On Allostery and dose-responses

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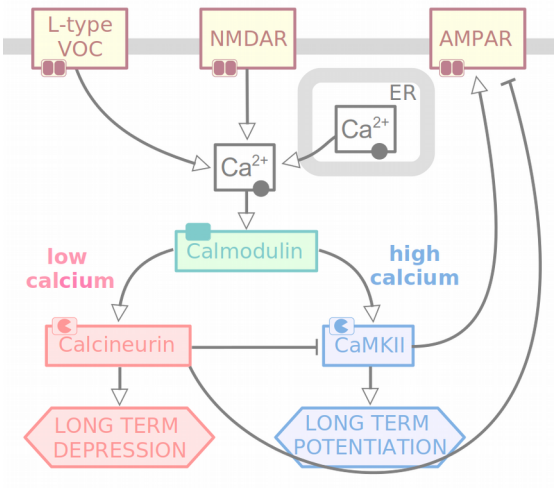
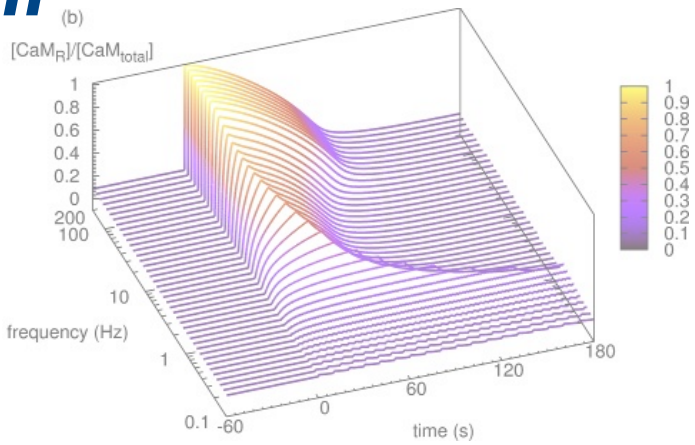
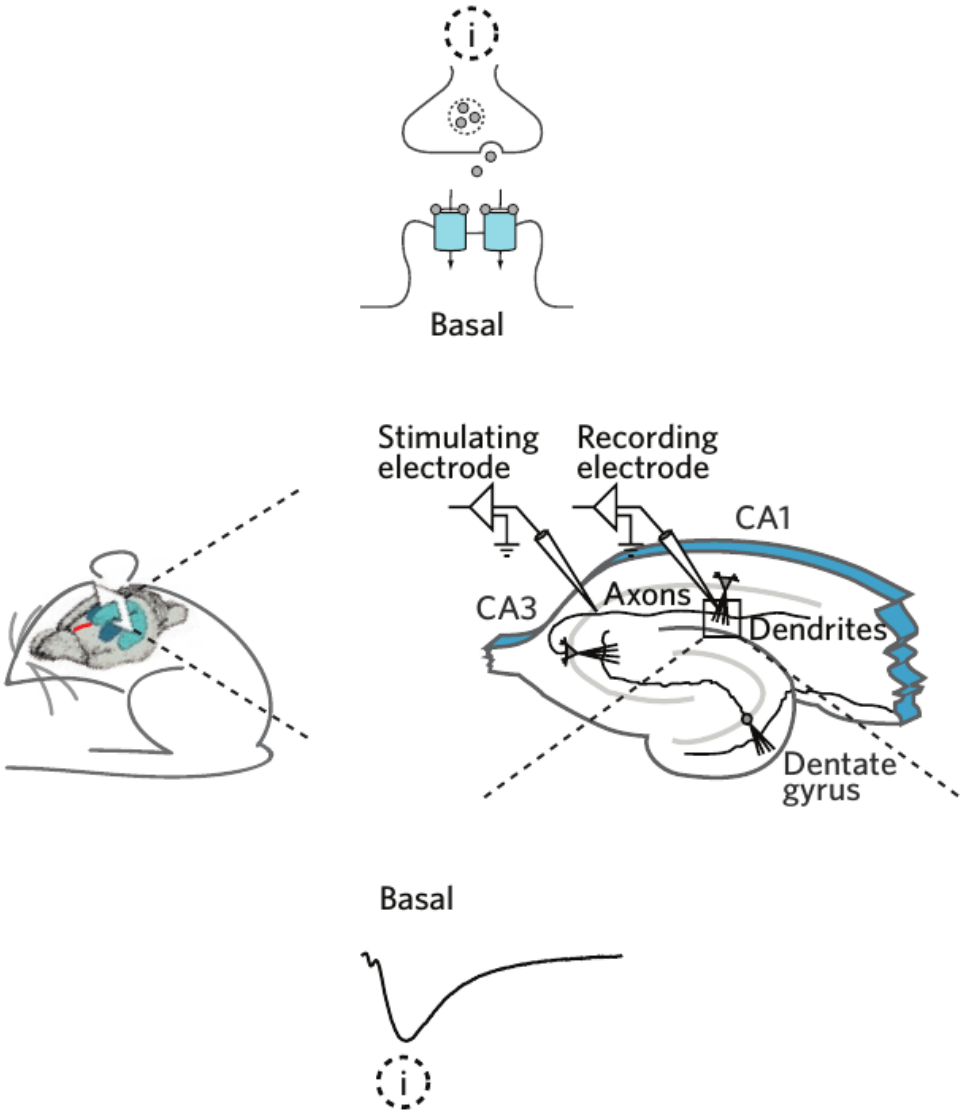
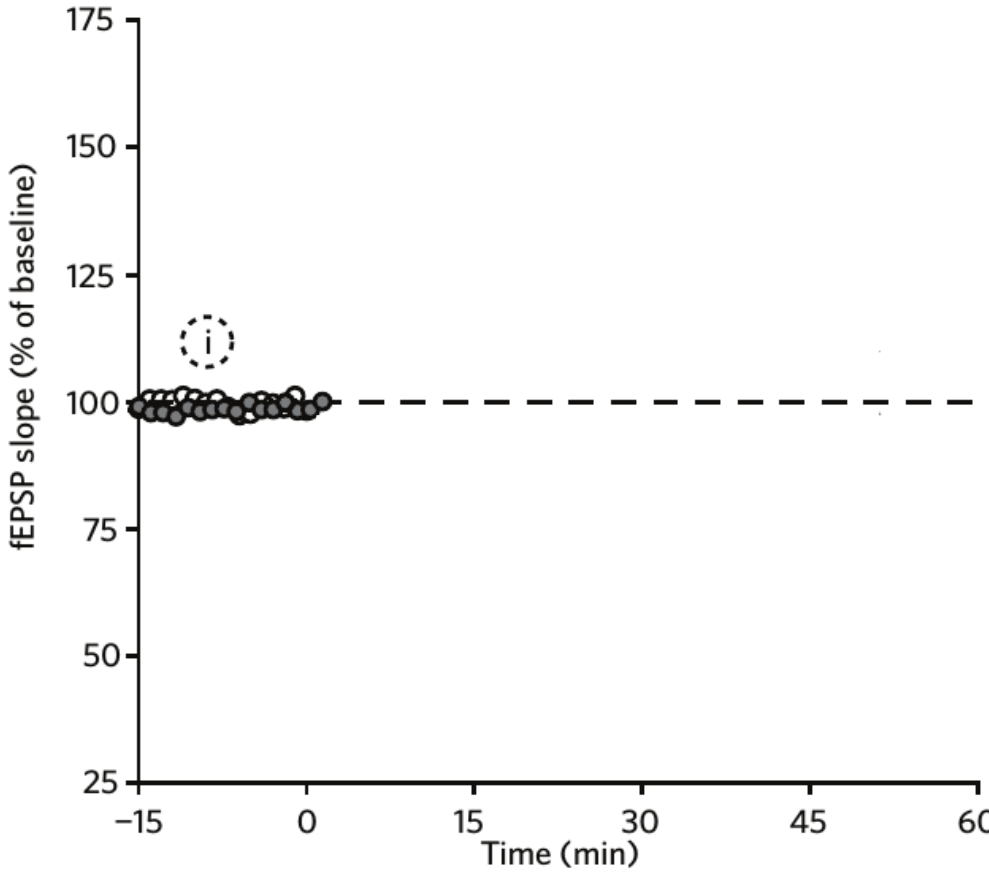
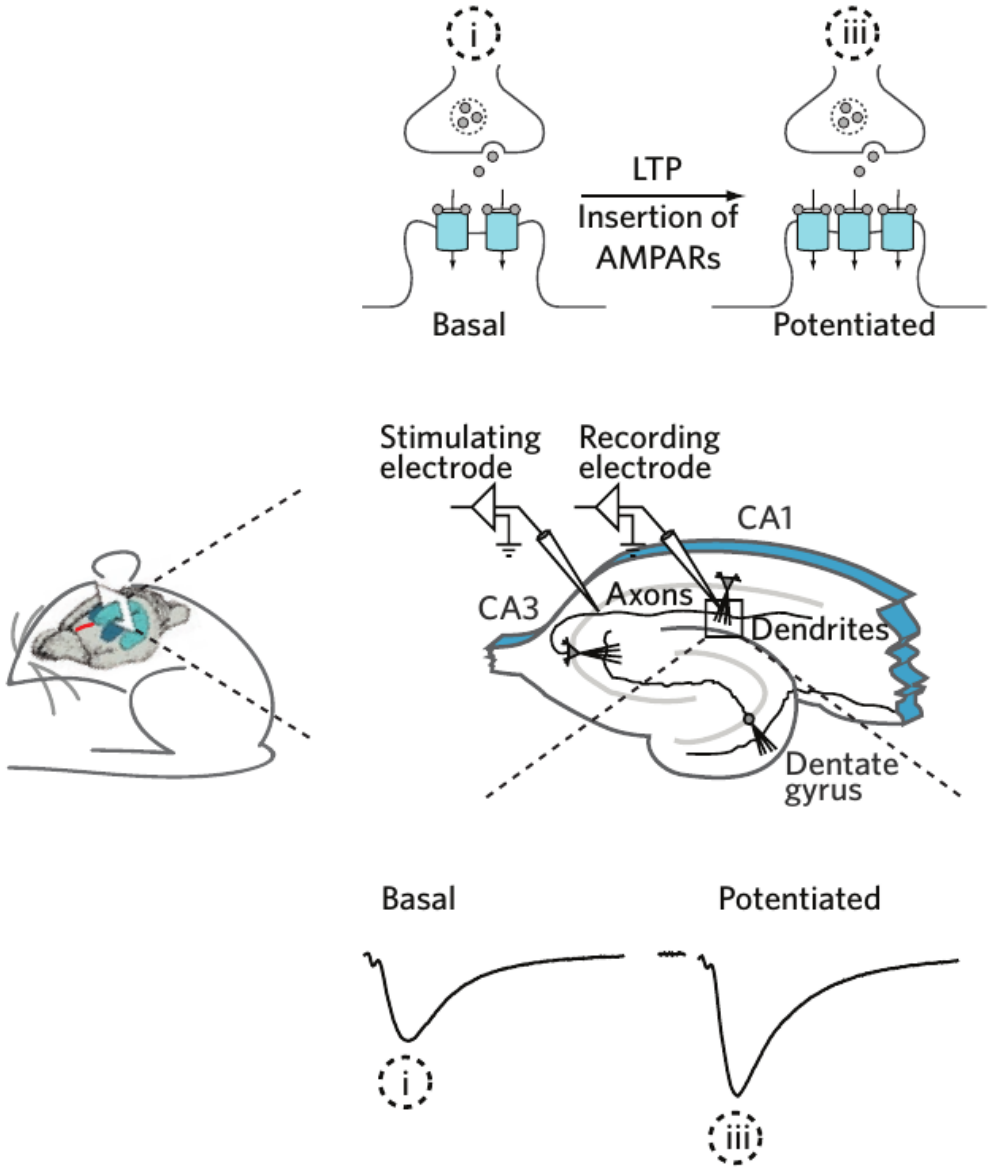


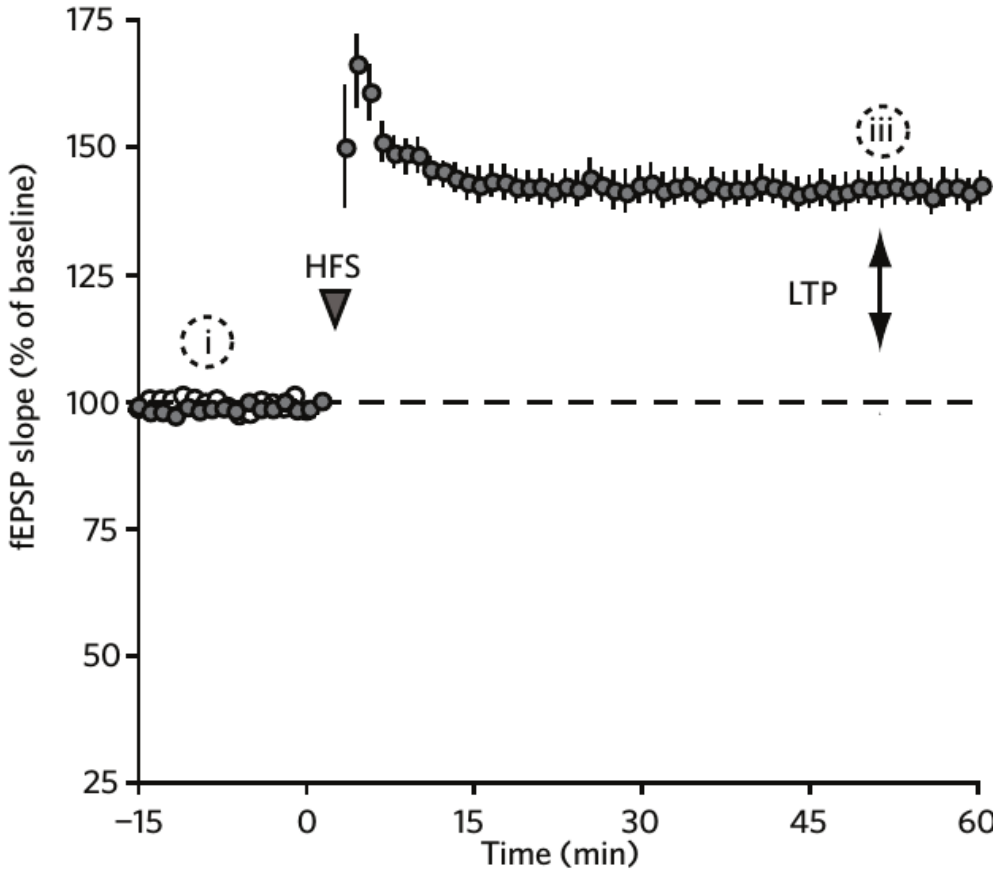




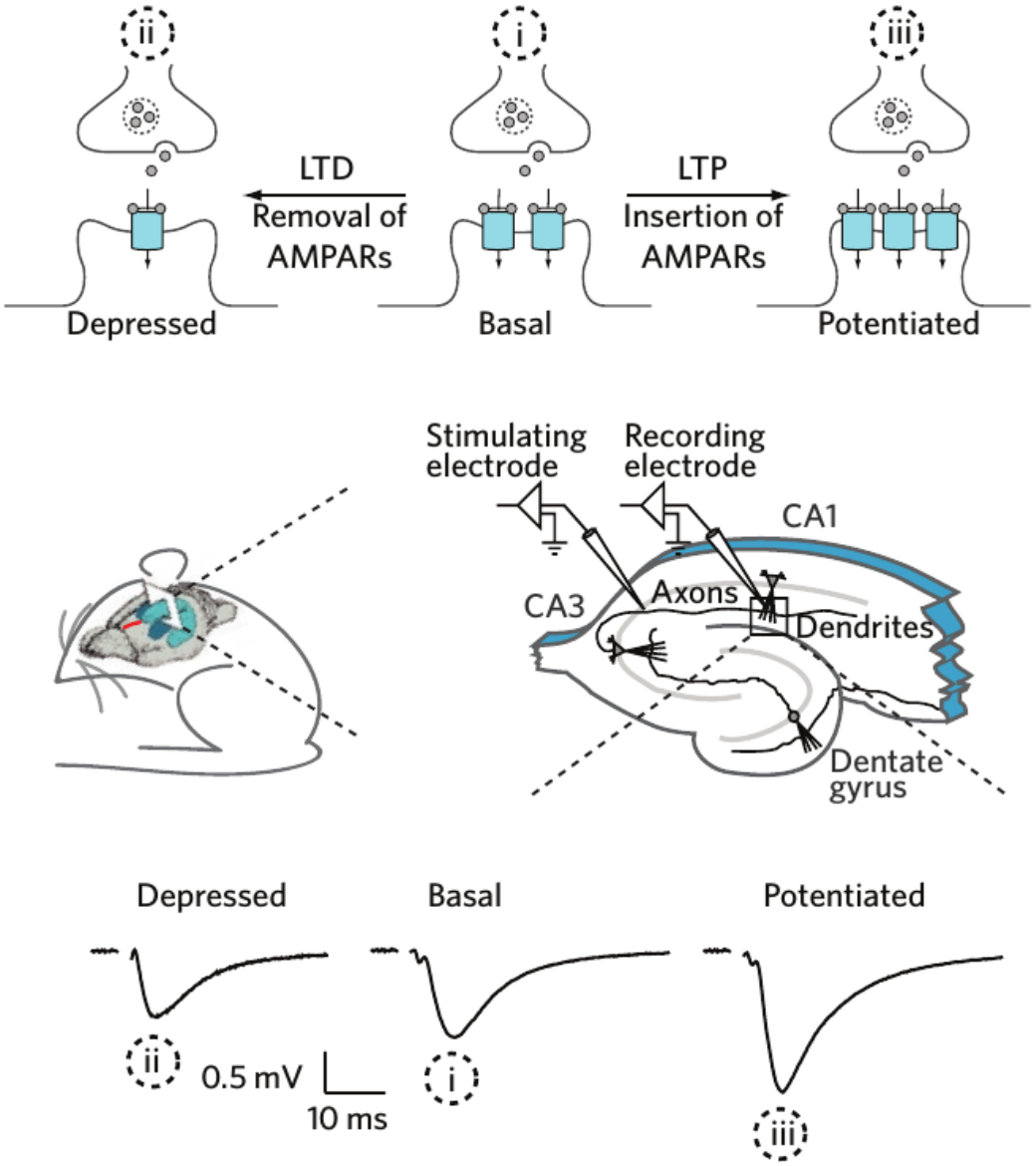


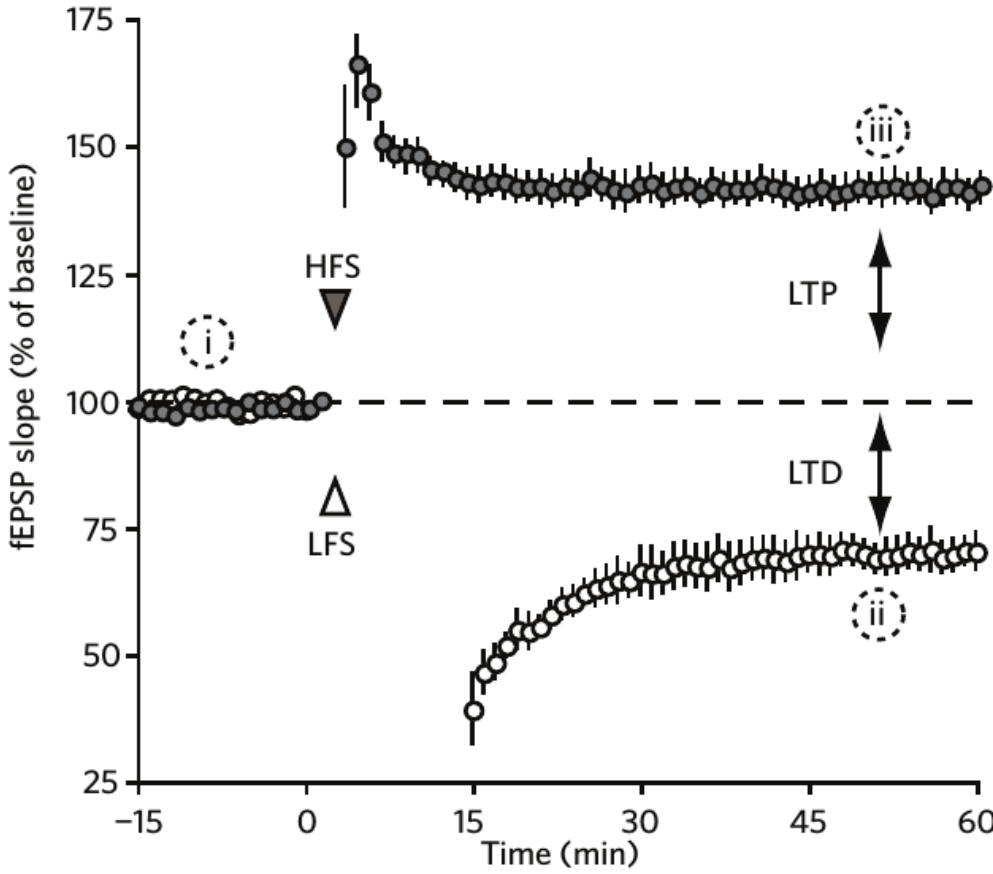
Fleming and England (2010) *Nat Chem Biol*





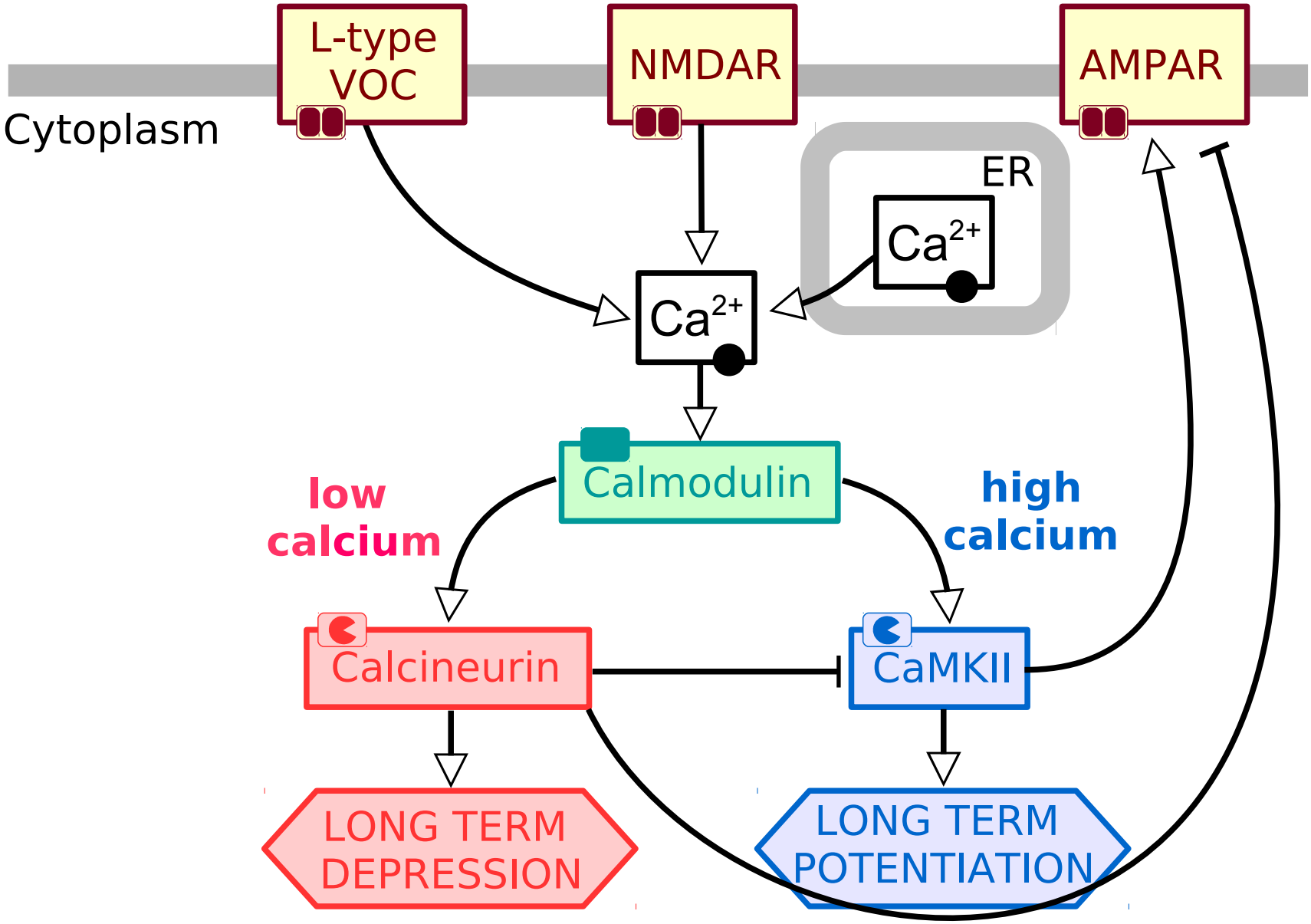
Fleming and England (2010) *Nat Chem Biol*



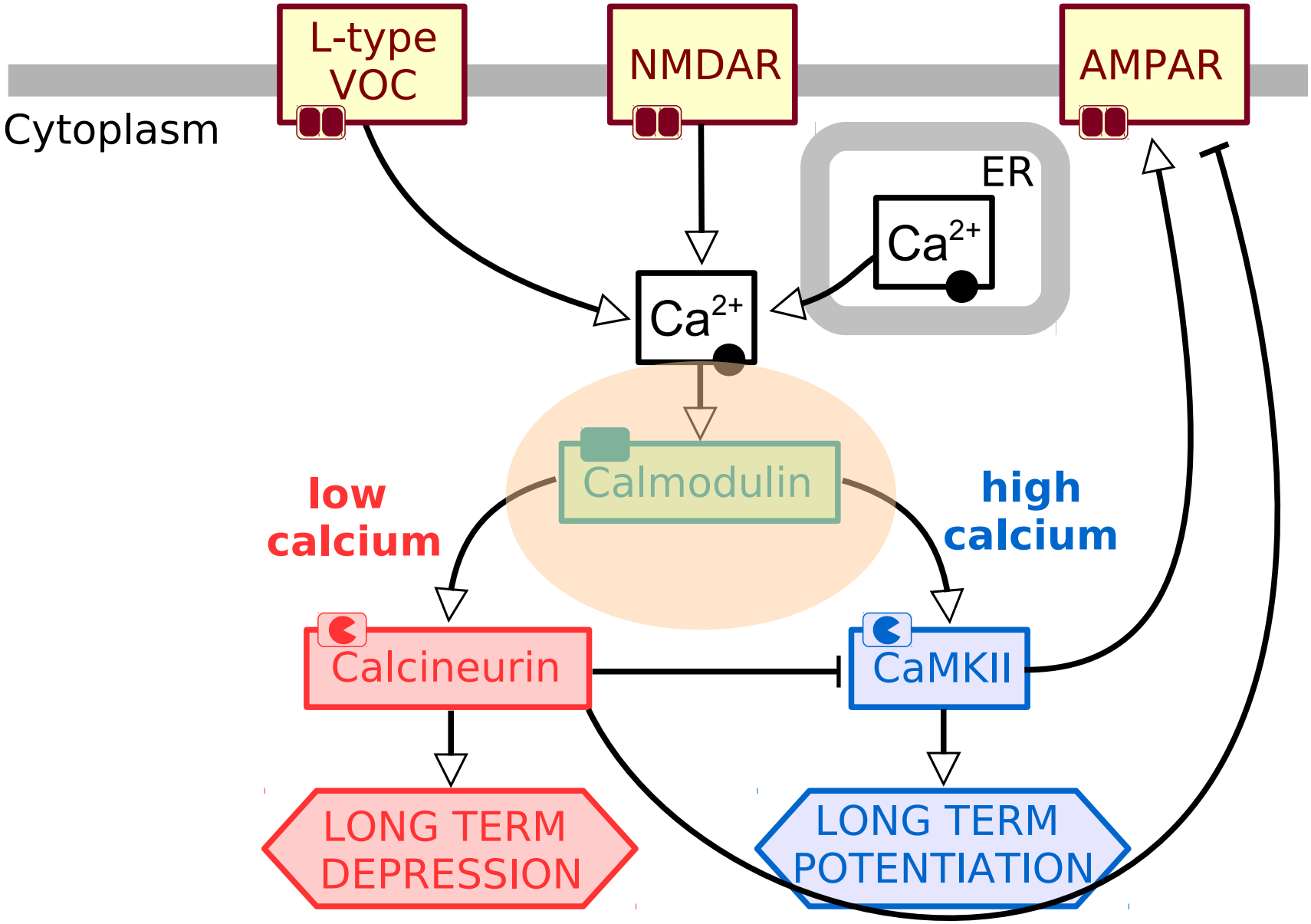


lasts for weeks

Fleming and England (2010) *Nat Chem Biol*

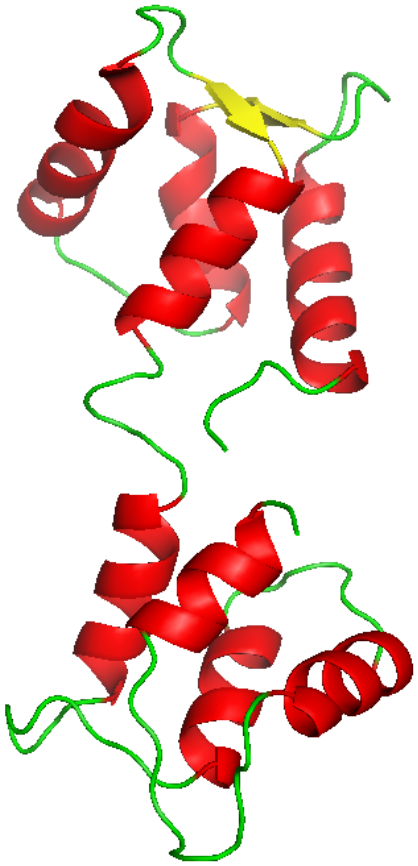


Lisman (1989) *PNAS*



Lisman (1989) *PNAS*

Closed (T)



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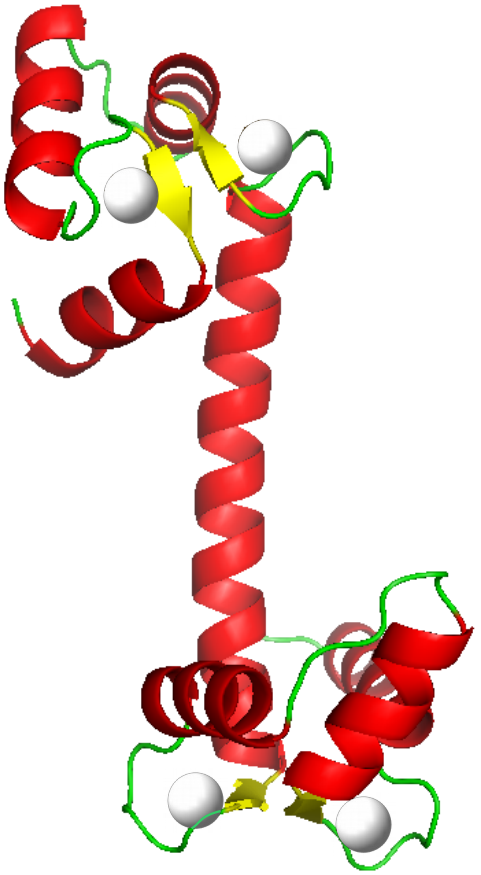
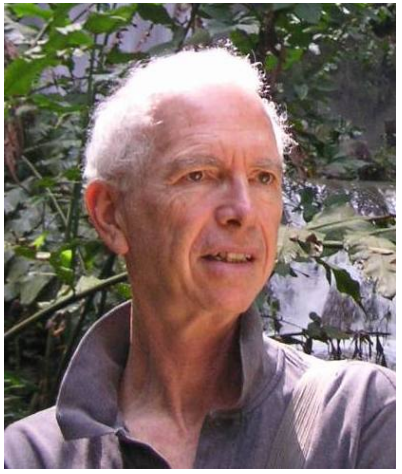
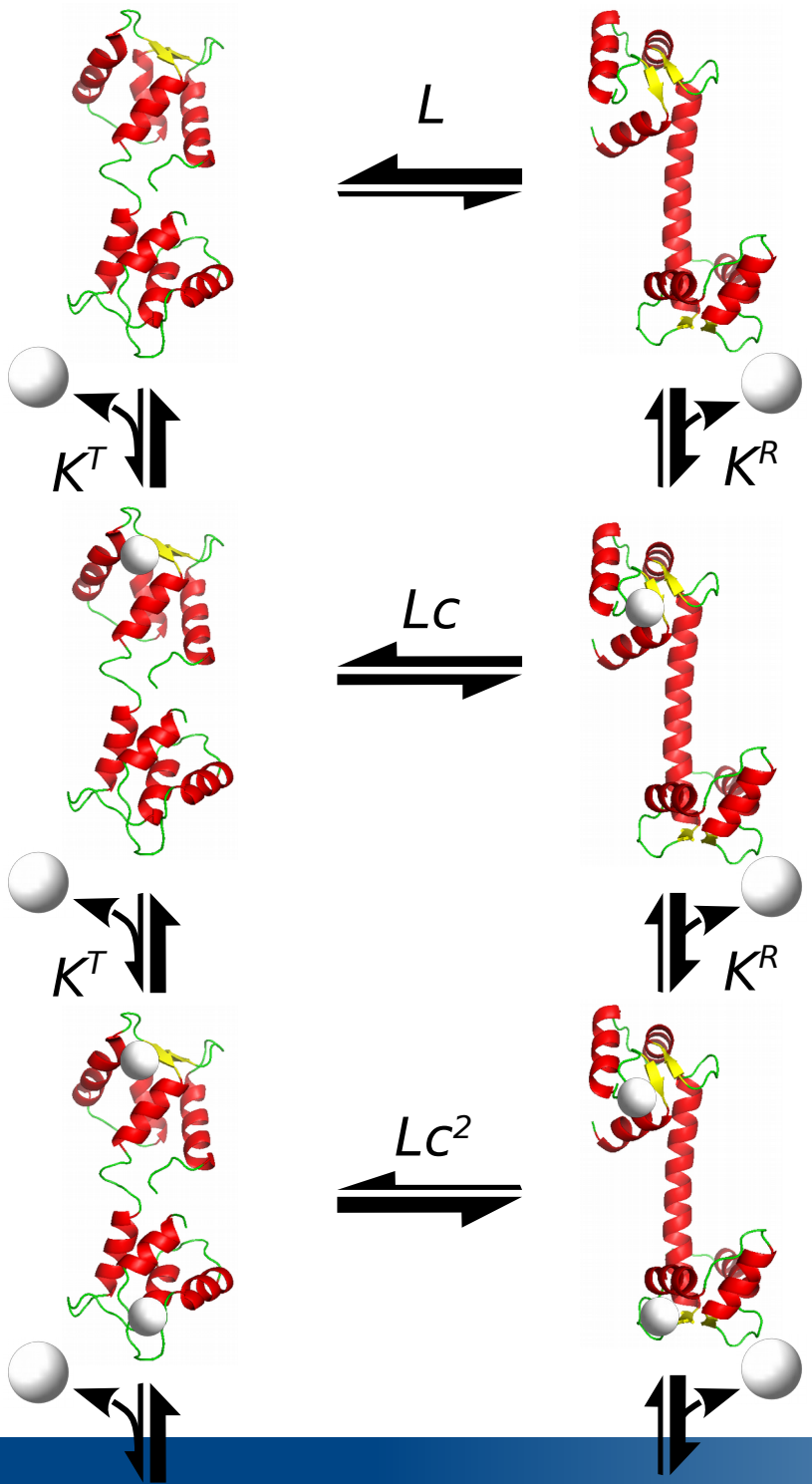


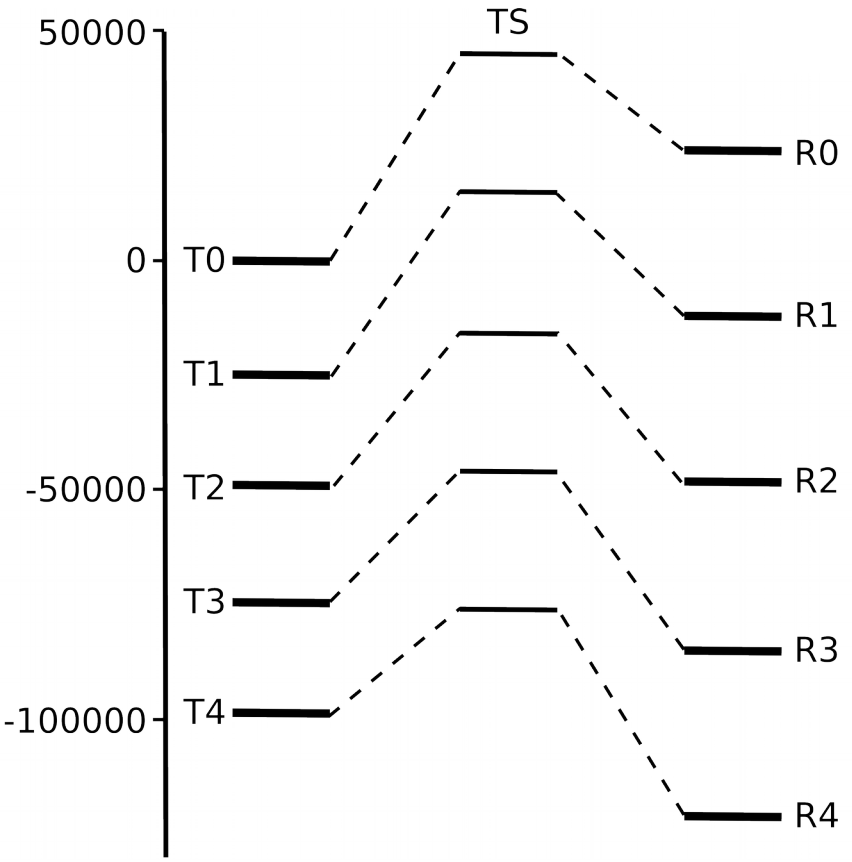
Melanie Stefan

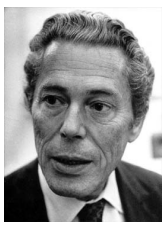


Stuart Edelstein

Stefan MI, Edelstein SJ, Le Novère N (2008)
Stefan MI, Edelstein SJ, Le Novère N (2009)
Edelstein SJ, Stefan MI, Le Novère N (2010)







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

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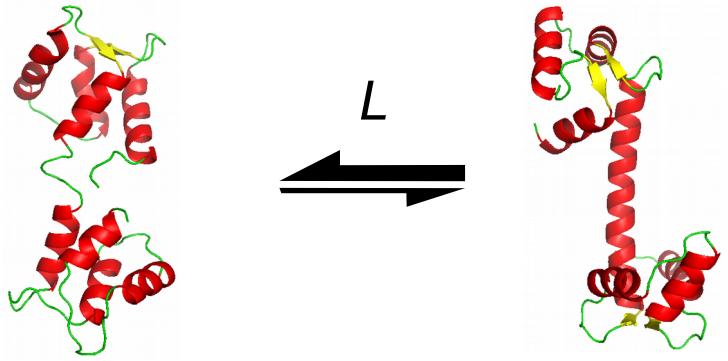
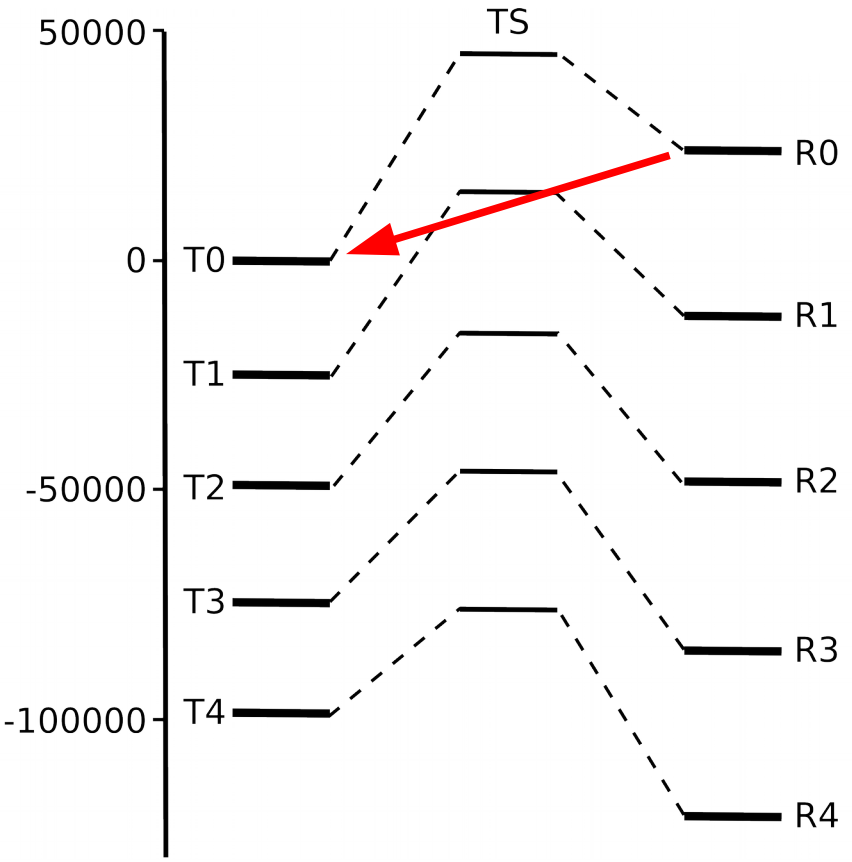

L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0
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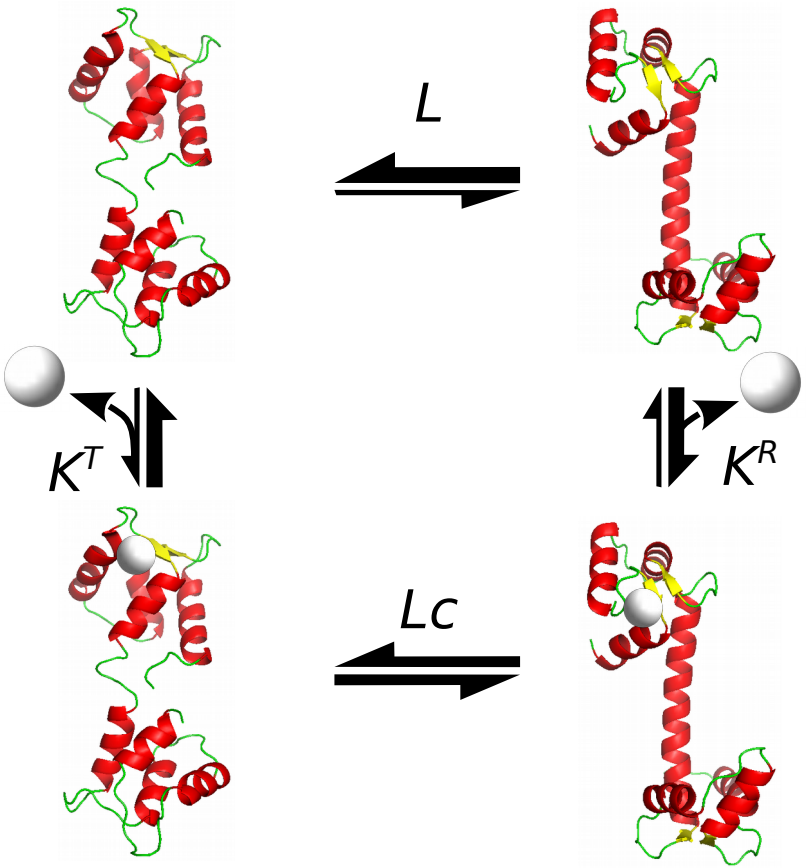
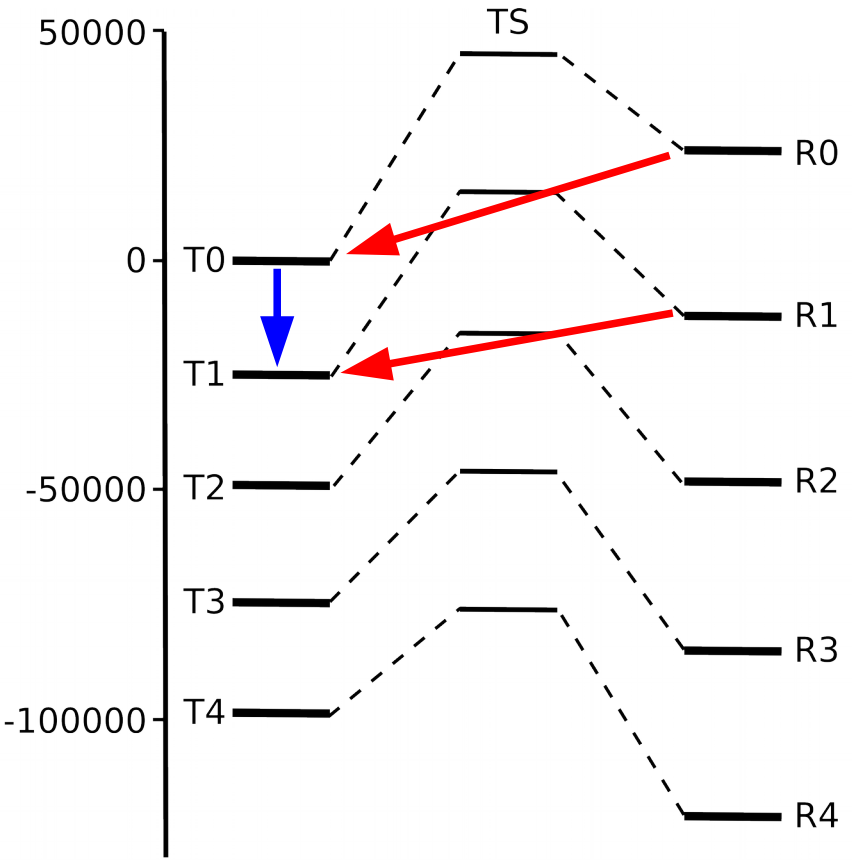
TS
T0
T1
T2
T3
T4
R0
R1
R2
R3
R4


