# What is Systems Biology?
# Where does it come from ?
# What are the challenges ahead?

Nicolas Le Novère, EMBL-EBI

# What happened to Biology at the end of XX$^{th}$ century?

Annu. Rev. Genomics Hum. Genet. 2001. 2:343–72


## A New Approach to Decoding Life:
## Systems Biology

Trey Ideker[1,2], Timothy Galitski[1], and Leroy Hood[1,2,3,4,5]
*Institute for Systems Biology[1], Seattle, Washington 98105; Departments of*

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

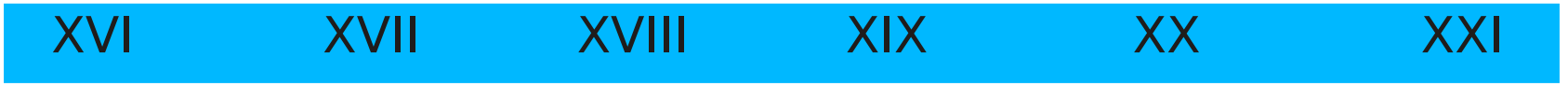
Invited Paper

## Perspectives on Systems Biology

Hiroaki KITANO
*Sony Computer Science Laboratories, Inc.*



# Emergence of the notion of system




Global Description of the world

"classical" mechanic, anatomy, physiology

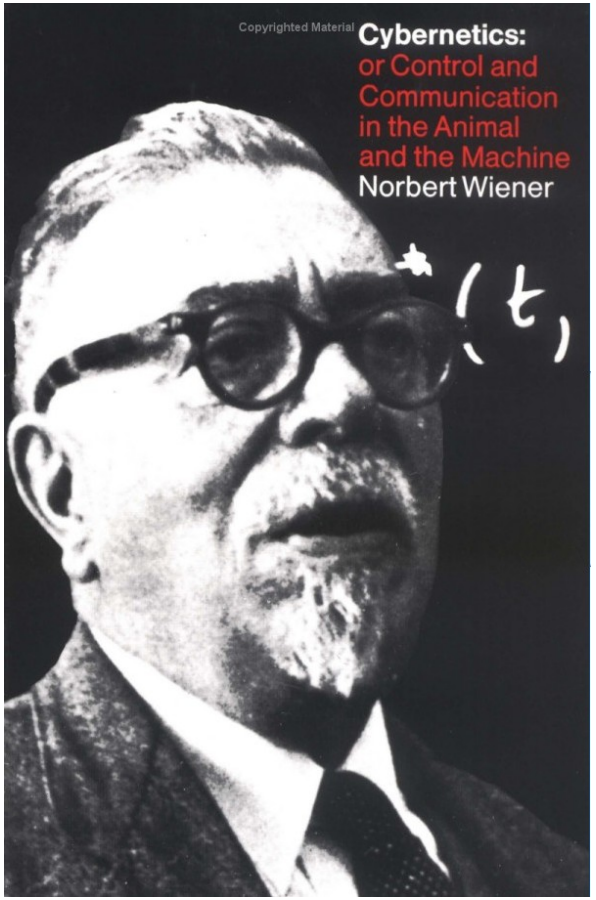
Description of the components of the world

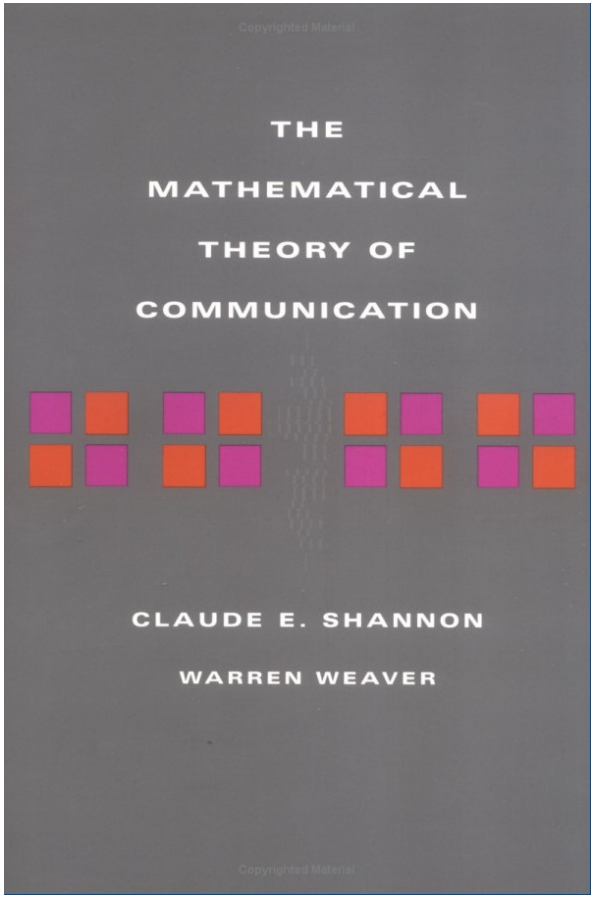
Statistical physics, thermodynamics, quantum mechanic, biochemistry, structural biology, molecular biology

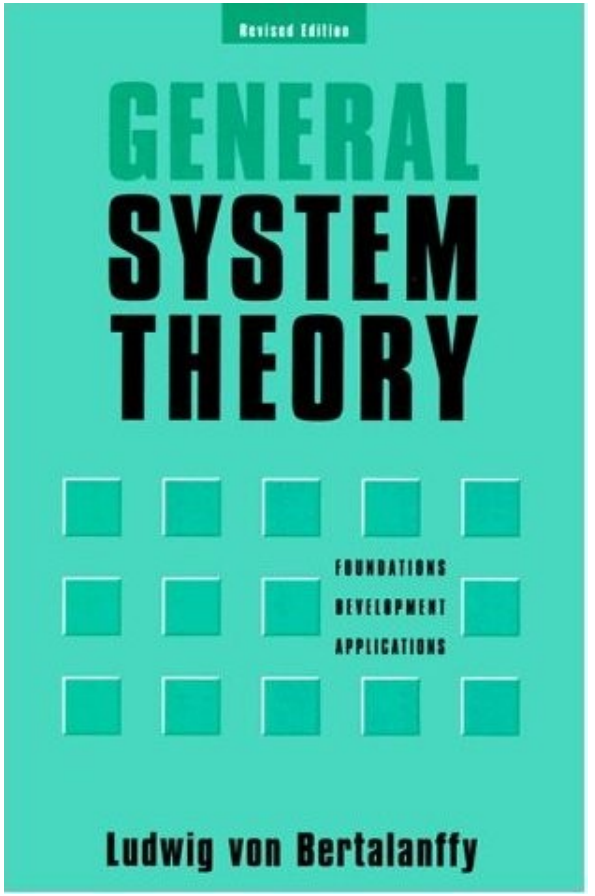
Description of interacting components

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

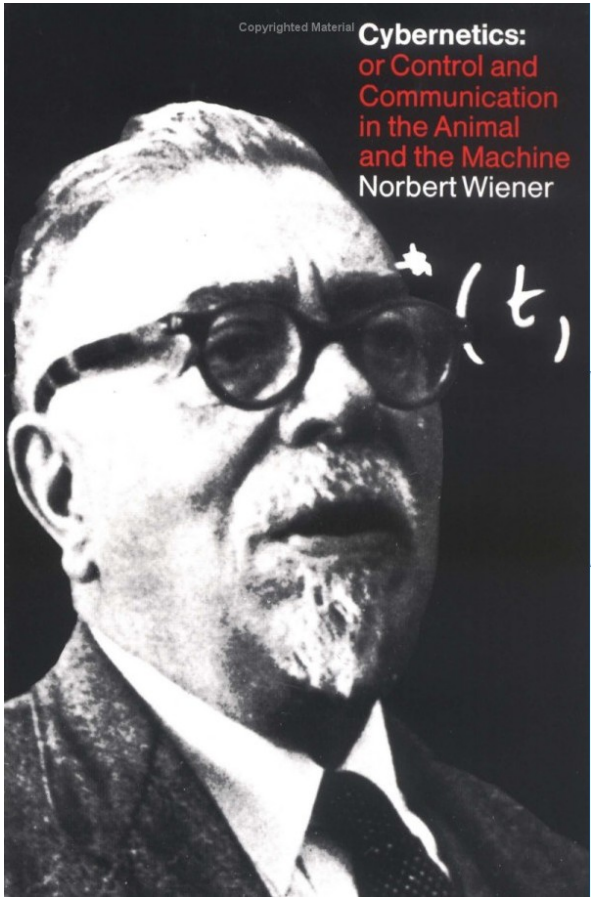
# Systems are formalised mid-XXth

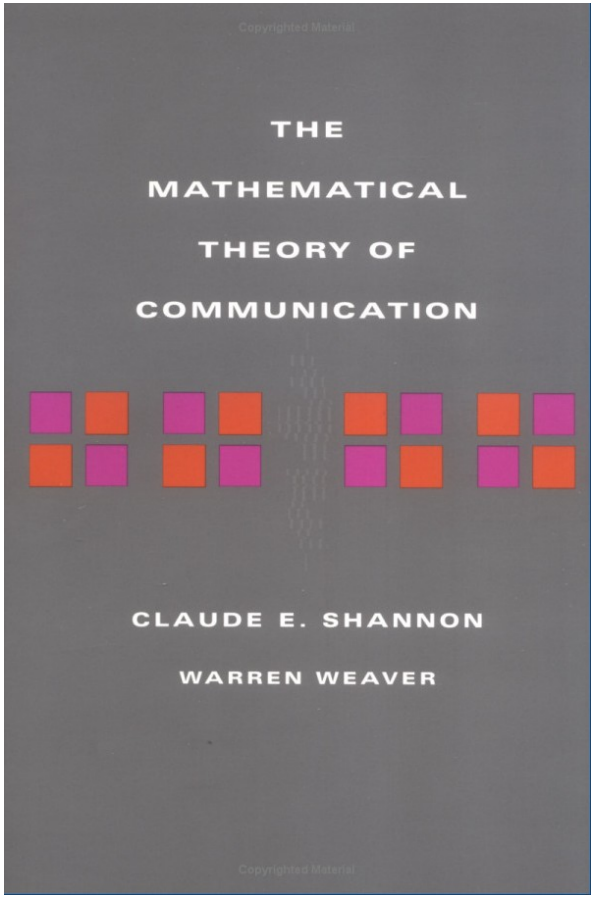


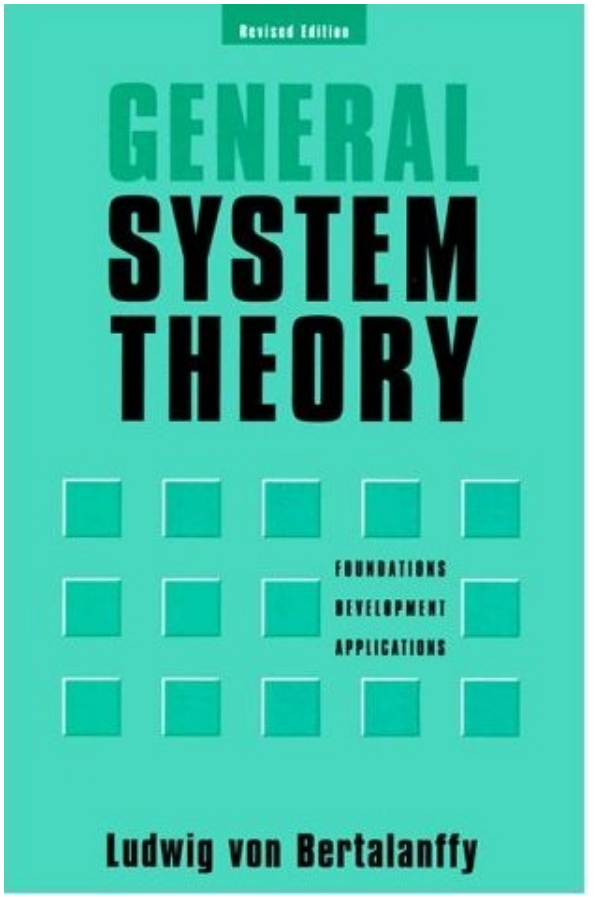



# Systems are formalised mid-XXth

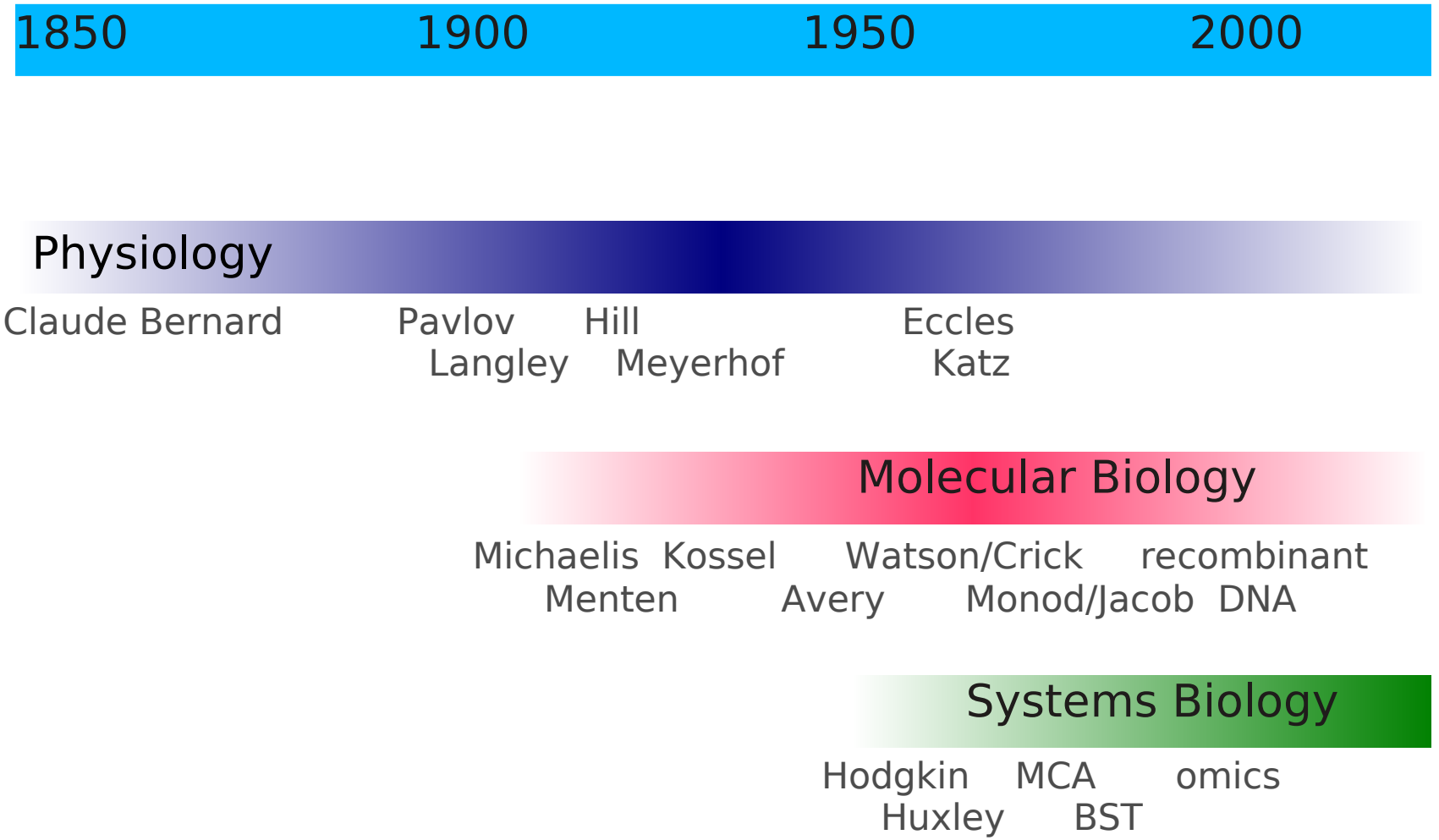



*"[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems*"
Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

# The three paradigms of Biology



# Computer simulations Vs. mathematical models



## 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



## 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

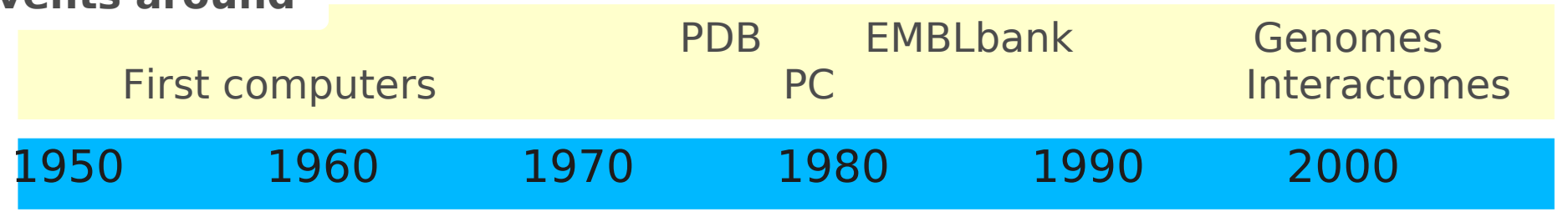
*From the Physiological Laboratory, University of Cambridge*

(*Received* 10 *March* 1952)

