The Truth about Systems Biology ...

Nicolas Le Novère, EMBL-EBI (*)

* I did not choose the title ...

Why is the definition of SB so fuzzy?

Why is the definition of SB so fuzzy?

"There are many definitions available for systems biology; these range from the overly ambitious to the opportunist. The latter category is frequently associated with scientists working in genomics and bioinformatics, who seek to re-label their work as systems biology. Such scientific opportunism is open to criticism that their research areas have been unsuccessful. This is excessively harsh [...]"

Preface of *Essays in Biochemistry - Systems Biology*, edited by O Wolkenhauer, P Wellstead and KH Cho.

Emergence of the notion of system

XVI	XVII	XVIII	XIX	XX	XXI

Global Description of the world

“classical” mechanic, anatomy, physiology

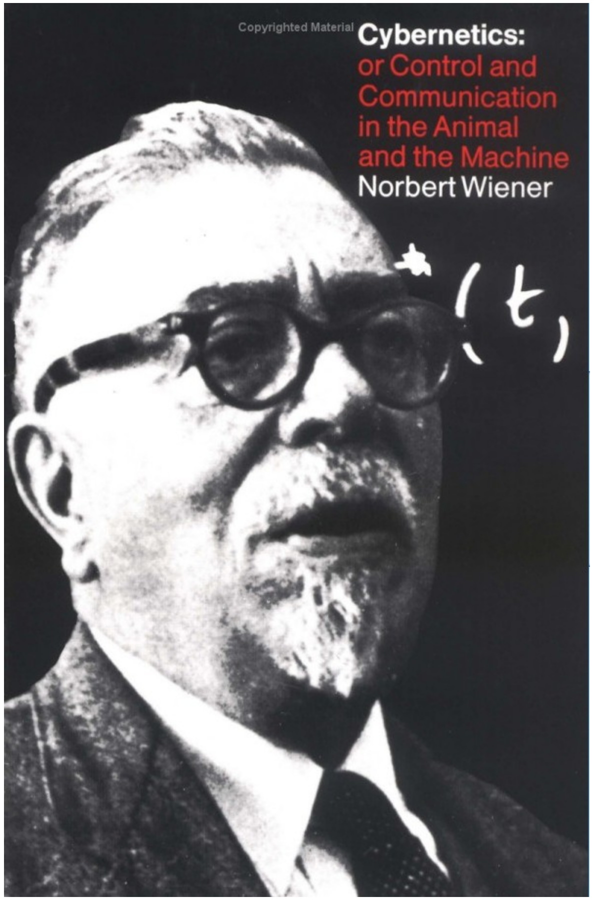
Description of the components of the world

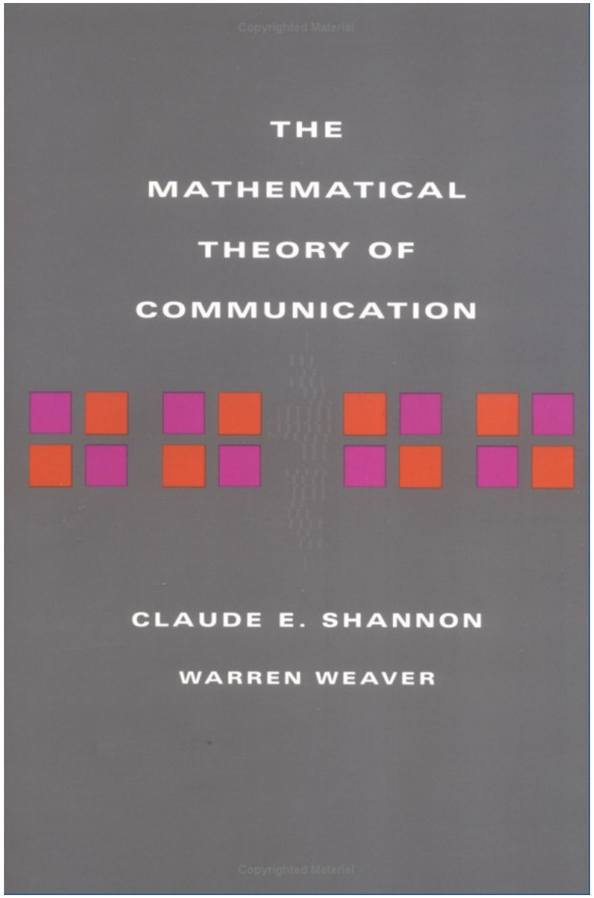
Statistical physics, thermodynamics, quantum mechanic, biochemistry, structural biology, molecular biology

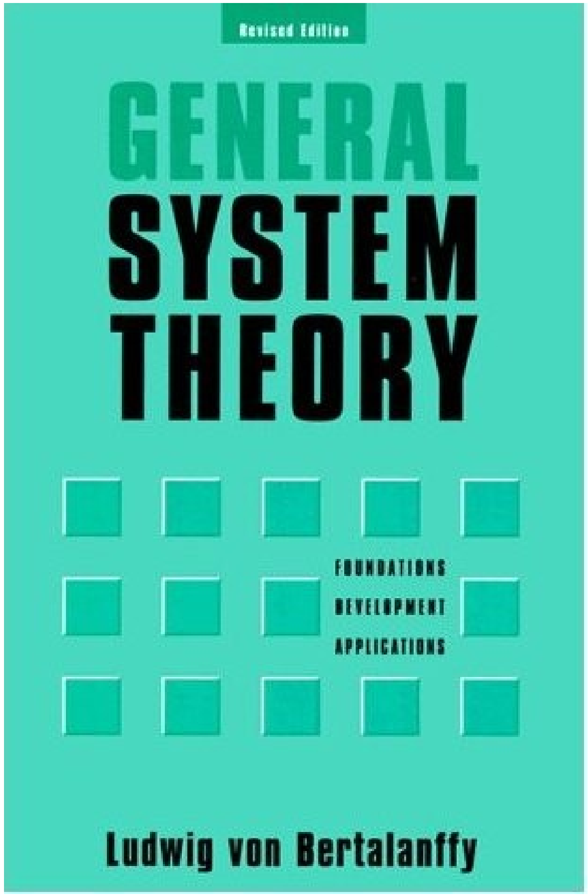
Description of interacting components

Cybernetics, Information theory, telecommunications, automata, multi-agents, Systems Biology

Systems have been formalised for a while







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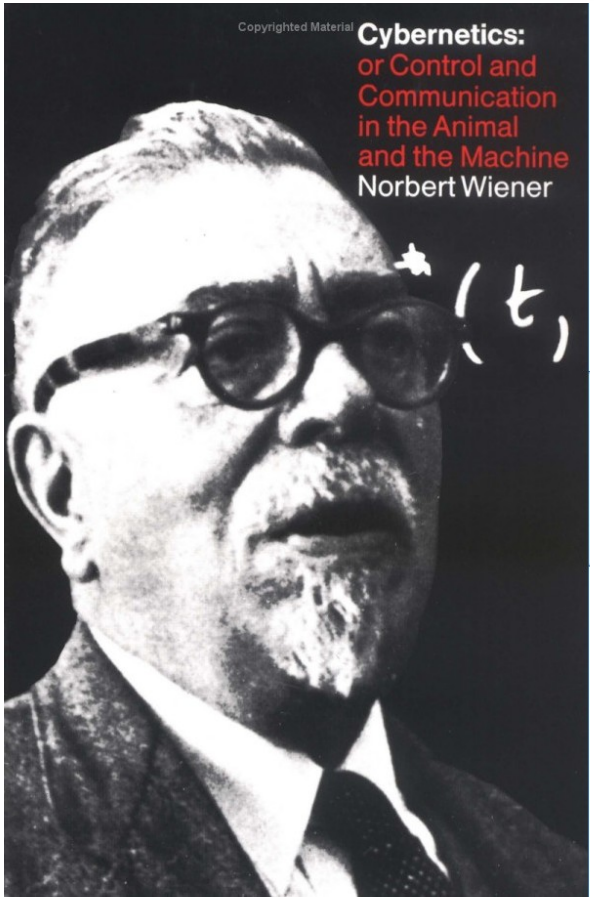
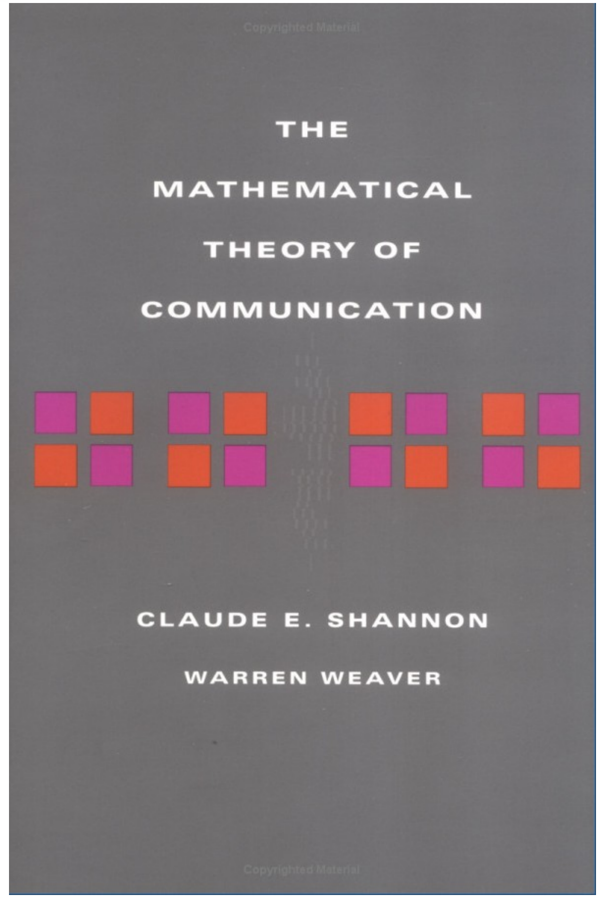
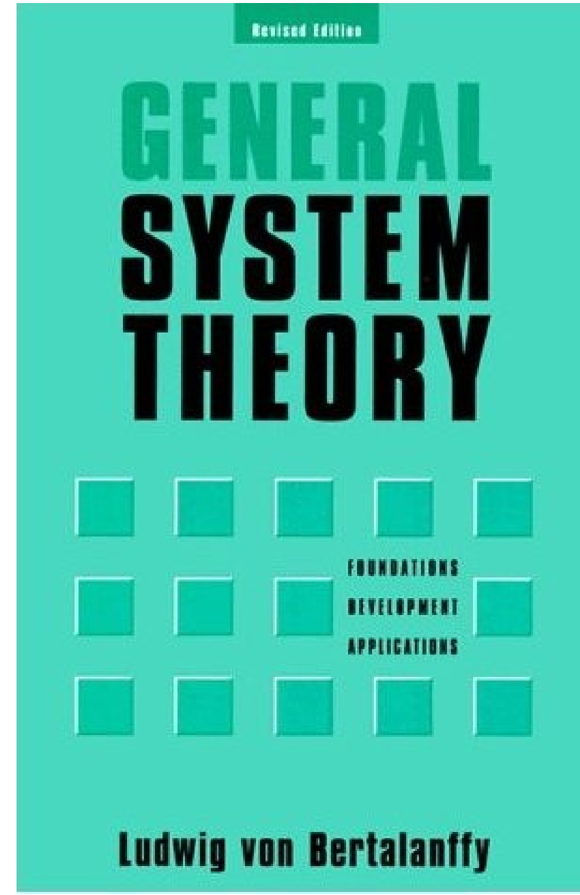
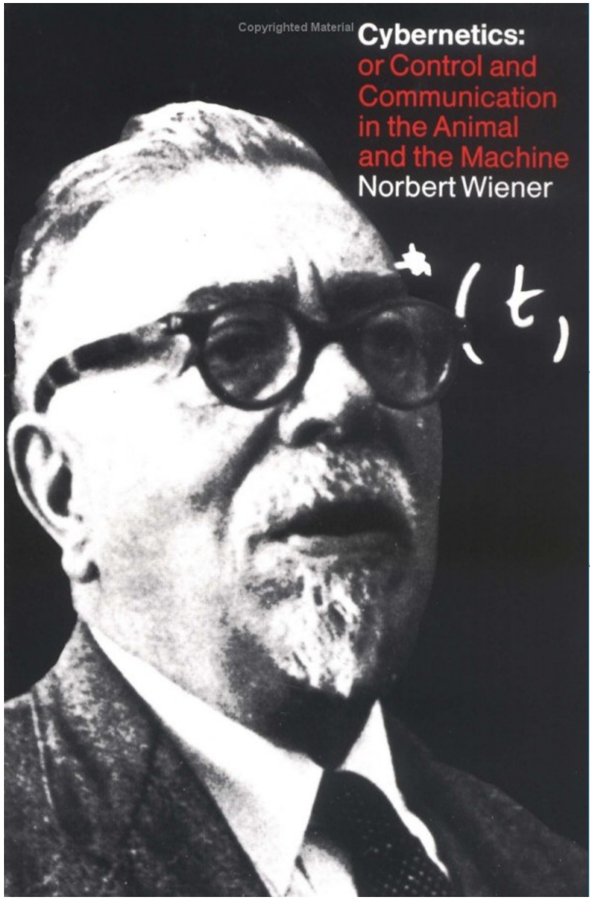


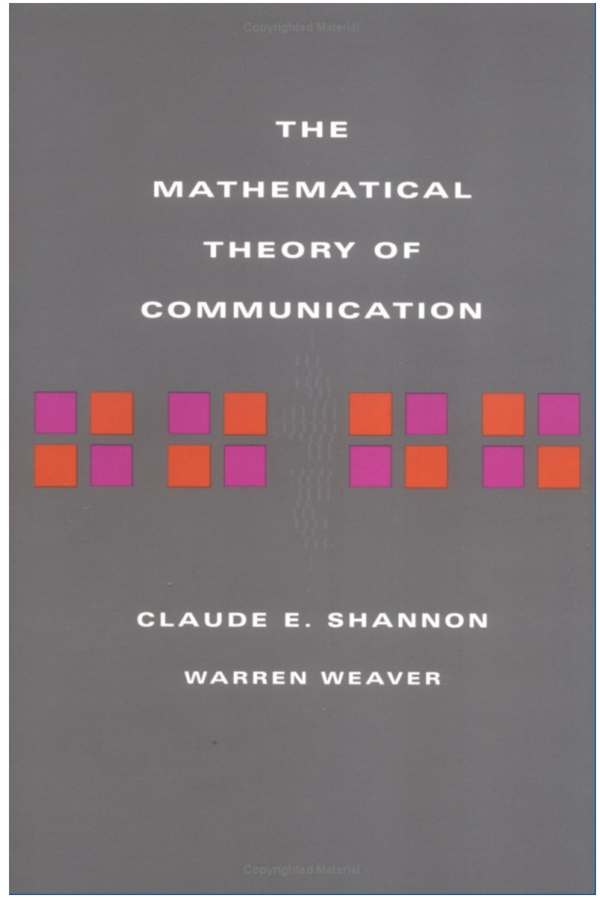


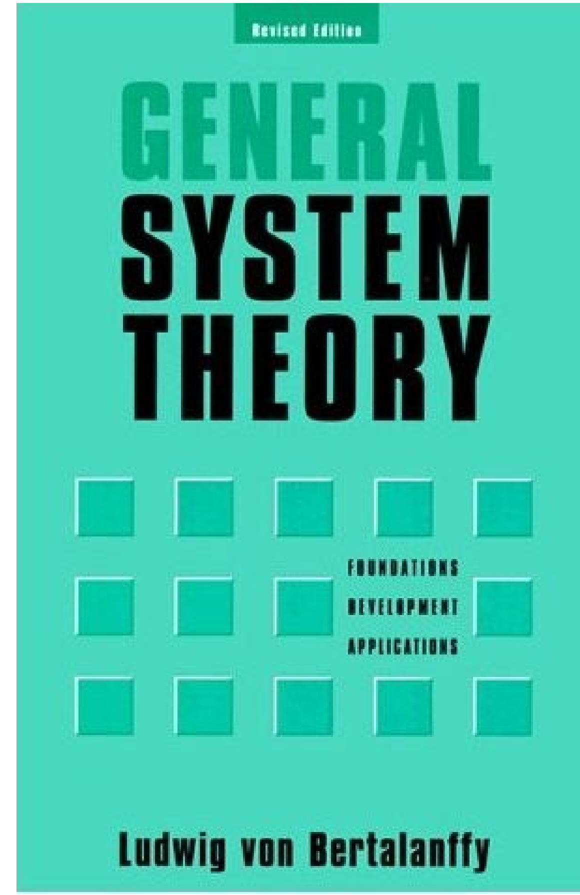


"[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems"
Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

Systems have been formalised for a while







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Mihajlo Mesarovic (1968) *Systems Theory and Biology*

Robert Rosen (1970) *Dynamical Systems Theory in Biology*

What is a "paradigm"?

- Thomas Kuhn: Set of practices that define a scientific discipline during a particular period of time
  - *what* is to be observed and scrutinized
  - *which* questions are supposed to be asked and probed for answers in relation to this subject
  - *how* these questions are to be structured
  - *how* the results of scientific investigations should be interpreted
  - *how* is an experiment to be conducted, and what equipment is available to conduct the experiment.

The three paradigms of explanatory Biology

1850 1900 1950 2000

Physiology

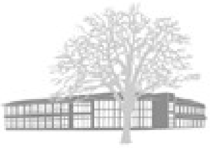
Claude Bernard
Pavlov
Langley
Hill
Meyerhof
Eccles
Katz

Molecular Biology

Michaelis
Menten
Kossel
Avery
Watson/Crick
Monod/Jacob
recombinant
DNA

Systems Biology

Hodgkin
Huxley
MCA
BST
omics



The three paradigms of explanatory Biology

1850 1900 1950 2000

Descriptive — Physiology

Claude Bernard, Pavlov, Langley, Hill, Meyerhof, Eccles, Katz

Explanatory — Molecular Biology

Michaelis, Menten, Kossel, Avery, Watson/Crick, Monod/Jacob, recombinant DNA

Predictive — Systems Biology

Hodgkin, Huxley, MCA, BST, omics

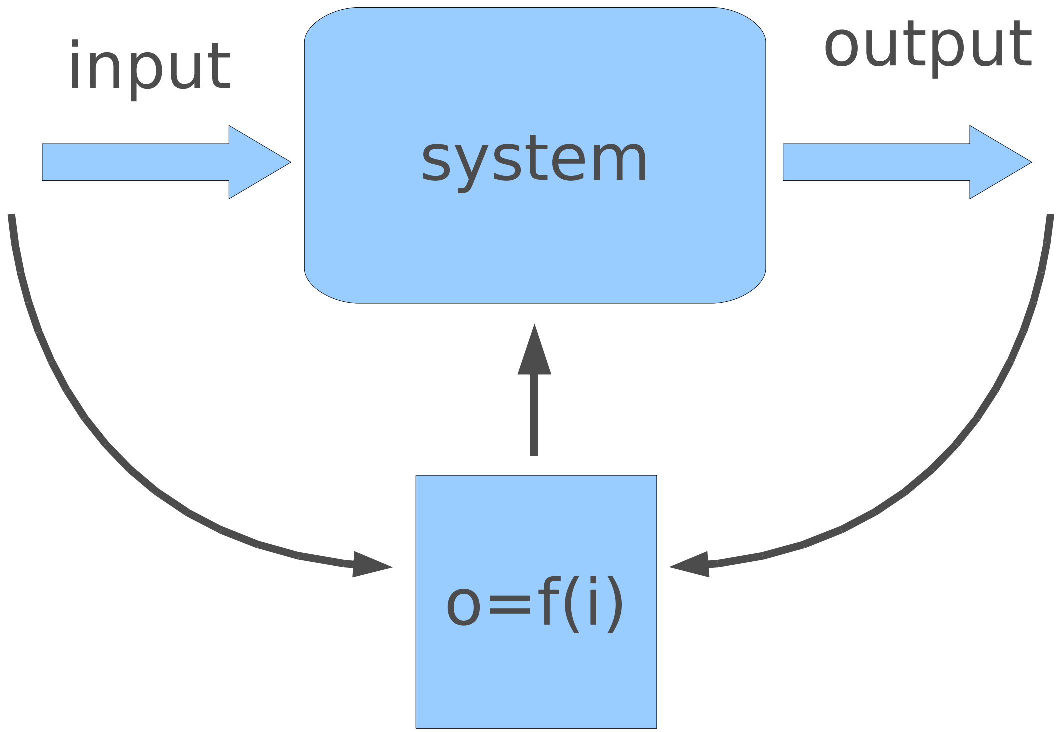
What Systems Biology is not ... only

- Modelling: This is Mathematical (theoretical) Biology
- High-throughput data generation: This is Functional Genomics
- Quantitative data measurement: That should always be the case in life science ... shouldn't it?

