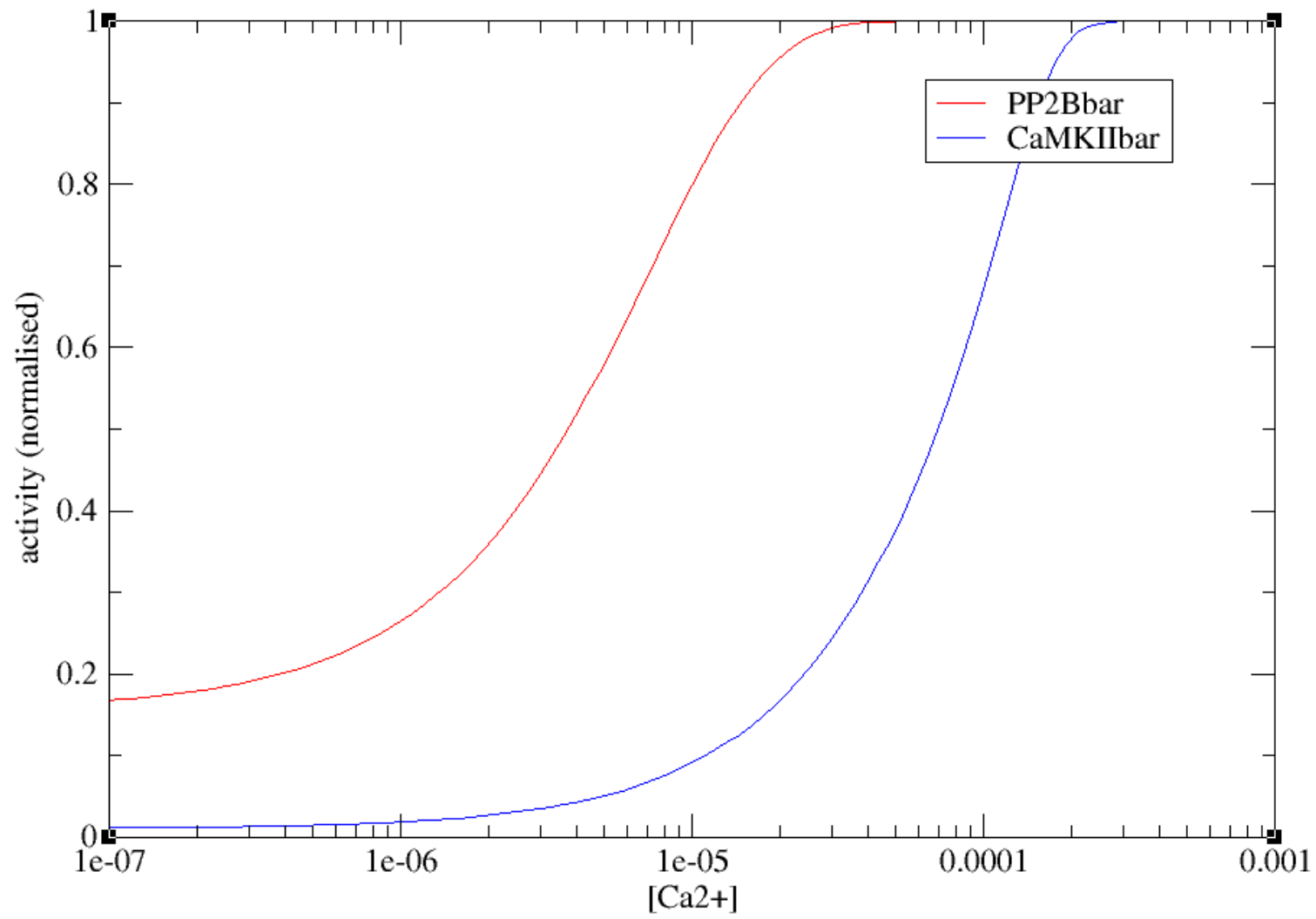
➡ Reduced equation



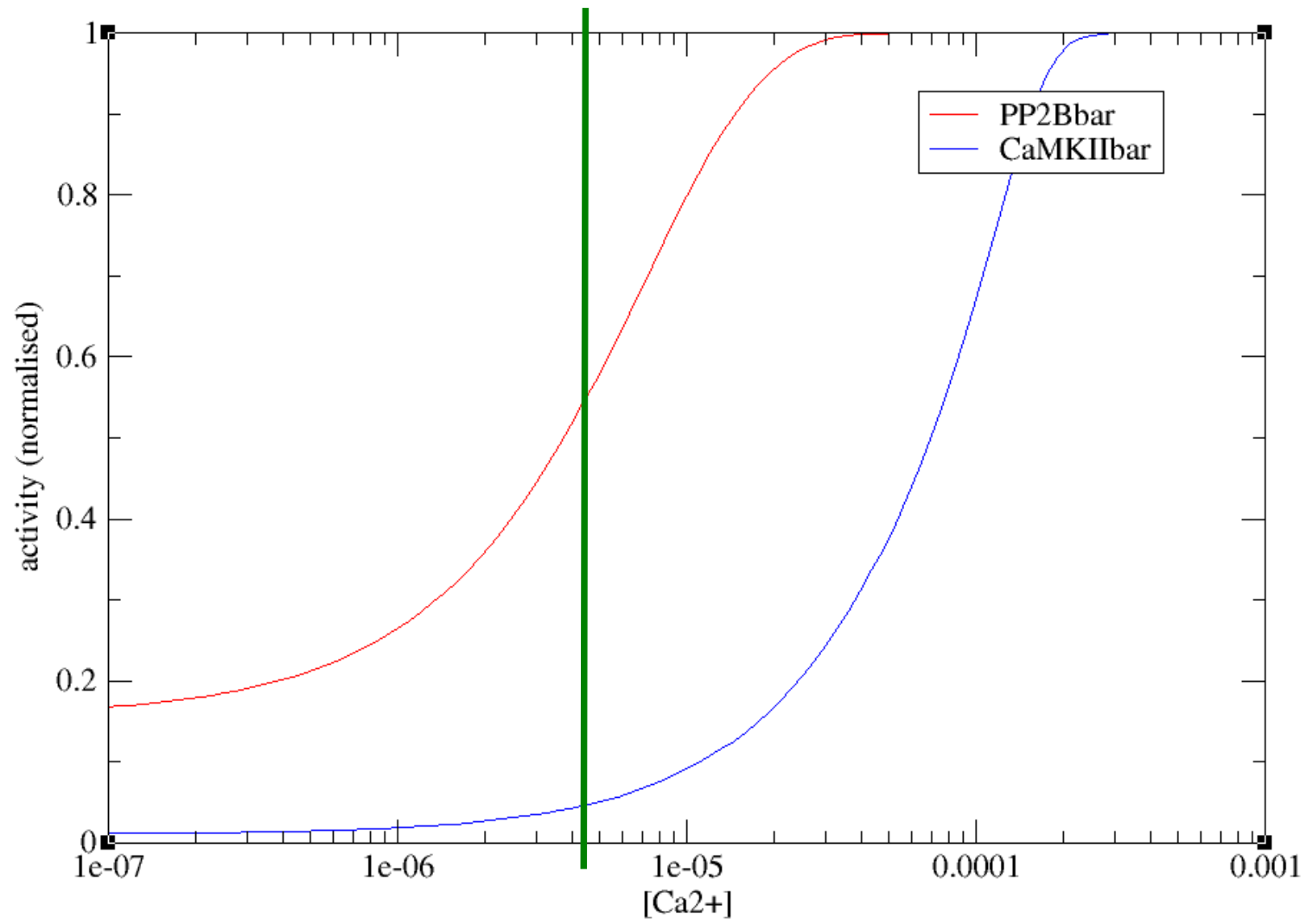
$$K_1 = 4 \frac{1 + L}{\frac{1}{K_A^R} + \frac{1}{K_B^R} + \frac{1}{K_C^R} + \frac{1}{K_D^R} + L \left(\frac{1}{K_A^T} + \frac{1}{K_B^T} + \frac{1}{K_C^T} + \frac{1}{K_D^T} \right)}$$