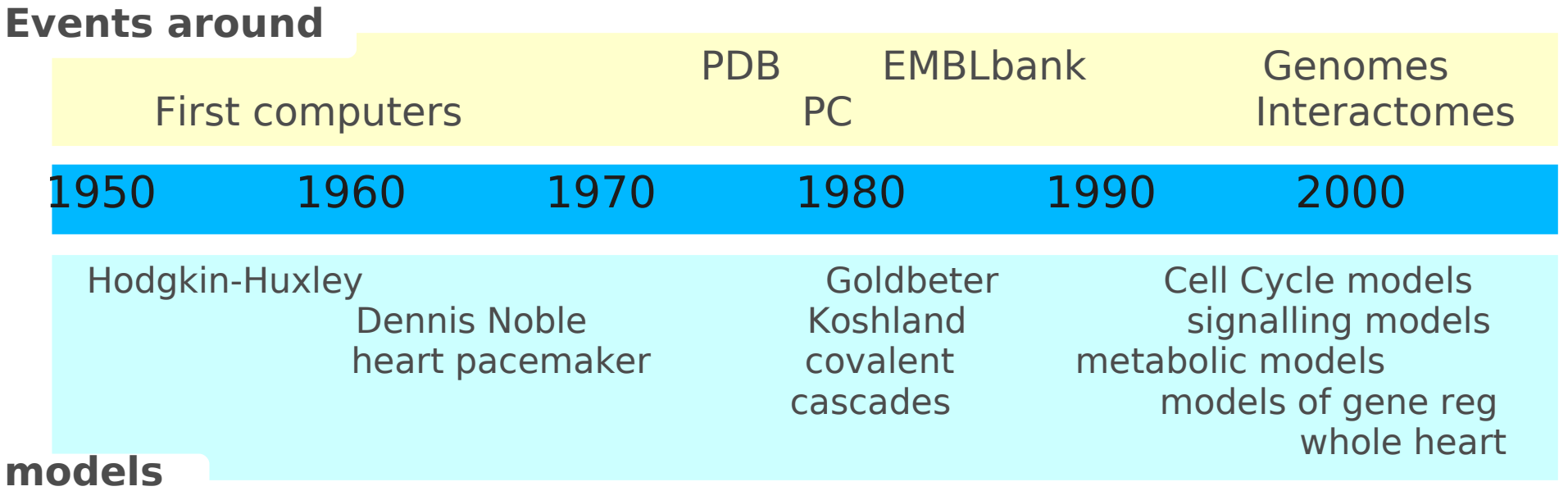
This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952 *a–c*). Its general object is to discuss the results of the preceding papers (Part I), to put them into mathematical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

# Towards Systems Biology

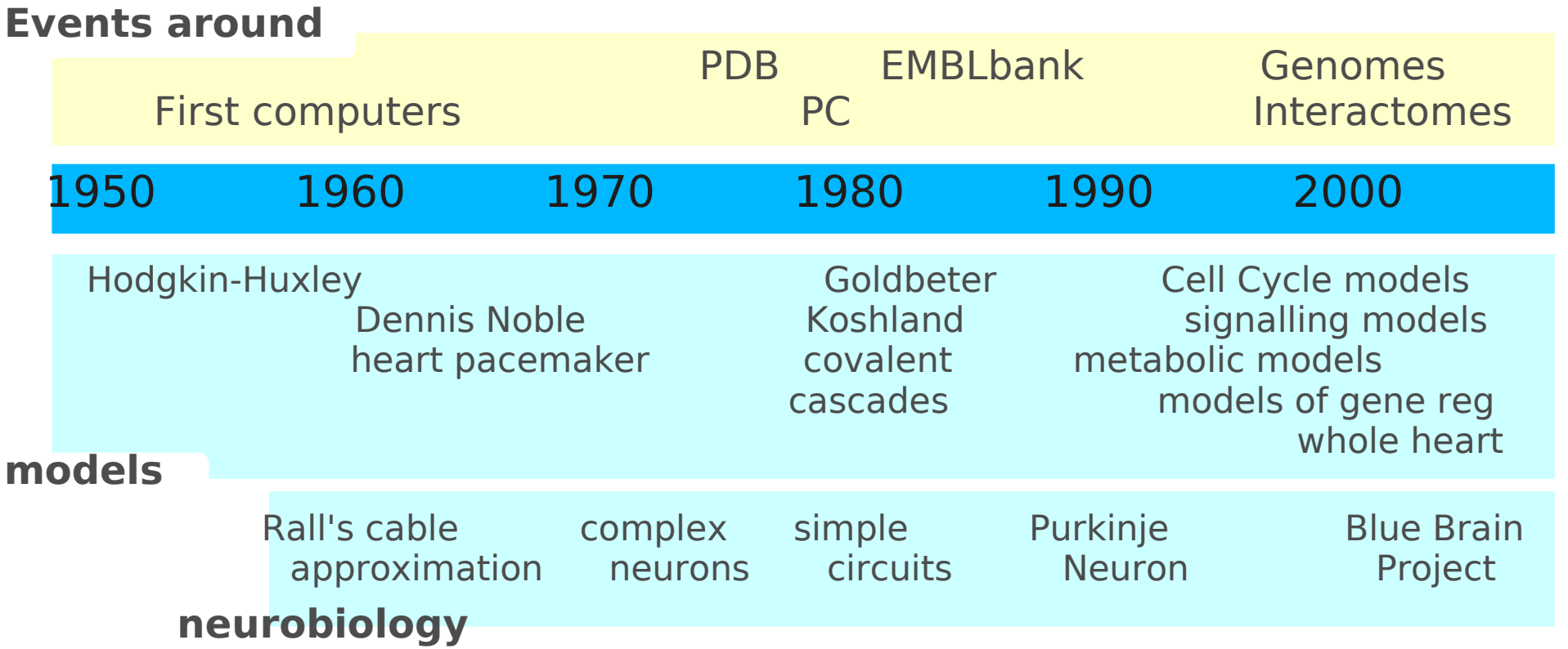
**Events around**



# Towards Systems Biology



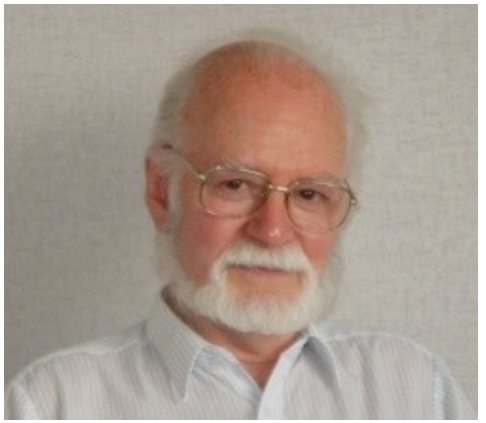
# Towards Systems Biology



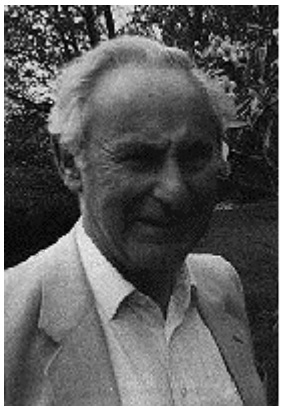
# 60s and 70s

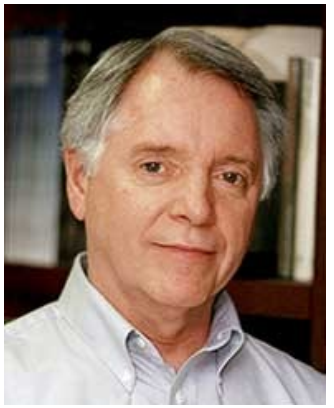
- Mihajlo Mesarovic: 1966 Symposium "general systems theory and biology

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

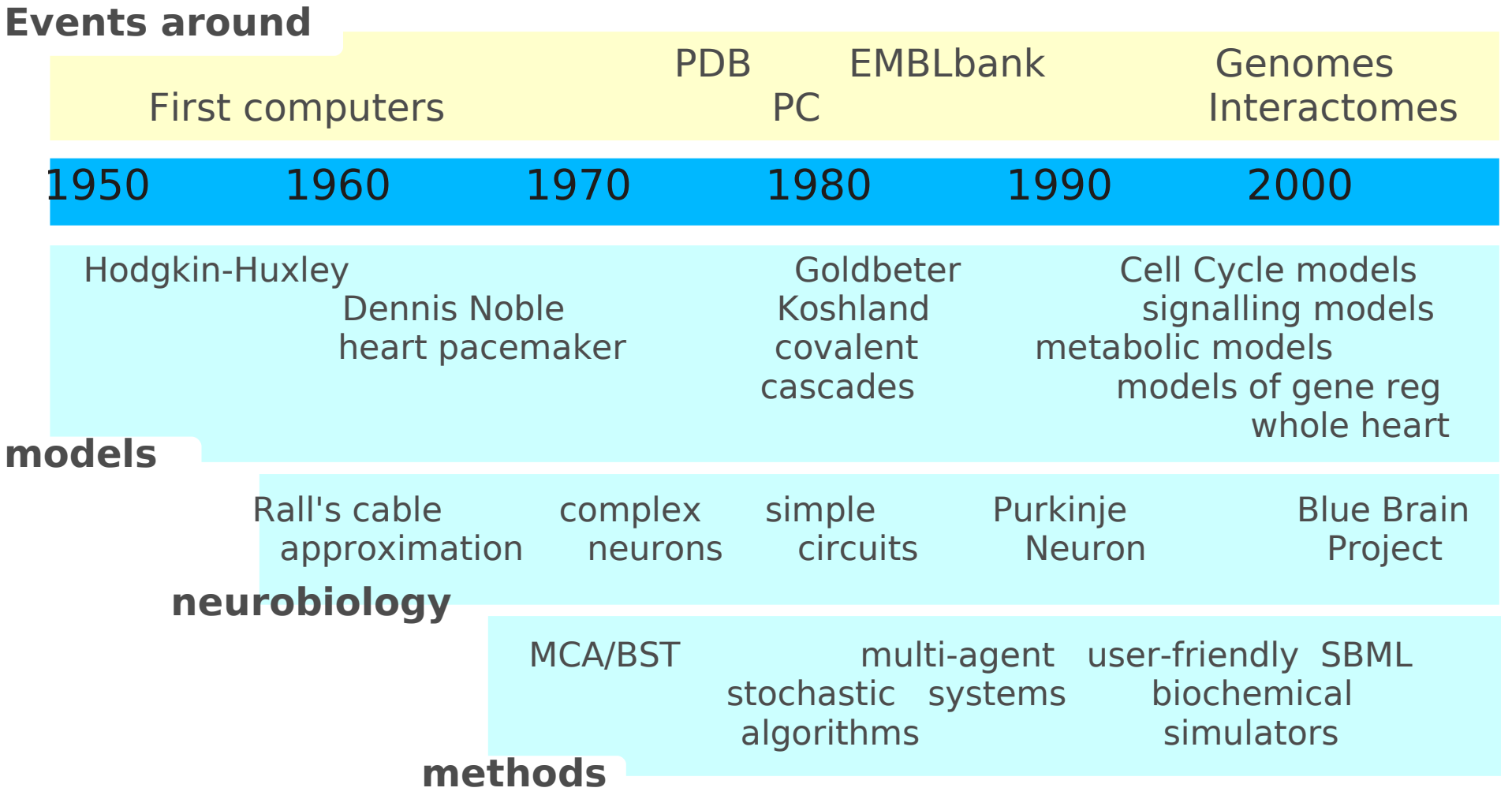


- Henri Kacser: Metabolic control analysis, Michel Savageau: Biochemical Systems Theory

