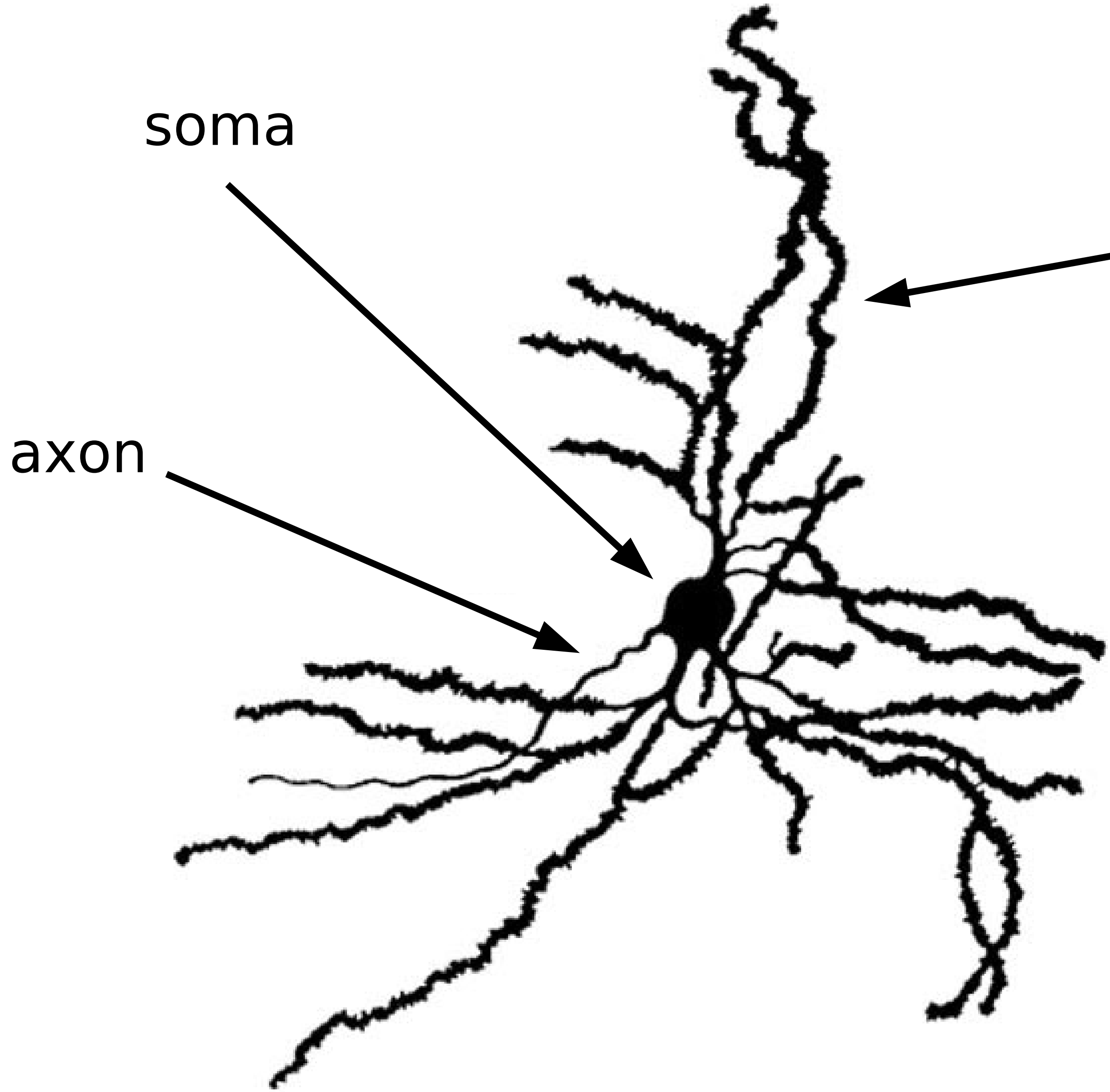
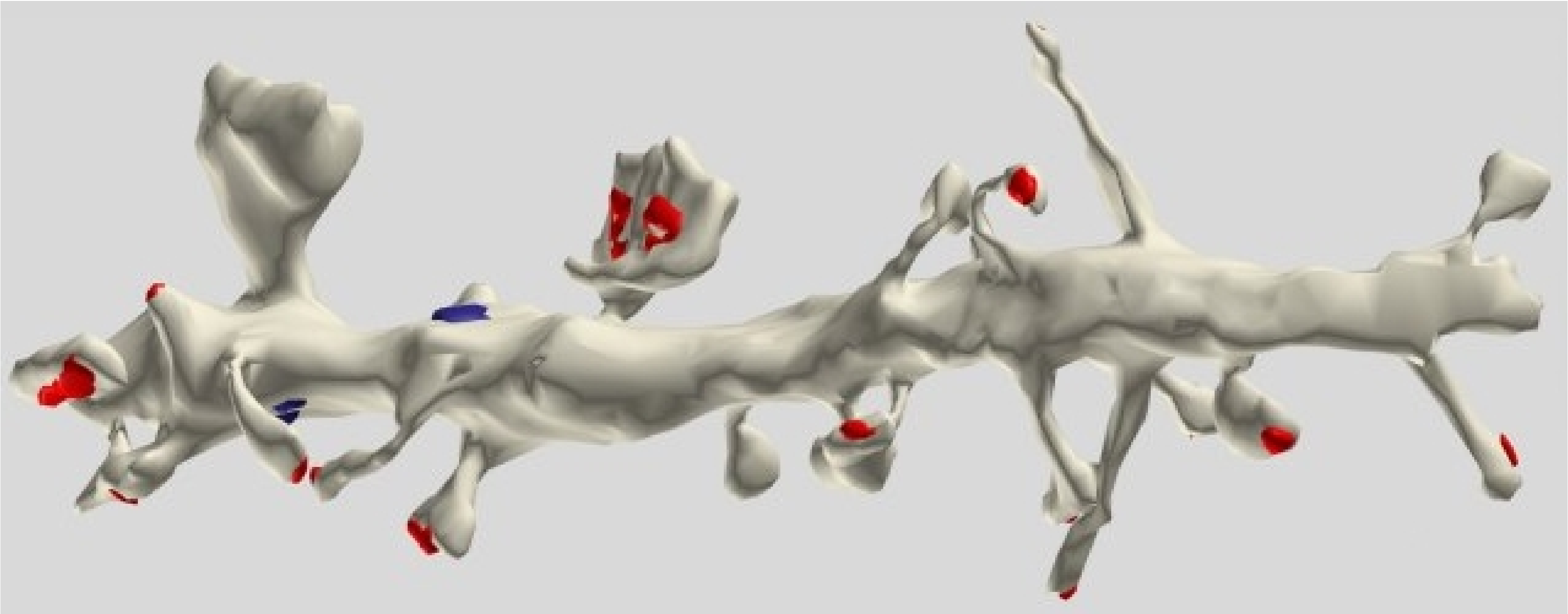
Linking biophysics and chemical kinetics to improve realism of models: calmodulin and synaptic plasticity

