What is Systems Biology?
What are the challenges ahead?

Nicolas Le Novère, EMBL-EBI

Emergence of the notion of system

XVI XVII XVIII XIX XX XXI

Global Description of the world

“classical” mechanic, anatomy, physiology

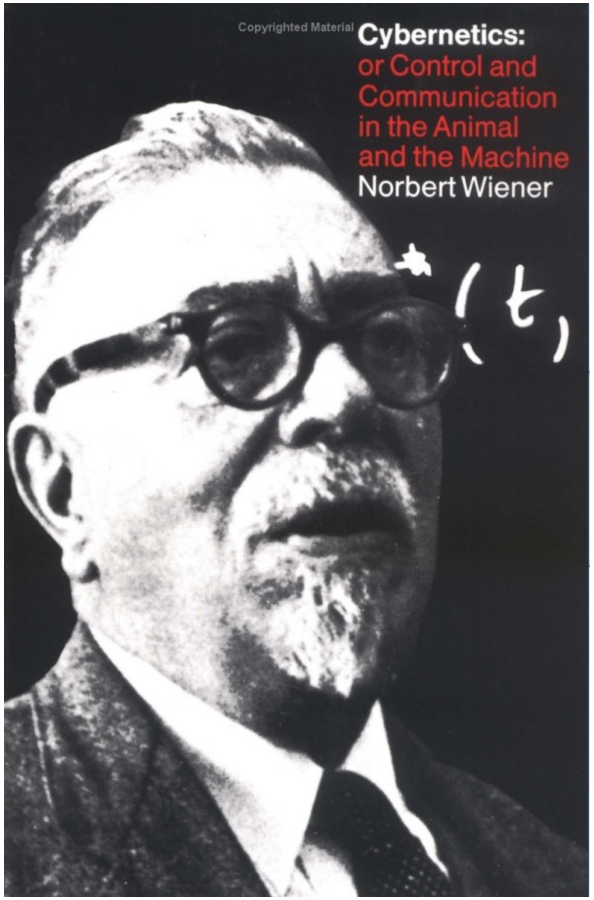
Description of the components of the world

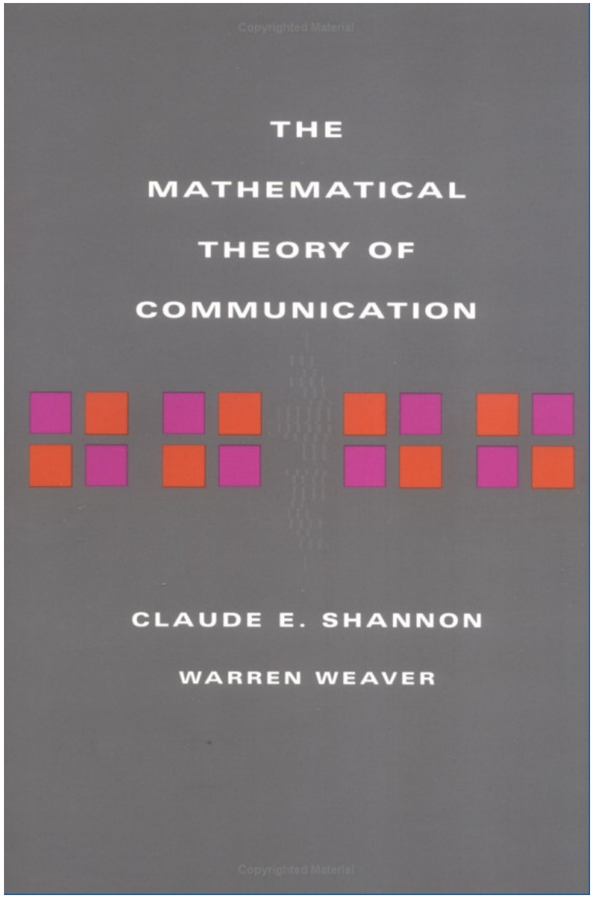
Statistical physics, thermodynamics, quantum mechanic,
biochemistry, structural biology, molecular biology

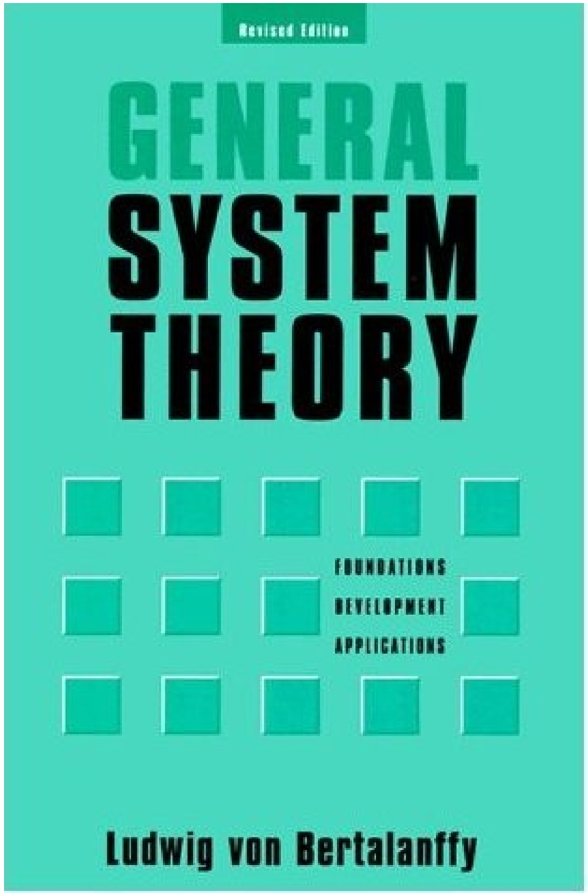
Description of interacting components

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

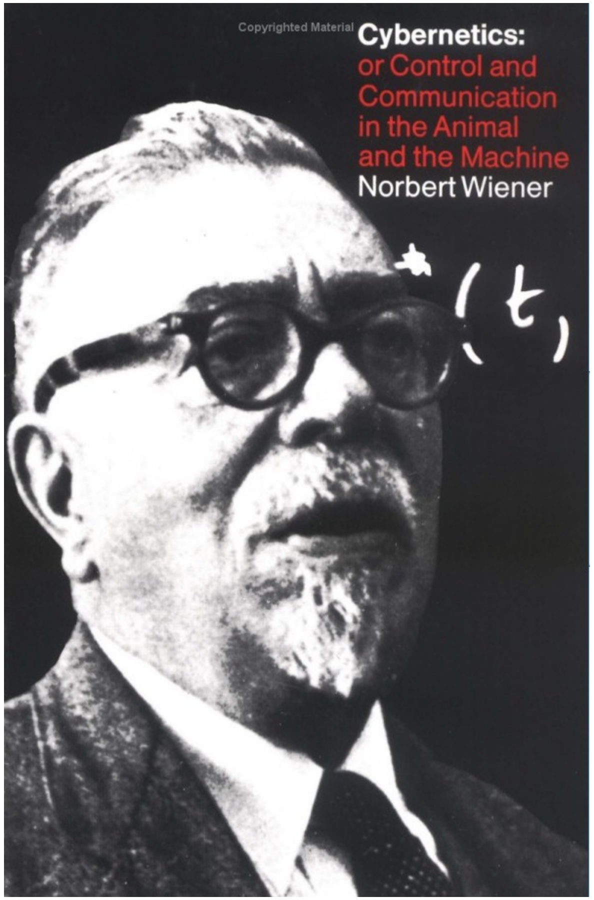
Systems have been formalised for a while

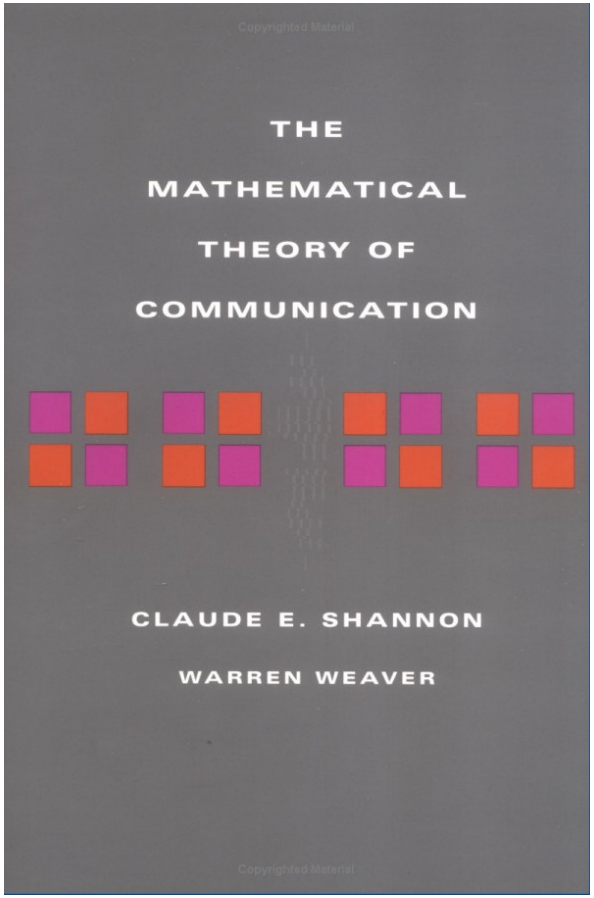


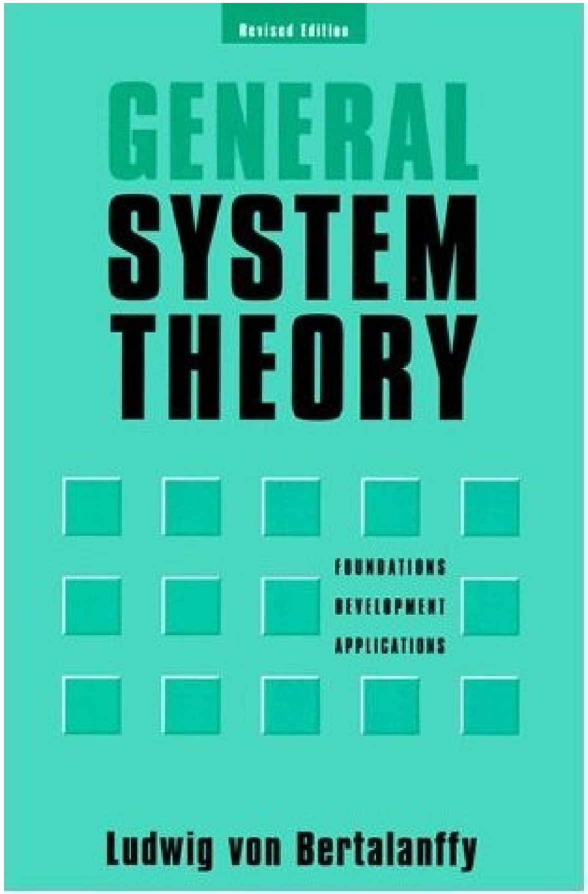




Systems have been formalised for a while

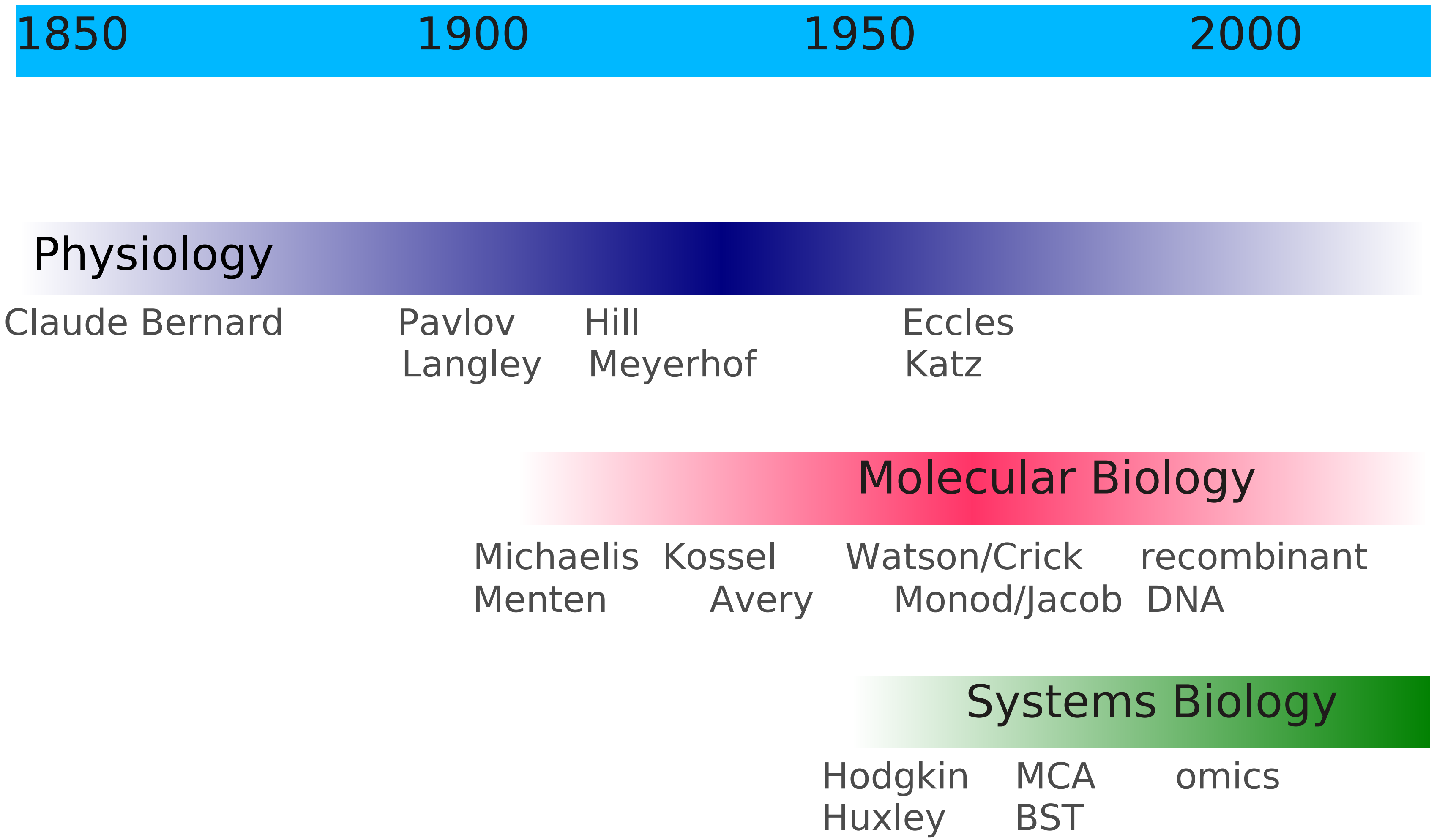






“[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems"
Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

