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

Nicolas Le Novère, Babraham Institute, EMBL-EBI

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


# A New Approach to Decoding Life: Systems Biology

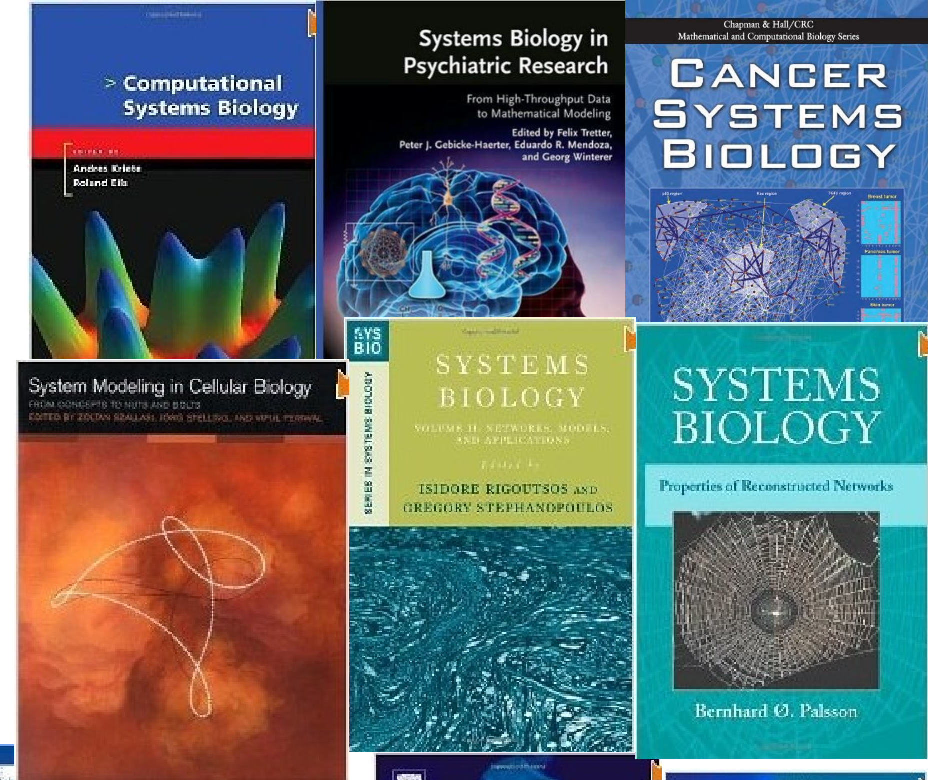
Trey Ideker[1,2], Timothy Galitski[1], and Leroy Hood[1,2,3,4,5]
*Institute for Systems Biology[1], Seattle, Washington 98105; Departments of*

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.*

NEW GENERATION COMPUTING


RESEARCH ARTICLE

# Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome

Daniel G. Gibson,[1] John I. Glass,[1] Carole Lartigue,[1] Vladimir N. Noskov,[1] Ray-Yuan Chuang,[1] Mikkel A. Algire,[1] Gwynedd A. Benders,[2] Michael G. Montague,[1] Li Ma,[1] Monzia M. Moodie,[1] Chuck Merryman,[1] Sanjay Vashee,[1] Radha Krishnakumar,[1] Nacyra Assad-Garcia,[1] Cynthia Andrews-Pfannkoch,[1] Evgeniya A. Denisova,[1] Lei Young,[1] Zhi-Qing Qi,[1] Thomas H. Segall-Shapiro,[1] Christopher H. Calvey,[1] Prashanth P. Parmar,[1] Clyde A. Hutchison III,[2] Hamilton O. Smith,[2] J. Craig Venter[1,2]*

2 JULY 2010 VOL 329 SCIENCE www.sciencemag.org

# EXTREME GENETIC ENGINEERING

## An Introduction to Synthetic Biology

January 2007

etc group

# Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Cell

Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,]*
[1] Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2] CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
*Contact: yamanaka@frontier.kyoto-u.ac.jp
DOI 10.1016/j.cell.2006.07.024
Cell 126, 663–676, August 25, 2006 ©2006 Elsevier Inc. 663

# A synthetic oscillatory network of transcriptional regulators

Michael B. Elowitz & Stanislas Leibler

*Departments of Molecular Biology and Physics, Princeton University, Princeton, New Jersey 08544, USA*

NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com


page discussion view source history teams

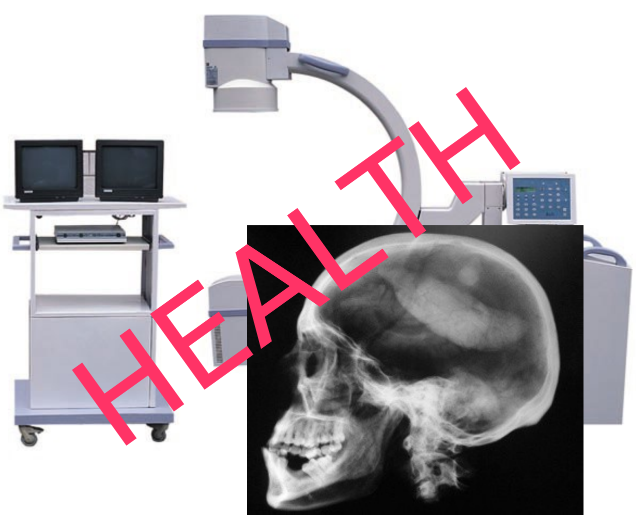
## About

The International Genetically Engineered Machine competition (iGEM) is
Biology competition. Student teams are given a kit of biological parts at the beginnin
Standard Biological Parts. Working at their own schools over the summer, they use t

# What did electrical engineering bring?





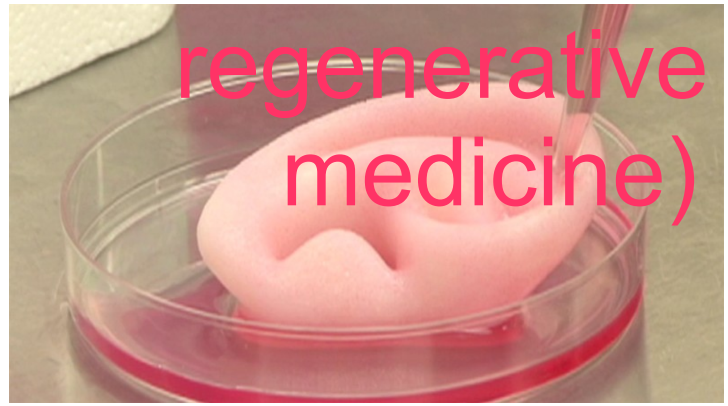



# What will biological engineering bring?

## HEALTH

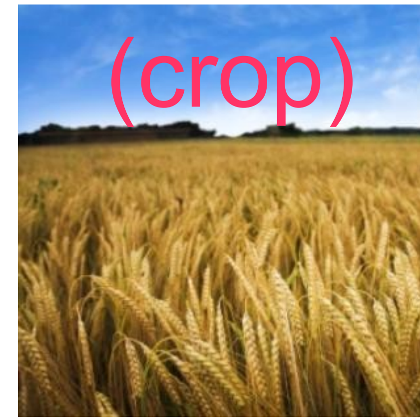
(drug production

regenerative medicine)



## FOOD

(crop)



## ENVIRONMENT

(biofuels

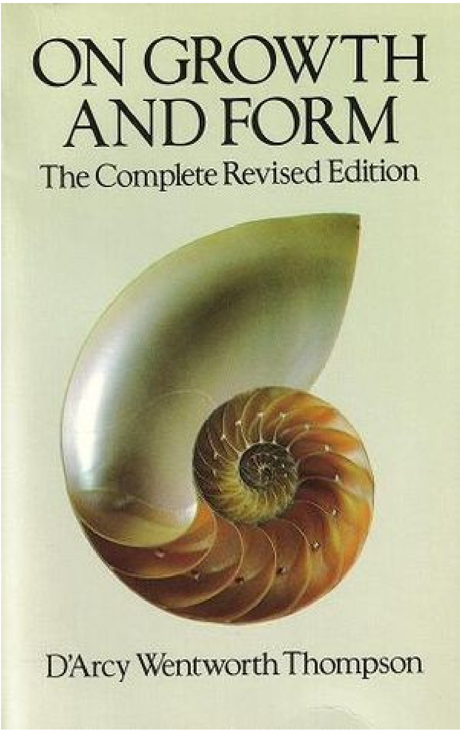
decontamination)

## SECURITY

(biosensors)

# Why using mathematical models?

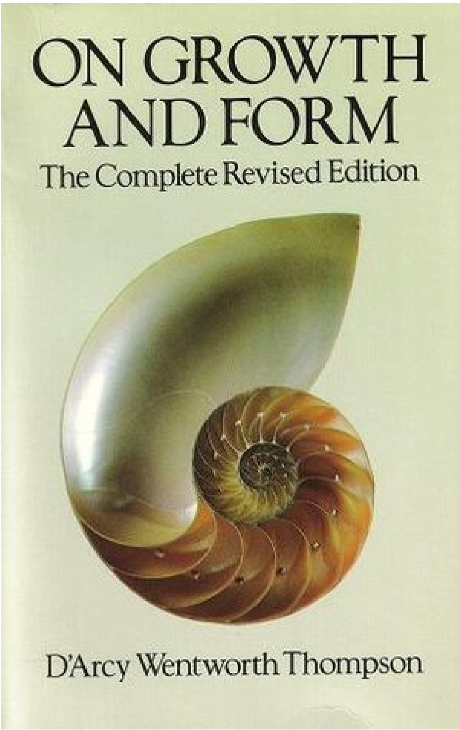
**Describe**

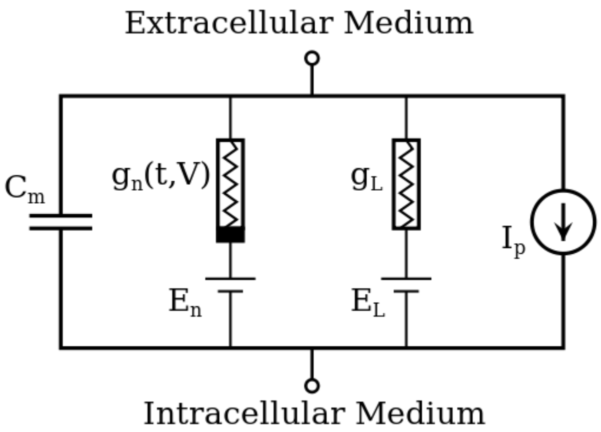


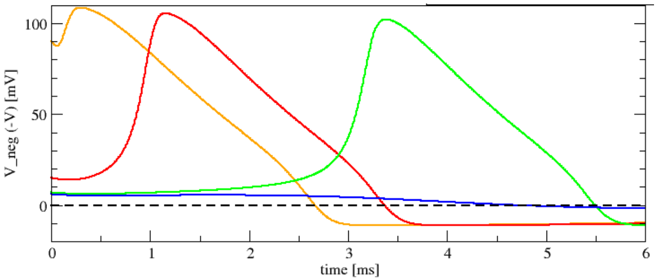

**1917**

# Why using mathematical models?

| Describe | Explain |
| --- | --- |



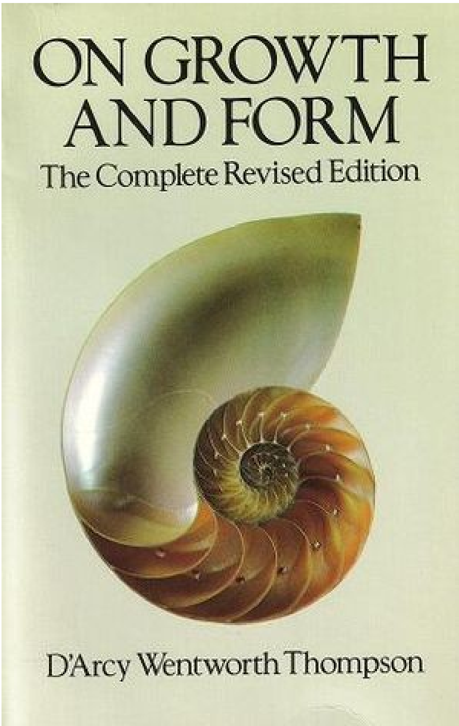



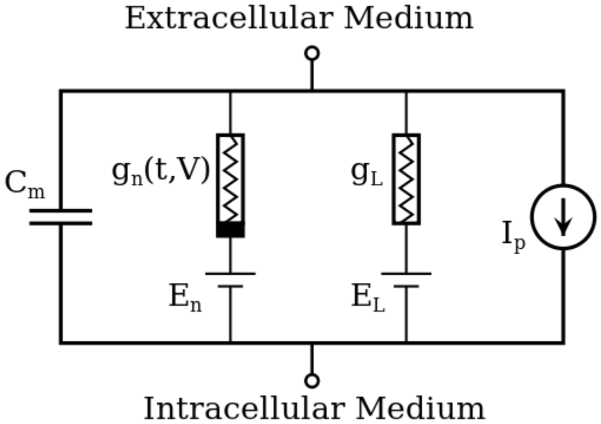

1917

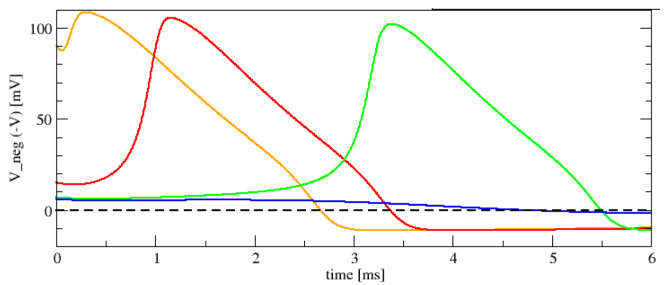
1952

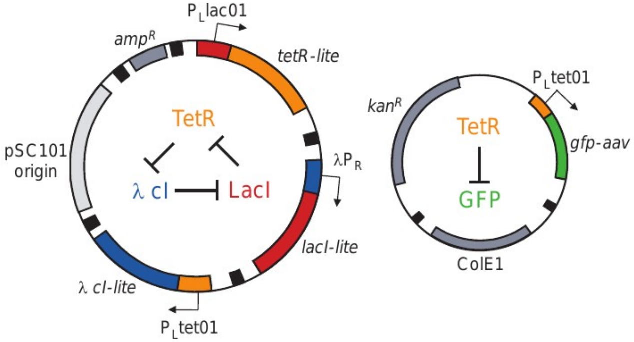
# Why using mathematical models?

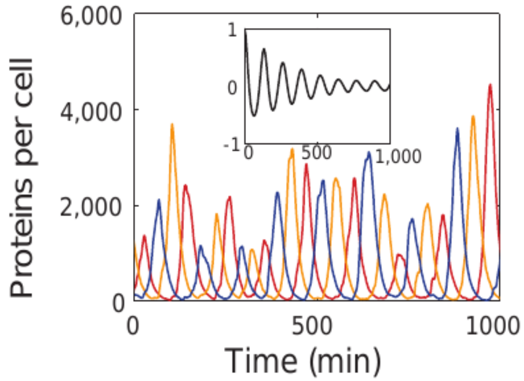
| Describe | Explain | Predict |
| --- | --- | --- |




1917

1952

2000

# What is a mathematical model?

Wikipedia (April 17th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

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Wikipedia (April 17th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

**variables**

[x]

Vmax

Kd

$EC_{50}$

length

$t_{1/2}$

# What is a mathematical model?

Wikipedia (April 17th 2013): "A mathematical model is a description of a system using mathematical concepts and language."

| variables | relationships |
|---|---|
| [x] | $K_d = \frac{[A] \cdot [B]}{[AB]}$ |
| Vmax | $d[X]/dt = k \cdot [Y]^2$ |
| Kd | $\sum_i [X]_i - F(t) = 0$ |
| $EC_{50}$ | $k(t) \sim N(k, \sigma^2)$ |
| length | If $\text{mass}_t > \text{threshold}$ then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$ |
| $t_{1/2}$ | |

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$$k(t) \sim N(k, \sigma^2)$$

If $\mathrm{mass}_t > \mathrm{threshold}$
then $\mathrm{mass}_{t+\Delta t} = 0.5 \cdot \mathrm{mass}$

**constraints**

[x]>0

Energy conservation

Boundary conditions
(v < upper limit)

Objective functions
(maximise ATP)

Initial conditions

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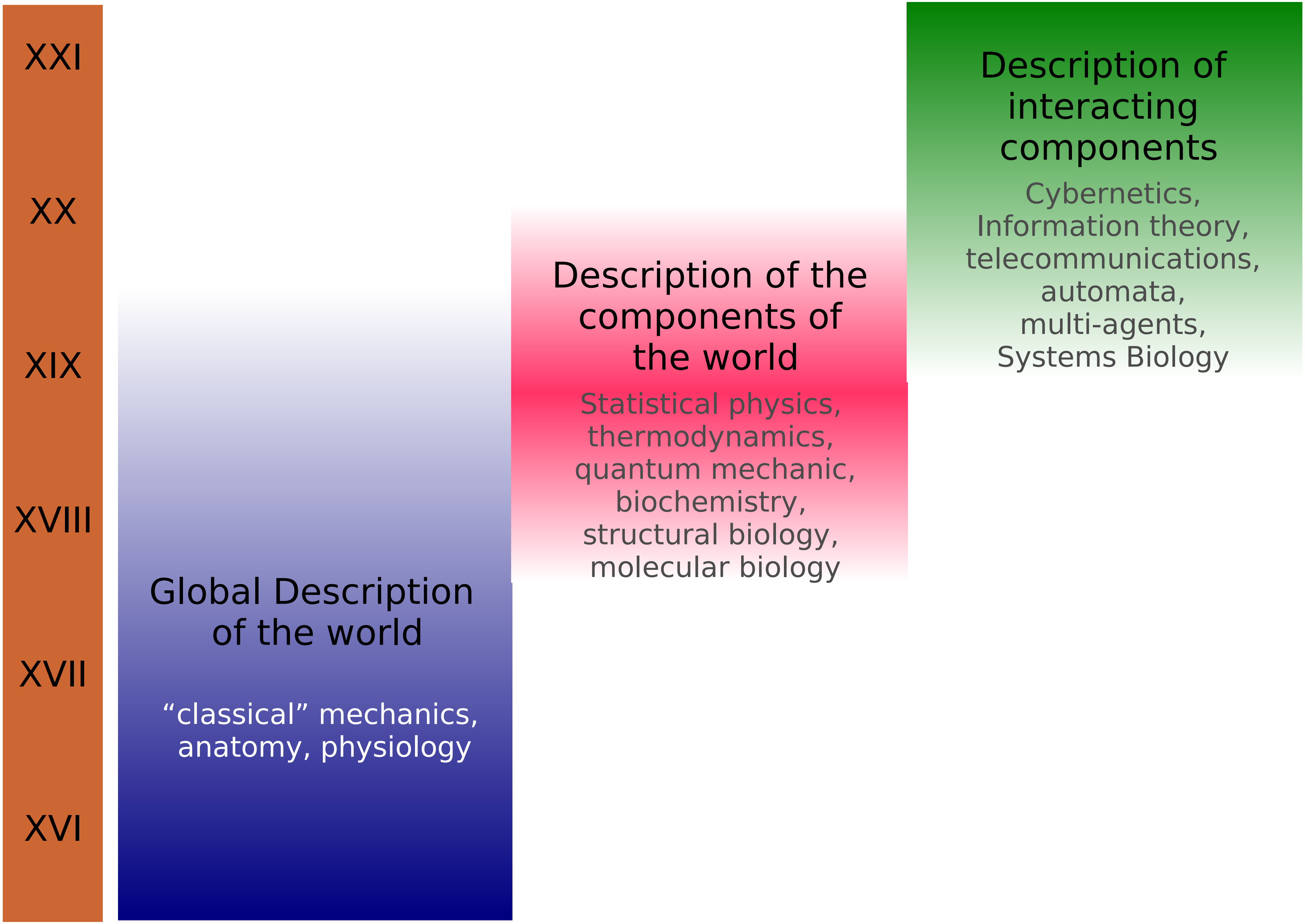
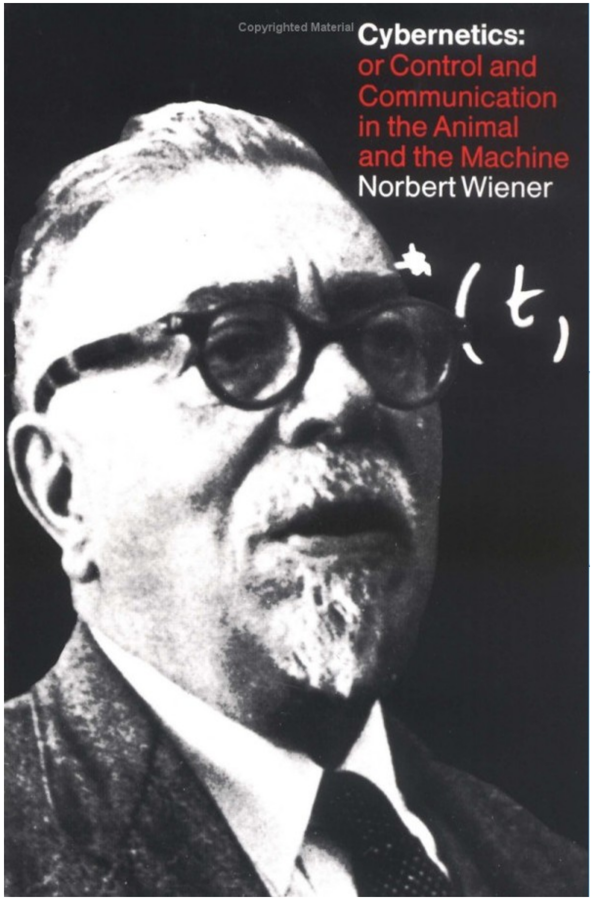
| length | If $\text{mass}_t > \text{threshold}$ then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$ | Initial conditions |
| $t_{1/2}$ | | |