Nicolas Le Novère, EMBL-EBI

Structure of a neuron

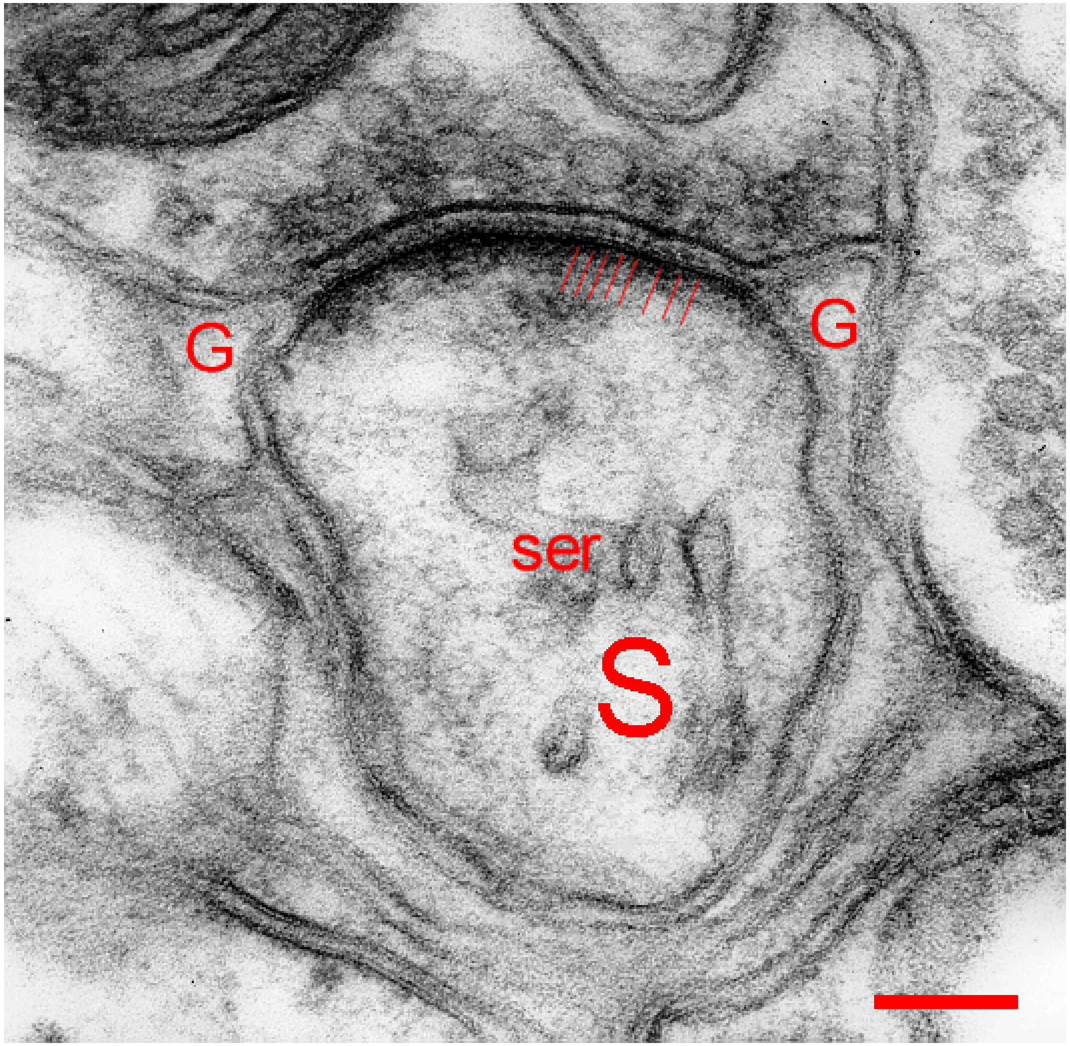


A spiny dendrite



Atlas of ultrastructural neurocytology (`http://synapse-web.org/`)

The spine as a “mini-cell”



