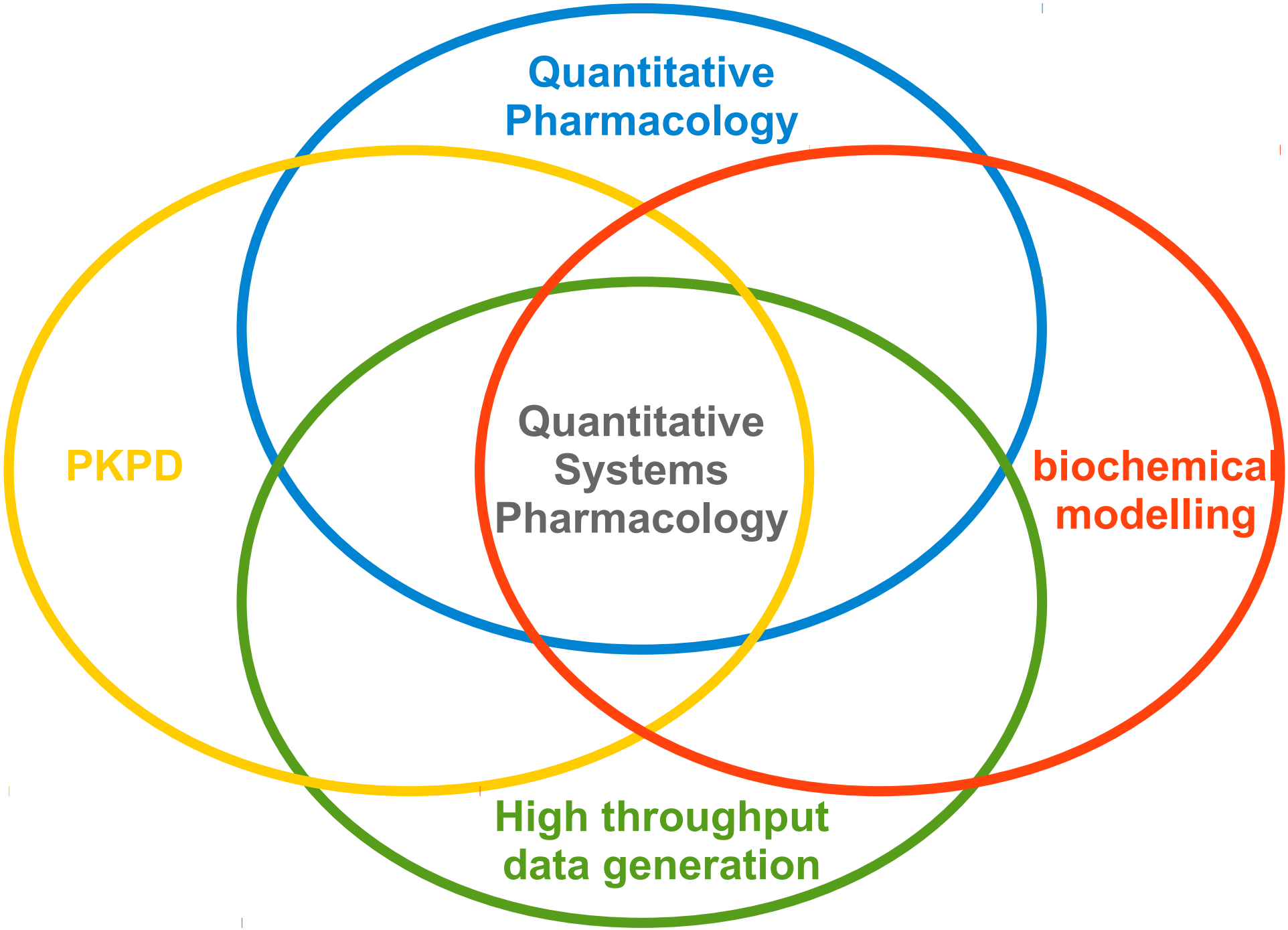
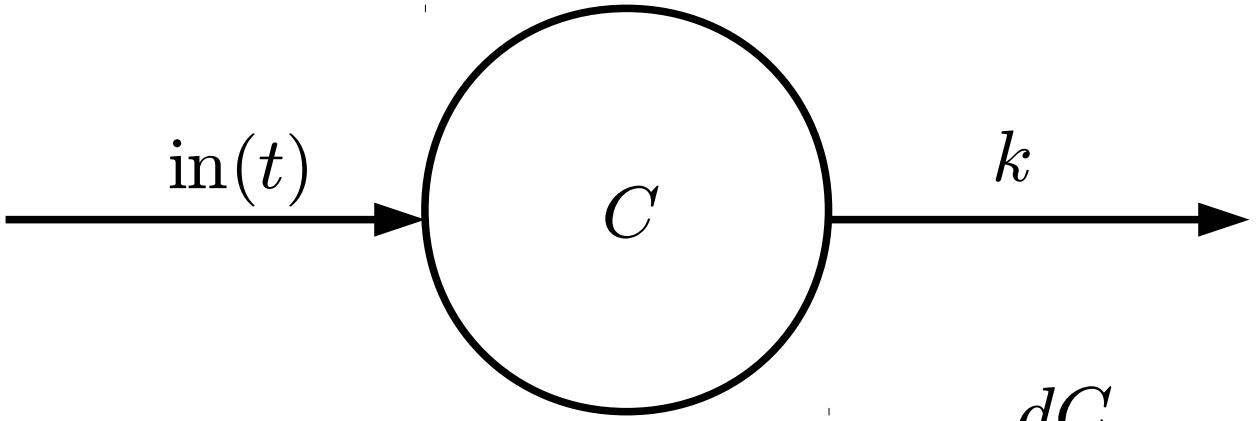
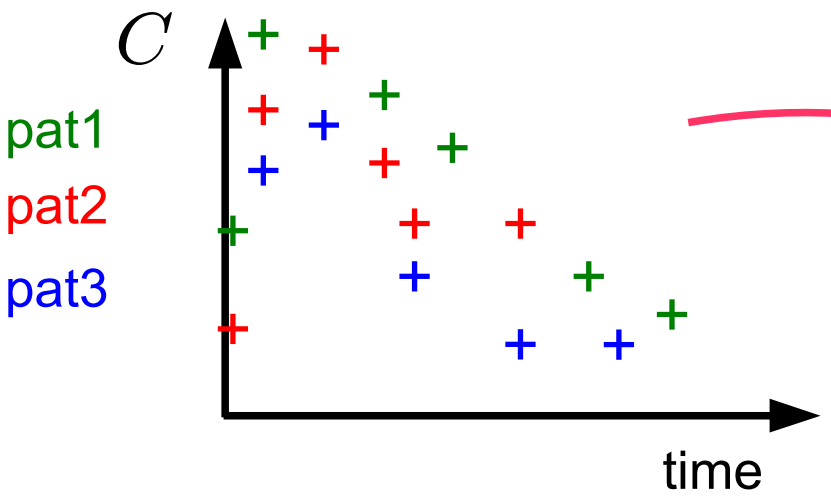
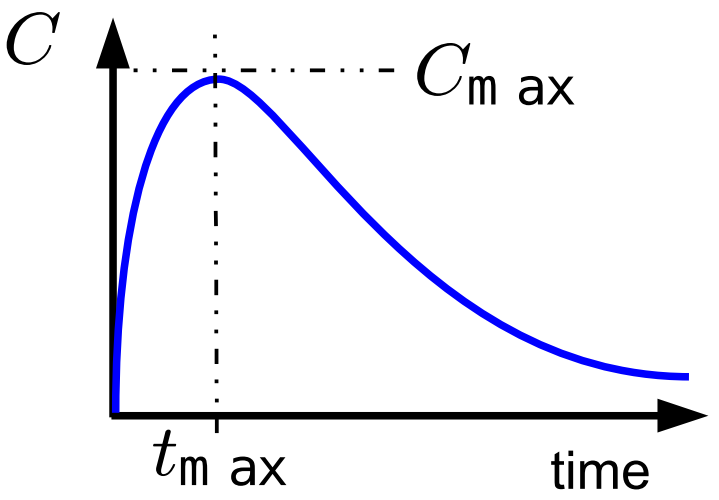

Quantitative Pharmacology
PKPD
Quantitative Systems Pharmacology
biochemical modelling
High throughput data generation

Drug discovery modelling: pharmacometrics

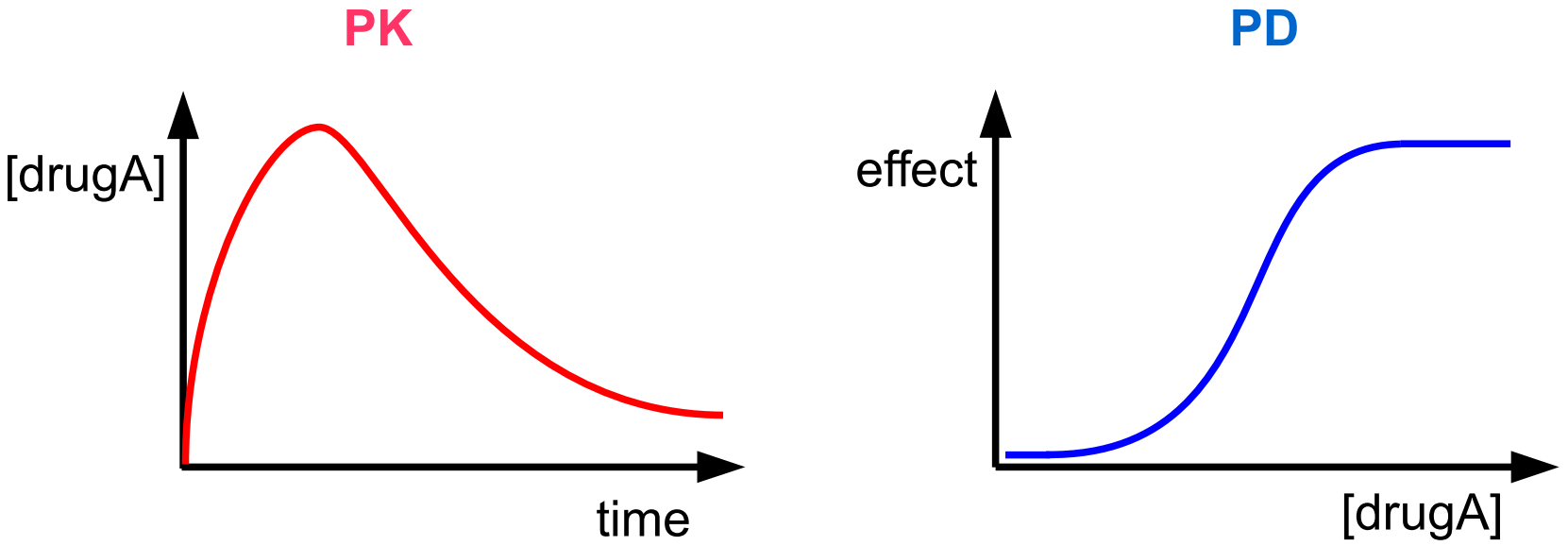


$$\frac{dC}{dt} = \text{in}(t) - k \times C$$

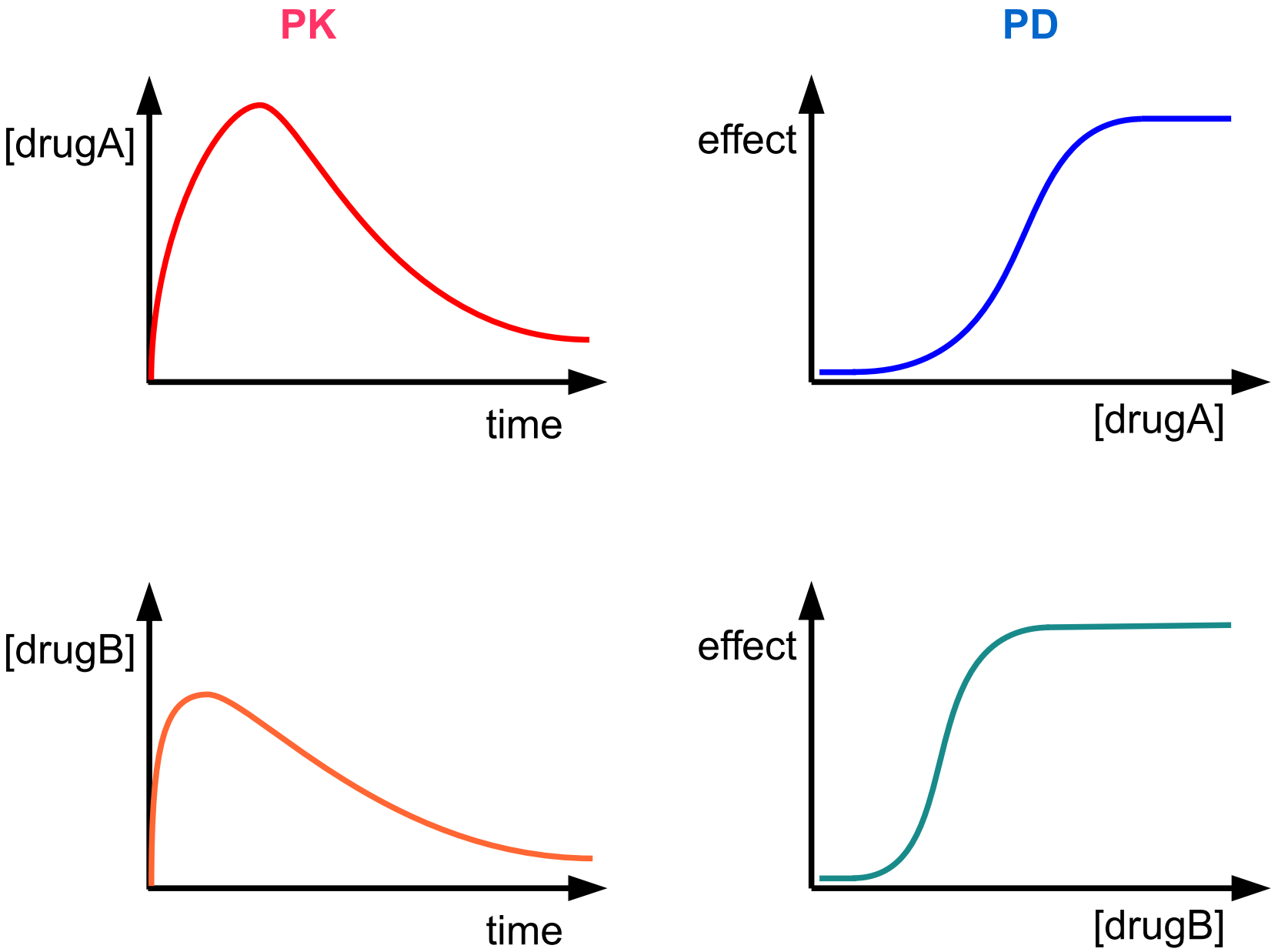




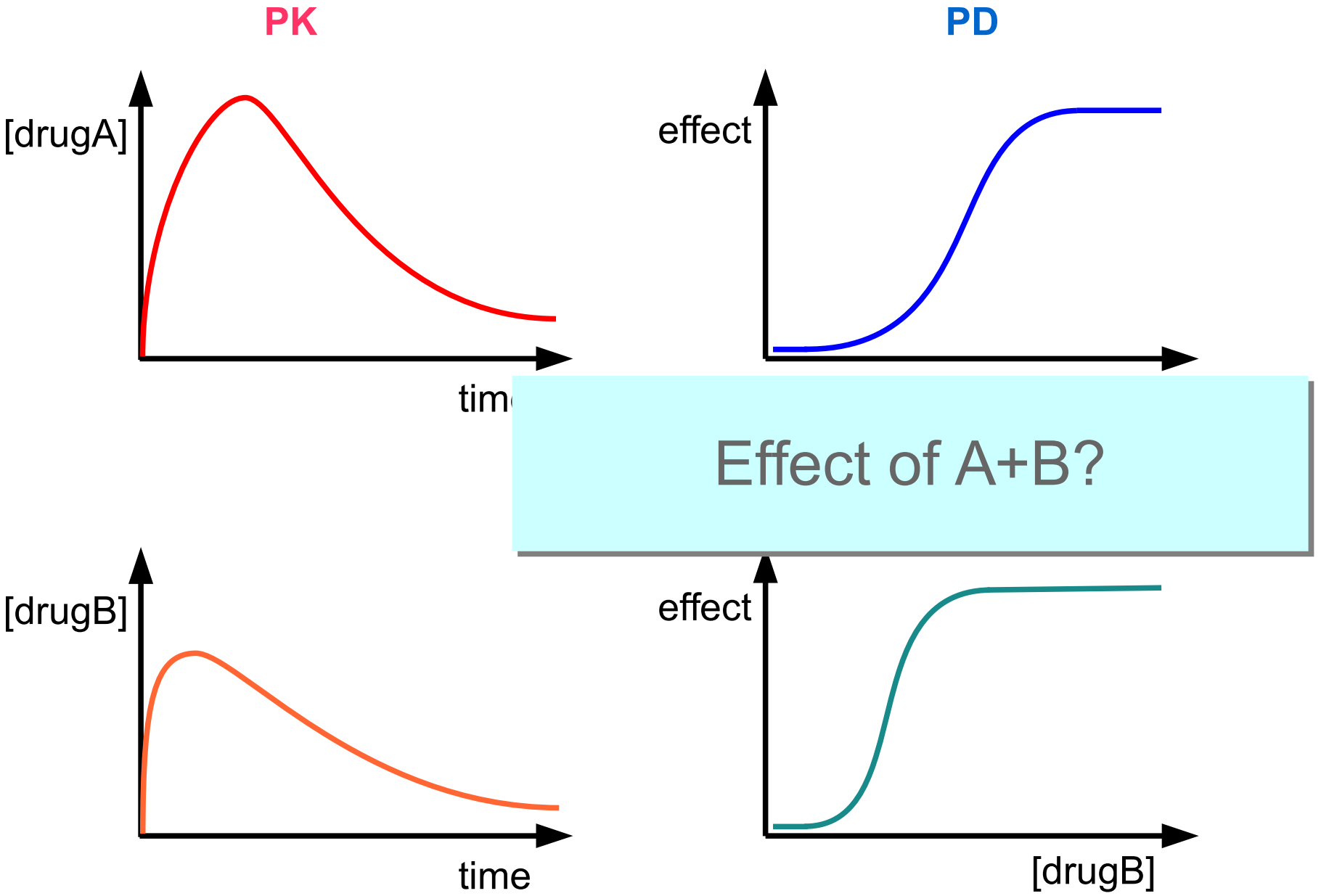
Drug discovery modelling: pharmacometrics



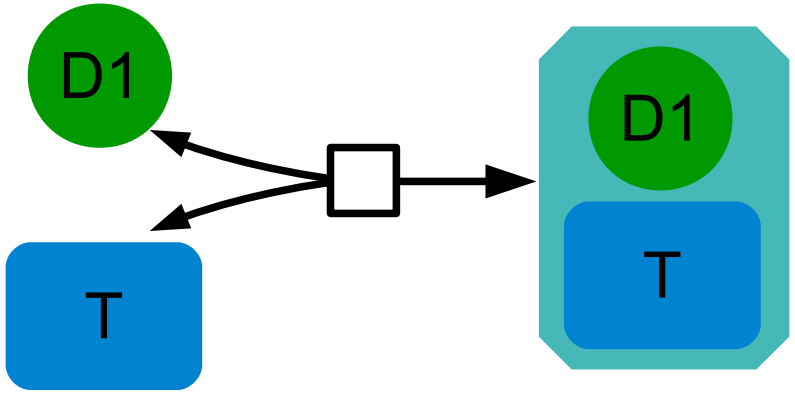
Drug discovery modelling: pharmacometrics



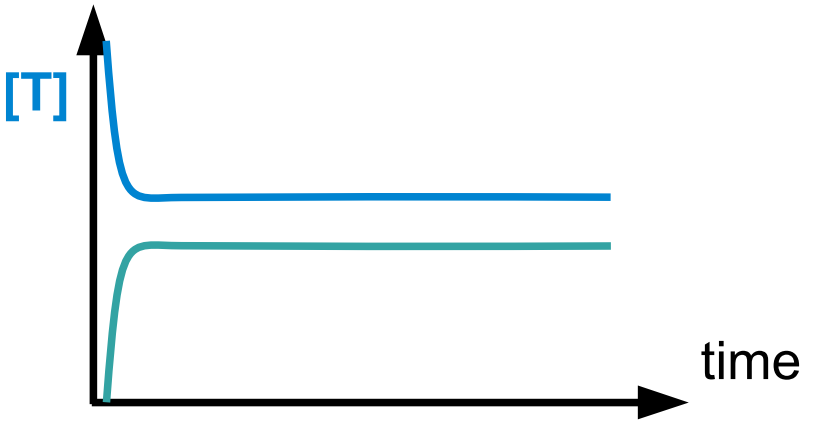
Drug discovery modelling: pharmacometrics

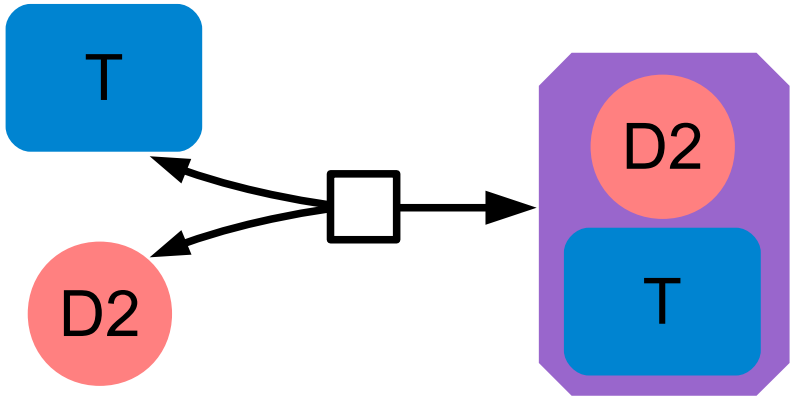


Systems modelling



$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1]$$

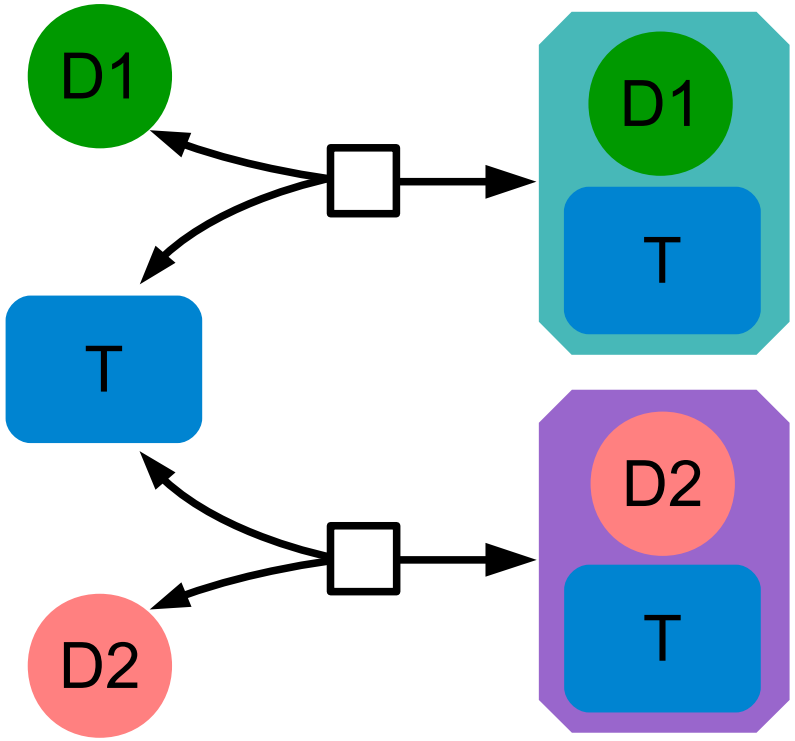


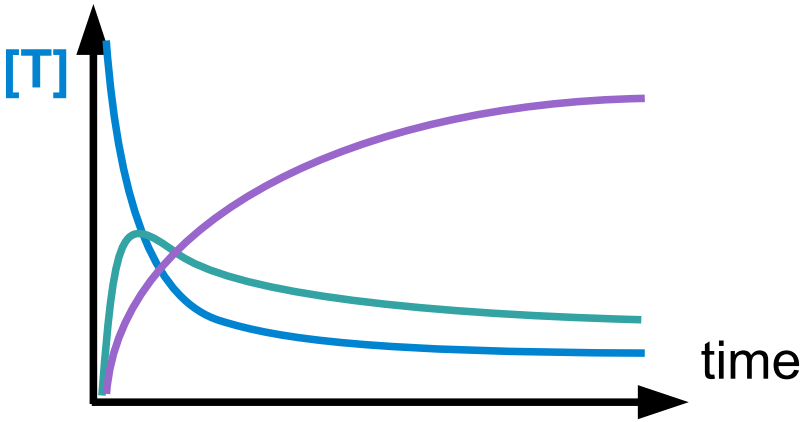


$$\frac{d[T]}{dt} = -k2 \times [T] \times [D2]$$

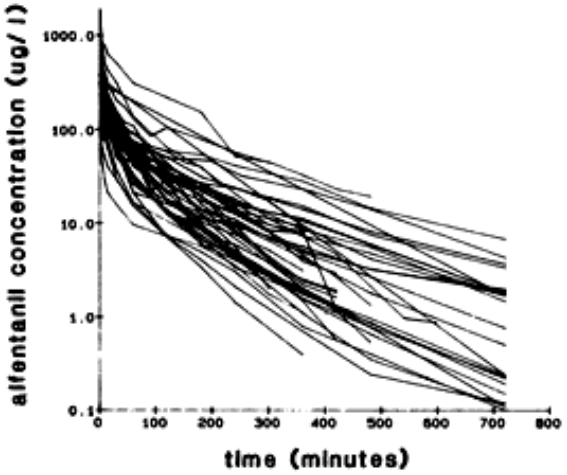
Systems modelling

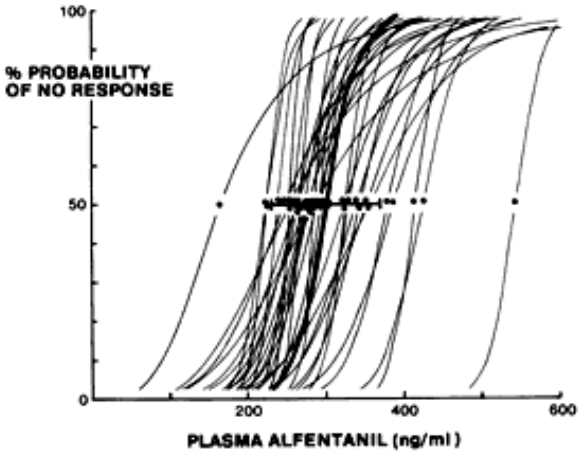
$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1] - k2 \times [T] \times [D2]$$

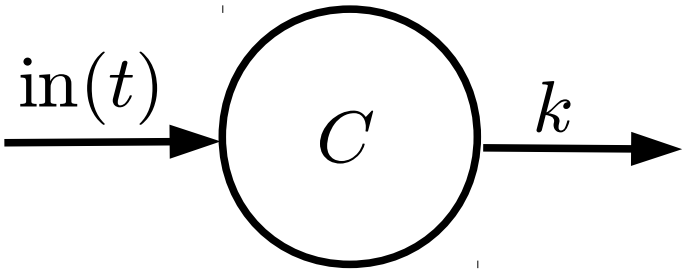


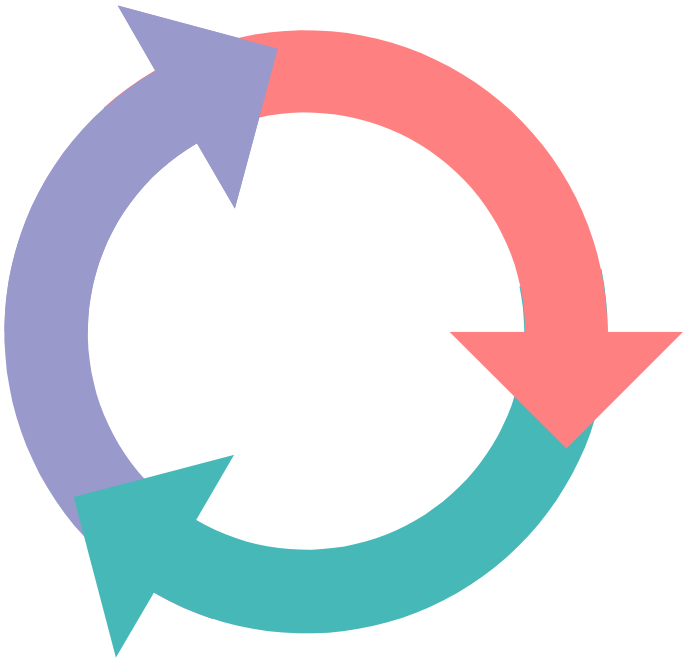


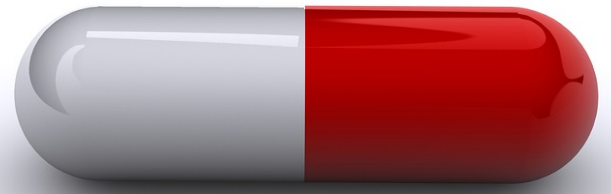
Drug discovery and pharmacometrics models



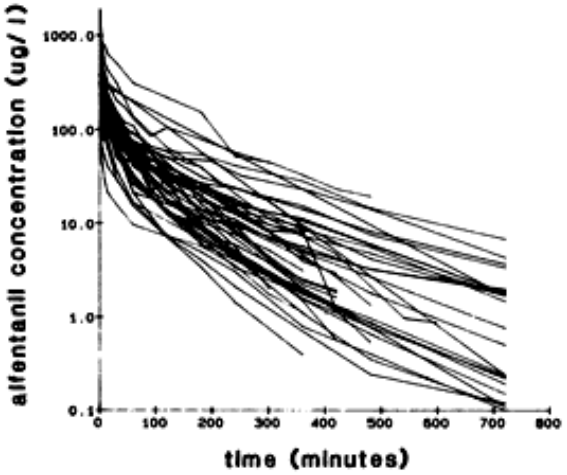


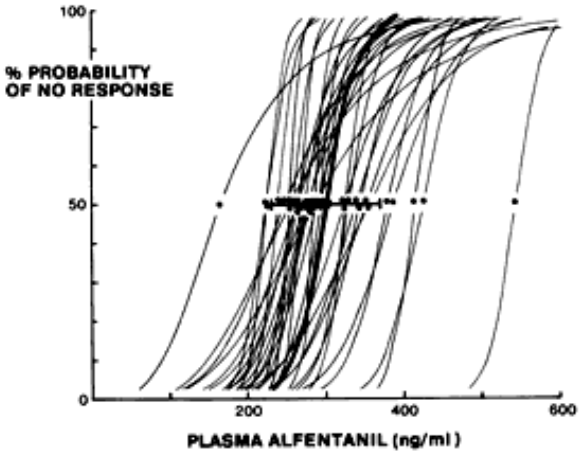


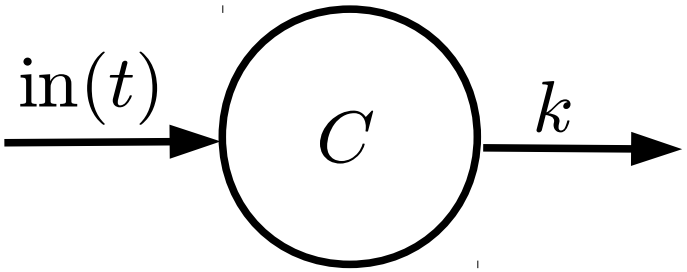


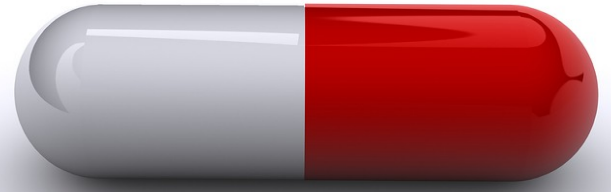


Drug discovery and pharmacometrics models

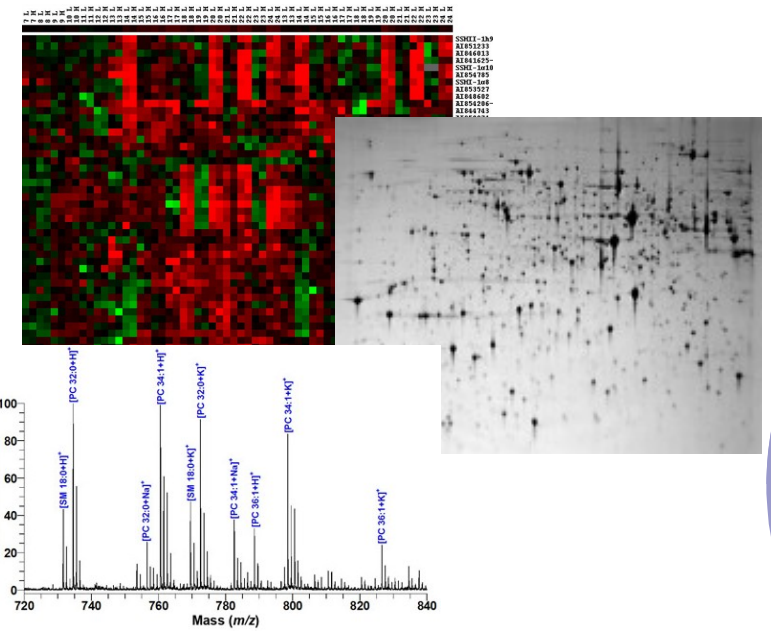


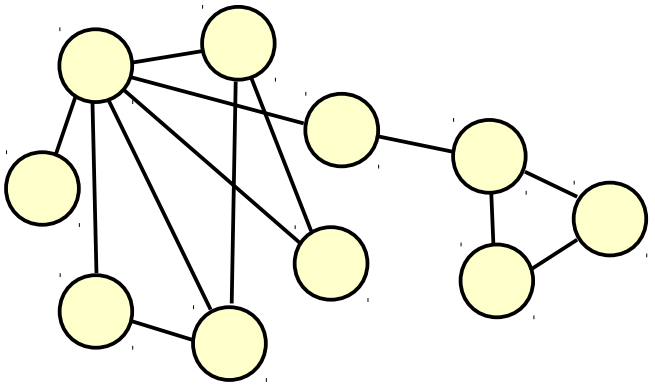


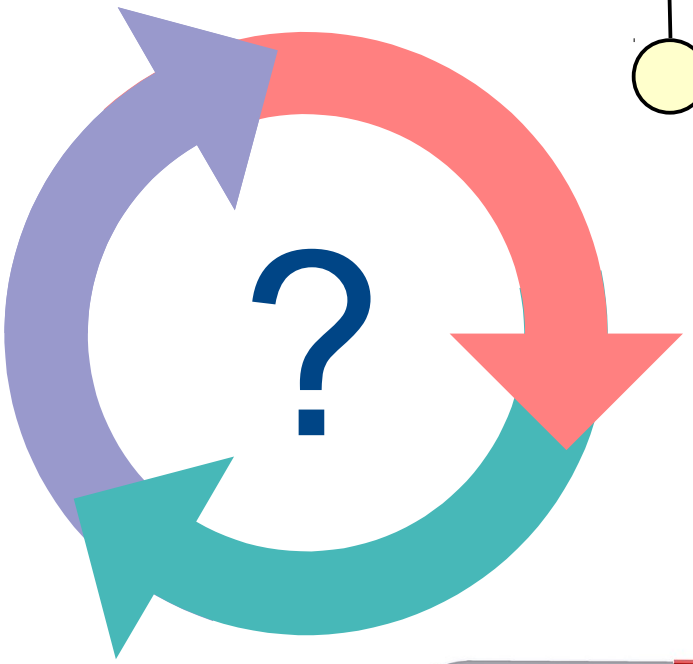


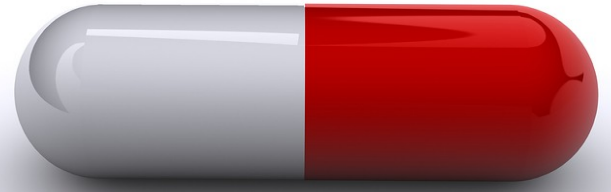


Drug discovery and omics







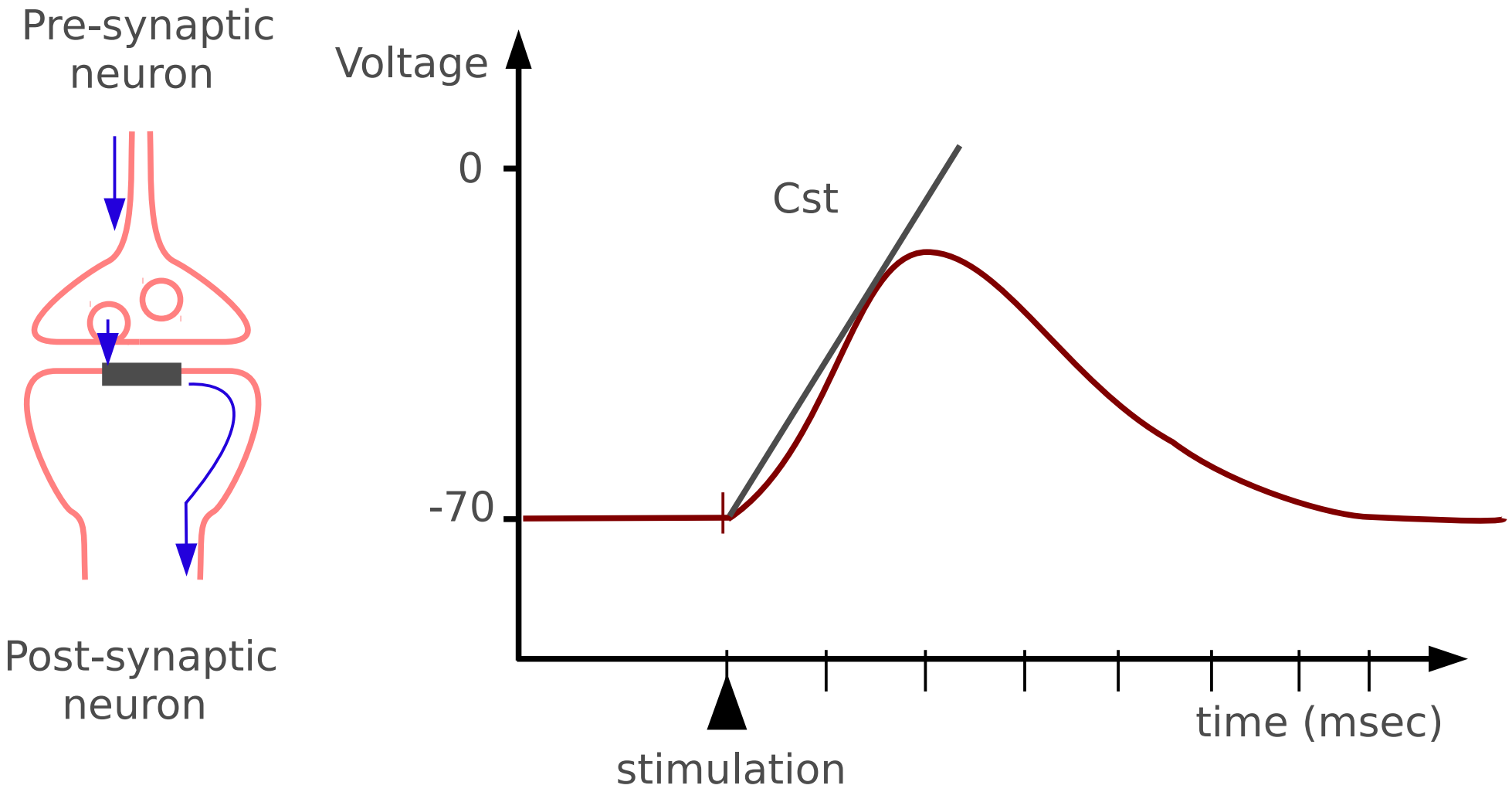


Allosteric calcium sensors in synaptic plasticity

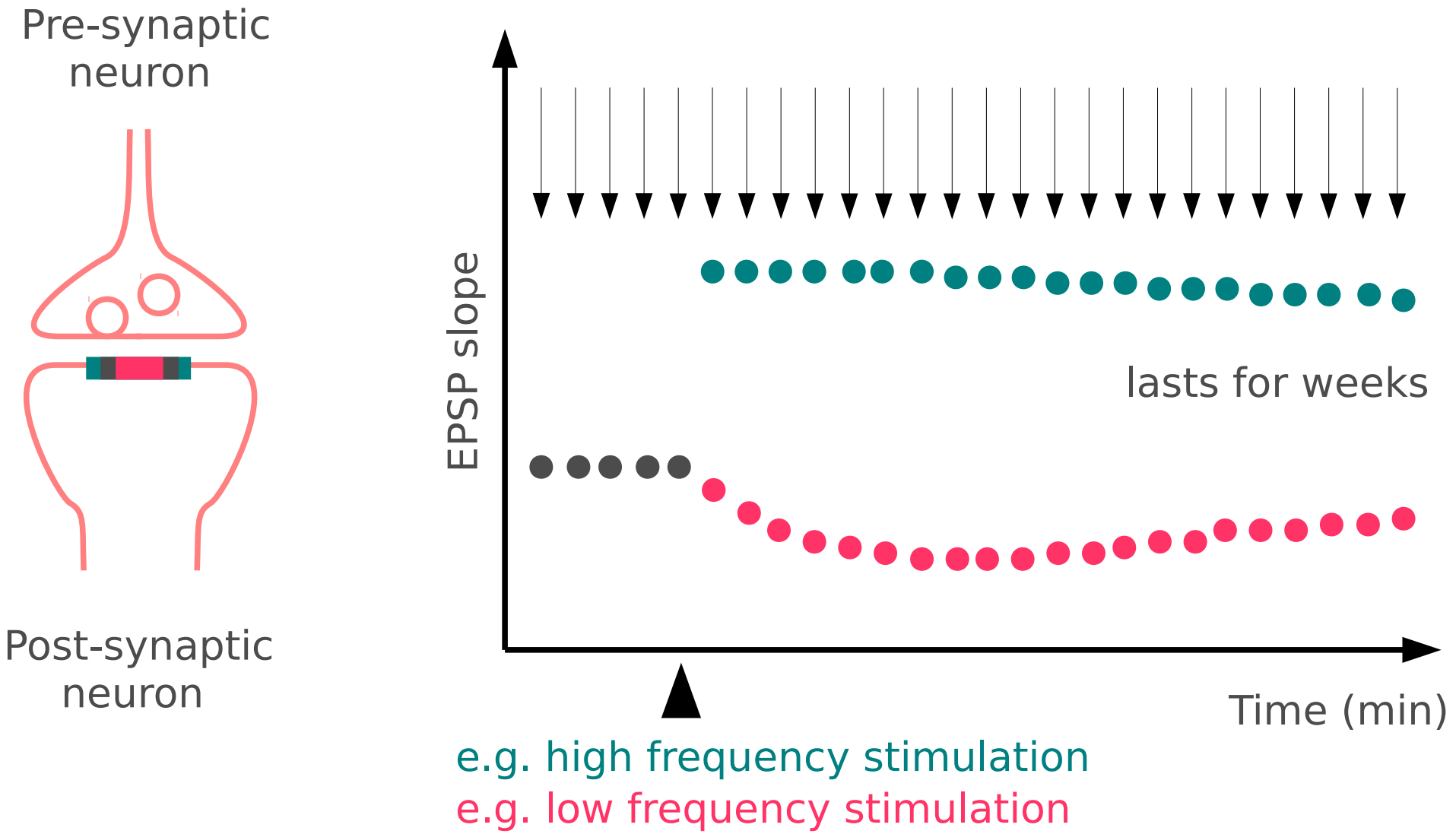
Nicolas Le Novère, Babraham Institute
n.lenovere@gmail.com
http://lenoverelab.org