The three paradigms of Biology



Computer simulations Vs. mathematical models

[37]

THE CHEMICAL BASIS OF MORPHOGENESIS

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

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

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

Computer simulations Vs. mathematical models

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THE CHEMICAL BASIS OF MORPHOGENESIS

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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

PDB EMBLbank Genomes

First computers PC Interactomes

1950 1960 1970 1980 1990 2000

Towards Systems Biology

Events around

PDB EMBLbank Genomes

First computers PC Interactomes

1950 1960 1970 1980 1990 2000

Hodgkin-Huxley

Dennis Noble
heart pacemaker

Goldbeter
Koshland
covalent
cascades

Cell Cycle models
signalling models
metabolic models
models of gene reg
whole heart

models

Towards Systems Biology

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Rall's cable
approximation

complex
neurons

simple
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Purkinje
Neuron

Blue Brain
Project

neurobiology

Towards Systems Biology

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models

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

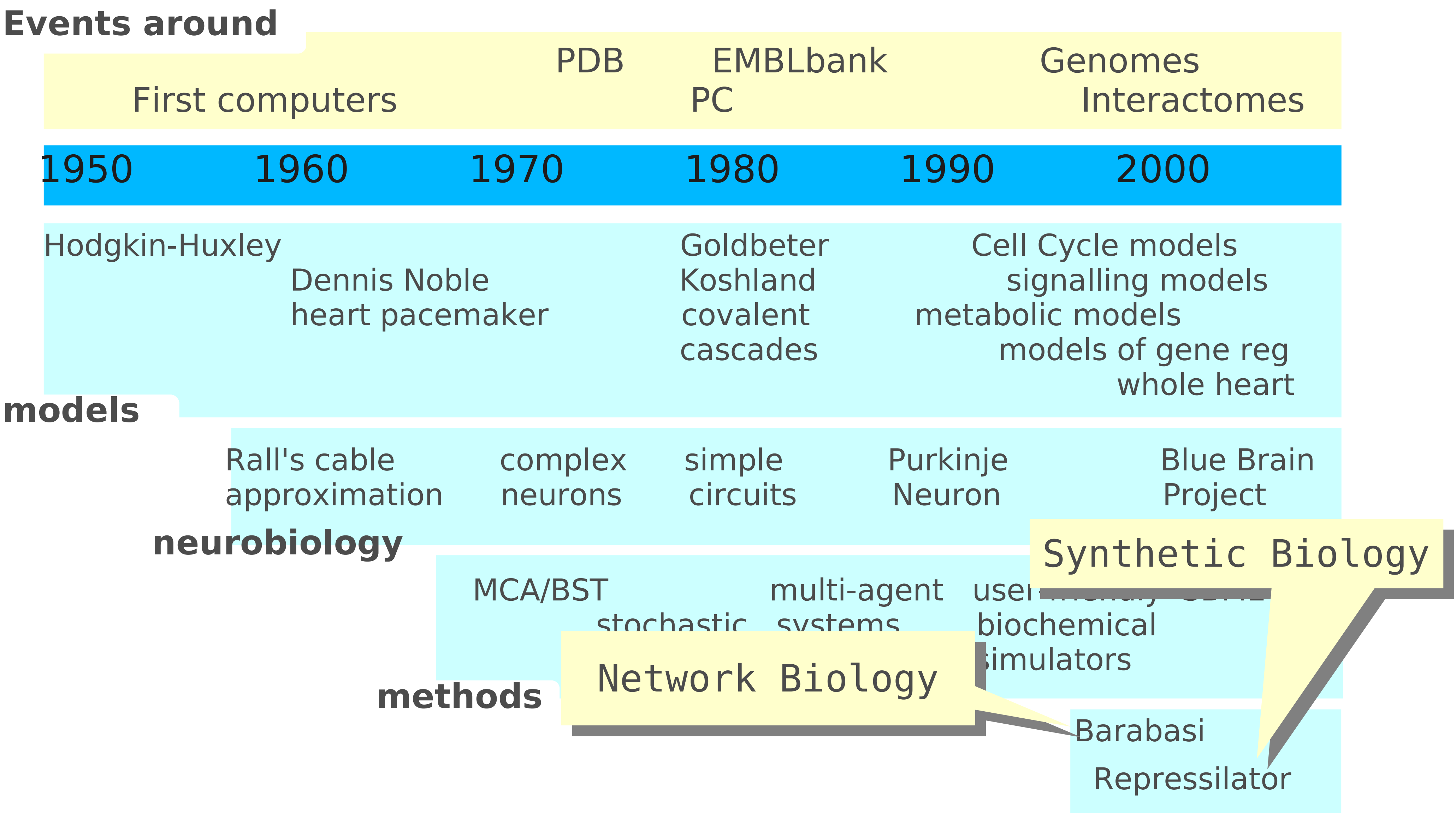
neurobiology

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

methods

Barabasi
Repressilator

Towards Systems Biology



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

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ERATO-Kitano

Alliance for Cellular Signaling

projects

SystemsX

HepatoSys

SysBio enters FP6

YSBN

ERASysBio

Rise of Systems Biology as a paradigm

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

projects

ERATO-Kitano
Alliance for Cellular Signaling
SystemsX
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publications

ECell
Von Dassow
SBML
Klipp
Alon
Choi
Annual Review
Science
Kriete
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Ideker/Hood
special issue
Boogerd
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IEE Sys Bio
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Institutes

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

Rise of Systems Biology as a paradigm

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ERATO-Kitano
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End of BBSRC Systems Biology calls

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Institutes

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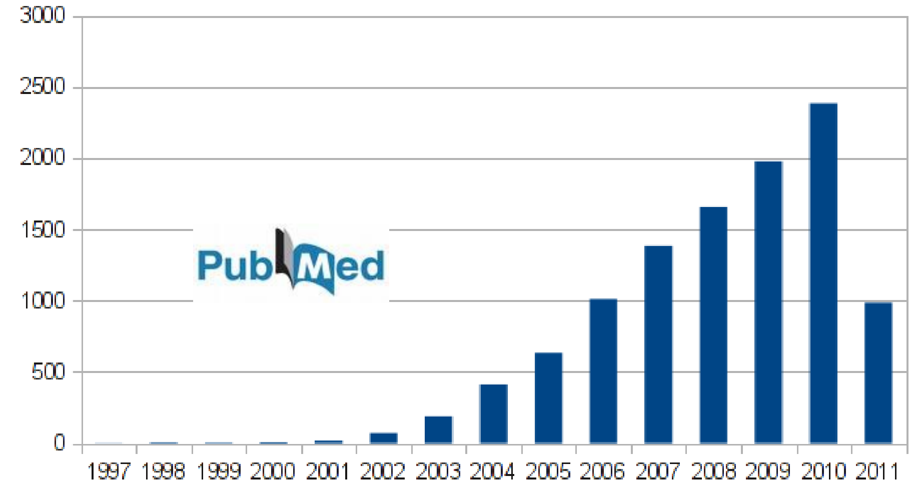
What is Systems Biology?

- First mention of the term: 1928 (L Von Bertallanfy)
- 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**.*

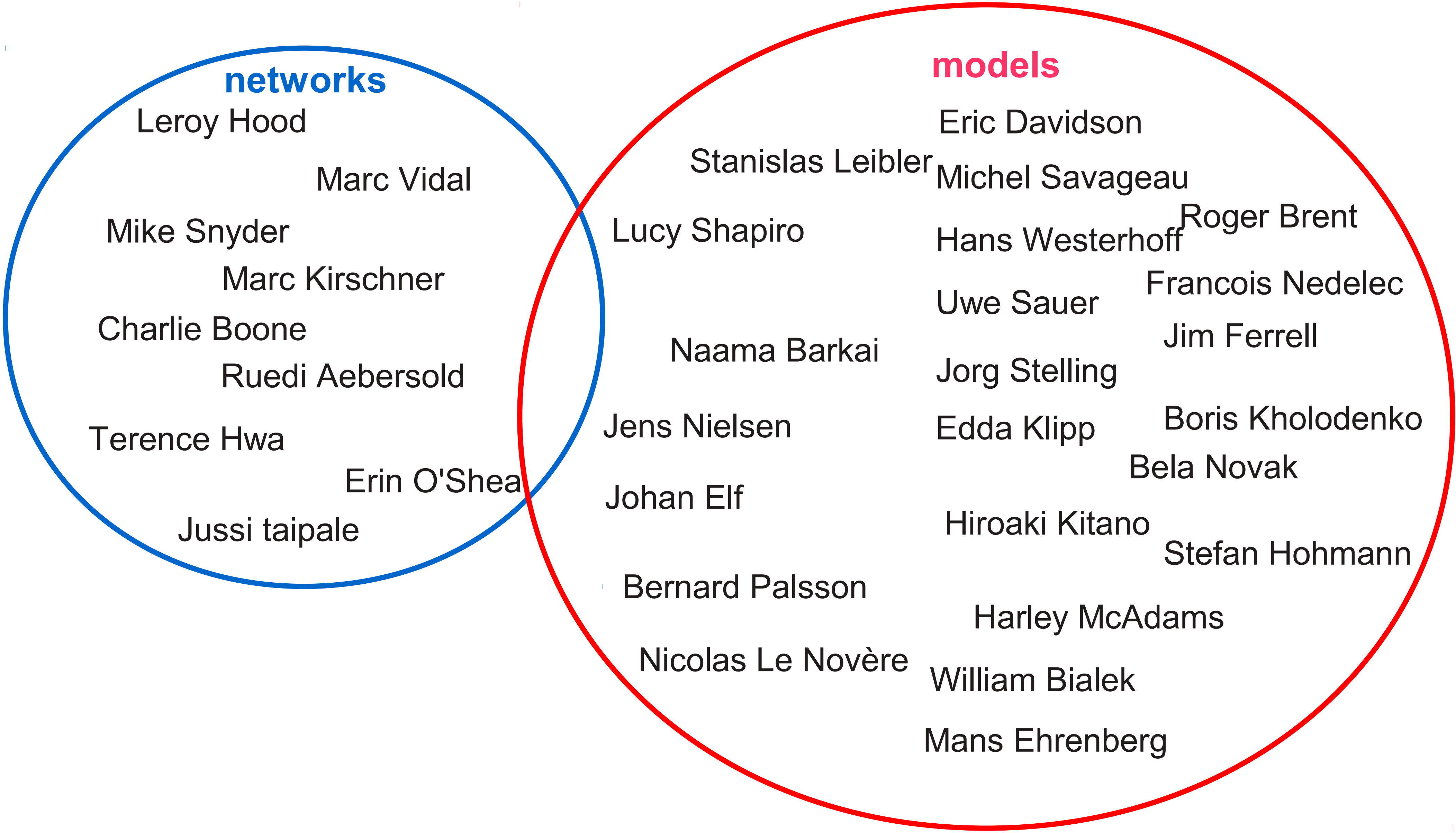
Systems-wide analysis (omics)

- 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)