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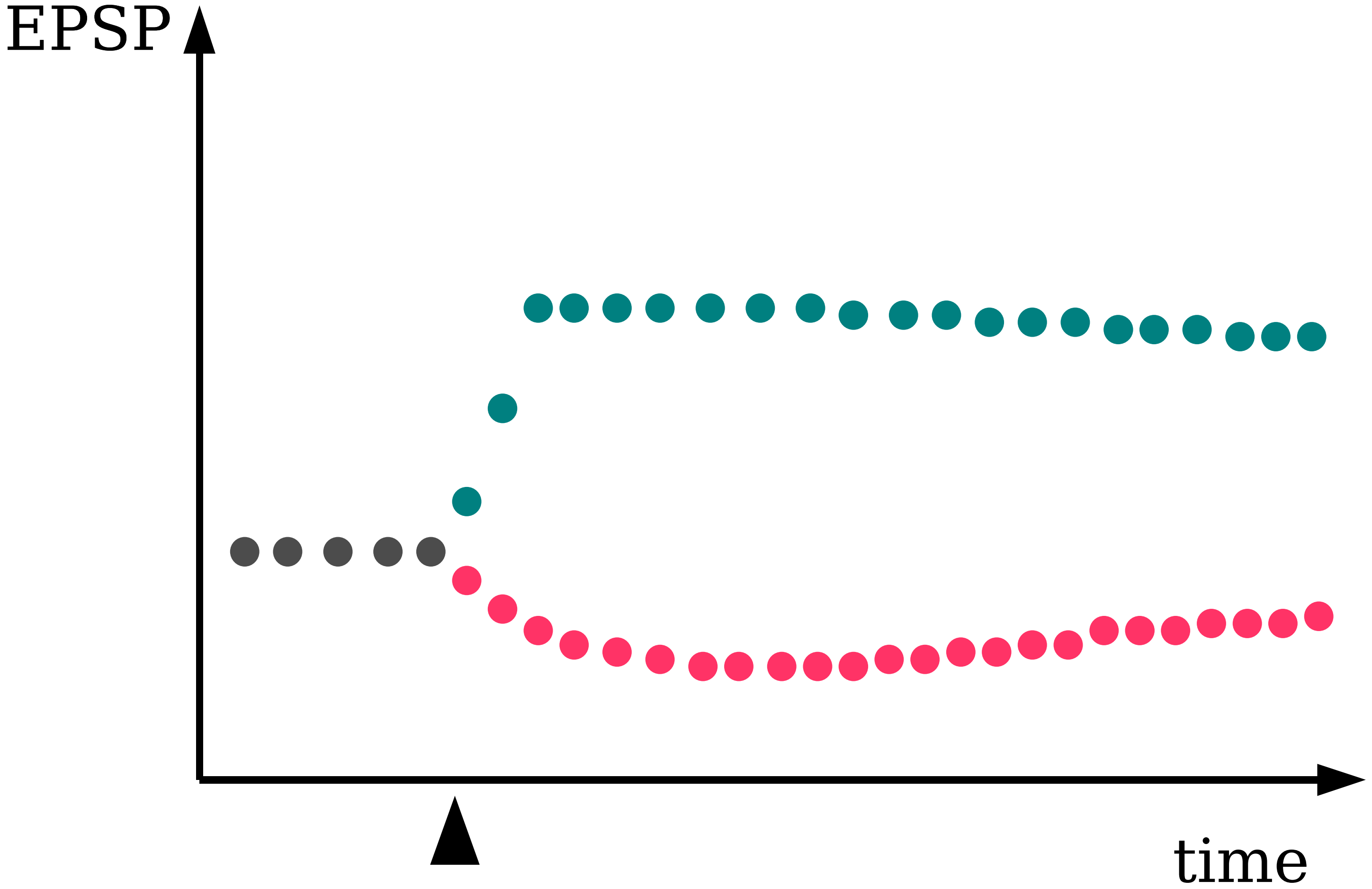
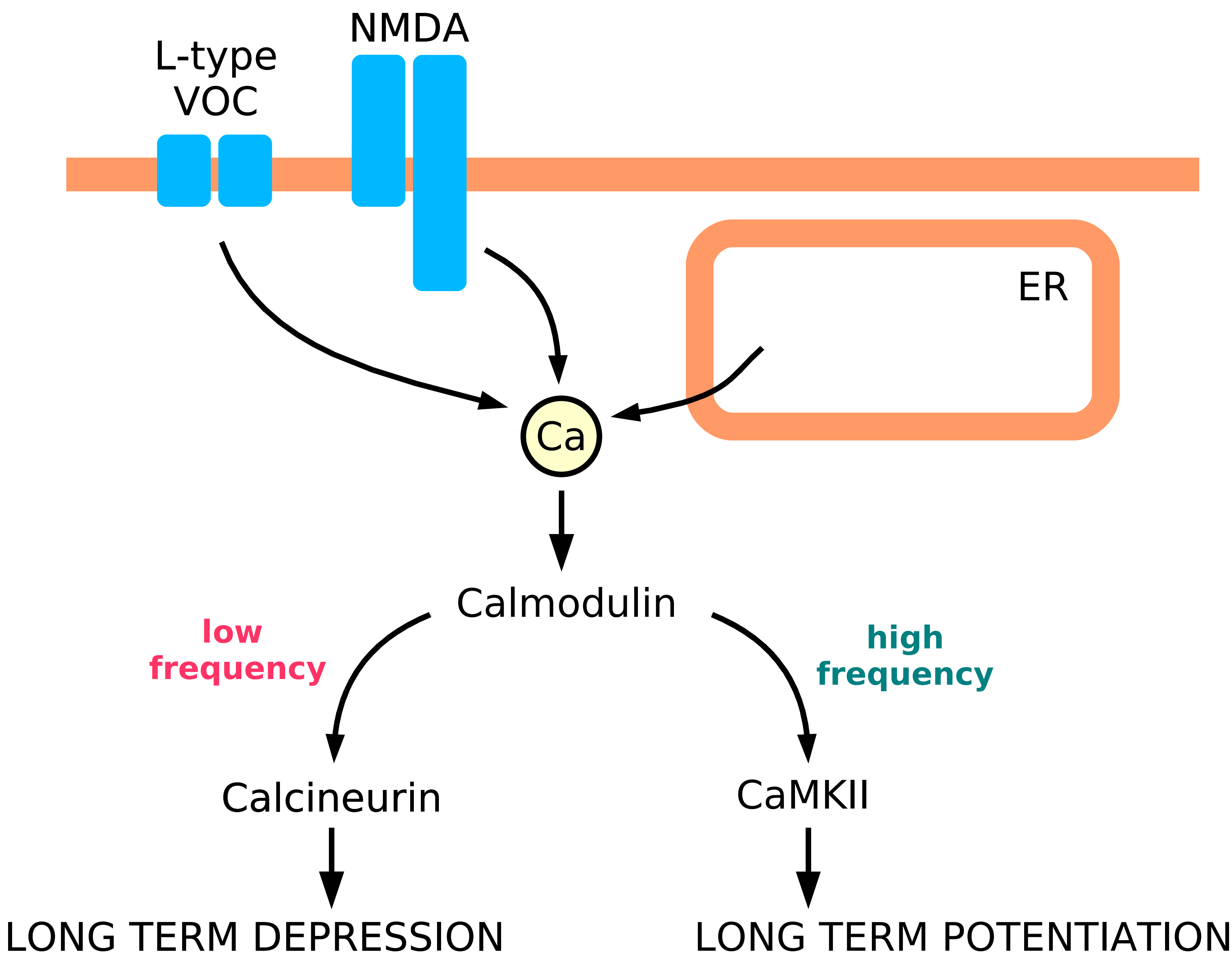
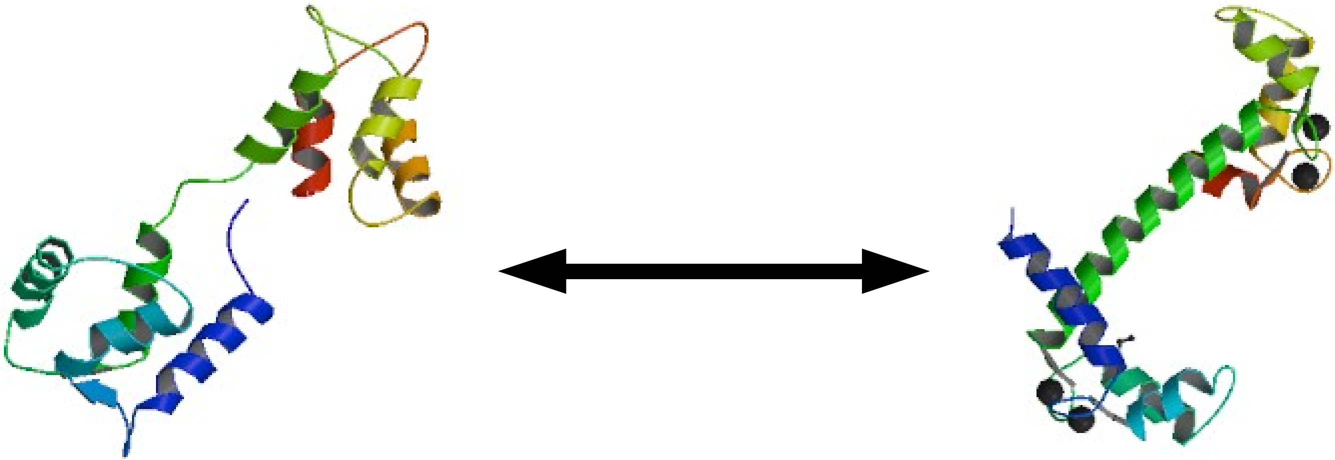
Synaptic plasticity