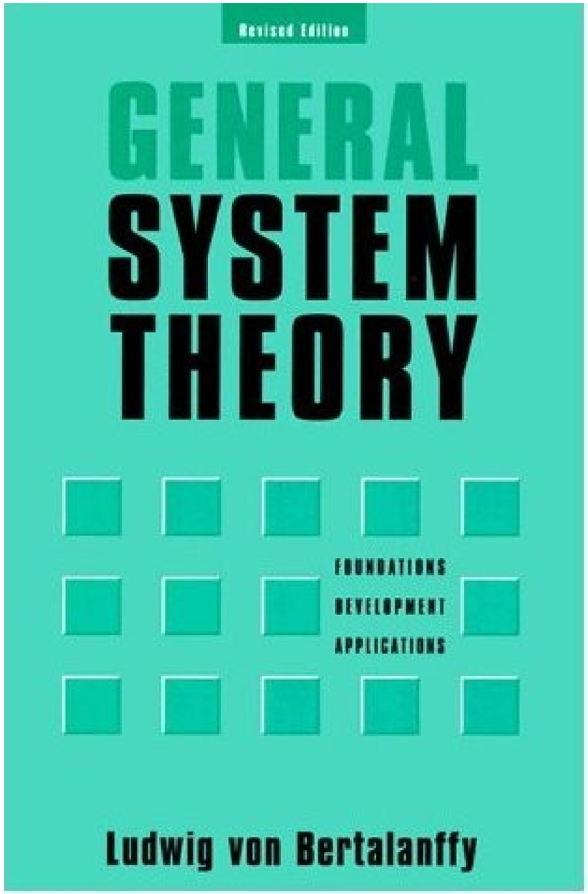
Different types: Dynamical models, logical models, rule-based models, multi-agent models, statistical models, etc.

# Emergence of the notion of system



# Systems are formalised mid-XXth



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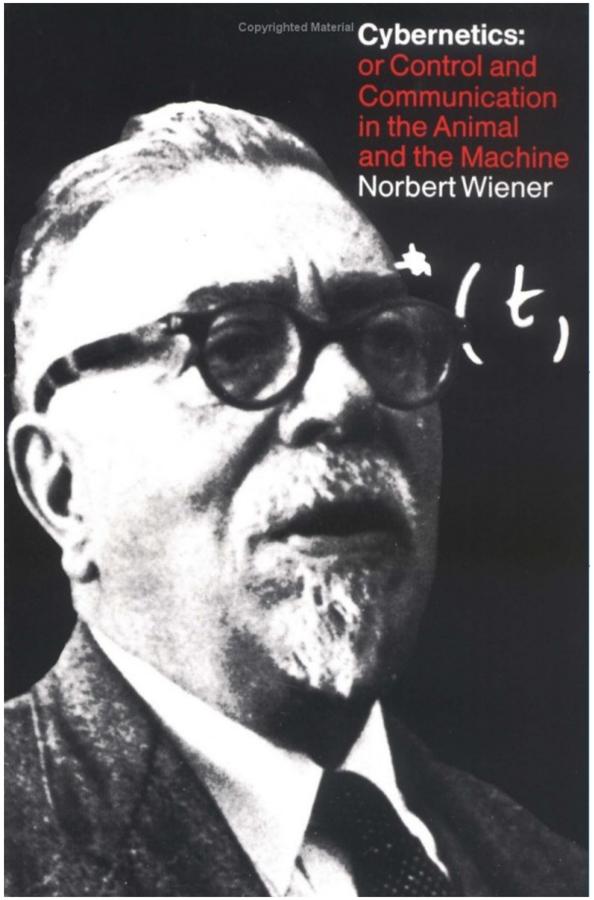
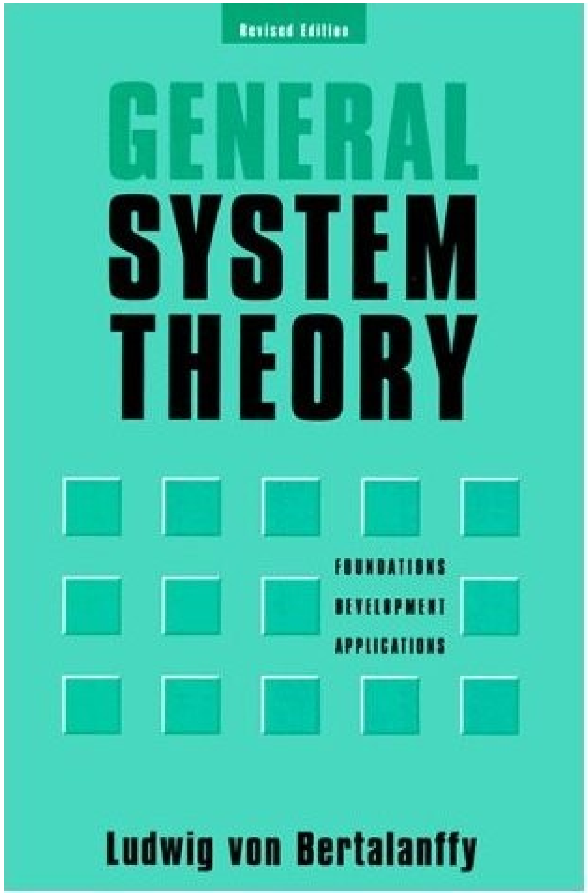
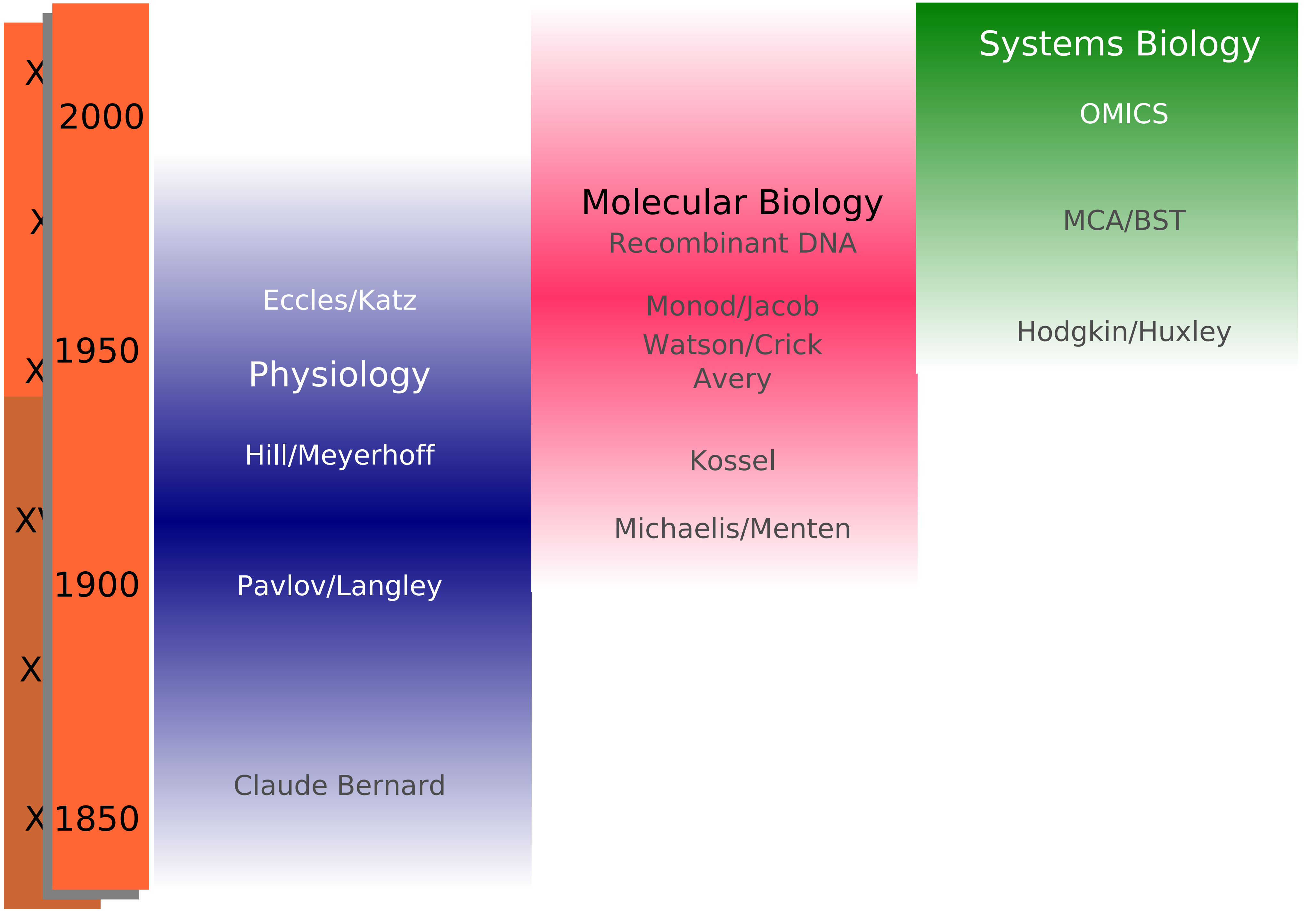


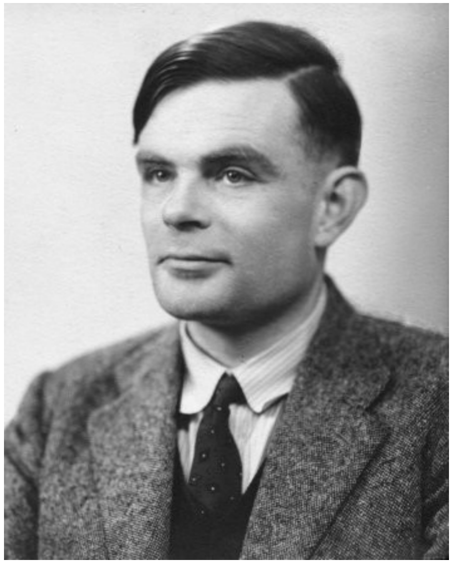




*“[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems*"
Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

# The three paradigms of Biology



# Computer simulations Vs. mathematical models





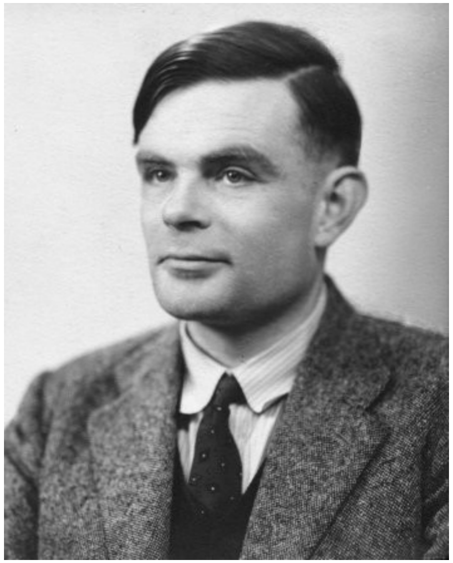
## THE CHEMICAL BASIS OF MORPHOGENESIS

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



[ 37 ]

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

# Birth of Computational Systems Biology

J. Physiol. (1952) 117, 500–544

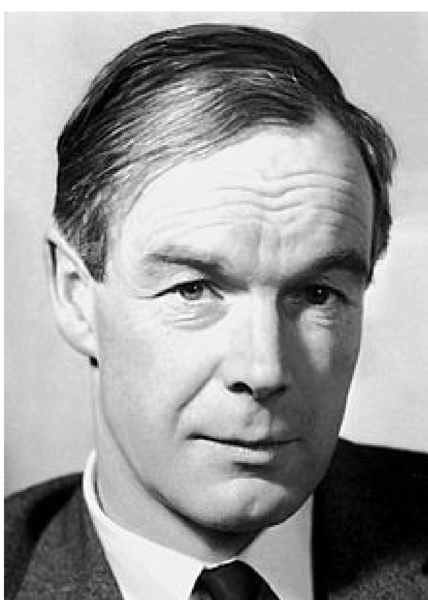
## A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

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

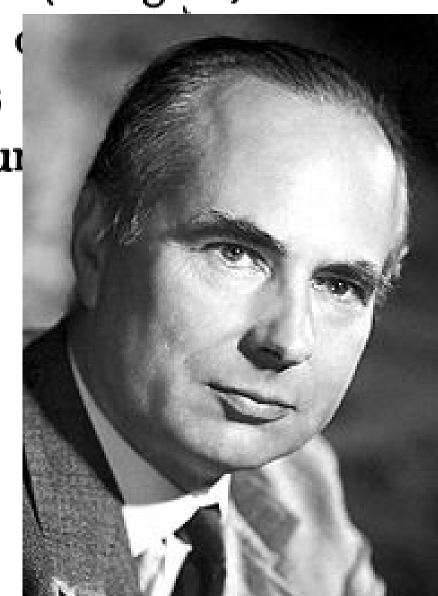
*From the Physiological Laboratory, University of Cambridge*

(*Received* 10 *March* 1952)

This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin,



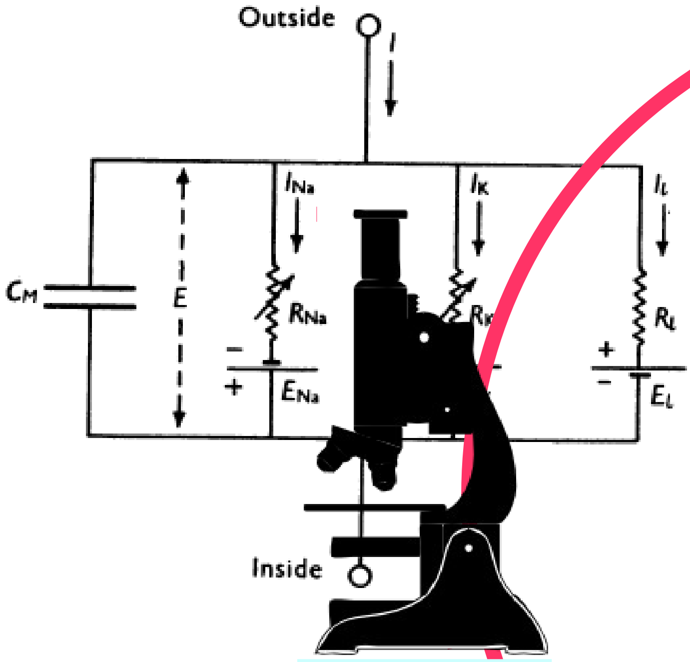
& Katz, 1952; Hodgkin & Huxley, 1952 *a–c*). Its general
the results of the preceding papers (Part I), to put
atical form (Part II) and to show that they will accou
and excitation in quantitative terms (Part III).