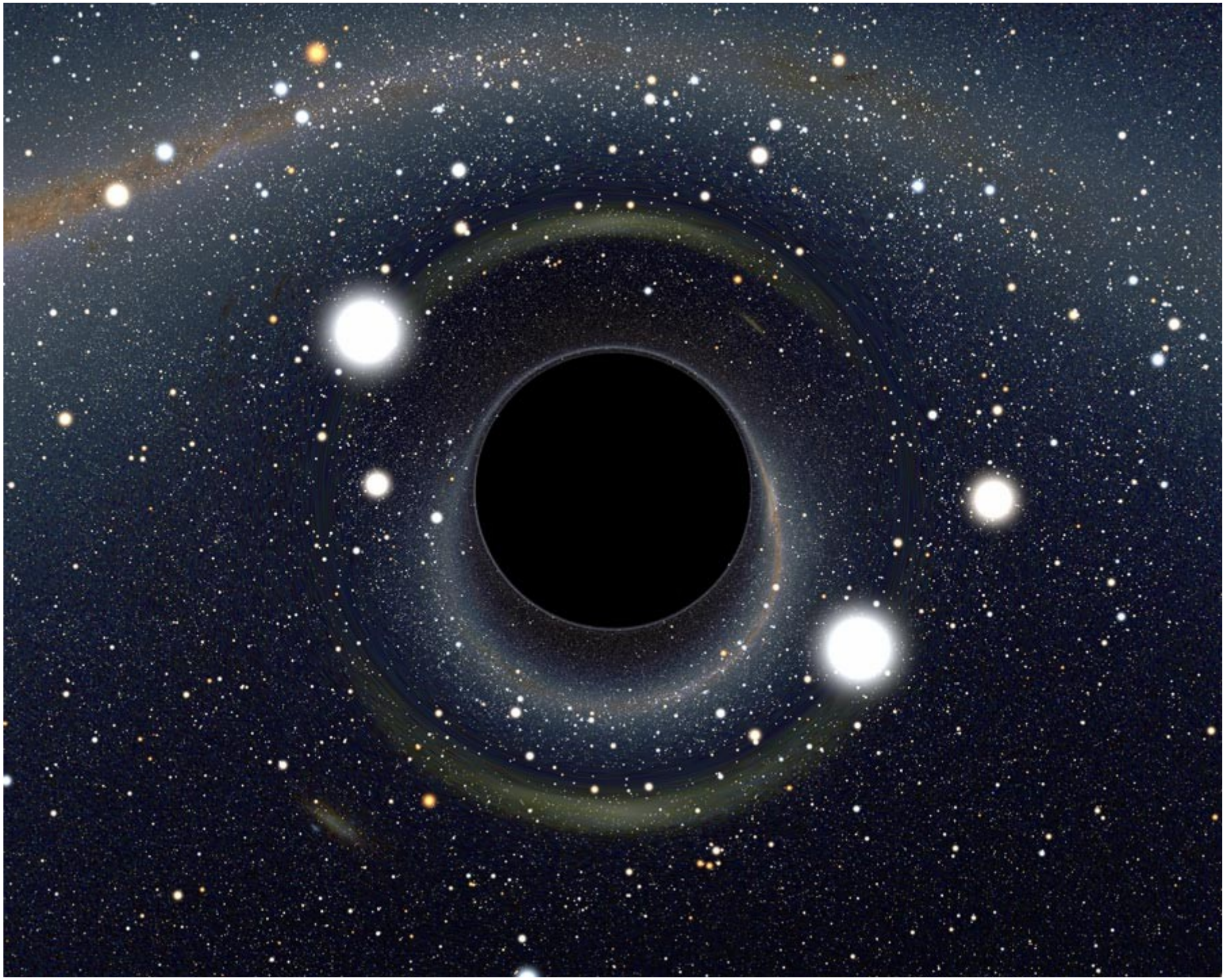




# Towards Systems Biology



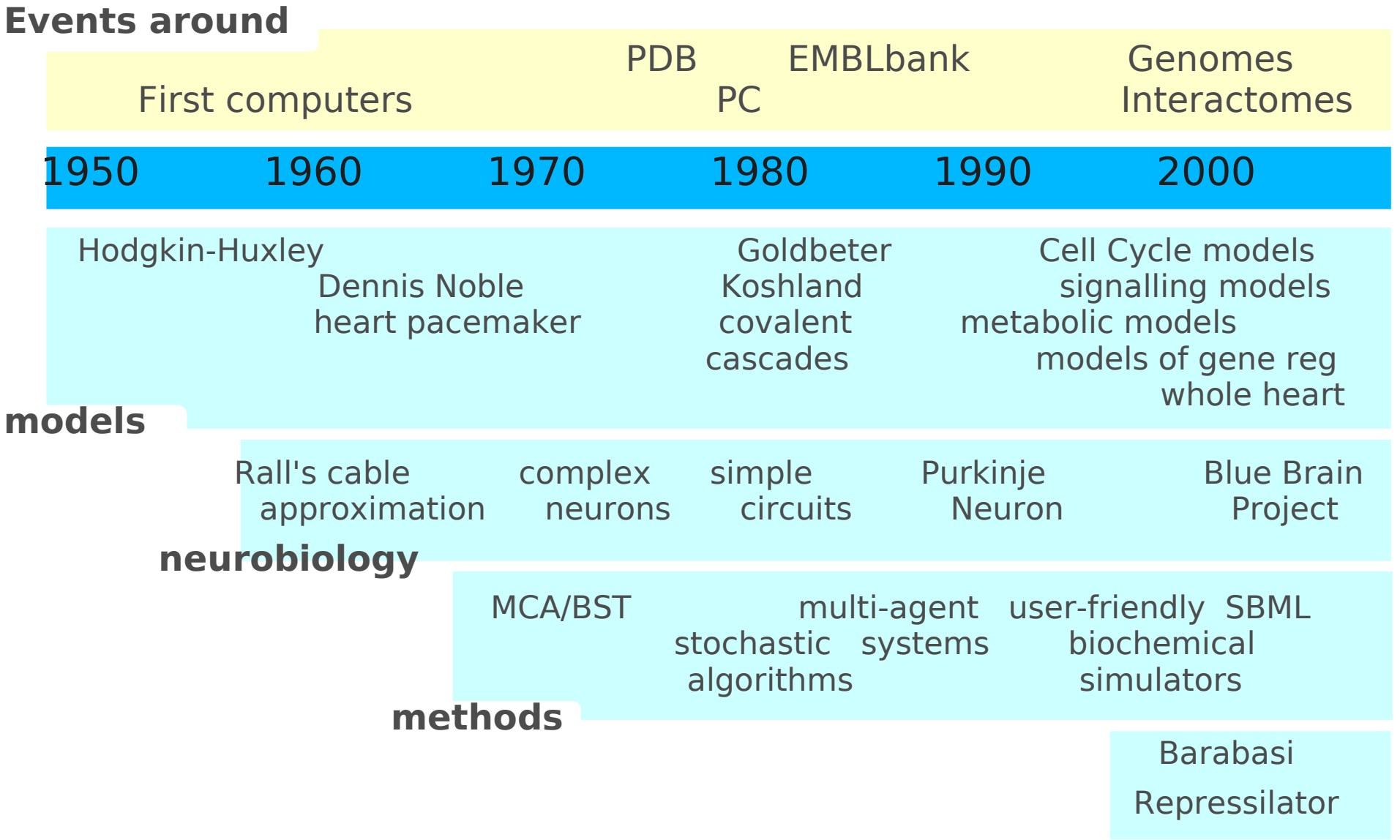
# 80s: The reign of Molecular Biology



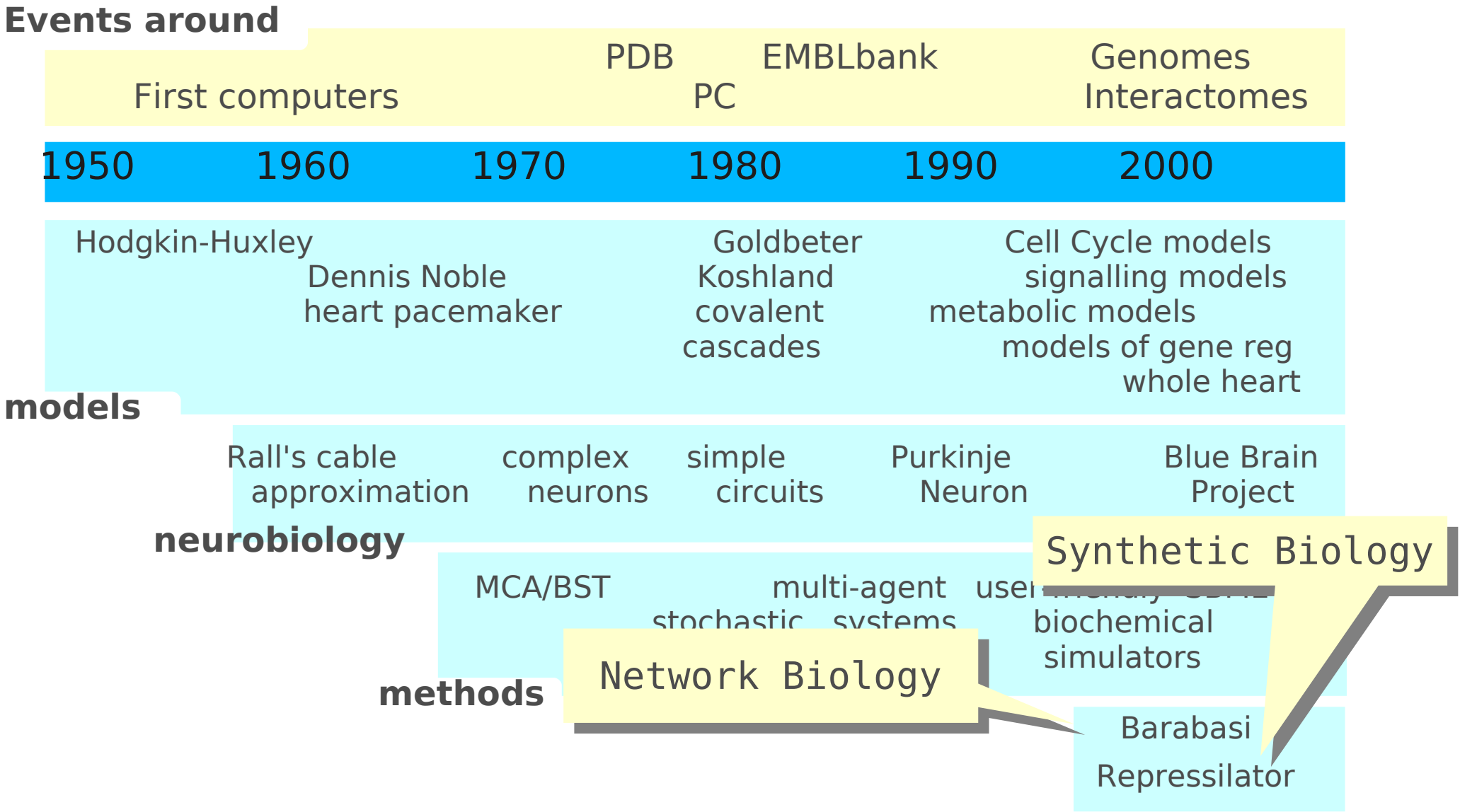
# 90s: maturation of the community

- 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
- Structuring 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

