

What is Systems Biology? What are the challenges ahead?

Nicolas Le Novère, EMBL-EBI

What happened to Biology at the end of XXth century?

Annu. Rev. Genomics Hum. Genet. 2001. 2:343-72
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A NEW APPROACH TO DECODING LIFE: Systems Biology

Trey Ideker^{1,2}, Timothy Galitski¹, and Leroy Hood^{1,2,3,4,5}
Institute for Systems Biology¹, Seattle, Washington 98105; Departments of

New Generation Computing, 18(2000)199-216
Ohmsha, Ltd. and Springer-Verlag

invited paper

Perspectives on Systems Biology

Hiroaki KITANO
Sony Computer Science Laboratories, Inc.

NEW
GENERATION
COMPUTING

©Ohmsha, Ltd.



Emergence of the notion of system

XVI

XVII

XVIII

XIX

XX

XXI

Global Description of the world

“classical” mechanic, anatomy, physiology

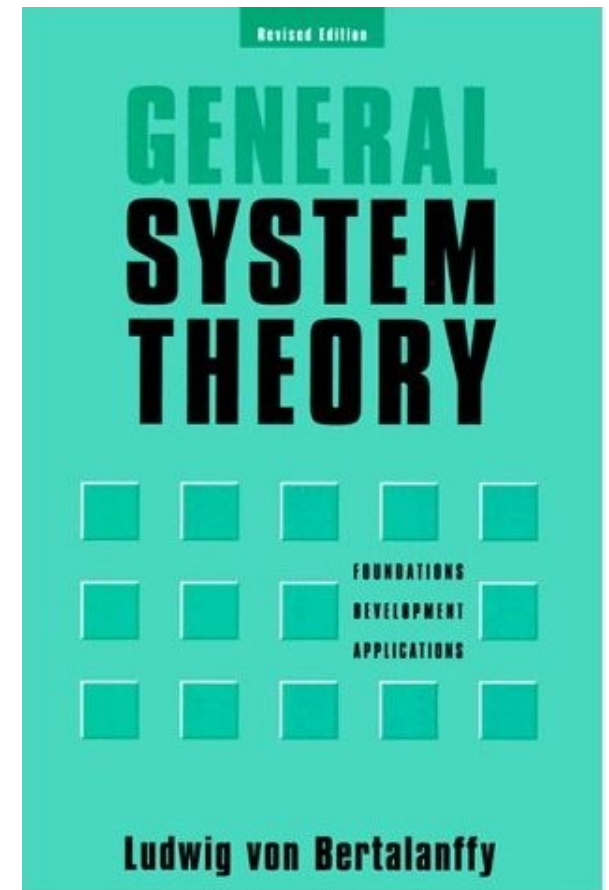
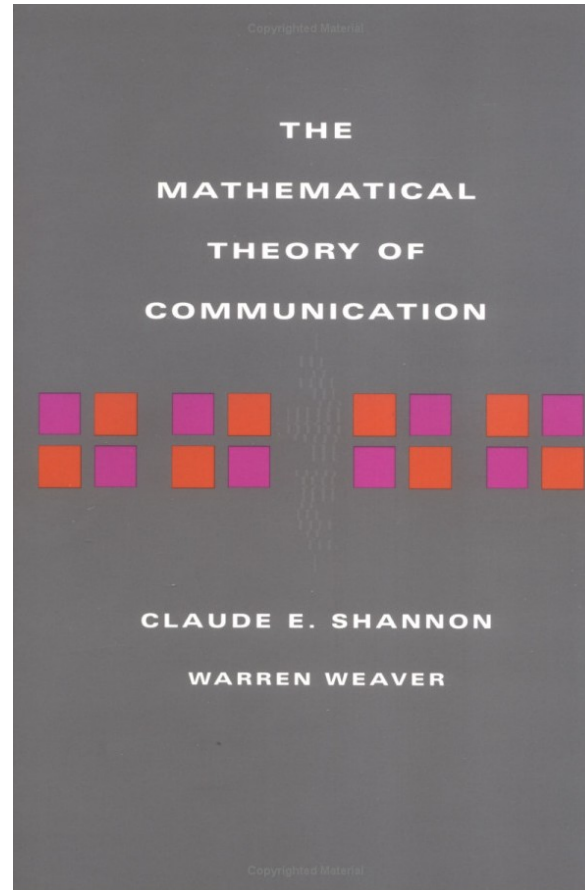
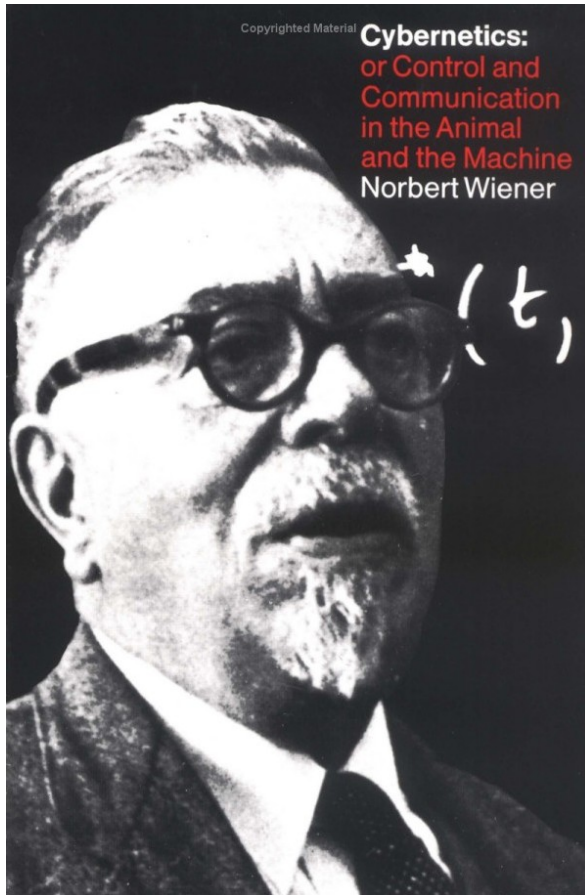
Description of the components of the world

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

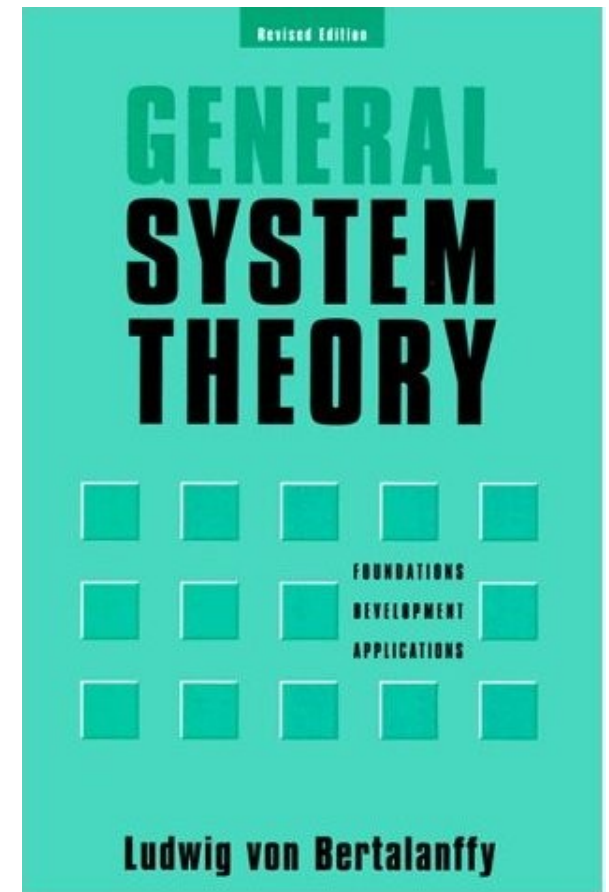
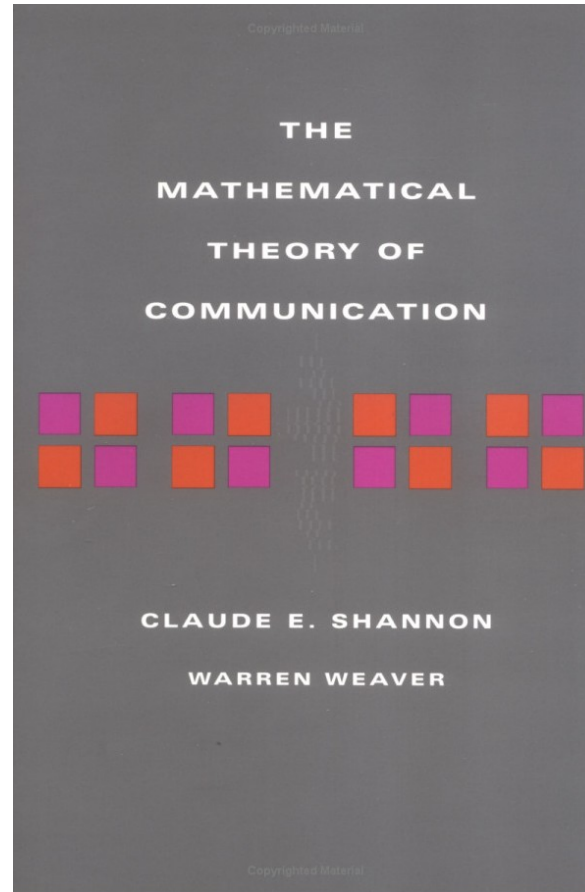
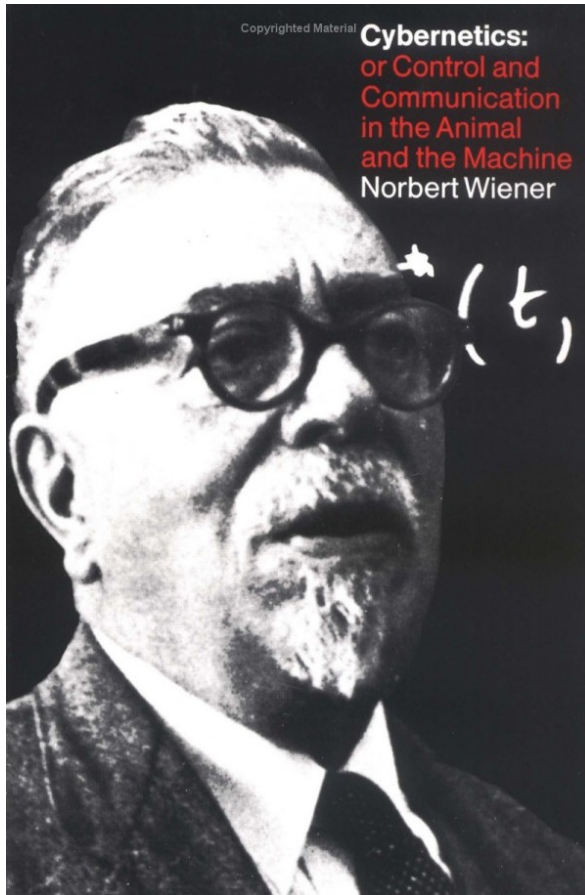
Description of interacting components

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

Systems are formalised mid-XXth



Systems are formalised mid-XXth



"[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 Bertalanffy, Kritische Theorie der Formbildung, 1928

The three paradigms of 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

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

[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.

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).

Towards Systems Biology

Events around

First computers		PDB	EMBLbank PC	Genomes Interactomes	
1950	1960	1970	1980	1990	2000

Towards Systems Biology

Events around

First computers		PDB	EMBLbank PC	Genomes Interactomes	
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1950	1960	1970	1980	1990	2000
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Hodgkin-Huxley	Goldbeter	Cell Cycle models
Dennis Noble	Koshland	signalling models
heart pacemaker	covalent	metabolic models
	cascades	models of gene reg
		whole heart

models

Towards Systems Biology

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

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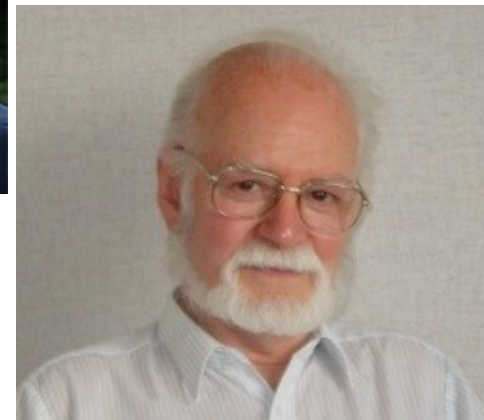
neurobiology

60s and 70s

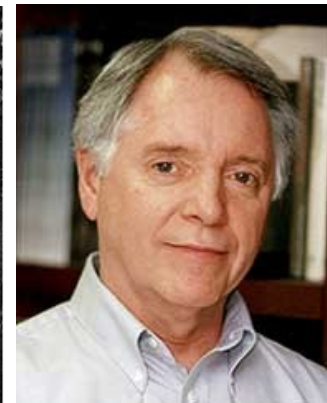
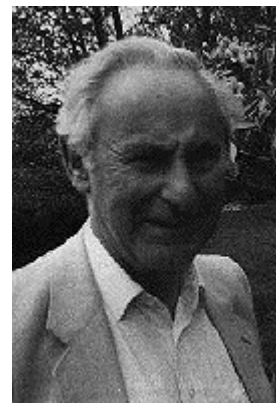
- Mihajlo Mesarovic: 1966 Symposium
“general systems theory and biology