R.I.P. 30 May 2012
Cambridge

# The Computational Systems Biology loop

"biological" model




mathematical model

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

$$dn/dt = \alpha_n(1-n) - \beta_n n,$$

$$dm/dt = \alpha_m(1-m) - \beta_m m,$$

$$dh/dt = \alpha_h(1-h) - \beta_h h,$$

$$\alpha_n = 0{\cdot}01\,(V+10)\Big/\left(\exp\frac{V+10}{10} - 1\right),$$

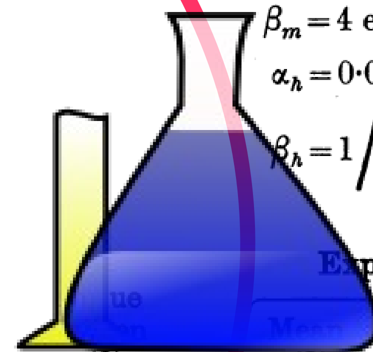
$$\beta_n = 0{\cdot}125\,\exp\,(V/80),$$

$$\alpha_m = 0{\cdot}1\,(V+25)\Big/\left(\exp\frac{V+25}{10} - 1\right),$$

$$\beta_m = 4\,\exp\,(V/18),$$

$$\alpha_h = 0{\cdot}07\,\exp\,(V/20),$$

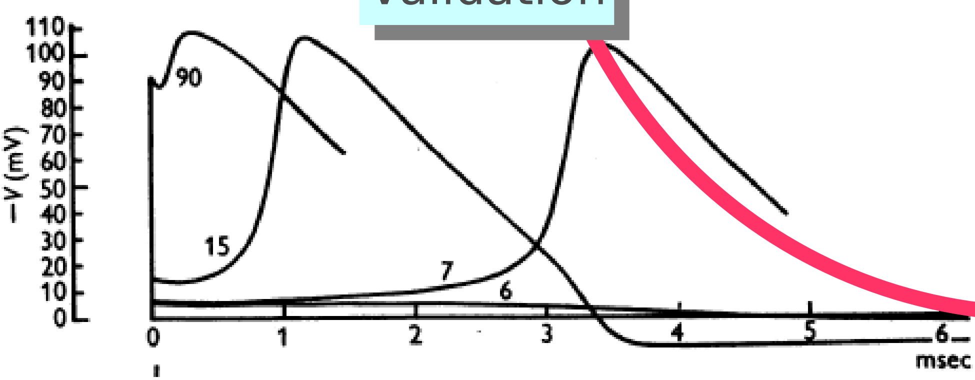
$$\beta_h = 1\Big/\left(\exp\frac{V+30}{10} + 1\right).$$



| Constant (1) | [illegible] (2) | Experimental values: Mean (3) | Experimental values: Range (4) |
|---|---|---|---|
| $C_M$ ($\mu$F/cm²) | [illegible] | [illegible] | 0·8 to 1·5 |
| $V_{Na}$ (mV) | [illegible] | [illegible] | −95 to −119 |
| $V_K$ (mV) | [illegible] | [illegible] | + 9 to + 14 |
| $V_l$ (mV) | −10·613 | − 11 | − 4 to − 22 |
| $\bar{g}_{Na}$ (m.mho/cm²) | 1?0 | 80<br>160 | 65 to 90<br>120 to 260 |
| $\bar{g}_K$ (m.mho/cm²) | 36 | 34 | 26 to 49 |
| $\bar{g}_l$ (m.mho/cm²) | 0·3 | 0·26 | 0·13 to 0·50 |

validation

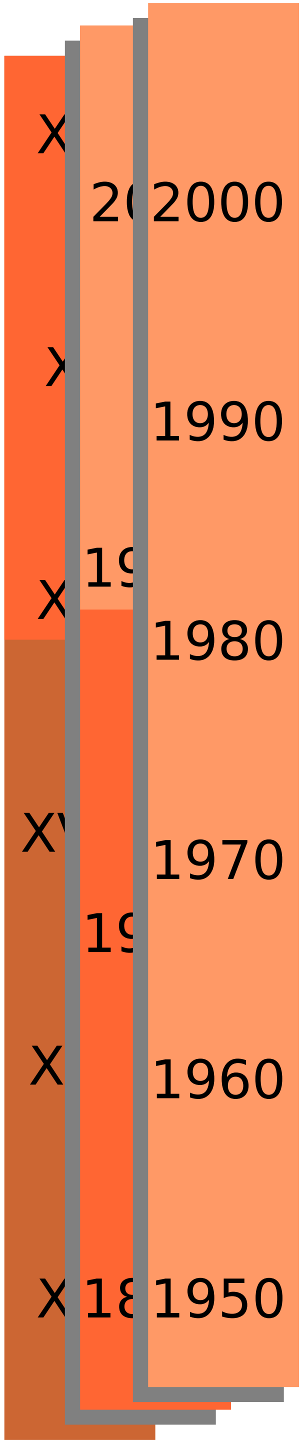
parameterisation




simulation

computational model

# Towards Systems Biology



# Towards Systems Biology

2000

Signalling pathways

Gene regulatory networks

1990

Cell cycle

Goldbeter/Koshland
Covalent cascades

1980

Metabolic networks

1970

Denis Noble
Heart pacemaker

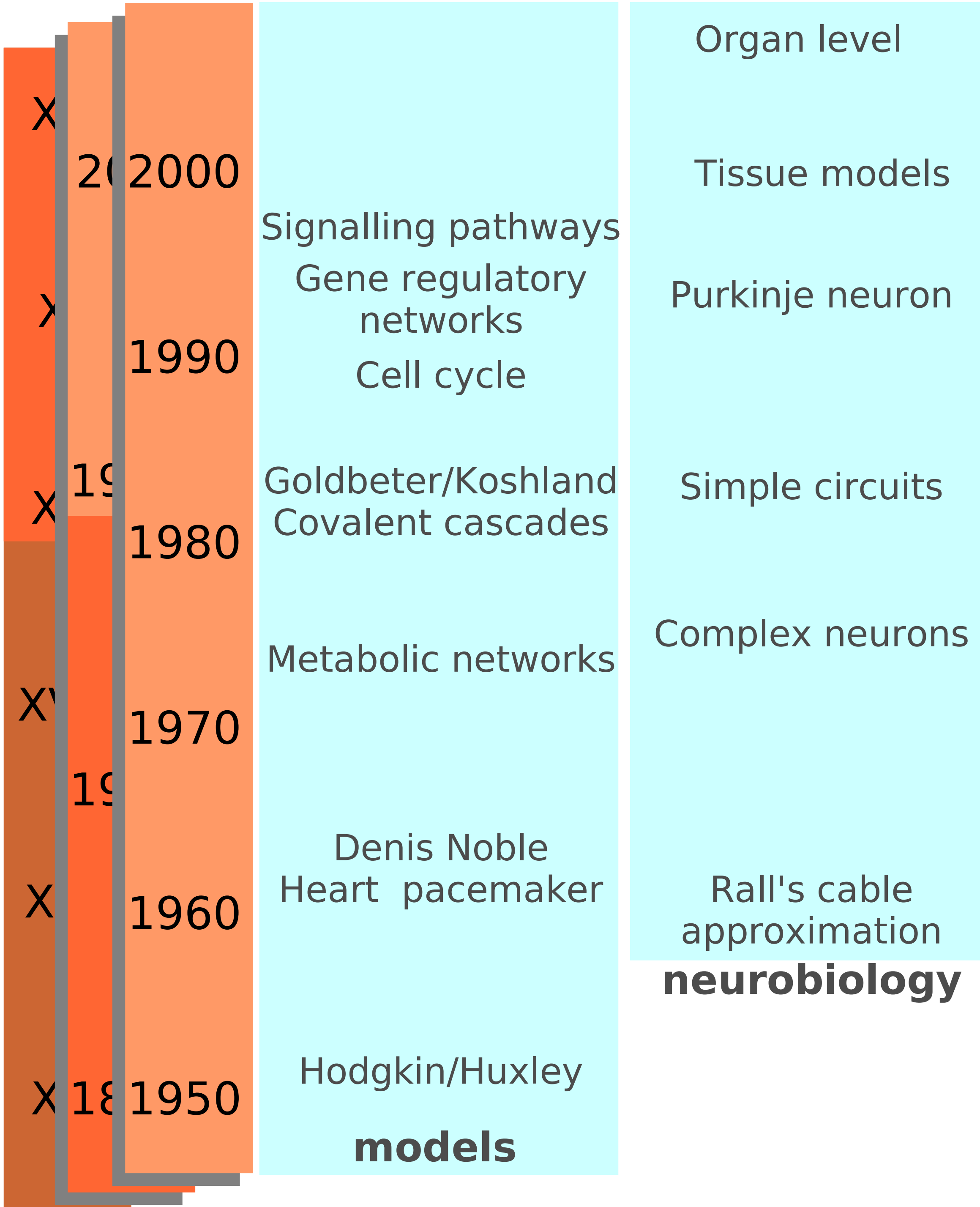
1960

Hodgkin/Huxley

1950

**models**

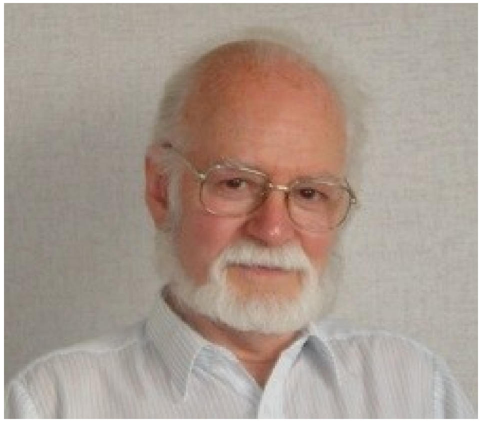
# Towards Systems Biology



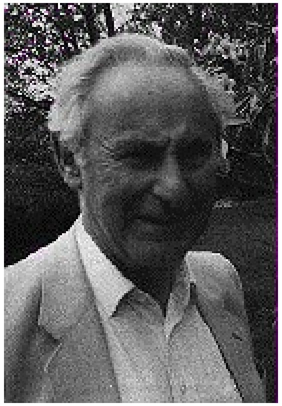
# 60s and 70s

- 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

2000
1990
1980
1970
1960
1950

**models**

- Signalling pathways
- Gene regulatory networks
- Cell cycle
- Goldbeter/Koshland Covalent cascades
- Metabolic networks
- Denis Noble Heart pacemaker
- Hodgkin/Huxley

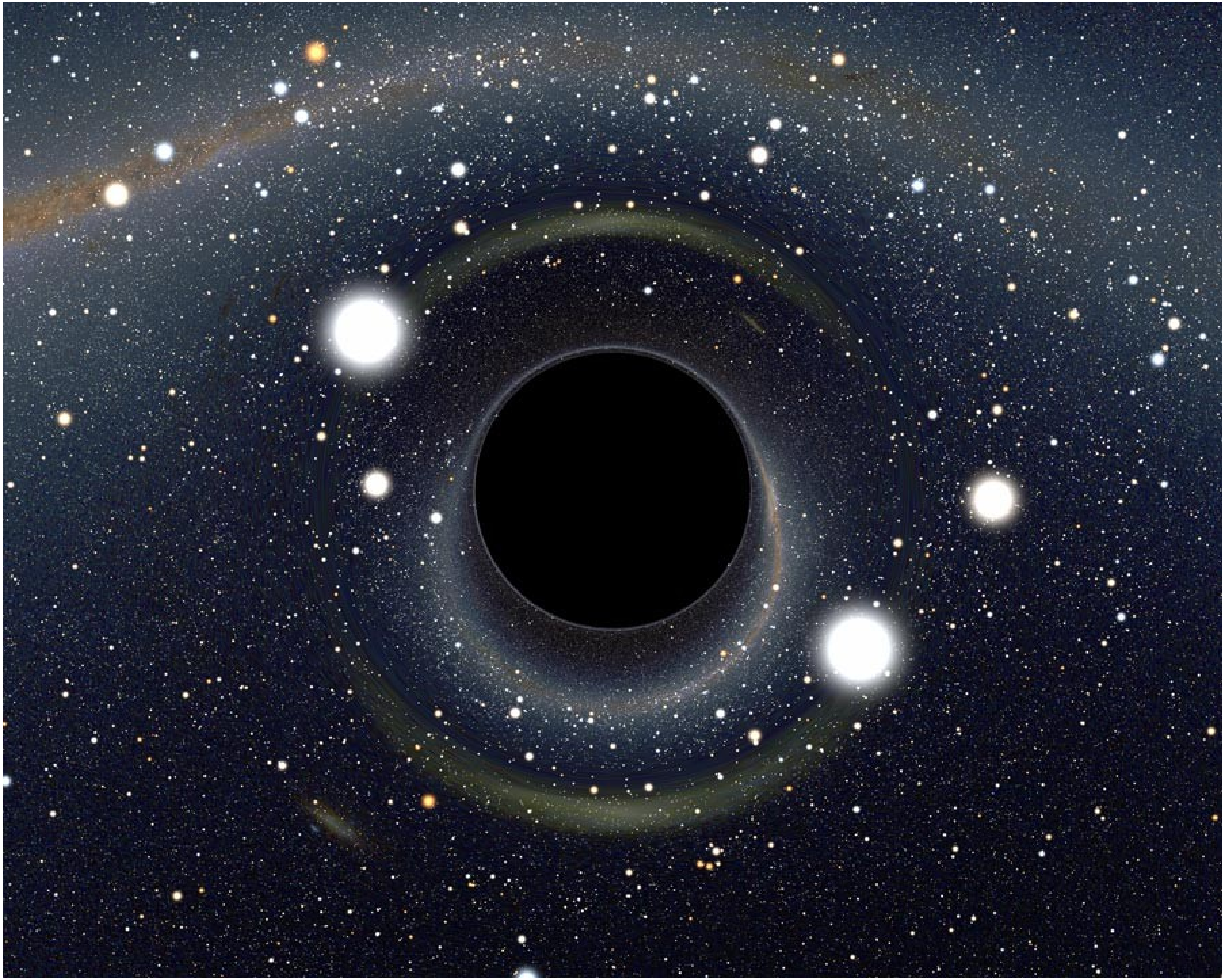
**neurobiology**

- Organ level
- Tissue models
- Purkinje neuron
- Simple circuits
- Complex neurons
- Rall's cable approximation

**methods**

- SBML
- User-friendly simulators
- Multi-agent systems
- Stochastic algorithms
- MCA/BST
- Boolean networks

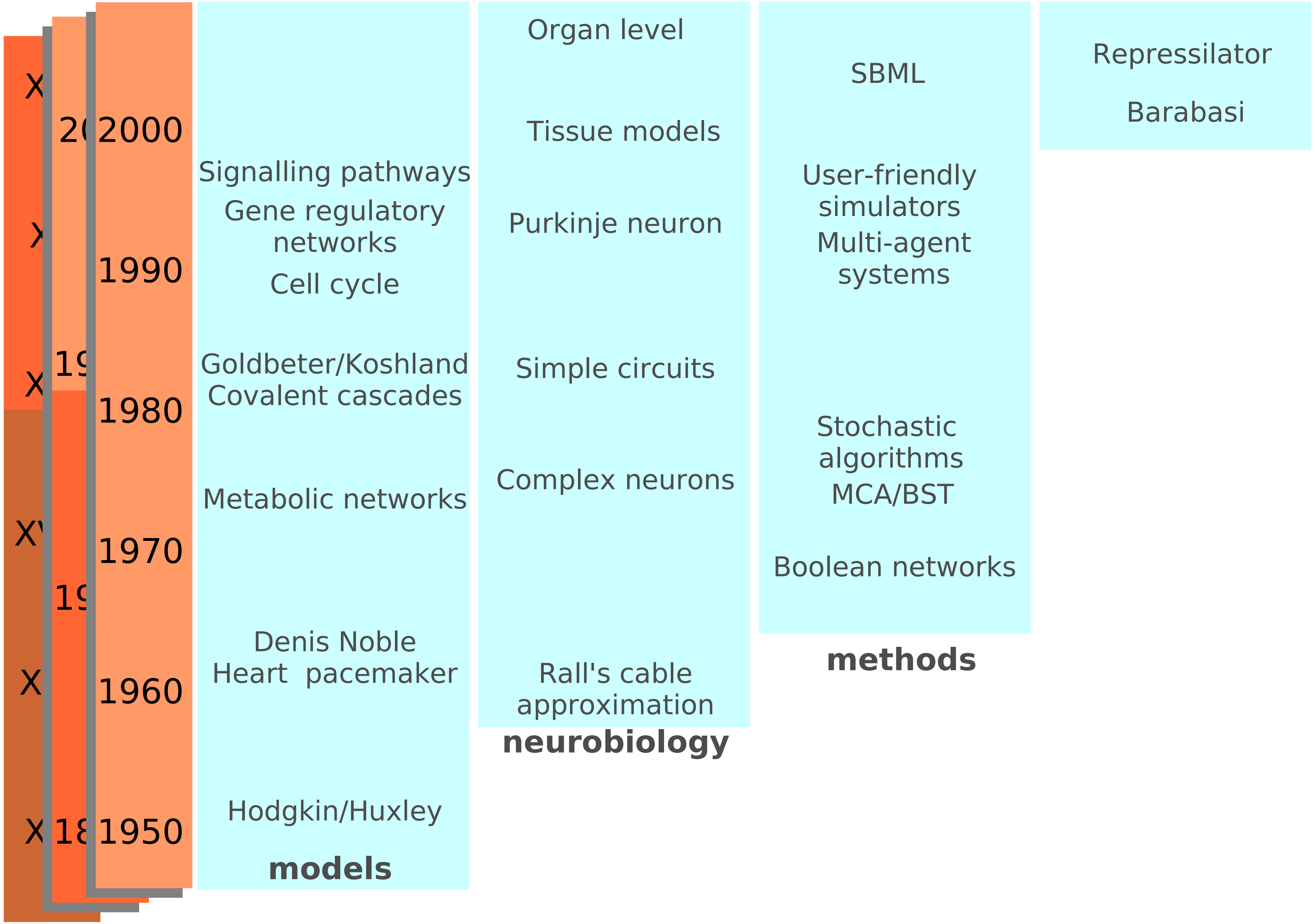
# 80s: The reign of Molecular Biology



# 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

2000
1990
1980
1970
1960
1950

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- Stochastic algorithms
- MCA/BST
- Boolean networks