# Towards Systems Biology



# Towards Systems Biology



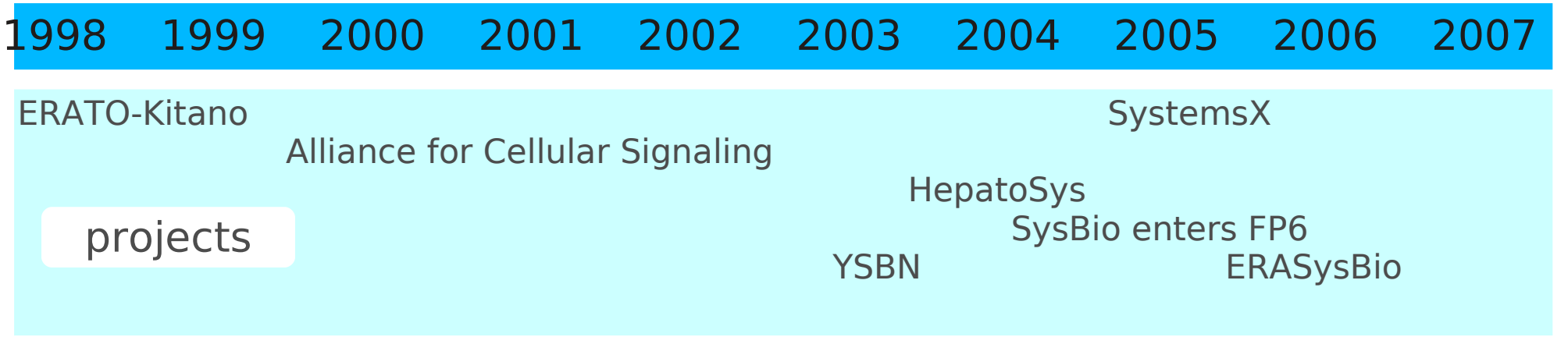
# Formal revival of Systems Biology

- "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

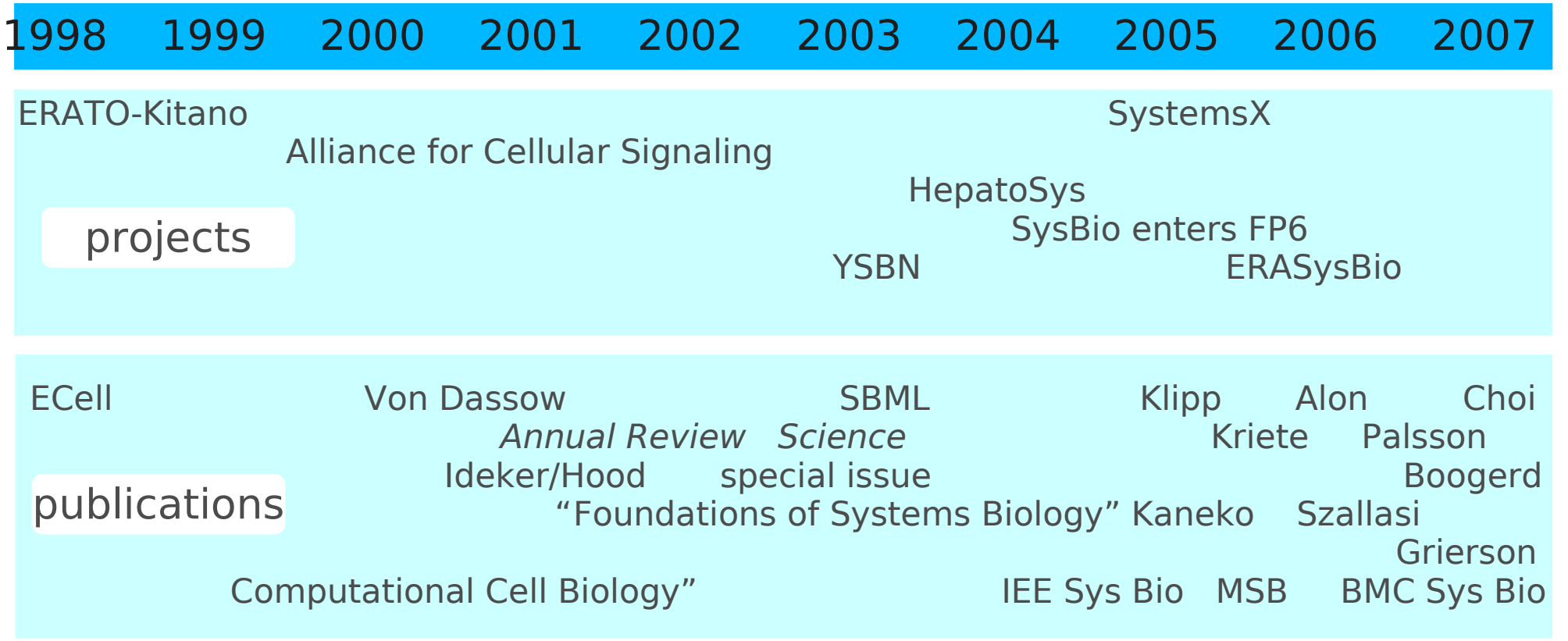
# Rise of Systems Biology as a paradigm

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

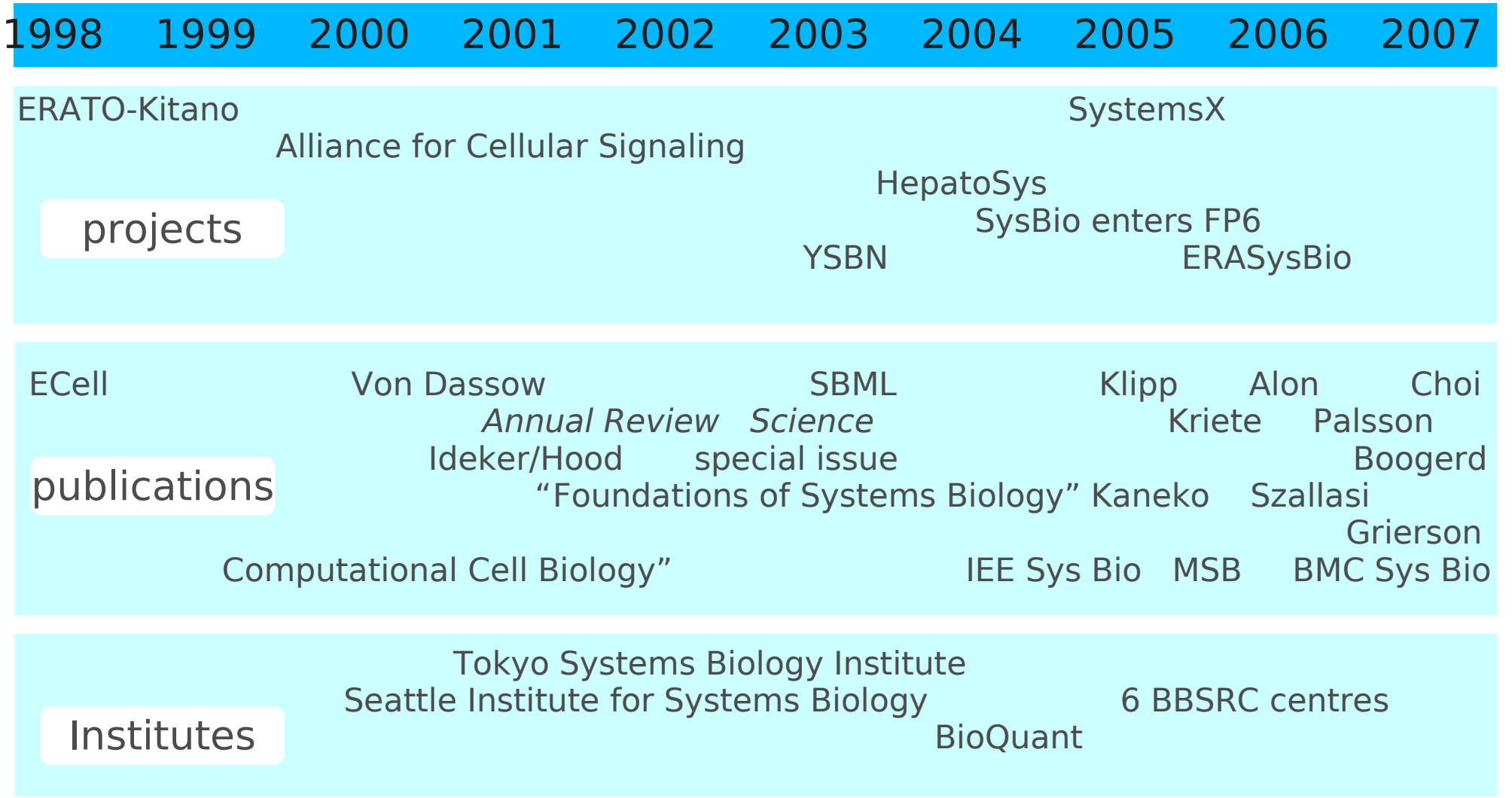
# Rise of Systems Biology as a paradigm



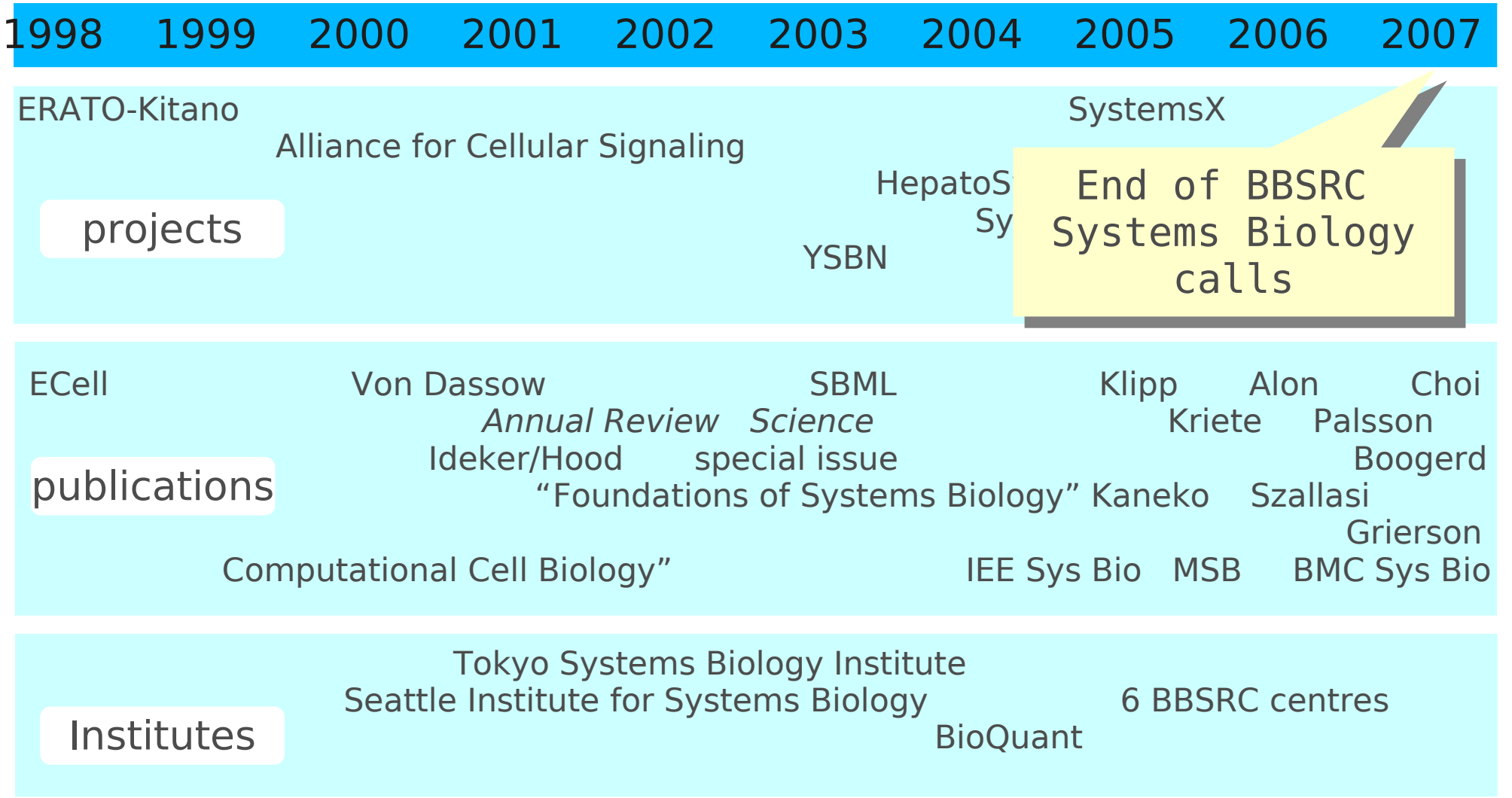
# Rise of Systems Biology as a paradigm



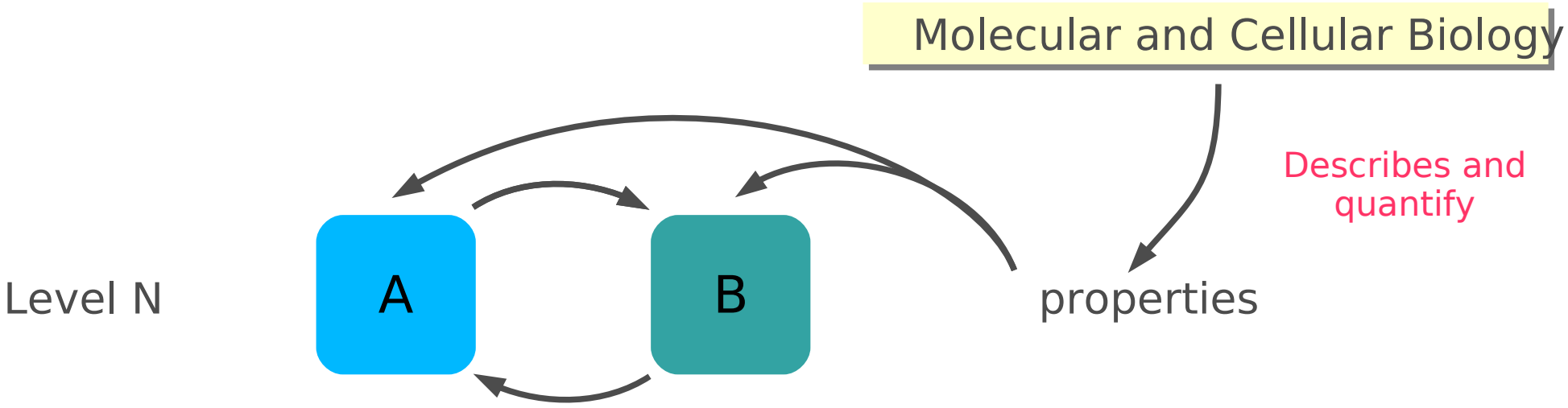
# Rise of Systems Biology as a paradigm



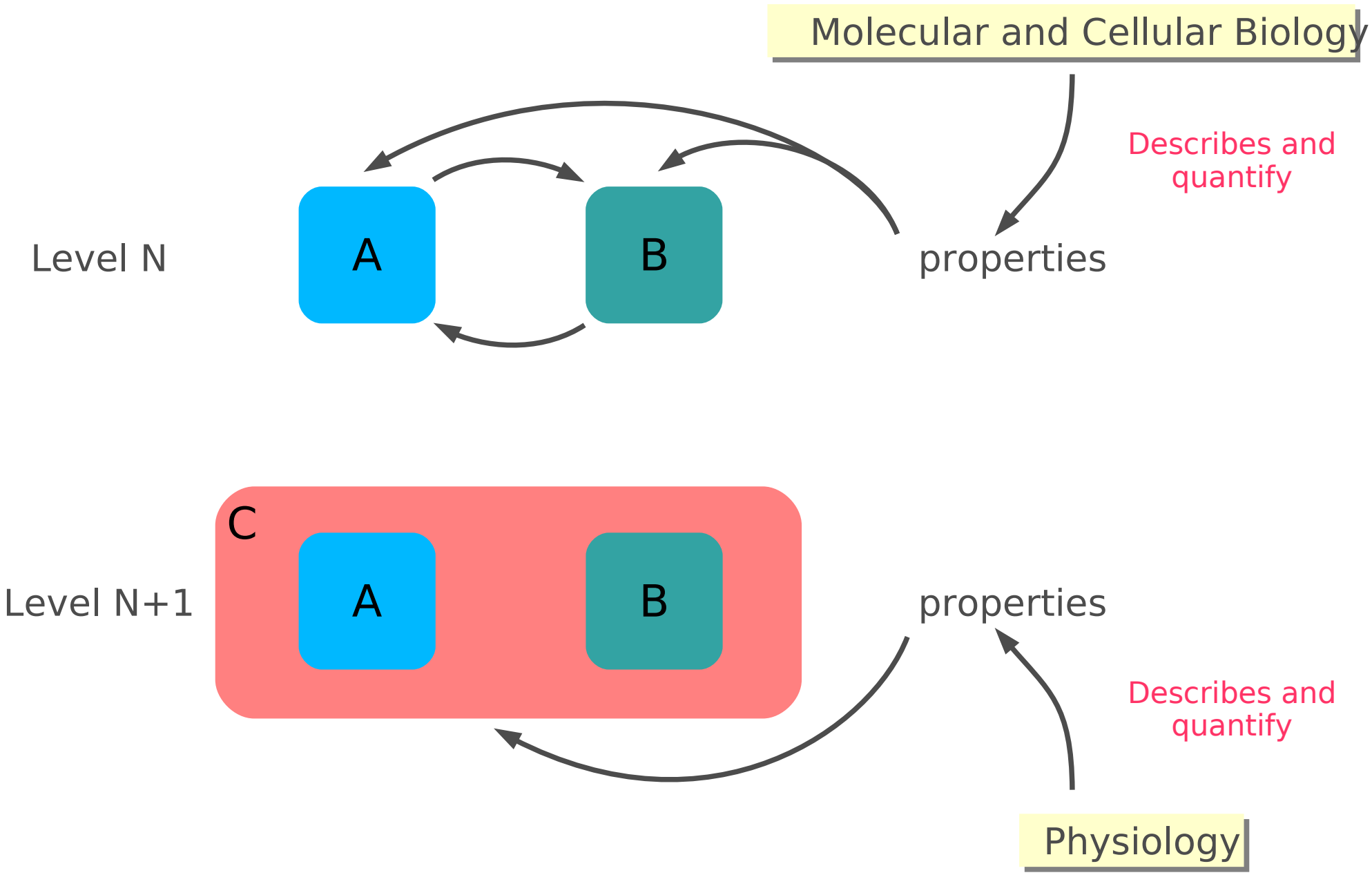
# Rise of Systems Biology as a paradigm



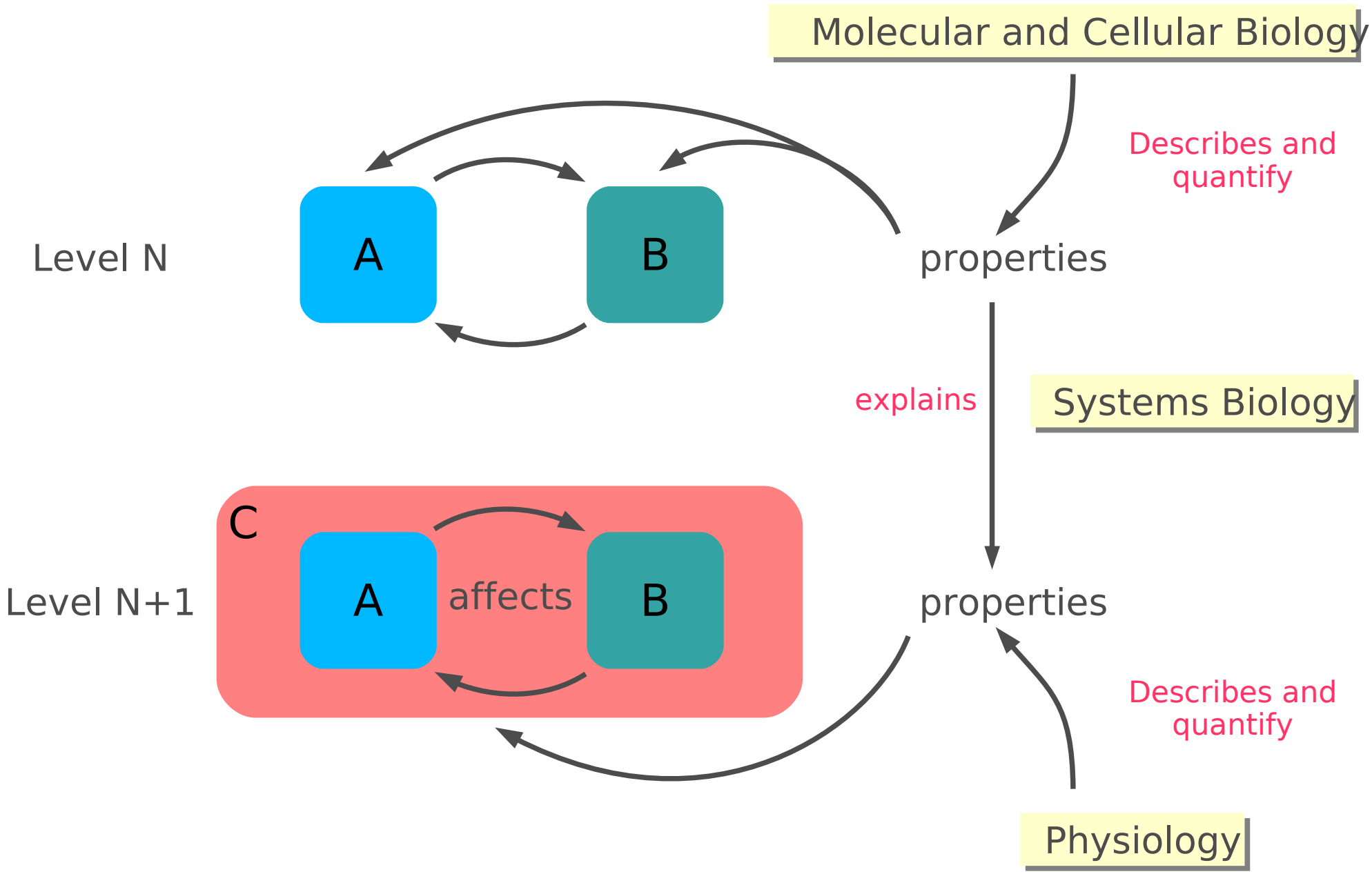
# What is Systems Biology?



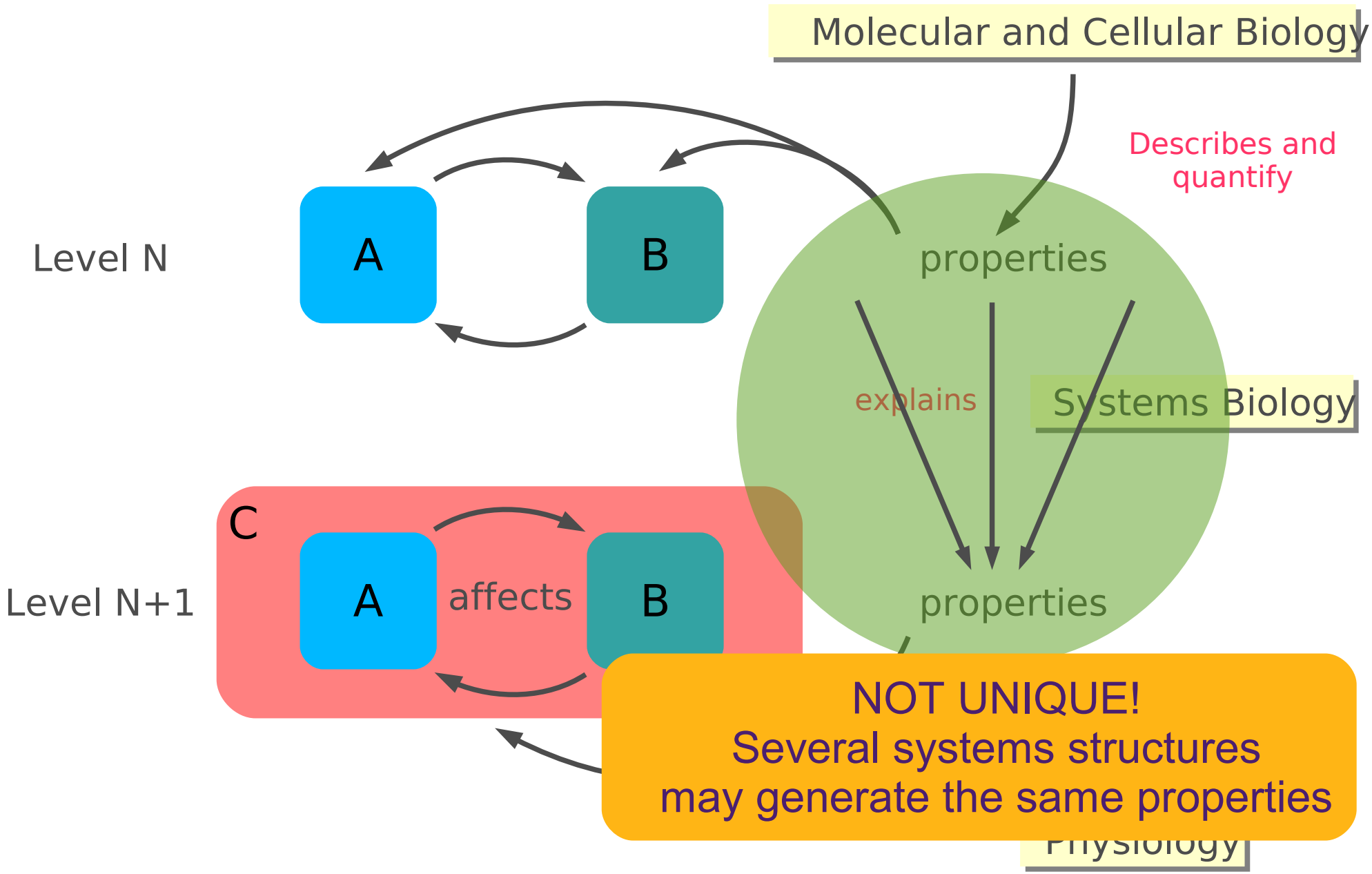
# What is Systems Biology?



# What is Systems Biology?



# What is Systems Biology?



# What Systems Biology is not

Purely theoretical: Most systems biologists are actually experimental biologists

# What Systems Biology is not

Purely theoretical: Most systems biologists are actually experimental biologists

Based on large datasets: in a system of two enzymes, the behaviour of both reactions is different than the ones observed in isolation

# What Systems Biology is not

Purely theoretical: Most systems biologists are actually experimental biologists

Based on large datasets: in a system of two enzymes, the behaviour of both reactions is different than the ones observed in isolation

Focused on biomolecular systems: systems biology is scale-free, and a biological system can be made up of molecules, cells, organs or individuals

# What Systems Biology is not

Purely theoretical: Most systems biologists are actually experimental biologists

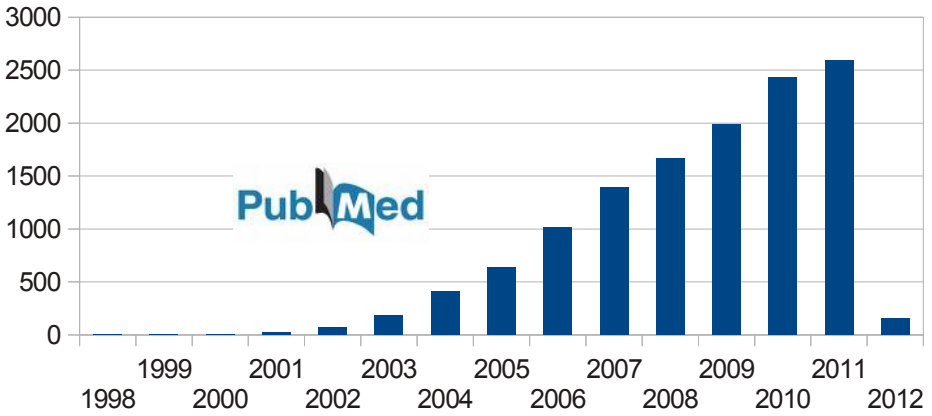
Based on large datasets: in a system of two enzymes, the behaviour of both reactions is different than the ones observed in isolation

Focused on biomolecular systems: systems biology is scale-free, and a biological system can be made up of molecules, cells, organs or individuals

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 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

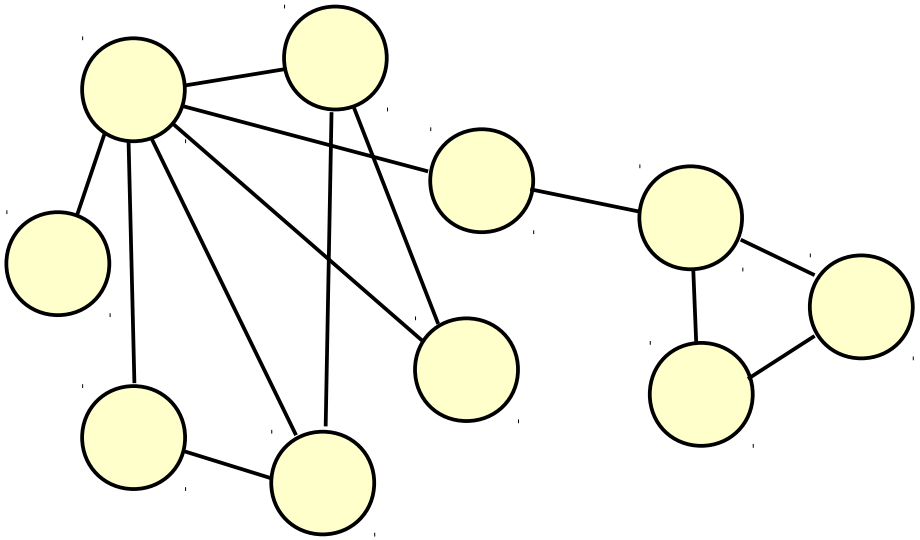
# The challenges ahead: Bridging the gaps