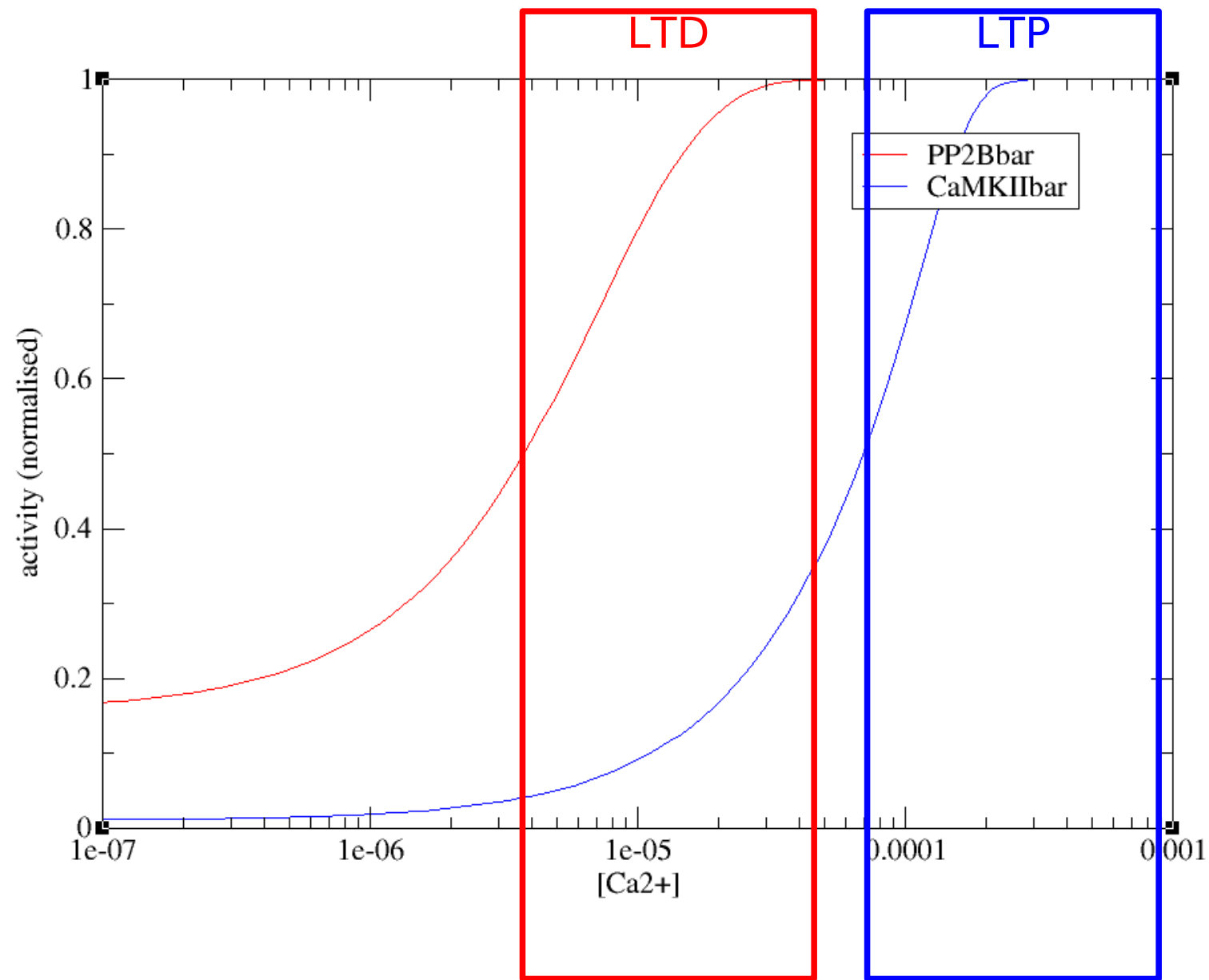






half saturation of calmodulin





- COPASI developers
(Virginia Bioinformatics Institute
EML-research)

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Pedro Mendes
Stefan Hoops
Sven Sahle
Ralf Gauges

- Compneur group
(EBI)

Prof Stuart Edelstein, visitor
Melanie Stefan, PhD student
David Marshall, undergraduate



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$$K_1 = \frac{\text{concentration of ligand binding sites} \times \text{ligand concentration}}{\text{concentration of protein bound to exactly one ligand molecule}}$$

$$= \frac{4[P_0][X]}{[P_1]}$$



$$K_1 = \frac{4([R_0] + [T_0])[X]}{[R_1] + [T_1]}$$



$$K_1 = 4 \frac{([R_0] + [T_0])[X]}{([R_A] + [R_B] + [R_C] + [R_D]) + ([T_A] + [T_B] + [T_C] + [T_D])}$$





$$K_1 = 4 \frac{([R_0] + L[R_0])[X]}{\left(\frac{[R_0][X]}{K_A^R} + \frac{[R_0][X]}{K_B^R} + \frac{[R_0][X]}{K_C^R} + \frac{[R_0][X]}{K_D^R} \right) + \left(\frac{[T_0][X]}{K_A^T} + \frac{[T_0][X]}{K_B^T} + \frac{[T_0][X]}{K_C^T} + \frac{[T_0][X]}{K_D^T} \right)}$$

$$= 4 \frac{[R_0][X](1 + L)}{[R_0][X] \left(\frac{1}{K_A^R} + \frac{1}{K_B^R} + \frac{1}{K_C^R} + \frac{1}{K_D^R} \right) + [T_0][X] \left(\frac{1}{K_A^T} + \frac{1}{K_B^T} + \frac{1}{K_C^T} + \frac{1}{K_D^T} \right)} =$$

$$= 4 \frac{[R_0][X](1 + L)}{[R_0][X] \left(\frac{1}{K_A^R} + \frac{1}{K_B^R} + \frac{1}{K_C^R} + \frac{1}{K_D^R} \right) + L[R_0][X] \left(\frac{1}{K_A^T} + \frac{1}{K_B^T} + \frac{1}{K_C^T} + \frac{1}{K_D^T} \right)}$$





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

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

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