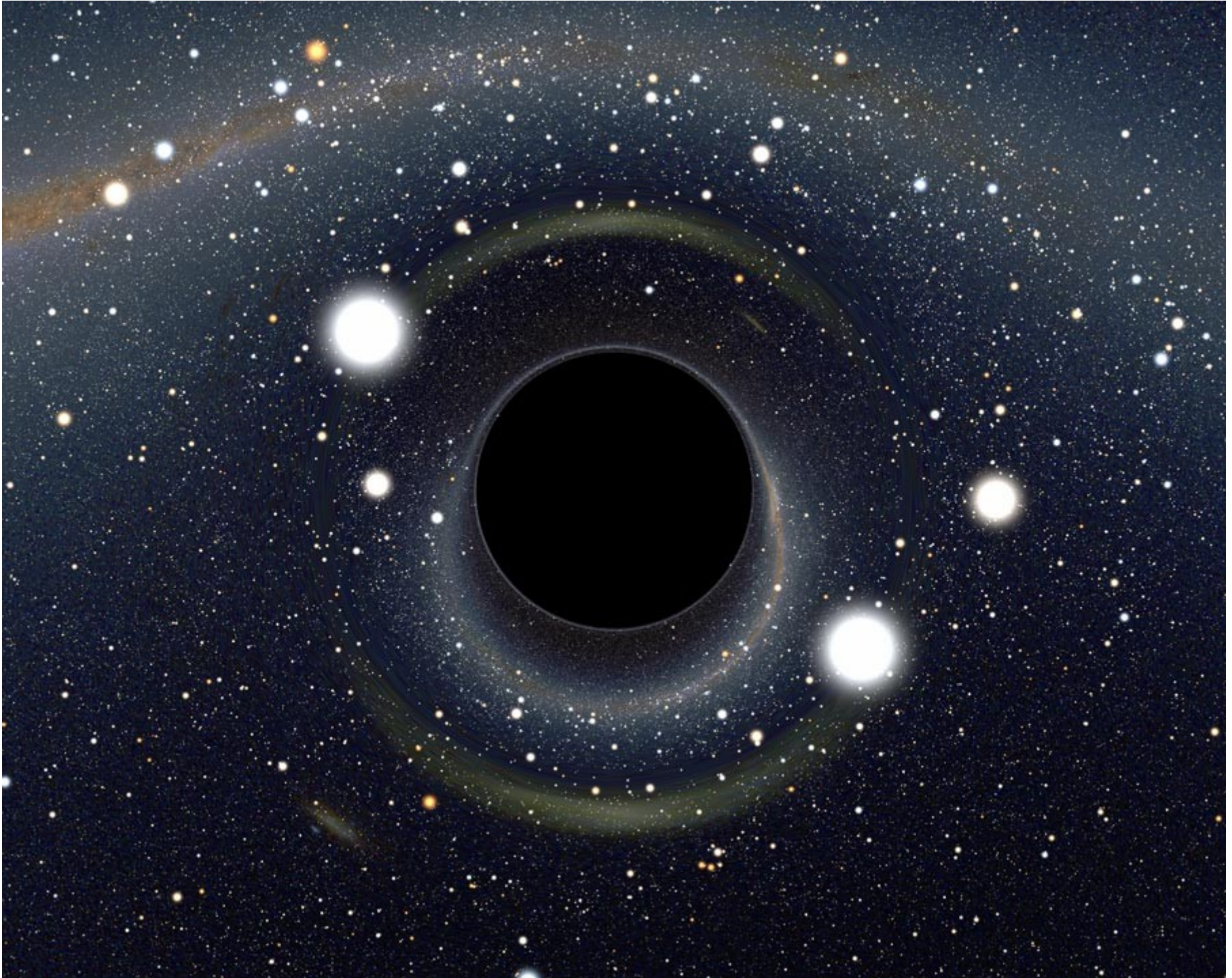
- Stuart Kaufmann,
Rene Thomas: 1969-73
boolean networks for
gene regulation



- Henri Kacser:
Metabolic control analysis,
Michel Savageau:
Biochemical Systems Theory



80s: The reign of Molecular Biology



Towards Systems Biology

Events around

First computers			PDB	EMBLbank PC	Genomes Interactomes
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1950	1960	1970	1980	1990	2000
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Hodgkin-Huxley	Dennis Noble heart pacemaker		Goldbeter Koshland covalent cascades	Cell Cycle models signalling models metabolic models models of gene reg whole heart	
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models

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

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

Towards Systems Biology

Events around

First computers			PDB	EMBLbank PC	Genomes Interactomes
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models

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

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

Barabasi Repressilator

Towards Systems Biology

Events around

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models

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

MCA/BST	stochastic	multi-agent systems	user-friendly biochemical simulators	Synthetic Biology
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methods

Network Biology

Barabasi
Repressilator

90s: maturation of the community

- Publication of modelling work in high visibility journals, e.g.:
 - Tyson. modeling the cell-division cycle - cdc2 and cyclin interactions. *PNAS* 1991; McAdams and Shapiro. Circuit simulation of genetic networks. *Science* 1995; Barkai and Leibler. Robustness in simple biochemical networks. *Nature* 1997; Neuman et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. *Science* 1998; Yue et al. Genomic cis-regulatory logic: Experimental and computational analysis of a sea urchin gene . *Science* 1998; Bray et al. Receptor clustering as a cellular mechanism to control sensitivity. *Nature* 1998; Bhalla ad Iyengar. Emergent properties of signaling pathways. *Science* 1998
- Structuration of the community modelling metabolism
- Large-scale modelling and simulation projects
 - E-Cell project 1996; The Virtual Cell 1998
- Availability of high-throughput data on parts and interactions
 - Two-hybrids (1989); microarrays (1995) etc.
- Large-scale funding for wet+dry studies of biological systems
 - Alliance For Cellular Signalling (<http://www.afcs.org/>). First of the NIH “glue grants”. 1998

Formal revival of Systems Biology

- “Modelling” Systems Biology
 - 1998 - Hiroaki Kitano founds the Systems Biology Institute in Tokyo
 - First appearance: Kyoda, Kitano. Virtual Drosophila project: Simulation of drosophila leg formation. *Genome Informatics Series* (1998)
 - Kitano, H. Perspectives on systems biology. *New Generation Computing* Volume 18, Issue 3, 2000, Pages 199-216
- “Network” Systems Biology
 - First appearance: Leroy Hood. Systems biology: new opportunities arising from genomics, proteomics and beyond. *Experimental Hematology*. Volume 26, Issue 8, 1998, Page 681
 - Schwikowski B, Uetz P, Fields S. A network of protein-protein interactions in yeast. *Nat Biotechnol*. 2000 Dec;18(12):1257-61.
 - 2000 - Leroy Hood founds the Systems Biology Institute in Seattle

Rise of Systems Biology as a paradigm

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

Rise of Systems Biology as a paradigm

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

ERATO-Kitano

Alliance for Cellular Signaling

SystemsX

HepatoSys

SysBio enters FP6

ERASysBio

YSBN

projects

Rise of Systems Biology as a paradigm

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ECell

Von Dassow

SBML

Klipp

Alon

Choi

Annual Review

Science

Kriete

Palsson

publications

Ideker/Hood

special issue

Boogerd

“Foundations of Systems Biology”

Kaneko

Szallasi

Grierson

Computational Cell Biology”

IEE Sys Bio

MSB

BMC Sys Bio

Rise of Systems Biology as a paradigm

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

ERATO-Kitano
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Tokyo Systems Biology Institute

Seattle Institute for Systems Biology

6 BBSRC centres

Institutes

BioQuant

Rise of Systems Biology as a paradigm

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

ERATO-Kitano
Alliance for Cellular Signaling

projects

SystemsX

HepatoS
Sy

YSBN

End of BBSRC
Systems Biology
calls

ECell

Von Dassow

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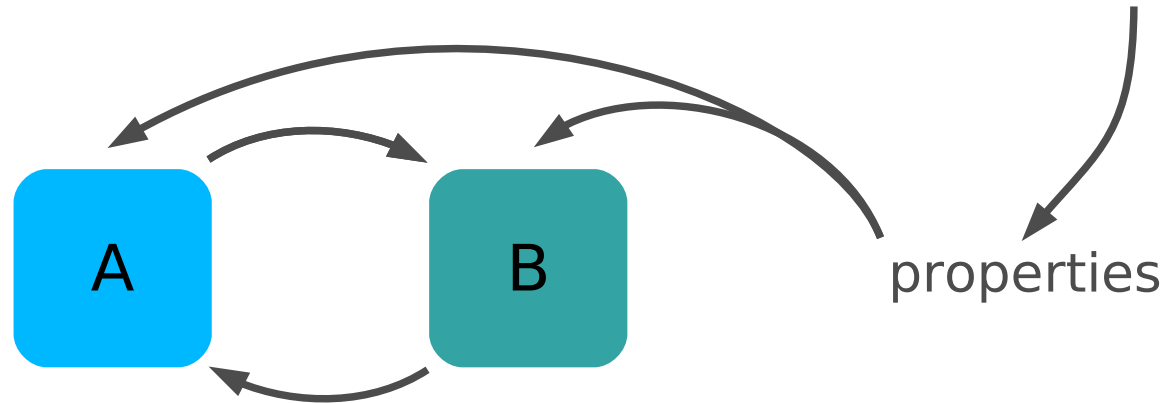
Institutes

BioQuant

What is Systems Biology?