L
K^T
K^R
Lc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0
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T0
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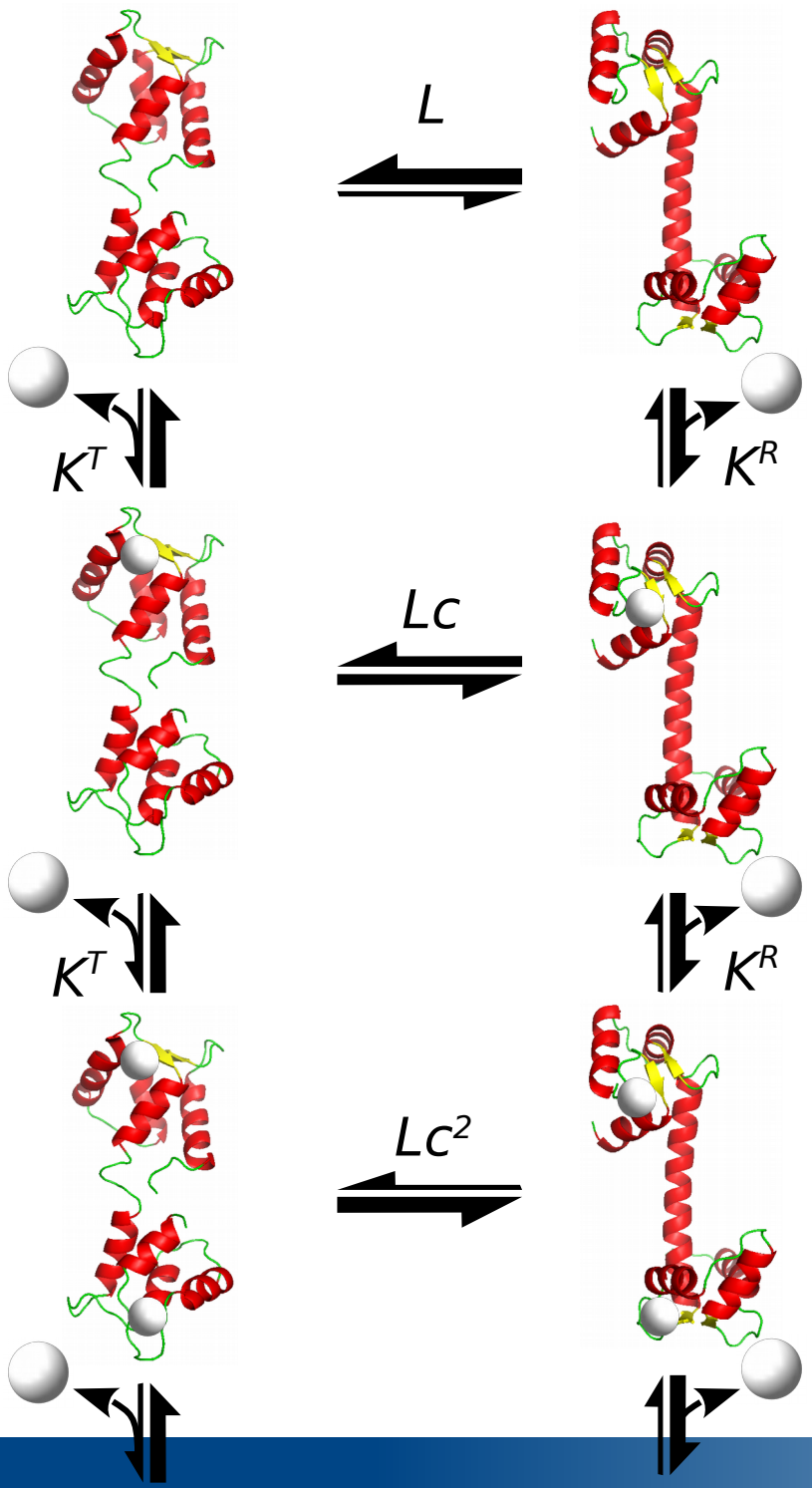
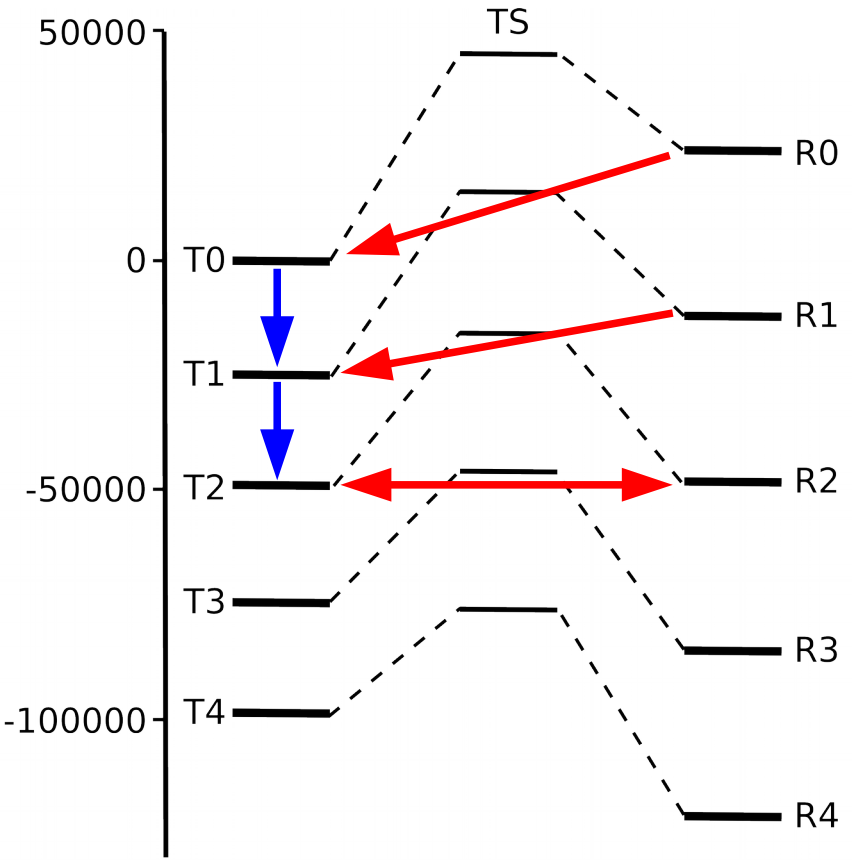
T2
T3
T4
R0
R1
R2
R3
R4





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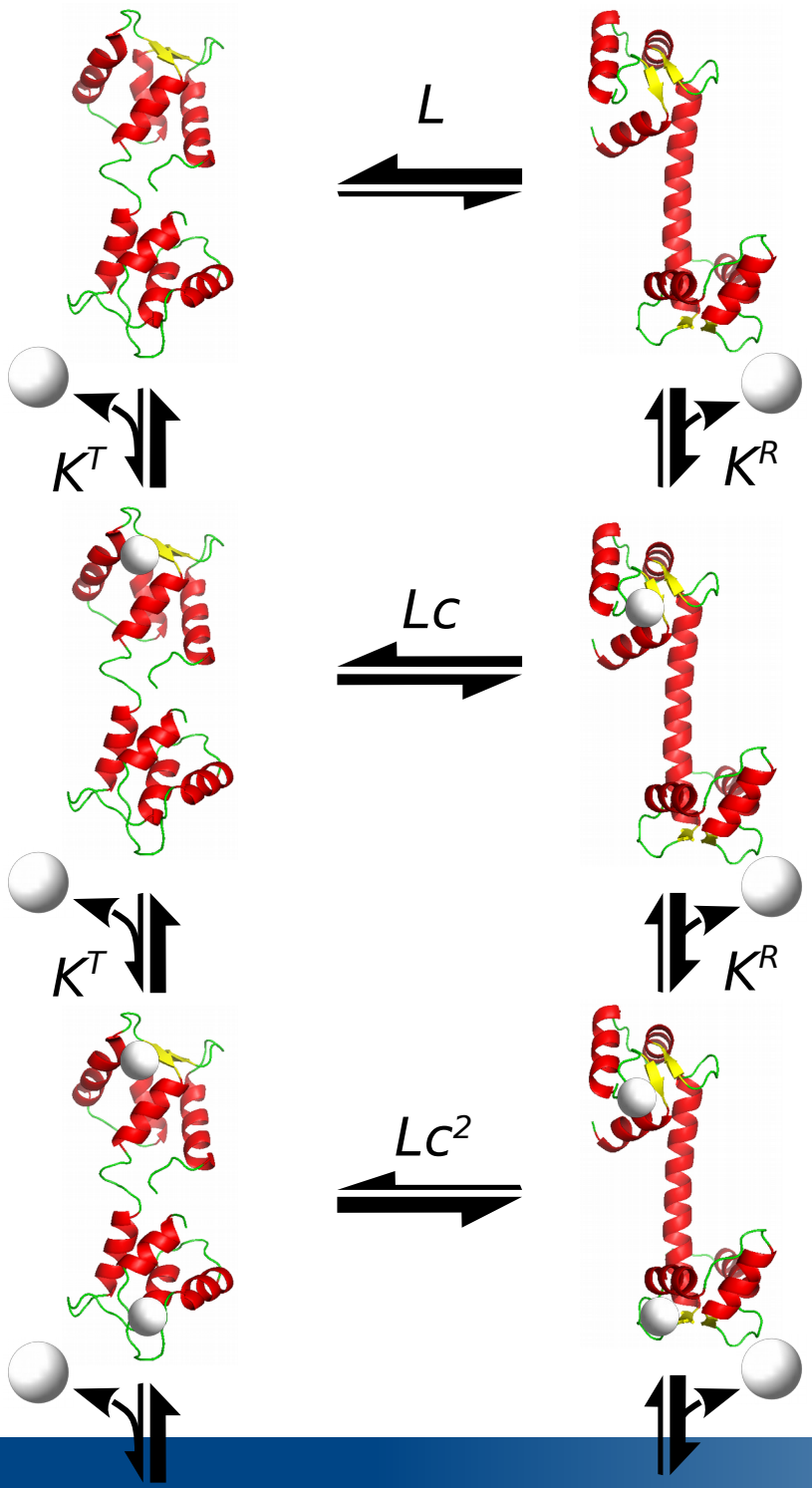

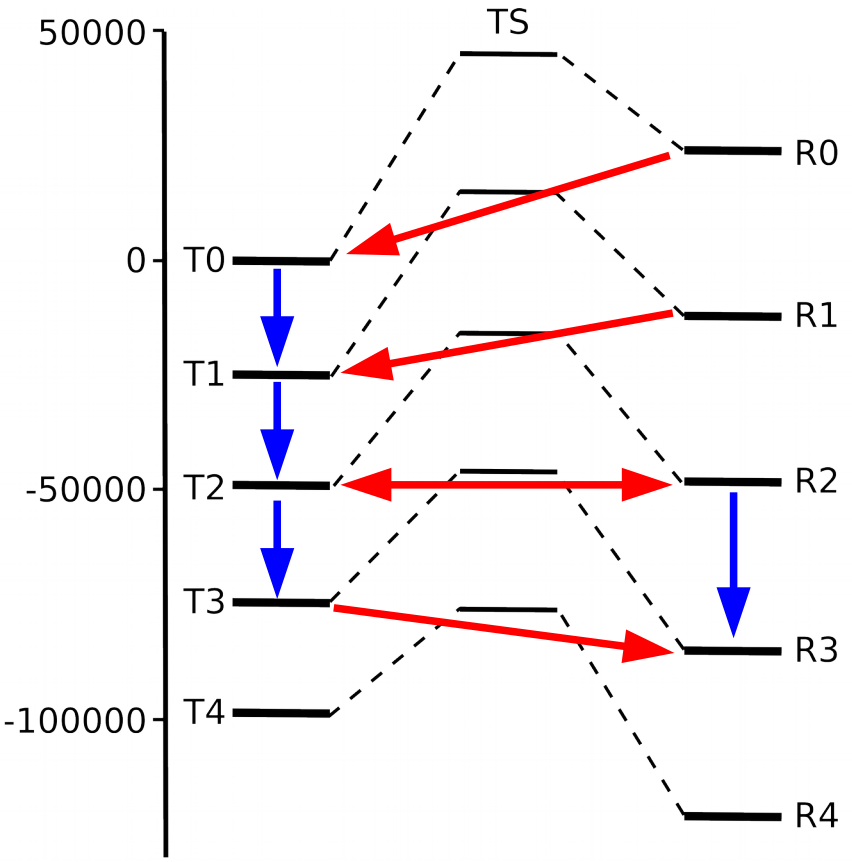

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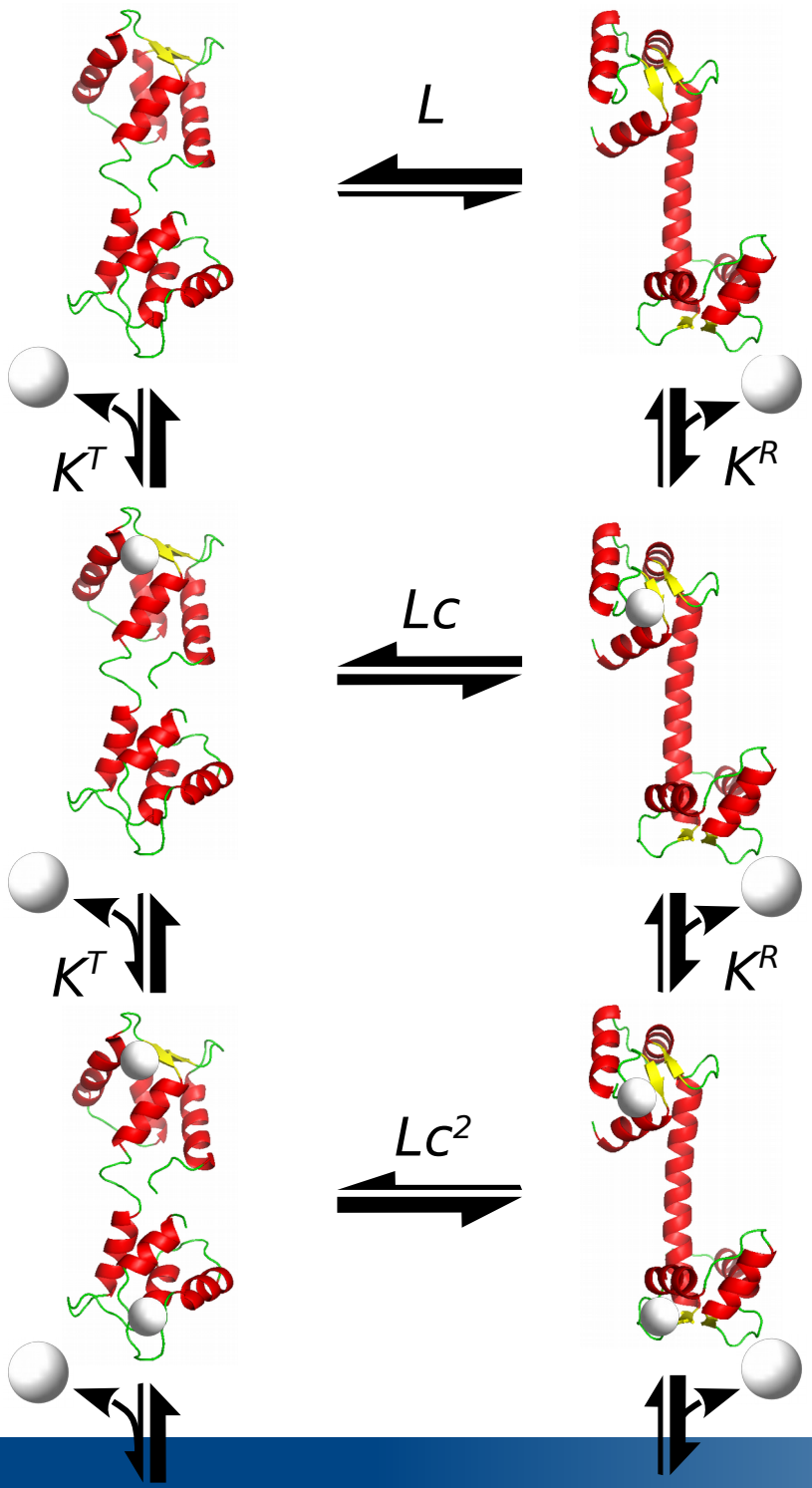
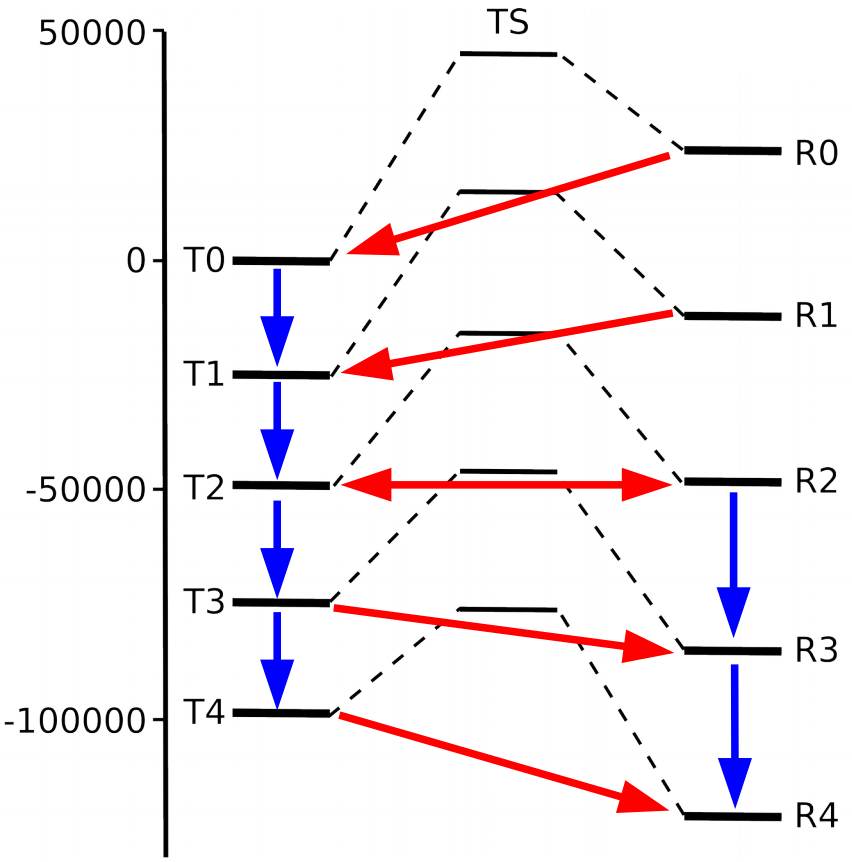
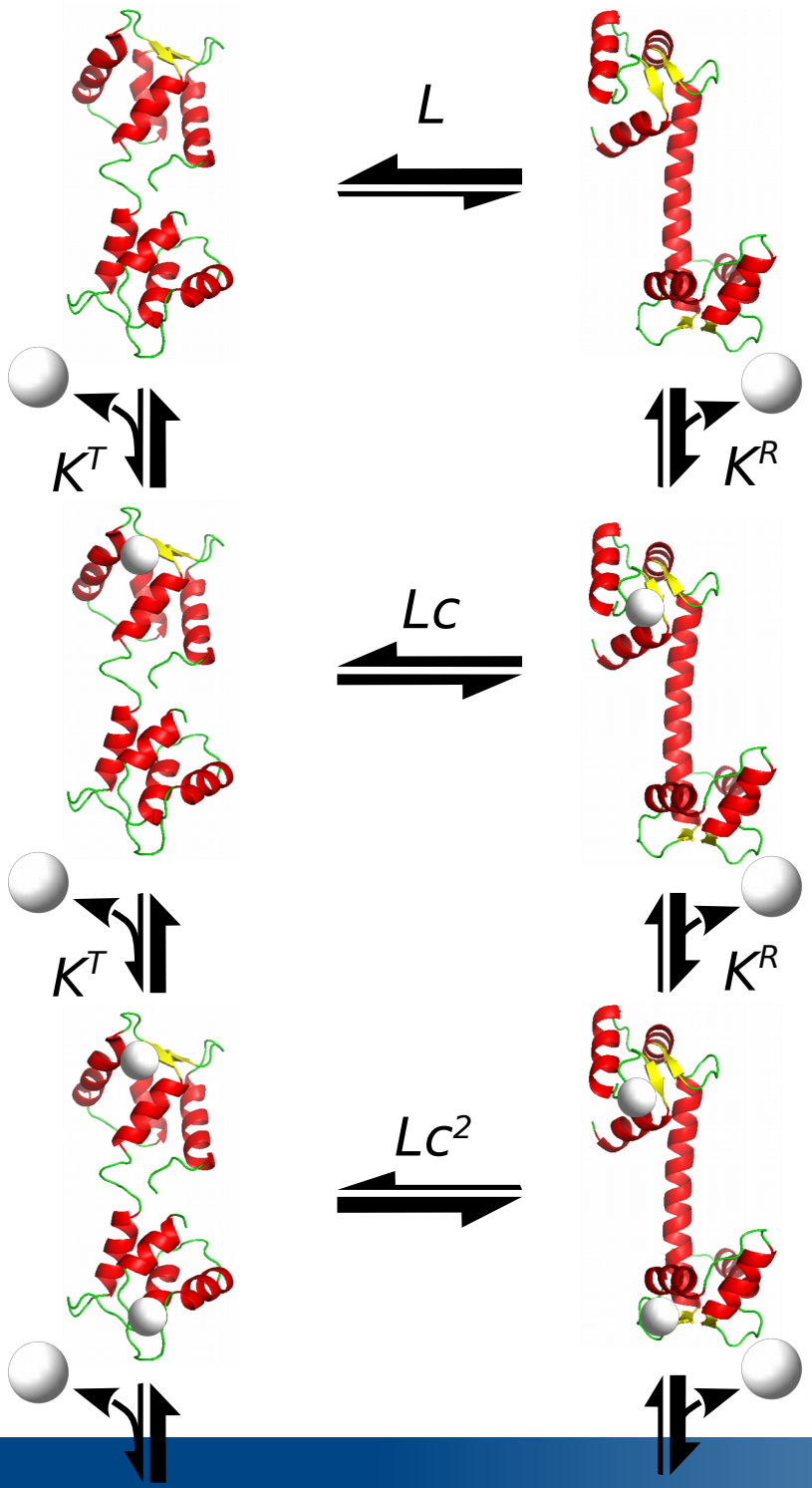






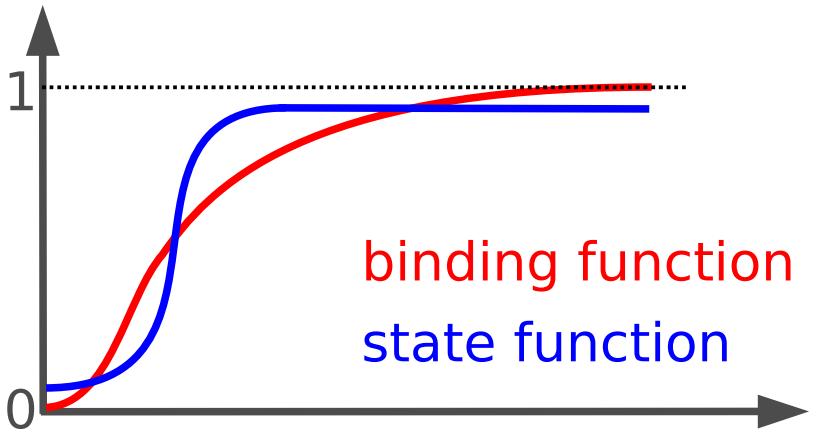
$$\bar{Y} = \frac{\alpha(1+\alpha)^{n-1} + Lc\alpha(1+c\alpha)^{n-1}}{(1+\alpha)^n + L(1+c\alpha)^n}$$

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

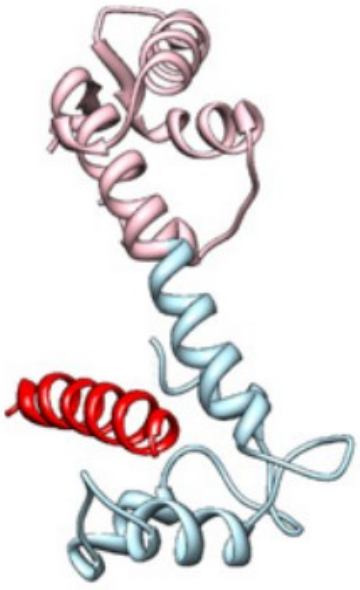
$$L = \frac{[T_0]}{[R_0]} \quad c = \frac{K^R}{K^T} \quad \alpha = \frac{[Ca^{2+}]}{[K^R]}$$

$L \gg 1 \Rightarrow$ Equilibrium strongly biased

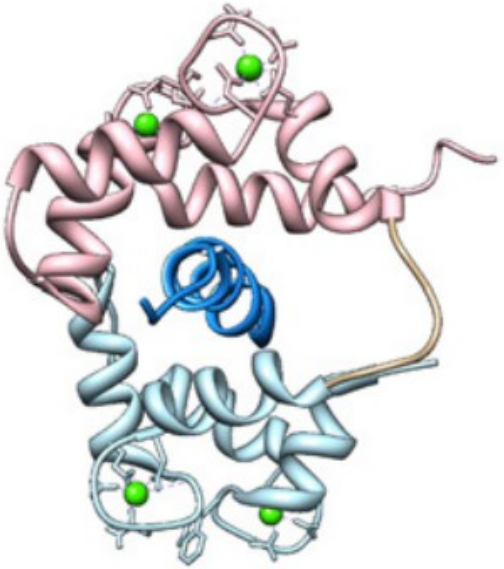
$c \ll 1 \Rightarrow$ strong effect of ligand



Different targets stabilise CaM in different states

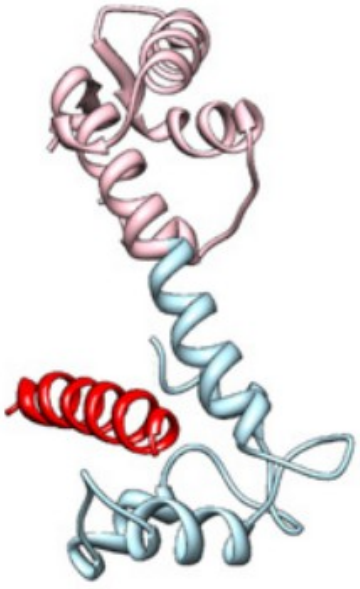


Neurogranin

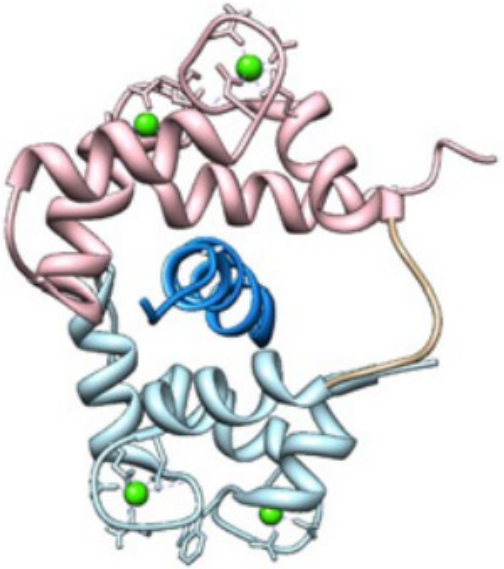


MLCK

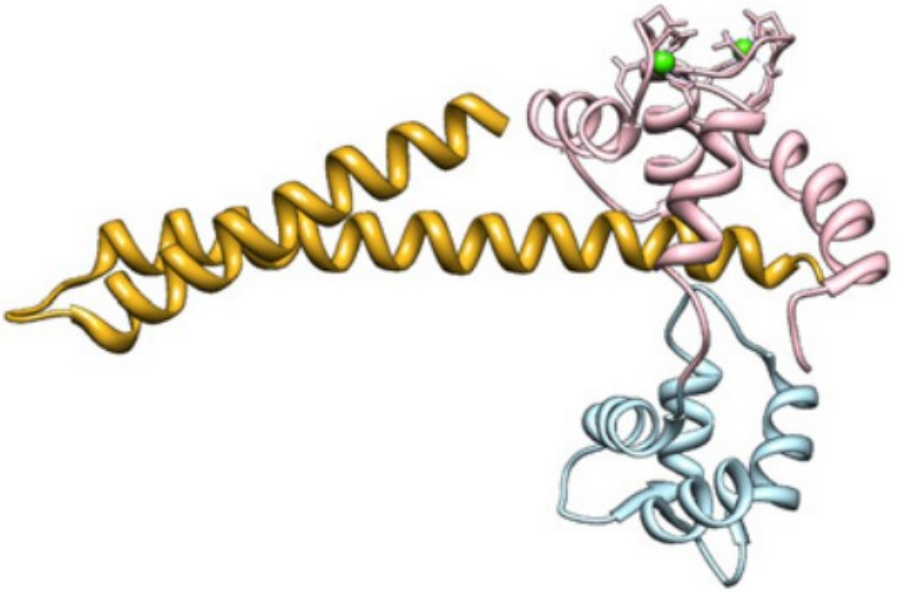
Different targets stabilise lobes in different states



Neurogranin



MLCK



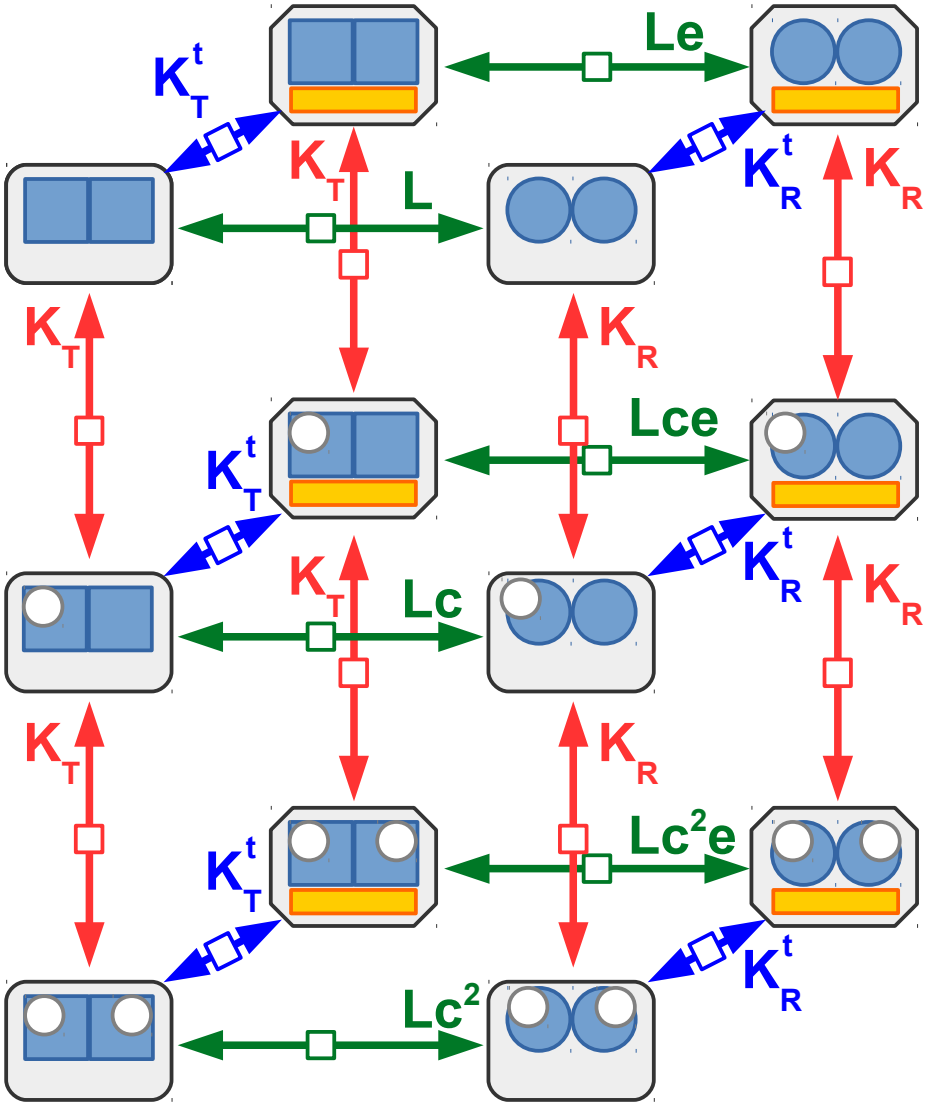
SK channel

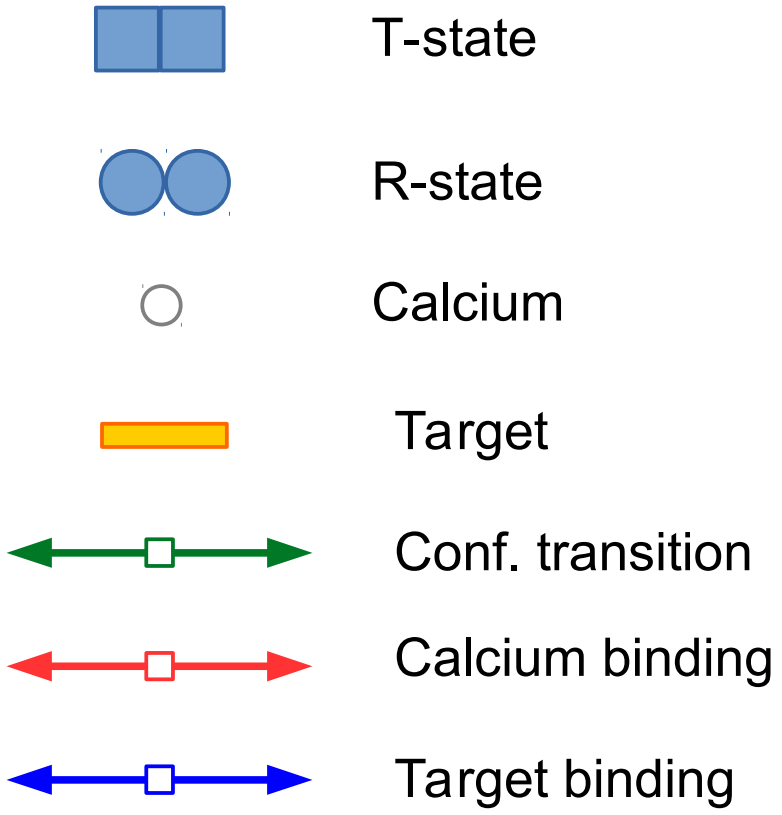
Massimo Lai

Denis Brun

Lai M, Brun D, Edelstein SJ, Le Novère N (2015)

Bindings of calcium and targets (one lobe)

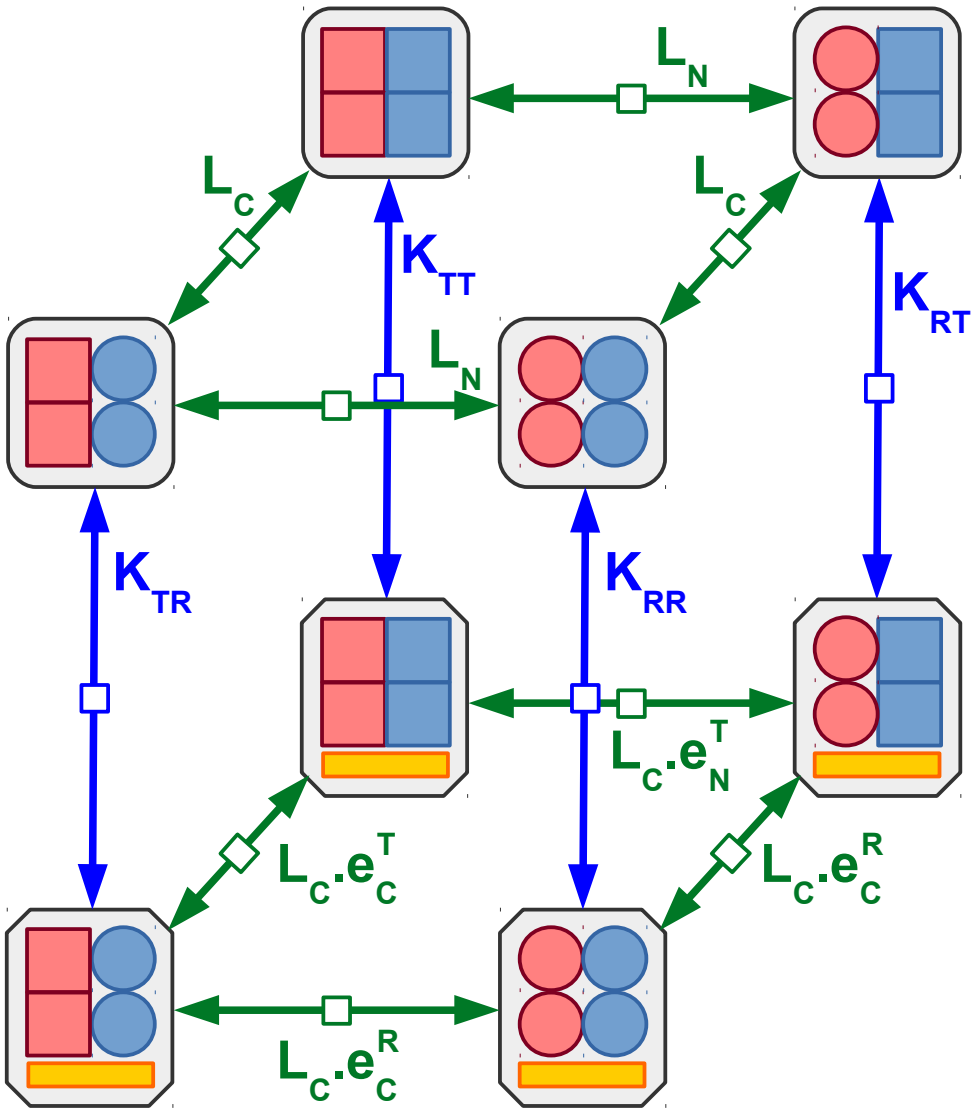


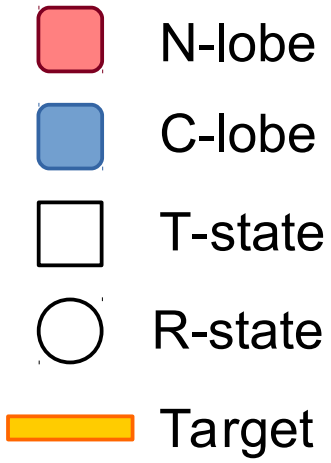


$$c = \frac{K_R}{K_T}$$

$$e = \frac{K_R^t}{K_T^t}$$

Hemiconcerted model of calmodulin



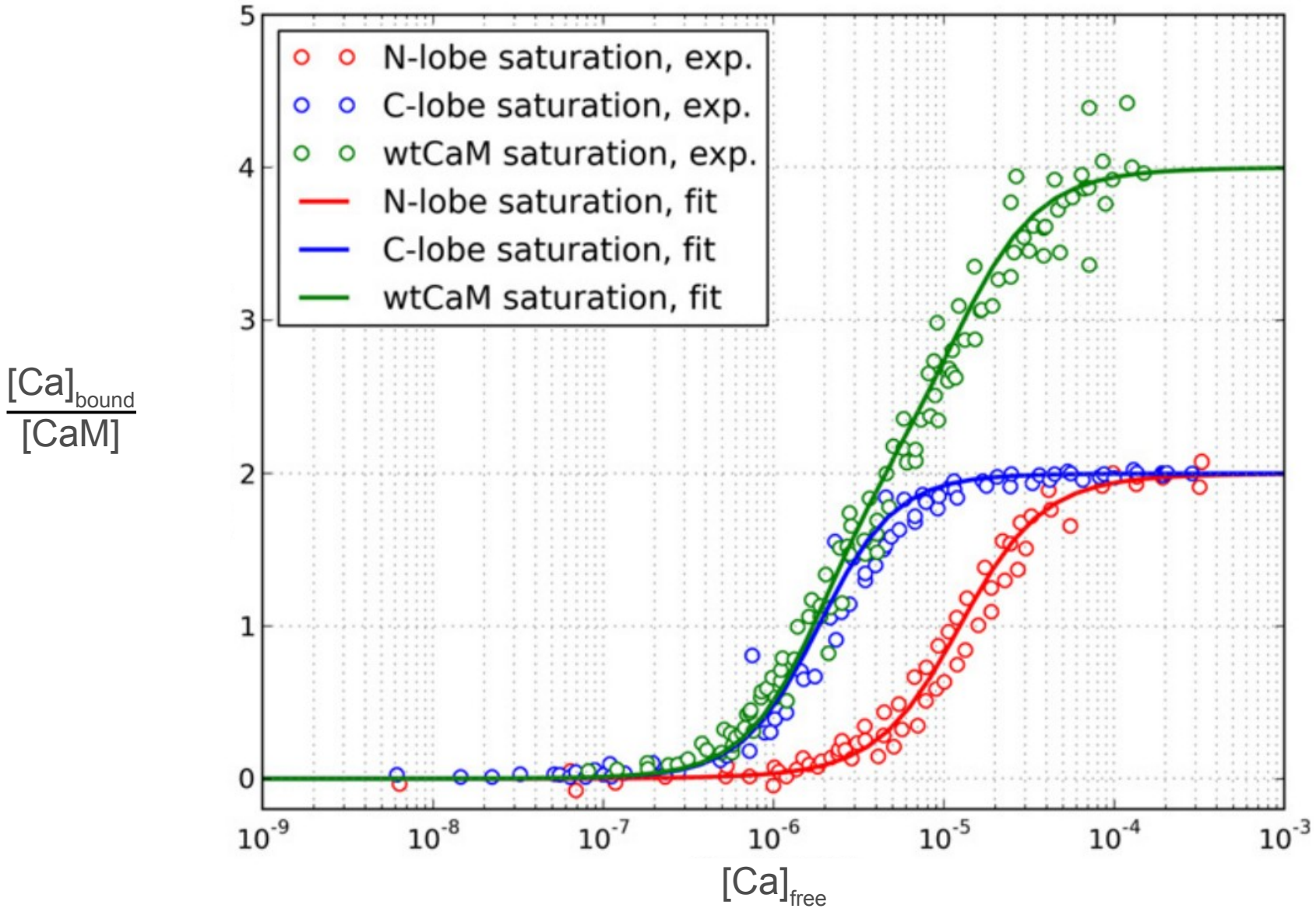


$$L_N = \frac{[TT]}{[RT]} = \frac{[TR]}{[RR]} \qquad L_C = \frac{[TT]}{[TR]} = \frac{[RT]}{[RR]}$$