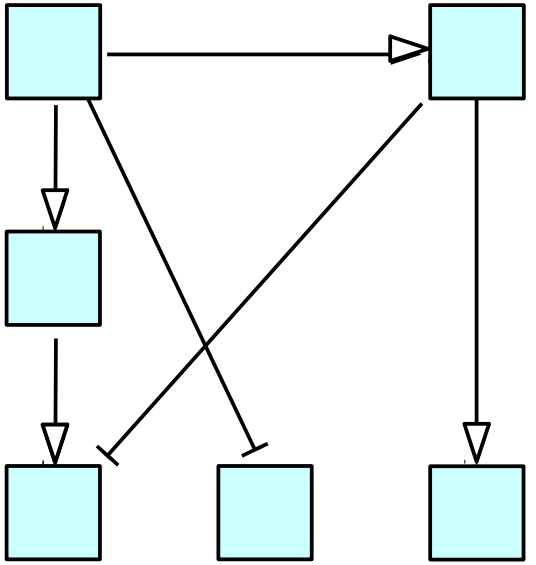
Types of representation

Scales and the mesoscopic gap

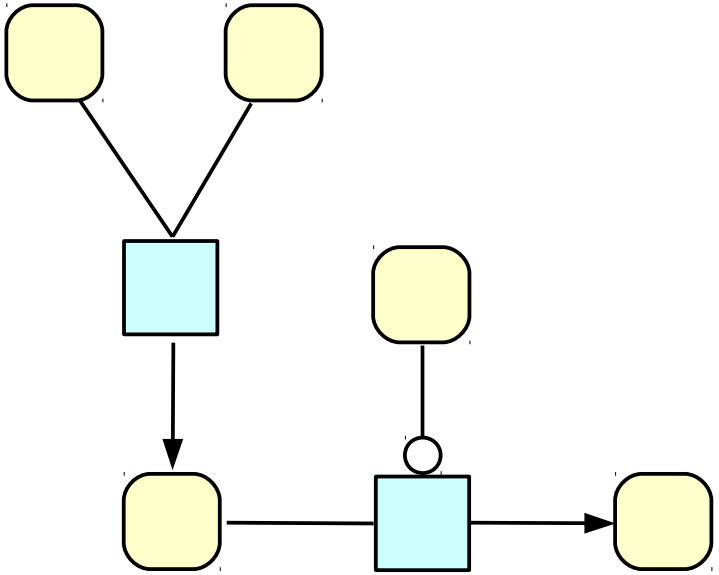
Drug discovery models
Vs systems modelling

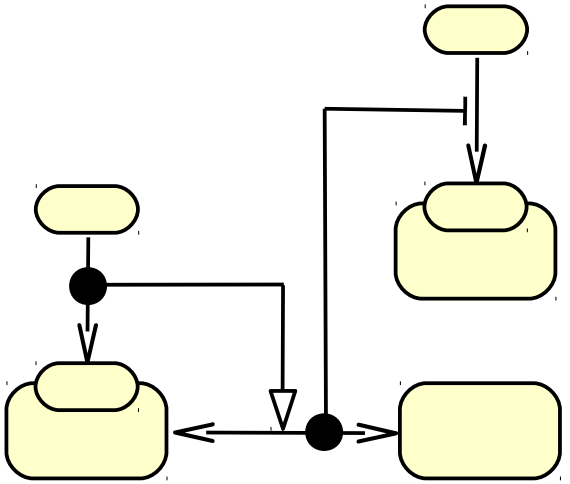
Drug discovery models
Vs “omics” data



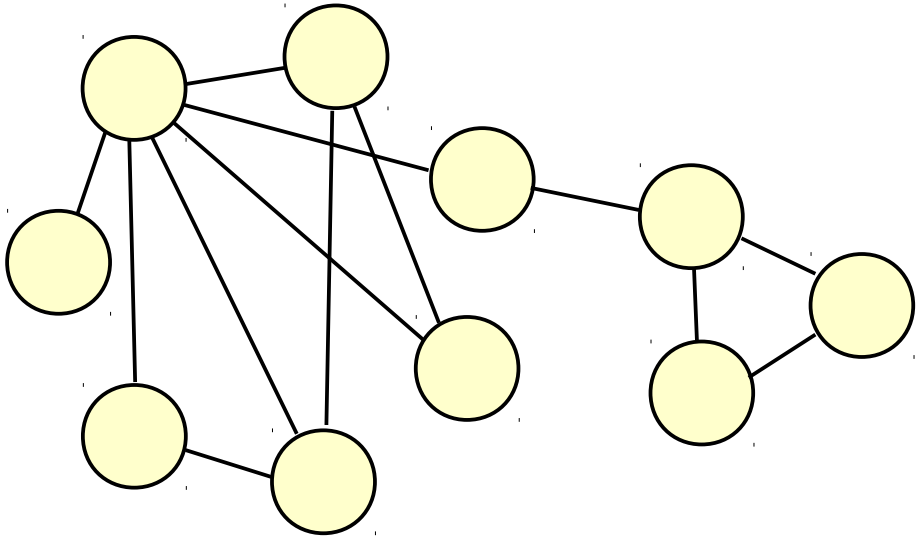


# The four views of systems biology



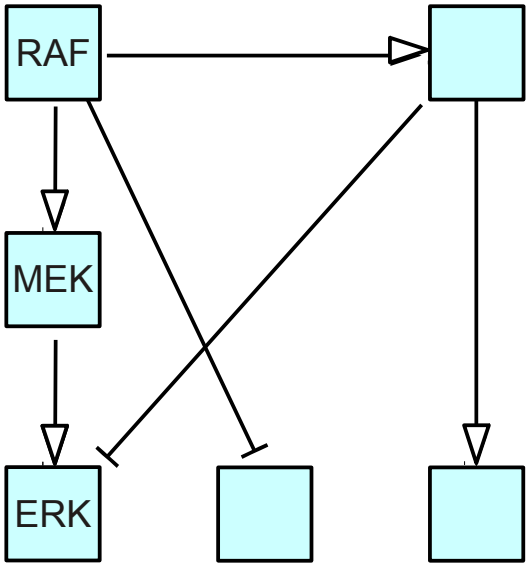


# Interaction networks



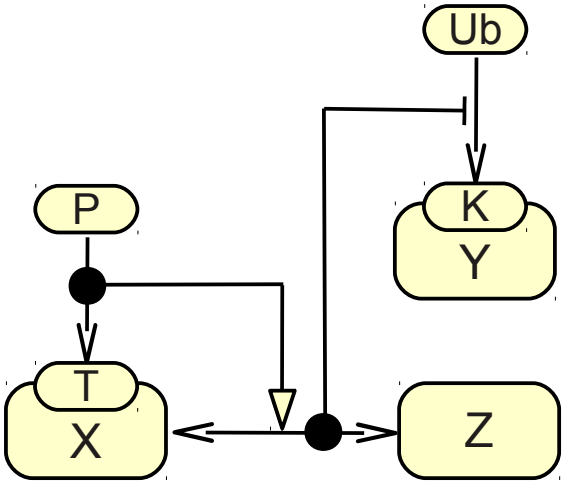
- Non-directional
- Non-sequential
- Non-mechanistic
- Statistical modelling
- Functional genomics
- IntAct, DIP, String

# Activity-Flows



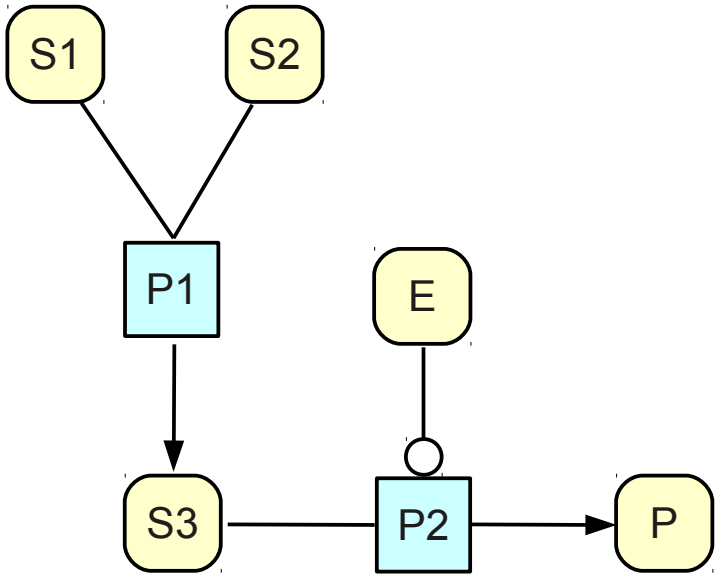

- Directional
- Sequential
- Non-mechanistic
- Logical modelling
- Signalling pathways, gene regulatory networks
- KEGG, STKEs

# Entity Relationships

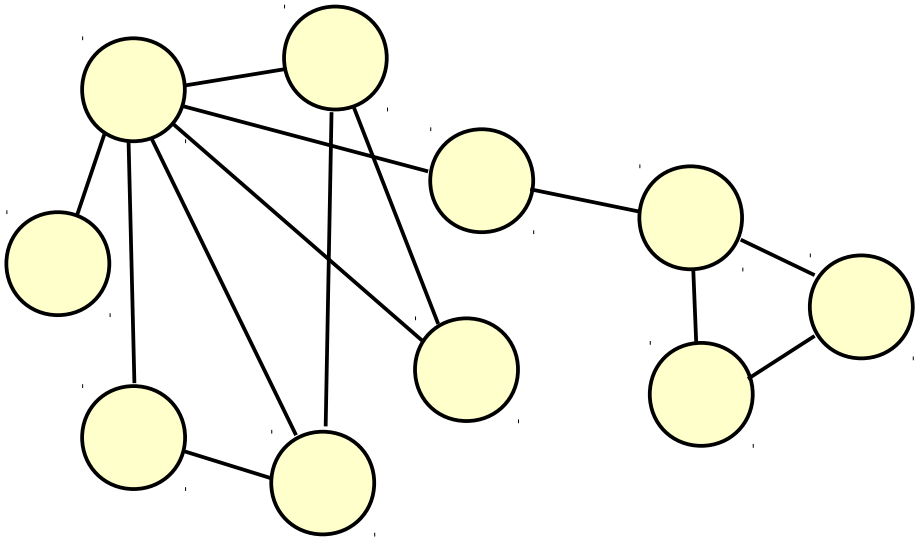


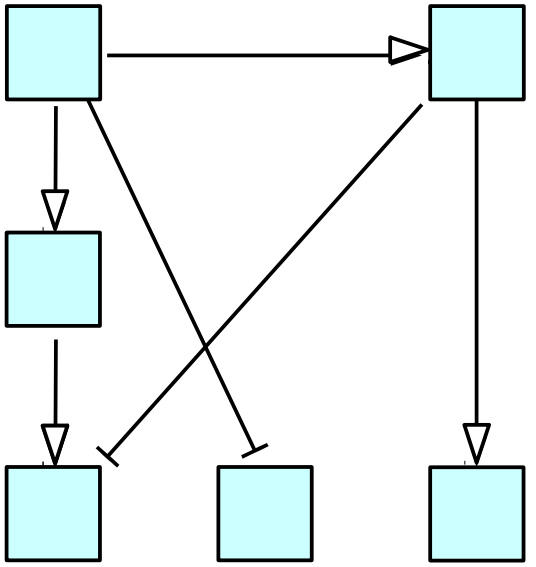

- Directional
- Non-sequential
- Mechanistic
- Independent rules: no explosion
- Rule-based modelling
- Molecular Biology
- MIM

# Process Descriptions

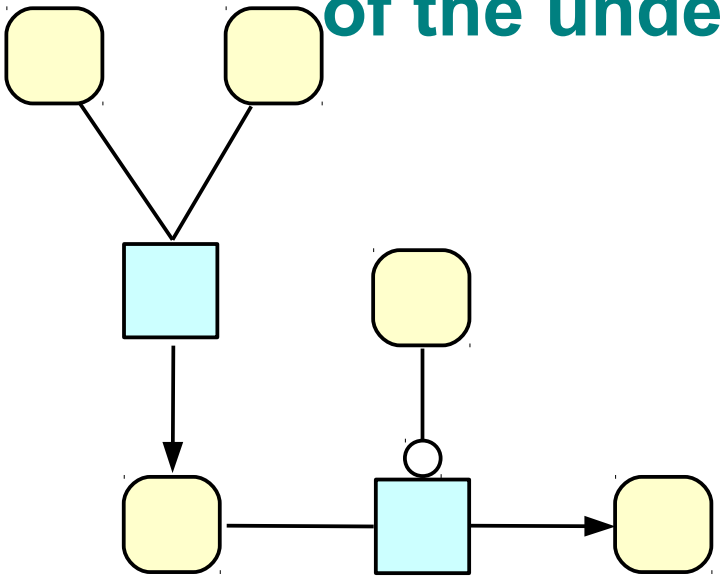


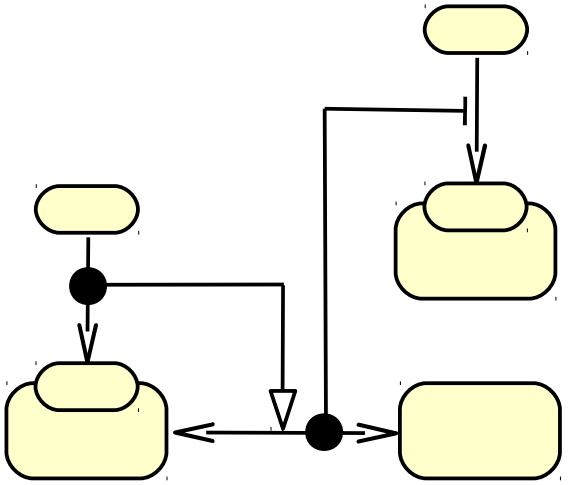

- Directional
- Sequential
- Mechanistic
- Subjected to combinatorial explosion
- Process modelling
- Biochemistry, Metabolic networks
- KEGG, Reactome

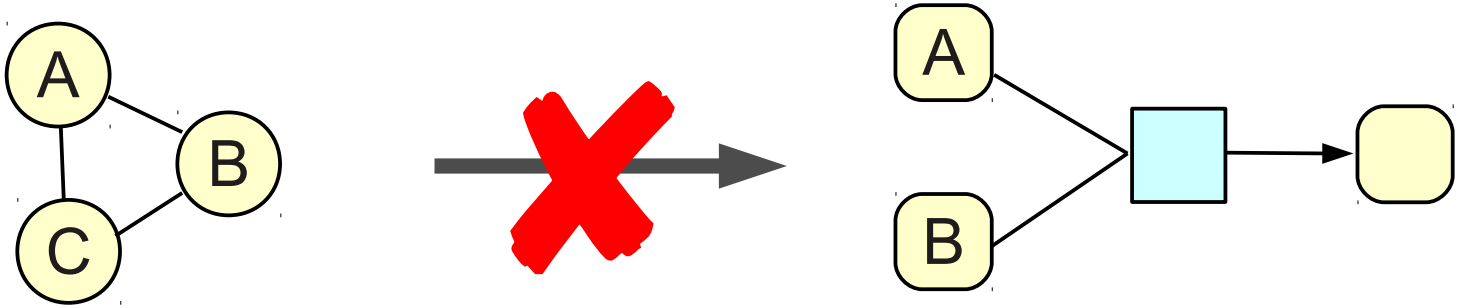




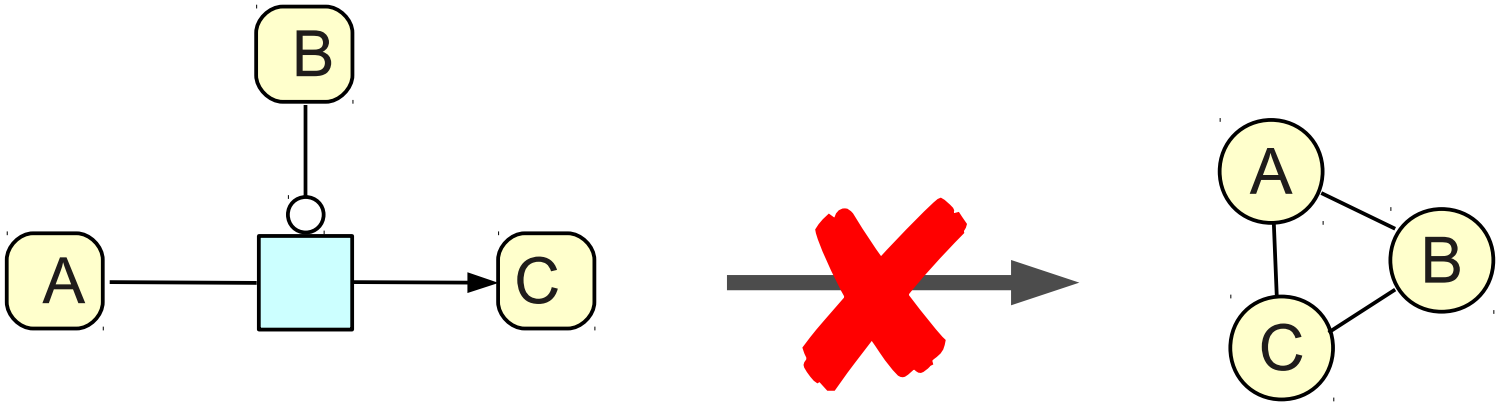
**The four views are orthogonal projections of the underlying biological phenomena**