Synthetic Biology

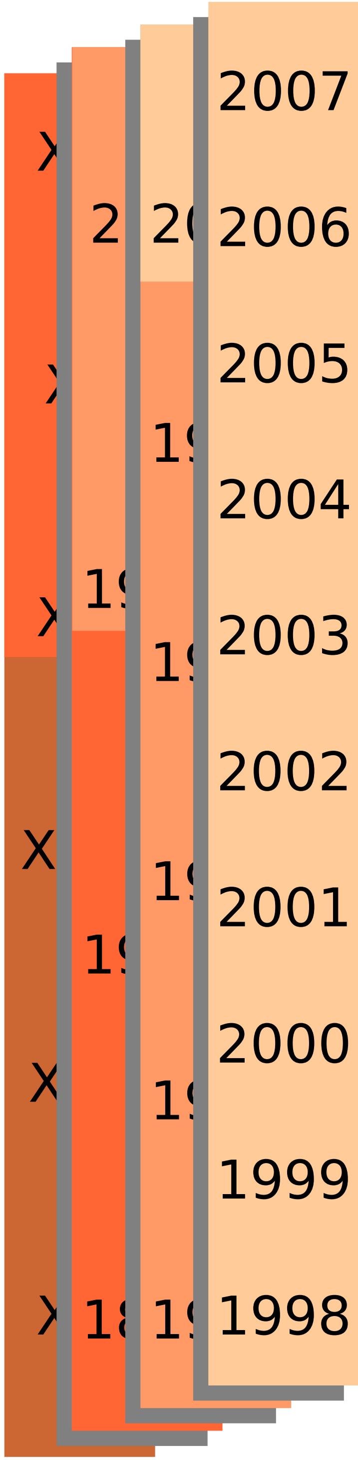
- Repressilator
- Barabasi

Network Biology

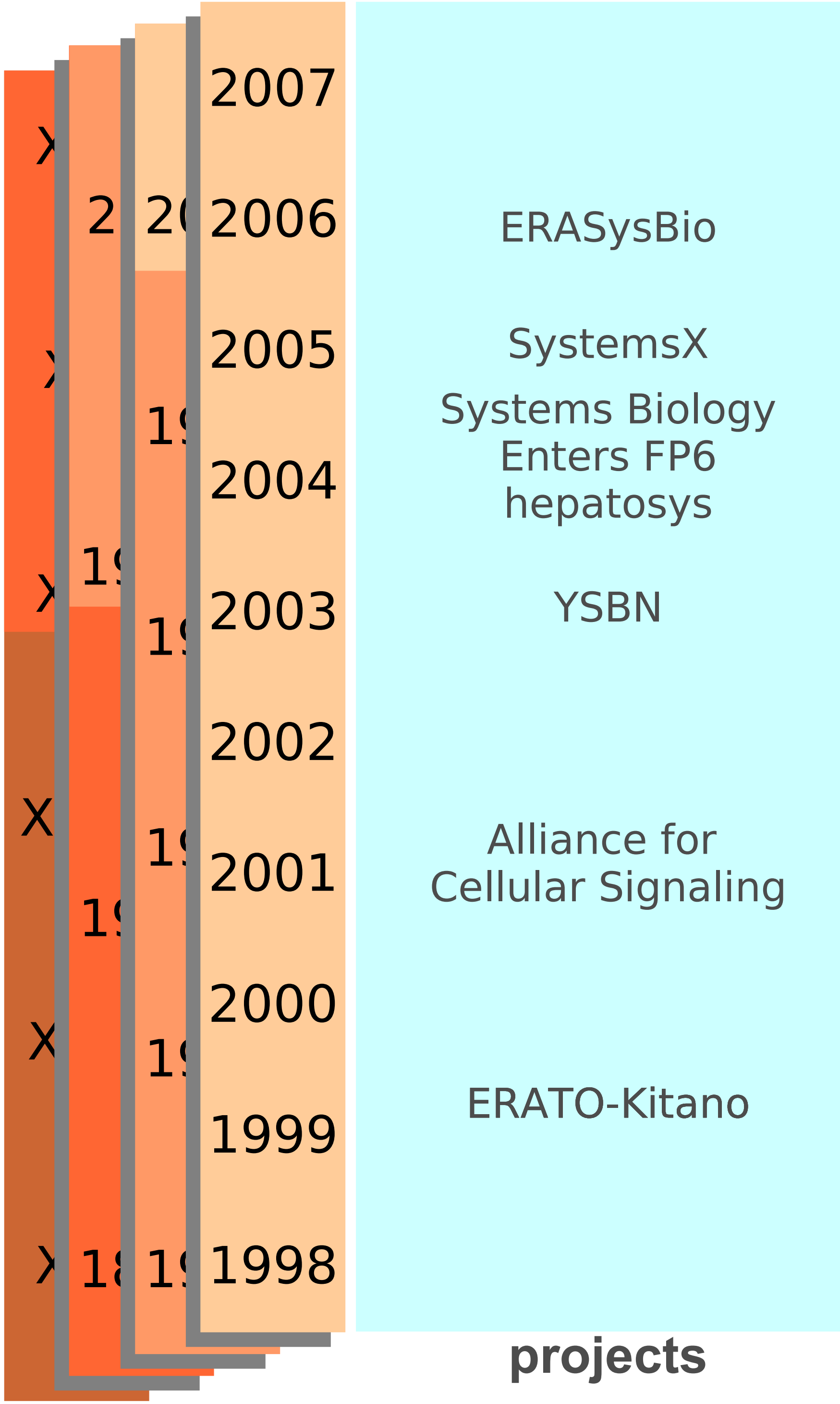
# Formal revival of Systems Biology

- “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

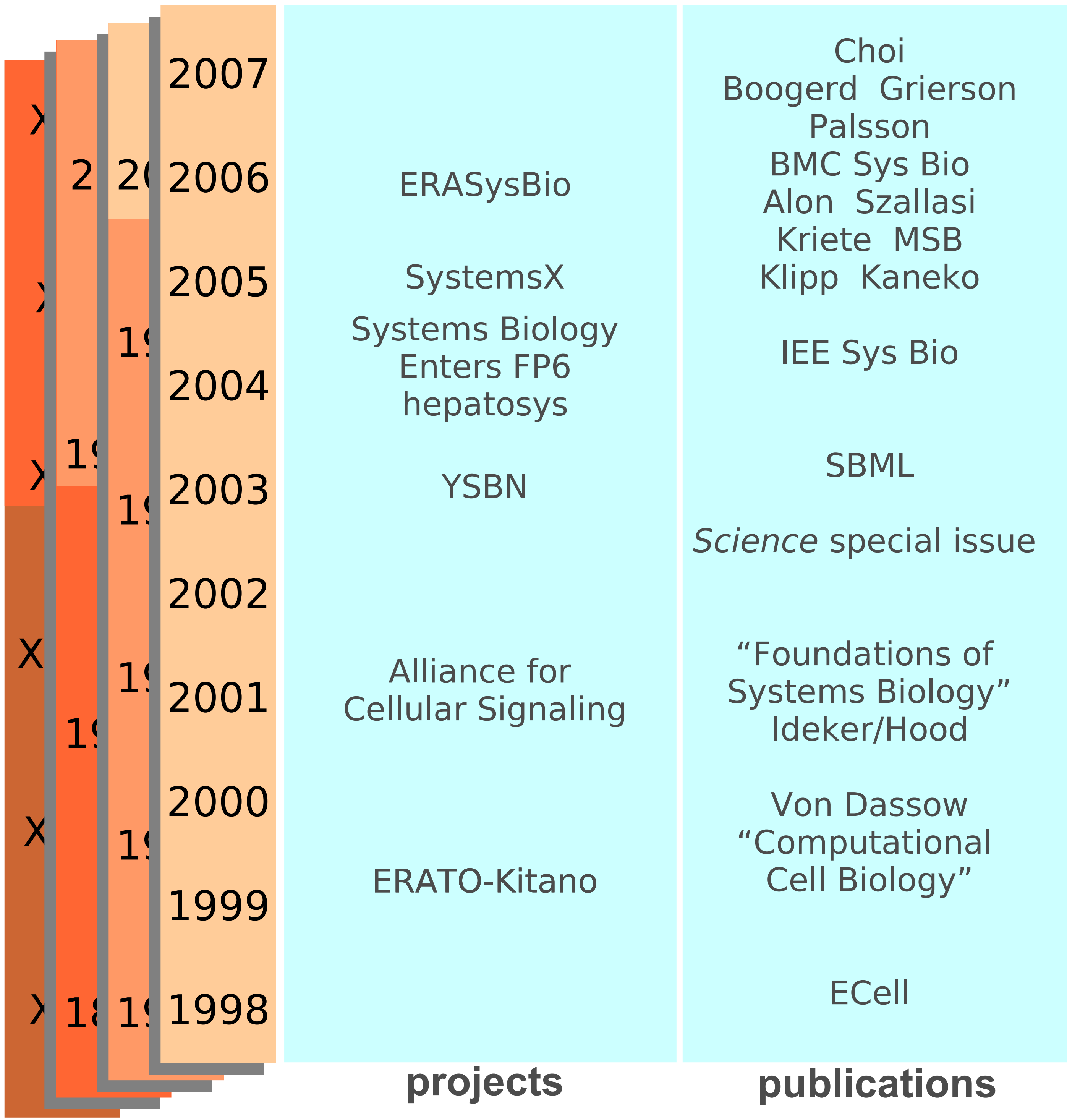
# Rise of Systems Biology as a paradigm



# Rise of Systems Biology as a paradigm



# Rise of Systems Biology as a paradigm



# Rise of Systems Biology as a paradigm

2007
2006
2005
2004
2003
2002
2001
2000
1999
1998

**projects**

ERASysBio

SystemsX

Systems Biology
Enters FP6
hepatosys

YSBN

Alliance for
Cellular Signaling

ERATO-Kitano

**publications**

Choi
Boogerd Grierson
Palsson
BMC Sys Bio
Alon Szallasi
Kriete MSB
Klipp Kaneko

IEE Sys Bio

SBML

*Science* special issue

“Foundations of
Systems Biology”
Ideker/Hood

Von Dassow
“Computational
Cell Biology”

ECell

**Institutes**

6 BBSRC centres

BioQuant

Tokyo Systems
Biology Institute

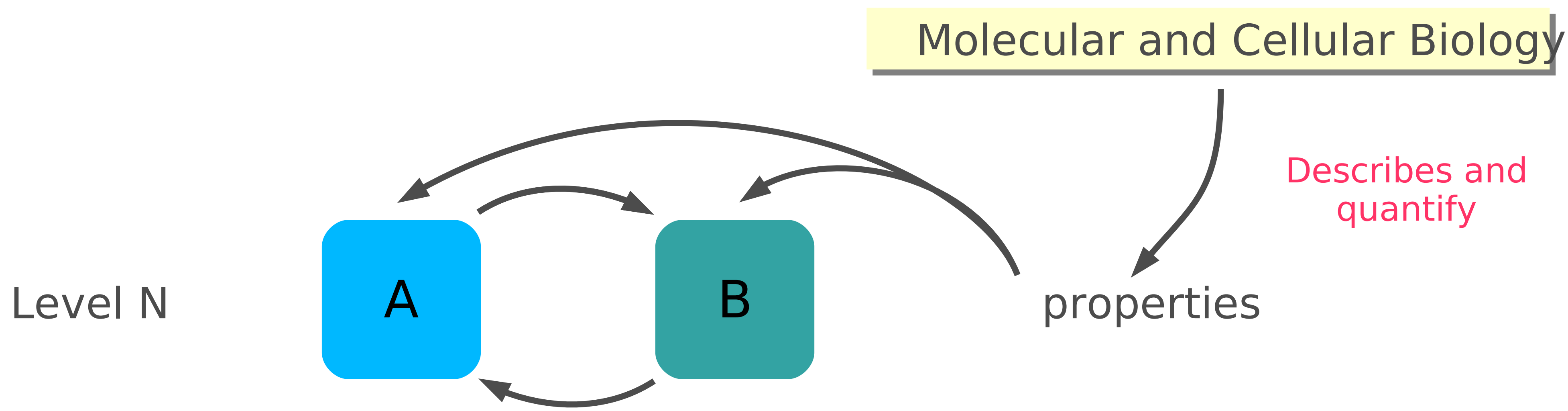
Seattle Institute
for Systems Biology

# Rise of Systems Biology as a paradigm

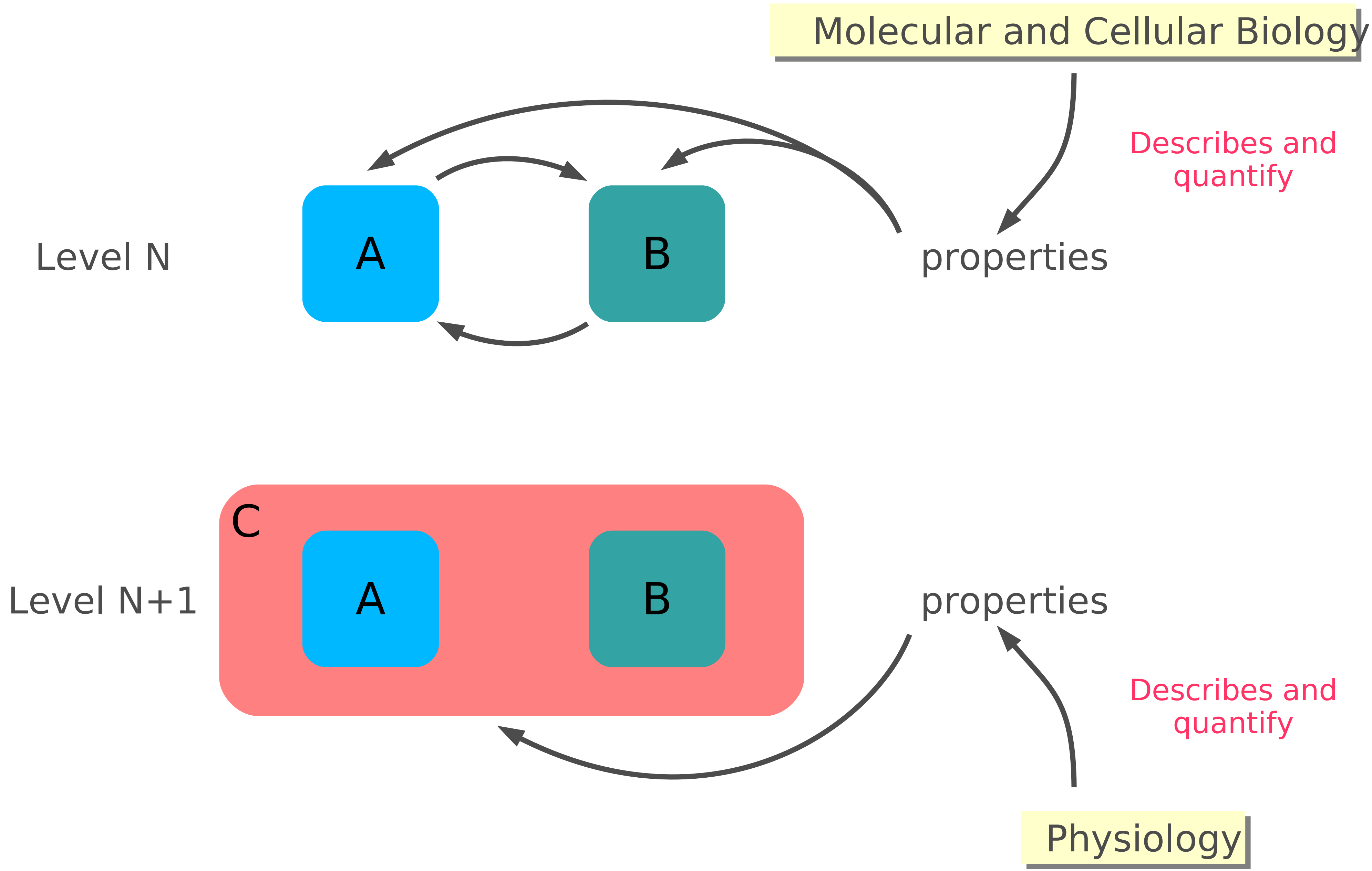
End of BBSRC Systems Biology calls

| | projects | publications | Institutes |
|---|---|---|---|
| 2007 | | Choi | |
| 2006 | ERASysBio | Palsson<br>BMC Sys Bio<br>Alon Szallasi<br>Kriete MSB | |
| 2005 | SystemsX | Klipp Kaneko | 6 BBSRC centres |
| 2004 | Systems Biology Enters FP6<br>hepatosys | IEE Sys Bio | BioQuant |
| 2003 | YSBN | SBML | |
| 2002 | | *Science* special issue | |
| 2001 | Alliance for Cellular Signaling | "Foundations of Systems Biology" Ideker/Hood | Tokyo Systems Biology Institute |
| 2000 | | Von Dassow<br>"Computational Cell Biology" | Seattle Institute for Systems Biology |
| 1999 | ERATO-Kitano | | |
| 1998 | | ECell | |

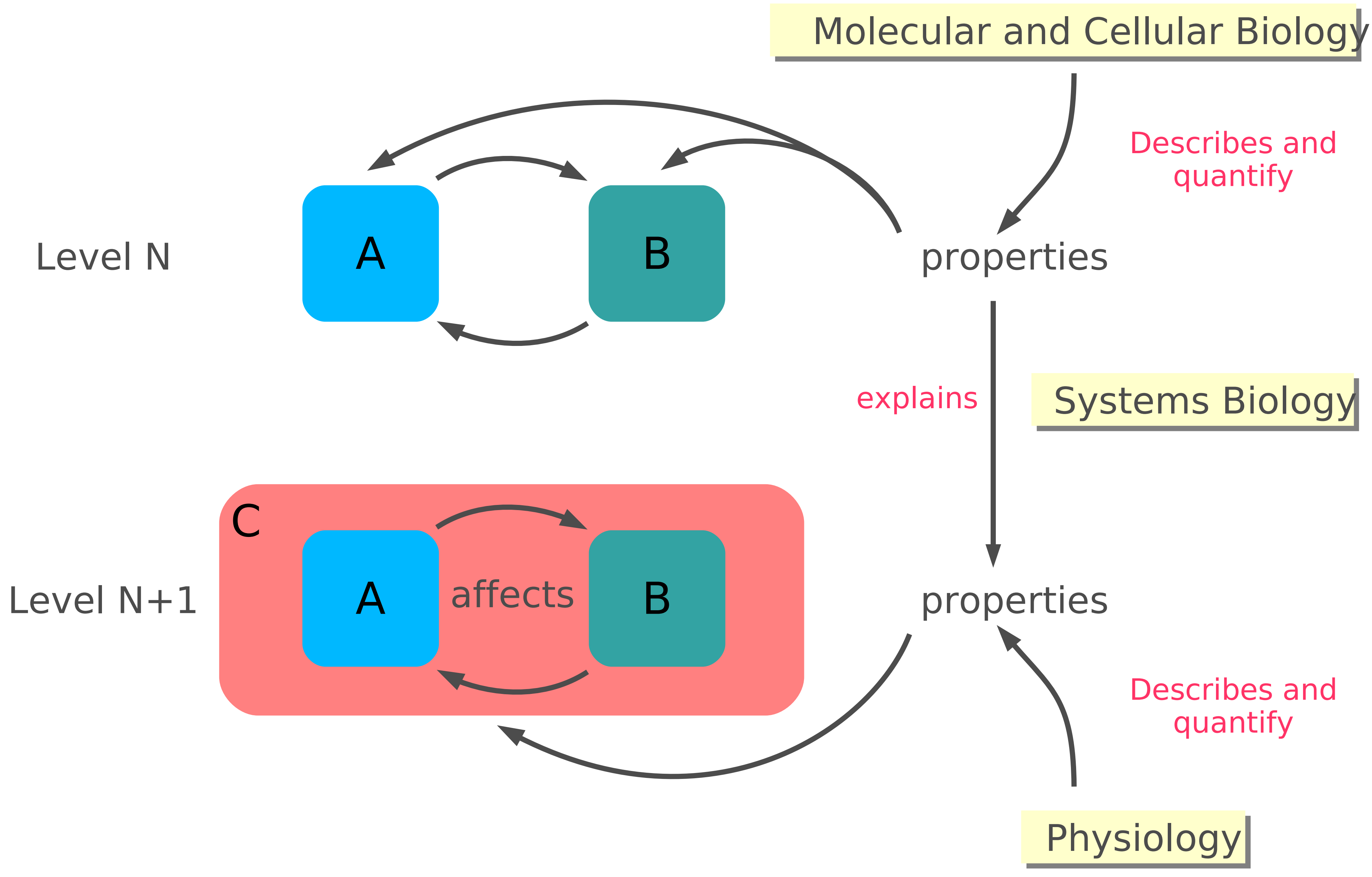
# But what is Systems Biology???



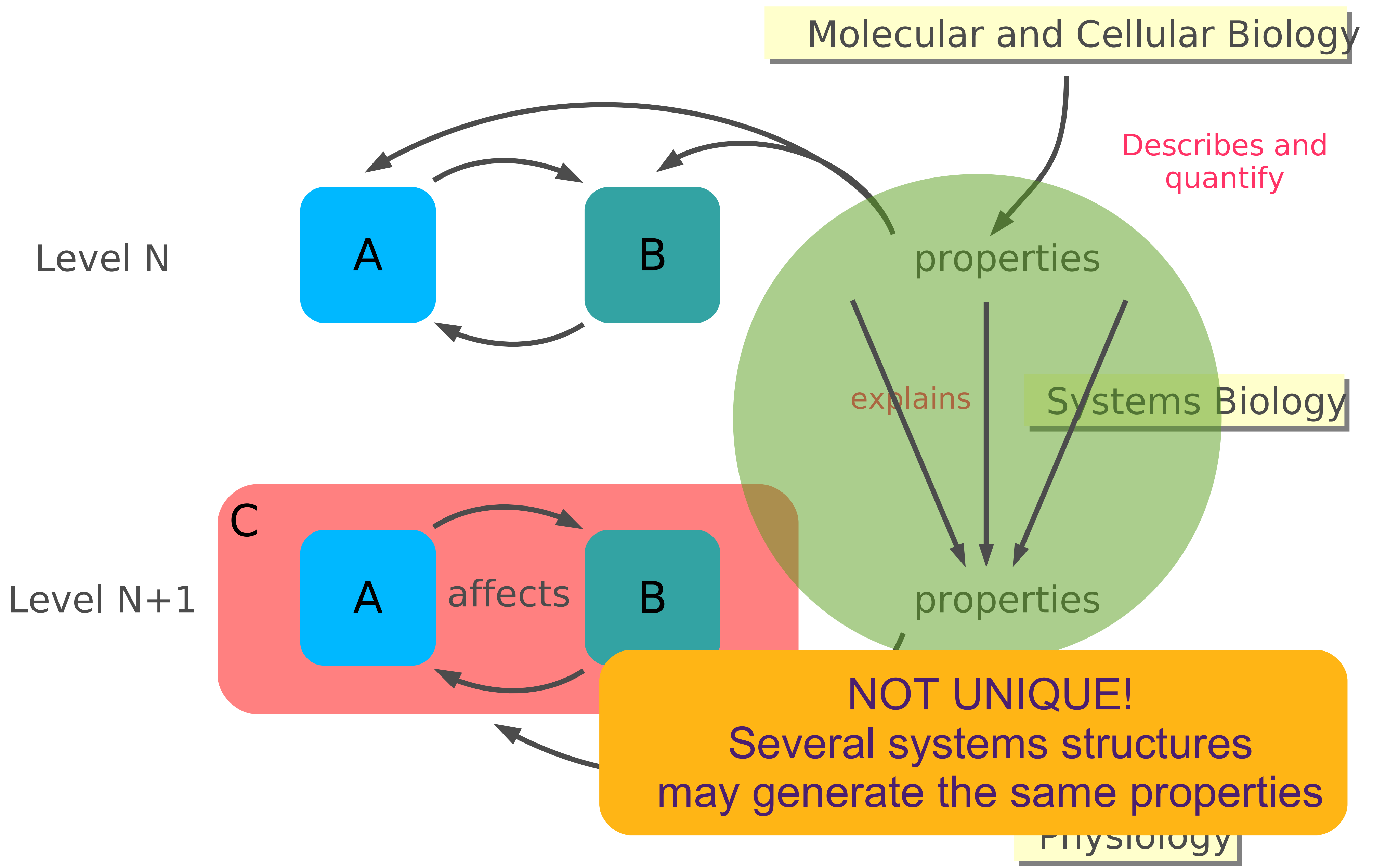
# But what is Systems Biology???