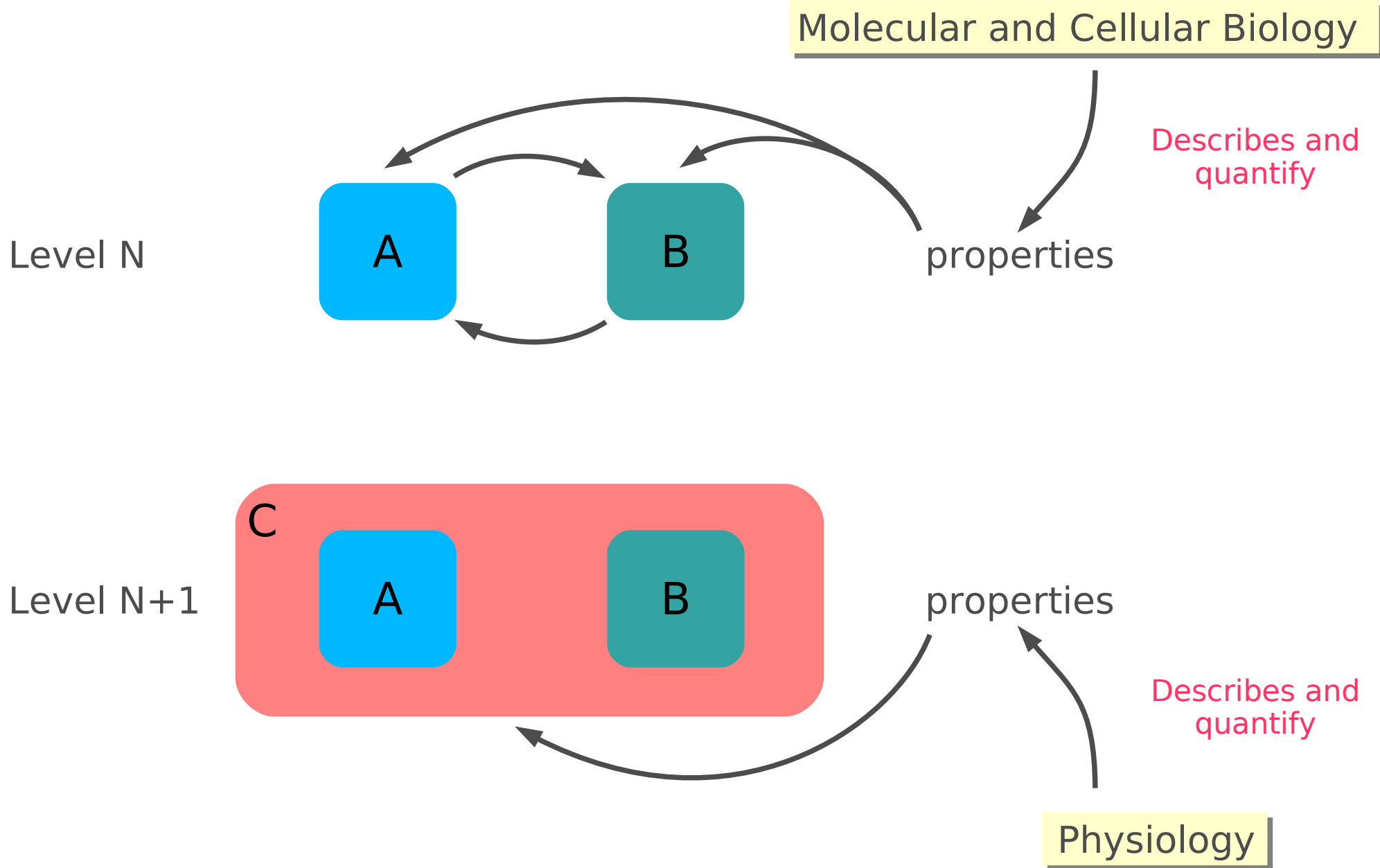
Molecular and Cellular Biology

Describes and
quantify

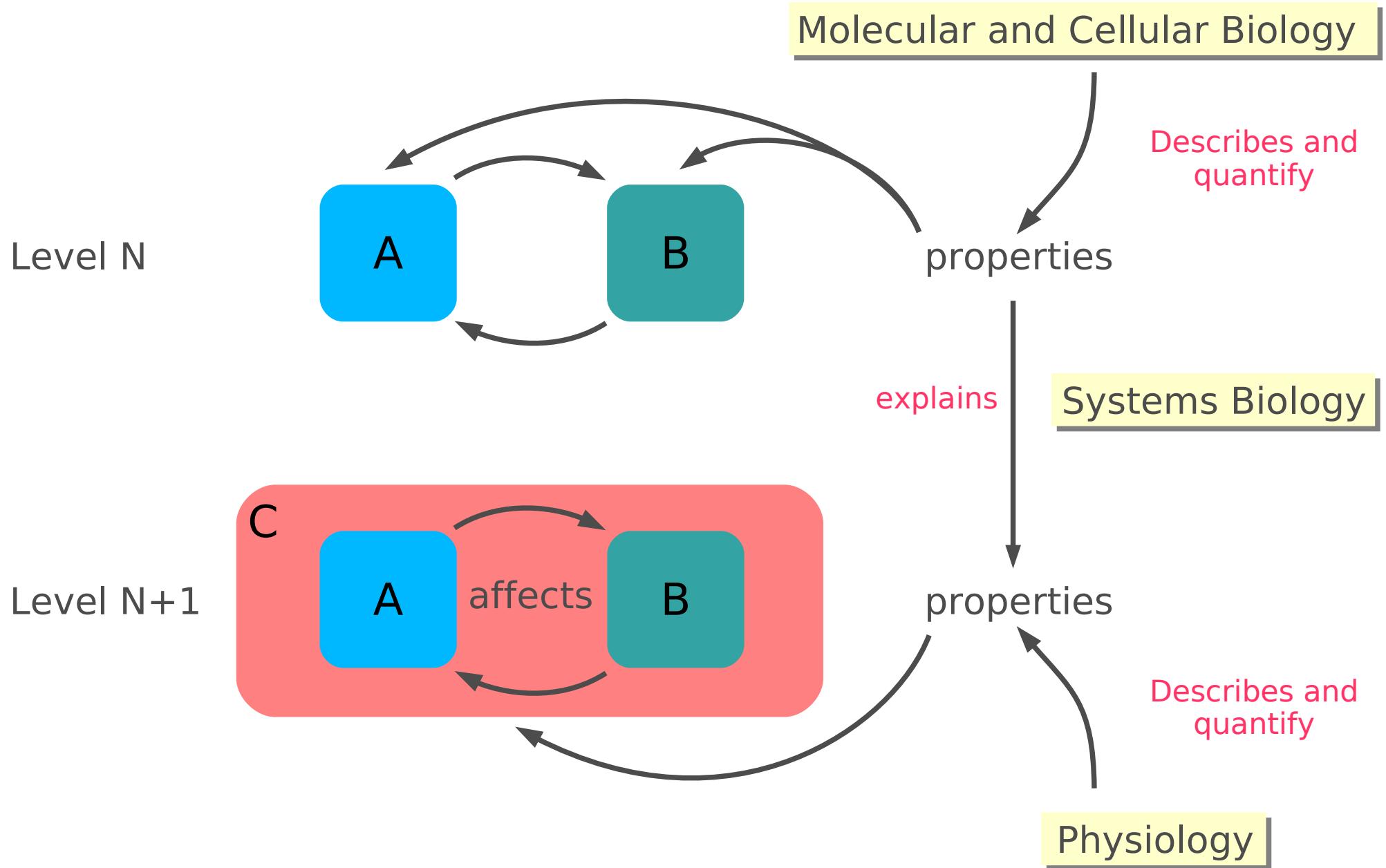


Level N

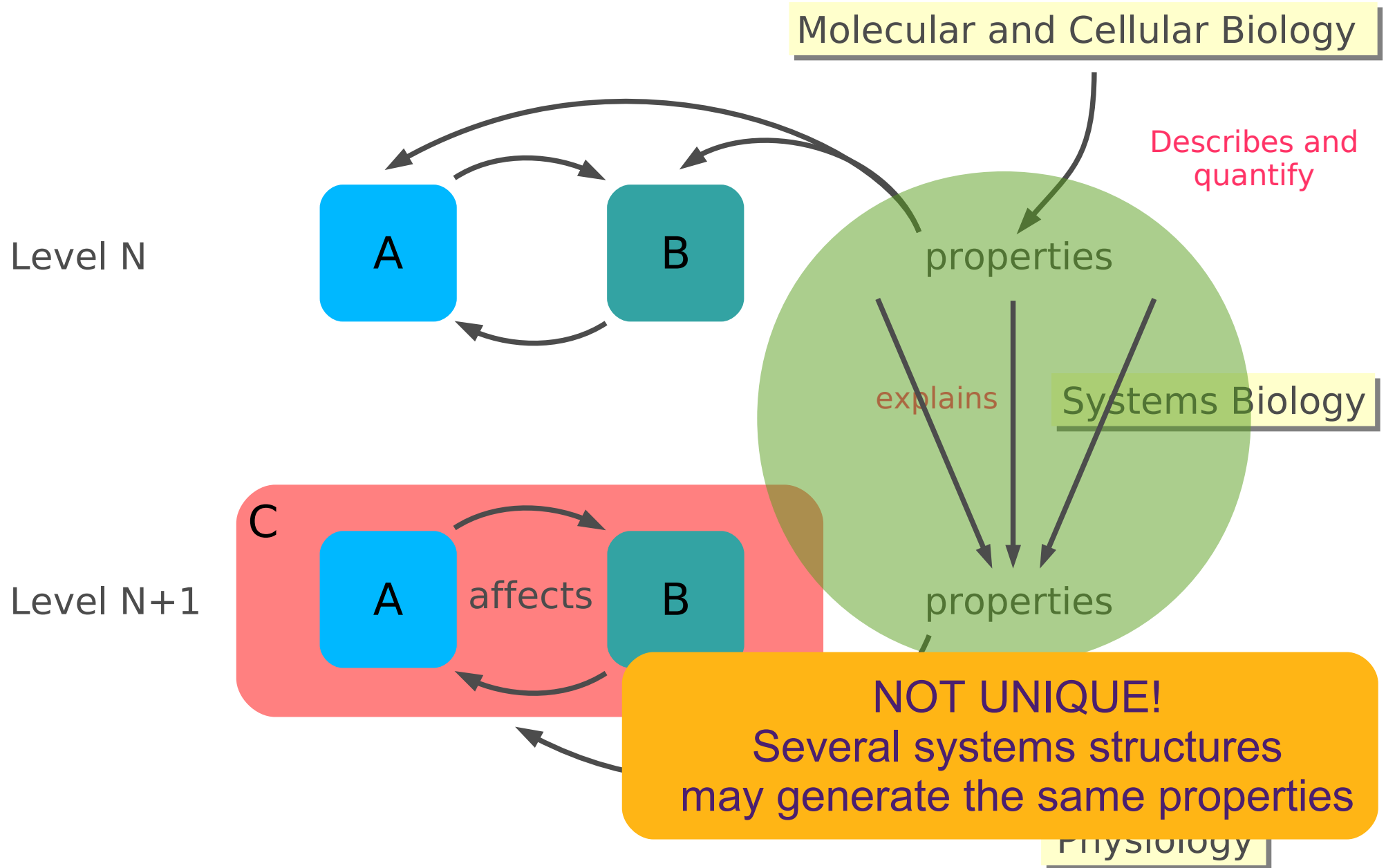
What is Systems Biology?



What is Systems Biology?



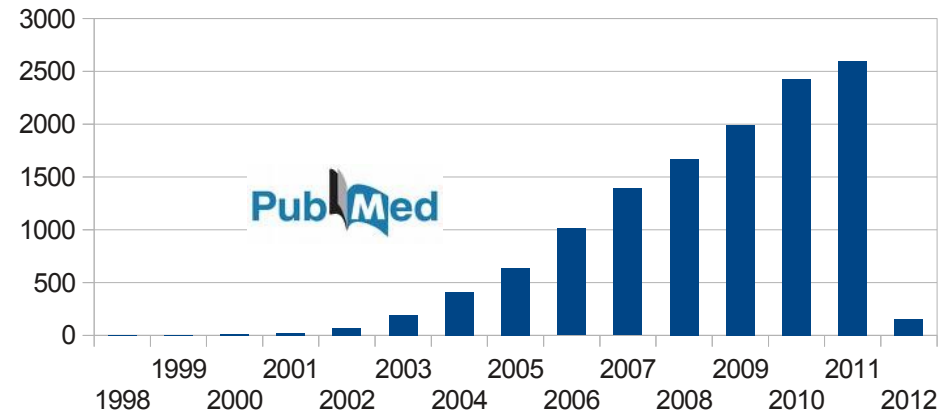
What is Systems Biology?



Systems Biology is the study of the ***emerging*** properties of a biological system, taking into account all the ***necessary*** constituents, their ***relationships*** and their ***dynamics***

What is Systems Biology?

- First mention of the term: 1928 (L Von Bertalanffy)
- Modern revival of the term: 1998 (L Hood, H Kitano)



*Systems Biology is the study of the **emerging** properties of a biological system, taking into account all the **necessary** constituents, their **relationships** and their **dynamics**.*

Systems-wide analysis (omics)

- Born: 1990s
- Technologies: high-throughput, statistics
- People's background: molecular biologists, mathematicians
- Key lesson: the selection of a phenotype is done at the level of the system, not of the component (gene expression puzzle)

Application of systems-theory

- Born: 1960s
- Technologies: quantitative measurements, modelling
- People's background: biochemists, engineers
- Key lesson: the properties at a certain level are emerging from the dynamic interaction of components at a lower level

Nobel Symposium on Systems Biology (June 2009)

networks

Leroy Hood
Marc Vidal
Mike Snyder
Marc Kirschner
Charlie Boone
Ruedi Aebersold
Terence Hwa
Erin O'Shea
Jussi Taipale

models

Eric Davidson
Stanislas Leibler
Michel Savageau
Lucy Shapiro
Hans Westerhoff
Roger Brent
Naama Barkai
Francois Nedelec
Jens Nielsen
Jim Ferrell
Johan Elf
Boris Kholodenko
Bernard Palsson
Bela Novak
Nicolas Le Novère
Hiroaki Kitano
Stefan Hohmann
Harley McAdams
William Bialek
Mans Ehrenberg



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Jussi Taipale

Avid Regev

Luis Serrano Jeff Hasty

Michael Elowitz

Yoshihide Hayashizaki

Richard Young

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Uwe Sauer
Jorg Stelling
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synthetic biology cell reprogramming



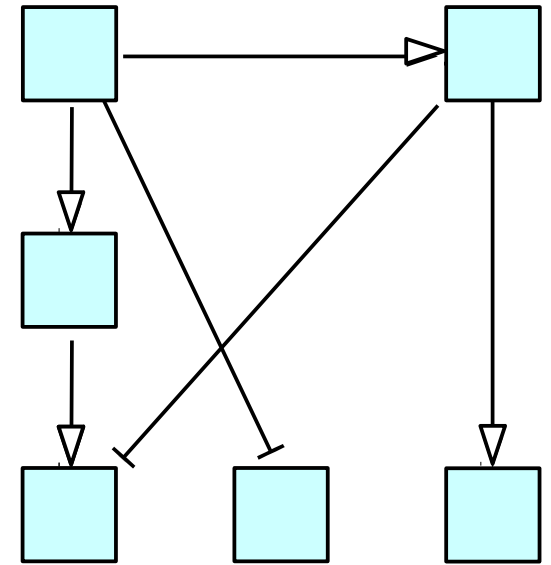
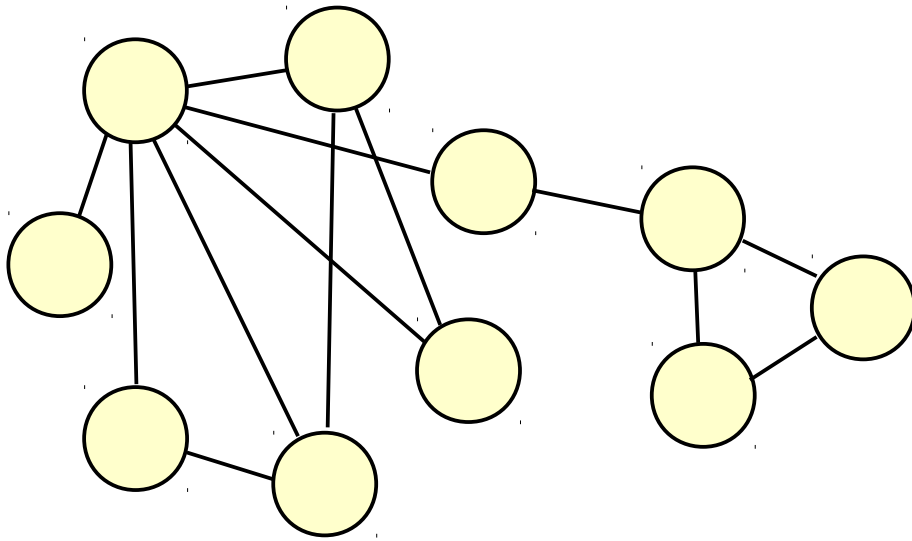
The challenges ahead: Bridging the gaps

