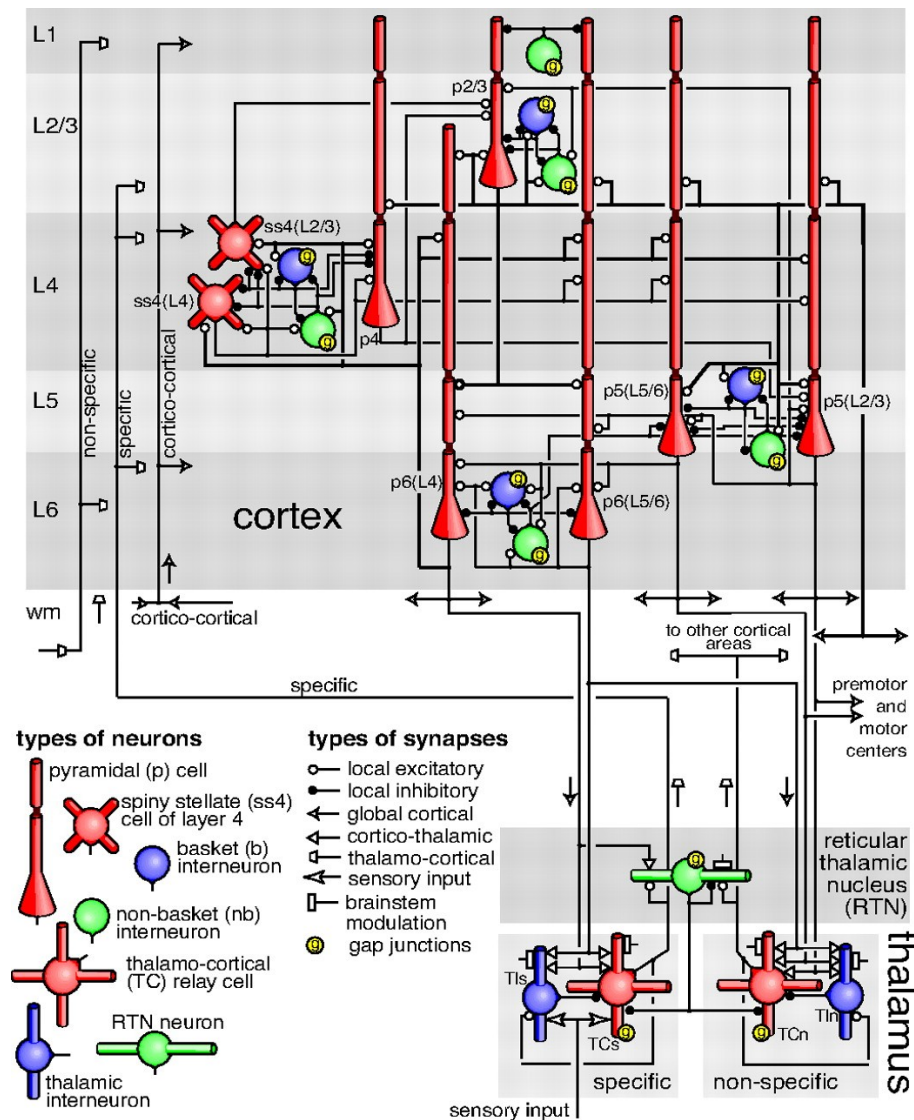


Allosteric calcium sensors in synaptic plasticity

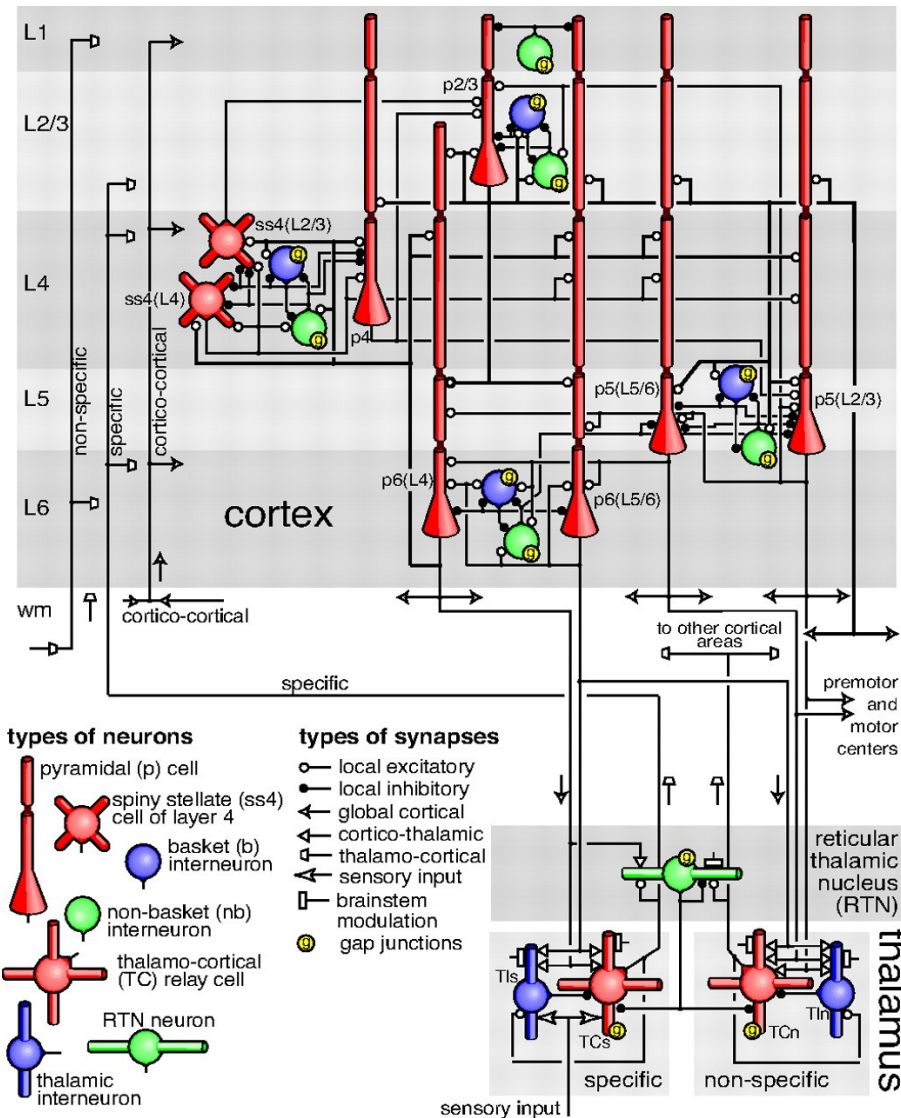
*Nicolas Le Novère, Babraham Institute
n.lenovere@gmail.com
<http://lenoverelab.org>*

The brain as an electrical circuit?



Izhikevich, Edelman (2008) *PNAS* 105: 3593-3598

The brain as an electrical circuit?



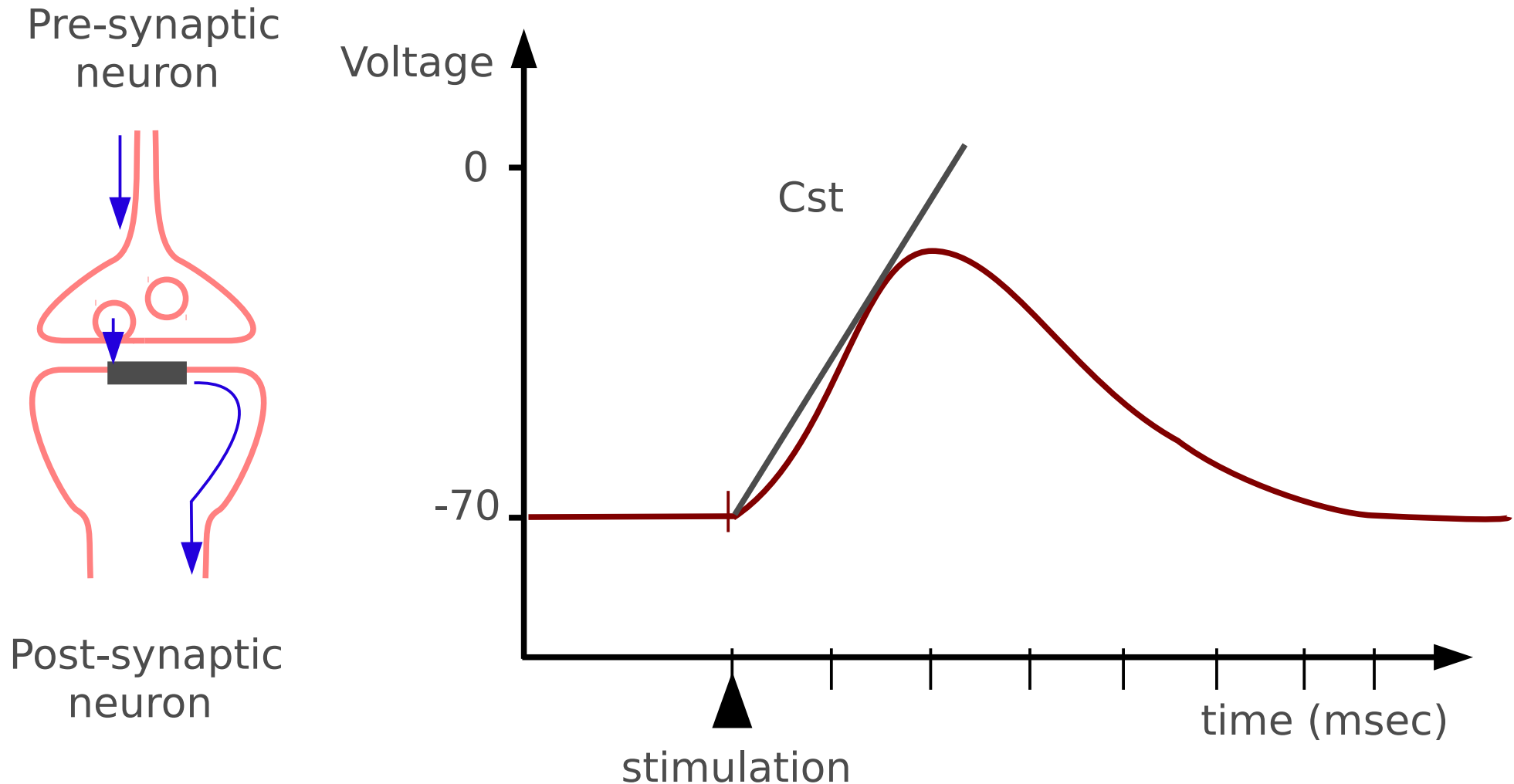
BUT

With variable topology

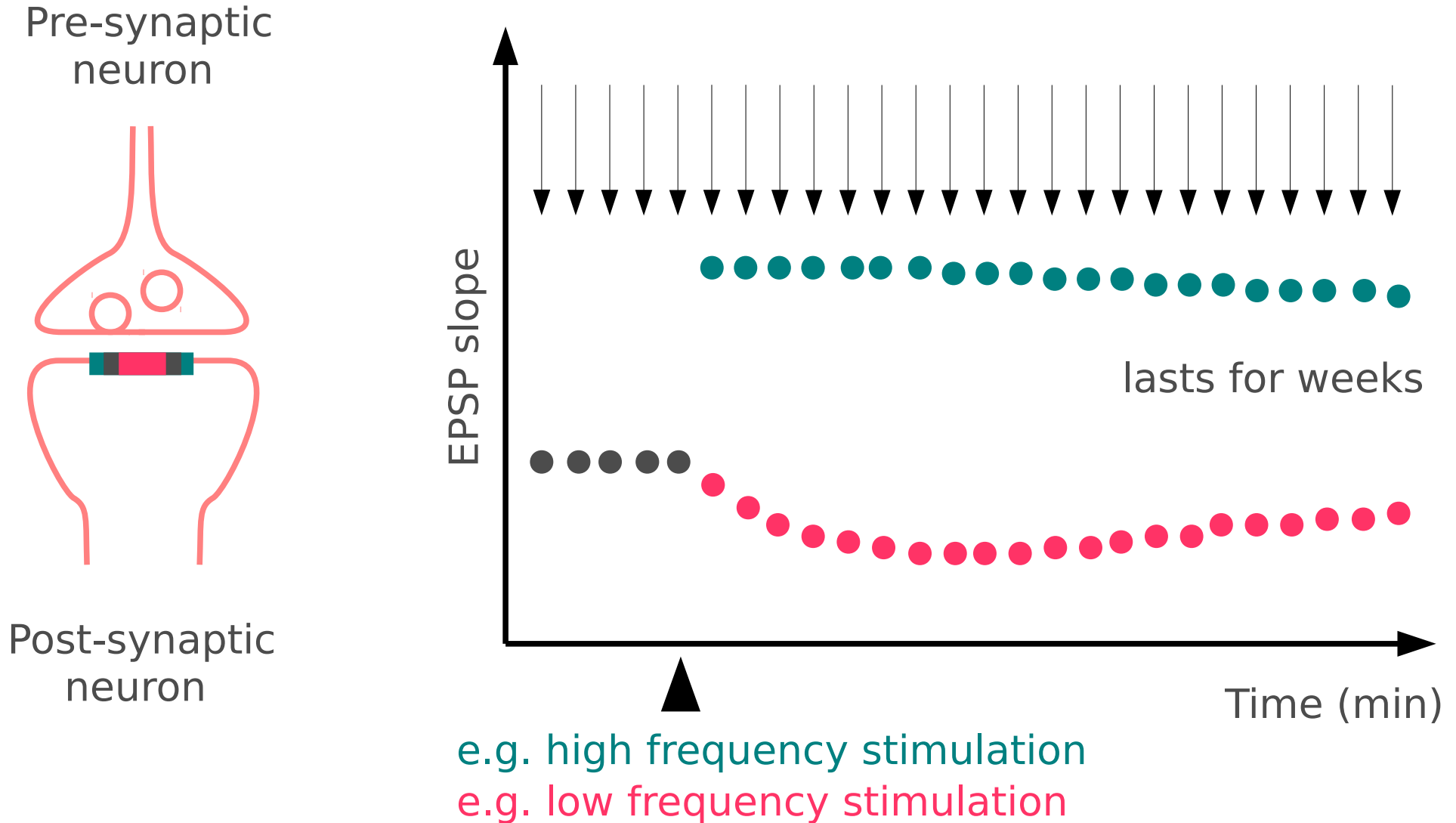
With variable connexions

Izhikevich, Edelman (2008) *PNAS* 105: 3593-3598

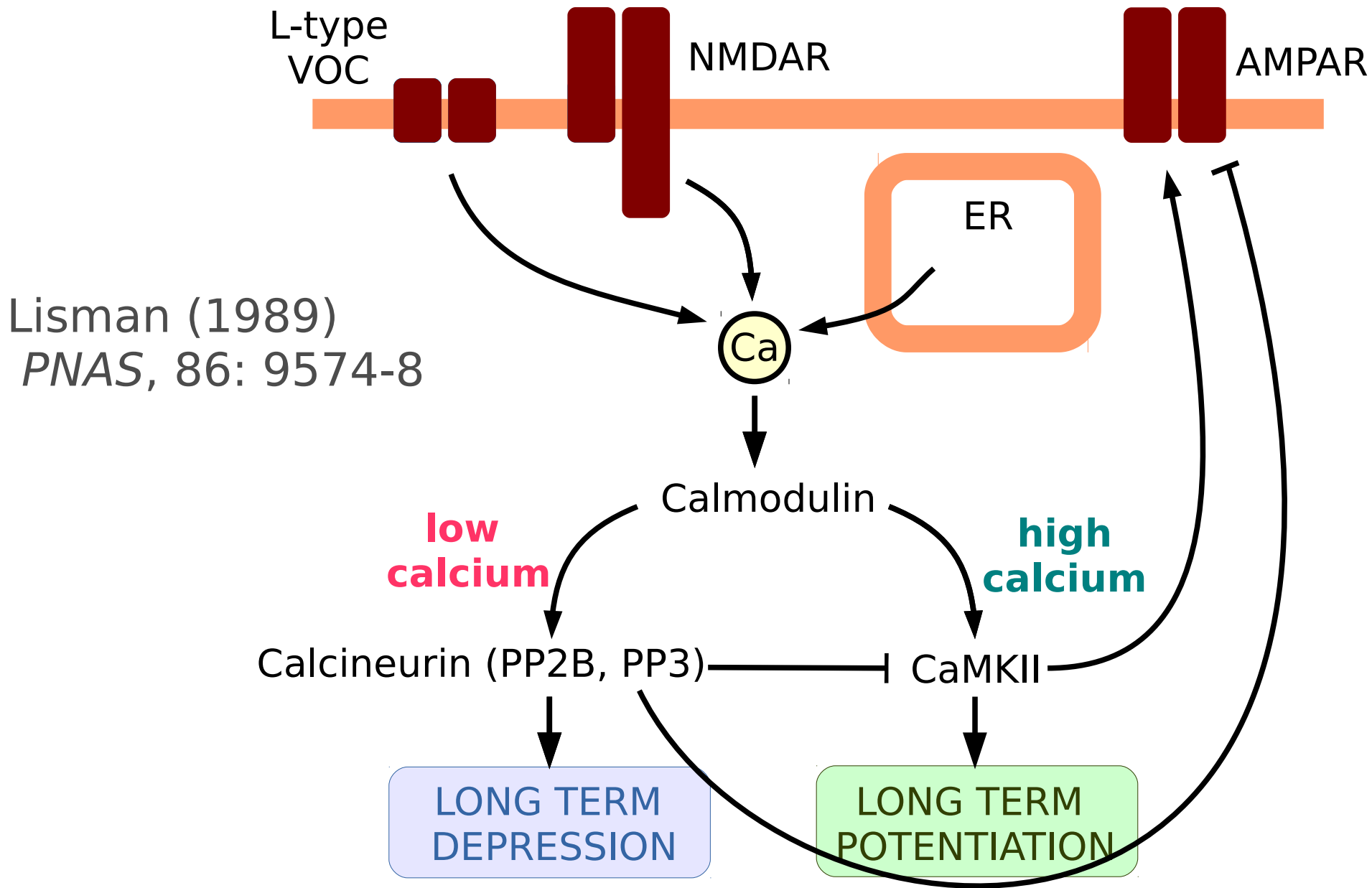
Excitatory post-synaptic potential



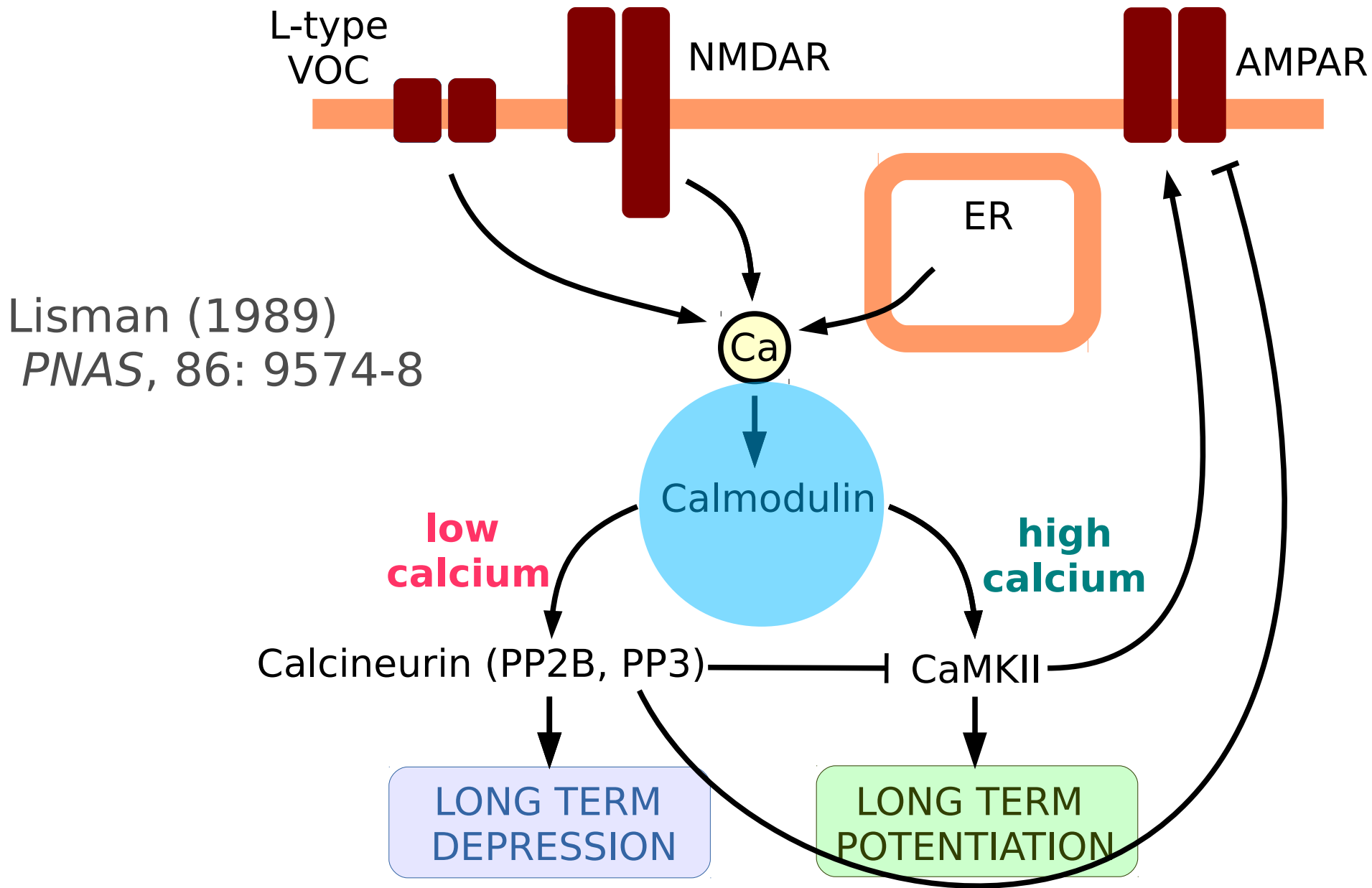
Bidirectional synaptic plasticity



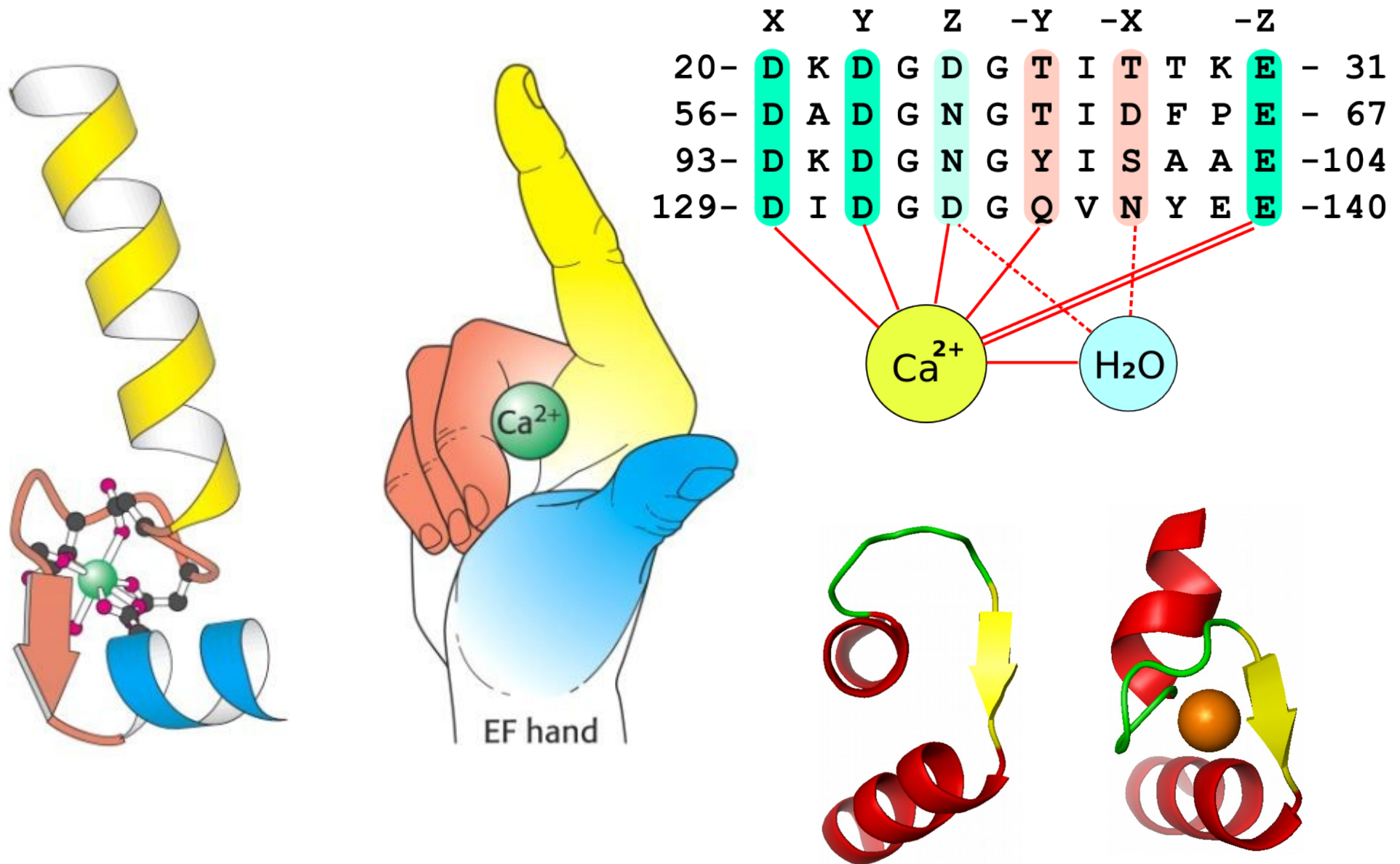
Calmodulin, the memory switch



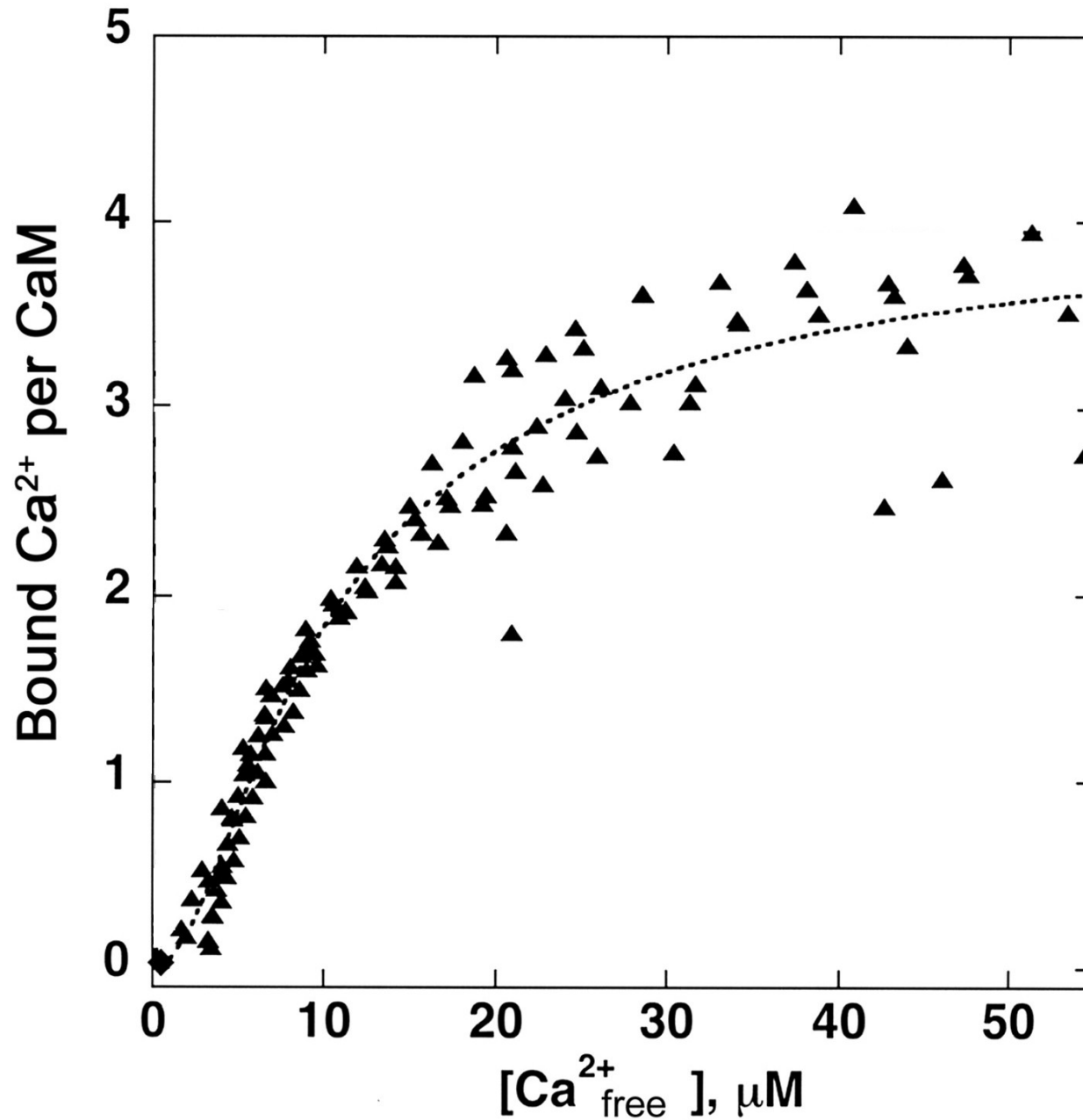
Calmodulin, the memory switch



Structure of a Calmodulin Ca^{2+} binding domain

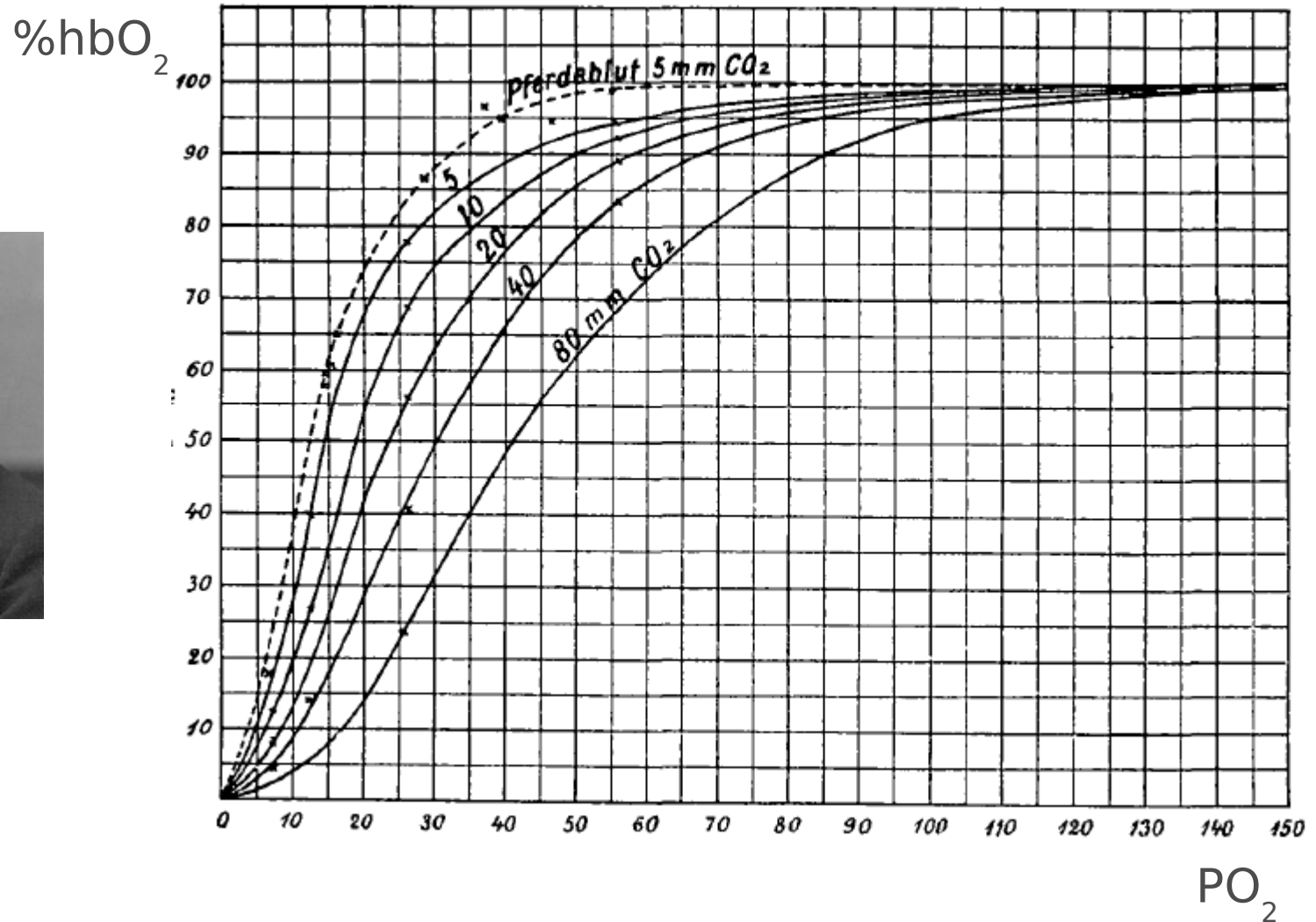


Calmodulin is ultra-sensitive



Shifman et al (2006)
PNAS, 103: 13968-13973

Origins of cooperativity: Bohr



Bohr C (1903) Theoretische behandlung der quantitativen verhältnisse bei der sauerstoff aufnahme des hämoglobins *Zentralbl Physiol* 17: 682

Origins of cooperativity: Hill

iv PROCEEDINGS OF THE PHYSIOLOGICAL

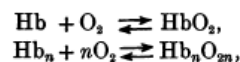
The possible effects of the aggregation of the molecules of hæmoglobin on its dissociation curves. By A. V. HILL.

In a previous communication Barcroft and I gave evidence which seemed to us to prove conclusively that dialysed hæmoglobin consists simply of molecules containing each one atom of iron. The molecular weight is therefore $Hb = 16,660$. These experiments have not been published yet, but I shall assume the results.

Other observers (Reid, Roaf, Hüfner and Gansser) working on different solutions have obtained divergent results. The method used by all of them was the direct estimation of the osmotic pressure, by means of a membrane permeable to salts, but not to hæmoglobin. The method involves a relatively large error, because the quantity measured is small. It is doubtful however whether this can explain the discordant results.

Our work led me to believe that the divergence between the results of different observers was due to an aggregation of the hæmoglobin molecules by the salts present in the solution, a consequent lowering of the number of molecules, and an increase in the average molecular weight as observed by the osmotic pressure method. To test this hypothesis I have applied it to several of the dissociation curves obtained by Barcroft and Camis with hæmoglobin in solutions of various salts, and with hæmoglobin prepared by Bohr's method.

The equation for the reaction would be



where Hb_n represents the aggregate of n molecules of Hb . I have supposed that in every solution there are many different sized aggregates, corresponding to many values of n .

If there were in the solution only Hb and Hb_2 the dissociation curve would be

$$y = \lambda \frac{K'x^2}{1 + K'x^2} + (100 - \lambda) \frac{Kx}{1 + Kx} \dots\dots\dots (A),$$

where $\lambda\%$ is as Hb_2 , $(100 - \lambda)\%$ as Hb , K' is the equilibrium constant of the reaction $Hb_2 + 2O_2 \rightleftharpoons Hb_2O_4$ and K that of $Hb + O_2 \rightleftharpoons HbO_2$: K has the value .125 (Barcroft and Roberts).

Hill (1910) *J Physiol* 40: iv-vii.



Origins of cooperativity: Hill

iv PROCEEDINGS OF THE PHYSIOLOGICAL

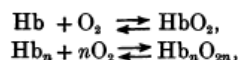
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Now it is unlikely that in either of these cases there is only Hb and Hb_2 ; and as the calculation of the constants in these equations is very tedious I decided to try whether the equation

$$y = 100 \frac{Kx^n}{1 + Kx^n} \dots\dots\dots (B)$$

would satisfy the observations.

Origins of cooperativity: Hill

iv PROCEEDINGS OF THE PHYSIOLOGICAL

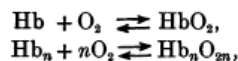
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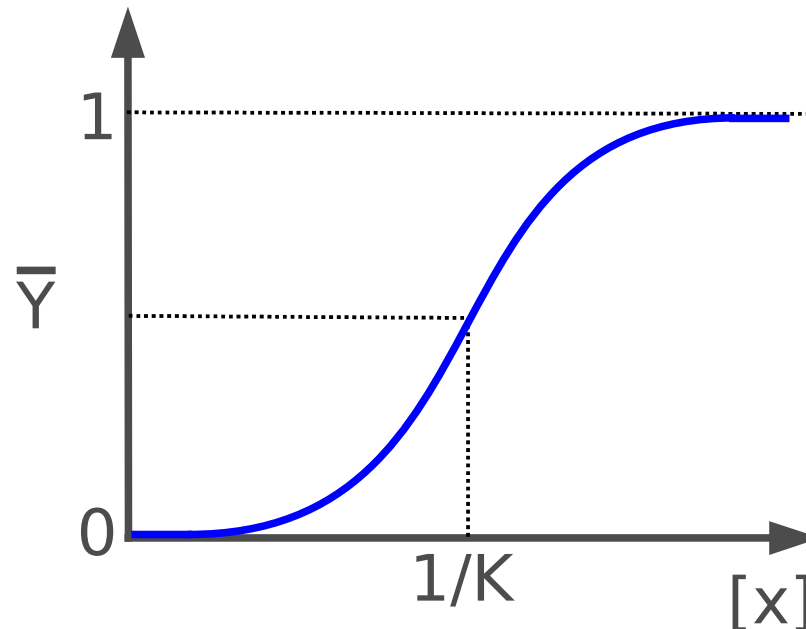
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Hill equation can be linearised

$$\bar{Y} = \frac{K^n [X]^n}{1 + K^n [X]^n}$$

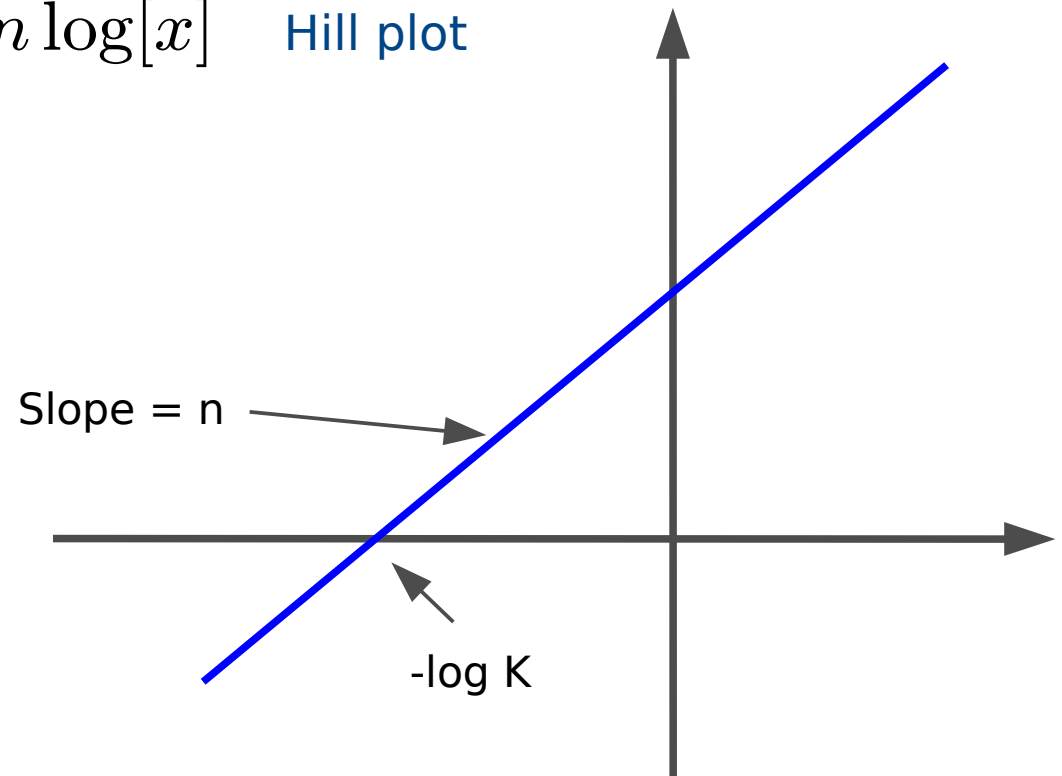
Hill equation

$$\log \frac{\bar{Y}}{1 - \bar{Y}} = n \log K + n \log [x]$$

Hill plot

Effect increases in function of the signal to the power of n:
n>1, ultra-sensitive
n<1, infra-sensitive

BUT cooperativity of ligand,
not of binding sites: unique affinity



Origins of cooperativity: Adair-Klotz

THE HEMOGLOBIN SYSTEM.

VI. THE OXYGEN DISSOCIATION CURVE OF HEMOGLOBIN

By G. S. ADAIR.

WITH THE COLLABORATION OF A. V. BOCK AND H. FIELD, JR.
(From the Medical Laboratories of the Massachusetts General Hospital, Boston.)

(Received for publication, January 7, 1925.)