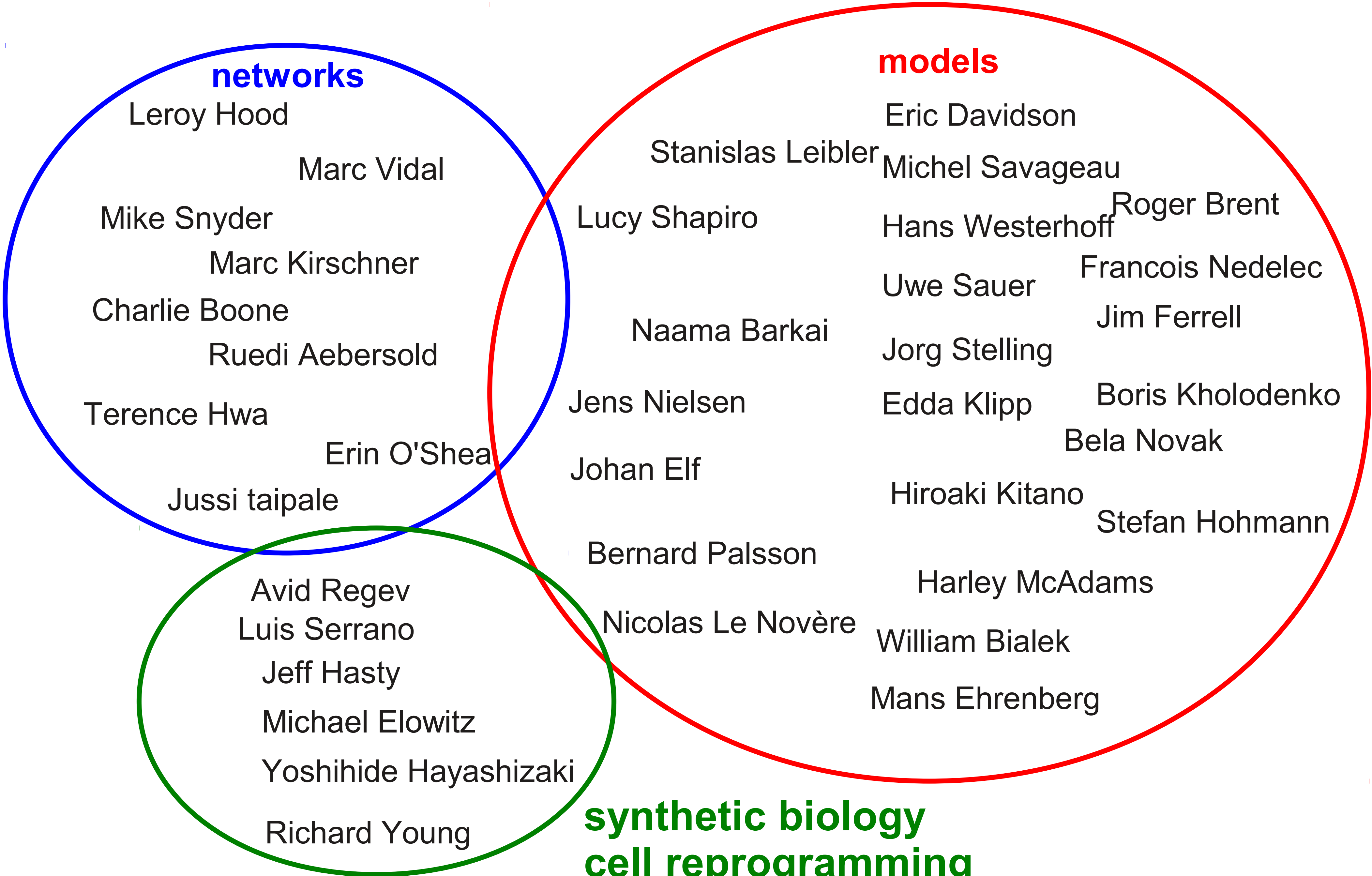
Application of systems-theory

- 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

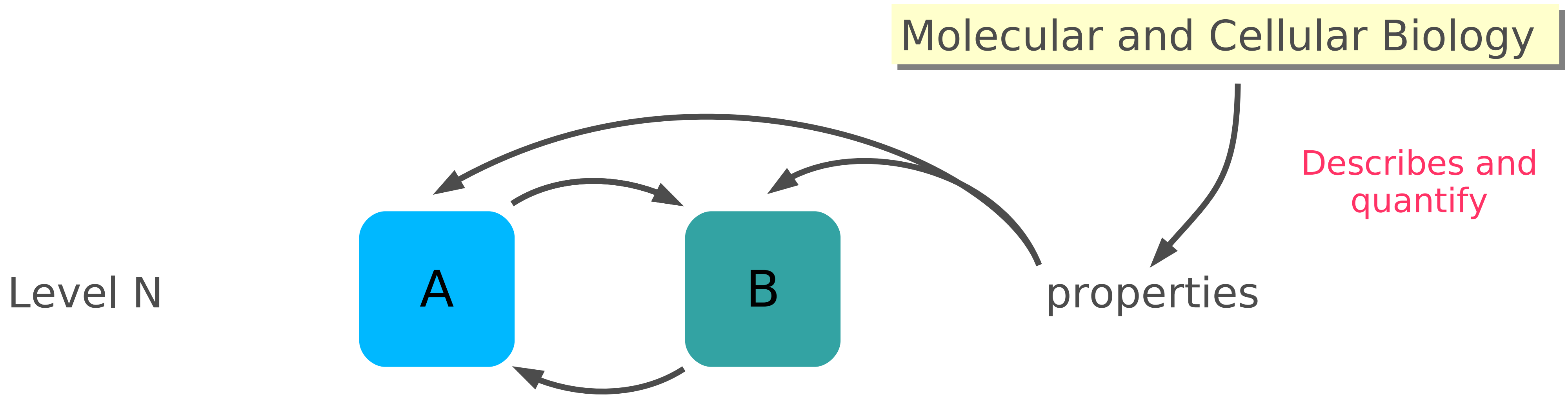
Nobel Symposium on Systems Biology (June 2009)



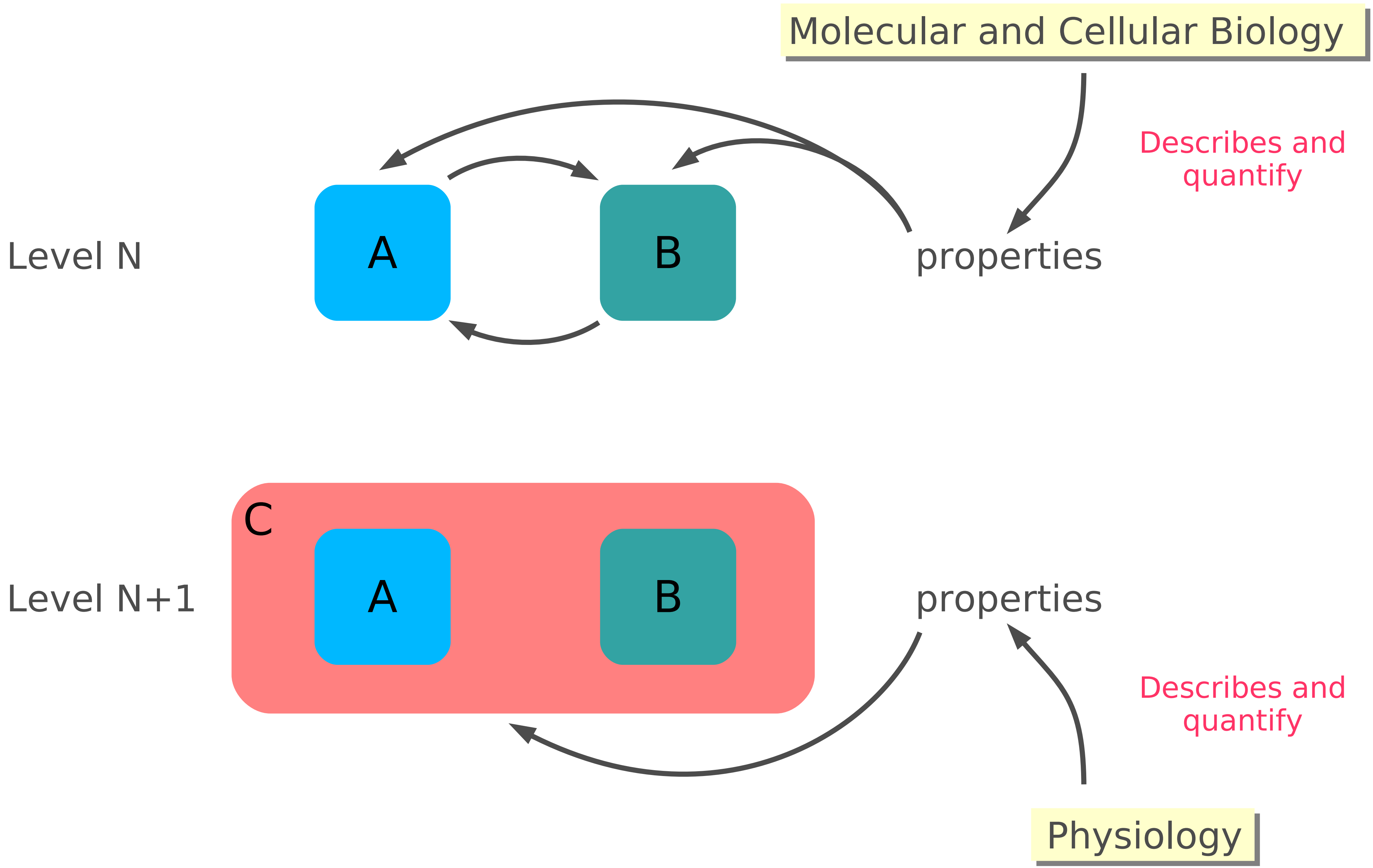
Nobel Symposium on Systems Biology (June 2009)



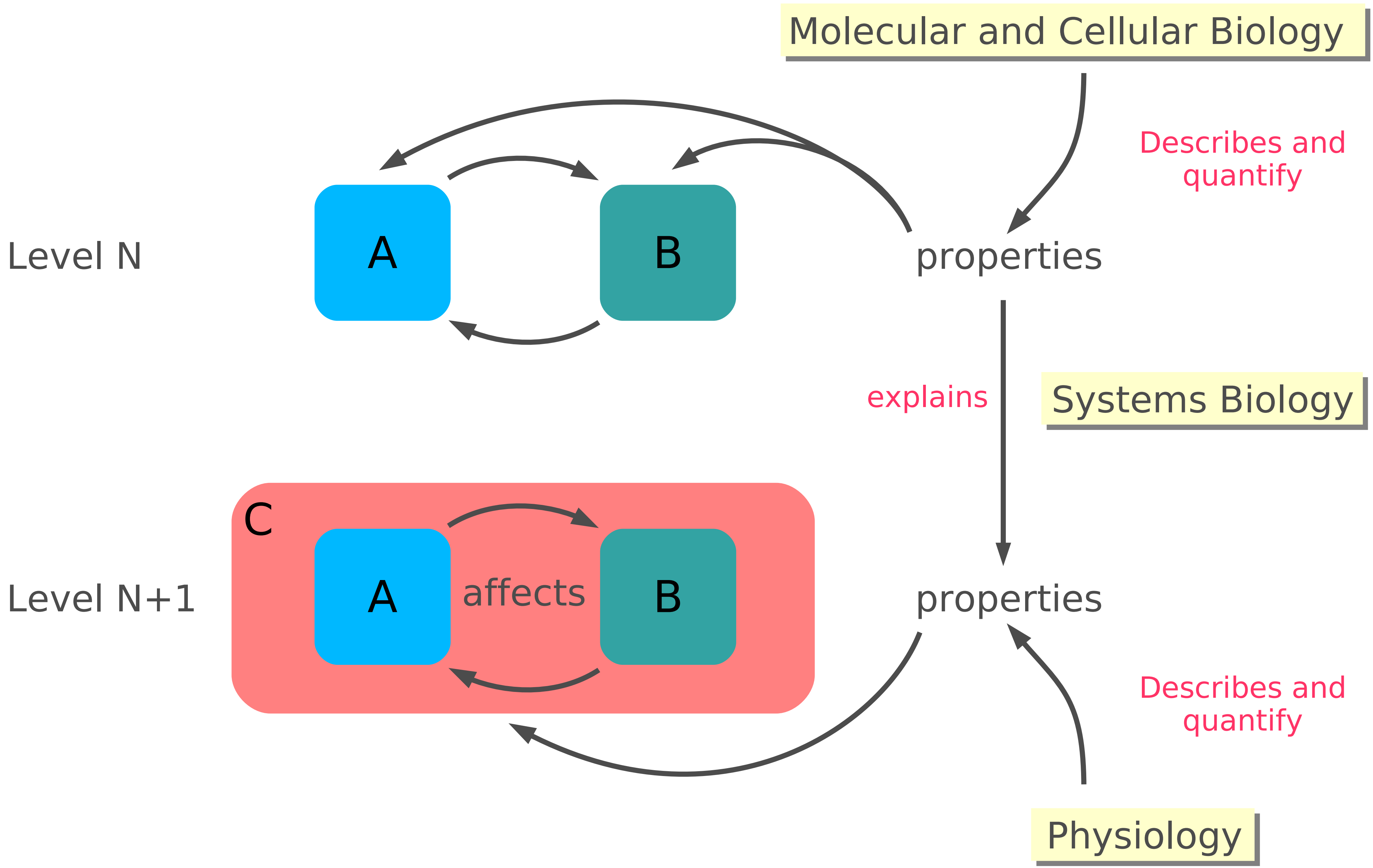
What is Systems Biology?



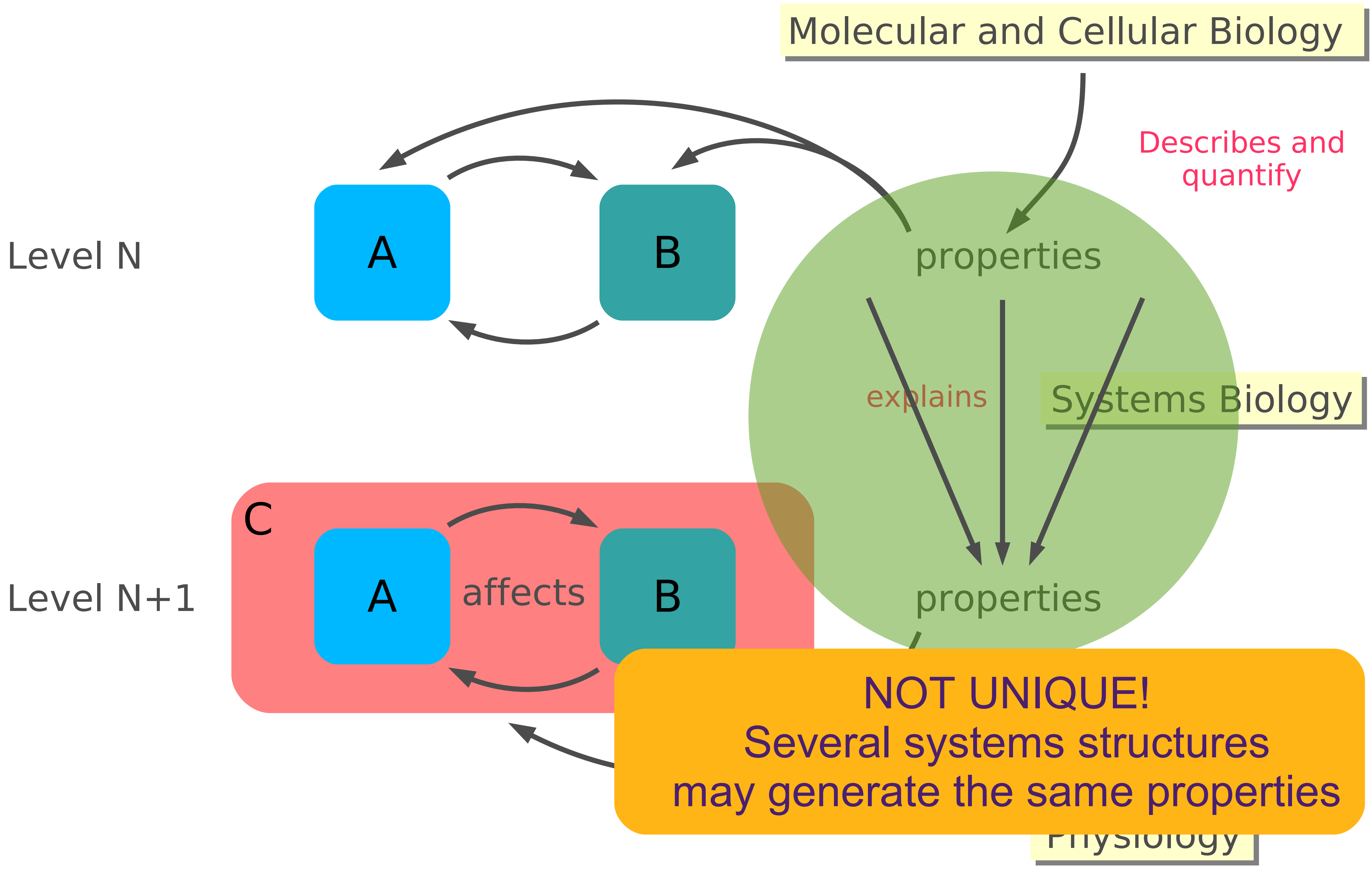
What is Systems Biology?