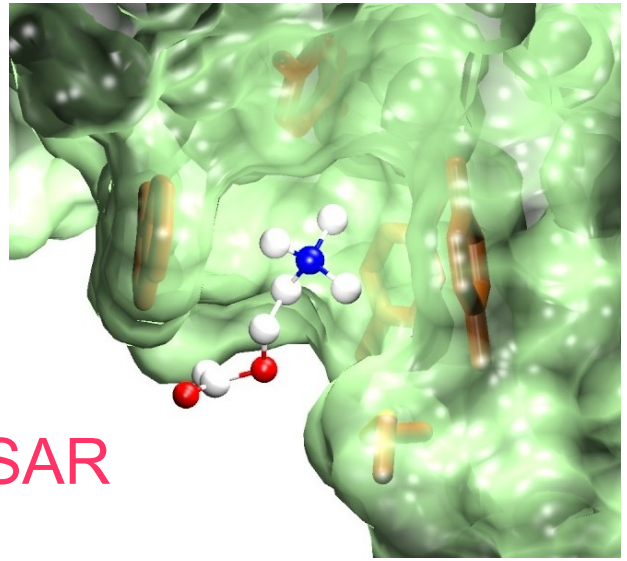



Think scaffolding proteins

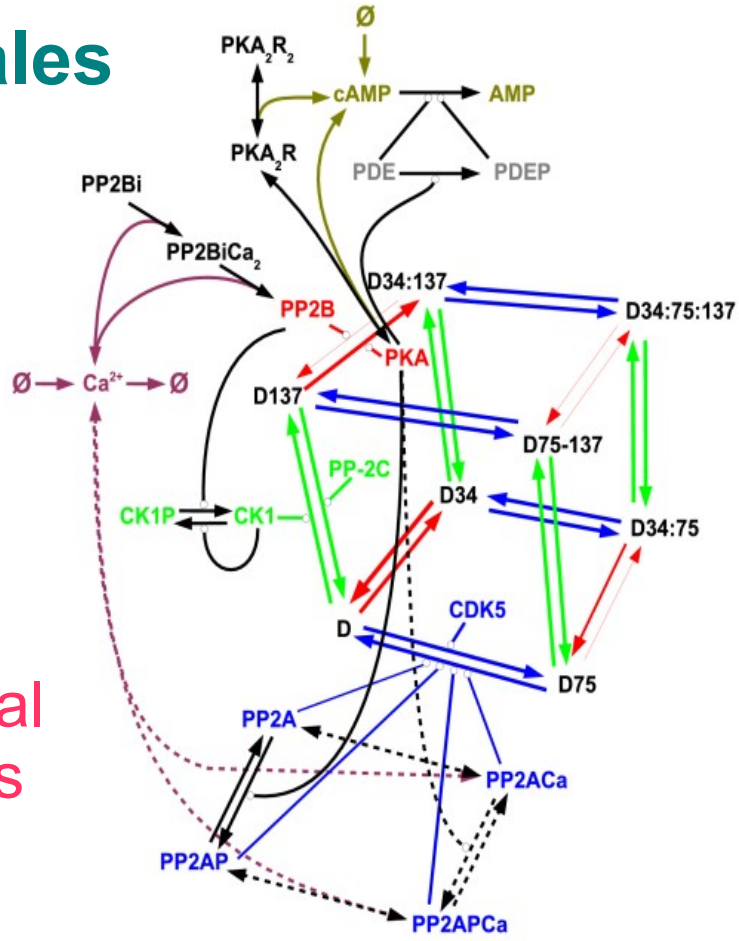



Think phosphorylated signals

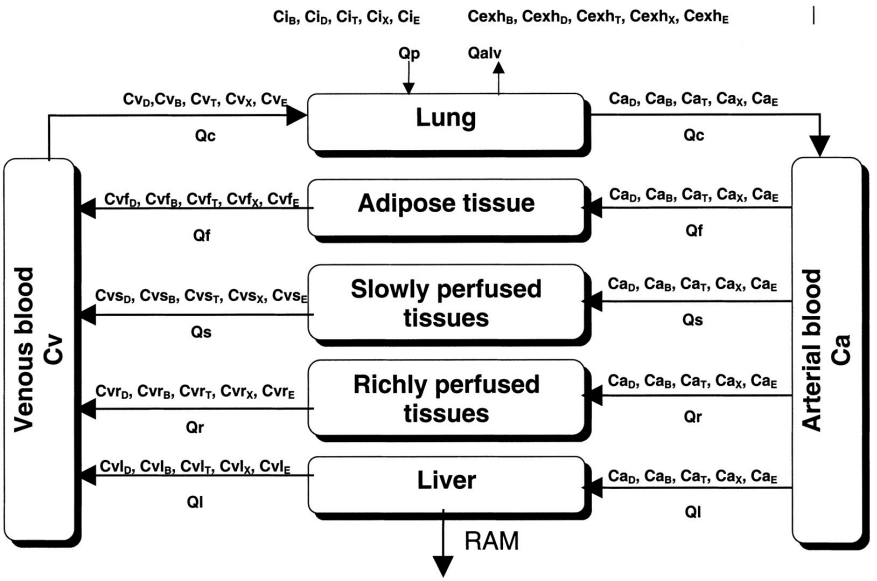
# The problem of scales



QSAR



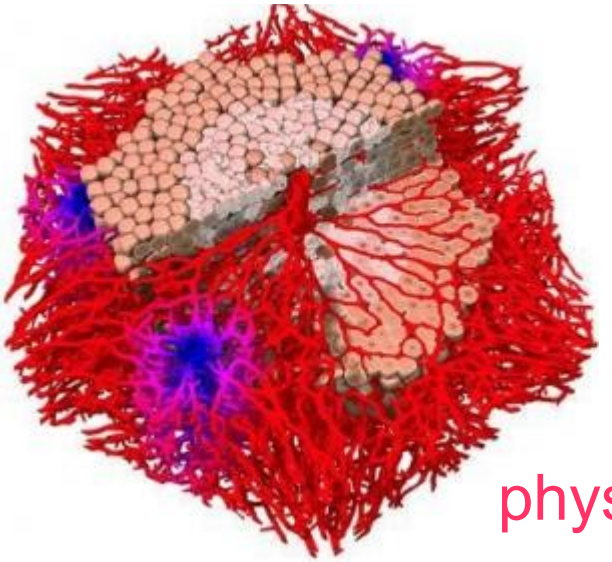

chemical kinetics




$$RAM_D = \frac{Vmax_D \; Cvl_D}{Km_D\left(1+\frac{Cvl_B}{Ki_{BD}}+\frac{Cvl_T}{Ki_{TD}}+\frac{Cvl_X}{Ki_{XD}}+\frac{Cvl_E}{Ki_{ED}}\right)+Cvl_D}$$

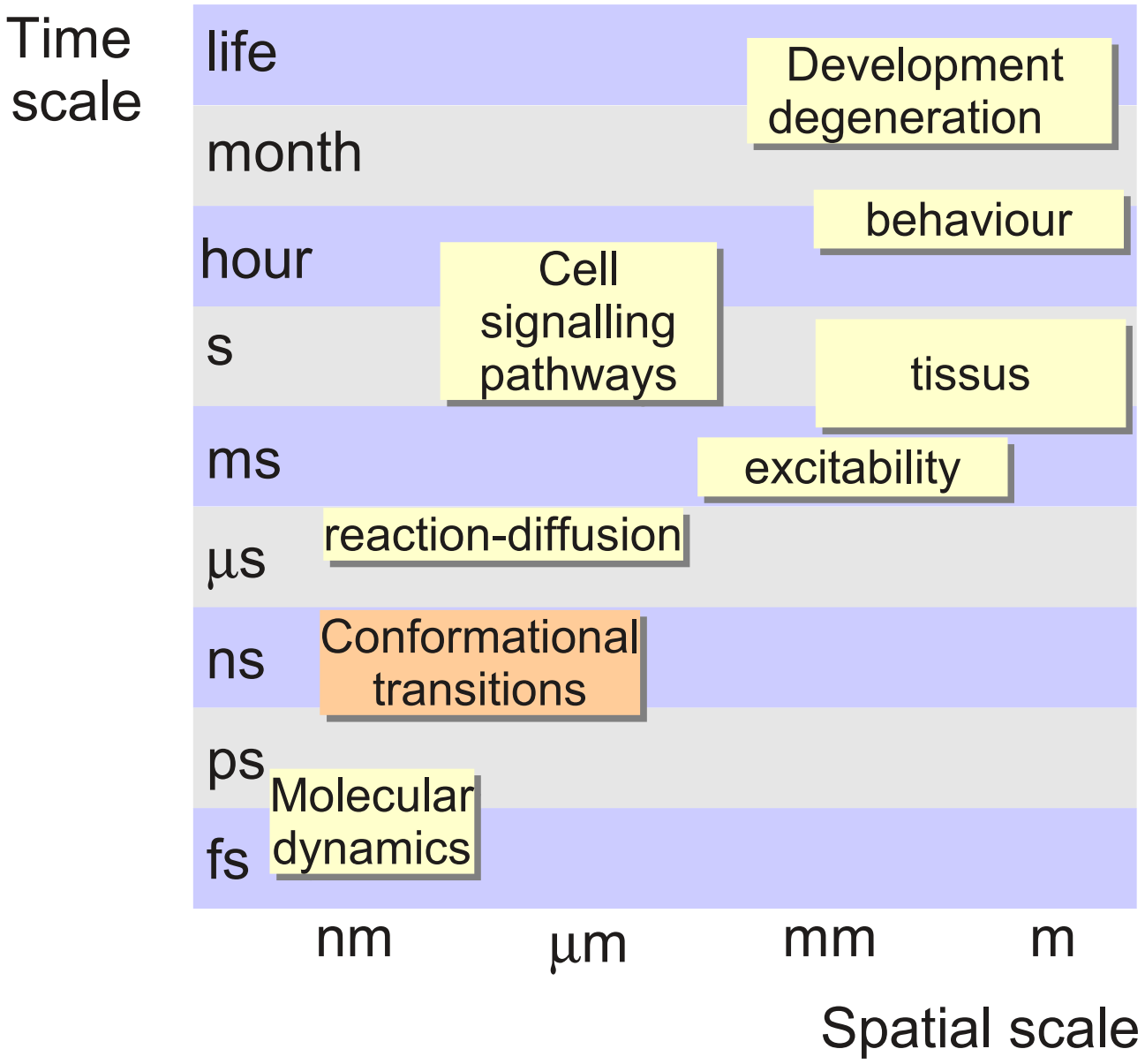
$$RAM_B = \frac{Vmax_B \; Cvl_B}{Km_B\left(1+\frac{Cvl_D}{Ki_{DB}}+\frac{Cvl_T}{Ki_{TB}}+\frac{Cvl_E}{Ki_{EB}}+\frac{Cvl_X}{Ki_{XB}}\right)+Cvl_B}$$

pharmacometrics

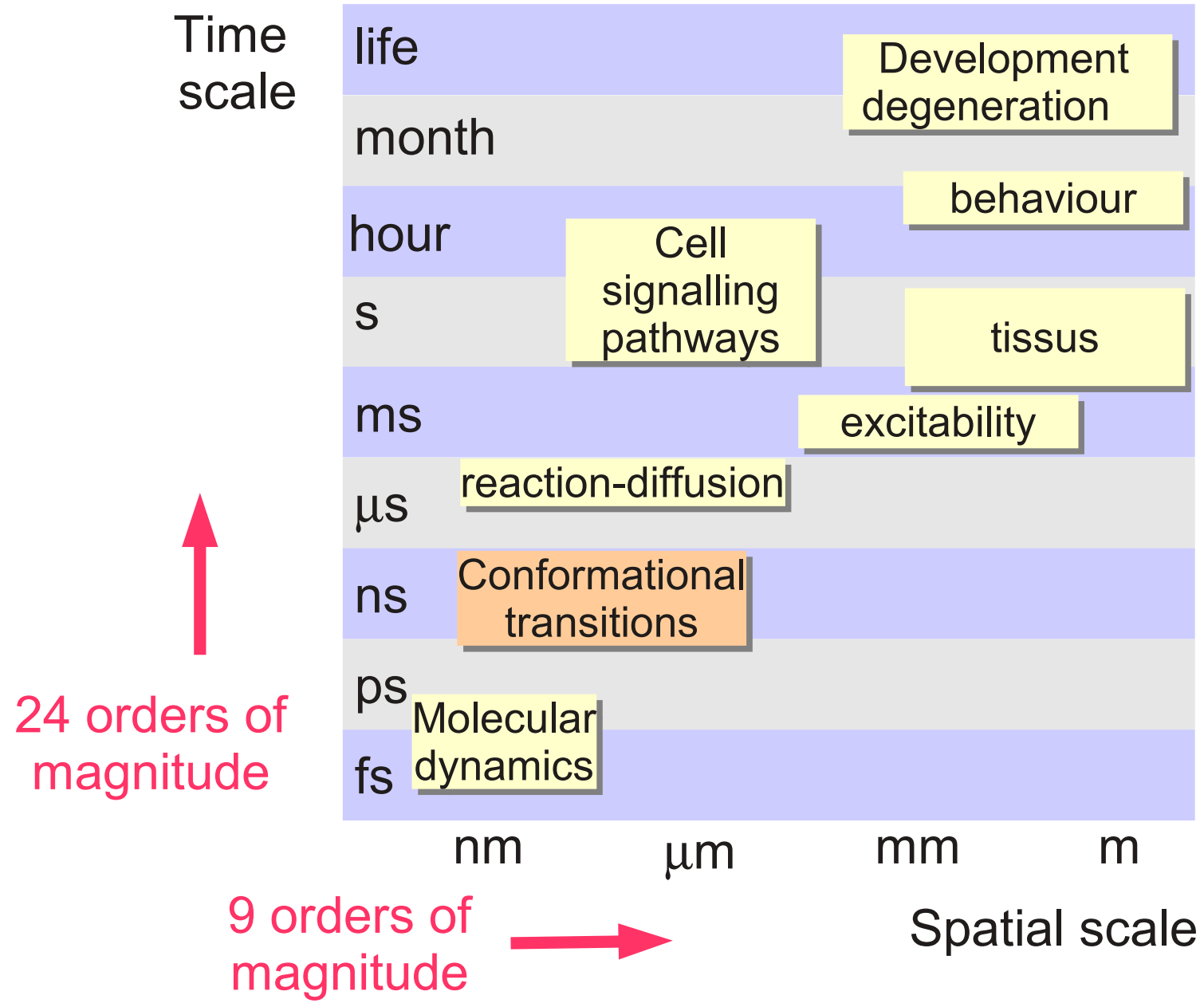


physiology

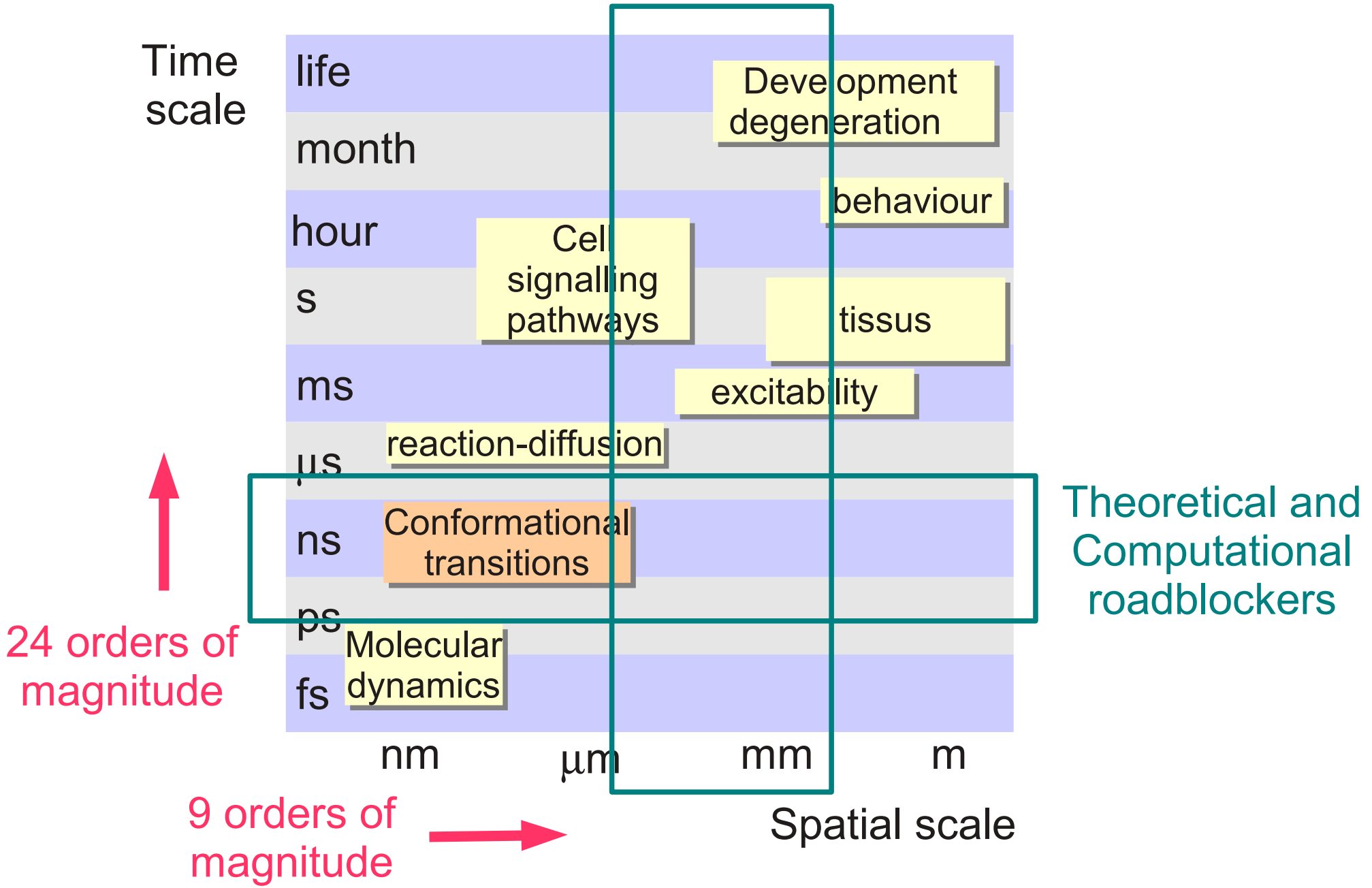
# The mesoscopic gap



# The mesoscopic gap



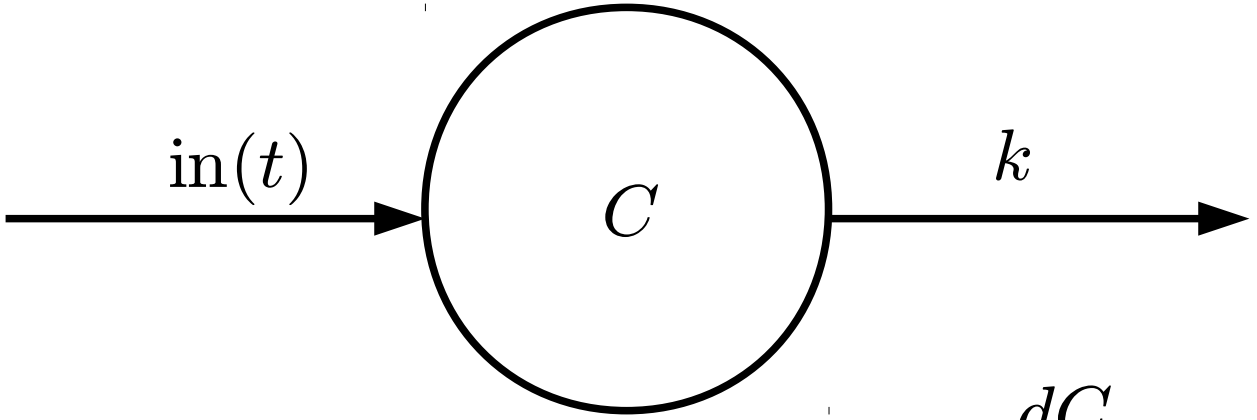
# The mesoscopic gap



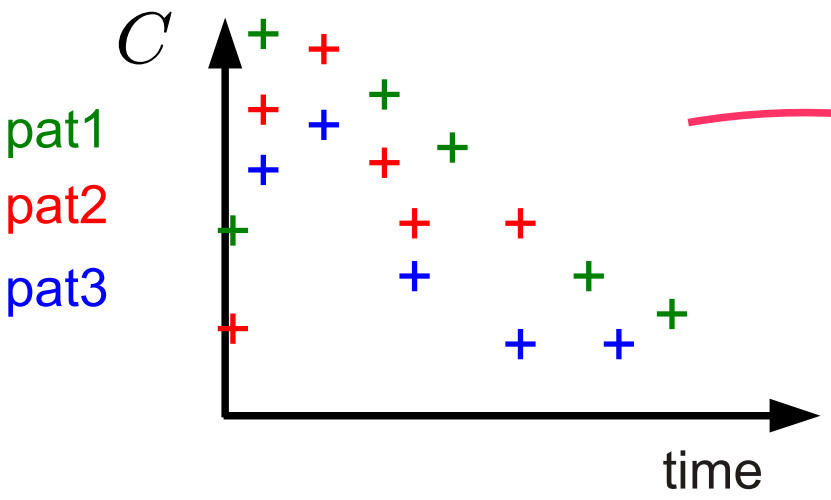
# Multi-scale does not mean fine scale plus massive power