This work gives the oxygen dissociation curves of so previously investigated in regard to their acid-binding and

Adair (1925) *J Biol Chem* 63: 529

$$\bar{Y} = \frac{1}{n} \frac{K_1[x] + 2K_2[x]^2 + 3K_3[x]^3 + 4K_4[x]^4}{1 + K_1[x] + K_2[x]^2 + K_3[x]^3 + K_4[x]^4}$$

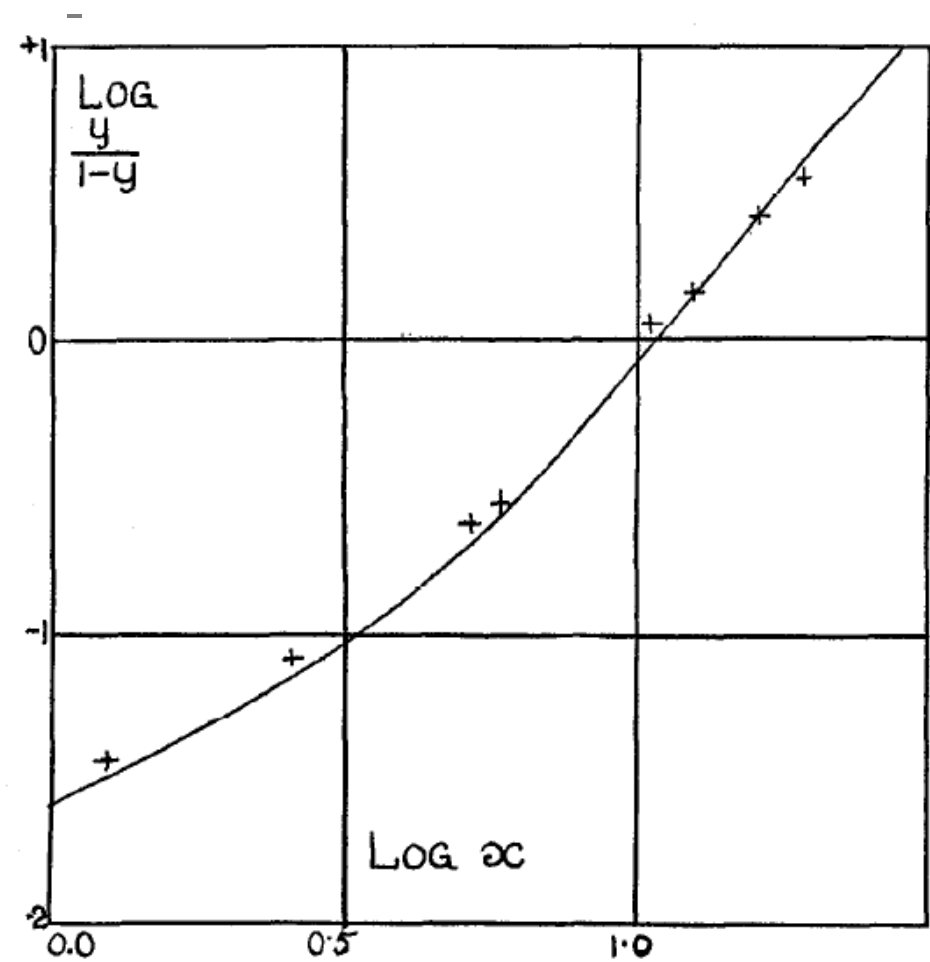


FIG. 2. Test of formula (6). Curve drawn from 6 experimental points from Table IV.

Origins of cooperativity: Adair-Klotz

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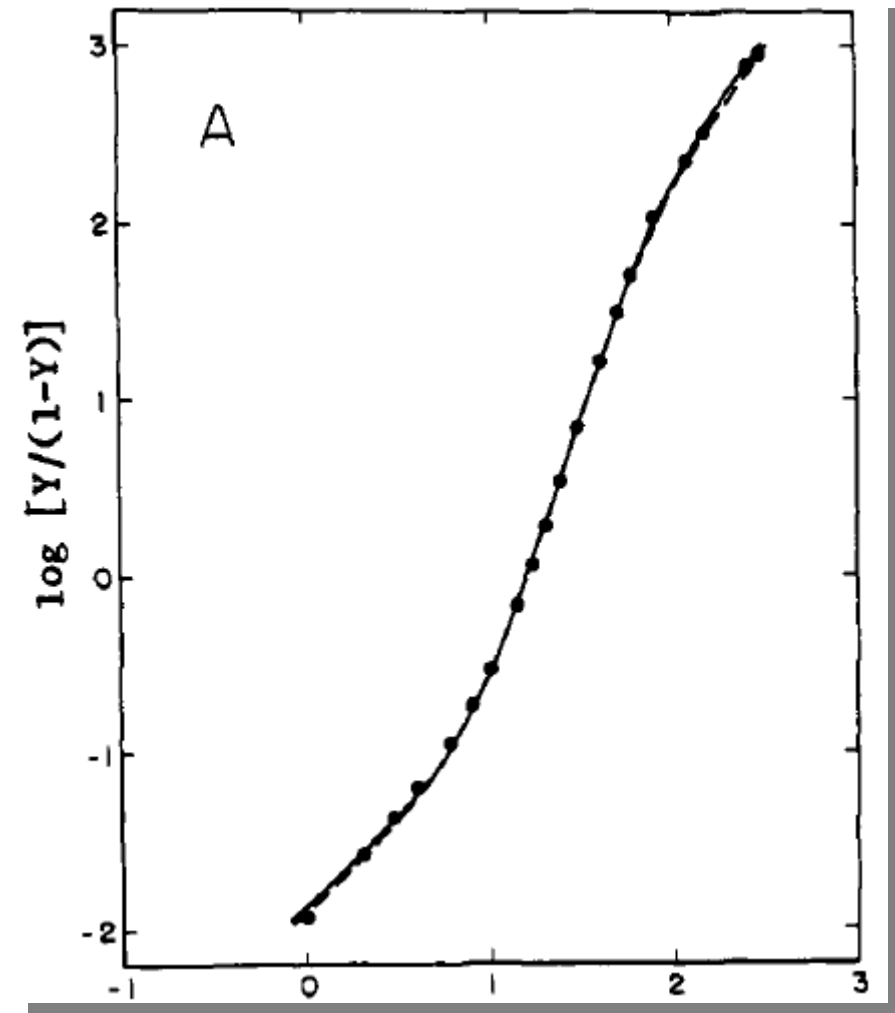
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Imai (1973) *Biochemistry* 12: 798-808

Adair-Klotz model applied to Calmodulin

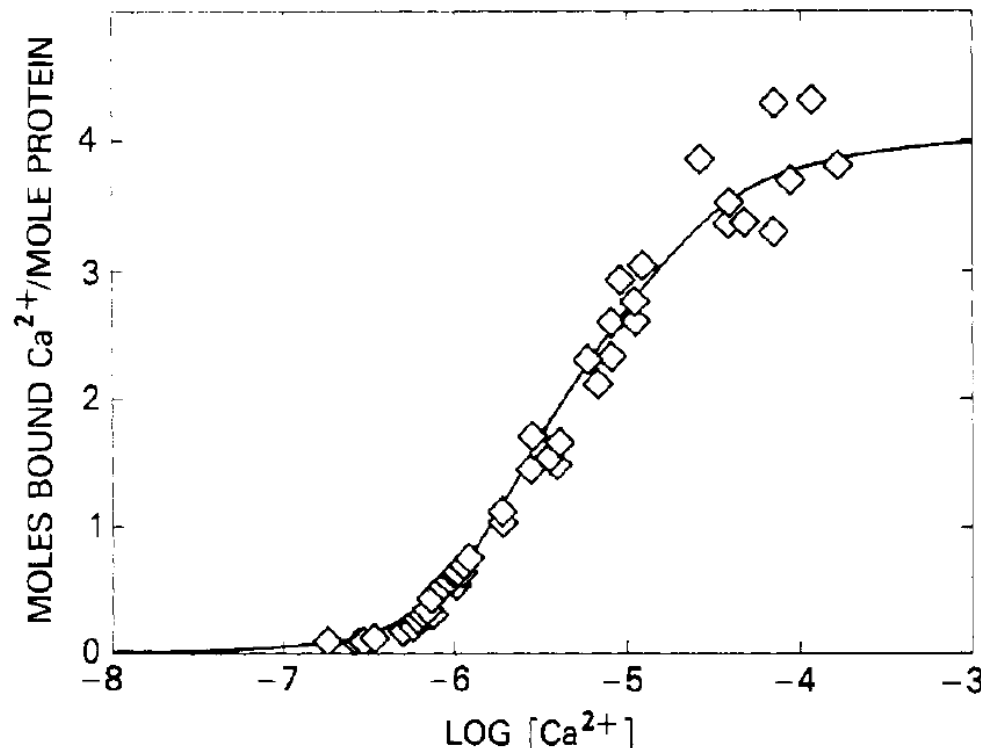
Klotz (1946) The Application of the Law of Mass Action to Binding by Proteins. Interactions with Calcium. *Arch Biochem*, 9:109-117.

1st calcium

2nd calcium

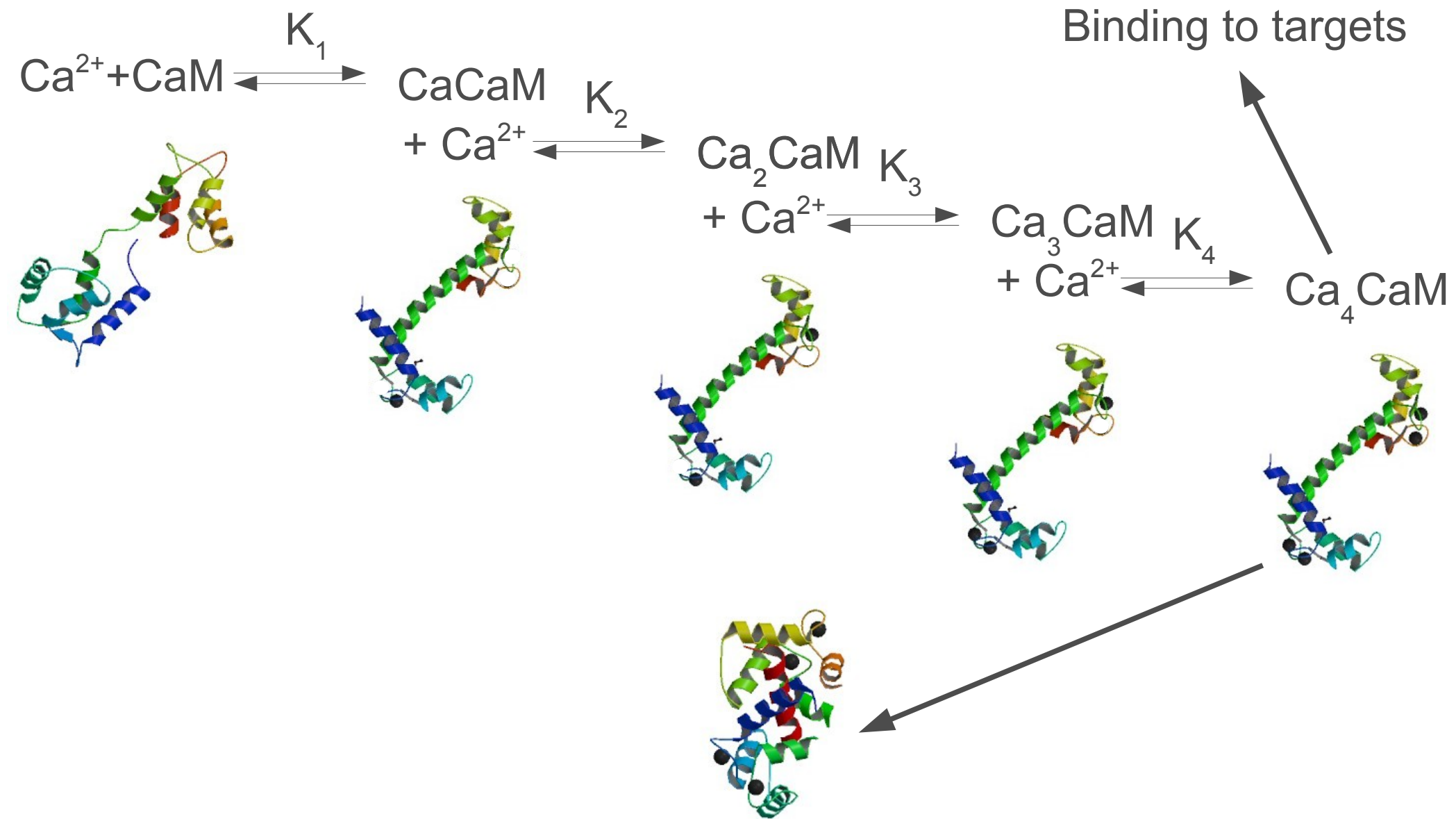
...

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

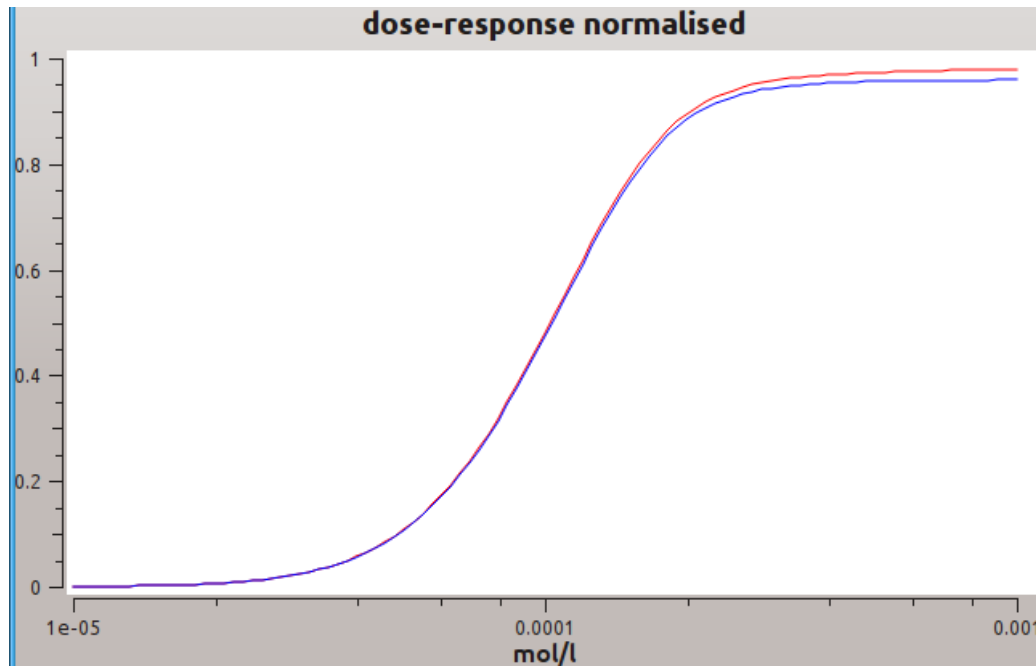


Crouch and Klee (1980)
Biochemistry, 19: 3692-3698b

Corresponding induced-fit model

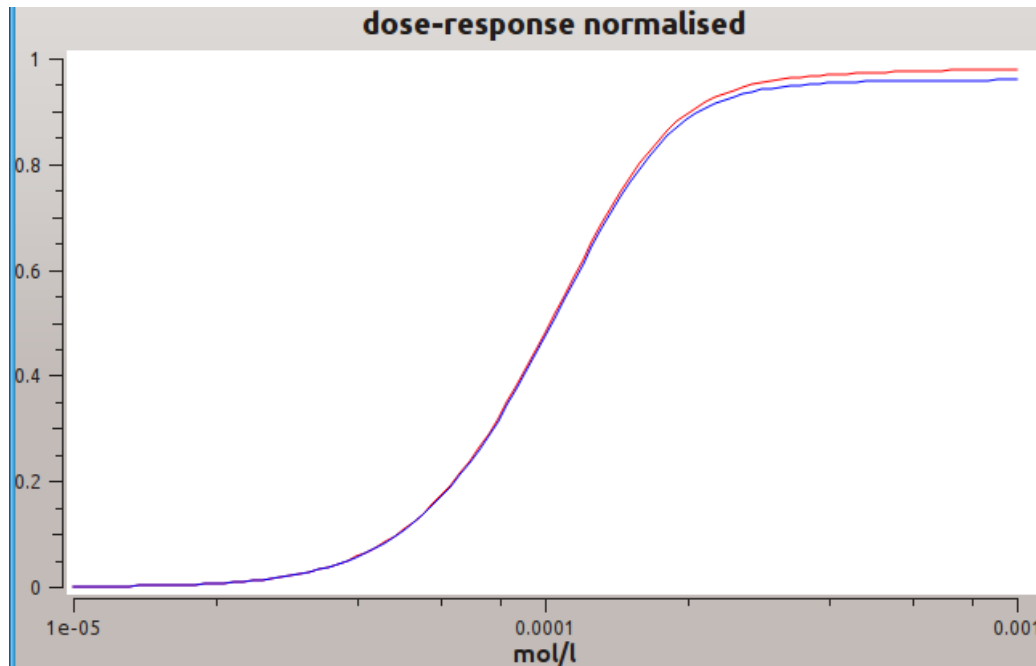


That does not work ...



[CaN]=[CamKII]=[CaM]/10 ;
Kd_CaMKII = 10xKd_CaN;
Software COPASI

We knew it would not work



[CaN]=[CamKII]=[CaM]/10 ;
Kd_CaMKII = 10xKd_CaN;
Software COPASI

- Calmodulin can activate calcineurin with 3 Ca^{2+} (Kincaid and Vaughan (1986). *PNAS*, 83: 1193-1197)
- Calmodulin can bind CaMKII with 2 Ca^{2+} (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])

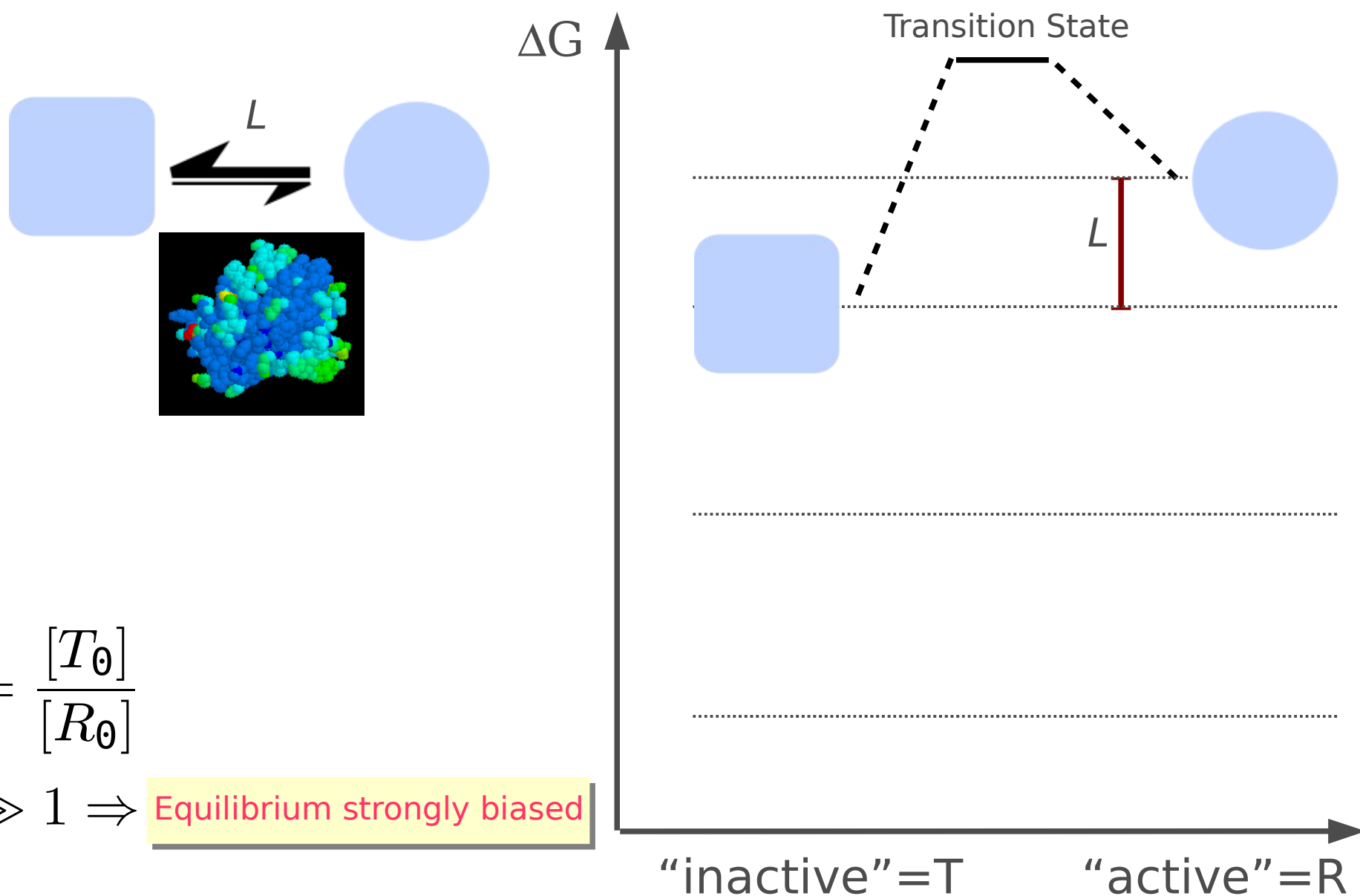
Monod, Wyman, Changeux (1965)

**On the nature of allosteric transitions:
a plausible model**

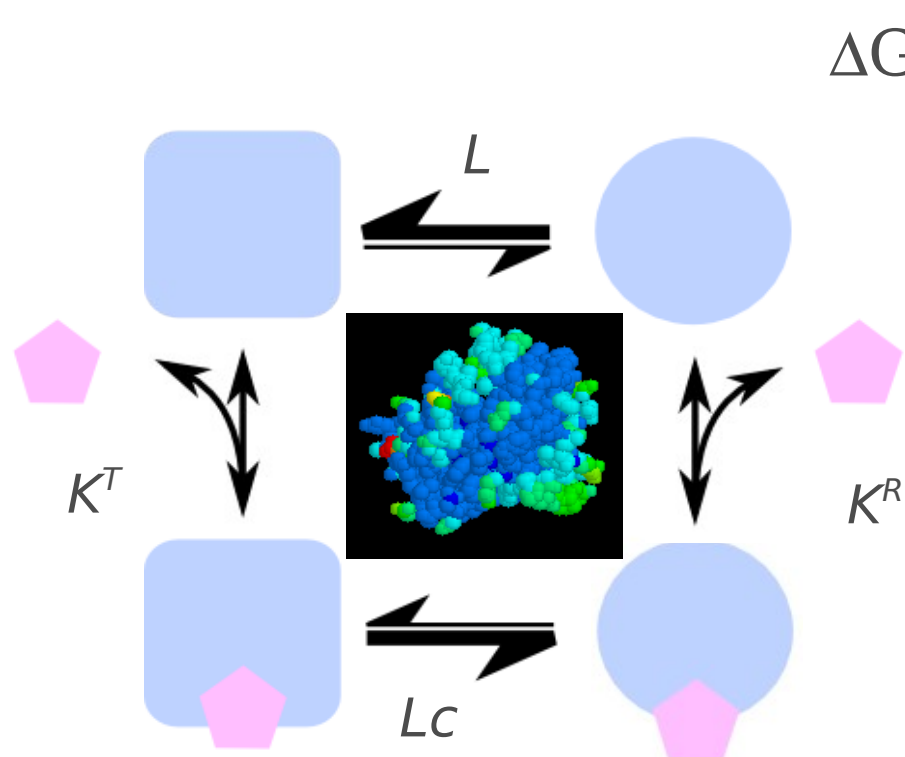
J Mol Biol, 12: 88-118



1 Modulation of thermal equilibria $\neq$ induced-fit



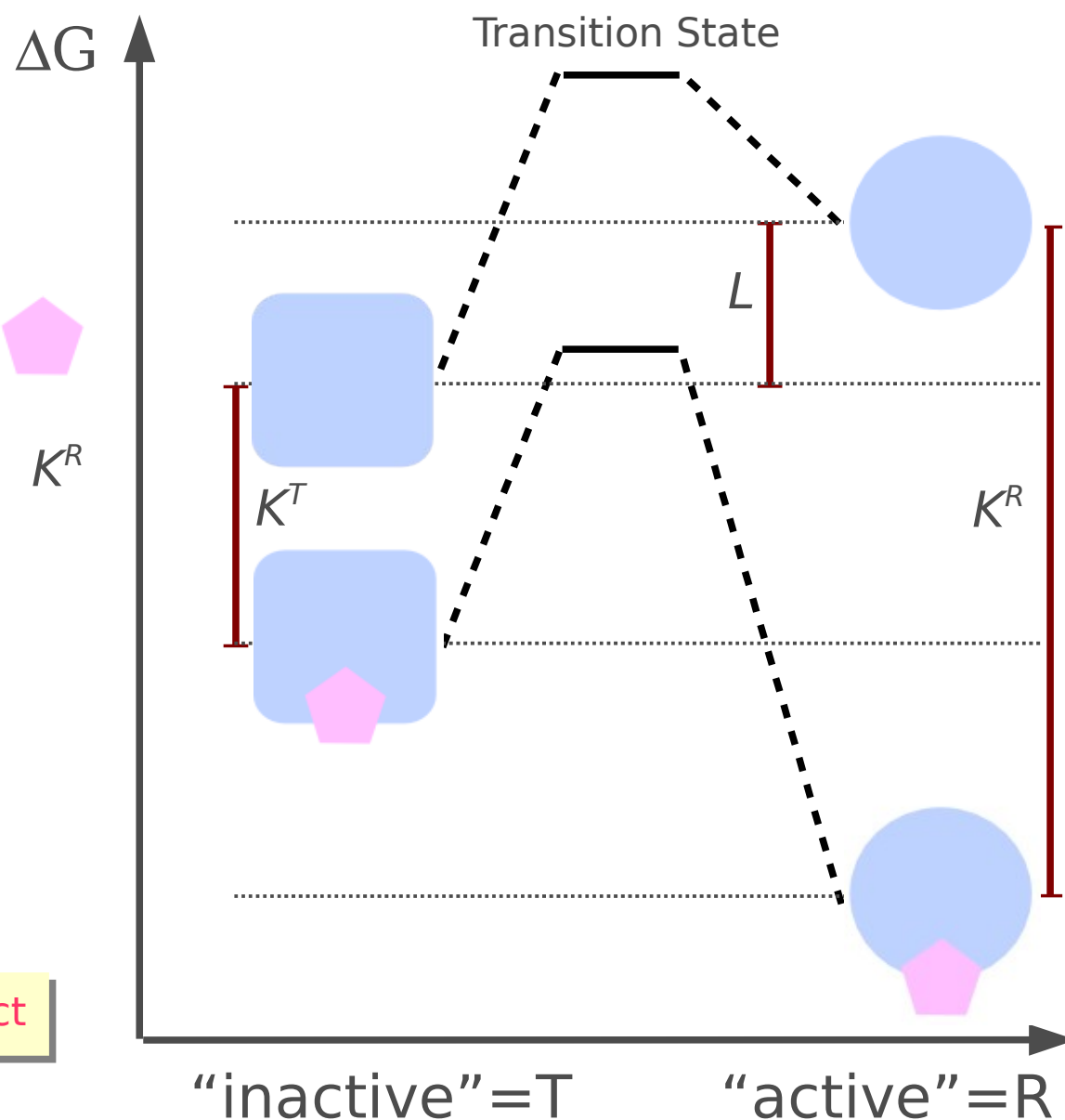
1 Modulation of thermal equilibria $\neq$ induced-fit



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

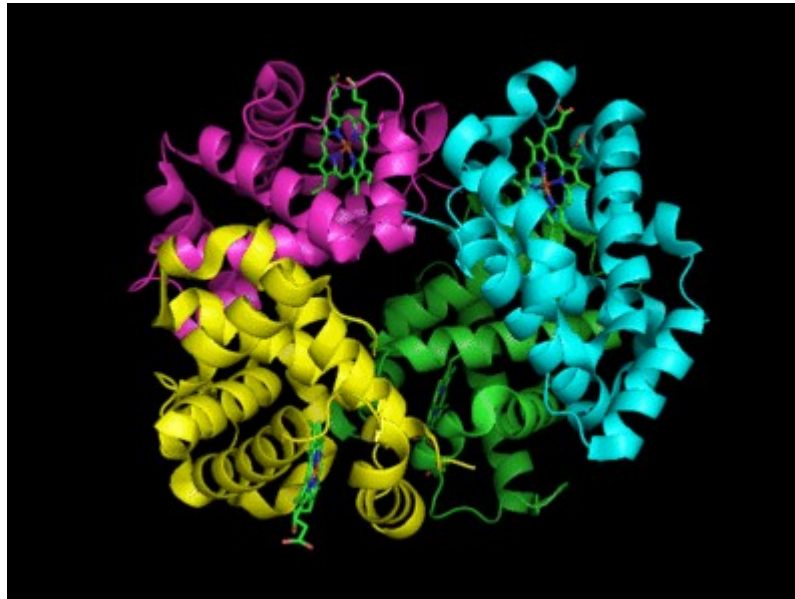
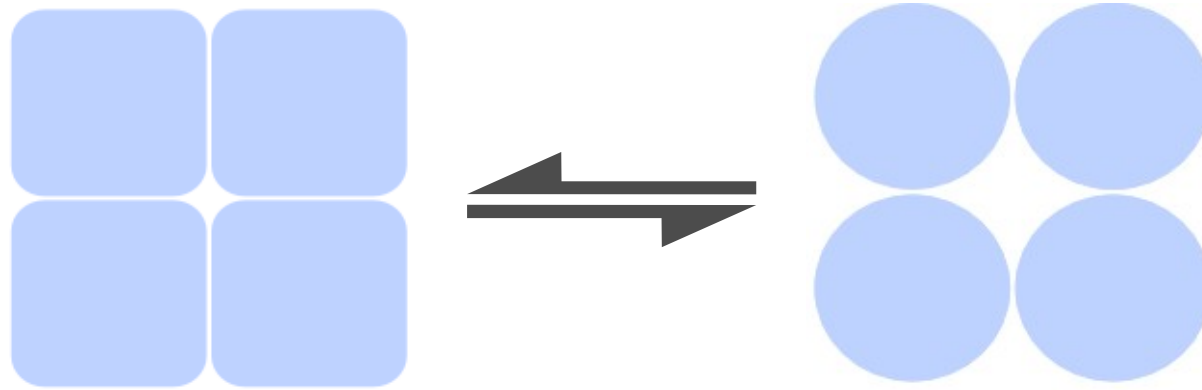
$$c = \frac{K^R}{K^T}$$

$c \ll 1 \Rightarrow$ ligand has strong effect

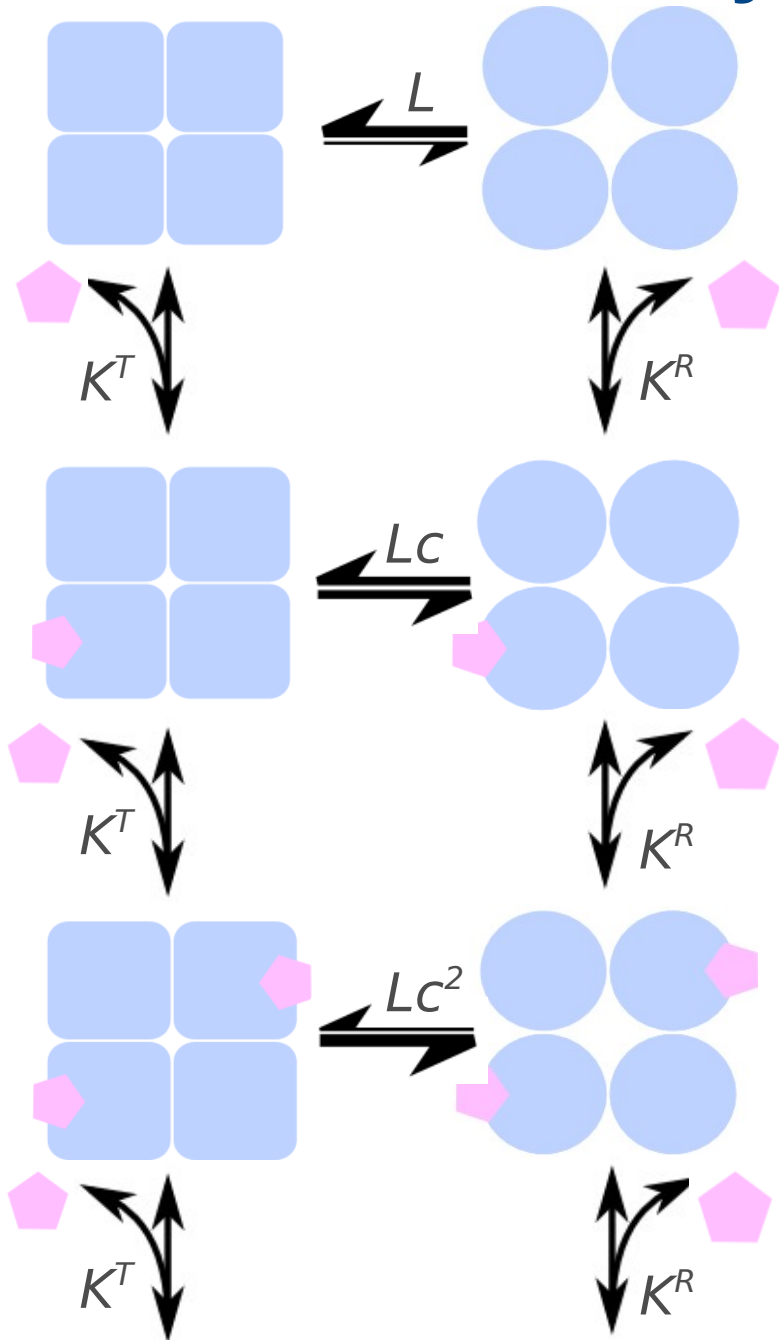


2

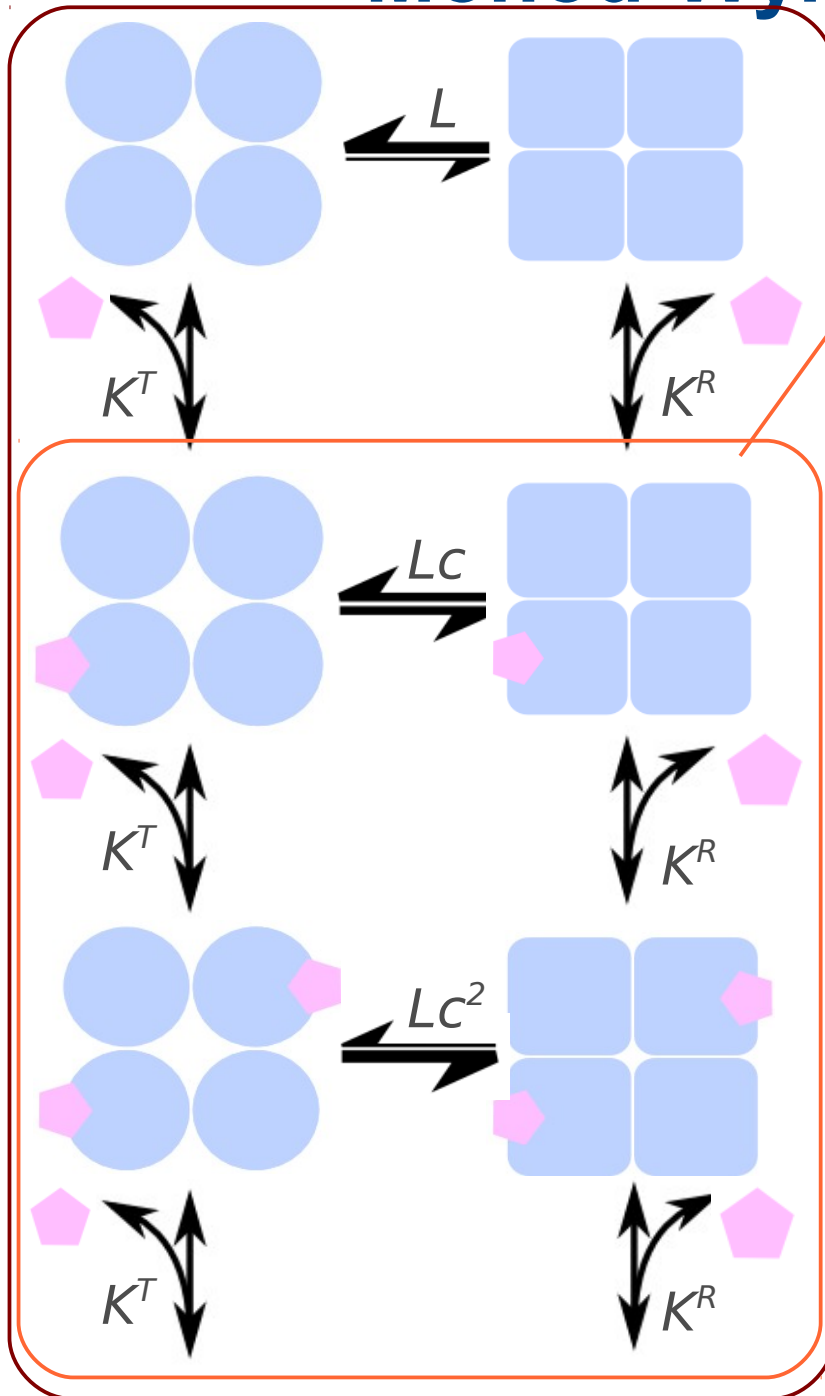
Concerted transitions $\neq$ sequential model