# But what is Systems Biology???



# But what is Systems Biology???



# What Systems Biology is not!

Purely theoretical: Most systems biologists are actually experimental biologists

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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***

# Two kinds of Systems Biology?

## 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

# Procedure does not depend on directionality

| | **Bottom-up** | **Top-down** |
|---|---|---|
| Build the system | literature | “pathway” database |
| Put numbers | biochemistry | “omics” |
| Parametrise | parameter search | hmm.... |
| Analyse | Simulation | structural analysis, steady-state analysis |
| perturb | Inhibition, stimulation, suppression, overexpression | |

# The challenges ahead

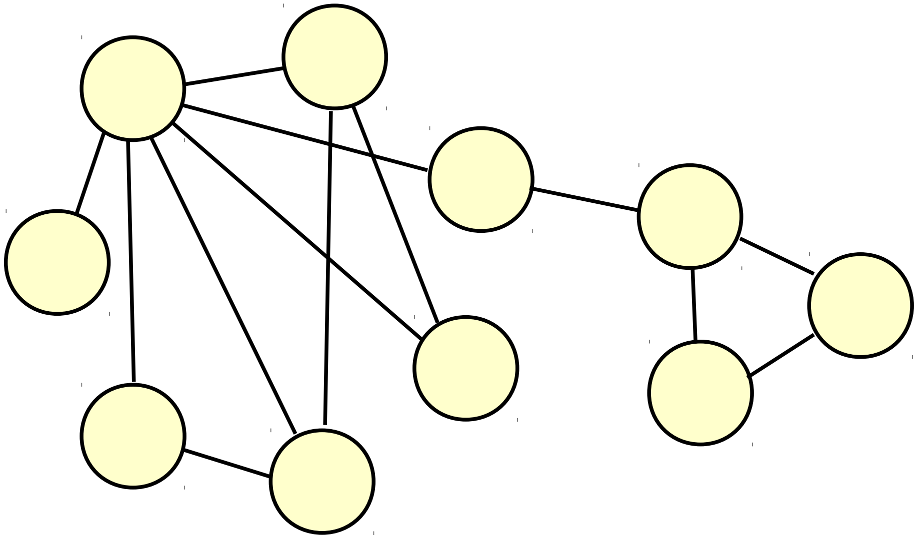
Types of representation

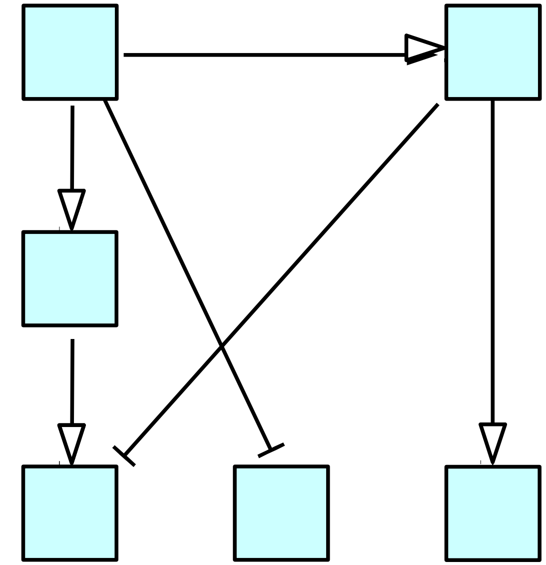
Scales and the mesoscopic gap

Genotype-system-phenotype problem

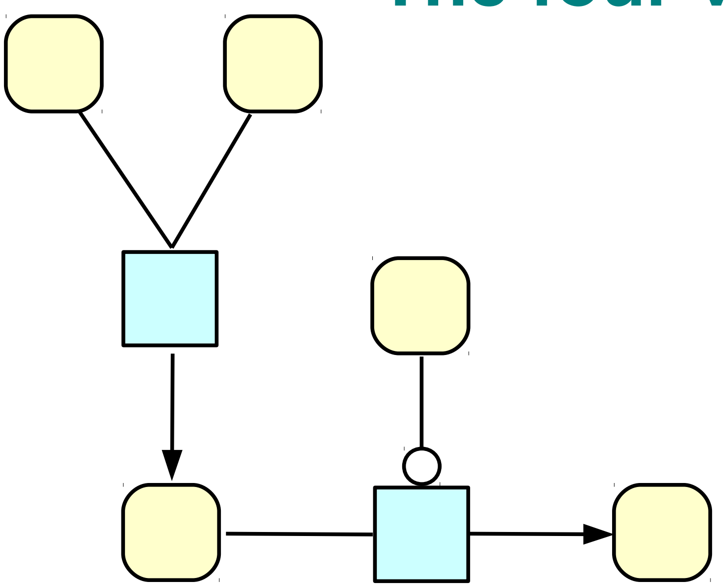
Drug discovery models
Vs systems modelling

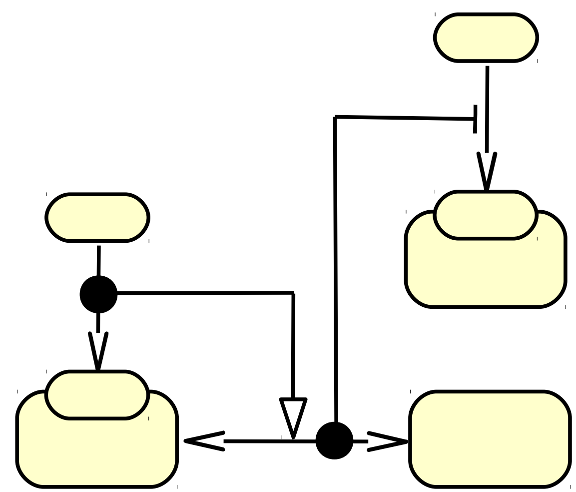
Drug discovery models
Vs “omics” data



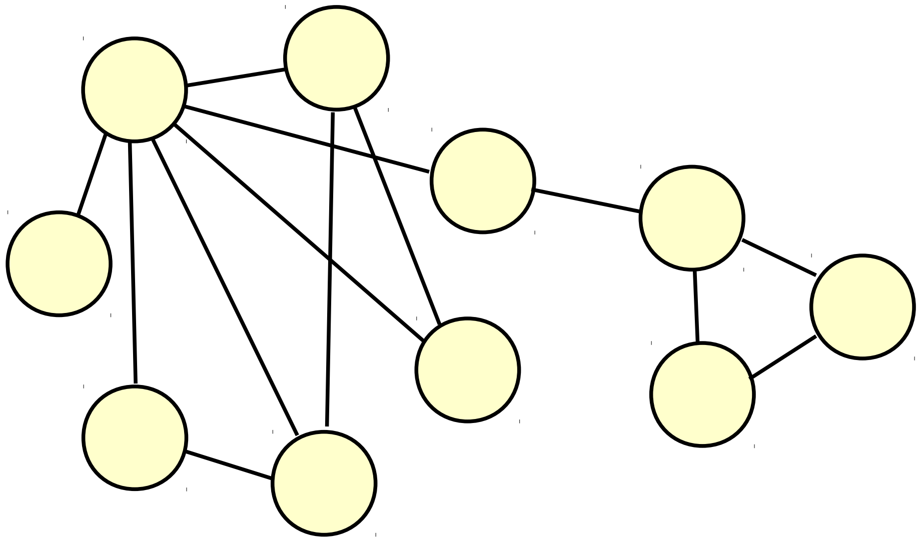


## The four views of systems biology



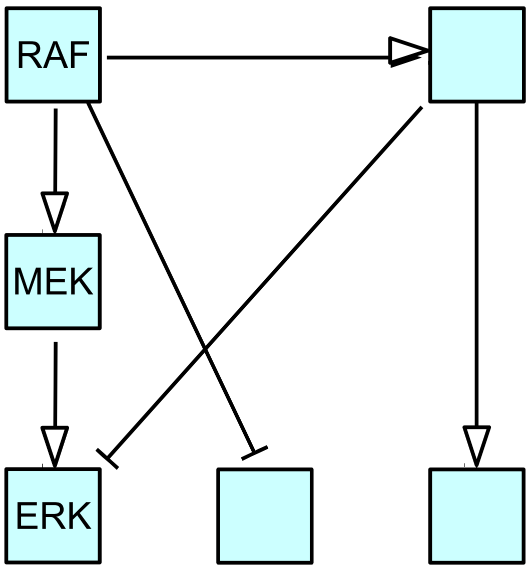


# Interaction networks



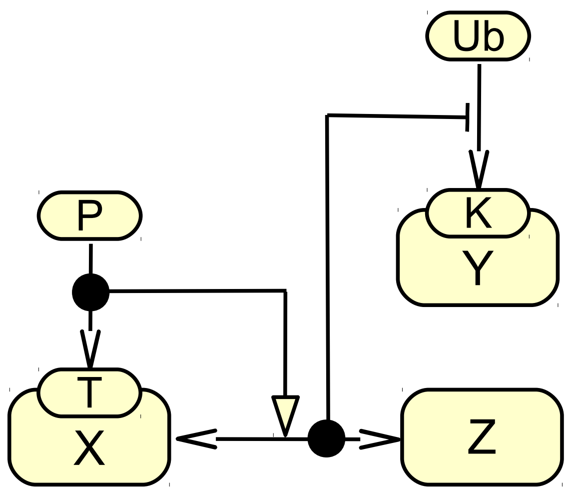
- Non-directional
- Non-sequential
- Non-mechanistic
- Statistical modelling
- Functional genomics
- IntAct, DIP, String

# Activity-Flows



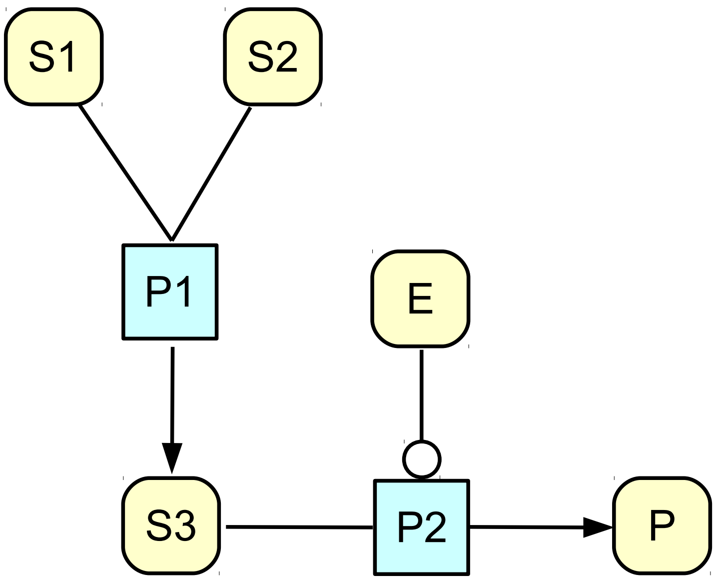

- Directional
- Sequential
- Non-mechanistic
- Logical modelling
- Signalling pathways, gene regulatory networks
- KEGG, STKEs

# Entity Relationships

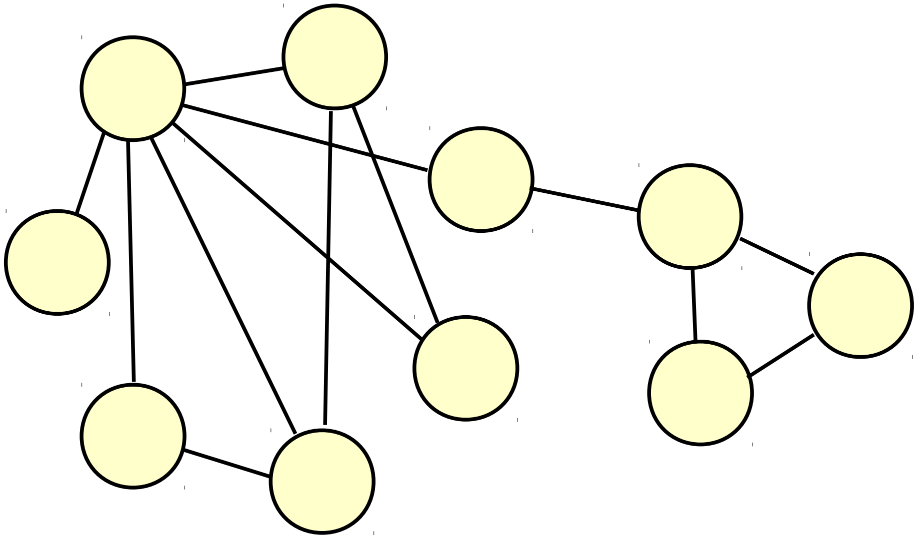


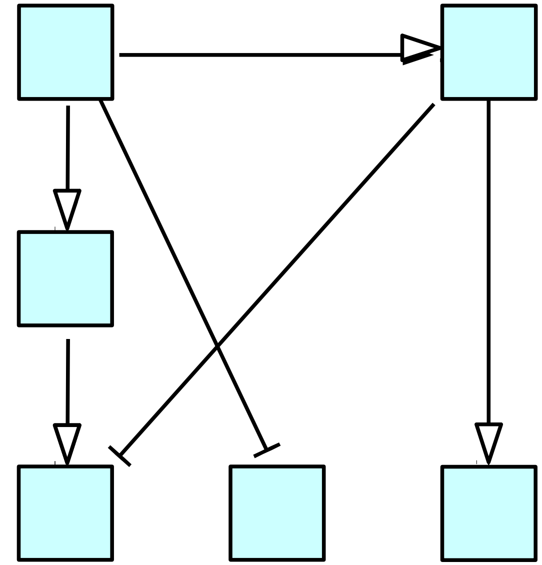

- Directional
- Non-sequential
- Mechanistic
- Independent rules: no explosion
- Rule-based modelling
- Molecular Biology
- MIM

# Process Descriptions

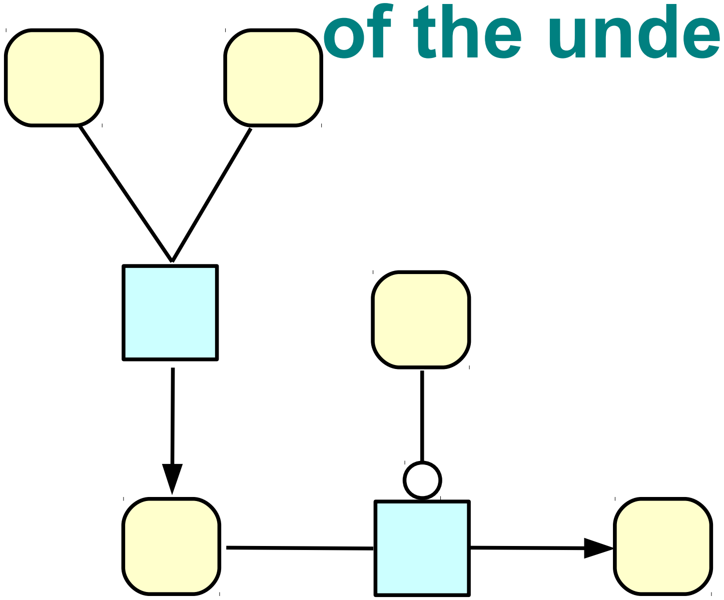


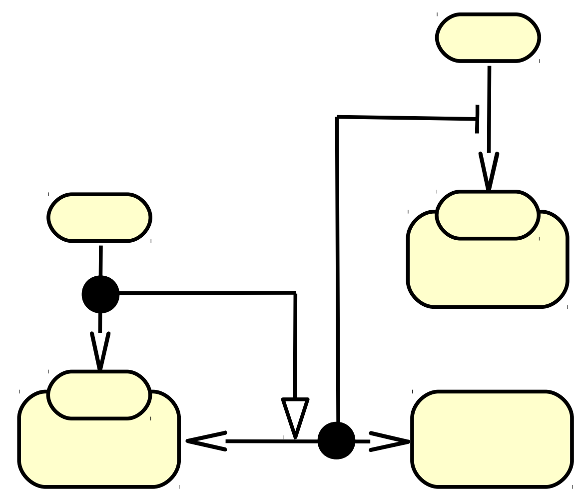

- Directional
- Sequential
- Mechanistic
- Subjected to combinatorial explosion
- Process modelling
- Biochemistry, Metabolic networks
- KEGG, Reactome

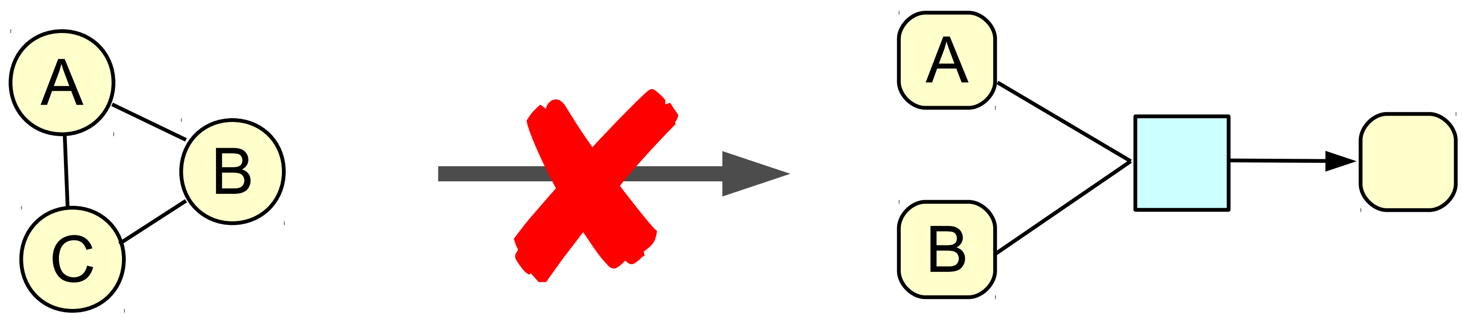




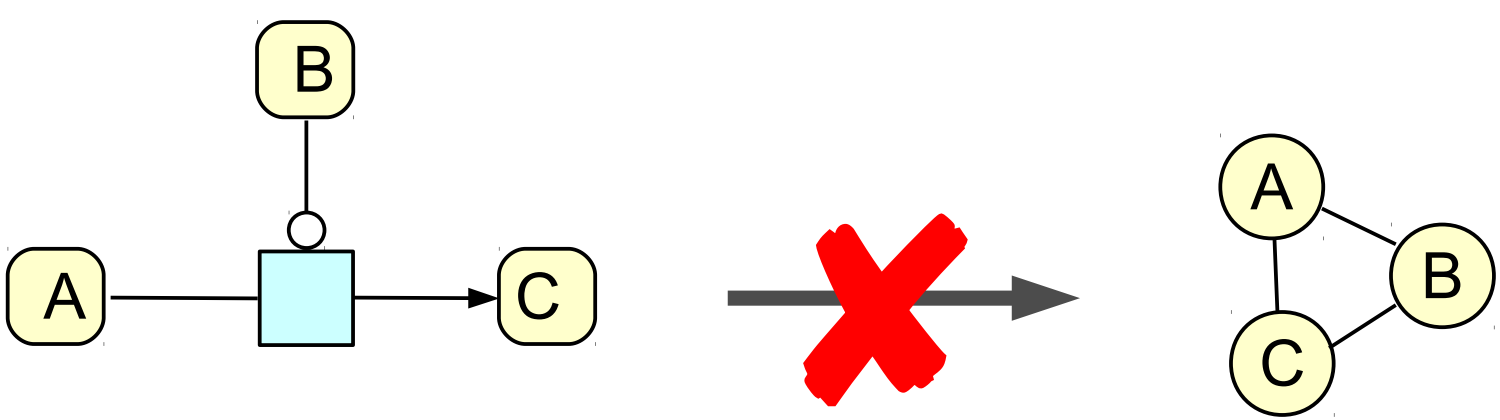
**The four views are <u>orthogonal</u> projections of the underlying biological phenomena**