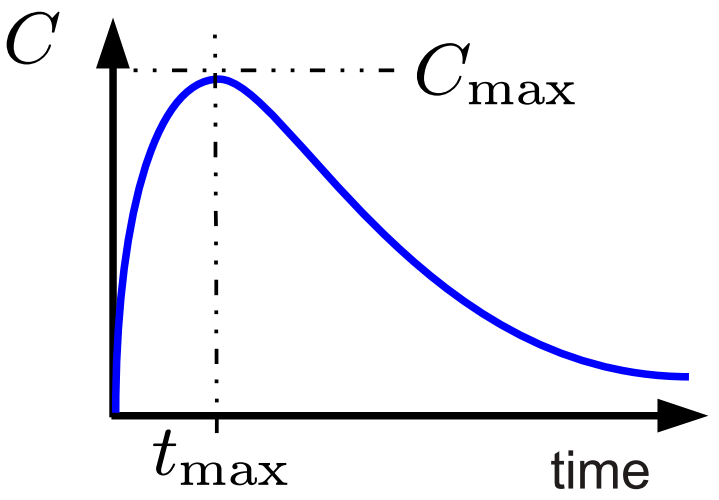
- Computational issues
  - In 2008, largest simulations were 1 million atoms for 50 ns (using > 30 years CPU) and 10000 atoms for 0.5 ms.
  - E-coli ~ 1 million million atoms ...
  - We need at least $10^{14}$ more power to simulate E coli during 1 s
- Theoretical issues
  - Molecular dynamics does not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

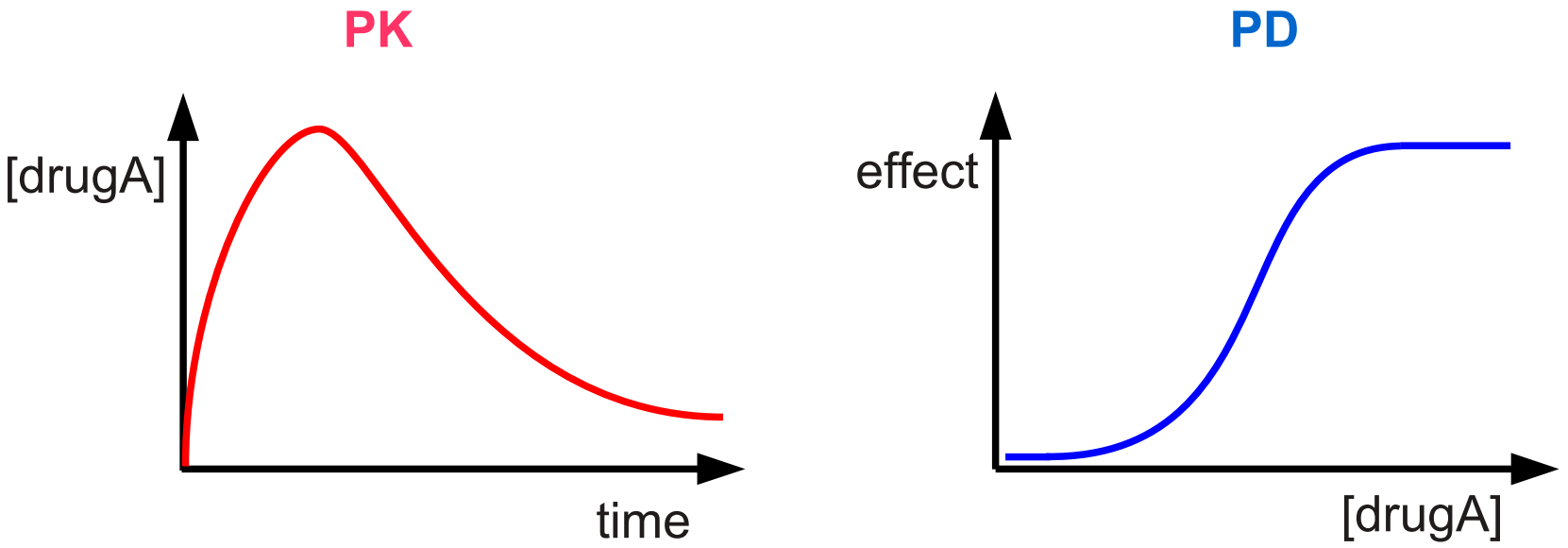



$$\frac{dC}{dt} = \text{in}(t) - k \times C$$

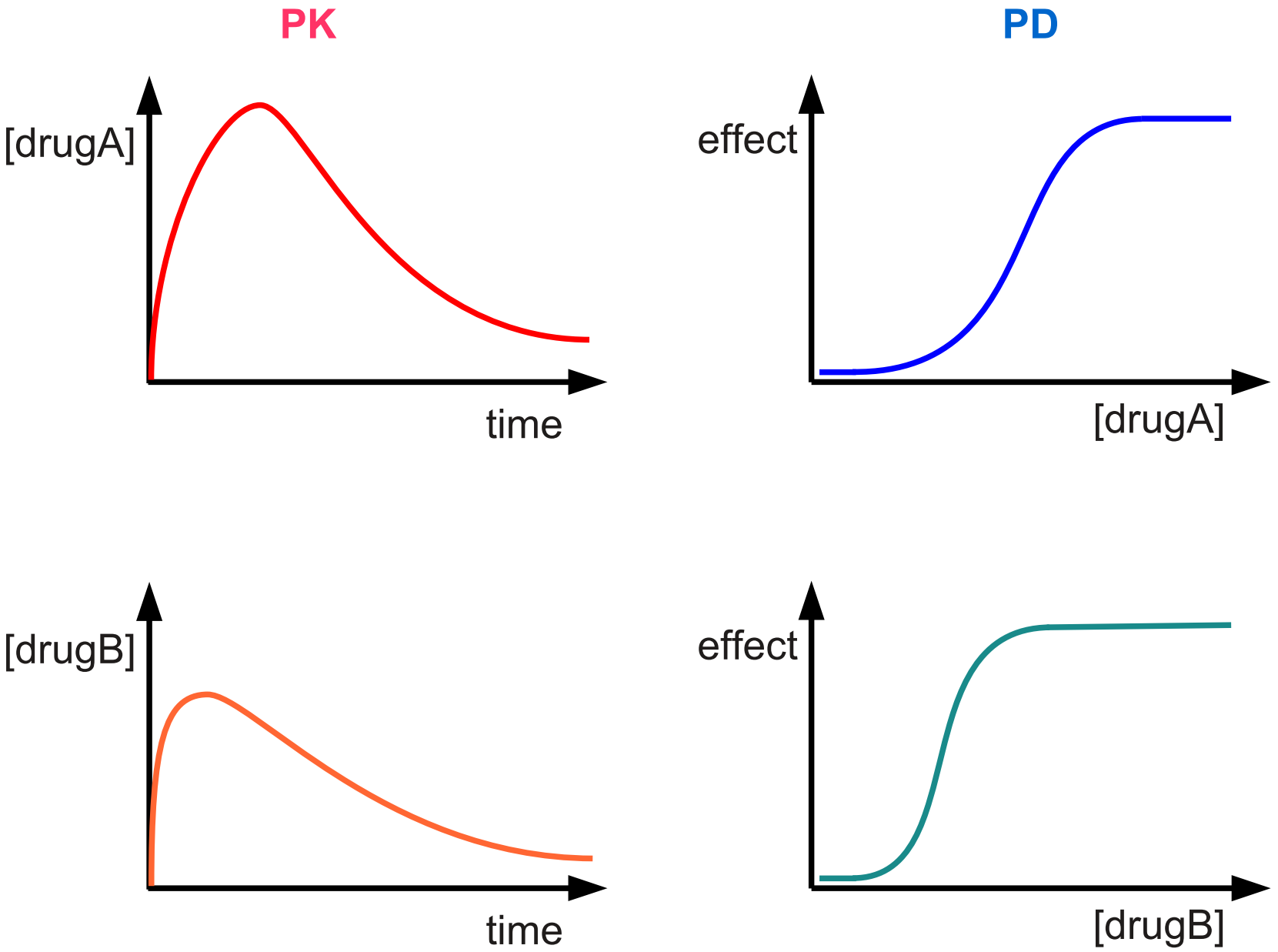


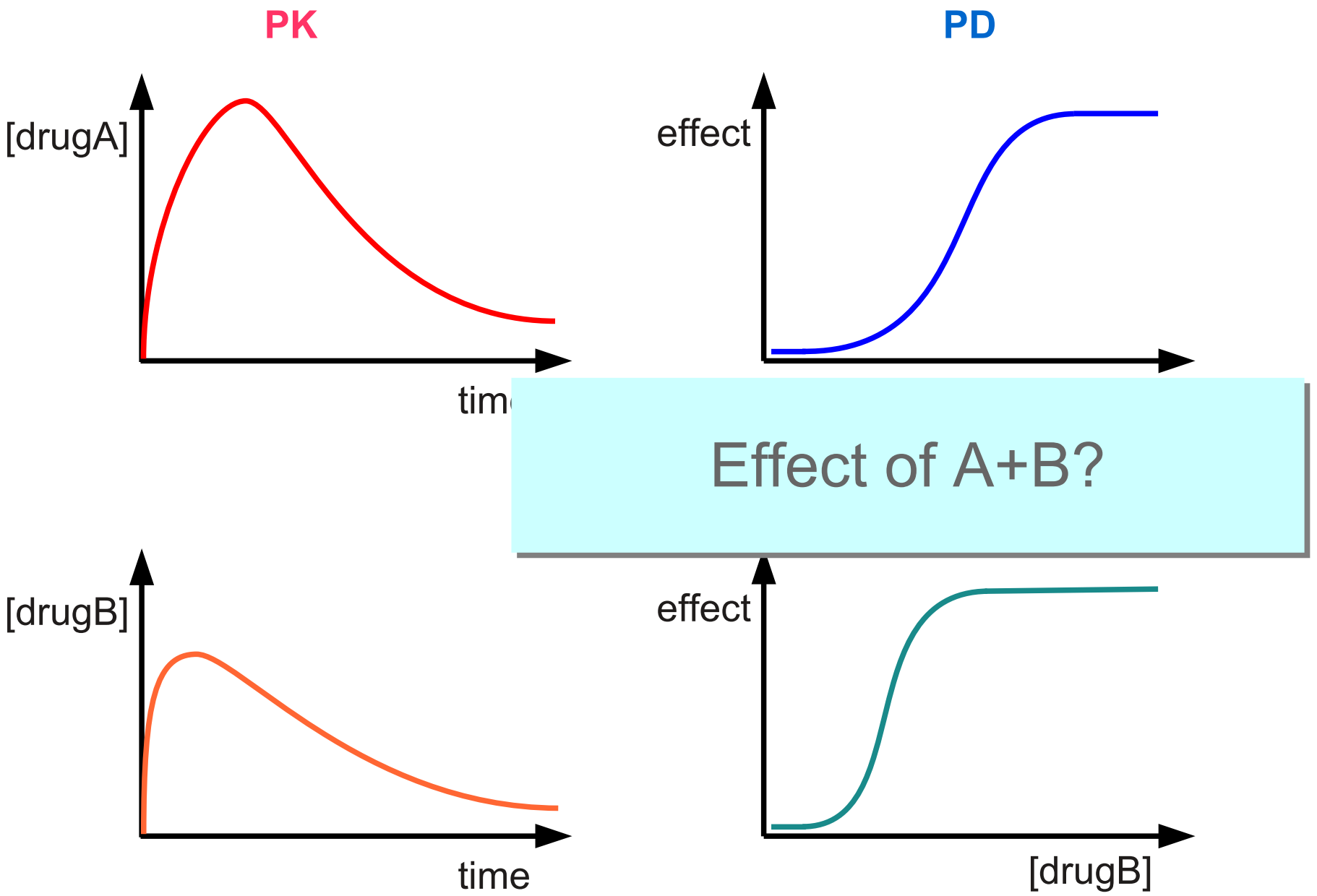
# Drug discovery modelling: pharmacometrics



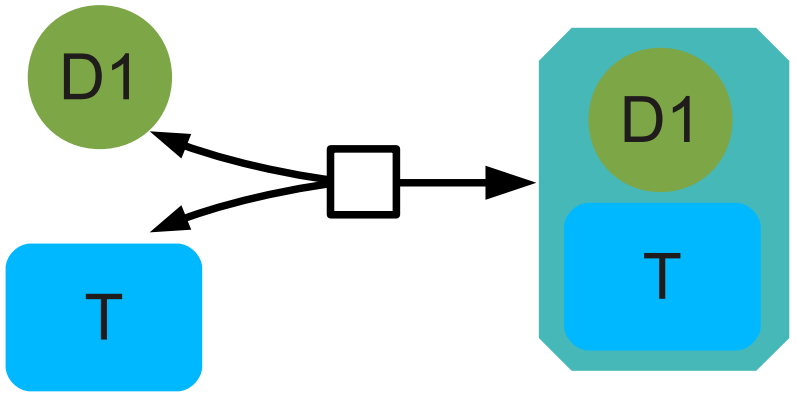
# Drug discovery modelling: pharmacometrics



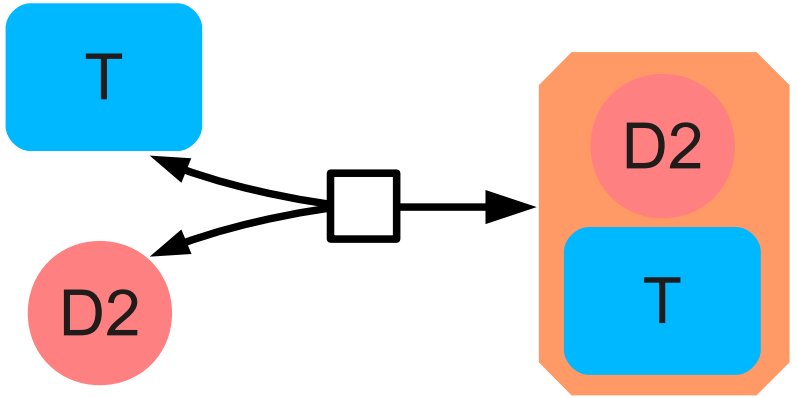
# Drug discovery modelling: pharmacometrics