Monod-Wyman-Changeux model



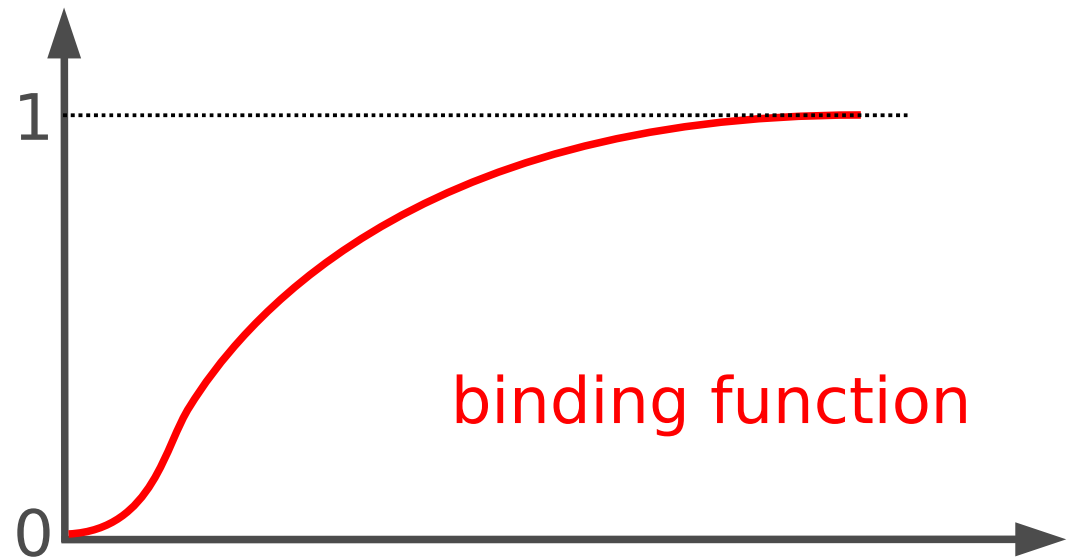
Monod-Wyman-Changeux model



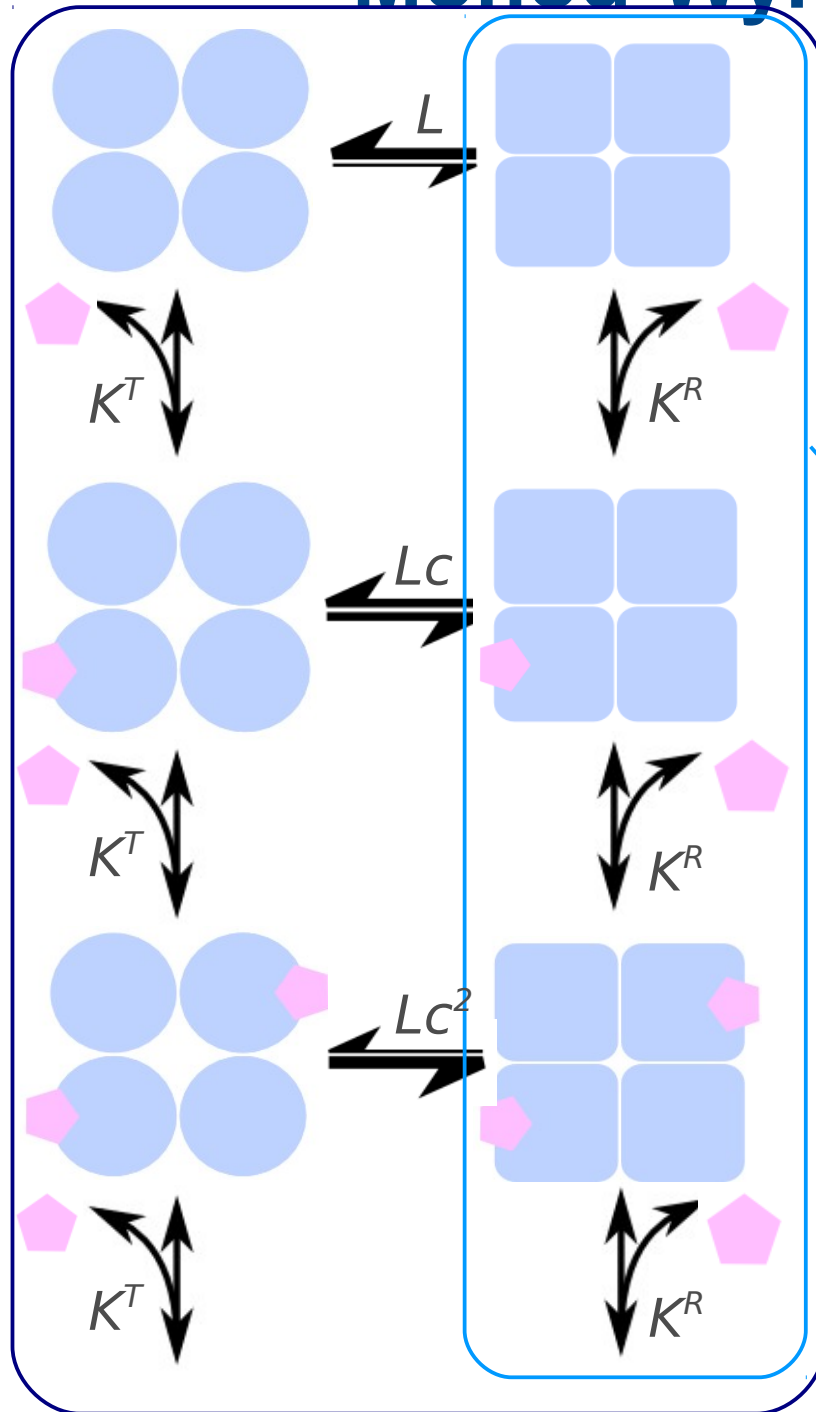
this
that

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

$$\alpha = \frac{[x]}{K^R}$$



Monod-Wyman-Changeux model

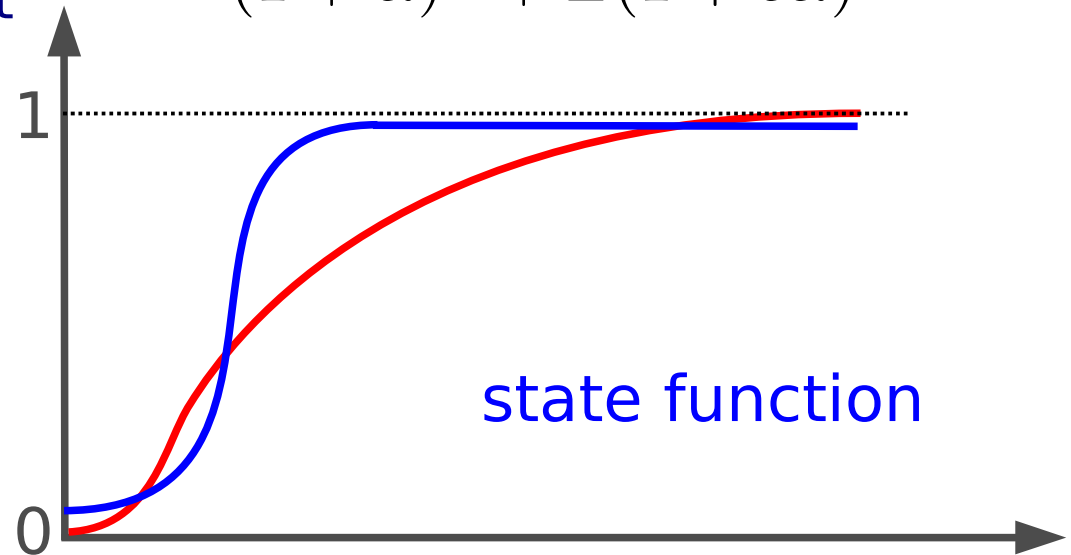


$$\alpha = \frac{[x]}{K^R}$$

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

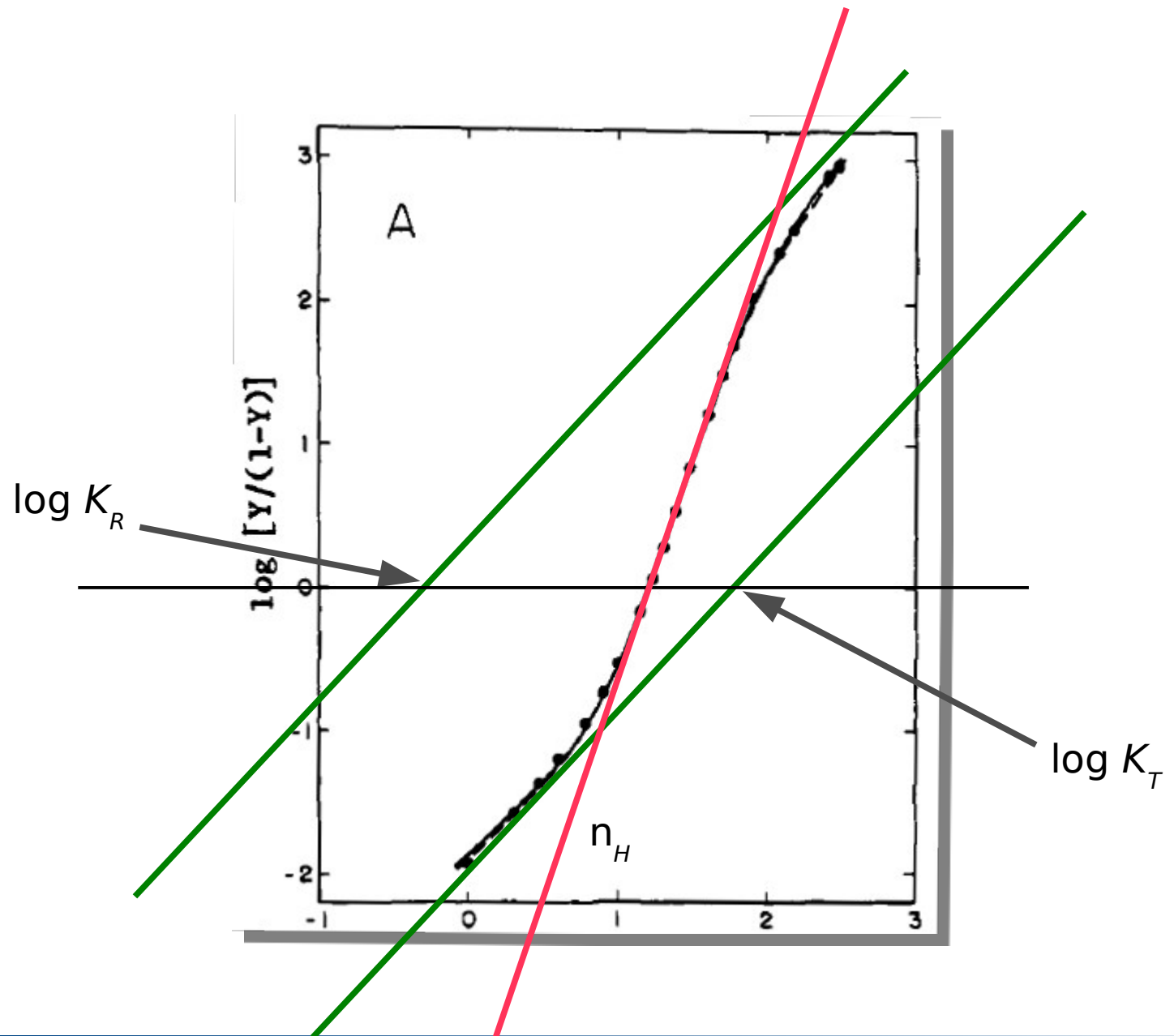
this
that

$$\bar{R} = \frac{(1 + \alpha)^n}{(1 + \alpha)^n + L(1 + c\alpha)^n}$$

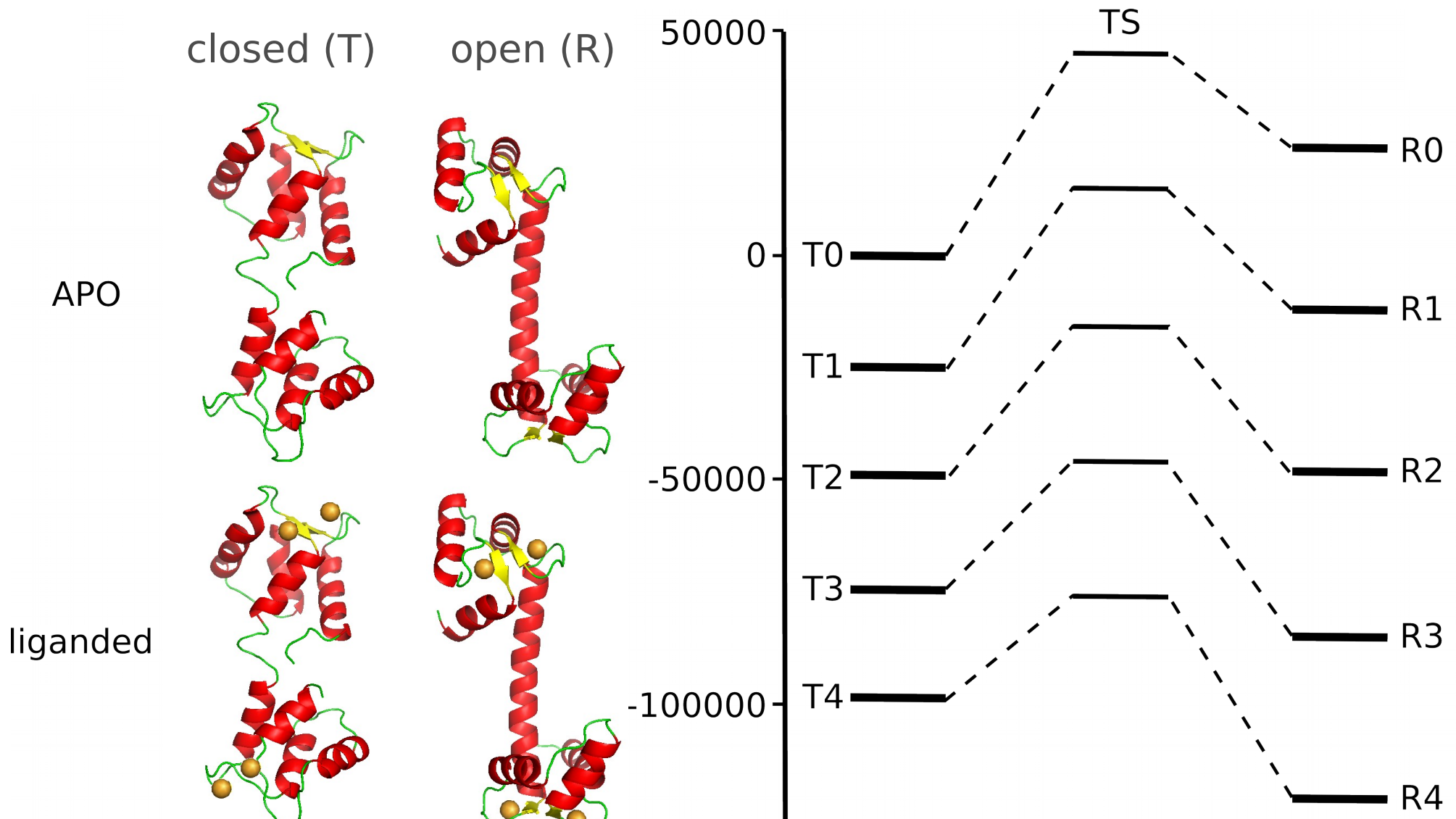


state function

“Hill” Plot for MWC model

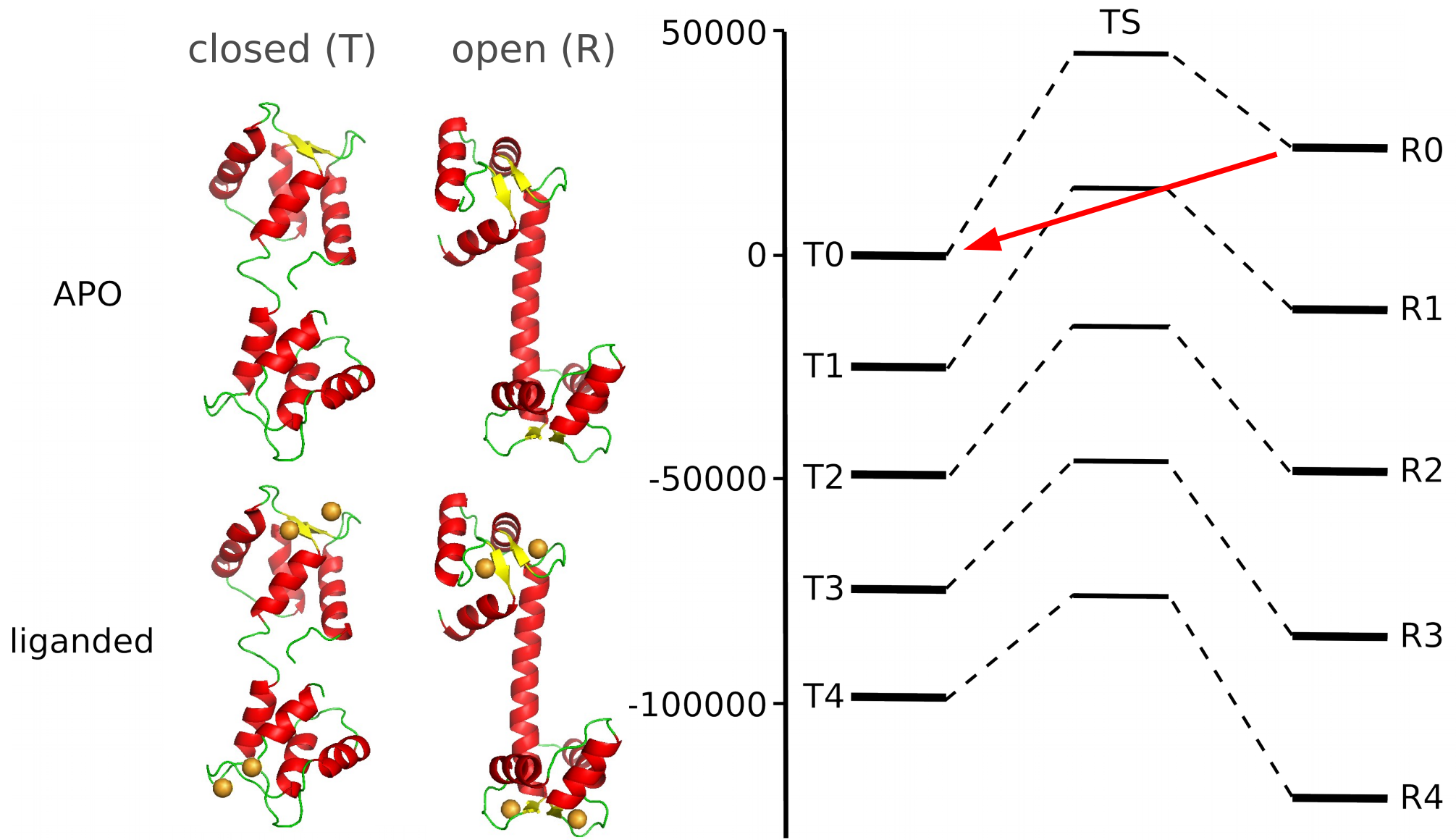


Allosteric model of Calmodulin activation

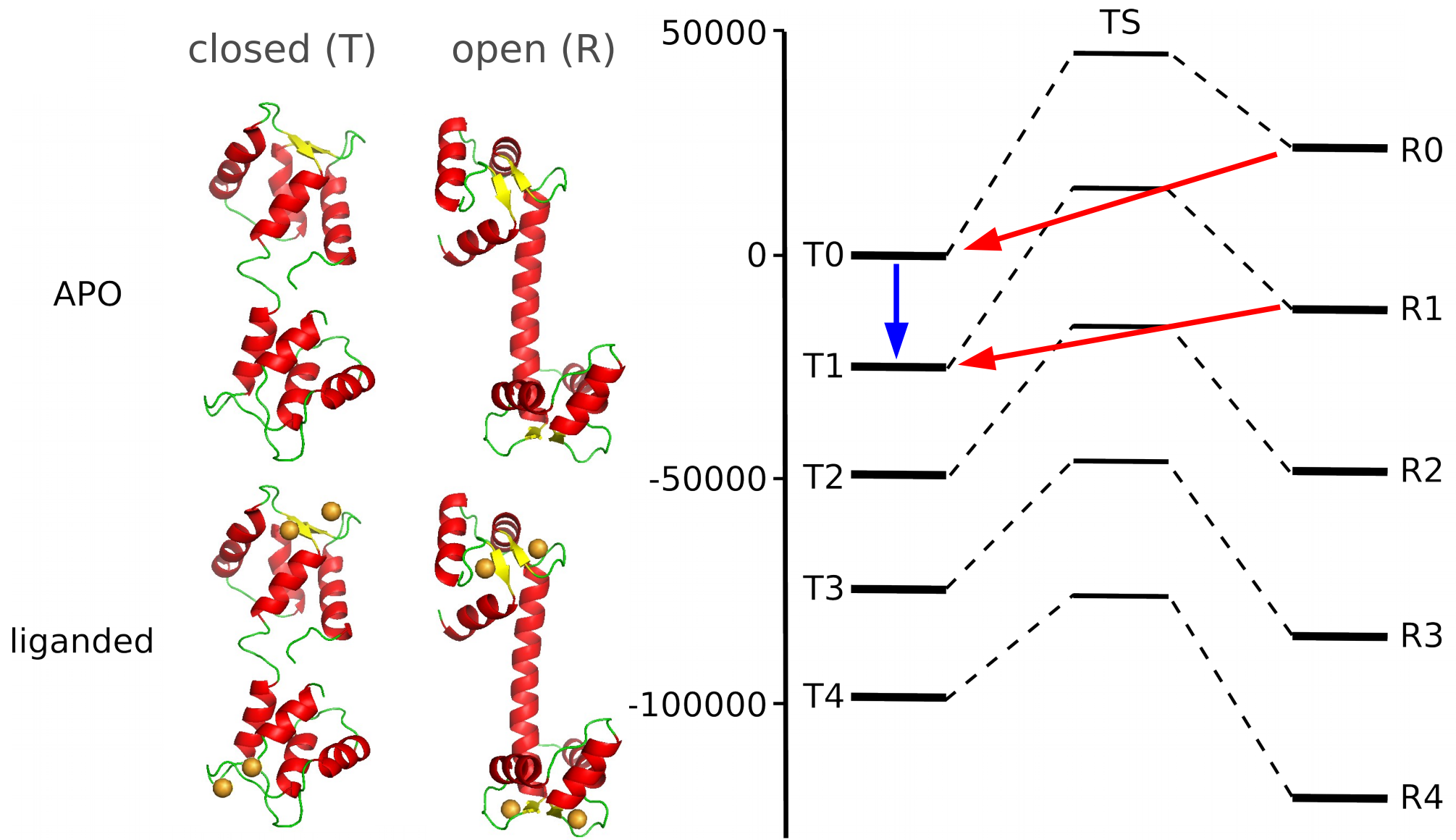


Stefan MI, Edelstein SJ, Le Novère N (2008) *Proc Natl Acad Sci USA*, 105:10768-10773

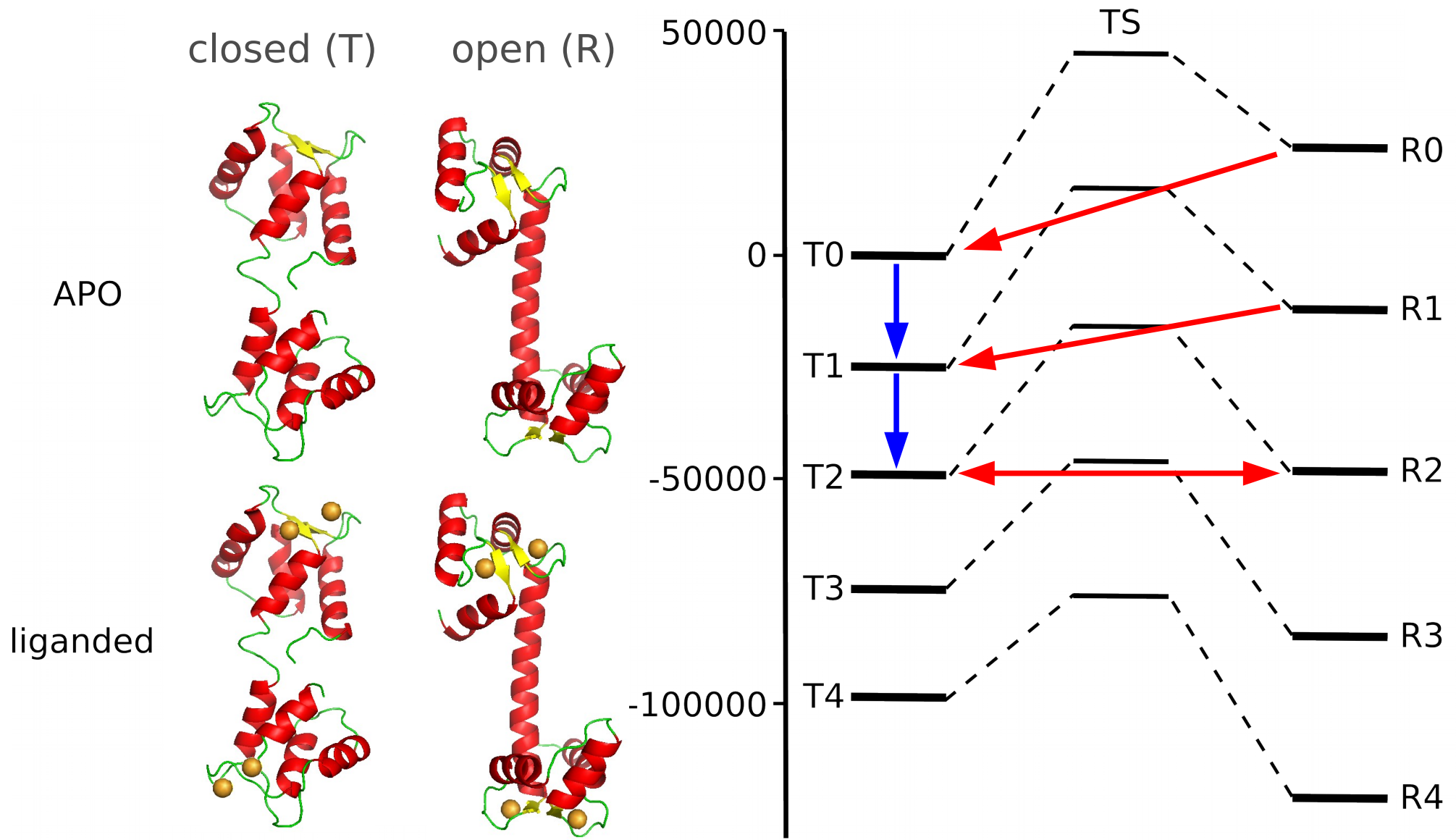
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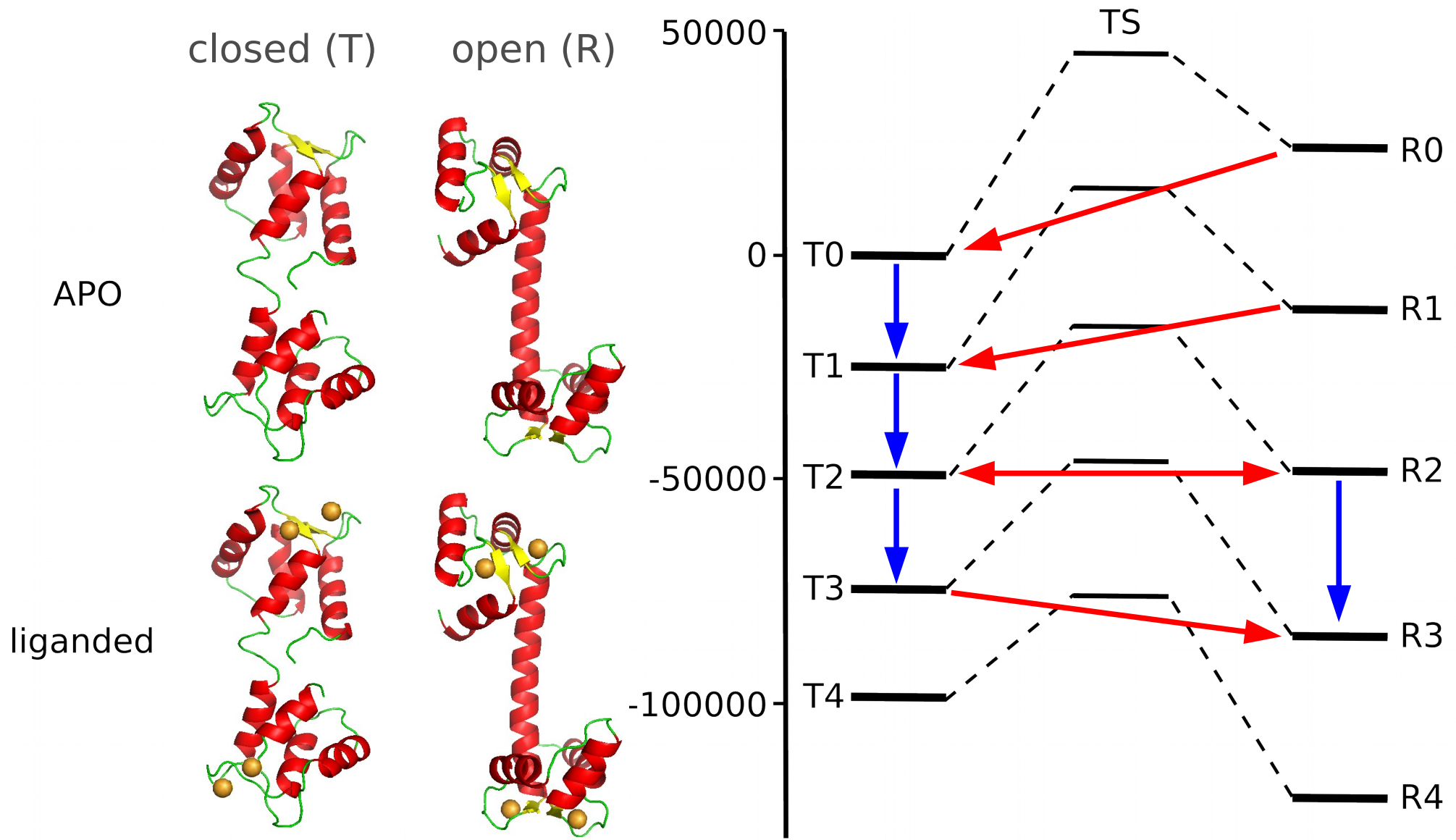
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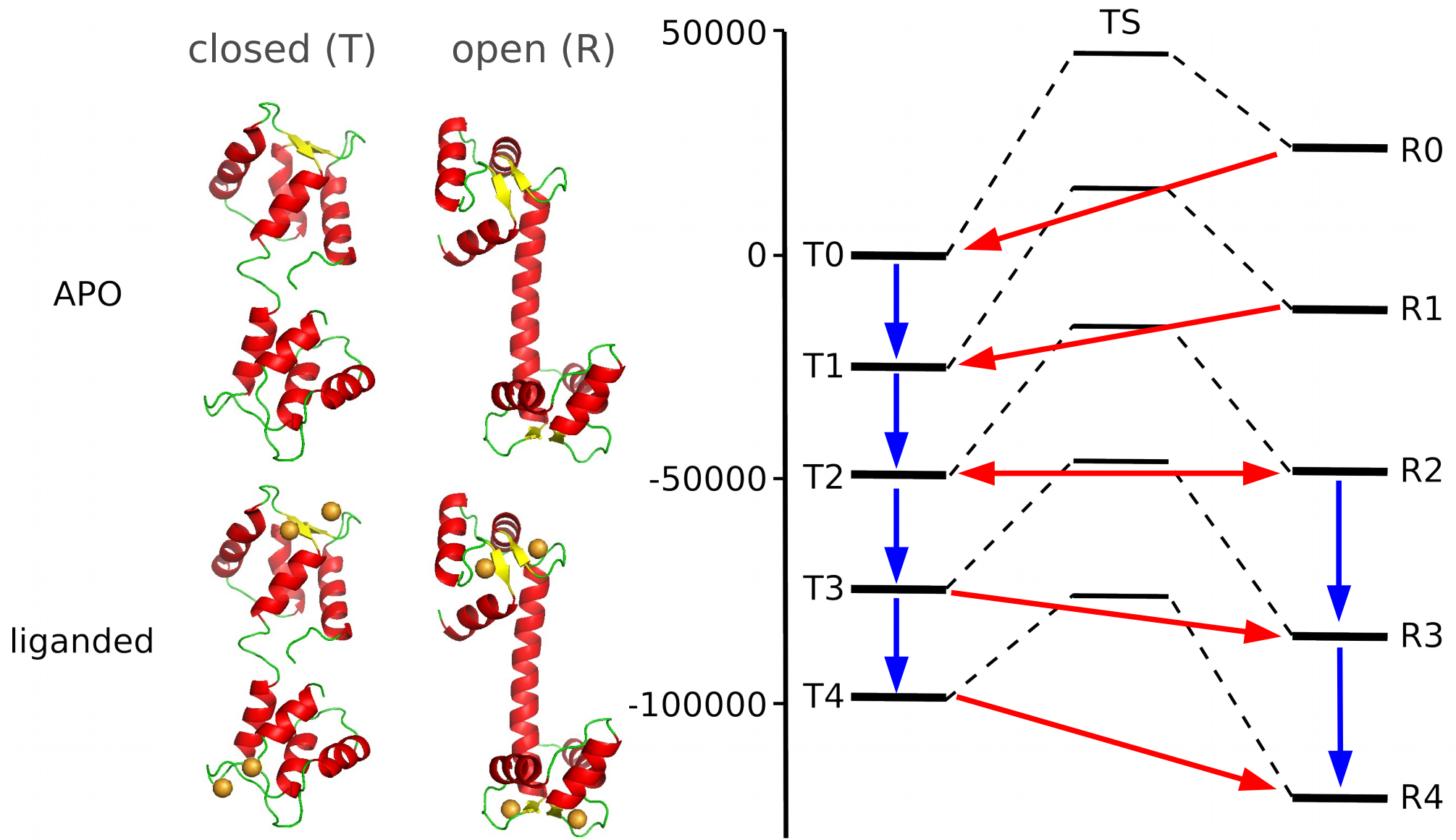
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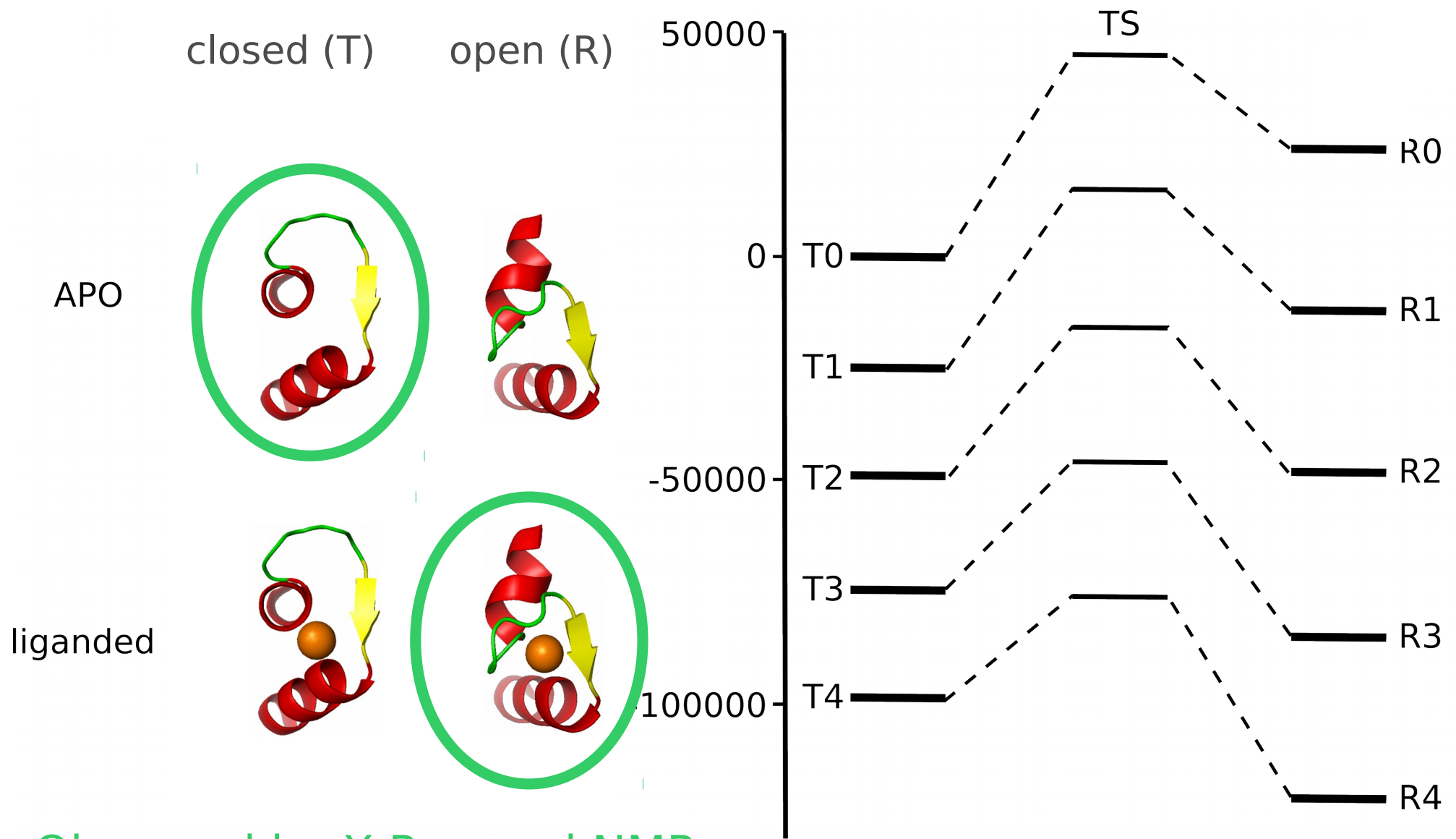
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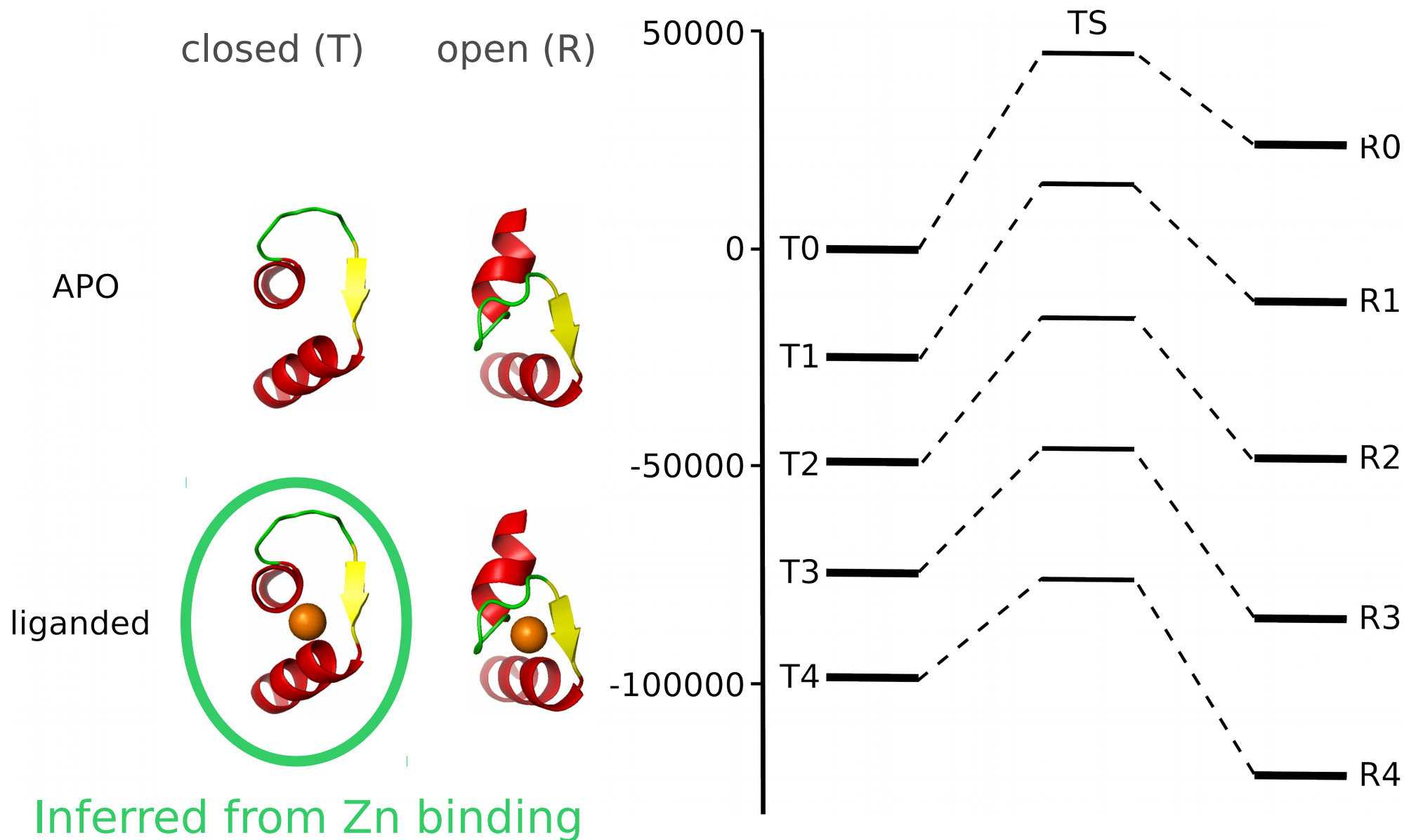