Babraham Institute

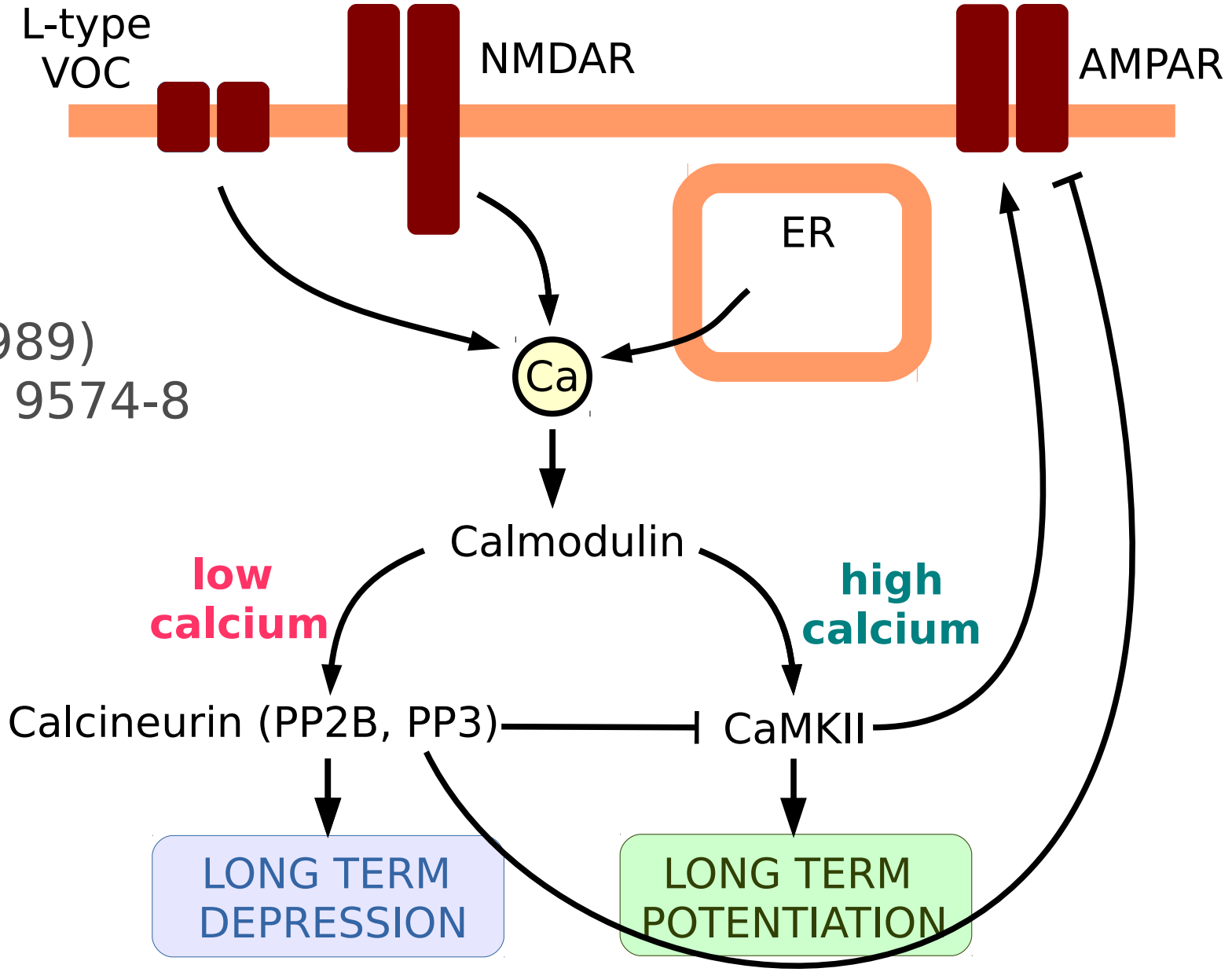
Excitatory post-synaptic potential



Bidirectional synaptic plasticity

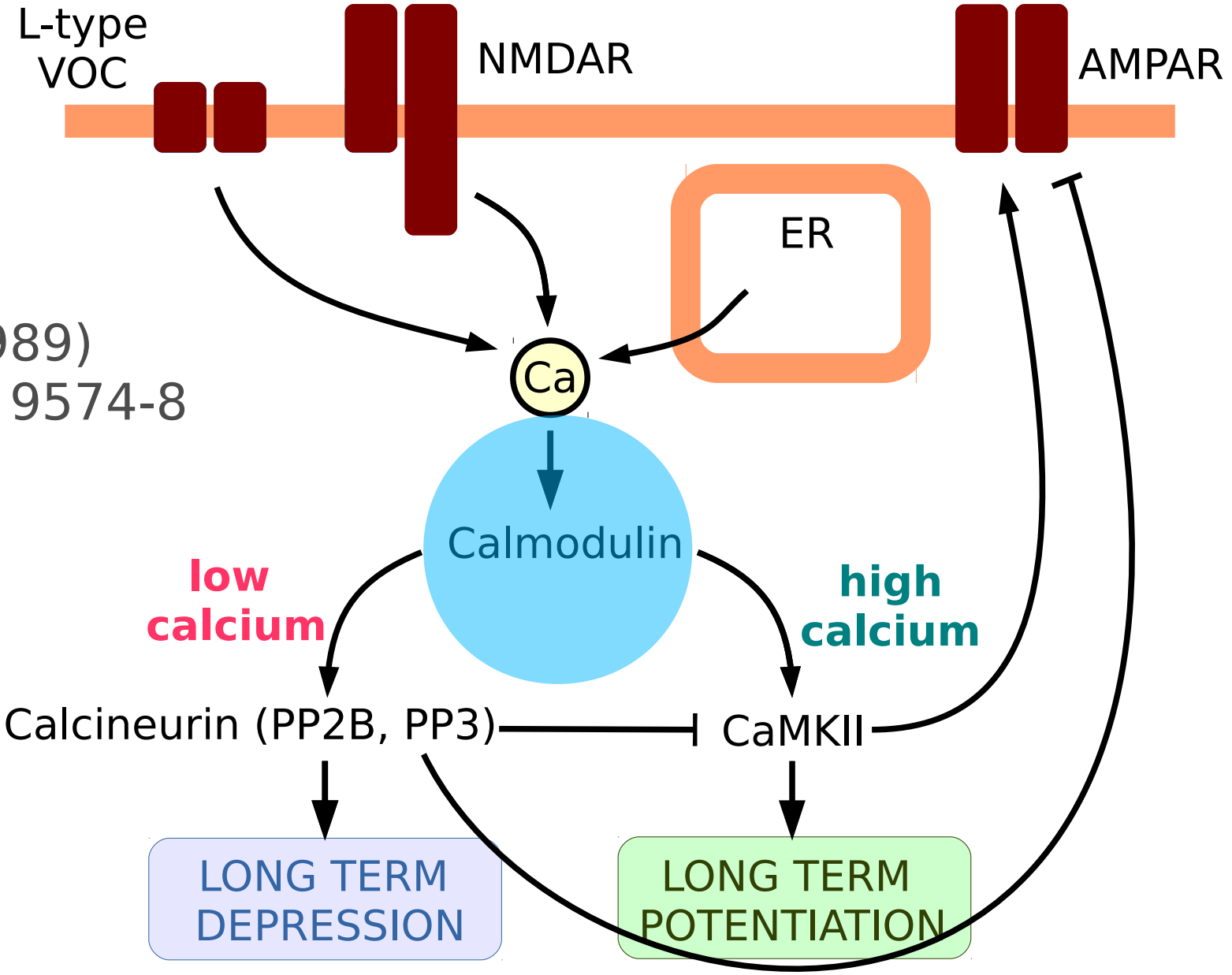


Calmodulin, the memory switch



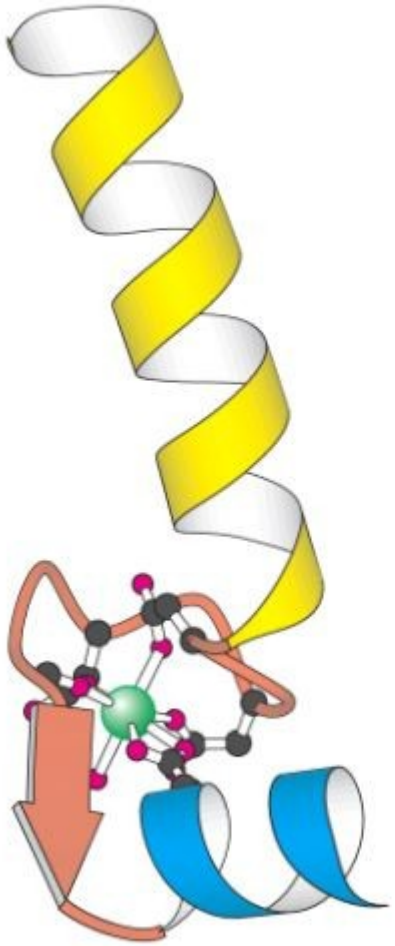
Lisman (1989)
PNAS, 86: 9574-8

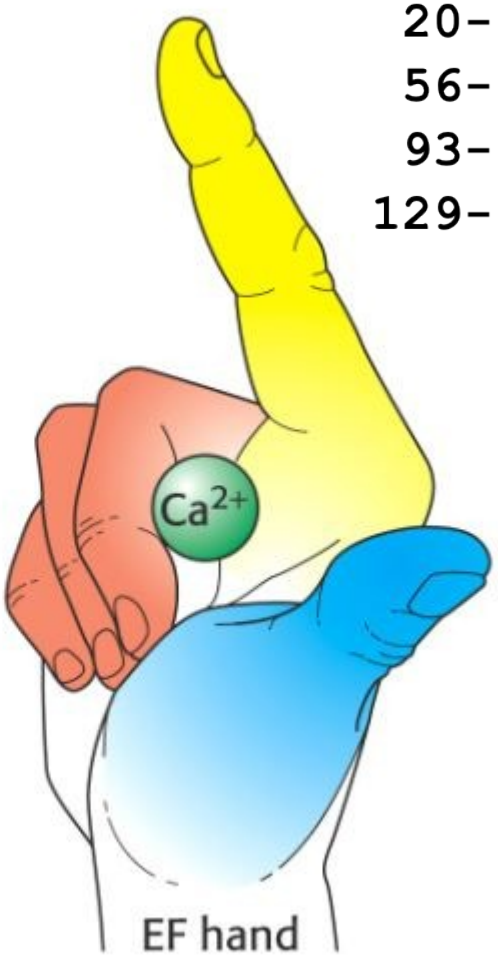
Calmodulin, the memory switch



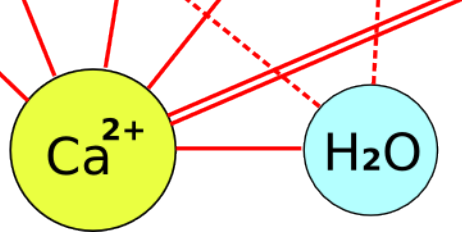
Lisman (1989)
PNAS, 86: 9574-8

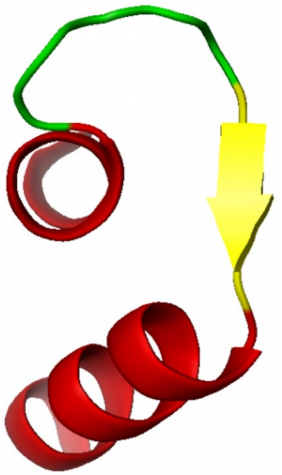
Structure of a Calmodulin Ca^{2+} binding domain

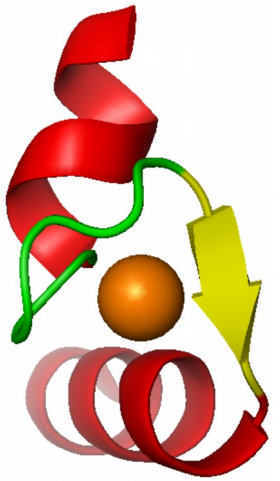




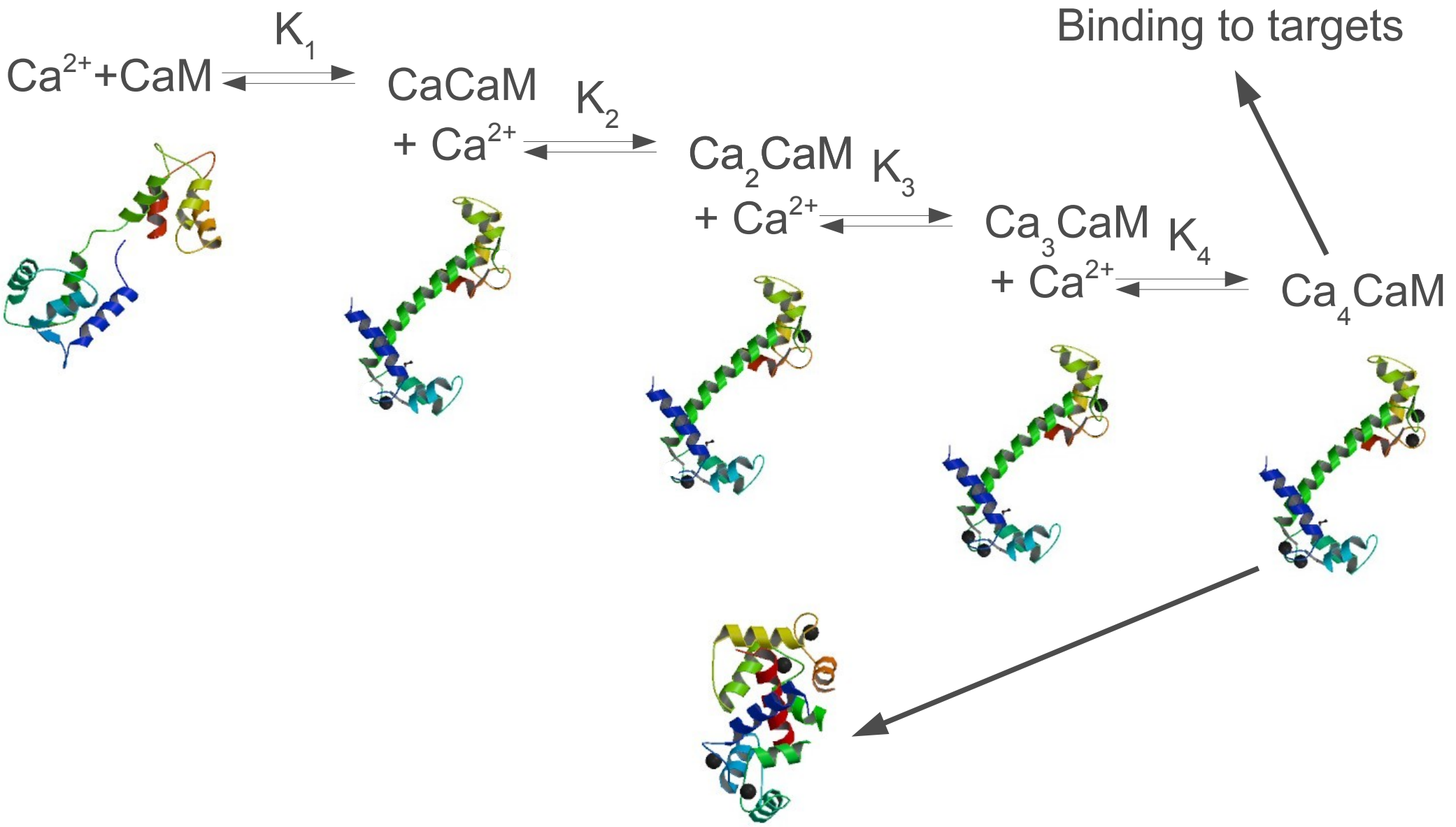
	X	Y	Z	-Y	-X	-Z	
20-	D	K	D	G	D	G	T	I	T	T	K	E	- 31
56-	D	A	D	G	N	G	T	I	D	F	P	E	- 67
93-	D	K	D	G	N	G	Y	I	S	A	A	E	-104
129-	D	I	D	G	D	G	Q	V	N	Y	E	E	-140



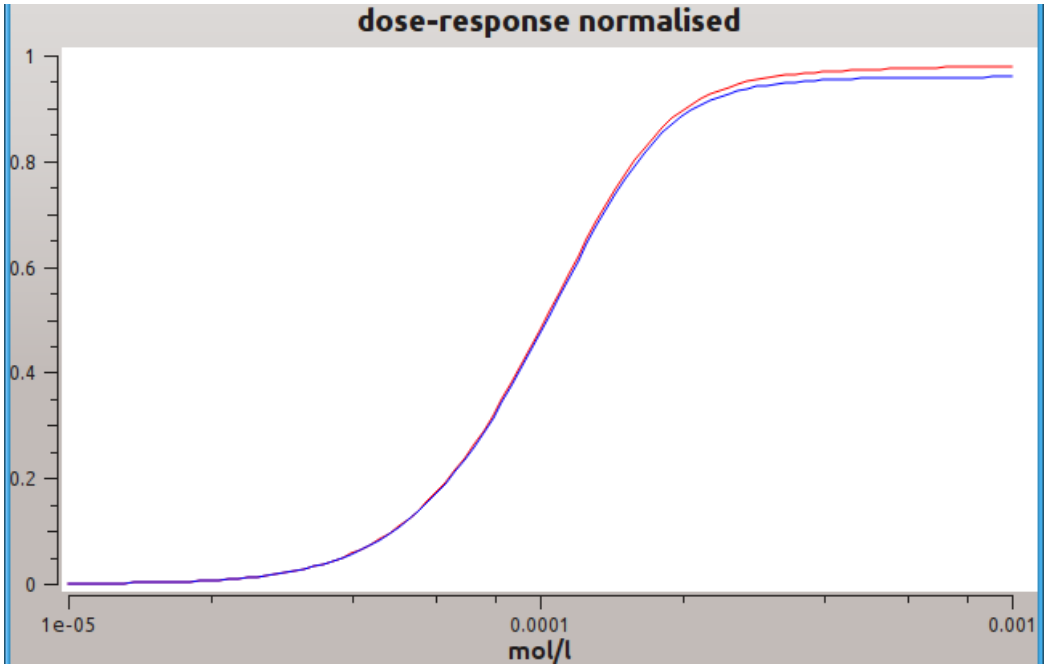




Corresponding induced-fit model

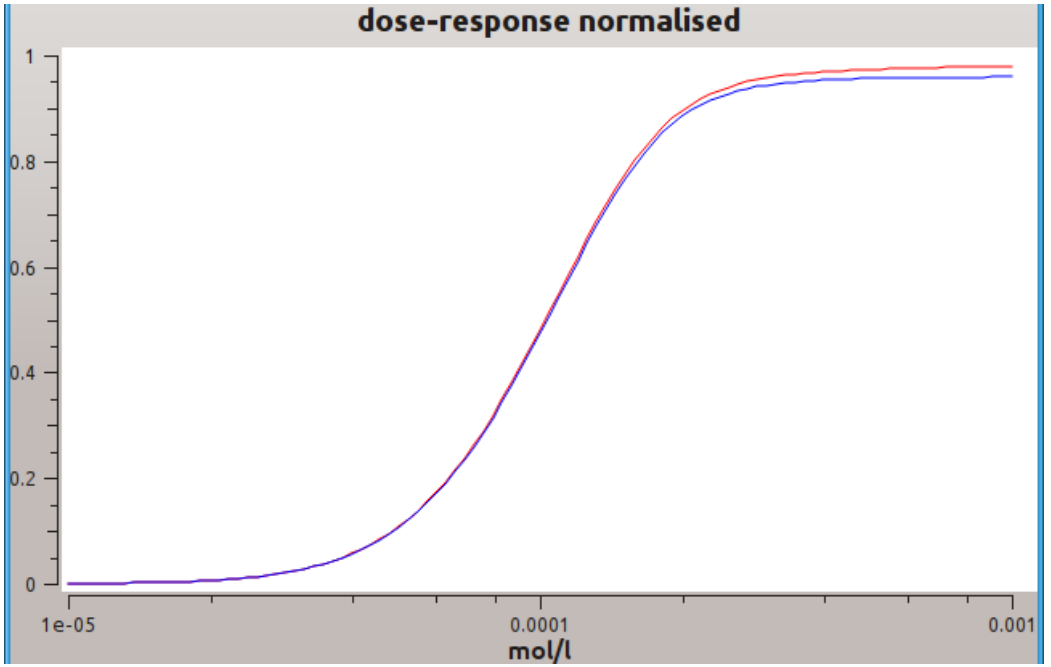


That does not work ...



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

We knew it would not work



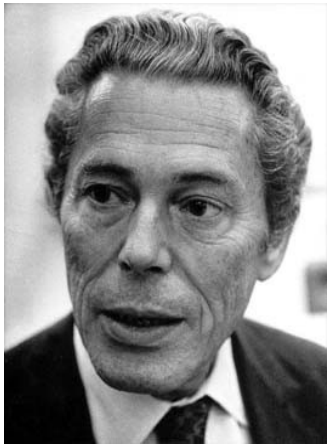
[CaN]=[CamKII]=[CaM]/10 ;
Kd_CaMKII = 10xKd_CaN;
Software COPASI

- 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])

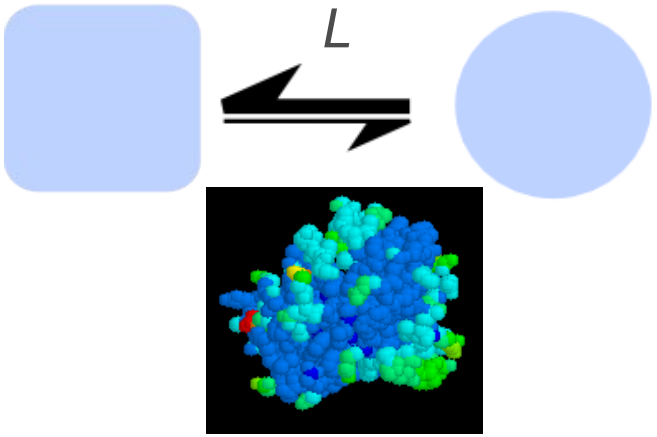
Monod, Wyman, Changeux (1965)

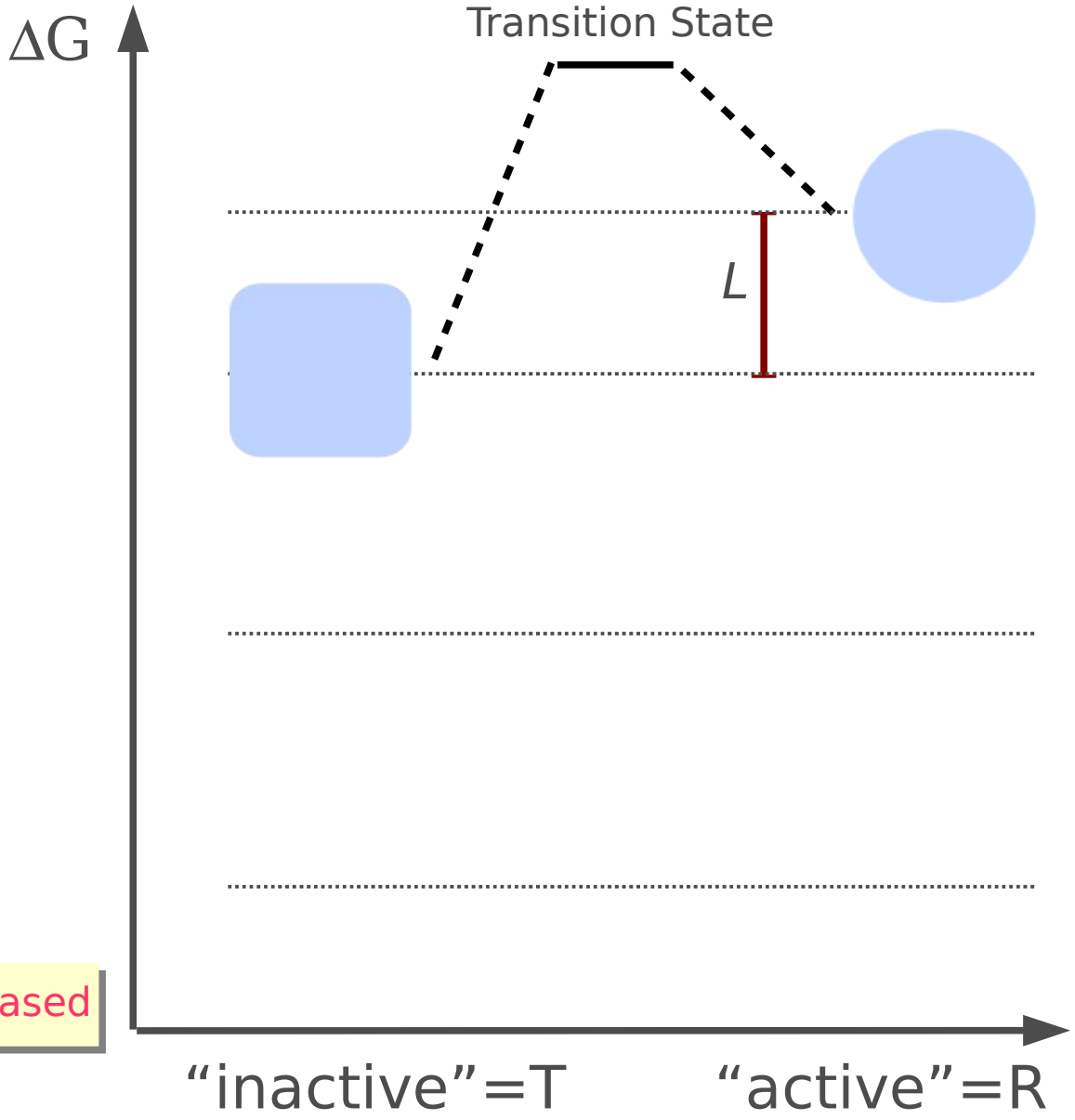
On the nature of allosteric transitions: a plausible model

J Mol Biol, 12: 88-118



1 Modulation of thermal equilibria ≠ induced-fit

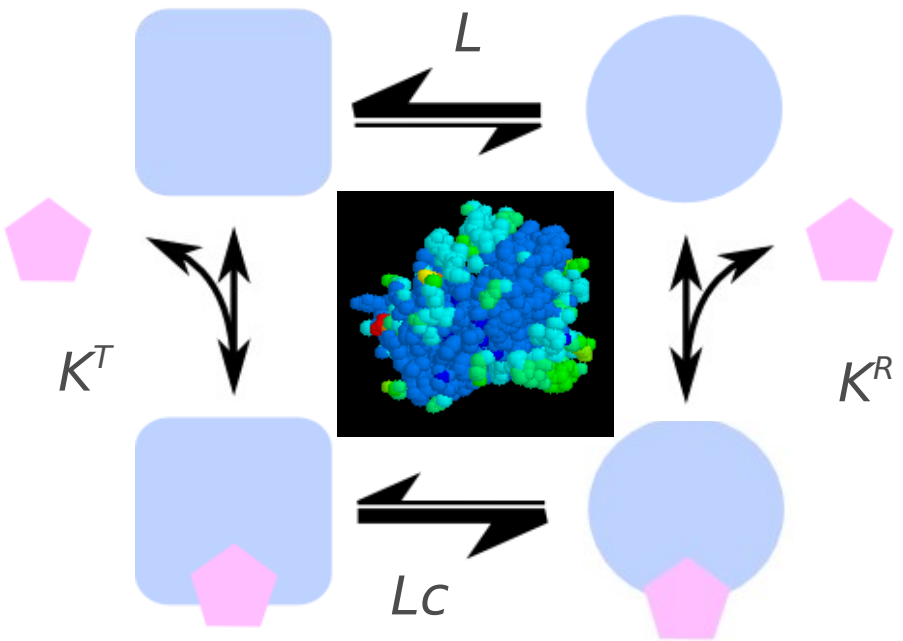




$$L = \frac{[T_0]}{[R_0]}$$

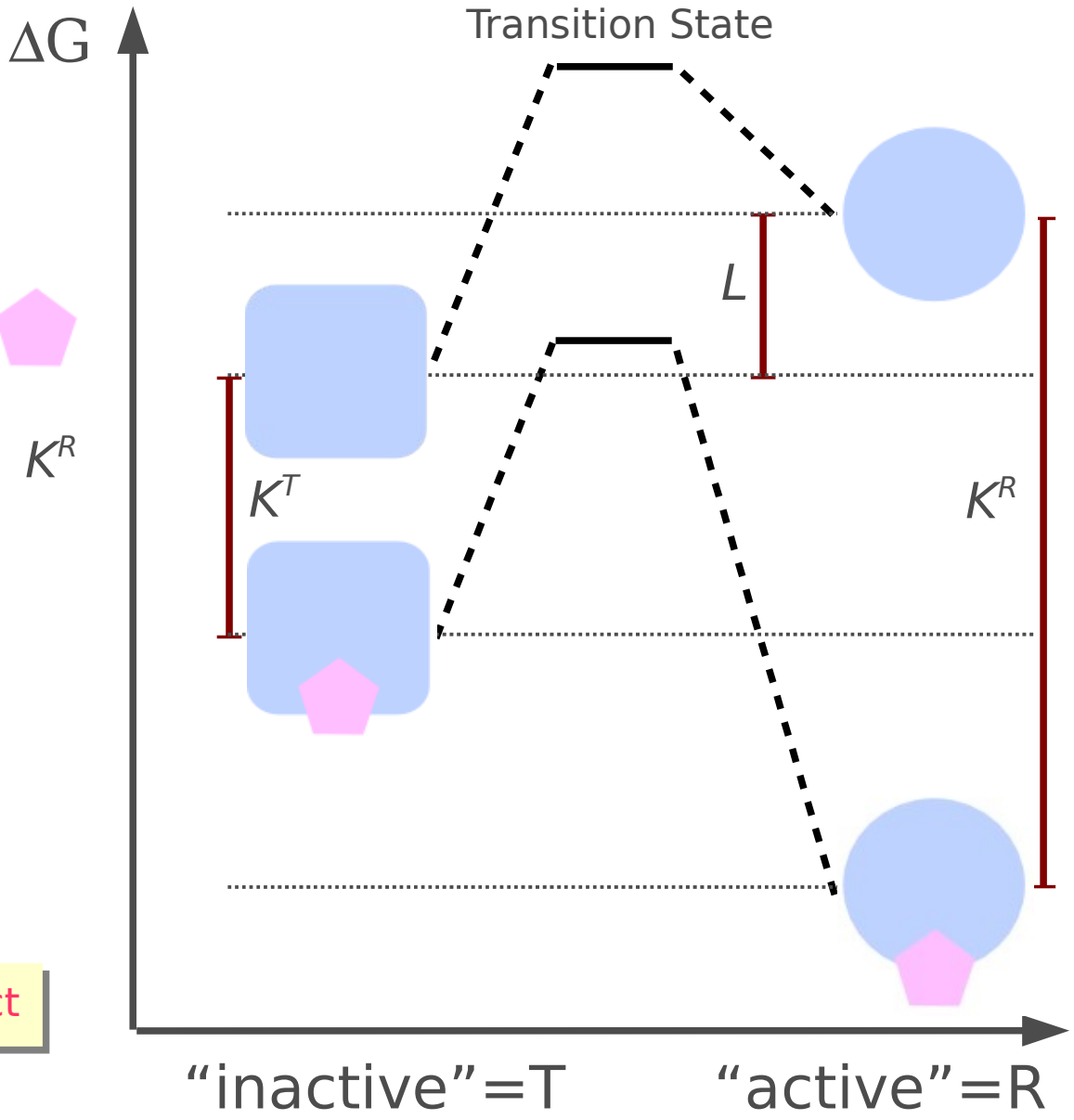
$L \gg 1 \Rightarrow$ Equilibrium strongly biased

1 Modulation of thermal equilibria ≠ induced-fit



$$L = \frac{[T_0]}{[R_0]} \qquad c = \frac{K^R}{K^T}$$

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



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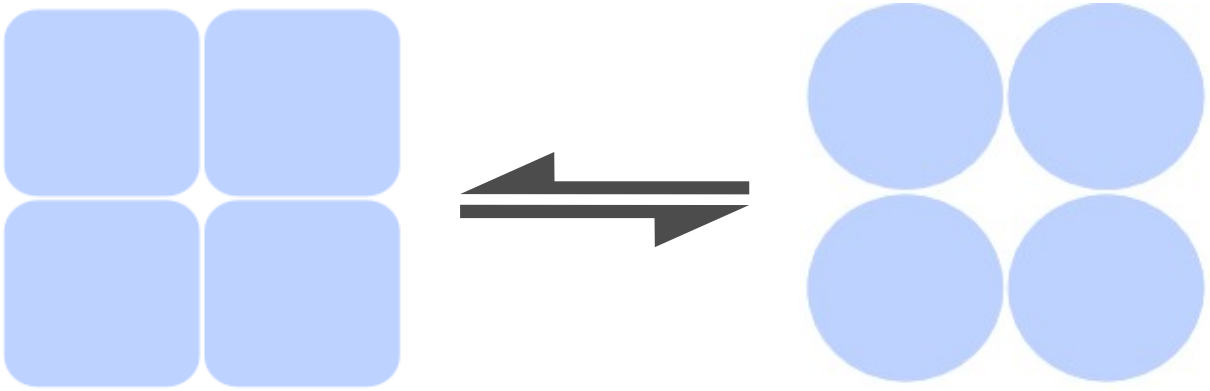
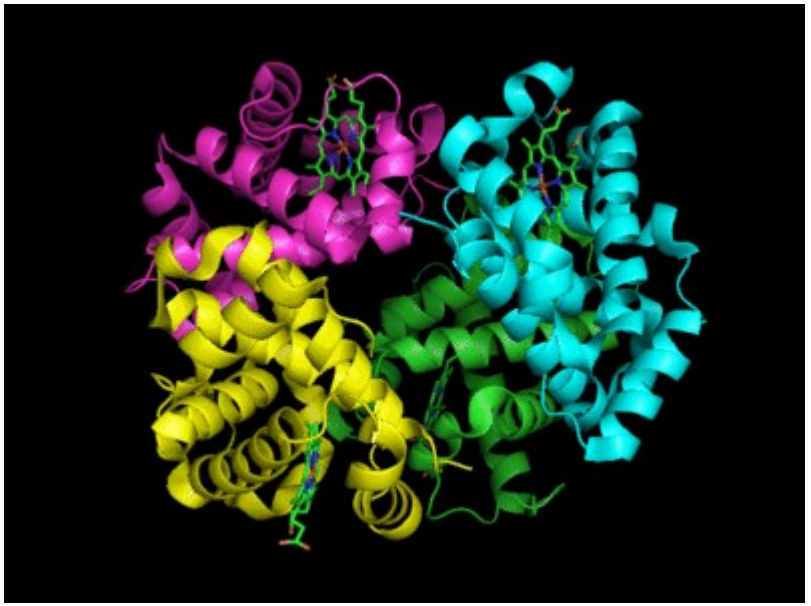
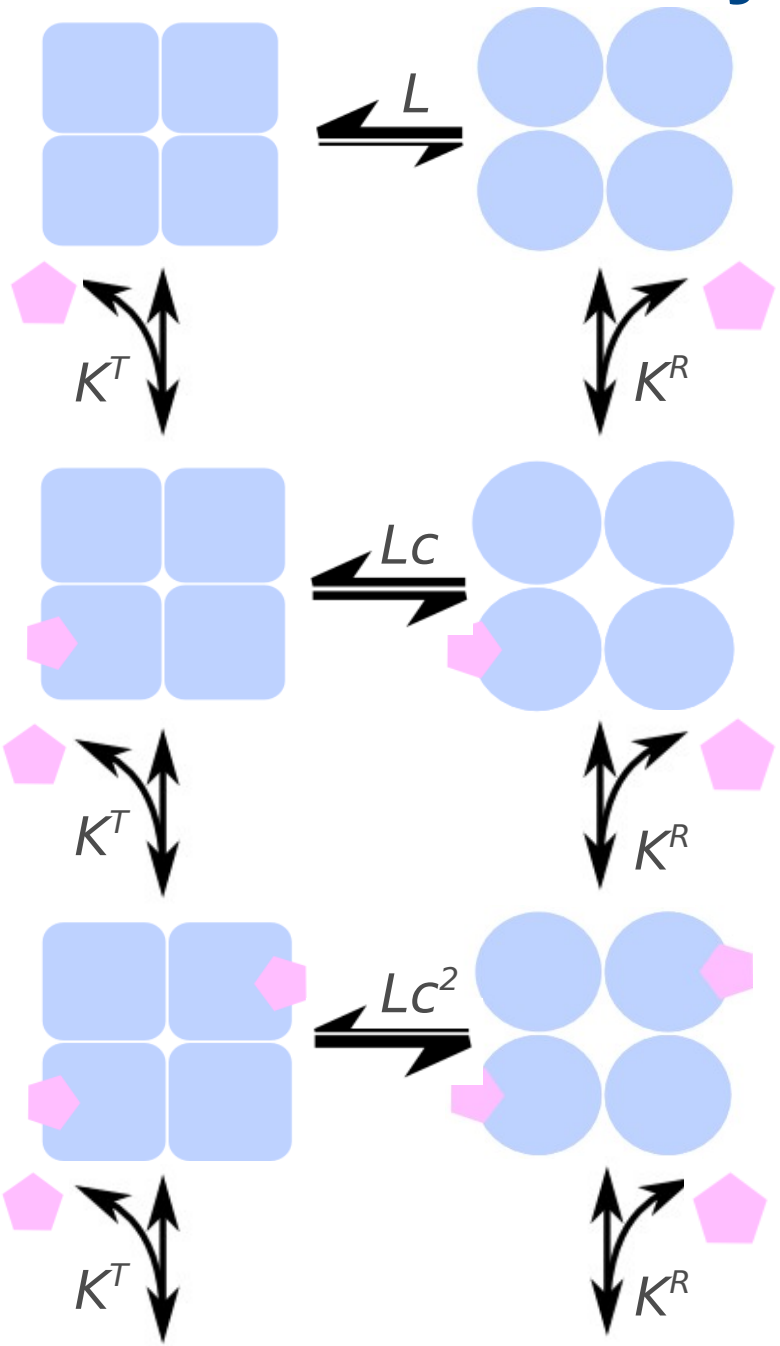
2 Concerted transitions ≠ sequential model