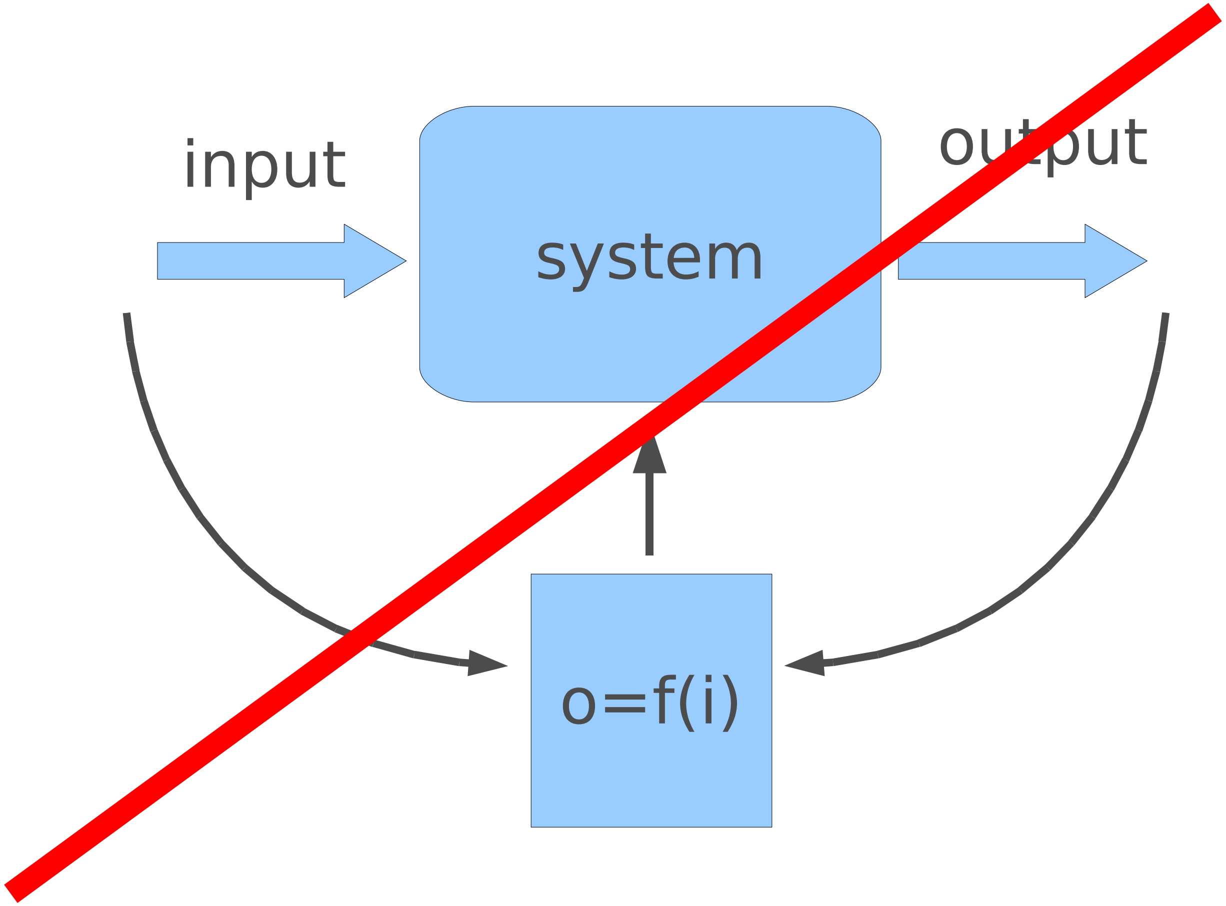
  Those are techniques. Systems Biology is a scientific paradigm, a way of thinking life

  (Molecular Biology is not defined by the use of restriction enzymes ... or is it?)

Systems Biology is REALLY NOT



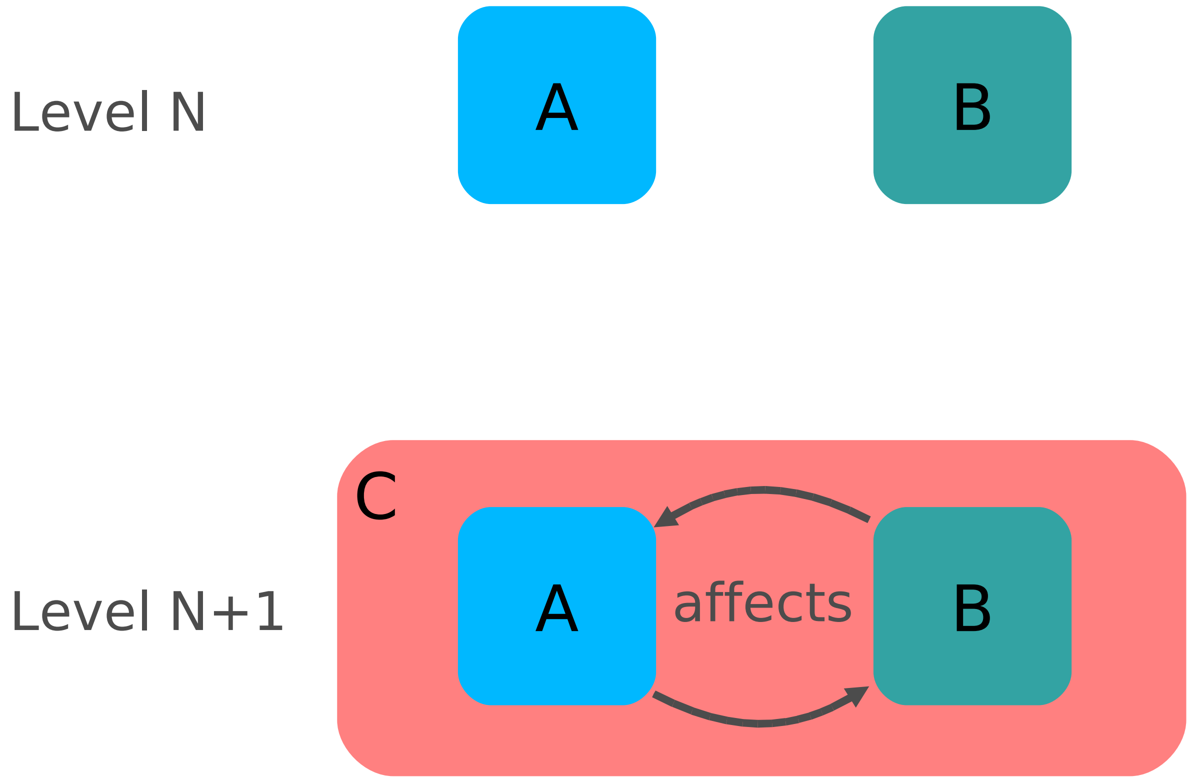
Systems Biology is REALLY NOT



This is physiology!

Level N

What is Systems Biology?



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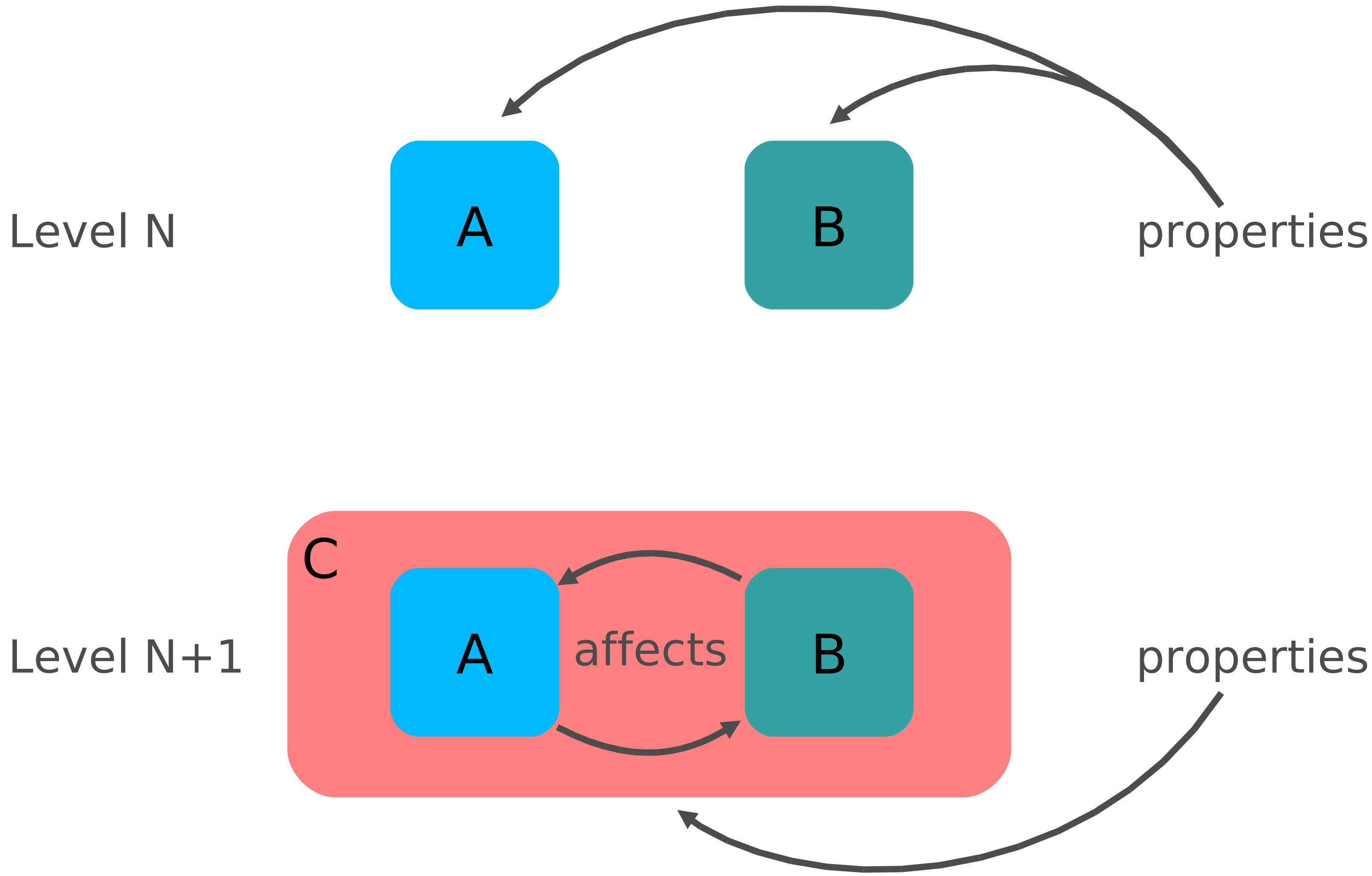

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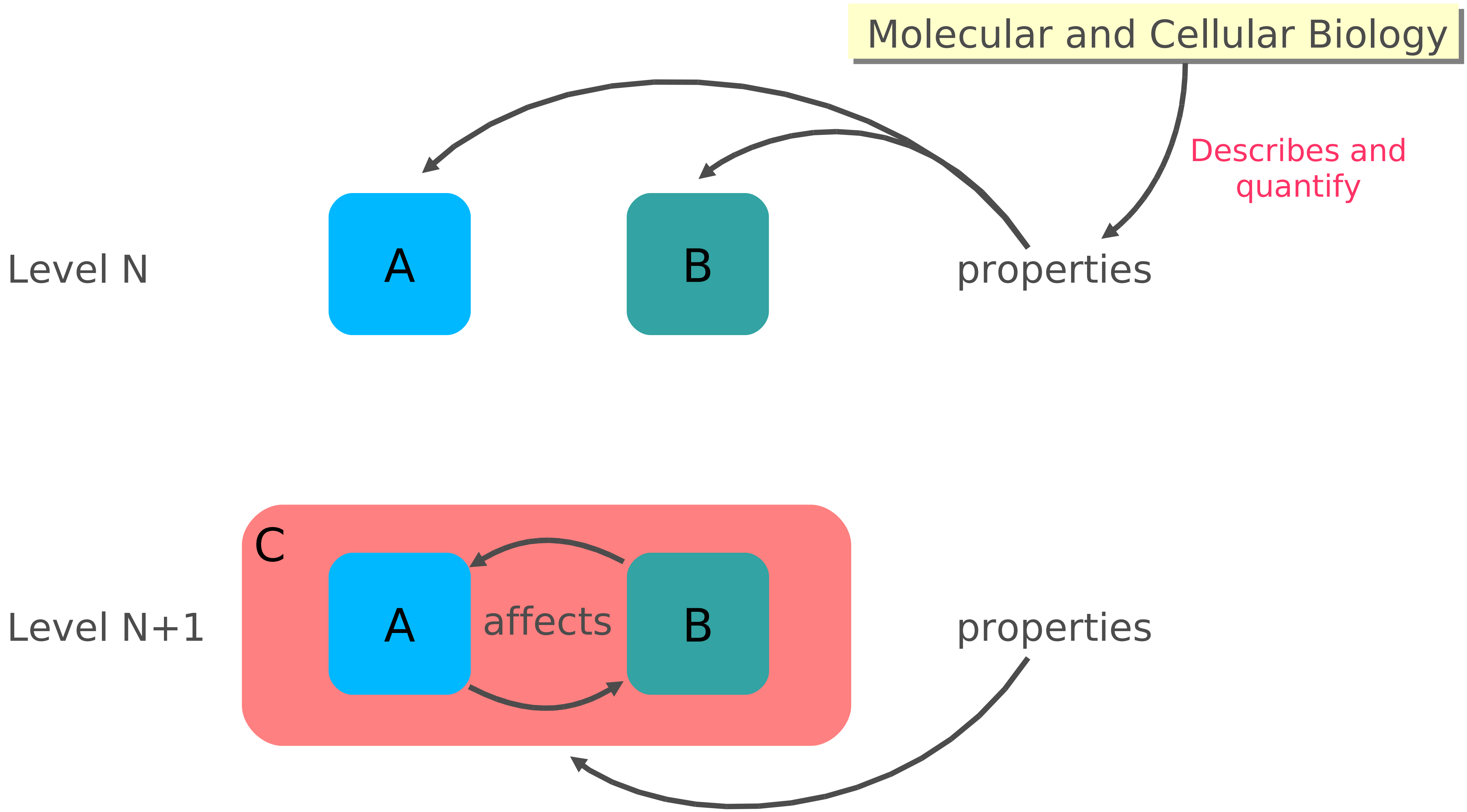

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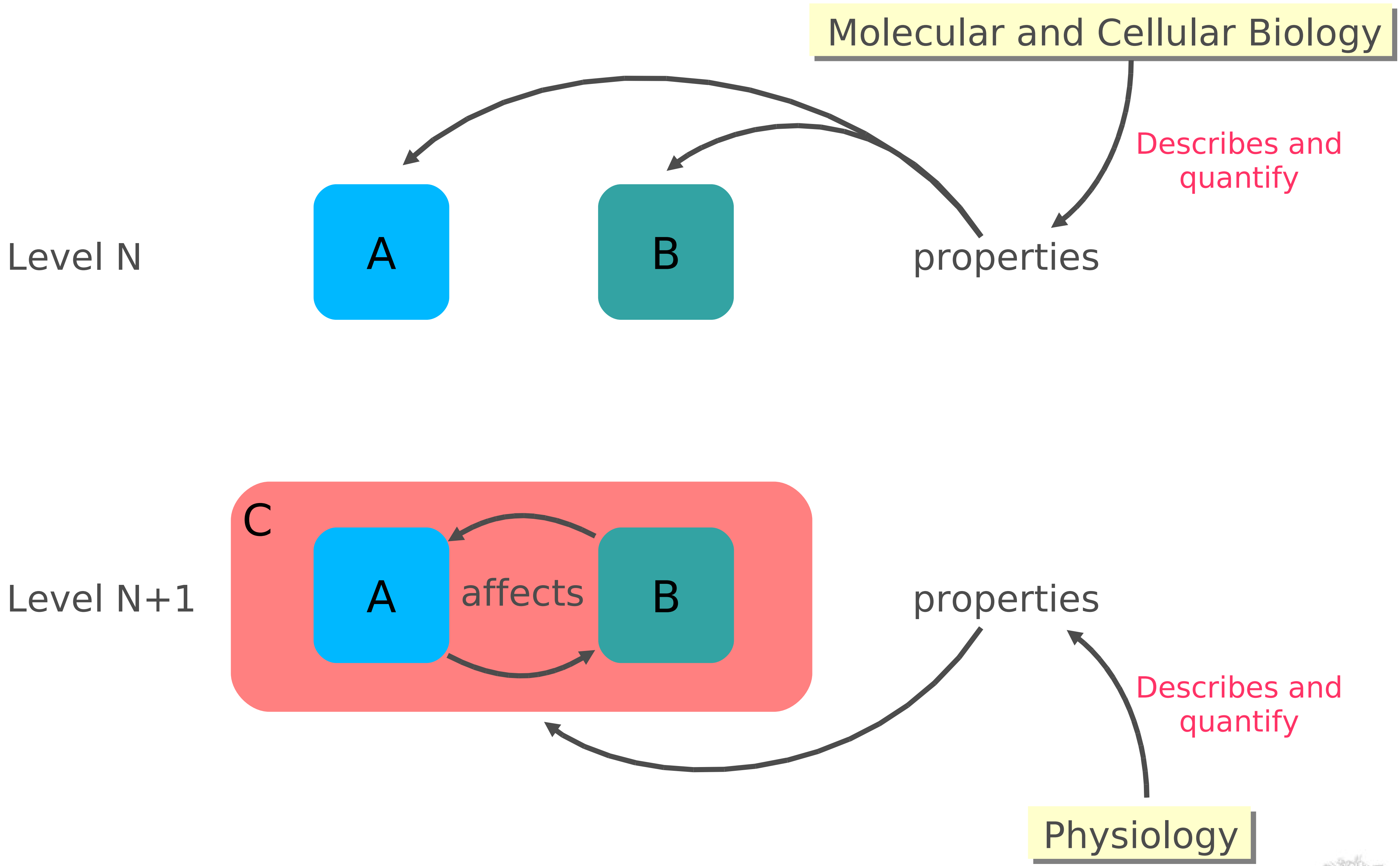