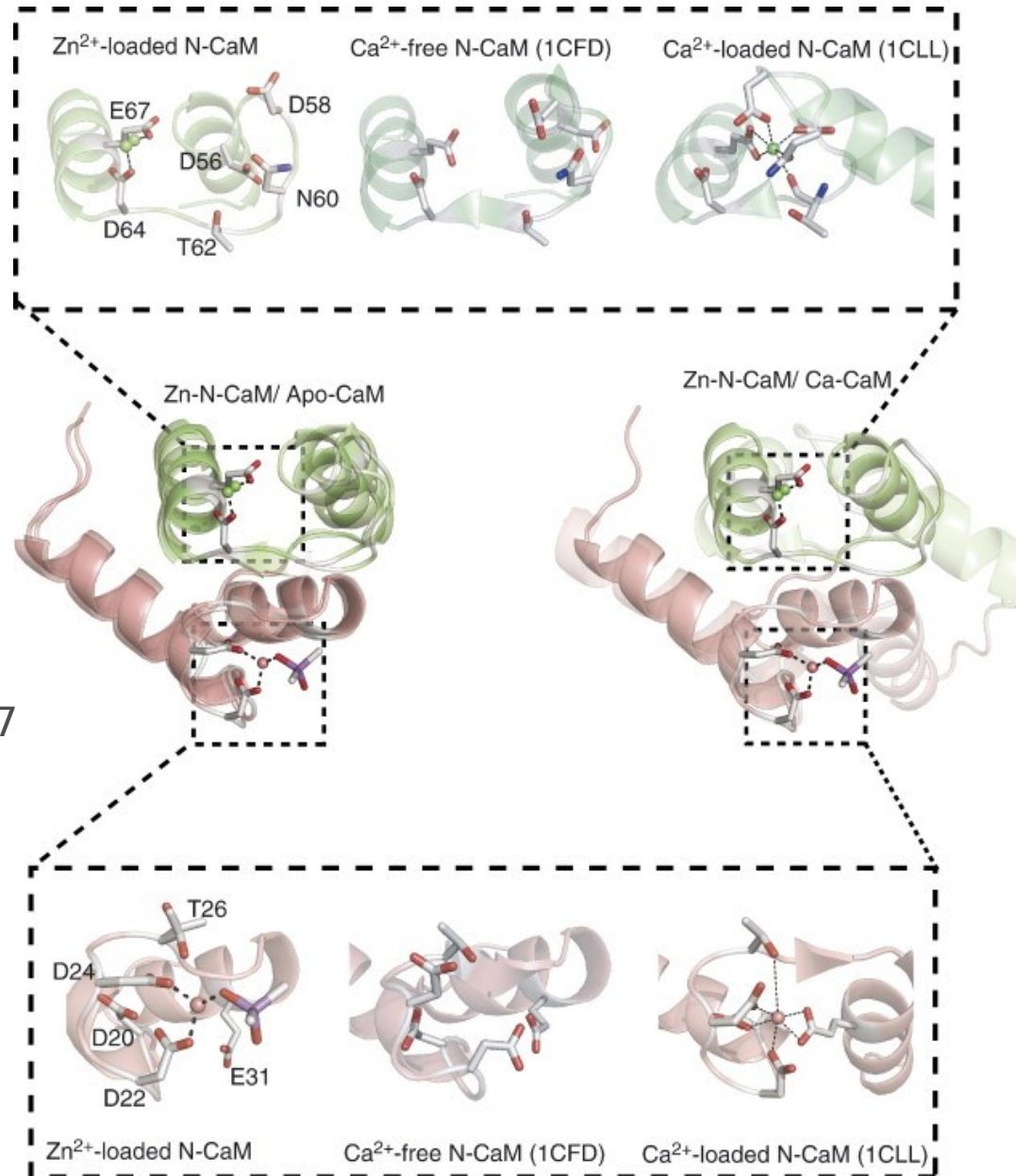
Observation Vs. Prediction



Observed by X-Ray and NMR

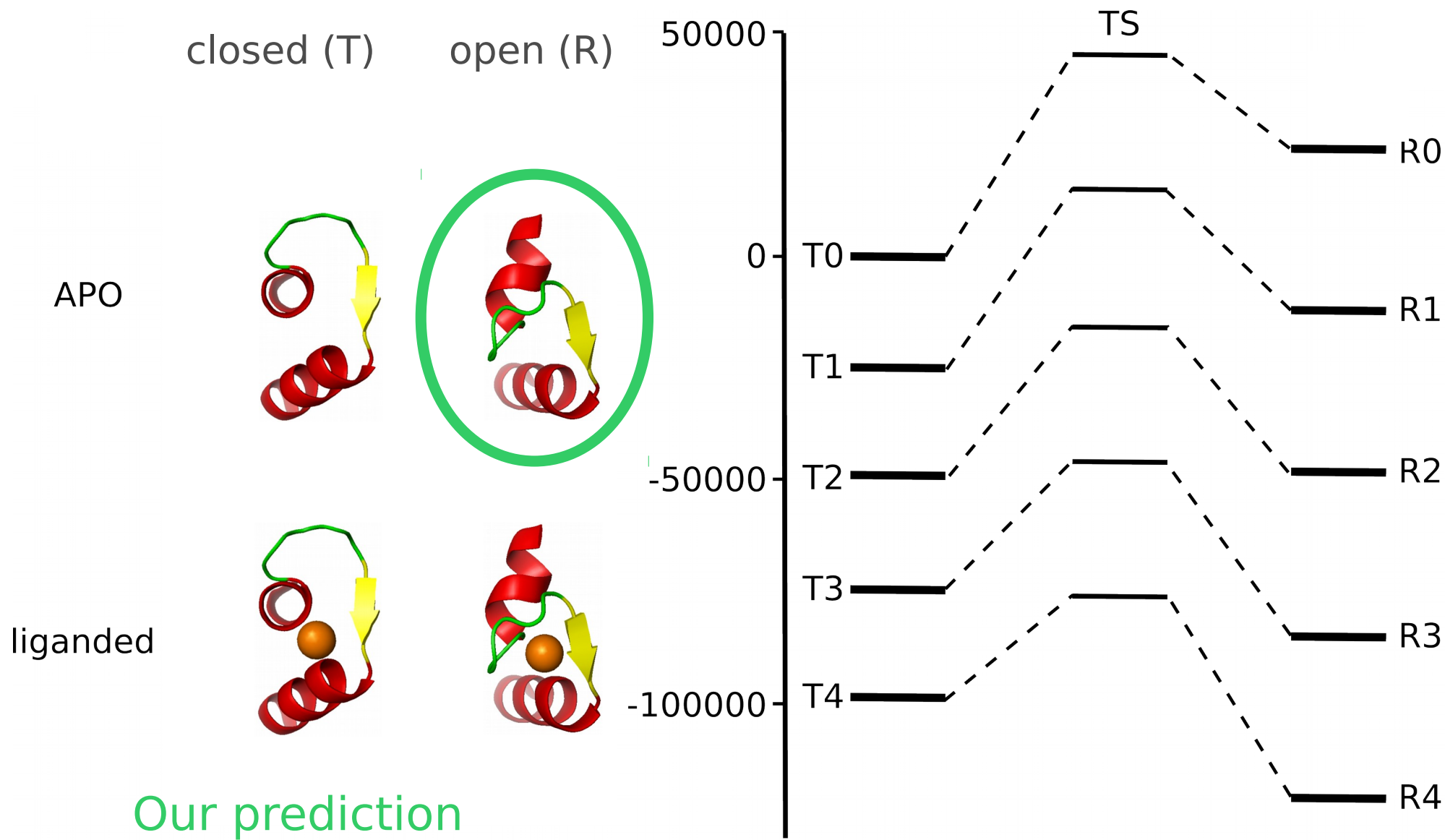
Observation Vs. Prediction





Warren *et al.* (2007).
J Mol Biol 374: 517-527

Observation Vs. Prediction



Parameterisation using accurate measurements

- Ca^{2+} binding in presence of targets: none, skMLCK, PhK5, CaATPase
- Ca^{2+} dissociation constants for complete calmodulin and N and C term mutants

1 in 20000 active w/o Ca^{2+}

$$L=20670$$

$$C=3.96 \cdot 10^{-3}$$

Affinity of Ca^{2+} for “open state” 250 times higher than for “closed state”

$$K_A^R = 8.32 \cdot 10^{-6}$$

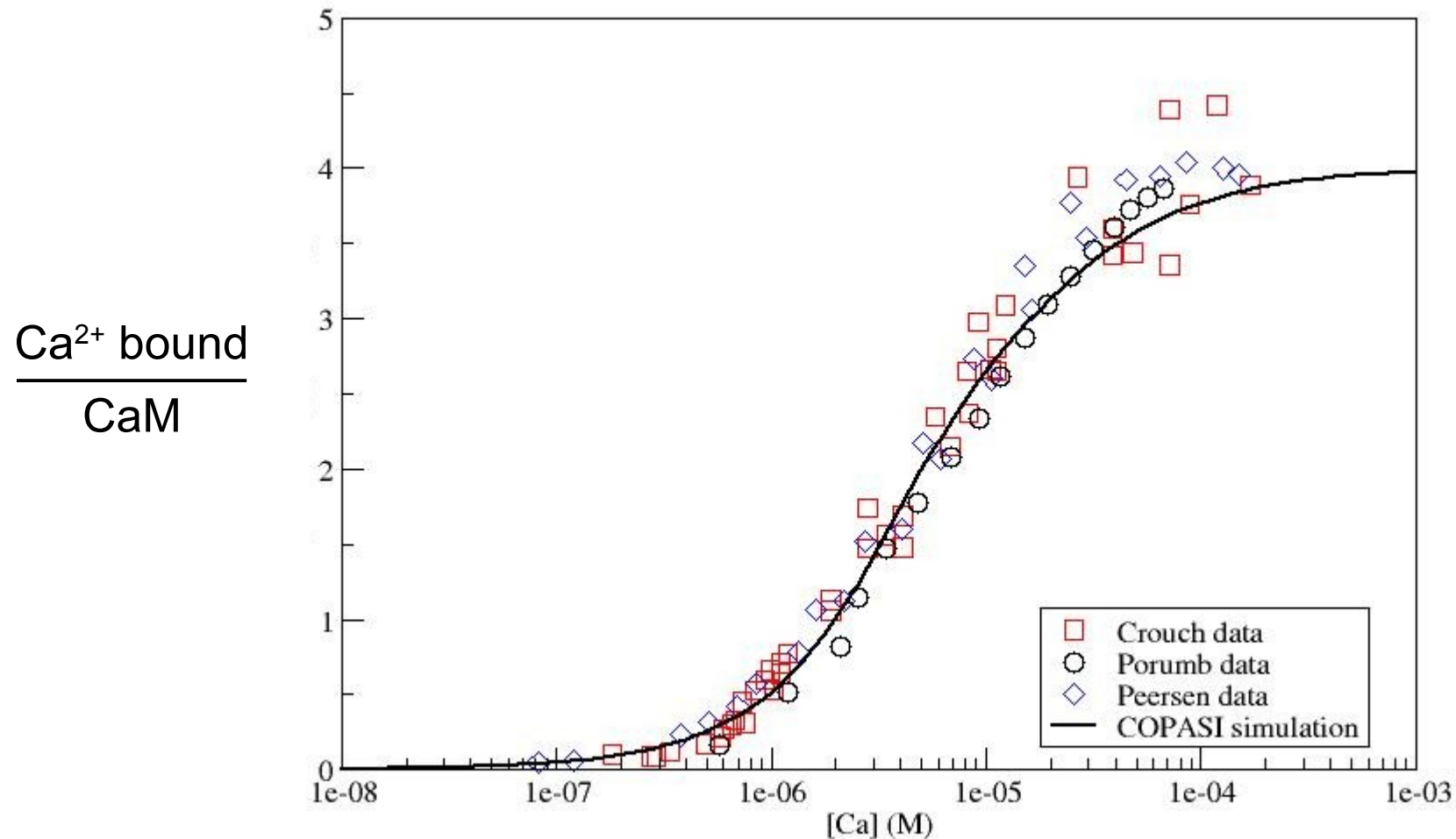
$$K_B^R = 1.66 \cdot 10^{-8}$$

$$K_C^R = 1.74 \cdot 10^{-5}$$

$$K_D^R = 1.45 \cdot 10^{-8}$$

2 high, 2 low, as expected

Comparison with experiments (binding function)



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

Porumb et al (1994) *Anal Biochem* 220: 227-237

Peersen et al (1997) *Prot Sci* 6: 794-807

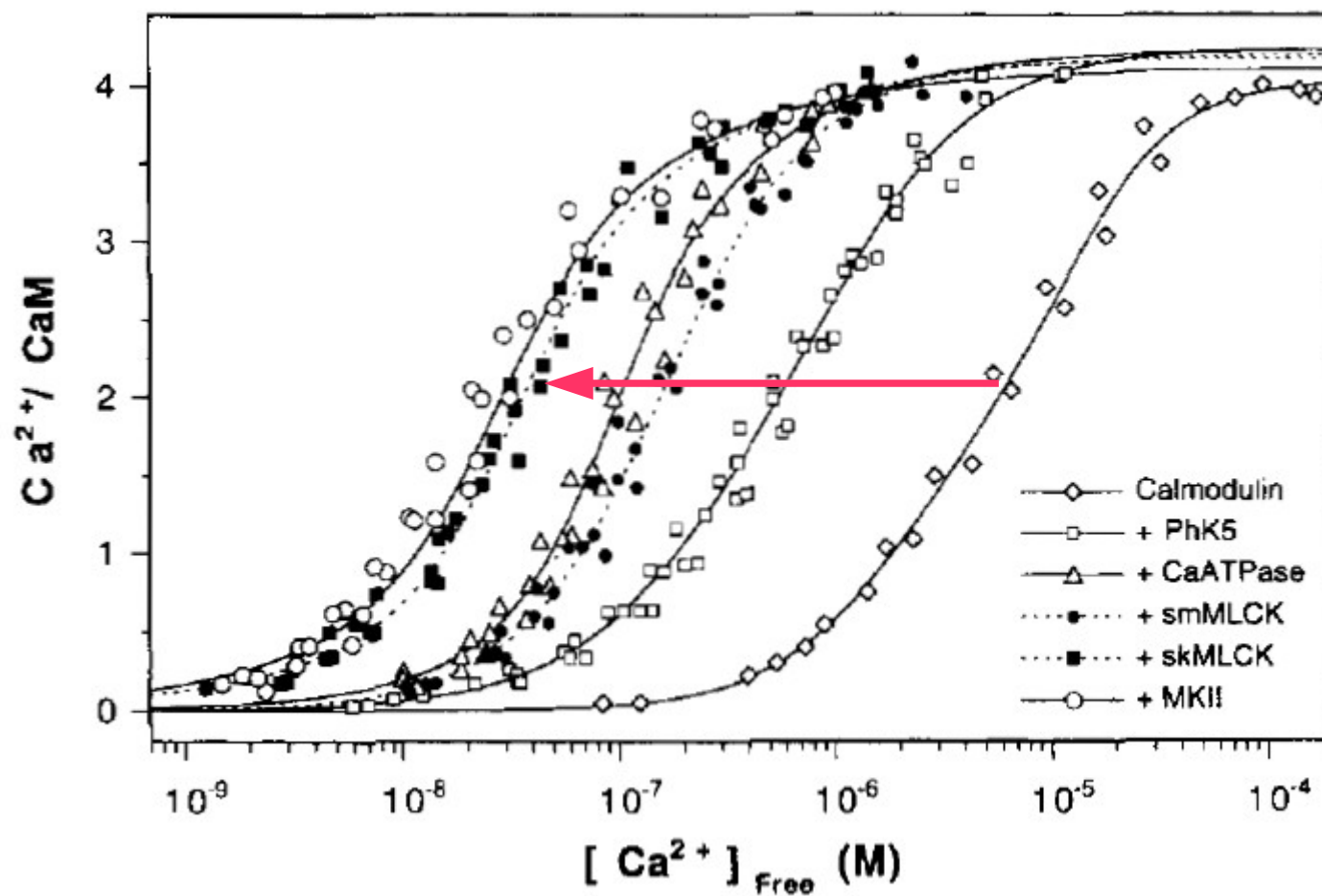
Activity of unsaturated calmodulin (state function)

- Fractional activity depends on the number of calcium ions bound

$$\frac{R_2}{T_2} = \frac{1}{L \cdot c^2}$$

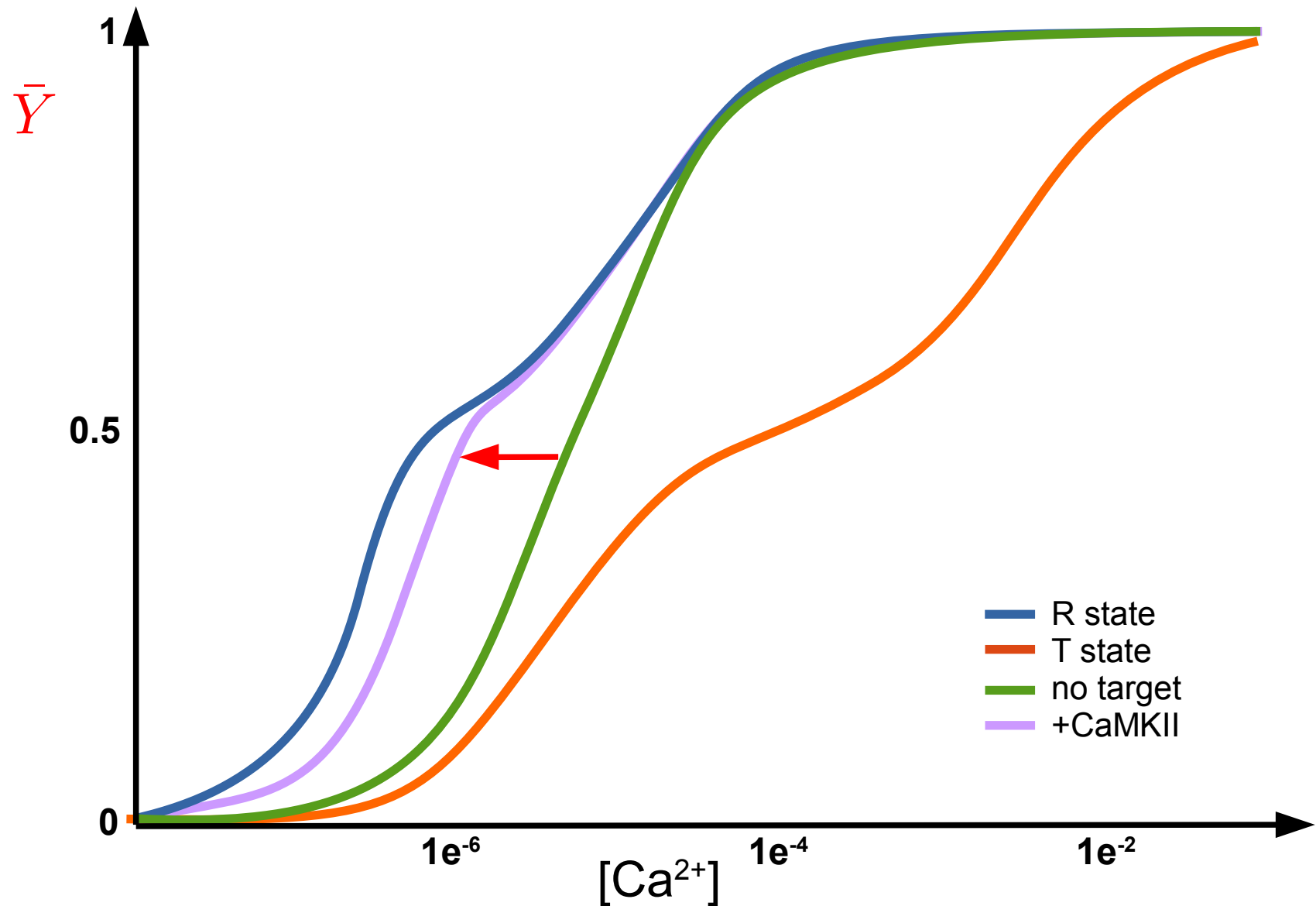
- $R_0/T_0 = 1/20000$ (1/L)
- $R_1/T_1 = 1/170$
- $R_2/T_2 = 0.69$ → half-saturation $\approx$ equi-probability
- $R_4/T_4 = 10000$

Targets as allosteric effectors

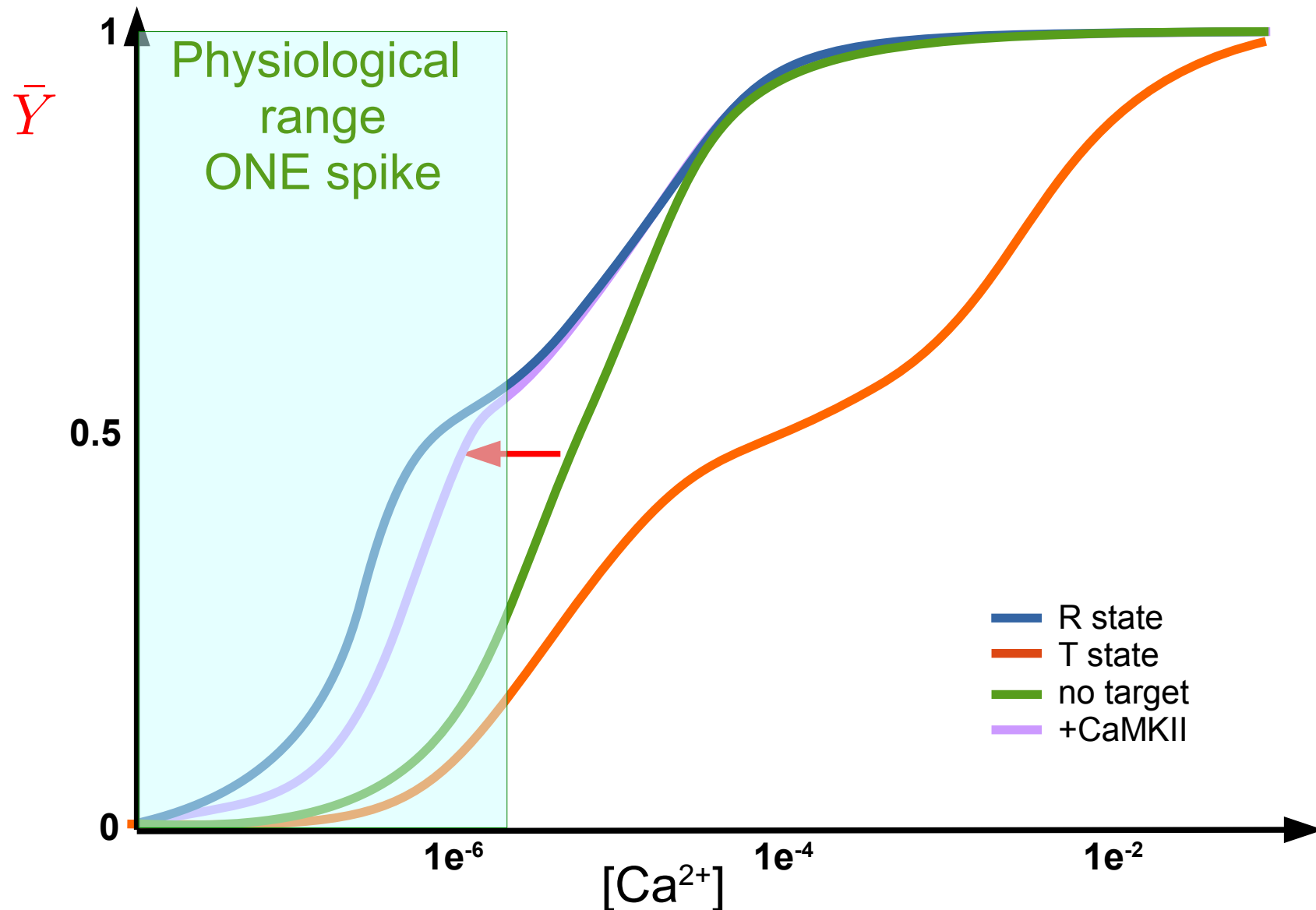


Peersen et al. (1997) *Prot Sci*, 6: 794-807

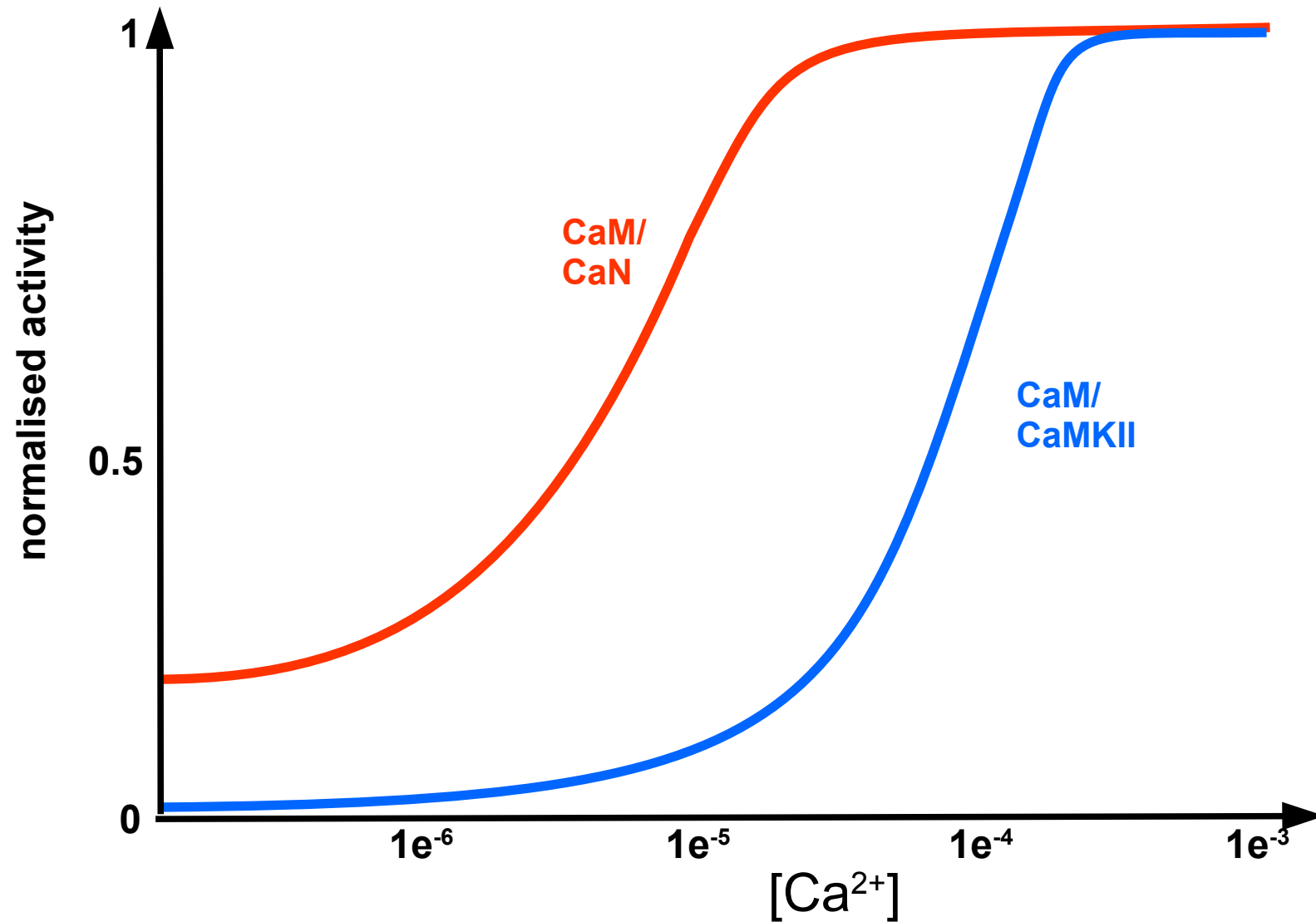
Binding to target increases the affinity for Ca^{2+}



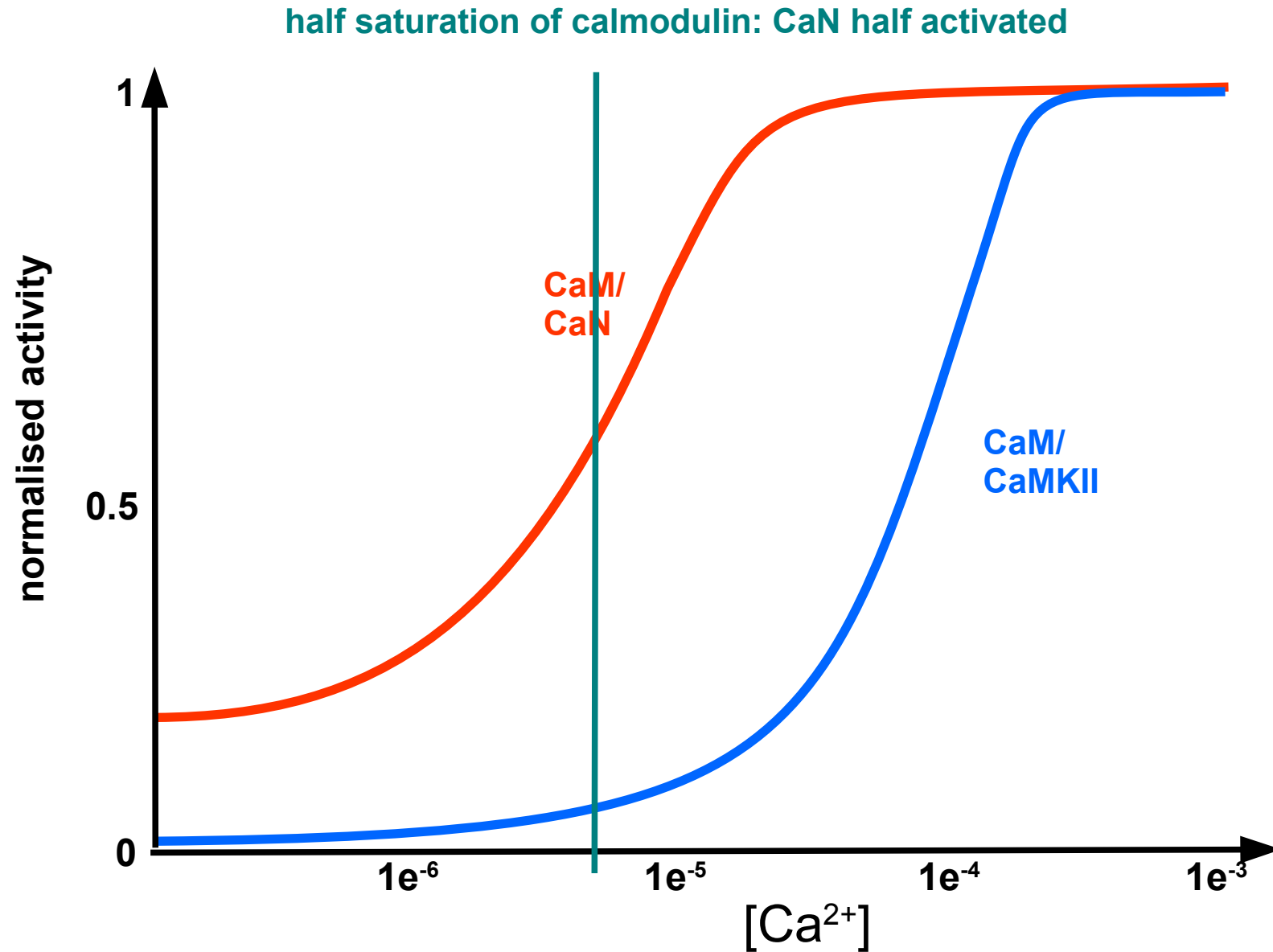
Targets stabilises Ca^{2+} binding into the physiological range



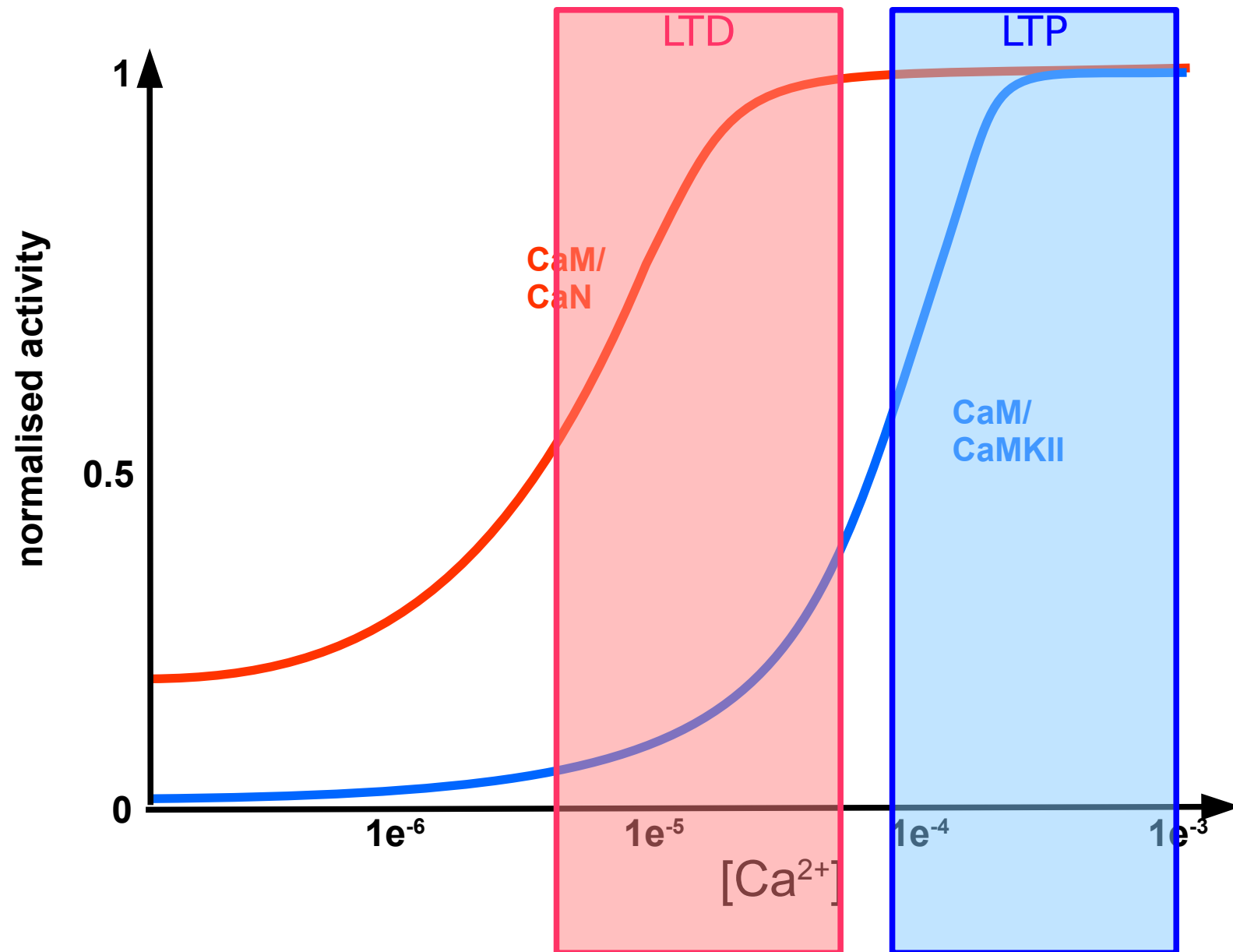
Bidirectional synaptic plasticity



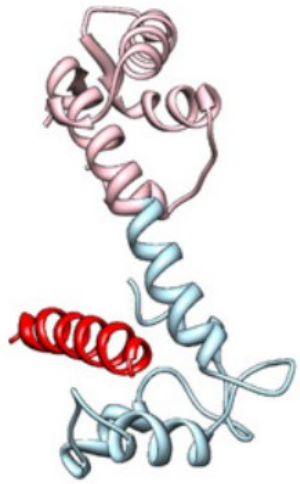
Bidirectional synaptic plasticity



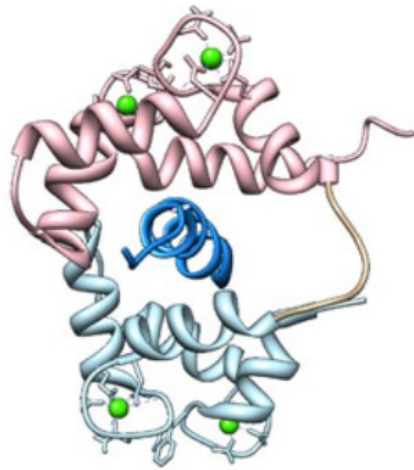
Bidirectional synaptic plasticity



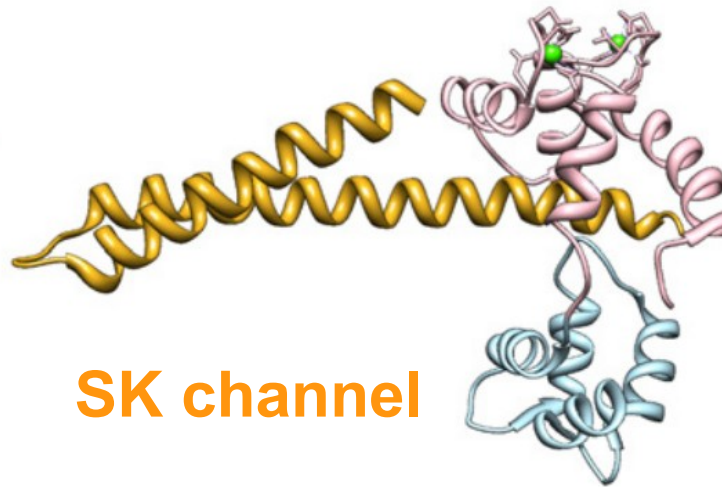
Different binding to different targets



Neurogranin

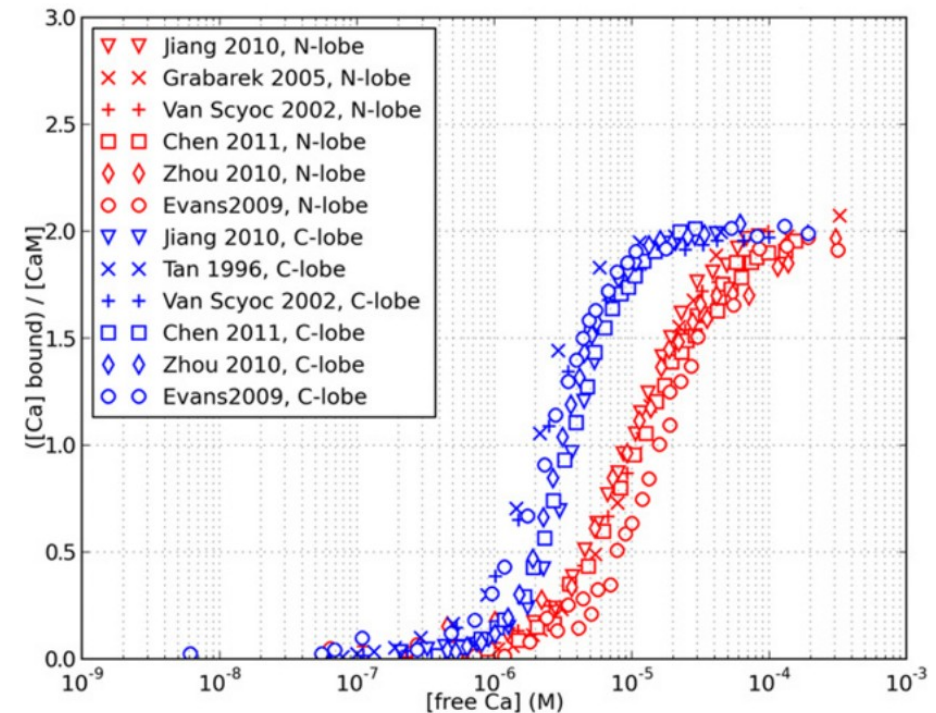


MLCK

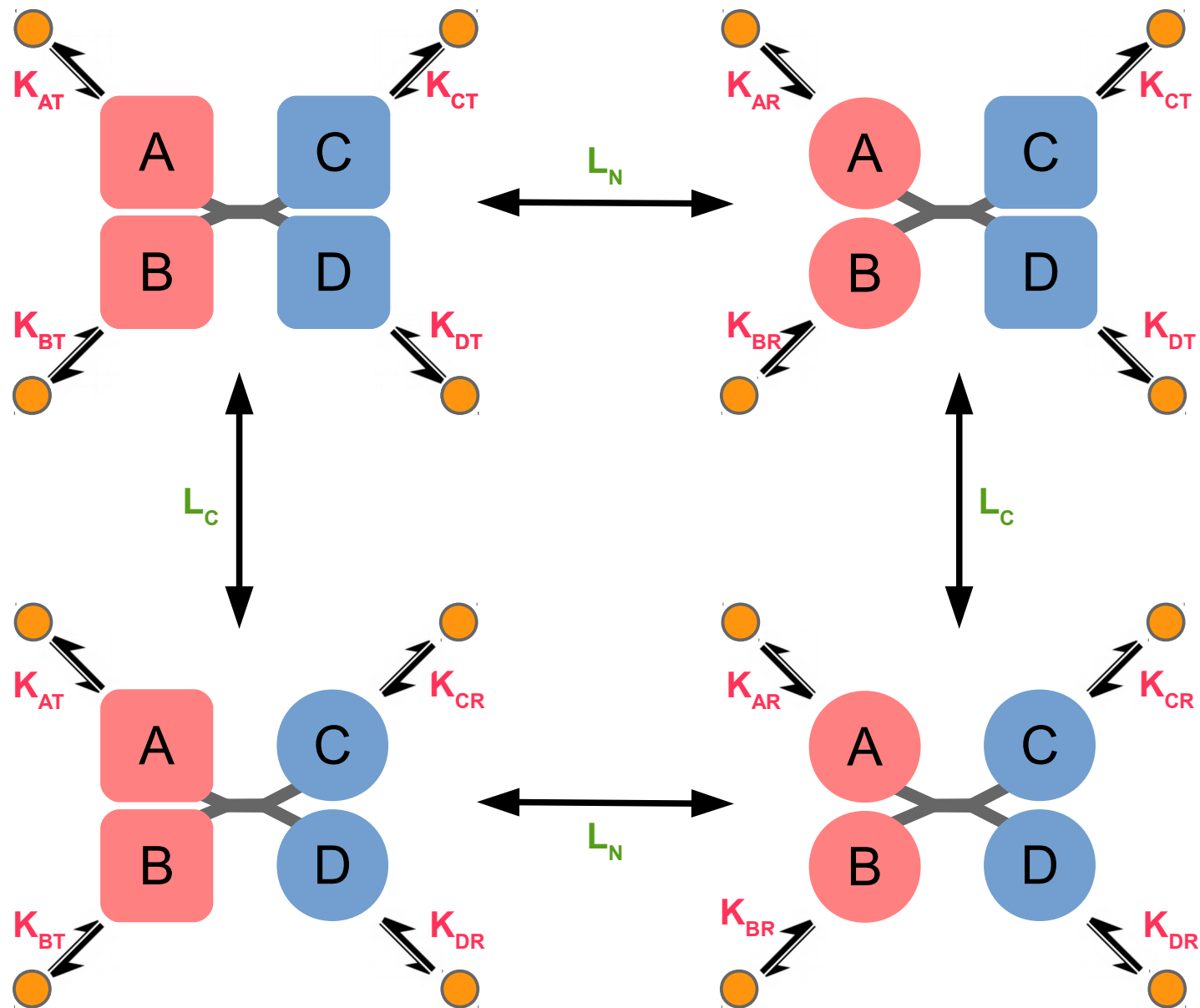


SK channel

Lai M, Brun D, Edelstein SJ, Le Novère N (2015)
PloS Comput Biol, 11(1): e1004063