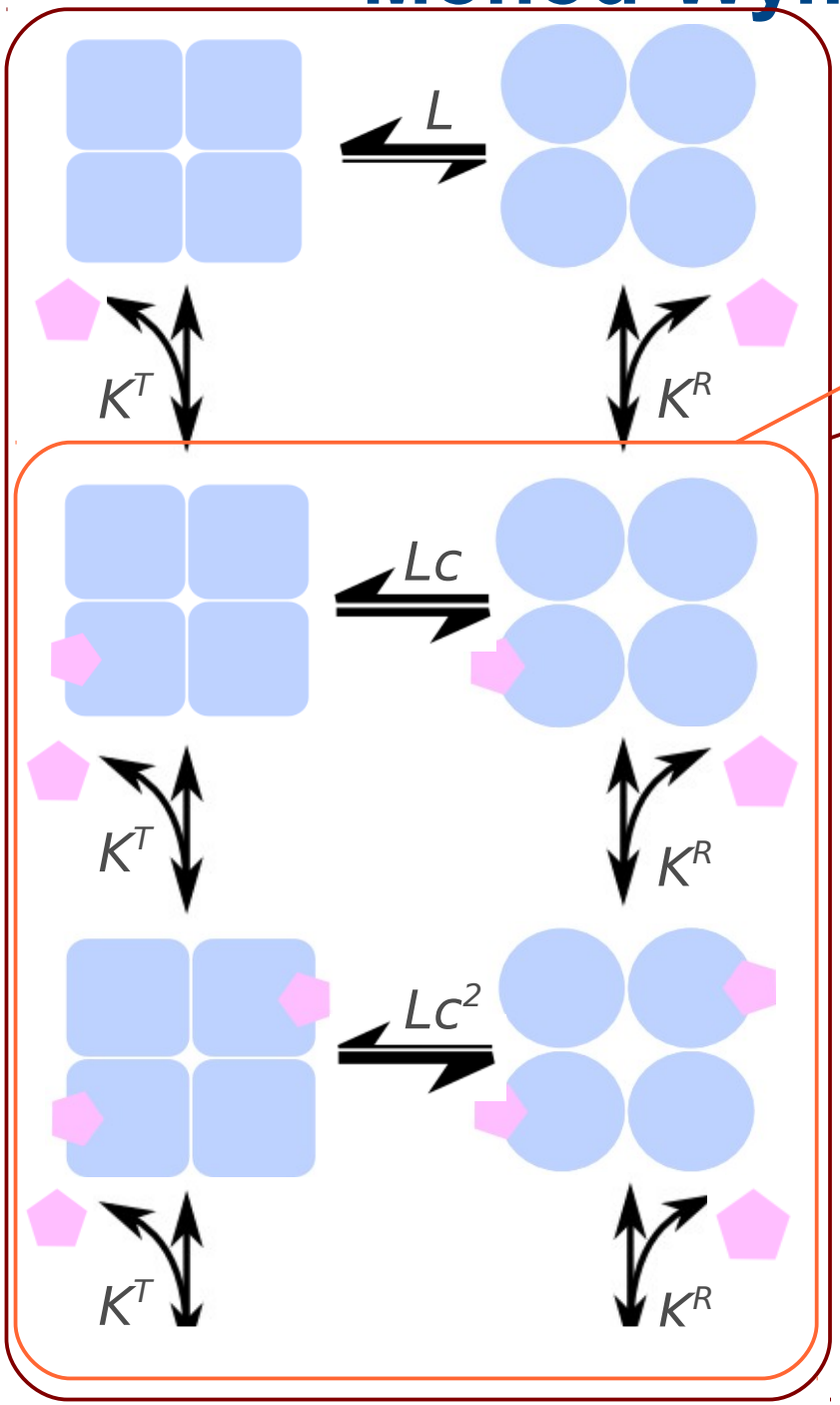




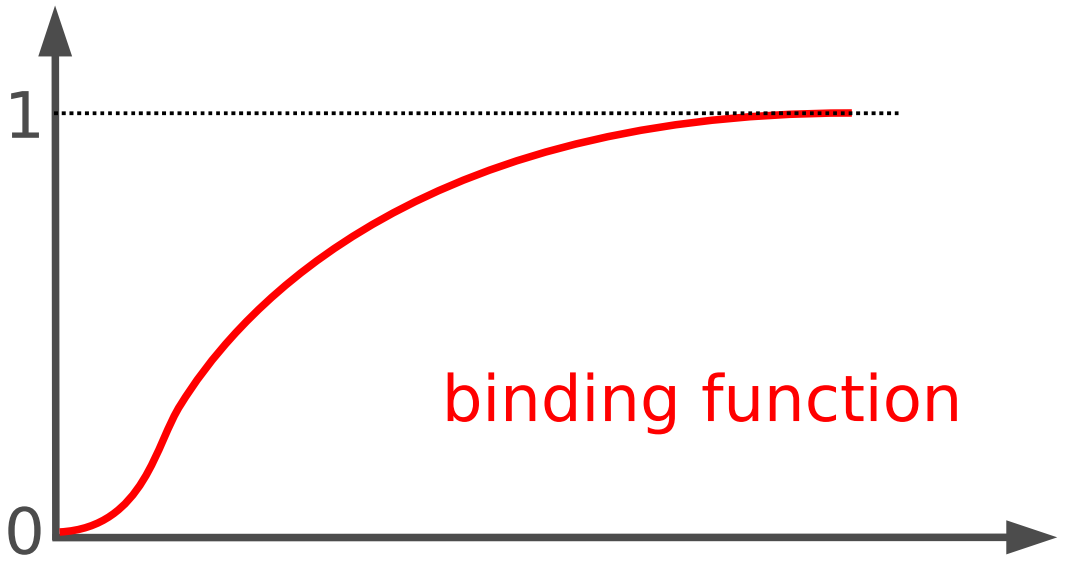
Monod-Wyman-Changeux model



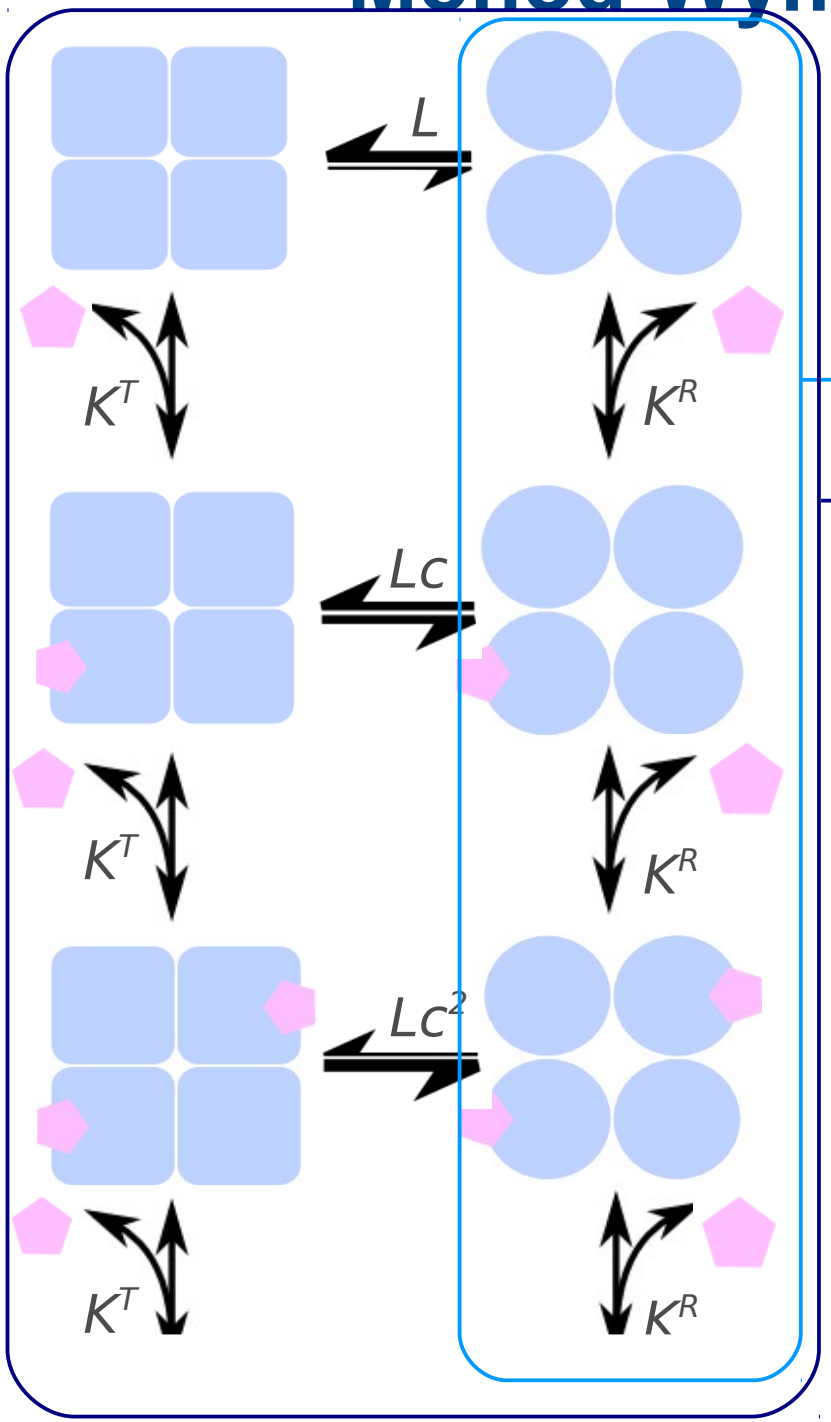
Monod-Wyman-Changeux model



$$\frac{\text{this}}{\text{that}} = \bar{Y}$$

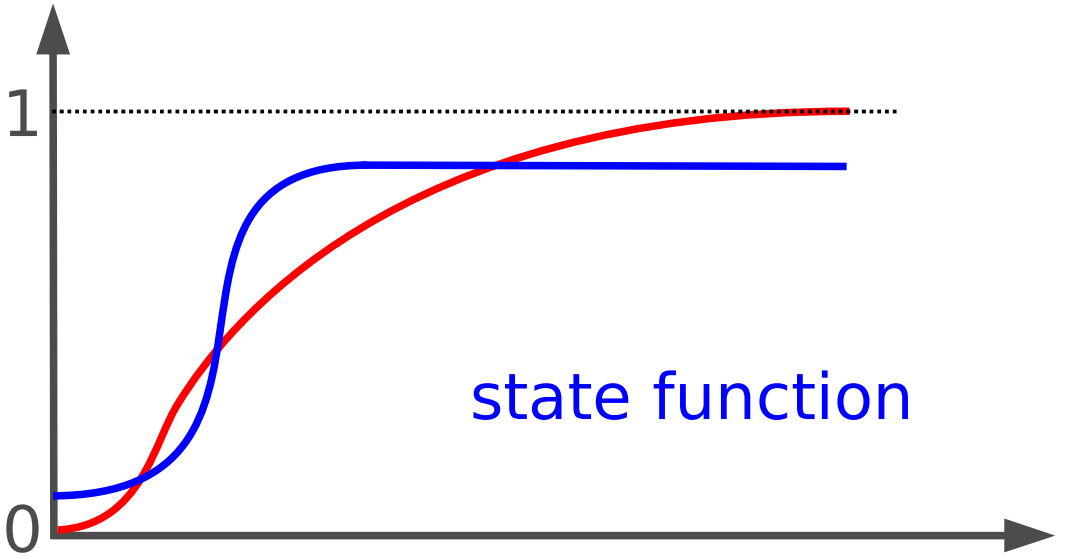


Monod-Wyman-Changeux model



$\bar{Y}$

this
—— = $\bar{R}$
that



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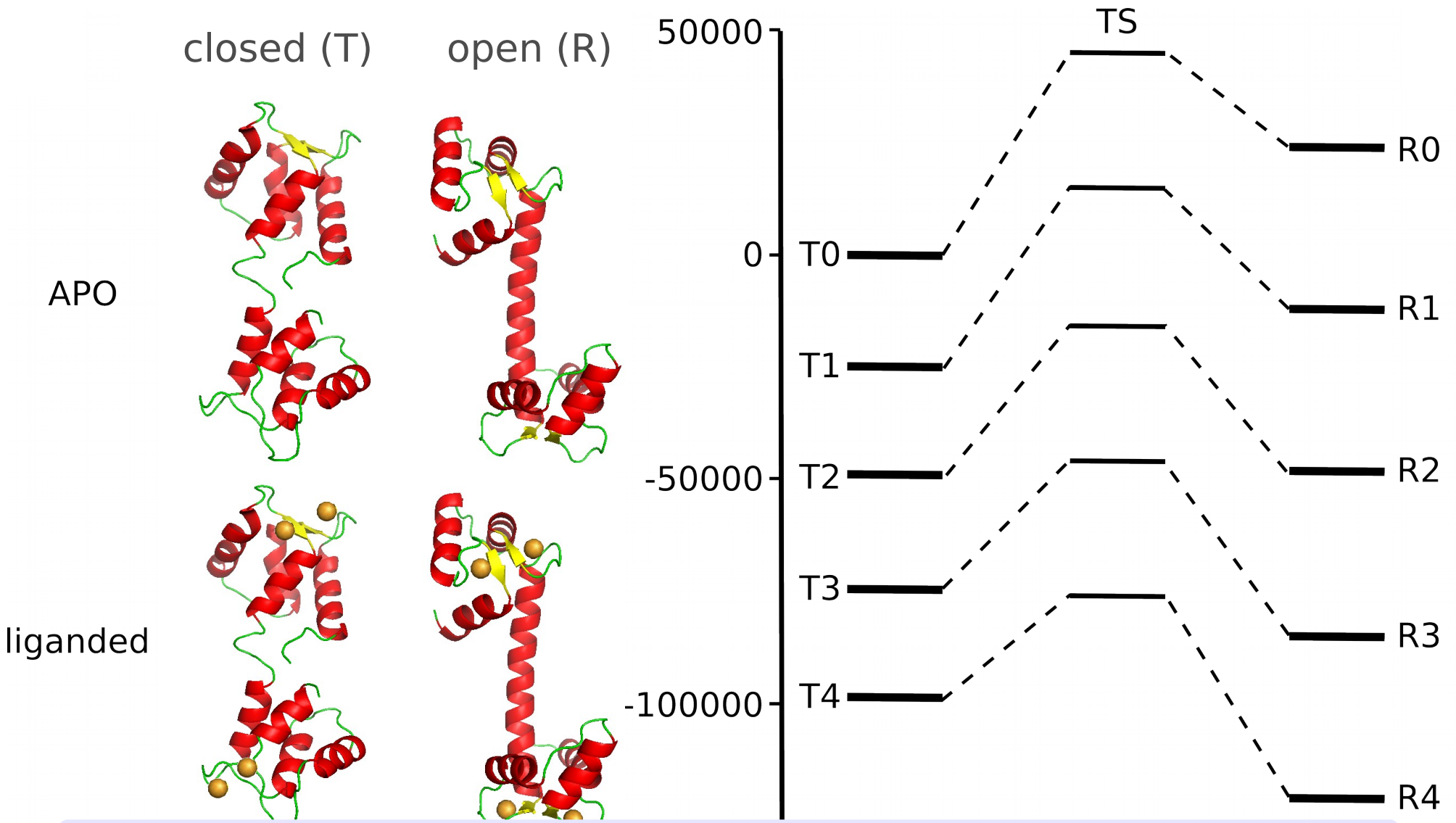
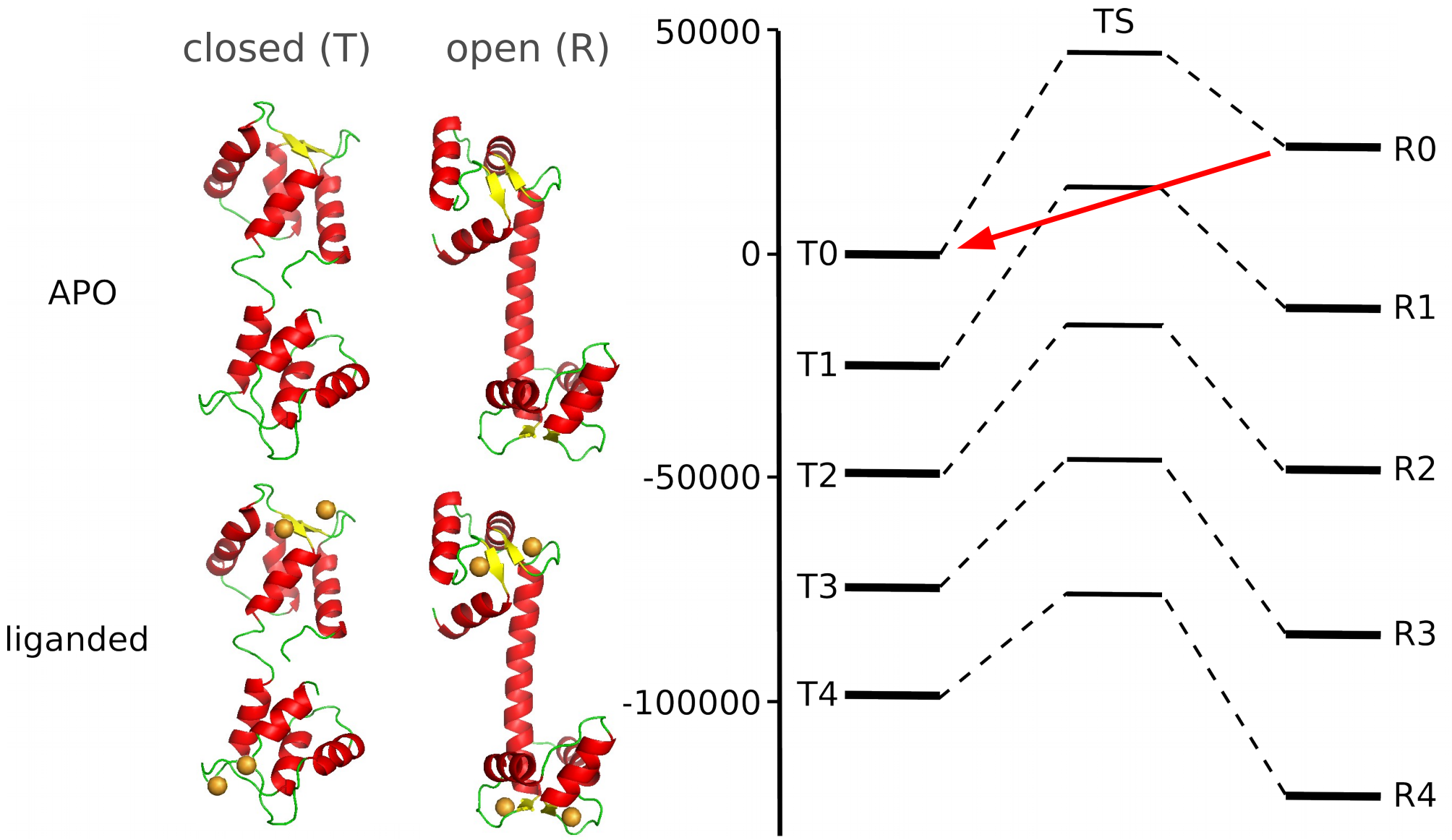
Allosteric model of Calmodulin activation

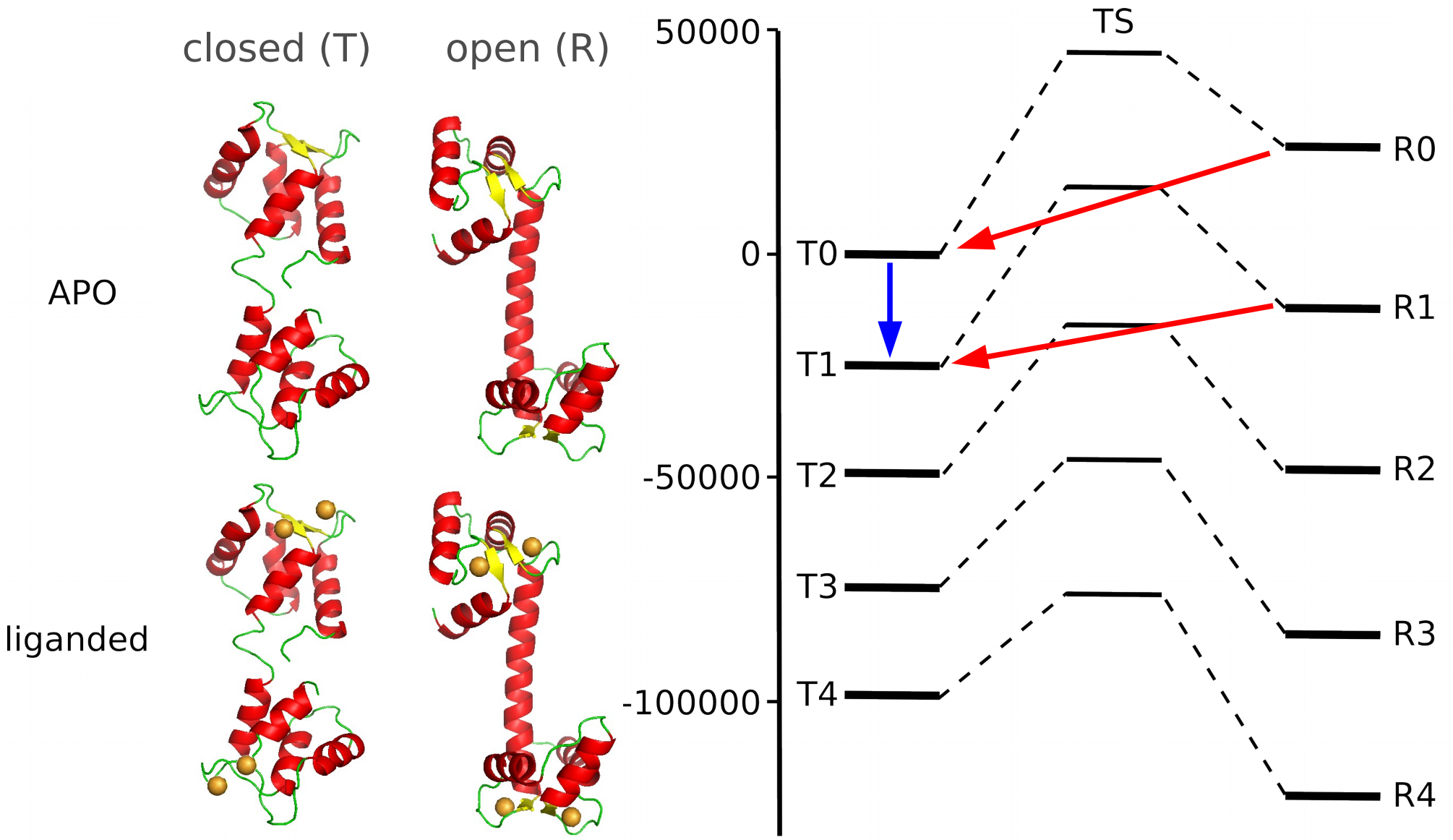


Stefan MI, Edelstein SJ, Le Novère N (2008) *Proc Natl Acad Sci USA*, 105:10768-10773

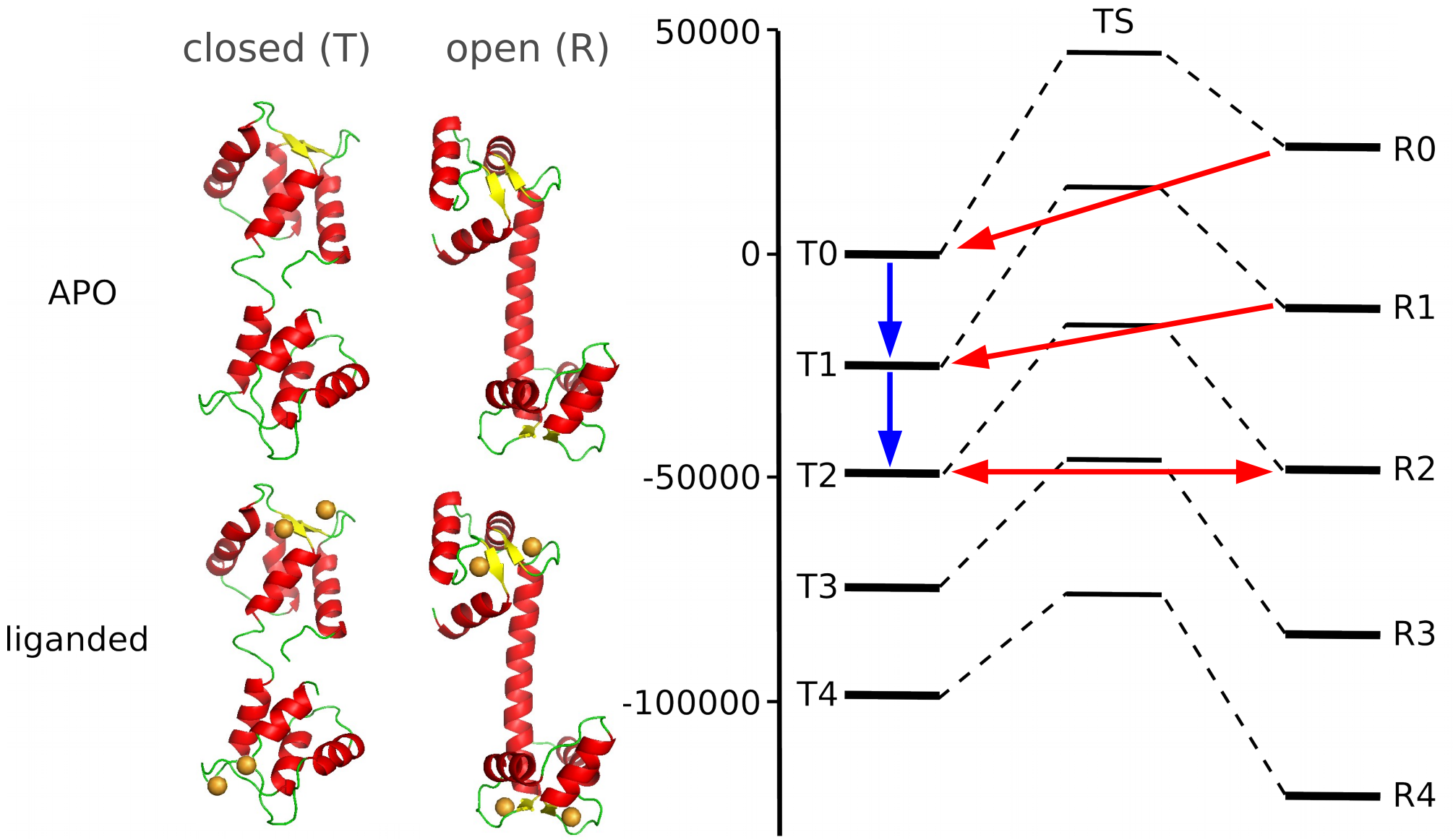
Allosteric model of Calmodulin activation



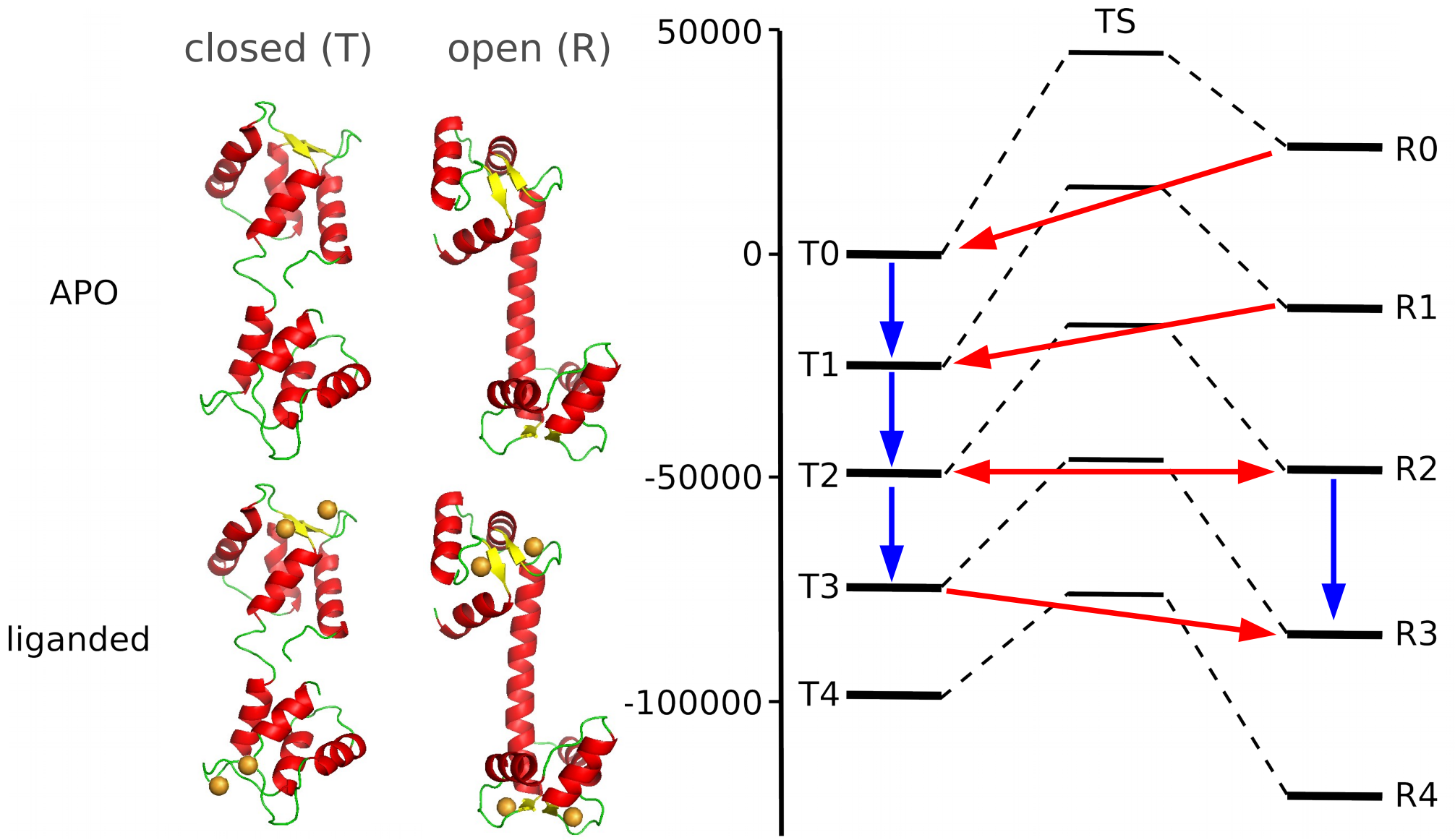
Allosteric model of Calmodulin activation



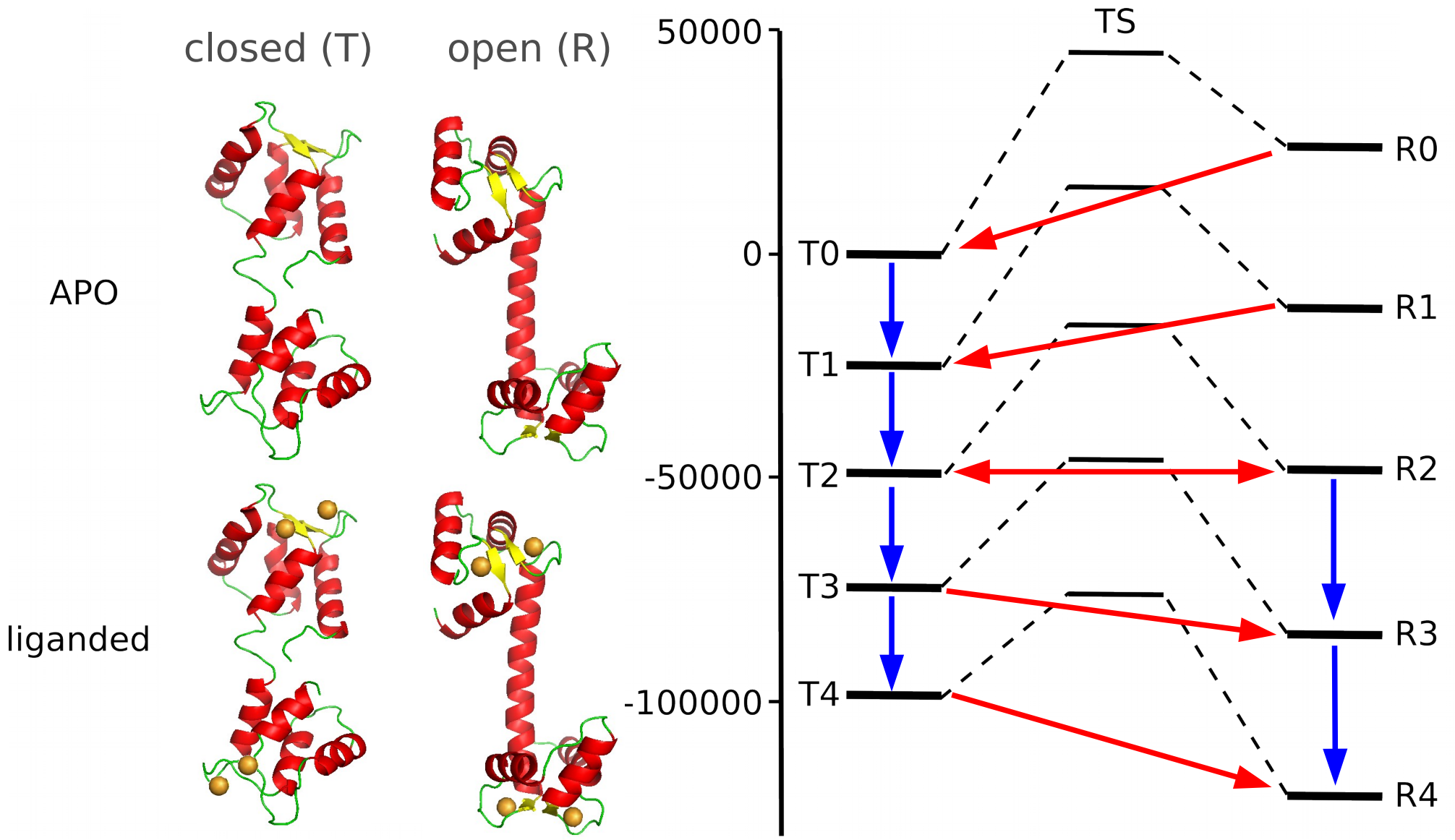
Allosteric model of Calmodulin activation



Allosteric model of Calmodulin activation



Allosteric model of Calmodulin activation



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+}

$L=20670$

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

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

$K^R_A=8.32\ 10^{-6}$

$K^R_B=1.66\ 10^{-8}$

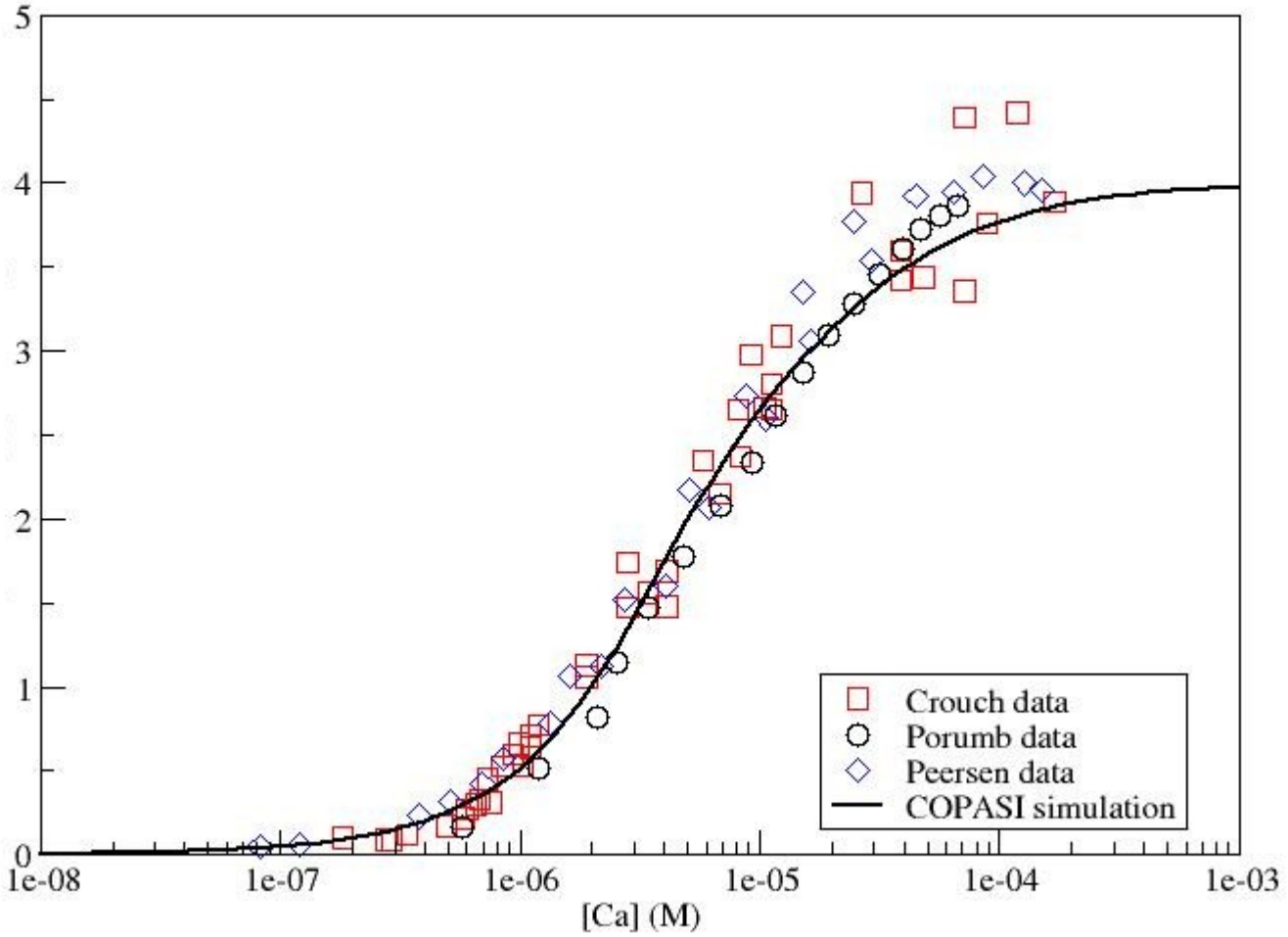
$K^R_C=1.74\ 10^{-5}$

$K^R_D=1.45\ 10^{-8}$

2 high, 2 low, as expected

Comparison with experiments (binding function)

$\frac{Ca^{2+}\ bound}{CaM}$



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

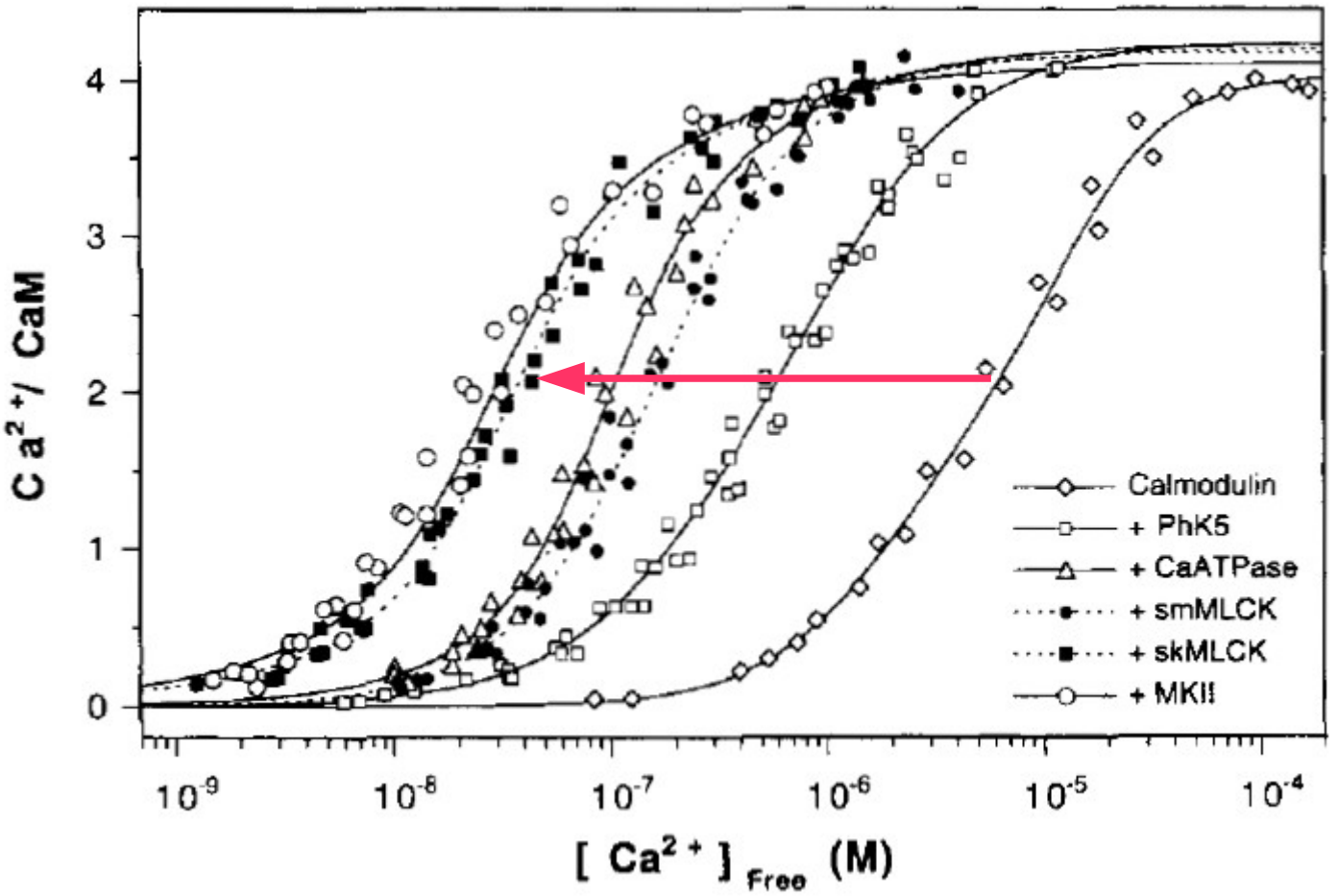
Activity of unsaturated calmodulin (state function)

- Fractional activity depends on the number of calcium ions bound

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

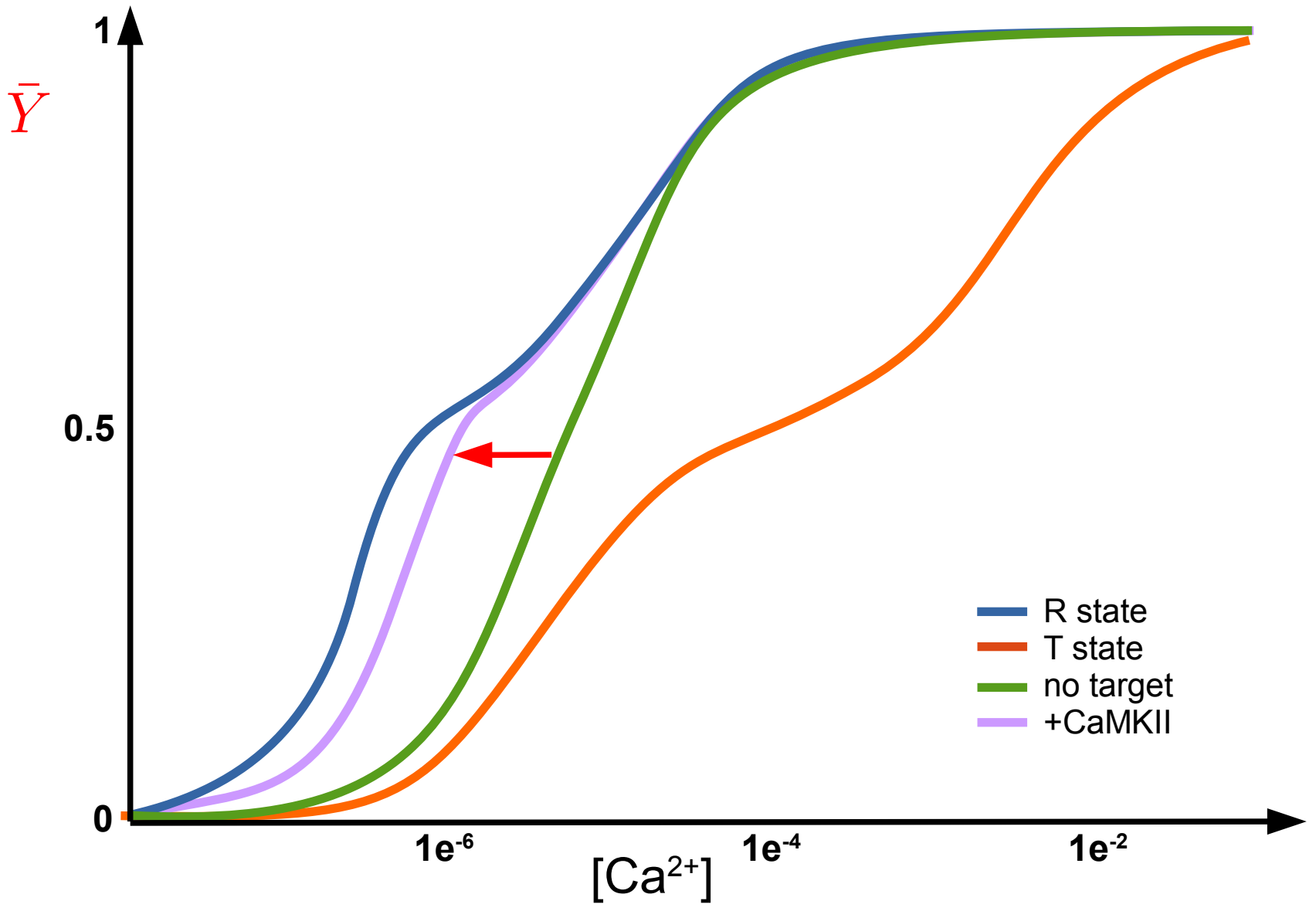
- $R_0/T_0 = 1/20000$ (1/L)
- $R_1/T_1 = 1/170$
- $R_2/T_2 = 0.69$ → half-saturation ≈ equi-probability
- $R_4/T_4 = 10000$

Targets as allosteric effectors

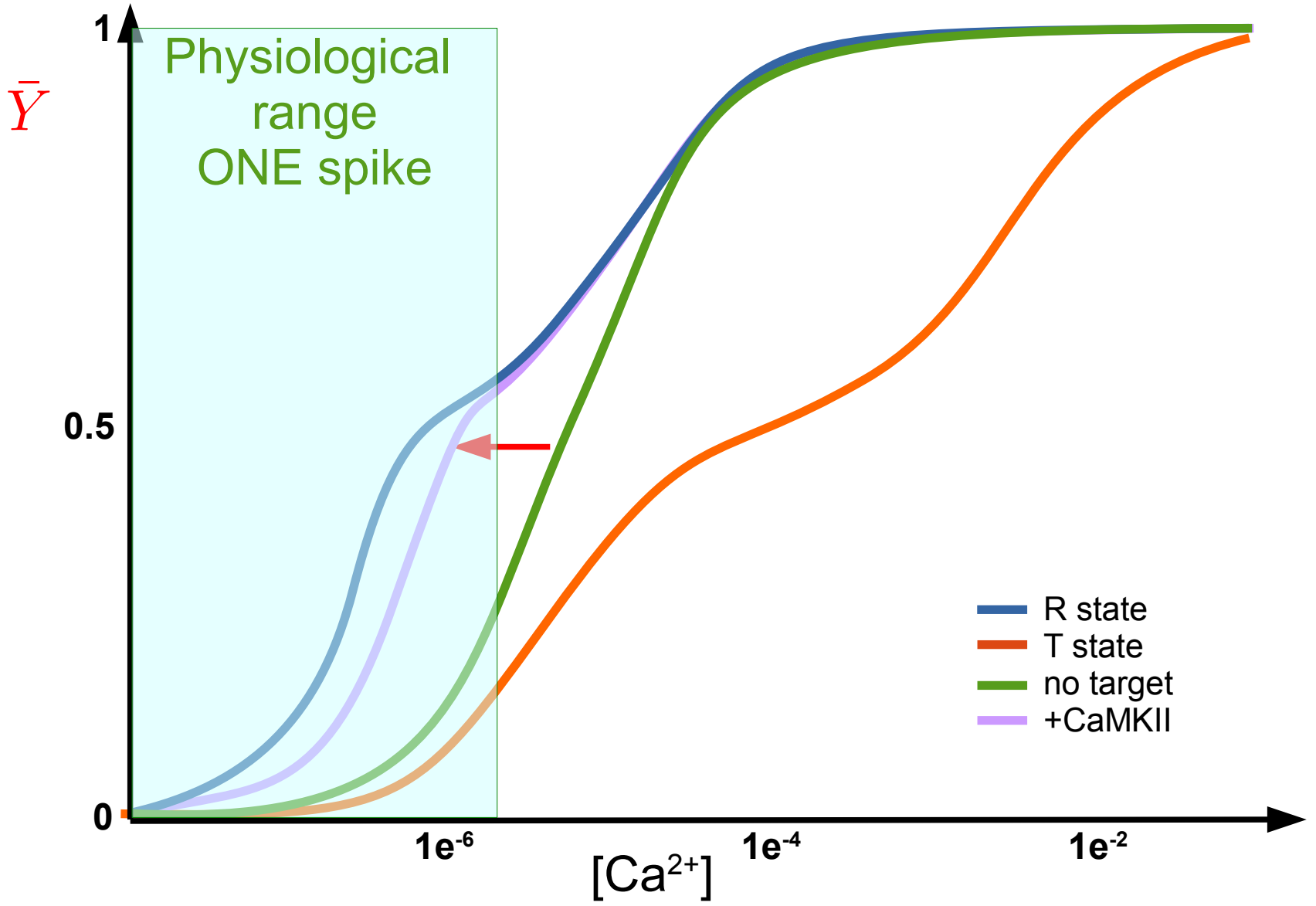


Peersen et al. (1997) *Prot Sci*, 6: 794-807

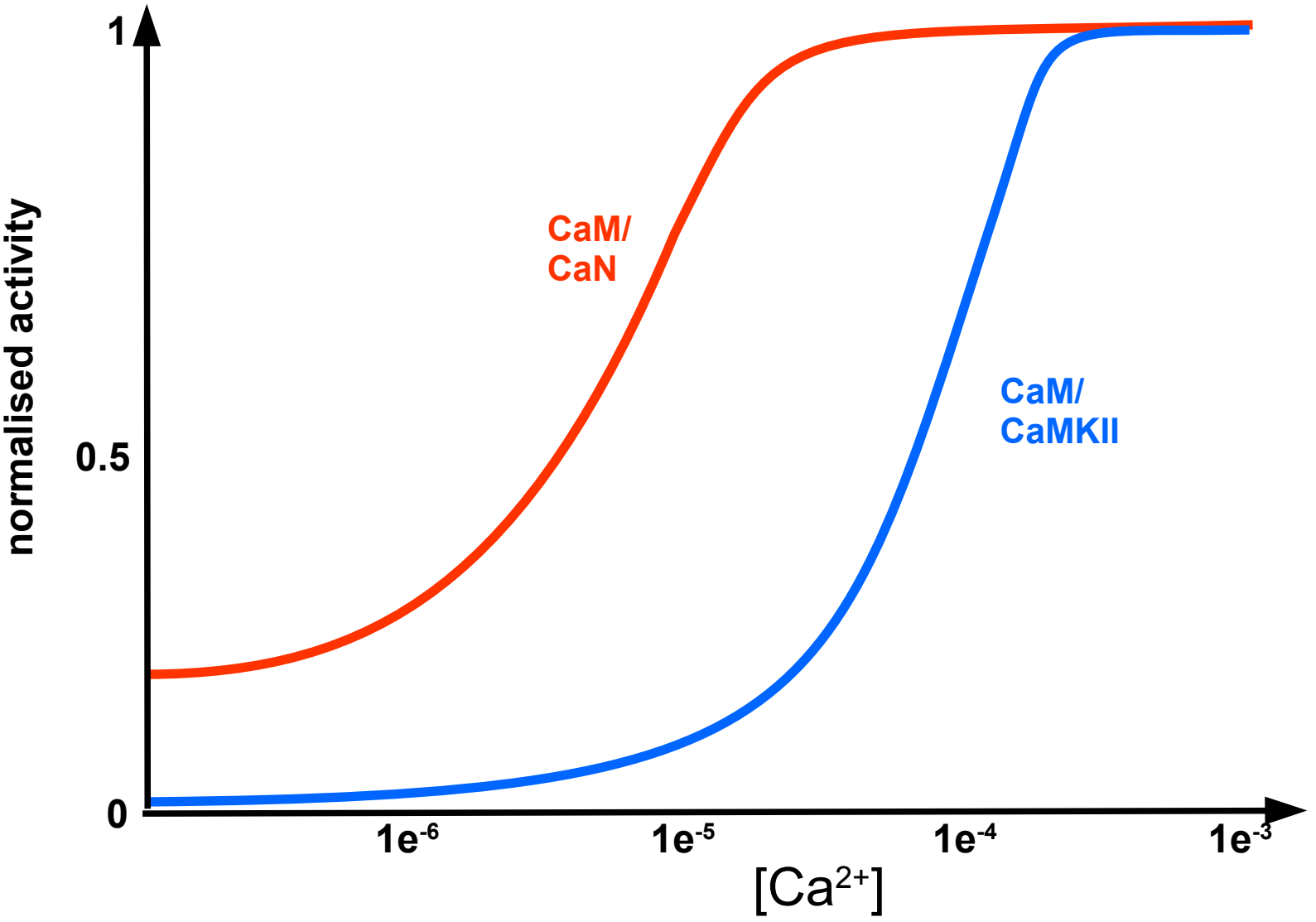
Binding to target increases the affinity for Ca^{2+}