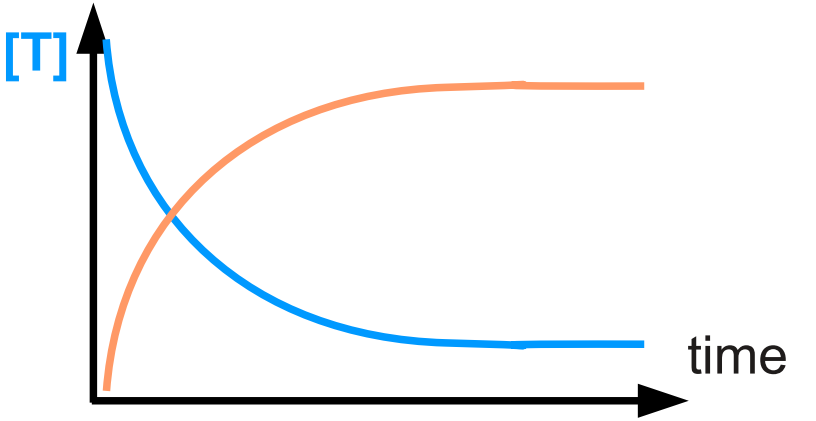
# Systems modelling




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

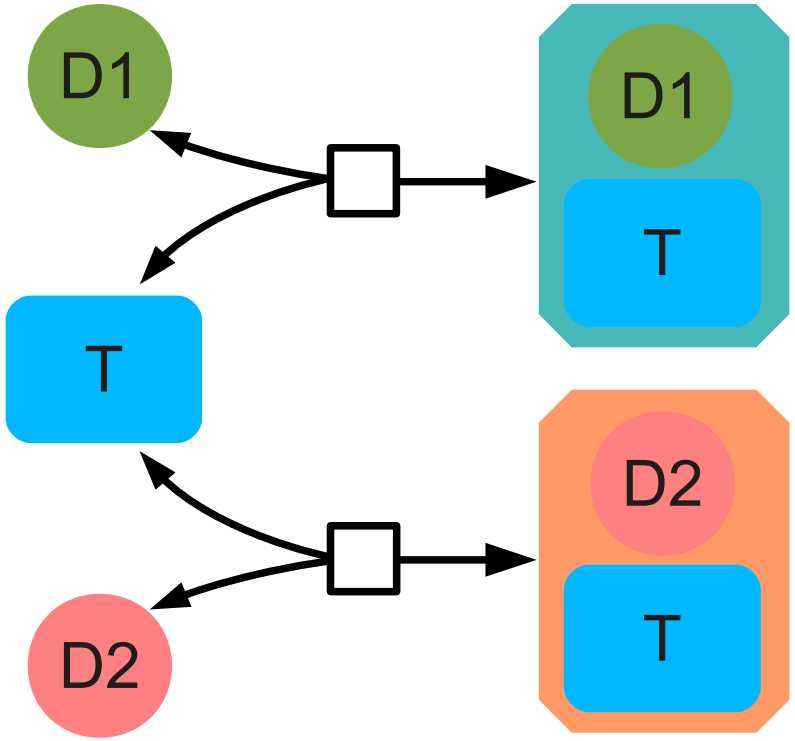



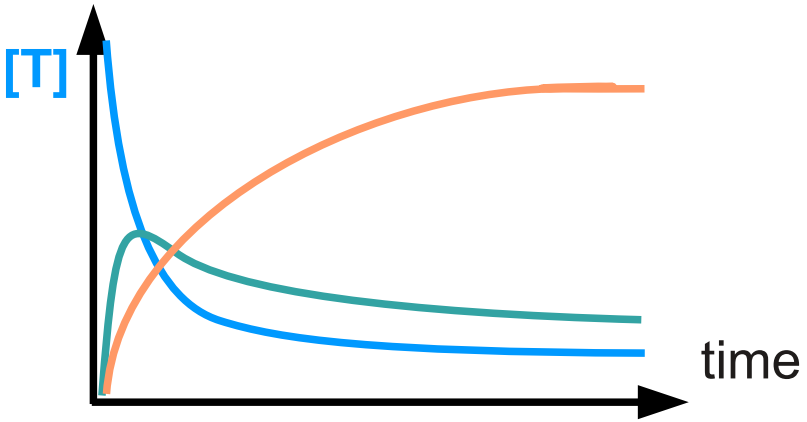

$$\frac{d[T]}{dt} = -k2 \times [T] \times [D2]$$



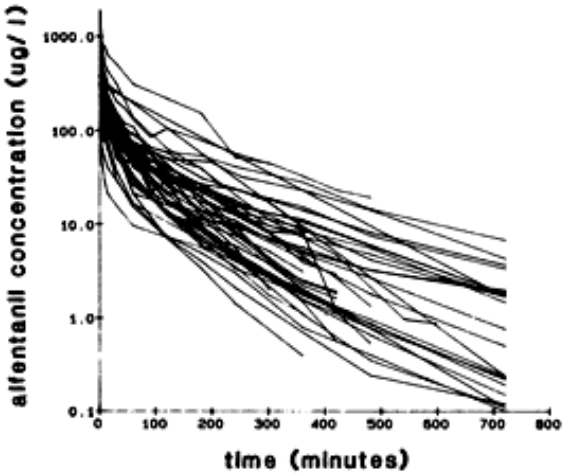
# Systems modelling

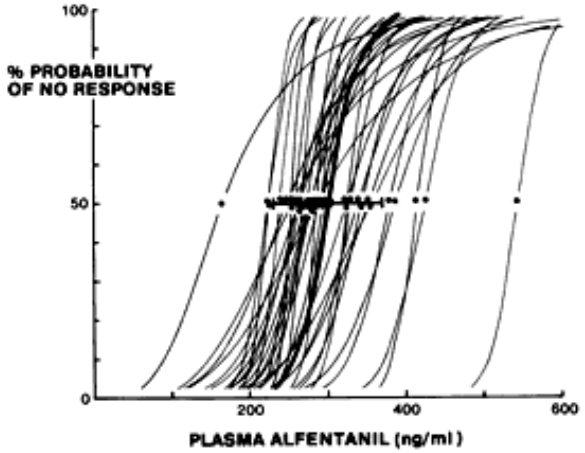
$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1] - k2 \times [T] \times [D2]$$

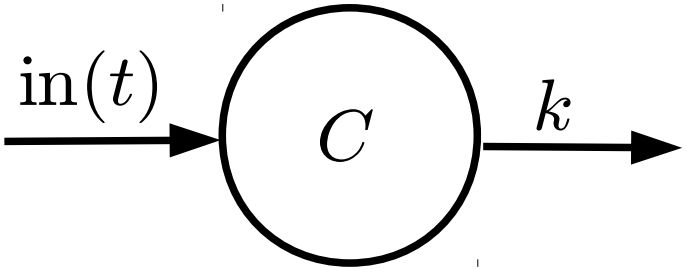


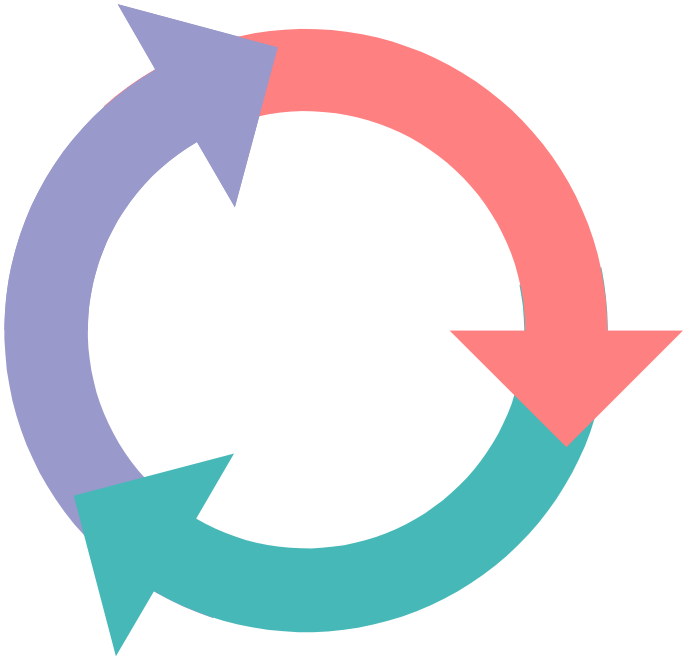



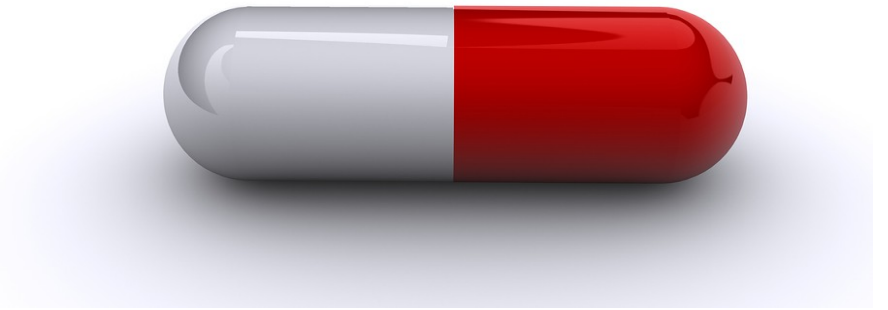
# Drug discovery and pharmacometrics models



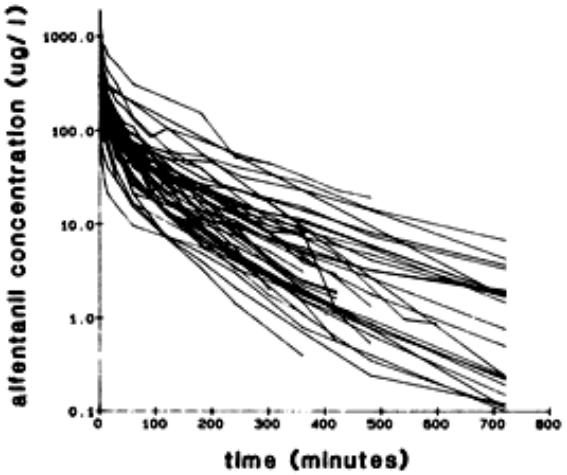



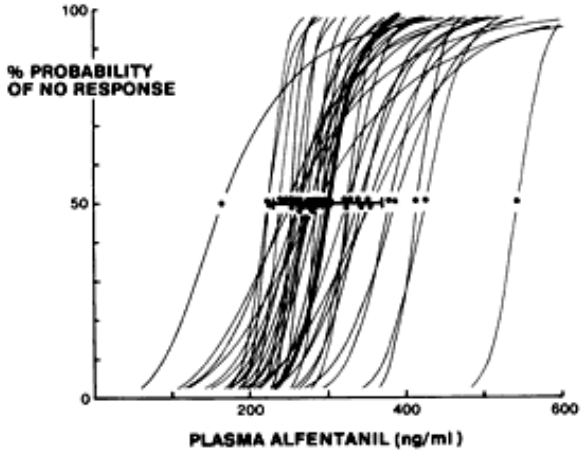



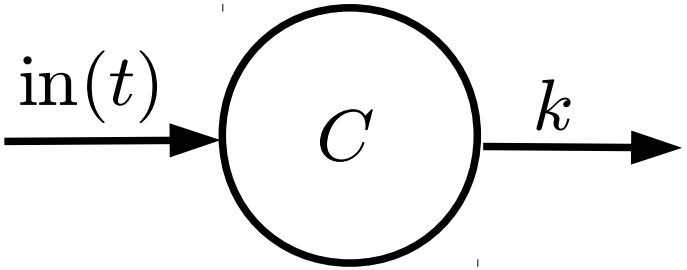



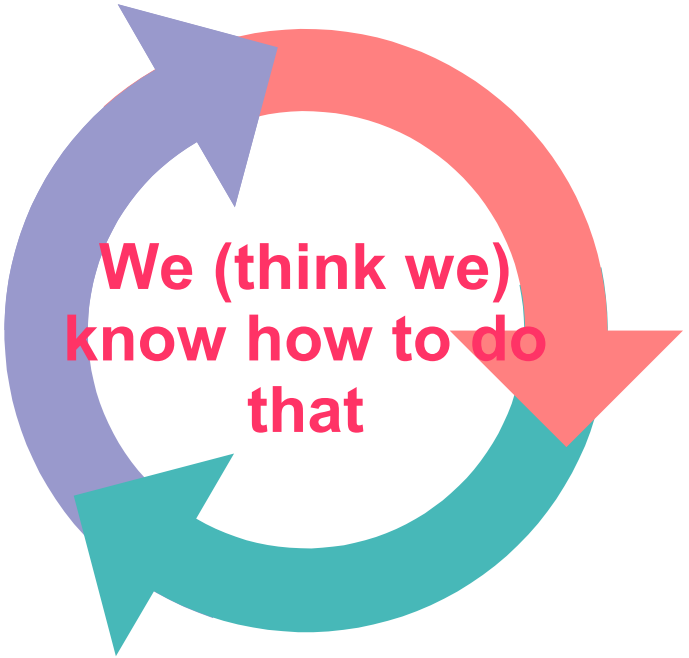


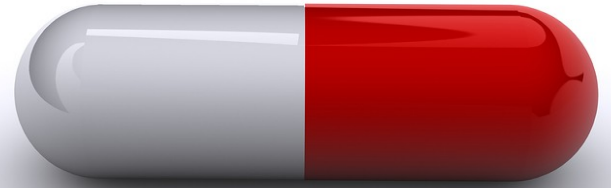
# Drug discovery and pharmacometrics models



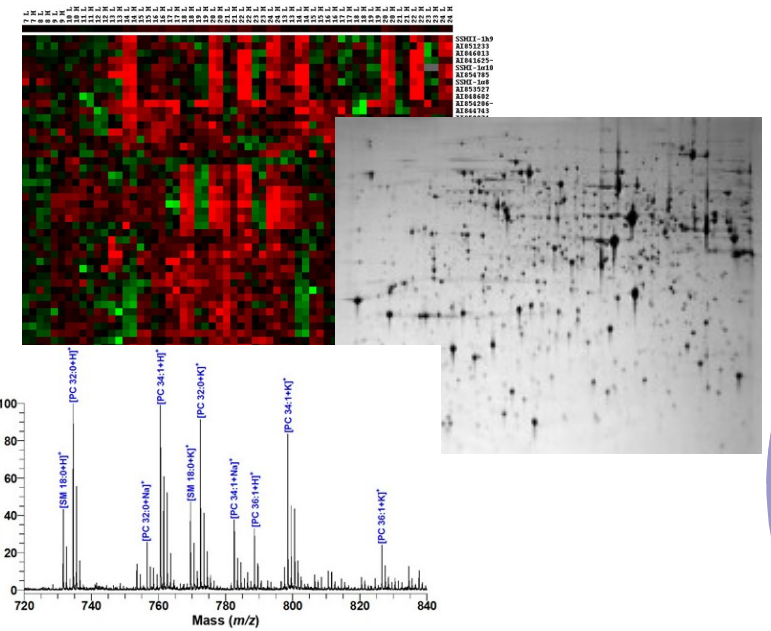



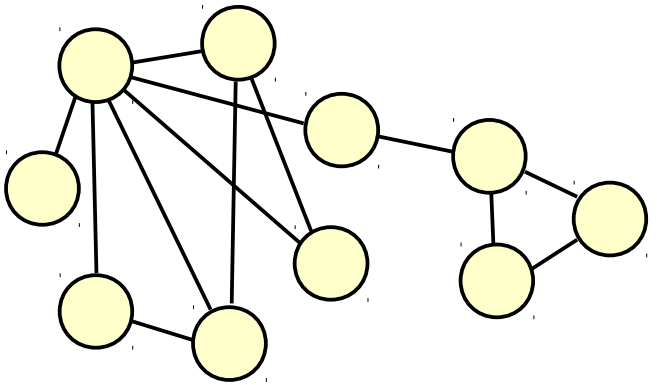



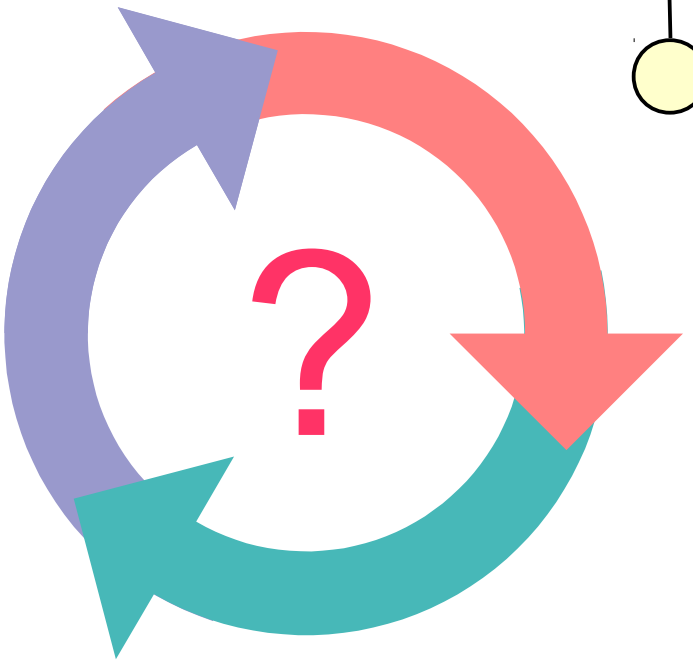



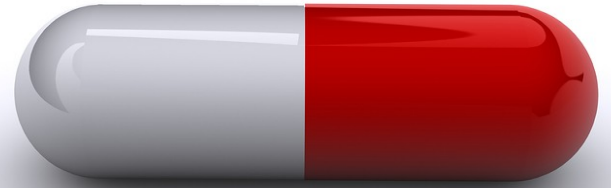



# Drug discovery and omics





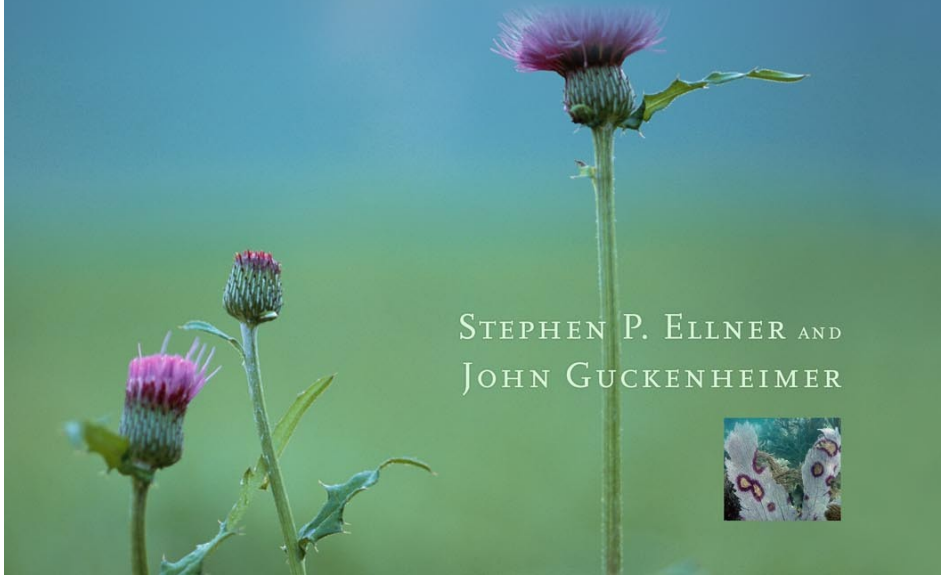
# Systems Biology

Edda Klipp, Wolfram Liebermeister, Christoph Wierling,
Axel Kowald, Hans Lehrach, and Ralf Herwig

A Textbook

WILEY-
BLACKWELL

# Dynamic Models in Biology



Stephen P. Ellner and
John Guckenheimer