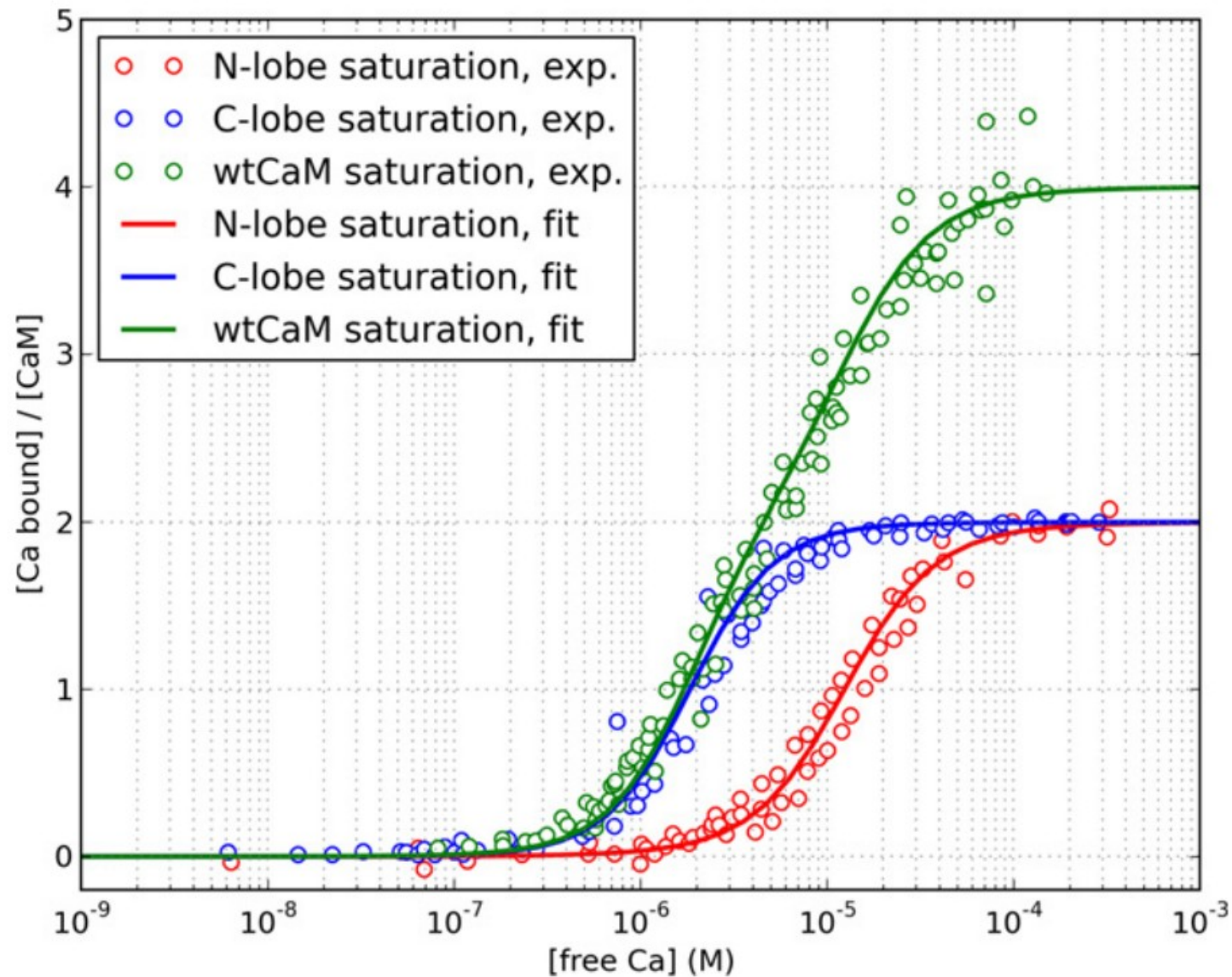


Hemiconcerted model of calmodulin



Lai M, Brun D, Edelstein SJ, Le Novère N (2015) *PLoS Comput Biol*, 10(1):e0116616

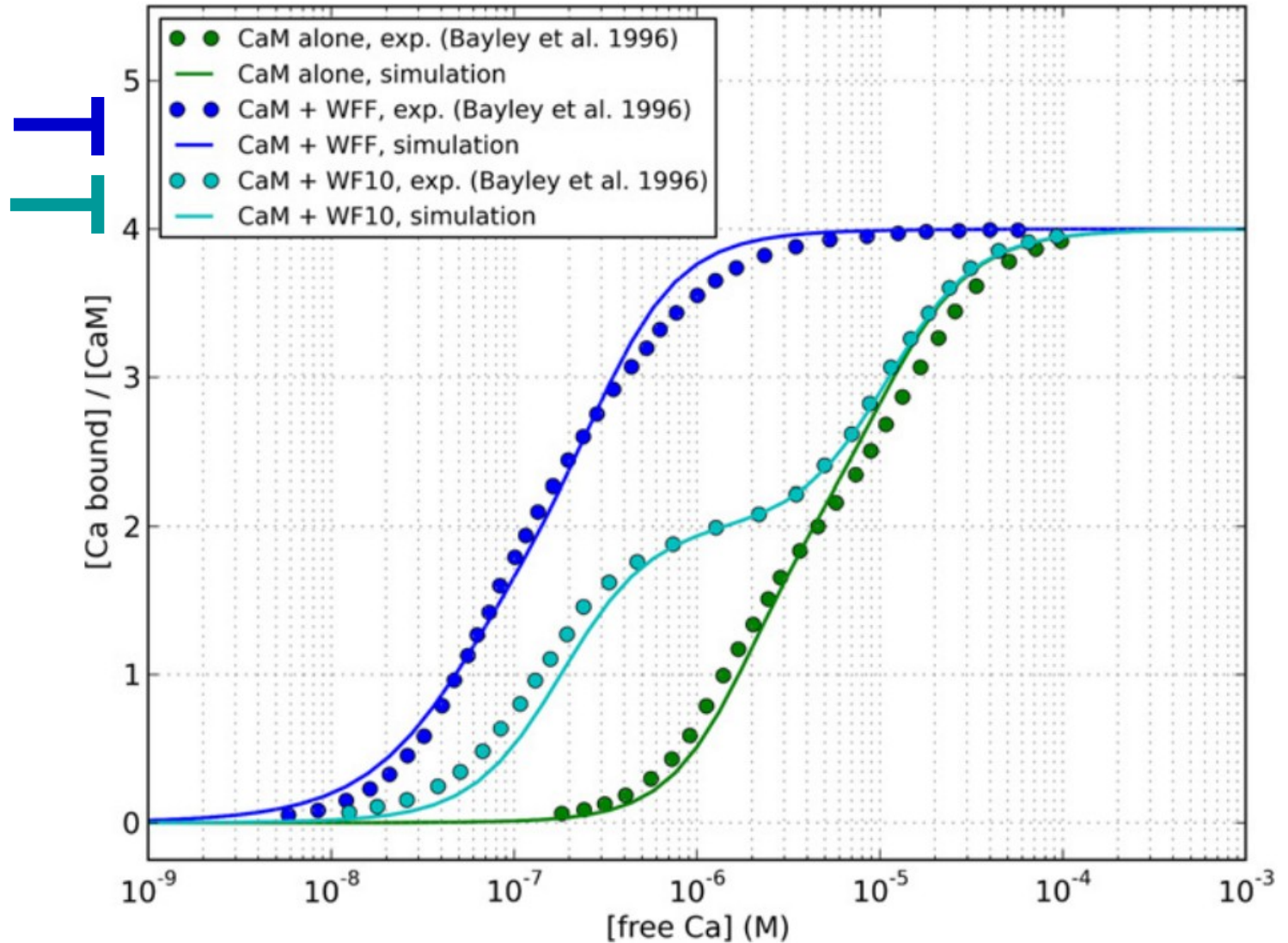
Calcium binding to lobes and whole CaM



Effect of R-stabilising targets

Stabilise R state
of both lobes

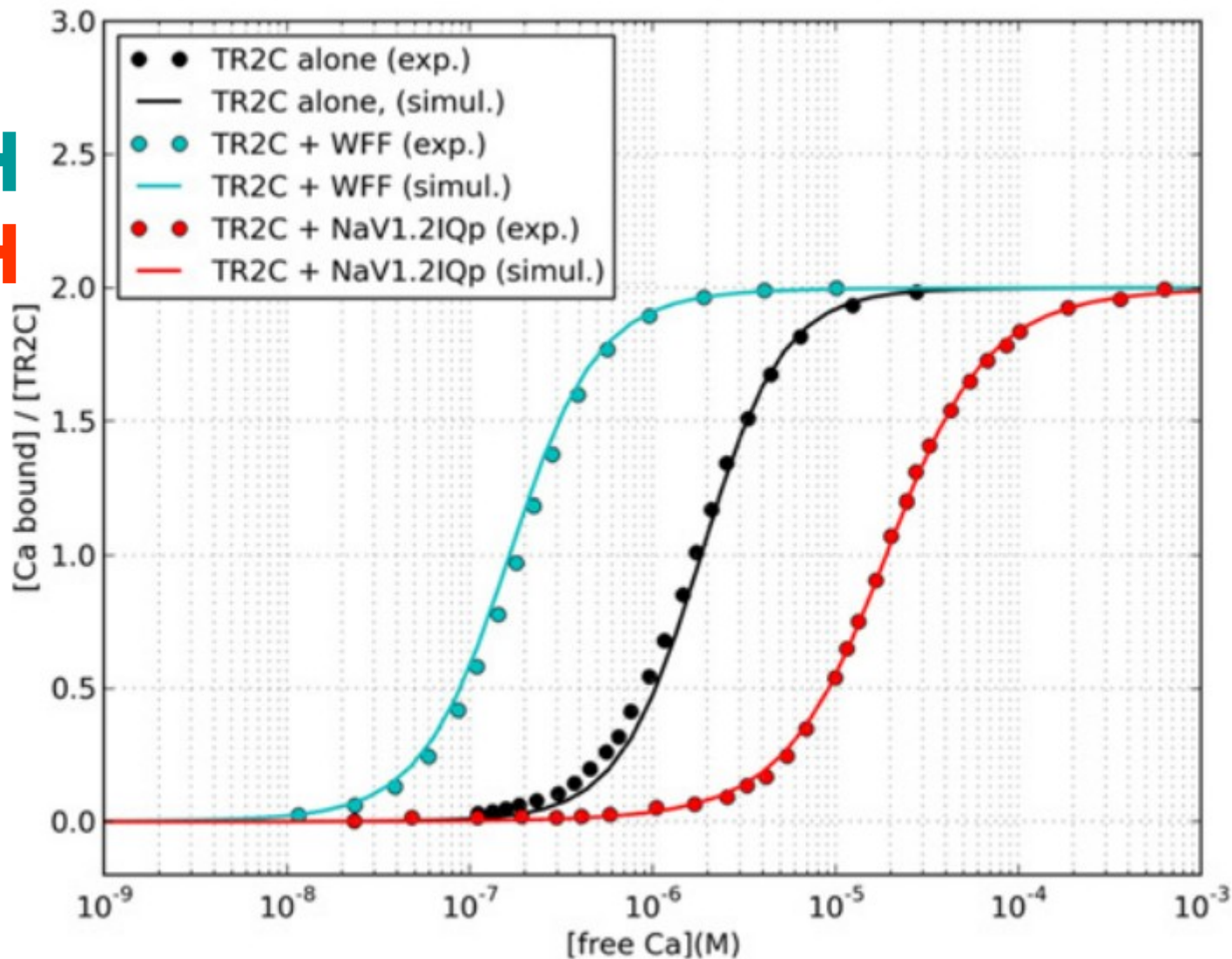
Stabilise R state
of C lobe



Effect of R and T stabilising targets

Peptide from
skMLCK $\rightarrow$ R

IQ domain from
NaV1.2 $\rightarrow$ T



Conclusions of part 1

Allosteric model of Calmodulin, with only two states for the EF hands, binding calcium with different affinities, and concerted transitions of the EF hands. Parameters estimated from experimental data-sets.

Model fits independent experimental datasets.

Affinity for calcium increases upon binding of the target.

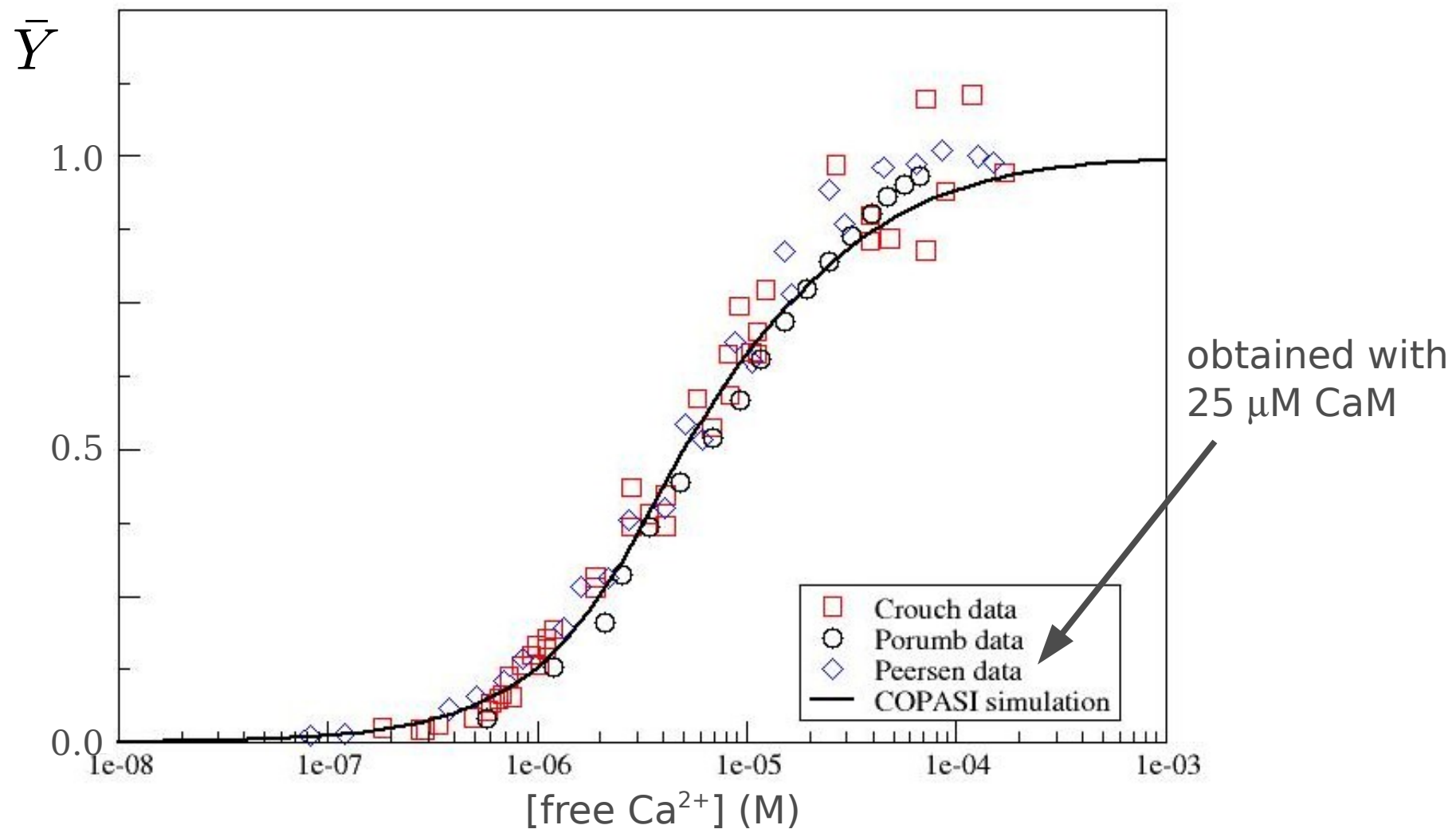
CaM significantly “active” with less than 4 Ca^{2+} bound.

CaM bind its targets with less than 4 Ca^{2+} bounds.

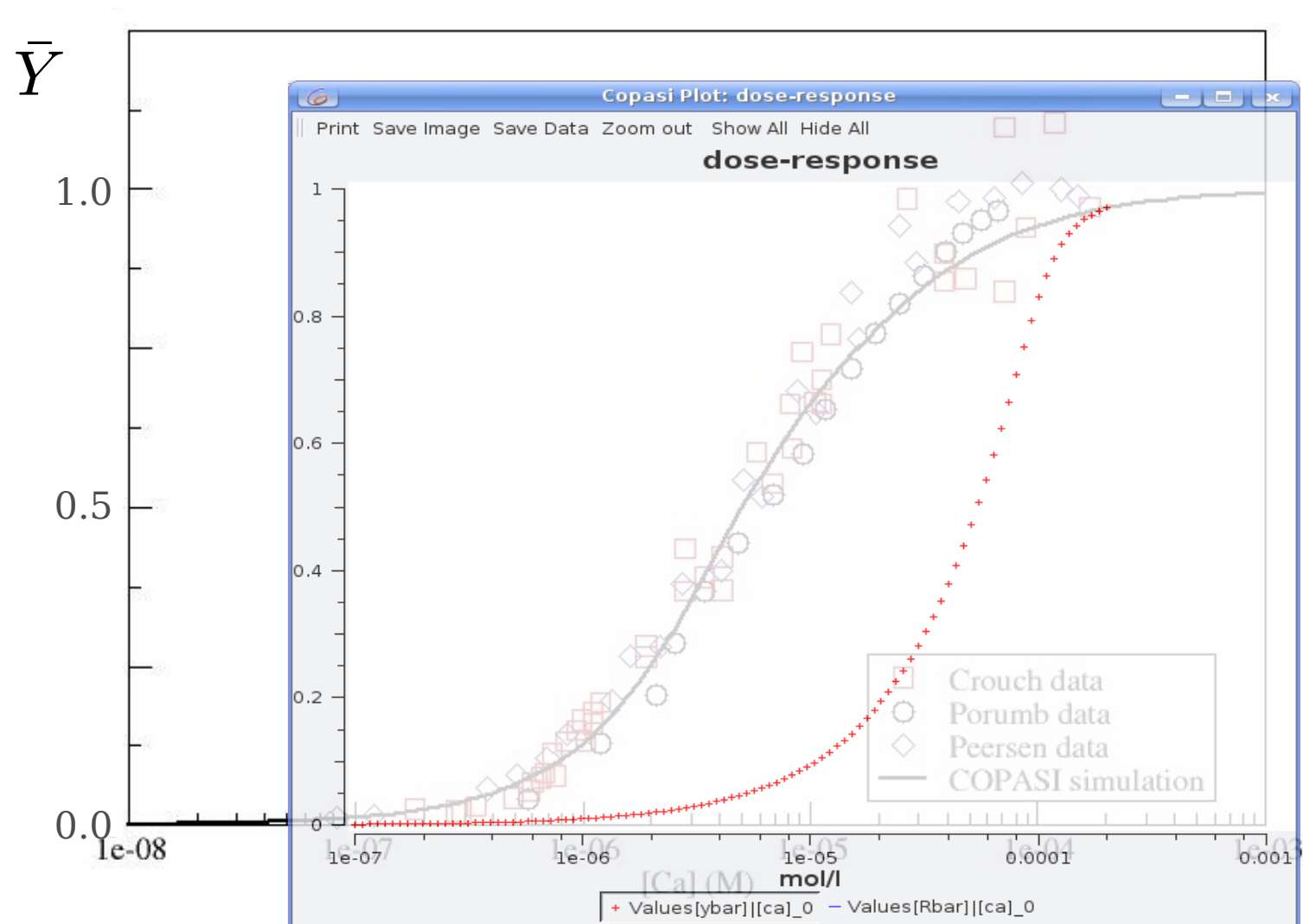
The model displays an activation of the sole **CaN** at low concentration of calcium, while high concentrations activate both **CaN** and **CaMKII**.

Digression: on ligand depletion

Allosteric model of Calmodulin function

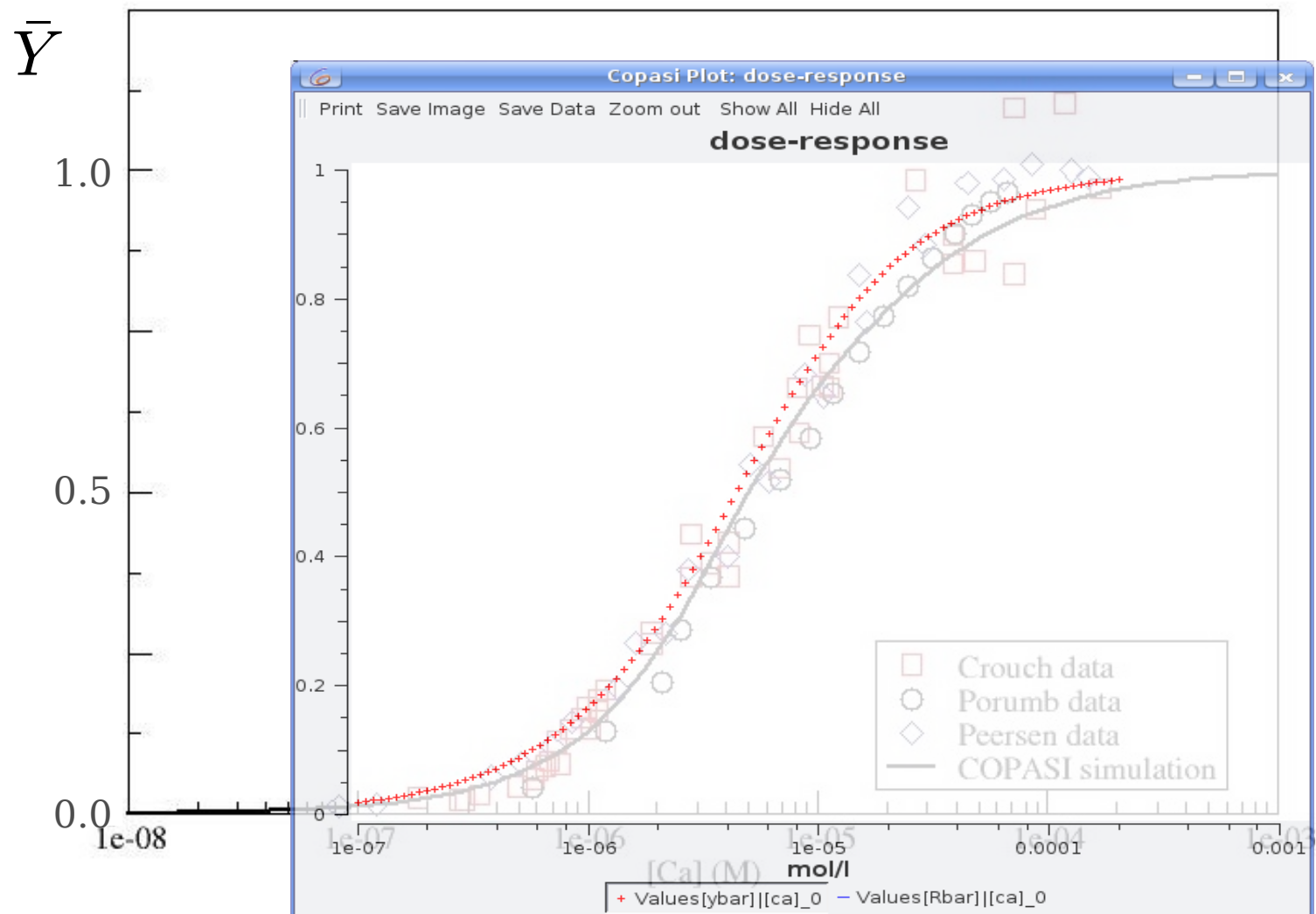


Calcium dose-response on 25 μM Calmodulin



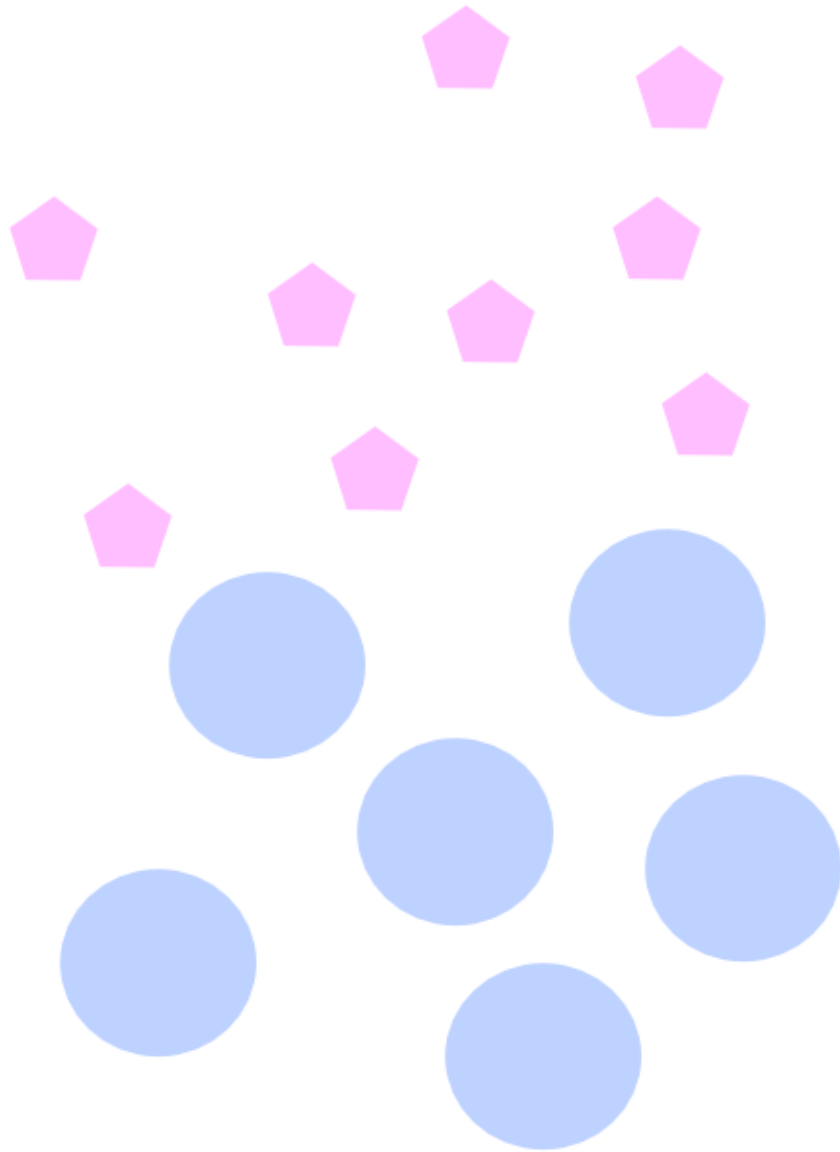
Numerical simulation with COPASI (<http://www.copasi.org>)

Calcium dose-response on 0.1 μM Calmodulin

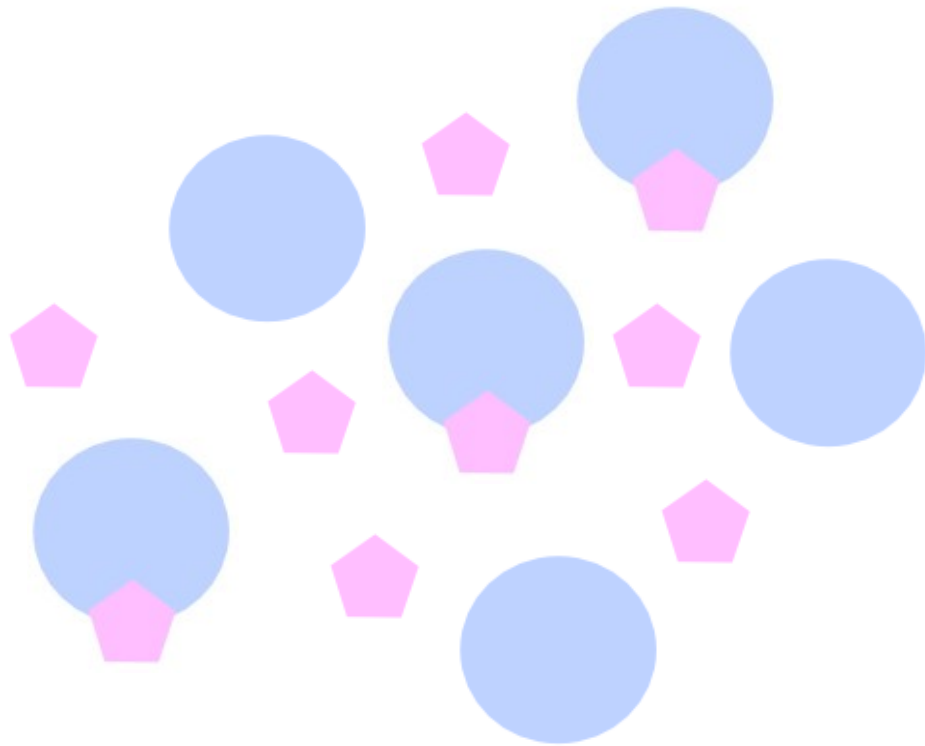


Edelstein S.J., Stefan M.I, Le Novère N. Ligand depletion in vivo modulates the dynamic range and cooperativity of signal transduction. *PLoS One* (2010), 5(1): e8449

What is ligand depletion?

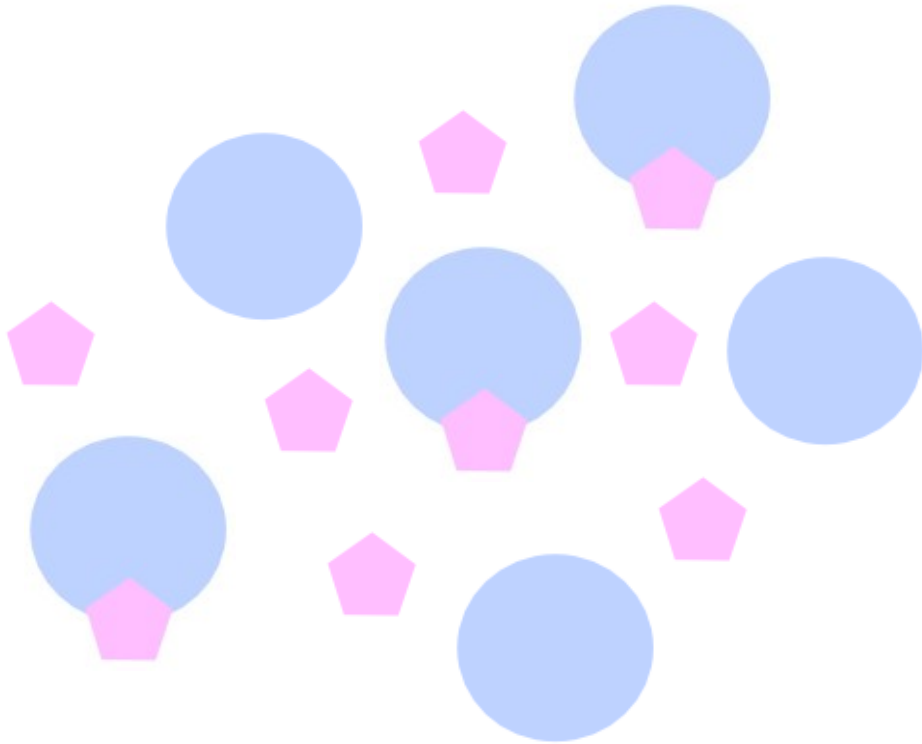
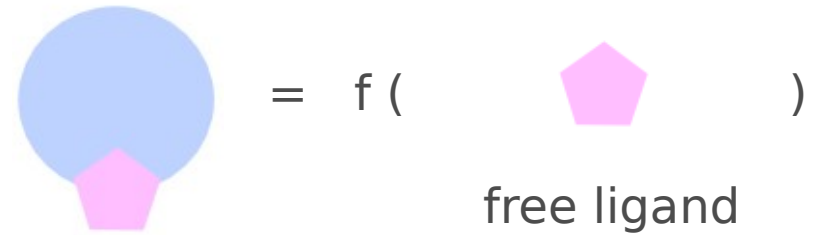


What is ligand depletion?



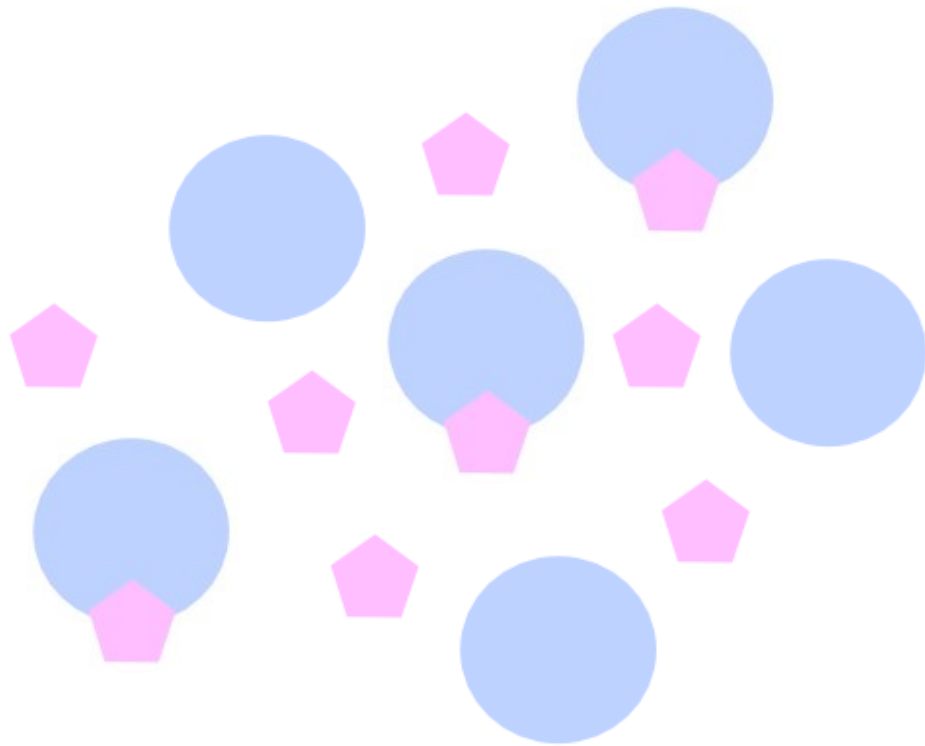
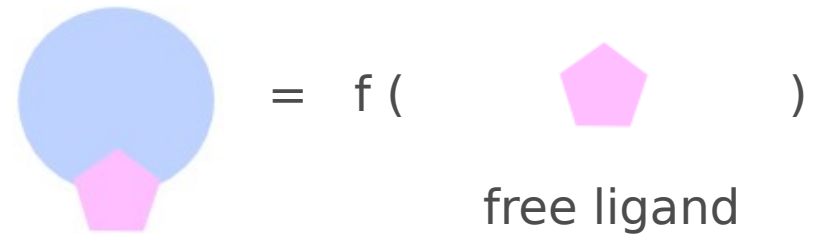
What is ligand depletion?

Chemistry (mass-action law)

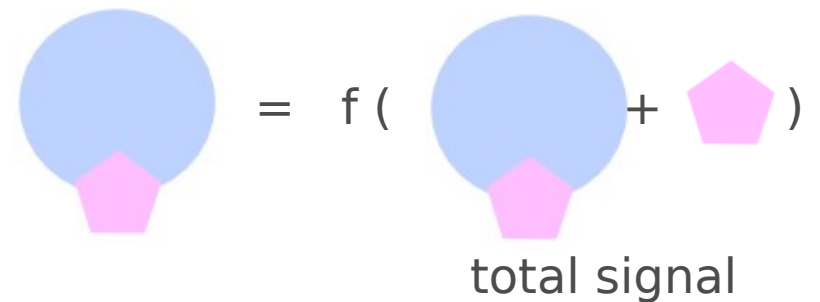


What is ligand depletion?

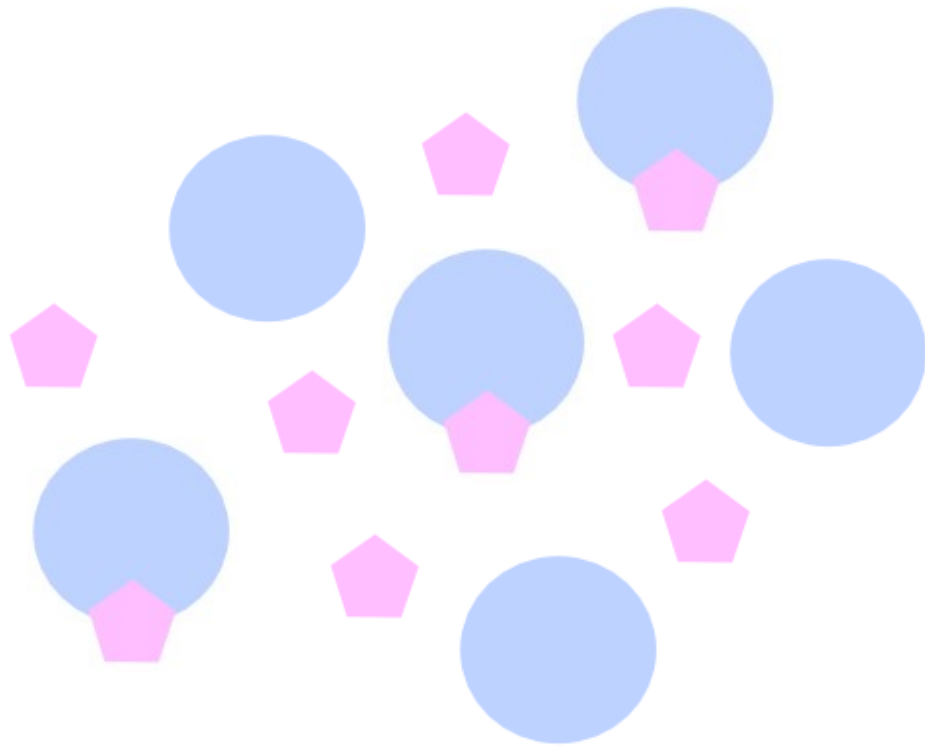
Chemistry (mass-action law)



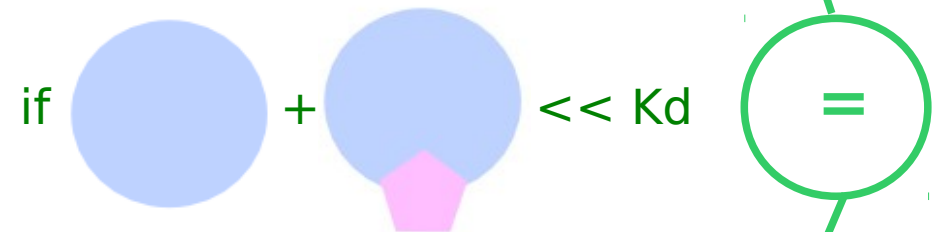
Cellular signalling



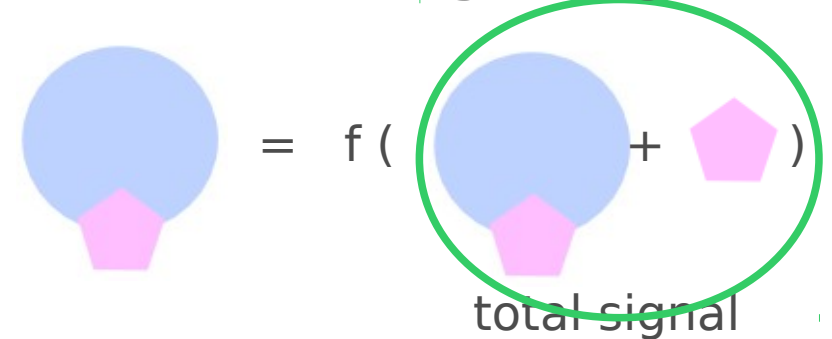
What is ligand depletion?



Chemistry (mass-action law)

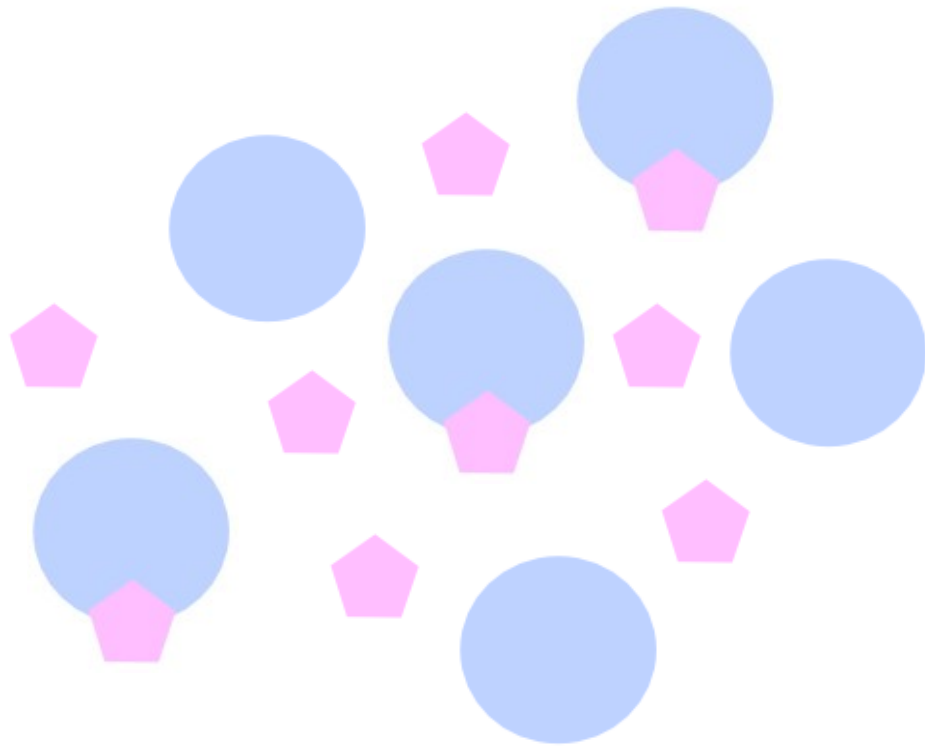


Cellular signalling

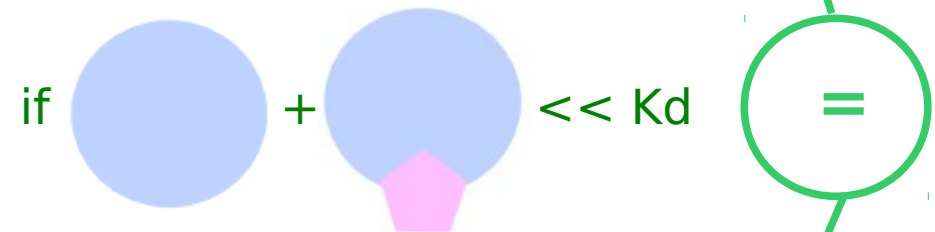
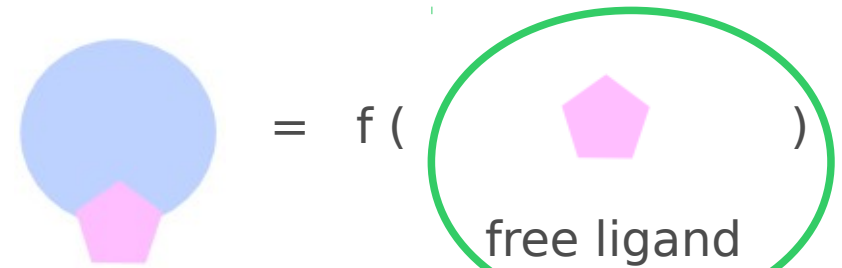


What is ligand depletion?