$$e_N^R = \frac{K_{RR}}{K_{TR}} \qquad e_C^R = \frac{K_{RR}}{K_{RT}}$$

$$e_N^T = \frac{K_{RT}}{K_{TT}} \qquad e_C^T = \frac{K_{TR}}{K_{TT}}$$

Calcium binding to lobes and whole CaM



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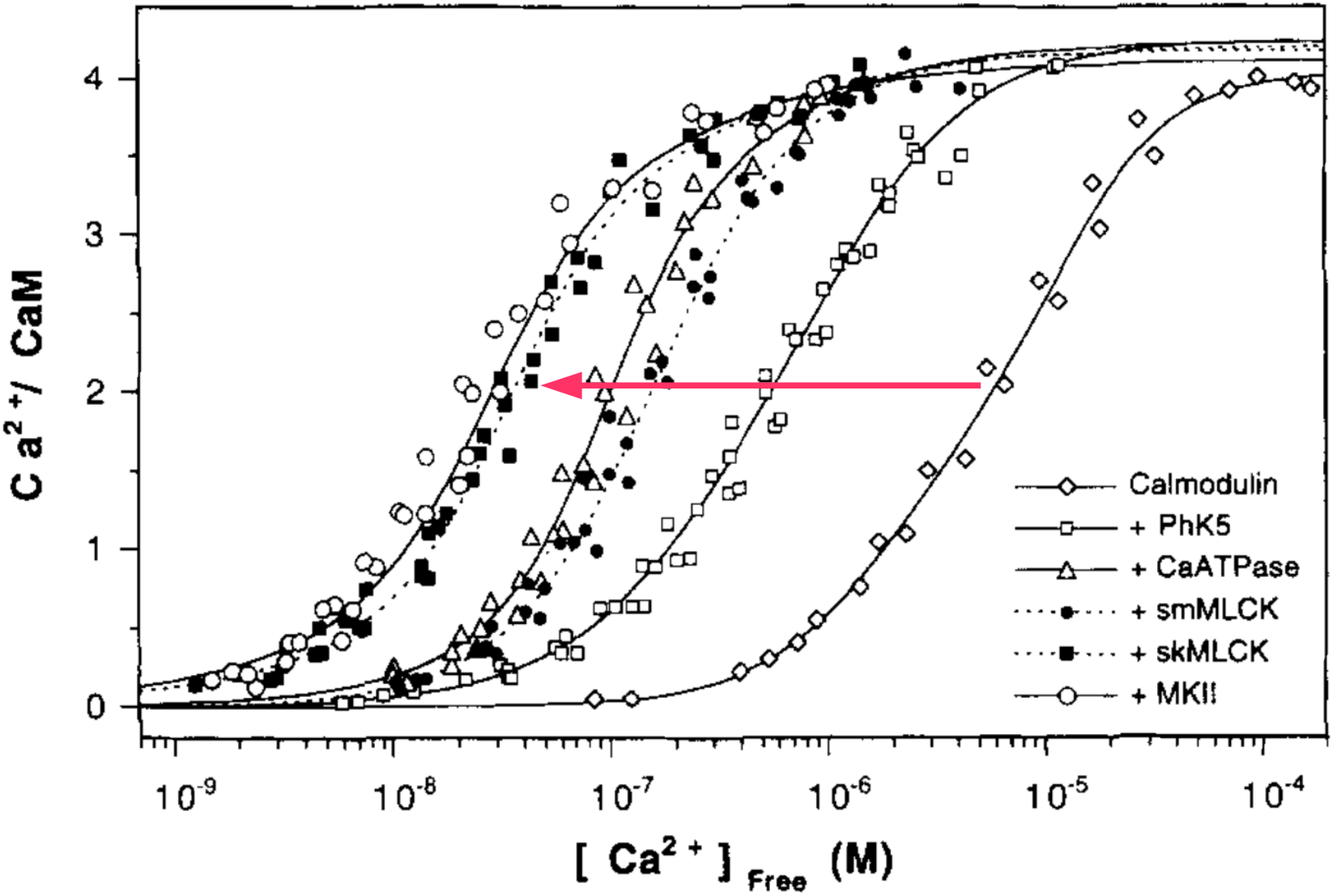
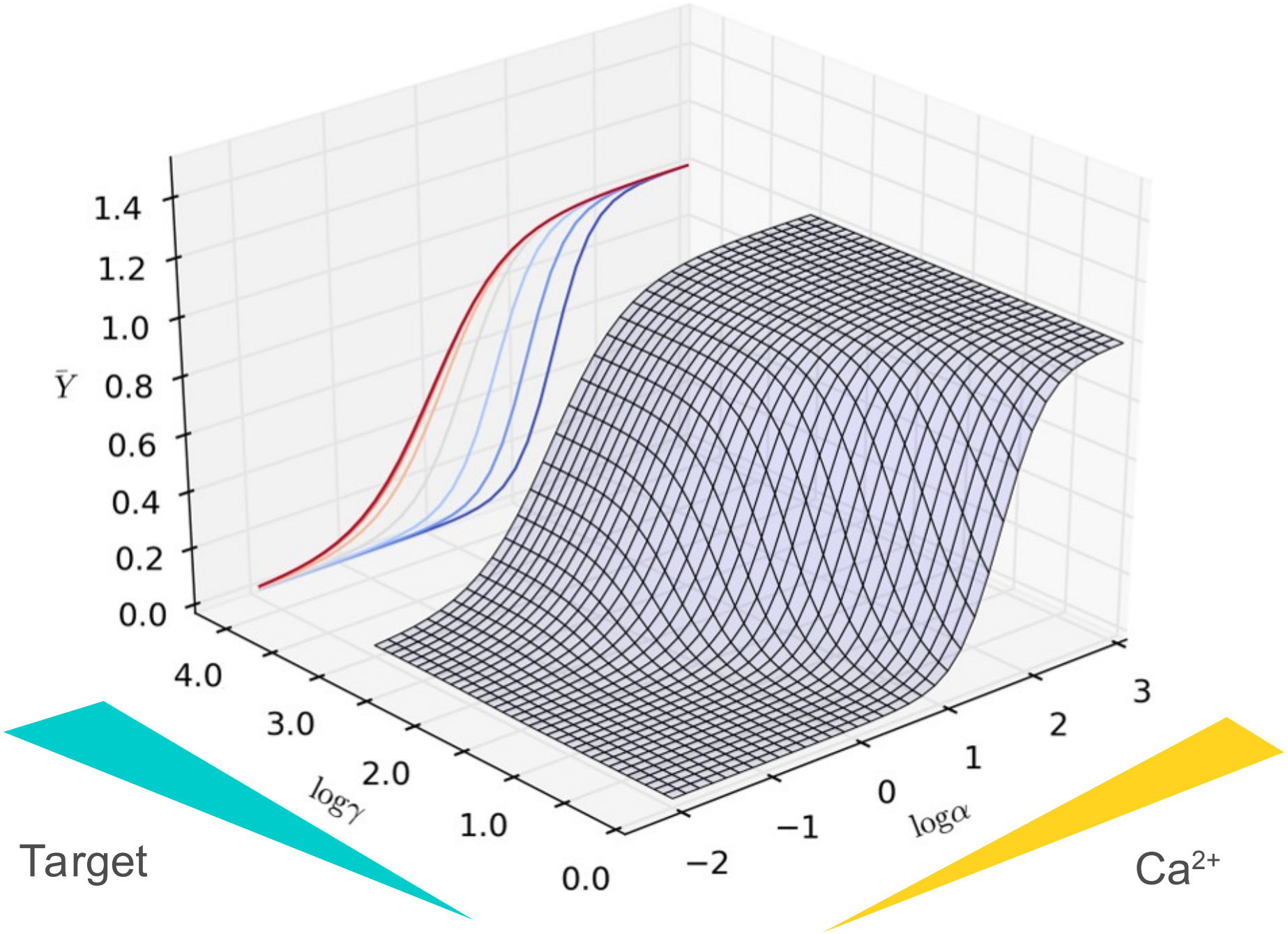
Targets are allosteric effectors



Peersen et al. (1997)



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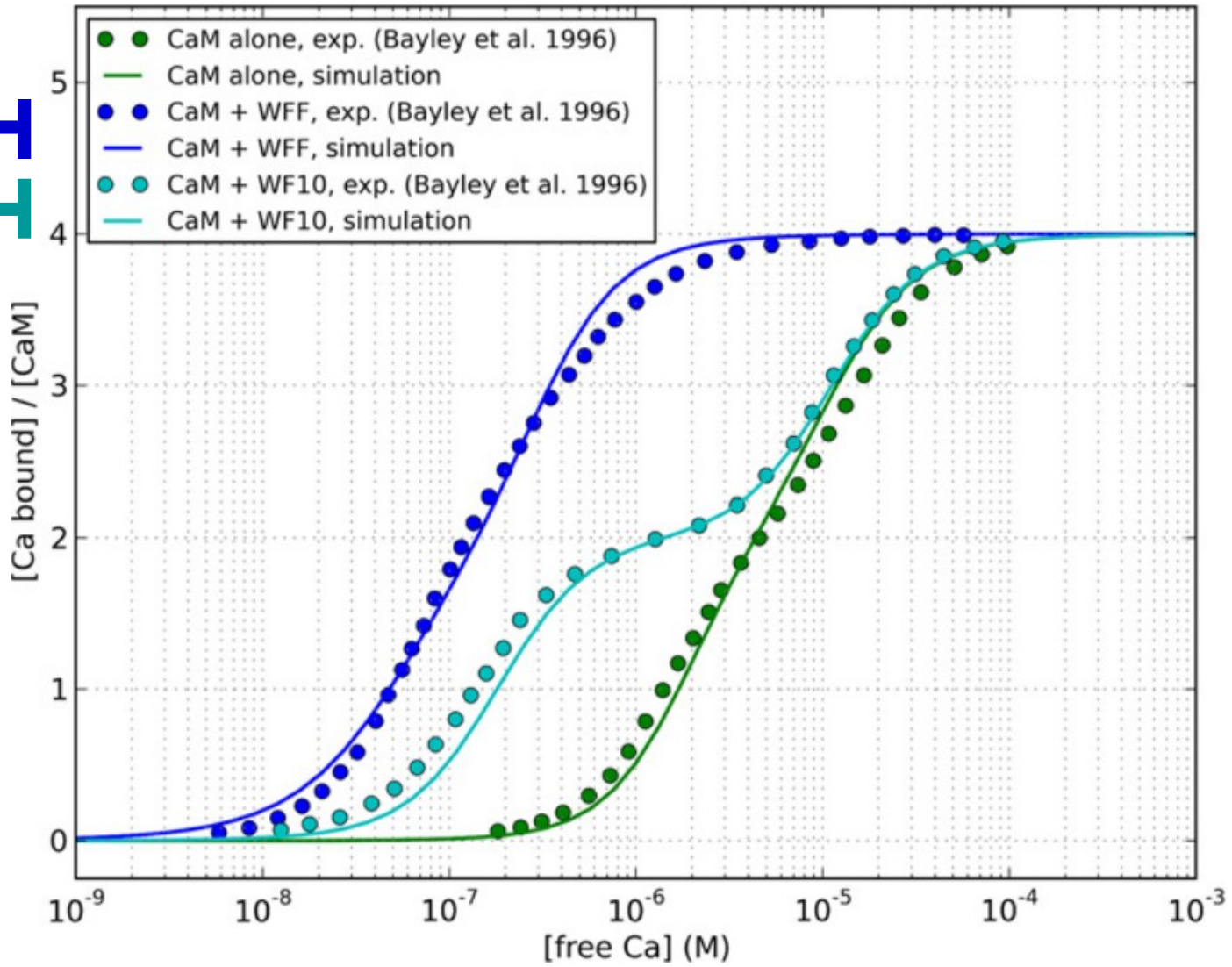
Stabilise R state of both lobes

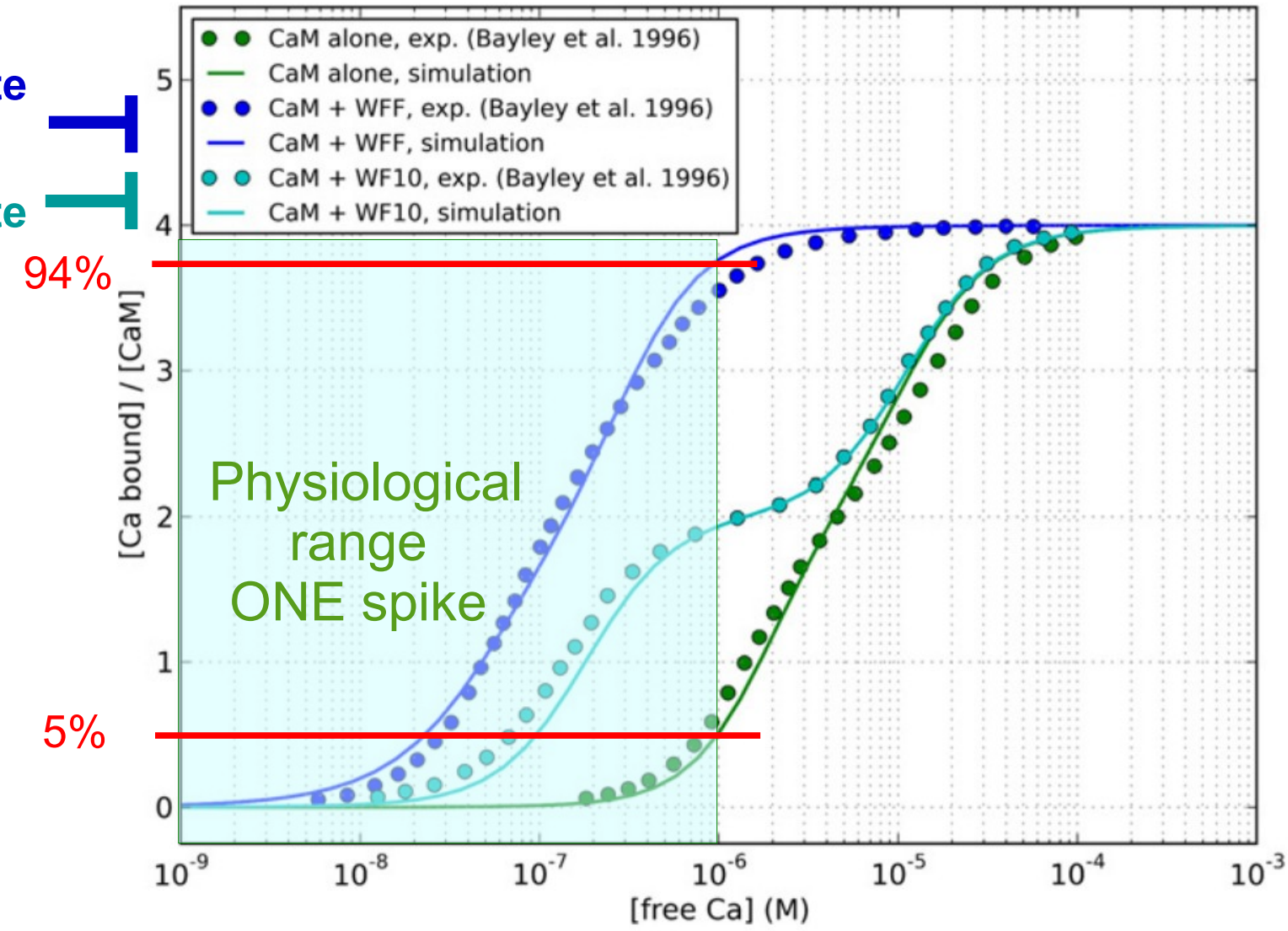
Stabilise R state of C lobe



Targets move Ca^{2+} binding into physiological range

Stabilise R state of both lobes

Stabilise R state of C lobe



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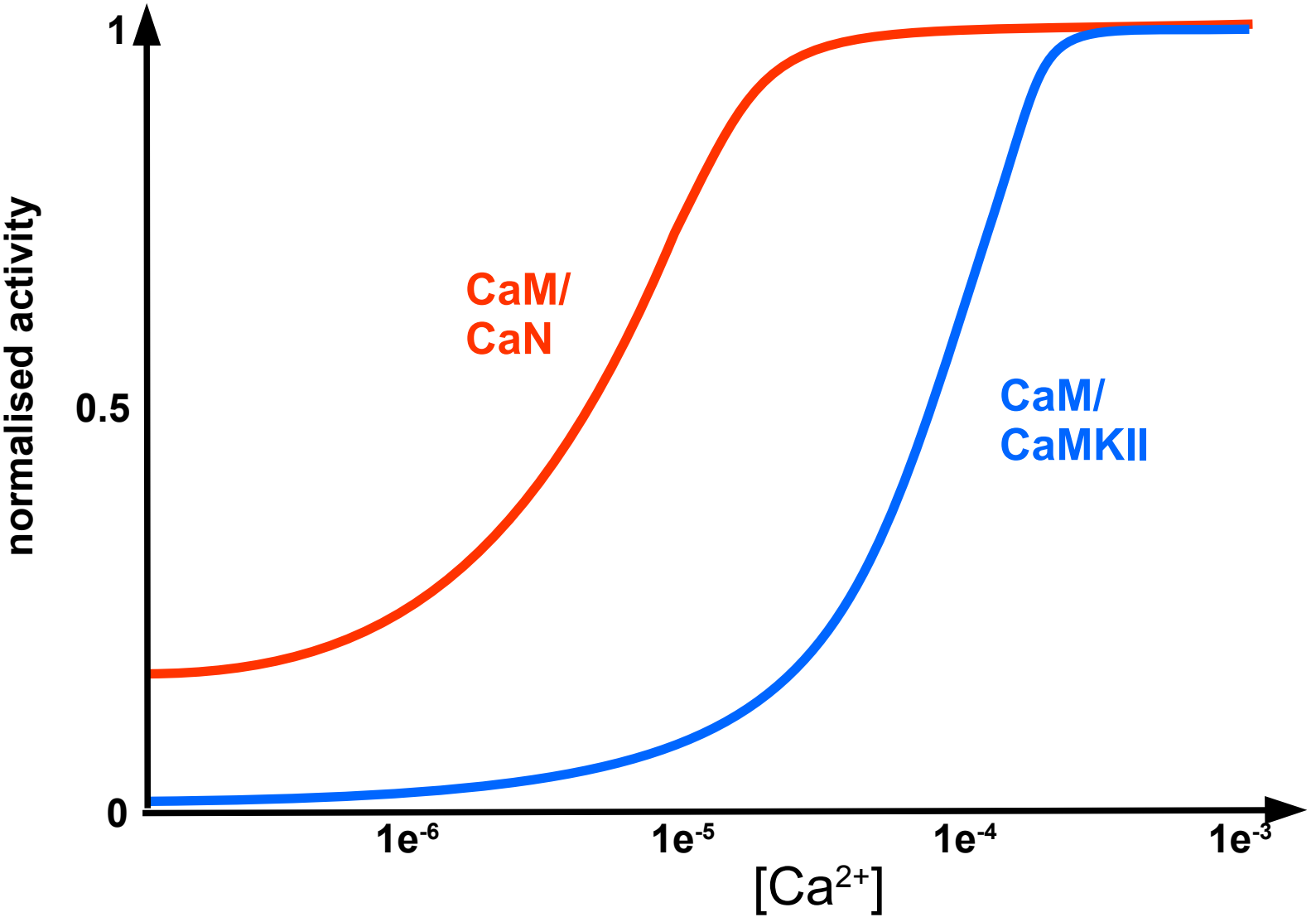
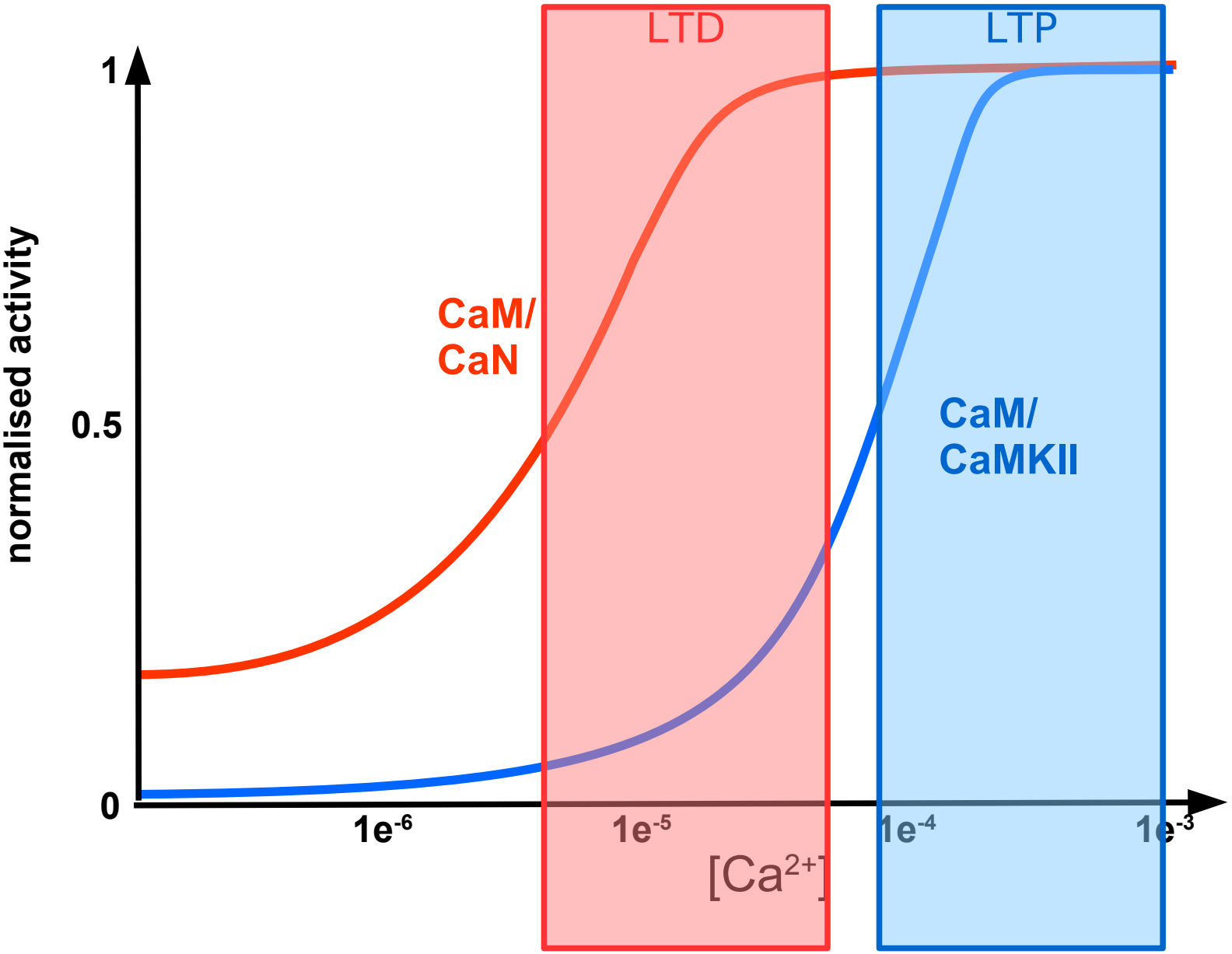
Calmodulin, its ligand and its targets



Bidirectional synaptic plasticity

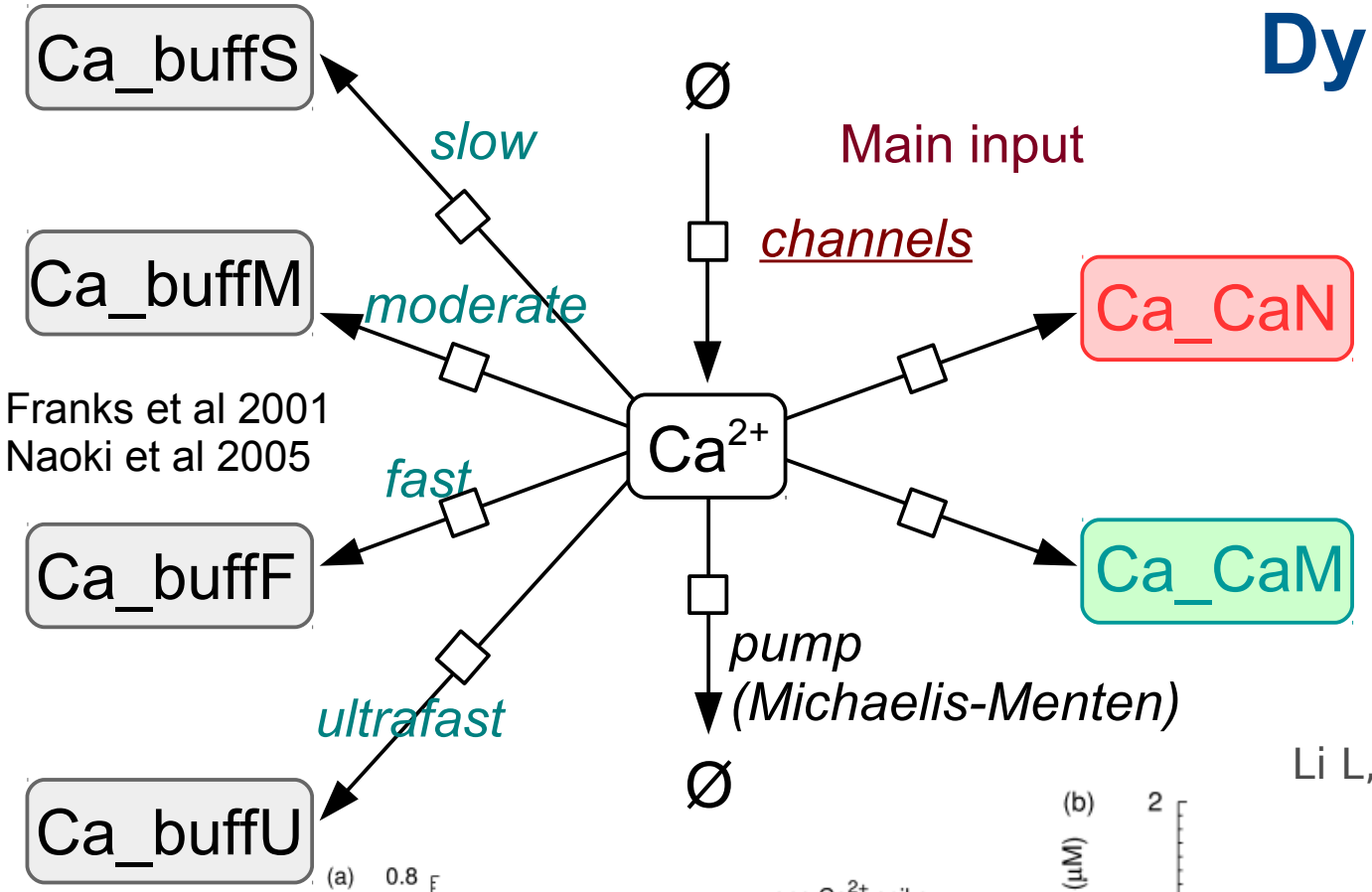


Wait a minute!
Signal transduction is not at equilibrium!

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

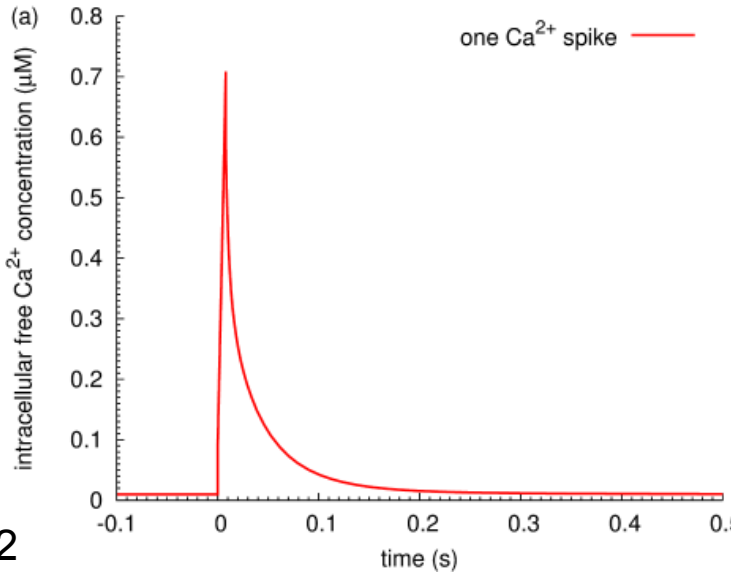


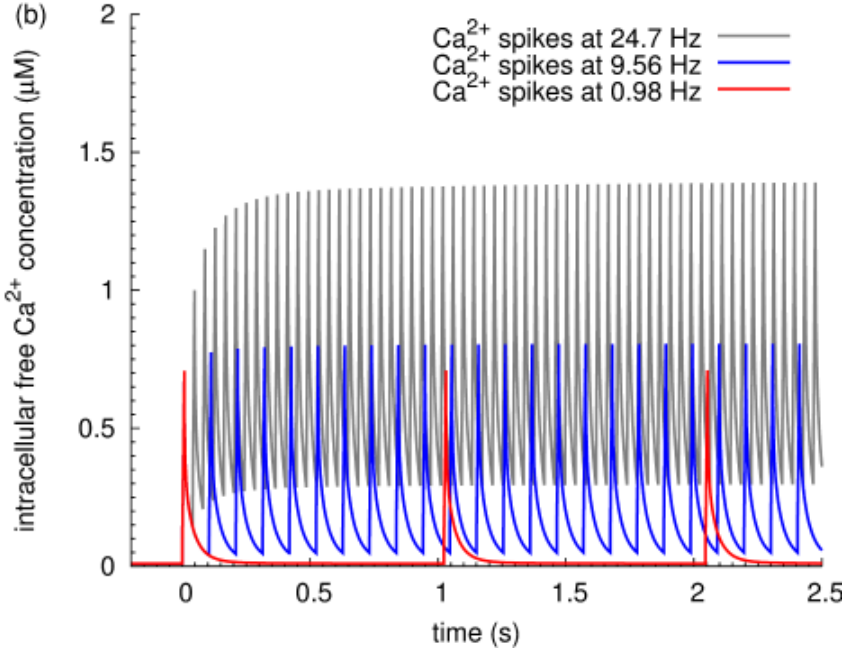
Franks et al 2001
Naoki et al 2005

Lu Li

Li L, Stefan MI, Le Novère N (2012)

Sabatini et al 2002





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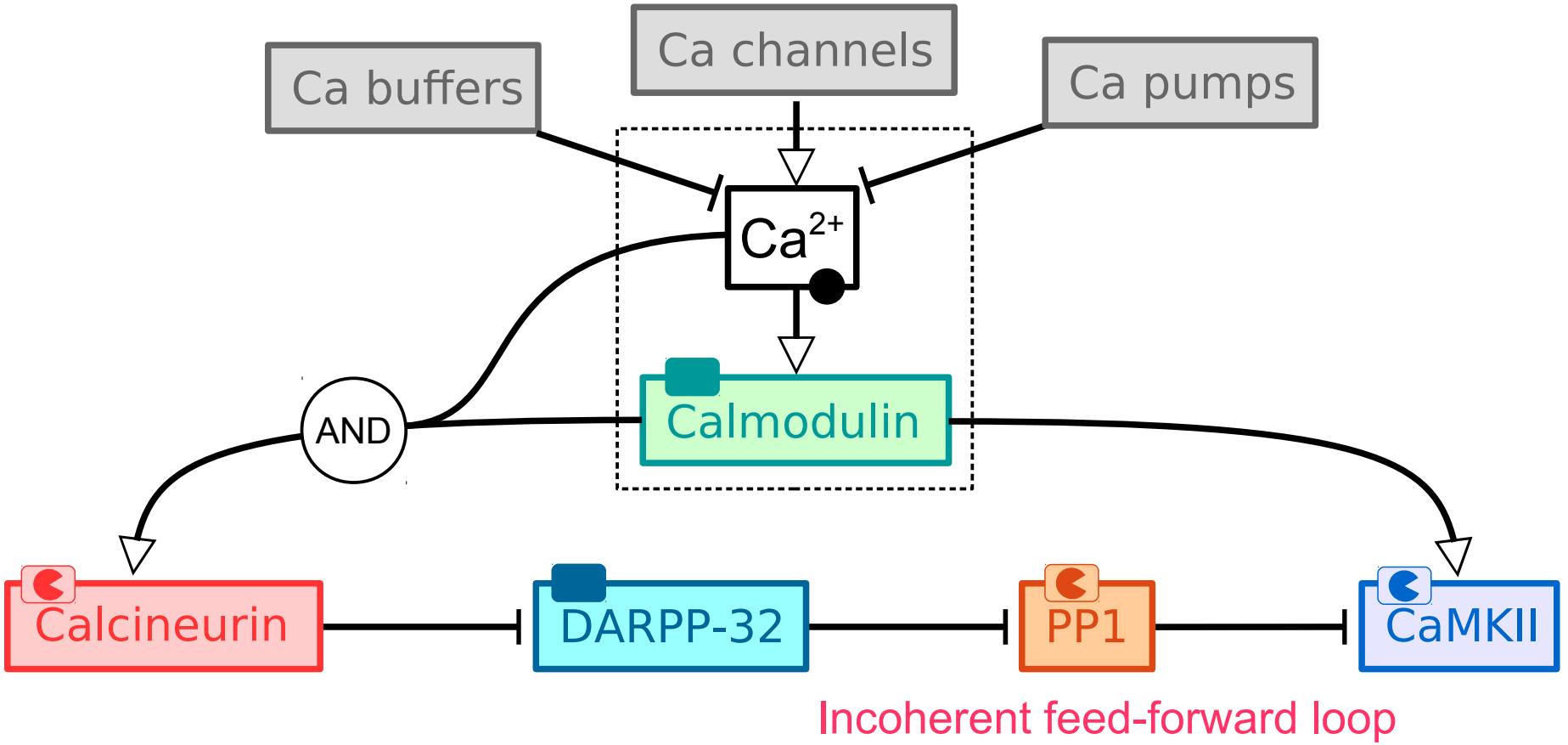
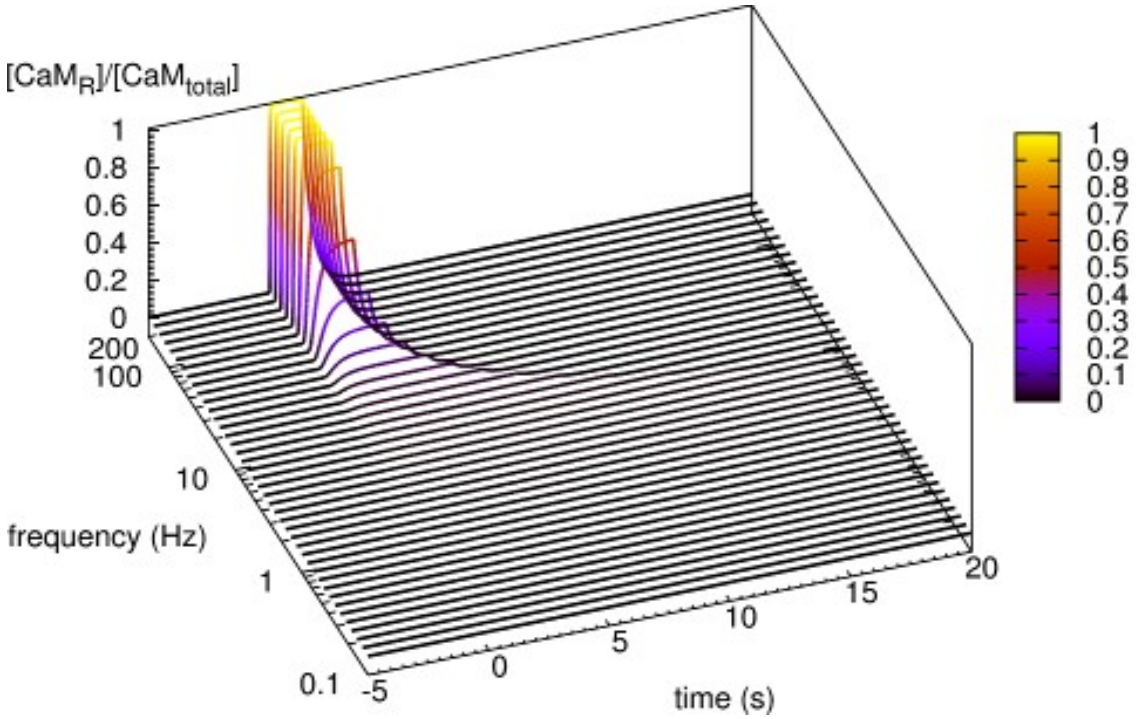
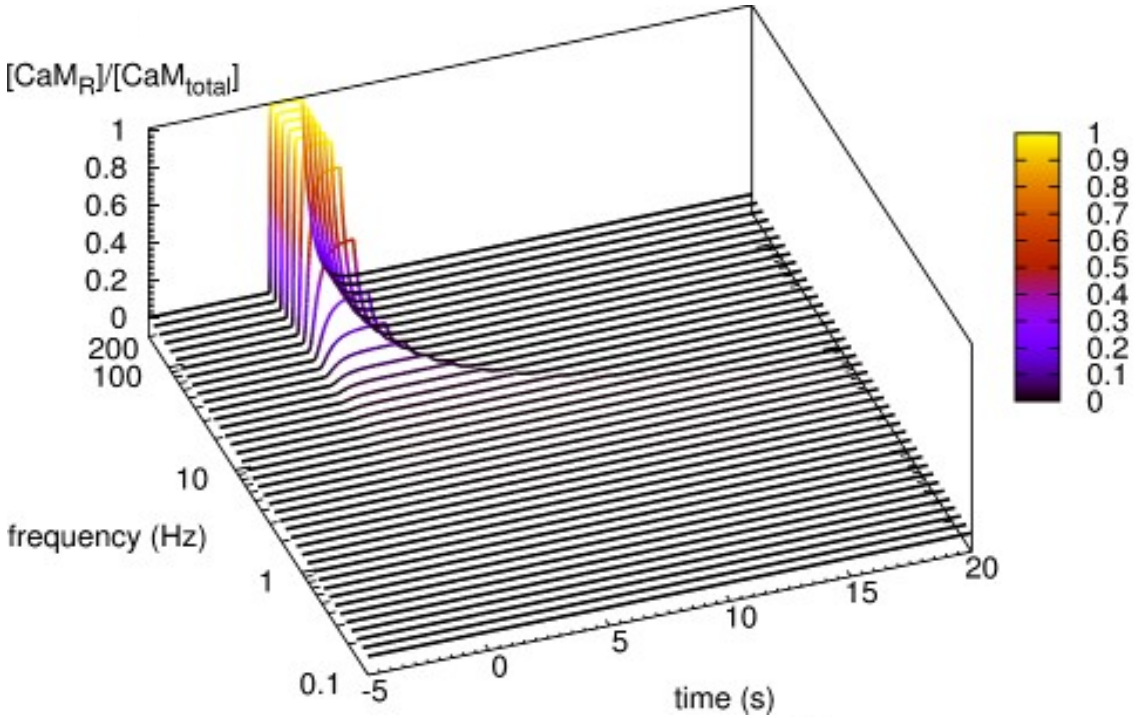


342 “molecular species”, representing 7 actual molecular entities
1295 reactions
184 mathematical rules
7 conditional discrete events



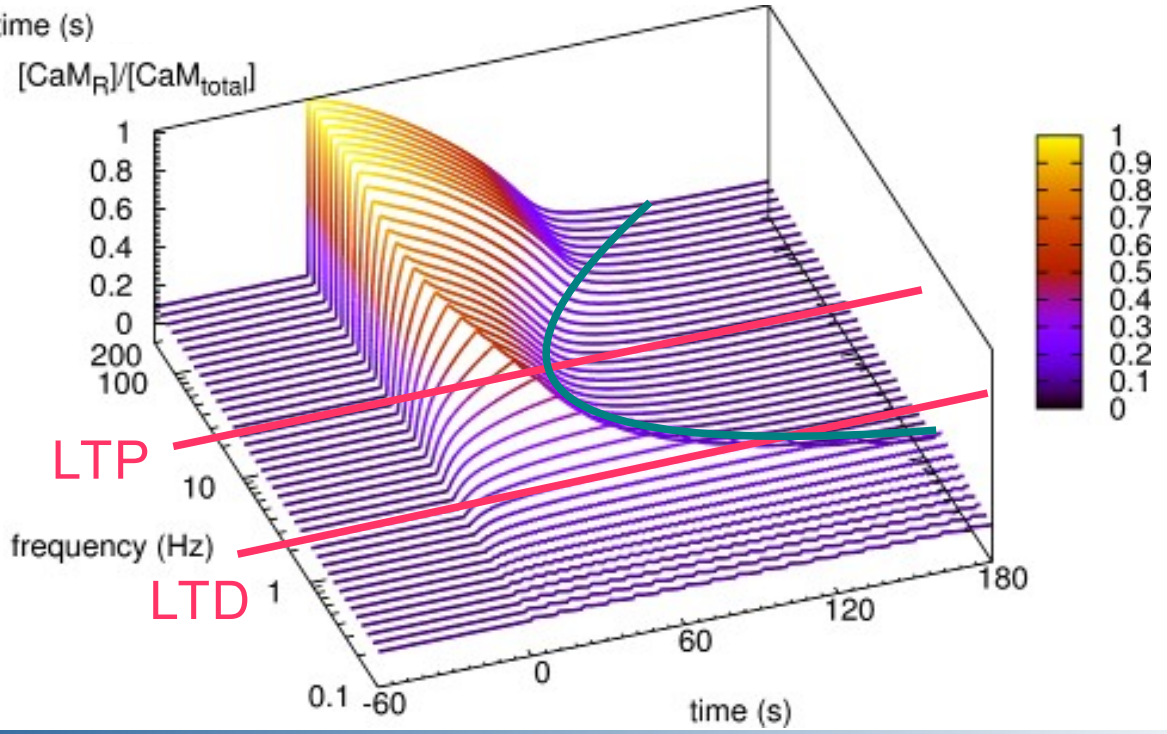
CaM without targets. Low frequencies do not activate calmodulin (binding events without conformational changes)