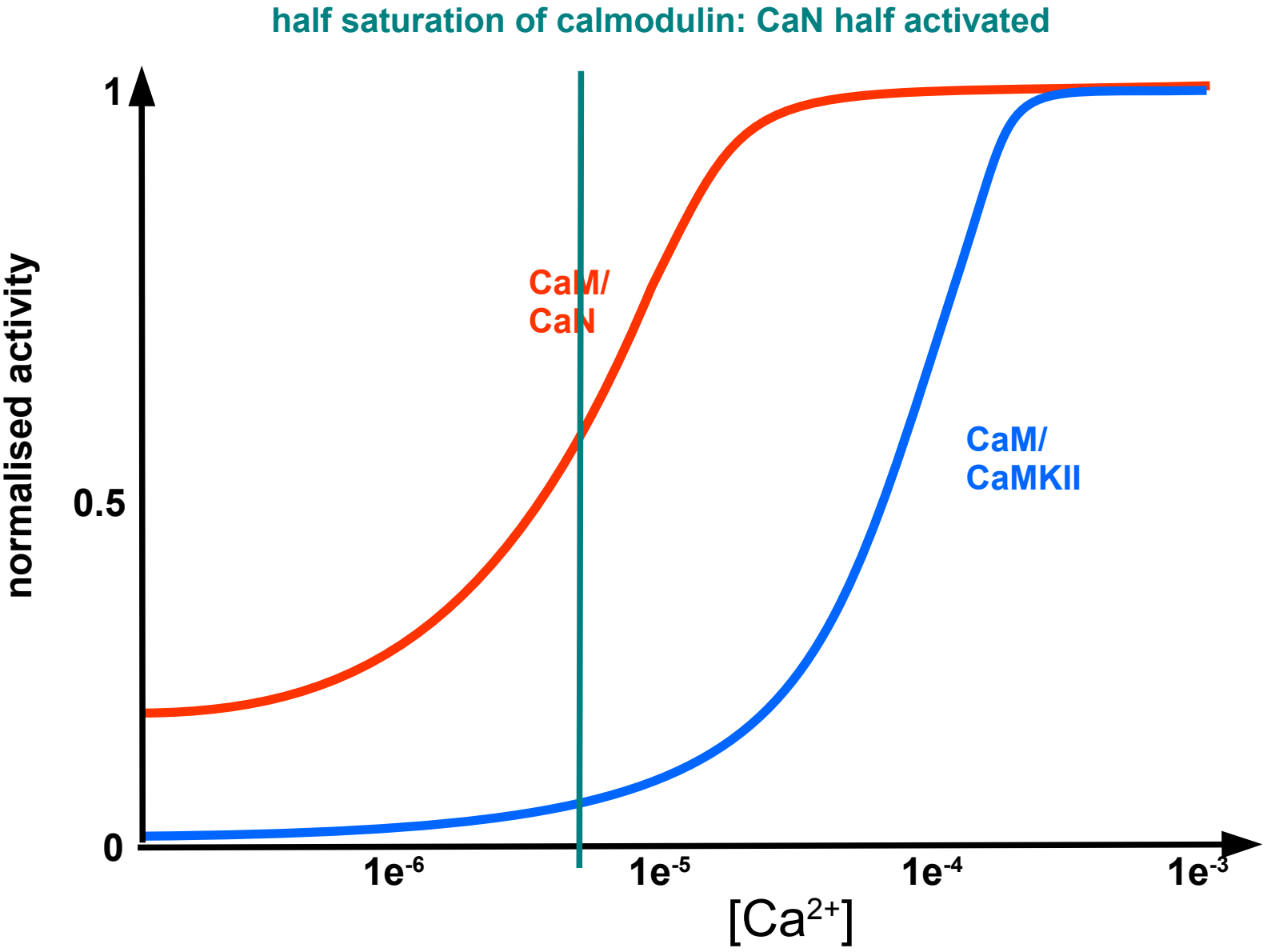
Targets stabilises Ca^{2+} binding into the physiological range



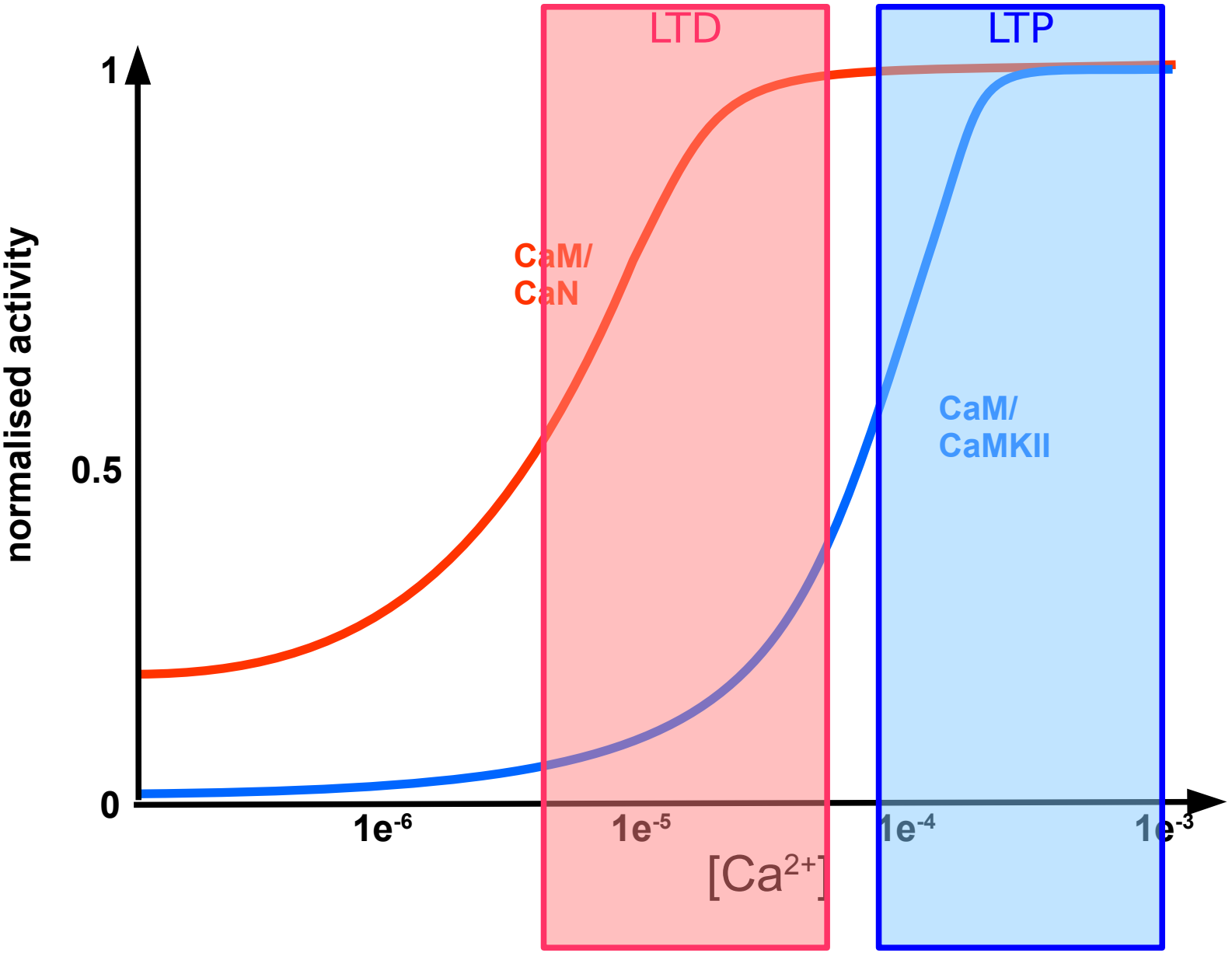
Bidirectional synaptic plasticity



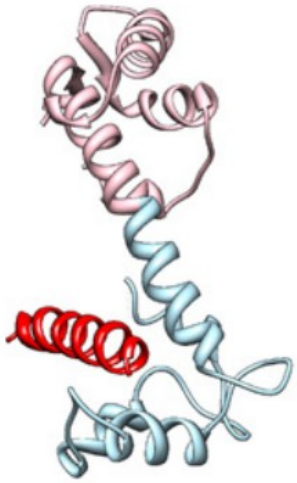
Bidirectional synaptic plasticity



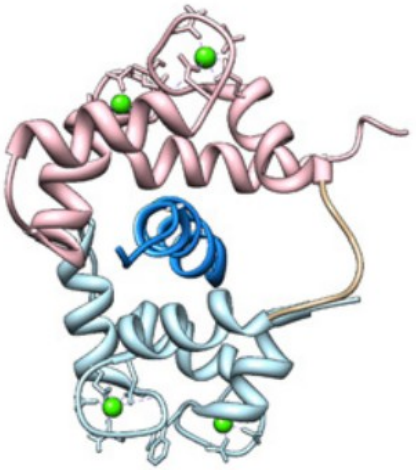
Bidirectional synaptic plasticity



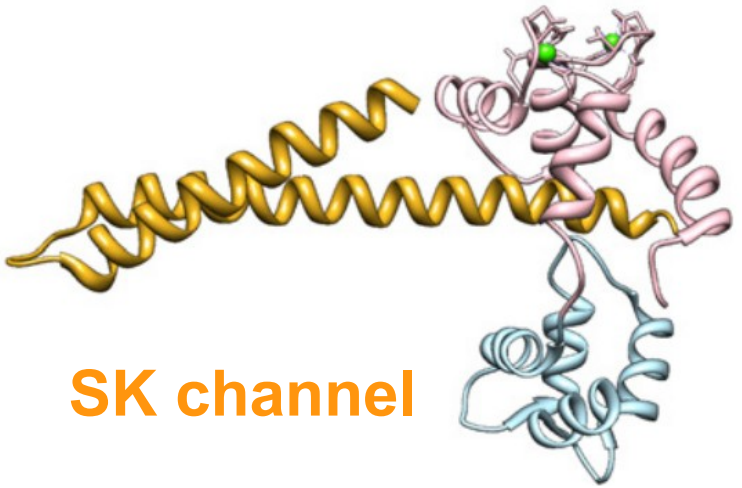
Different binding to different targets



Neurogranin

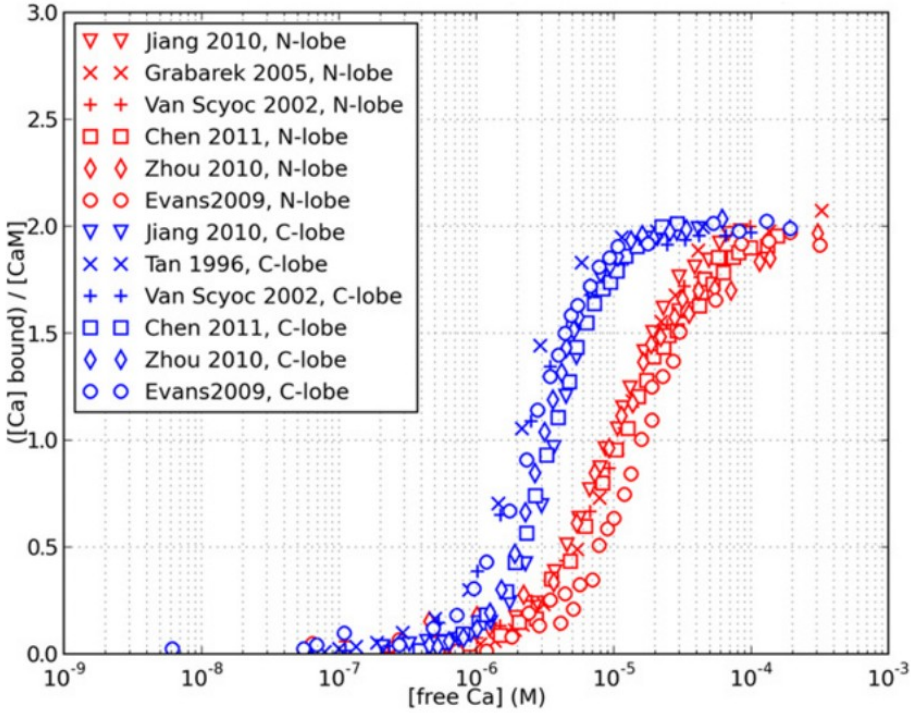


MLCK

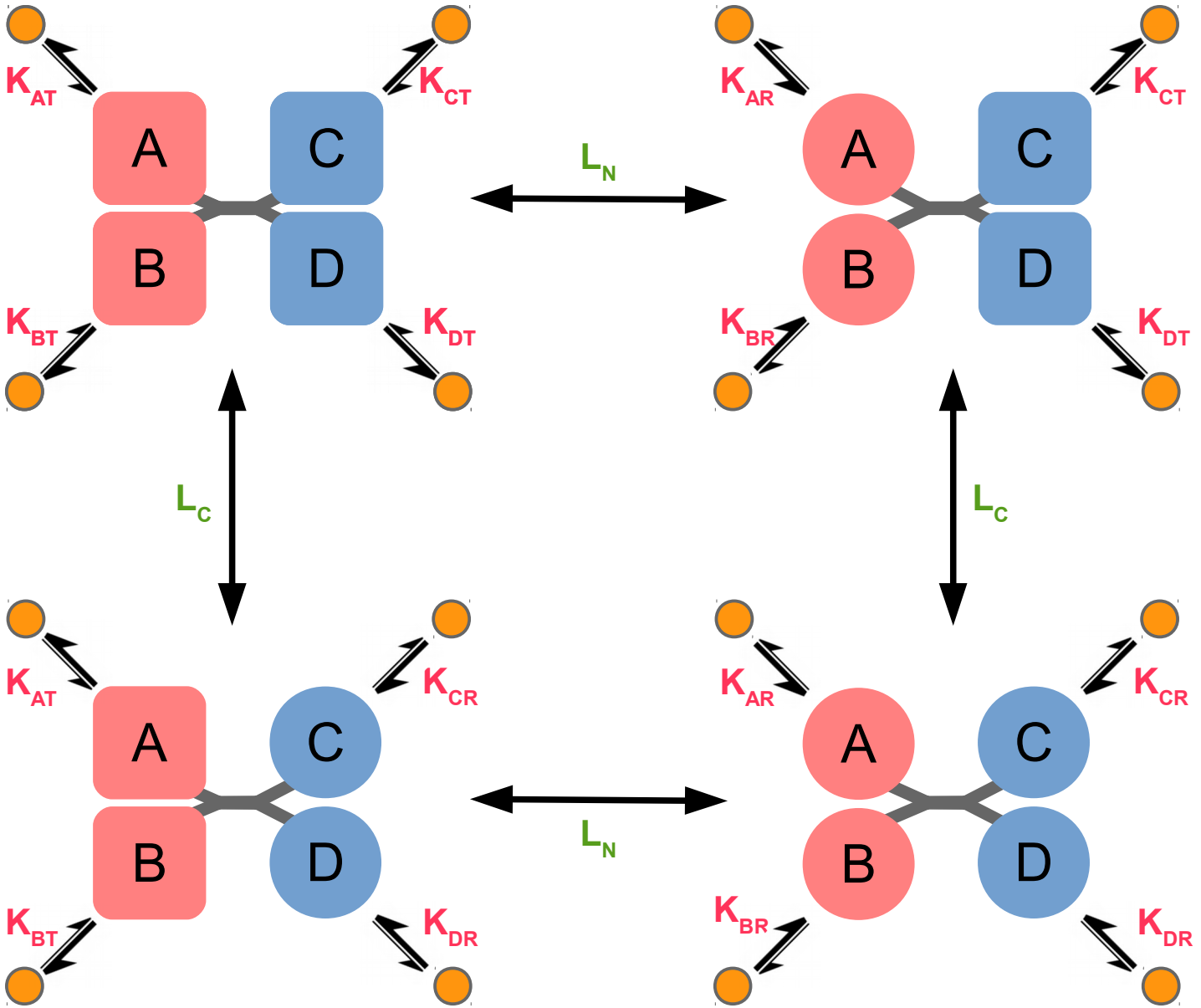


SK channel

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

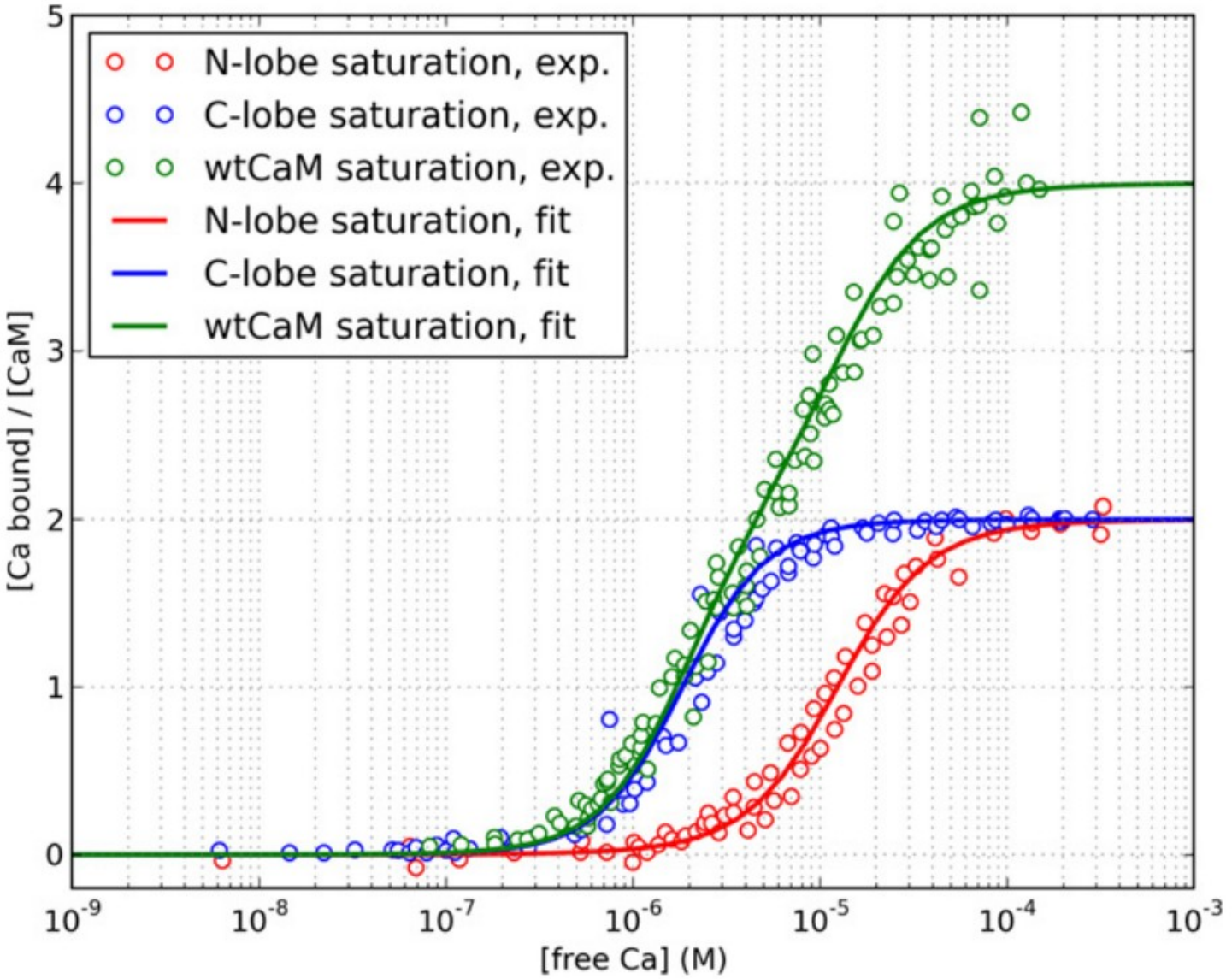


Hemiconcerted model of calmodulin



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

Calcium binding to lobes and whole CaM



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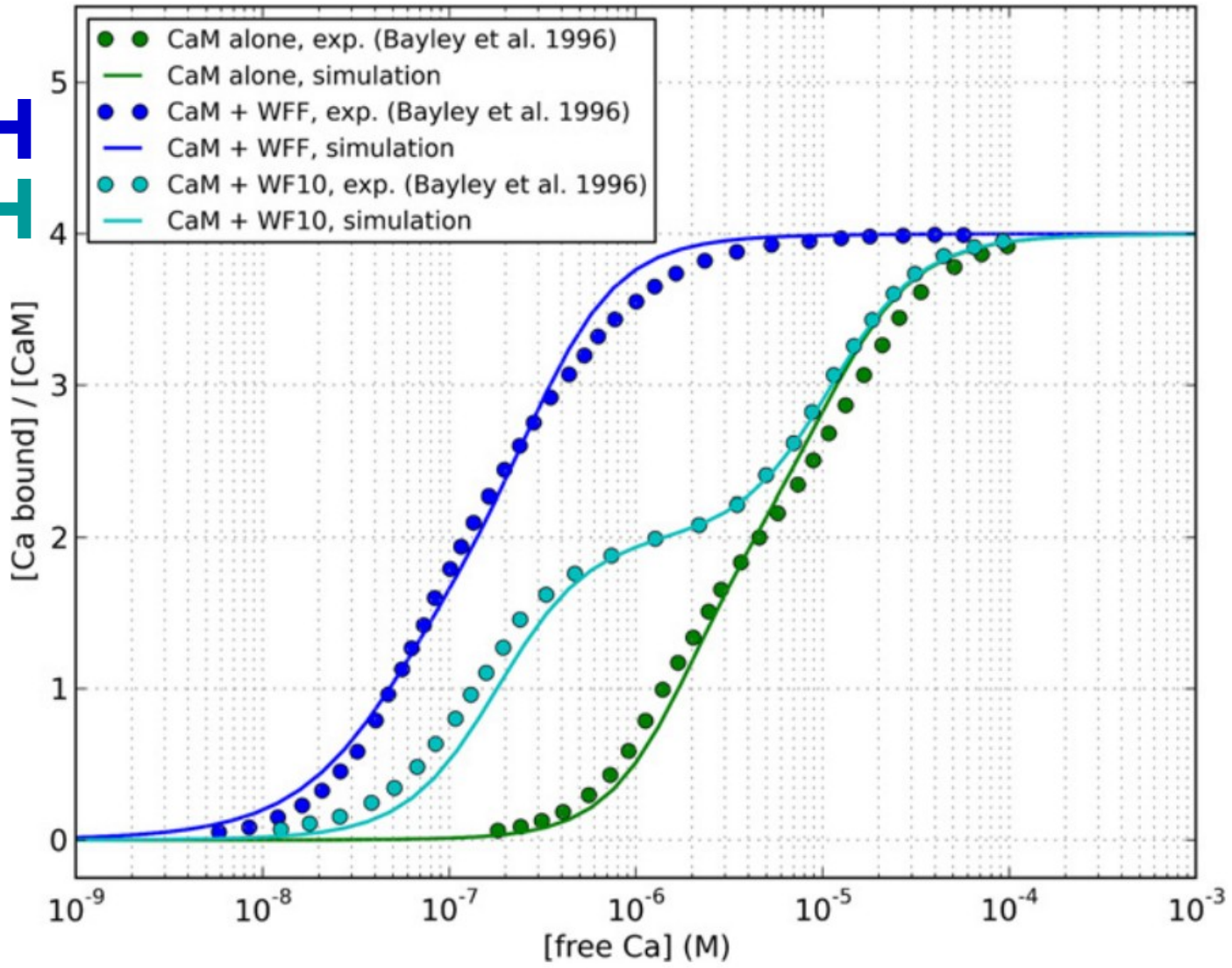
Effect of R-stabilising targets

Stabilise R state of both lobes

Stabilise R state of C lobe



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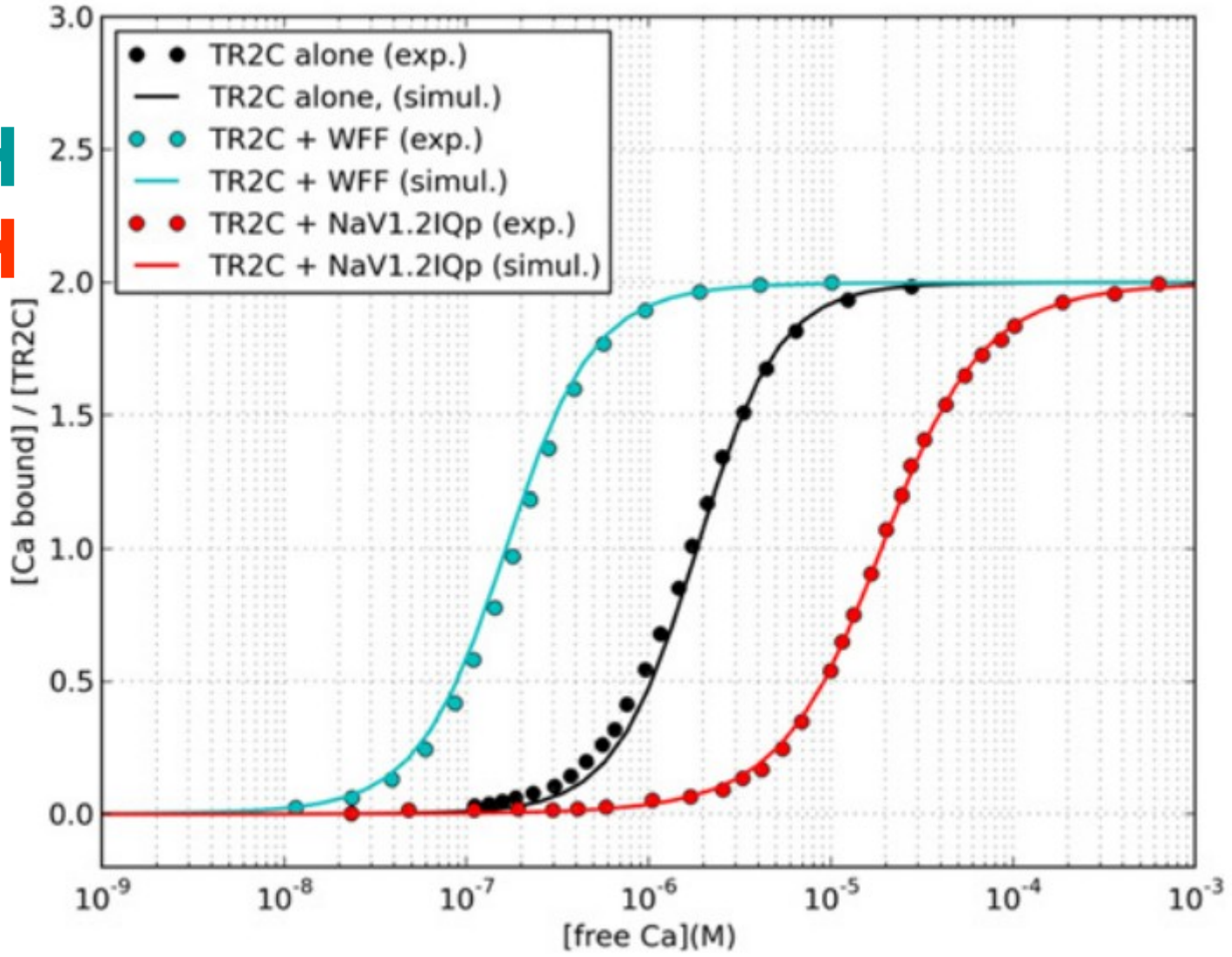
Effect of R and T stabilising targets

Peptide from skMLCK → R

IQ domain from NaV1.2 → T



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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.

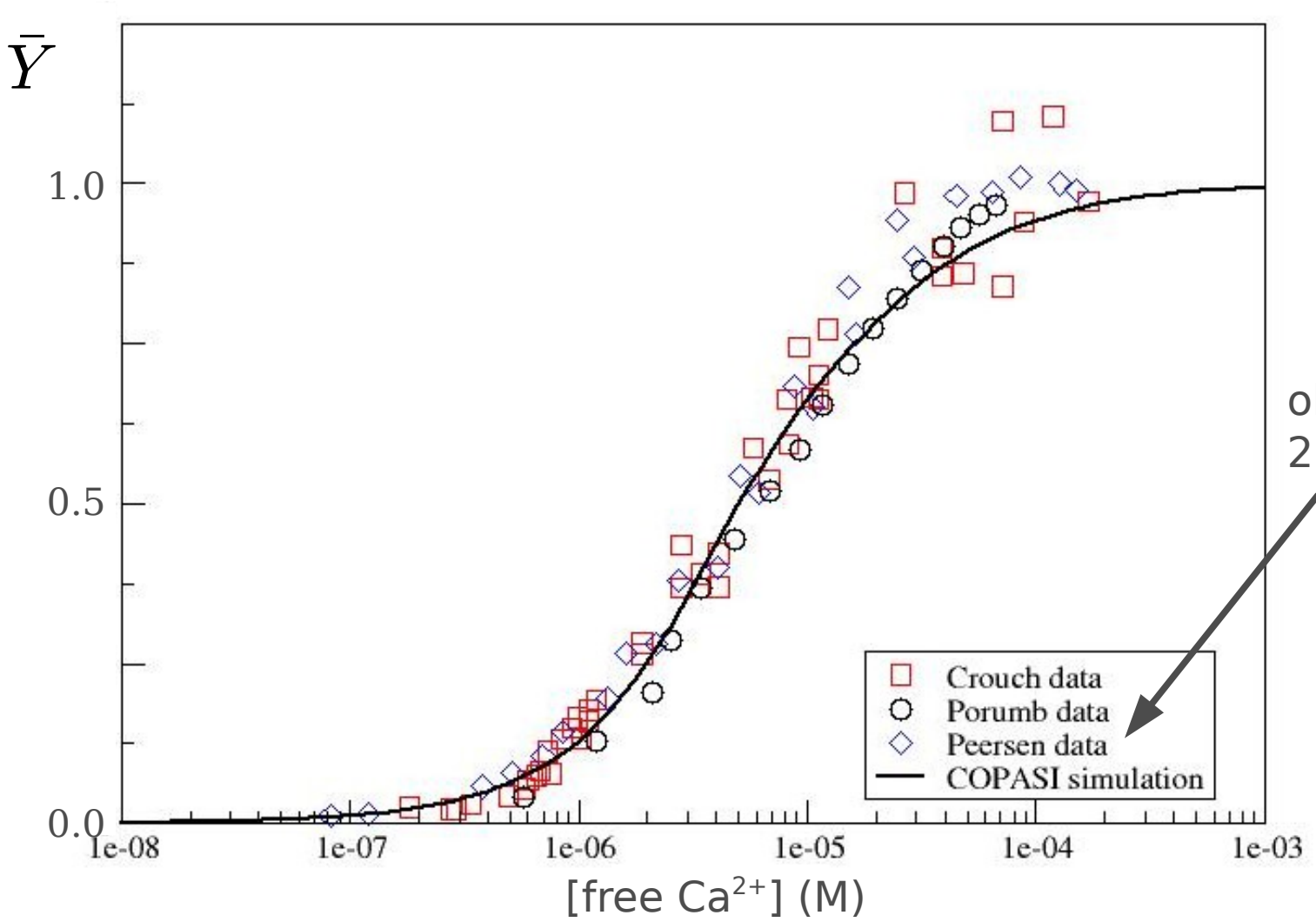
CaM significantly “active” with less than 4 Ca^{2+} bound.

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.

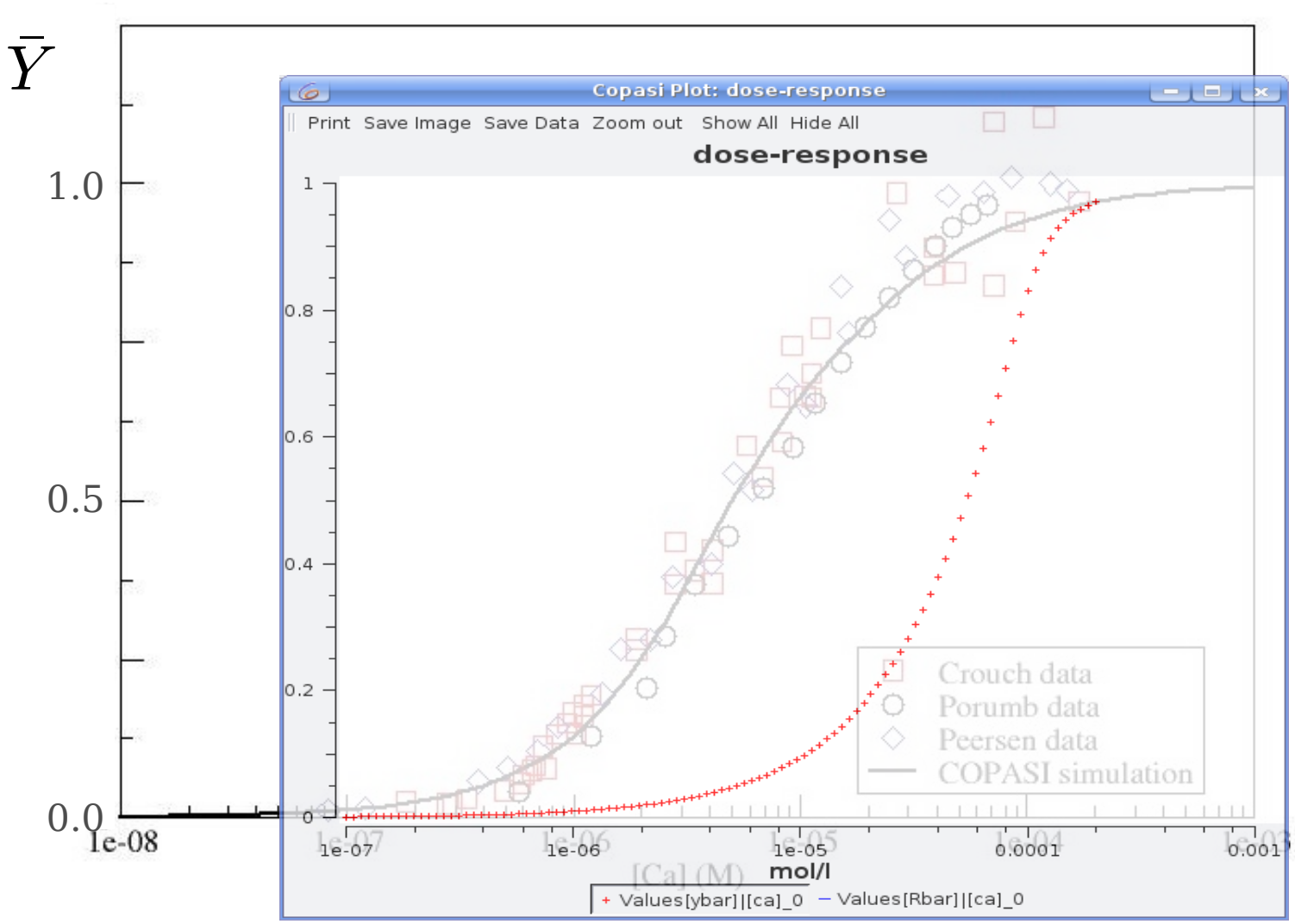
Digression: on ligand depletion

Allosteric model of Calmodulin function



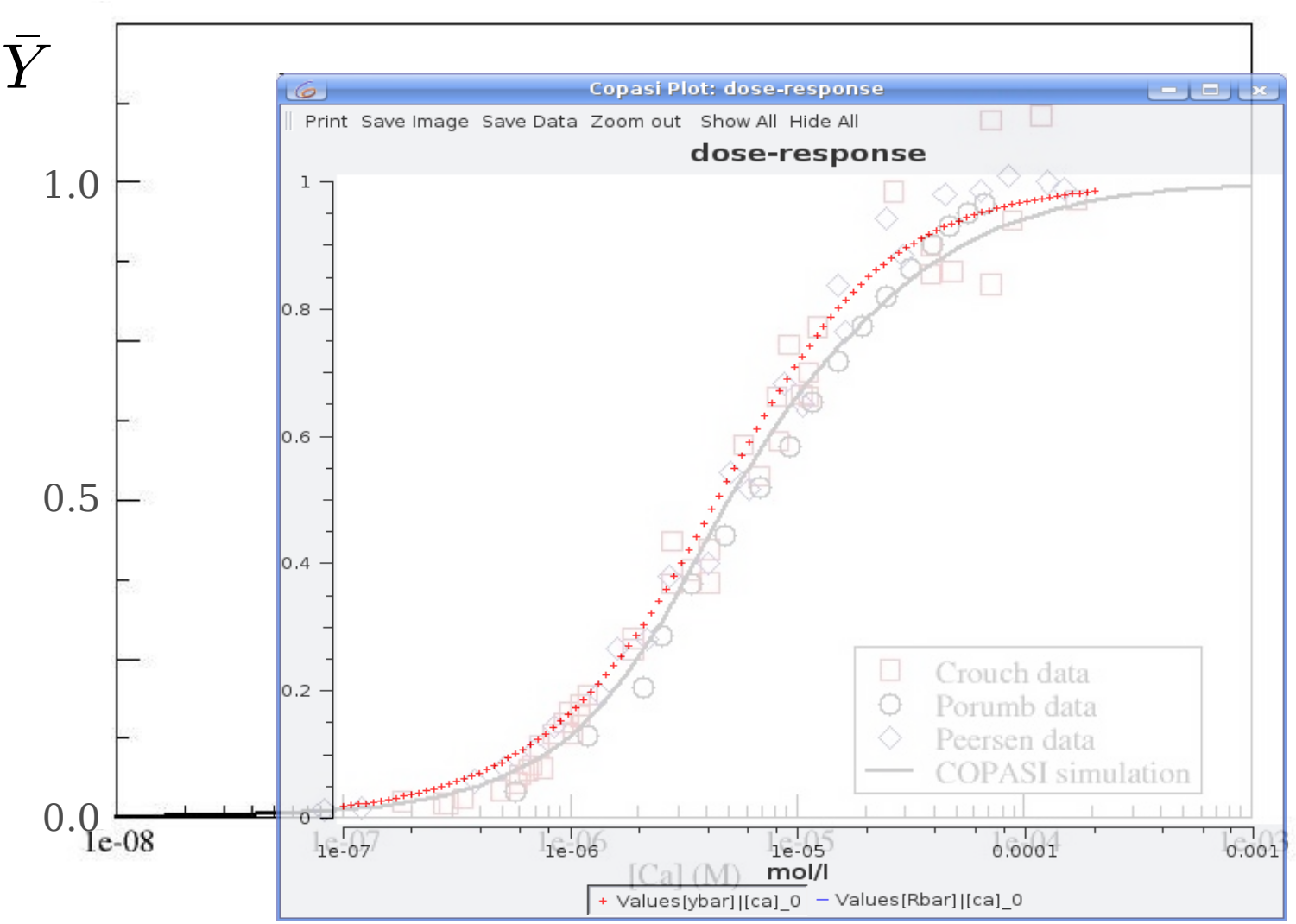
obtained with
25 μM CaM

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?

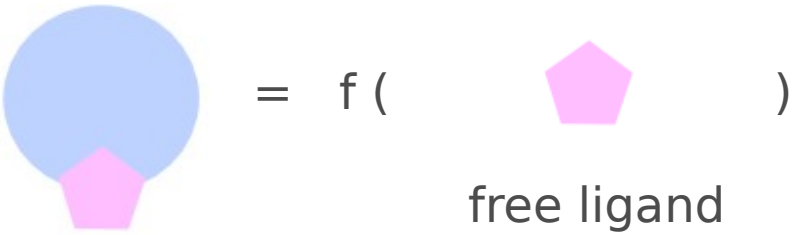
Chemistry (mass-action law)

= f ( )

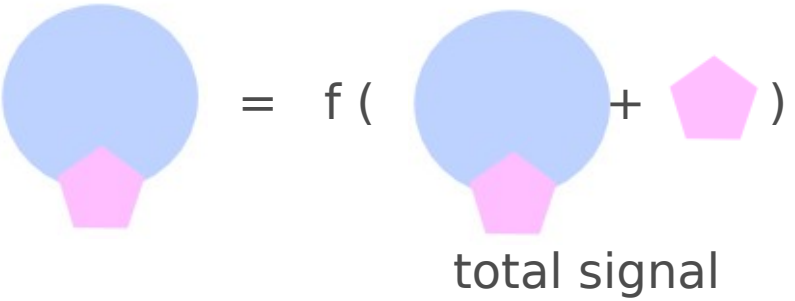
free ligand

What is ligand depletion?

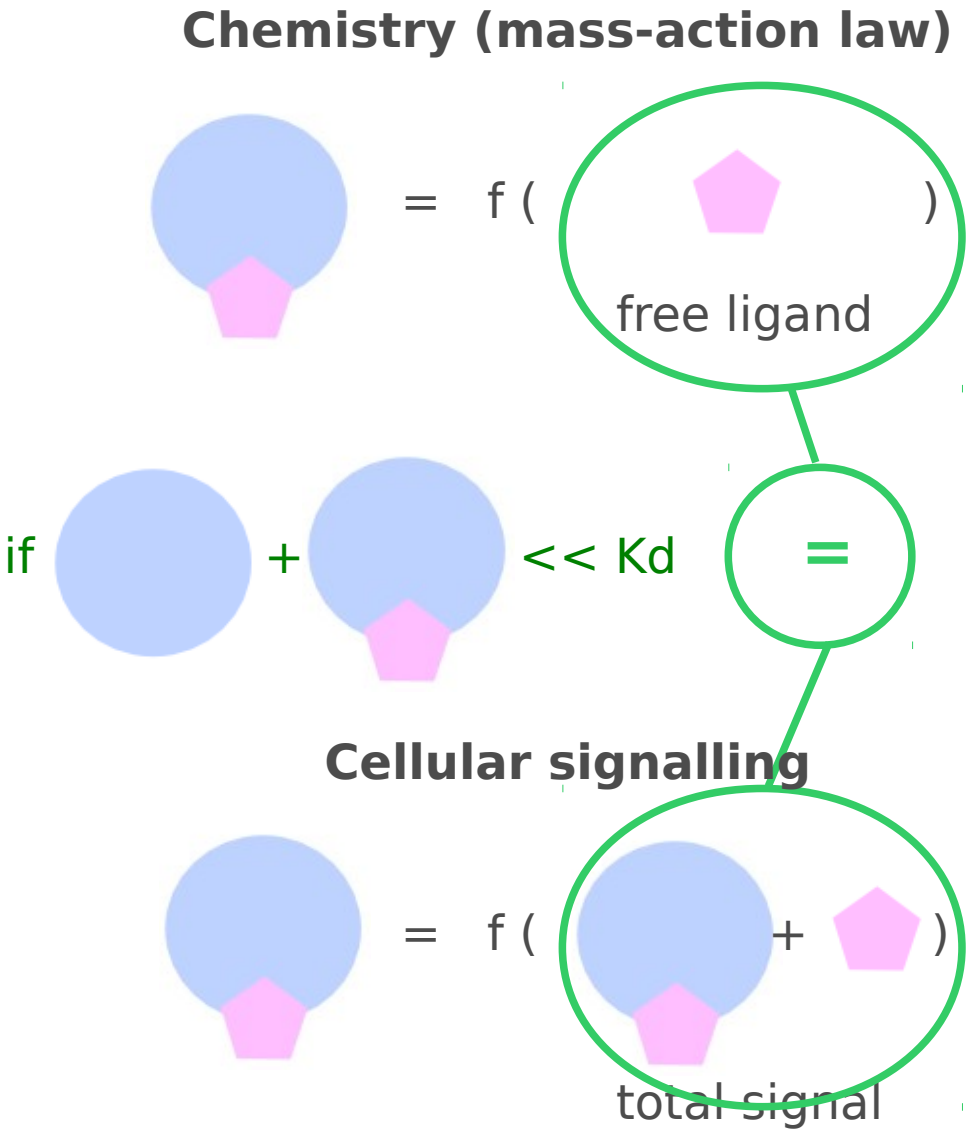
Chemistry (mass-action law)



Cellular signalling



What is ligand depletion?