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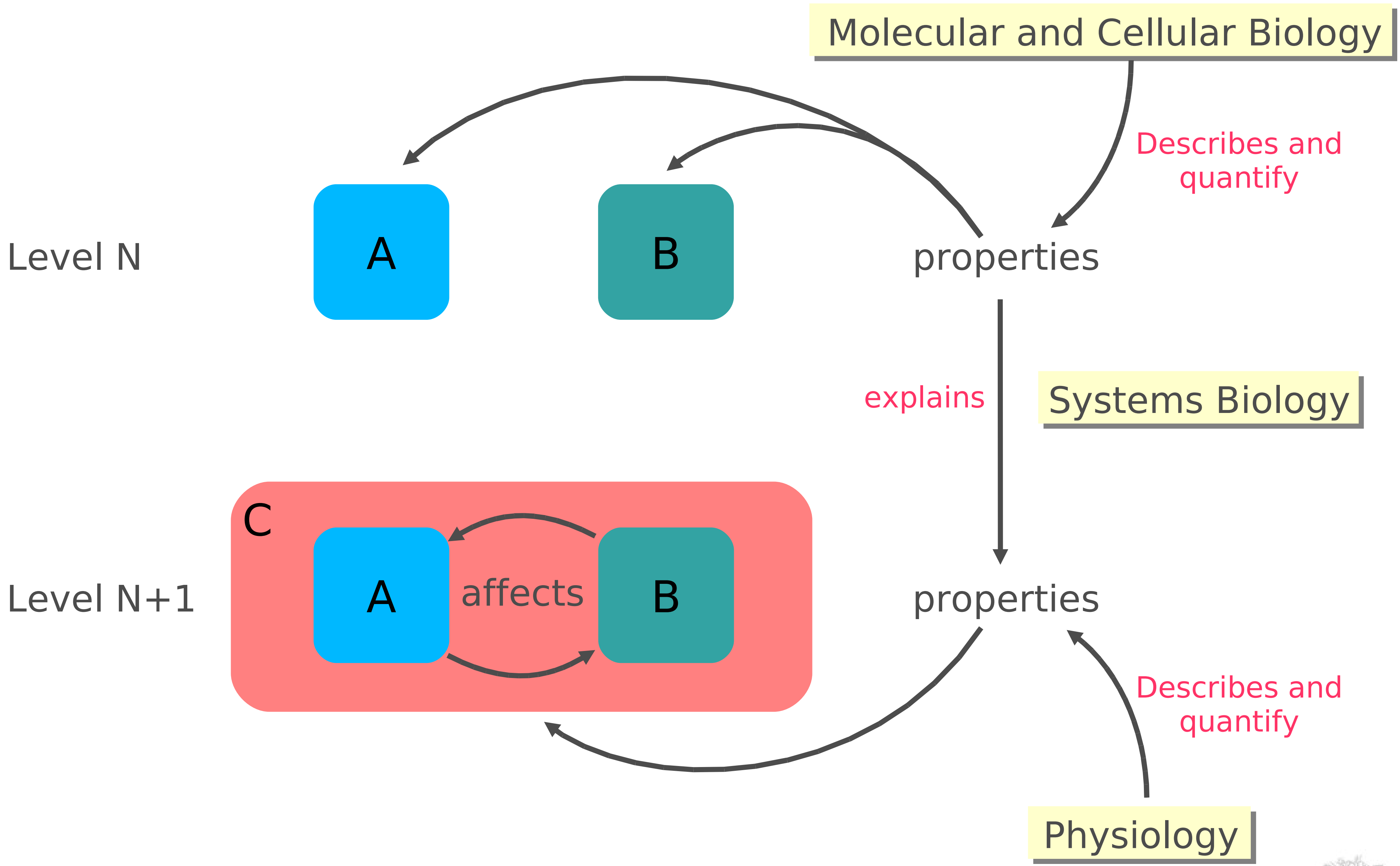

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Computer simulations Vs. mathematical models

[37]

THE CHEMICAL BASIS OF MORPHOGENESIS

By A. M. TURING, F.R.S. *University of Manchester*

(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system. The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on *Hydra* and for whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two

Computer simulations Vs. mathematical models

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One would like to be able to follow this more general process mathematically also. The difficulties are, however, such that one cannot hope to have any very embracing theory of such processes, beyond the statement of the equations. It might be possible, however, to treat a few particular cases in detail ***with the aid of a digital computer****. This method has the advantage that it is not so necessary to make simplifying assumptions as it is when doing a more theoretical type of analysis.*

Birth of Computational Systems Biology

J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

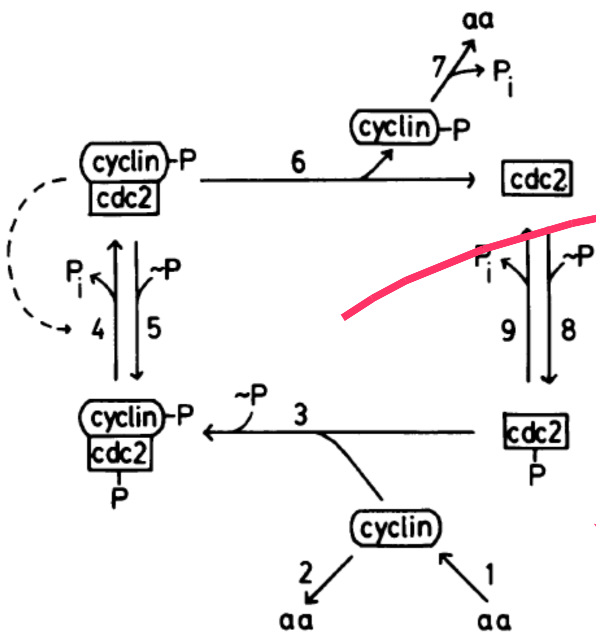
BY A. L. HODGKIN AND A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

(*Received* 10 *March* 1952)

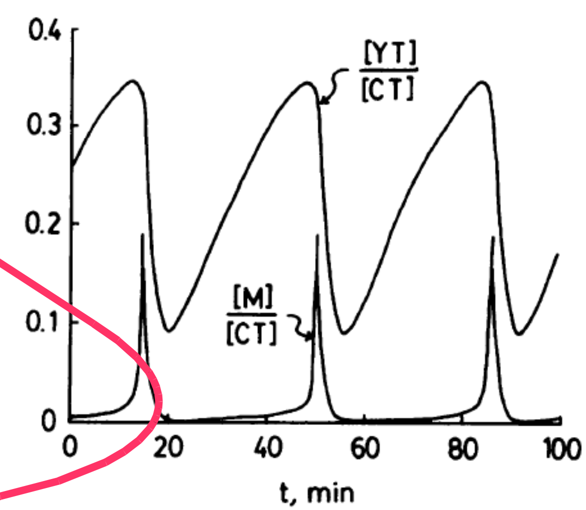
This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952 *a–c*). Its general object is to discuss the results of the preceding papers (Part I), to put them into mathematical form (Part II) and to show that they will account for conduction and excitation in quantitative terms (Part III).

Simple example of Systems Biology



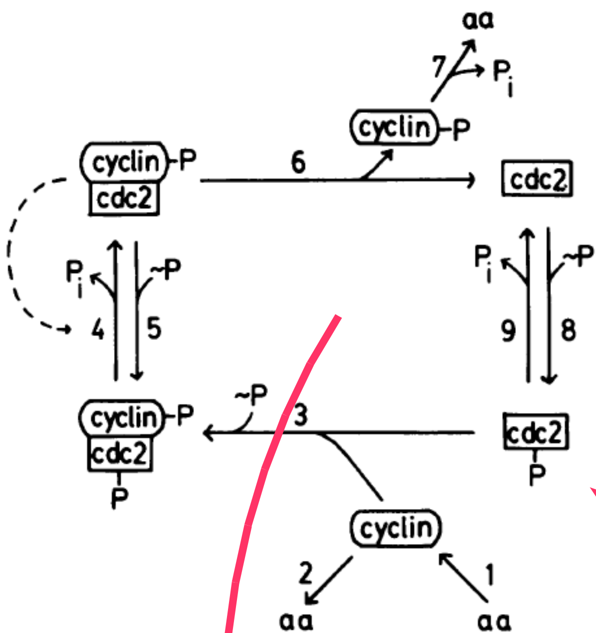
$$
\begin{aligned}
d[\mathrm{C2}]/dt &= k_6[\mathrm{M}] - k_8[\sim P][\mathrm{C2}] + k_9[\mathrm{CP}]\\
d[\mathrm{CP}]/dt &= -k_3[\mathrm{CP}][\mathrm{Y}] + k_8[\sim P][\mathrm{C2}] - k_9[\mathrm{CP}]\\
d[\mathrm{pM}]/dt &= k_3[\mathrm{CP}][\mathrm{Y}] - [\mathrm{pM}]F([\mathrm{M}]) + k_5[\sim P][\mathrm{M}]\\
d[\mathrm{M}]/dt &= [\mathrm{pM}]F([\mathrm{M}]) - k_5[\sim P][\mathrm{M}] - k_6[\mathrm{M}]\\
d[\mathrm{Y}]/dt &= k_1[\mathrm{aa}] - k_2[\mathrm{Y}] - k_3[\mathrm{CP}][\mathrm{Y}]\\
d[\mathrm{YP}]/dt &= k_6[\mathrm{M}] - k_7[\mathrm{YP}]
\end{aligned}
$$

Parameter	Value	Notes
$k_1[\mathrm{aa}]/[\mathrm{CT}]$	$0.015\ \mathrm{min}^{-1}$	*
k_2	0	†
$k_3[\mathrm{CT}]$	$200\ \mathrm{min}^{-1}$	*
k_4	10–$1000\ \mathrm{min}^{-1}$ (adjustable)	
k_4'	$0.018\ \mathrm{min}^{-1}$	
$k_5[\sim P]$	0	‡
k_6	0.1–$10\ \mathrm{min}^{-1}$ (adjustable)	
k_7	$0.6\ \mathrm{min}^{-1}$	†
$k_8[\sim P]$	$>>k_9$	§
k_9	$>>k_6$	§



Tyson et al (1991) PNAS 88(1):7328-32

Simple example of Systems Biology



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d[\mathrm{pM}]/dt &= k_3[\mathrm{CP}][\mathrm{Y}] - [\mathrm{pM}]F([\mathrm{M}]) + k_5[\sim P][\mathrm{M}]\\
d[\mathrm{M}]/dt &= [\mathrm{pM}]F([\mathrm{M}]) - k_5[\sim P][\mathrm{M}] - k_6[\mathrm{M}]\\
d[\mathrm{Y}]/dt &= k_1[\mathrm{aa}] - k_2[\mathrm{Y}] - k_3[\mathrm{CP}][\mathrm{Y}]\\
d[\mathrm{YP}]/dt &= k_6[\mathrm{M}] - k_7[\mathrm{YP}]
\end{aligned}
$$

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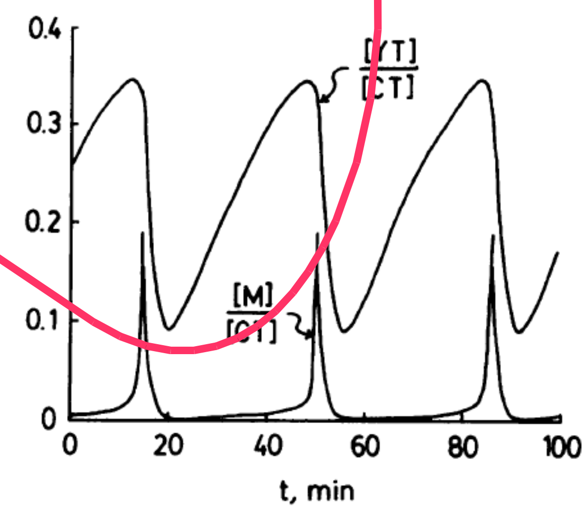
k_9	$>>k_6$	§



Tyson et al (1991) PNAS 88(1):7328-32

History of Systems Biology

Events around

PDB EMBLbank Genomes
First computers PC Interactomes

1950 1960 1970 1980 1990 2000

models

Hodgkin-Huxley
Dennis Noble heart pacemaker
Goldbeter Koshland covalent cascades
Cell Cycle models
signalling models
metabolic models
whole heart

neurobiology

Rall's cable approximation
complex neurons
simple circuits
Purkinje Neuron
Blue Brain Project

methods

MCA/BST
stochastic algorithms
multi-agent systems
user-friendly biochemical simulators
SBML

Network Biology ← Barabasi
Synthetic Biology ← Repressilator

EMBL-EBI

Rise of Systems Biology as a paradigm

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

projects

ERATO-Kitano
SystemsX
Alliance for Cellular Signaling
HepatoSys
SysBio enters FP6
YSBN
ERASysBio

publications

ECell
Von Dassow
SBML
Klipp
Alon
Choi
Annual Review Science
Kriete
Palsson
Ideker/Hood
special issue
Boogerd
"Foundations of Systems Biology"
Kaneko
Szallasi
"Computational Cell Biology"
Grierson
IEE Sys Bio
MSB
BMC Sys Bio

Institutes

Tokyo Systems Biology Institute
Seattle Institute for Systems Biology
6 BBSRC centres
BioQuant

Rise of Systems Biology as a paradigm

1998	1999	2000	2001	2002	2003	2004	2005	2006	2007

projects

ERATO-Kitano

Alliance for Cellular Signaling

HepatoS

Sy

YSBN

SystemsX

End of BBSRC Systems Biology calls

publications

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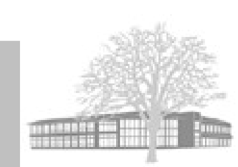
BioQuant

6 BBSRC centres

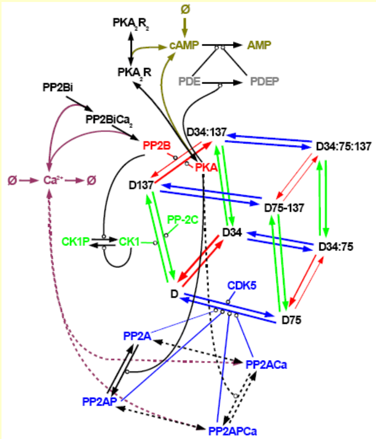


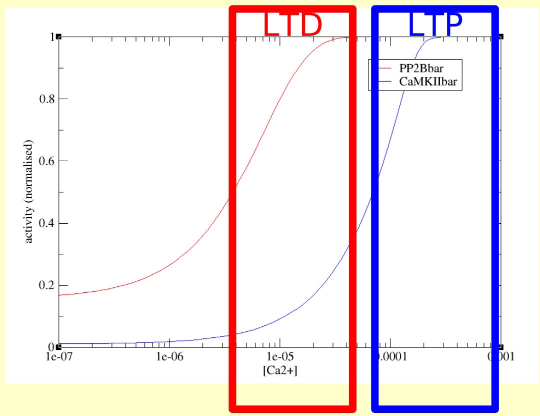
The "two" Systems Biology

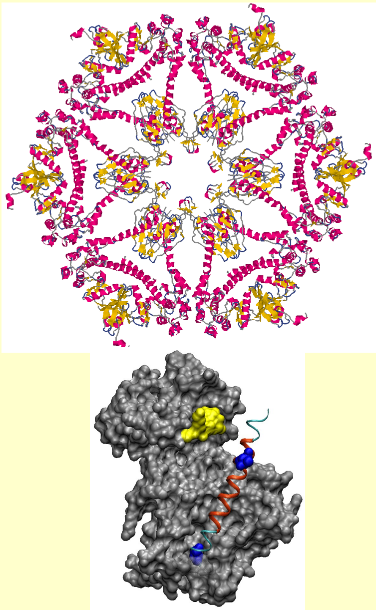
What	Computation Systems Biology: kinetic modelling, simulation, numerical analysis. Mainly metabolic networks and signalling pathways	Network Systems Biology: interactomes, regulatory networks, boolean models. Mainly gene regulatory networks
Who	Originate from Biochemistry, Physics and Engineering *Arkin, Bhalla, Bray, Fell, Ferrell, Hunter, Kell, Kholodenko, Kitano, Leibler, Noble, Palsson, Tyson, Westerhoff* International Society for Systems Biology	Originate from Functional Genomics, Bioinformatics and Mathematics *Birney, Bork, Brunak, Hood, Ideker, Snyder, Vidal* International Society of Computational Biology
When	International Conference on Systems Biology	Intelligent Systems in Molecular Biology, International Conference on Pathways, Networks, and Systems Medicine
Where	Biochemical journals, BMC Systems Biology, IET Systems Biology, Molecular Systems Biology	Bioinformatics, PloS Computational Biology