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



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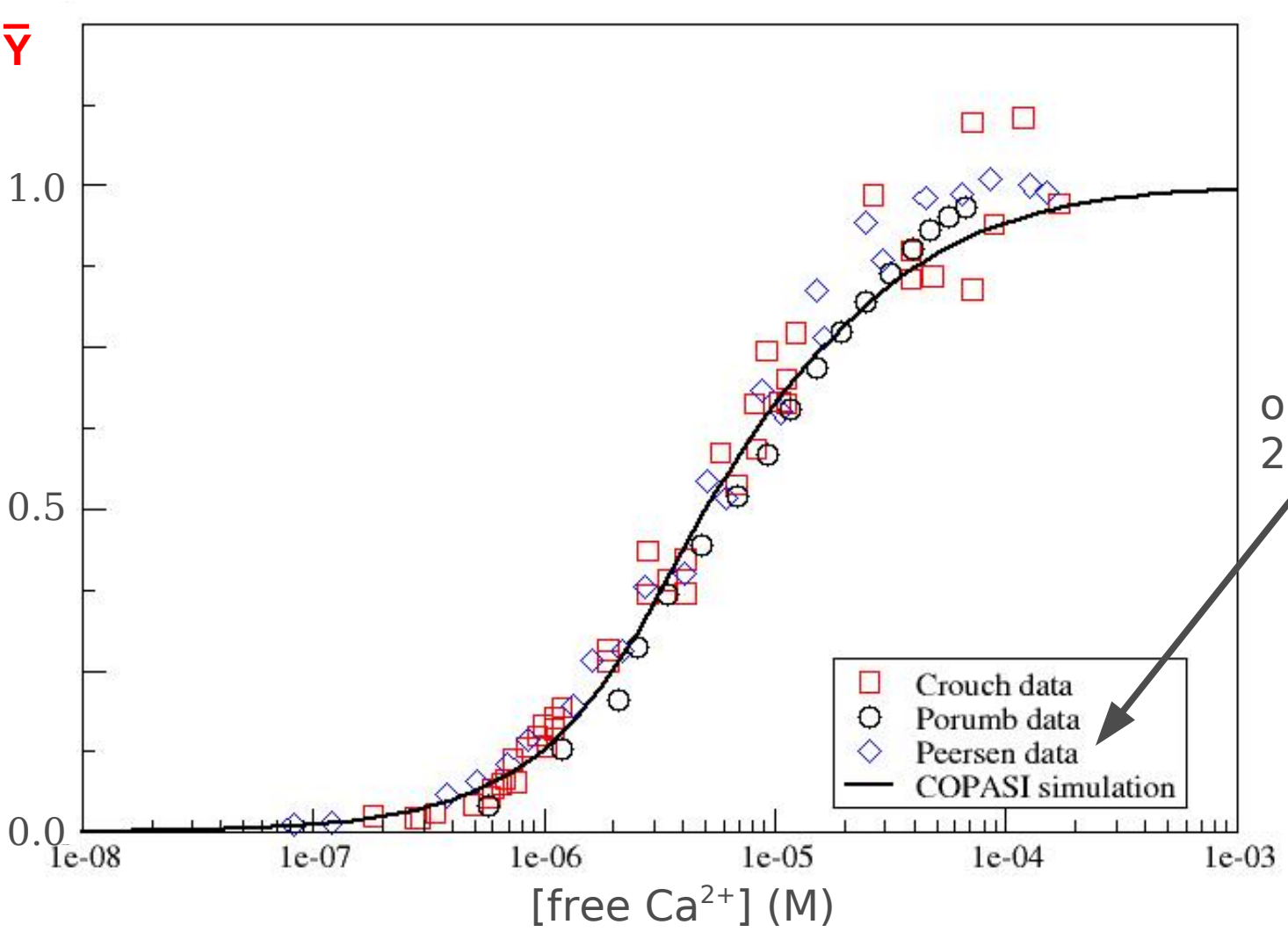
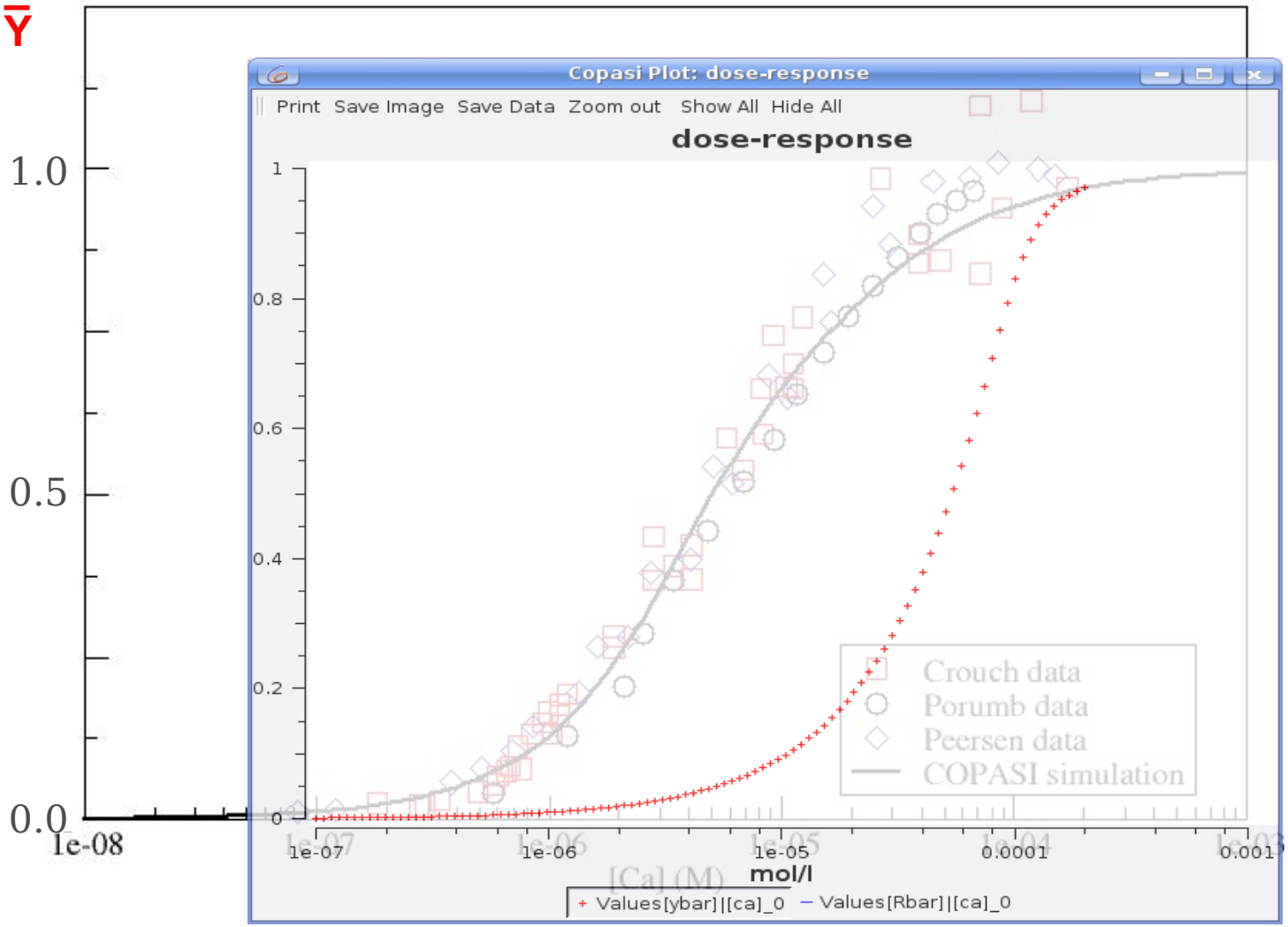

$\bar{Y}$
1.0
0.5
0.0
1e-08
1e-07
1e-06
1e-05
1e-04
1e-03
[free Ca^{2+}] (M)
Crouch data
Porumb data
Peersen data
COPASI simulation
obtained with
25 μM CaM

Calcium dose-response with 25 μM Calmodulin



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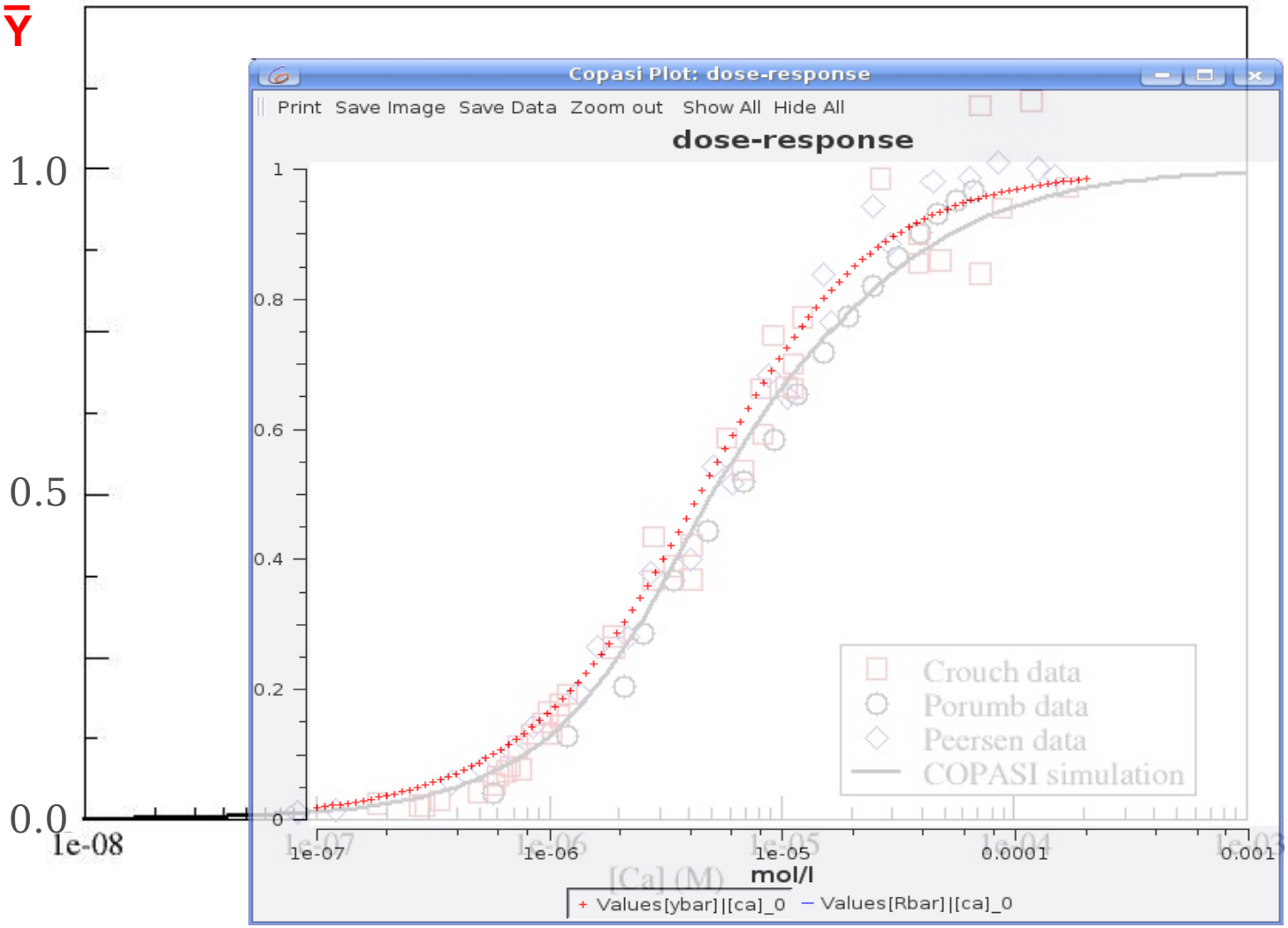
Calcium dose-response with 0.1 μM Calmodulin



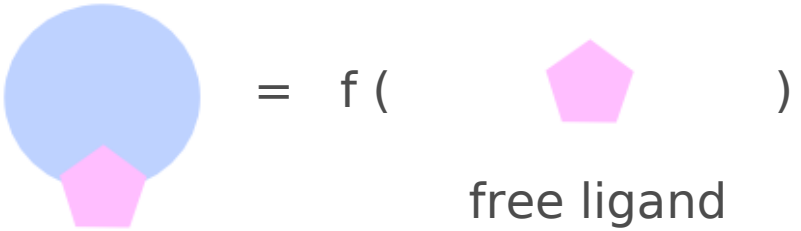
Edelstein SJ, Stefan MI, Le Novère N (2010)

Beware the ligand depletion

Beware the ligand depletion

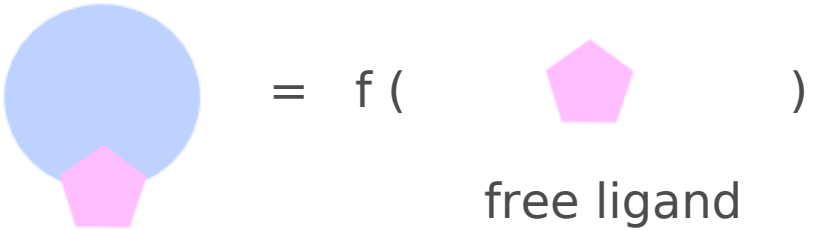
Beware the ligand depletion

Chemistry (mass-action law)

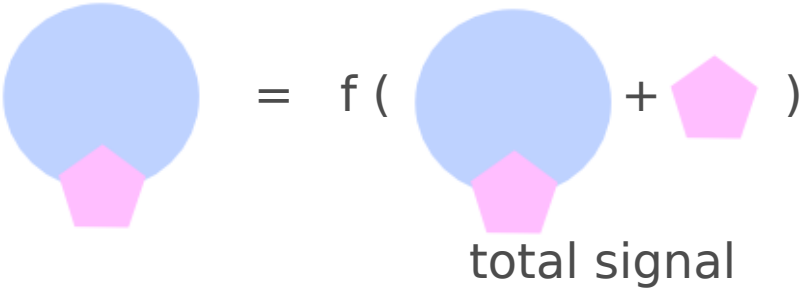


Beware the ligand depletion

Chemistry (mass-action law)



Cellular signalling



Beware the ligand depletion

Chemistry (mass-action law)

= f (free ligand)

if + << Kd =

Cellular signalling

= f (+ total signal)

Beware the ligand depletion

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

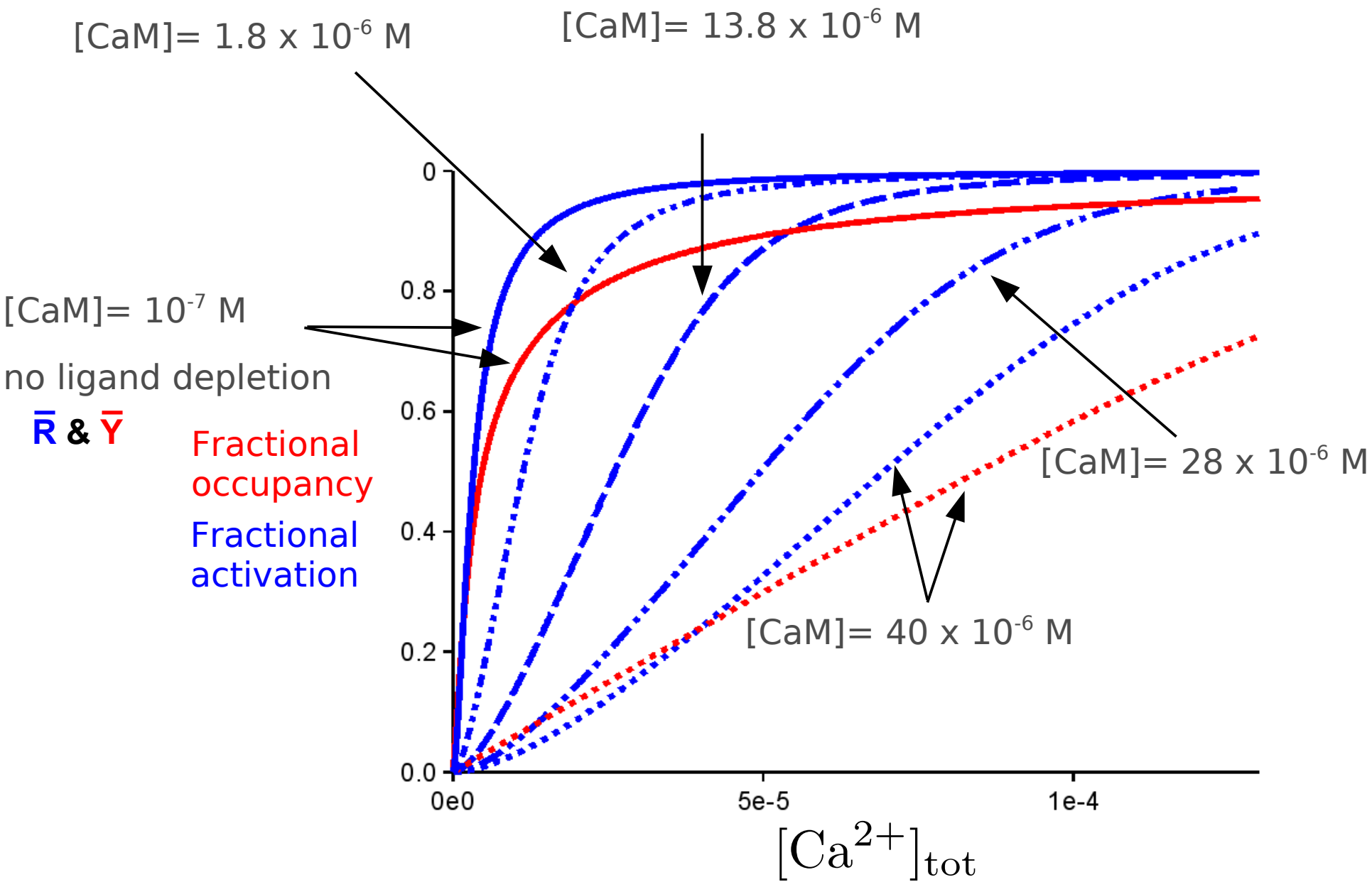
Chemistry (mass-action law)

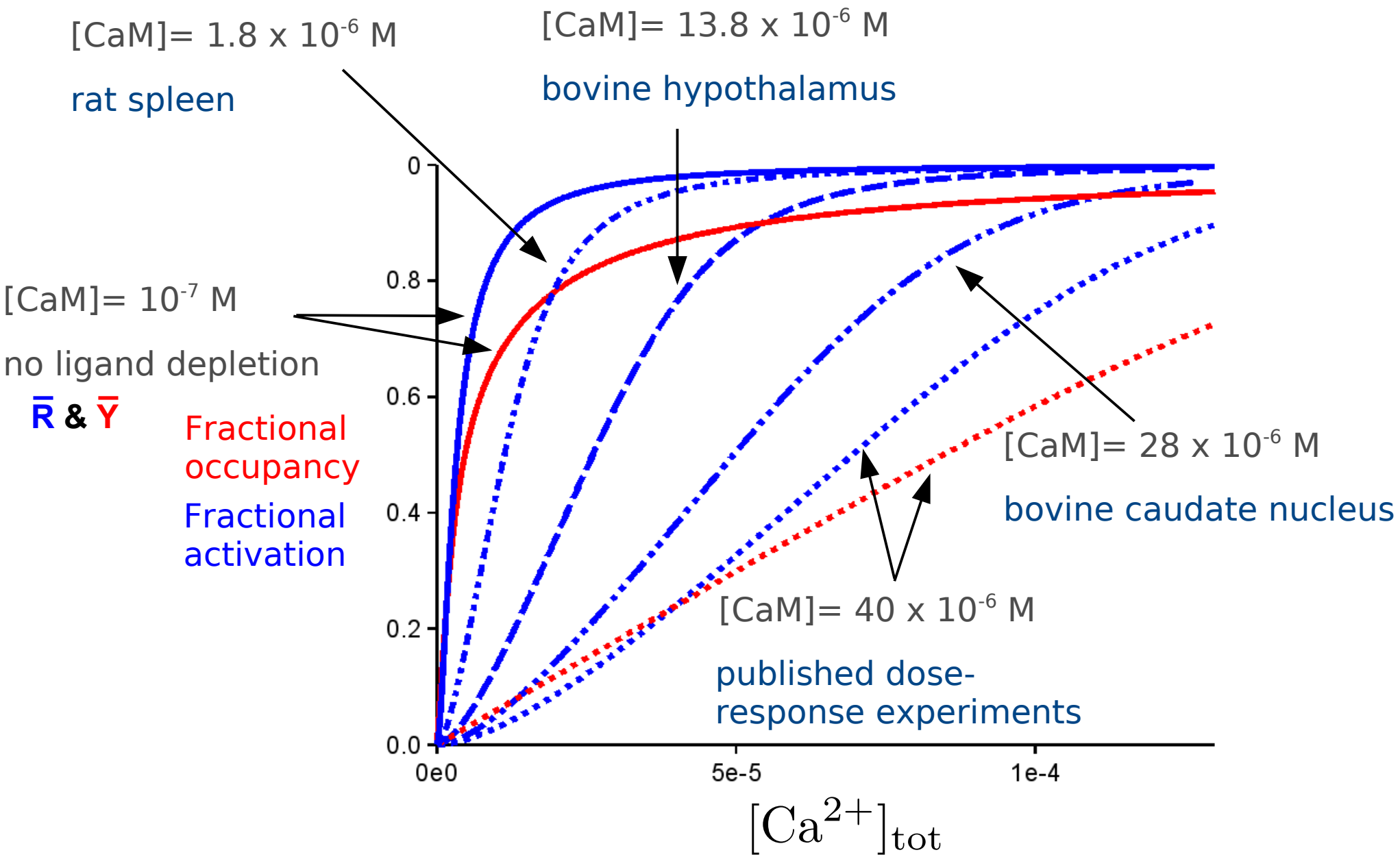
= f (free ligand)

if + << Kd =

Cellular signalling

= f (+ total signal)


[CaM]= 1.8 x 10-6 M
[CaM]= 13.8 x 10-6 M
[CaM]= 10-7 M
no ligand depletion
R̄ & Ȳ
Fractional occupancy
Fractional activation
[CaM]= 28 x 10-6 M
[CaM]= 40 x 10-6 M
0
0.8
0.6
0.4
0.2
0.0
0e0
5e-5
1e-4
[Ca2+]tot


[CaM]= 1.8 x 10-6 M
rat spleen
[CaM]= 13.8 x 10-6 M
bovine hypothalamus
[CaM]= 10-7 M
no ligand depletion
R̄ & Ȳ
Fractional occupancy
Fractional activation
[CaM]= 28 x 10-6 M
bovine caudate nucleus
[CaM]= 40 x 10-6 M
published dose-response experiments
0
0.8
0.6
0.4
0.2
0.0
0e0
5e-5
1e-4
[Ca2+]tot

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

rat spleen

~1 μM to 45 μM

[CaM]= 10^{-7} M

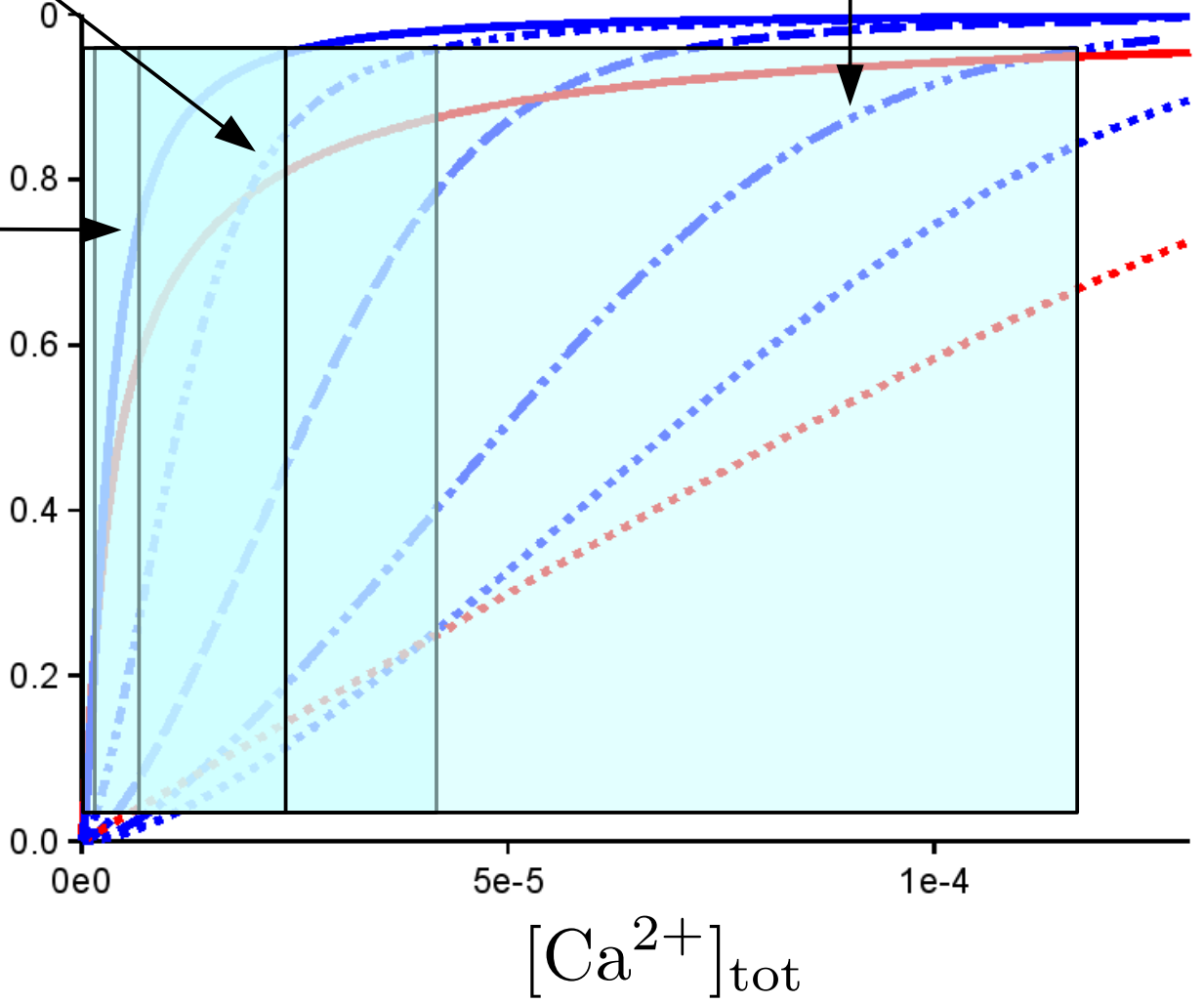
no ligand depletion

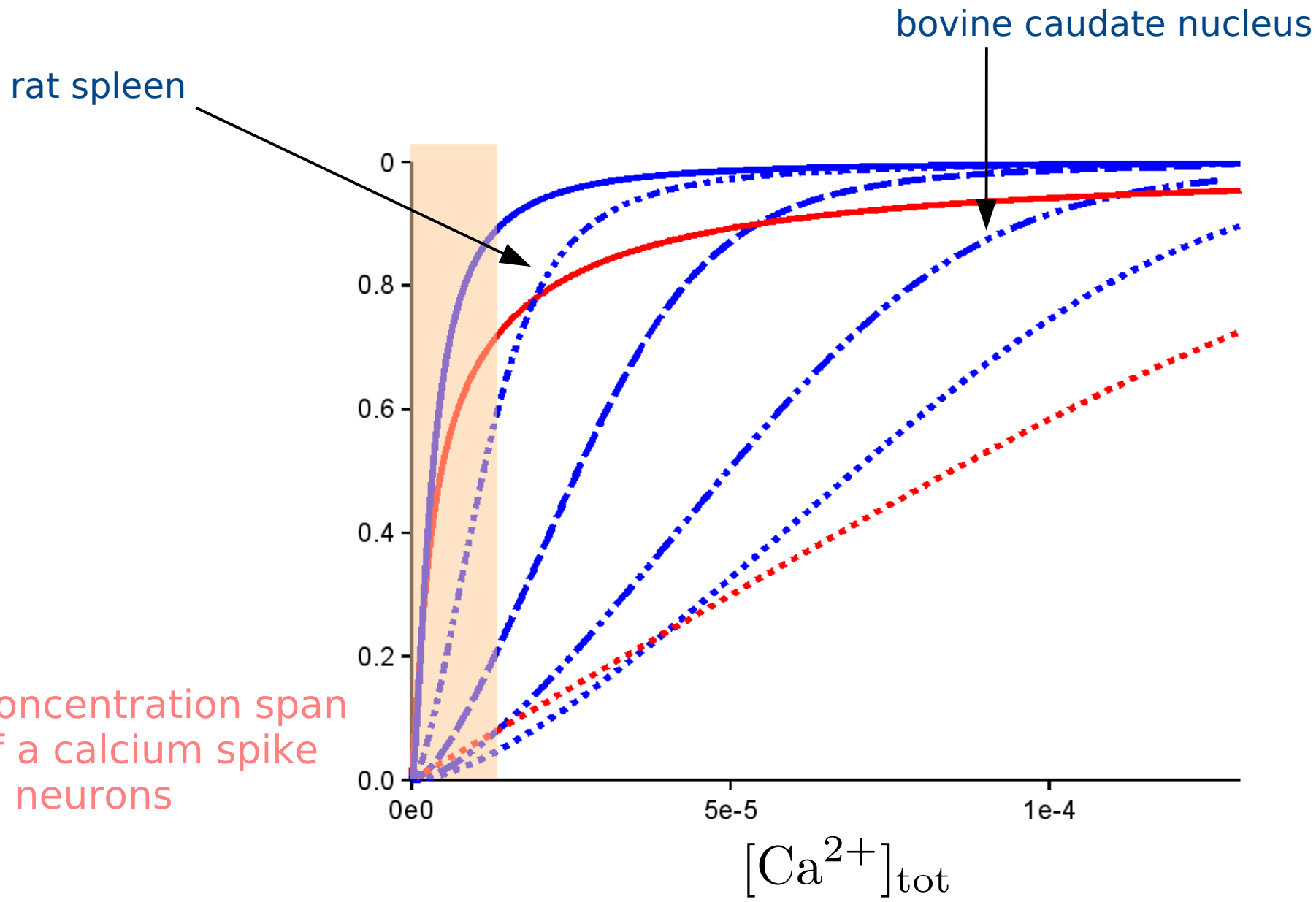
~100 nM to 25 μM

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

bovine caudate nucleus

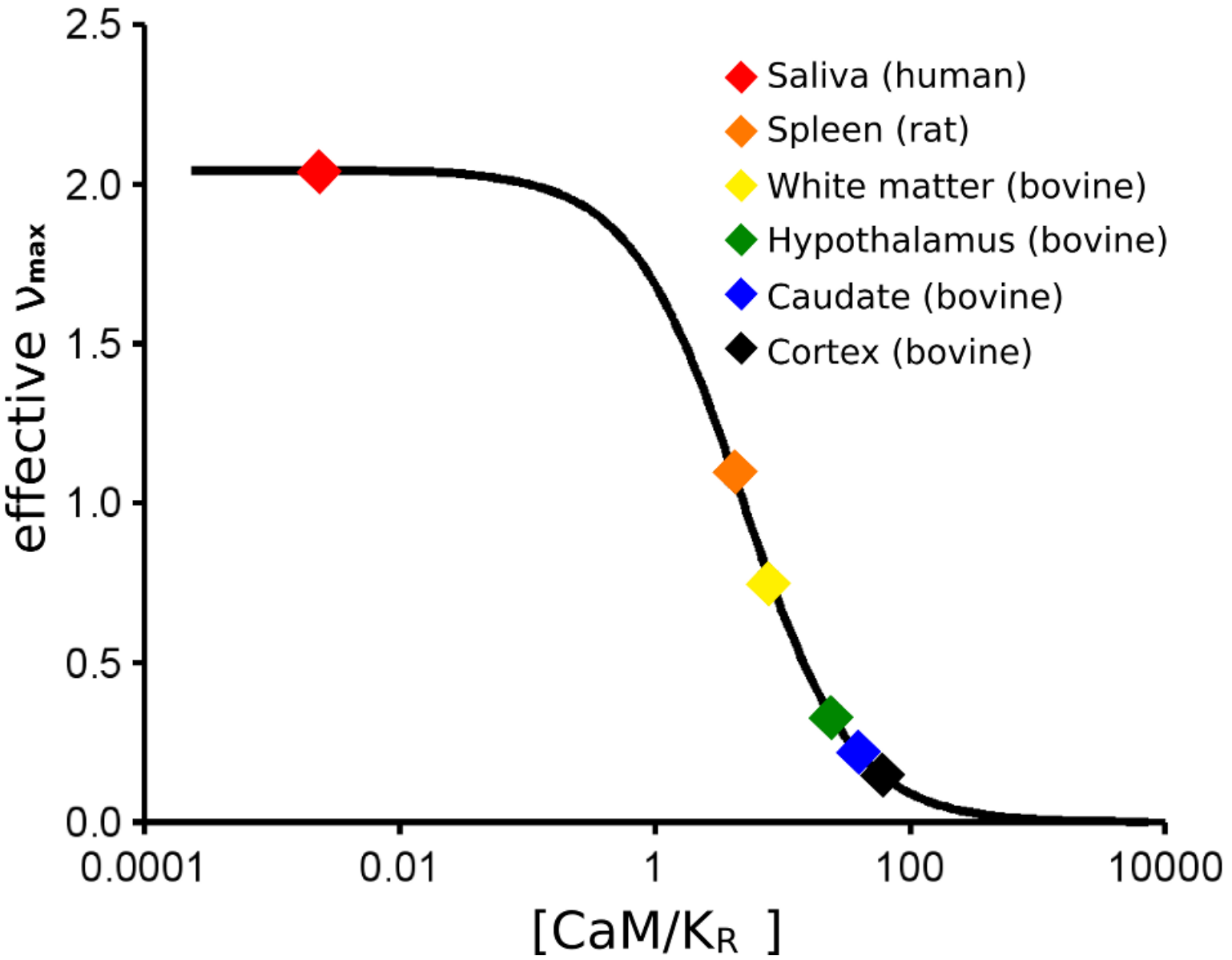
~5 μM to 120 μM



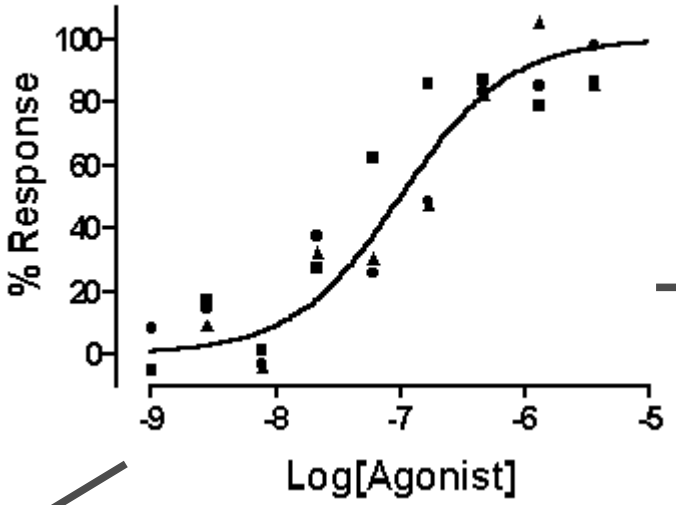


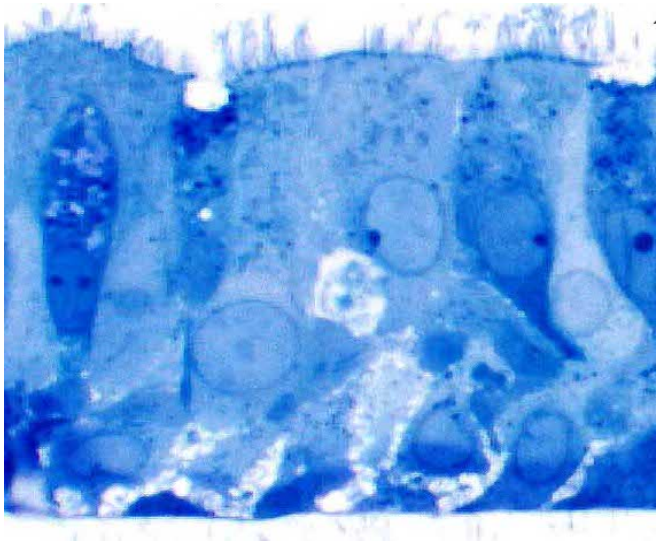
Concentration span of a calcium spike in neurons

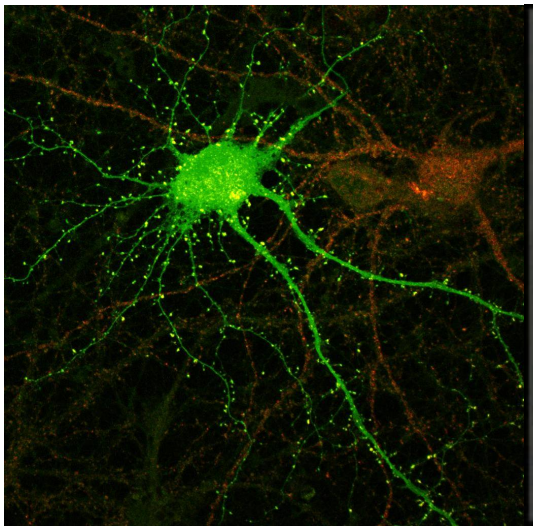
Ligand-depletion decreases effective cooperativity

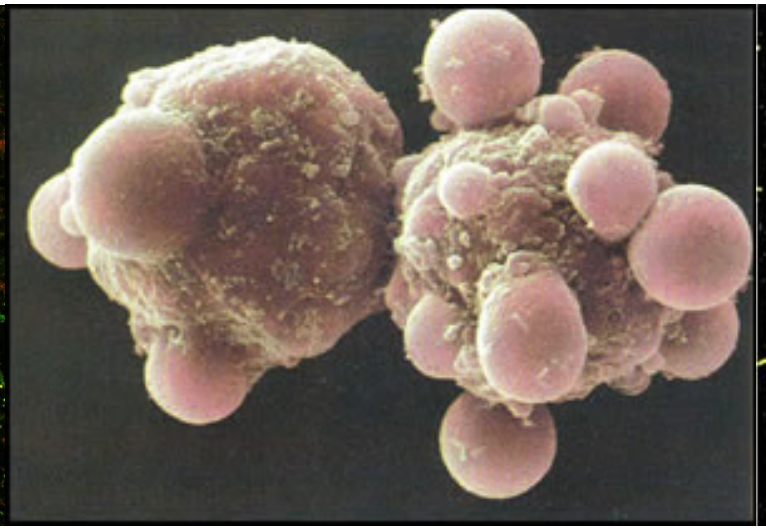


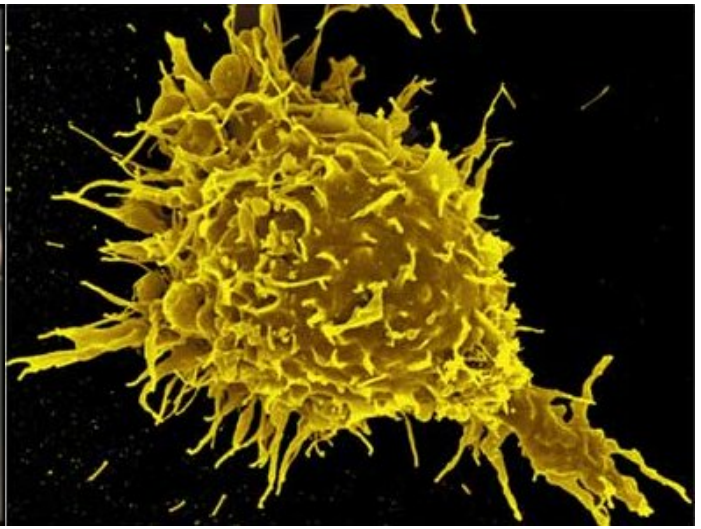
How general is an *in vitro* dose-response?



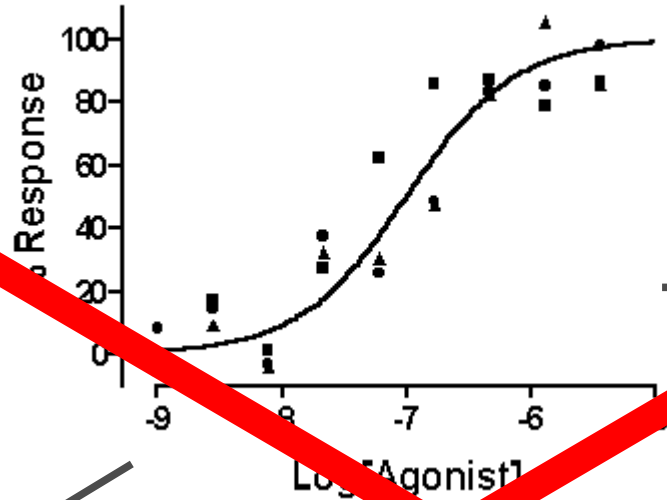


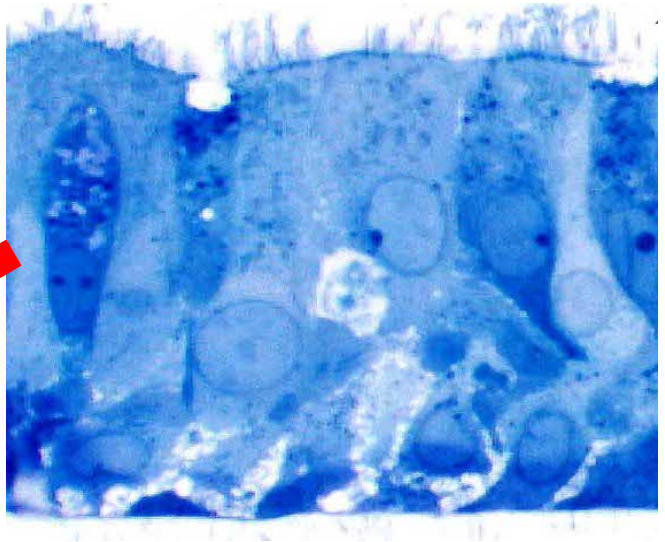


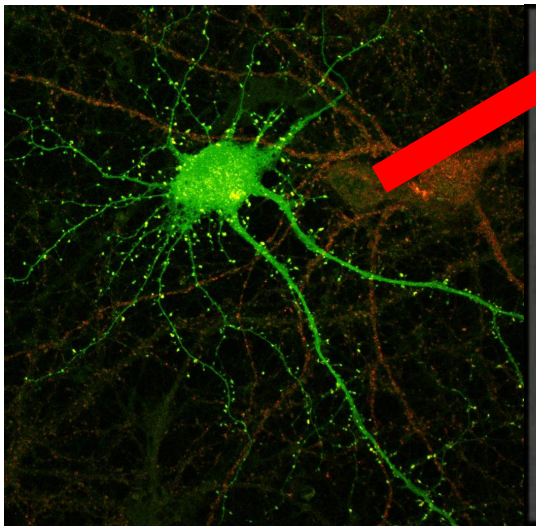


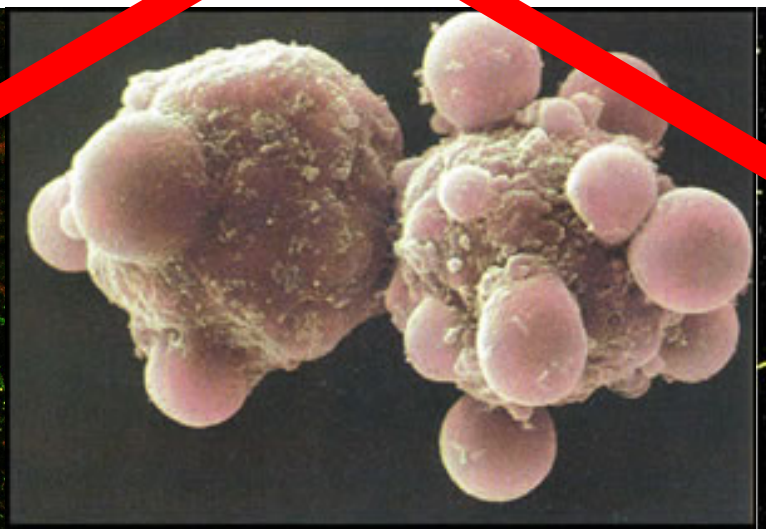


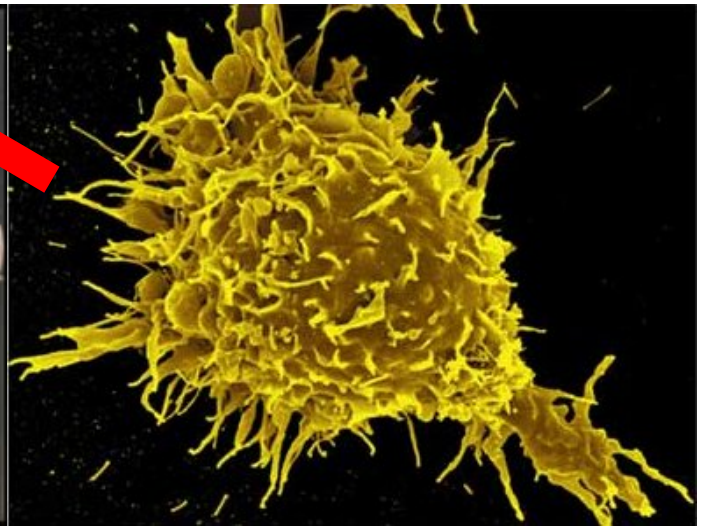
How general is an *in vitro* dose-response?