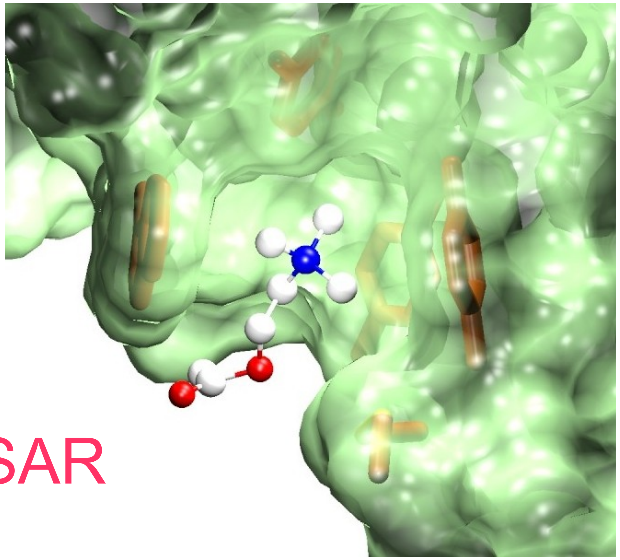



Think scaffolding proteins



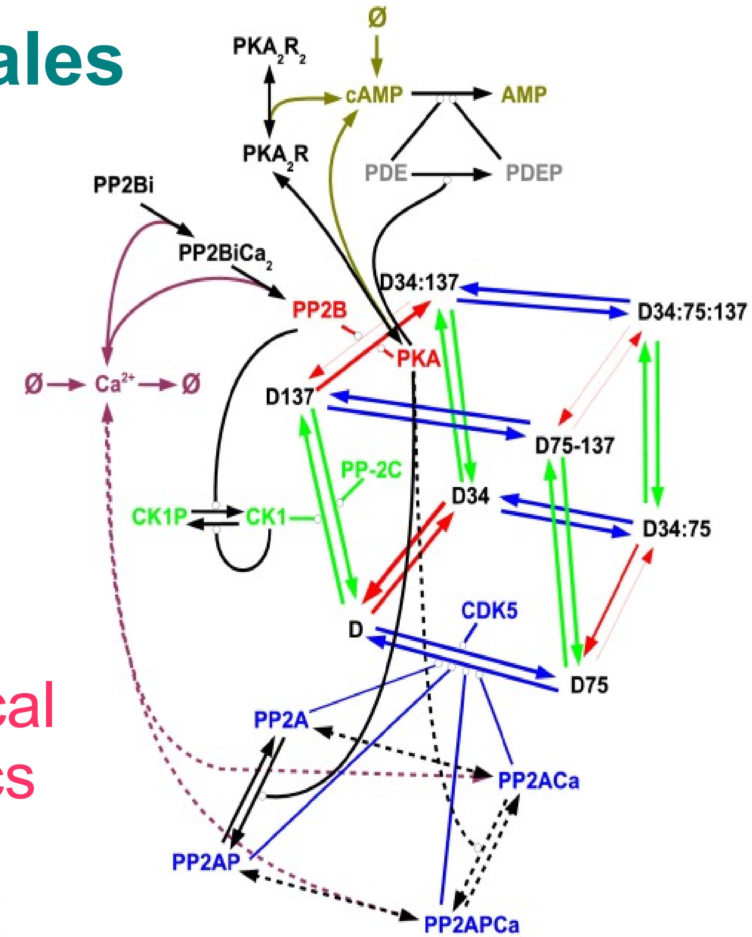

Think phosphorylated signals

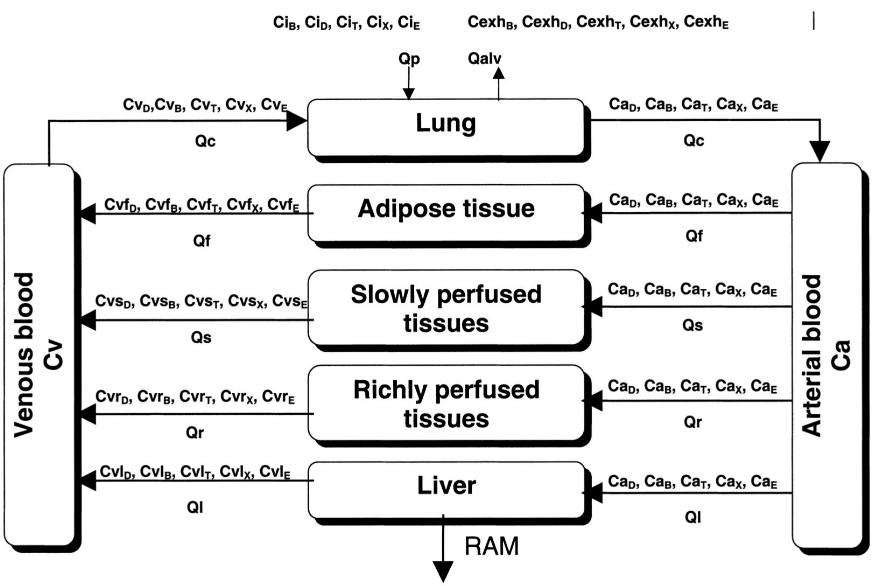
# The problem of scales



QSAR

chemical kinetics

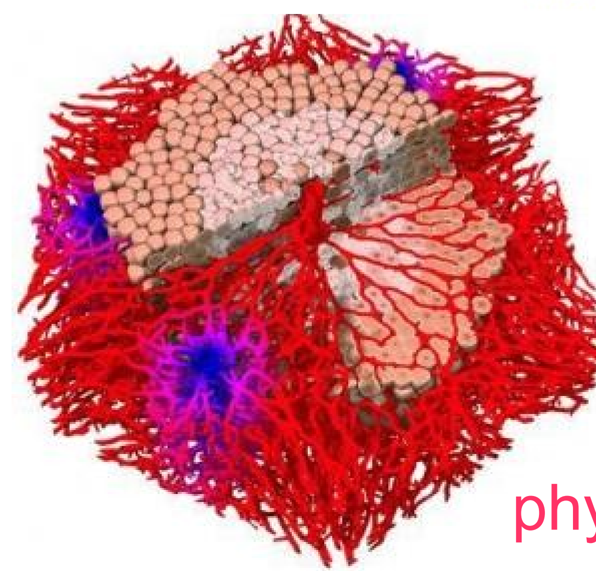



$$RAM_D = \frac{Vmax_D \;\; Cvl_D}{Km_D\left(1+\frac{Cvl_B}{Ki_{BD}}+\frac{Cvl_T}{Ki_{TD}}+\frac{Cvl_X}{Ki_{XD}}+\frac{Cvl_E}{Ki_{ED}}\right)+Cvl_D}$$

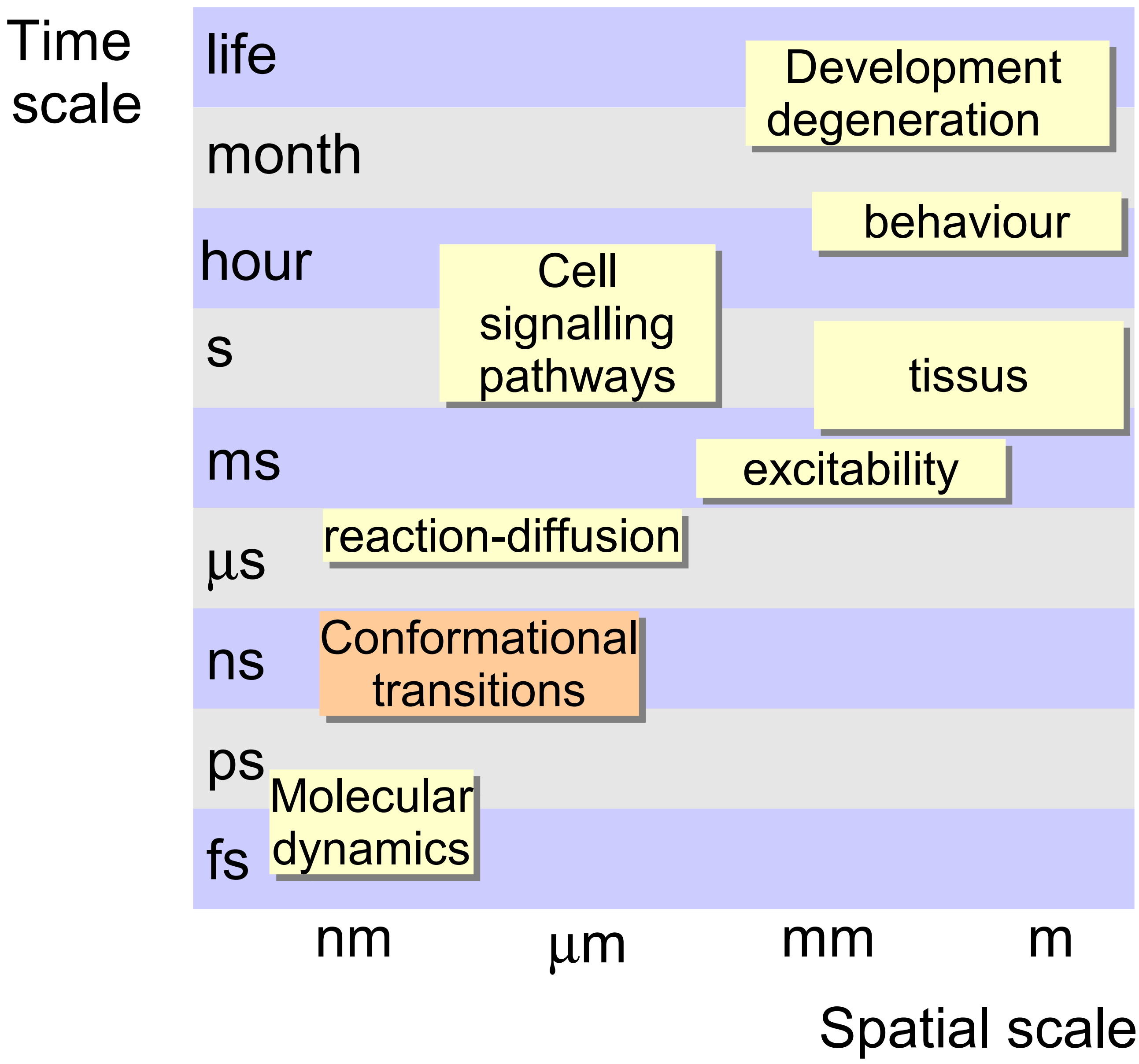
$$RAM_B = \frac{Vmax_B \;\; Cvl_B}{Km_B\left(1+\frac{Cvl_D}{Ki_{DB}}+\frac{Cvl_T}{Ki_{TB}}+\frac{Cvl_E}{Ki_{EB}}+\frac{Cvl_X}{Ki_{XB}}\right)+Cvl_B}$$

pharmacometrics



physiology

# The mesoscopic gap



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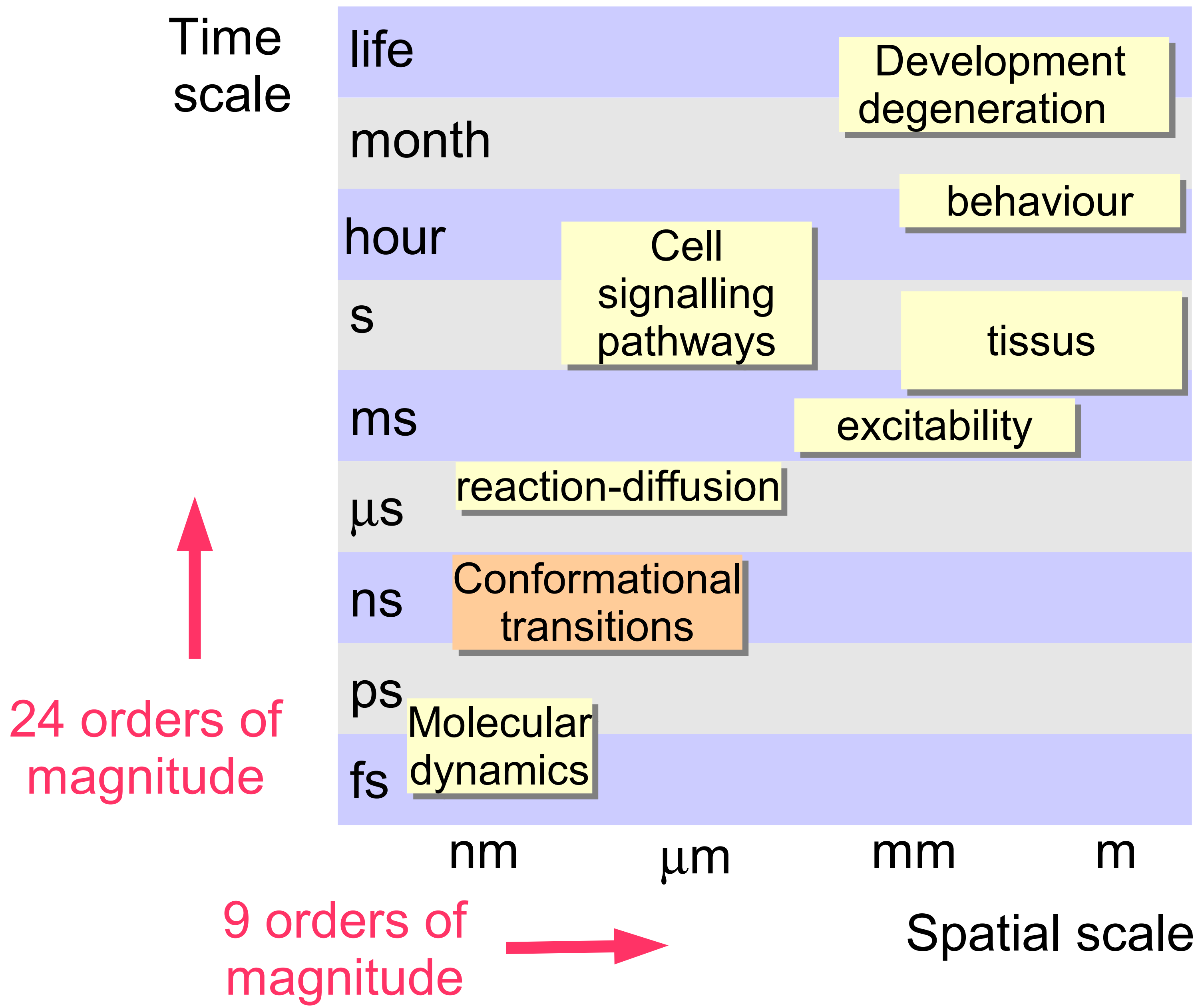