What is Systems Biology?



What is Systems Biology?



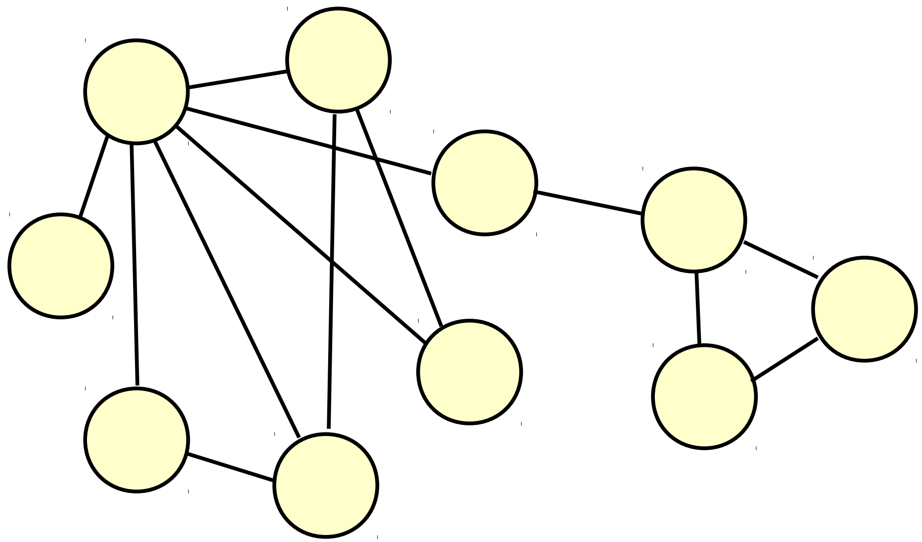
The challenges ahead: Bridging the gaps

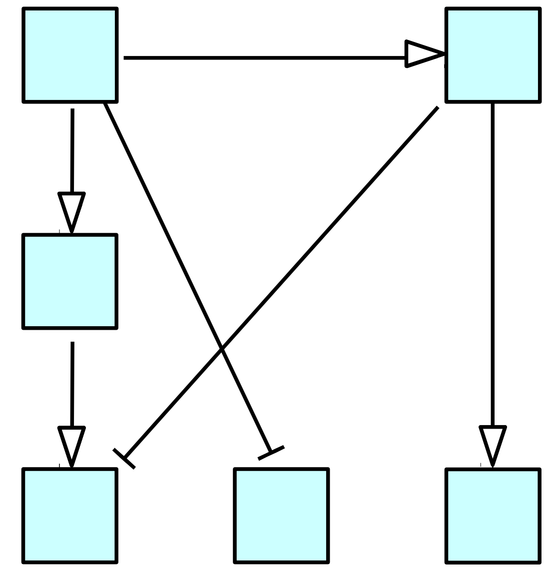
Types of representation

Scales and the mesoscopic gap

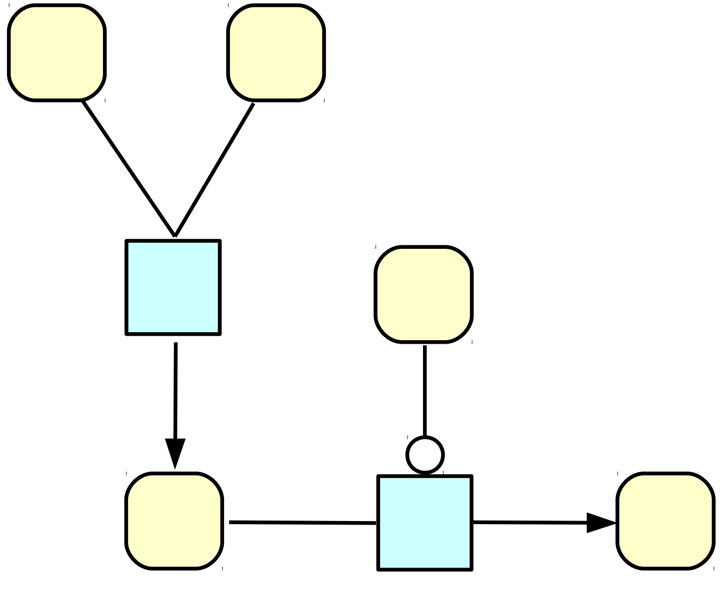
Drug discovery models
Vs systems modelling

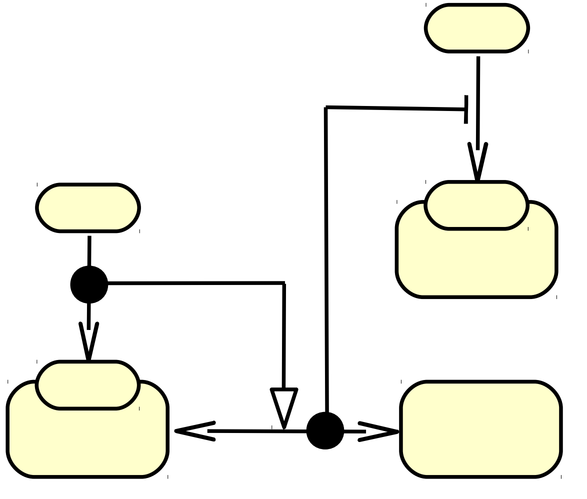
Drug discovery models
Vs “omics” data



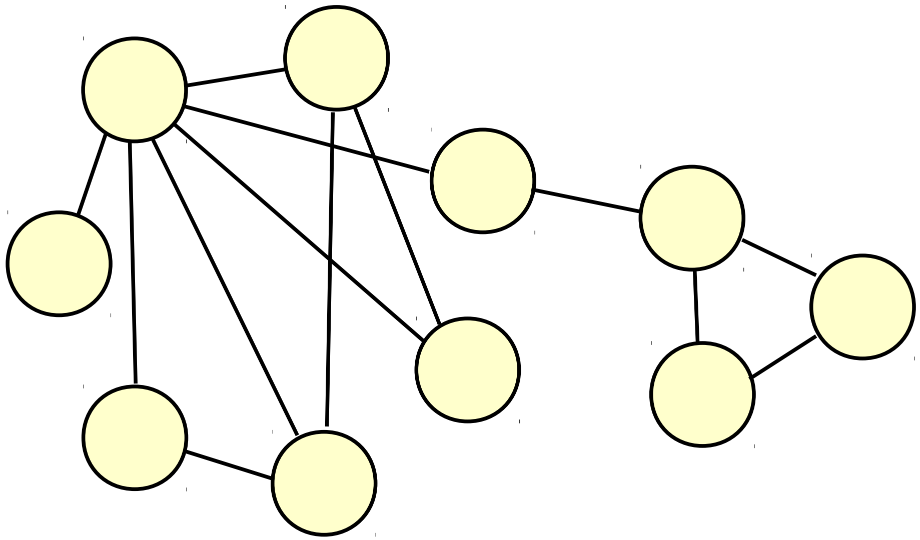


The four views of systems biology



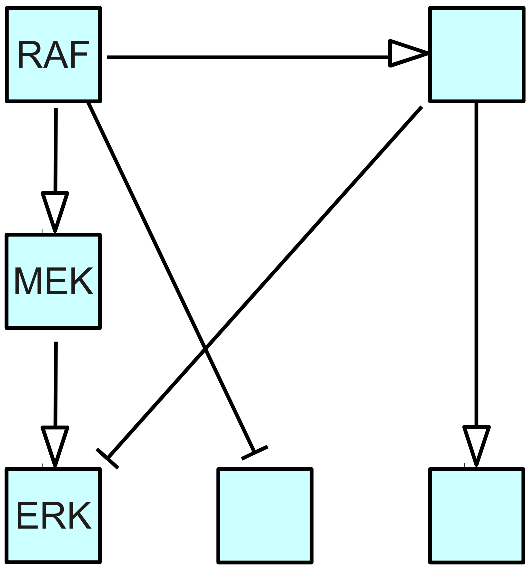


Interaction networks



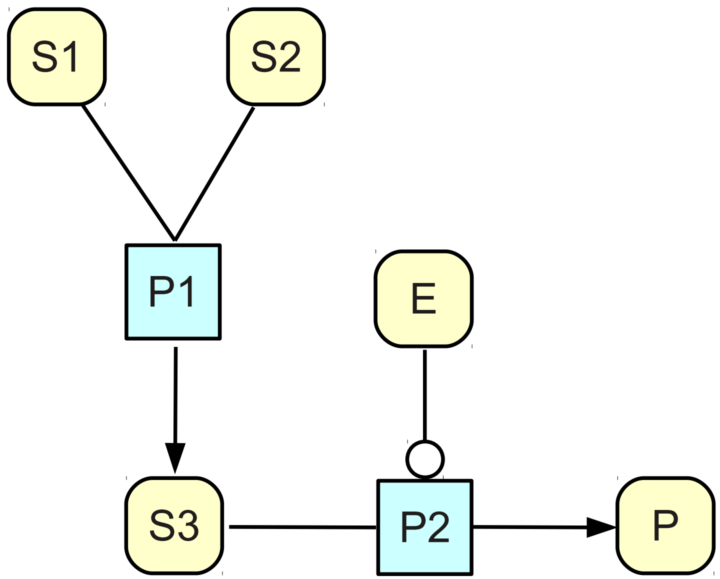
- Non-directional
- Non-sequential
- Non-mechanistic
- Statistical modelling
- Functional genomics
- IntAct, DIP, String

Activity-Flows



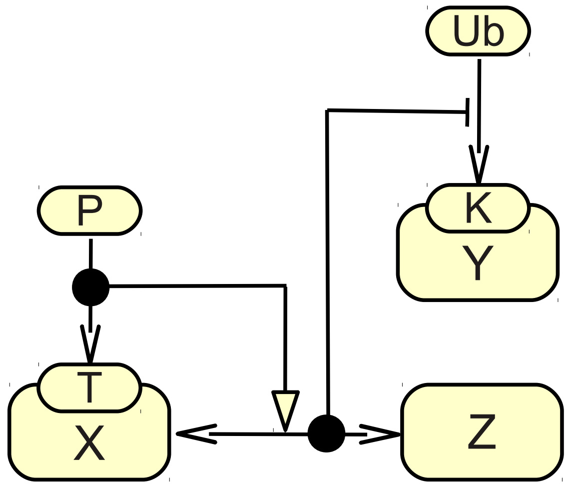
- Directional
- Sequential
- Non-mechanistic
- Logical modelling
- Signalling pathways, gene regulatory networks
- KEGG, STKEs

Process Descriptions

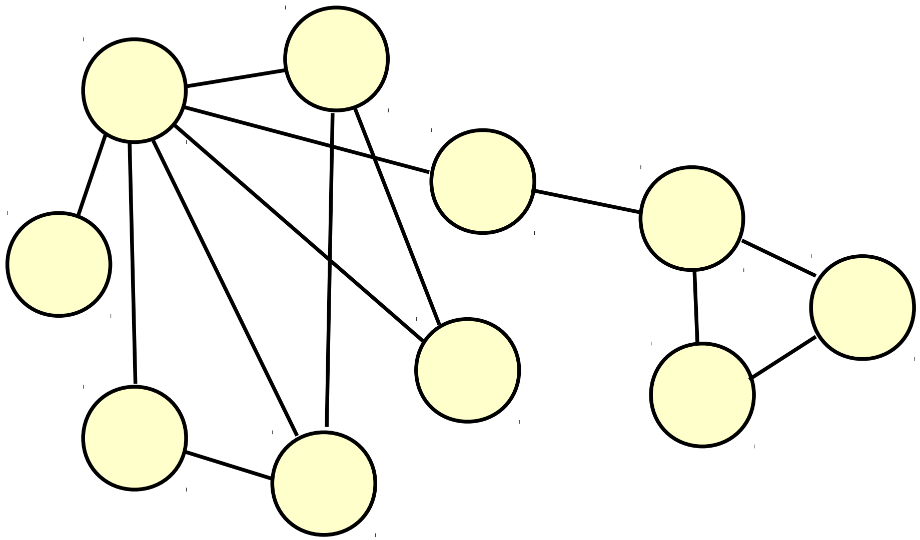


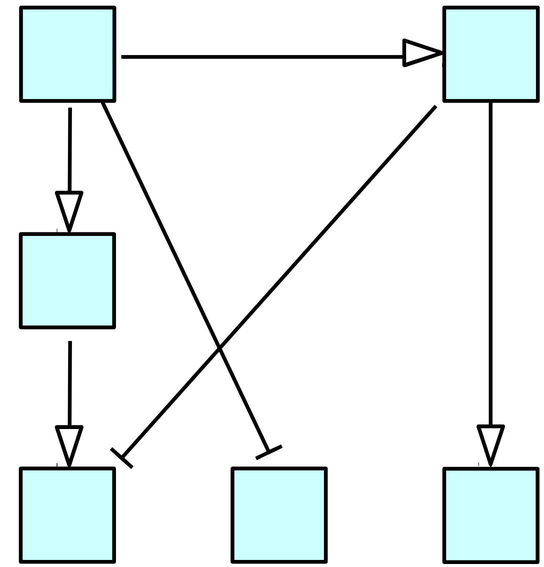
- Directional
- Sequential
- Mechanistic
- Subjected to combinatorial explosion
- Process modelling
- Biochemistry, Metabolic networks
- KEGG, Reactome