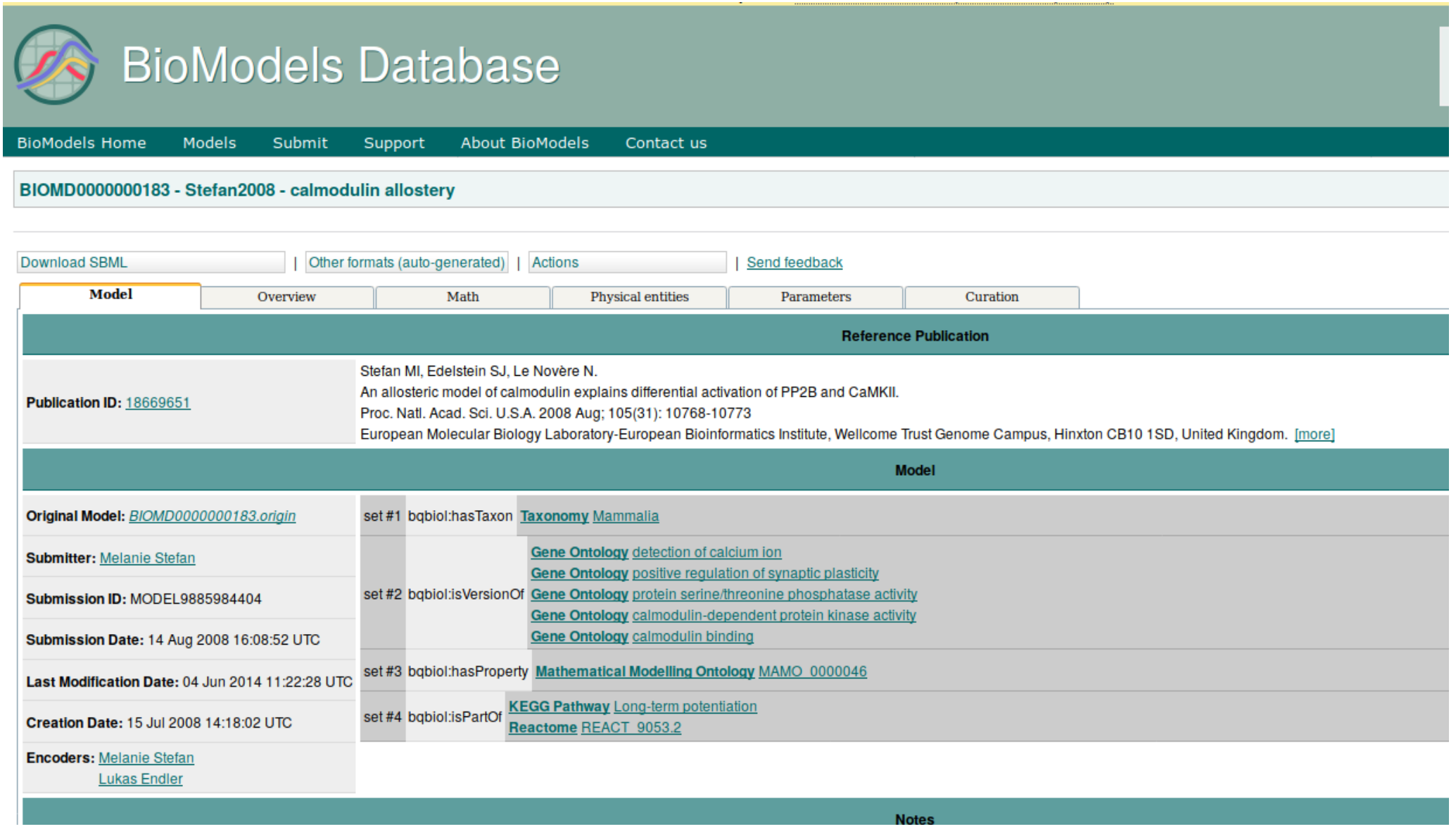












Le Novère N et al. (2006), Chelliah et al. (2015)

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BIOMD0000000183 - Stefan2008 - calr

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Model Overview

Publication ID: 18669651

Original Model: BIOMD0000000183.origin

Submitter: Melanie Stefan

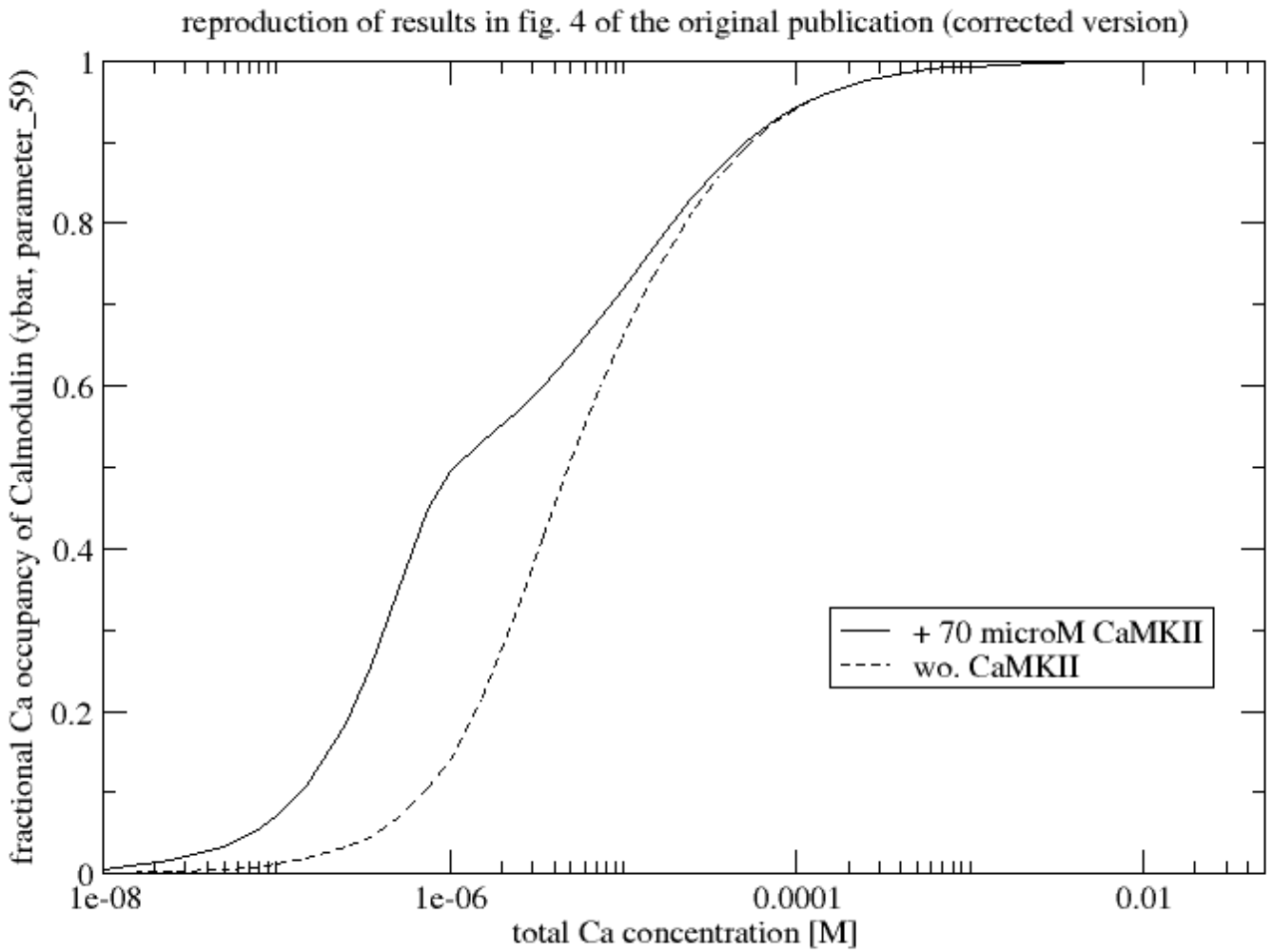
Submission ID: MODEL9885984404

Submission Date: 14 Aug 2008 16:08:52 UTC

Last Modification Date: 04 Jun 2014 11:22:28

Creation Date: 15 Jul 2008 14:18:02 UTC

Encoders: Melanie Stefan
Lukas Endler



Curation figure

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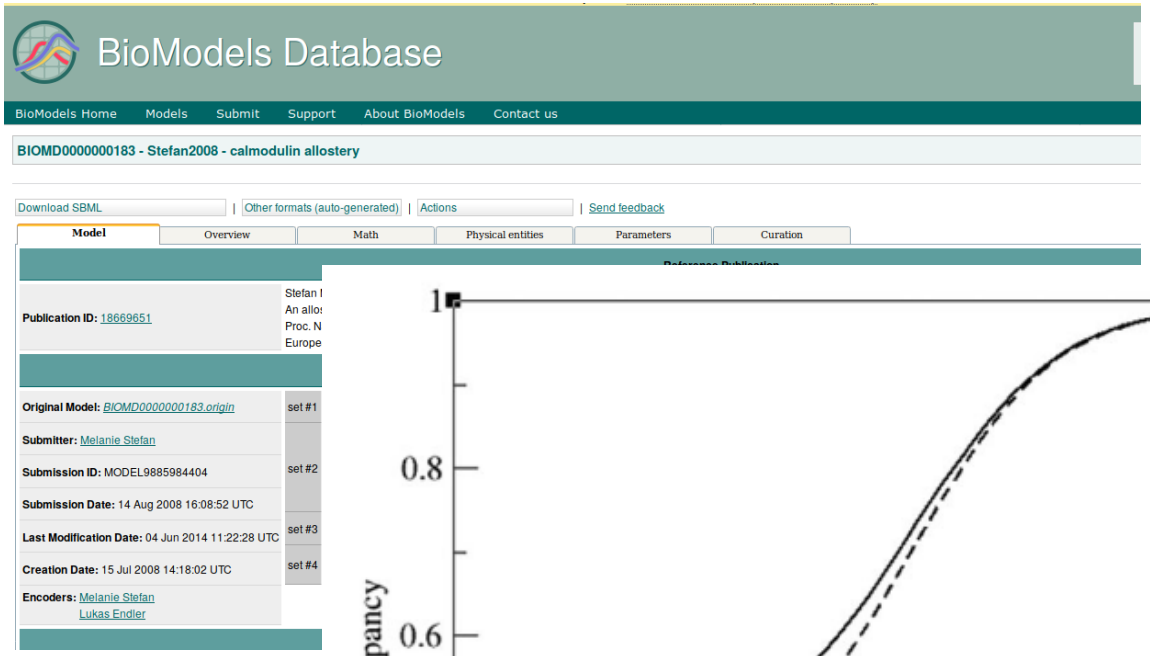
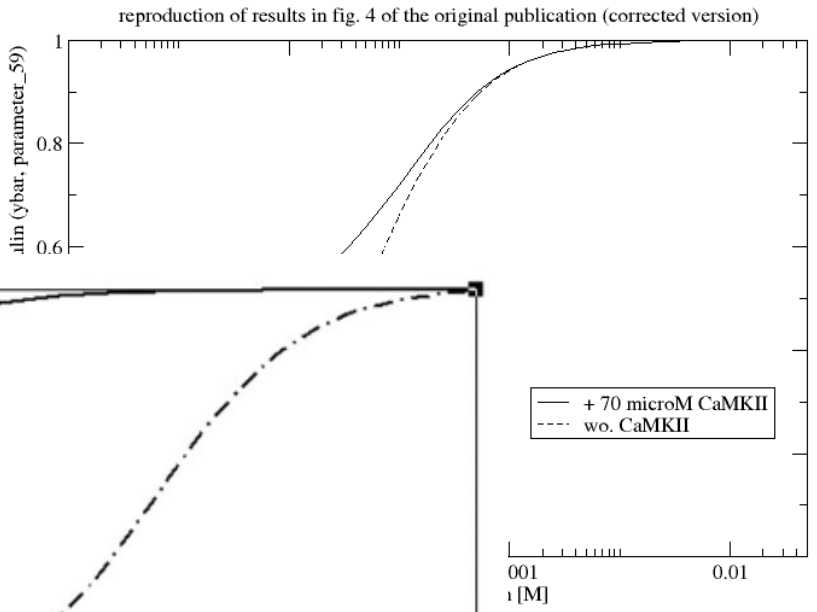
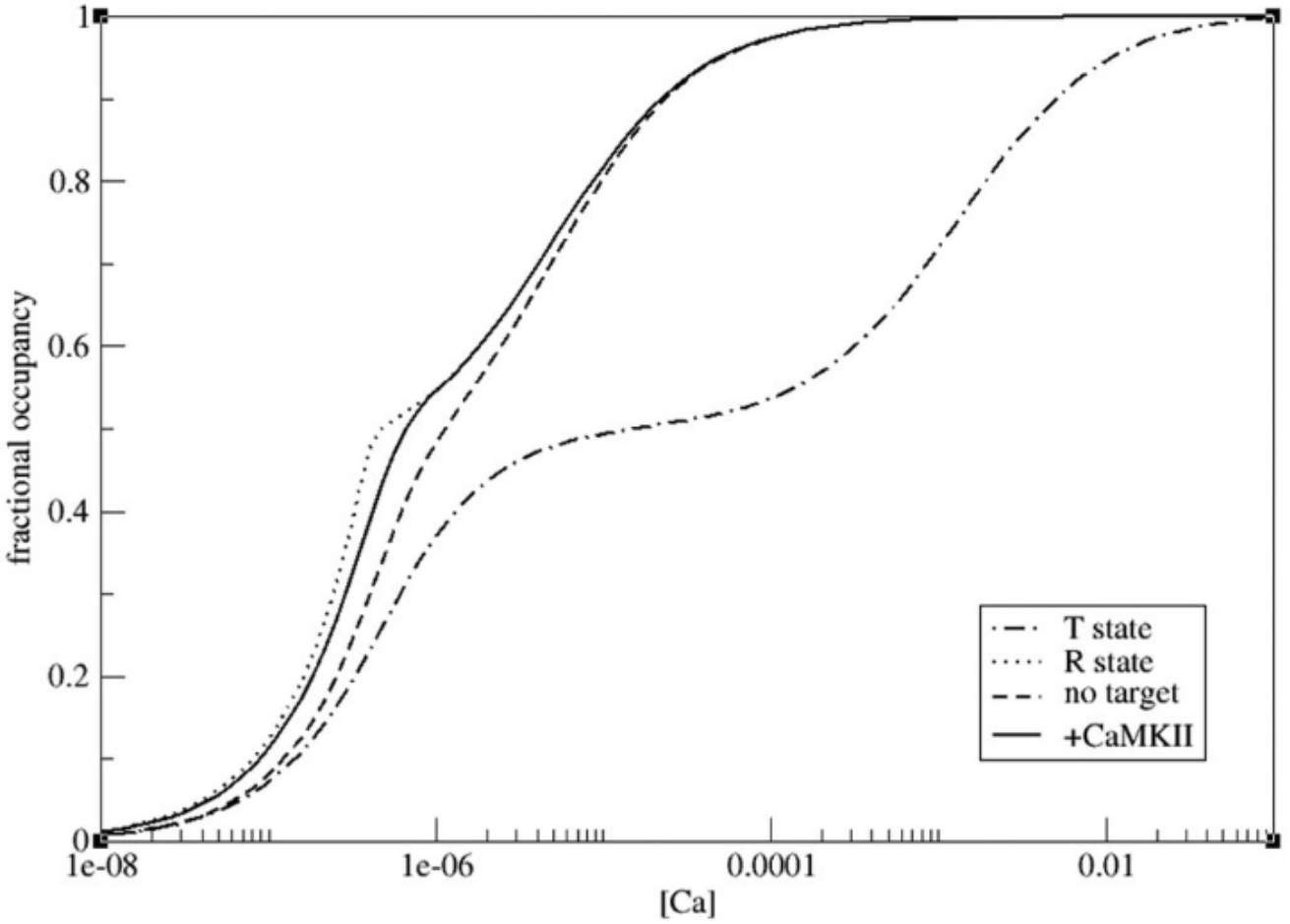
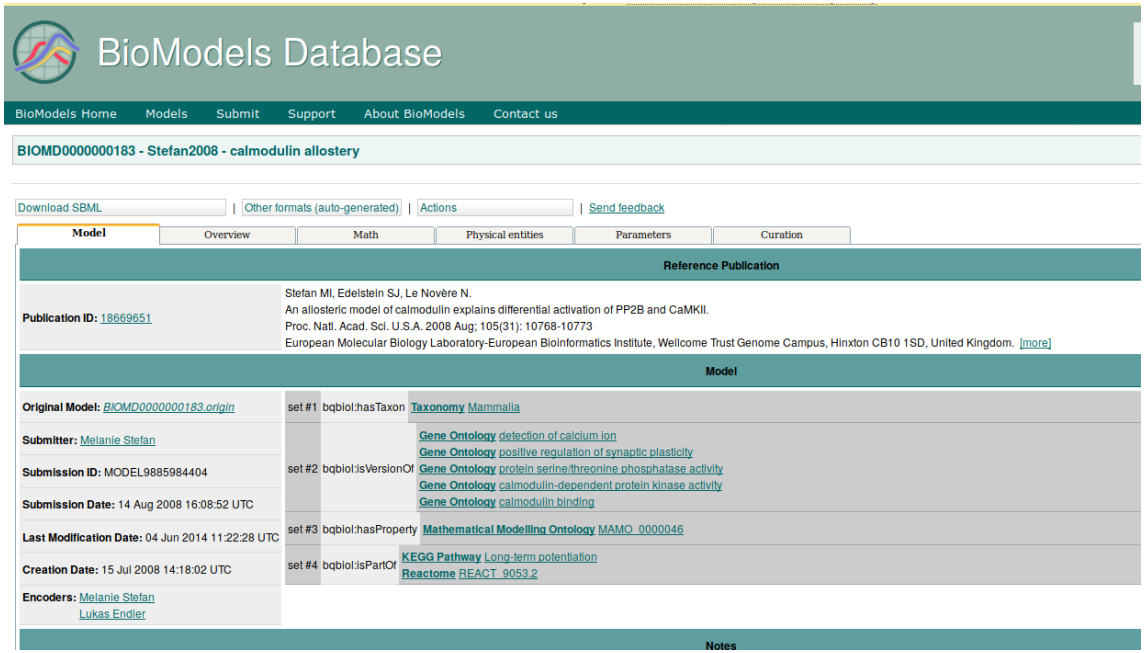
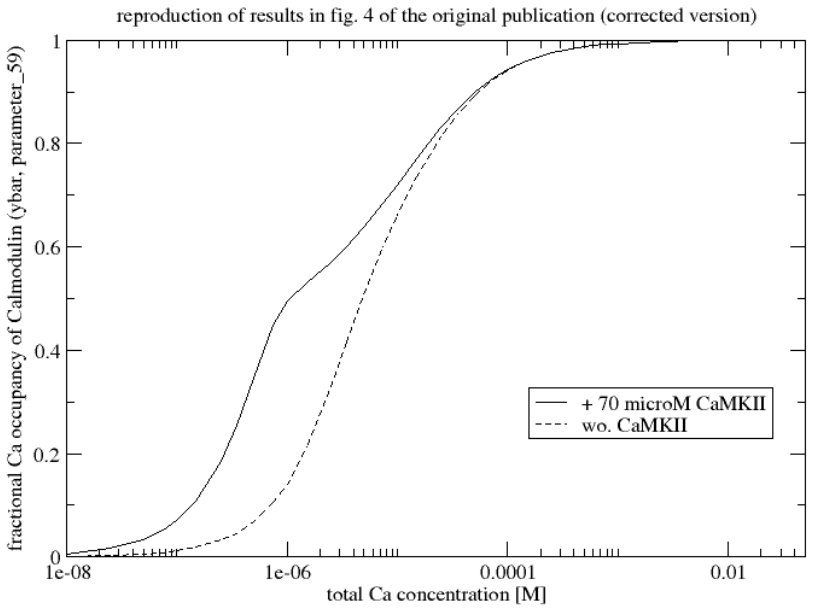


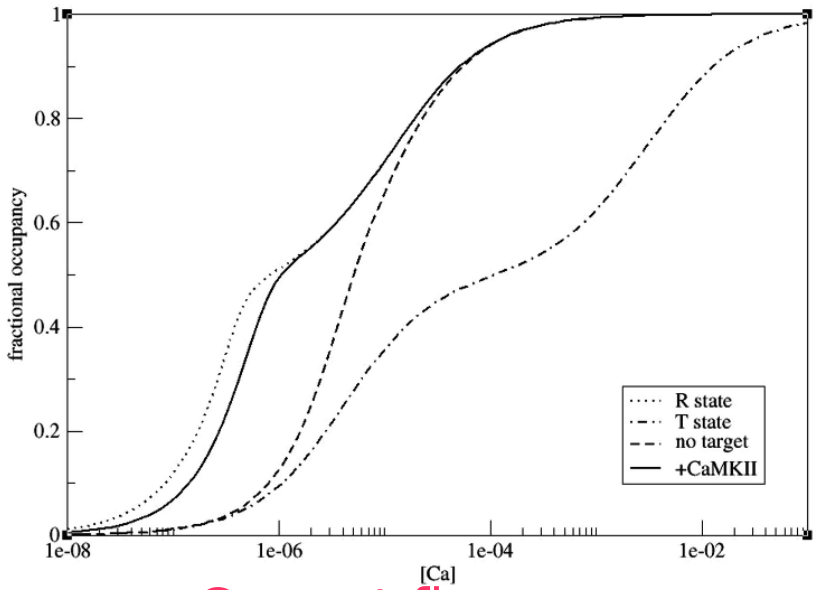


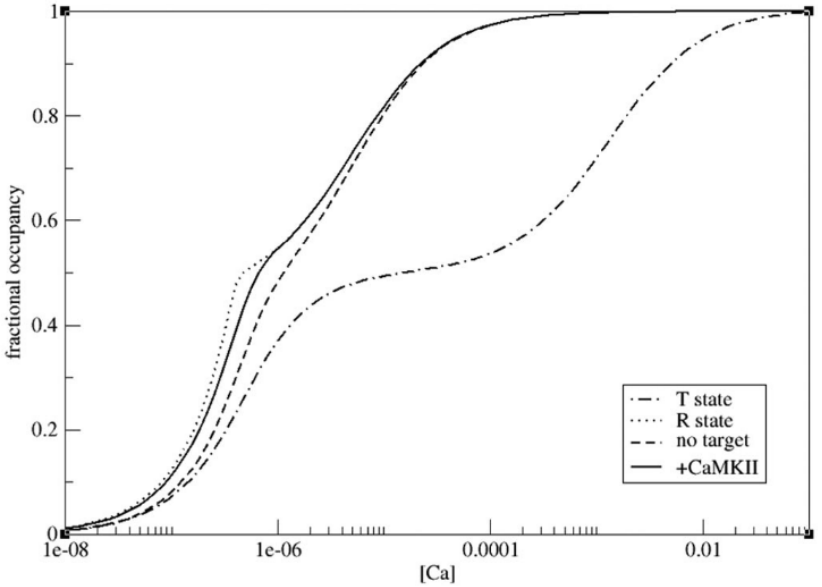


Published figure!









Correct figure ....

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BIOMD0000000183 - Stefan2008 - calmodulin allostery

Download SBML | Other formats (auto-generated) | Actions | Send feedback

Model | Overview | Math | Physical entities | Parameters | Curation

Reference Publication

Publication ID: 18669651

Stefan MI, Edelstein SJ, Le Novère N.
An allosteric model of calmodulin explains differential activation of PP2B and CaMKII.
Proc. Natl. Acad. Sci. U.S.A. 2008 Aug; 105(31): 10768-10773
European Molecular Biology Laboratory-European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton CB10 1SD, United Kingdom. [more]

Model

Original Model: *BIOMD0000000183.origin*

Submitter: Melanie Stefan

Submission ID: MODEL9885984404

Submission Date: 14 Aug 2008 16:08:52 UTC

Last Modification Date: 04 Jun 2014 11:22:28 UTC

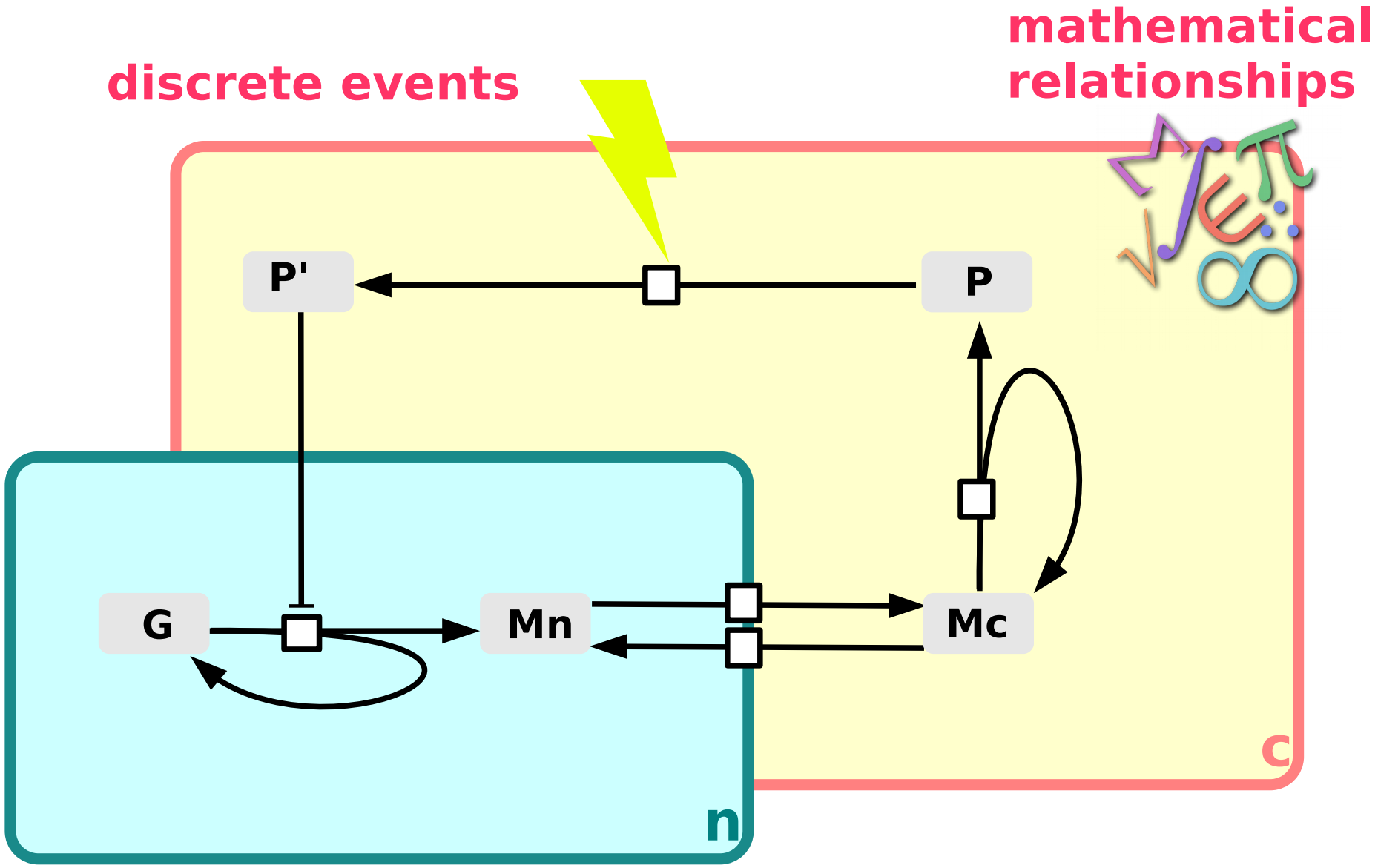
Creation Date: 15 Jul 2008 14:18:02 UTC

Encoders: Melanie Stefan
Lukas Endler

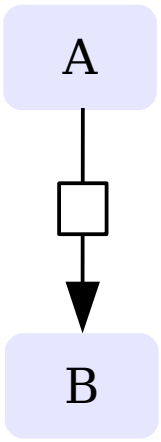
set #1	bqbiol:hasTaxon	**Taxonomy** Mammalia
set #2	bqbiol:isVersionOf	**Gene Ontology** detection of calcium ion **Gene Ontology** positive regulation of synaptic plasticity **Gene Ontology** protein serine/threonine phosphatase activity **Gene Ontology** calmodulin-dependent protein kinase activity **Gene Ontology** calmodulin binding
set #3	bqbiol:hasProperty	**Mathematical Modelling Ontology** MAMO_0000046
set #4	bqbiol:isPartOf	**KEGG Pathway** Long-term potentiation **Reactome** REACT_9053.2

Notes

Standard format to encode models



Hucka et al. (2003)



$$\frac{d[B]}{dt} = k1 \times [A]$$

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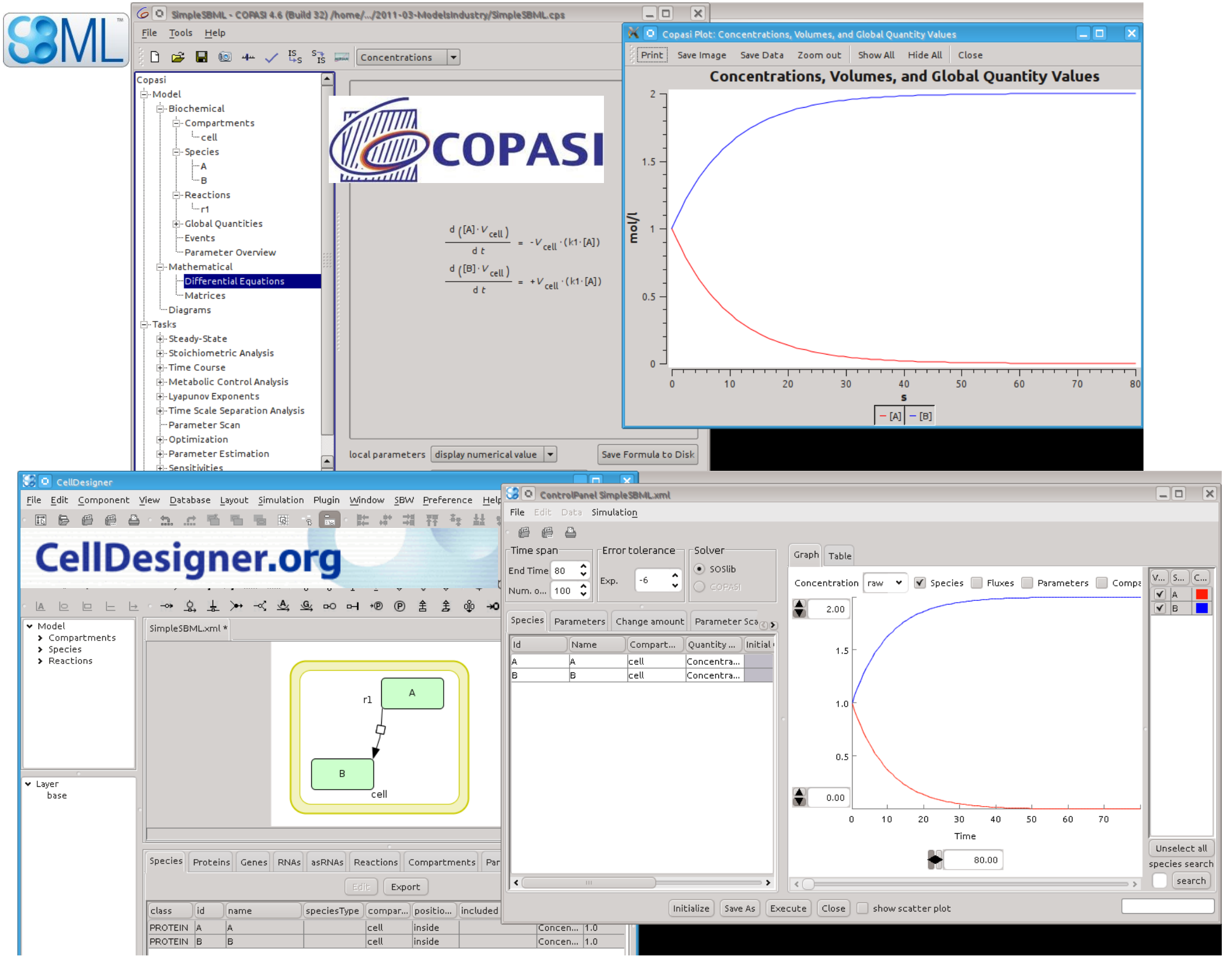
A very simple SBML file


SBML
SimpleSBML - COPASI 4.6 (Build 32) /home/.../2011-03-ModelsIndustry/SimpleSBML.cps
File Tools Help
Concentrations
Copasi
Model
Biochemical
Compartments
cell
Species
A
B
Reactions
r1
Global Quantities
Events
Parameter Overview
Mathematical
Differential Equations
Matrices
Diagrams
Tasks
Steady-State
Stoichiometric Analysis
Time Course
Metabolic Control Analysis
Lyapunov Exponents
Time Scale Separation Analysis
Parameter Scan
Optimization
Parameter Estimation
Sensitivities
COPASI
d([A]·V_cell)/dt = -V_cell·(k1·[A])
d([B]·V_cell)/dt = +V_cell·(k1·[A])
local parameters
display numerical value
Save Formula to Disk
Copasi Plot: Concentrations, Volumes, and Global Quantity Values
Print Save Image Save Data Zoom out Show All Hide All Close
Concentrations, Volumes, and Global Quantity Values
mol/l
s
[A] [B]
CellDesigner
File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help
CellDesigner.org
Model
Compartments
Species
Reactions
Layer
base
SimpleSBML.xml *
r1
A
B
cell
Species Proteins Genes RNAs asRNAs Reactions Compartments
Edit Export
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PROTEIN A A cell inside Concen... 1.0
PROTEIN B B cell inside Concen... 1.0
ControlPanel SimpleSBML.xml
File Edit Data Simulation
Time span
End Time 80
Num. o... 100
Error tolerance
Exp. -6
Solver
SOSlib
COPASI
Species Parameters Change amount Parameter Sca
Id Name Compart... Quantity ... Initial
A A cell Concentra...
B B cell Concentra...
Graph Table
Concentration raw
Species Fluxes Parameters Compa
2.00
0.00
Time
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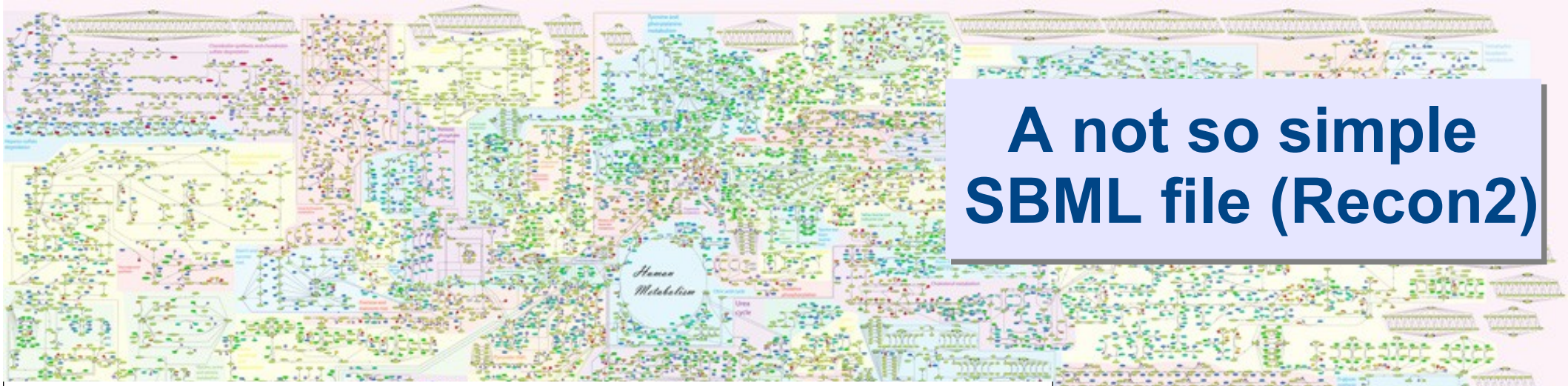
V... S... C...
A
B
Unselect all
species search
search
Initialize Save As Execute Close show scatter plot



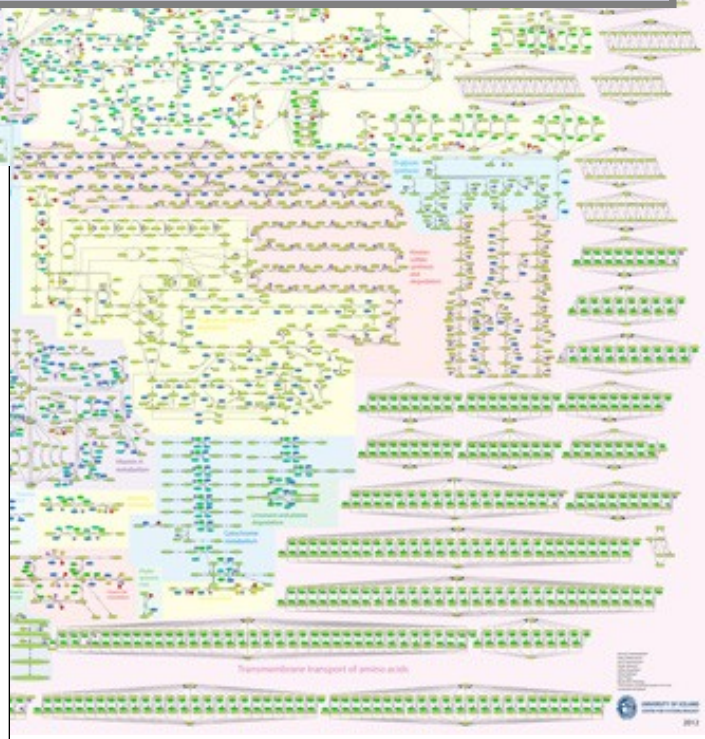
A not so simple SBML file (Recon2)

A community-driven global reconstruction of human metabolism

Ines Thiele[1,2,37], Neil Swainston[3,4,37], Ronan M T Fleming[1,5], Andreas Hoppe[6], Swagatika Sahoo[1], Maike K Aurich[1], Hulda Haraldsdottir[1], Monica L Mo[7], Ottar Rolfsson[1], Miranda D Stobbe[8,9], Stefan G Thorleifsson[1], Rasmus Agren[10], Christian Bölling[6], Sergio Bordel[10], Arvind K Chavali[11], Paul Dobson[12], Warwick B Dunn[3,13], Lukas Endler[14], David Hala[15], Michael Hucka[16], Duncan Hull[4], Daniel Jameson[3,4], Neema Jamshidi[7], Jon J Jonsson[5], Nick Juty[17], Sarah Keating[17], Intawat Nookaew[10], Nicolas Le Novère[17,18], Naglis Malys[3,19,20], Alexander Mazein[21], Jason A Papin[11], Nathan D Price[22], Evgeni Selkov, Sr[23], Martin I Sigurdsson[1], Evangelos Simeonidis[22,24], Nikolaus Sonnenschein[25], Kieran Smallbone[3,26], Anatoly Sorokin[21,27], Johannes H G M van Beek[28–30], Dieter Weichart[3,31], Igor Goryanin[21,32], Jens Nielsen[10], Hans V Westerhoff[3,28,33,34], Douglas B Kell[3,35], Pedro Mendes[3,4,36] & Bernhard Ø Palsson[1,7]

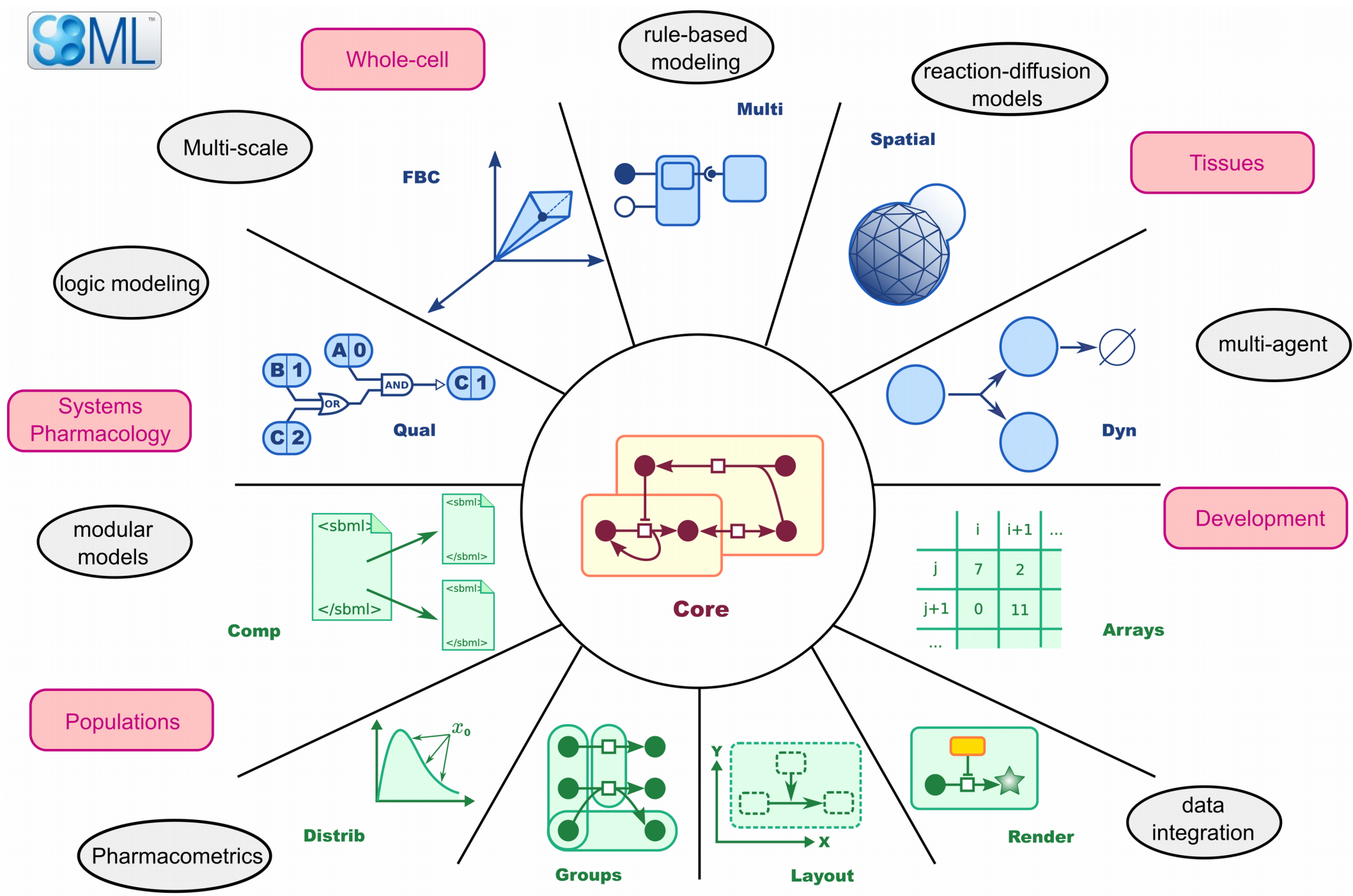
Multiple models of human metabolism have been reconstructed, but each represents only a subset of our knowledge. Here we describe Recon 2, a community-driven, consensus 'metabolic reconstruction', which is the most comprehensive representation of human metabolism that is applicable to computational modeling. Compared with its predecessors, the reconstruction has improved topological and functional features, including ~2× more reactions and ~1.7× more unique metabolites. Using Recon 2 we predicted changes in metabolite biomarkers for 49 inborn errors of metabolism with 77% accuracy when compared to experimental data. Mapping metabolomic data and drug information onto Recon 2 demonstrates its potential for integrating and analyzing diverse data types. Using protein expression data, we automatically generated a compendium of 65 cell type–specific models, providing a basis for manual curation or investigation of cell-specific metabolic properties. Recon 2 will facilitate many future biomedical studies and is freely available at http://humanmetabolism.org/.