Calcium theory of Synaptic Plasticity



Alternative structures of calmodulin



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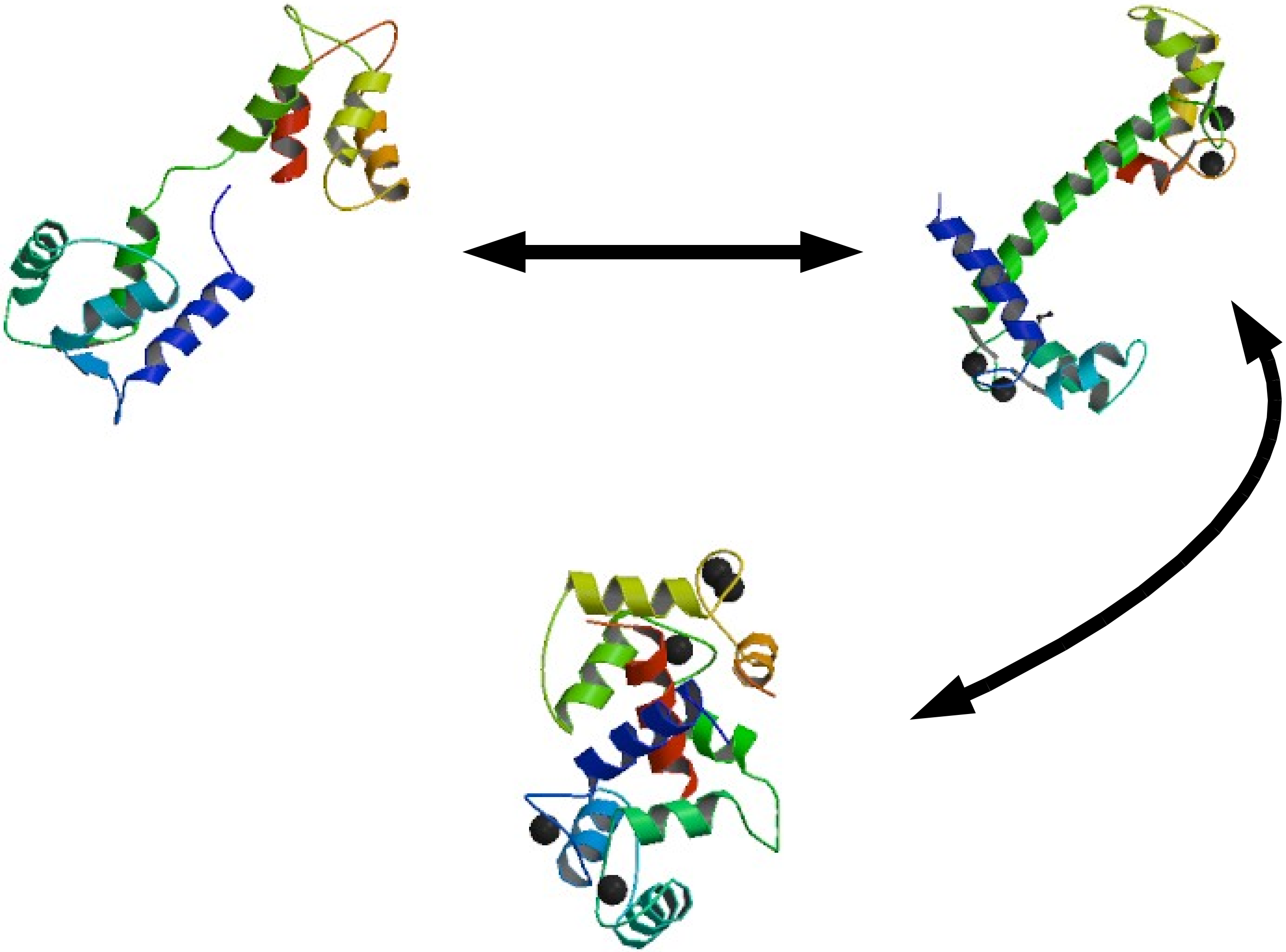


Phenomenological models

- 4 independent binding sites
- One affinity per site

$$4\ Ca^{2+} + CaM \overset{K}{\rightleftharpoons} CaM^*$$

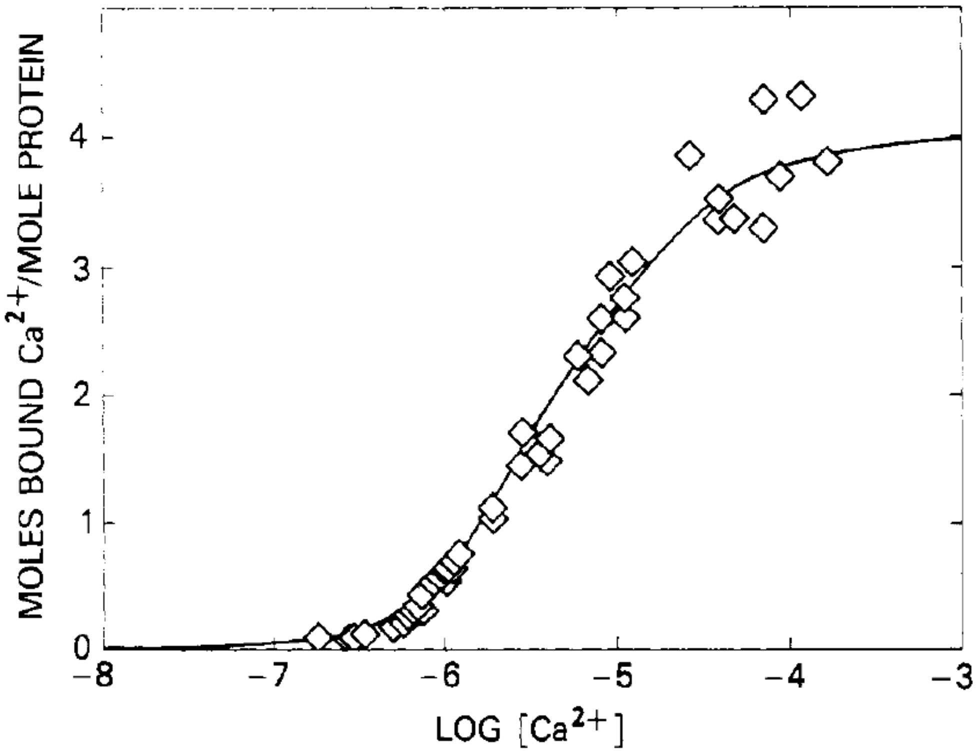
Waage and Guldberg (1964).