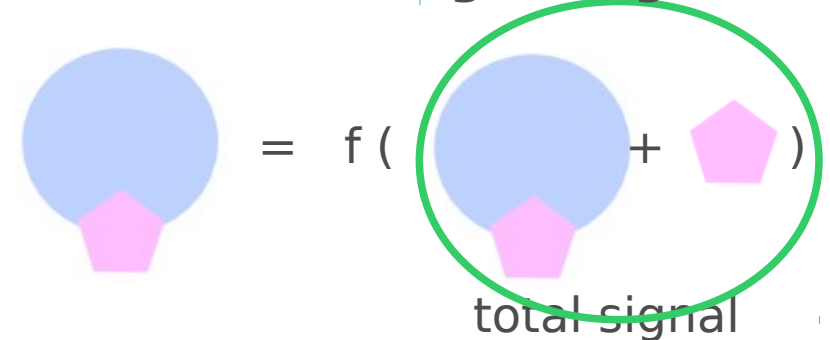
This is generally not the case in signalling:
Concentrations of sensors are in micromolar range, as are the dissociation constants.



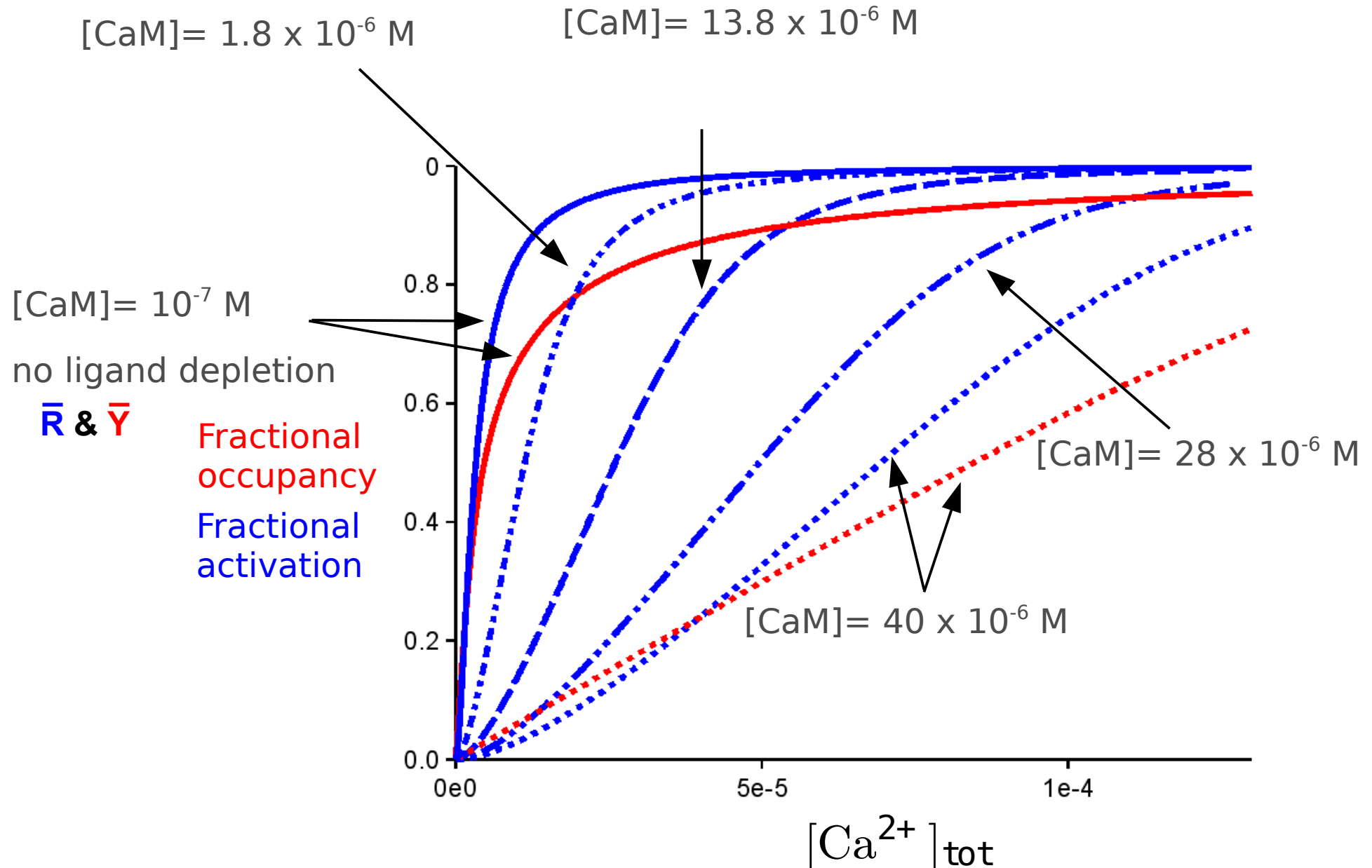
Chemistry (mass-action law)



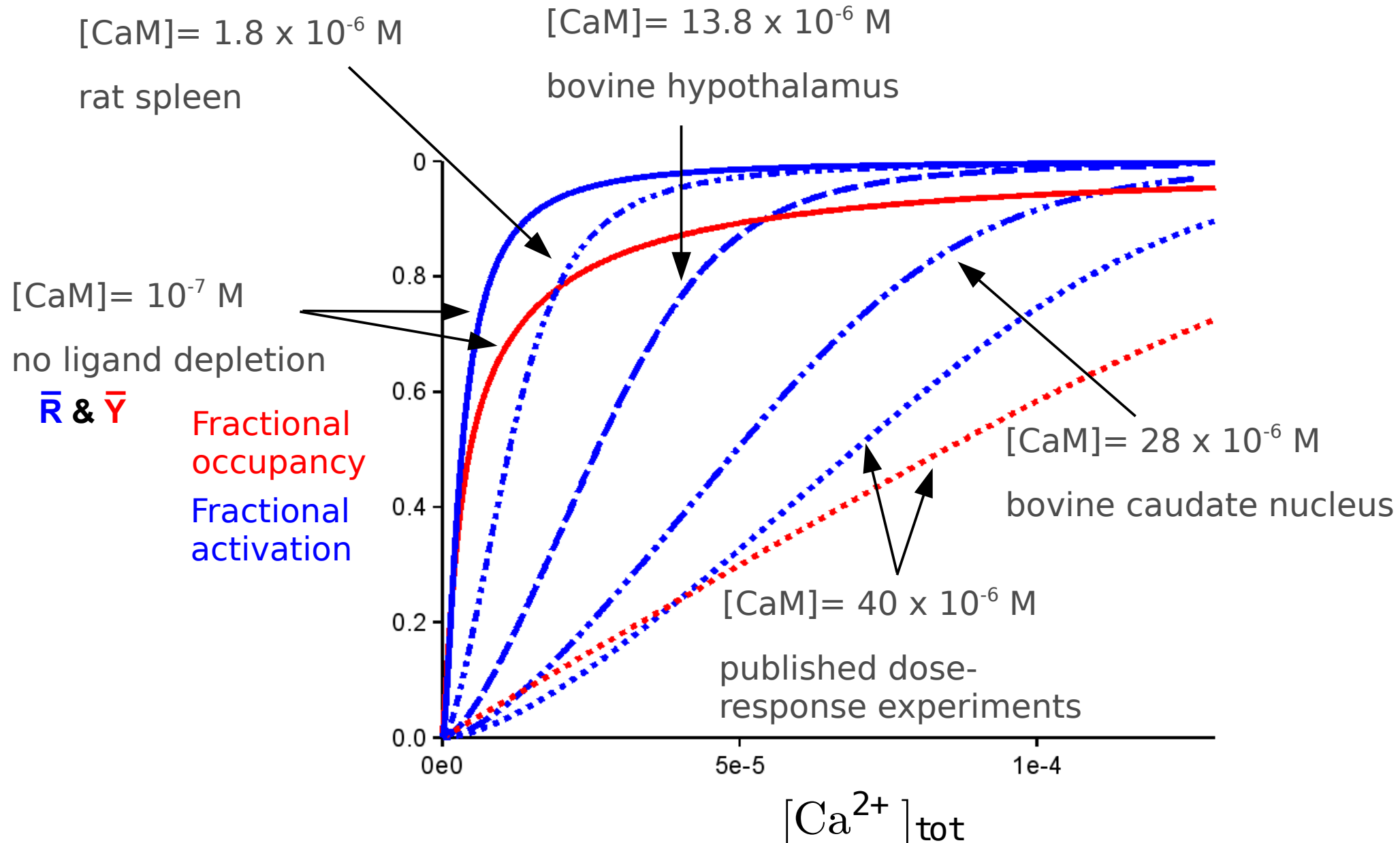
Cellular signalling



Dose-response depends on Calmodulin concentration



Dose-response depends on Calmodulin concentration



Ligand-depletion modifies sensitivity

$[\text{CaM}] = 28 \times 10^{-6} \text{ M}$

bovine caudate nucleus

$\sim 5 \mu\text{M}$ to $120 \mu\text{M}$

$[\text{CaM}] = 1.8 \times 10^{-6} \text{ M}$

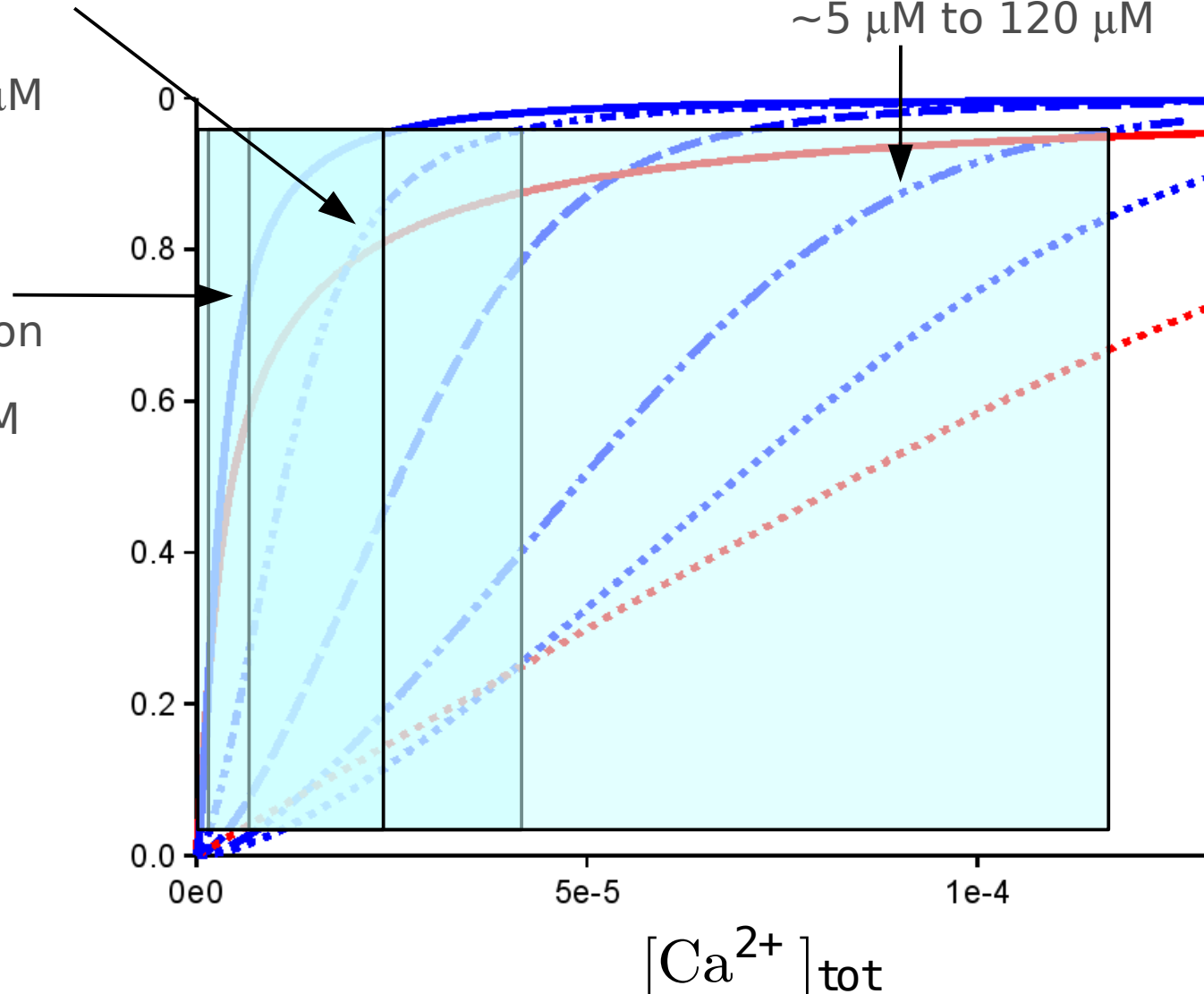
rat spleen

$\sim 1 \mu\text{M}$ to $45 \mu\text{M}$

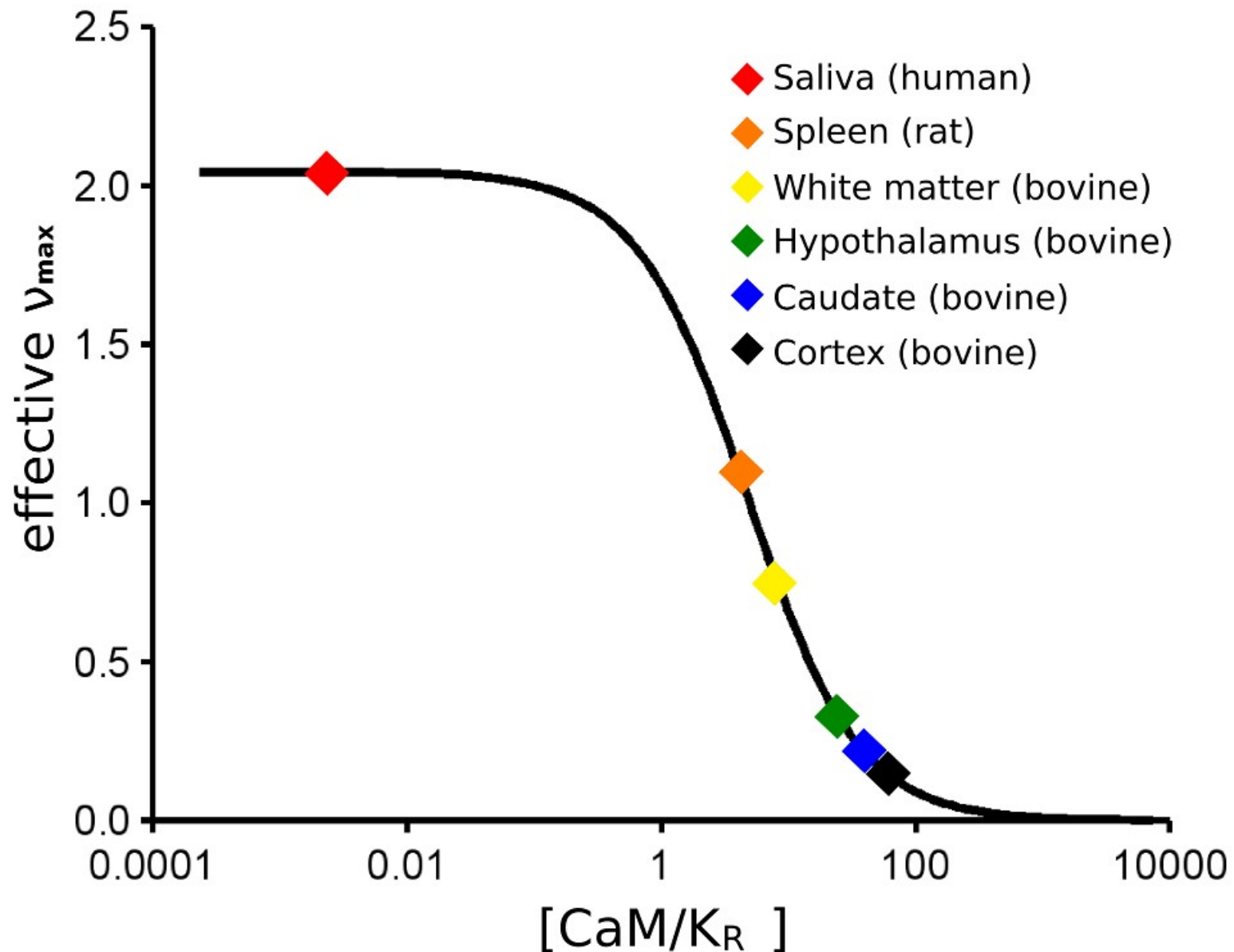
$[\text{CaM}] = 10^{-7} \text{ M}$

no ligand depletion

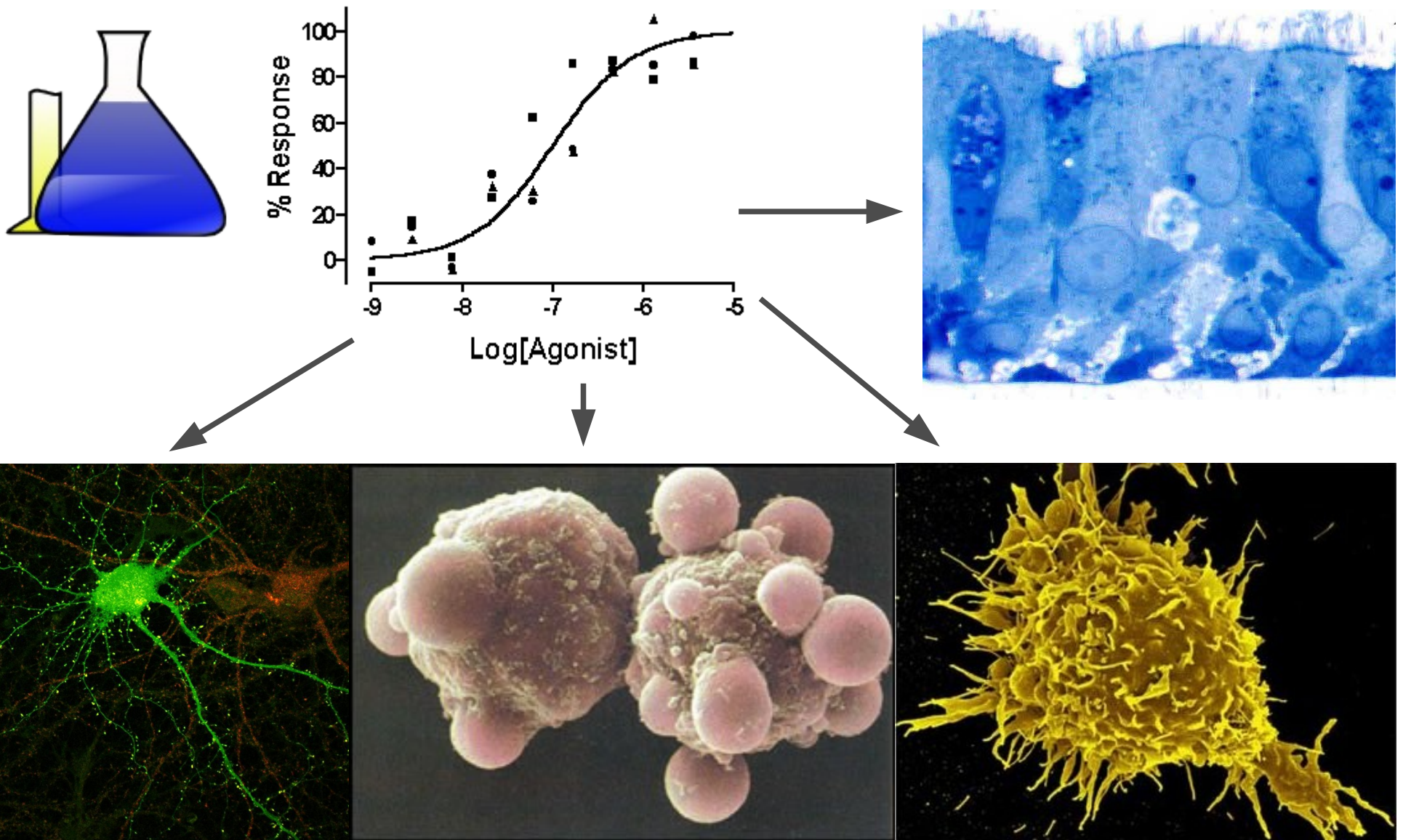
$\sim 100 \text{ nM}$ to $25 \mu\text{M}$



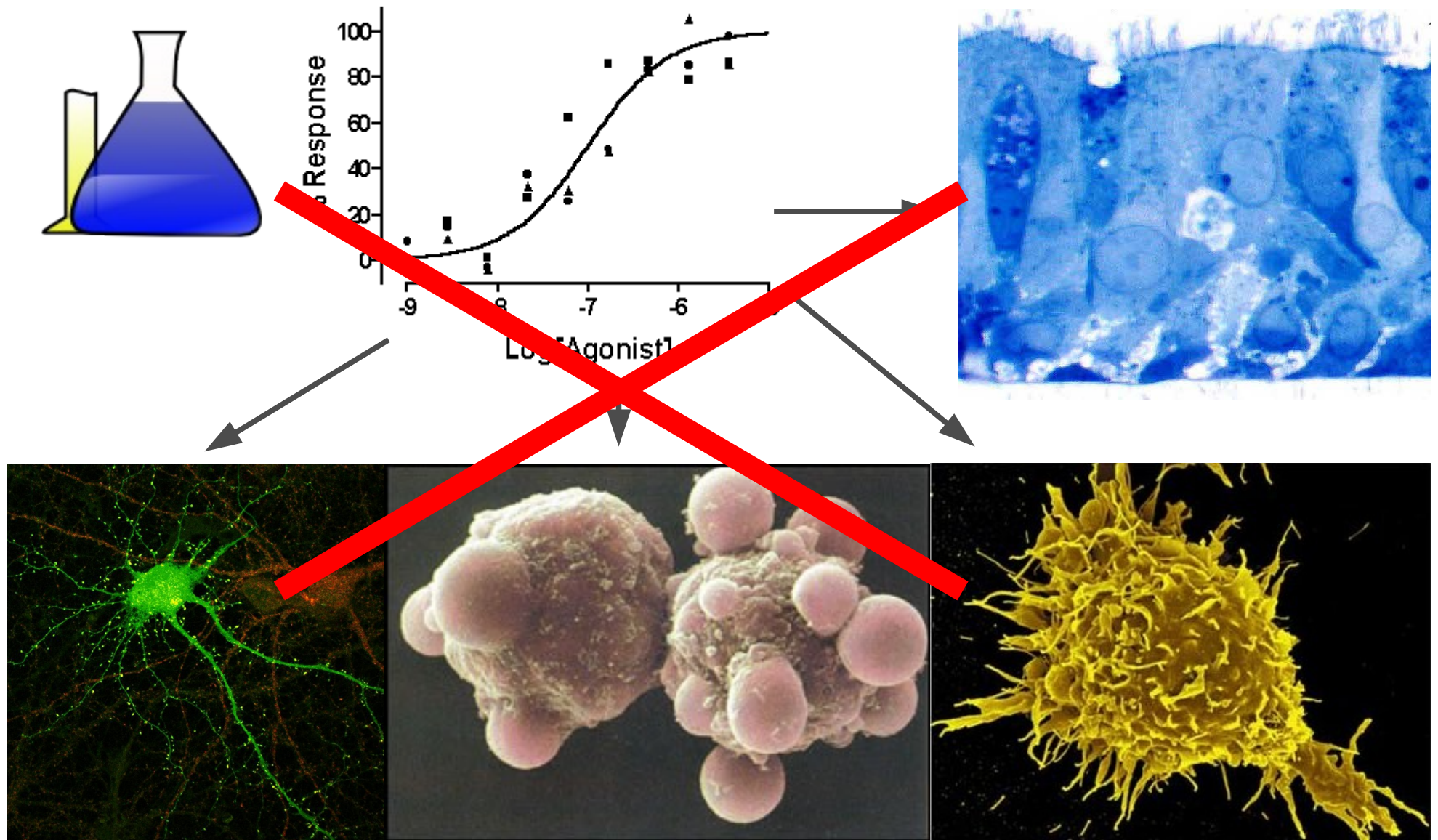
Ligand-depletion decreases effective cooperativity



How general is a dose-response?



A “dose-response” cannot be reused directly!

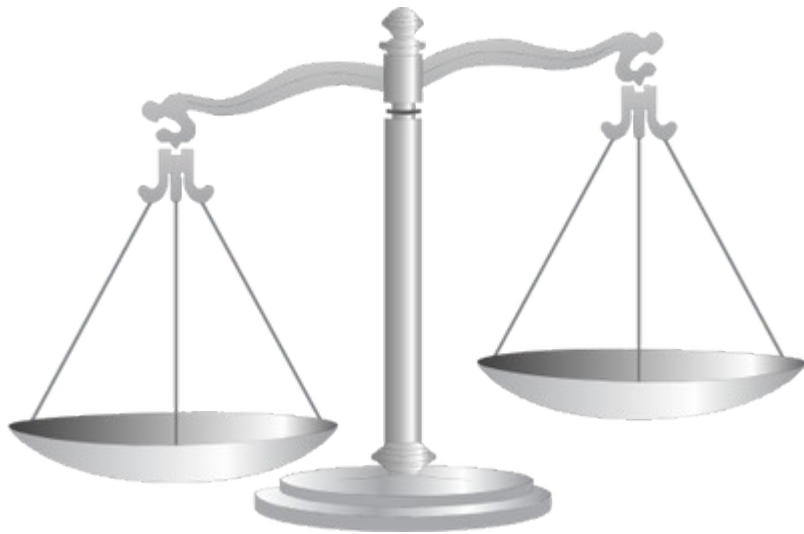


End of digression

Wait a minute!

Signal transduction is not at equilibrium!

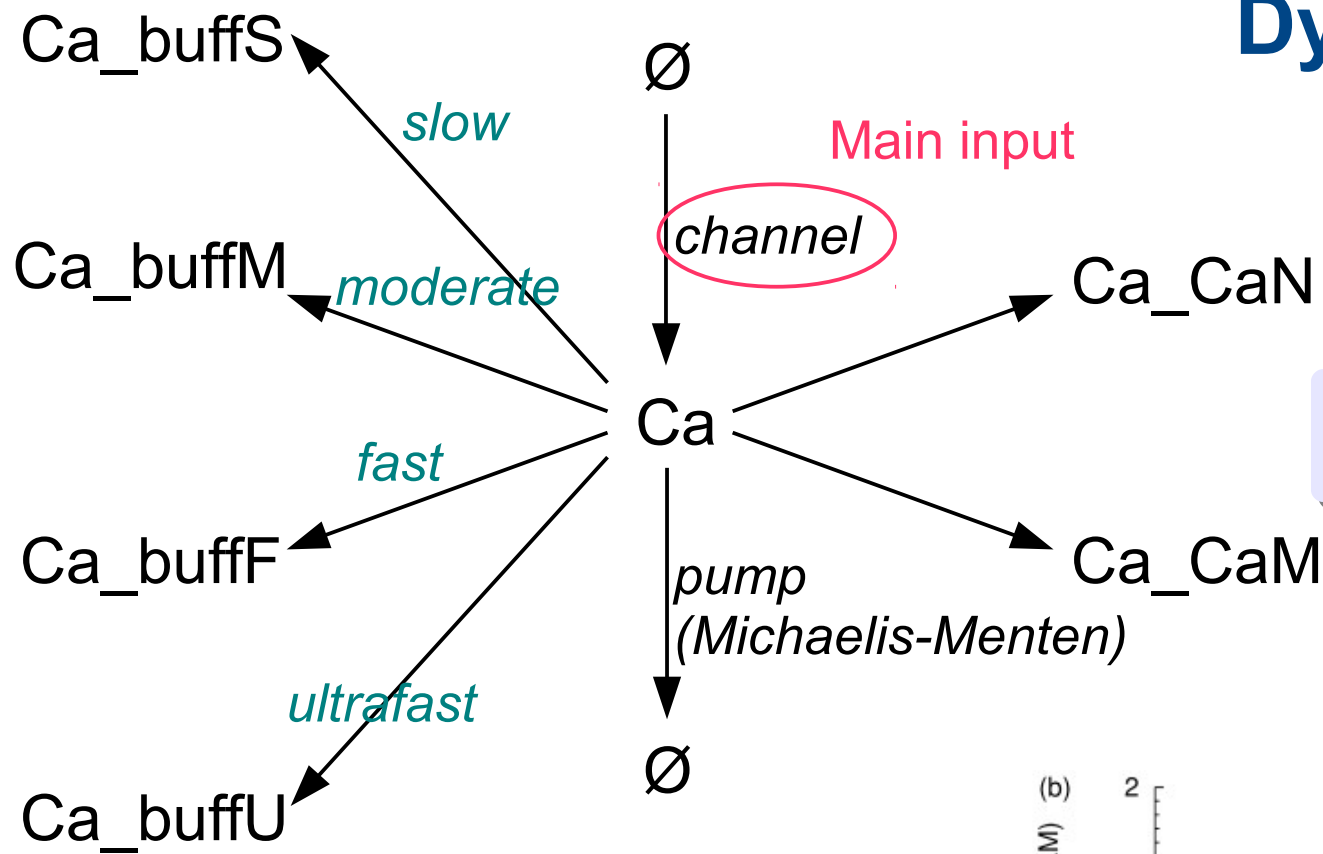
AMPAR post-synaptic potential:	5 ms
Calcium spike:	50 ms
Half saturation calmodulin ($k_{on}=1.5e6$, $k_{off}=100$):	5 ms
Relaxation between calmodulin states:	1 ms
autophosphorylation of CaMKII ($k_{on}=6$):	100 ms



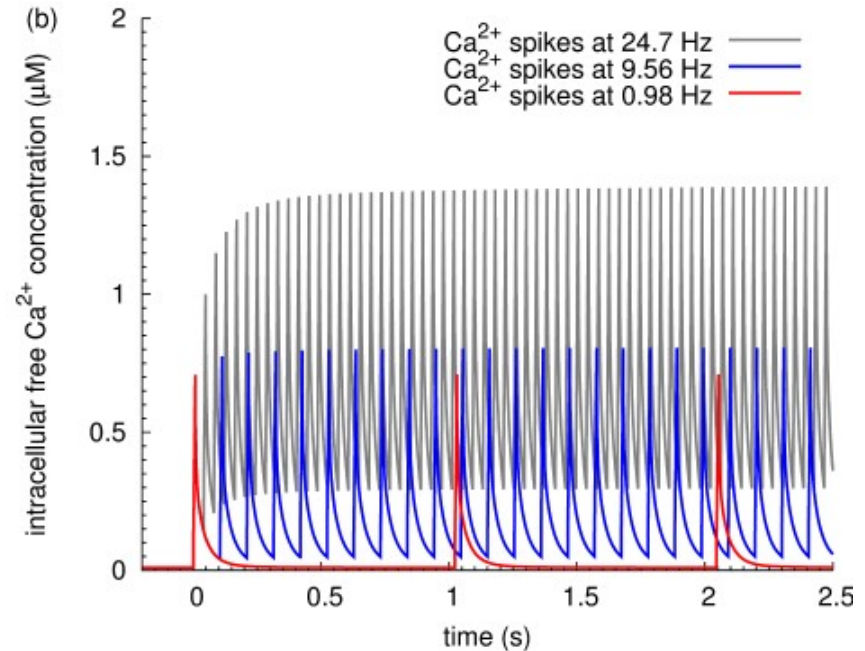
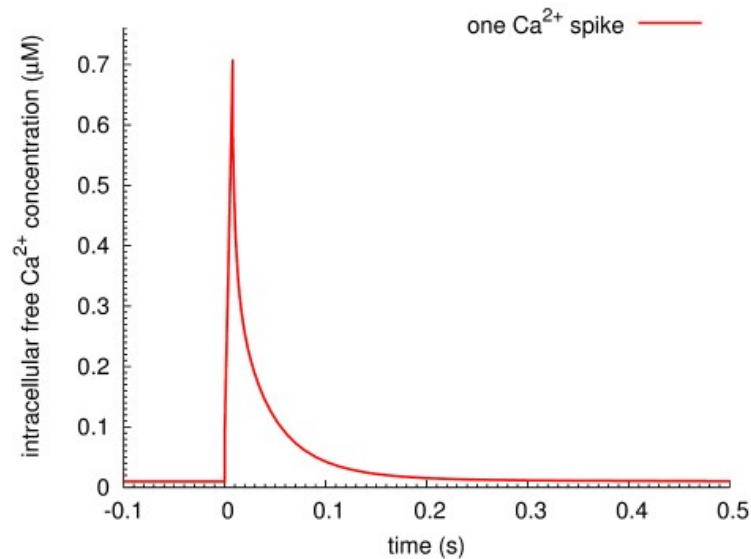
≠



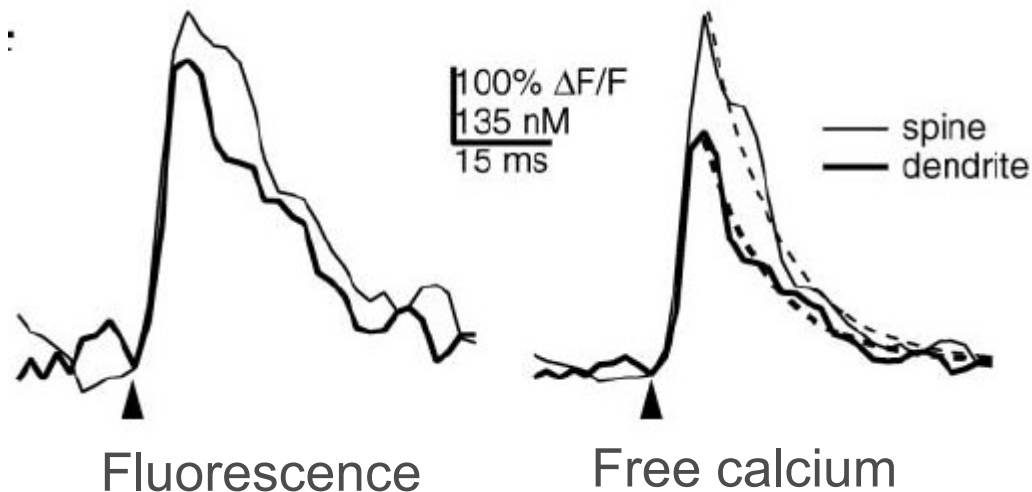
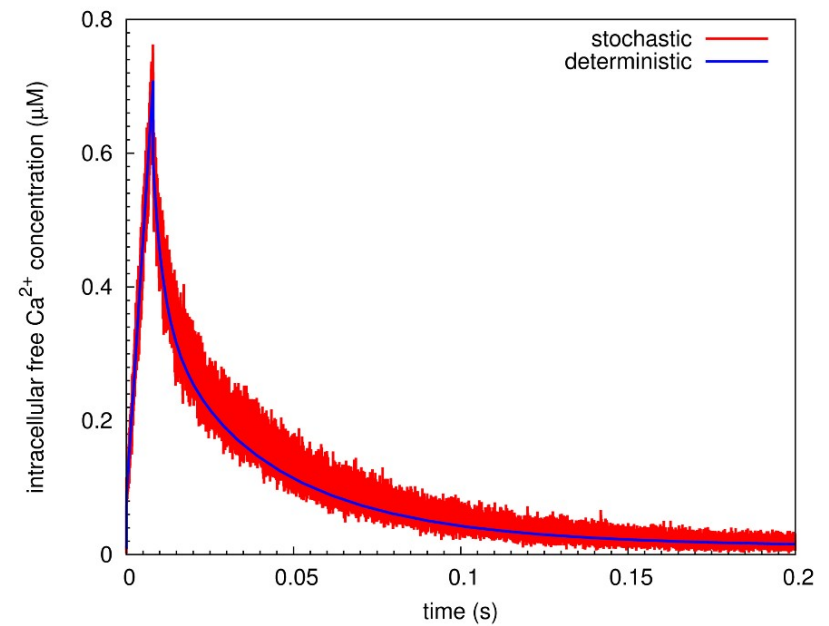
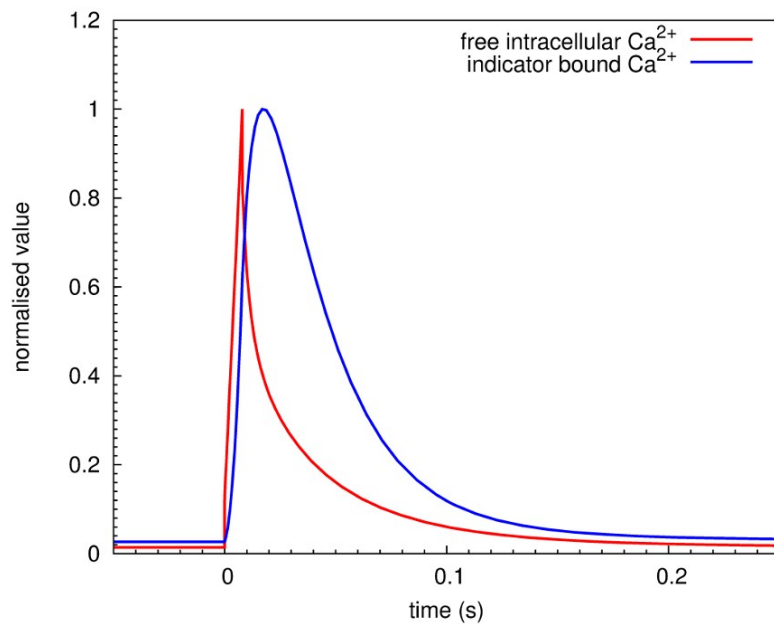
Dynamic of calcium in the spine



Li L, Stefan MI, Le Novère N
(2012) *PLoS ONE*, 7(9): e43810



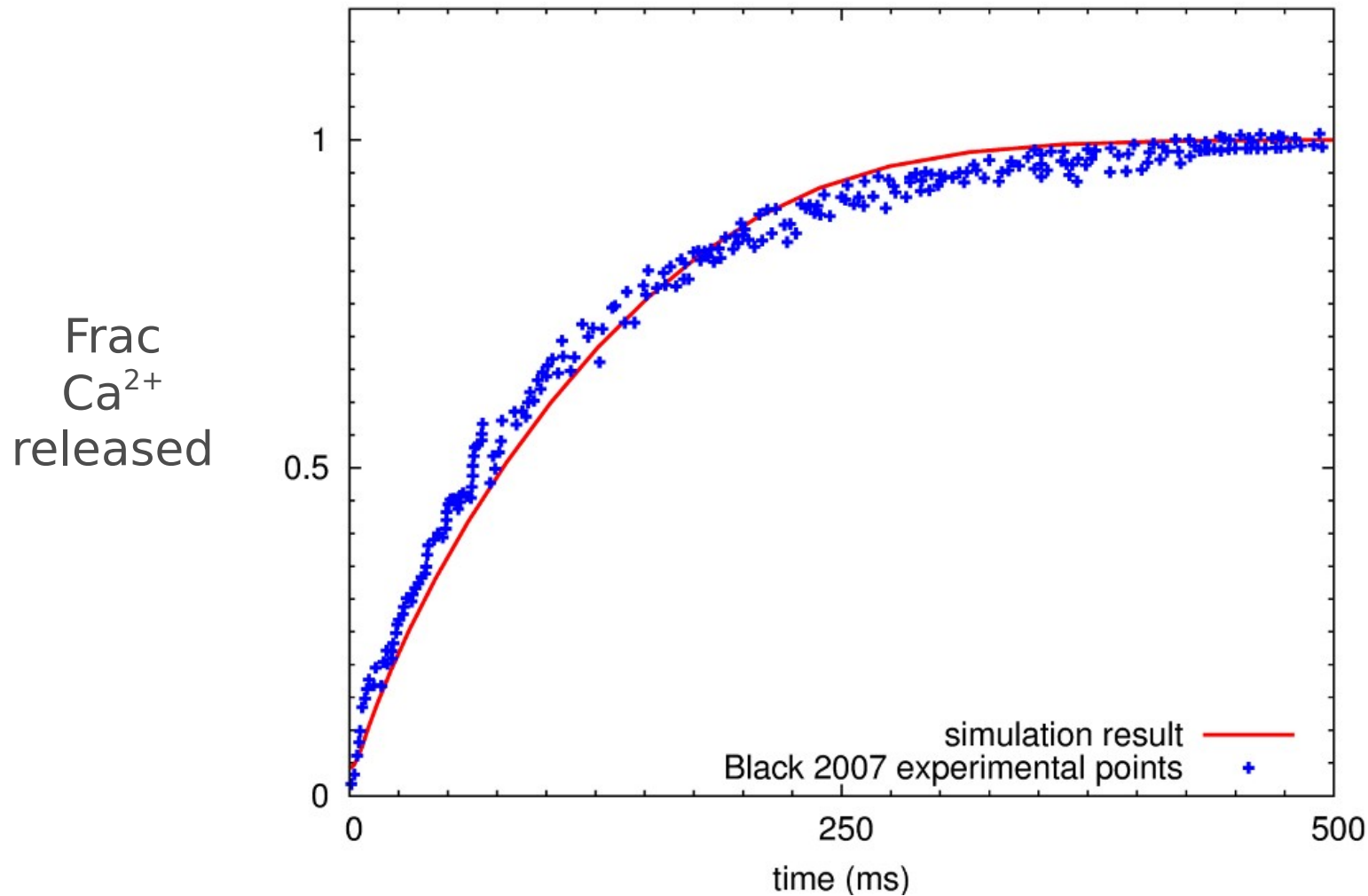
Are those spikes realistic?