An understanding of metabolism is fundamental to comprehending the phenotypic behavior of all living organisms, including humans, where metabolism is integral to health and is involved in much of human disease. High quality, genome-scale 'metabolic reconstructions' are at the heart of bottom-up systems biology analyses and represent the entire network of metabolic reactions that a given organism is known to exhibit[1]. The metabolic-network reconstruction procedure is now well-established[2] and has been applied to a growing number of model organisms[3]. Metabolic reconstructions allow for the conversion of biological knowledge into a mathematical format and the subsequent computation of physiological states[1,4,5] to address a variety of scientific and applied questions[3,6]. Reconstructions enable network-wide mechanistic investigations of the genotype-phenotype relationship. A high-quality reconstruction of the metabolic network is thus

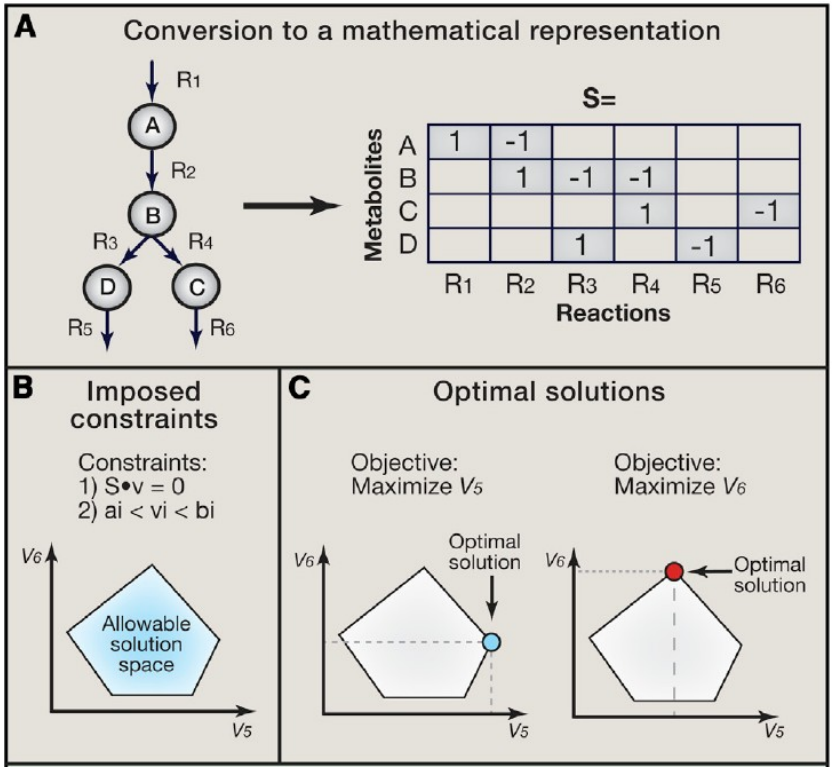


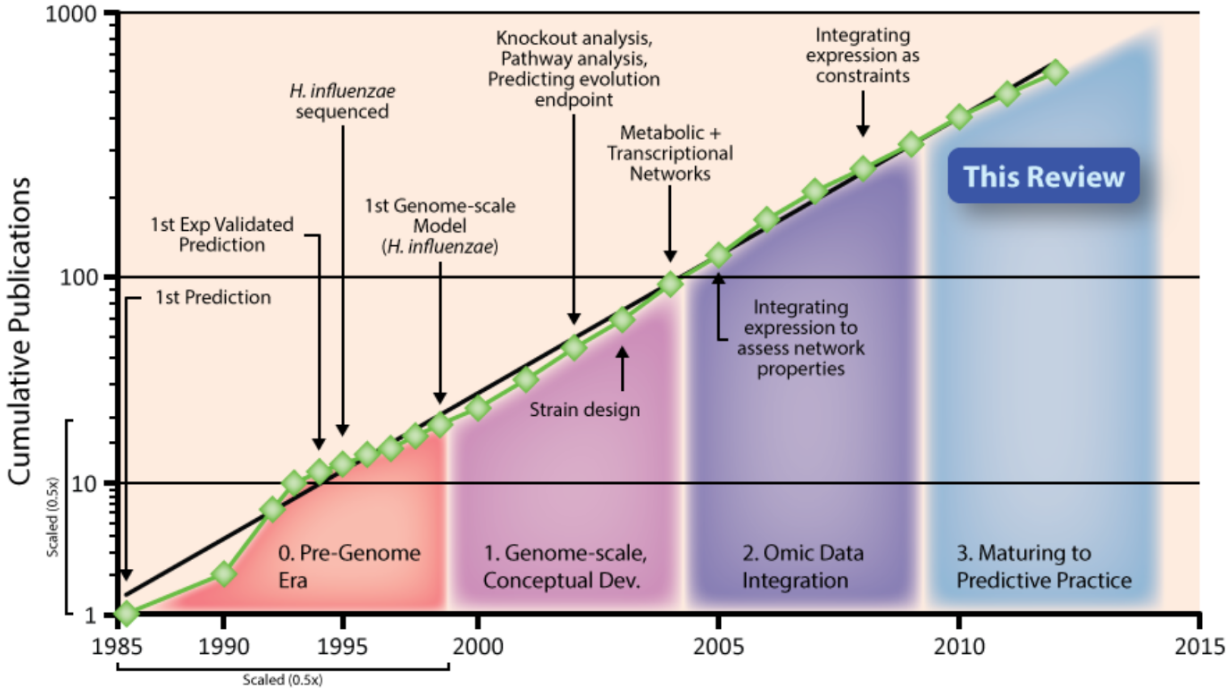
- 8 compartments
- 5 063 metabolites
- 2 194 proteins
- 7 440 reactions

MODEL1109130000



Babraham Institute





SBML Level 3 Package Specification

Do genome-scale models need exact solvers or clearer standards?

Ali Ebrahim, Eivind Almaas, Eugen Bauer, Aarash Bordbar, Anthony P Burgard, Roger L Chang, Andreas Dräger, Iman Famili, Adam M Feist, Ronan MT Fleming, Stephen S Fong, Vassily Hatzimanikatis, Markus J Herrgård, Allen Holder, Michael Hucka, Daniel Hyduke, Neema Jamshidi, Sang Yup Lee, Nicolas Le Novère, Joshua A Lerman, Nathan E Lewis, Ding Ma, Radhakrishnan Mahadevan, Costas Maranas, Harish Nagarajan, Ali Navid, Jens Nielsen, Lars K Nielsen, Juan Nogales, Alberto Noronha, Csaba Pal, Bernhard O Palsson, Jason A Papin, Kiran R Patil, Nathan D Price, Jennifer L Reed, Michael Saunders, Ryan S Senger, Nikolaus Sonnenschein, Yuekai Sun, Ines Thiele

Author Affiliations

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Molecular Systems Biology (2015) 11, 831

SBML Level 3 Package: Flux Balance Constraints ('fbc')

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Version 2, Release 1

September 12, 2015

Parent pages: SBML.org

Events

An important aspect of SBML development is face-to-face meetings, where developers, researchers and other interested persons meet each other and discuss their experiences and ongoing work. There are different kinds of events. *SBML Forum Meetings* are the annual working meetings of the SBML community and provide an opportunity to discuss SBML, its continued evolution, and software efforts to support SBML. *SBML Hackathons* are annual meetings of developers and provide an opportunity to discuss software interoperability of SBML-aware software. Finally, the community also organizes occasional special workshops aimed at pushing forward the development of specific SBML features.

Upcoming Events

COMBINE 2017 *(Coordinating Standards for Modeling in Biology)*
October 9–13, Milan, Italy.

All Events

SBML Forum Meetings [collapse]

Date(s)	Event	Location	Host(s)
Sept. 19–24, 2016	COMBINE 2016	Newcastle University, Newcastle upon Tyne, UK	Multiple groups
Oct. 12–16, 2015	COMBINE 2015	University of Utah, Salt Lake City, United States	Myers Group
Aug. 18–22, 2014	COMBINE 2014	University of Southern California, Los Angeles, United States	Keck School of Medicine of USC
Sep. 16–20, 2013	COMBINE 2013	Institut Curie, Paris, France	U900 Computationa Systems Biology of

Parent pages: SBML.org

Downloads

Software by the SBML Team and the BioModels.net Team

The SBML Project helps develop a variety of software packages for working with SBML. (Many more third-party packages also support SBML—visit the **SBML Software Guide** to find out more about them!)

LibSBML
A free, open-source **API** library for working with SBML content. It supports many programming languages and operating systems.

JSBML
A free, open-source, pure-Java library for working with SBML. It emulates libSBML's API, with more Java idioms and without native object code.

SBMLToolbox
A free, open-source package for working with SBML in **MATLAB**. It provides functions for reading, writing, manipulating, and simulating SBML models.

SBML Test Suite
A conformance testing suite for assessing a simulator's support for SBML. Includes test cases, a standalone runner, an online system, and a database.

MOCCASIN
A free, open-source package for translating ODE models written in MATLAB into models in SBML format.

Deviser
A system for defining and prototyping SBML Level 3 package definitions and code for libSBML.

SBMLeditor
A portable (written in Java), low-level, tree-structured editor for SBML. It supports annotations and validation.

SBML Converters
Today, there exist many converters that can translate between SBML and other formats; some were written by the BioModels Database team, and some by other groups. Visit our **Converters** page for more information.

SBML™

The Systems Biology Markup Language (SBML):
Language Specification for Level 3 Version 2 Core

Michael Hucka (Chair) — *California Institute of Technology, US*
Frank T. Bergmann — *California Institute of Technology, US*
Andreas Dräger — *University of Tübingen, DE*
Stefan Hoops — *Virginia Bioinformatics Institute, US*
Sarah M. Keating — *European Bioinformatics Institute, GB*
Nicolas Le Novère — *Babraham Institute, GB*
Chris J. Myers — *University of Utah, US*
Brett G. Olivier — *VU University Amsterdam, NL*
Sven Sahle — *University of Heidelberg, DE*
James C. Schaff — *University of Connecticut, US*
Lucian P. Smith — *University of Washington, US*
Dagmar Waltemath — *University of Rostock, DE*
Darren J. Wilkinson — *Newcastle University, GB*

sbml-editors@sbml.org

SBML Level 3 Version 2 Core

Release 1

05 December 2017

Corrections and other changes to this SBML language specification may appear over time. Notifications of new releases are broadcast on the mailing list sbml.org/forums/sbml-announce

The latest release of the SBML Level 3 Version 2 Core specification is available at http://sbml.org/specifications/sbml-level-3/version-2/core

This release of the specification is available at http://sbml.org/specifications/sbml-level-3/version-2/core/release-1/

The list of known issues in all releases of SBML Level 3 Version 2 Core is available at http://sbml.org/specifications/sbml-level-3/version-2/core/errata/

Formal schemas for use with XML are available at http://sbml.org/specifications/sbml-level-3/version-2/schemas/

SBML Systems Biology Markup Language

SBML.org The Systems Biology Markup Language

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Parent pages: SBML.org

SBML Software Guide

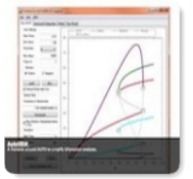
The following pages describe SBML-compatible software packages known to us. We offer different ways of viewing the information, all drawn from the same underlying data collected from the systems' developers via our **software survey**. The *Matrix* provides a table listing all known software and a variety of their features; the *Summary* provides general descriptions of most of the software; and the *Showcase* provides a sequential slideshow of a subset of the software.

Number of software packages listed in the matrix today: **290**.

Go to the SBML Software Matrix

Go to the SBML Software Summary

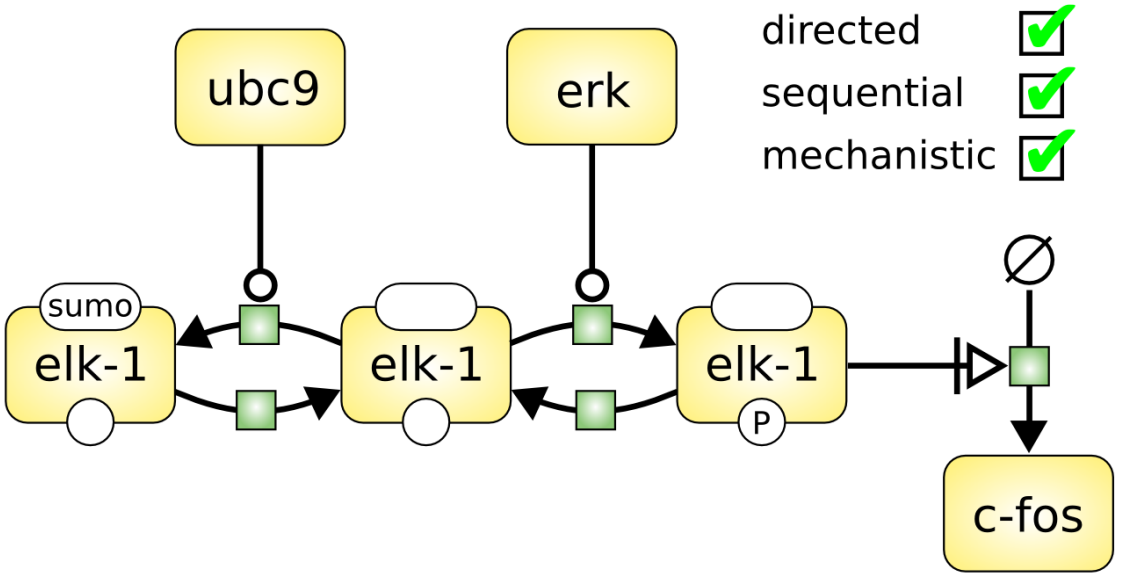
Go to the SBML Software Showcase



Please **tell us about additions and updates**.

Systems Biology Graphical Notation: One standard Three languages

process descriptions



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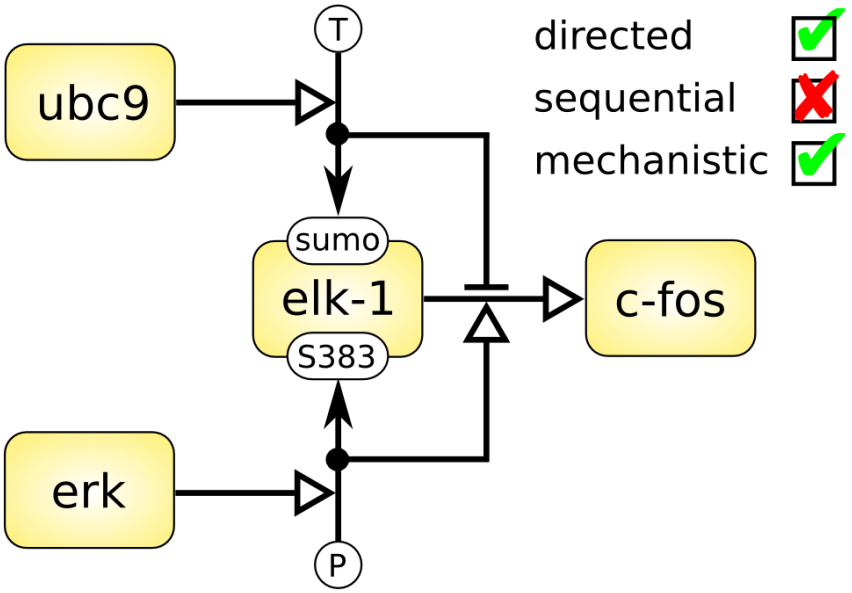
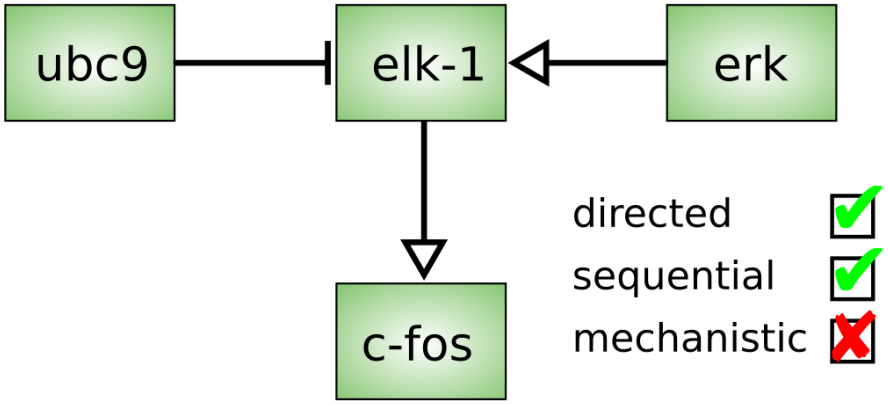


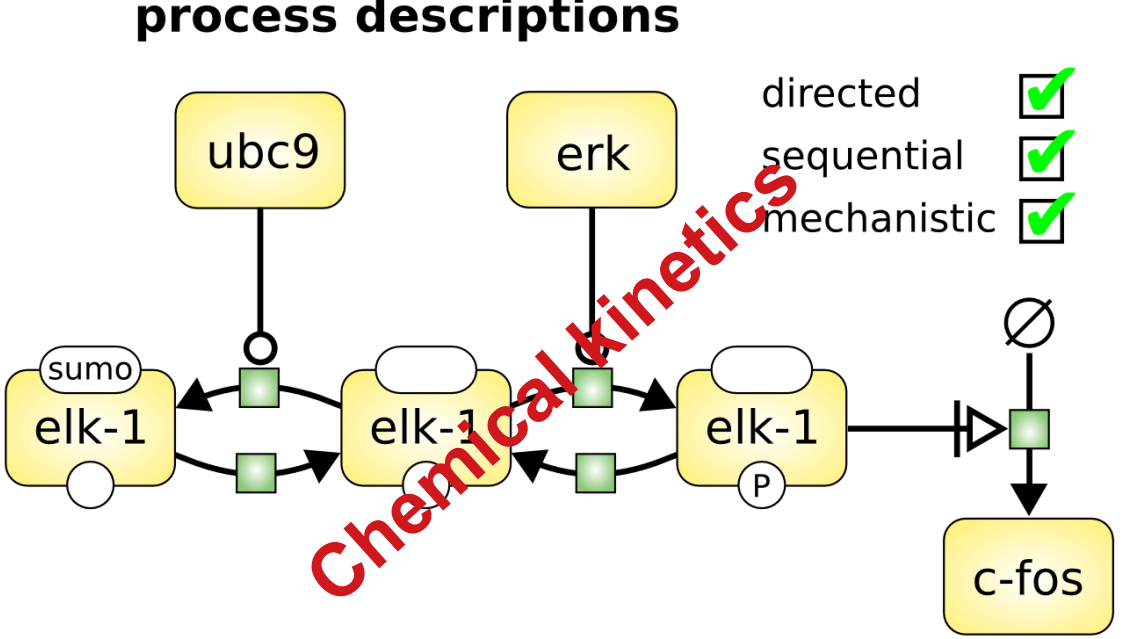
activity flows

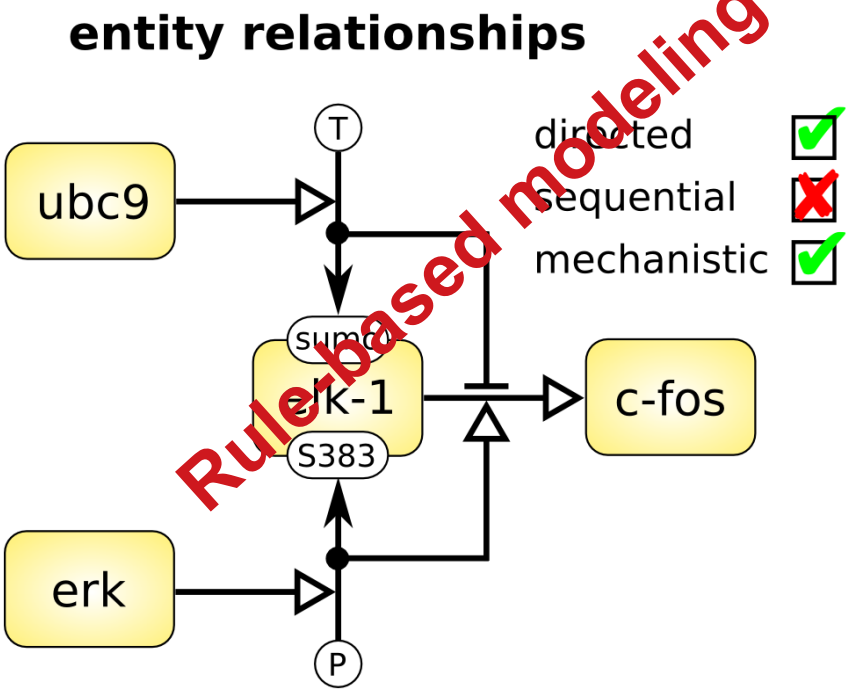


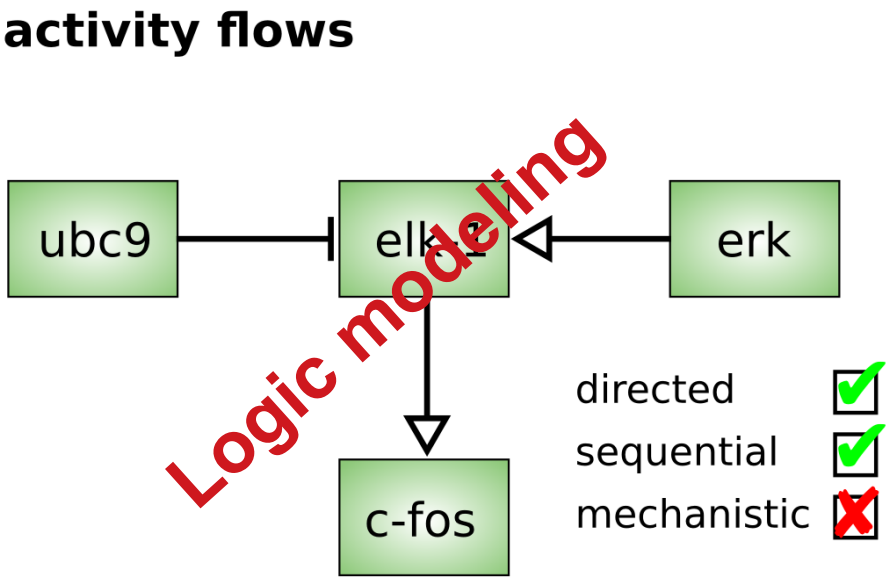
Le Novère et al. (2009)

http://sbgn.org/

Systems Biology Graphical Notation: One standard Three languages







Le Novère et al. (2009)

http://sbgn.org/

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  <map version="http://identifiers.org/combine.specifications/
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          <!-- Line breaks are allowed in the text attribute -->
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          <label text="Ethanal" />
          <bbox x="220" y="110" w="60" h="60"/>
      </glyph>
      <glyph class="macromolecule" id="glyph_adh1">
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      </glyph>
      <glyph class="simple chemical" id="glyph_h">
          <label text="H+" />
          <bbox x="220" y="190" w="60" h="60"/>
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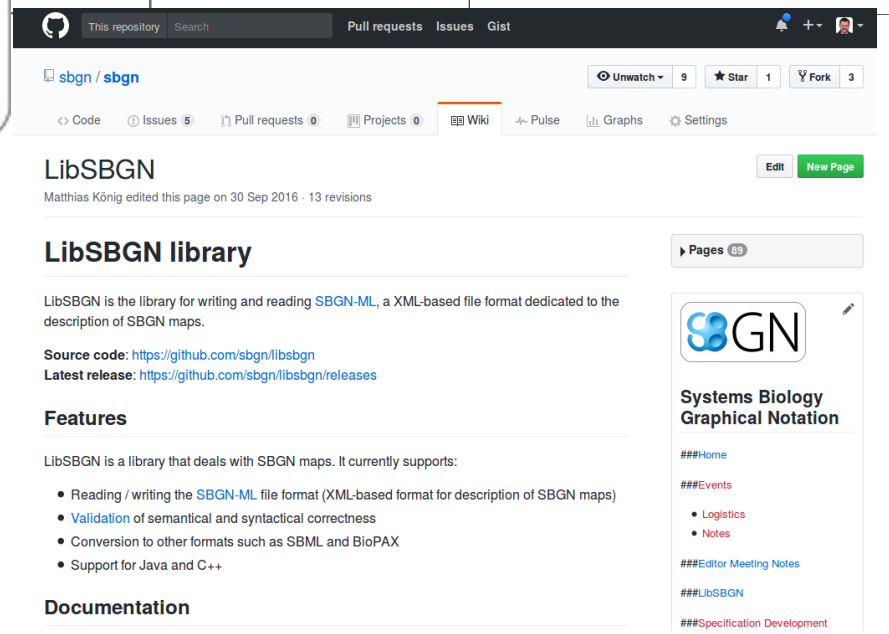
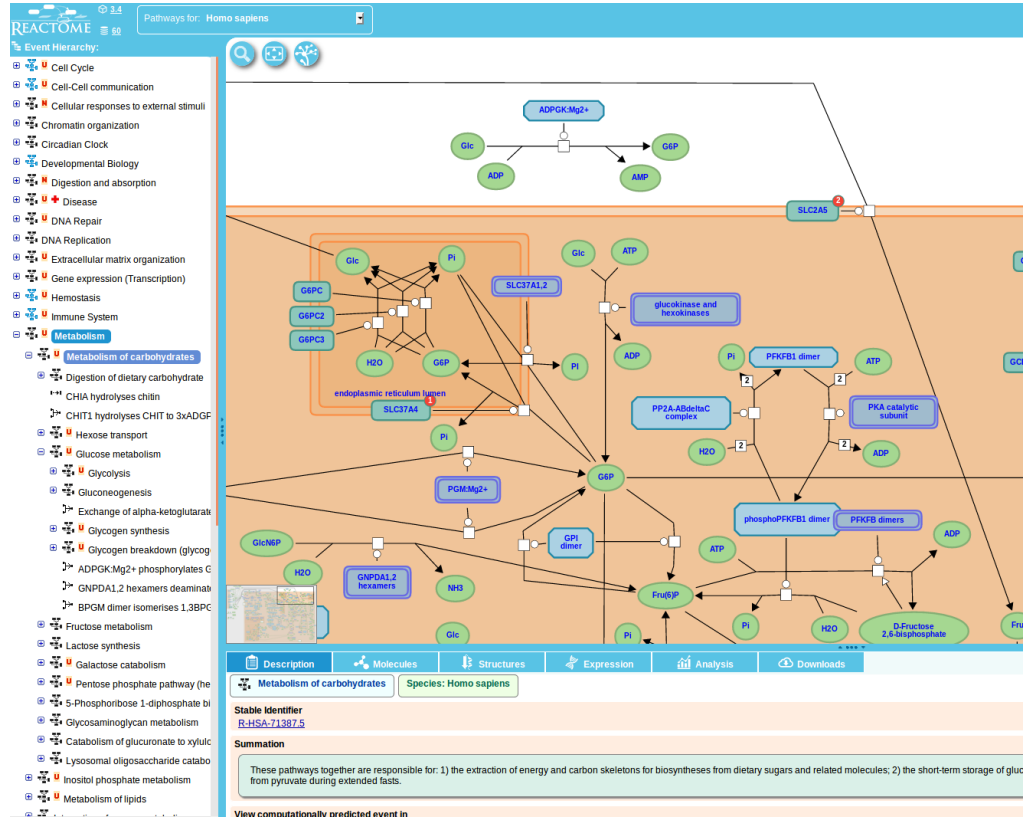
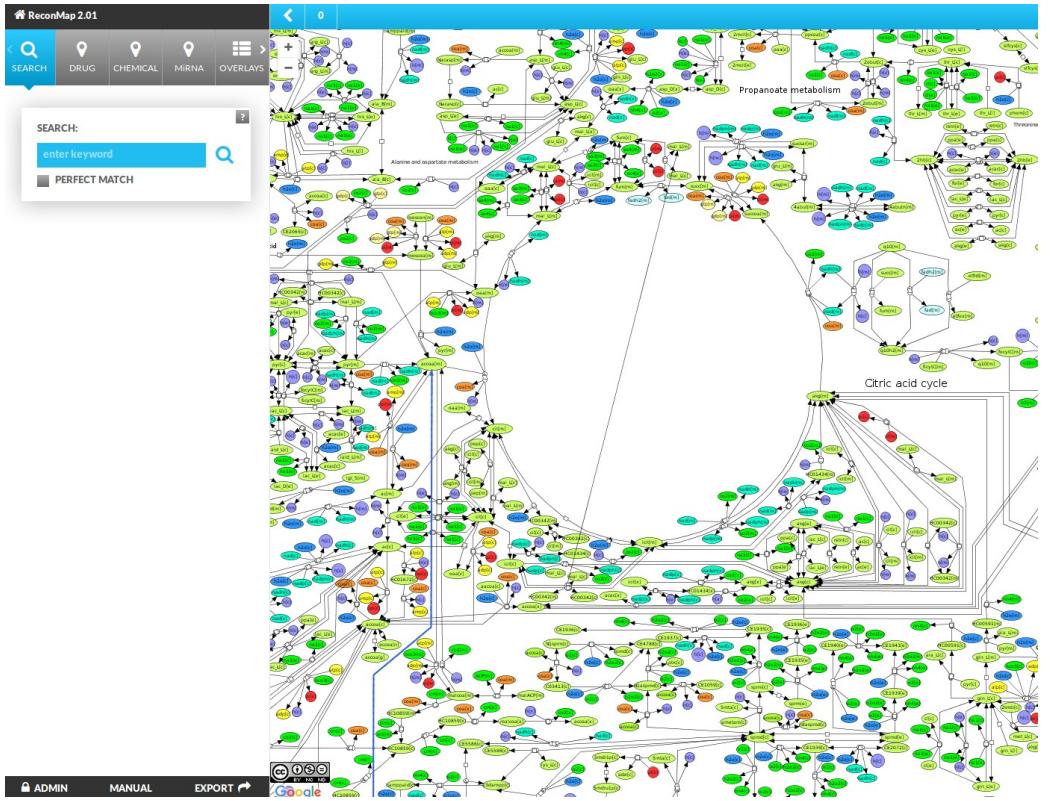


Babraham Institute


REACTOME
Pathways for: Homo sapiens
Event Hierarchy:
Cell Cycle
Cell-Cell communication
Cellular responses to external stimuli
Chromatin organization
Circadian Clock
Developmental Biology
Digestion and absorption
Disease
DNA Repair
DNA Replication
Extracellular matrix organization
Gene expression (Transcription)
Hemostasis
Immune System
Metabolism
Metabolism of carbohydrates
Digestion of dietary carbohydrate
CHIA hydrolyses chitin
CHIT1 hydrolyses CHIT to 3xADGF
Hexose transport
Glucose metabolism
Glycolysis
Gluconeogenesis
Exchange of alpha-ketoglutarate
Glycogen synthesis
Glycogen breakdown (glycog
ADPGK:Mg2+ phosphorylates G
GNPDA1,2 hexamers deaminate
BPGM dimer isomerises 1,3BPG
Fructose metabolism
Lactose synthesis
Galactose catabolism
Pentose phosphate pathway (he
5-Phosphoribose 1-diphosphate bi
Glycosaminoglycan metabolism
Catabolism of glucuronate to xyluc
Lysosomal oligosaccharide catabo
Inositol phosphate metabolism
Metabolism of lipids
ADPGK:Mg2+
Glc
G6P
ADP
AMP
SLC2A5
G6PC
G6PC2
G6PC3
Pi
SLC37A1,2
ATP
glucokinase and hexokinases
H2O
endoplasmic reticulum lumen
SLC37A4
PFKFB1 dimer
PP2A-ABdeltaC complex
PKA catalytic subunit
PGM:Mg2+
GlcN6P
GPI dimer
phosphoPFKFB1 dimer
PFKFB dimers
GNPDA1,2 hexamers
NH3
Fru(6)P
D-Fructose 2,6-bisphosphate
Description
Molecules
Structures
Expression
Analysis
Downloads
Metabolism of carbohydrates
Species: Homo sapiens
Stable Identifier
R-HSA-71387.5
Summation
These pathways together are responsible for: 1) the extraction of energy and carbon skeletons for biosynthesis from dietary sugars and related molecules; 2) the short-term storage of gluc
from pyruvate during extended fasts.
View computationally predicted event in


ReconMap 2.01
SEARCH
DRUG
CHEMICAL
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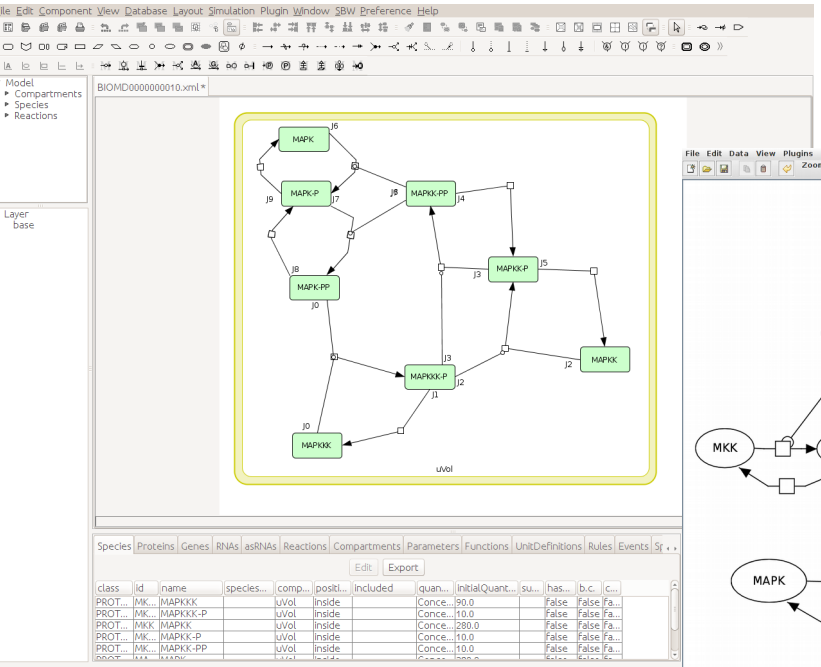
SEARCH:
enter keyword
PERFECT MATCH
ADMIN
MANUAL
EXPORT
Propanoate metabolism
Citric acid cycle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MAPK
MAPK-P
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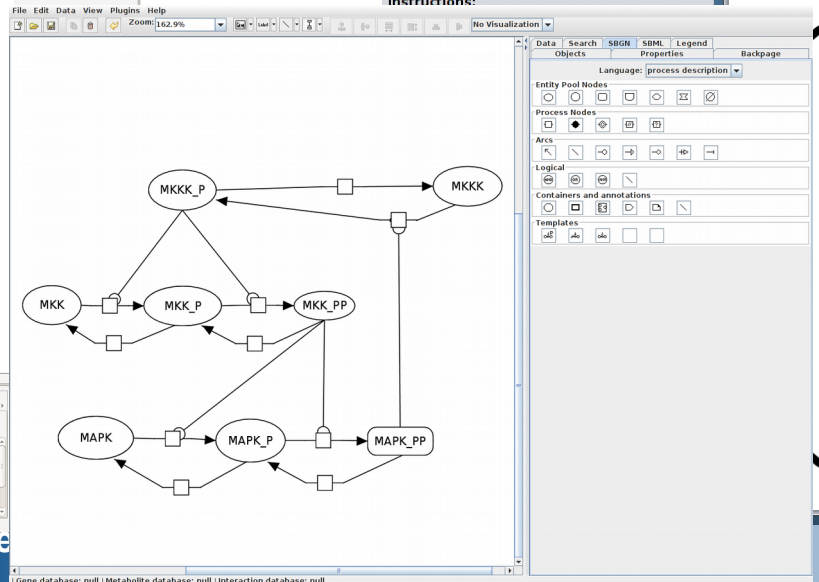
Proteins
Genes
RNAs
asRNAs
Reactions
Compartments
Parameters
Functions
UnitDefinitions
Rules
Events


MKKK_P
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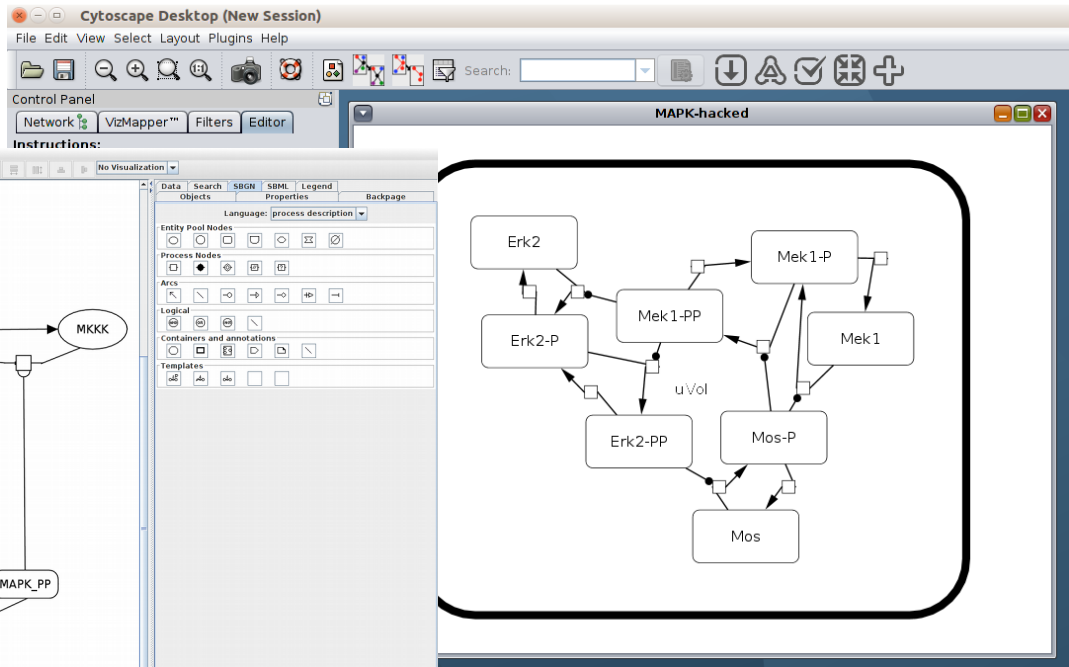
Data
Search
SBGN
SBML
Legend
Entity Pool Nodes
Process Nodes
Arcs
Logical
Containers and annotations
Templates


Cytoscape Desktop (New Session)
File Edit View Select Layout Plugins Help
Control Panel
Network
VizMapper™
Filters
Editor
MAPK-hacked
Erk2
Mek1-P
Mek1-PP
Mek1
Erk2-P
uVol
Erk2-PP
Mos-P
Mos

combine the computational modeling in biology network

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COMBINE

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lenov

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  - CoLoMoTo Page
  - HTML Page
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  - Panel
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  - URL aliases Admin
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- Administer
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- Junk

Coordinating standards for modeling in biology

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The 'COmputational Modeling in BIology' NEtwork (COMBINE) is an initiative to coordinate the development of the various community standards and formats for computational models. By doing so, it is expected that the federated projects will develop a set of interoperable and non-overlapping standards covering all aspects of modeling in biology.

Building on the experience of mature projects, which already have stable specifications, software support, user-base and community governance, COMBINE will help foster or support fledgling efforts aimed at filling gaps or new needs. As those efforts mature, they may become part of the core set of COMBINE standards.

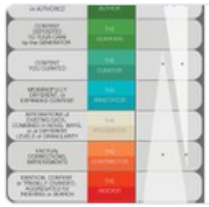
One of the initial activities of COMBINE is to coordinate the organization of scientific and technical events common to several standards. Those events, as others related to our field of research are gathered in a calendar.

To receive announcements from COMBINE, subscribe to the twitter [https://twitter.com/combine_coord COMBINE news]

To discuss the goals, organization and operation of COMBINE, subscribe to [https://groups.google.com/forum/?hl=en-GB#!forum/combine-discuss COMBINE discuss]. To report issues about the co.mbine.org website, send a mail to combine-support @ googlegroups.com

Tweets by @combine_coord

COMBINE @combine_coord
Best practises in building and using identifiers. Identifiers.org can help journals.plos.org/plosbiology/ar…



Identifiers for the 21st century: …
In many disciplines, data are highly decentralized across thousands of
journals.plos.org

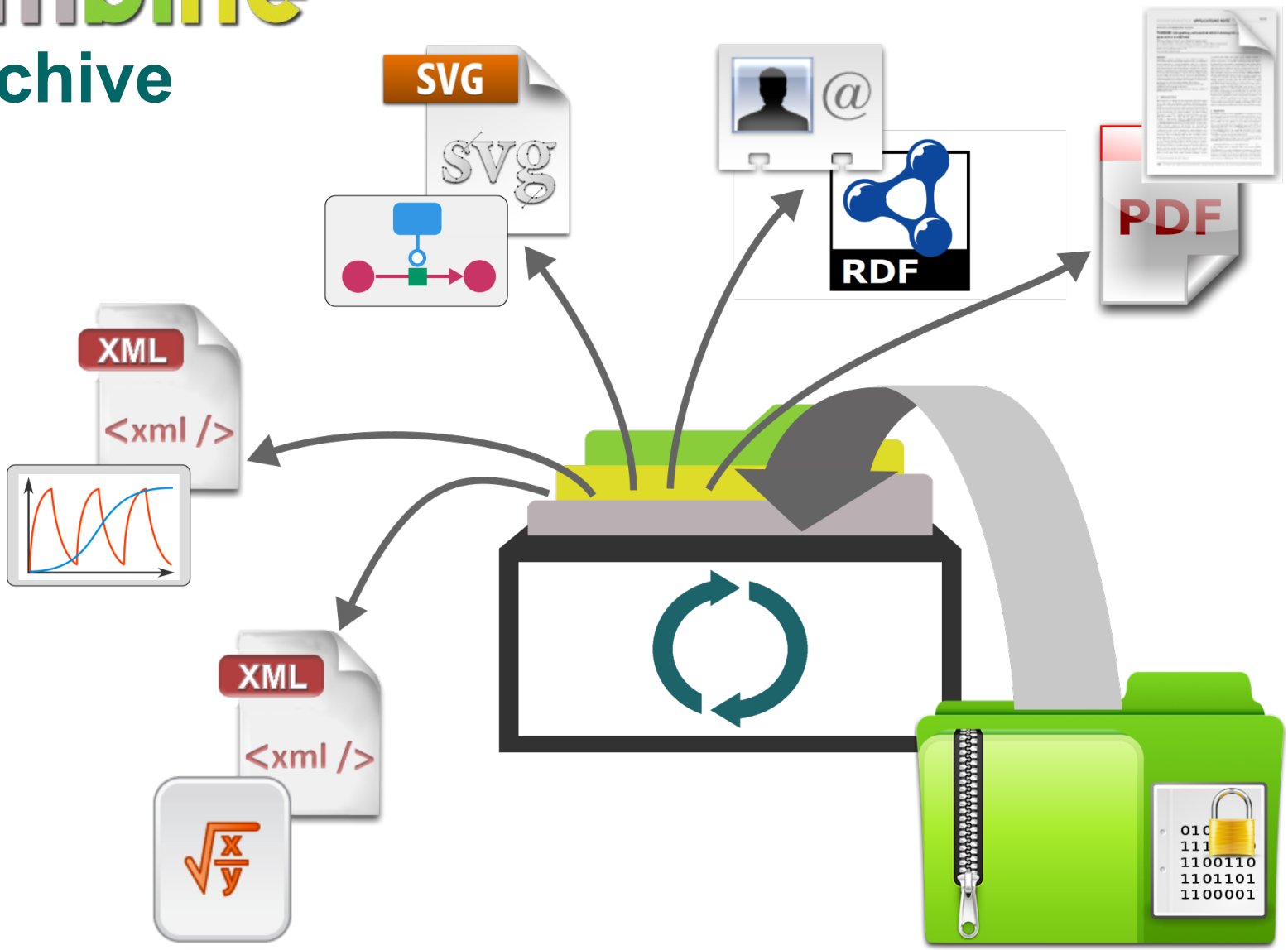
2h

COMBINE @combine_coord
COMBINE 2017, 9-13 Oct, Milano. Register before Aug 1st co.mbine.org/events/COMBINE… #SBML #SBGN #BioPAX #SBOL #SEDML #NeuroML #CellML

06 Jul

https://co.mbine.org

combine archive



https://co.mbine.org/standards/omex

Bergman *et al. BMC Syst Biol* (2014)

Pecunia est nervus belli

The Computational Modeling of Biological Systems (SysMod) Community of Special Interest (COSI) of the International Society for Computational Biology (ISCB) is a forum for discussion about the combined use of systems biology modeling and bioinformatics to understand biology and disease. SysMod encompasses all methods used in bioinformatics and systems biology, as well as all biological systems and all applications areas. The main activities of SysMod include an annual meeting at the Intelligent Systems for Molecular Biology (ISMB) conference organized by the ISCB and an online forum.

Annual meeting

The main activity of SysMod is an annual 1-day meeting at the annual Intelligent Systems in Molecular Biology (ISMB) conference organized by the International Society for Computational Biology (ISCB). The meeting is a forum for discussion about the integration of systems biology and bioinformatics. The meetings include keynote talks, contributed talks, and poster sessions. The third annual SysMod meeting will take place on July 7, 2018 in Chicago. Please see the meeting page for more information.

Google Group

The SysMod Google Group is an forum for discussion among systems biologists and bioinformaticians. Please visit Google Groups to join.

News

The third annual SysMod meeting will be held on July 7, 2018 during the ISMB conference in Chicago.