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

Hill (1910).

Phenomenological models

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



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

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

That does not work ...

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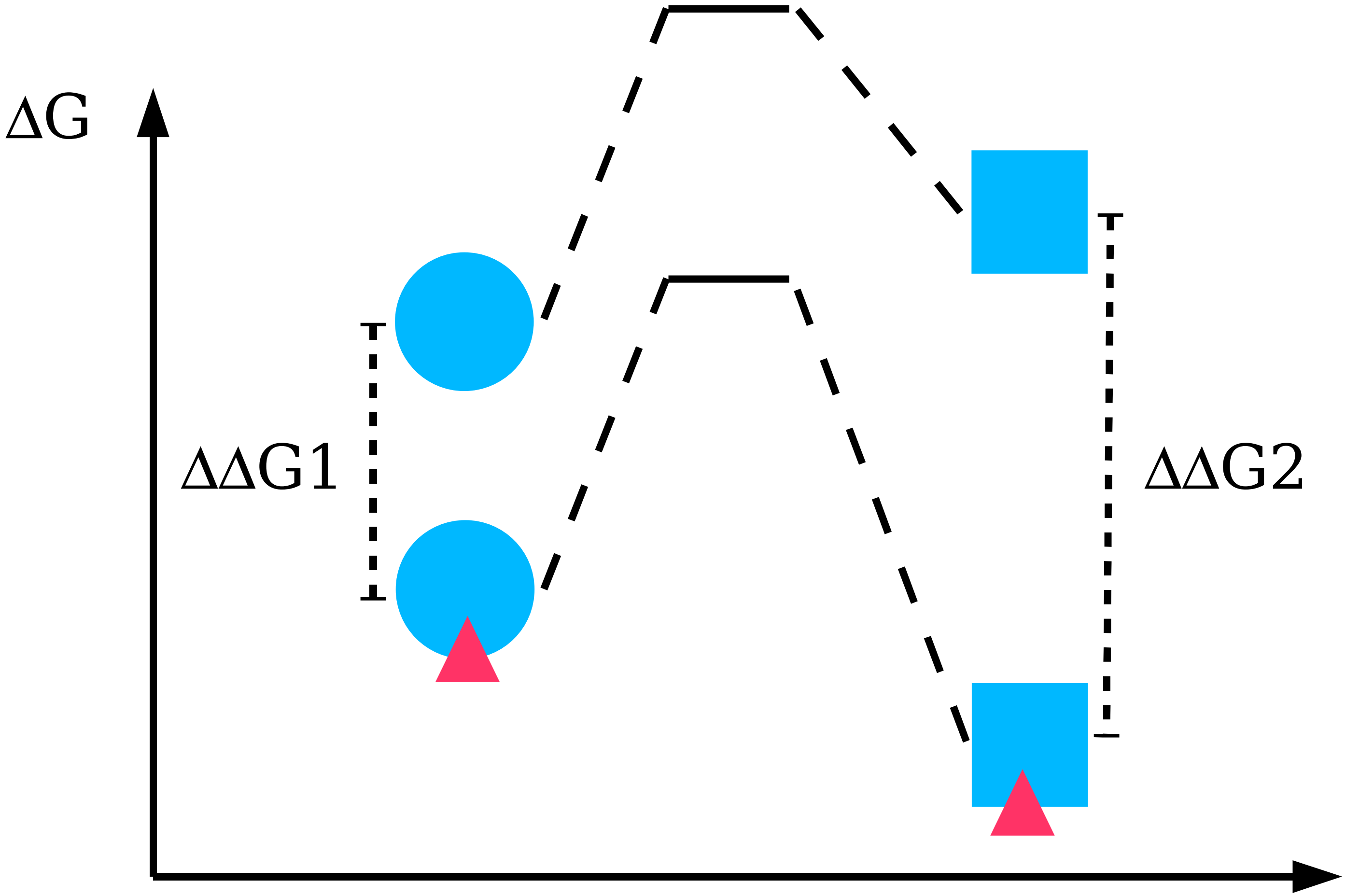
→ Monod, Wyman, Changeux (1965). *J Mol Biol*, 12: 88-118

Free energy, ligand binding and isomerisation



K ∝ e-(ΔΔG/RT)