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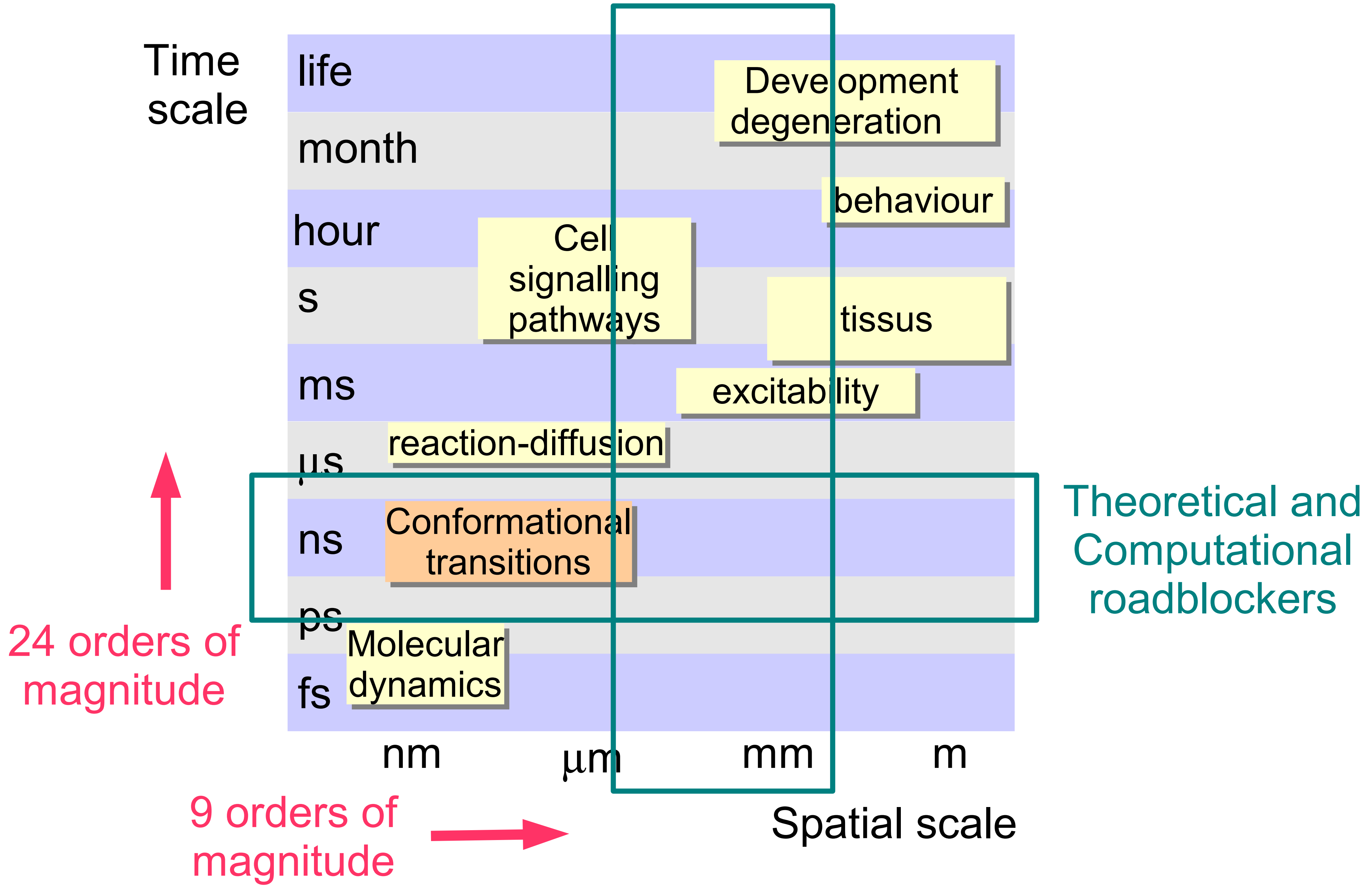
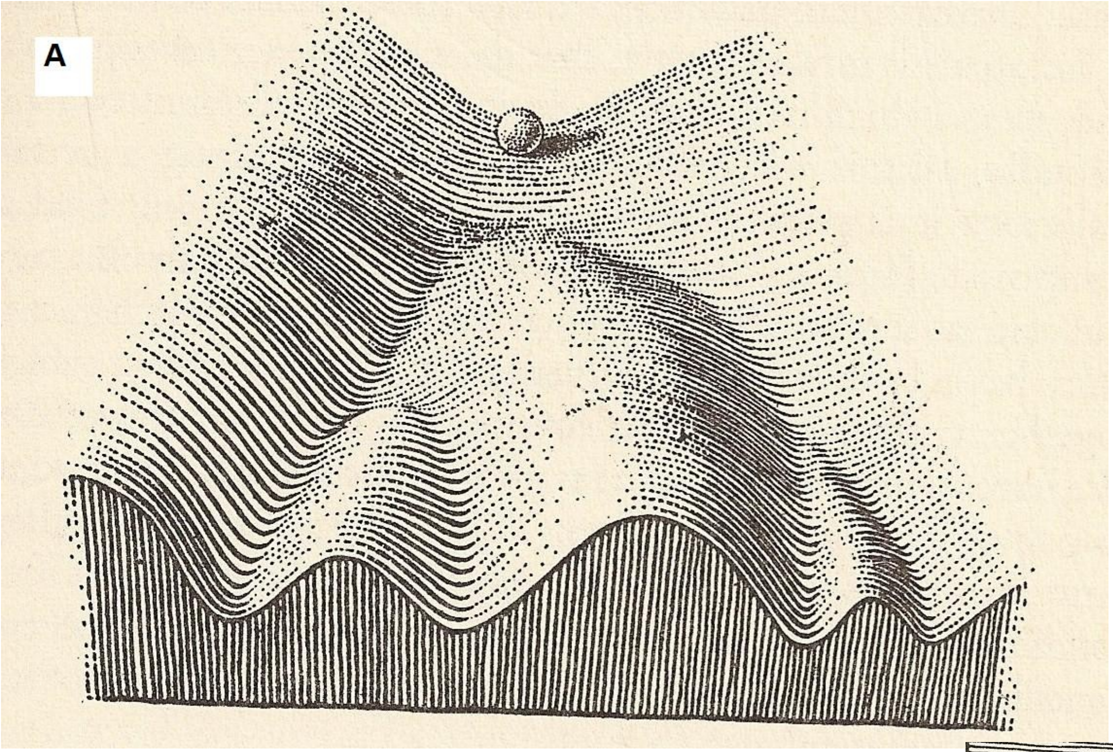


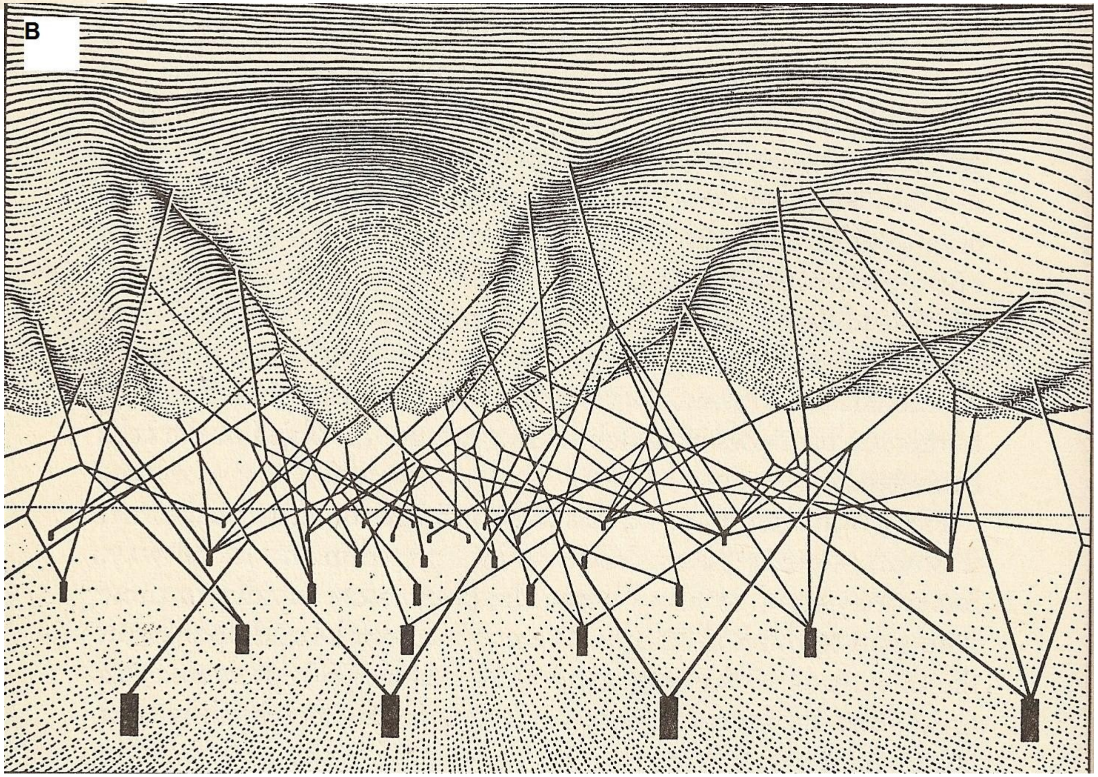
# *Multi*-scale does not mean fine scale plus massive power

- 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.

# Emergent properties and the gene-system-phenotype puzzle




Waddington C.H., Kacser H (1957)
The Strategy of the Genes:
A Discussion of Some Aspects of
Theoretical Biology.
George Allen & Unwin



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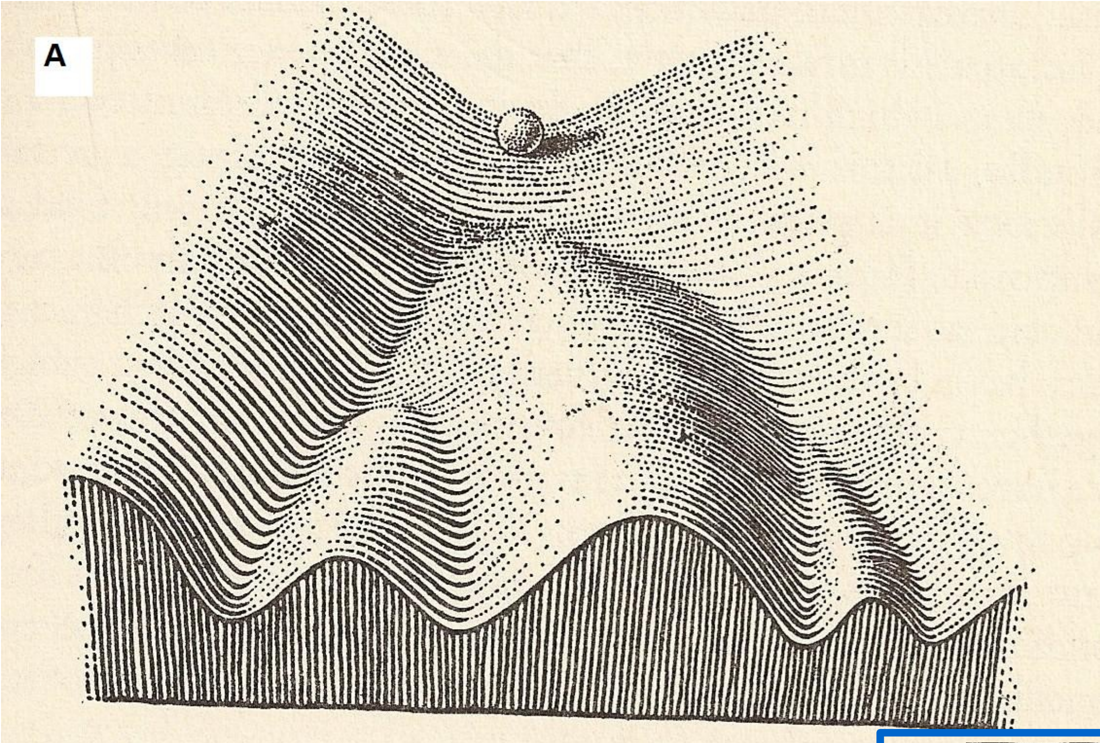


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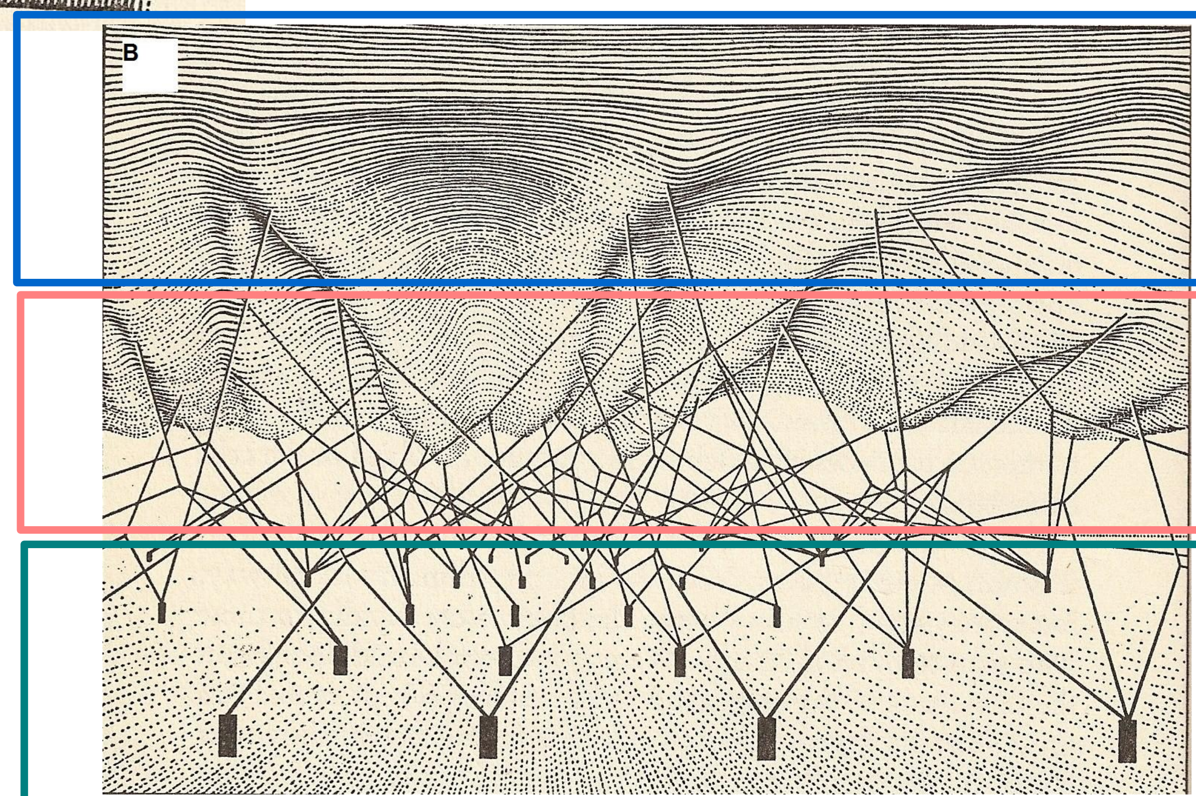
physiology ← phenotype

systems biology ← system

genetics ← genotype



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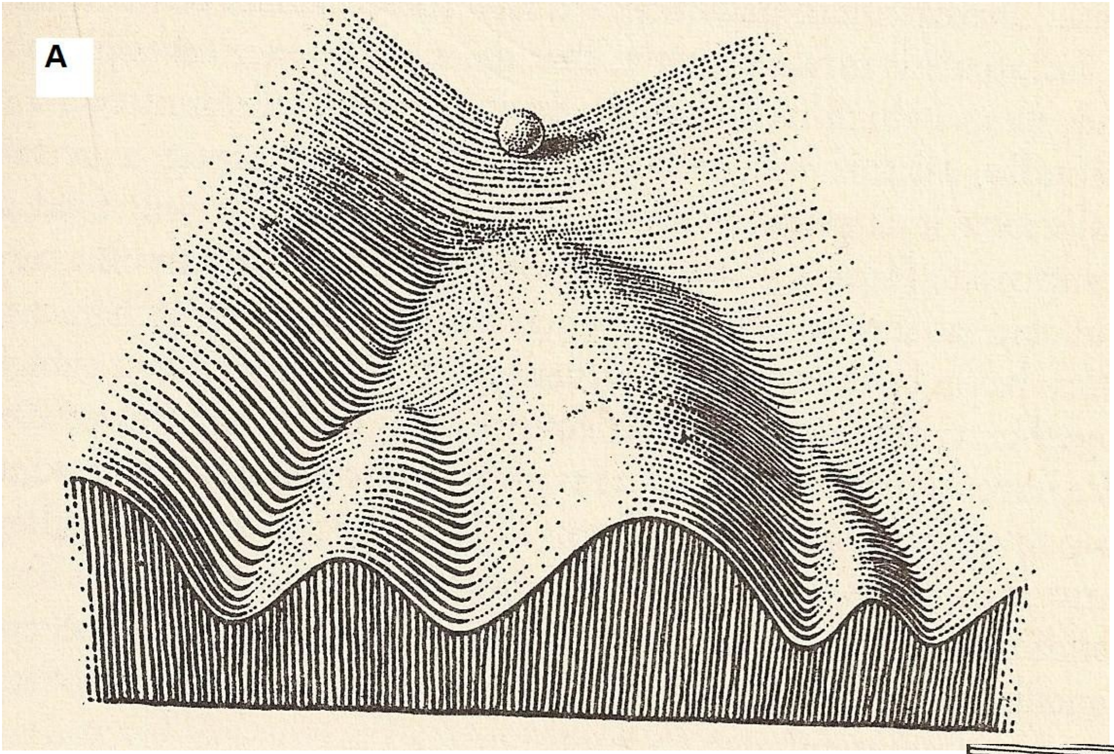


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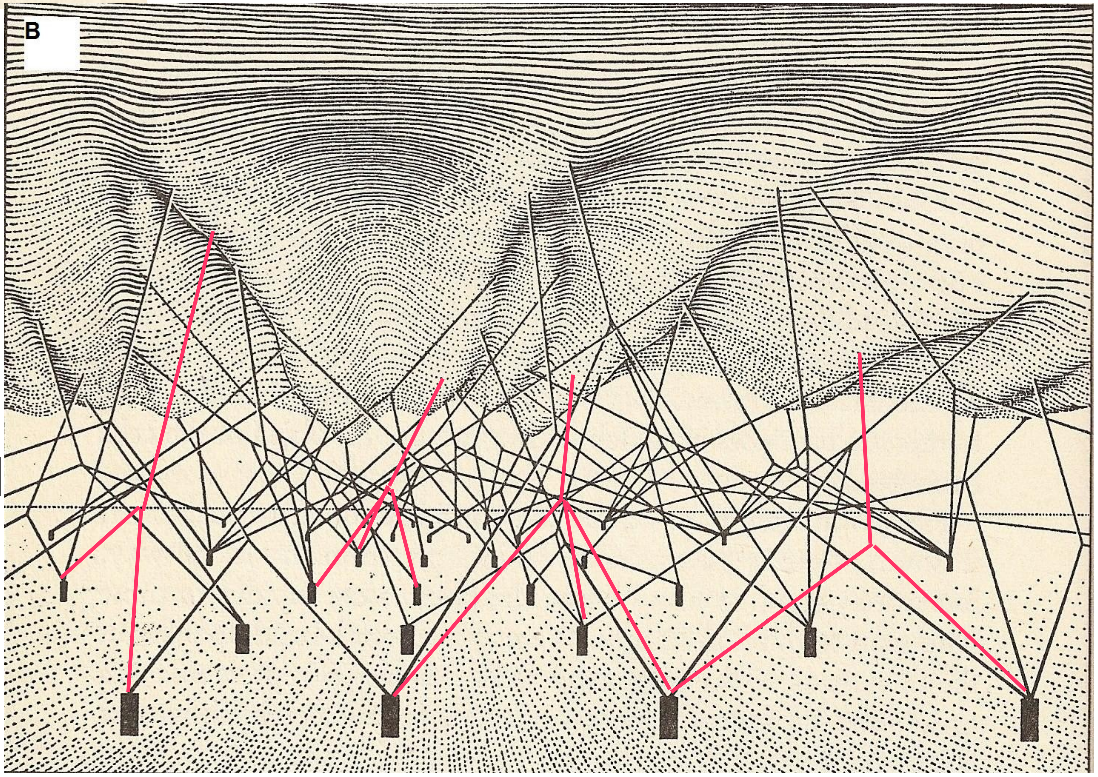
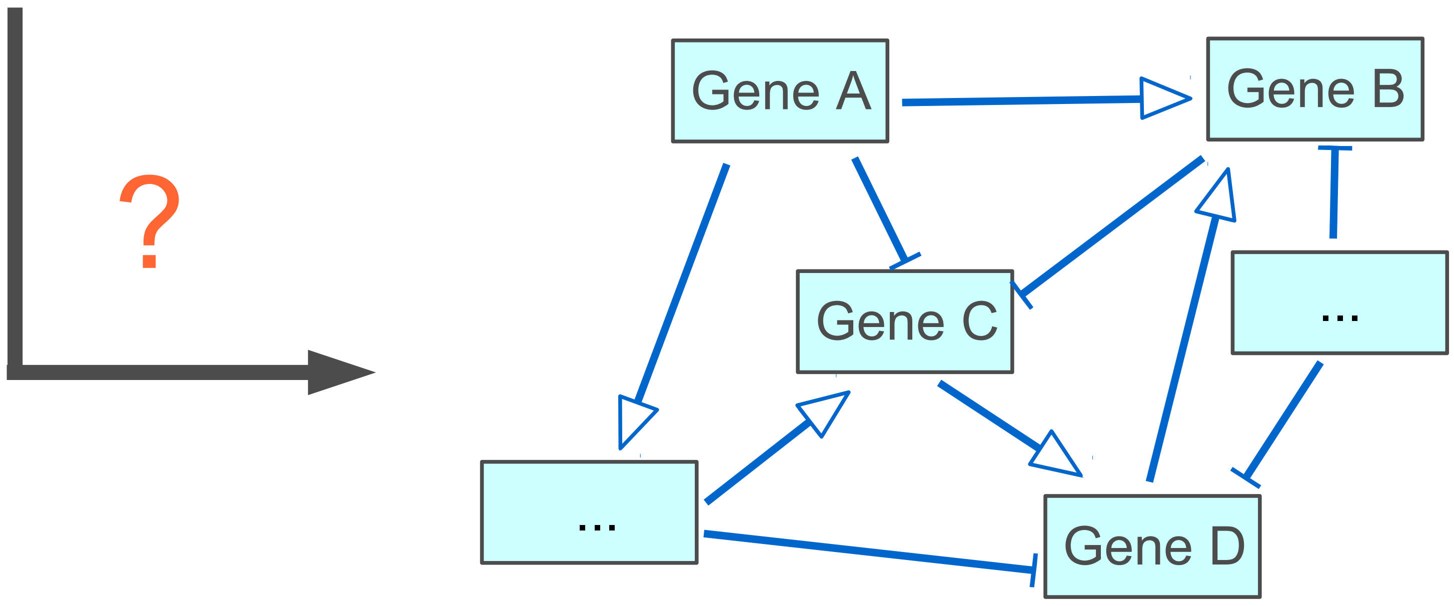