Entity Relationships

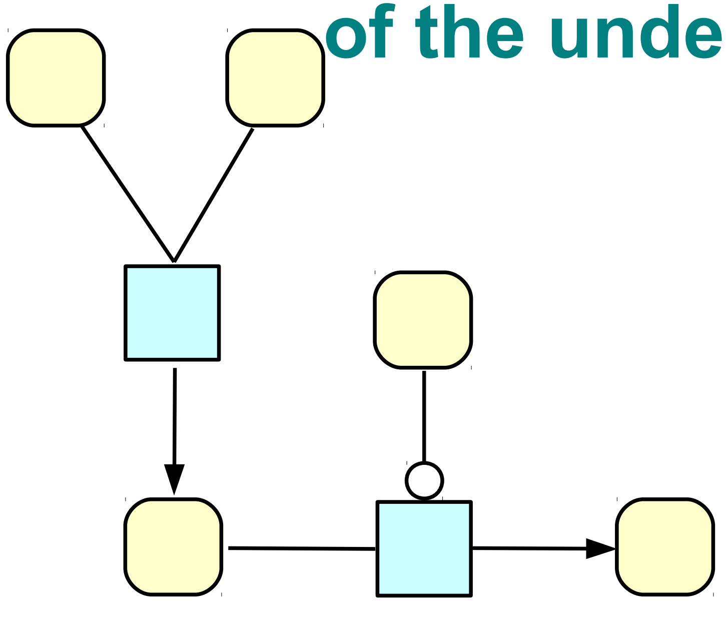


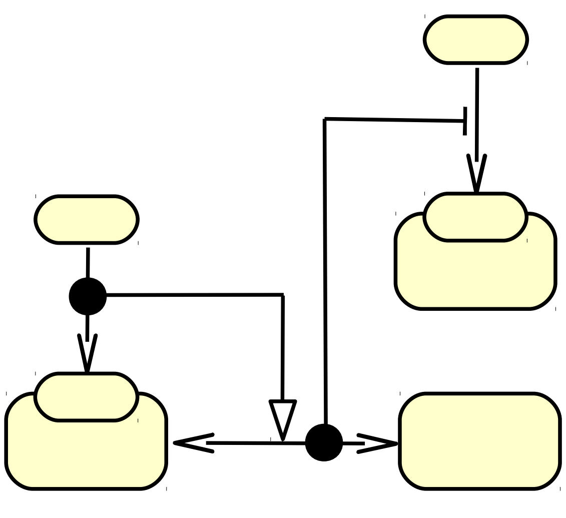
- Directional
- Non-sequential
- Mechanistic
- Independent rules: no explosion
- Rule-based modelling
- Molecular Biology
- MIM