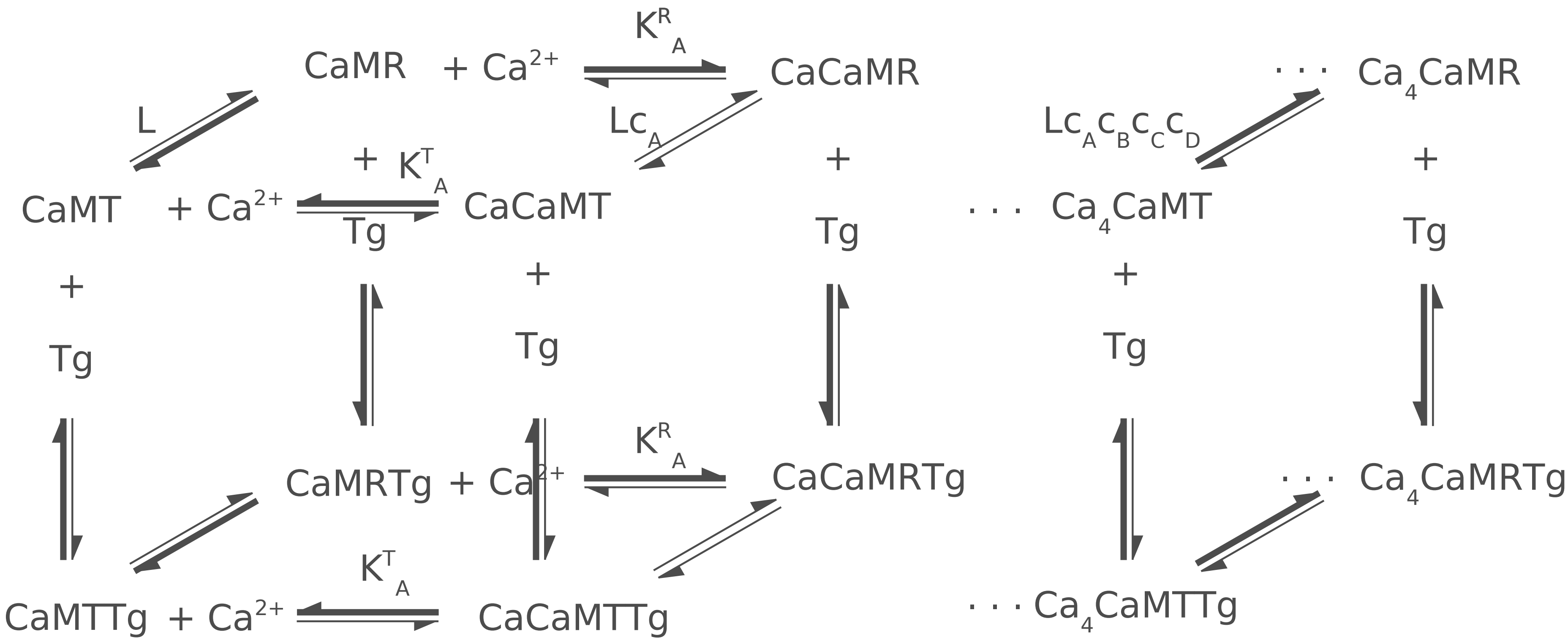
Allosteric regulation of calmodulin

$$\begin{array}{ccc}
\mathrm{CaMT} + \mathrm{Ca}^{2+} & \overset{L}{\rightleftharpoons} & \mathrm{CaMR} + \mathrm{Ca}^{2+} \\
K^{R}{}_{A} \updownarrow & & \updownarrow K^{T}{}_{A} \\
\mathrm{CaCaMT} & \underset{Lc_{A}}{\rightleftharpoons} & \mathrm{CaCaMR}
\end{array}$$

$$\begin{array}{ccc}
\mathrm{CaMT} + \mathrm{Tg} & \overset{L}{\rightleftharpoons} & \mathrm{CaMR} + \mathrm{Tg} \\
K^{R}{}_{Tg} \updownarrow & & \updownarrow K^{T}{}_{Tg} \\
\mathrm{CaMTTg} & \underset{Lc_{Tg}}{\rightleftharpoons} & \mathrm{CaMRTg}
\end{array}$$

$$L = \frac{[\mathrm{CaMT}]}{[\mathrm{CaMR}]} \qquad C_{I} = \frac{K^{R}{}_{I}}{K^{T}{}_{I}}$$