Twitter feed

SysMod Retweeted

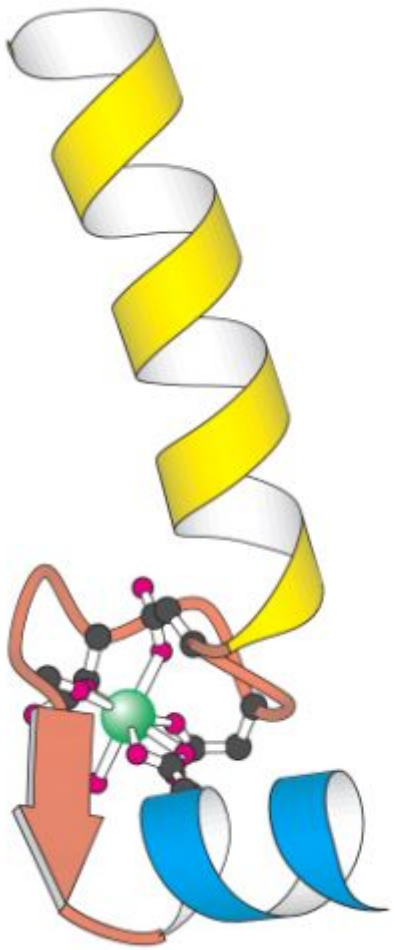
SysMod
@cosi_sysmod

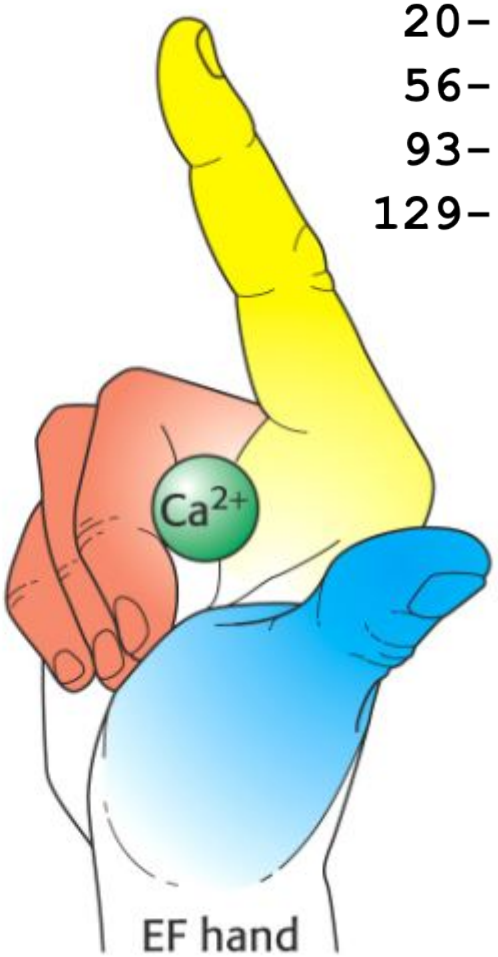
Tomorrow is the deadline to submit abstract for #sysmod #ismb2018. Submit athttps://www.iscb.org /ismb2018-submit/ismb2018-abstracts selecting SysMod in the proposed COSIs. NB: There will be a late poster call, but w/o option of talk.

Apr 4, 2018

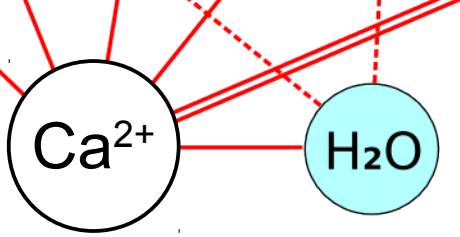
SysMod
@cosi_sysmod

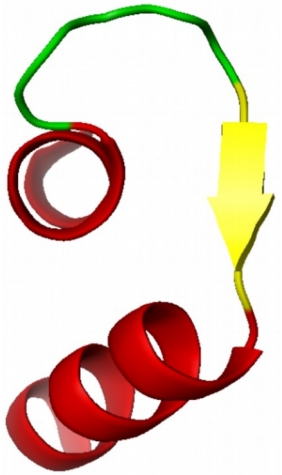
Calmodulin carries 4 Ca^{2+} binding domains

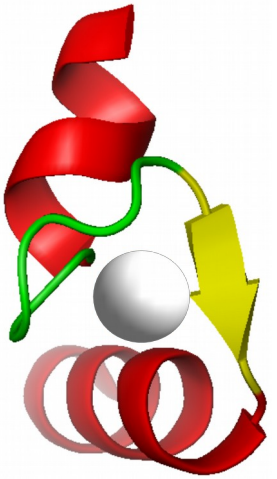


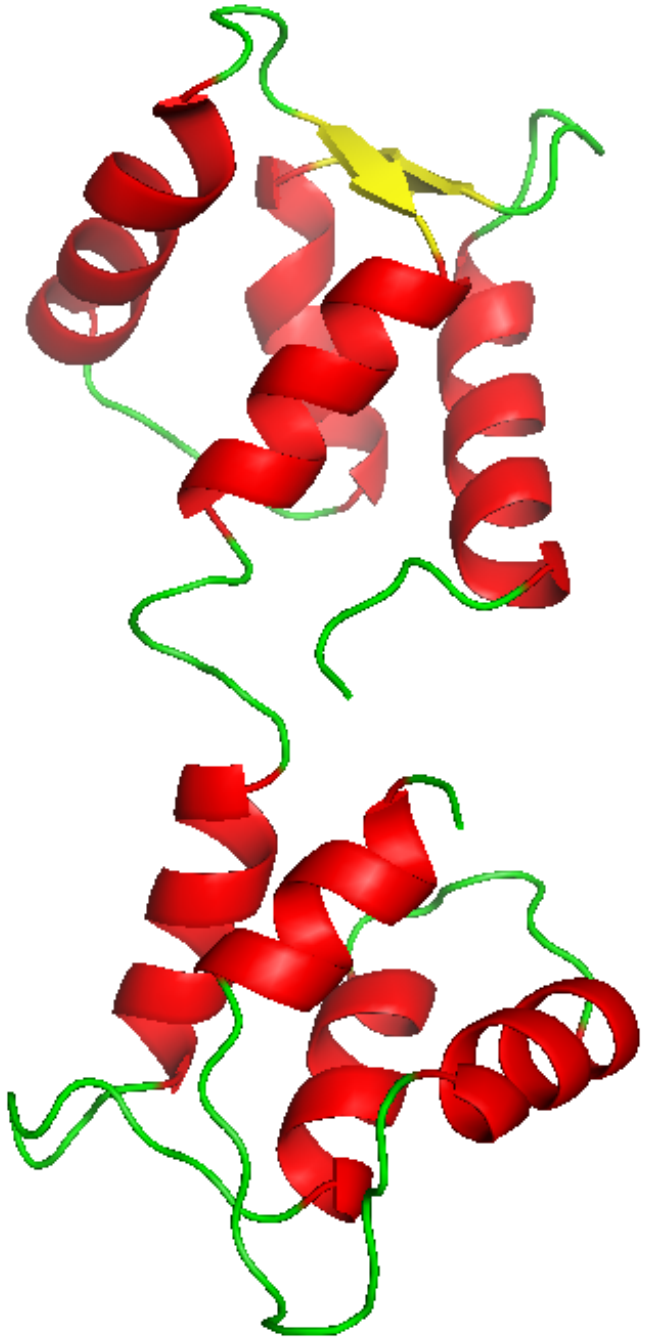


	X	Y	Z	-Y	-X	-Z	
20-	D	K	D	G	D	G	T	I	T	T	K	E	- 31
56-	D	A	D	G	N	G	T	I	D	F	P	E	- 67
93-	D	K	D	G	N	G	Y	I	S	A	A	E	-104
129-	D	I	D	G	D	G	Q	V	N	Y	E	E	-140

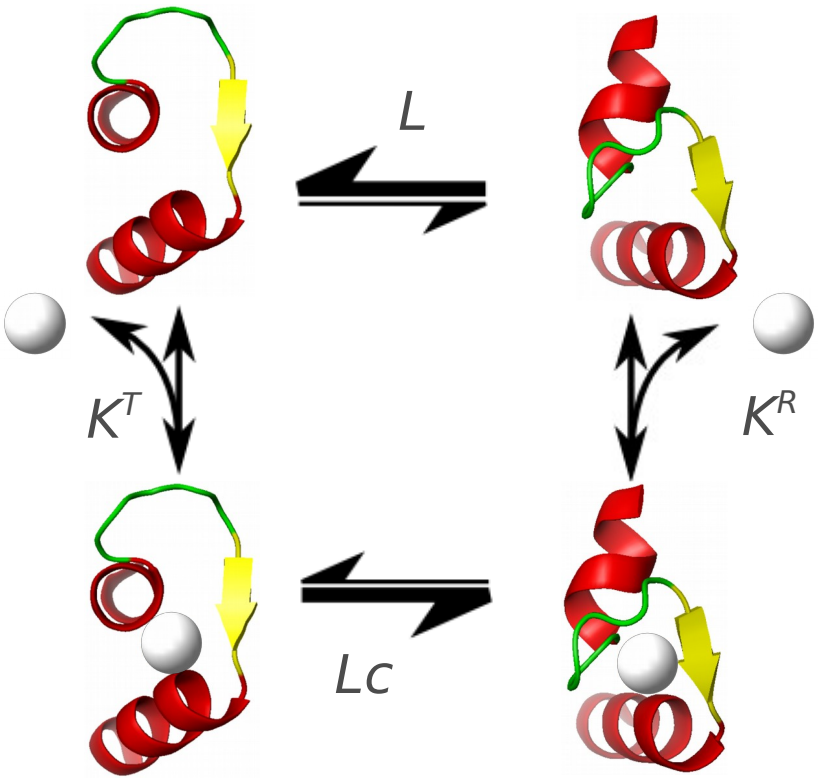


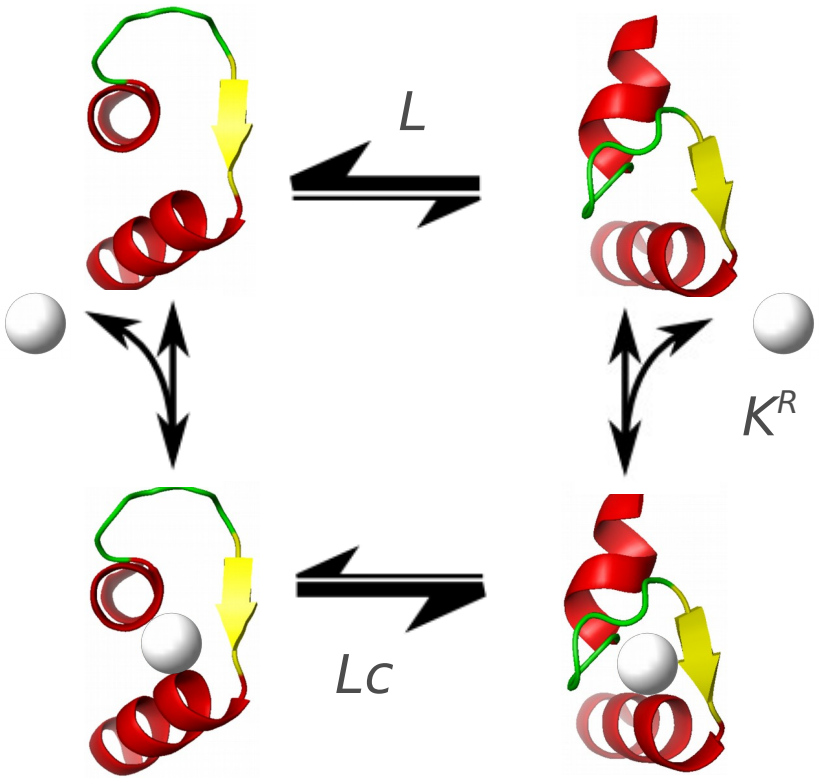


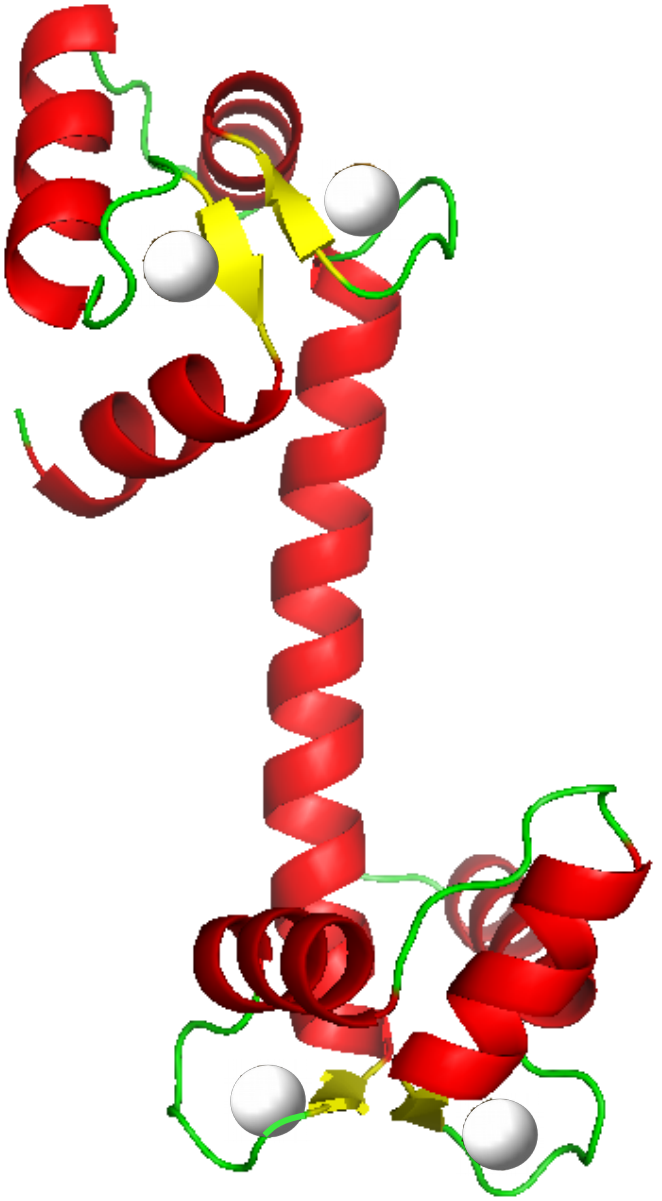




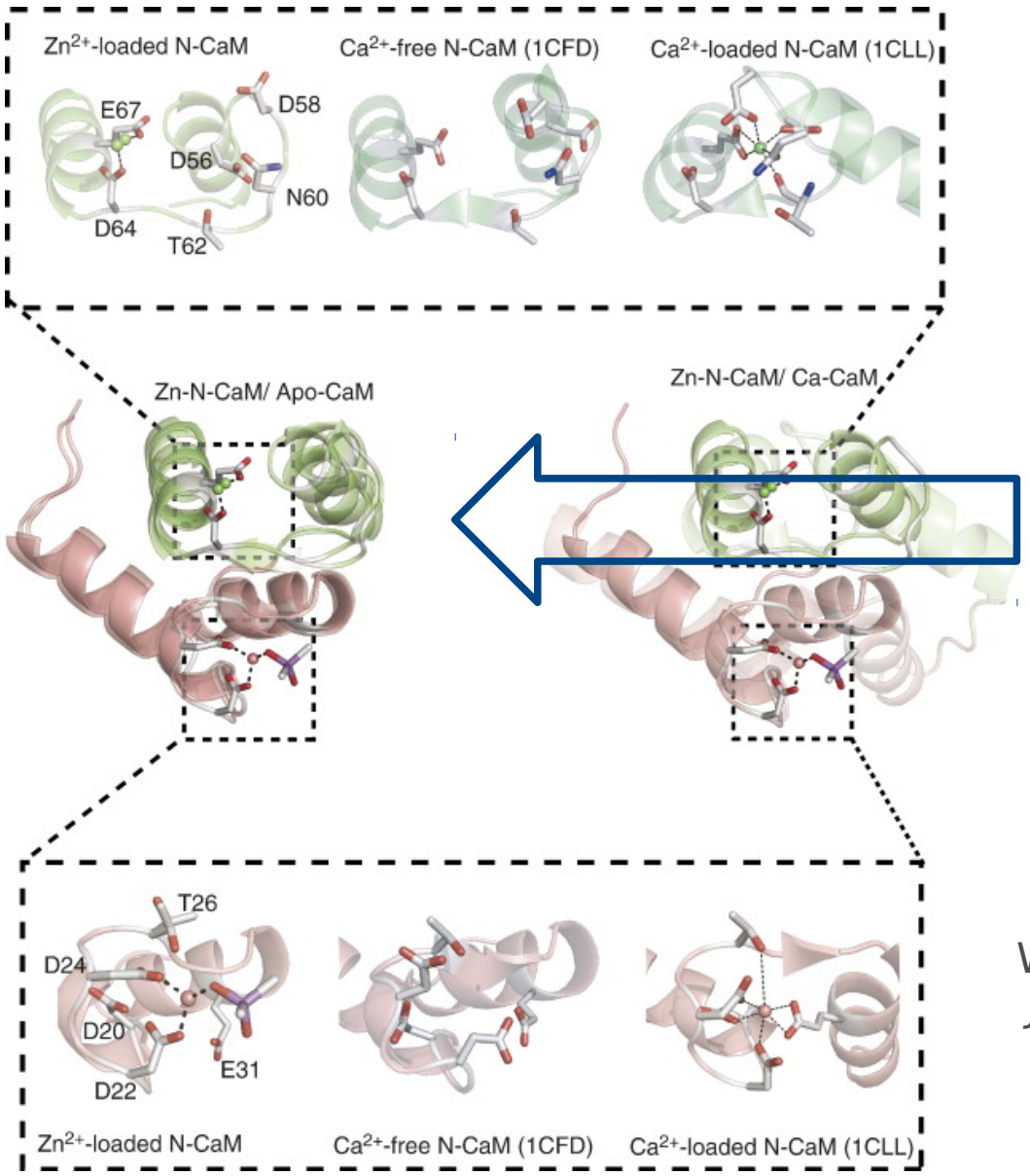
Kuboniwa *et al.* (1995).
Nat Struct Biol 2: 768-776

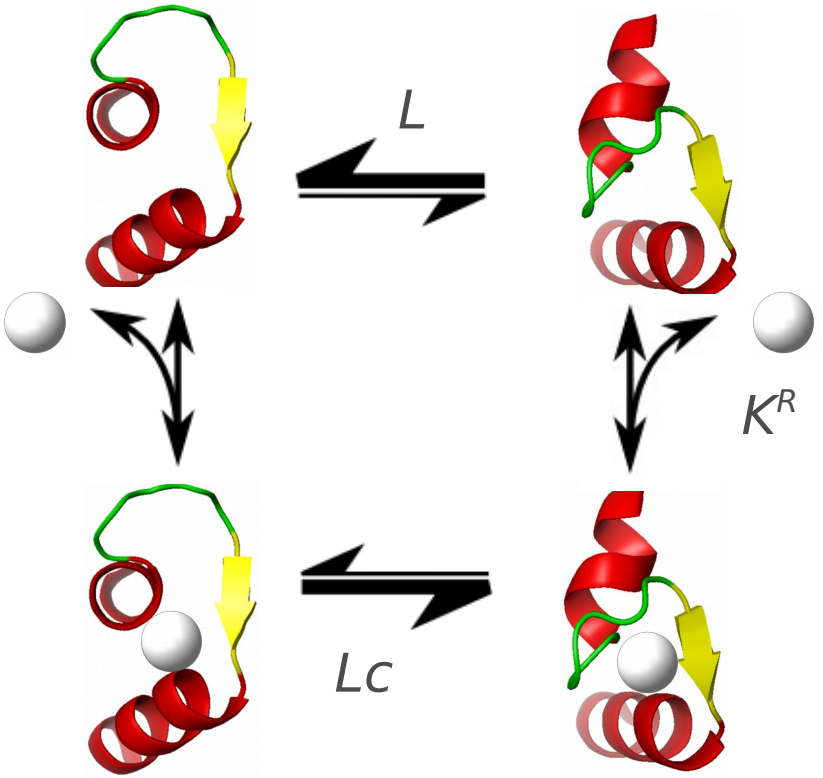






Babu *et al.* (1985).
Nature 315: 37-40





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

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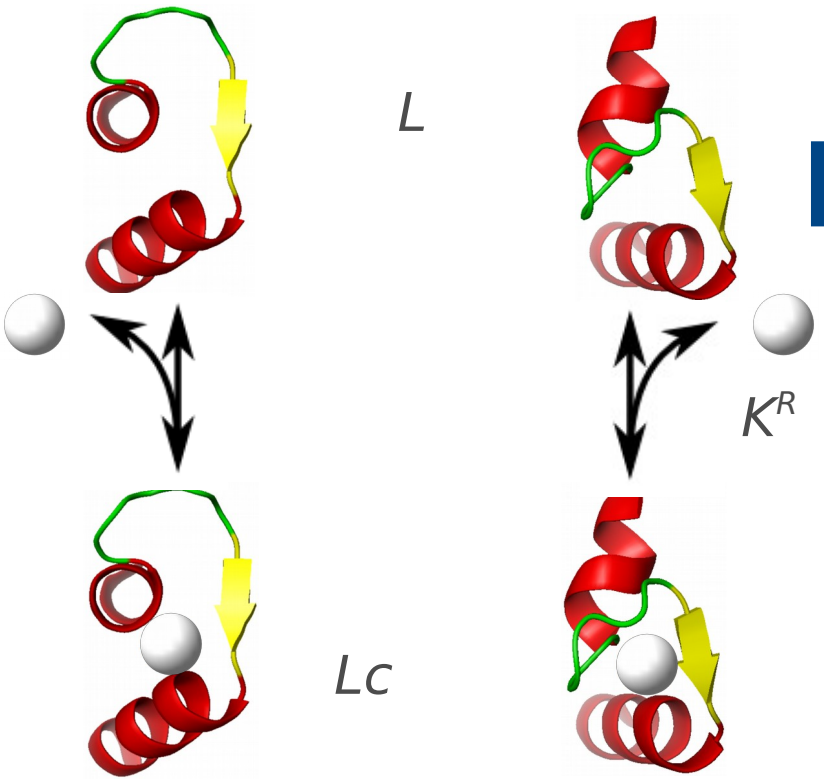
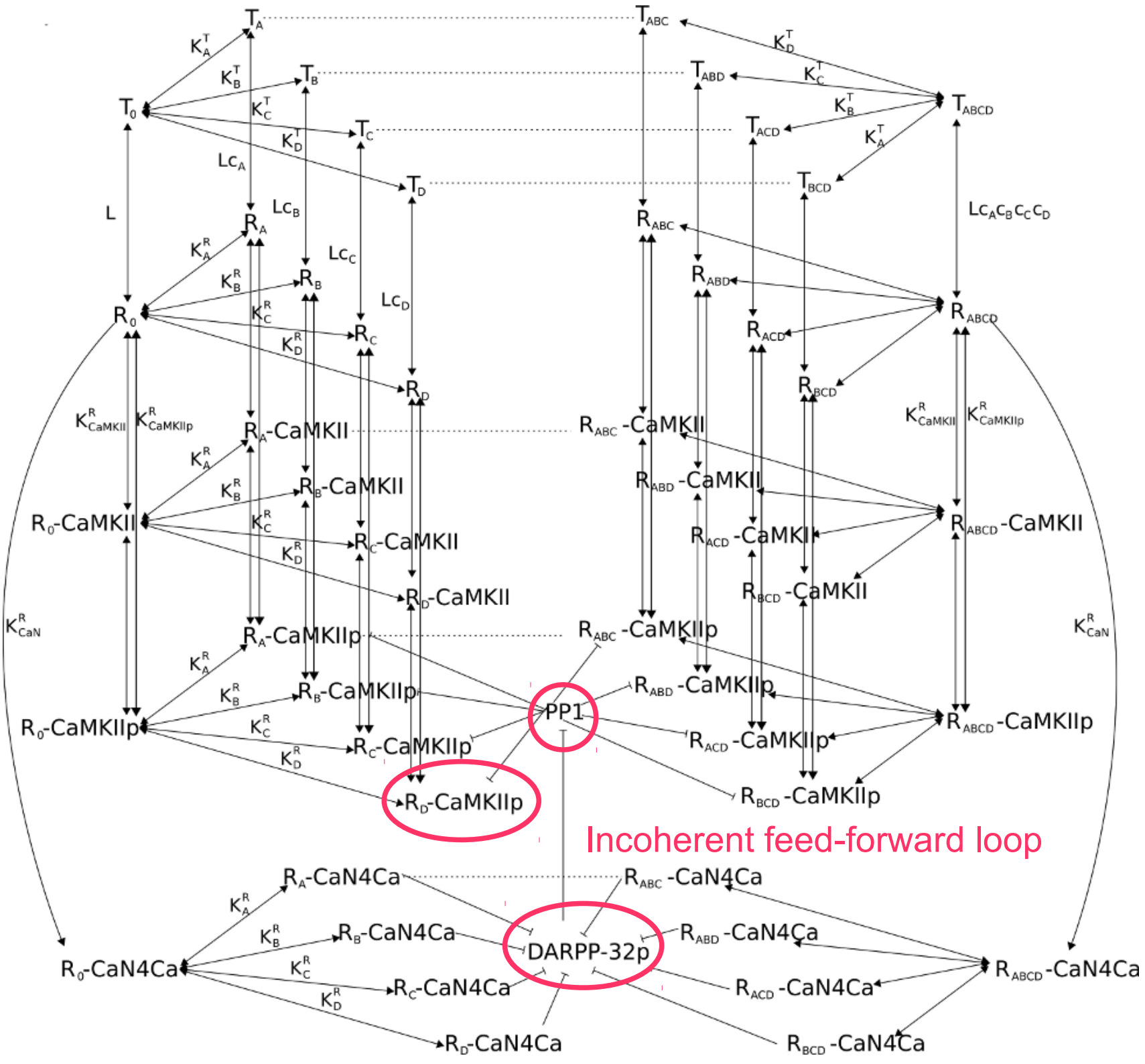

L
K^R
Lc

?


T0
TA
TB
TC
TD
TABC
TABD
TACD
TBCD
TABCD
KAT
KBT
KCT
KDT
LcA
LcB
LcC
LcD
LcAcBcCcD
L
R0
RA
RB
RC
RD
RABC
RABD
RACD
RBCD
RABCD
KRCaMKII
KRCaMKIIp
KRCaN
KAR
KBR
KCR
KDR
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
Incoherent feed-forward loop
R0-CaN4Ca
RA-CaN4Ca
RB-CaN4Ca
RC-CaN4Ca
RD-CaN4Ca
RABC-CaN4Ca
RABD-CaN4Ca
RACD-CaN4Ca
RBCD-CaN4Ca
RABCD-CaN4Ca
DARPP-32p

Parametrisation 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

Activity of unsaturated calmodulin (state function)

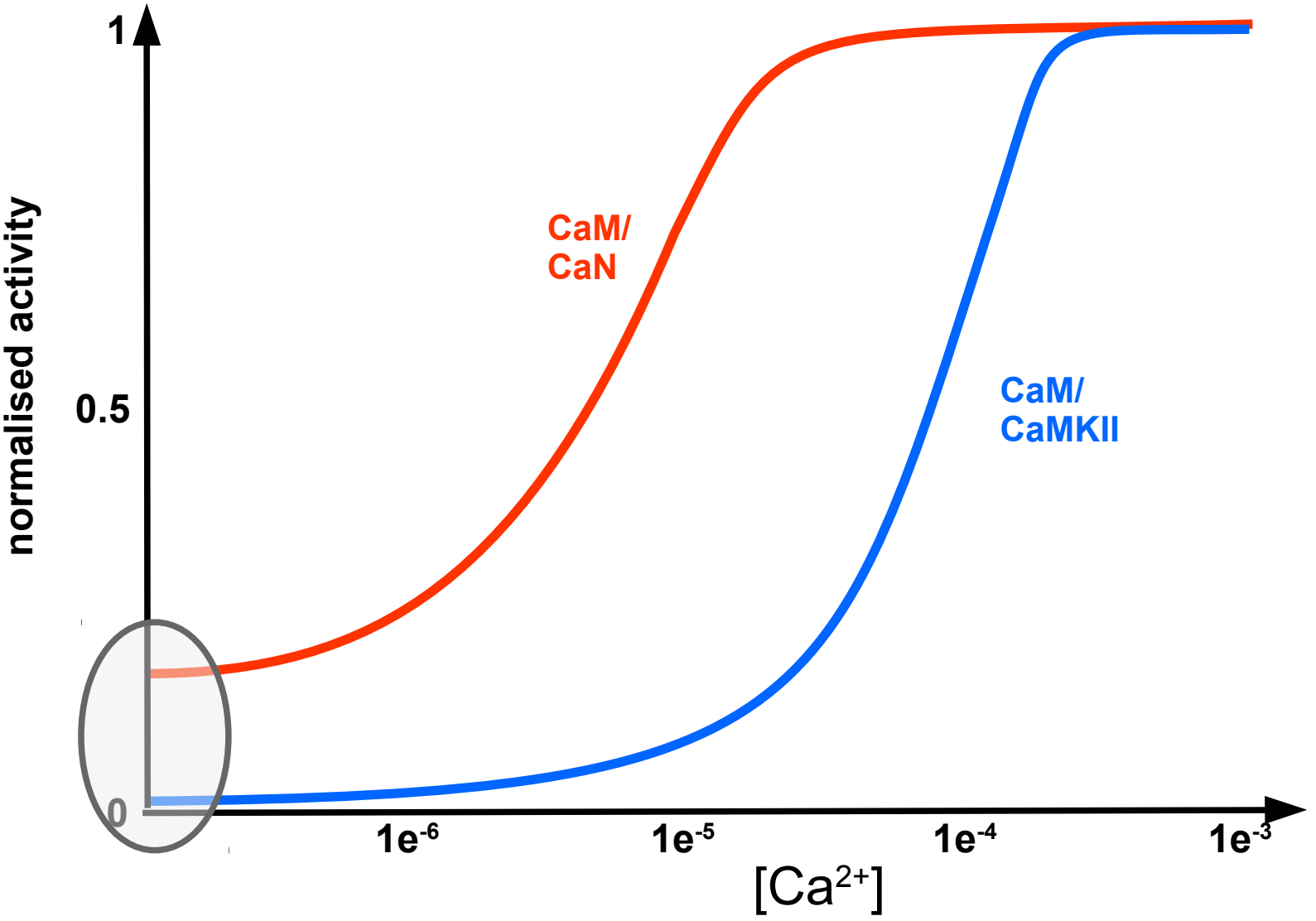
- Fractional activity depends on the number of calcium ions bound

$$\frac{R_i}{T_i} = \frac{1}{L \cdot c^i}$$

- $R_0/T_0 = 1/20000$ (1/L)
- $R_1/T_1 = 1/170$
- $R_2/T_2 = 0.69$ → half-saturation ≈ equi-probability
- $R_3/T_3 = 780$
- $R_4/T_4 = 10000$

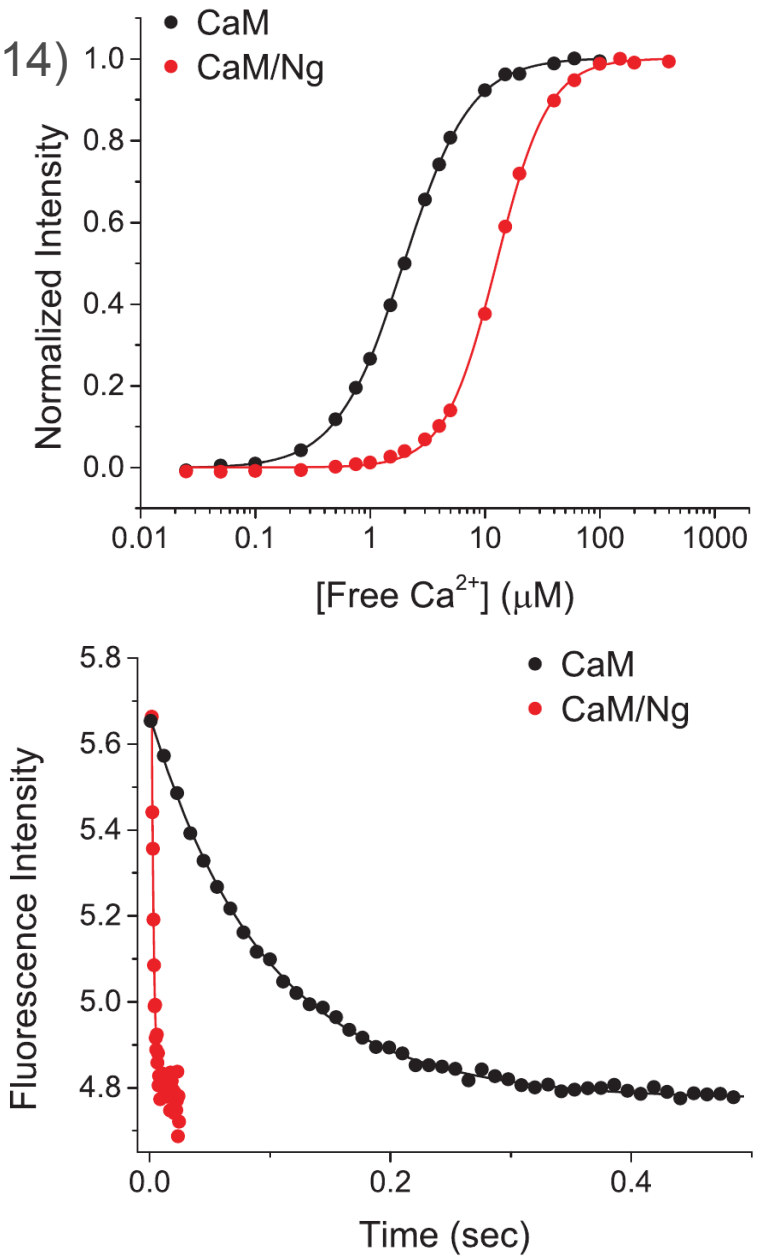
Do we need to represent the four calcium bindings to understand Calmodulin activation?

Calcineurin stabilises CaM R → no deactivation



Neurogranin affects Ca^{2+} binding to CaM

Hoffman *et al* (2014)



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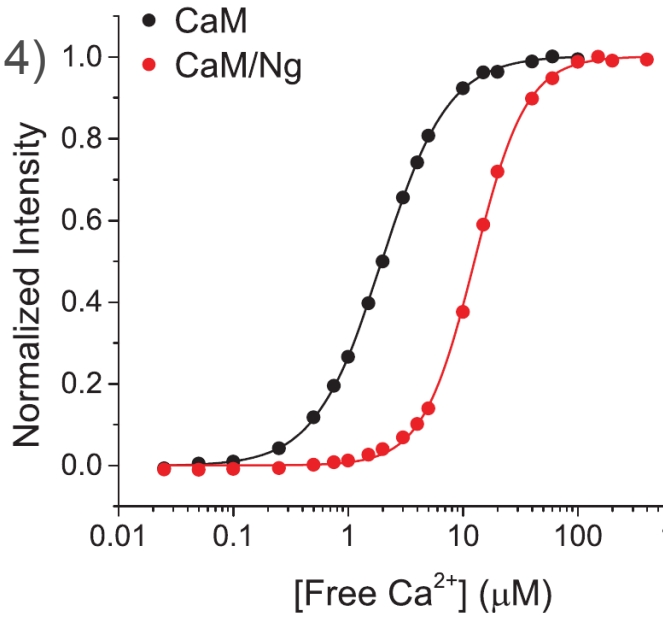
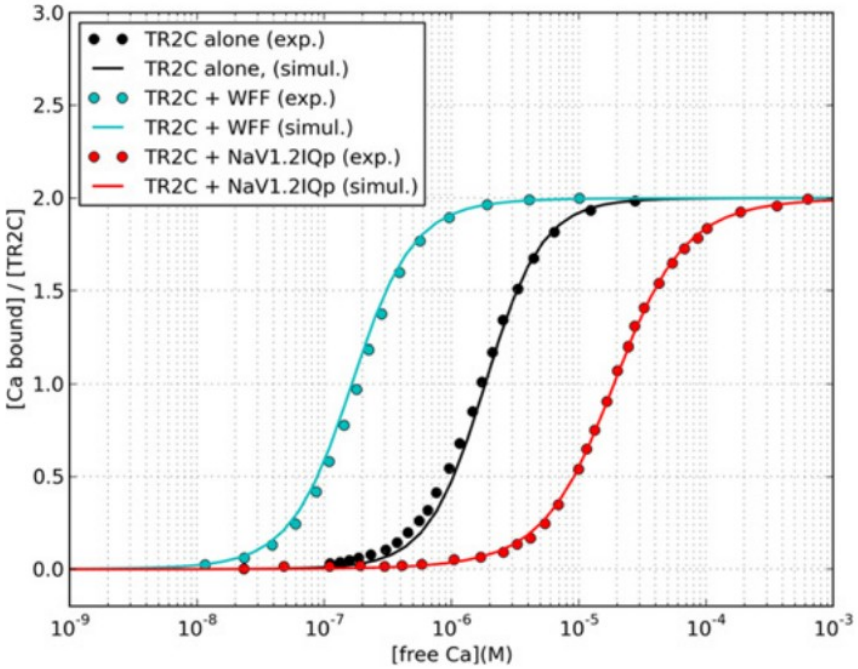
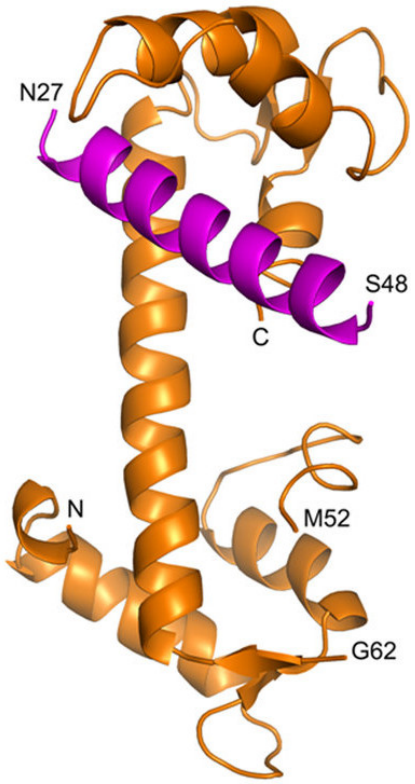
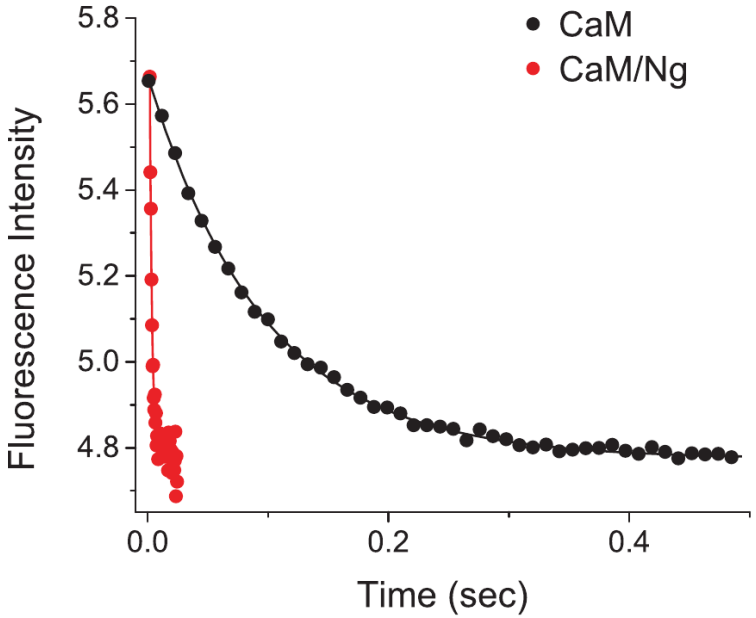
Hoffman *et al* (2014)

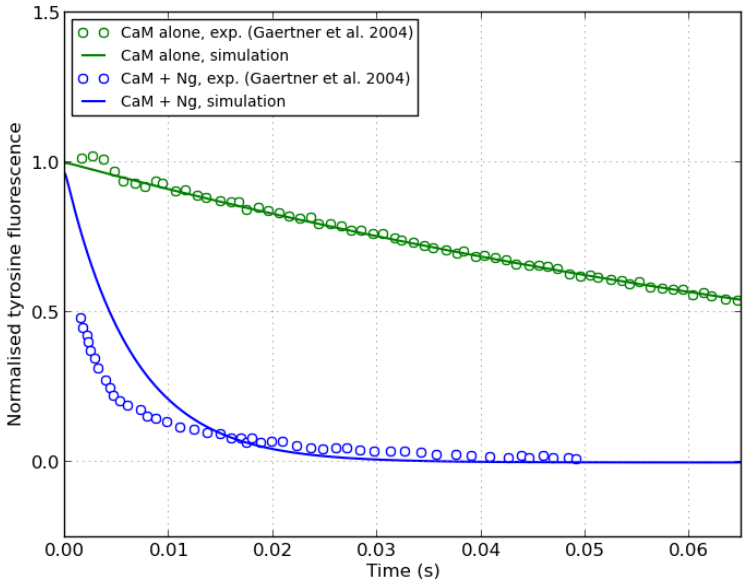






Kumar *et al* (2013)





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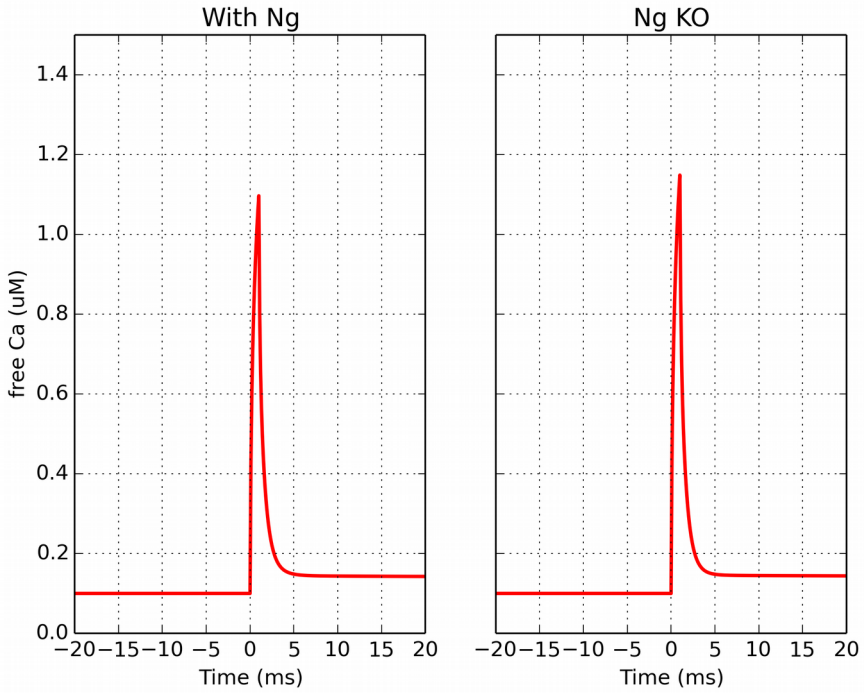
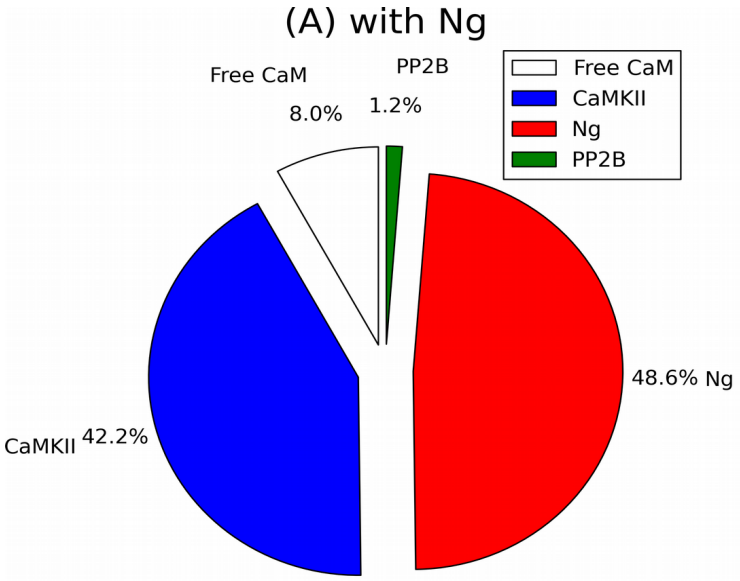
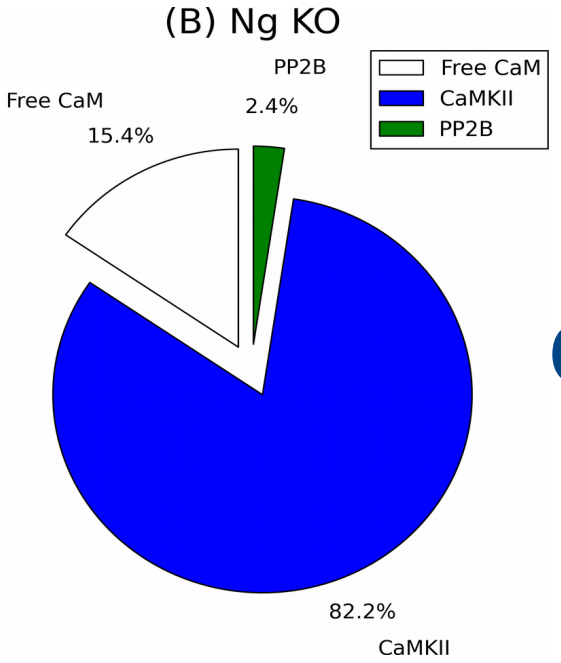
No large effect of Ng on [Ca^{2+}free]