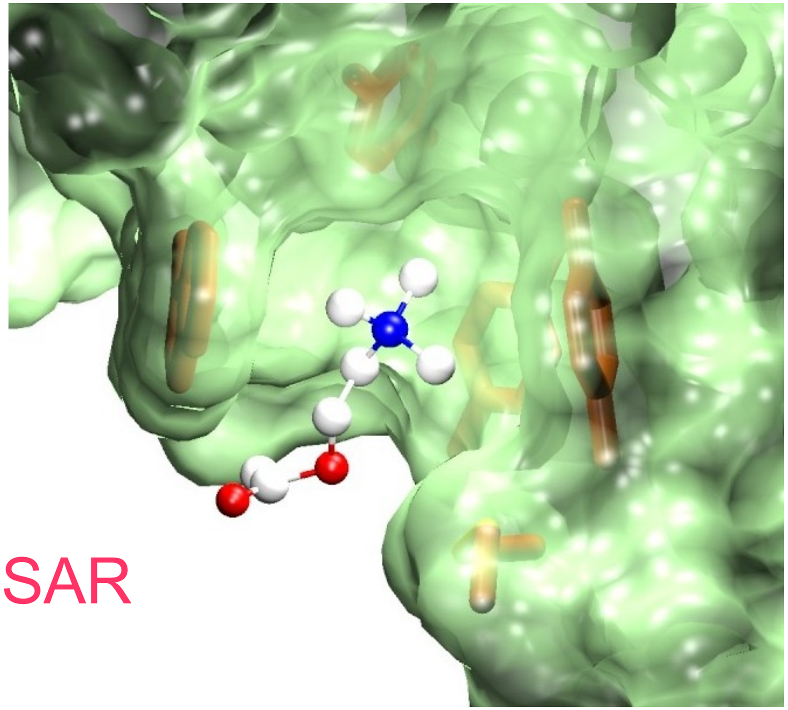


The four views are orthogonal projections of the underlying biological phenomena

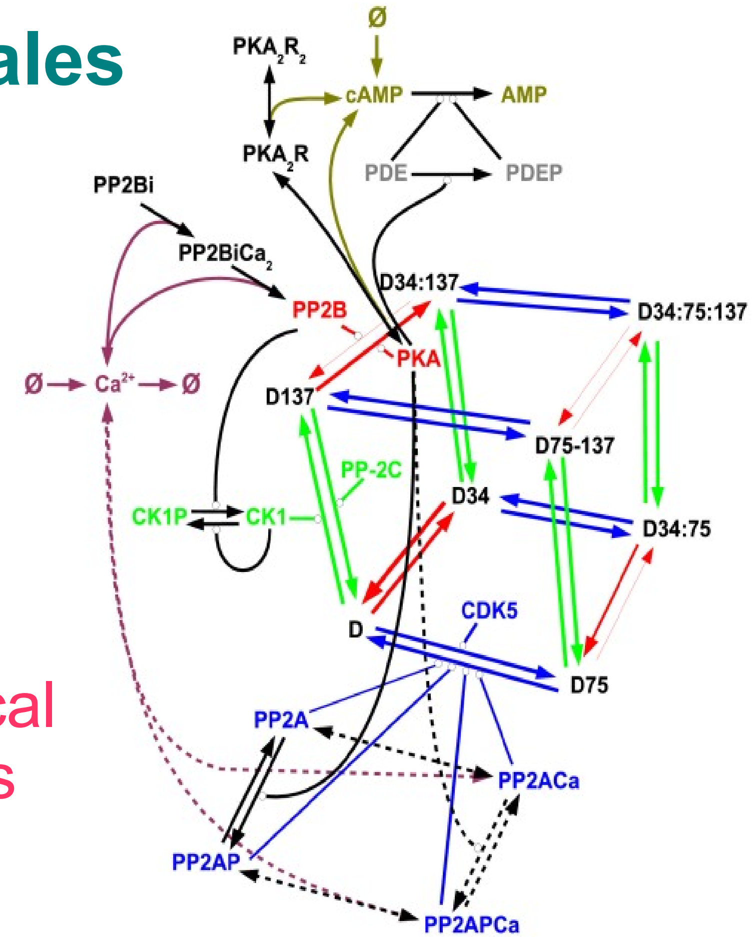




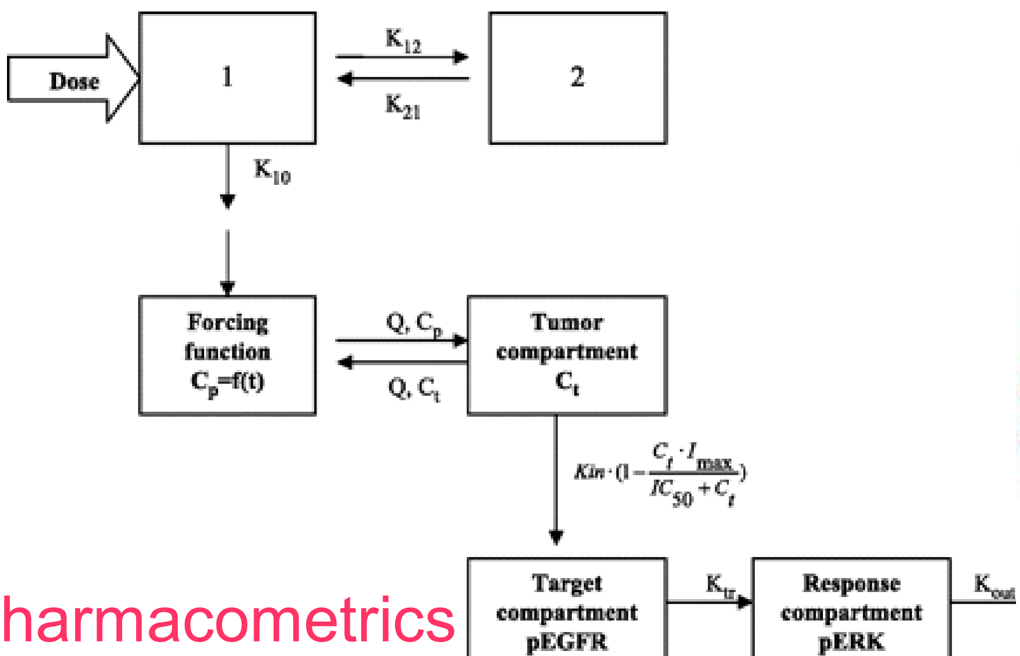
The problem of scales



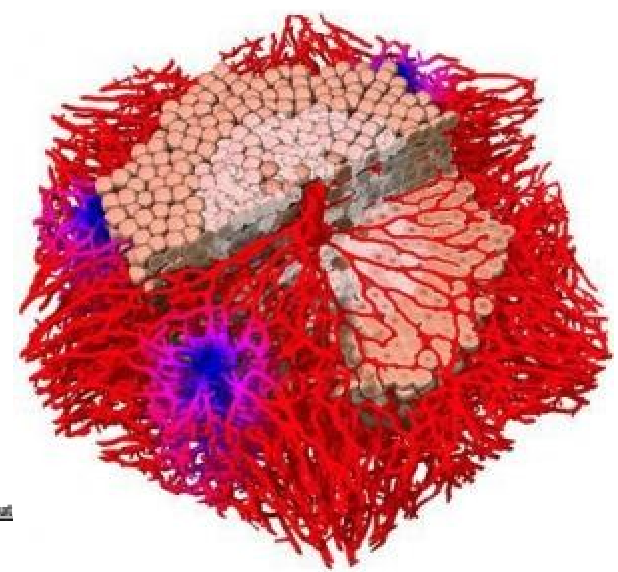
QSAR



chemical kinetics

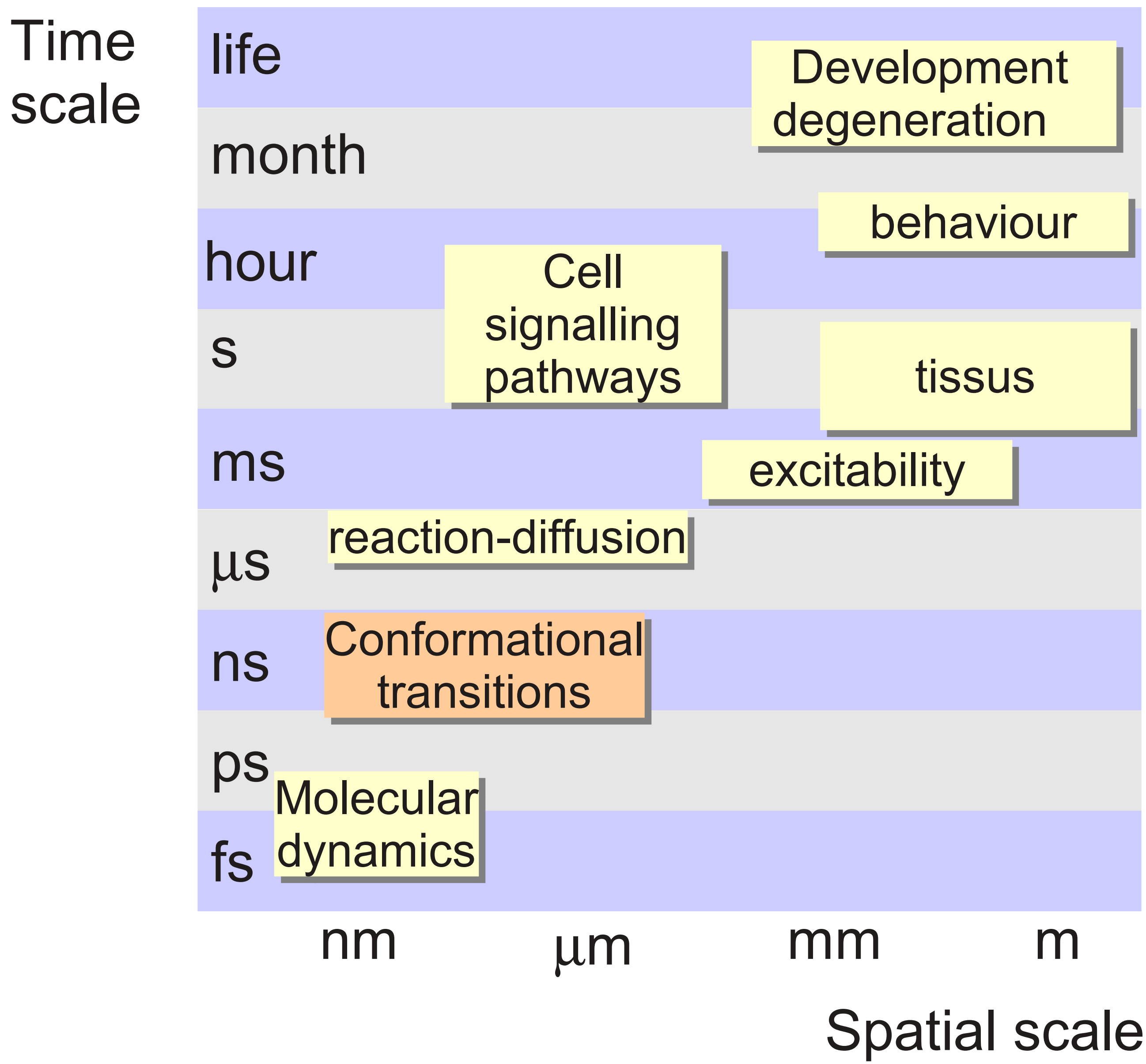


pharmacometrics

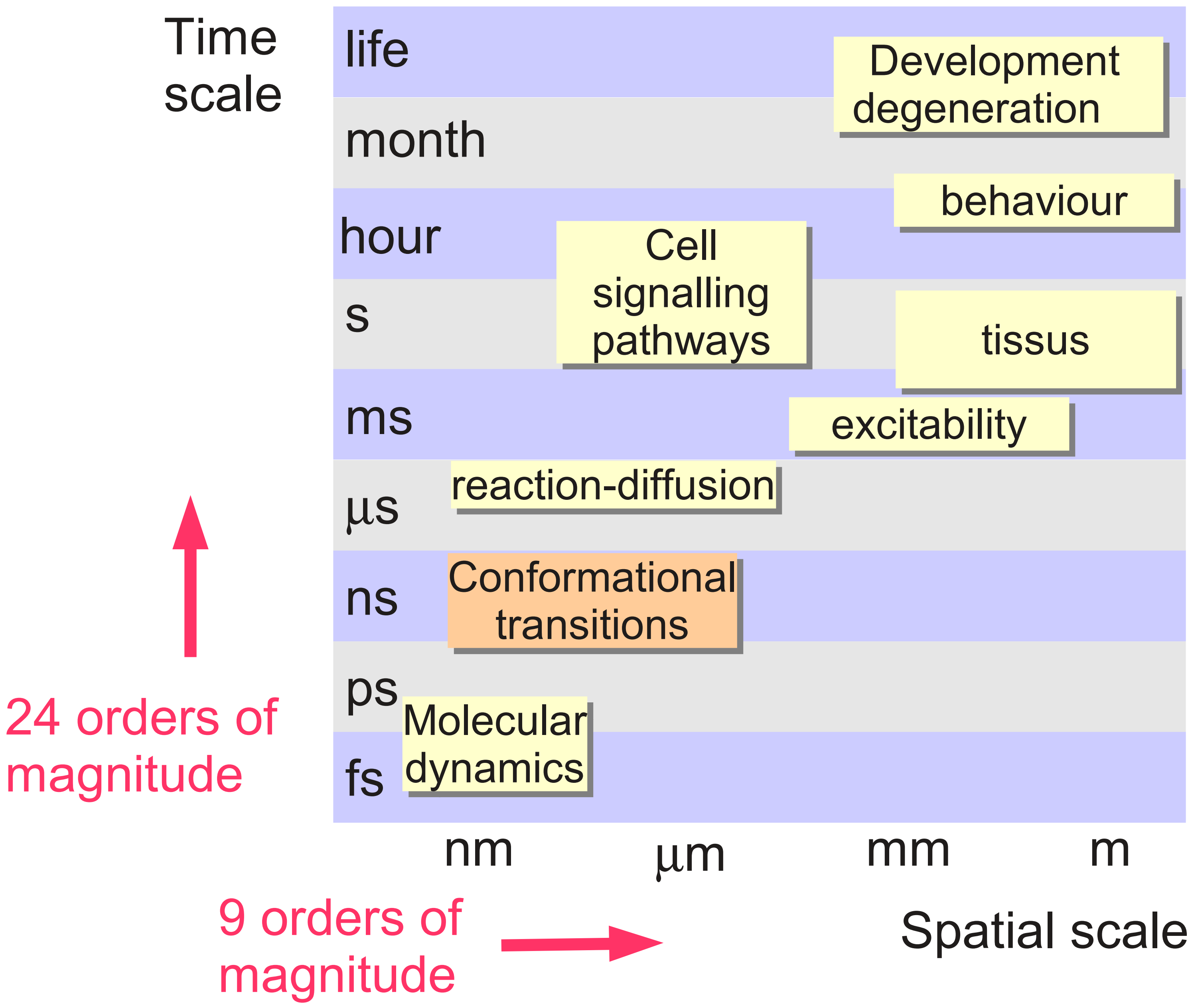


physiology

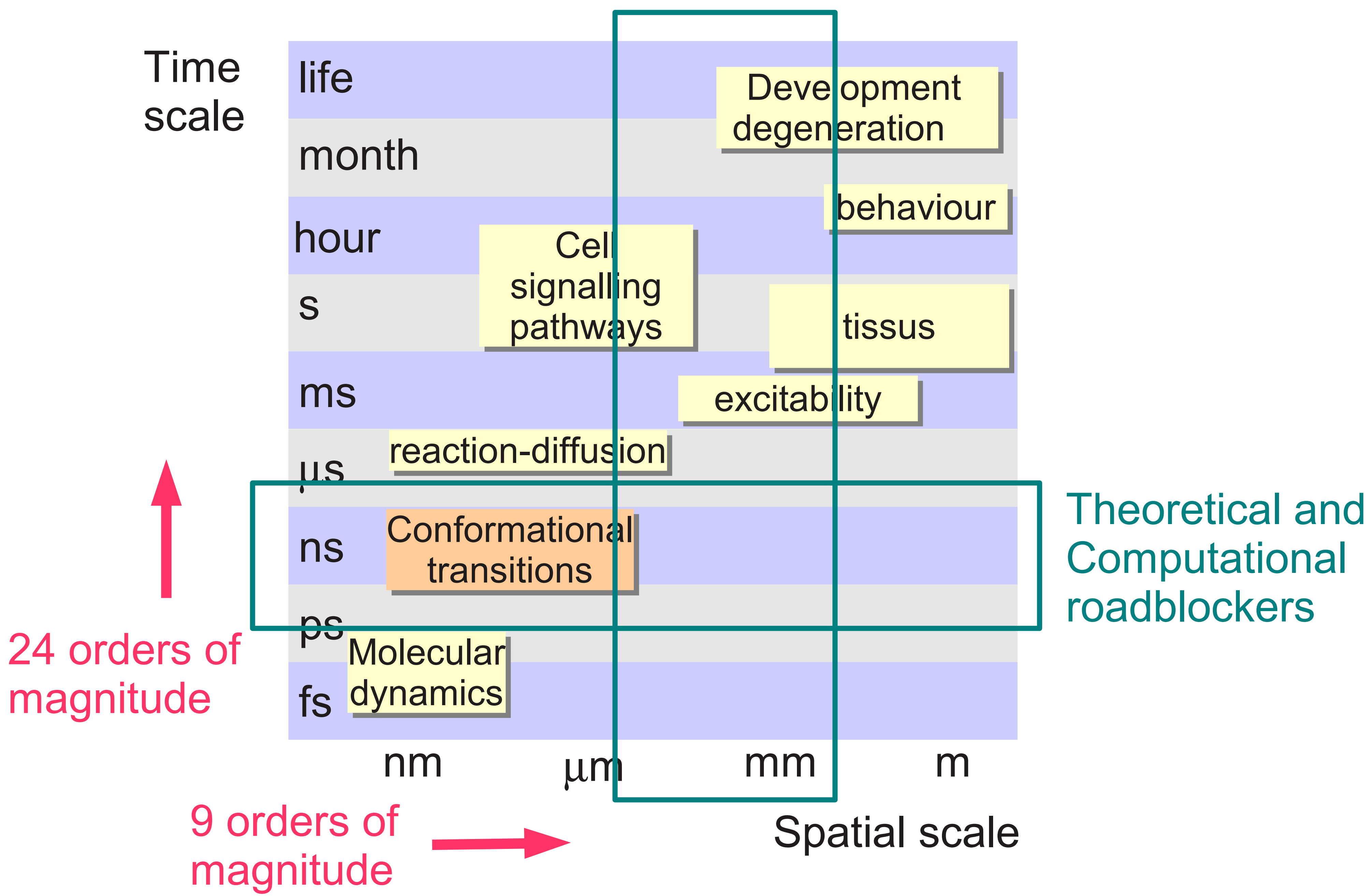
The mesoscopic gap



The mesoscopic gap



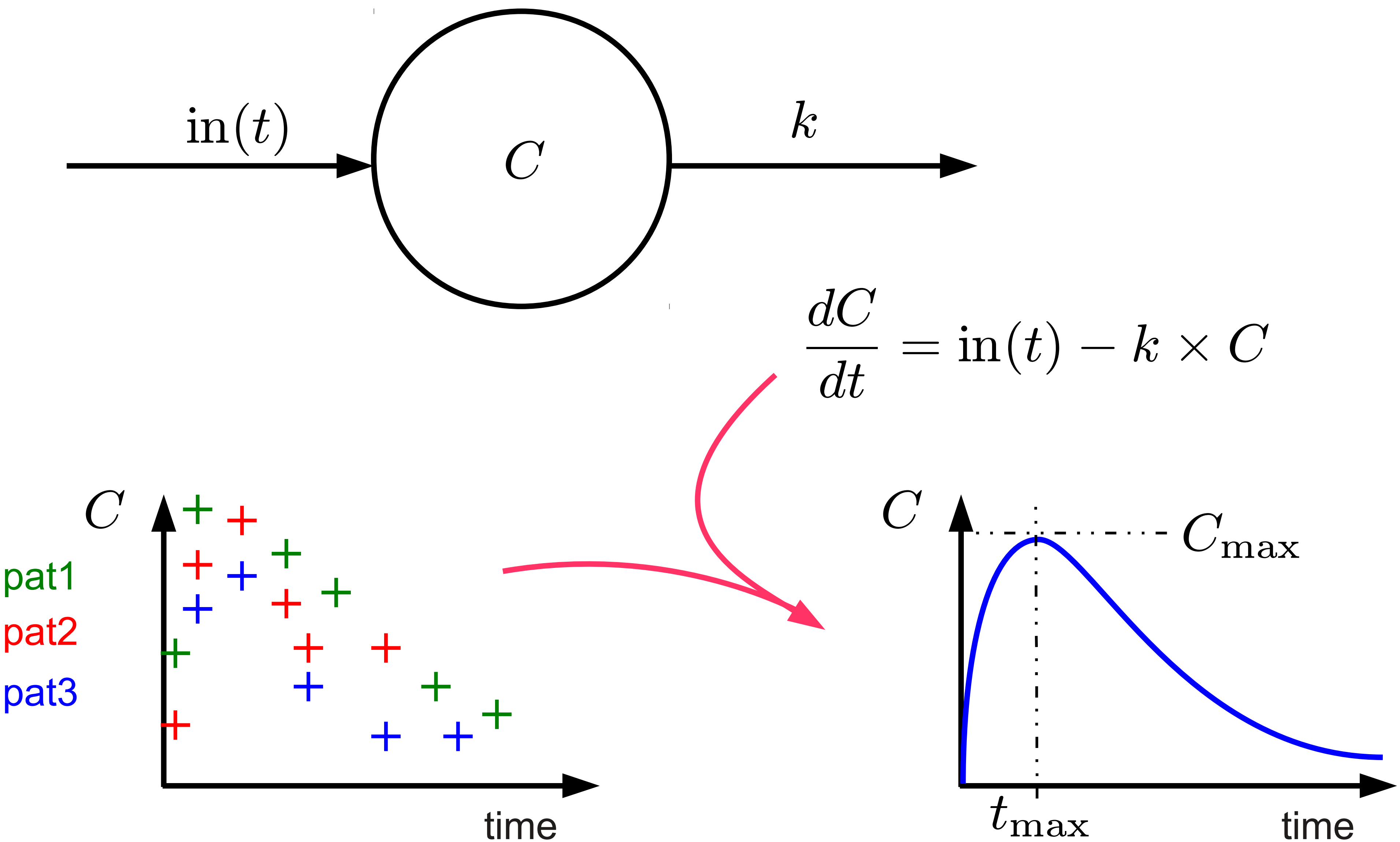
The mesoscopic gap



Multi-scale does not mean fine scale plus massive power

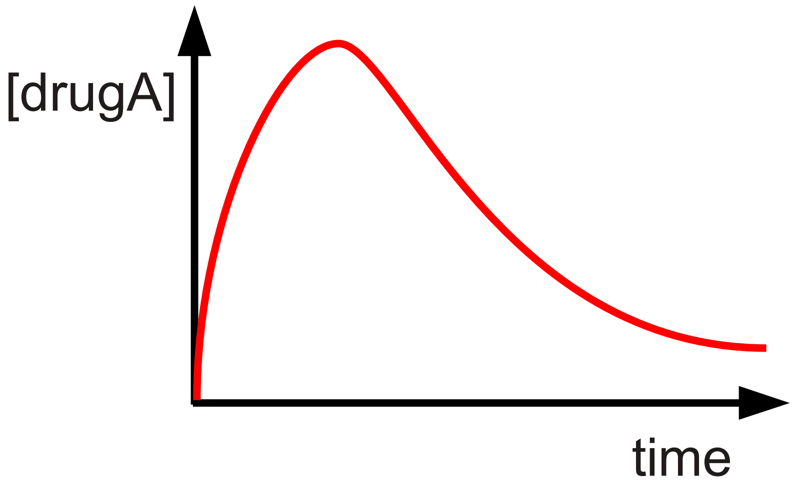
- Computational issues
  - In 2008, largest simulations were 1 million atoms for 50 ns (using > 30 years CPU) and 10000 atoms for 0.5 ms.
  - E-coli ~ 1 million million atoms ...
  - We need at least 10^{14} more power to simulate E coli during 1 s
- Theoretical issues
  - Molecular dynamics does not 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