Types of representation

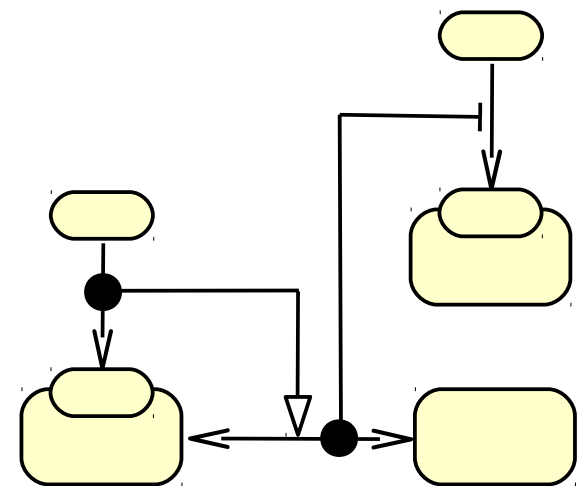
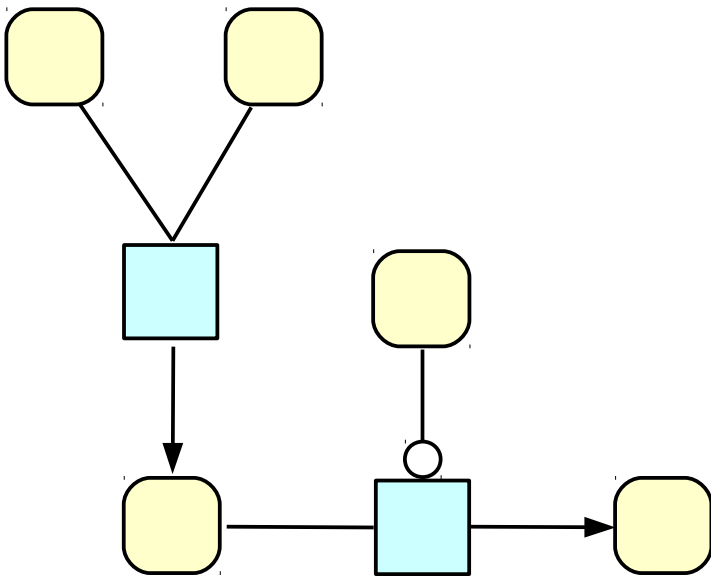
Scales and the mesoscopic gap

Drug discovery models
Vs systems modelling

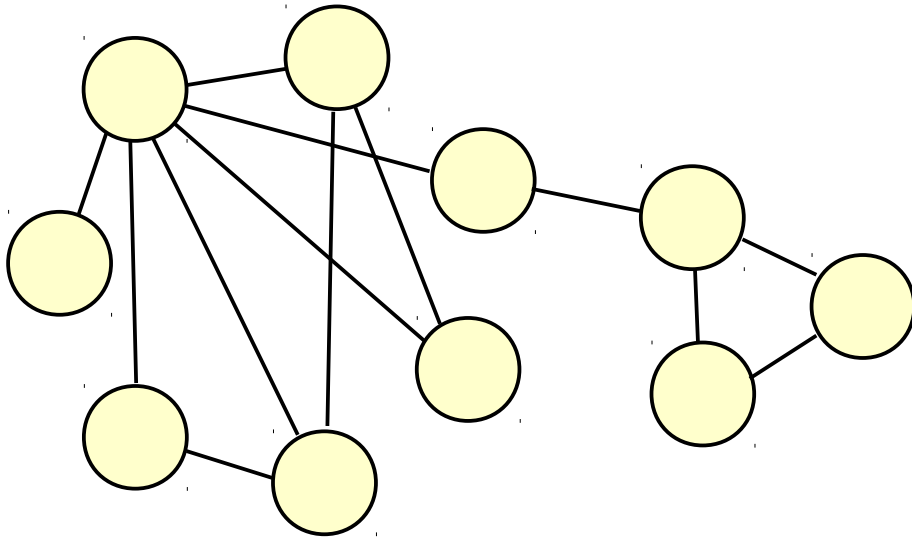
Drug discovery models
Vs “omics” data



The four views of systems biology

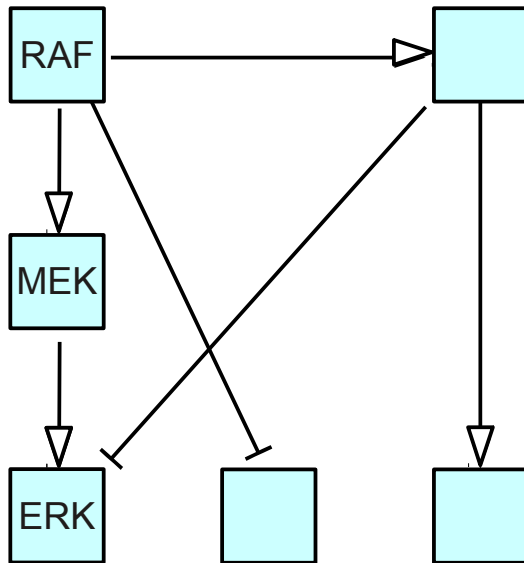


Interaction networks



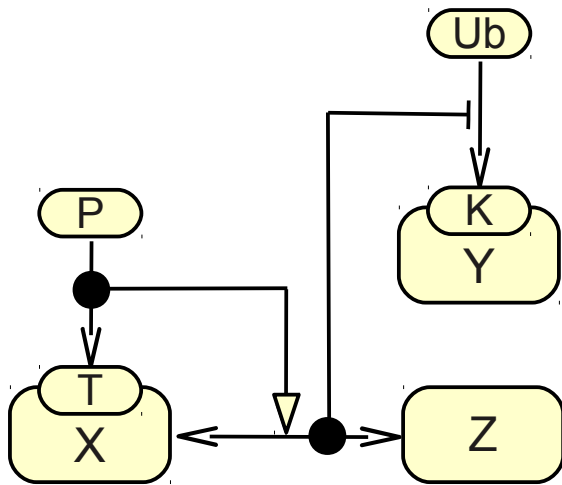
- Non-directional
- Non-sequential
- Non-mechanistic
- Statistical modelling
- Functional genomics
- IntAct, DIP, String

Activity-Flows



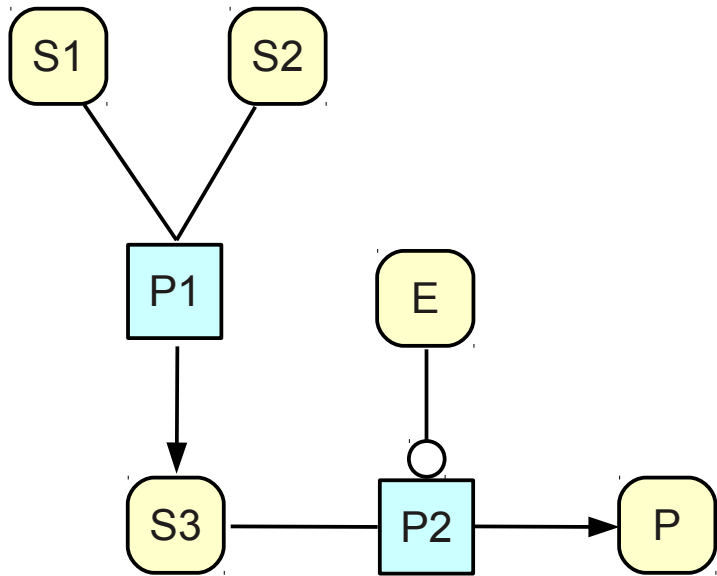
- Directional
- Sequential
- Non-mechanistic
- Logical modelling
- Signalling pathways, gene regulatory networks
- KEGG, STKEs

Entity Relationships

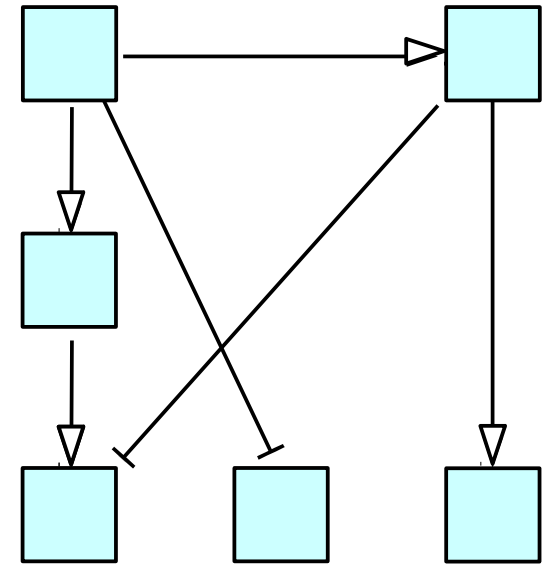
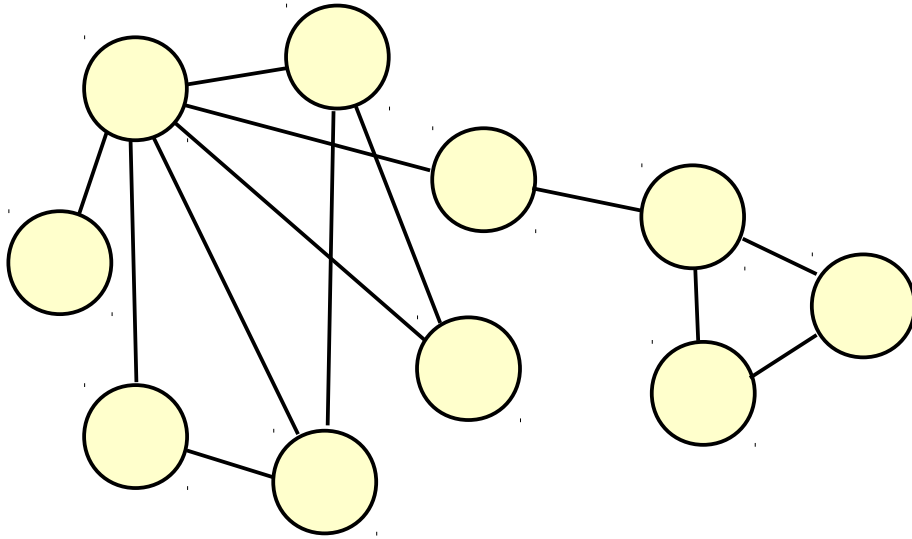


- Directional
- Non-sequential
- Mechanistic
- Independent rules: no explosion
- Rule-based modelling
- Molecular Biology
- MIM

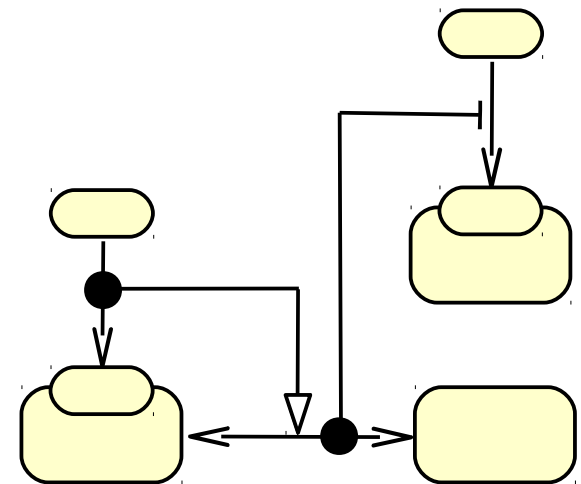
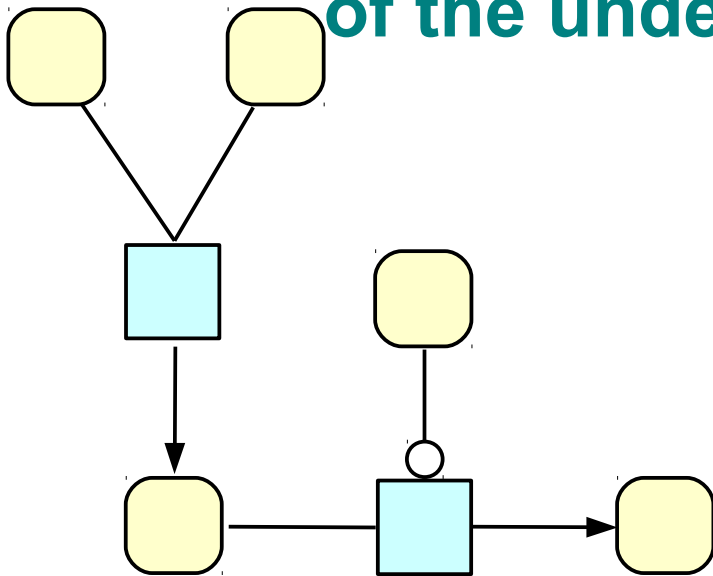
Process Descriptions



- Directional
- Sequential
- Mechanistic
- Subjected to combinatorial explosion
- **Process modelling**
- **Biochemistry**, Metabolic networks
- KEGG, Reactome