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)

= f (free ligand)

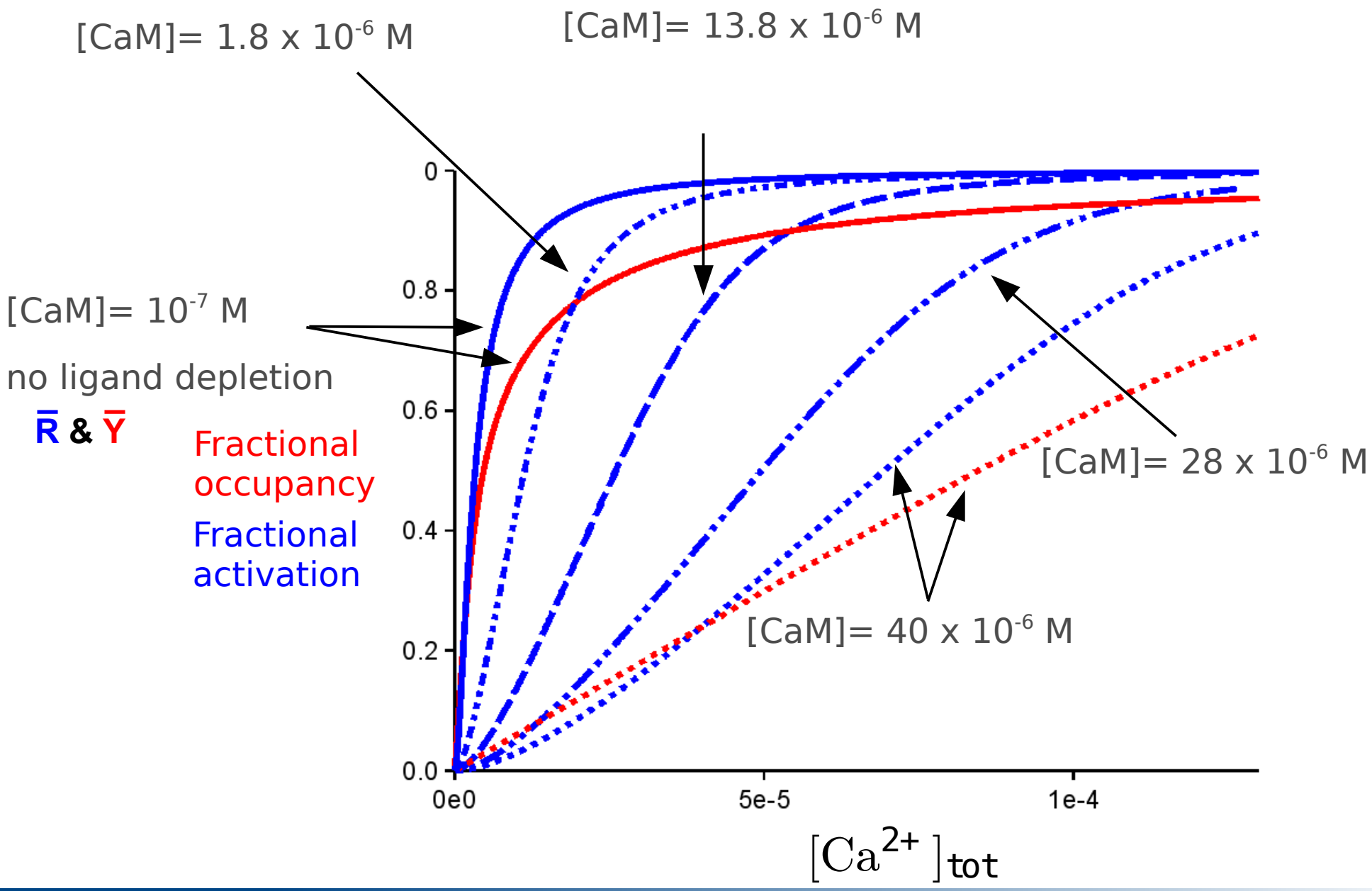
if + << Kd =

Cellular signalling

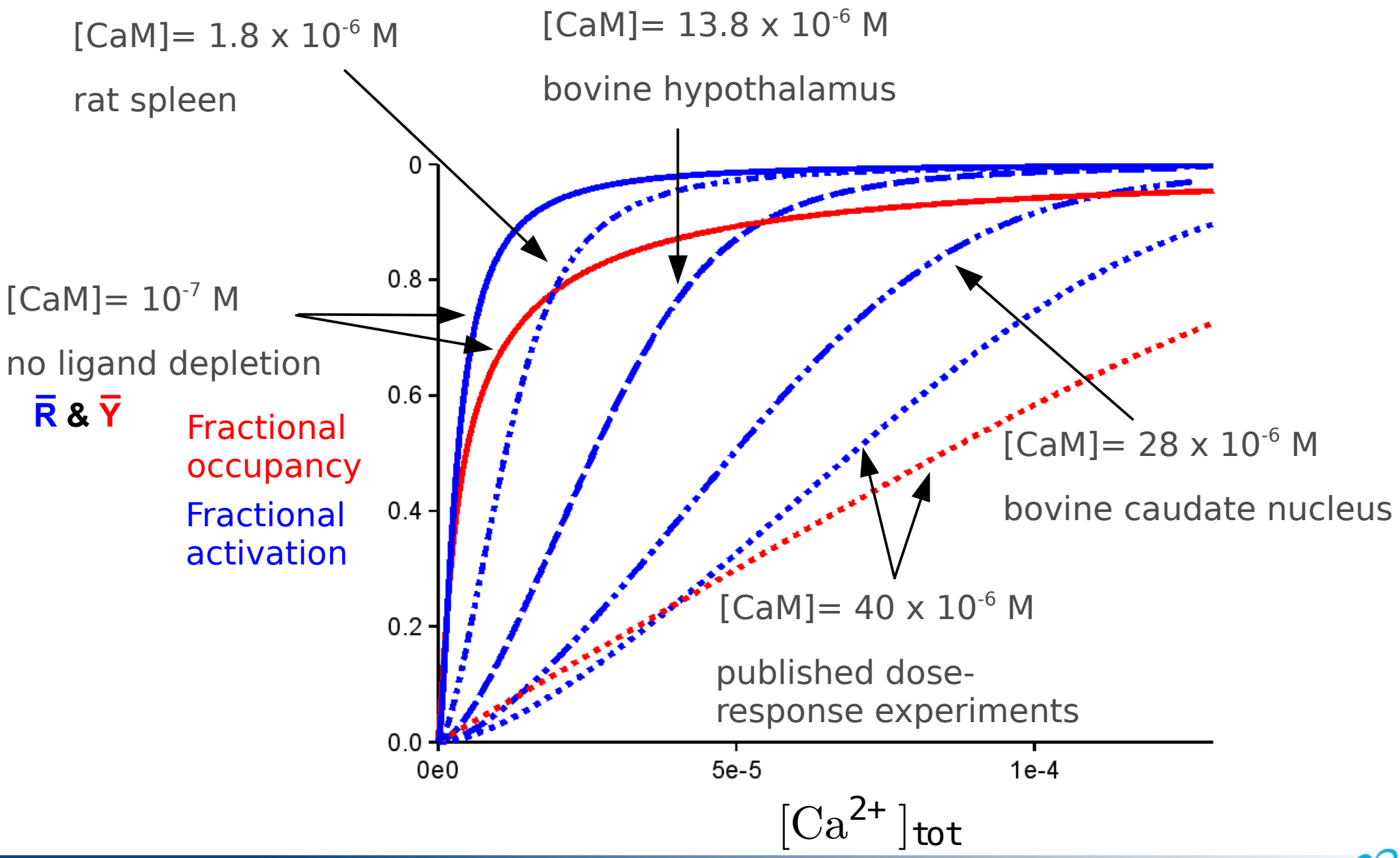
= f (+)

total signal

Dose-response depends on Calmodulin concentration



Dose-response depends on Calmodulin concentration



Ligand-depletion modifies sensitivity

[CaM]= 28 x 10^{-6} M

bovine caudate nucleus

~5 μM to 120 μM

[CaM]= 1.8 x 10^{-6} M

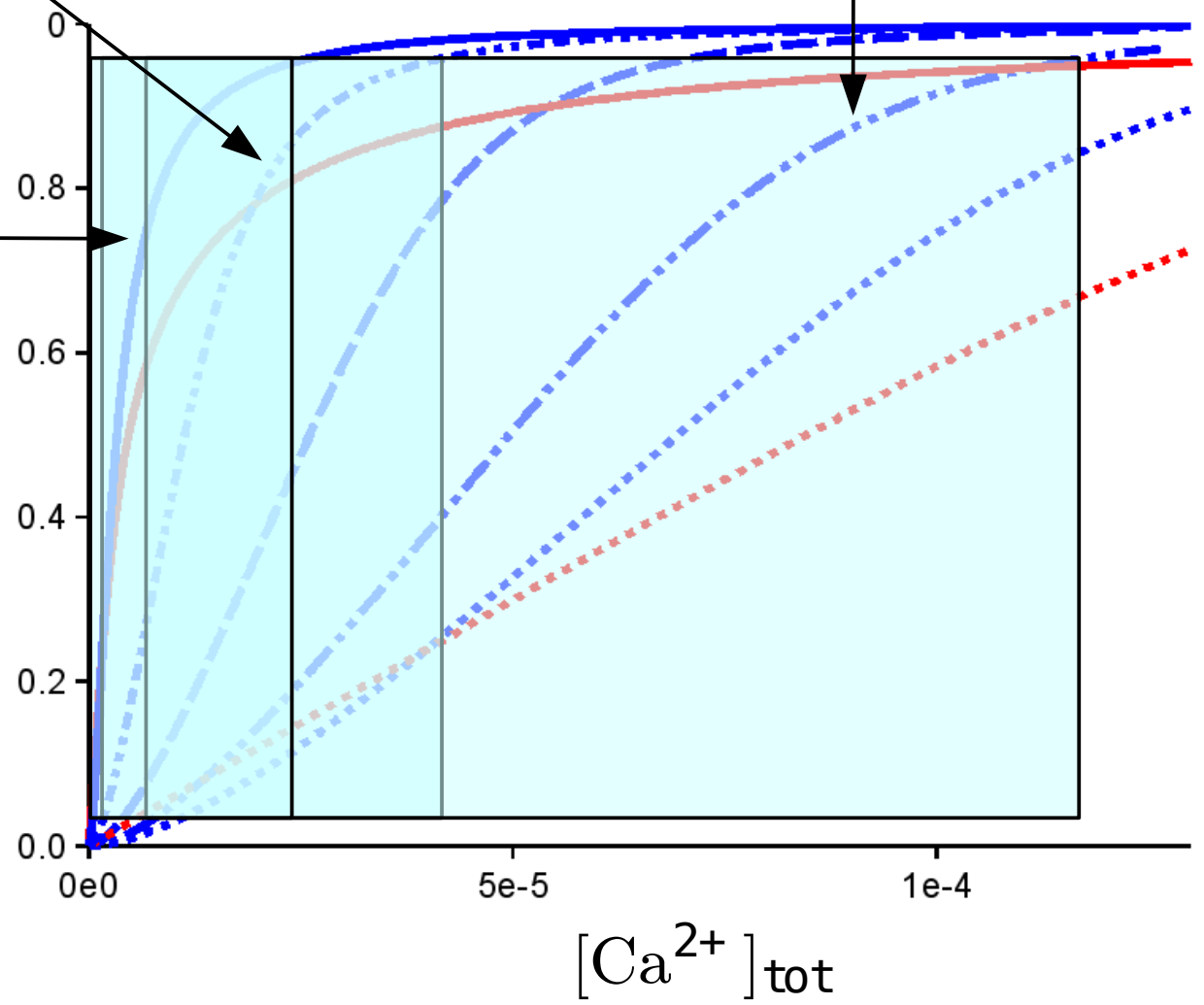
rat spleen

~1 μM to 45 μM

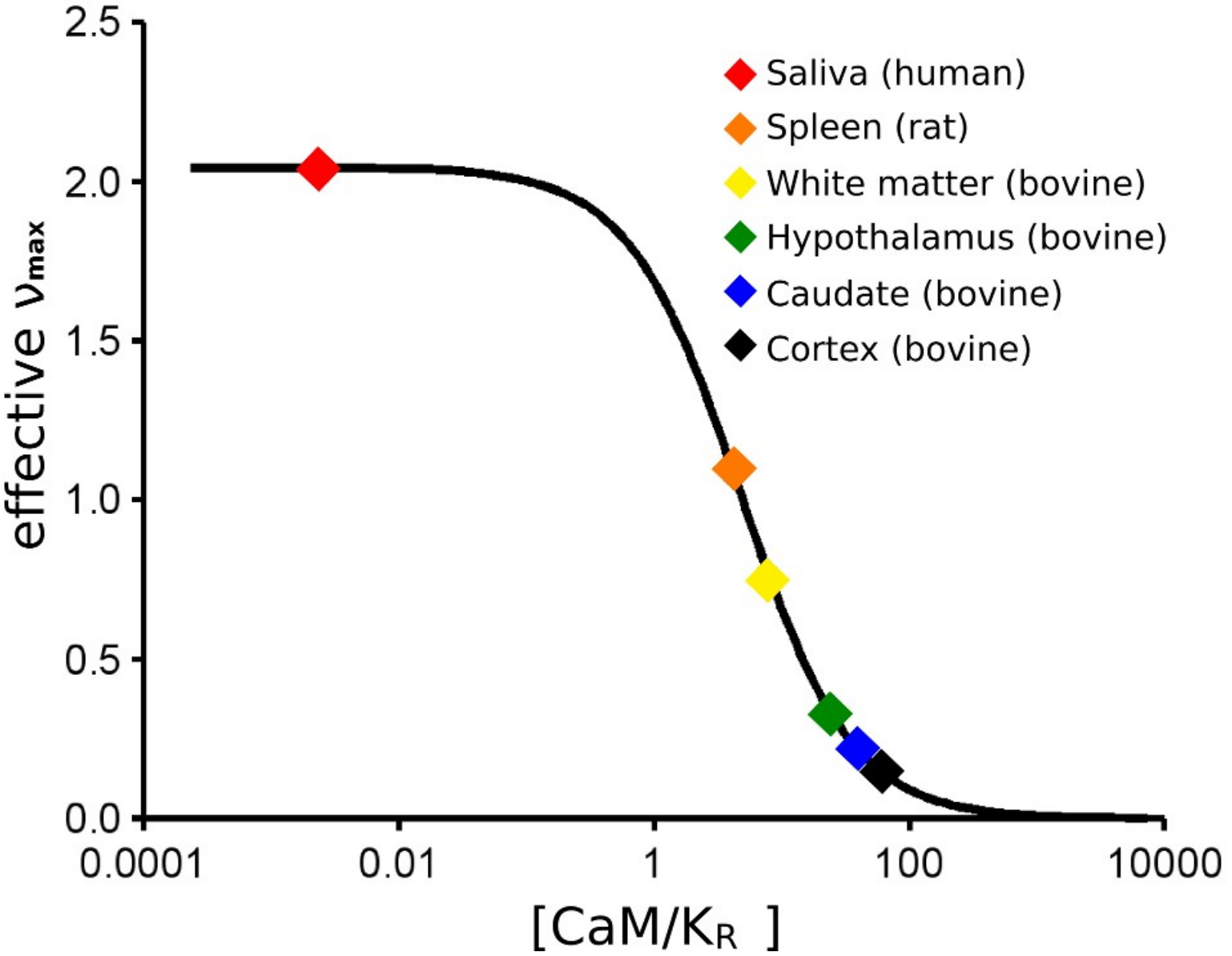
[CaM]= 10^{-7} M

no ligand depletion

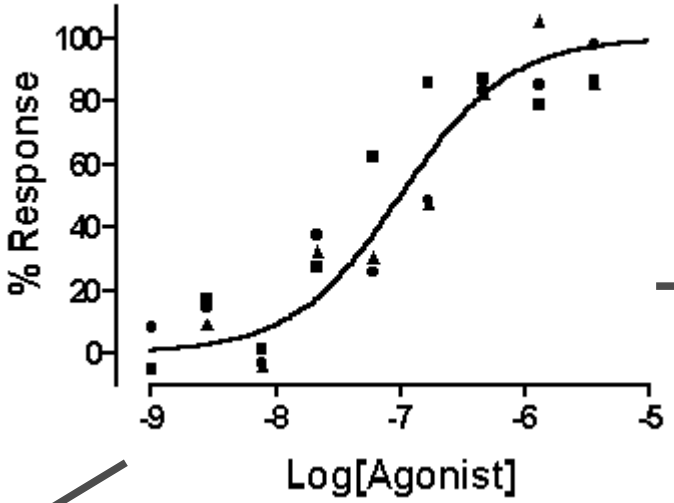
~100 nM to 25 μM

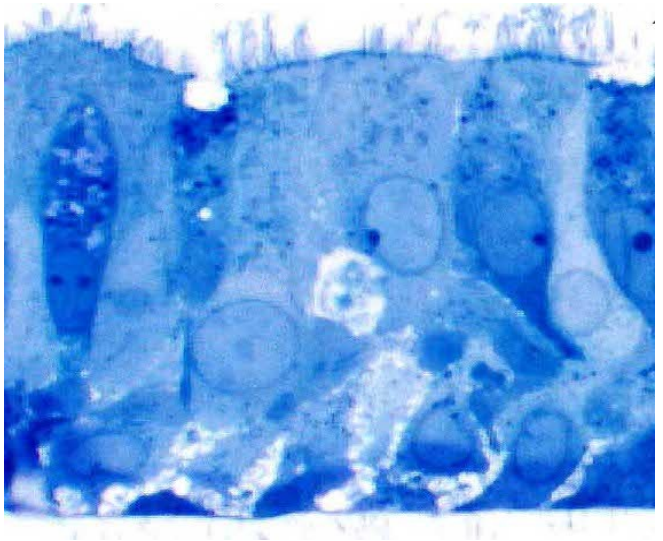


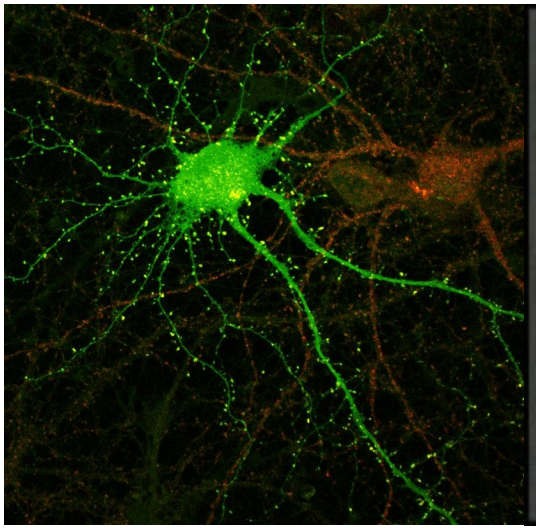
Ligand-depletion decreases effective cooperativity

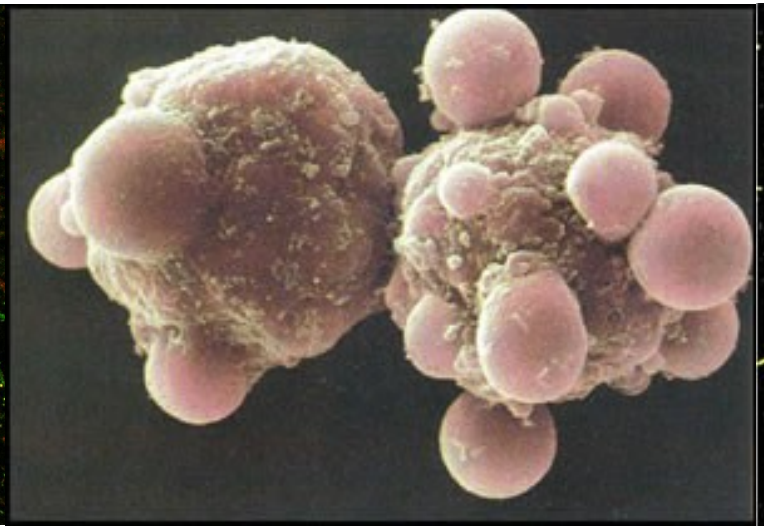


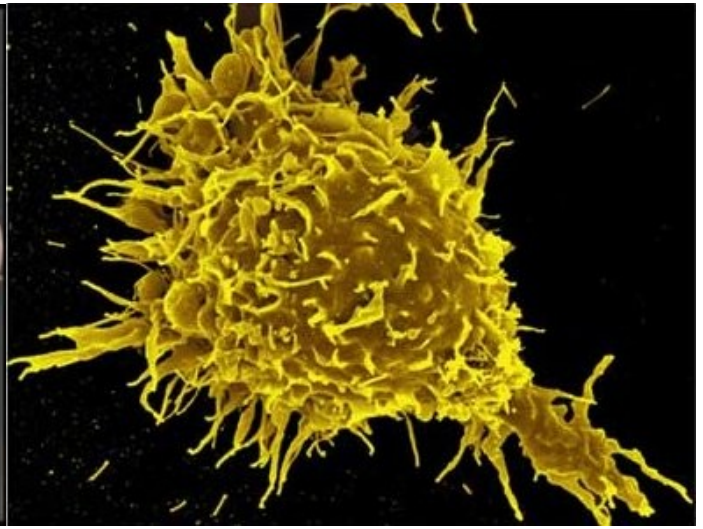
How general is a dose-response?



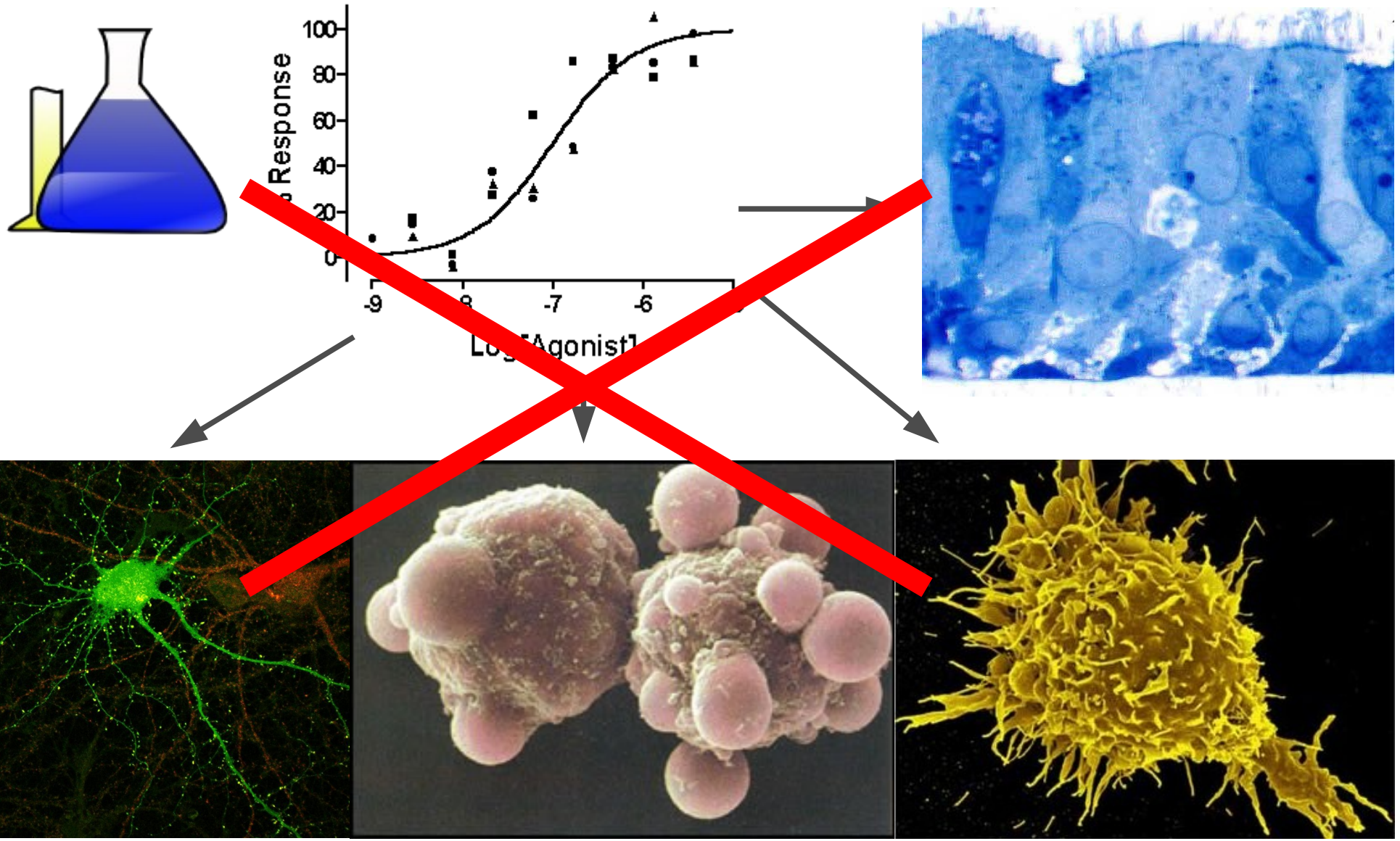








A “dose-response” cannot be reused directly!



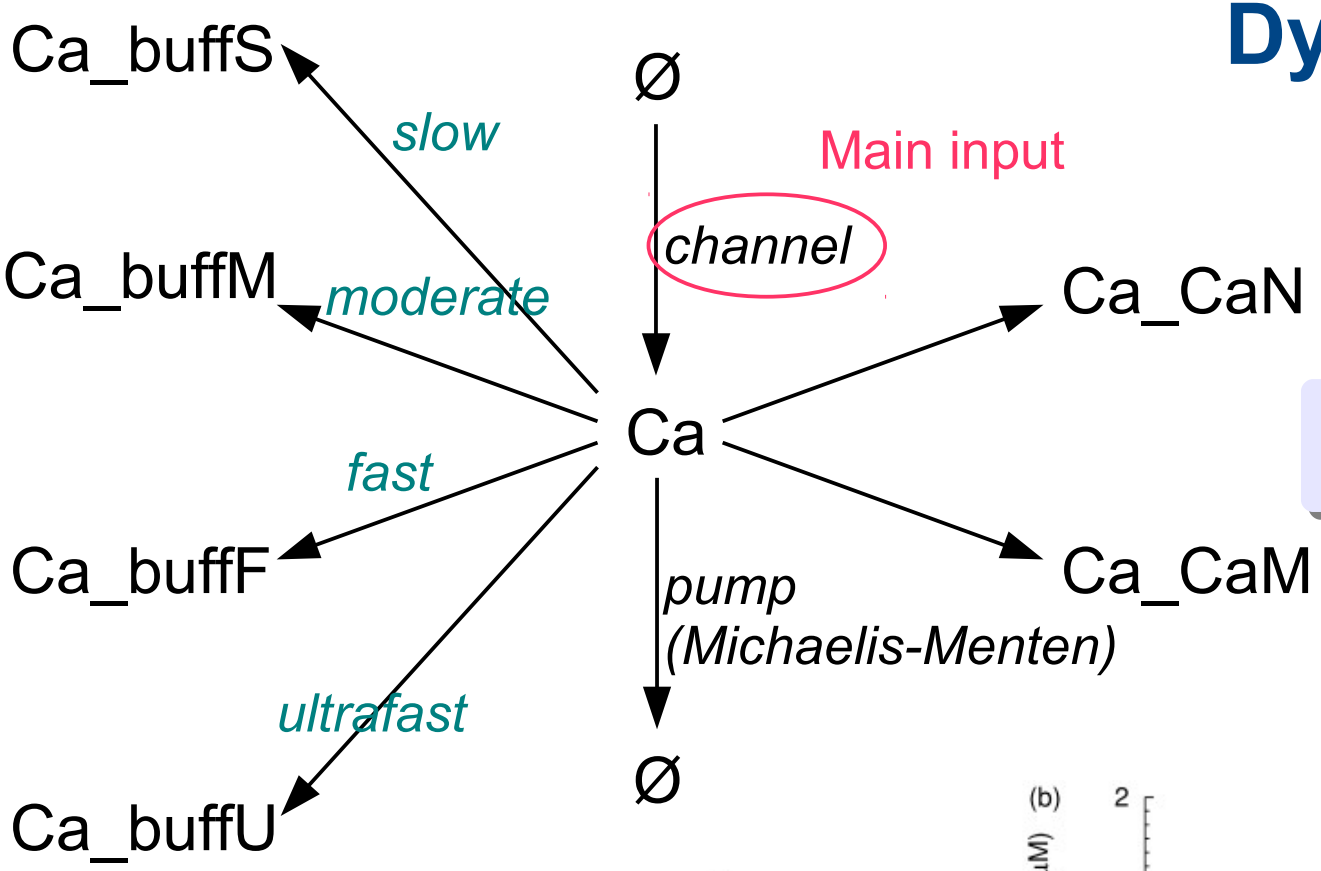
End of digression

Wait a minute!
Signal transduction is not at equilibrium!

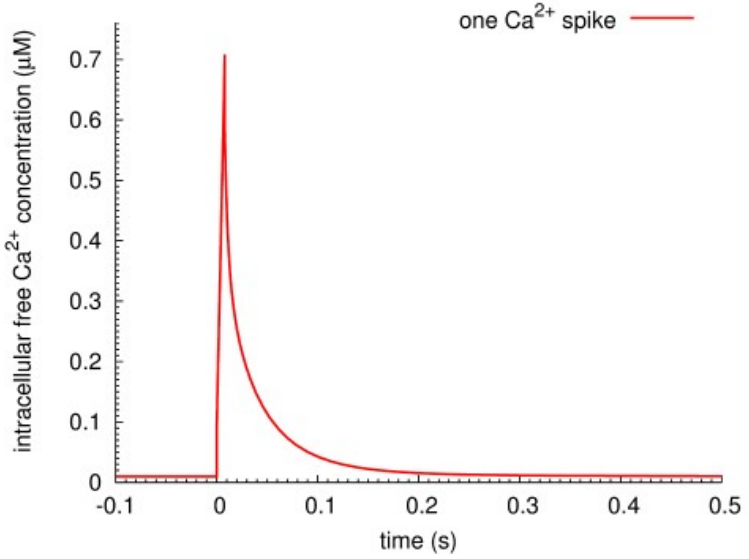
AMPAR post-synaptic potential:	5 ms
Calcium spike:	50 ms
Half saturation calmodulin (kon=1.5e6, koff=100):	5 ms
Relaxation between calmodulin states:	1 ms
autophosphorylation of CaMKII (kon=6):	100 ms

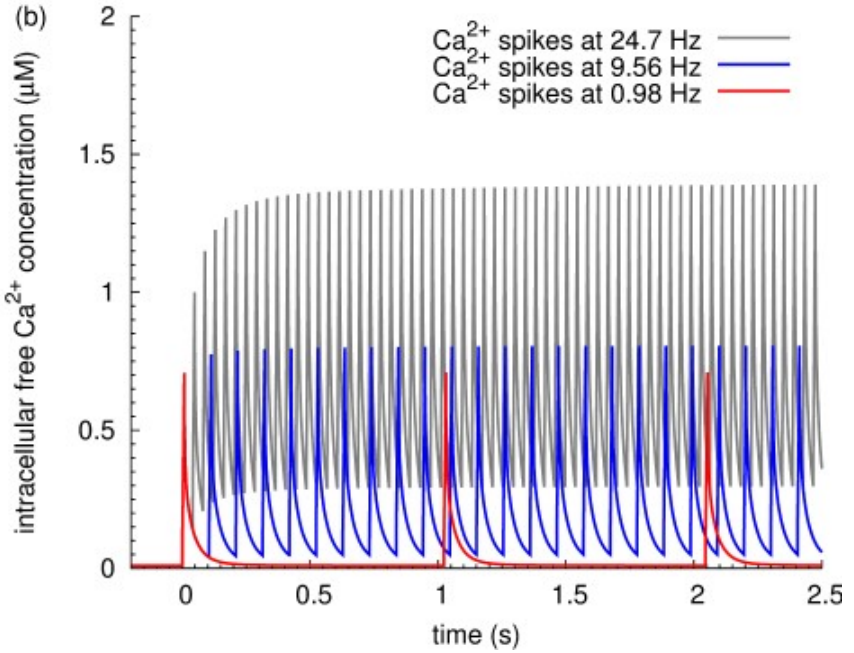
≠

Dynamic of calcium in the spine



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





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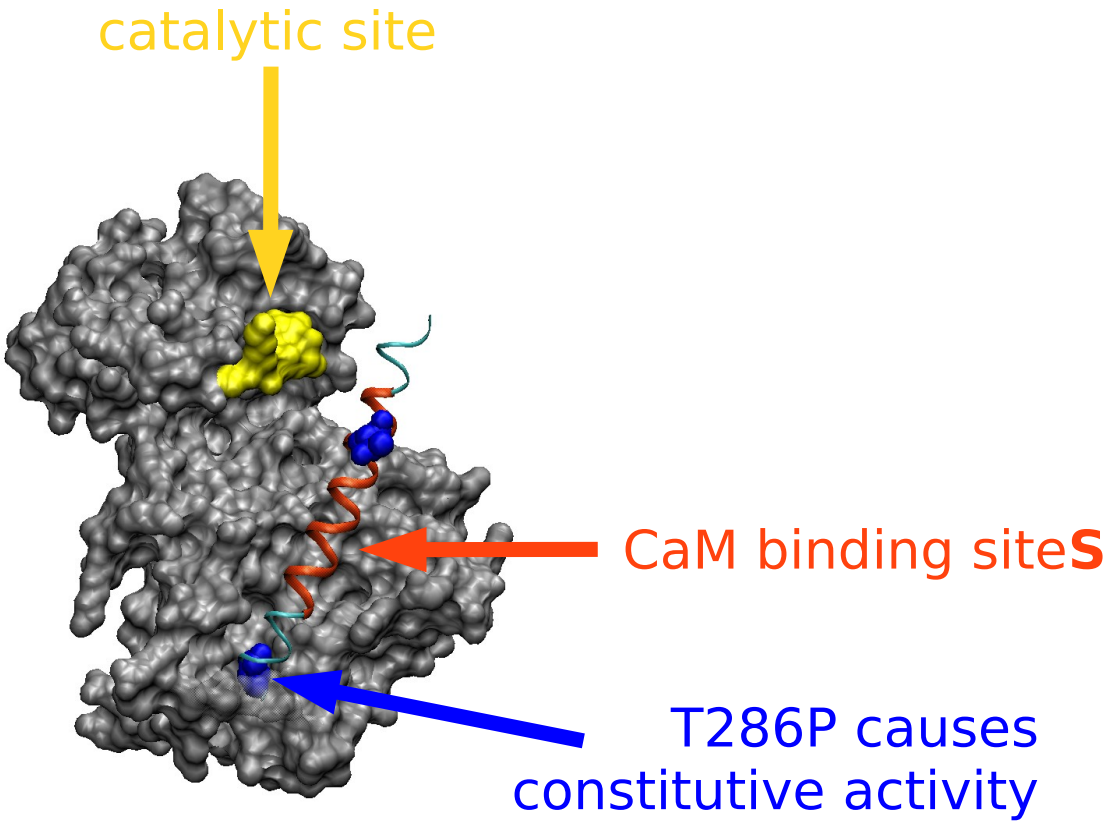
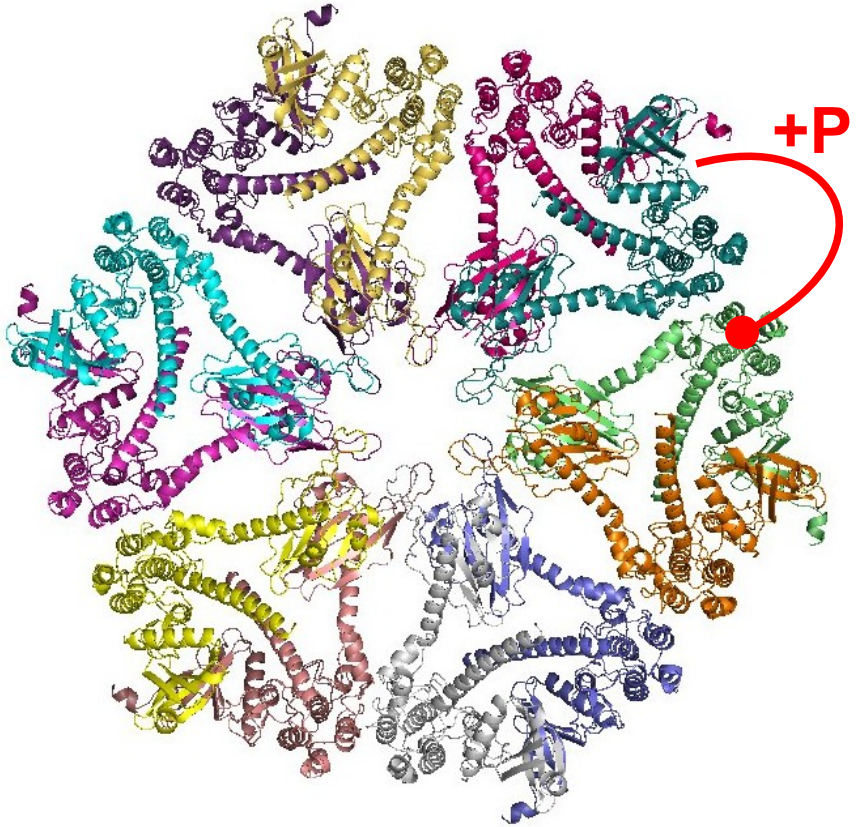
Calcium/calmodulin kinase II

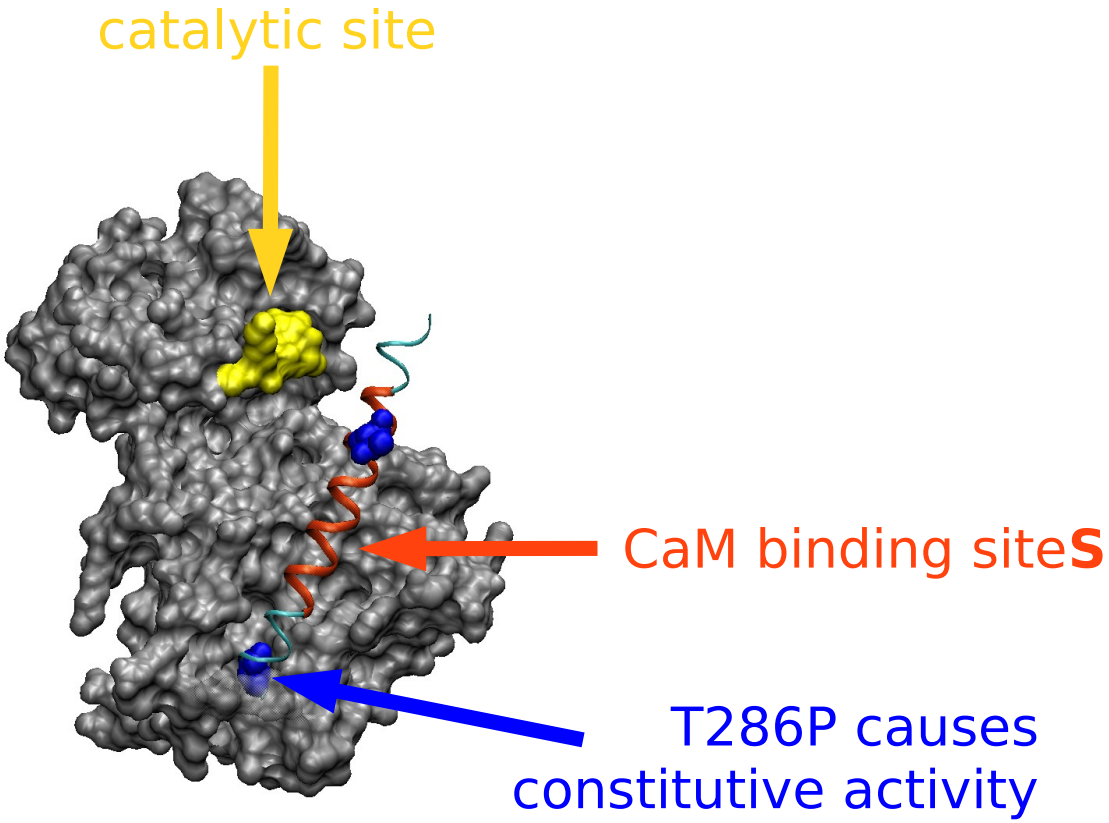


Calmodulin trapping is
an apparent increase of
affinity of CaMKII for CaM
when T286 is phosphorylated

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

Calcium/calmodulin kinase II

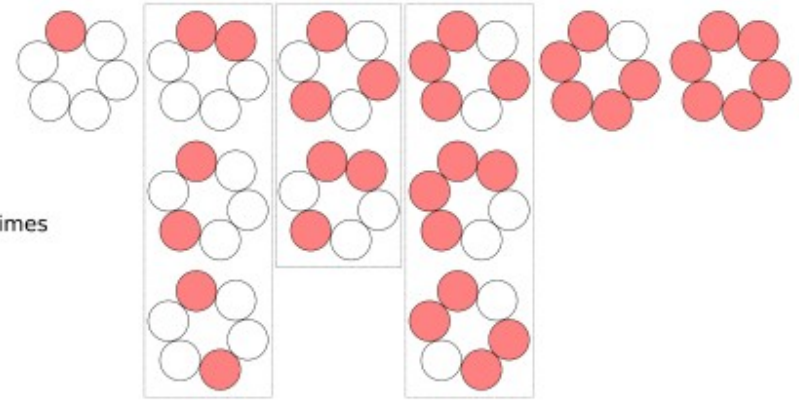




Dodecamer;
Trans-phosphorylation of T286
by neighbouring subunits

A given fraction of activated CaMKII monomers.

Randomly allocate activated monomers to CaMKII hexamers.
Record the number of hexamers containing different numbers of active monomers (in red) as the following:



Repeat 1000 times

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

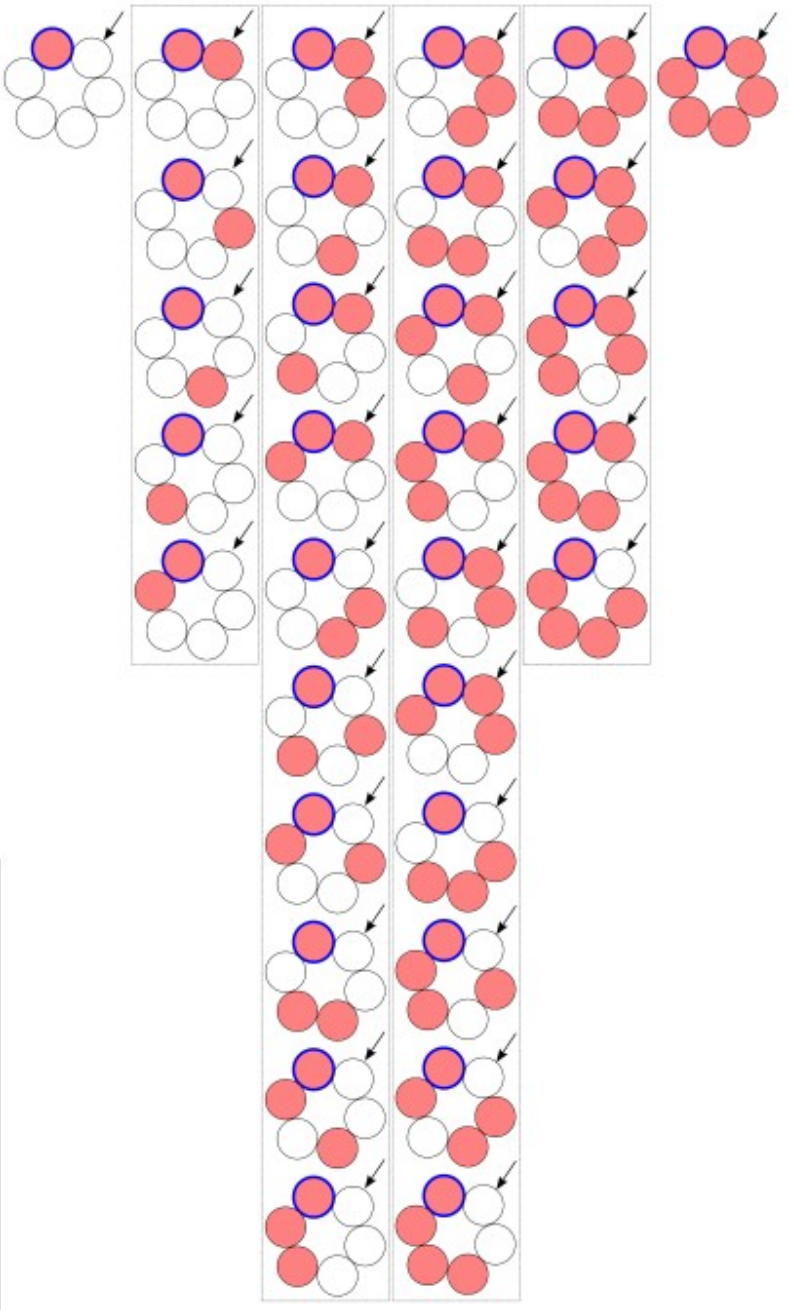
Repeat for every 1% increase of CaMKII active monomers

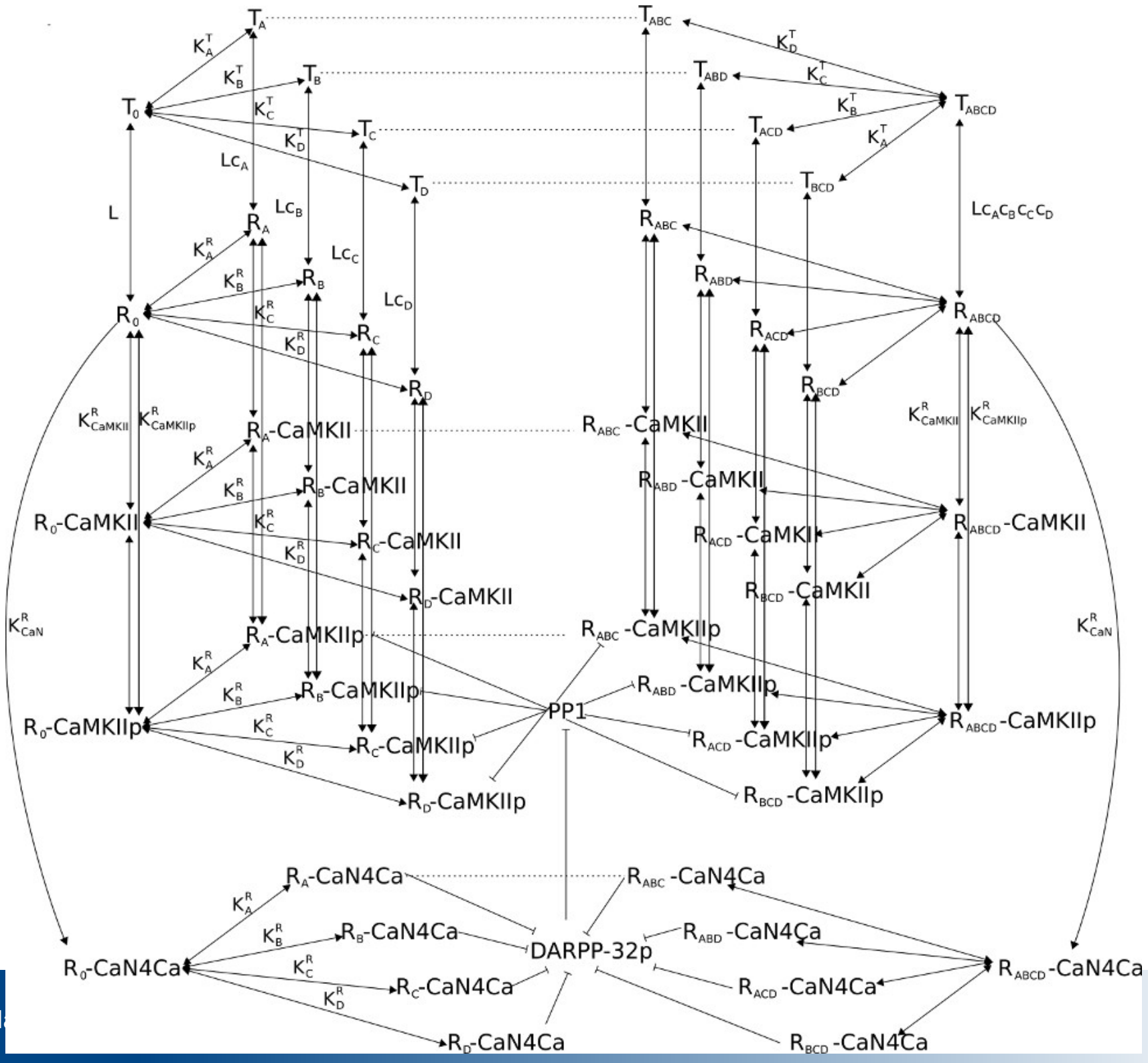
Multiply average populations of each number of active monomers per hexamer by their corresponding probabilities of having an active neighbour.