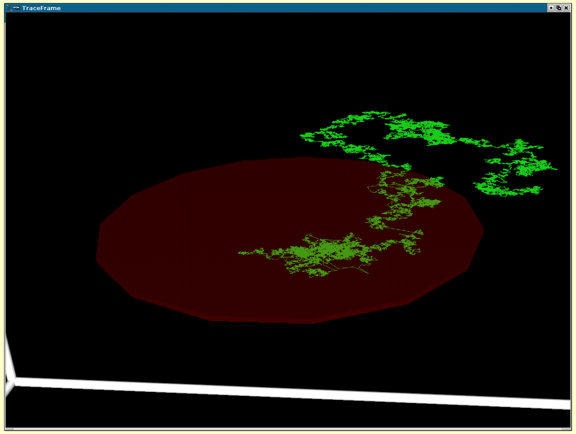
"Compneur" themes and projects

Computational Neurobiology



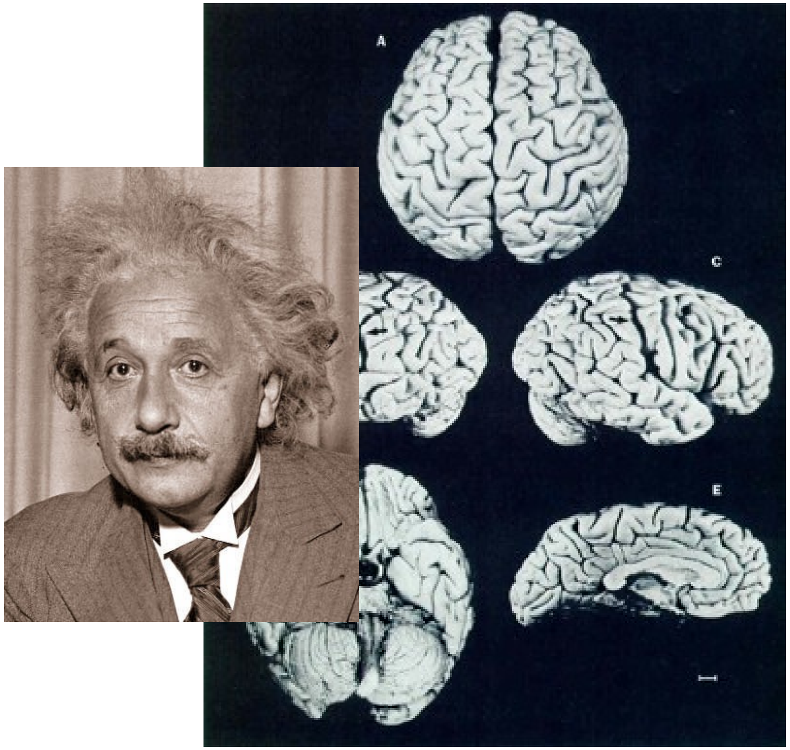




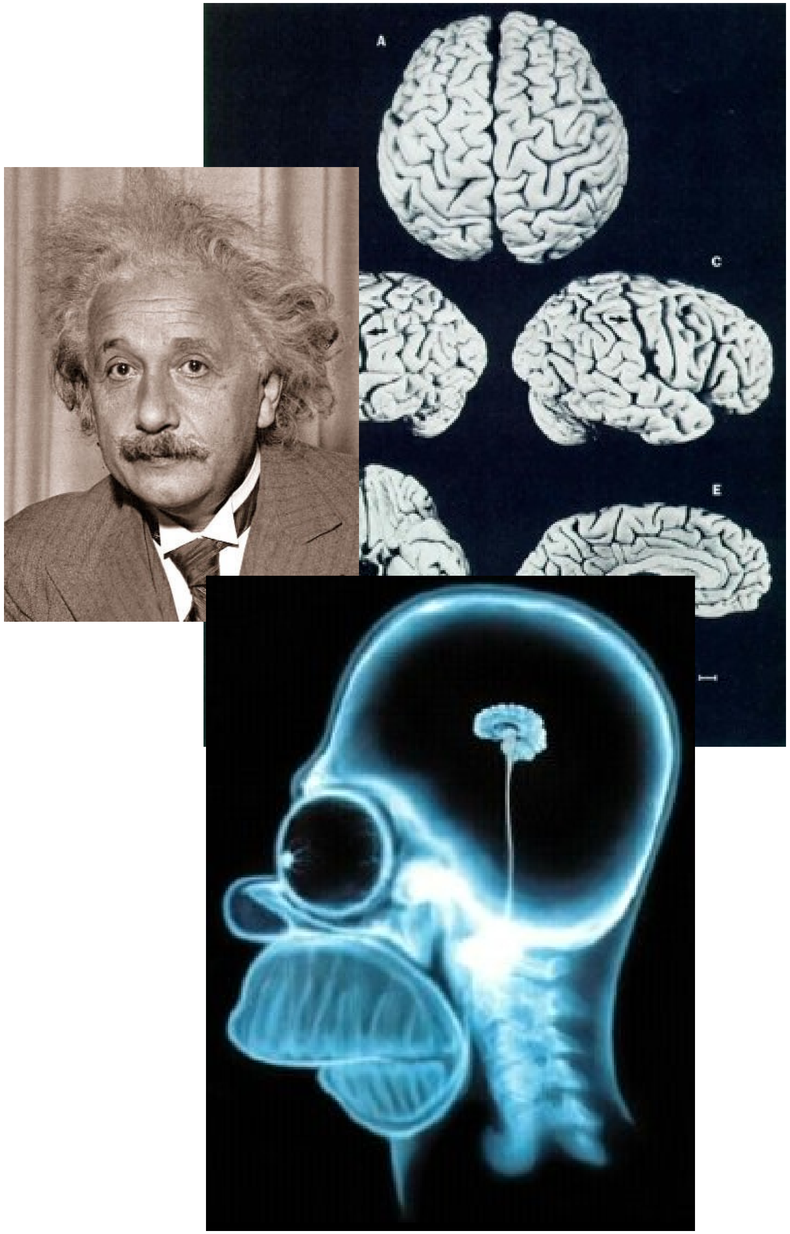


Systems Biology

The brain



The brain



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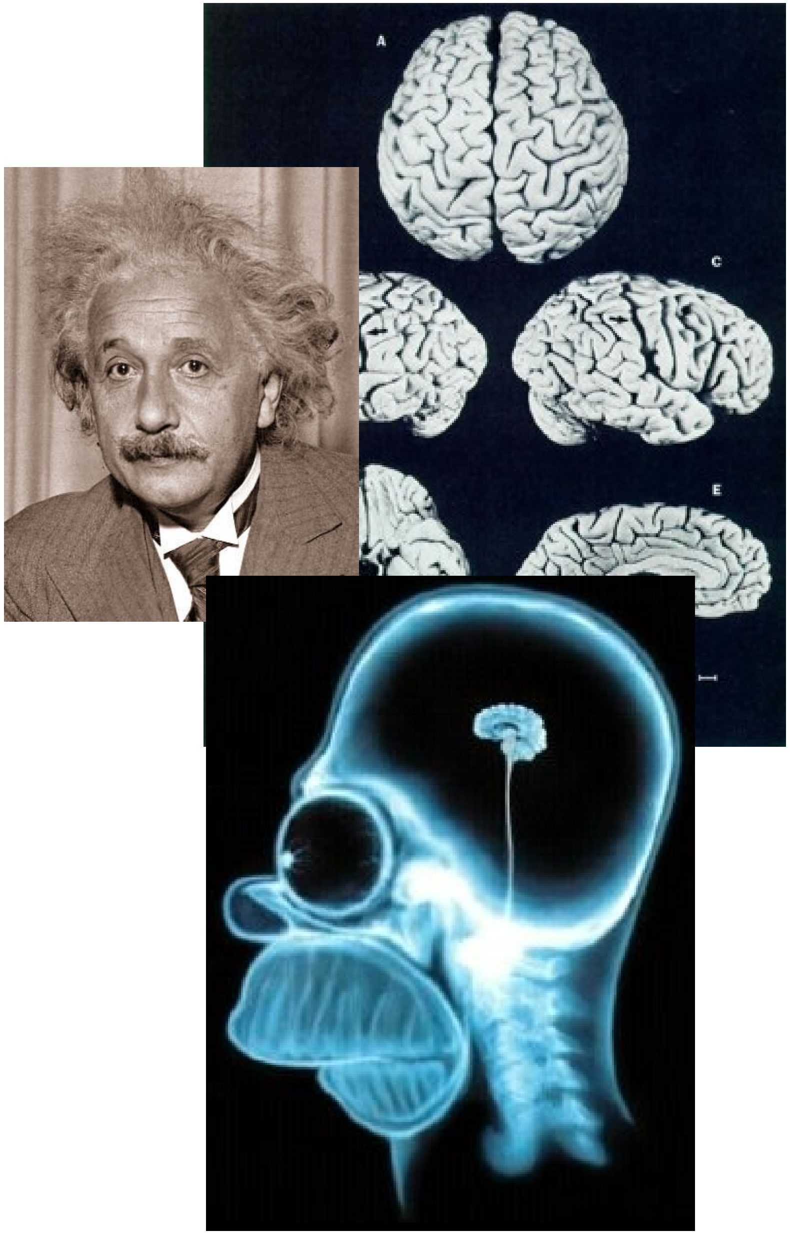
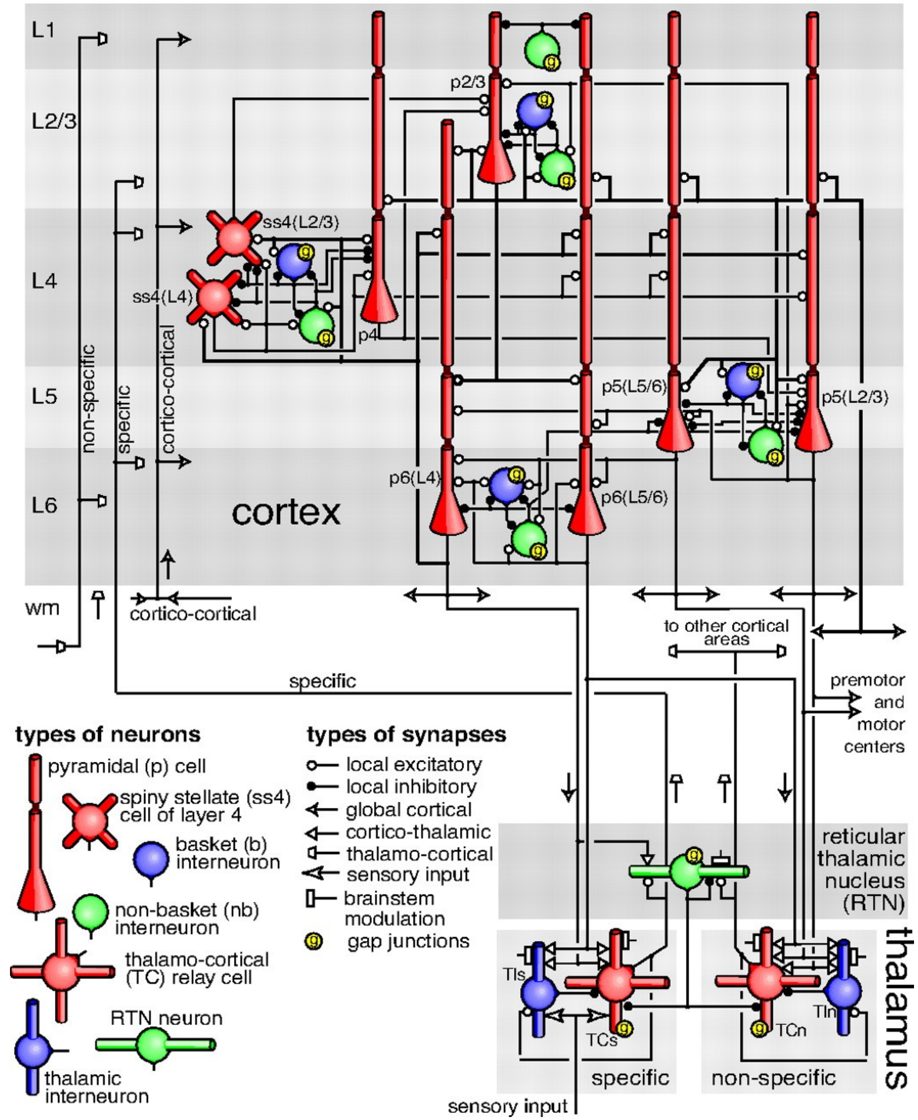
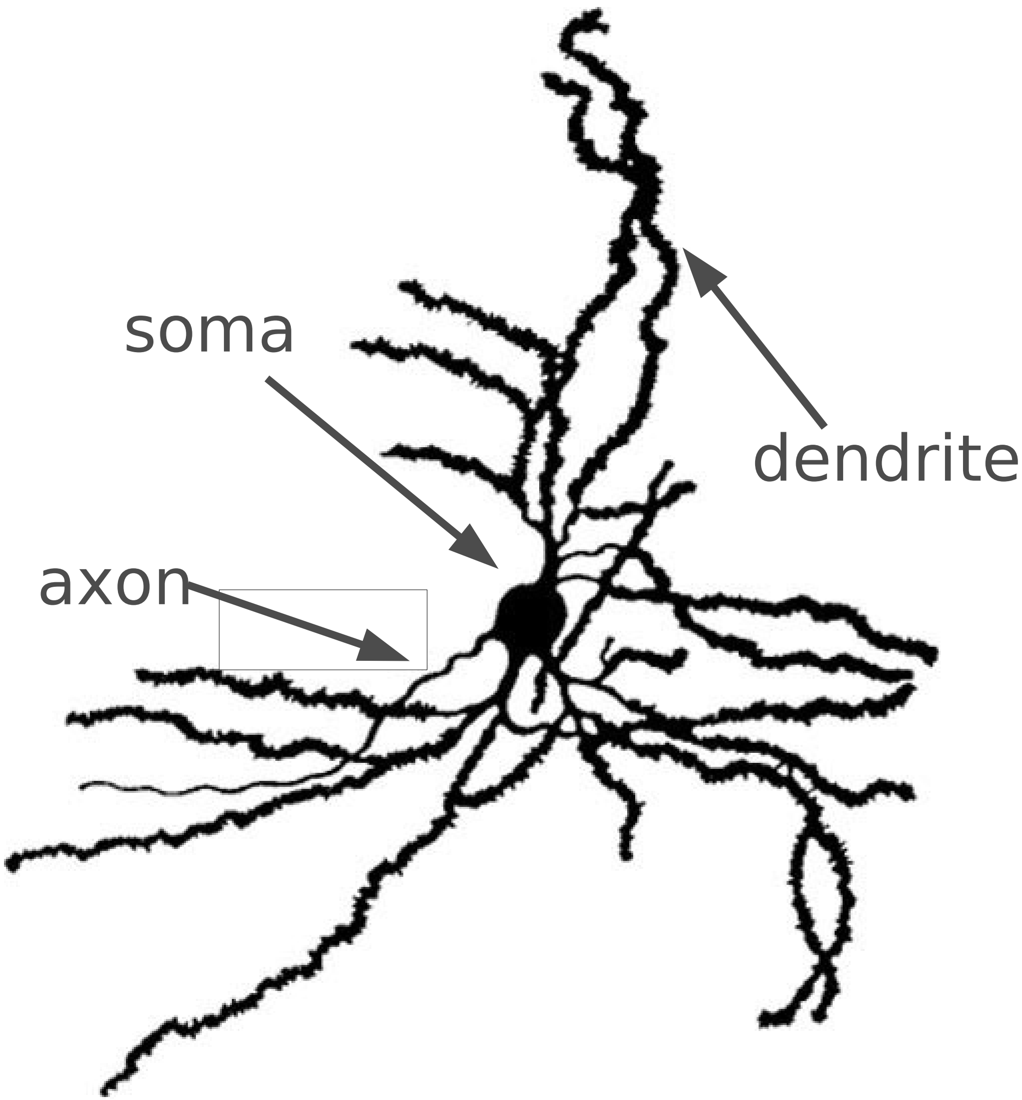
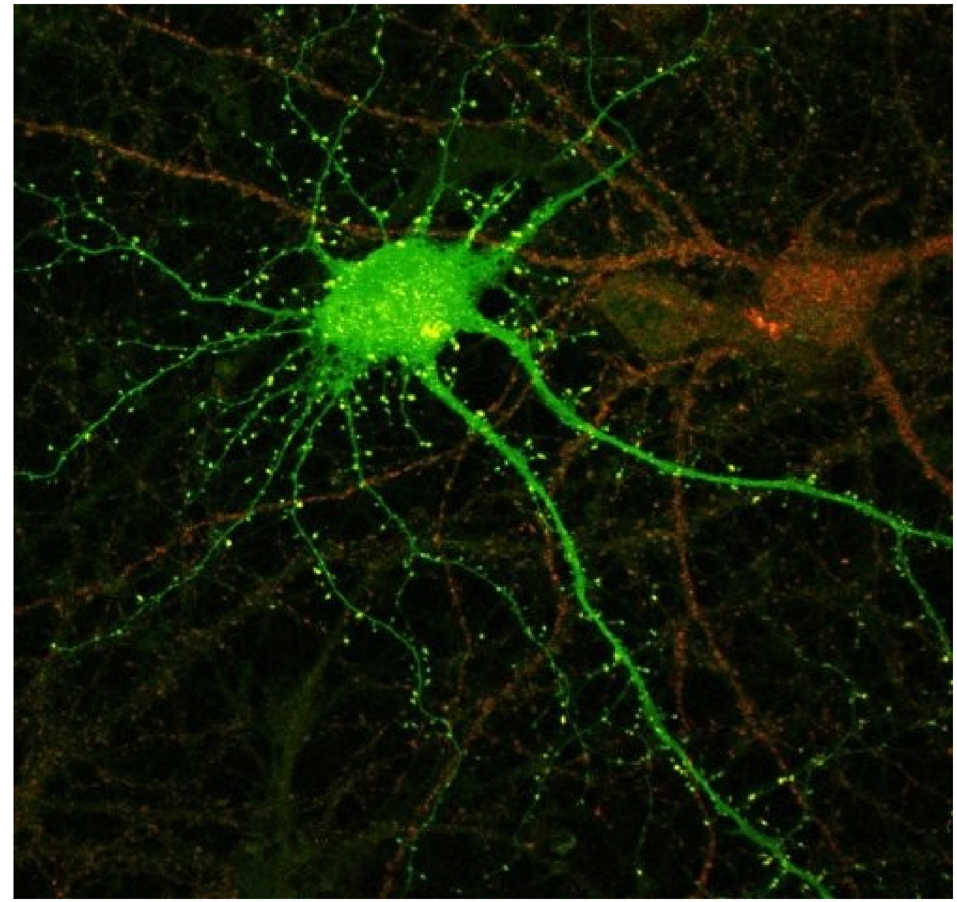




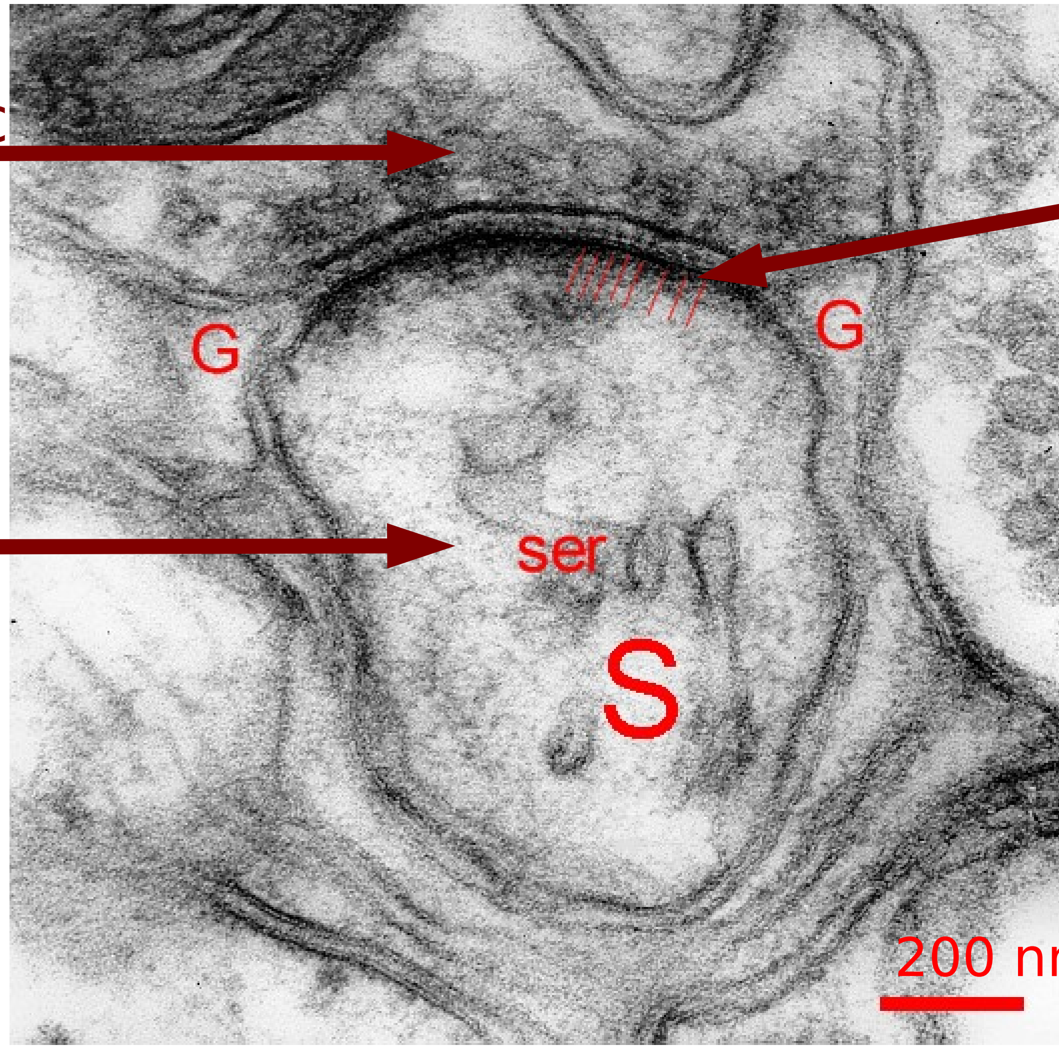
Izhikevich, Edelman (2008)
PNAS 105: 3593-3598