Full mechanistic thermodynamic model



$$L = \frac{[\mathrm{CaMT}]}{[\mathrm{CaMR}]} \qquad C_I = \frac{K^R_I}{K^T_I}$$

Derivation of Adair's constants

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

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

Derivation of Adair's constants

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

Derivation of Adair's constants

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

Derivation of Adair's constants

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

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

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

Derivation of Adair's constants

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

Derivation of Adair's constants

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

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

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

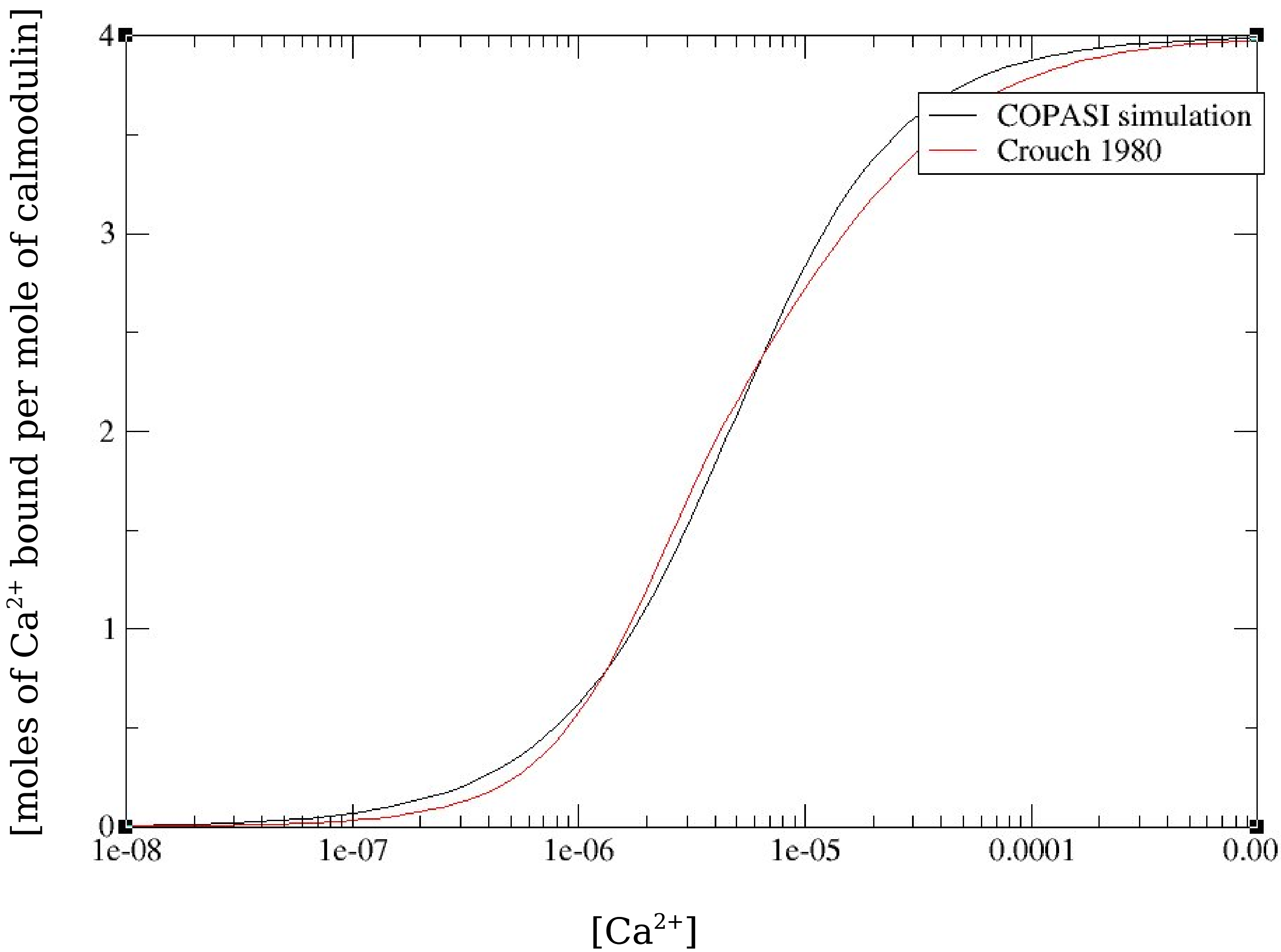
Creation of the kinetic model

Parameter estimation constrained by:

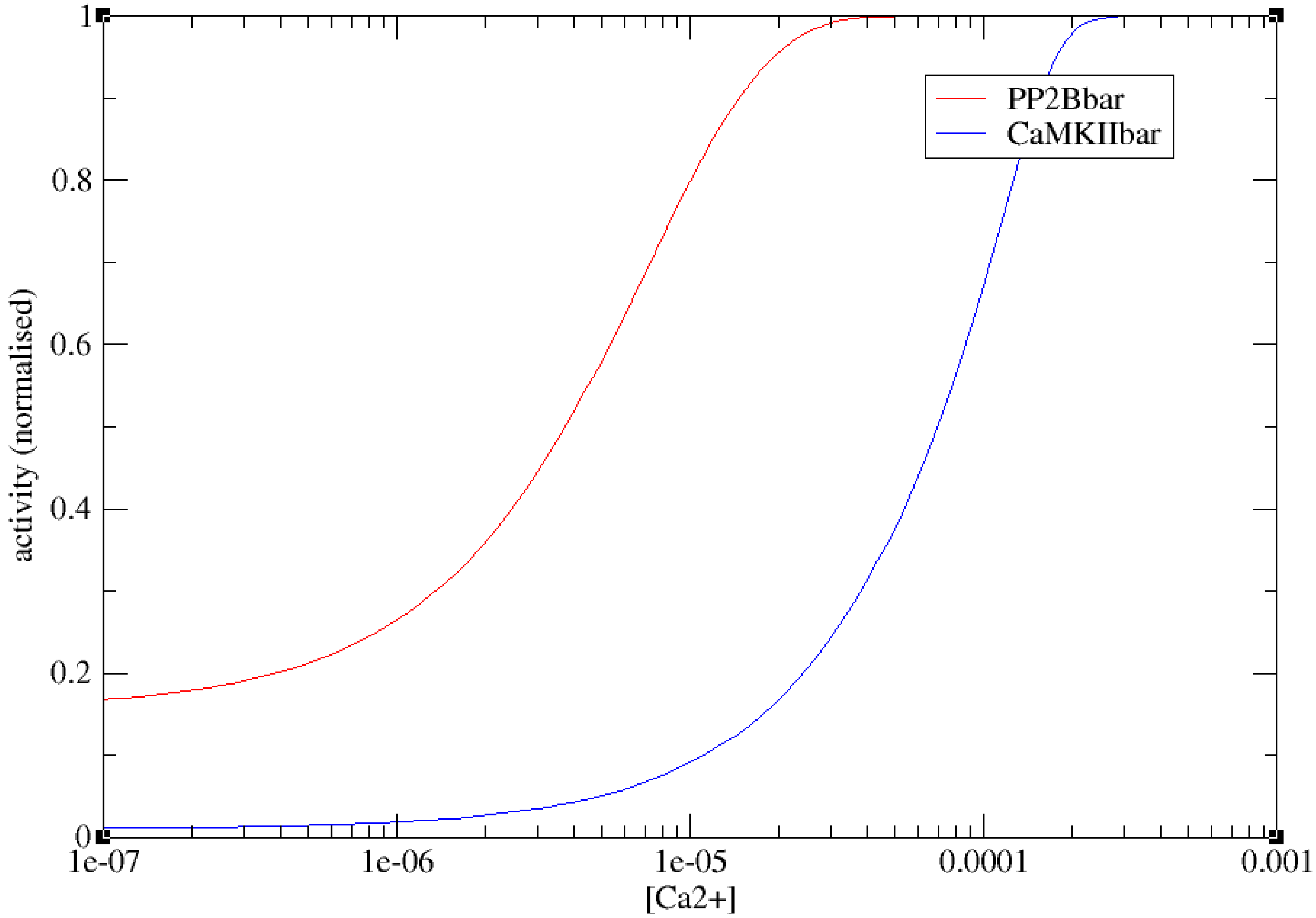
- Calcium binding R and T states
  - Crouch and Klee (1980) *Biochemistry*, 19: 3692-3698
- Calcium binding R state only (locked by troponin) and isomerisation constant
  - Keller et al (1982). *Biochemistry*, 21: 156-162
- Calcium binding of N and C terminals
  - Shifman et al (2006) *PNAS*, 103: 13968-13973