Relative uncertainty increases when concentration decreases, both in concentration and time, but no difference in dynamics.

Sabatini et al (2002)
Neuron 33: 439–452.

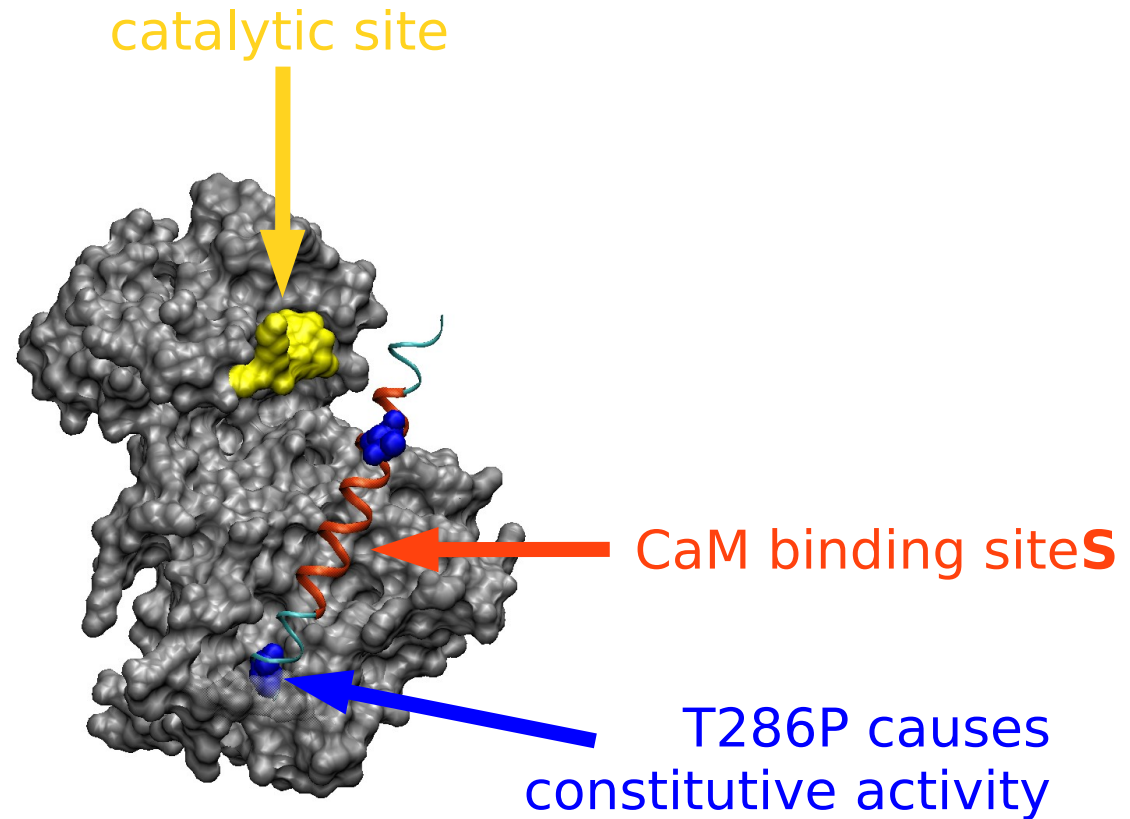
Validation of CaM kinetics



Black DJ, Selfridge JE, Persechini A (2007). *Biochemistry* 46: 13415–13424.



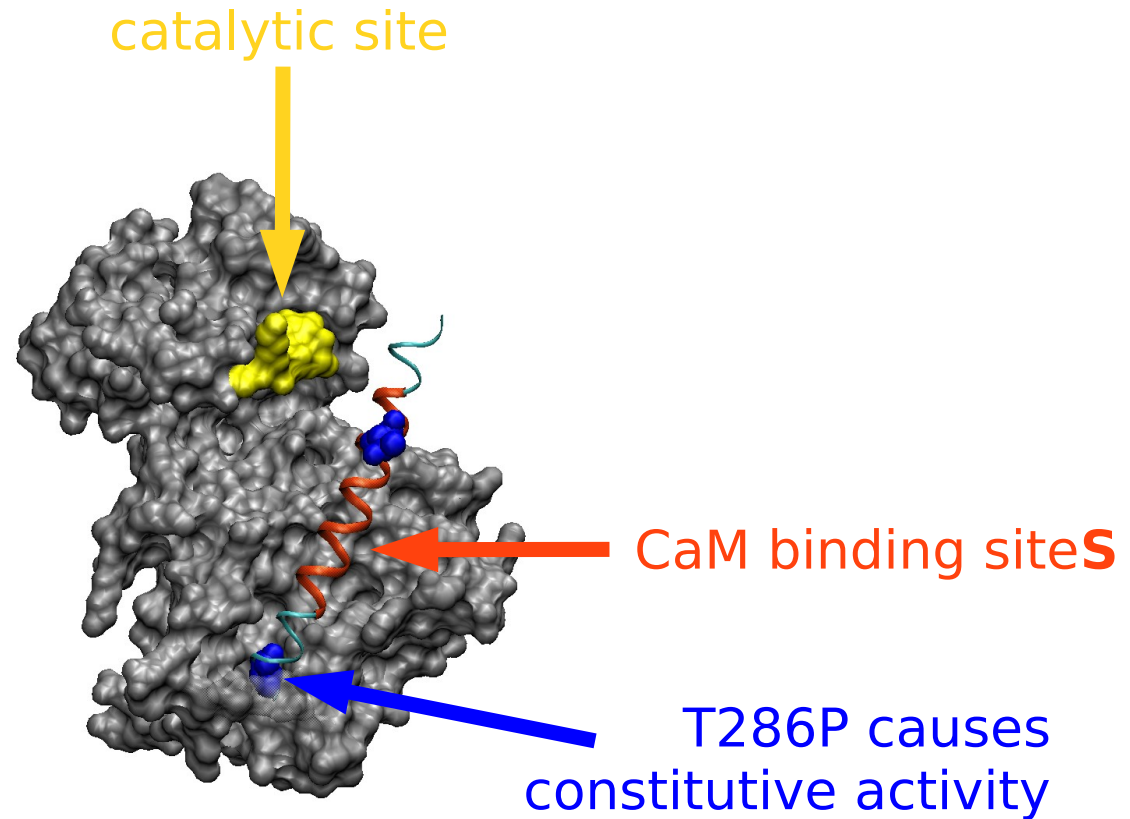
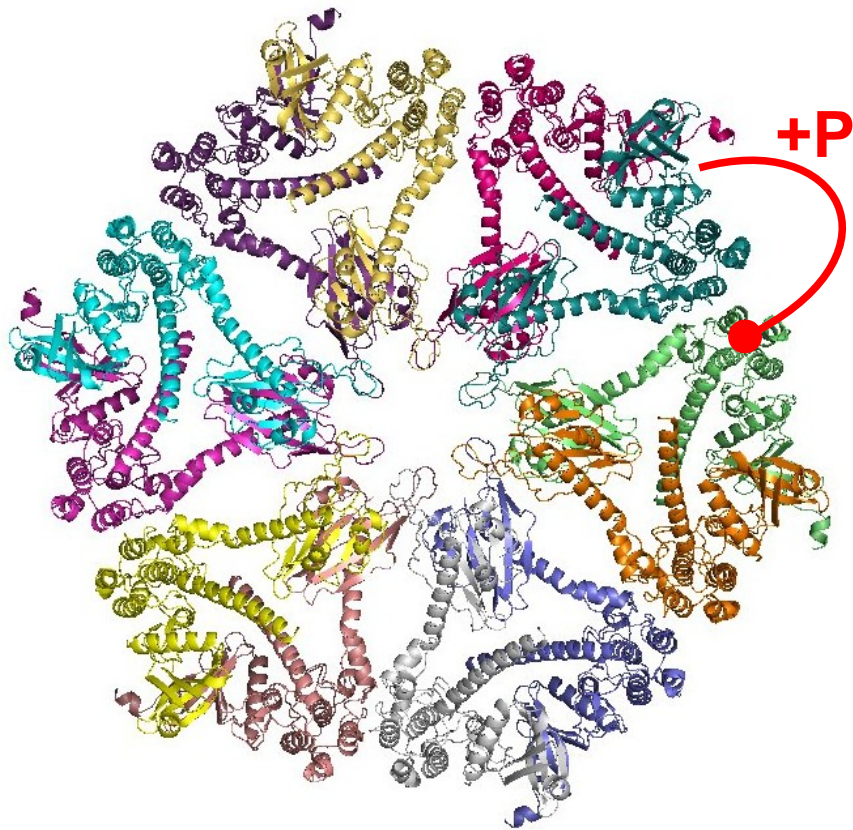
Calcium/calmodulin kinase II



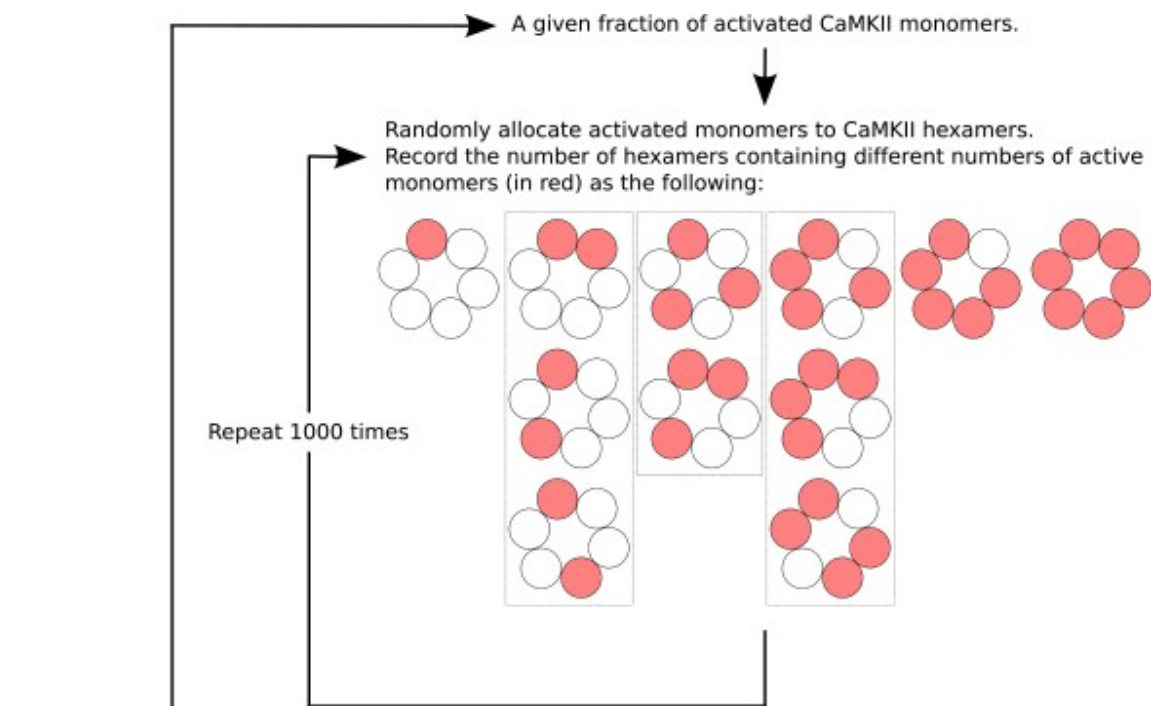
Calmodulin trapping is an apparent increase of affinity of CaMKII for CaM when T286 is phosphorylated

Stefan MI, Marshall D, Le Novère N (2012) *PLoS ONE*, 7(1): e29406

Calcium/calmodulin kinase II



Dodecamer;
Trans-phosphorylation of T286
by neighbouring subunits



Repeat for every 1% increase of CaMKII active monomers

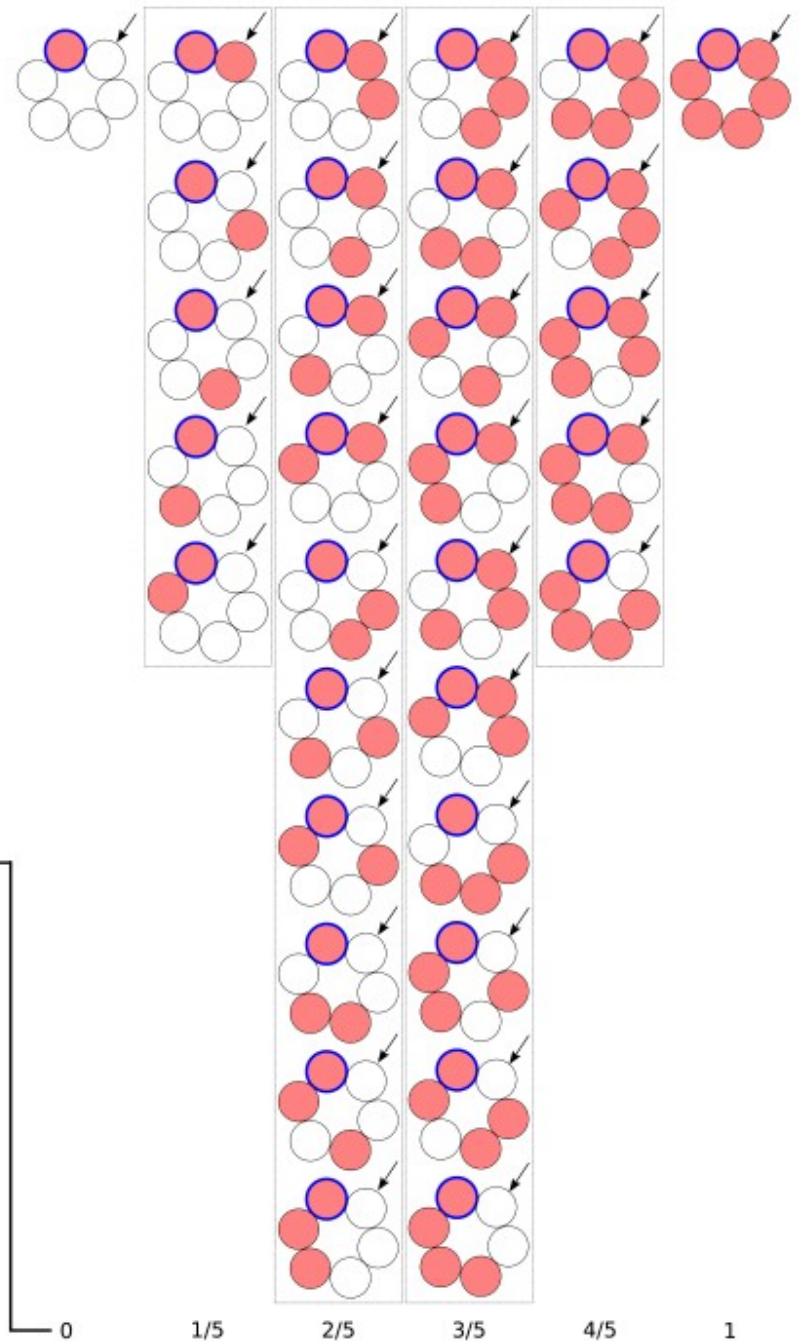
Calculate the average population for each number of active monomers per hexamer.

Multiply average populations of each number of active monomers per hexamer by their corresponding probabilities of having an active neighbour.

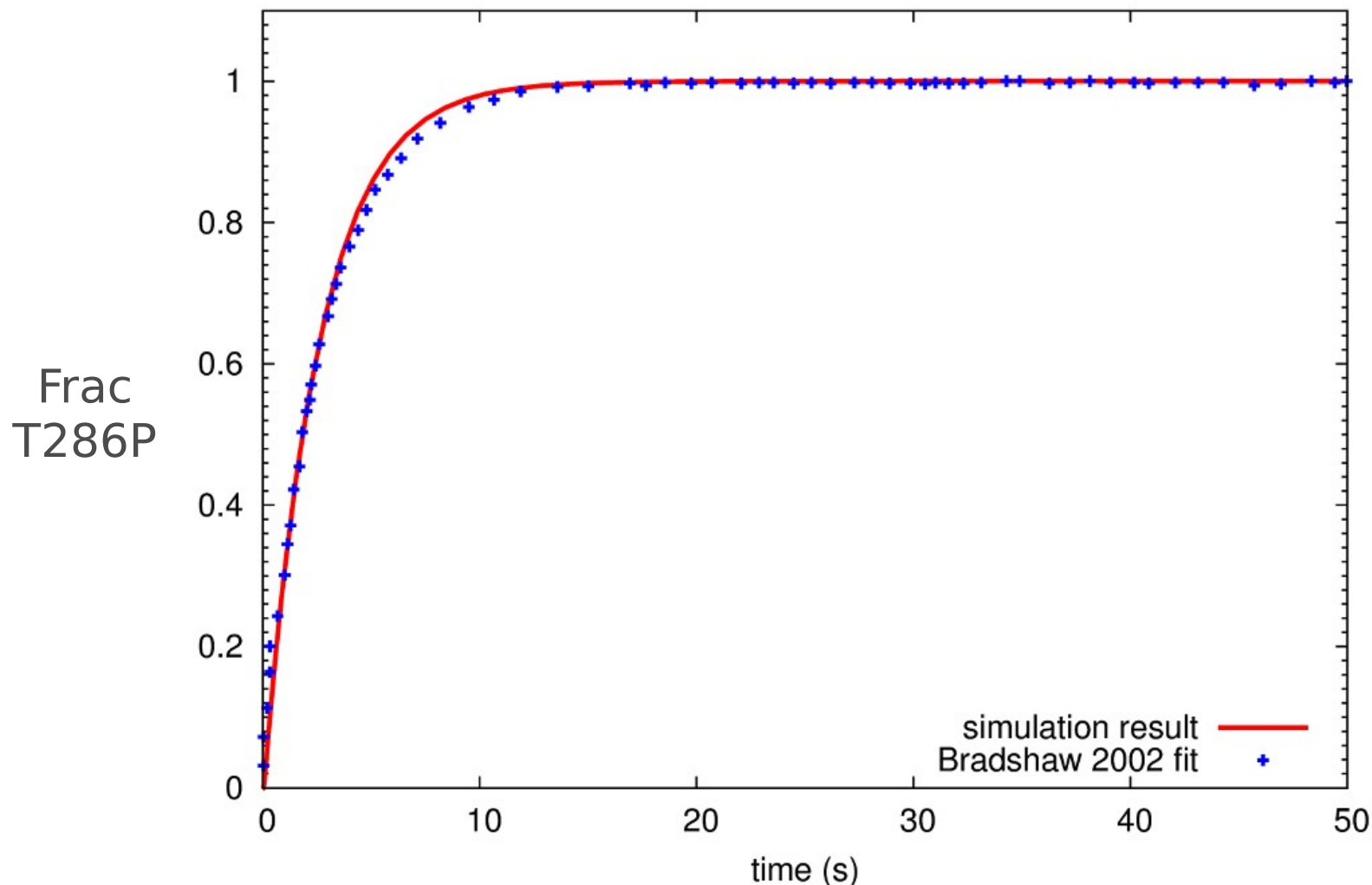
The sum of these six numbers is a coefficient that can be used to adjust CaMKII autophosphorylation rate.

Fit these 100 coefficients into a polynomial function of activated CaMKII monomers, and embed this function in the model.

Calculate the probabilities of having an active neighbour on one specific side (indicated by the arrow) of the activated monomer of interest (blue outline) (since only the asymmetrical situation is considered). The possible positions of activated monomers are listed as the following, with corresponding probabilities:

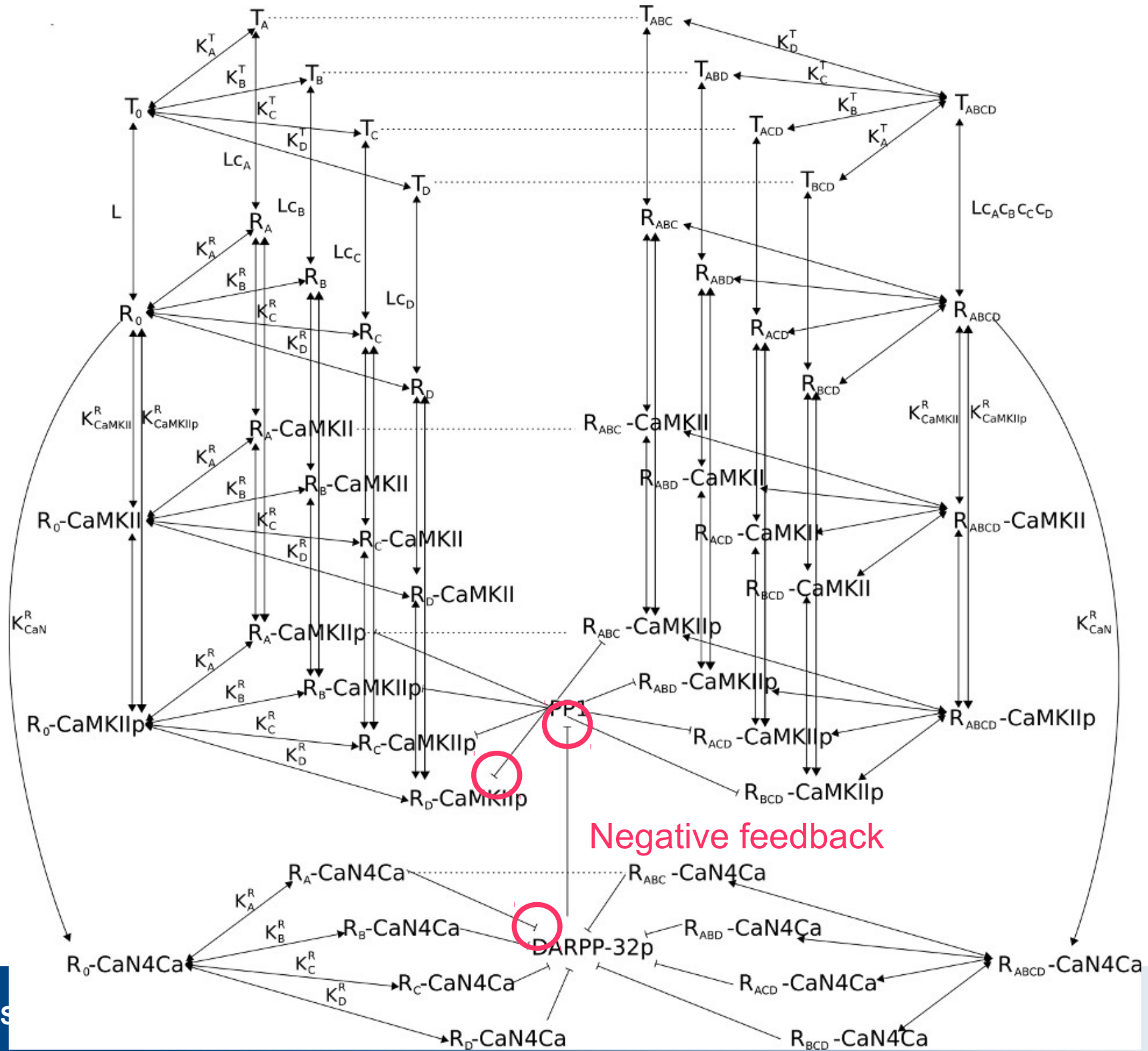


Validation of CaMKII kinetics

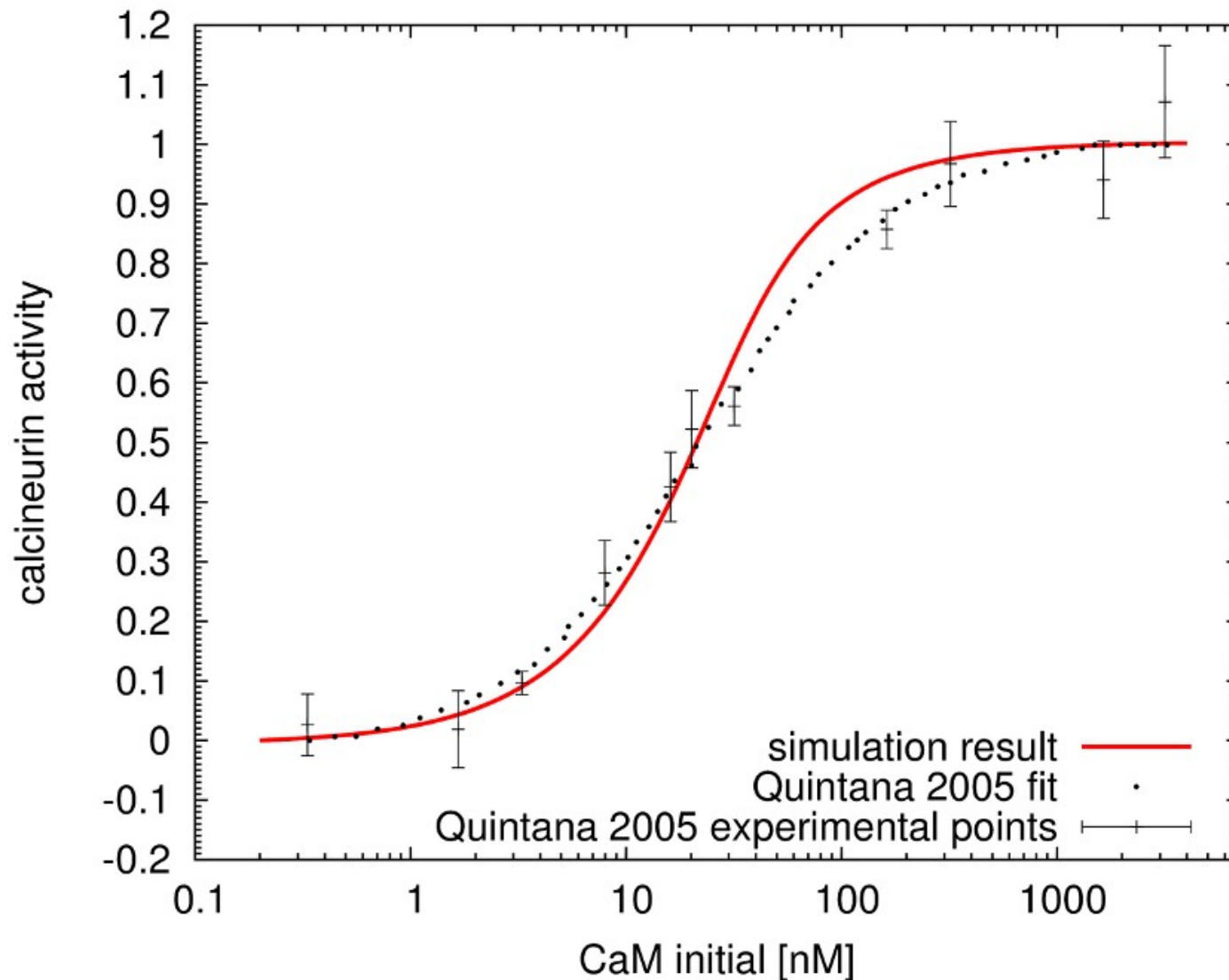


Bradshaw JM, Kubota Y, Meyer T, Schulman H (2003). *PNAS* 100: 10512–10517.



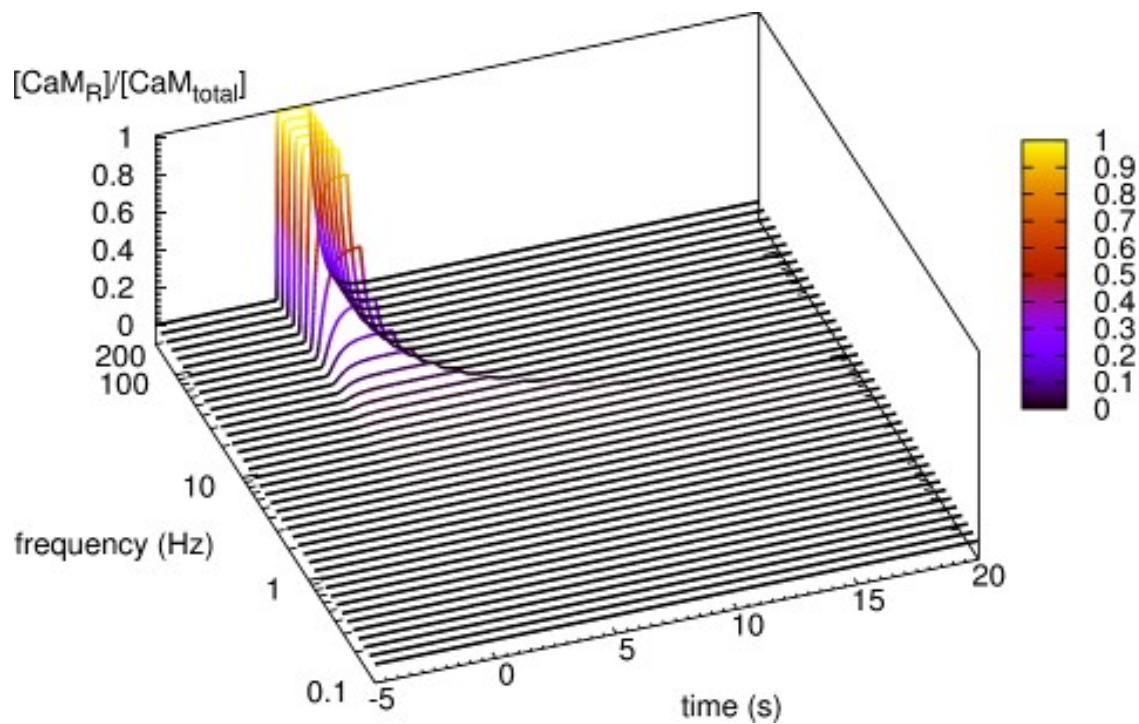


Validation of calcium-activation of CaN



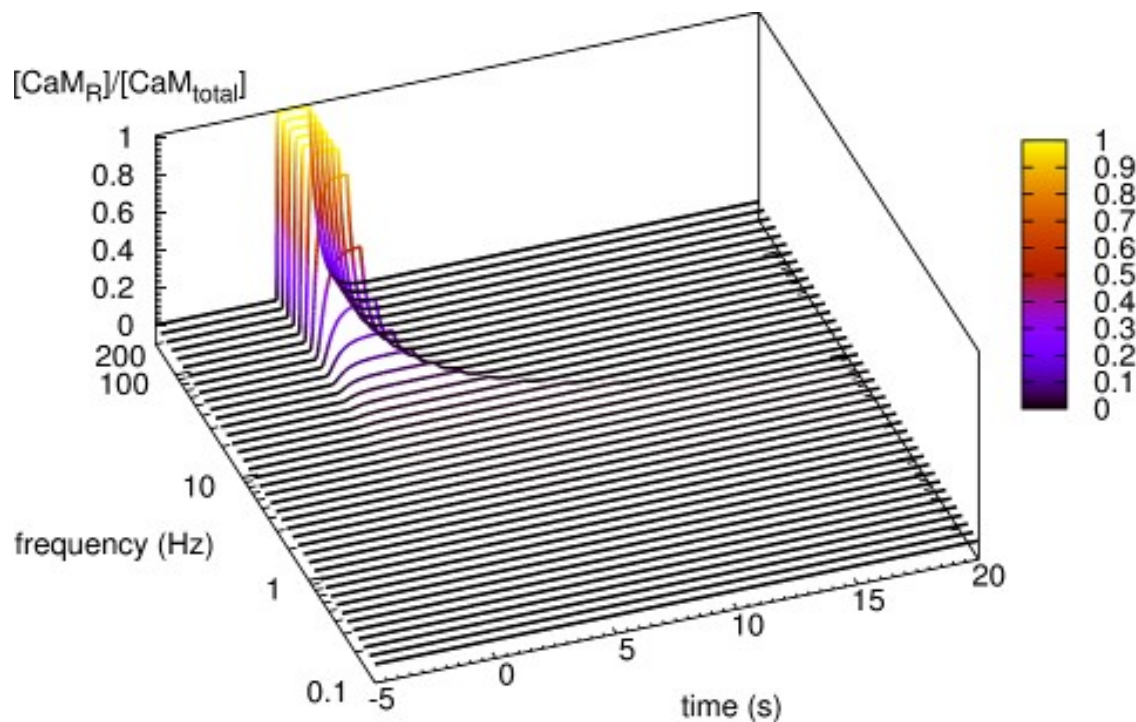
Quintana AR, Wang D, Forbes JE, Waxham MN (2005). *BBRC* 334: 674-680.

Calmodulin activation



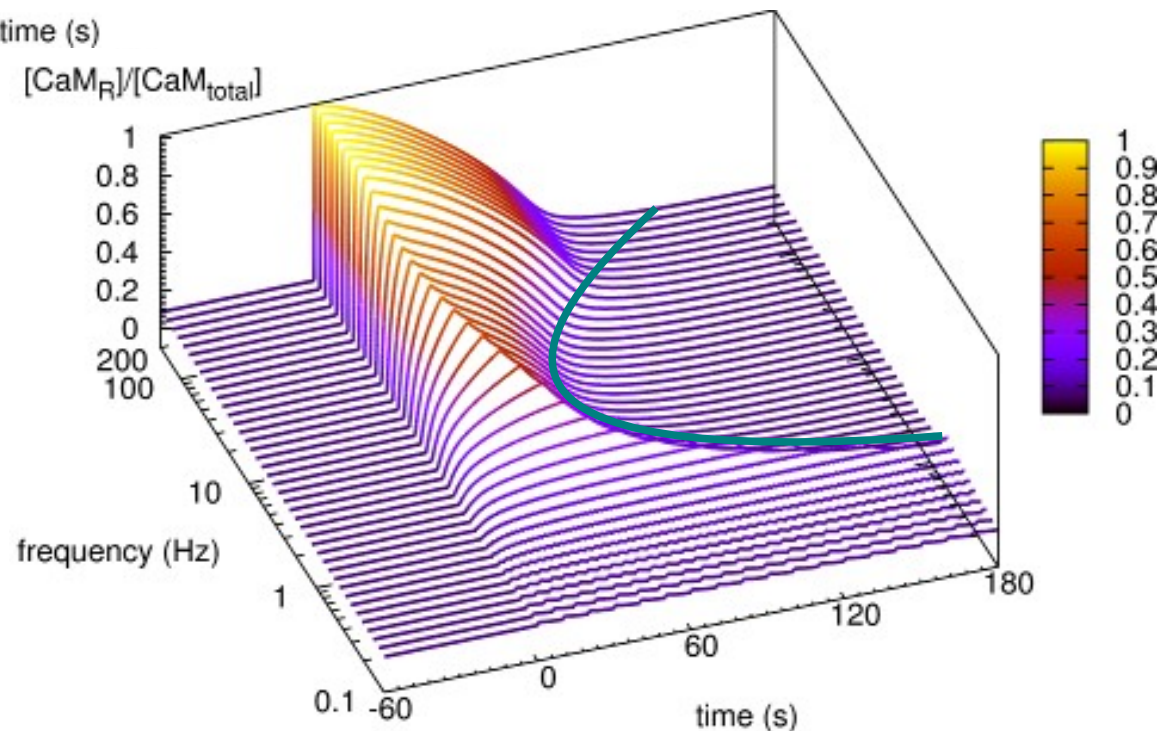
CaM without targets. Low frequencies do not activate calmodulin (binding events without conformational changes)

Calmodulin activation

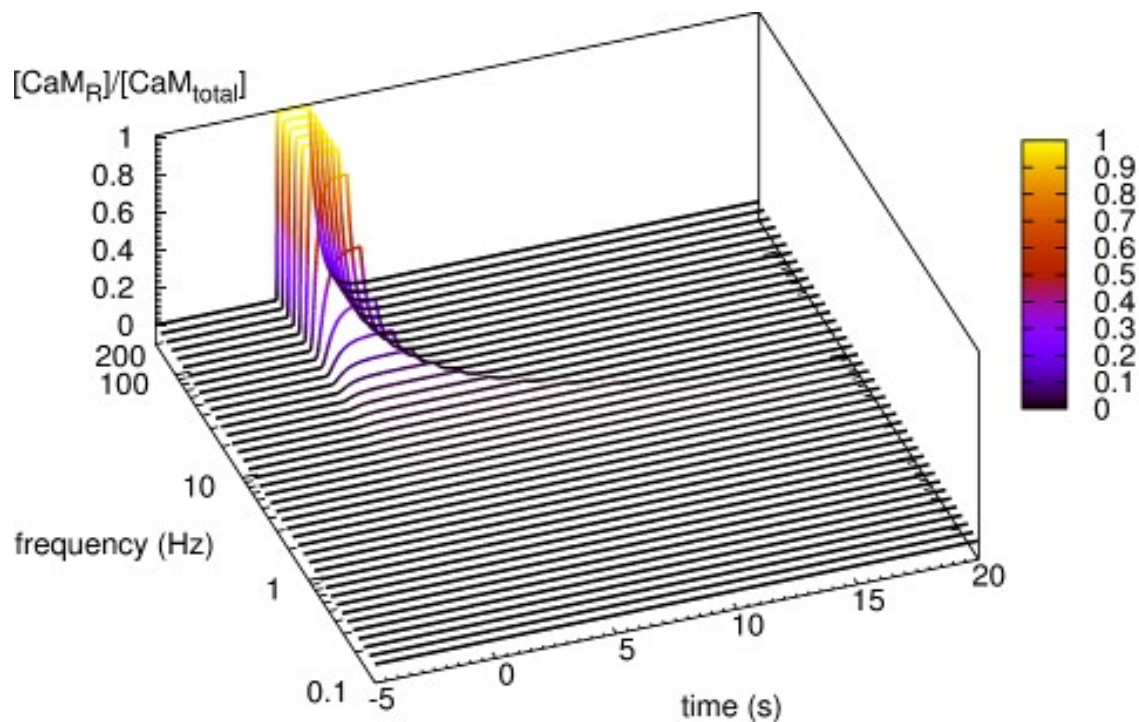


CaM without targets. Low frequencies do not activate calmodulin (binding events without conformational changes)

CaM with targets. Binding to CaN and CaMKII stabilises R state, with higher affinity. Positive feedback loop
→ bistability