The neuron



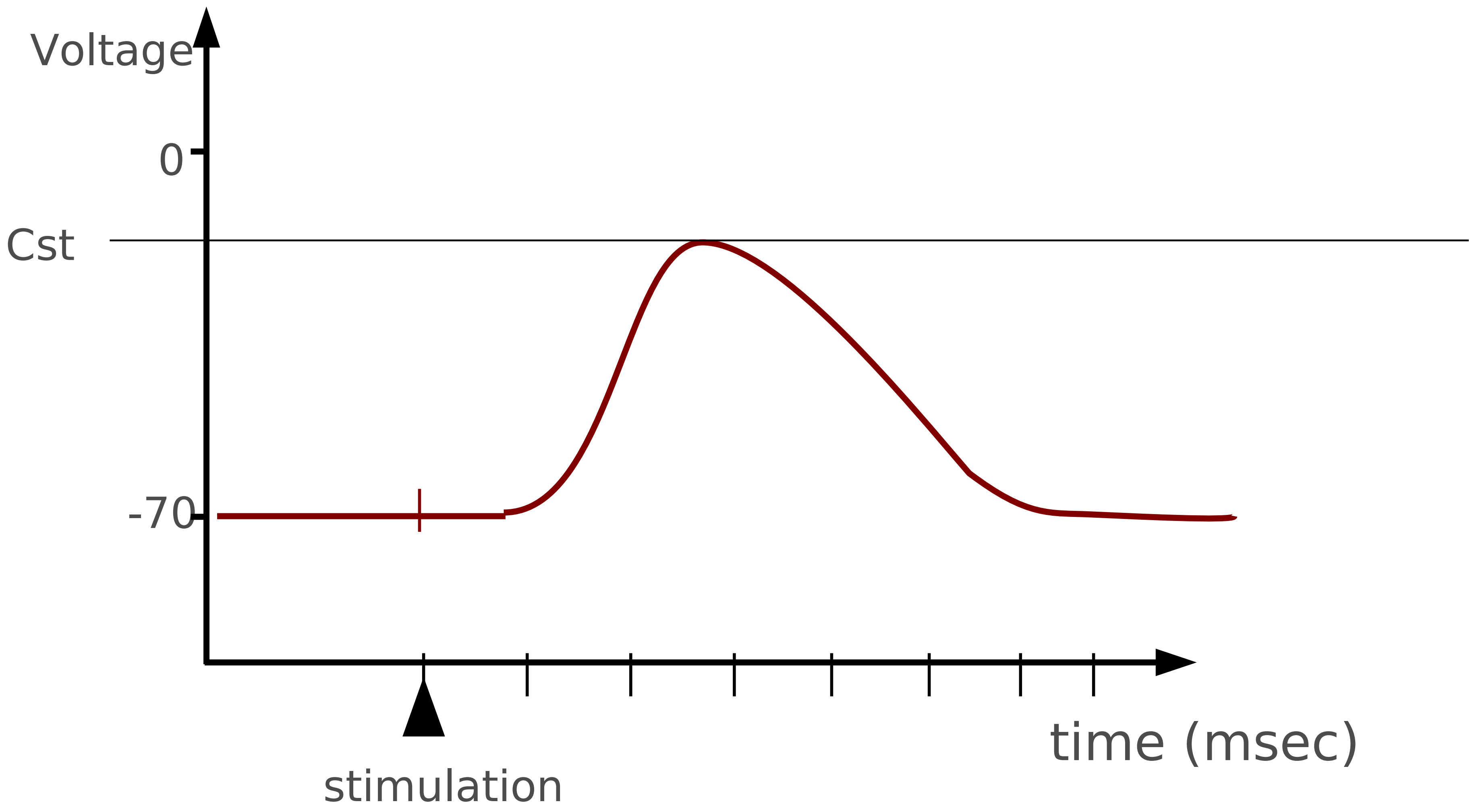


The spine

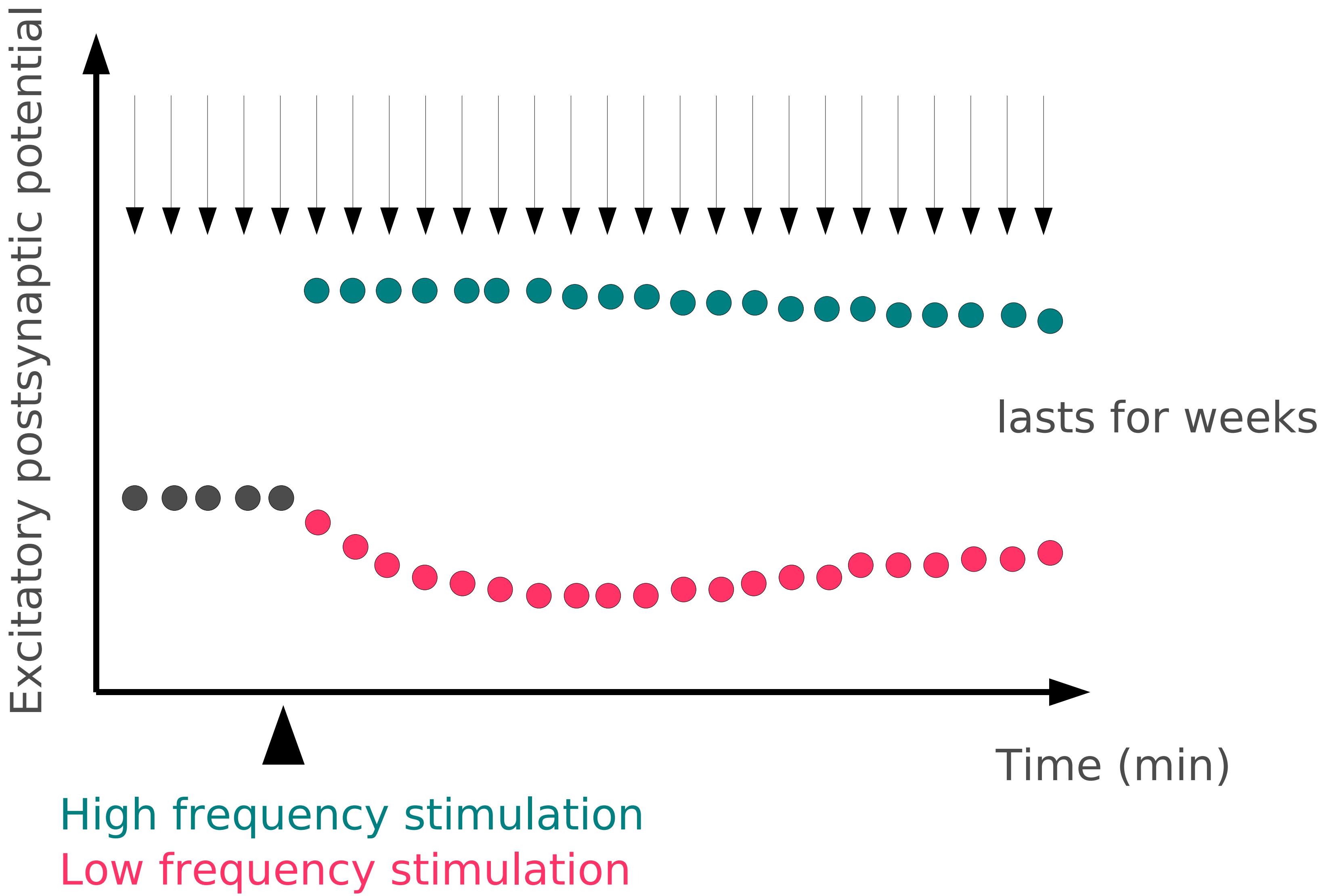


Atlas of ultrastructural neurocytology (http://synapse-web.org/)

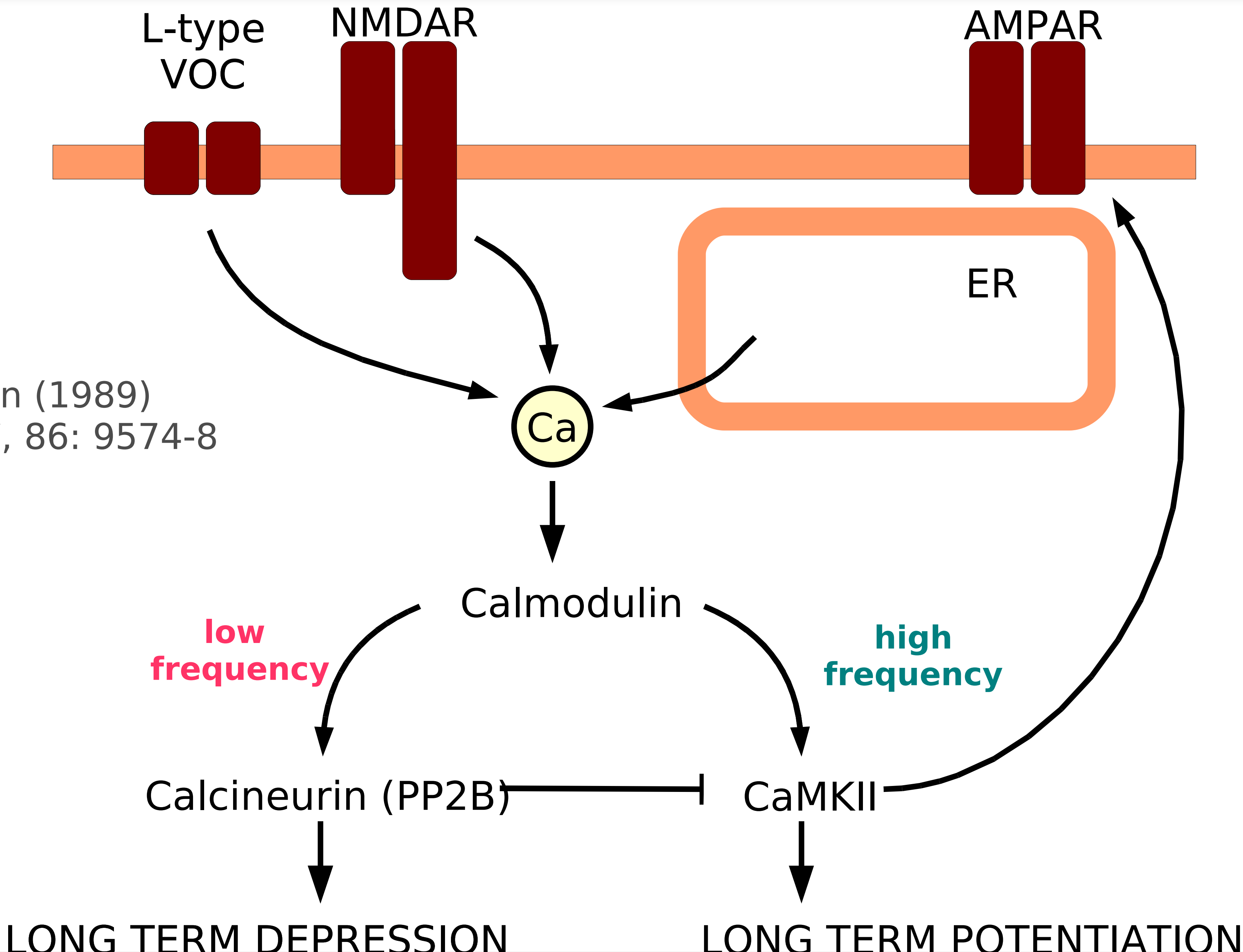
Excitatory post-synaptic potential



Bidirectional synaptic plasticity

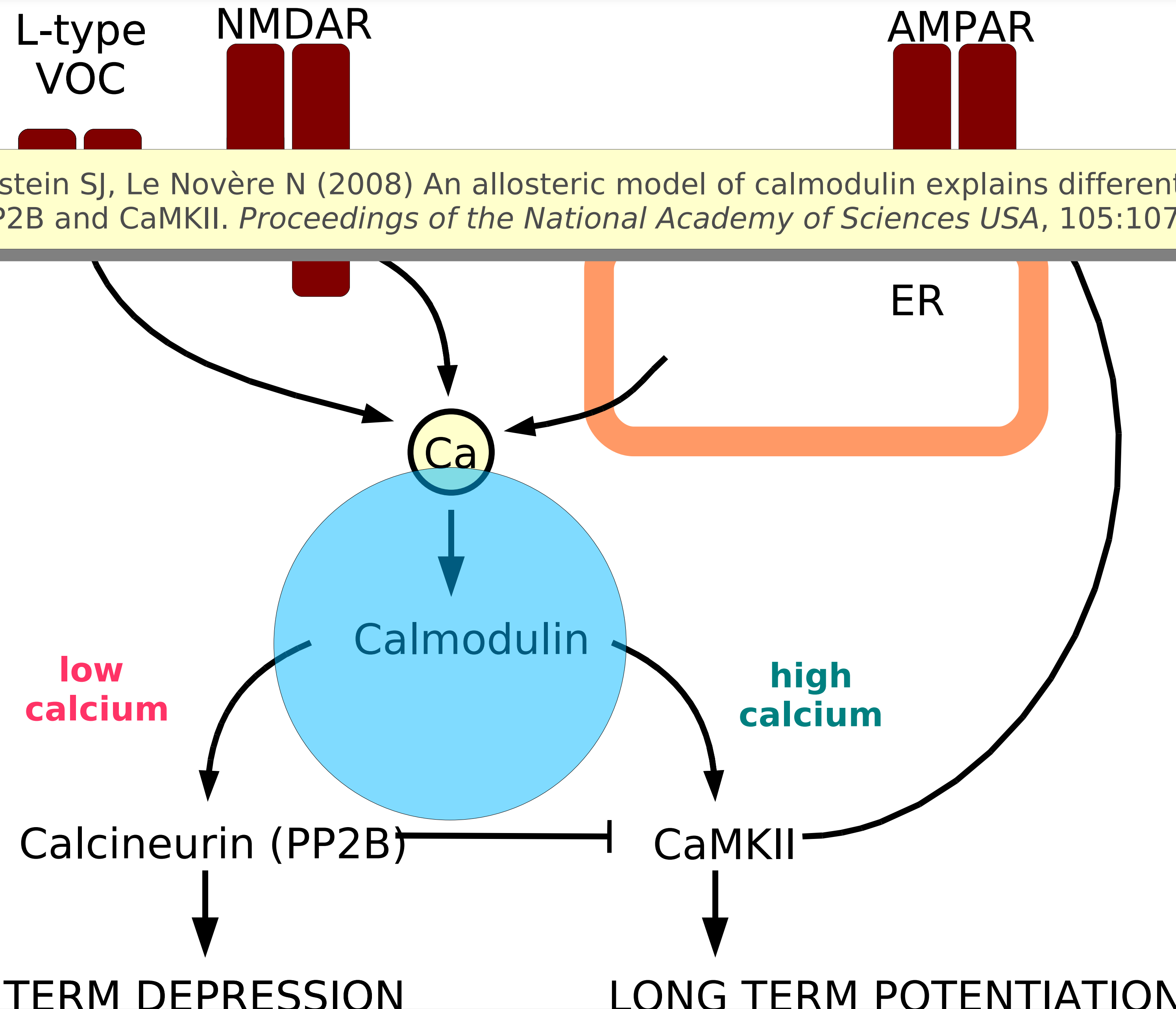


Calcium theory of Synaptic Plasticity



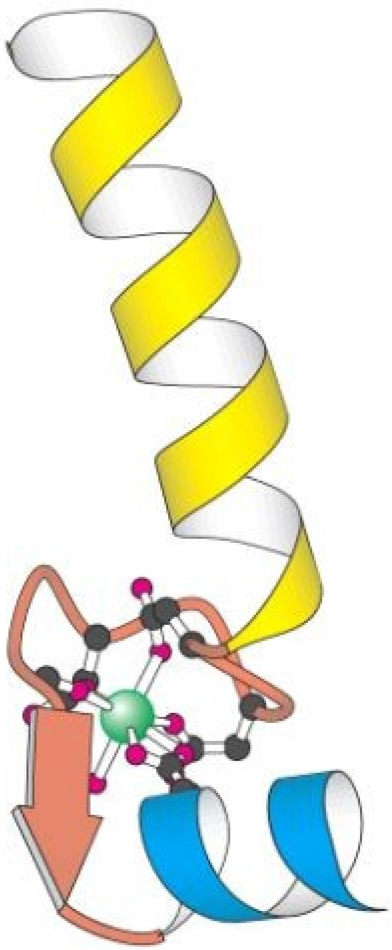
Lisman (1989)
PNAS, 86: 9574-8

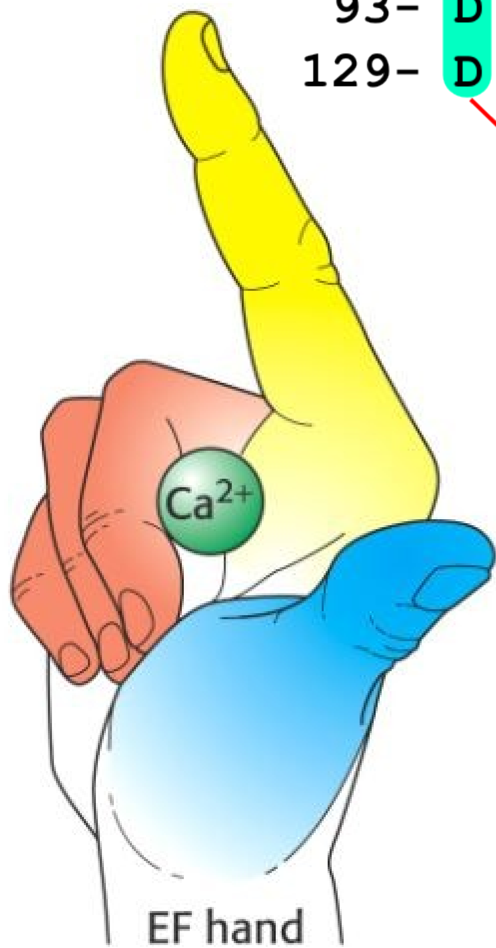
Calmodulin, the memory switch

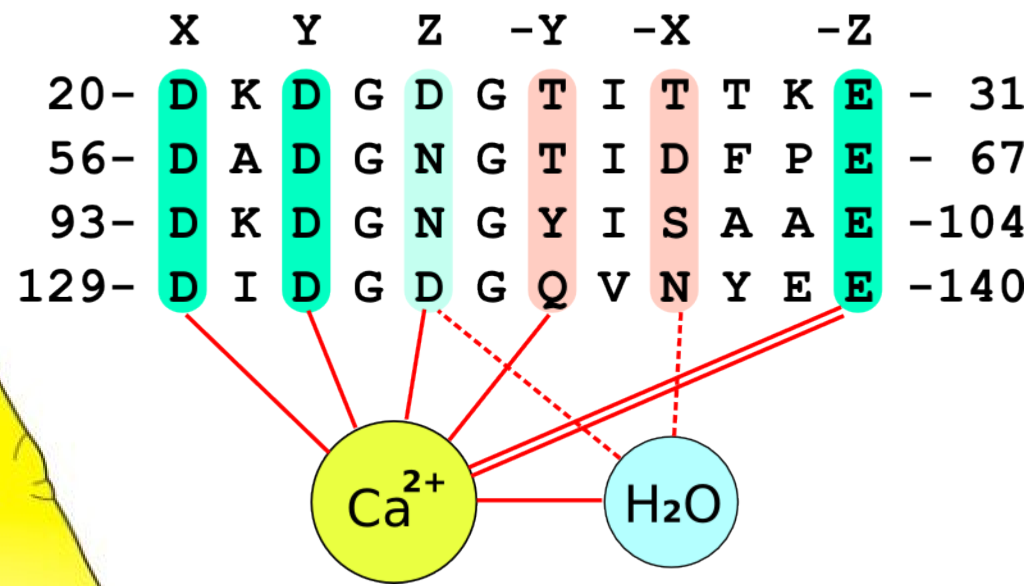


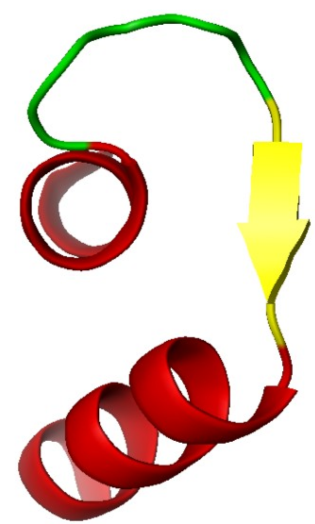
Stefan MI, Edelstein SJ, Le Novère N (2008) An allosteric model of calmodulin explains differential activation of PP2B and CaMKII. *Proceedings of the National Academy of Sciences USA*, 105:10768-10773