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

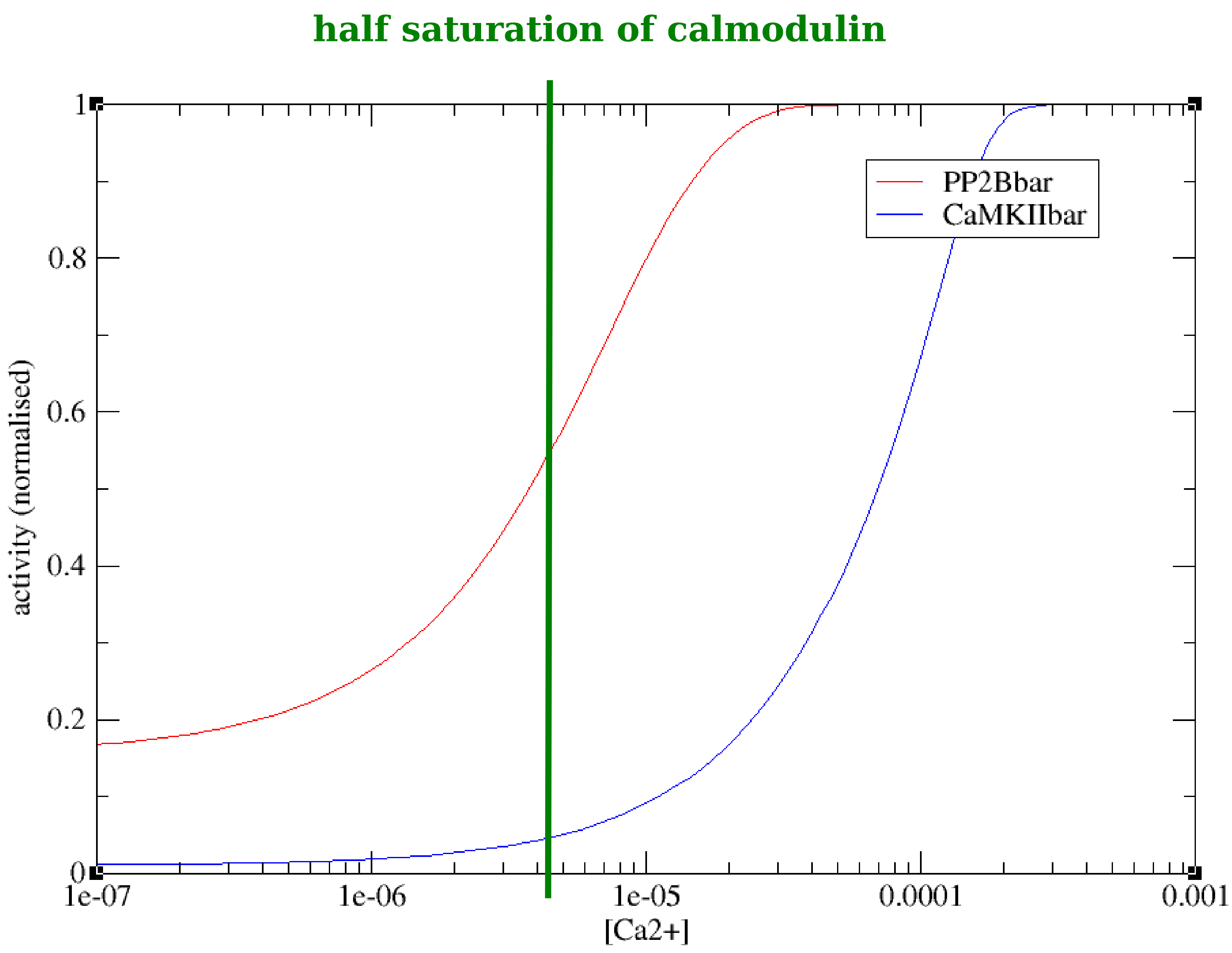
Parameter scan on kinetic simulations



Bidirectional synaptic plasticity



Bidirectional synaptic plasticity



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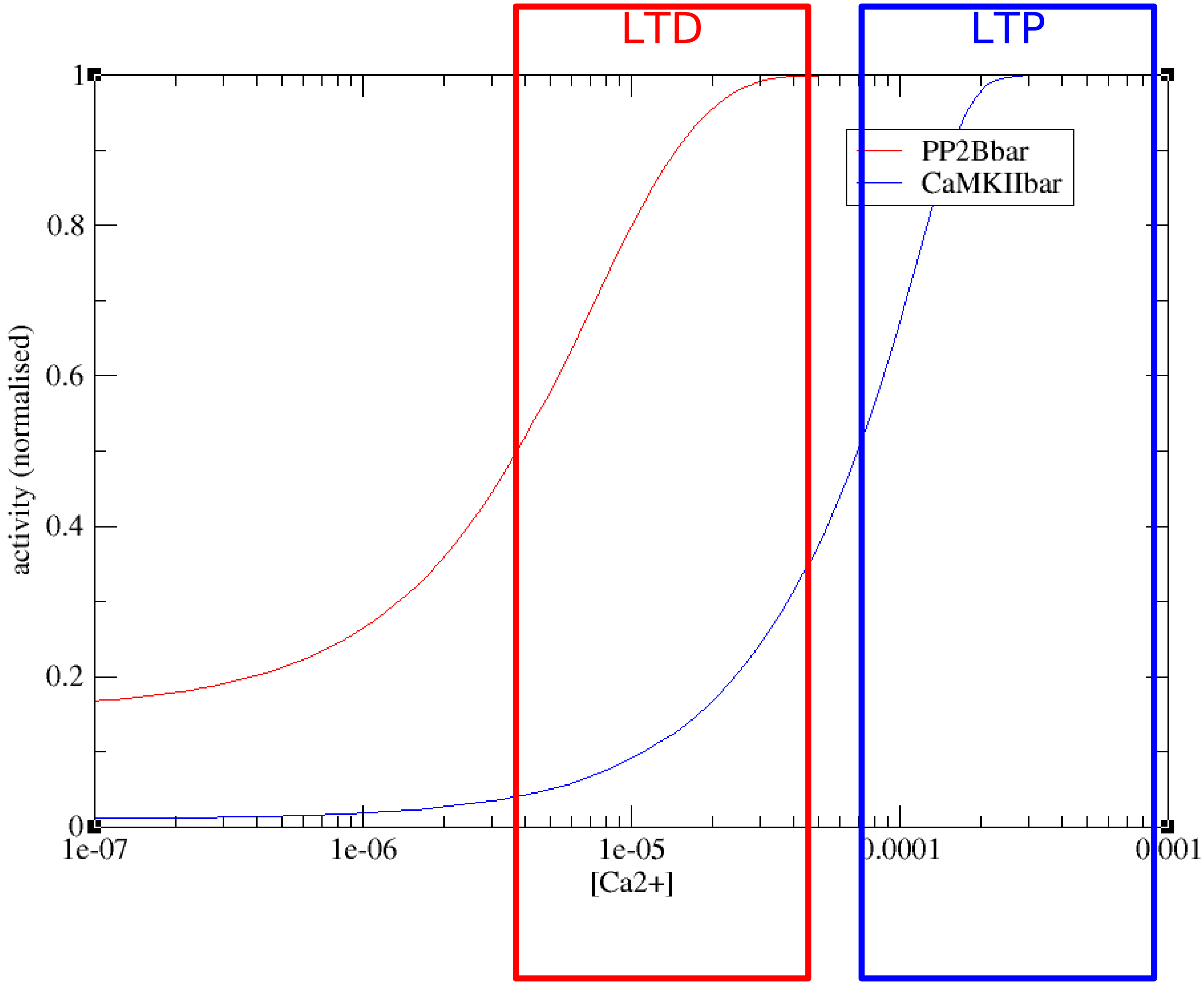

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