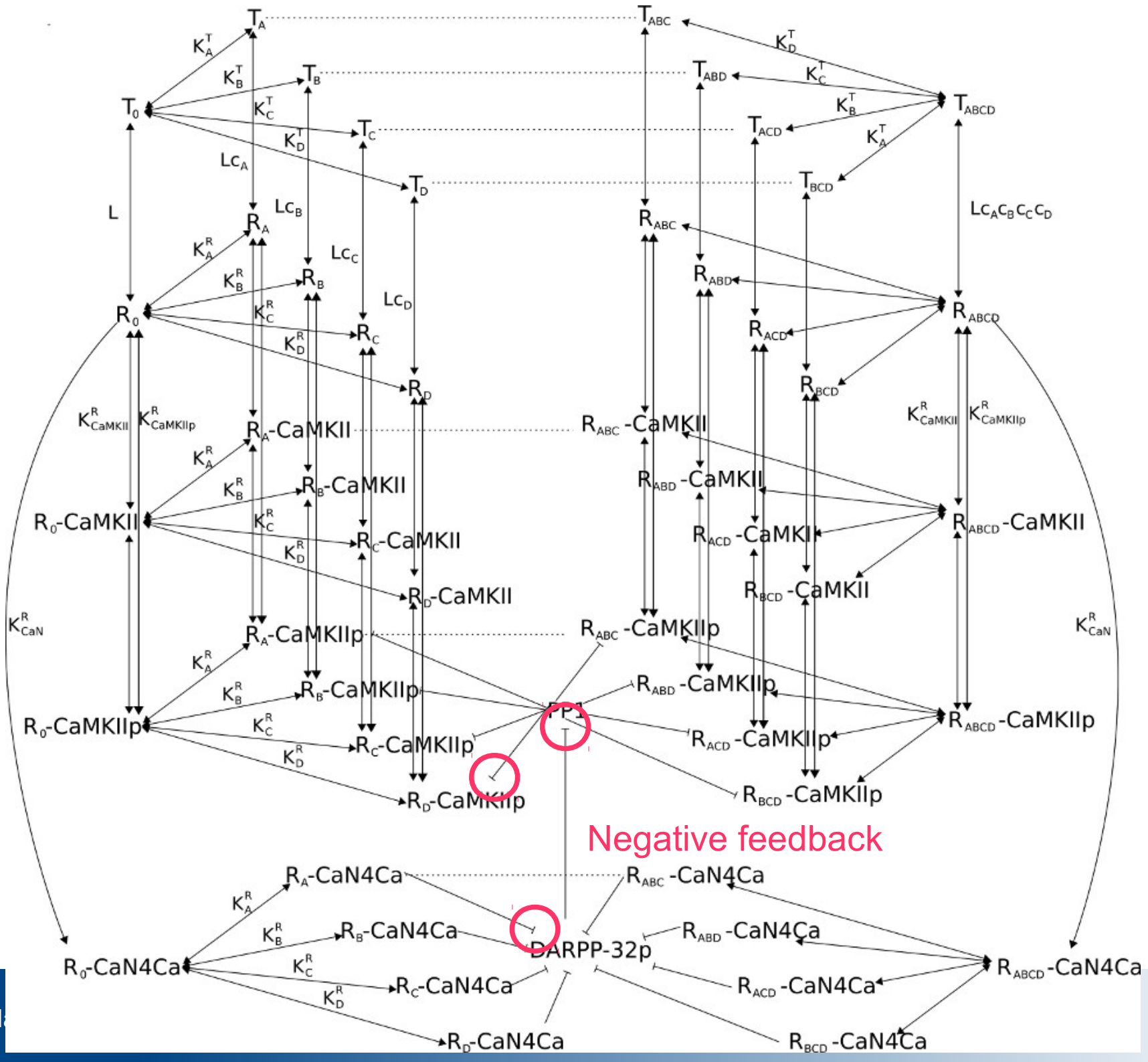
The sum of these six numbers is a coefficient that can be used to adjust CaMKII autophosphorylation rate.

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:




T0
TA
TB
TC
TD
TABC
TABD
TACD
TBCD
TABCD
R0
RA
RB
RC
RD
RABC
RABD
RACD
RBCD
RABCD
L
LcA
LcB
LcC
LcD
LcAcBccCD
R0-CaMKII
RA-CaMKII
RB-CaMKII
RC-CaMKII
RD-CaMKII
RABC-CaMKII
RABD-CaMKII
RACD-CaMKII
RBCD-CaMKII
RABCD-CaMKII
R0-CaMKIIp
RA-CaMKIIp
RB-CaMKIIp
RC-CaMKIIp
RD-CaMKIIp
RABC-CaMKIIp
RABD-CaMKIIp
RACD-CaMKIIp
RBCD-CaMKIIp
RABCD-CaMKIIp
PP1
R0-CaN4Ca
RA-CaN4Ca
RB-CaN4Ca
RC-CaN4Ca
RD-CaN4Ca
RABC-CaN4Ca
RABD-CaN4Ca
RACD-CaN4Ca
RBCD-CaN4Ca
RABCD-CaN4Ca
DARPP-32p



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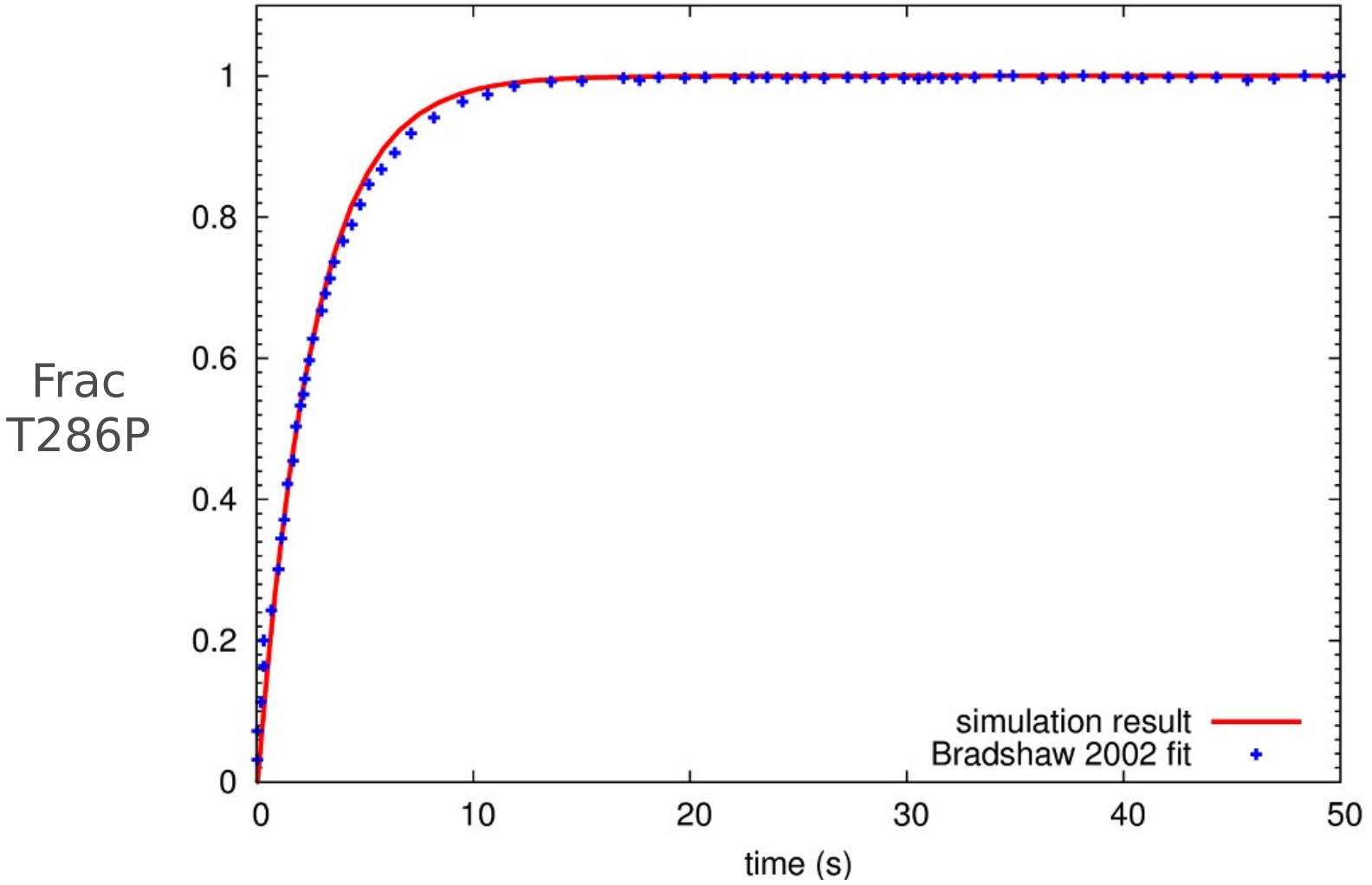
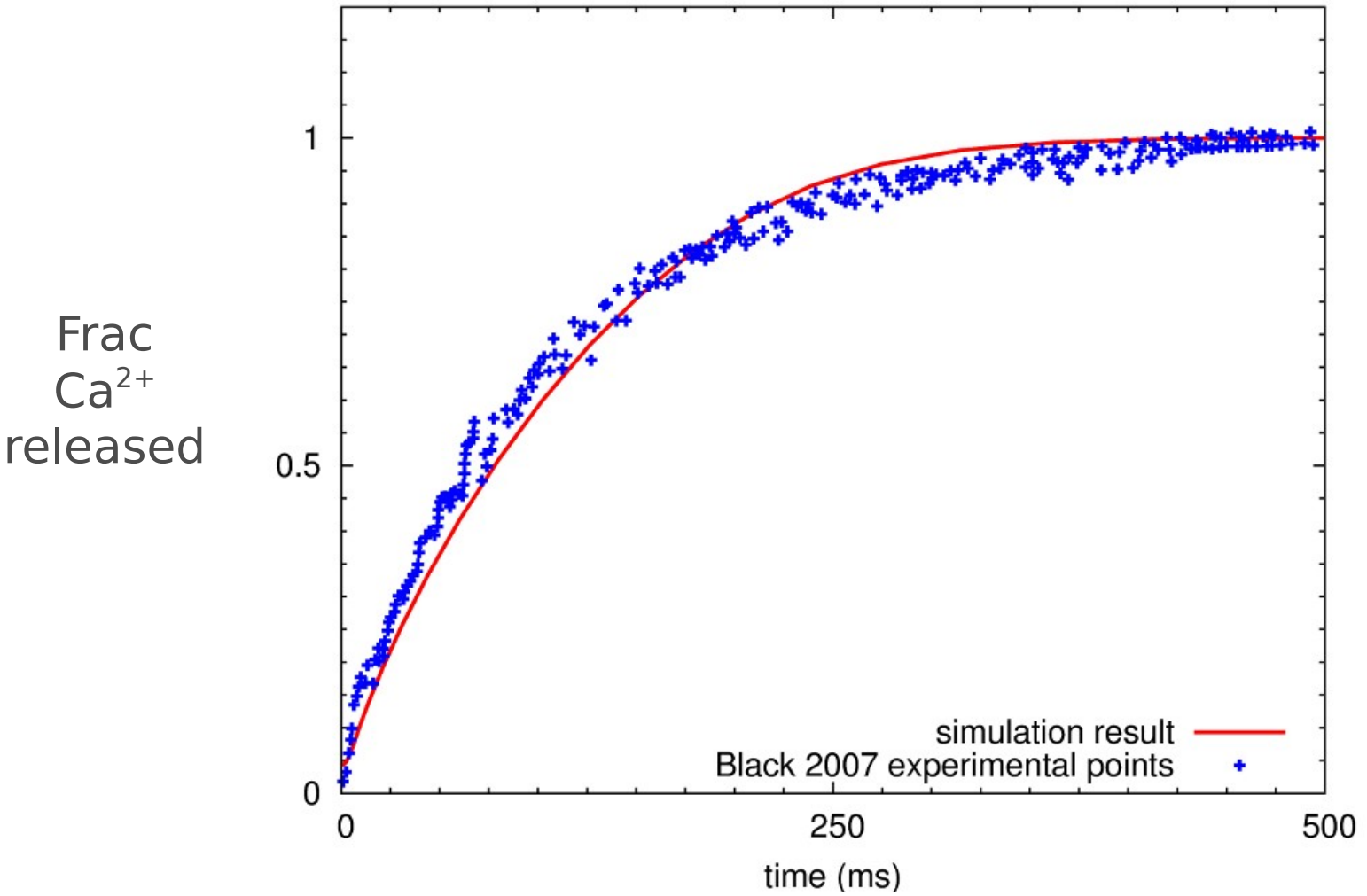
Validation of CaMKII kinetics



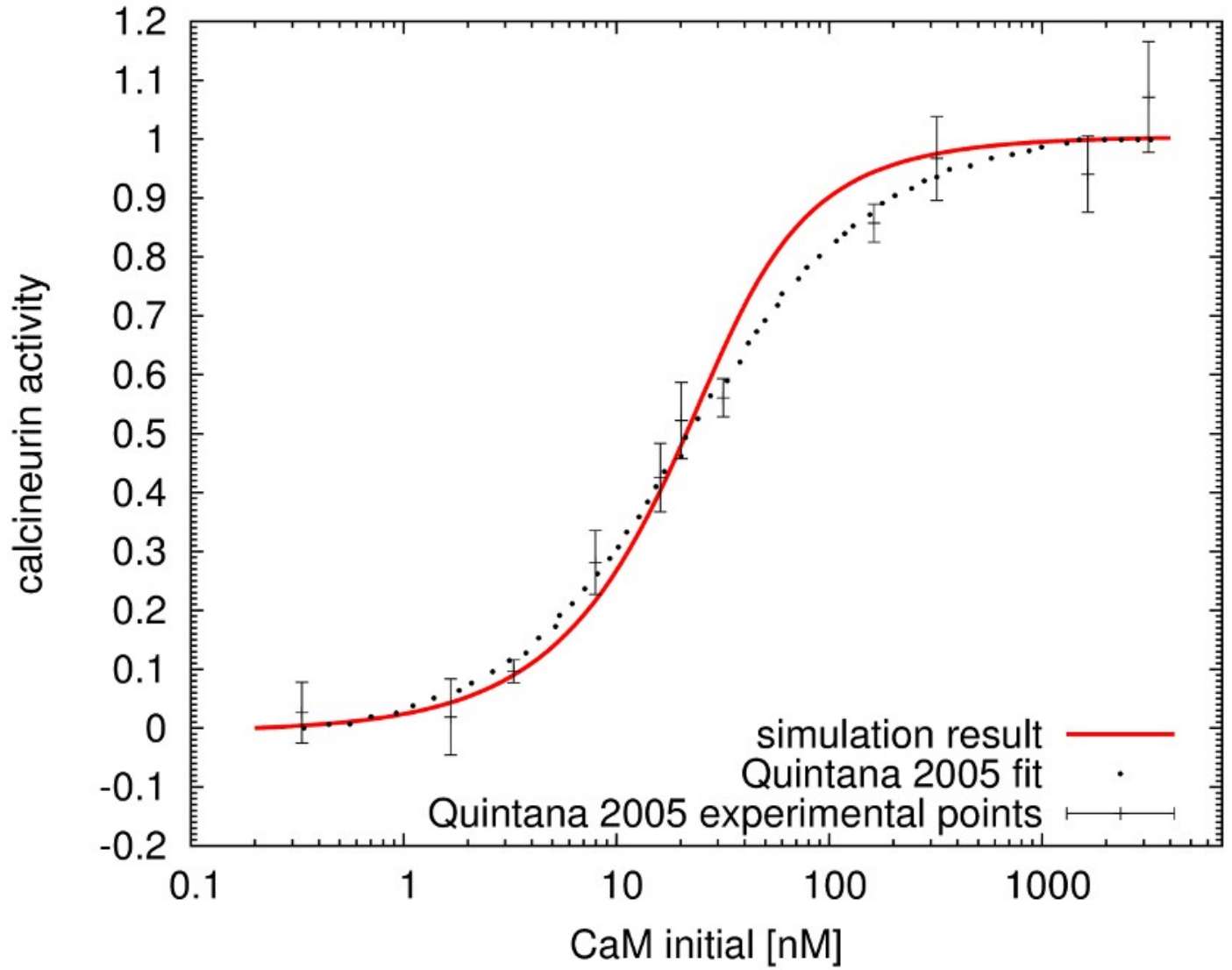
Bradshaw JM, Kubota Y, Meyer T, Schulman H (2003). *PNAS* 100: 10512–10517.

Validation of CaM kinetics



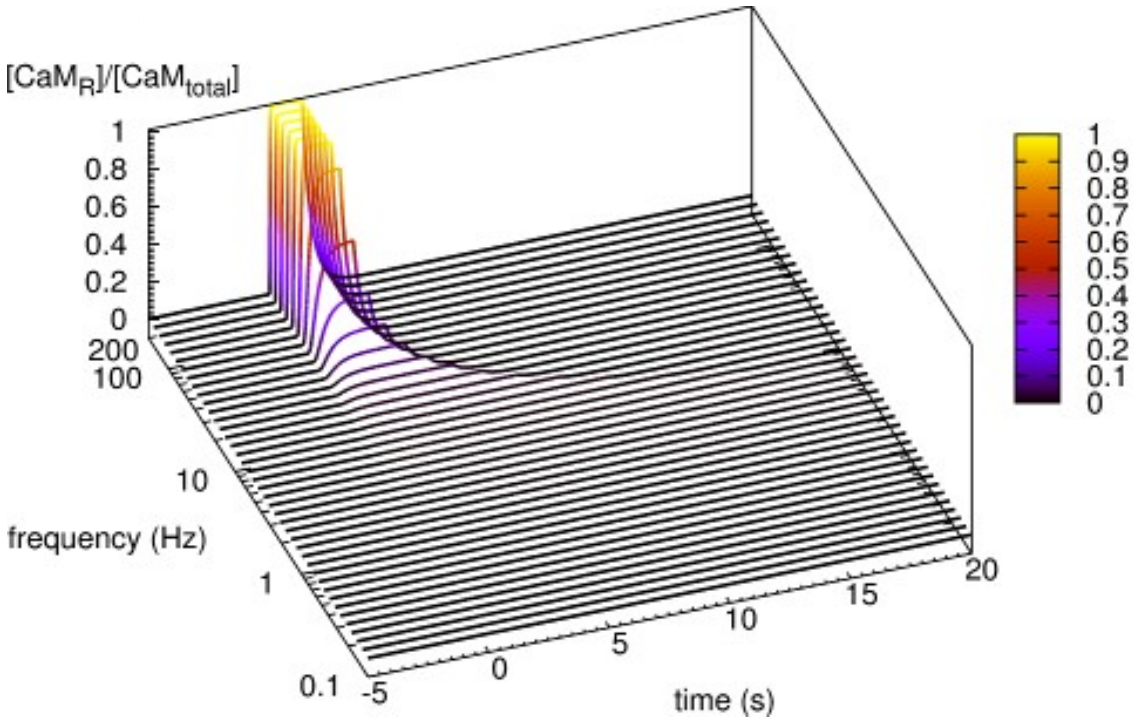
Black DJ, Selfridge JE, Persechini A (2007). *Biochemistry* 46: 13415–13424.

Validation of calcium-activation of CaN



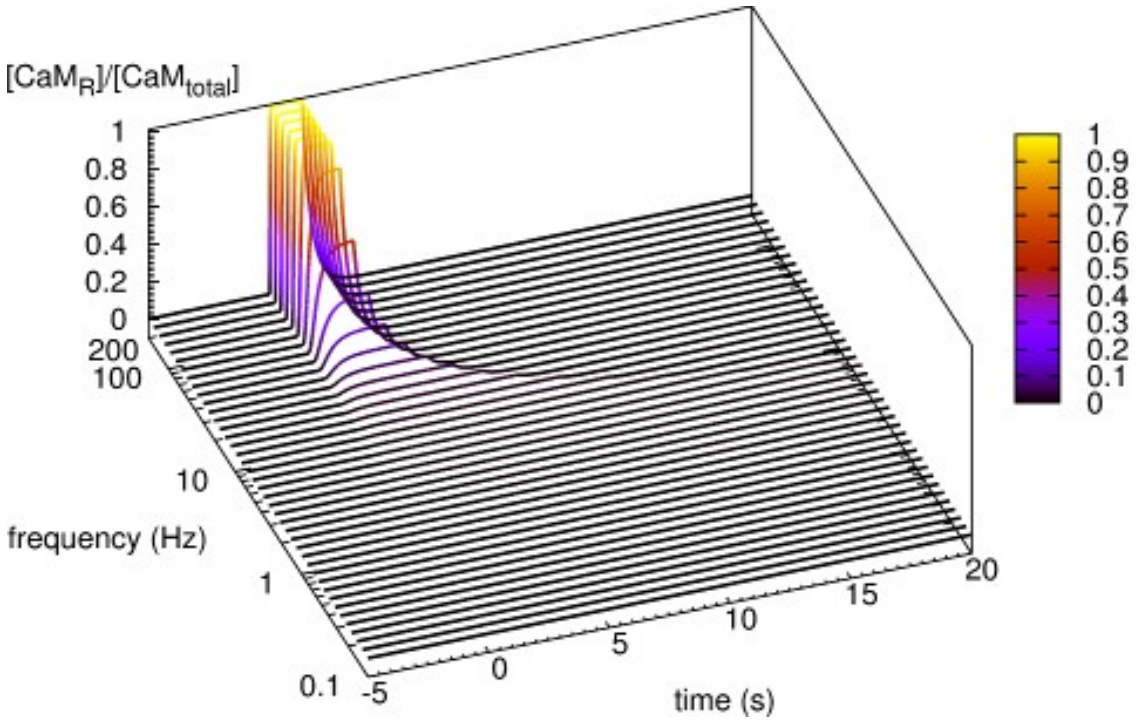
Quintana AR, Wang D, Forbes JE, Waxham MN (2005). *BBRC* 334: 674–680.

Calmodulin activation



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

Calmodulin activation



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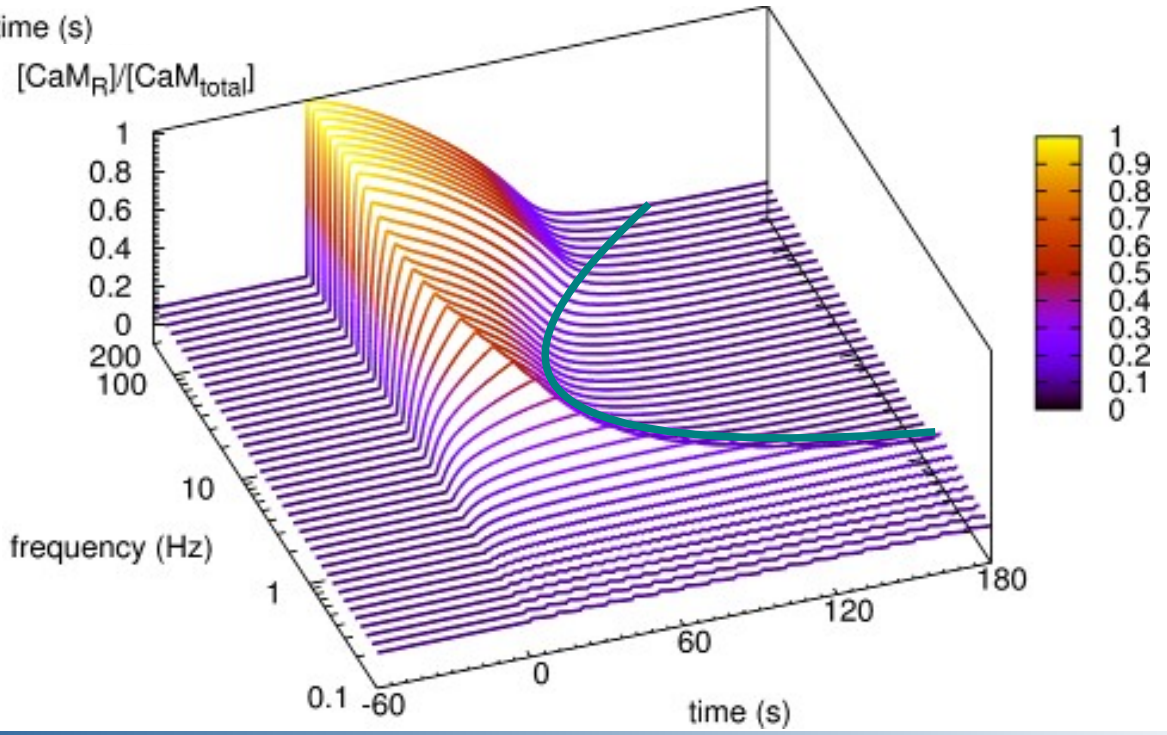
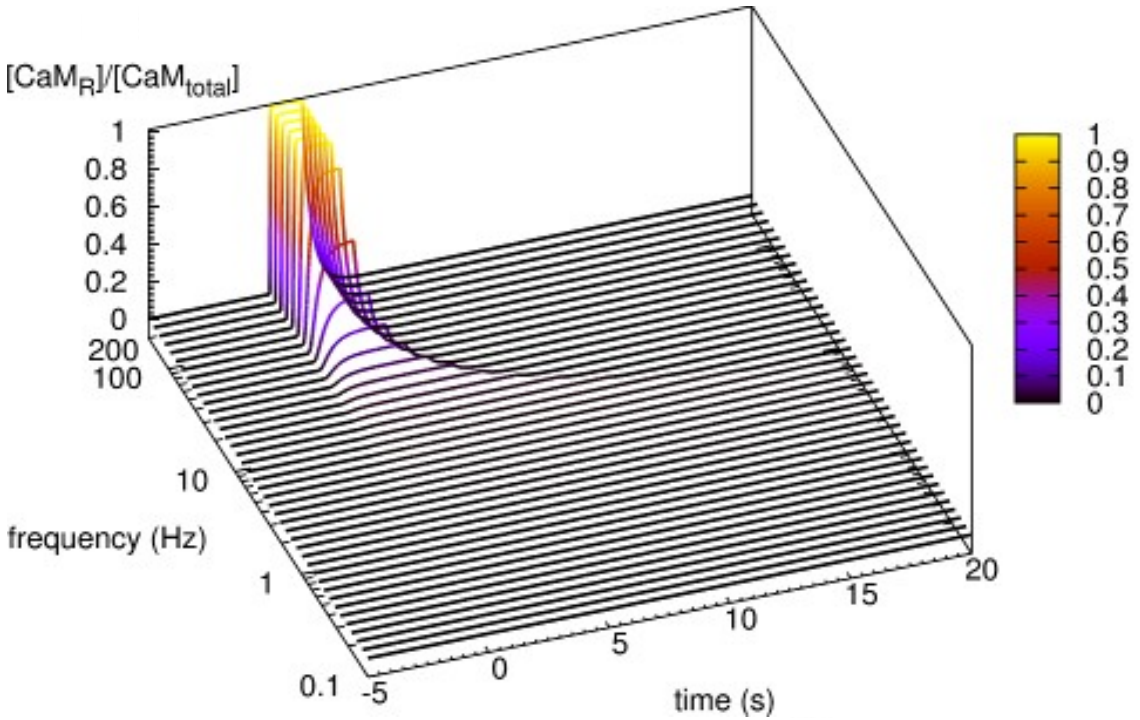


CaM with targets. Binding to CaN and CaMKII stabilises R state, with higher affinity. Positive feedback loop
➜ bistability

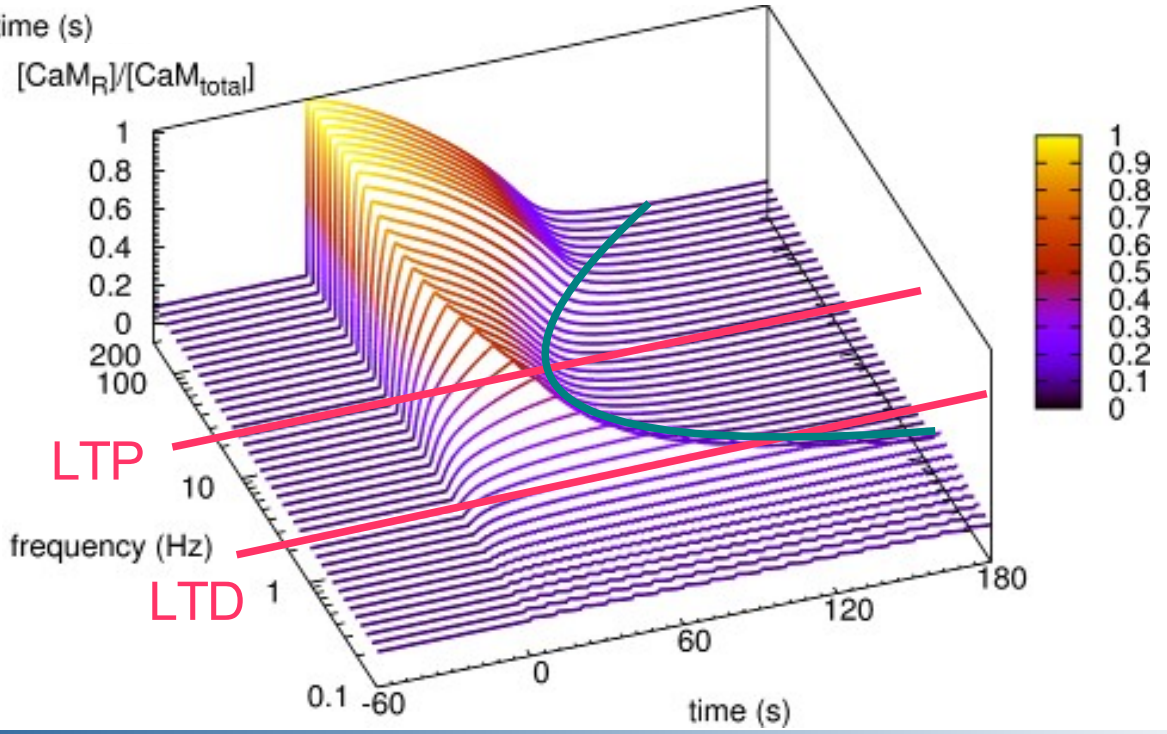
Calmodulin activation



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



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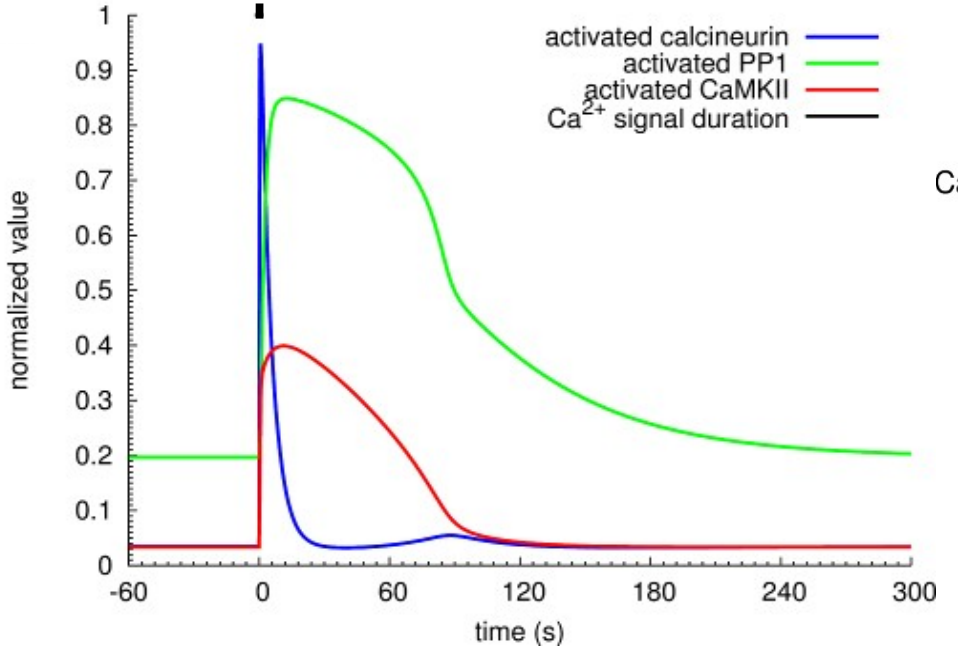
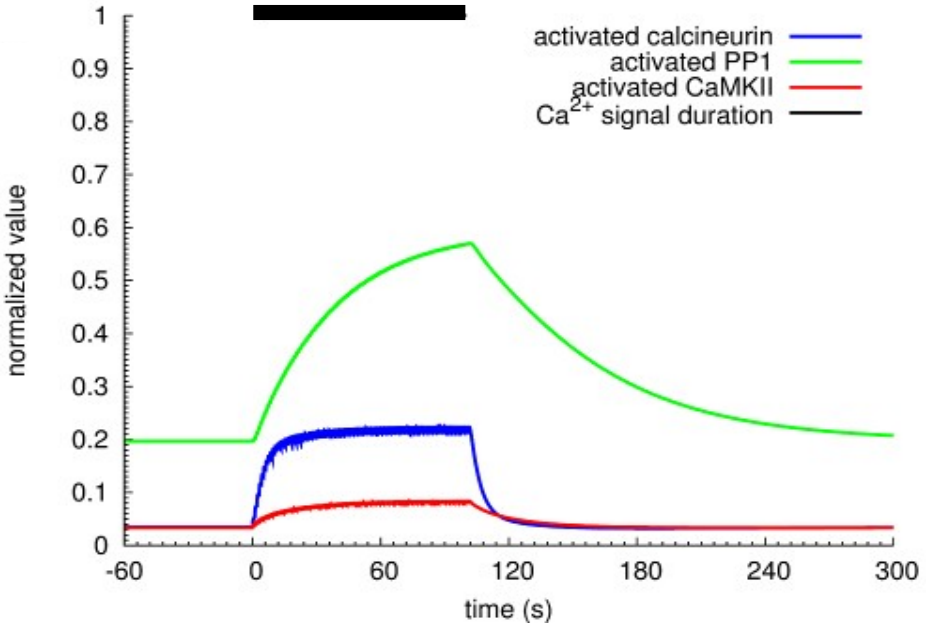
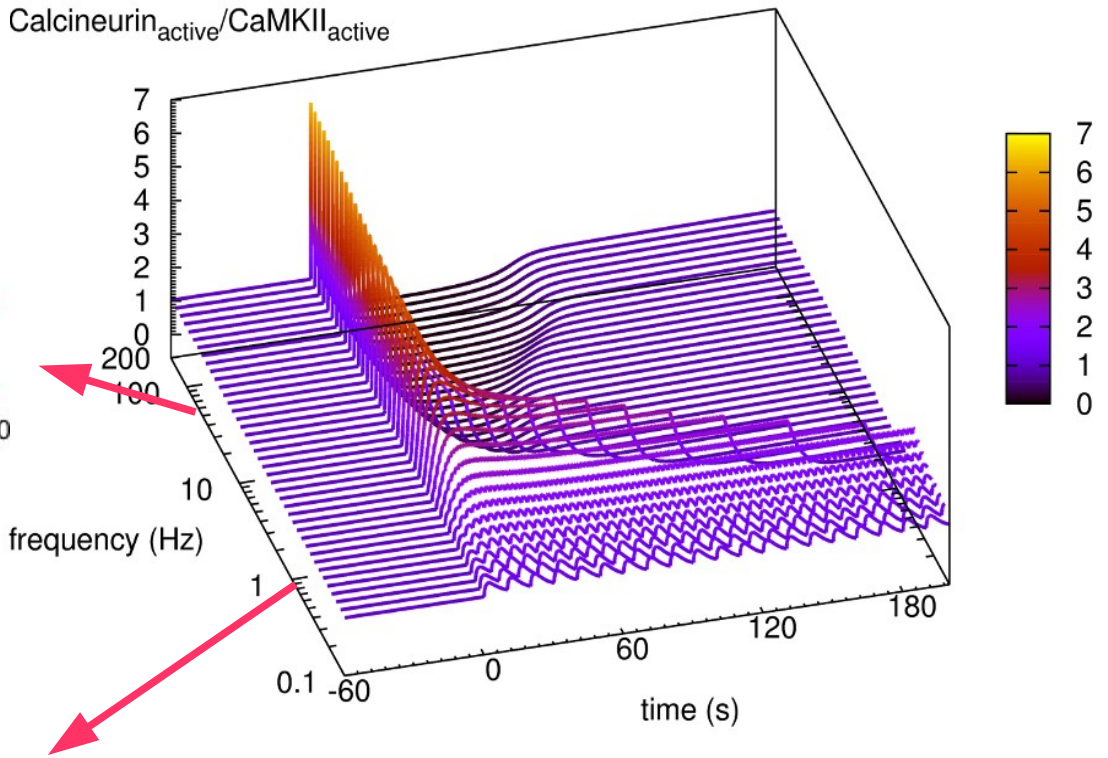
Temporal activation of CaMKII and CaN







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

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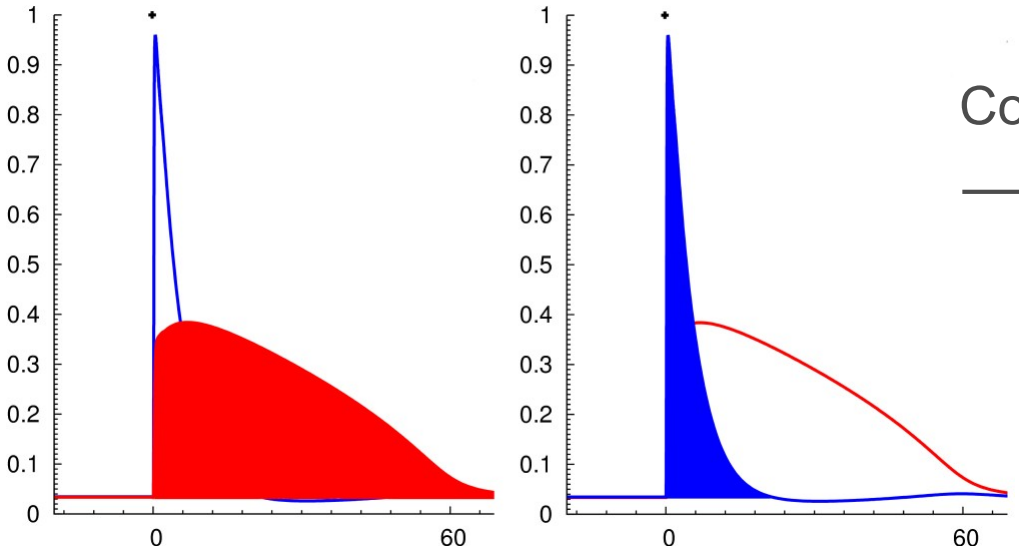
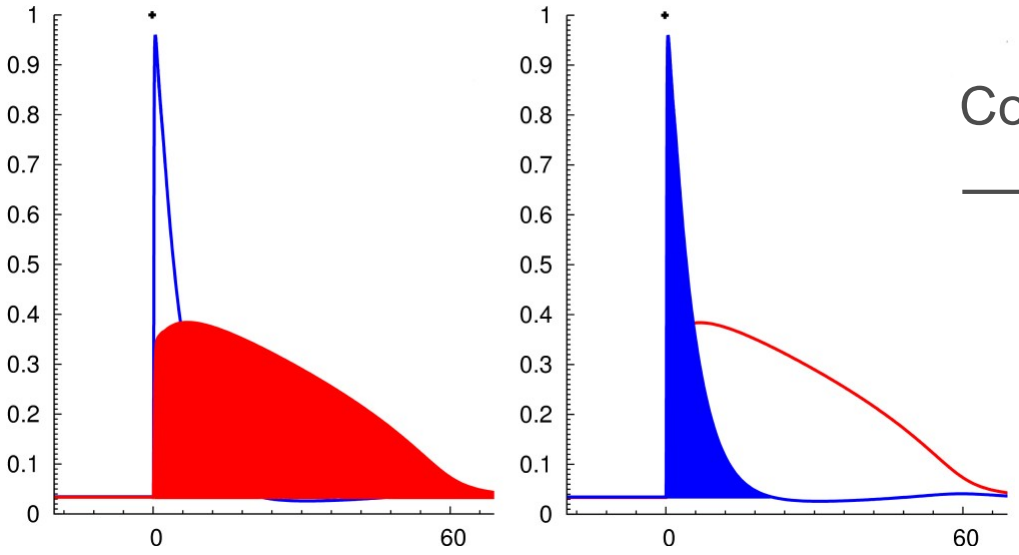
Bidirectional plasticity



Constant catalytic rates of active enzyme

$\longrightarrow$ quantity of catalysed reaction events prop to integral of the activation curve

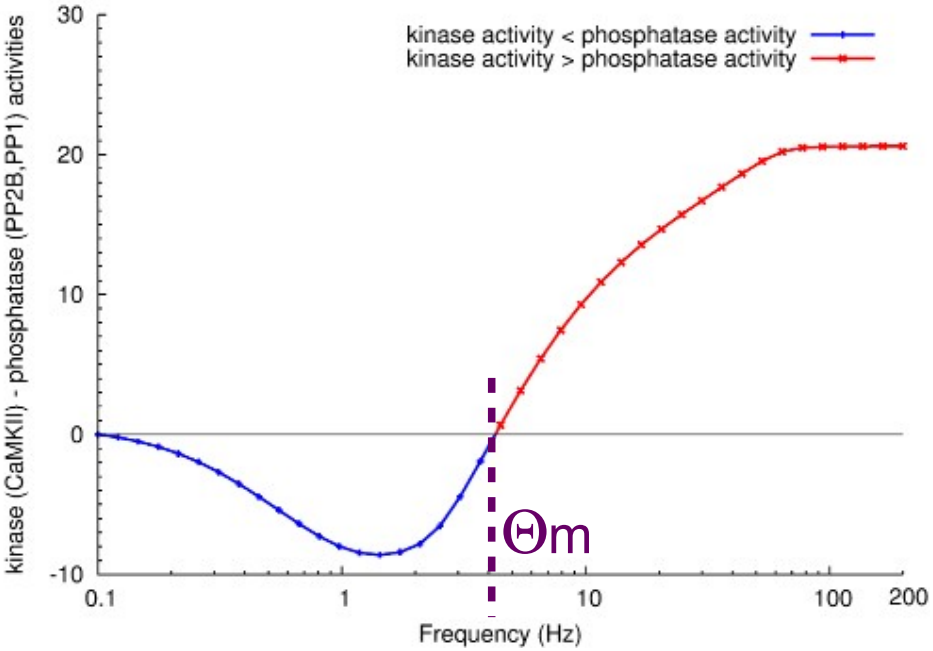
Bidirectional plasticity



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



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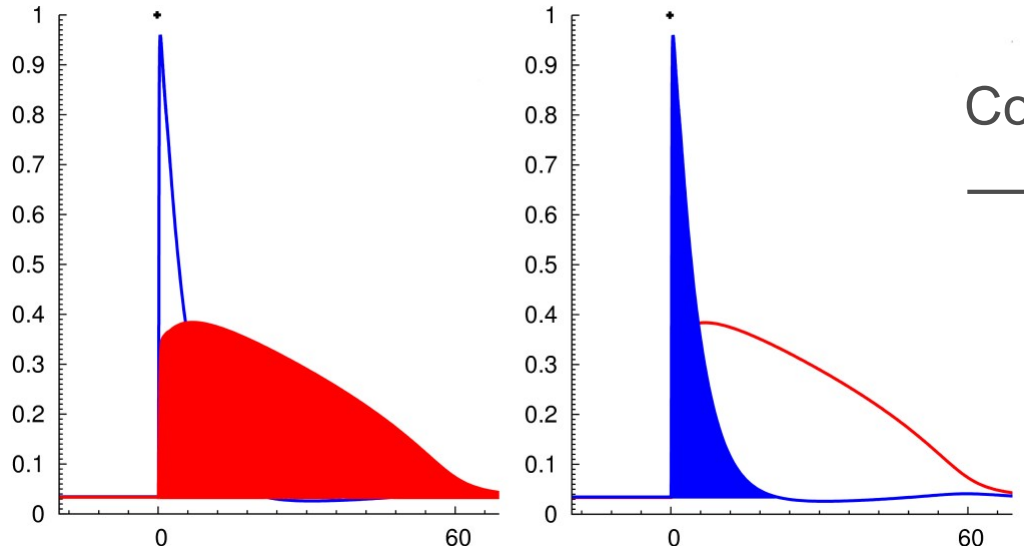
Bidirectional plasticity