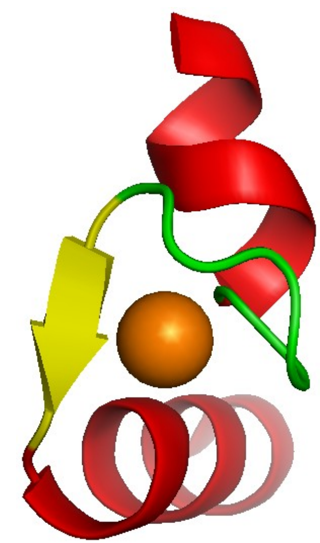
Structure of Calmodulin



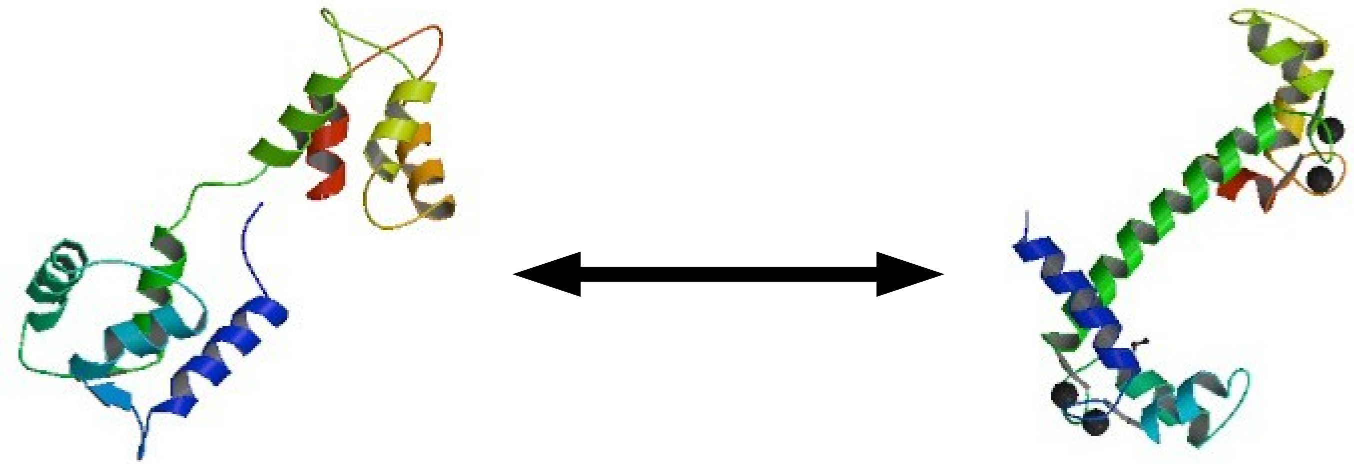




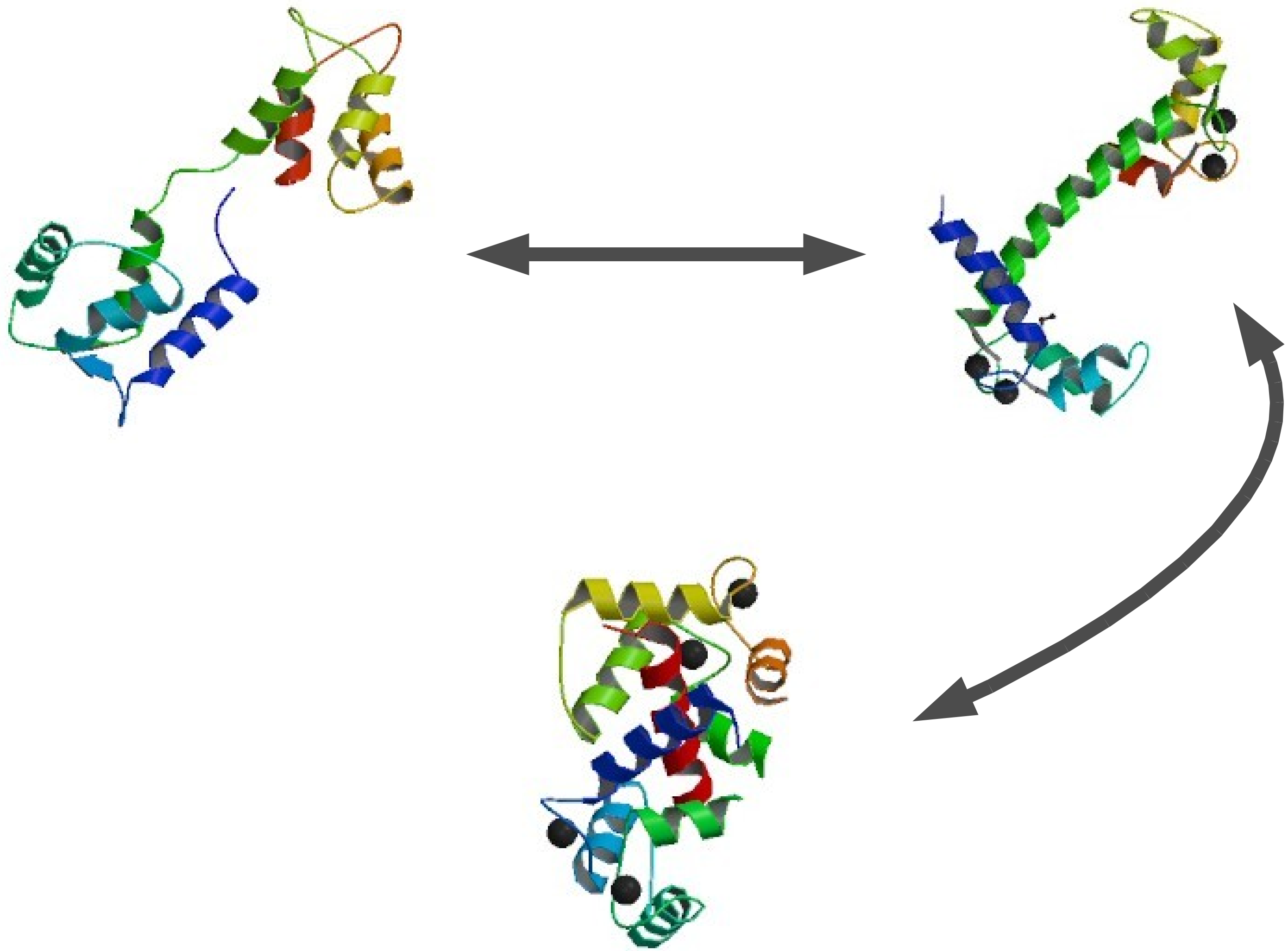




State transitions of calmodulin

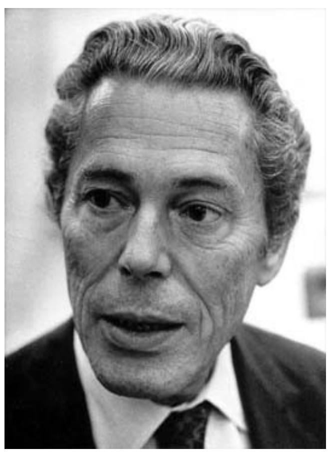


State transistions of calmodulin

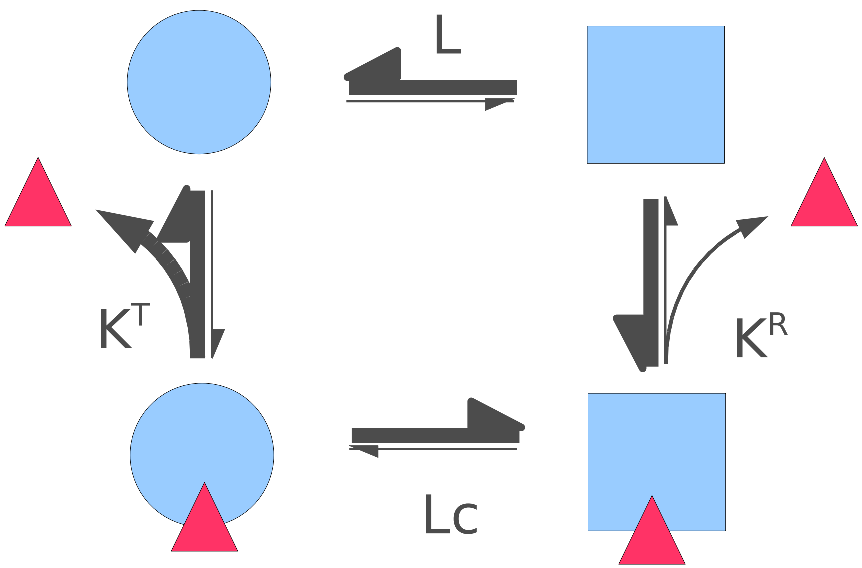


Allostery and state selection

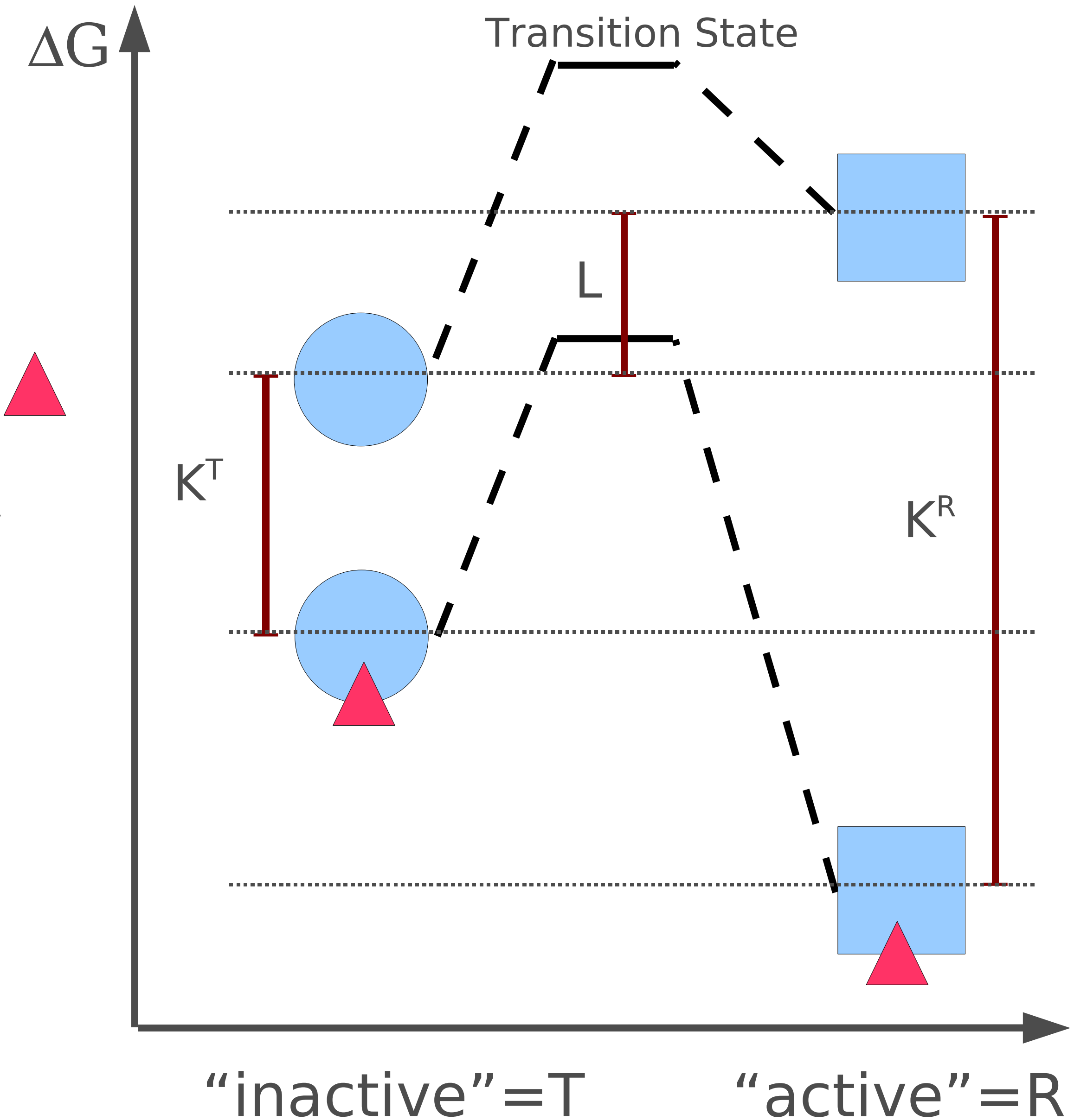
- Monod, Wyman, Changeux (1965). On the nature of allosteric transitions: a plausible model. *J Mol Biol*, 12: 88-118



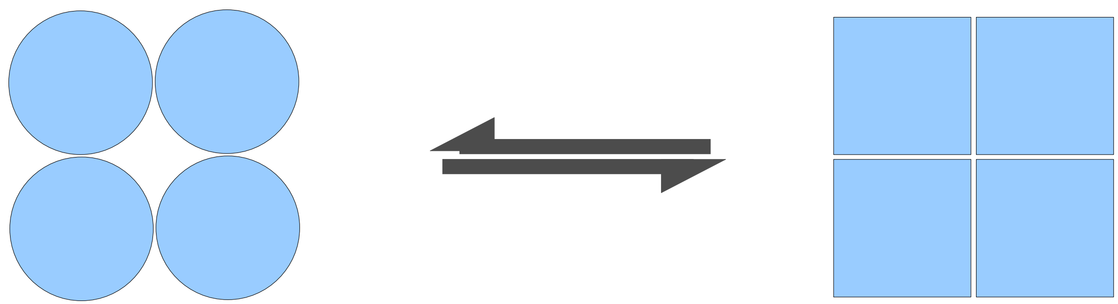
Modulation of thermal equilibria ≠ induced-fit



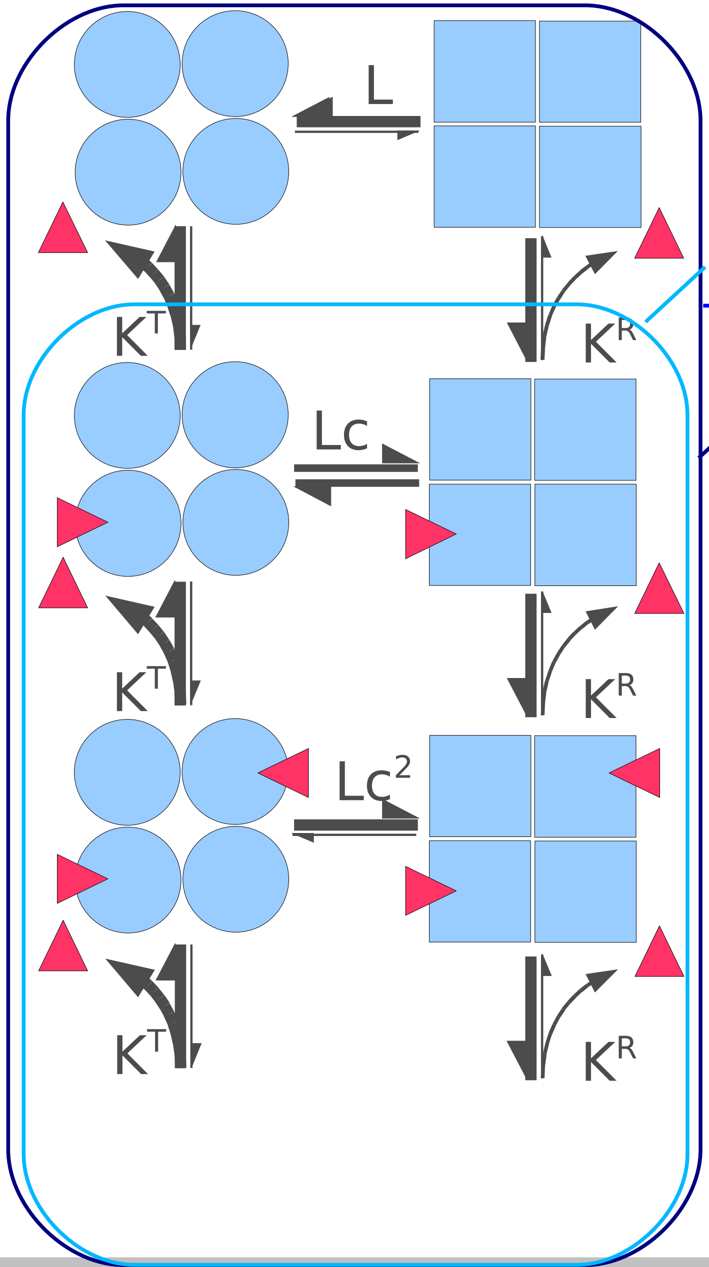
$$L = \frac{[T0]}{[R0]} \qquad C = \frac{K^R}{K^T}$$