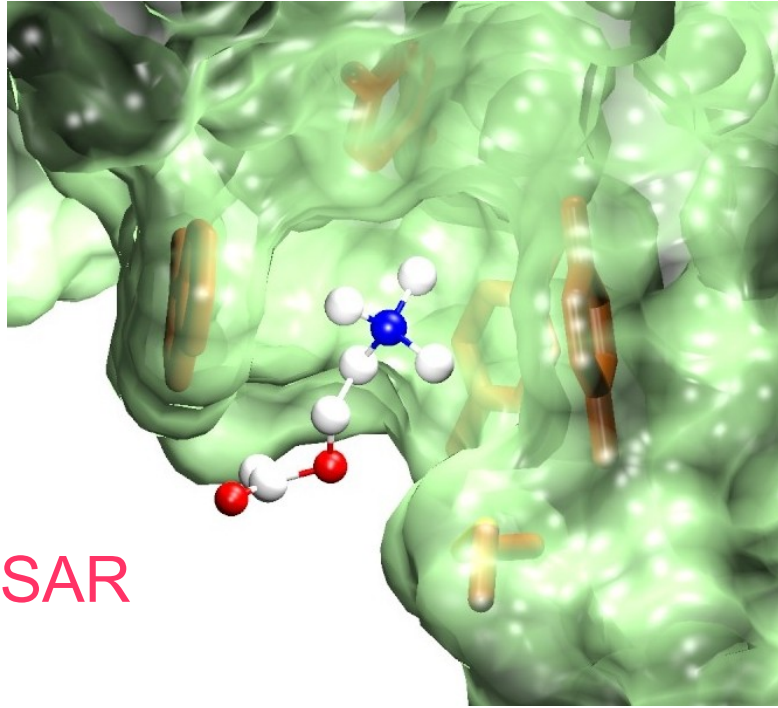


The four views are orthogonal projections of the underlying biological phenomena

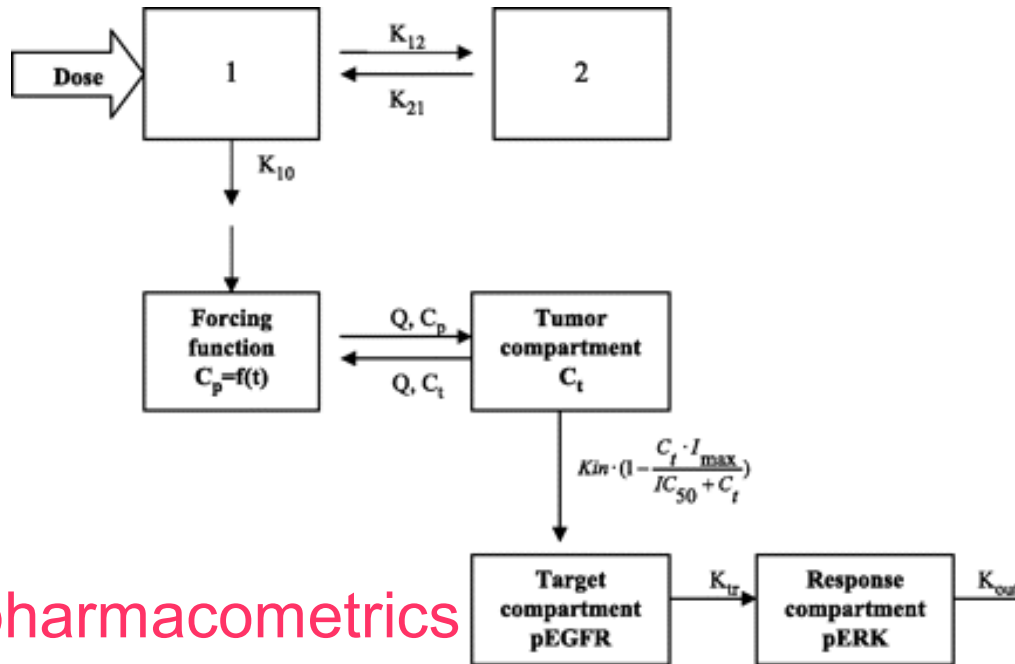


peroxysome

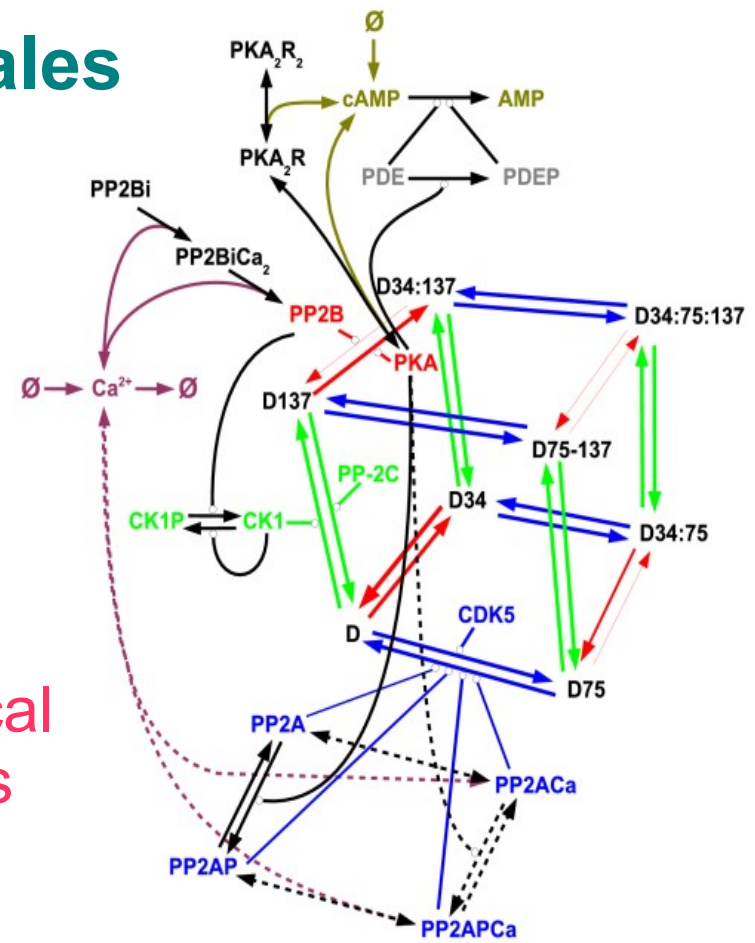
The problem of scales



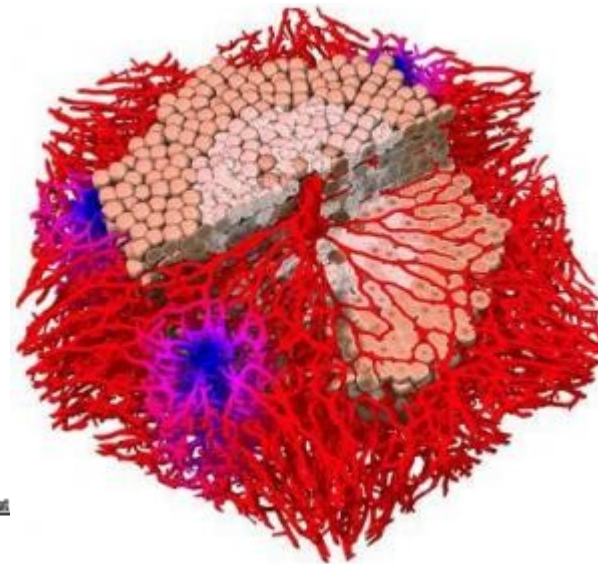
QSAR



pharmacometrics

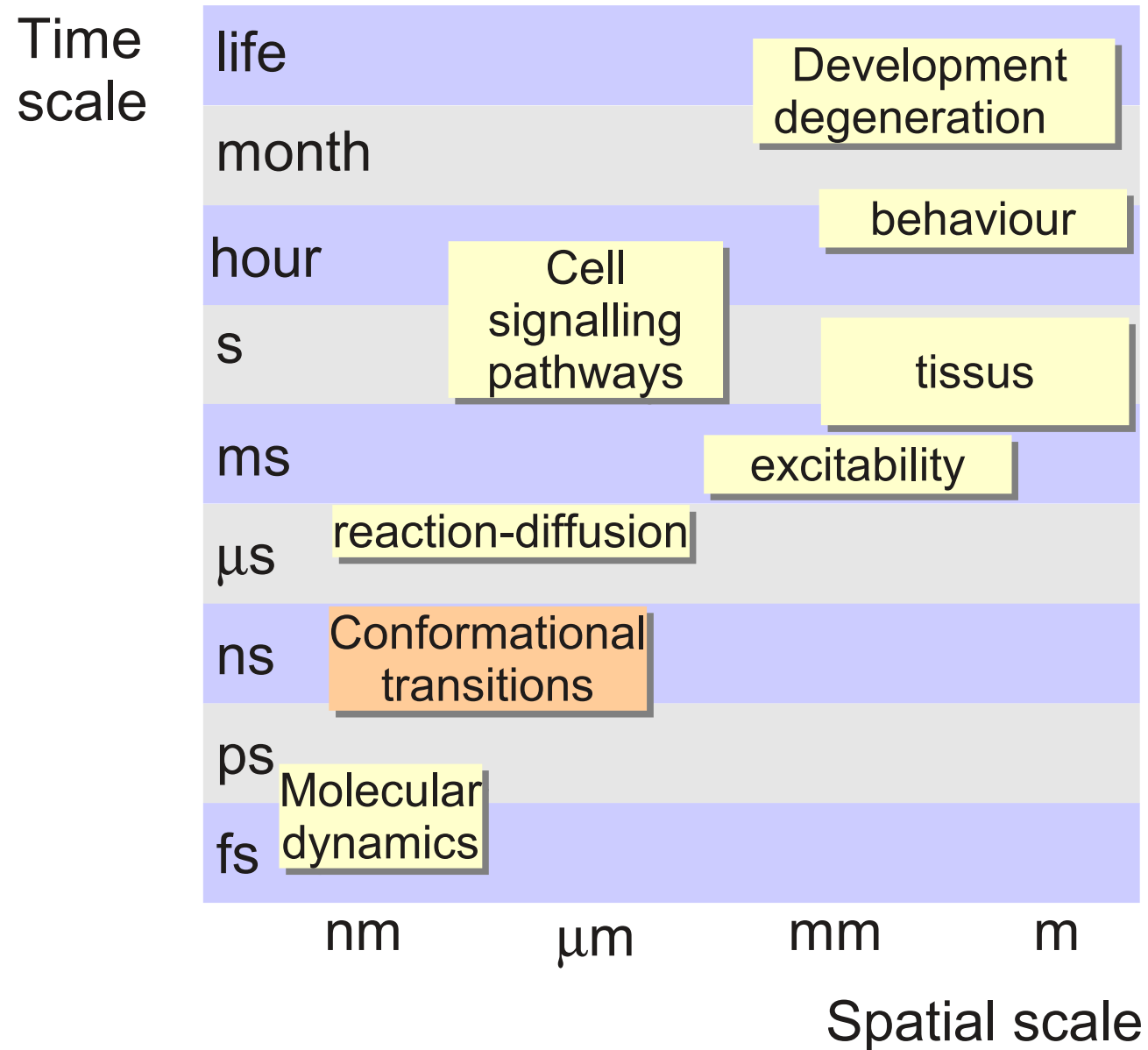


chemical kinetics

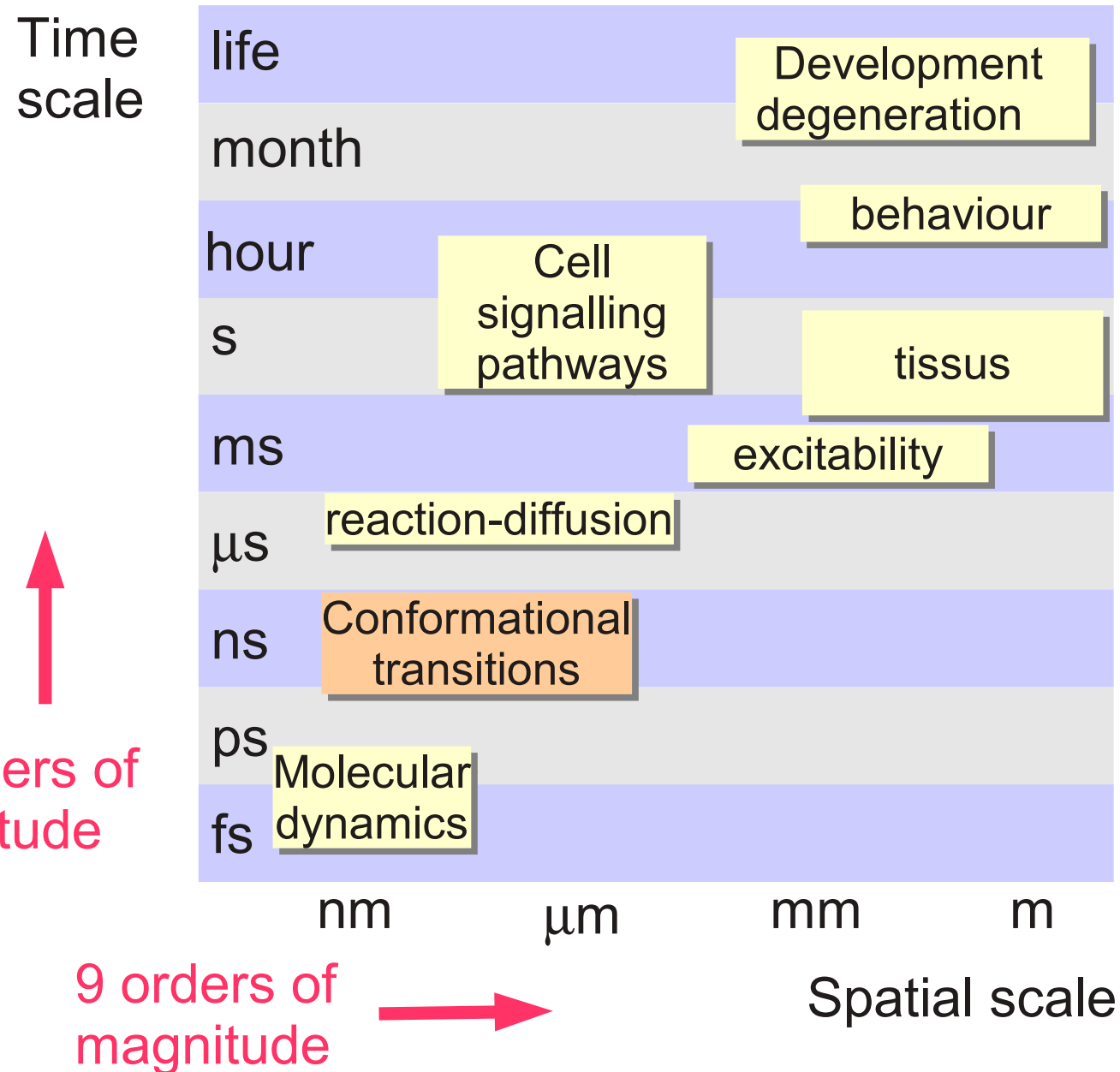


physiology

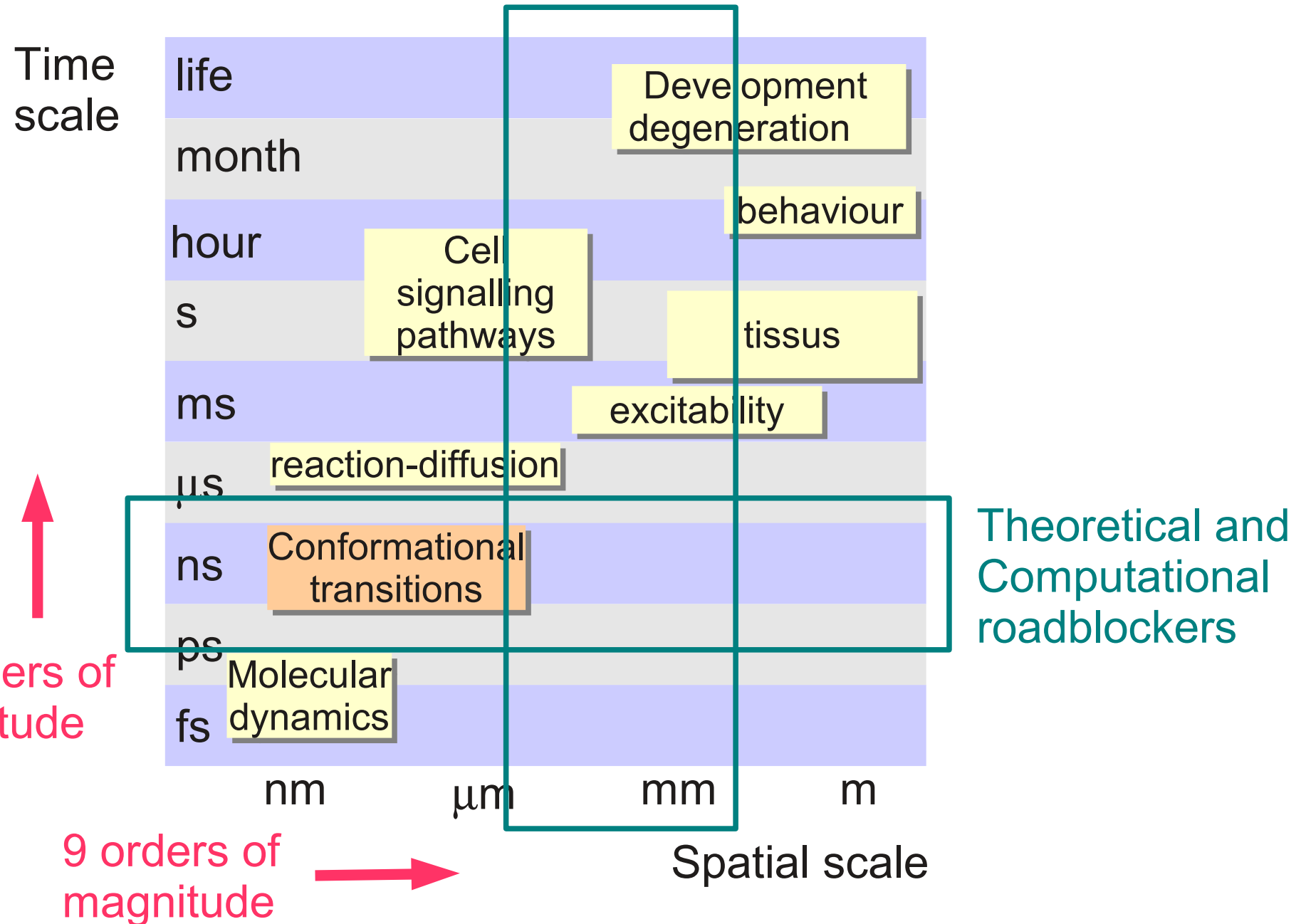
The mesoscopic gap



The mesoscopic gap



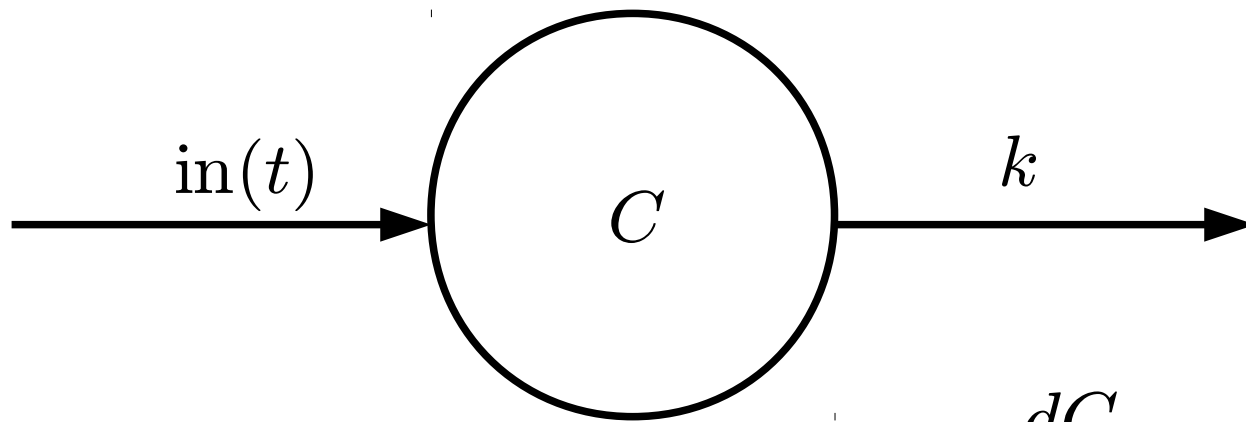
The mesoscopic gap