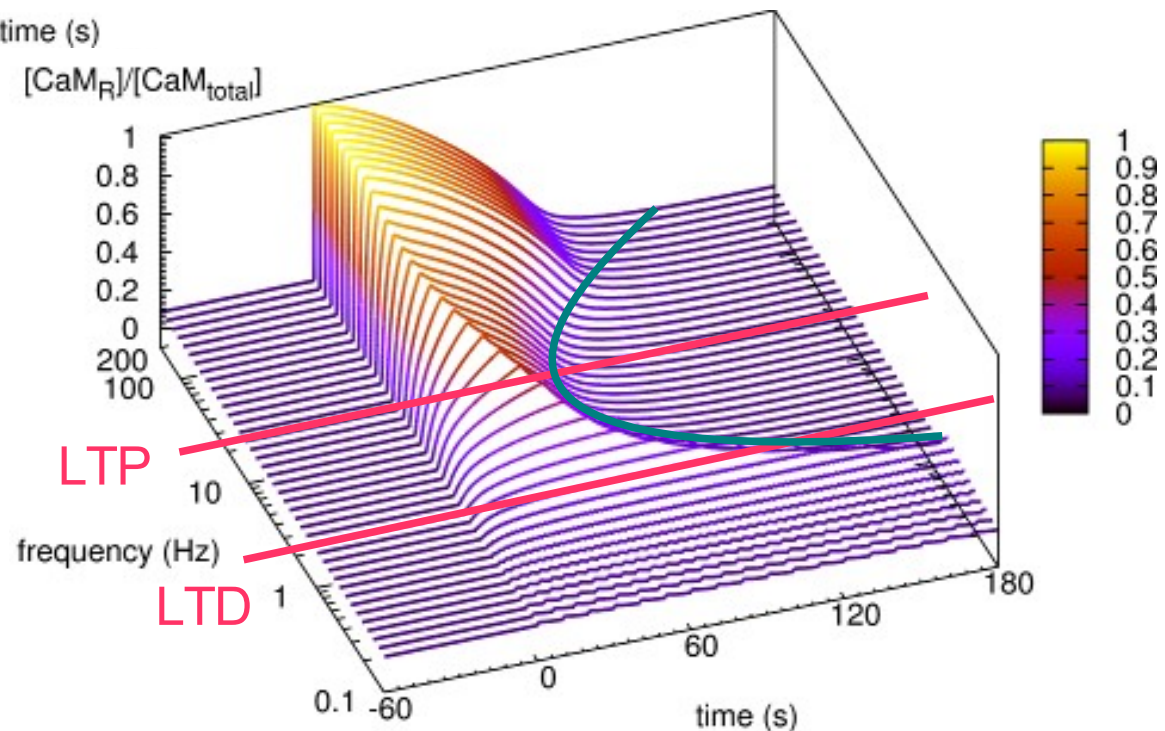
Calmodulin activation



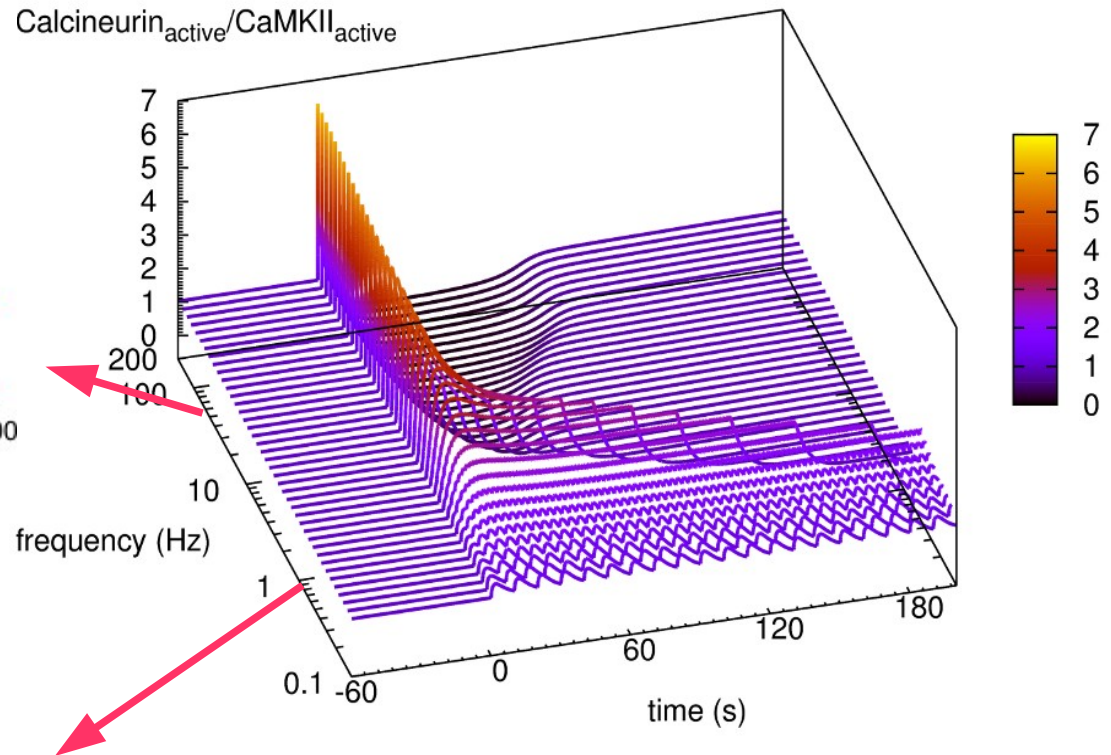
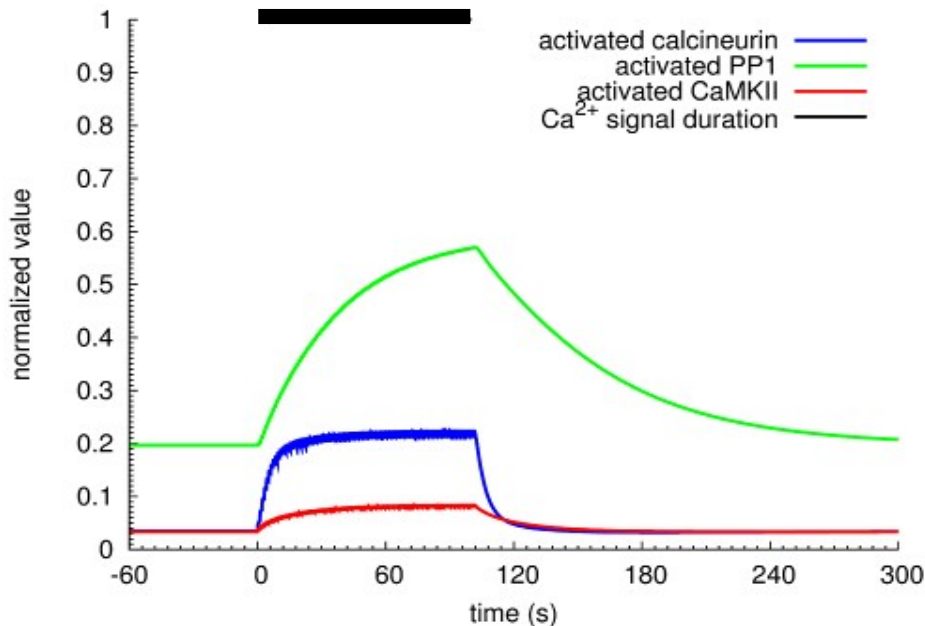
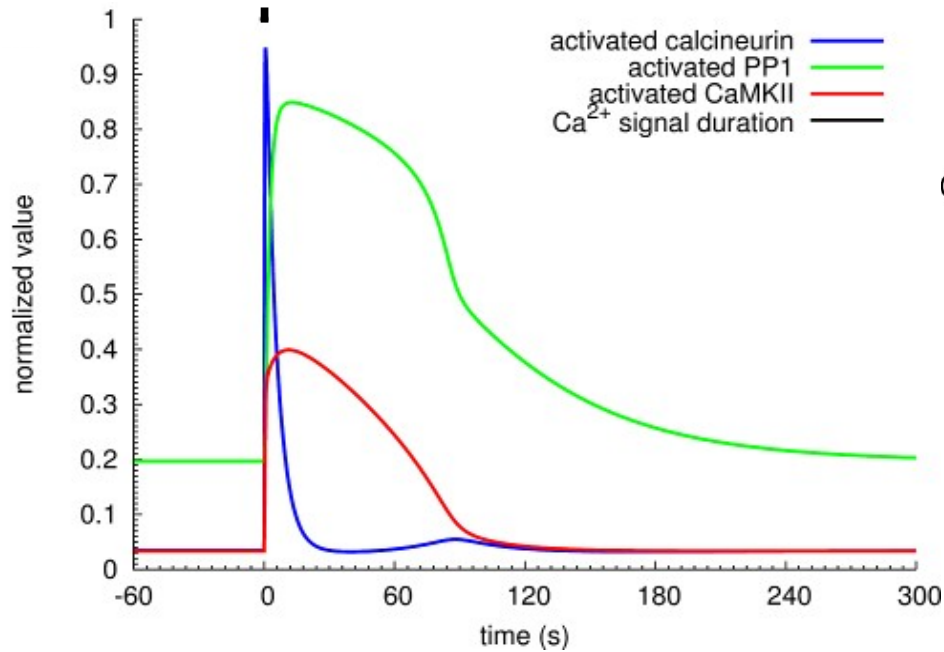
CaM without targets. Low frequencies do not activate calmodulin (binding events without conformational changes)

At high frequency, effects of calcium signals last much longer than the signal itself

CaM with targets. Binding to CaN and CaMKII stabilises R state, with higher affinity. Positive feedback loop → bistability



Temporal activation of CaMKII and CaN

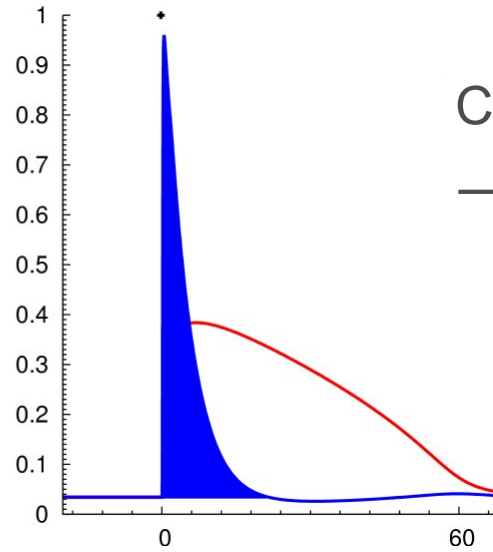
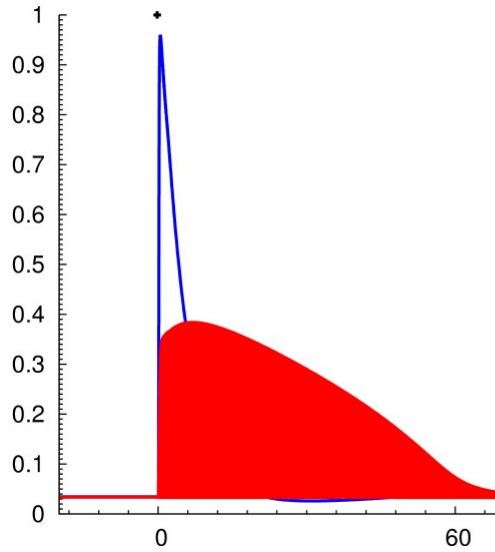


All calcium frequencies increase CaN **AND** CaMKII. It is not a Switch. But the ratio of activation changes

Bidirectional plasticity

Constant catalytic rates of active enzyme

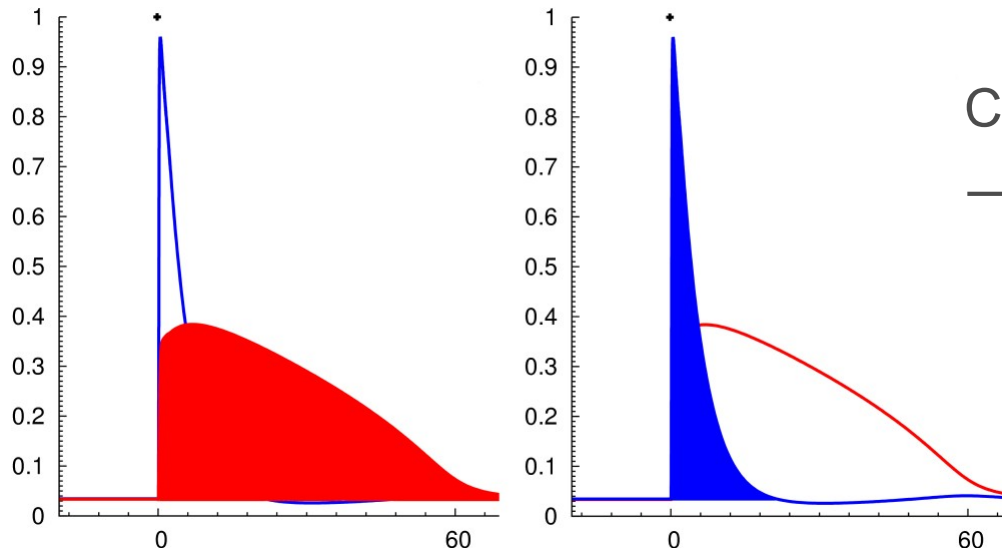
→ quantity of catalysed reaction events
prop to integral of the activation curve



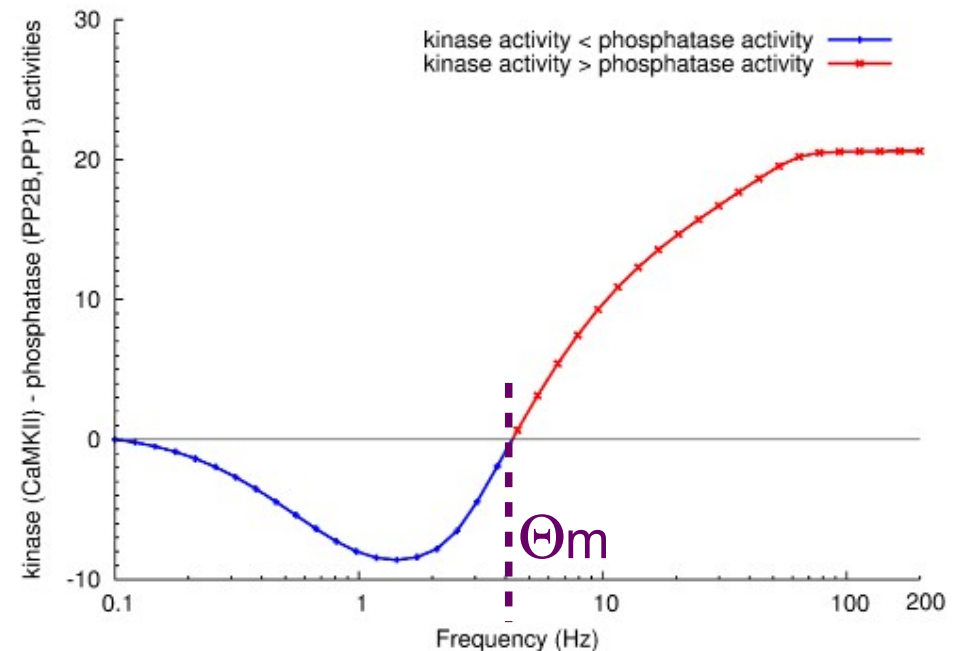
Bidirectional plasticity

Constant catalytic rates of active enzyme

→ quantity of catalysed reaction events
prop to integral of the activation curve



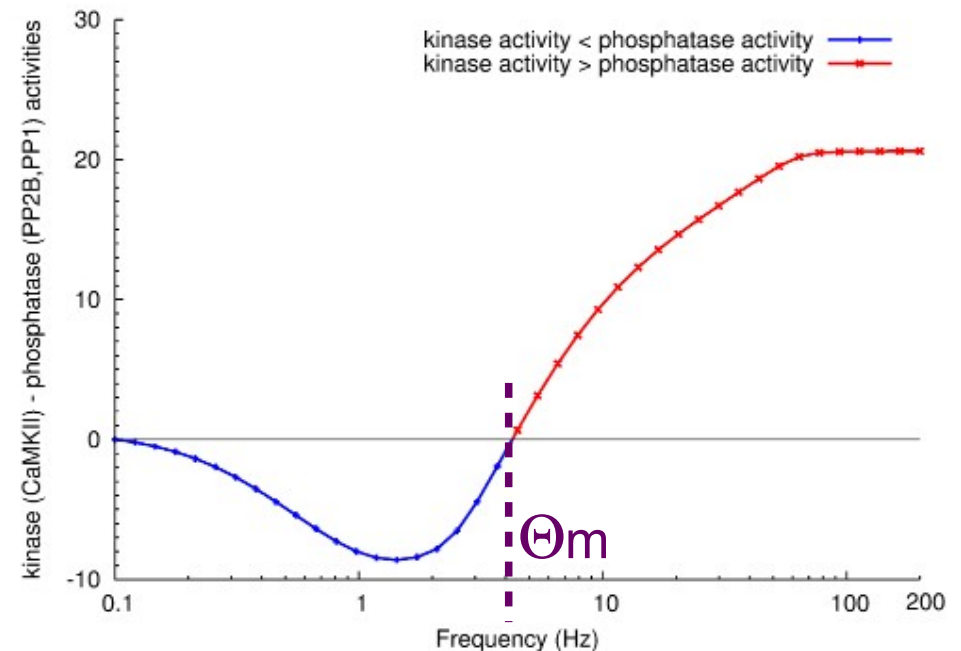
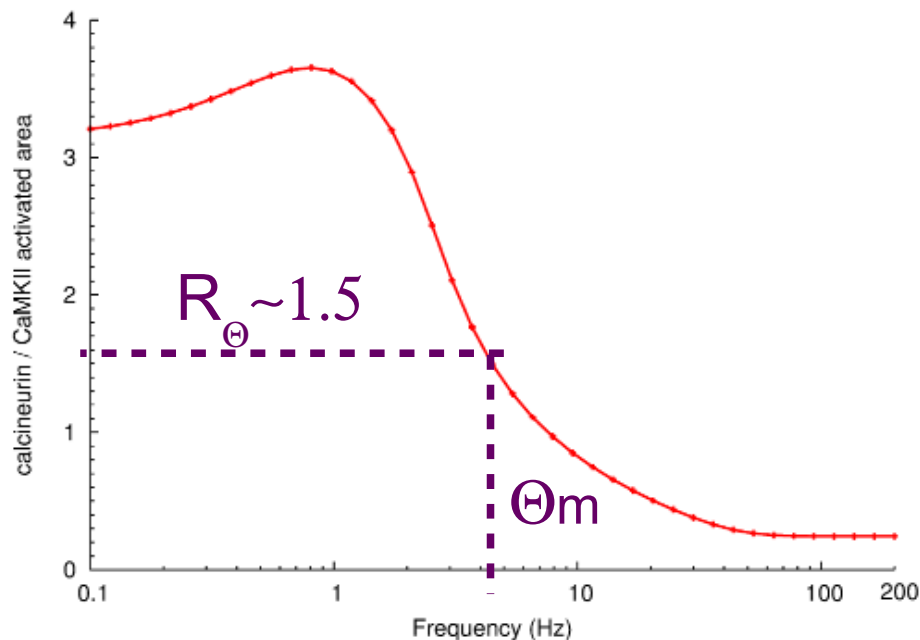
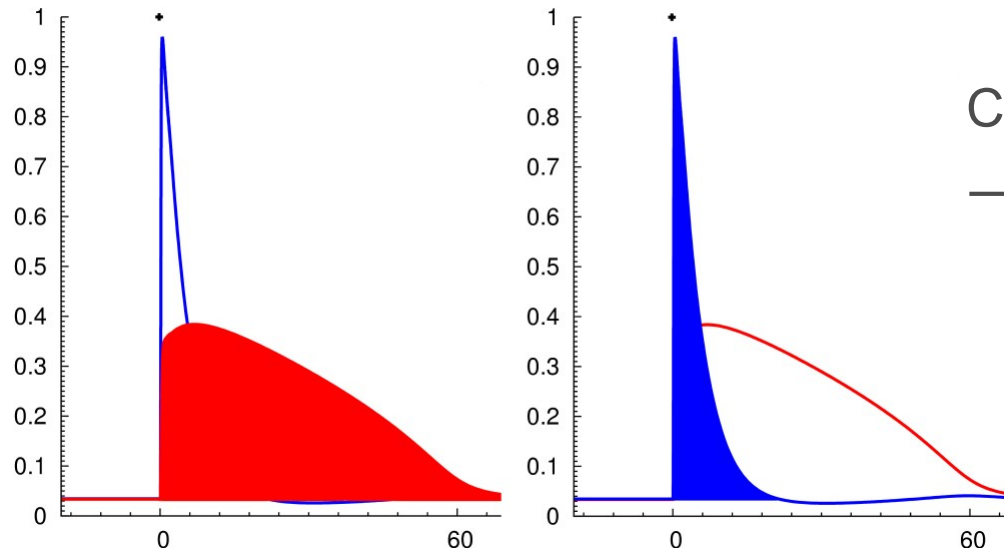
Bienestock-Cooper-Munro
(BCM) curve: difference of
active areas* catalytic activities



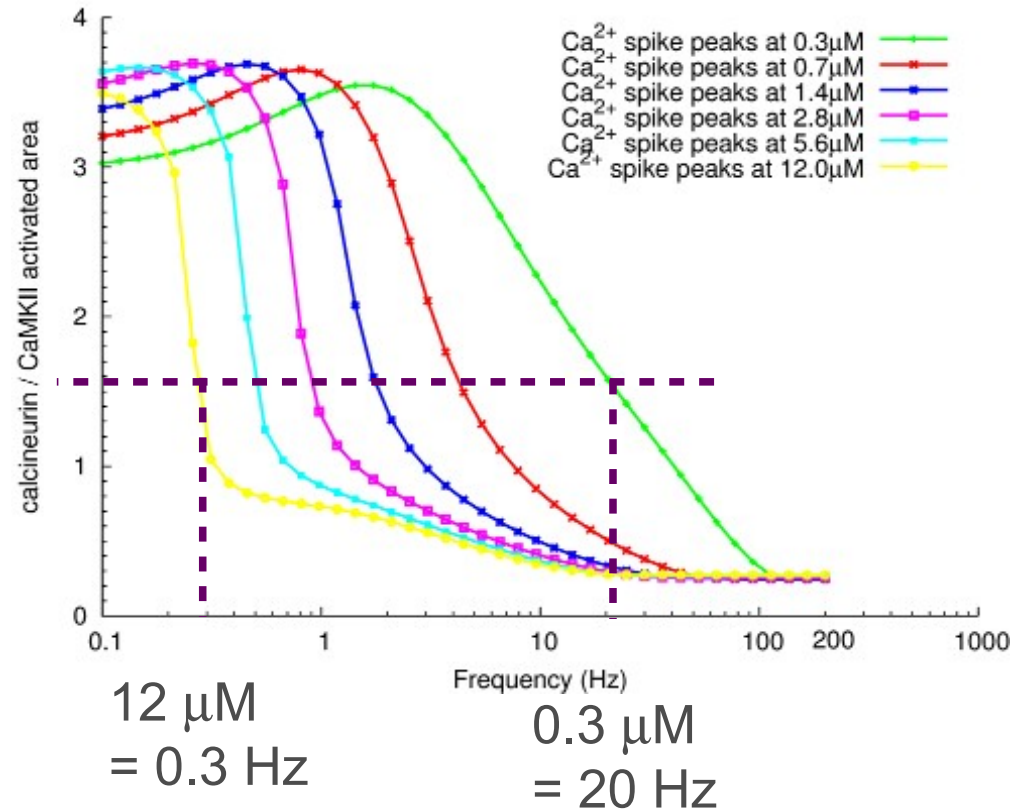
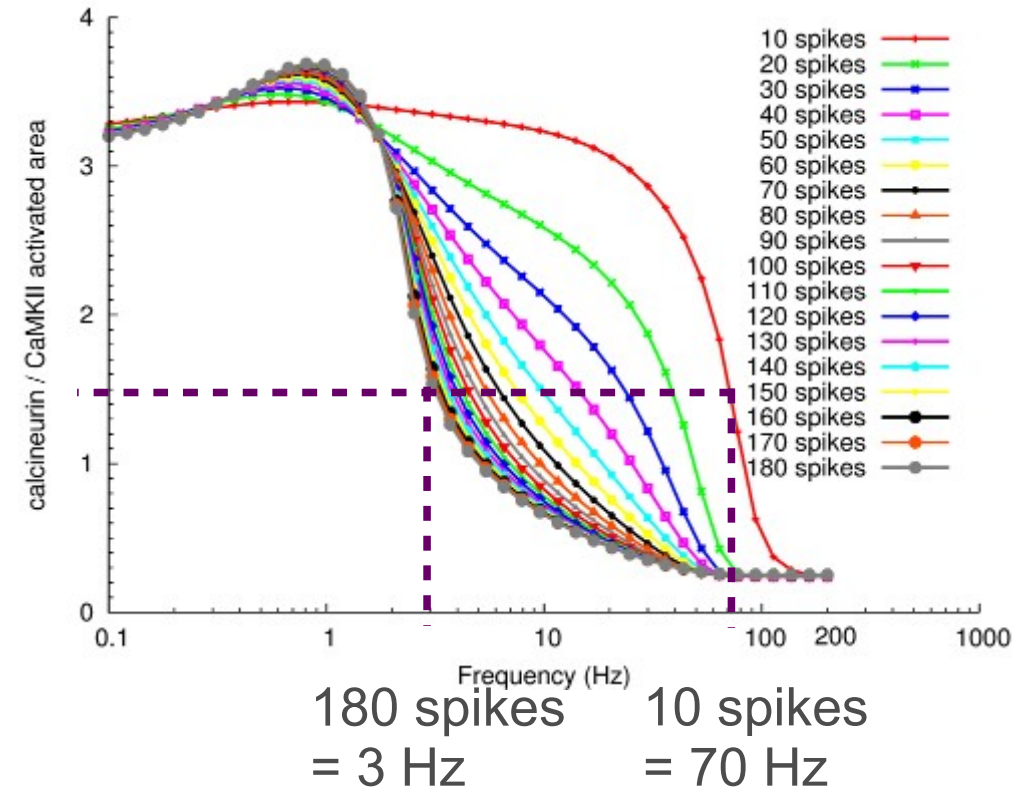
Bidirectional plasticity

Constant catalytic rates of active enzyme
 → quantity of catalysed reaction events
 prop to integral of the activation curve

Bienestock-Cooper-Munro
 (BCM) curve: difference of
 active areas* catalytic activities

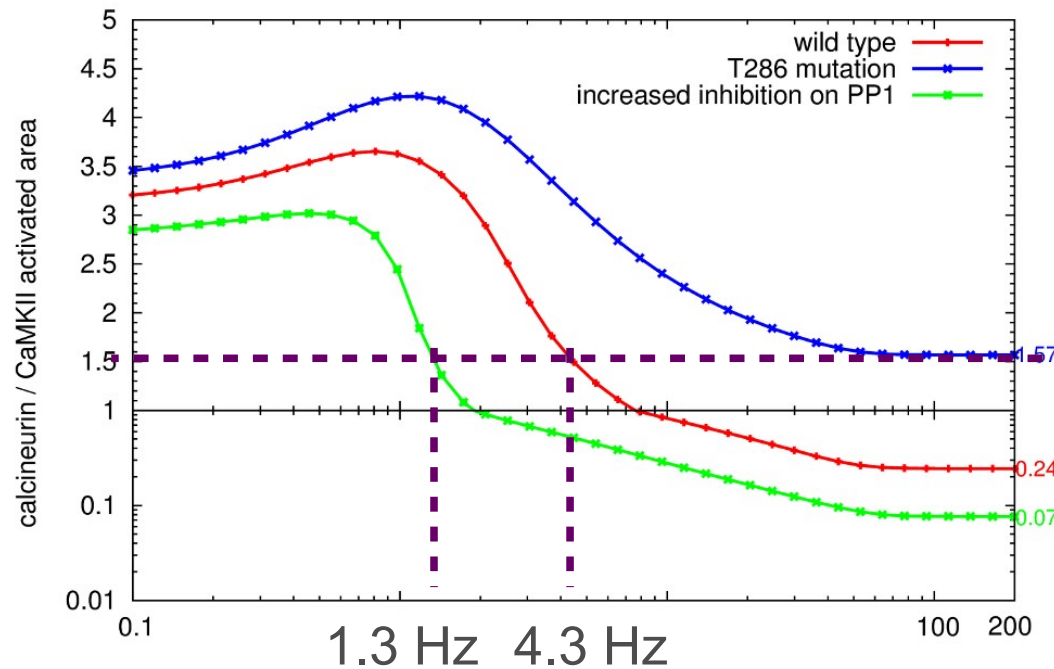


Effect of calcium duration and amount



Prolonged or intense signals decrease Θ_m : It is not an intrinsic property of the synapse

Effect of intrinsic system perturbations



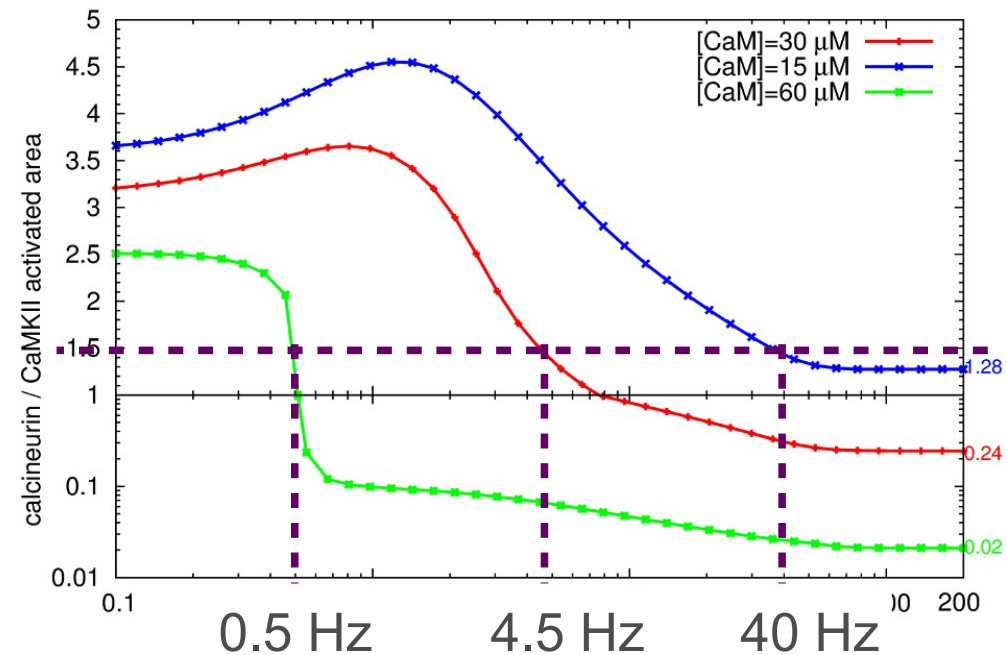
CaMKII not constitutively active
No CaM trapping

Never any positive plasticity
Giese et al (1998) *Science*, 279:870-873

Lower deactivation of CaMKII

Competition for CaM, and CaN wins

(Pi, Otmakhov, Lemelin, De Koninck, Lisman. (2010) Autonomous CaMKII can promote either long-term potentiation or long-term depression, depending on the state of T305/T306 phosphorylation. *J Neurosci*, 30:8704-9
Proposed some direct interactions between CaN and CaMKII.
They got it completely wrong!



Summary of part 2

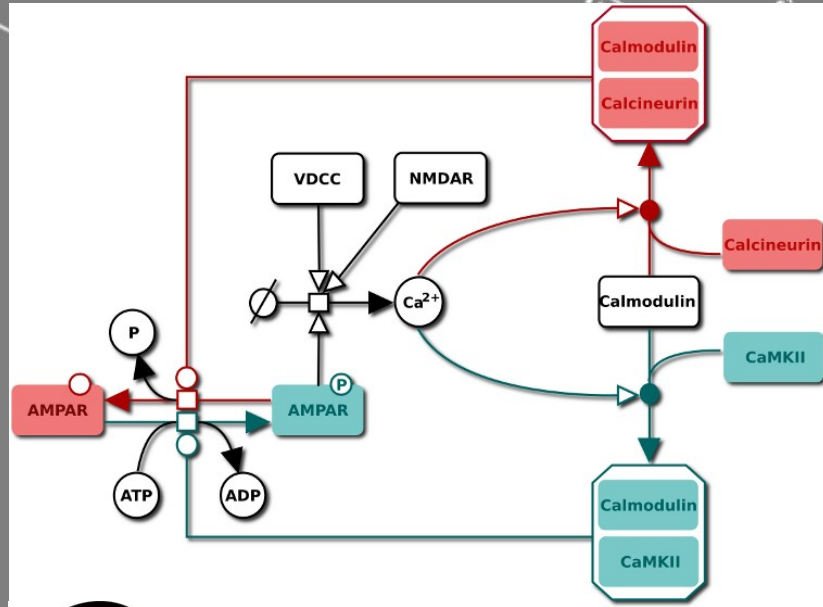
Allosteric stabilisation by targets triggers bistable CaM response to calcium. Above a certain frequency, CaM activation lasts longer than the initial signal.

Calcium signals do not choose between CaN and CaMKII, *BOTH* enzymes are activated at *ALL* frequencies. The ratio of activity changes.

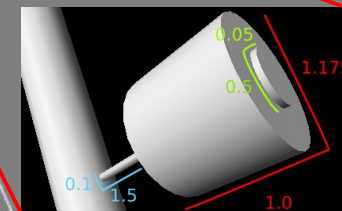
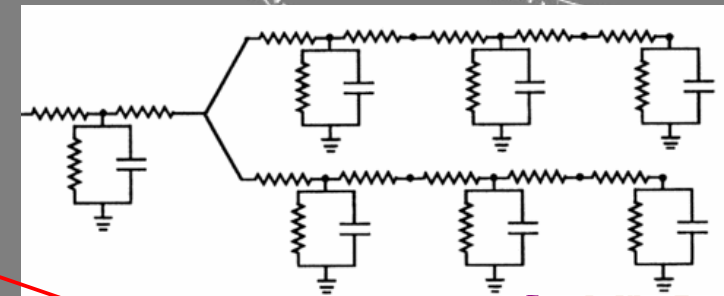
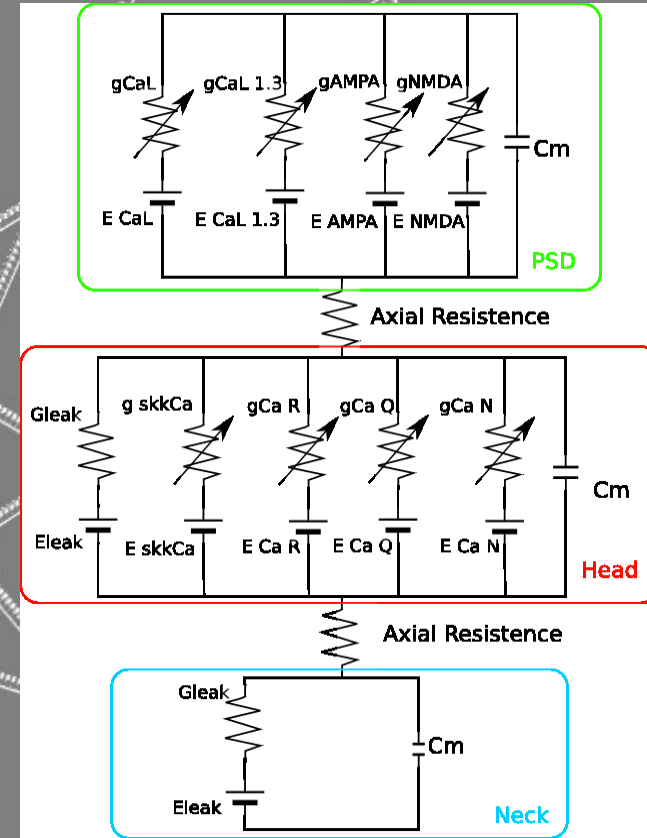
The frequency at which a synapse switches from a depression to a potentiation mode is not an intrinsic property of the synapse, but a dynamical one that depends on the length and amplitude of stimulations.

Modifications of topology, parameters and initial conditions affect both response intensity and threshold frequency. Some mutants can't have positive plasticity for any stimulation. [CaM] decides of the balance CaN/KII

Whole cell: electro-biochemical models



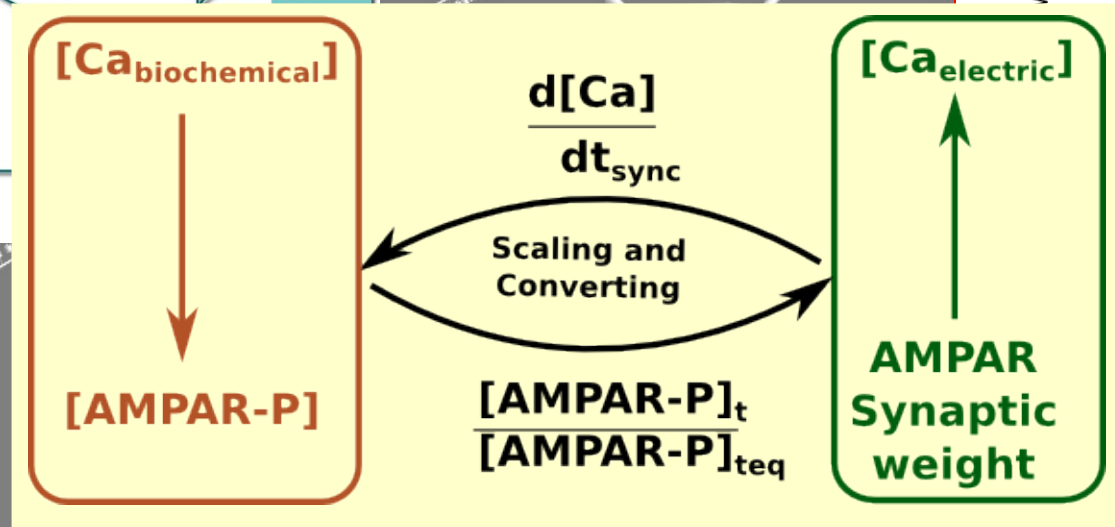
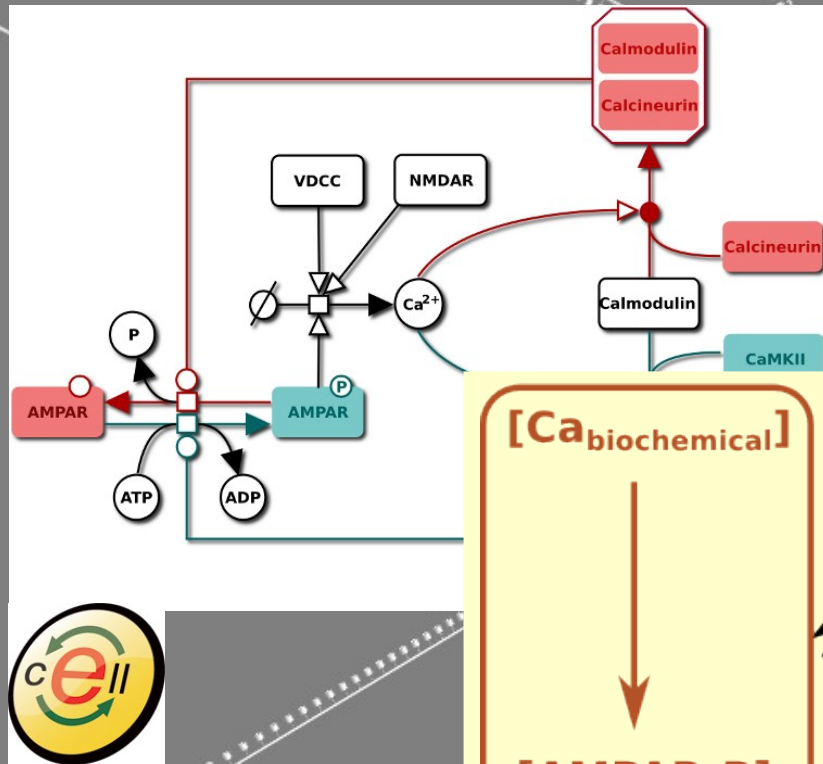
1504 spines
4761 compartments
16362 channels



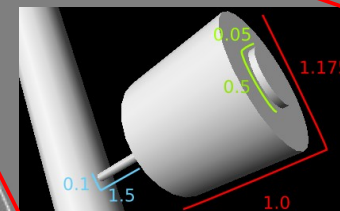
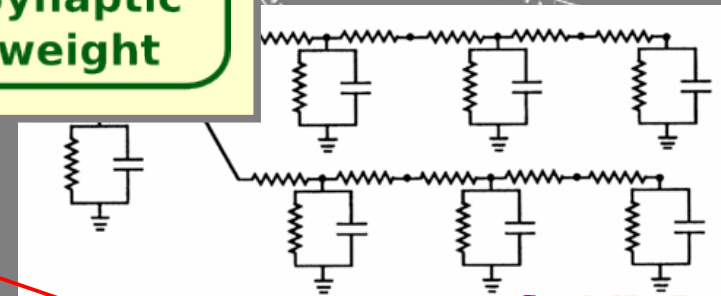
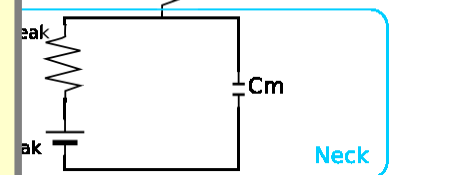
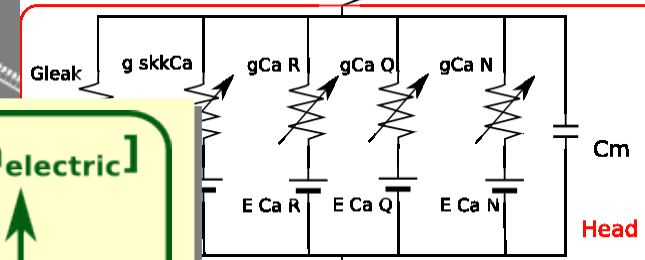
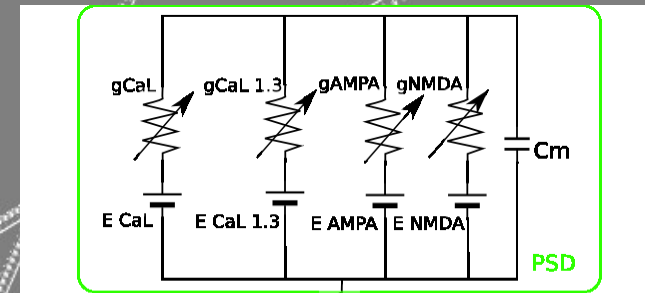
Mattioni M, Cohen U, Le Novère N (2012)
Frontiers Neuroinfo, 6:20

Mattioni M, Le Novère N (2013)
PLoS ONE, 8(7): e66811

Whole cell: electro-biochemical models



1504 spines
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