Concerted transi tions ≠ sequential model

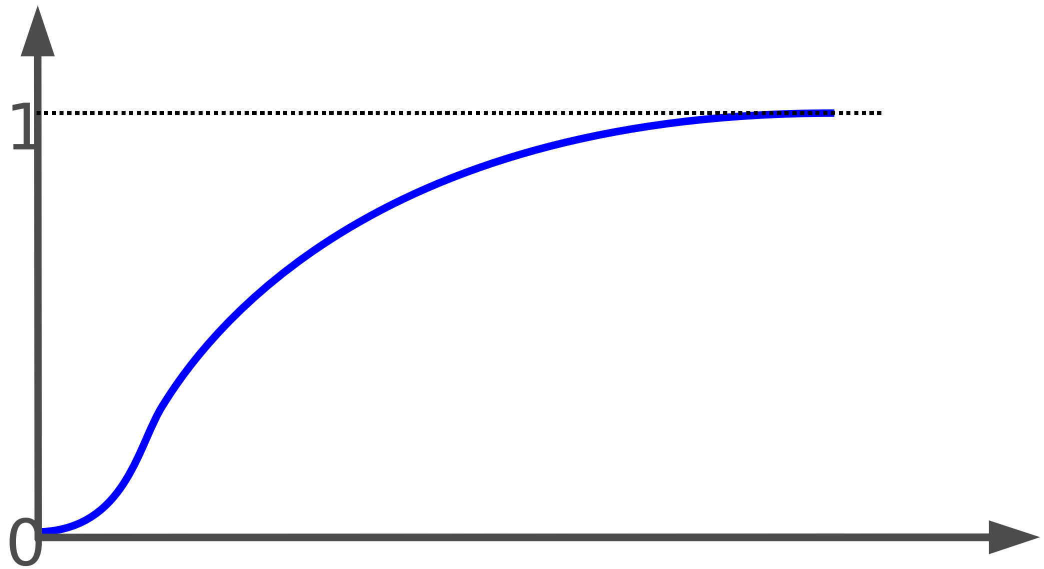


Monod-Wyman-Changeux model

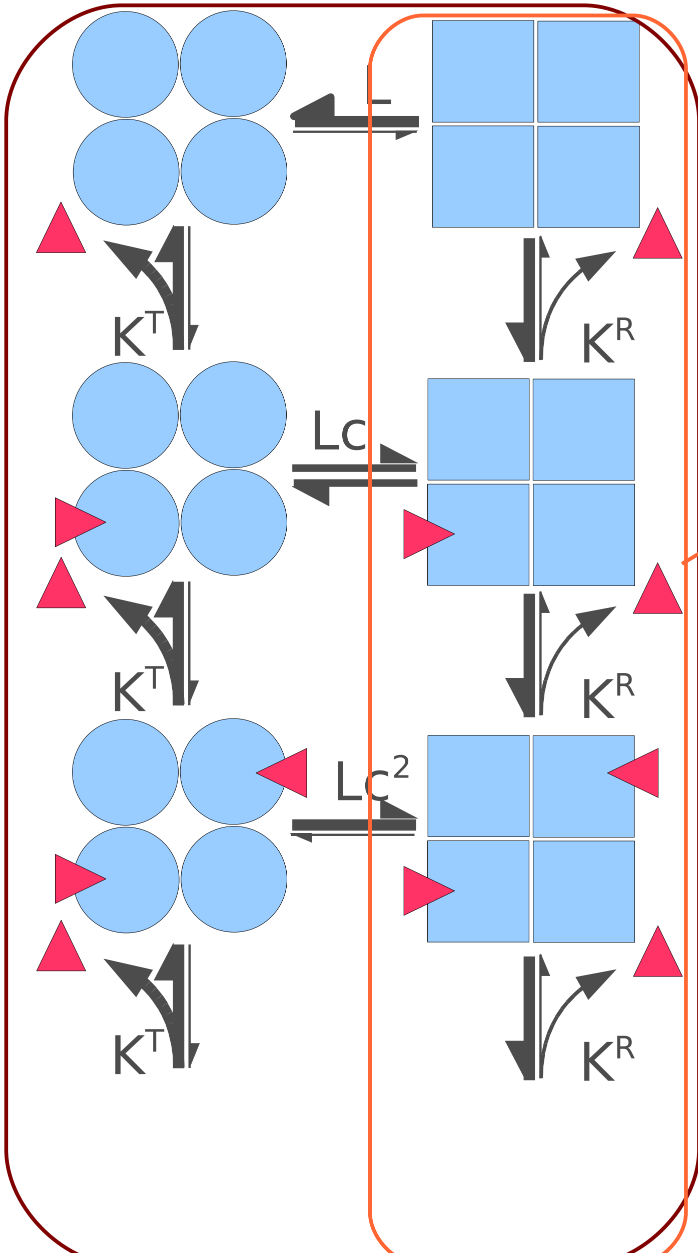


$$\alpha = \frac{[x]}{K^R}$$

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



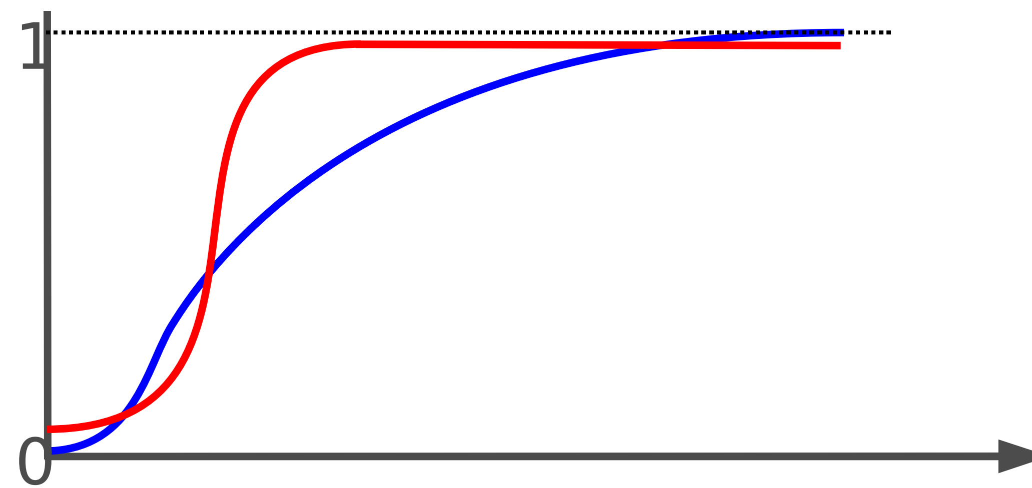
Monod-Wyman-Changeux model



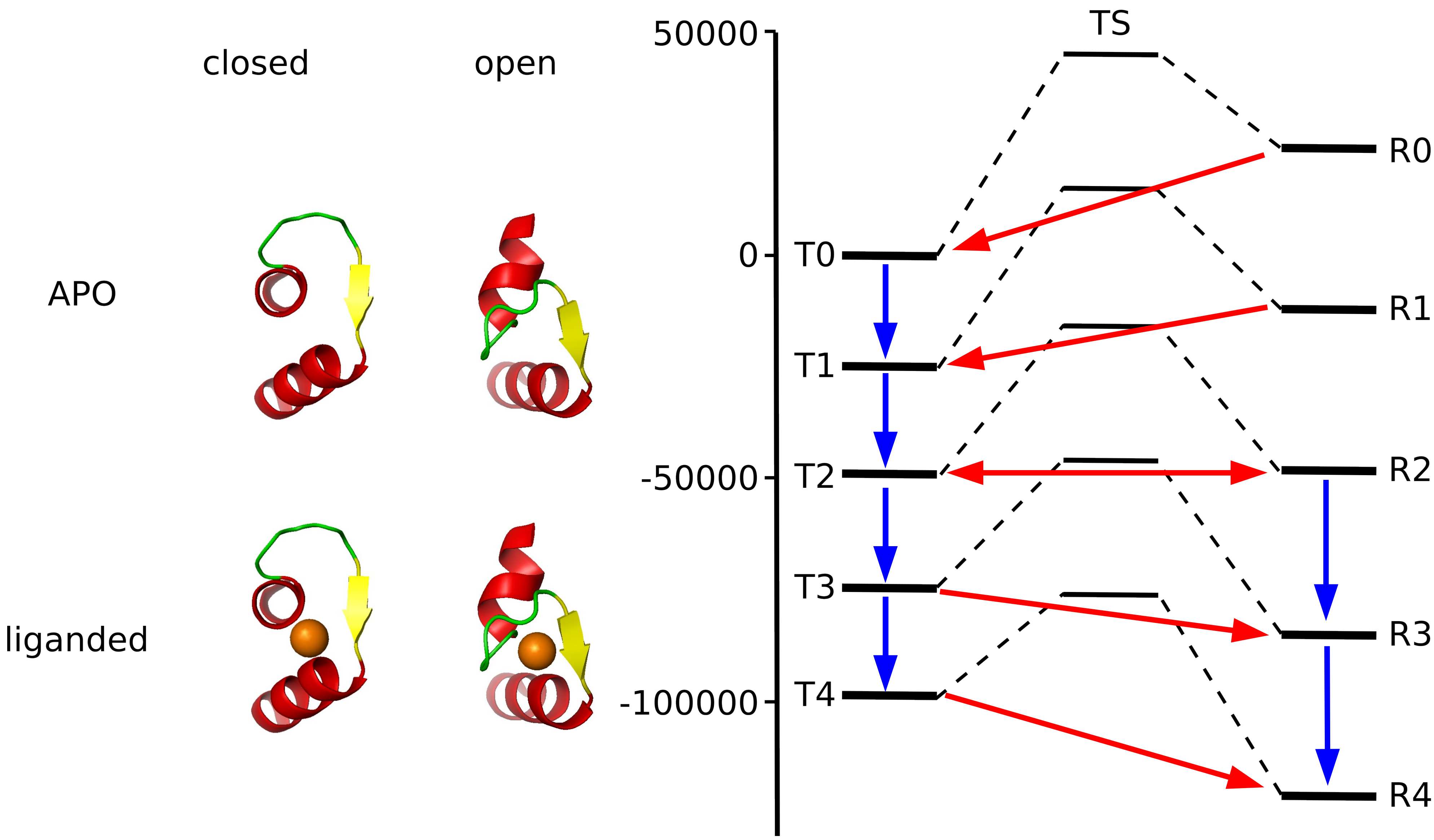
$$\alpha = \frac{[x]}{K^R}$$

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

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



Concerted transition



Obtaining L and c

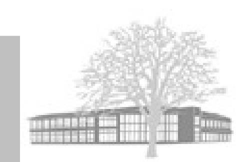
- Hypothesis for the whole model: free energy of conformational transition is evenly distributed: c is unique
- Additional simplification to determine L: affinities are identical

$$\bar{Y} = \frac{\alpha(1+\alpha)^3 + L\left(\frac{1+\gamma e}{1+\gamma}\right)c\alpha(1+c\alpha)^3}{(1+\alpha)^4 + L\left(\frac{1+\gamma e}{1+\gamma}\right)(1+c\alpha)^4}$$

L=20670

c=3.96.10^{-3}

- Model constraints for the determination of c and L
  - Ca binding in presence of target: none, skMLCK, PhK5, CaATPase (Peersen et al (1997) Prot Sci 6: 794-807). Concentration at 50% saturation.
  - 100 000 parameter sets plus least-square
  - 13 identical minima. e for skMLCK is e-15, which can be taken as skMLCK binding only to R state.



Obtaining the microscopic affinities

- Determination of individual affinities:

$$\bar{Y} = 0.25 \frac{\sum_i \left(\alpha_i \prod_j (1 + \alpha_j) \right) + L \sum_i \left(c\, \alpha_i \prod_j (1 + c\, \alpha_j) \right)}{\prod_i (1 + \alpha_i) + L \prod_i (1 + c\, \alpha_i)}$$

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

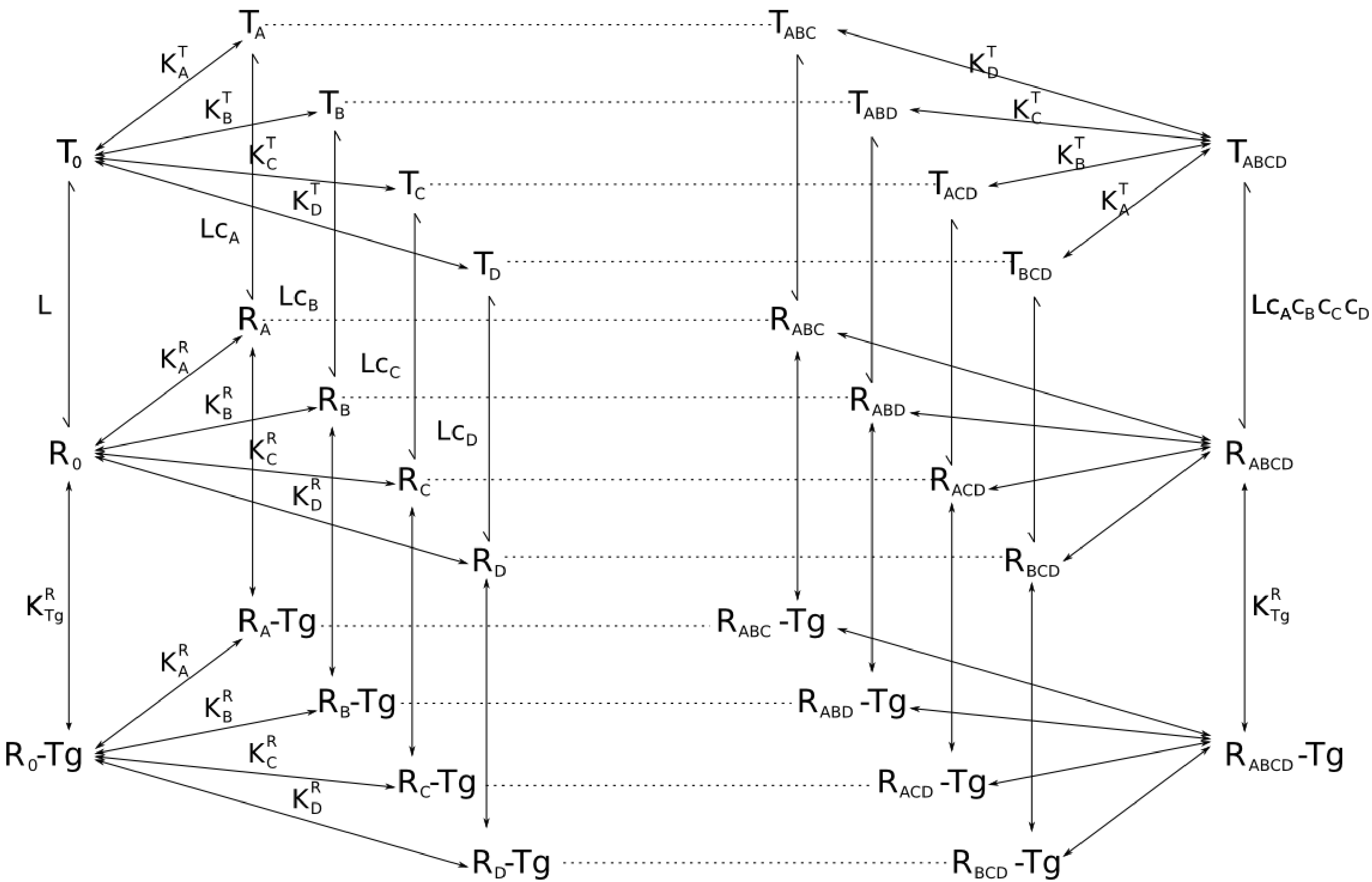
$K^R_B = 1.66\ 10^{-8}$

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

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

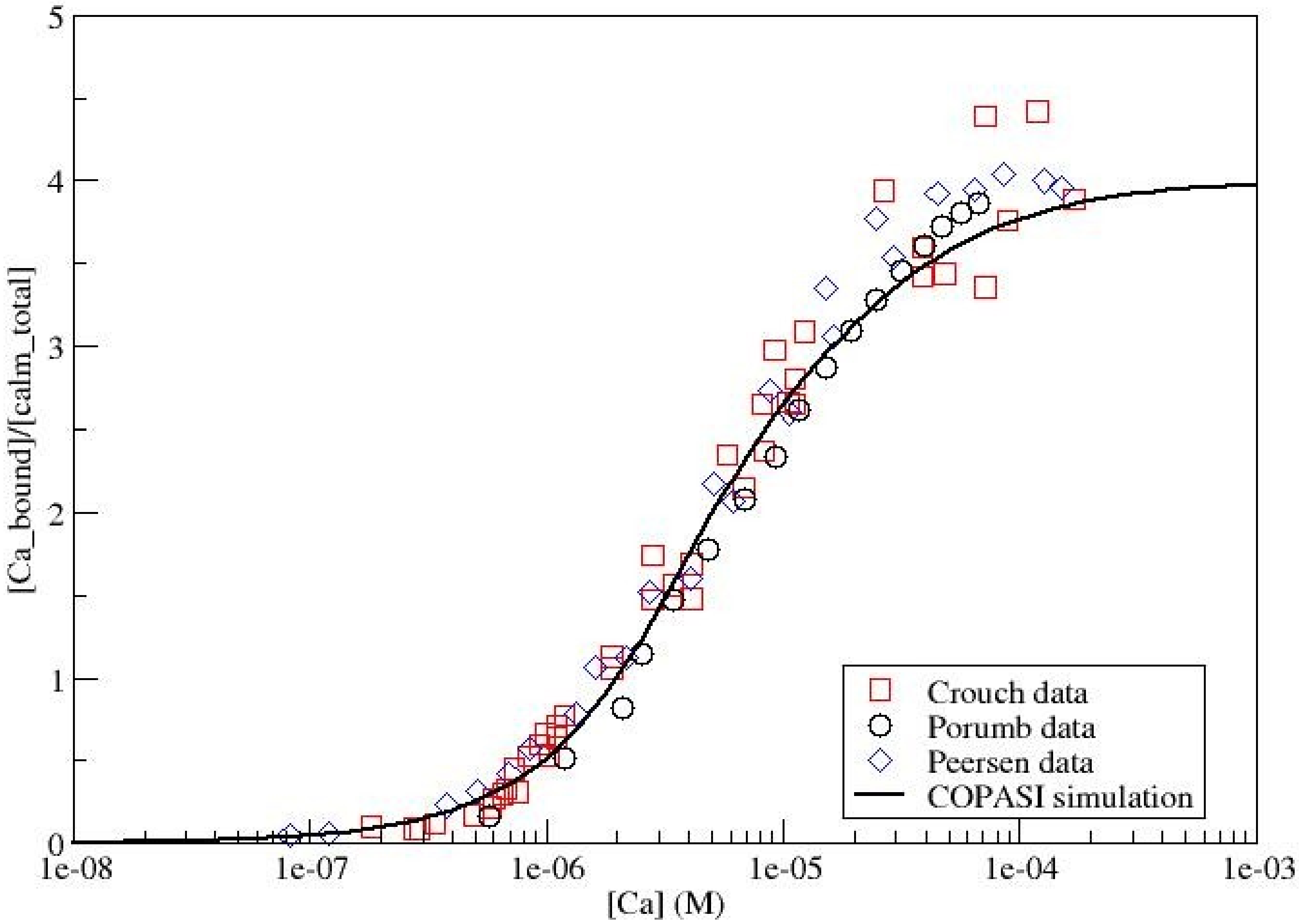
- Model constraints for calcium dissociation constants
  - Complete CaM (Bayley et al (1996) *Prot Sci* 5: 1215-1228)
  - N and C term Mutants (Shifman et al (2006) *PNAS*, 103: 13968-13973)
  - R-only - skMLCK(Peersen et al (1997) Prot Sci 6: 794-807)
  - Concentration at 25% and 50% saturation.
  - Systematic logarithmic sampling of the affinity space (coarse-grained, 50 values per affinity, then refined 66 values per affinity) = 25 millions parameter sets

Full mechanistic thermodynamic model



320 reactions

Comparison with experiments



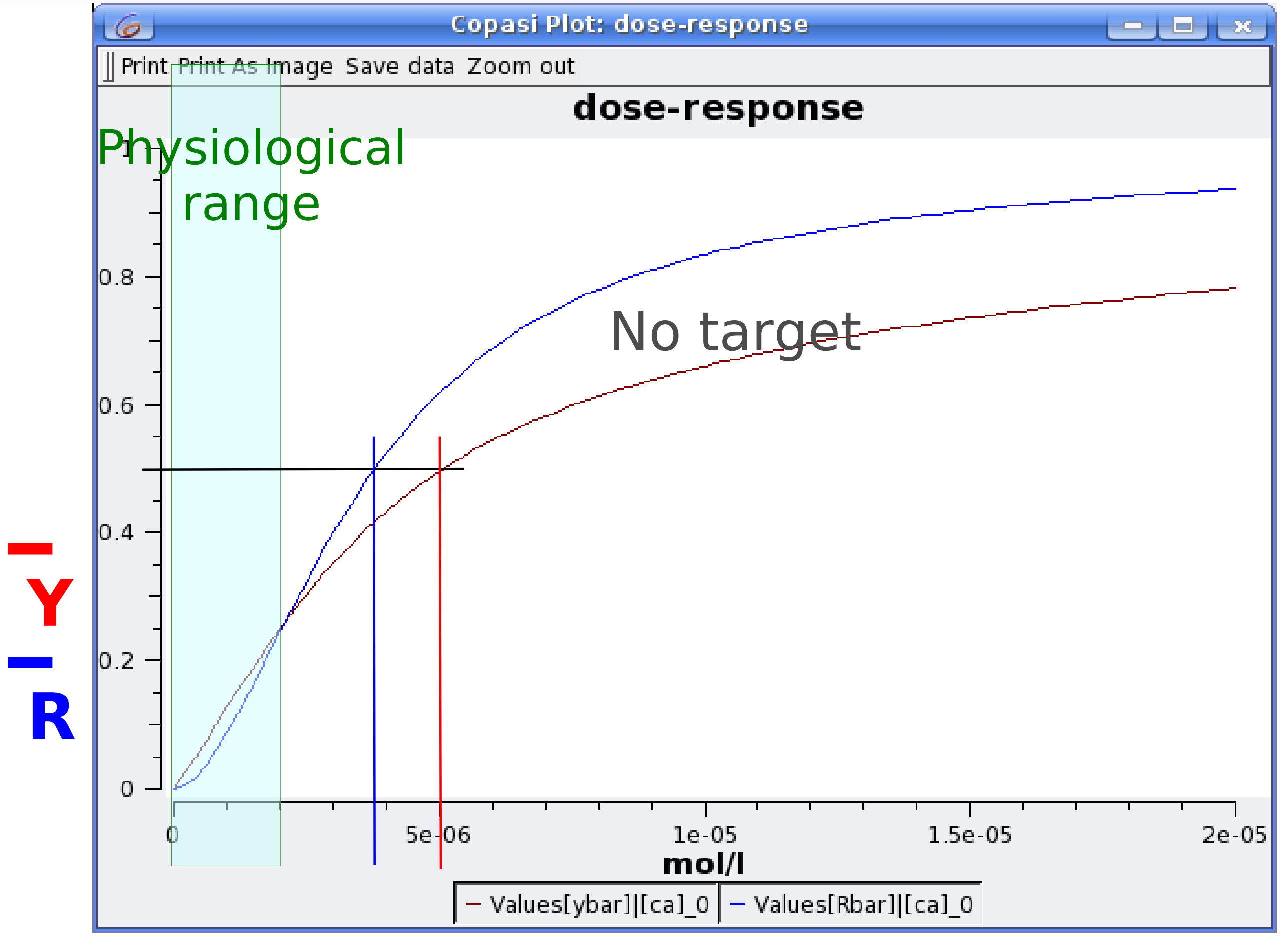
Activity of unsaturated calmodulin

- Fractional activity depends on the number of calcium ions bound. E.g.:

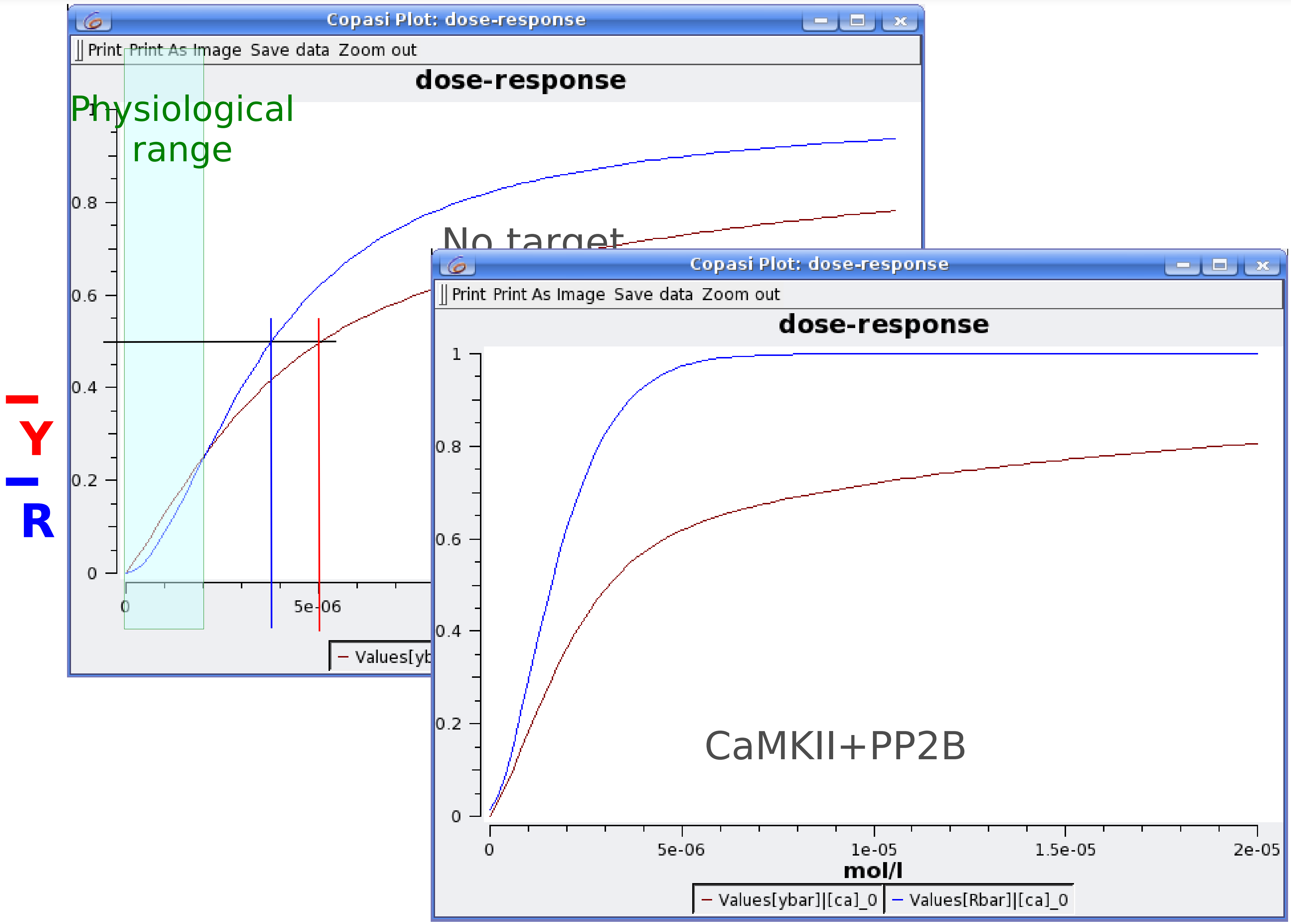
$$\frac{R_2}{T_2} = \frac{1}{L \, . \, c^2}$$

- $R_0/T_0 = 1/20000$ (1/L)
- $R_1/T_1 = 1/170$
- $R_2/T_2 = 0.69$ ➡ half-saturation = equi-probability
- $R_3/T_3 = 80$
- $R_4/T_4 = 10000$

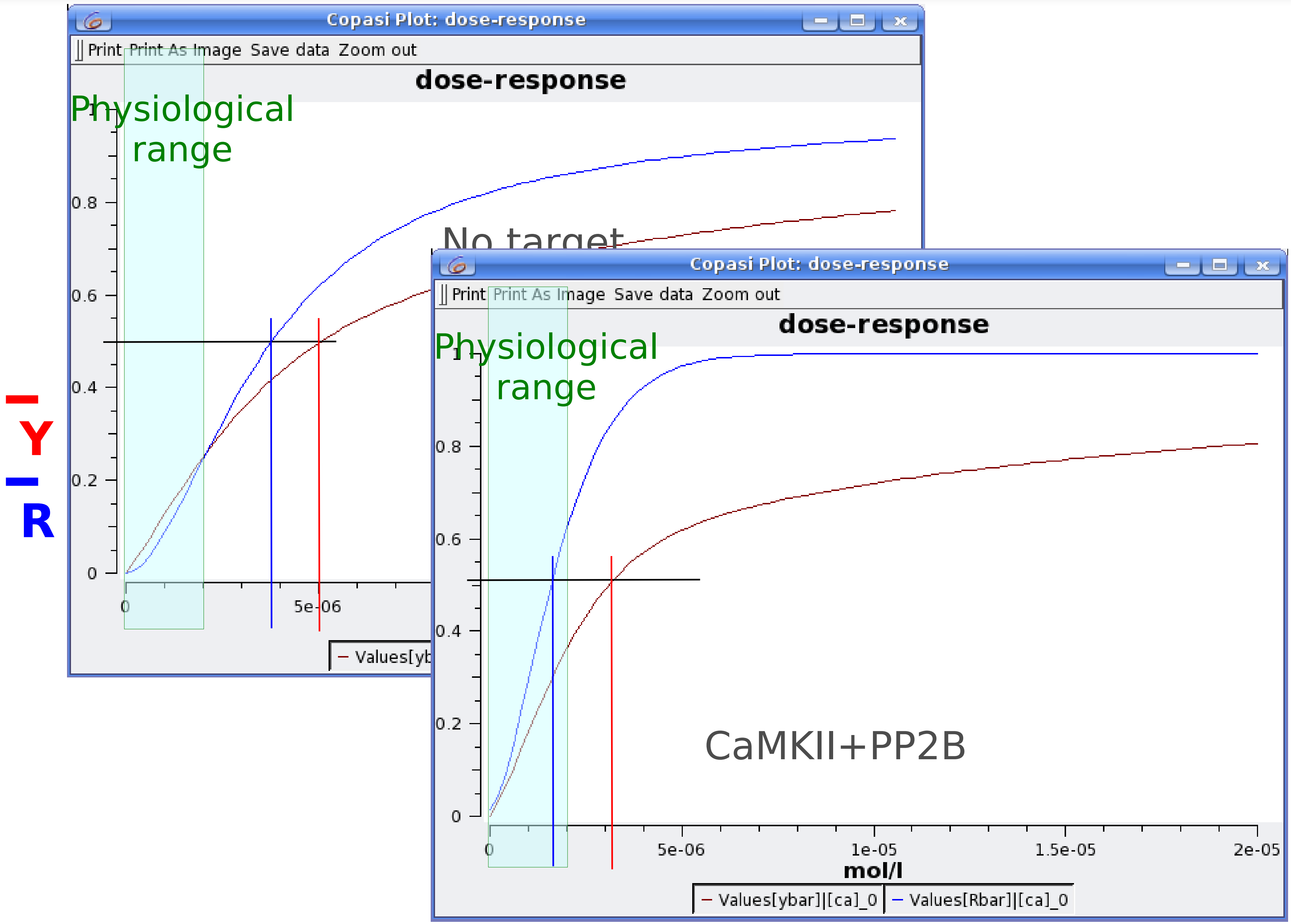
But ... we're out of the physiological range?



But ... we're out of the physiological range?

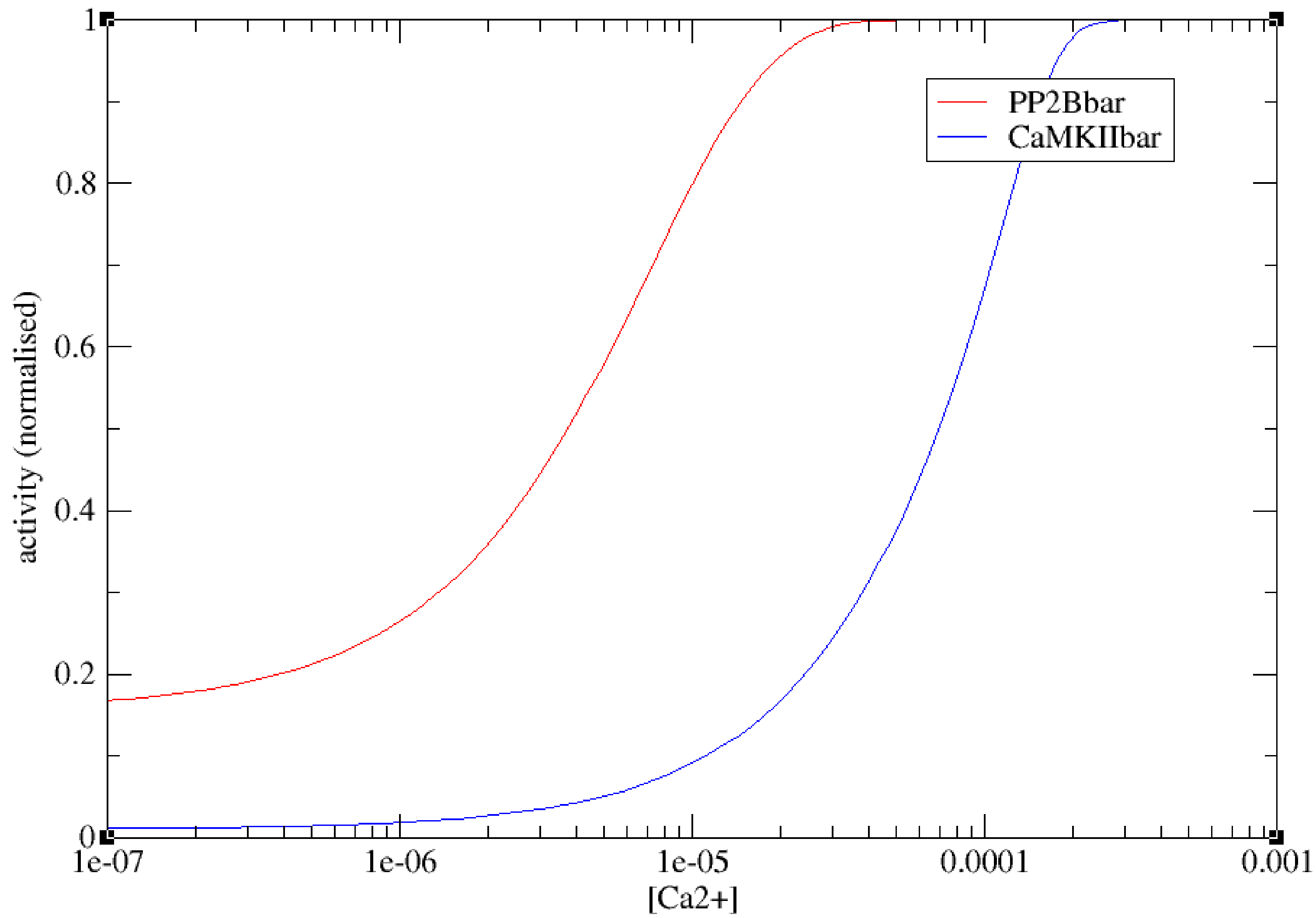


This is Systems Biology!

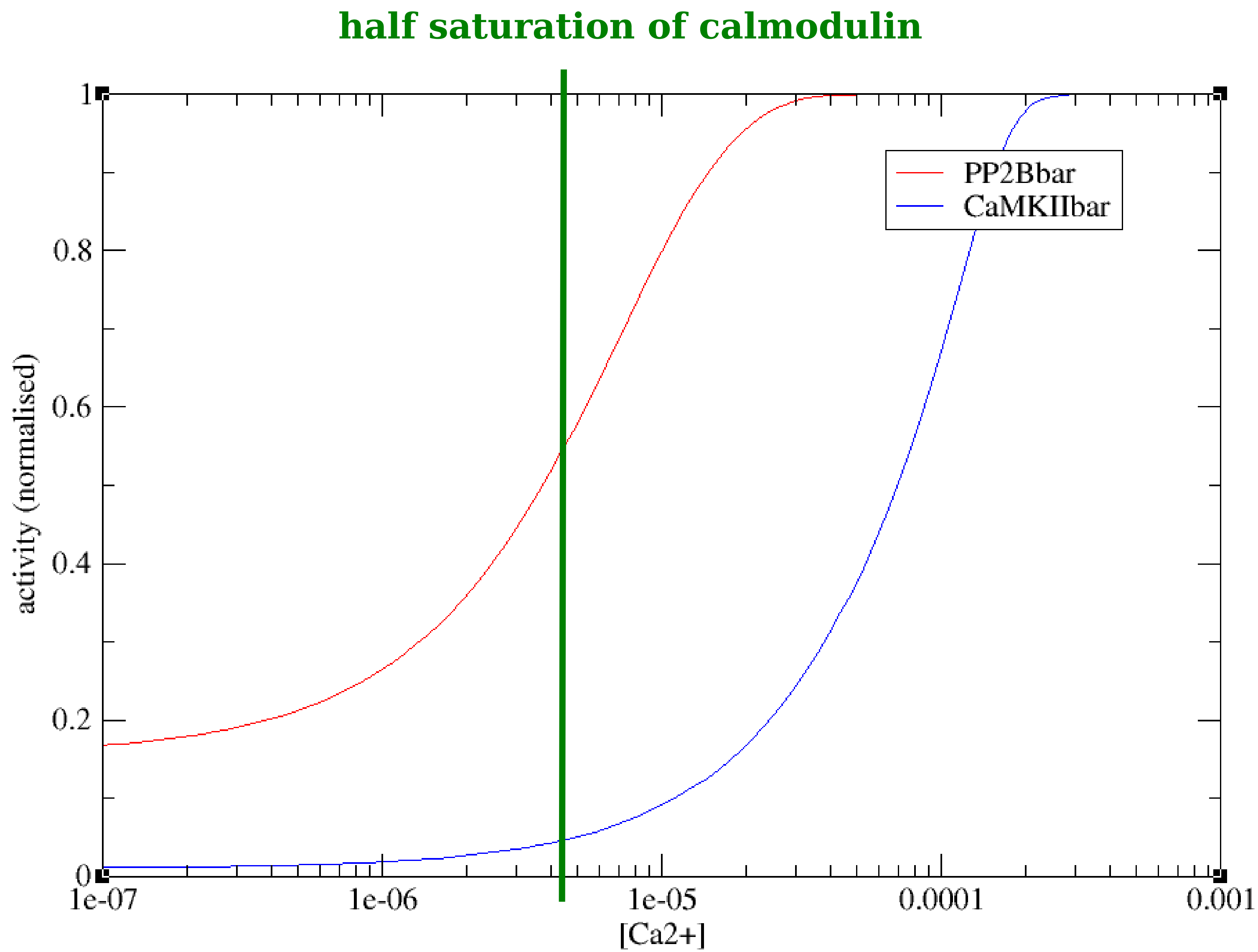


Bidirectional synaptic plasticity

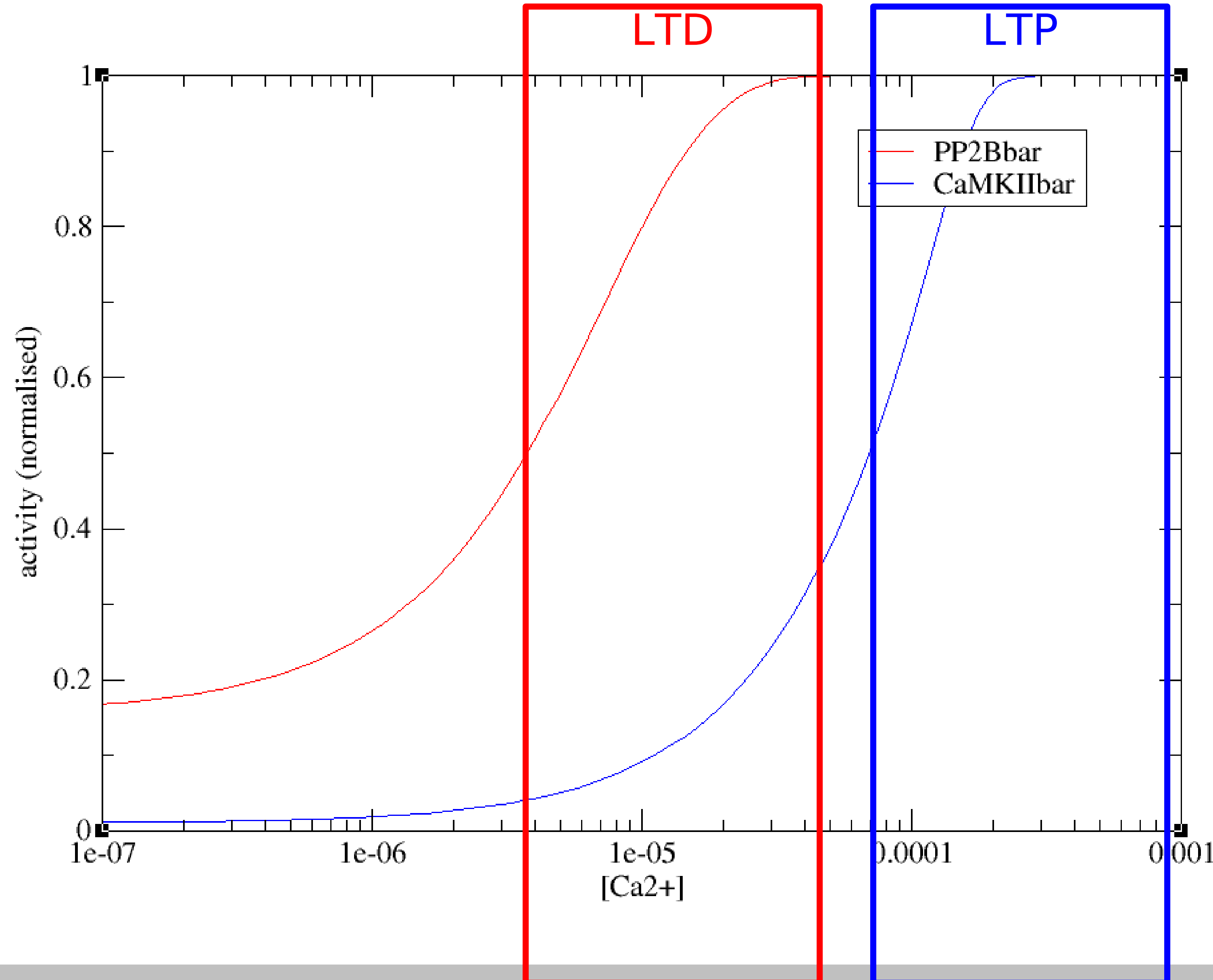
affinity for PP2B >> affinity for CaMKII
[PP2B] << [CaMKII}



Bidirectional synaptic plasticity

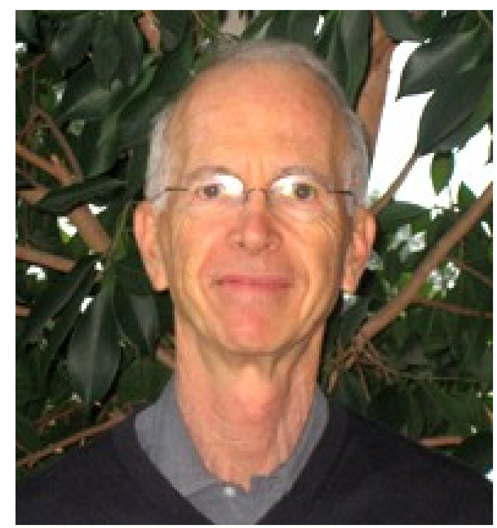


Bidirectional synaptic plasticity



- Developers of COPASI
  - Sven Sahle
  - Stefan Hoops
  - Ursula Kummer
  - Pedro Mendes
- Developers of Scilab
- Annalisa Pastore
- Stephen Martins

Melanie Stefan



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