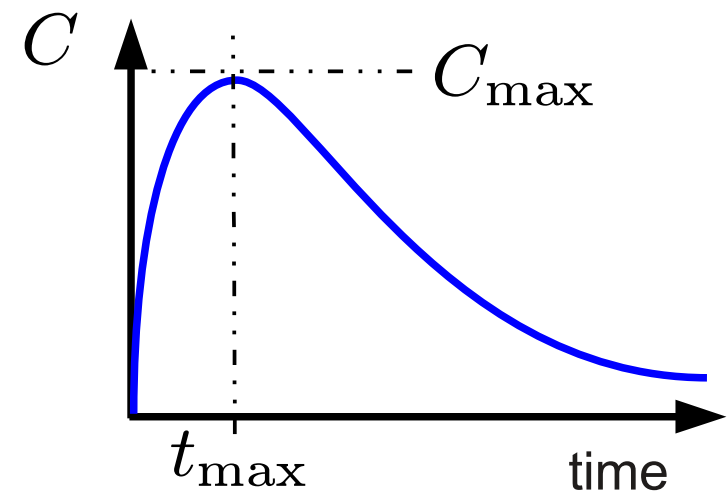
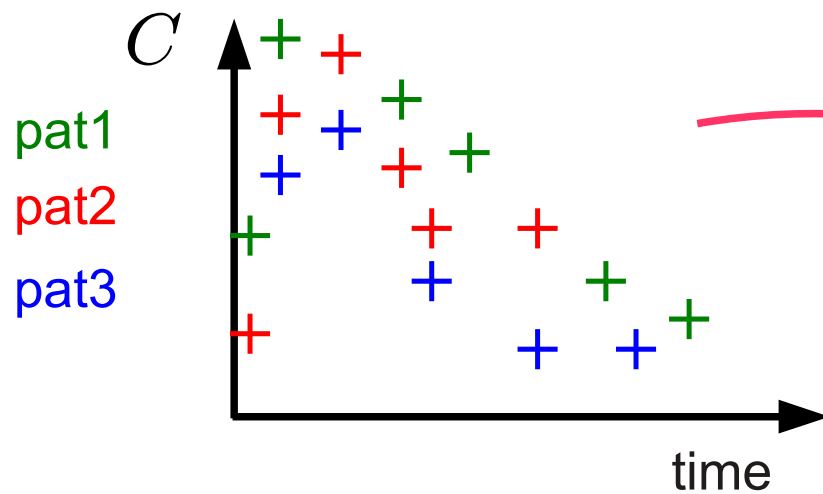
Multi-scale does not mean fine scale plus massive power

- Computational issues
 - In 2008, largest simulations were 1 million atoms for 50 ns (using > 30 years CPU) and 10000 atoms for 0.5 ms.
 - E-coli ~ 1 million million atoms ...
 - We need at least 10^{14} more power to simulate E coli during 1 s
- Theoretical issues
 - Molecular dynamics does not scale linearly with number of interactions
 - We do not know how to simulate mesoscopic phenomena: conformational transitions, secondary structure movements etc.