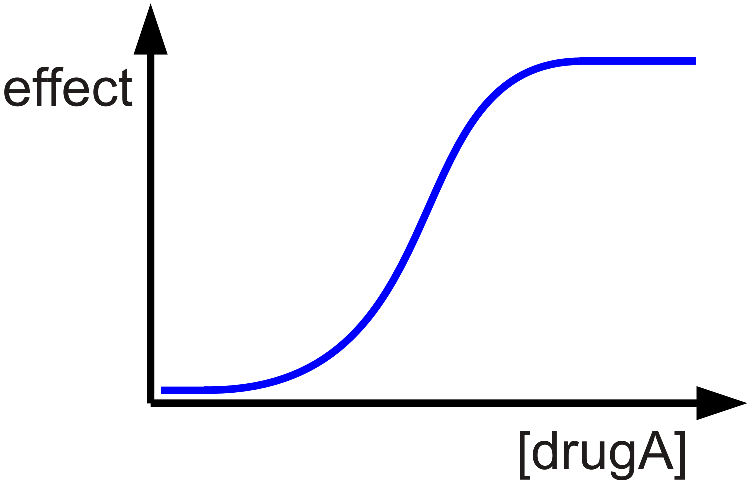


Drug discovery modelling: pharmacometrics

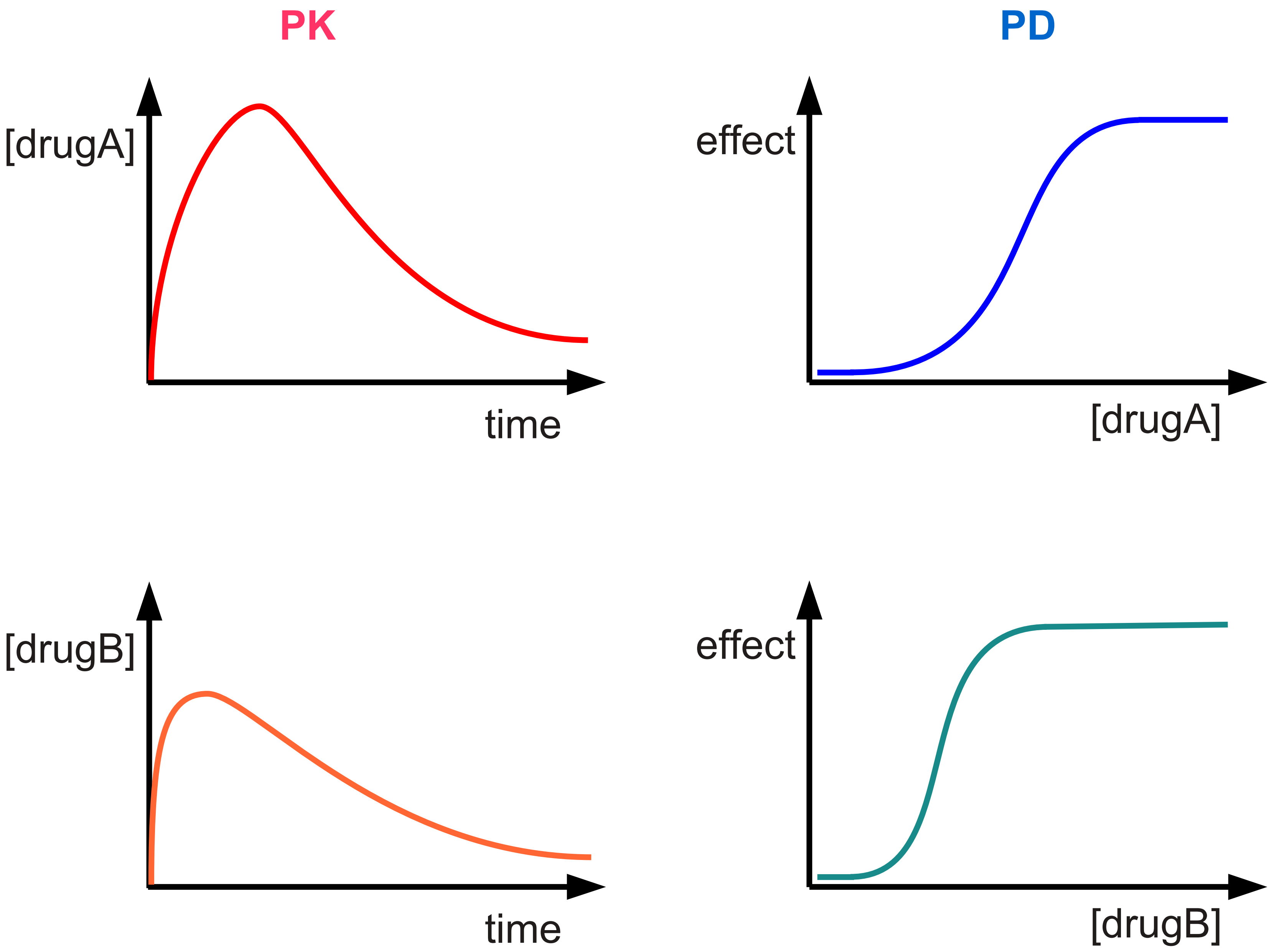
PK



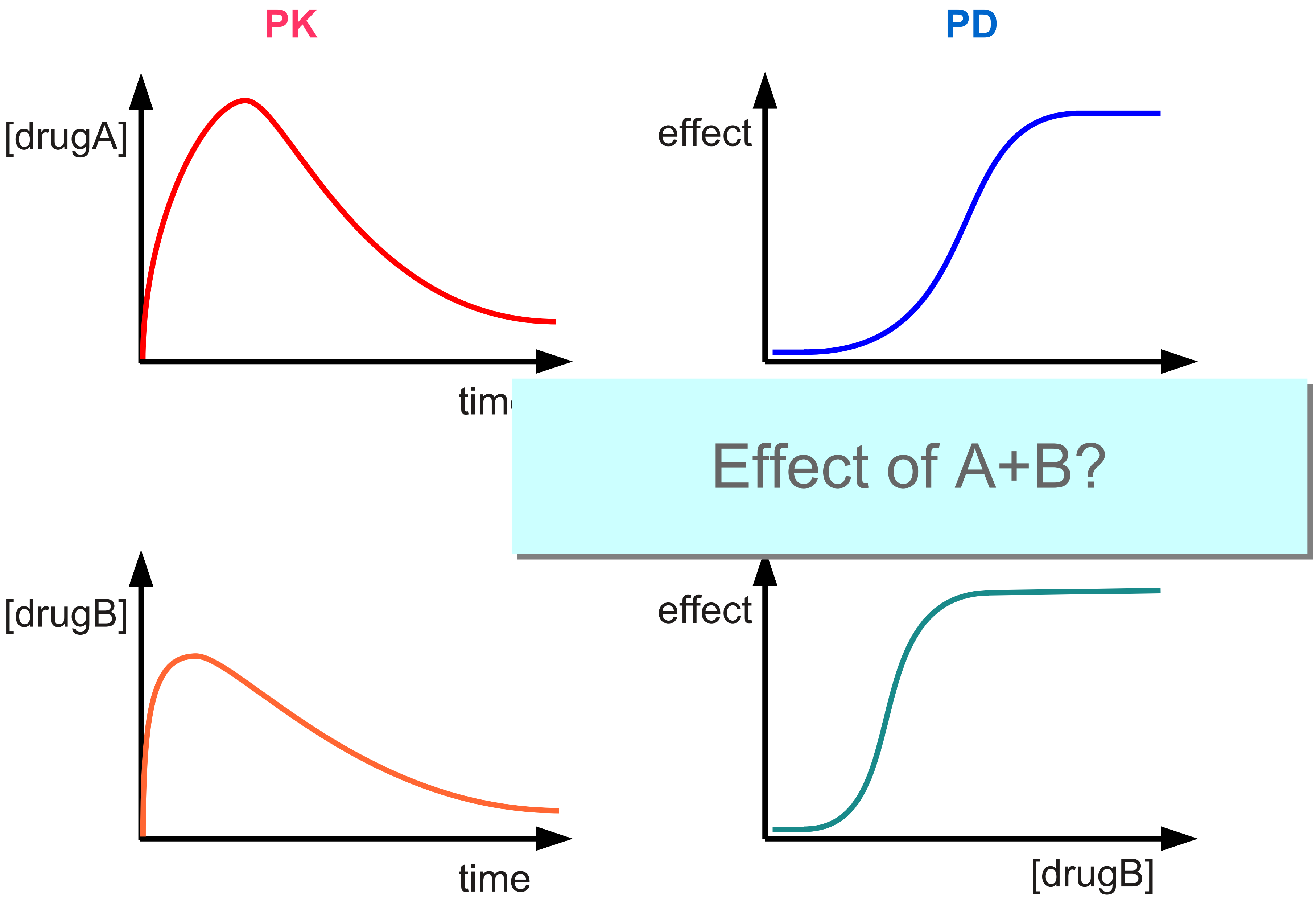
PD



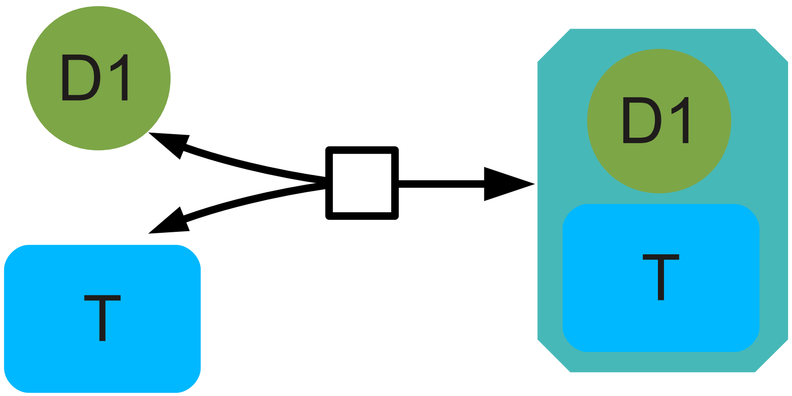
Drug discovery modelling: pharmacometrics



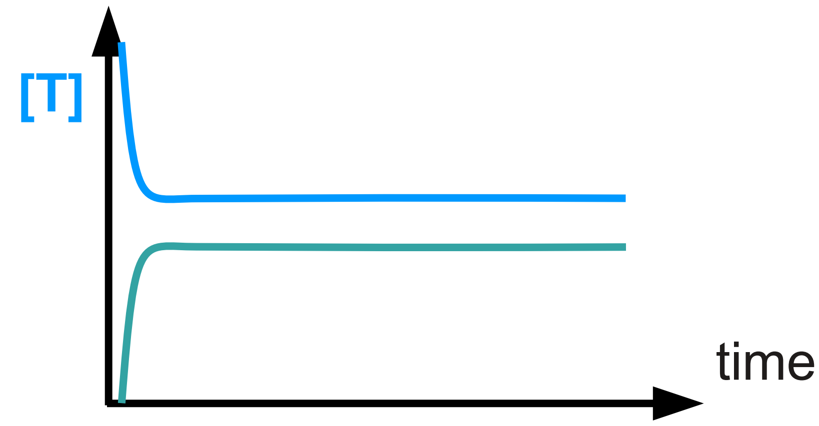
Drug discovery modelling: pharmacometrics

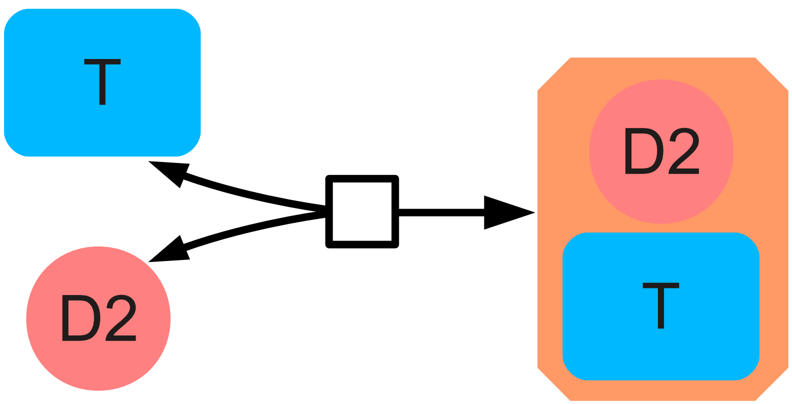


Systems modelling

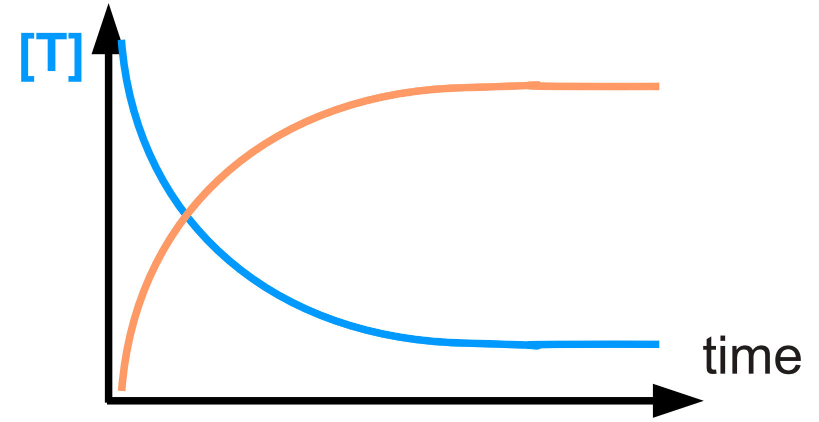


$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1]$$



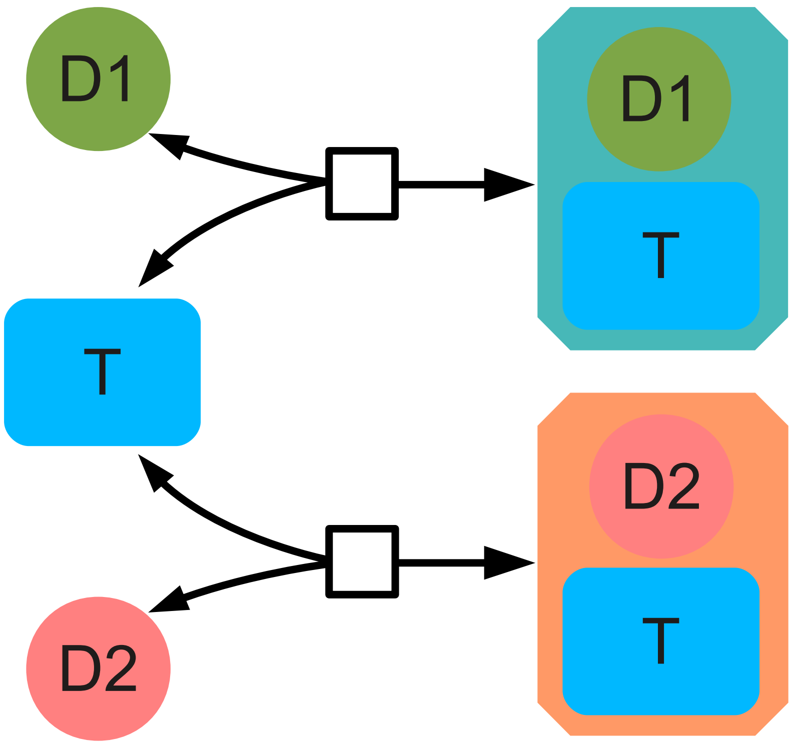


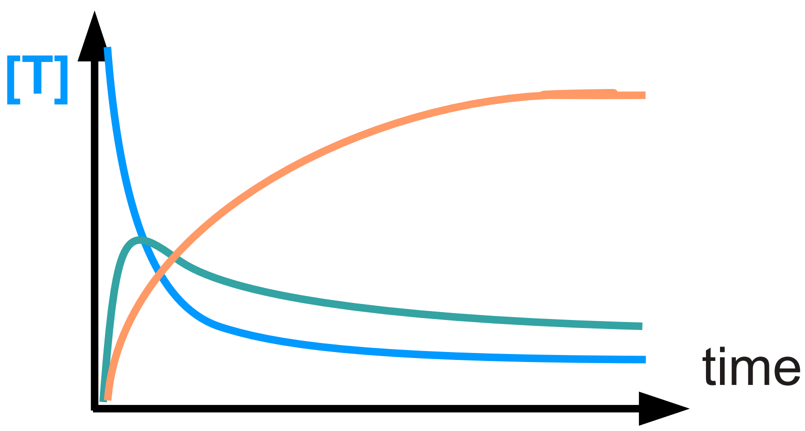
$$\frac{d[T]}{dt} = -k2 \times [T] \times [D2]$$