Ng affects CaM distribution

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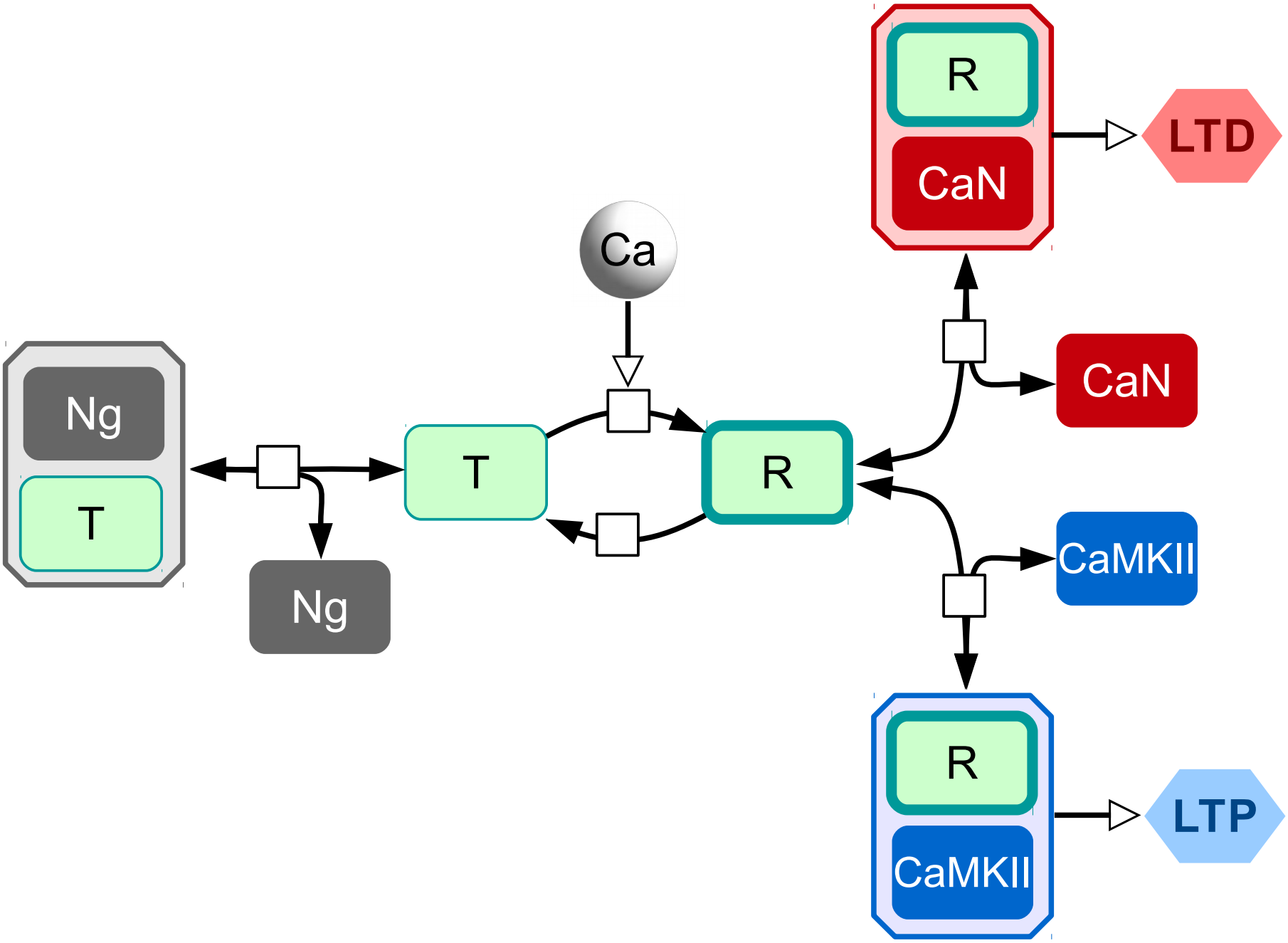
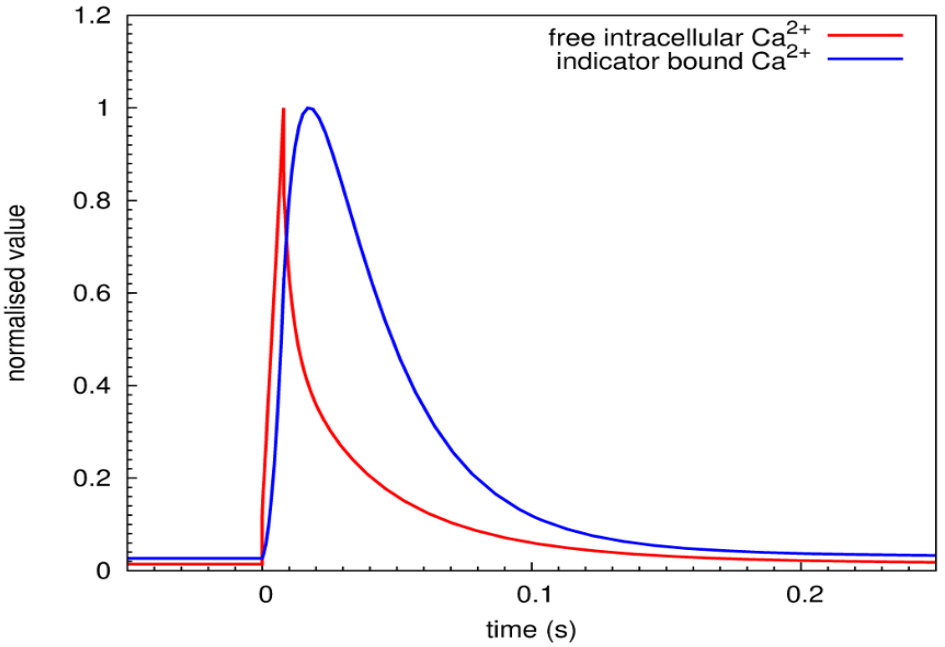
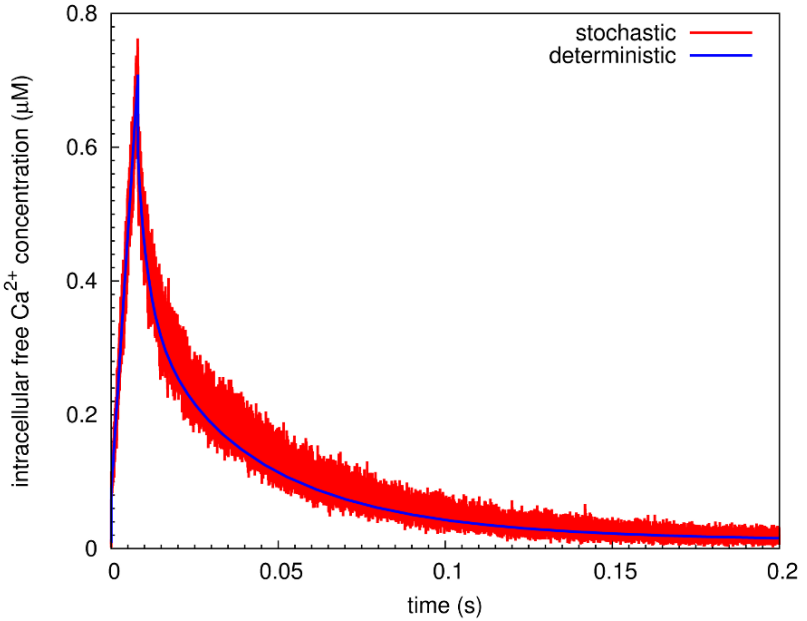
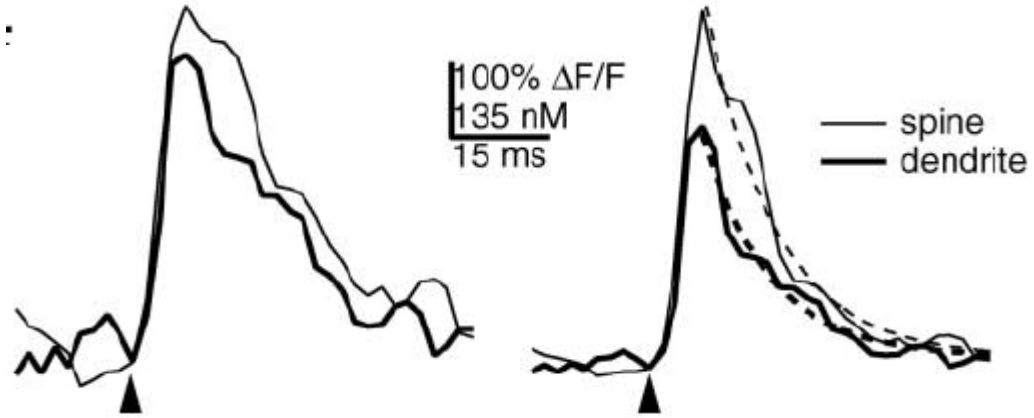

R
CaN
LTD
Ca
Ng
T
CaN
T
R
Ng
CaMKII
R
CaMKII
LTP

Are those spikes realistic?





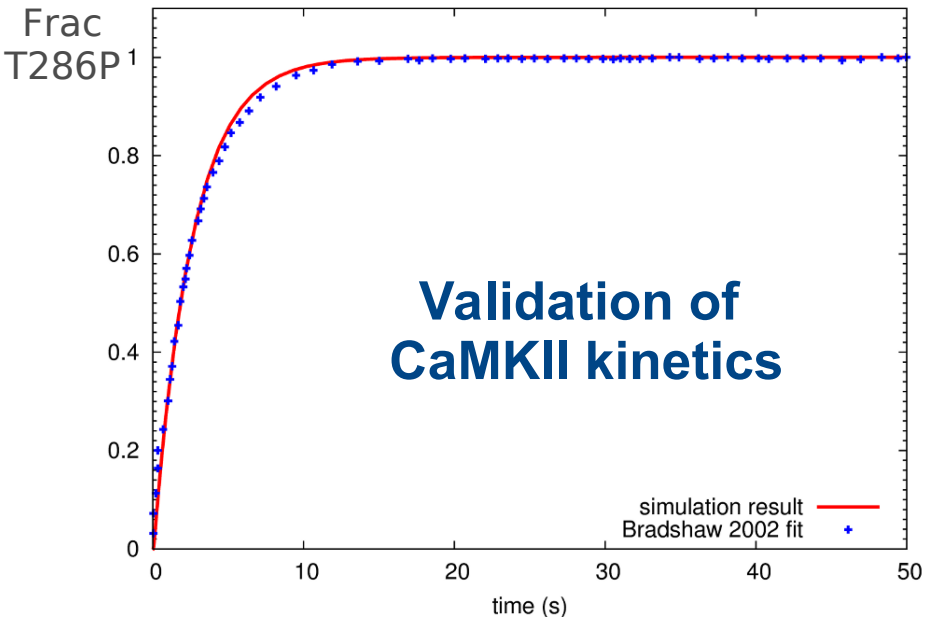
Relative uncertainty increases when concentration decreases, both in concentration and time, but no difference in dynamics.



Fluorescence

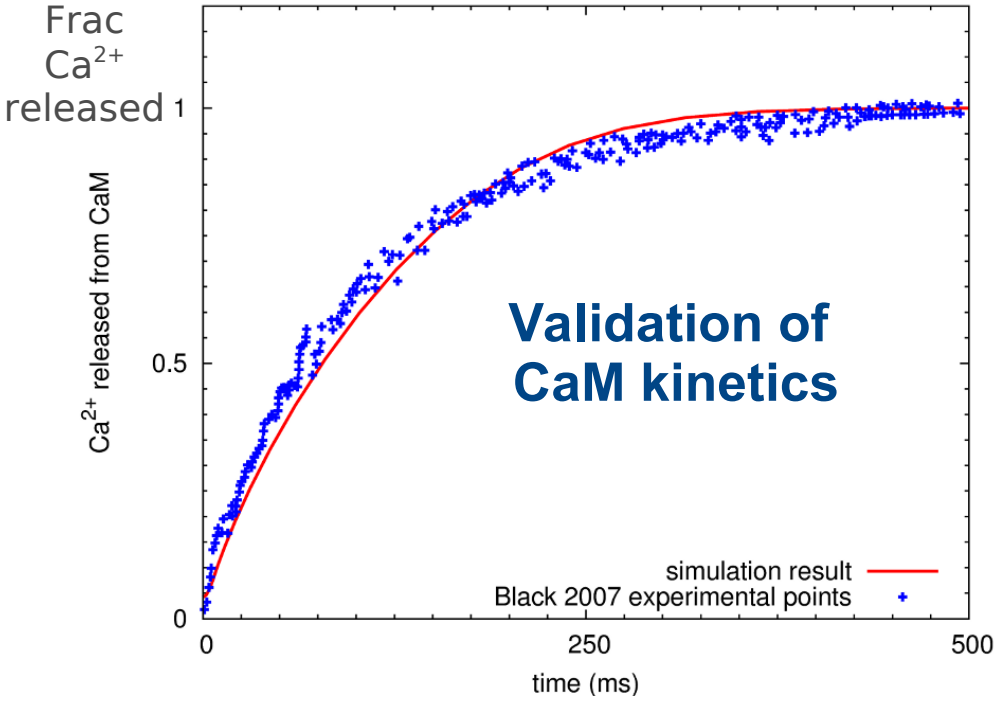
Free calcium

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



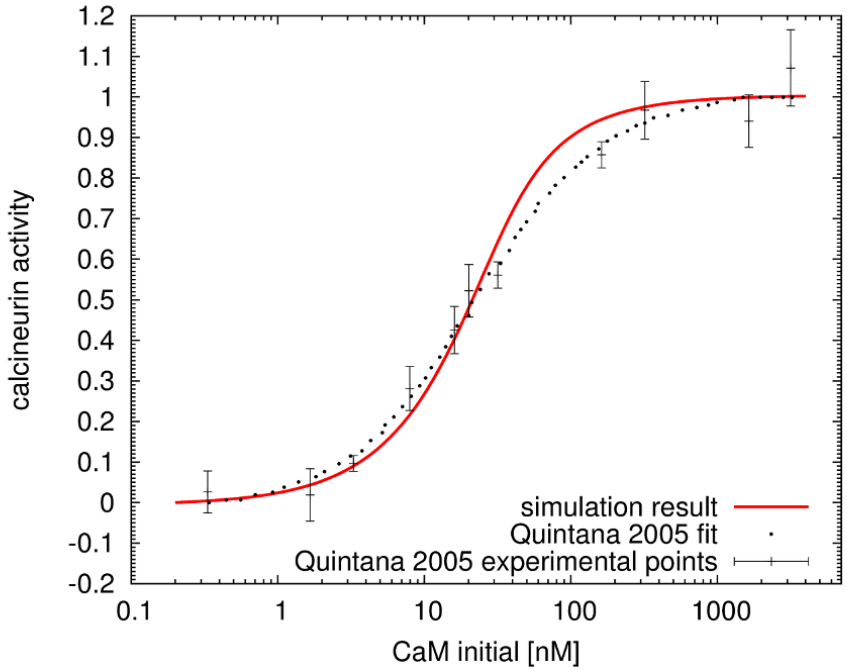
Validation of CaMKII kinetics

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



Validation of CaM kinetics

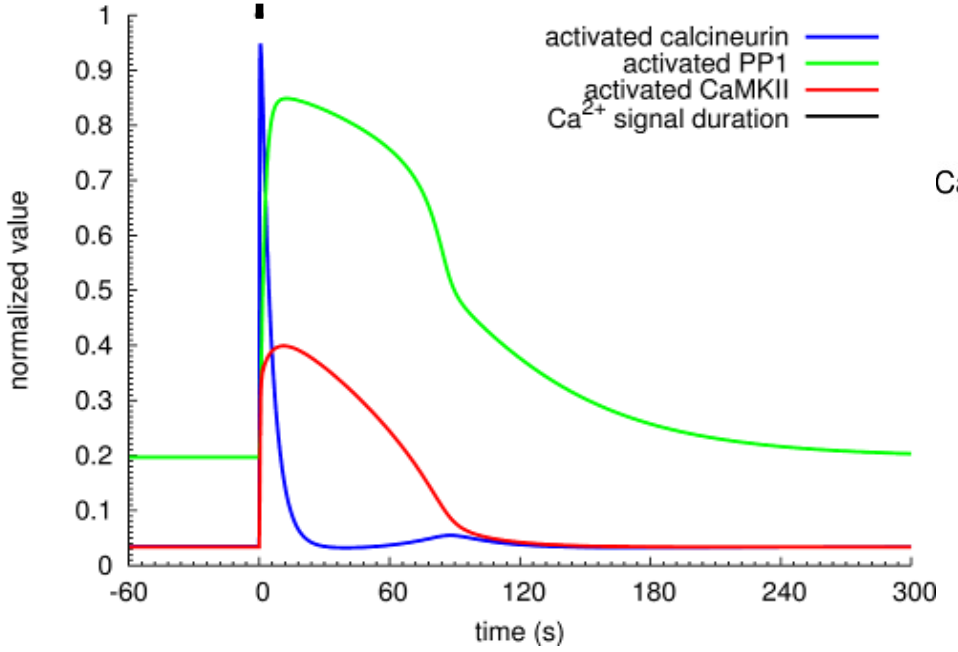
Black DJ, Selfridge JE, Persechini A (2007). *Biochemistry* 46: 13415–13424.

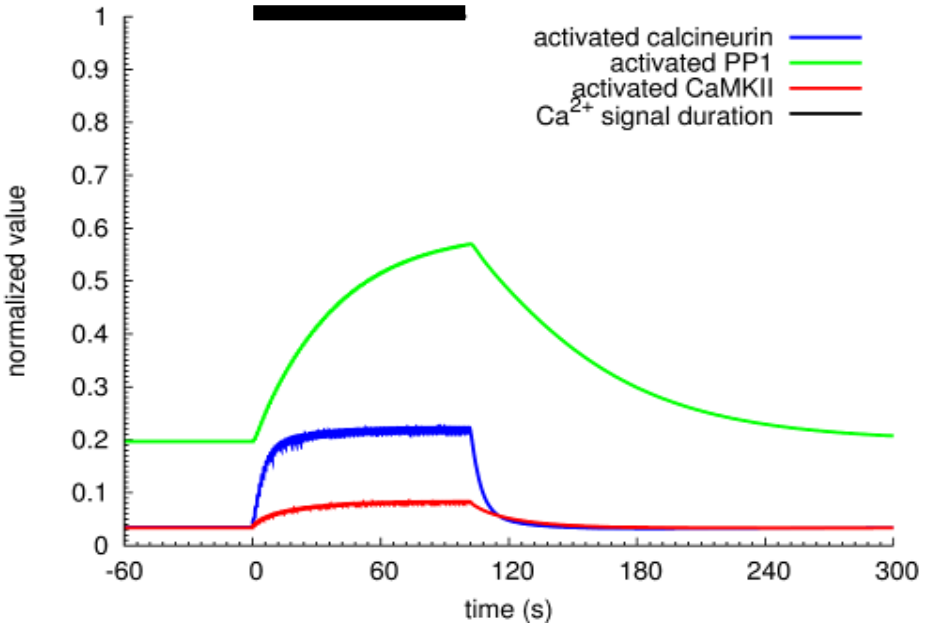


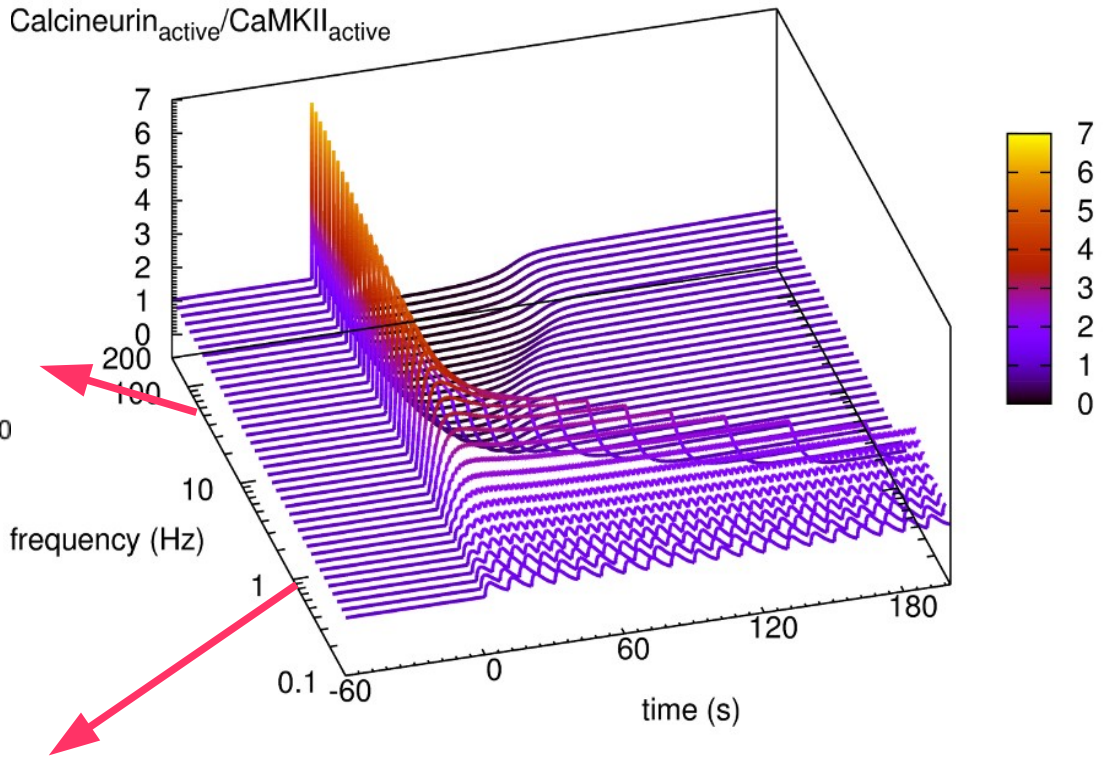
Validation of calcium-activation of CaN

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

CaMKII and CaN activation







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

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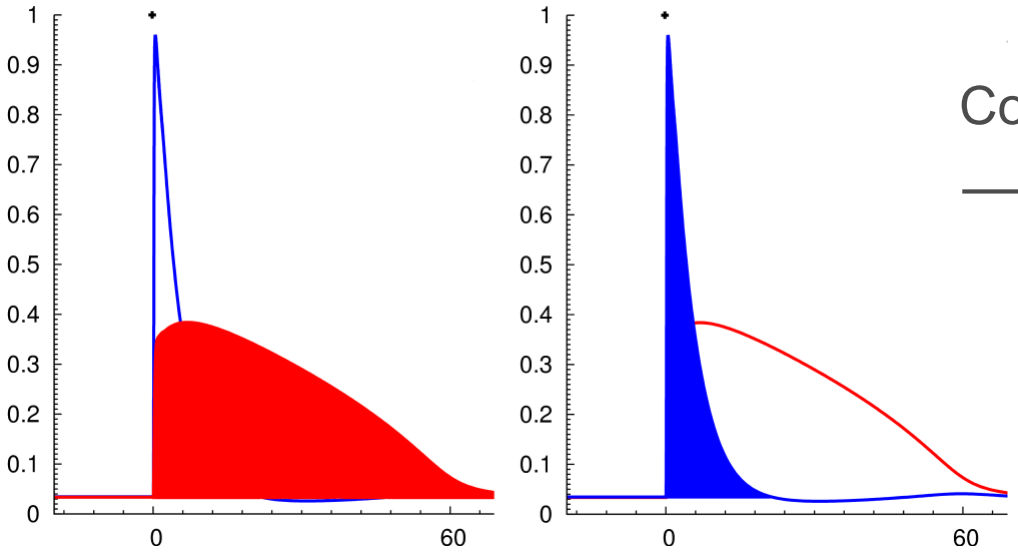
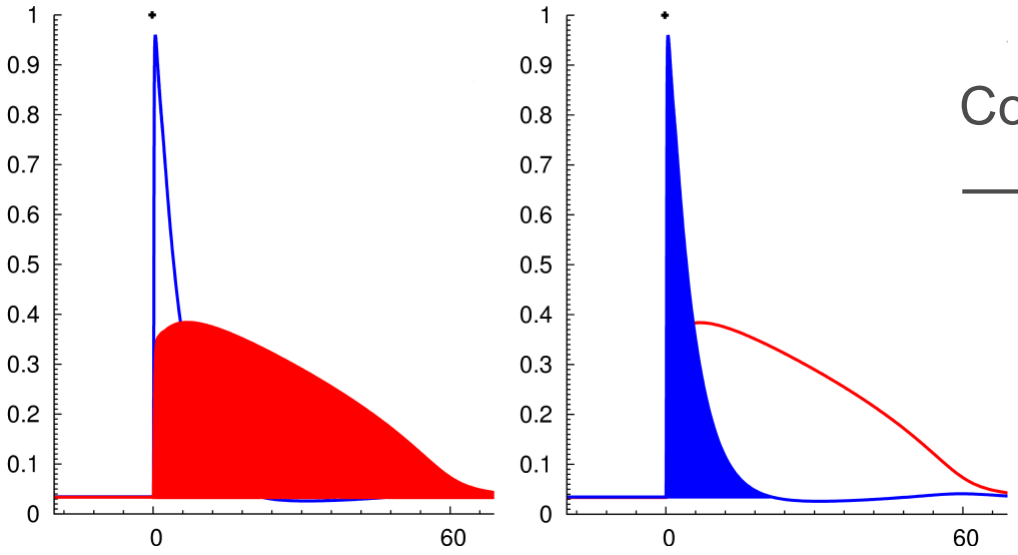
Bidirectional plasticity



Constant catalytic rates of active enzyme

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

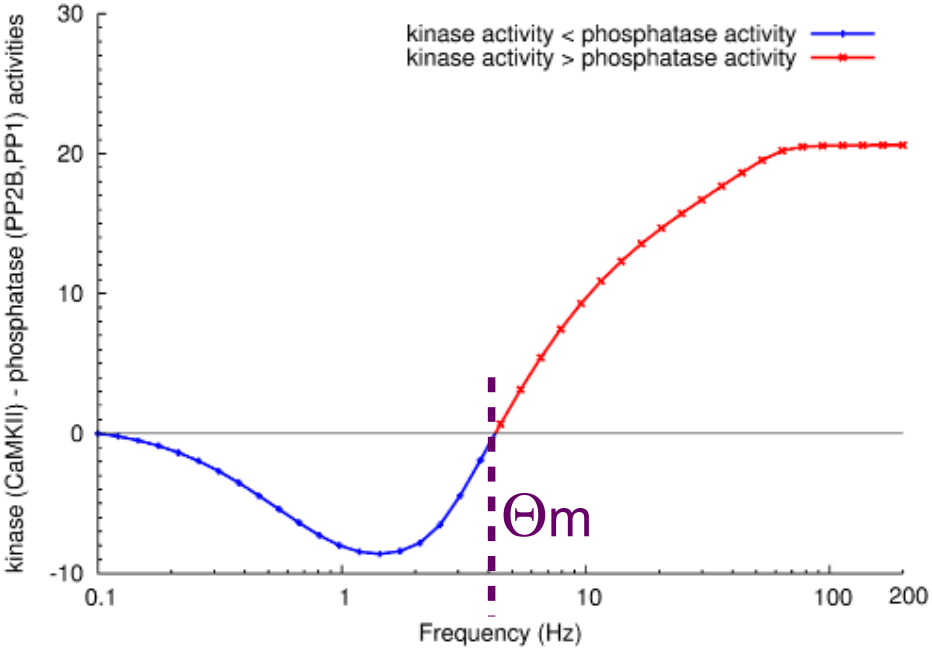
Bidirectional plasticity



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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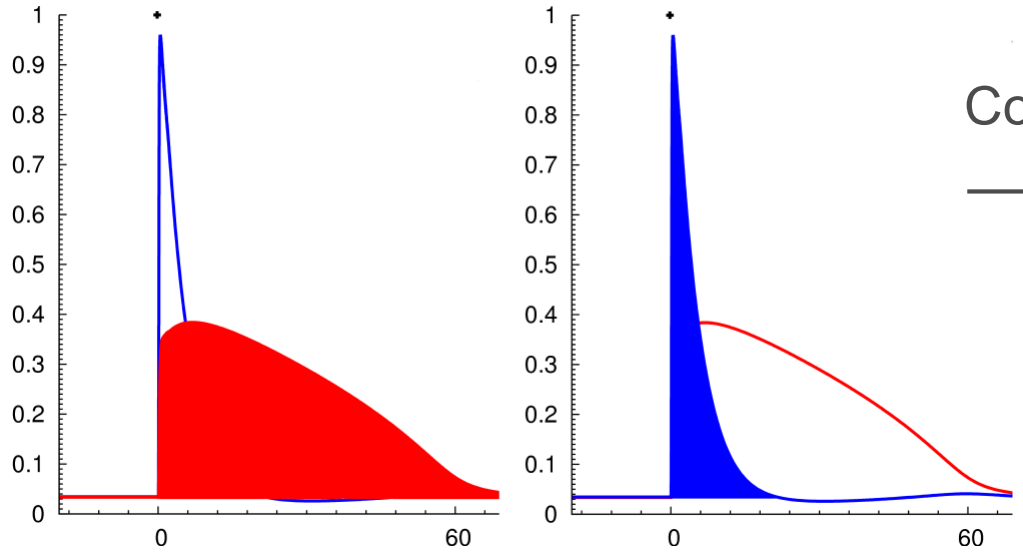
Bidirectional plasticity



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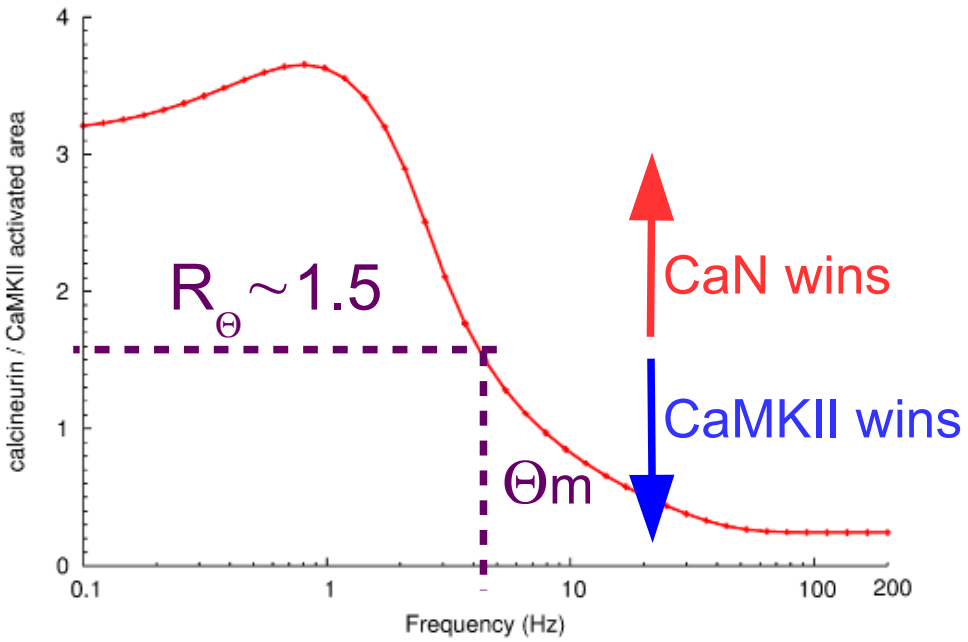

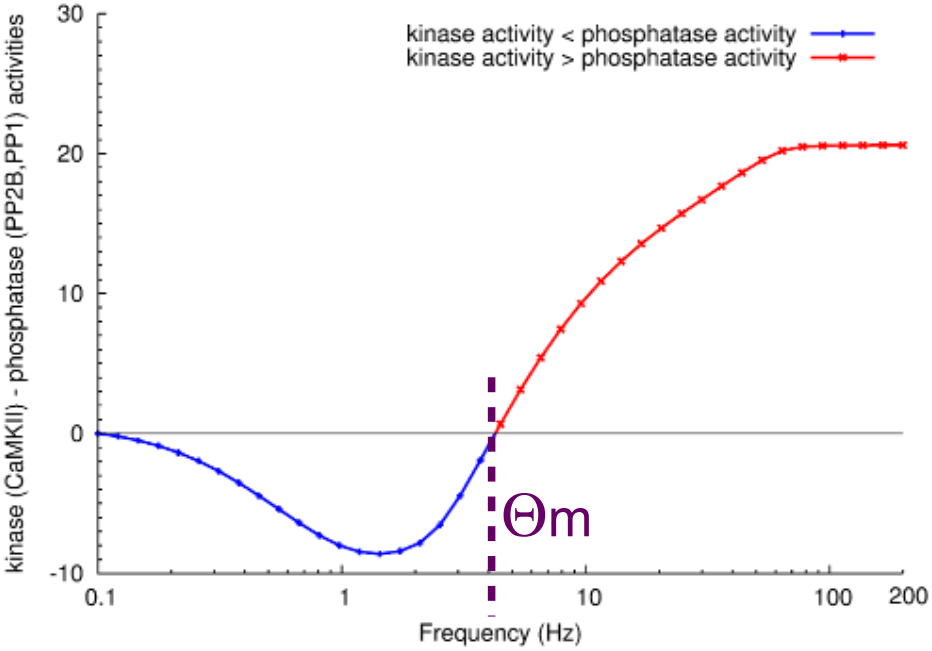

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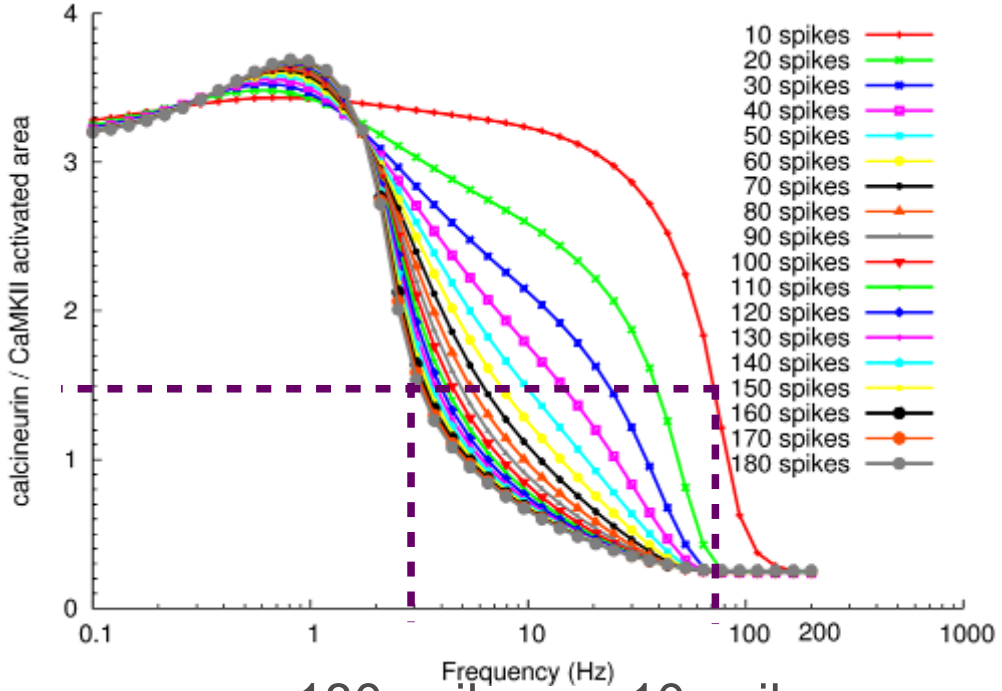
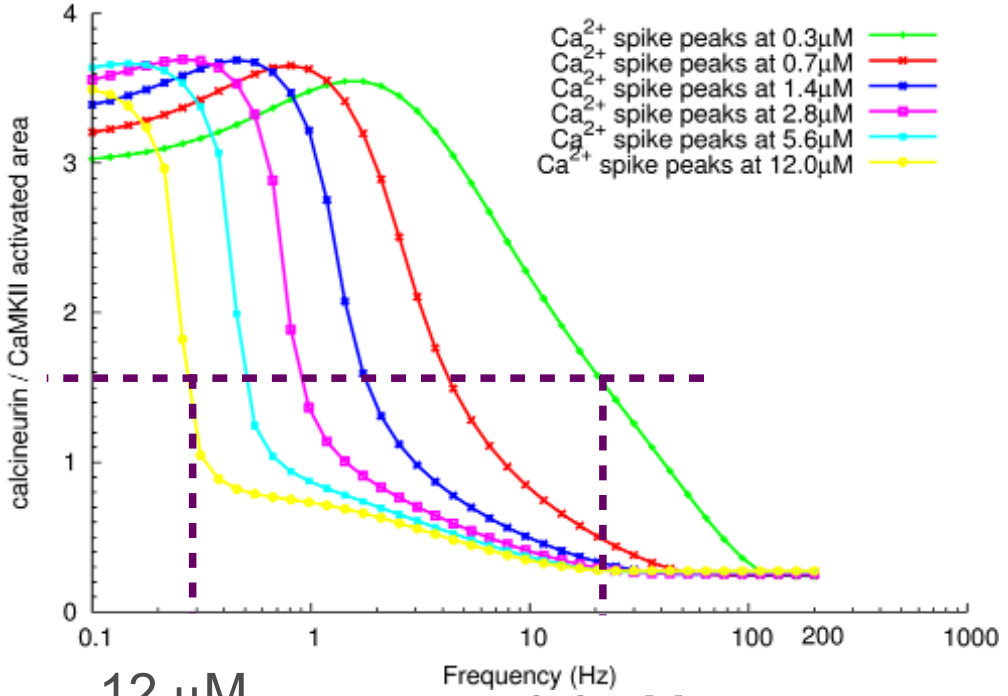
Effect of calcium duration and amount



180 spikes = 3 Hz

10 spikes = 70 Hz

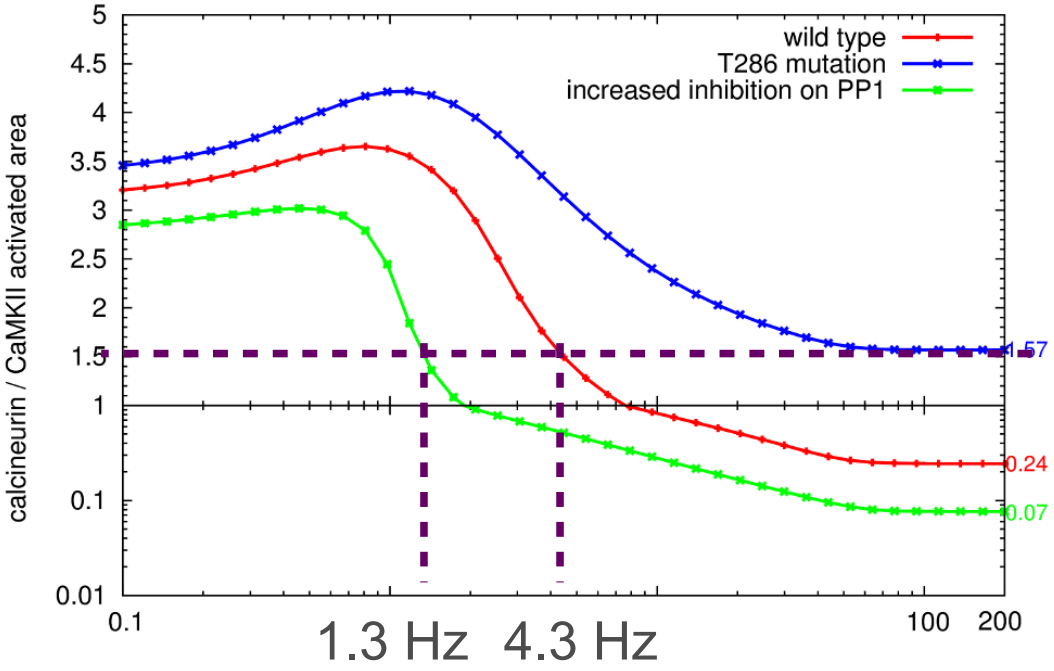


12 µM = 0.3 Hz

0.3 µM = 20 Hz

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

Effect of intrinsic system perturbations



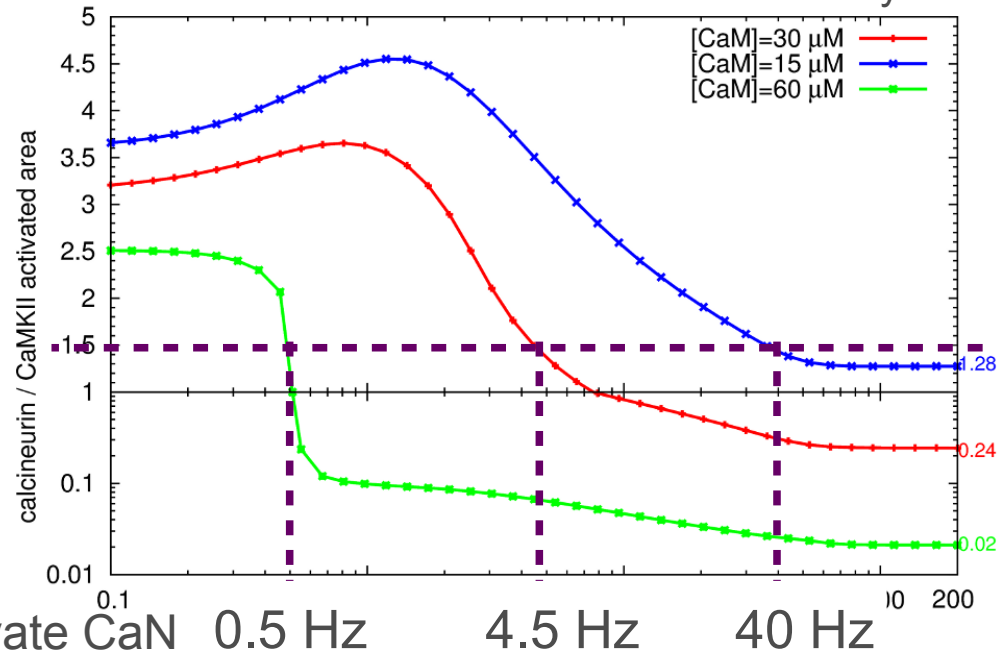
CaMKII not constitutively active
No CaM trapping

Never any positive plasticity

Giese et al (1998) *Science,* 279:870-873

Lower deactivation of CaMKII

Effect of I1 and DARPP-32 activation by cAMP



Competition for CaM, CaN wins

Effect of $Ng^{-/-}$ (Huang *et al* 2004).
Better performance at low frequencies.

NB: No need of direct interactions between CaN and CaMKII to explain paradoxical effects of T306 phosphorylation (Pi *et al* 2010) on CaN. T206P releases limiting CaM, that can then activate CaN

Rbar, Edelstein and Le Novère version

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

$$\alpha = \frac{[Ca^{2+}]}{[K^R]}$$

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

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

$$\bar{R} = \frac{1}{1 + L\Omega^n}$$

M ligands binding on different sites

$$\bar{R} = \frac{1}{1 + L\prod_{i=1}^{i=m}\Omega_i^{n_i}}$$