Drug discovery modelling: pharmacometrics

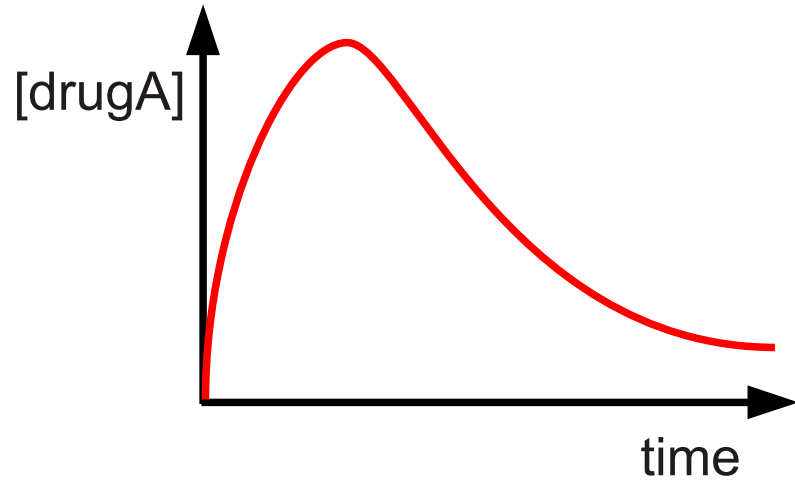


$$\frac{dC}{dt} = \text{in}(t) - k \times C$$

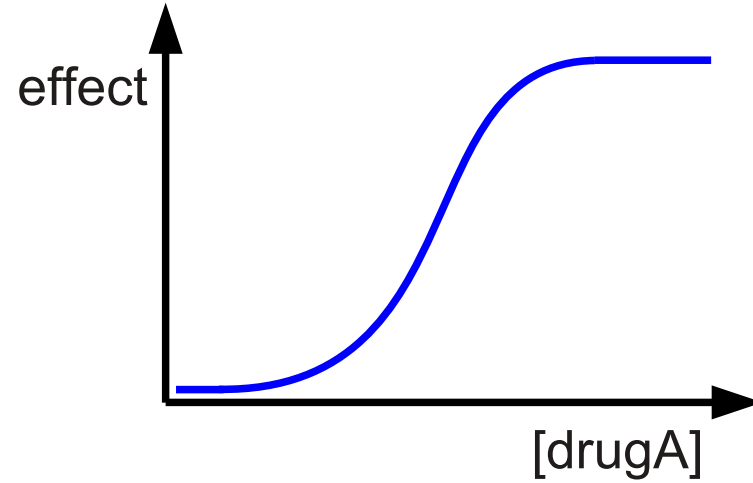


Drug discovery modelling: pharmacometrics

PK

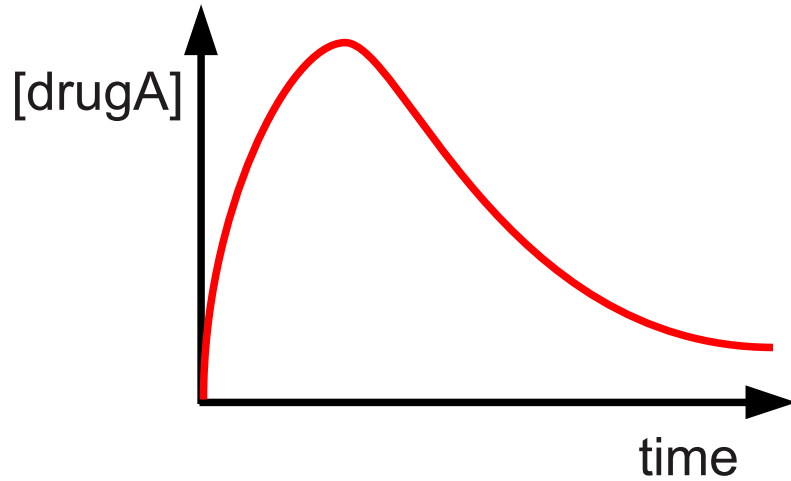


PD

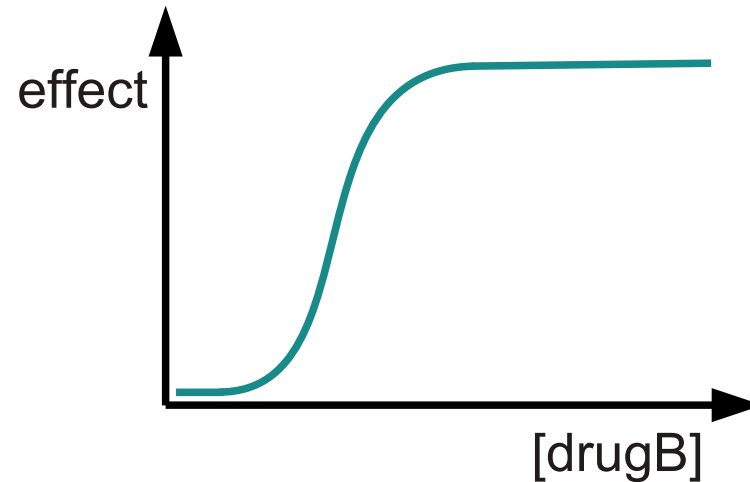
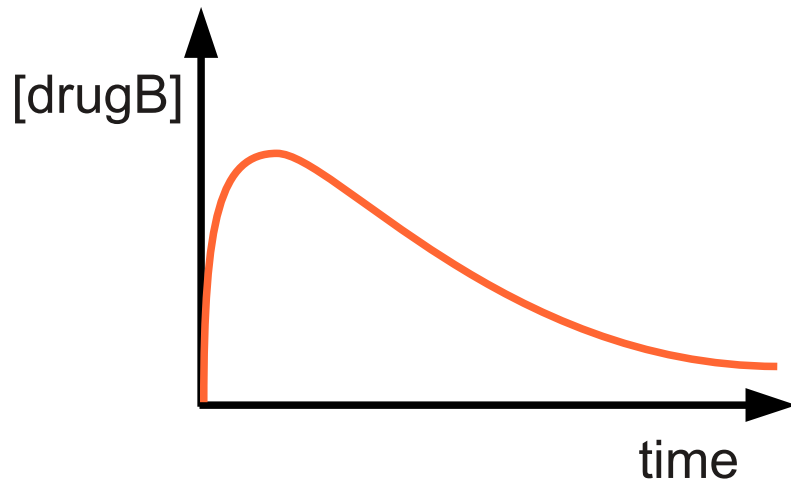
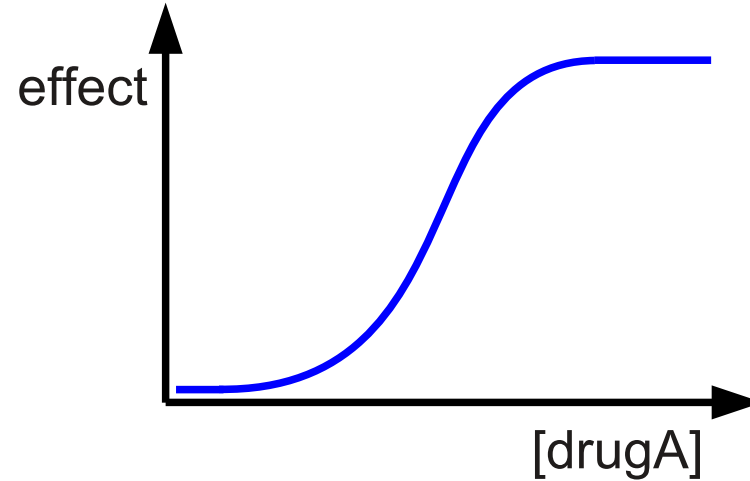


Drug discovery modelling: pharmacometrics

PK

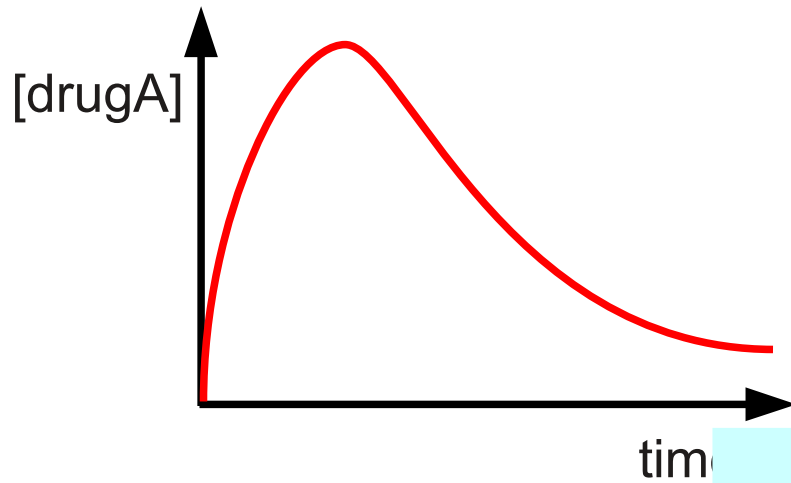


PD

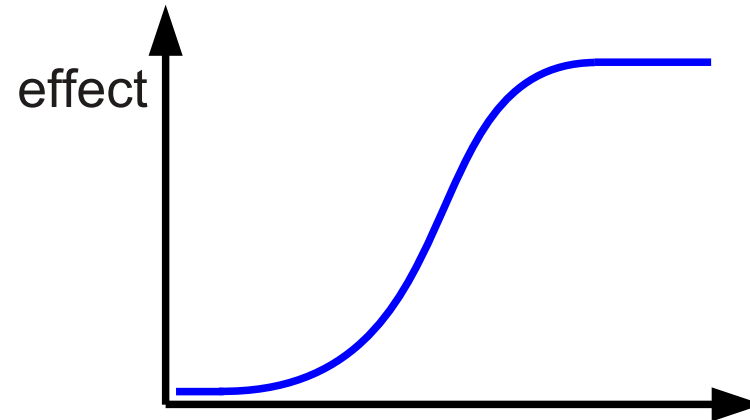


Drug discovery modelling: pharmacometrics

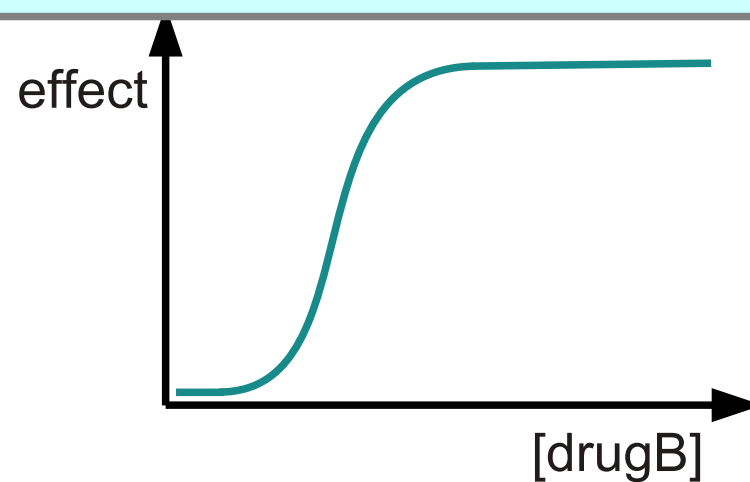
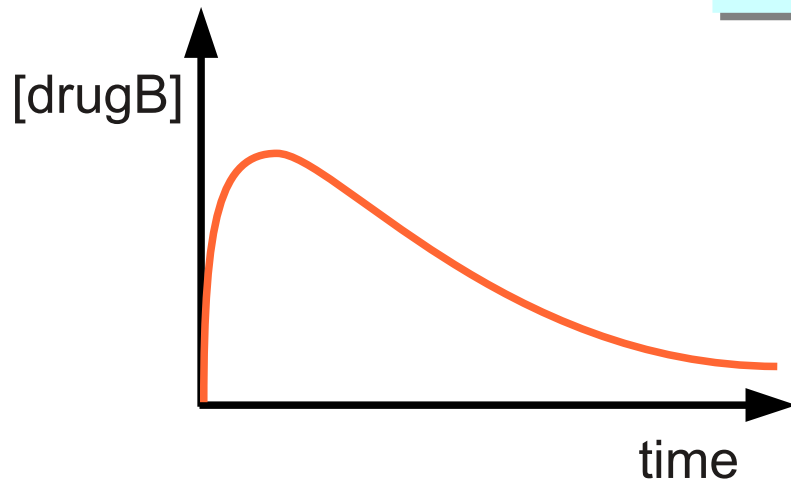
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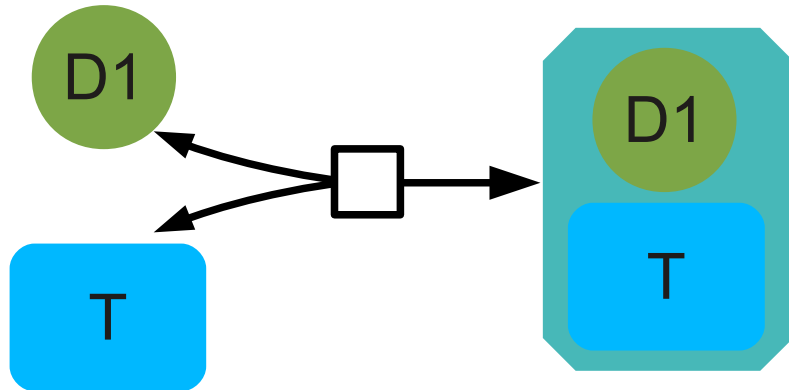
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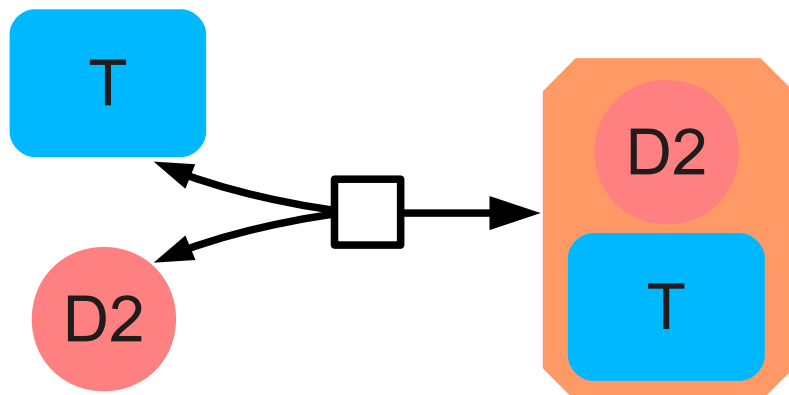
Effect of A+B?



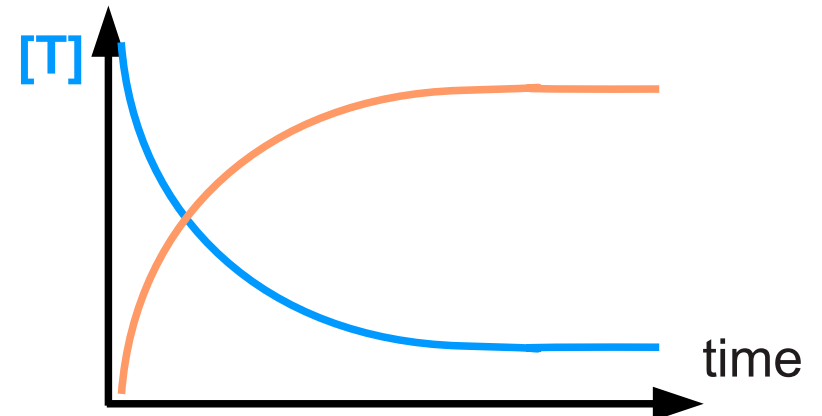
Systems modelling



$$\frac{d[T]}{dt} = -k_1 \times [T] \times [D1]$$

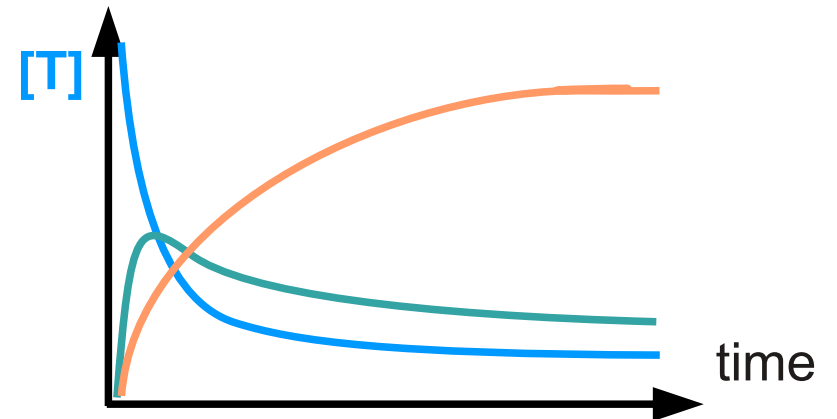
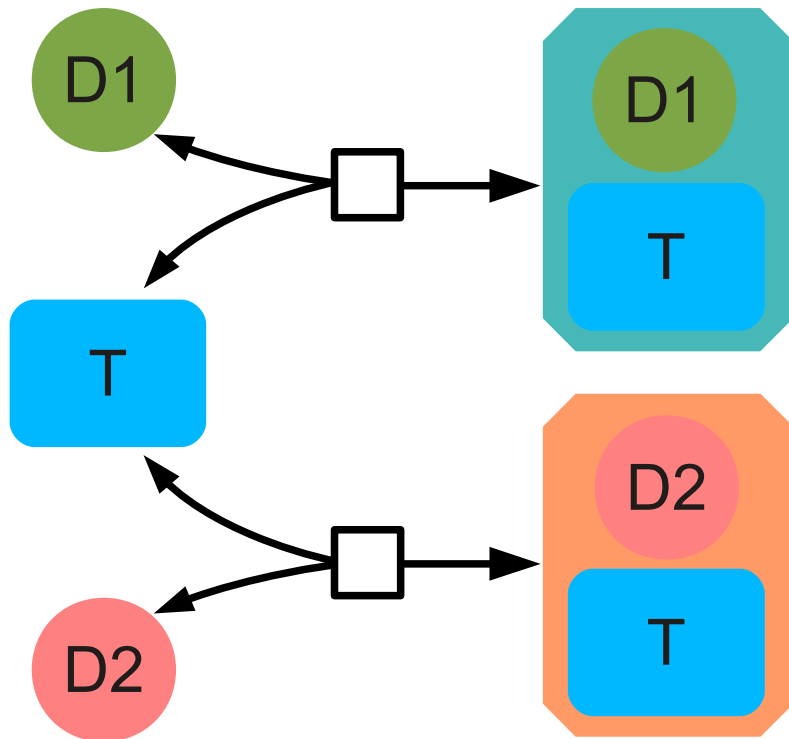