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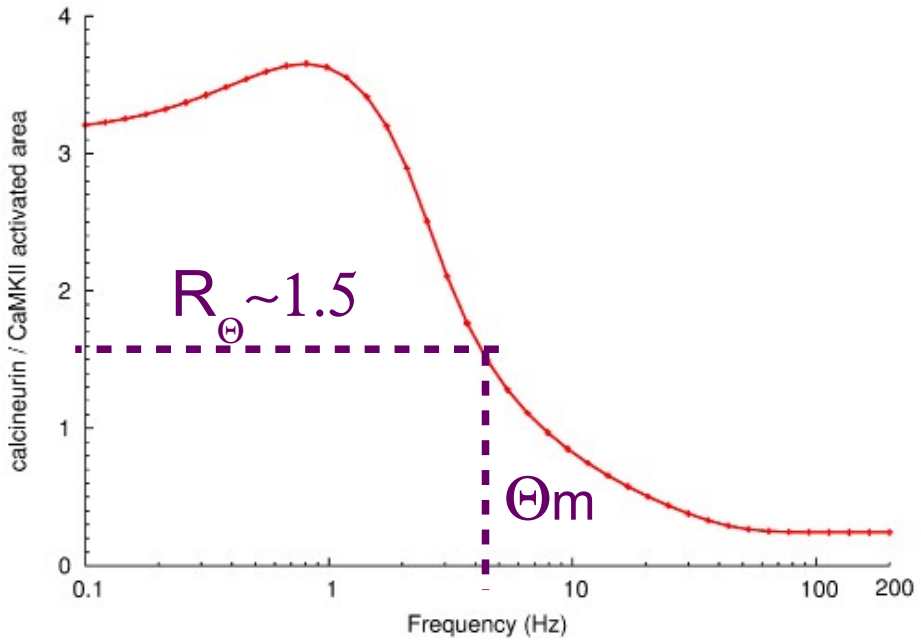

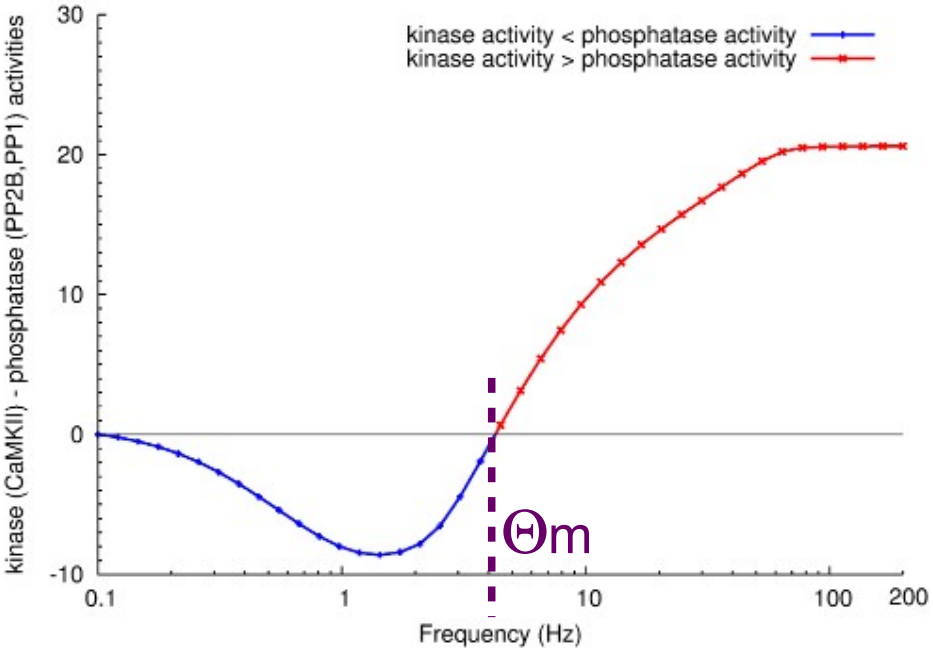

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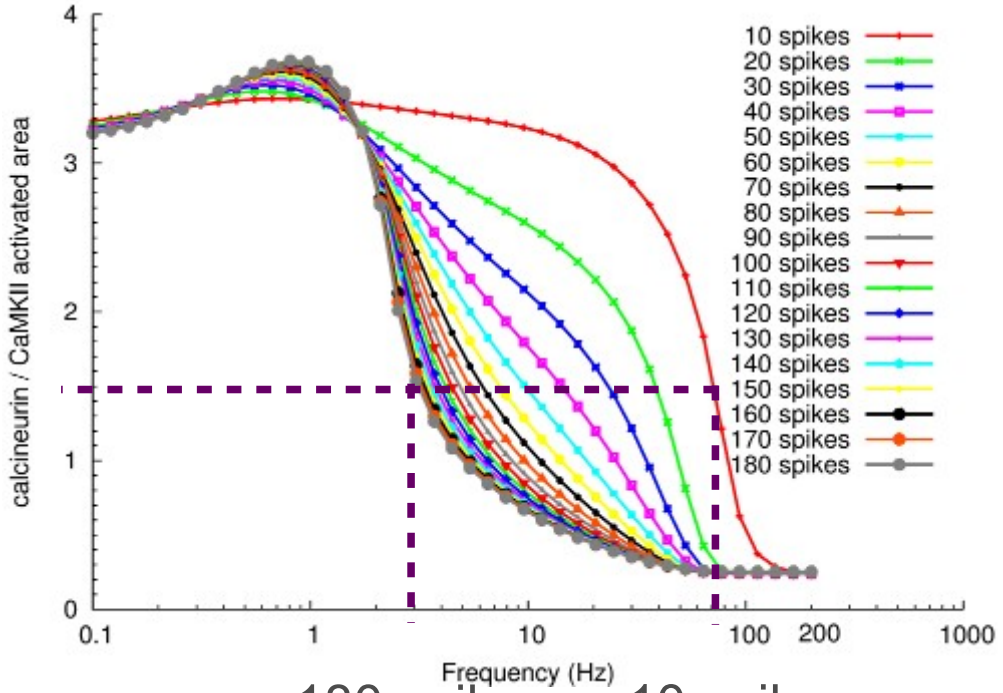
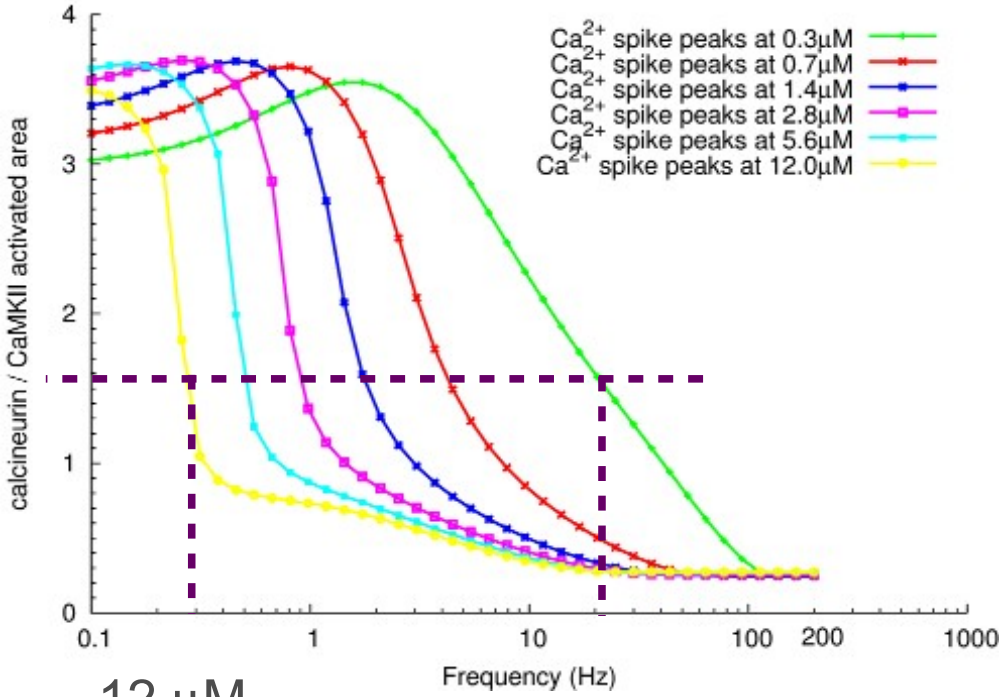
Effect of calcium duration and amount



180 spikes = 3 Hz

10 spikes = 70 Hz



12 µM = 0.3 Hz

0.3 µM = 20 Hz

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

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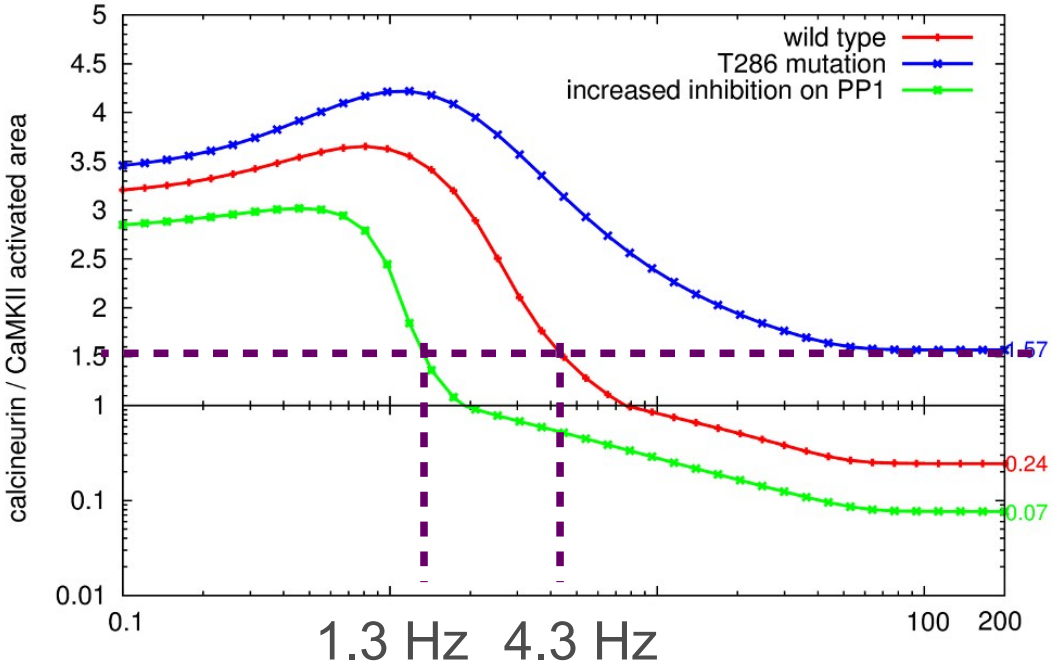
Effect of intrinsic system perturbations



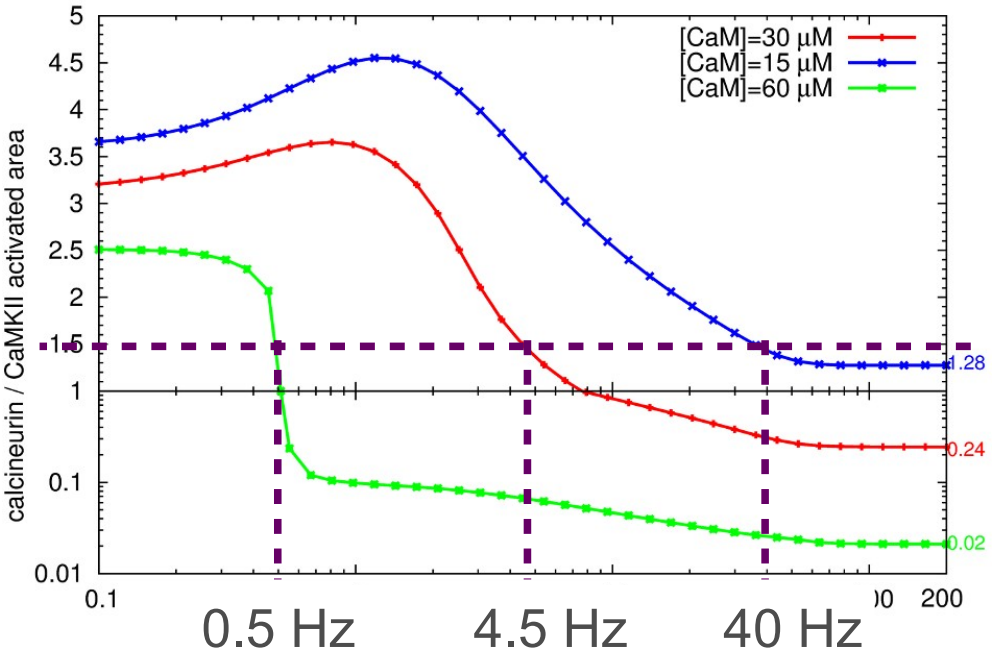
CaMKII not constitutively active
No CaM trapping

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

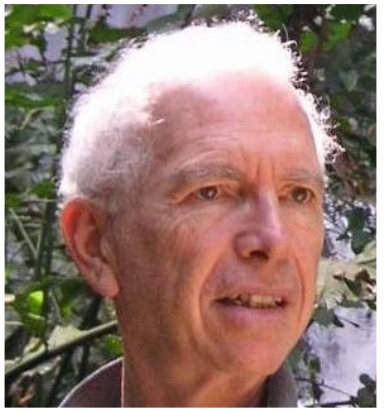
- Developers of ECell3, COPASI, Scilab

Melanie Stefan

Lu Li

Denis Brun

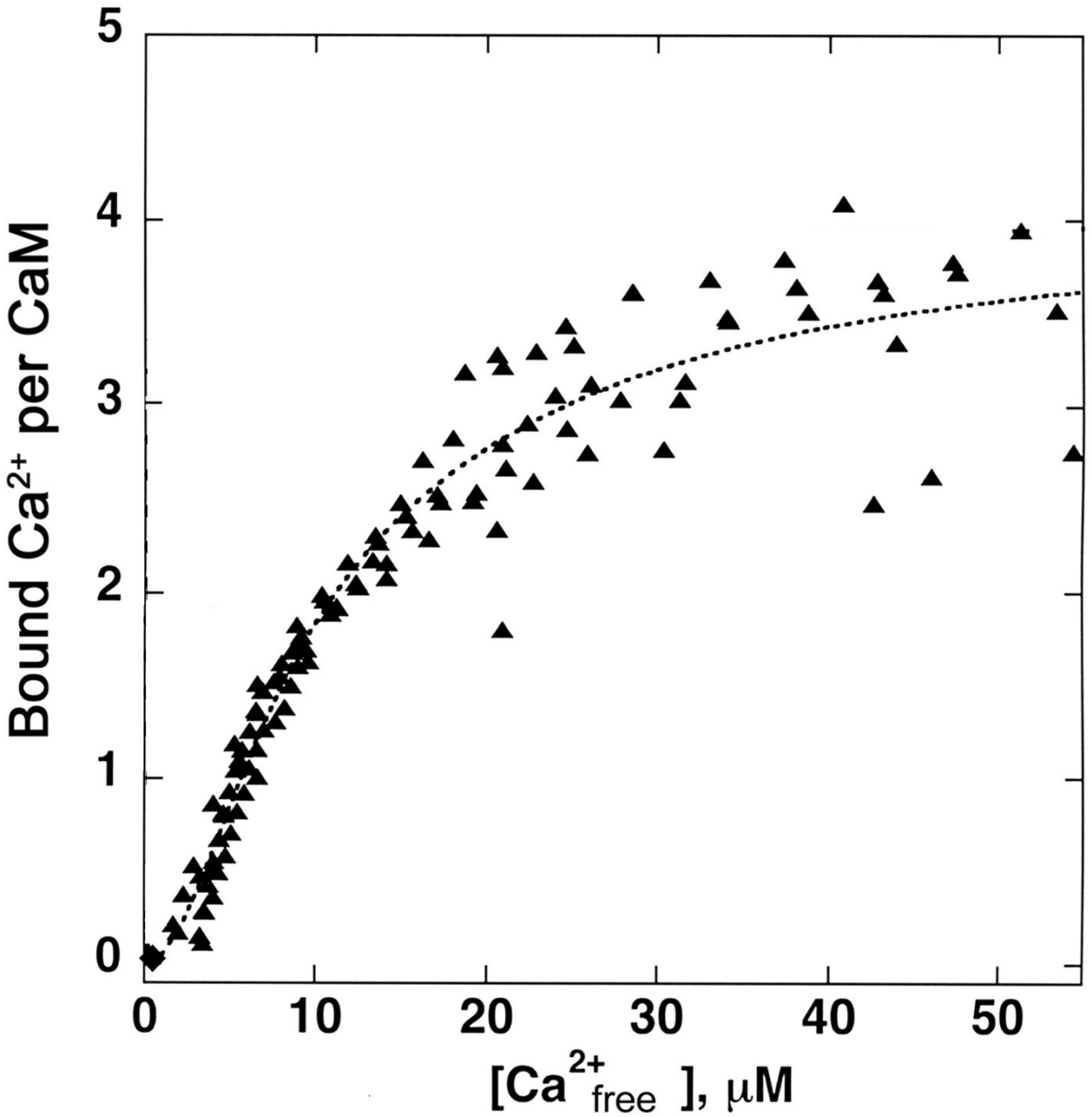
Michele Mattioni



Stuart Edelstein

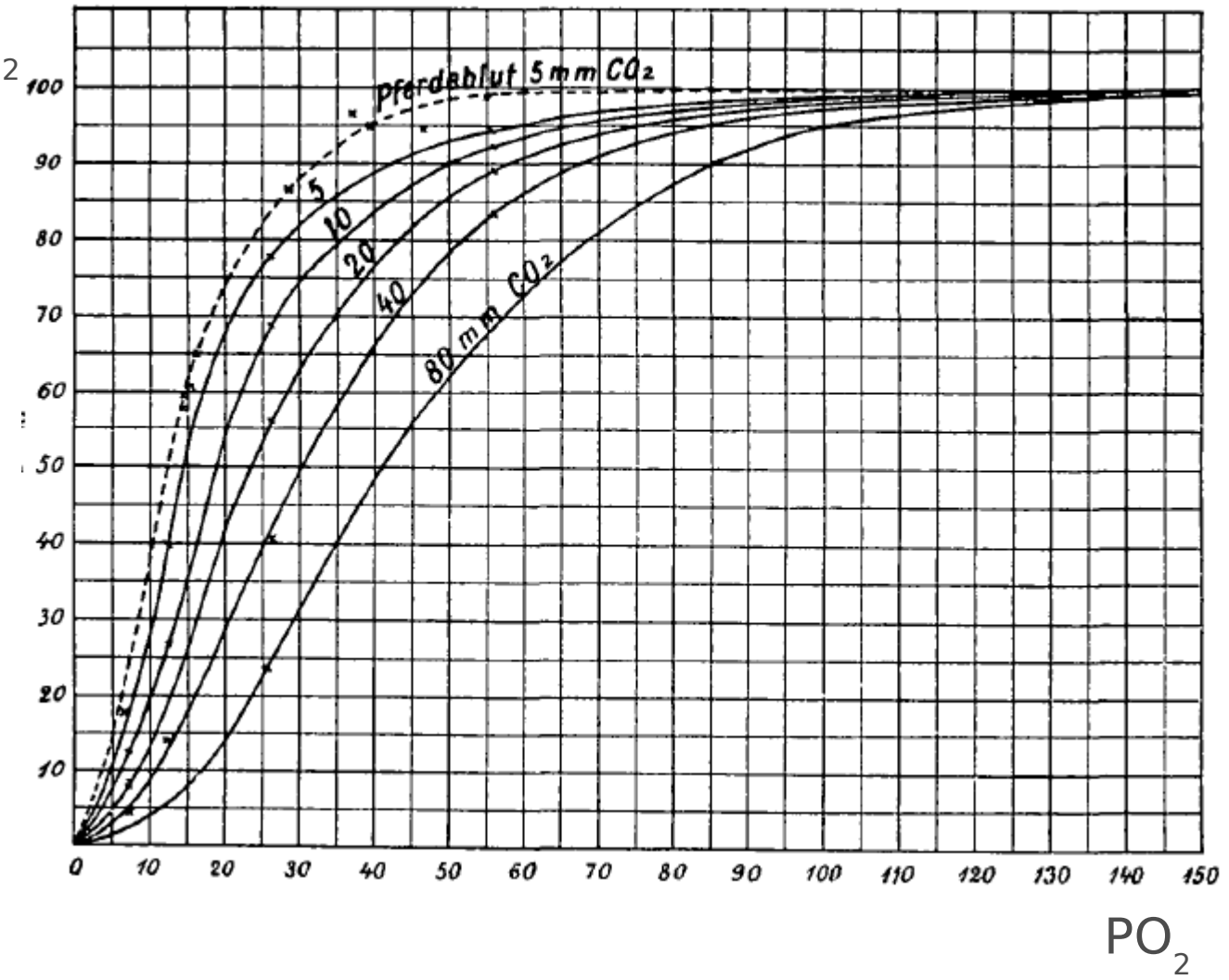
Massimo Lai

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

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

$$\mathrm{Hb} + \mathrm{O_2} \rightleftarrows \mathrm{HbO_2},$$
$$\mathrm{Hb}_n + n\mathrm{O_2} \rightleftarrows \mathrm{Hb}_n\mathrm{O}_{2n},$$

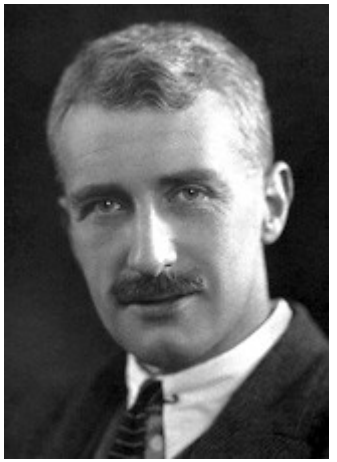
where Hb_n represents the aggregate of n molecules of Hb. I have supposed that in every solution there are many different sized aggregates, corresponding to many values of n.

If there were in the solution only Hb and $\mathrm{Hb_2}$ the dissociation curve would be

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

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

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



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

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

would satisfy the observations.

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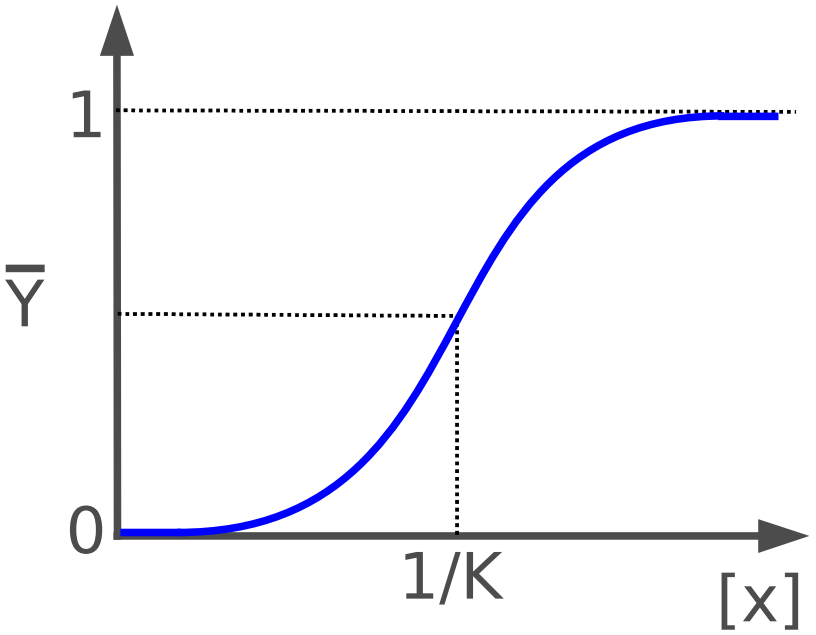

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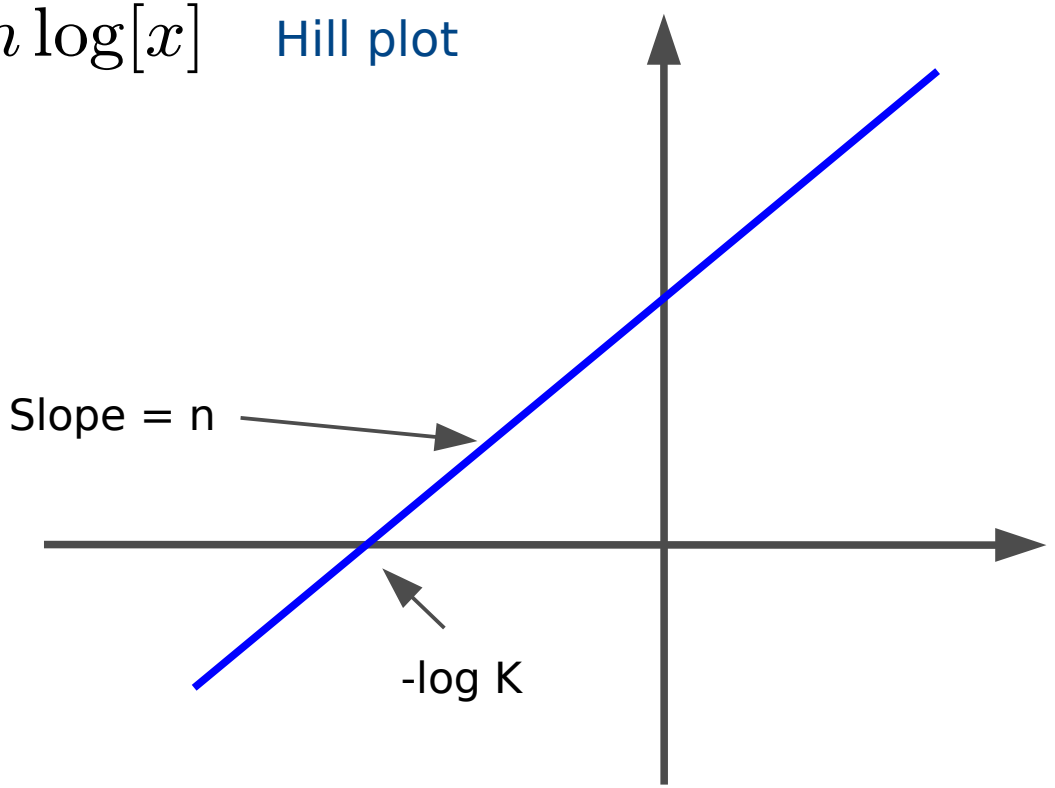
Hill equation can be linearised

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

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 HEMOGLOI

By G. S. ADAIR.

With the Collaboration of A. V. Bock and H. Field,

(*From the Medical Laboratories of the Massachusetts General Hos Boston.*)

(Received for publication, January 7, 1925.)

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

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

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

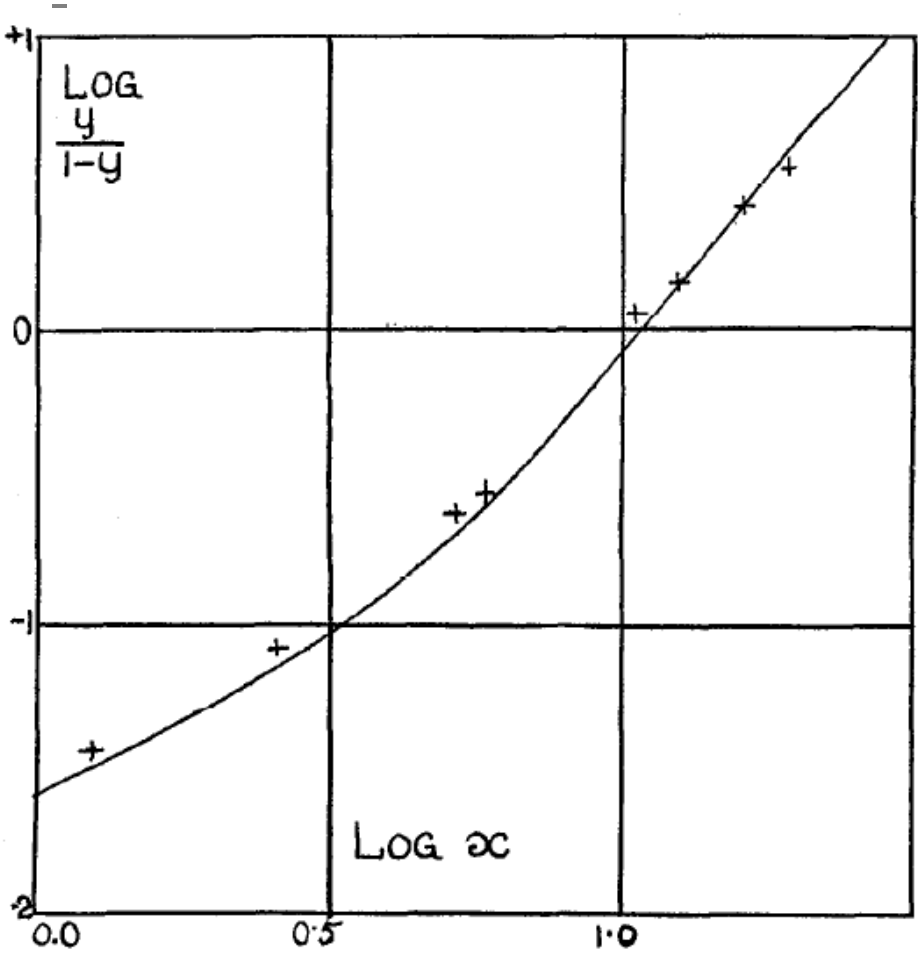


FIG. 2. Test of formula (6). Curve drawn from 6 experimental points from Table IV.

Origins of cooperativity: Adair-Klotz

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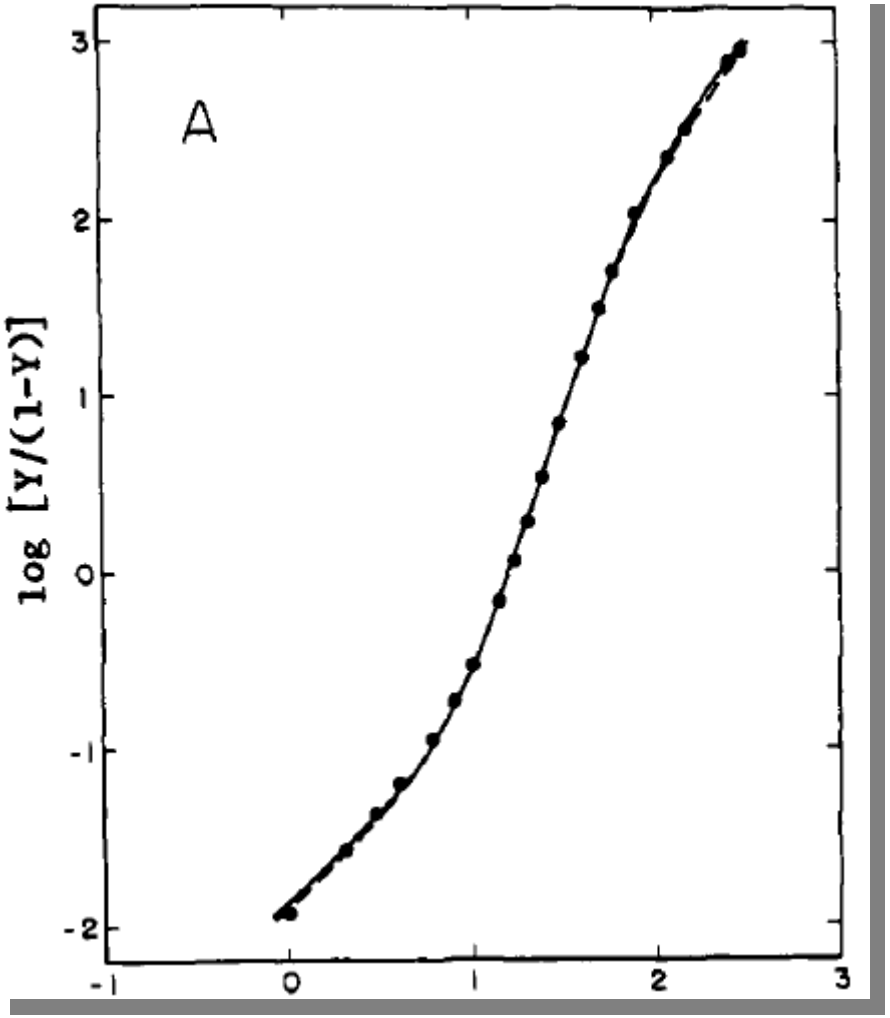


Imai (1973) *Biochemistry* 12: 798-808

Adair-Klotz model applied to Calmodulin

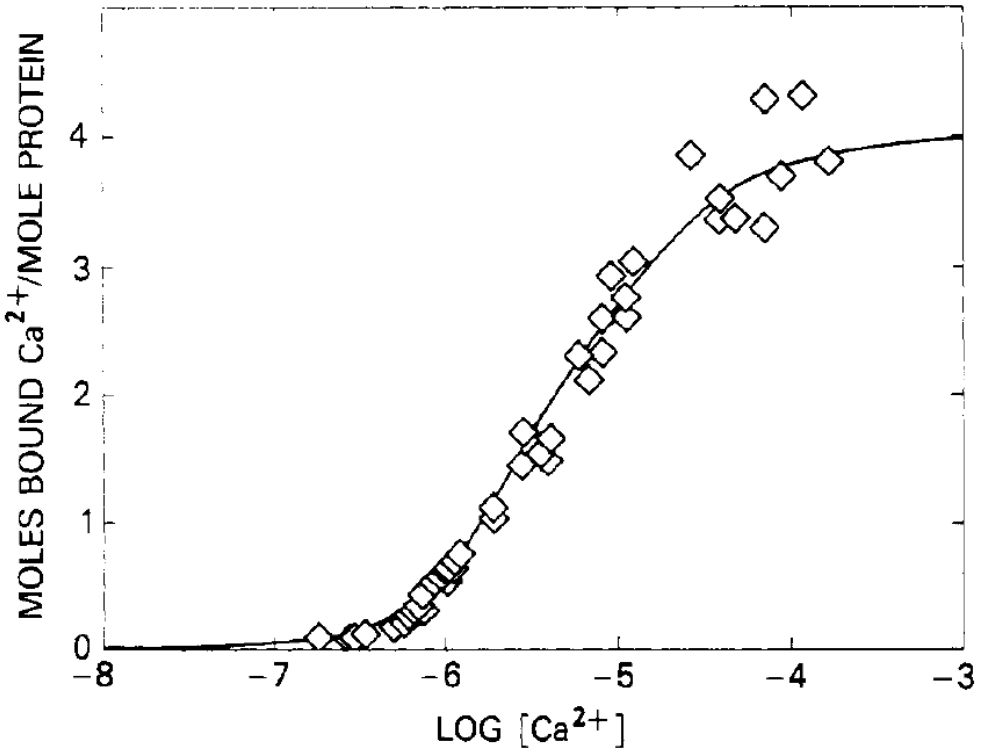
Klotz (1946) The Application of the Law of Mass Action to Binding by Proteins. Interactions with Calcium. *Arch Biochem*, 9:109–117.

1st calcium

2nd calcium

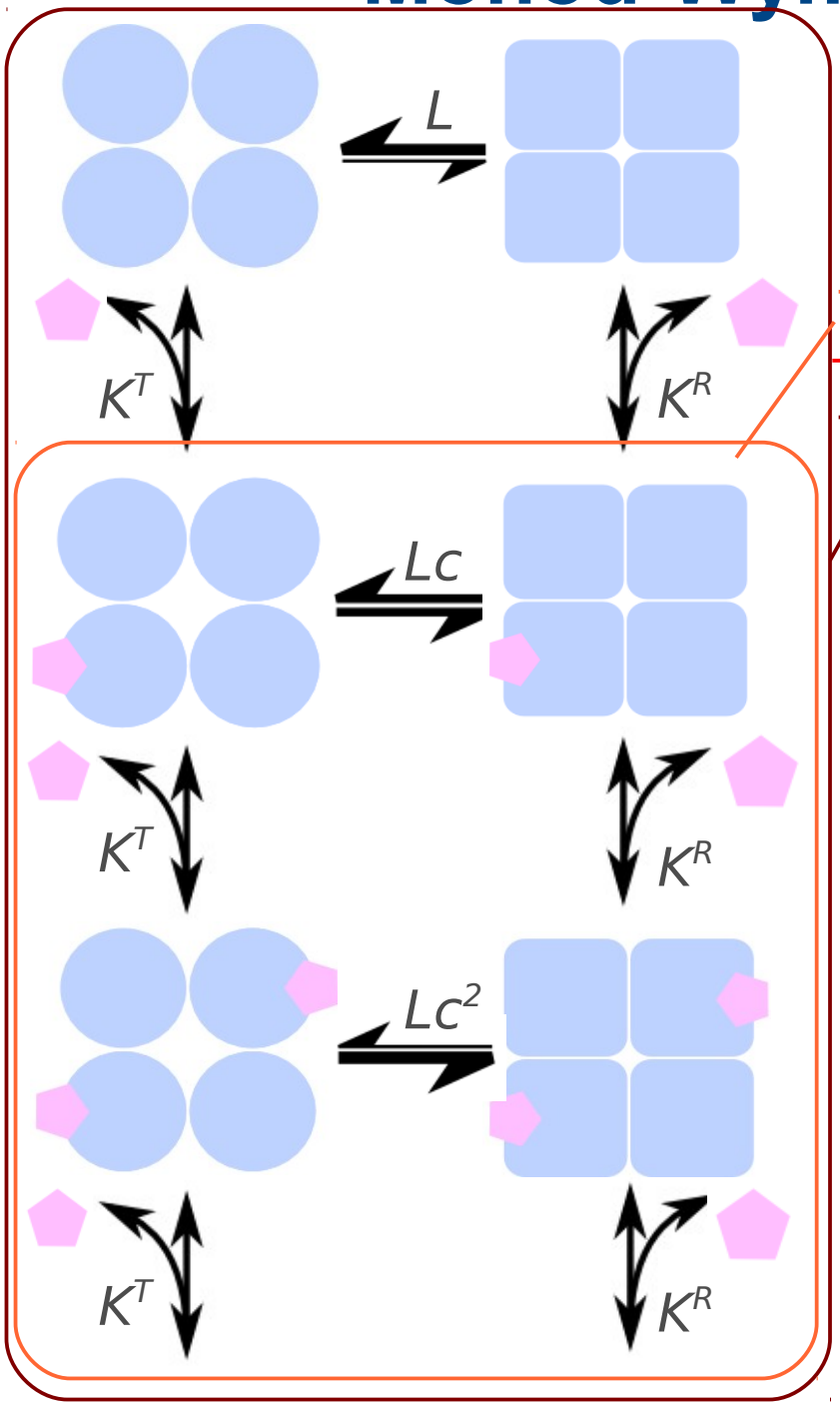
...