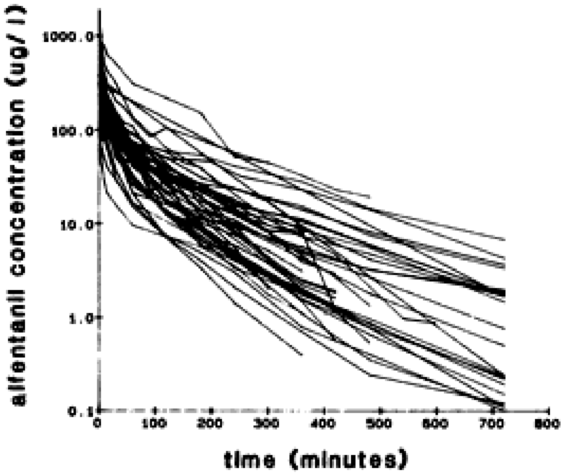
Systems modelling

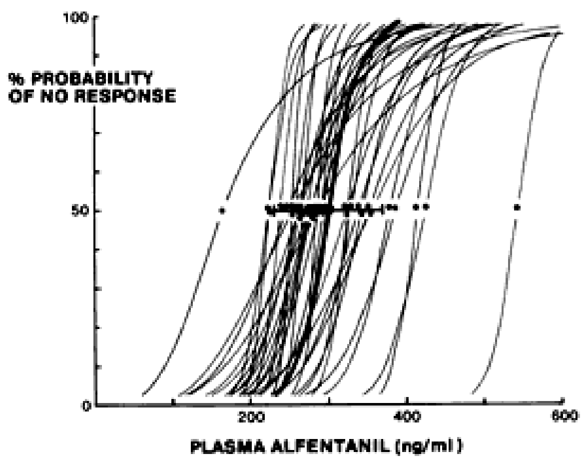
$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1] - k2 \times [T] \times [D2]$$

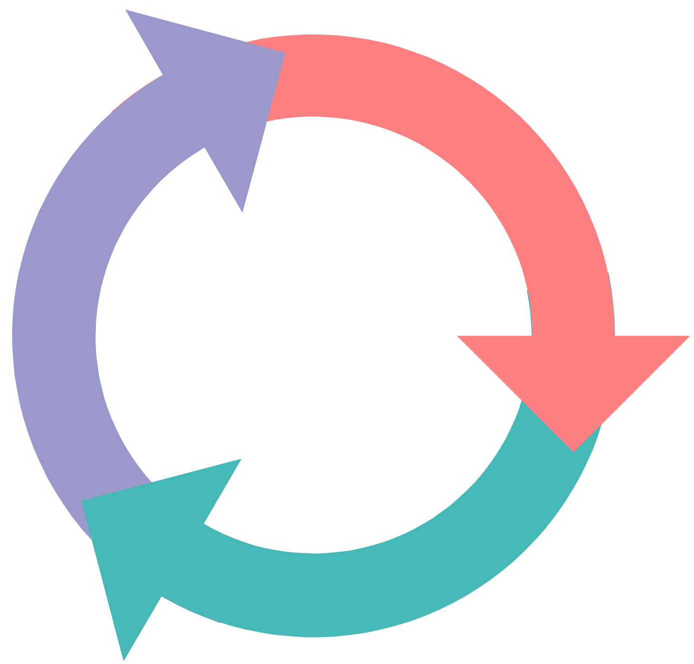


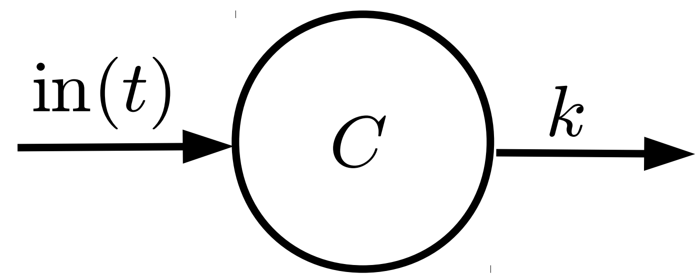


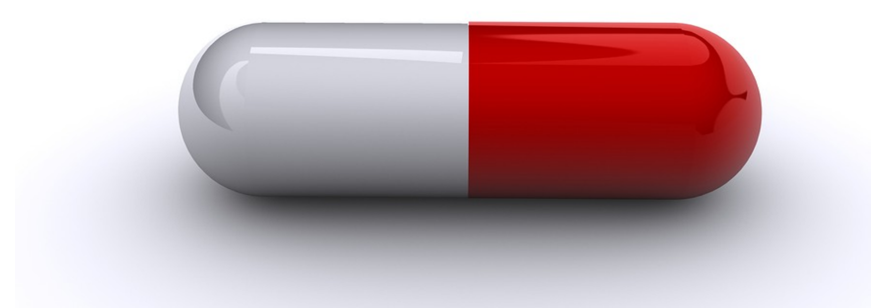
Drug discovery and pharmacometrics models



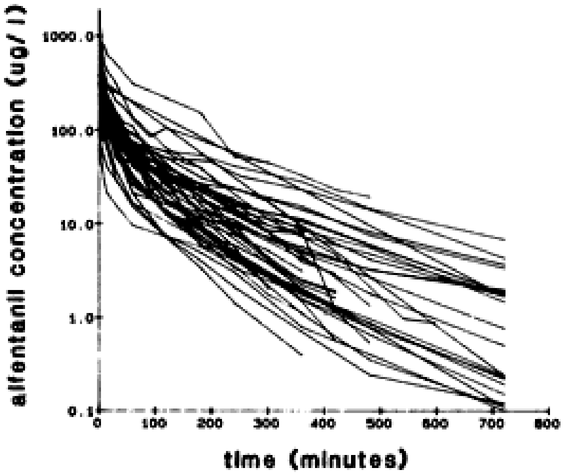


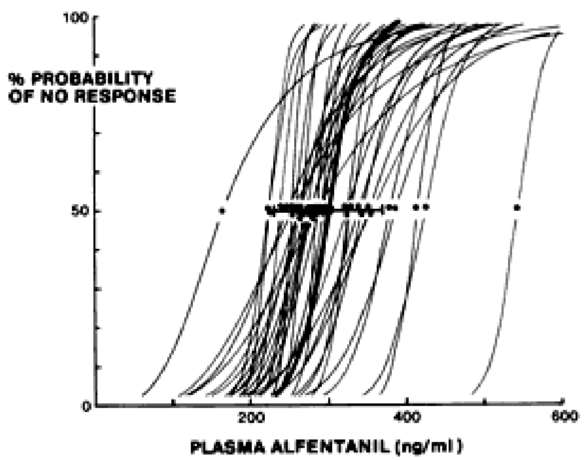


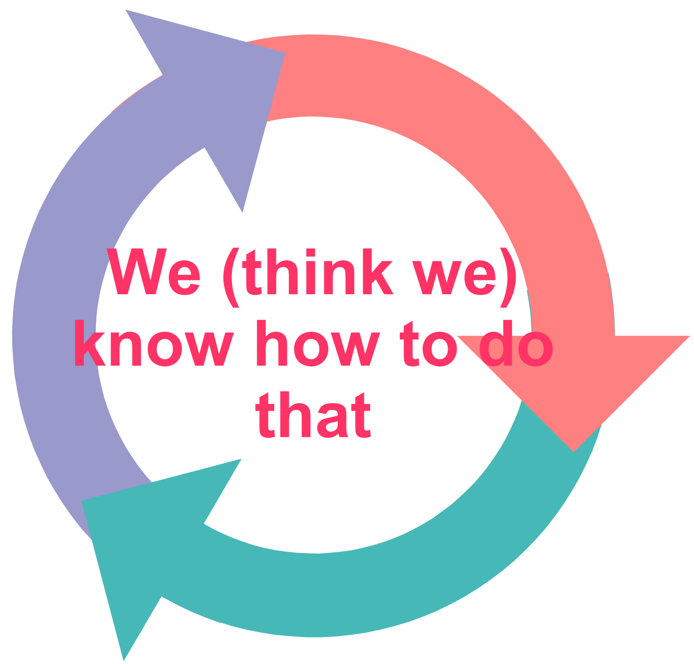


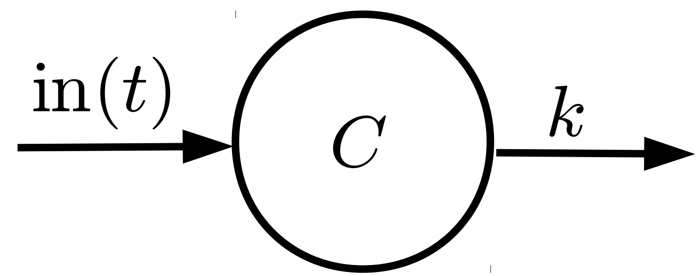


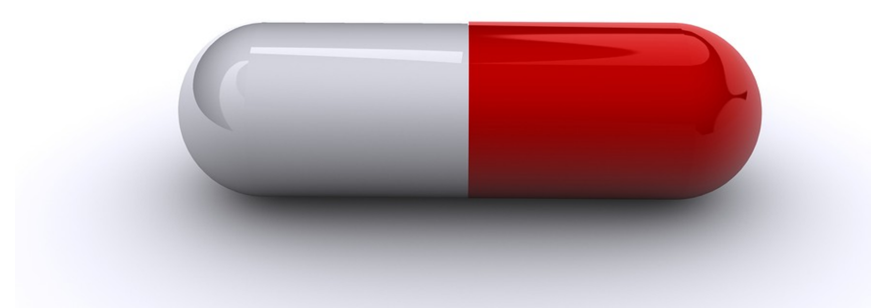
Drug discovery and pharmacometrics models



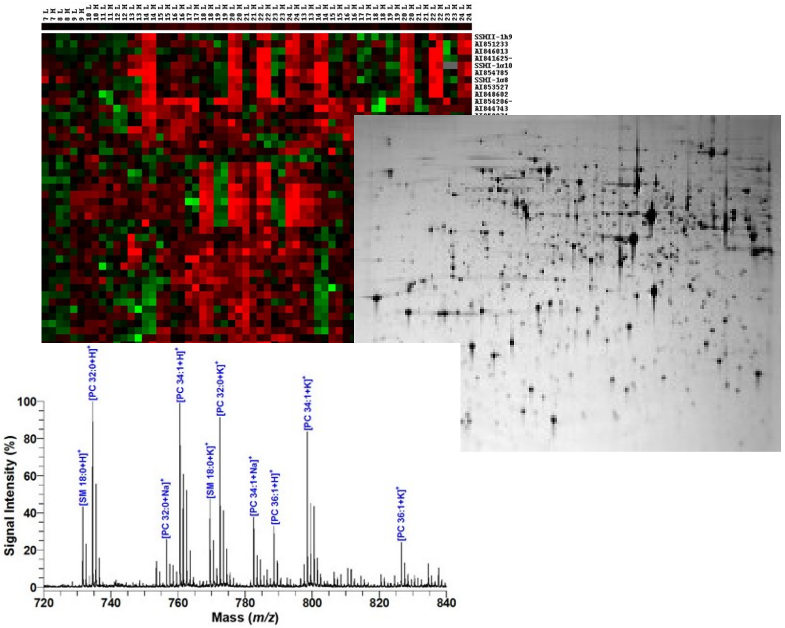


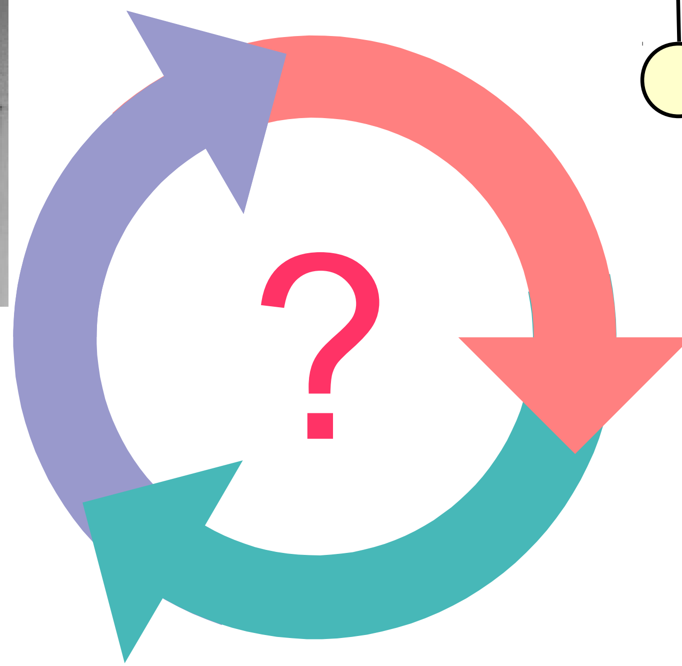


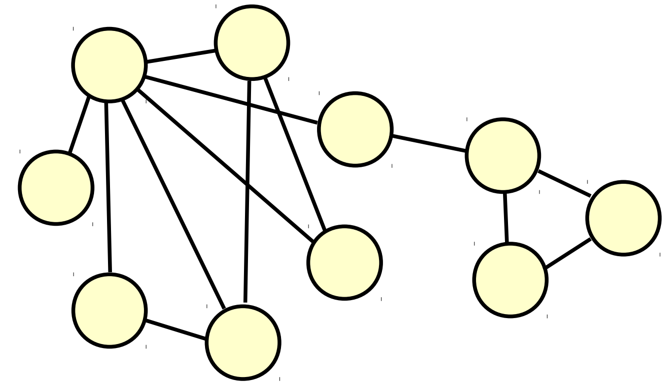


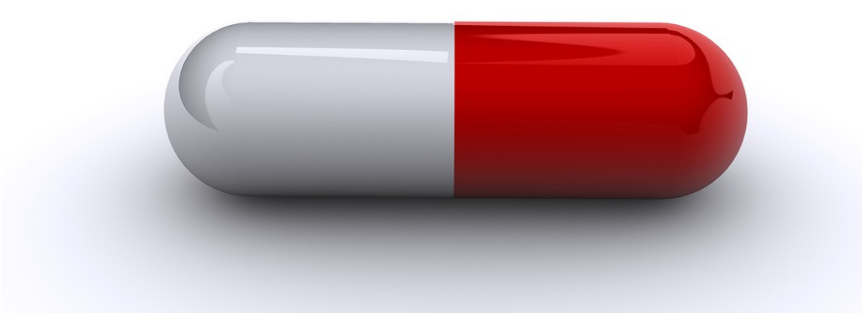


Drug discovery and omics









Thank-you for joining the meeting and discuss those issues over the next couple of days