$$\frac{d[T]}{dt} = -k_2 \times [T] \times [D2]$$

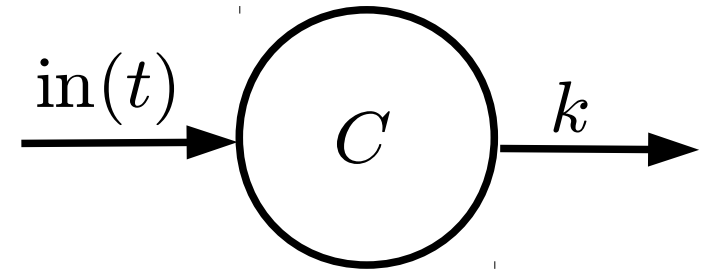
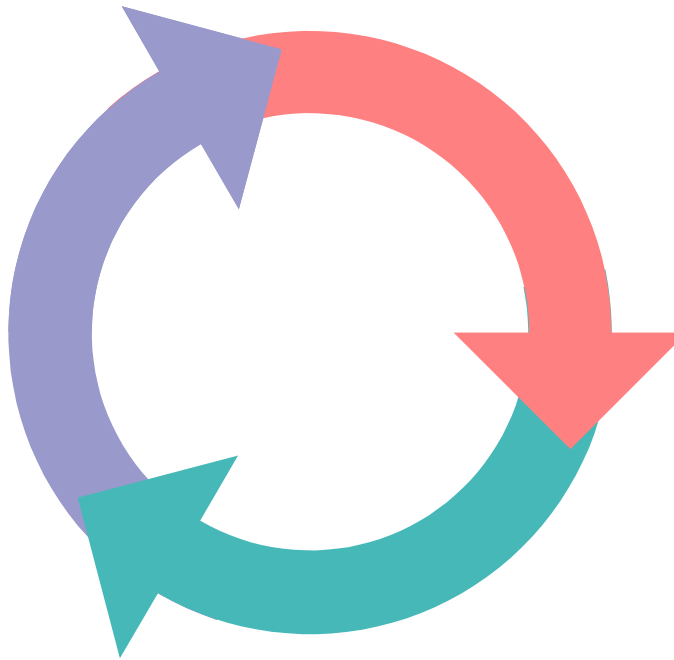
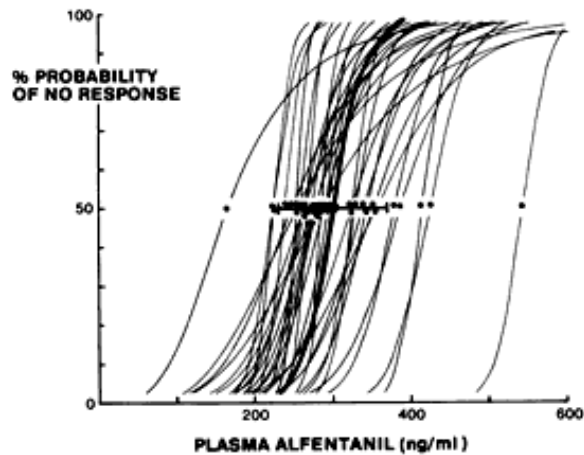
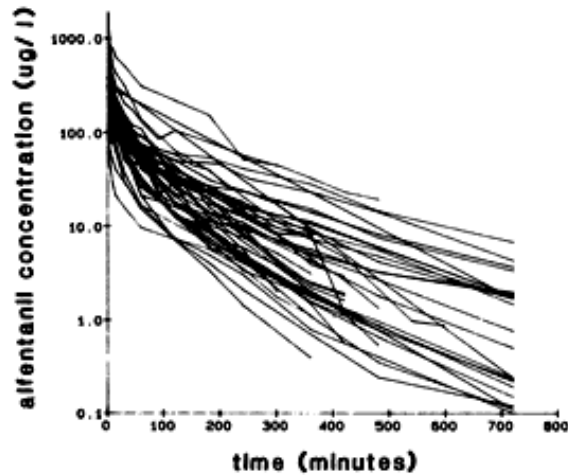


Systems modelling

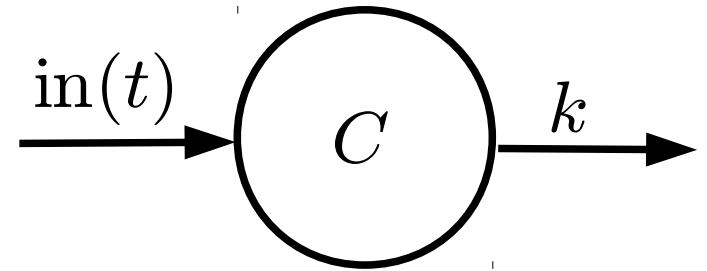
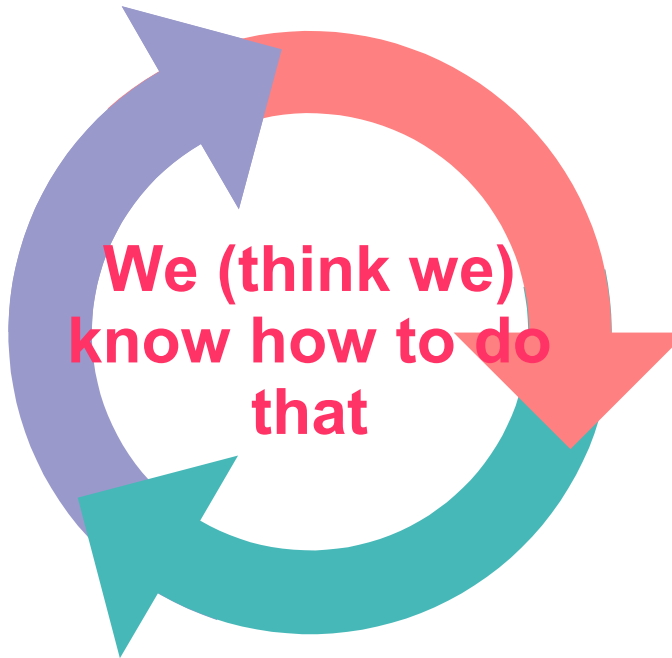
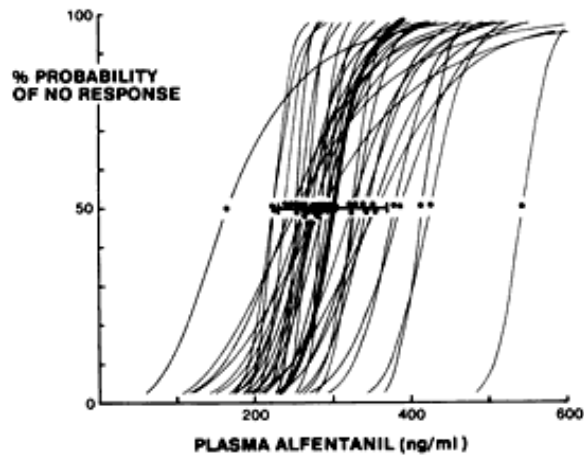
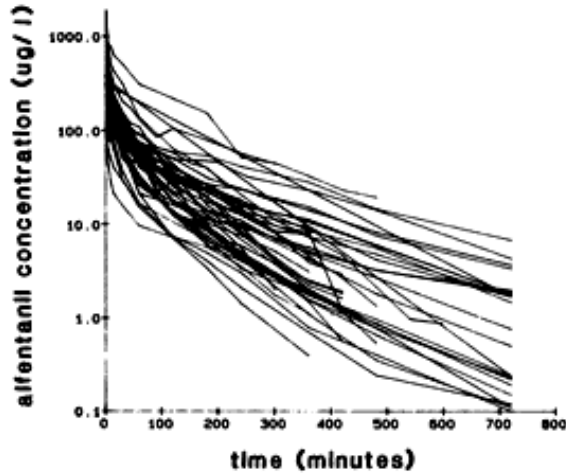
$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1] - k2 \times [T] \times [D2]$$



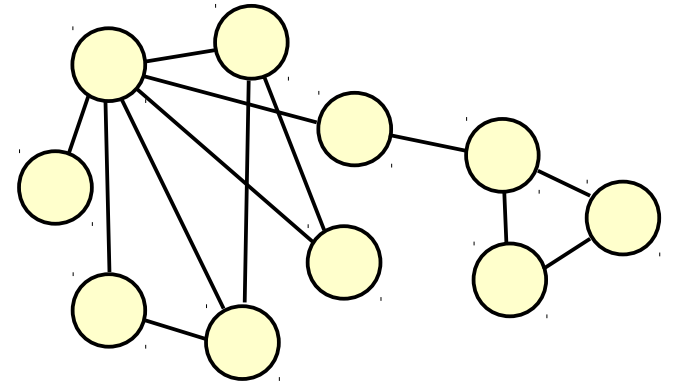
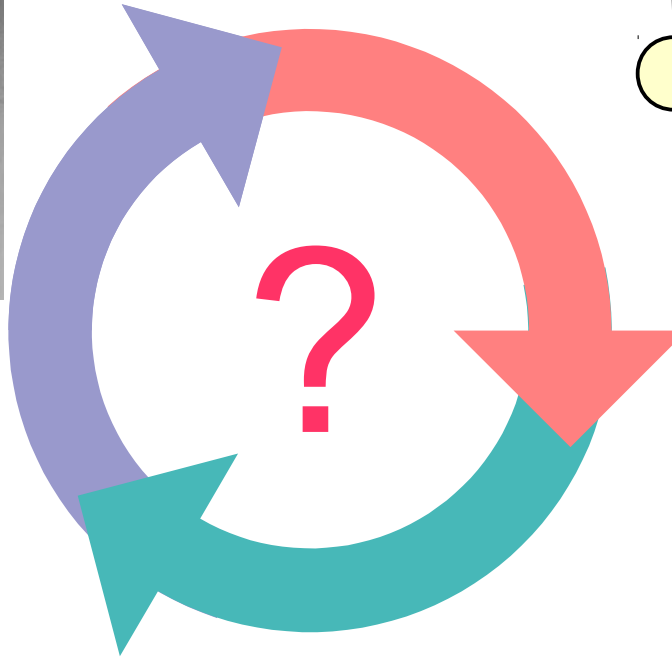
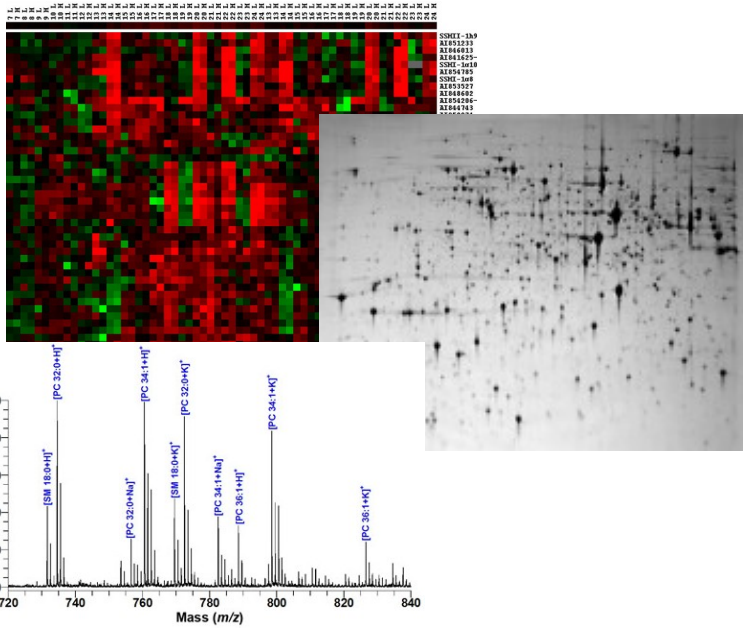
Drug discovery and pharmacometrics models



Drug discovery and pharmacometrics models



Drug discovery and omics



Systems Biology

Edda Klipp, Wolfram Liebermeister, Christoph Wierling,
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