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



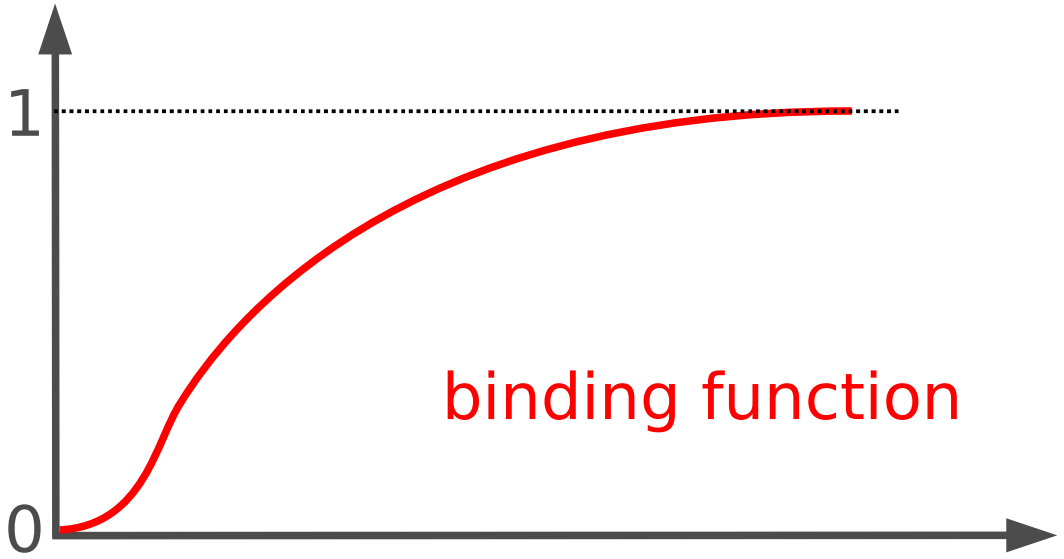
Crouch and Klee (1980) *Biochemistry*, 19: 3692-3698b

Monod-Wyman-Changeux model



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

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



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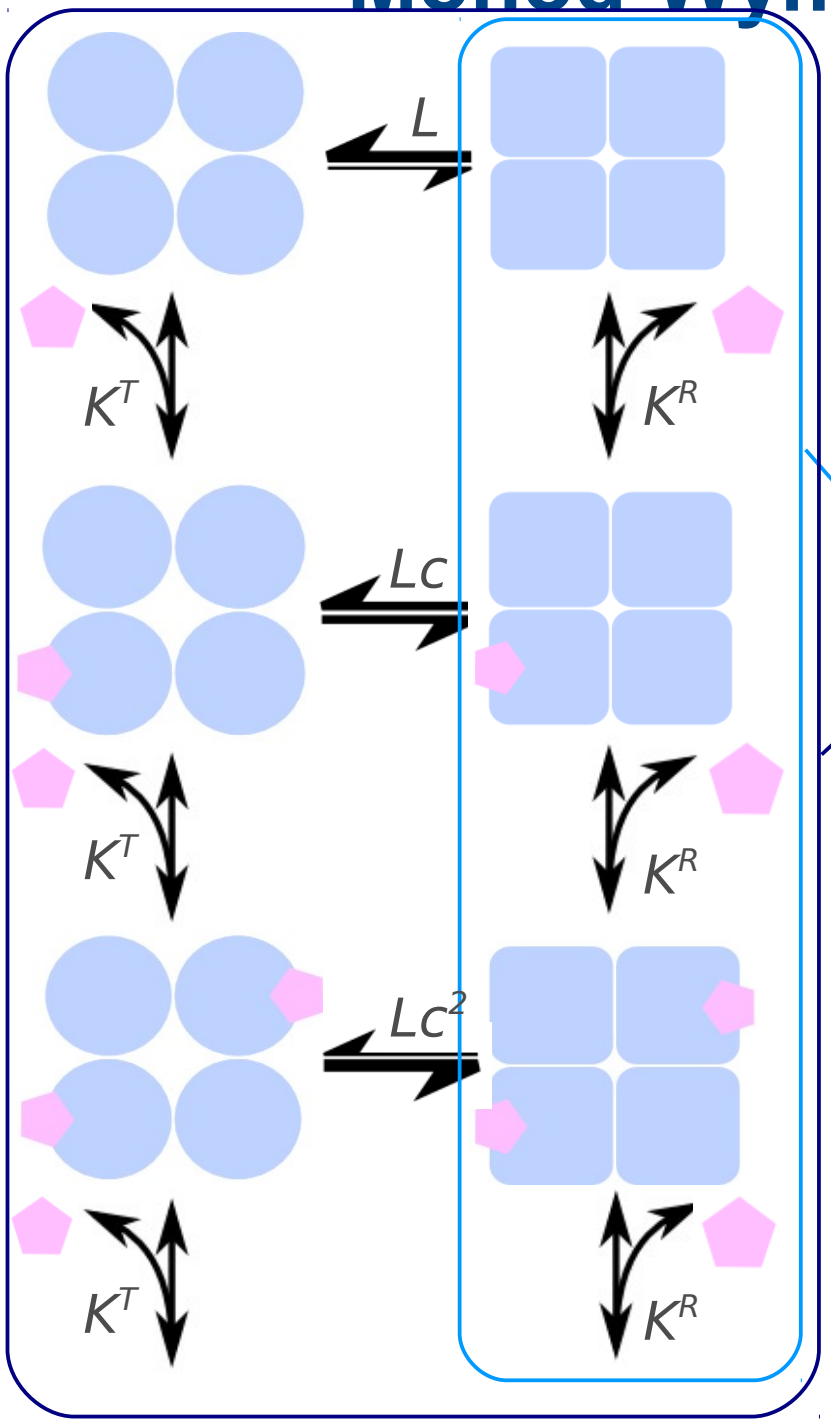
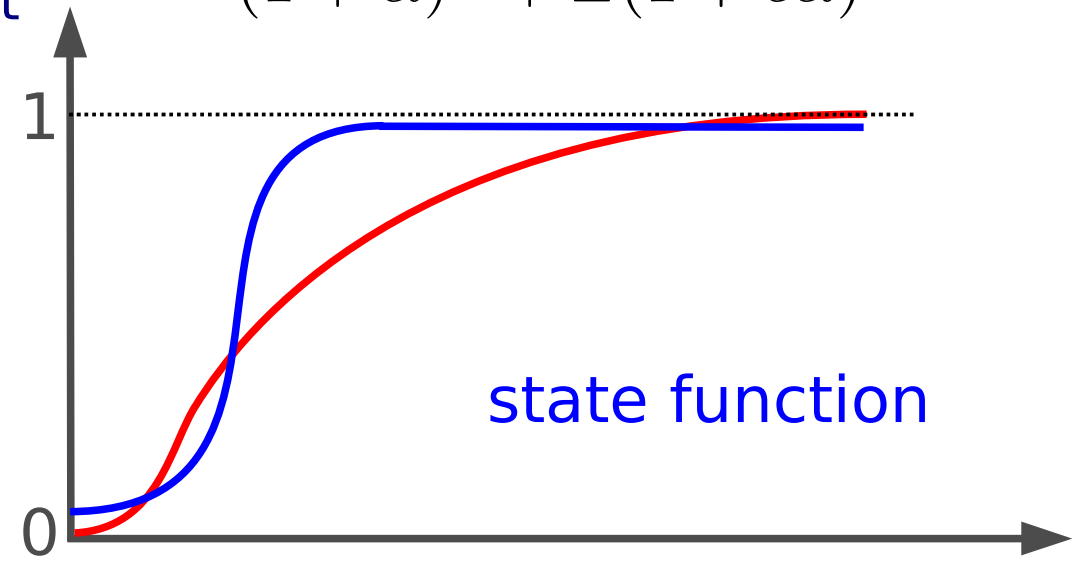
Monod-Wyman-Changeux model



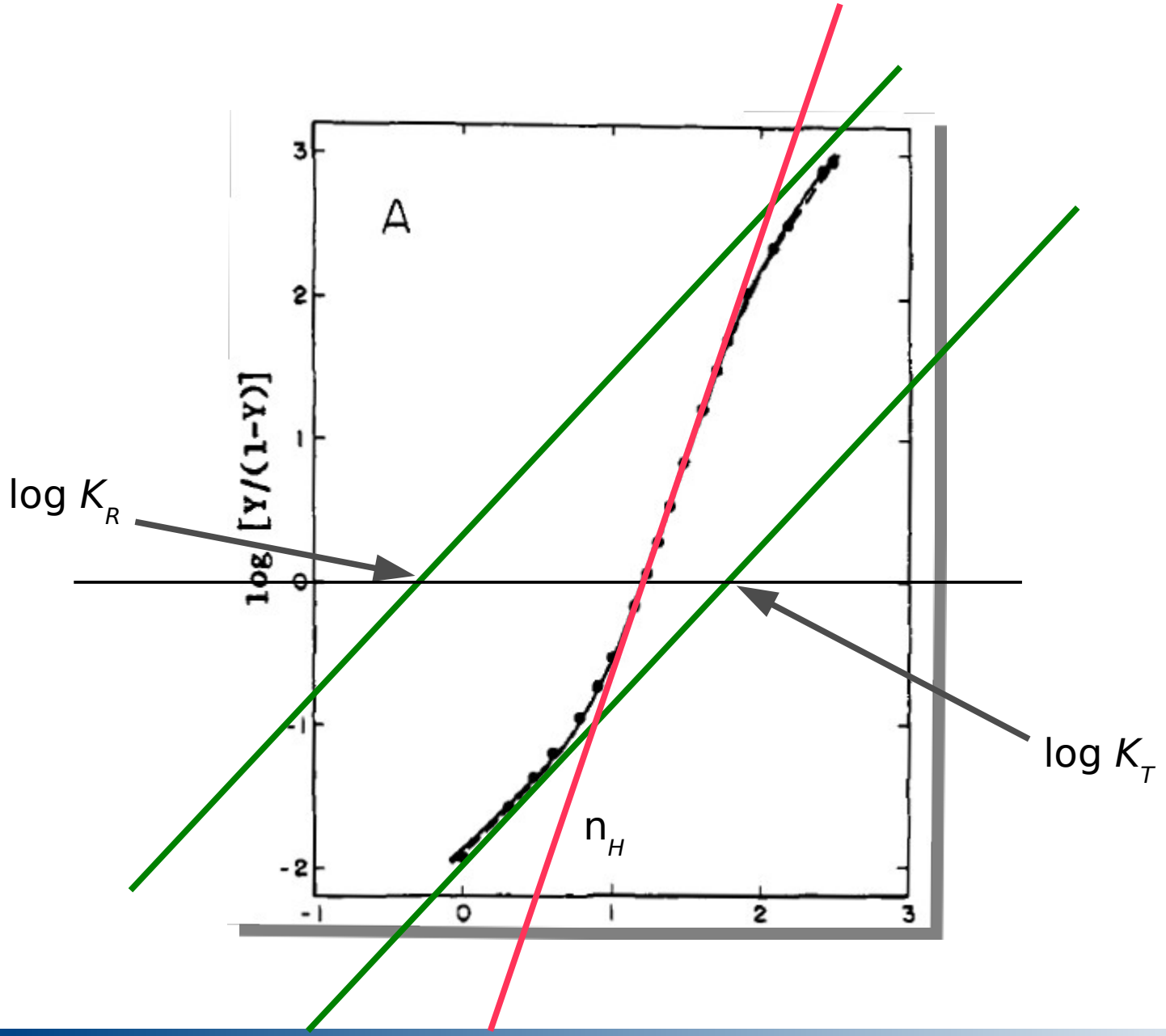
$$\alpha = \frac{[x]}{K^{\mathsf{R}}}$$

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

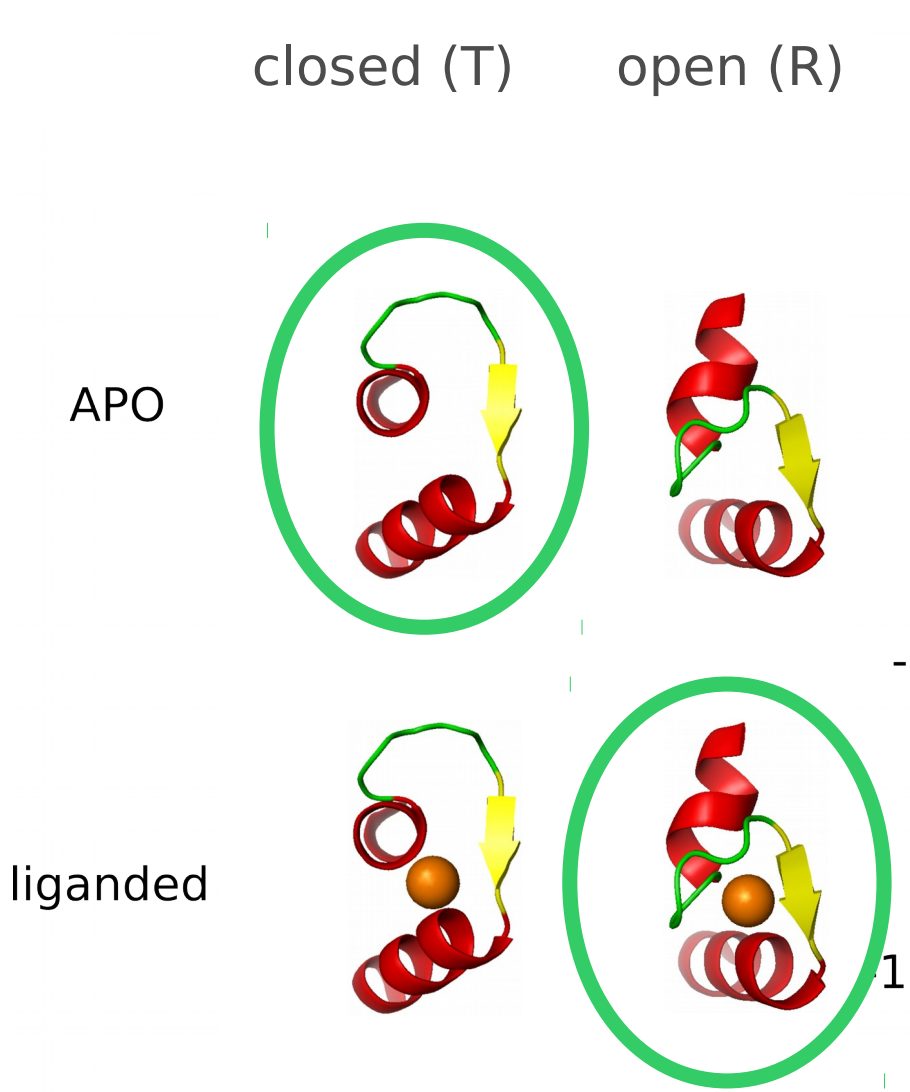
this = $\bar{R} = \dfrac{(1+\alpha)^n}{(1+\alpha)^n + L(1+c\alpha)^n}$ that

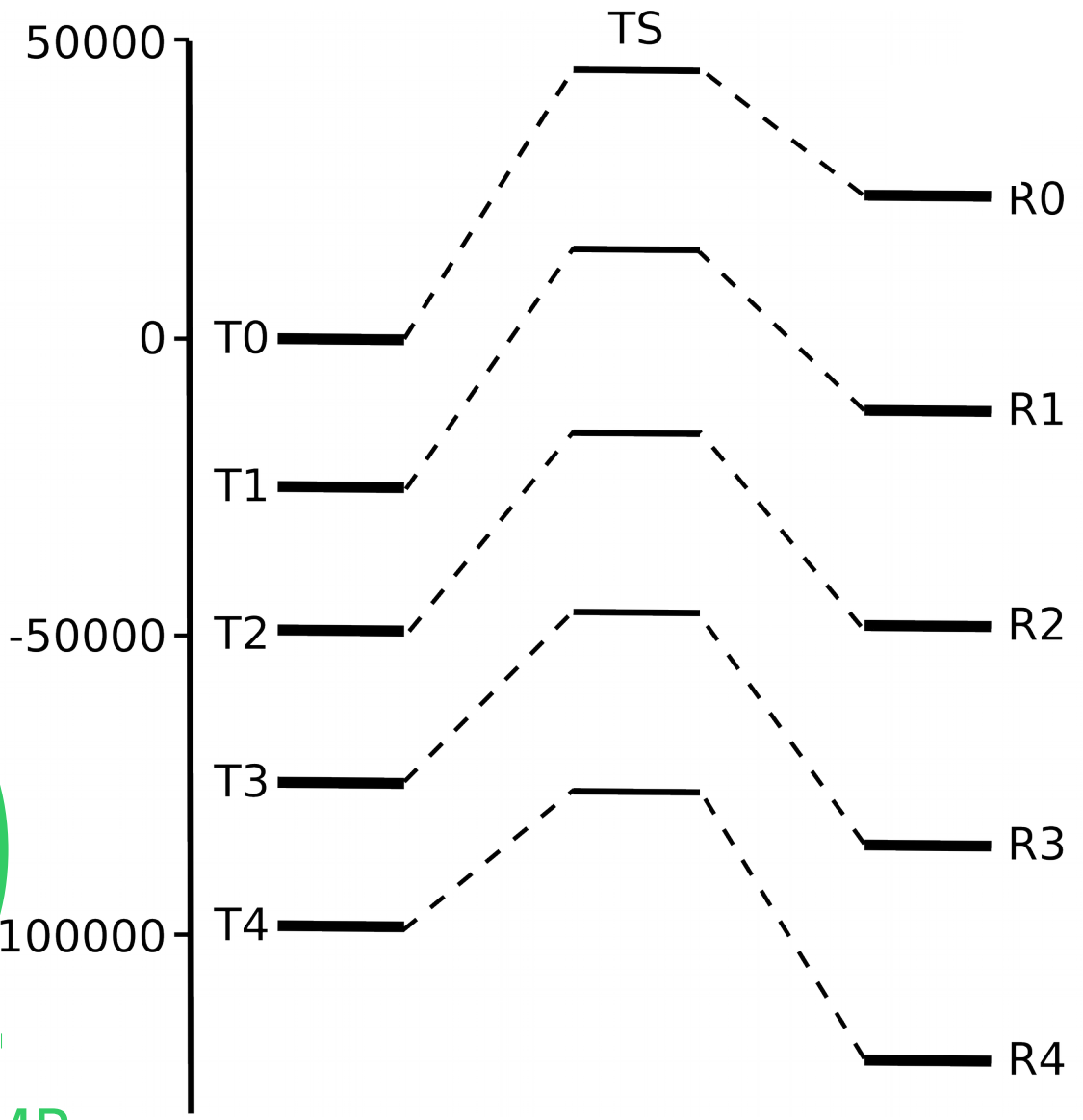


“Hill” Plot for MWC model



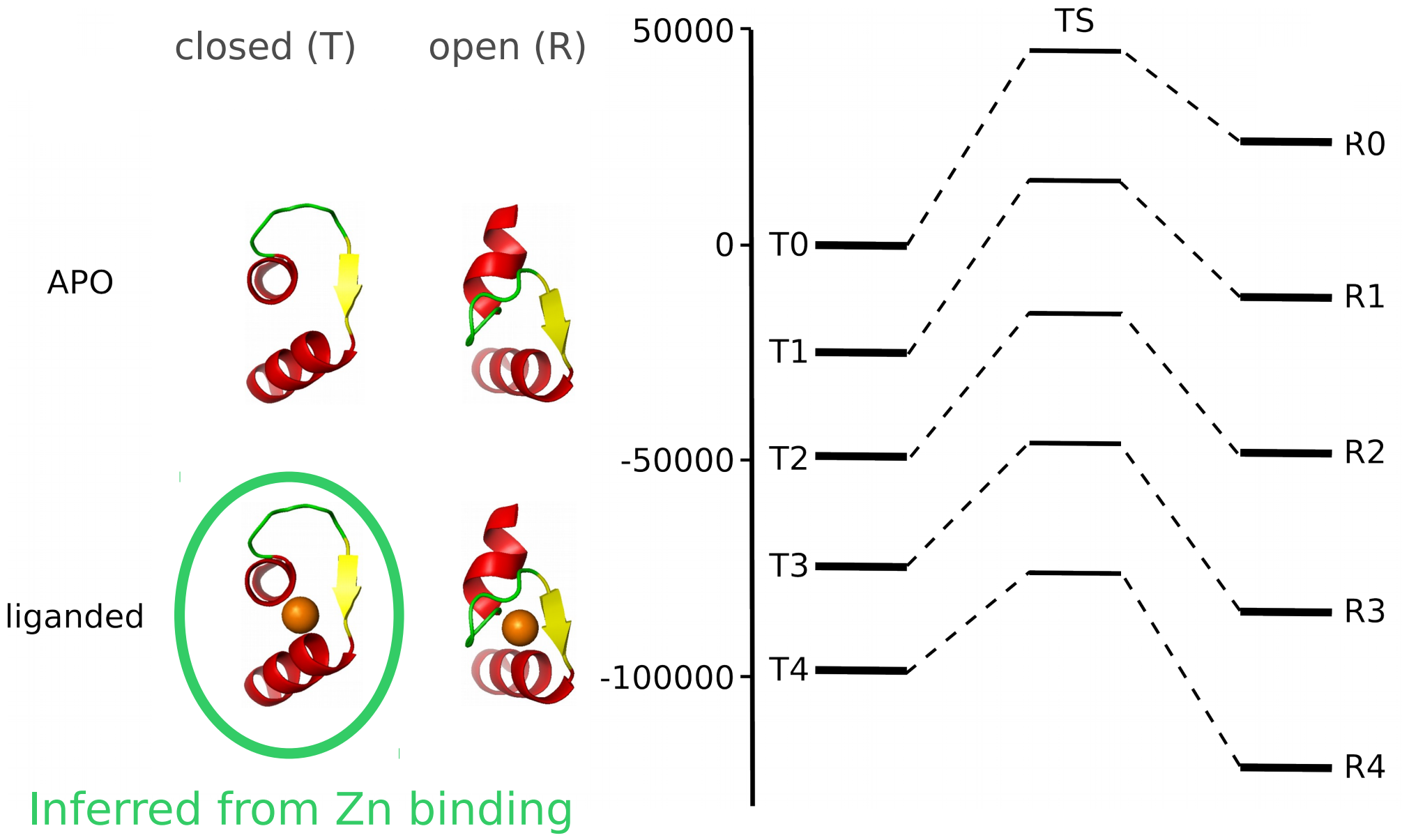
Observation Vs. Prediction





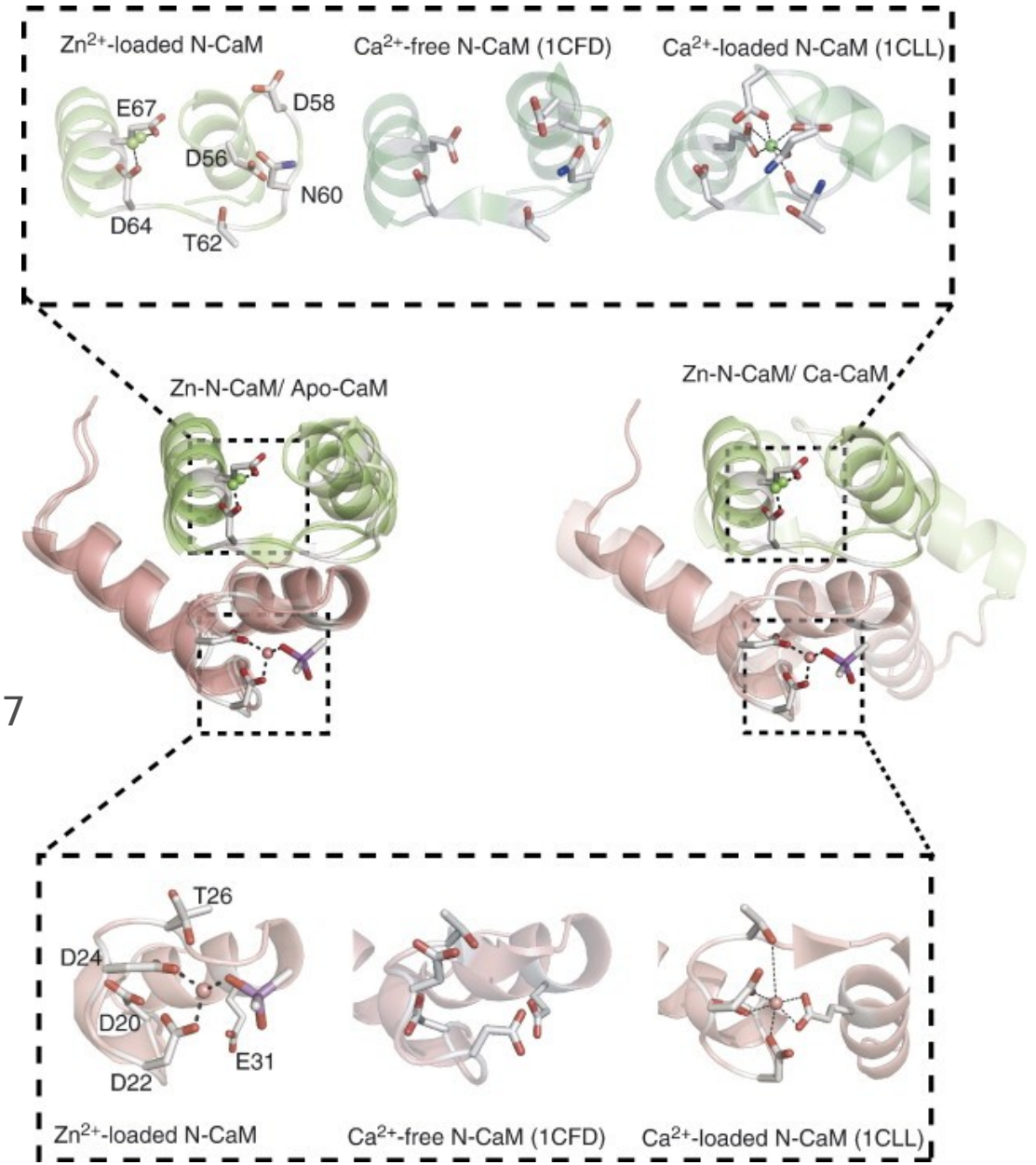
Observed by X-Ray and NMR

Observation Vs. Prediction

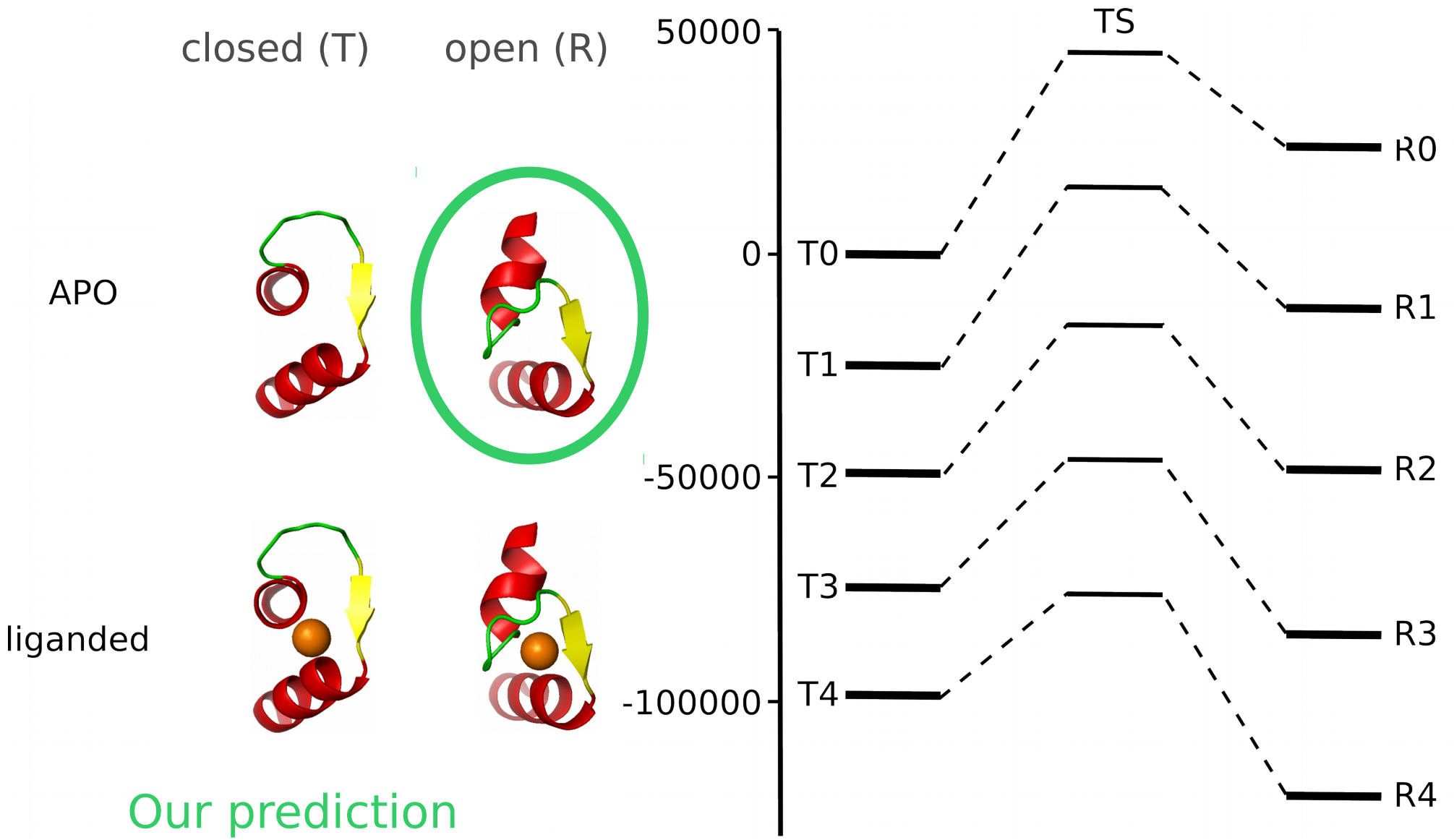


Inferred from Zn binding

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

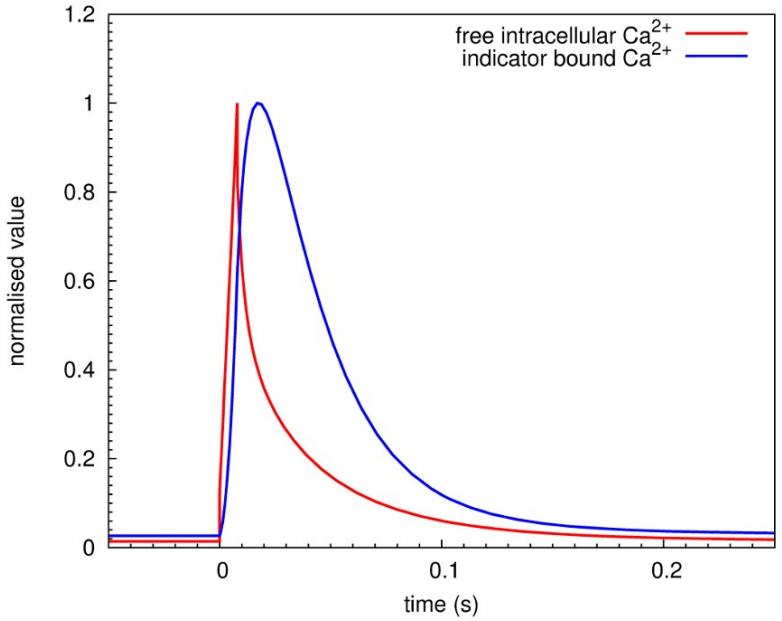


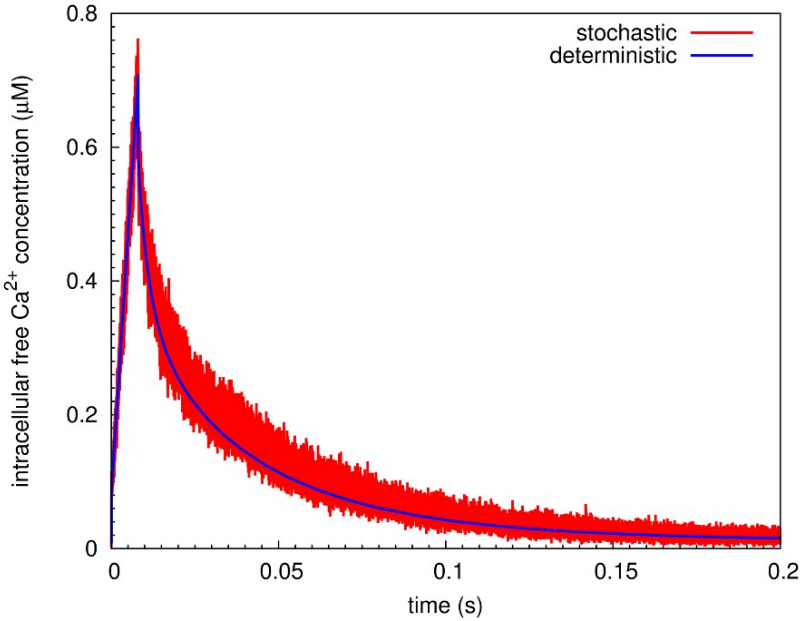
Observation Vs. Prediction

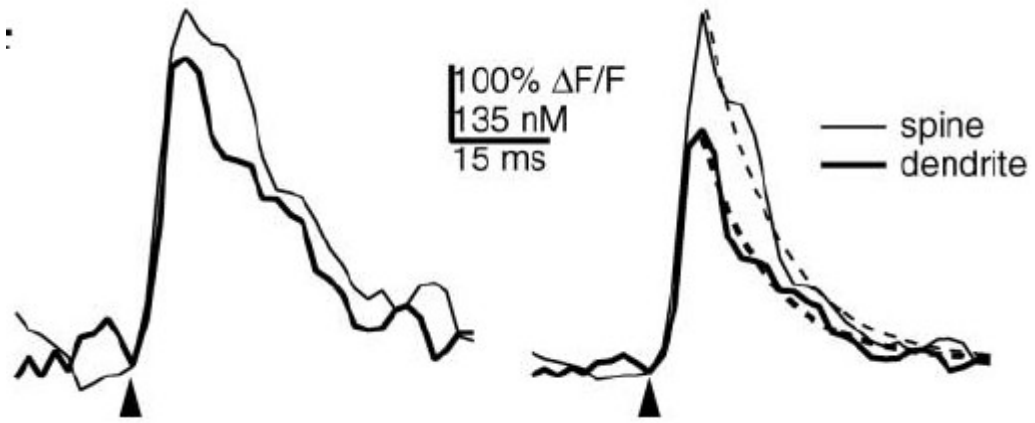


Babraham Institute

Are those spikes realistic?





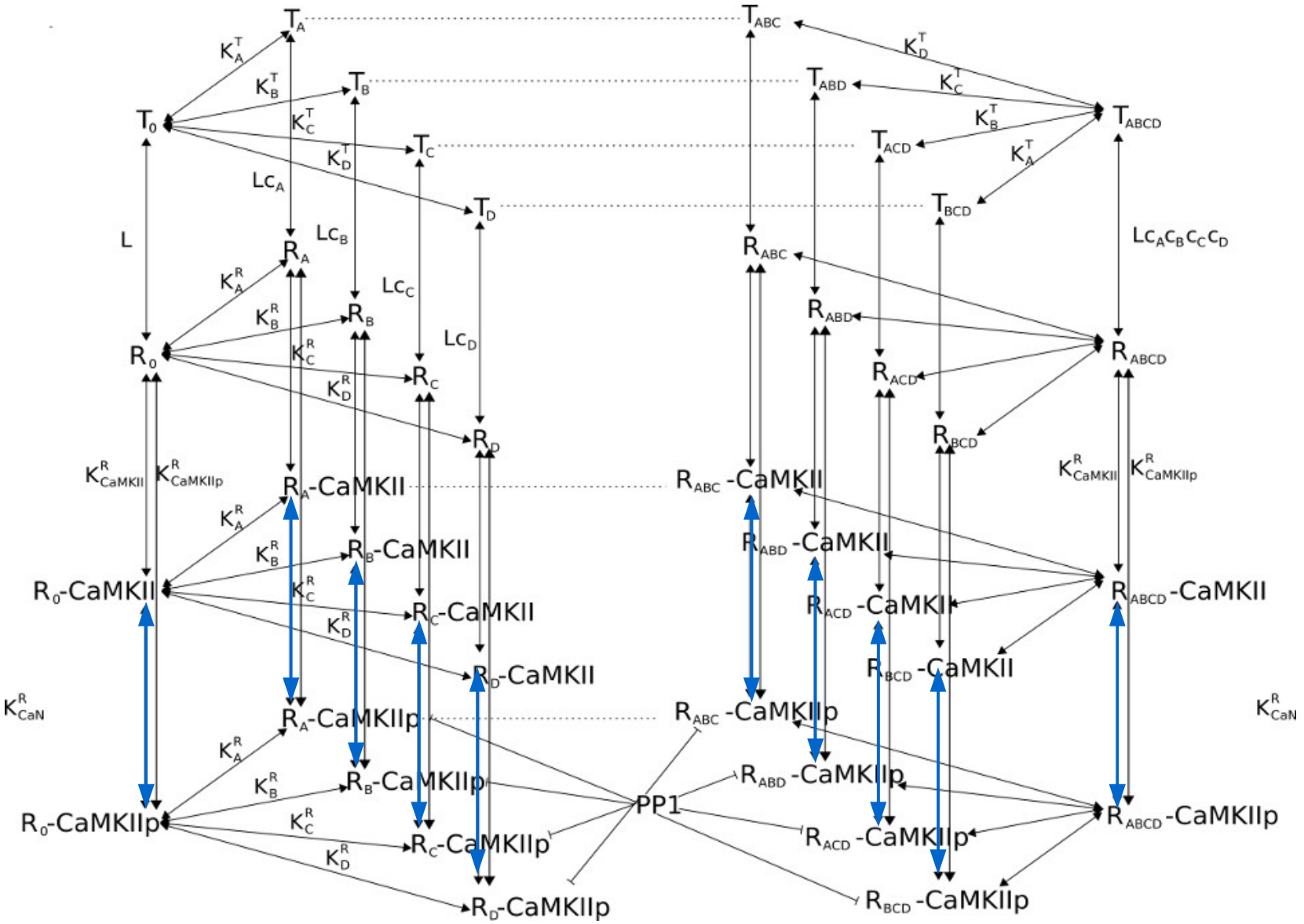


Fluorescence

Free calcium

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

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


T_A
T_B
T_C
T_D
T_0
T_ABC
T_ABD
T_ACD
T_BCD
T_ABCD
K_A^T
K_B^T
K_C^T
K_D^T
Lc_A
Lc_B
Lc_C
Lc_D
L
R_A
R_B
R_C
R_D
R_0
R_ABC
R_ABD
R_ACD
R_BCD
R_ABCD
Lc_A c_B c_C c_D
K_CaMKII^R
K_CaMKIIp^R
R_A-CaMKII
R_B-CaMKII
R_C-CaMKII
R_D-CaMKII
R_0-CaMKII
R_ABC-CaMKII
R_ABD-CaMKII
R_ACD-CaMKII
R_BCD-CaMKII
R_ABCD-CaMKII
K_CaN^R
R_A-CaMKIIp
R_B-CaMKIIp
R_C-CaMKIIp
R_D-CaMKIIp
R_0-CaMKIIp
R_ABC-CaMKIIp
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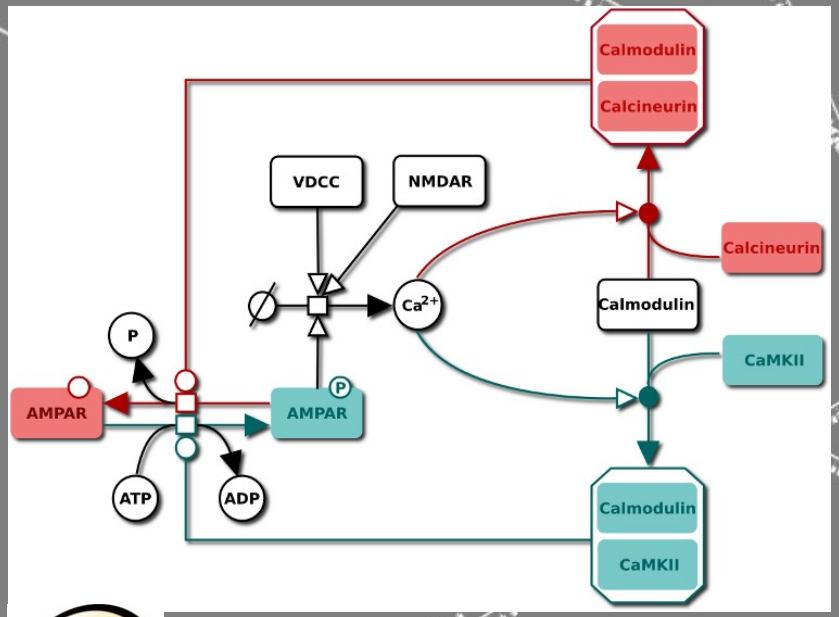
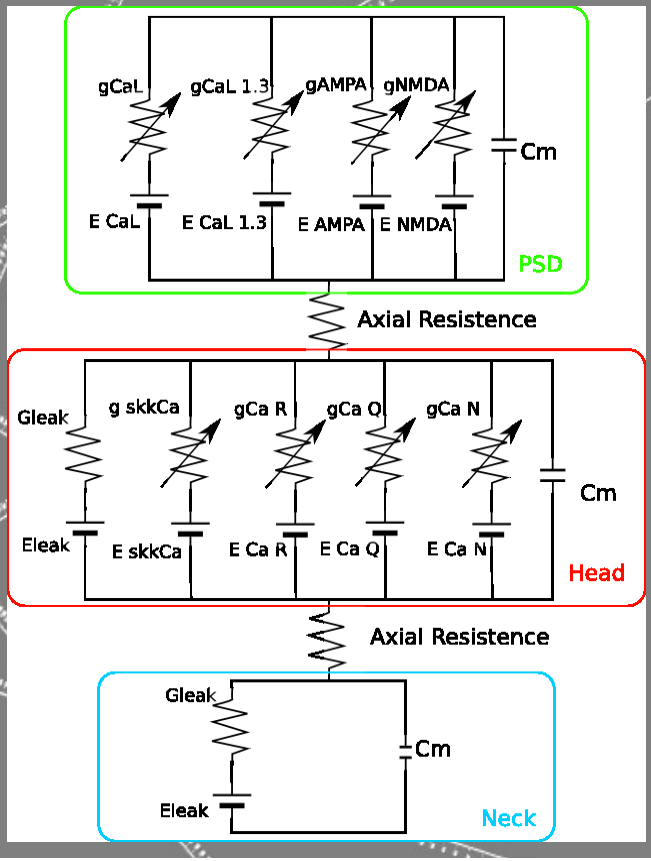
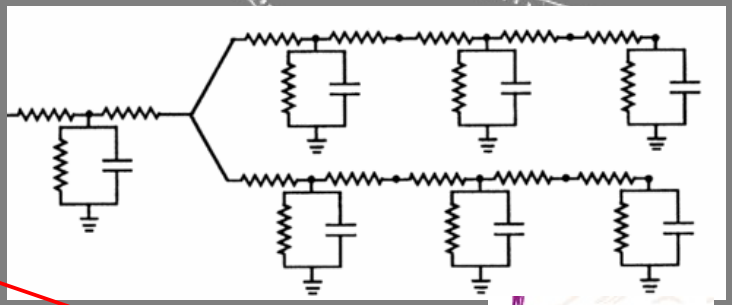
R_ACD-CaMKIIp
R_BCD-CaMKIIp
R_ABCD-CaMKIIp
PP1

Whole cell: electro-biochemical models



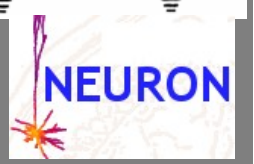


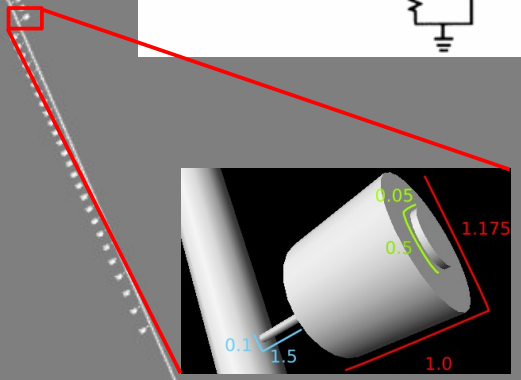


1504 spines

4761 compartments

16362 channels

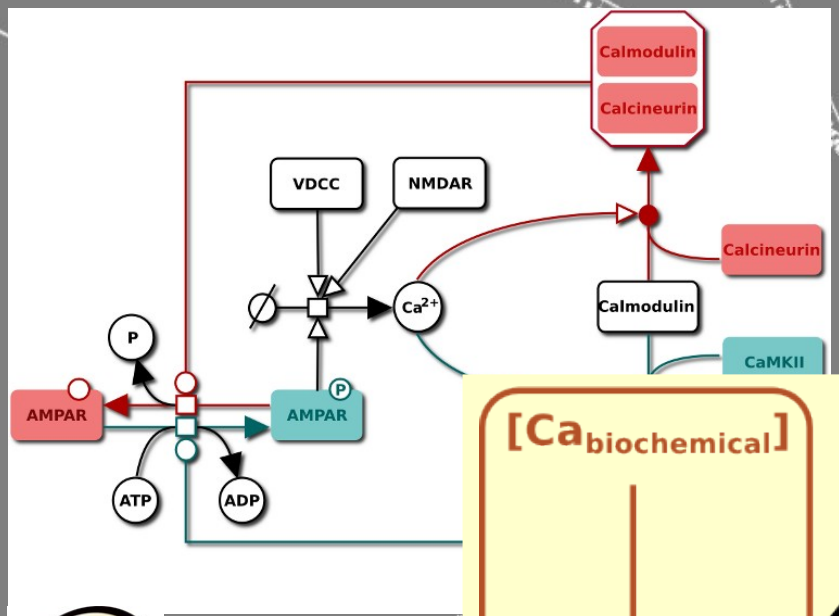


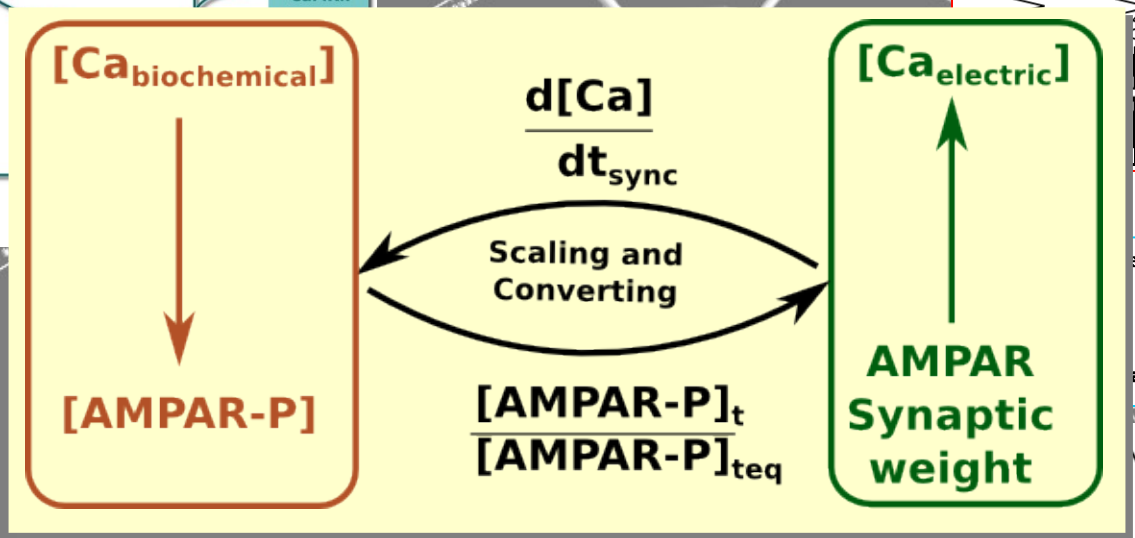


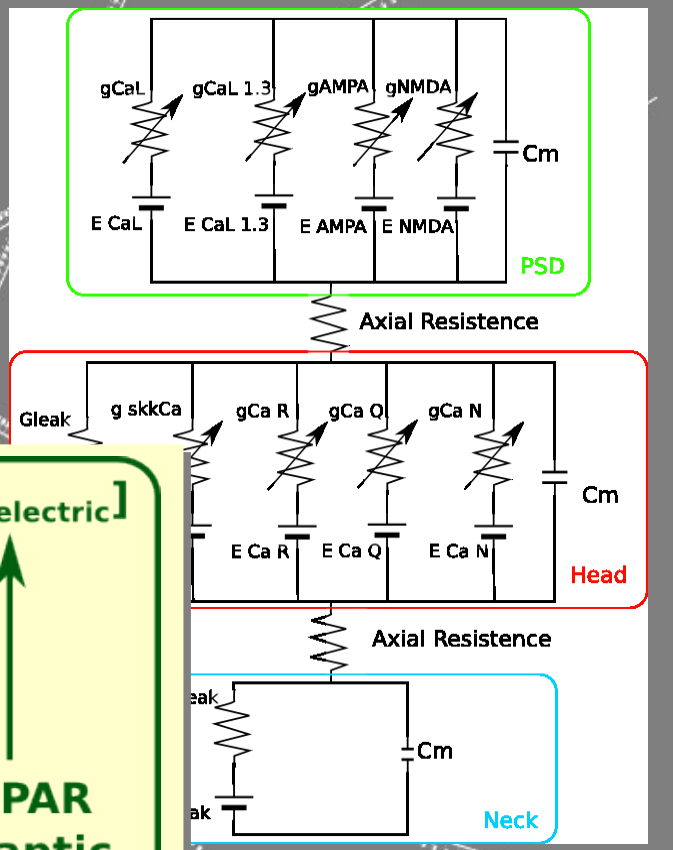
Mattioni M, Cohen U, Le Novère N (2012)
Frontiers Neuroinfo, 6:20

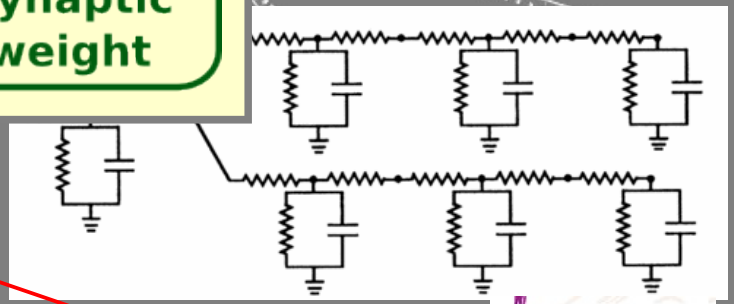
Mattioni M, Le Novère N (2013)
PLoS ONE, 8(7): e66811

Whole cell: electro-biochemical models









1504 spines

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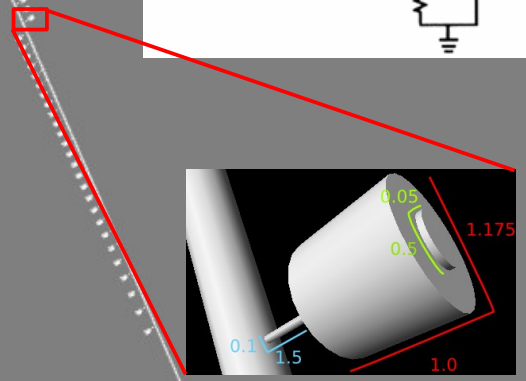

NEURON

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