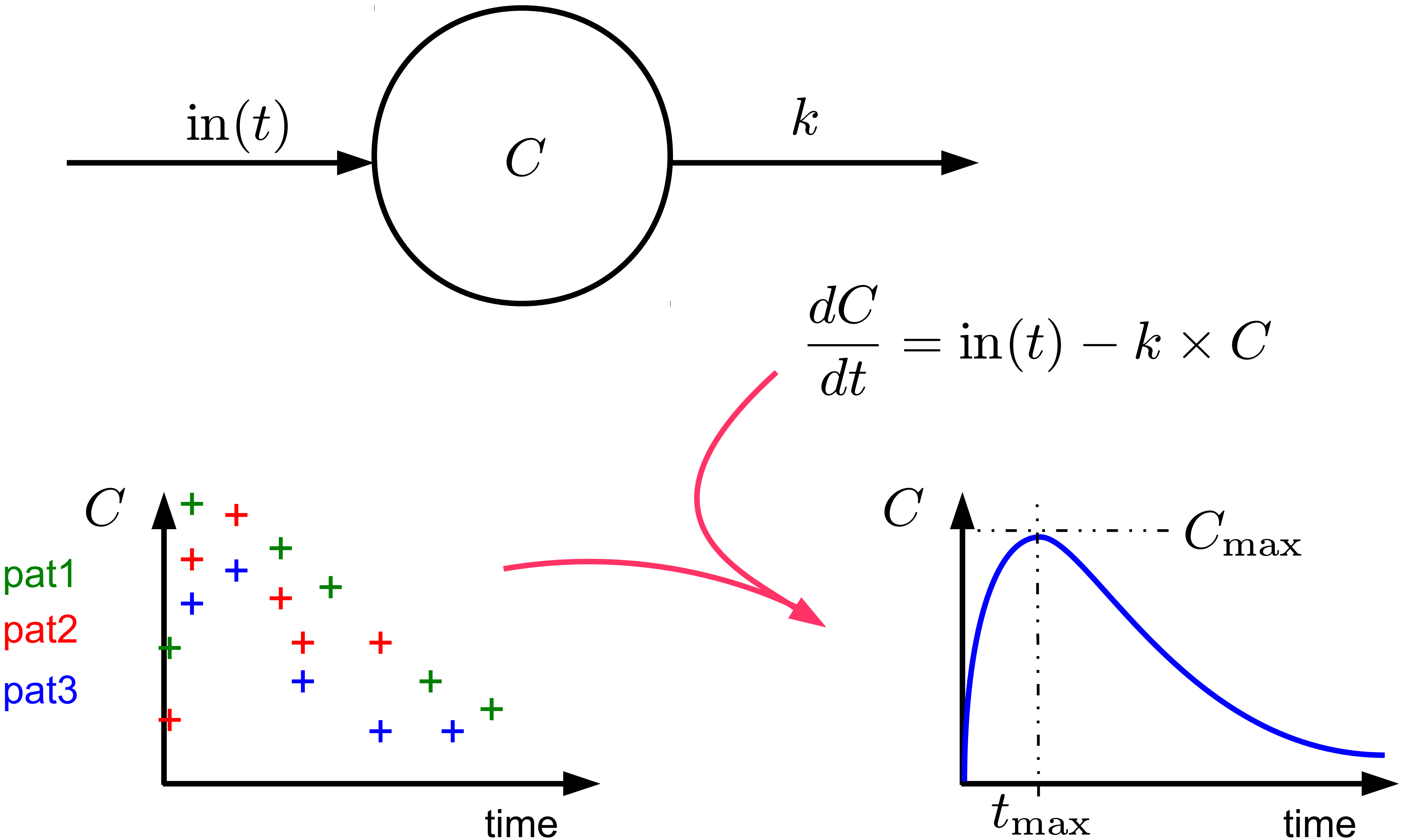

Many networks can theoretically generate the same phenotype, and this happens, in a synchronous (sister cells with same phenotype but different transcript/prote/metabol/omes) and diachronous manner (*omes of a cell changes over time but same phenotype).

# Reverse engineering is hard ...

| | Gene A | Gene B | Gene C | Gene D | ... |
|---|---|---|---|---|---|
| Phenotype X | ✔ | ✘ | ✔ | ✘ | |
| Phenotype Y | ✔ | ✘ | ✘ | ✔ | |
| Phenotype Z | ✘ | ✔ | ✔ | ✘ | |
| ... | | | | | |



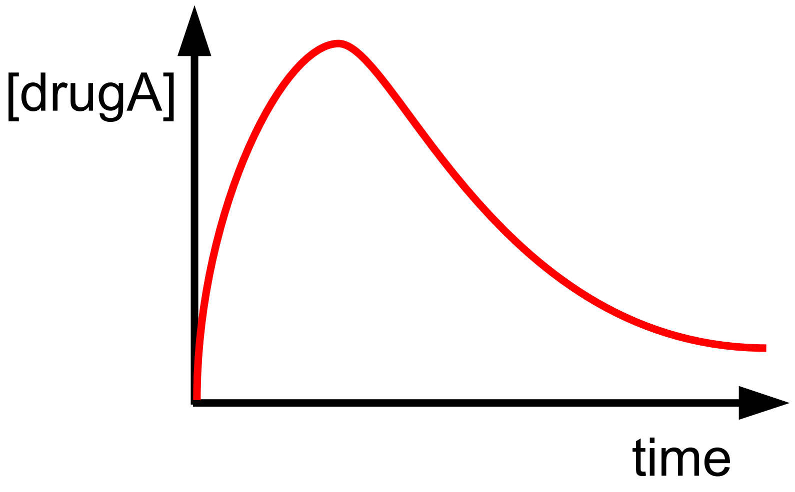
# Drug discovery modelling: pharmacometrics



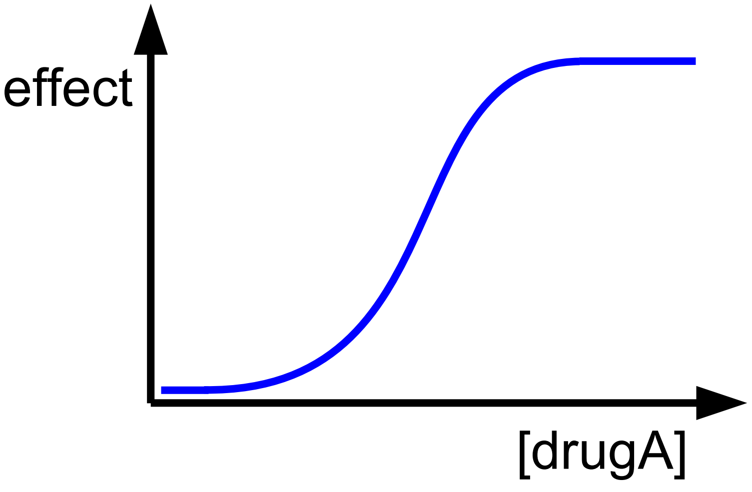

$$\frac{dC}{dt} = \mathrm{in}(t) - k \times C$$

# Drug discovery modelling: pharmacometrics

PK




PD



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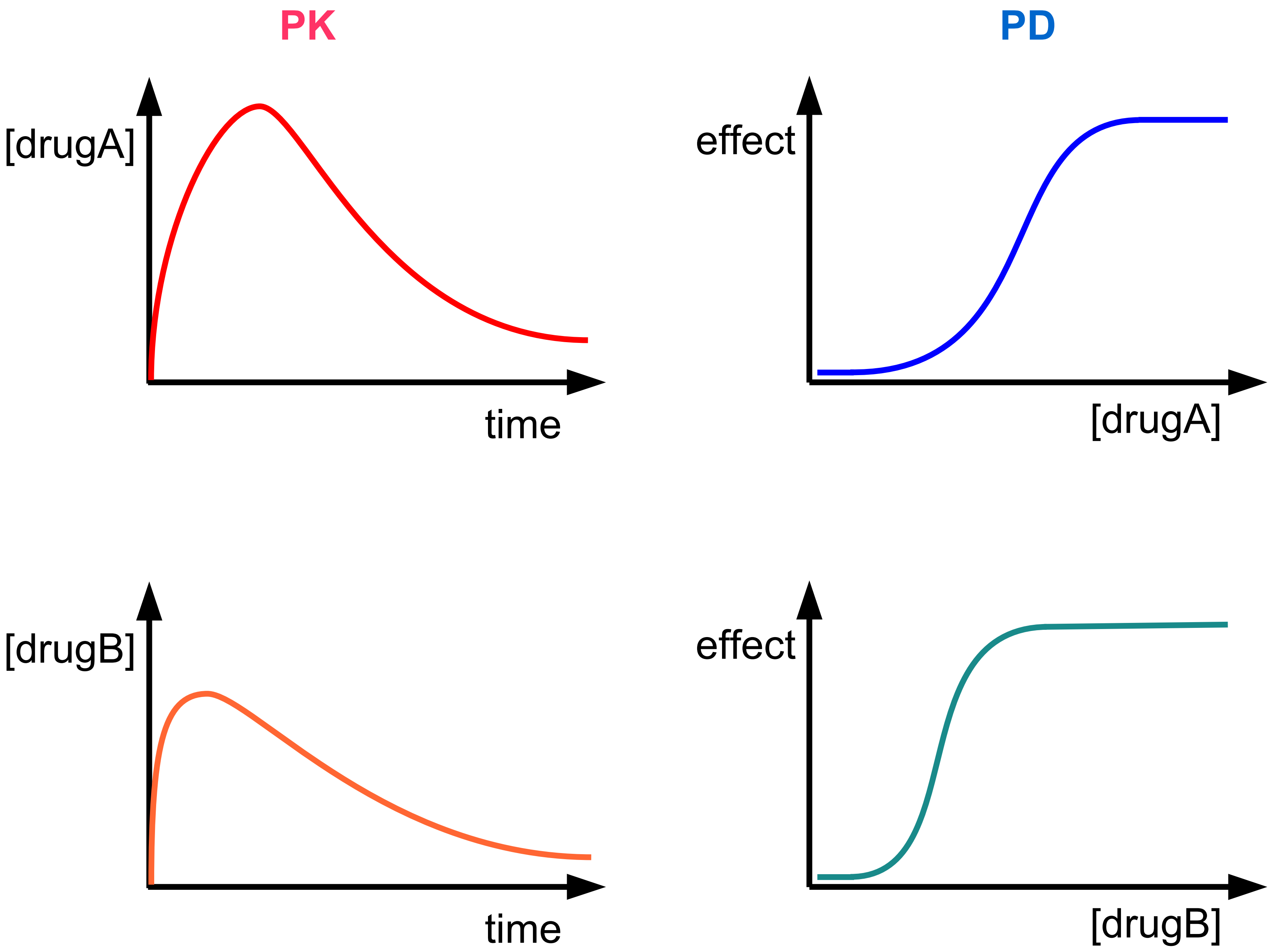

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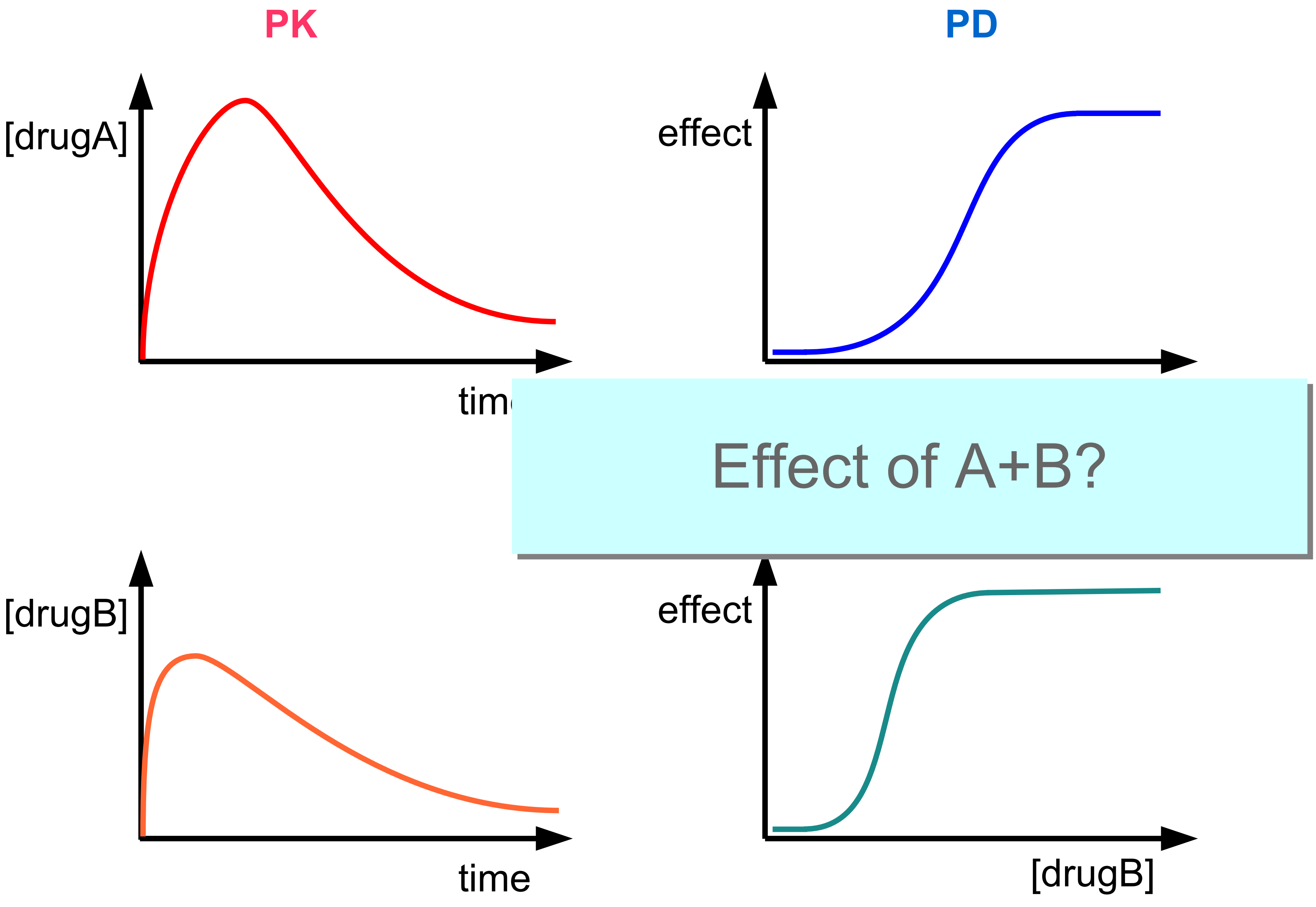
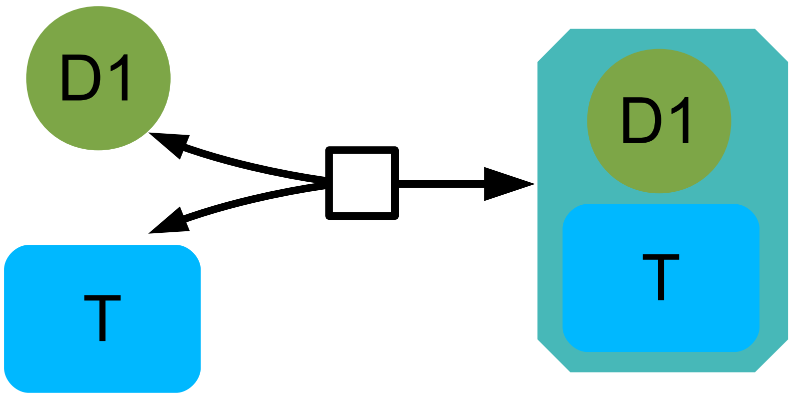
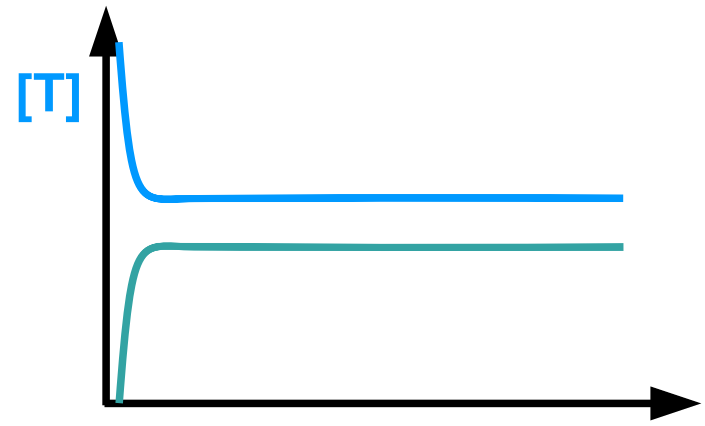
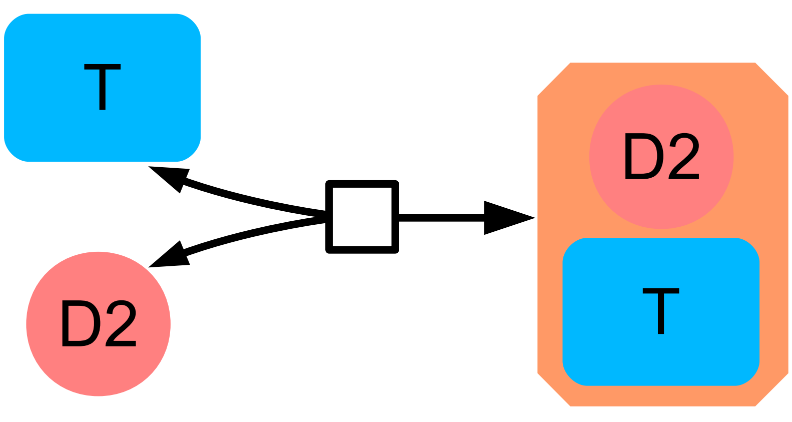


# Systems modelling

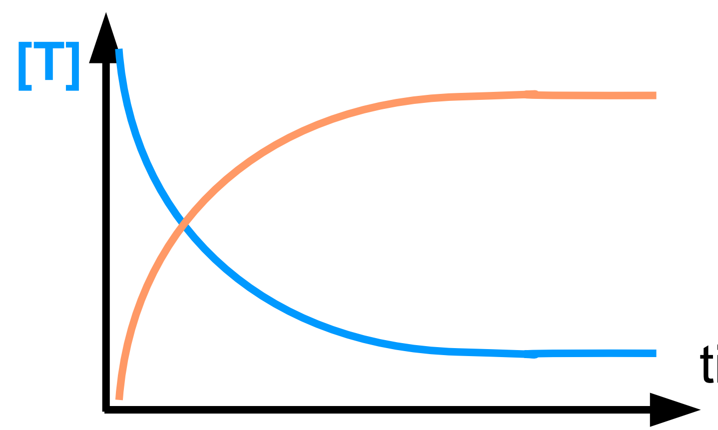



$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1]$$



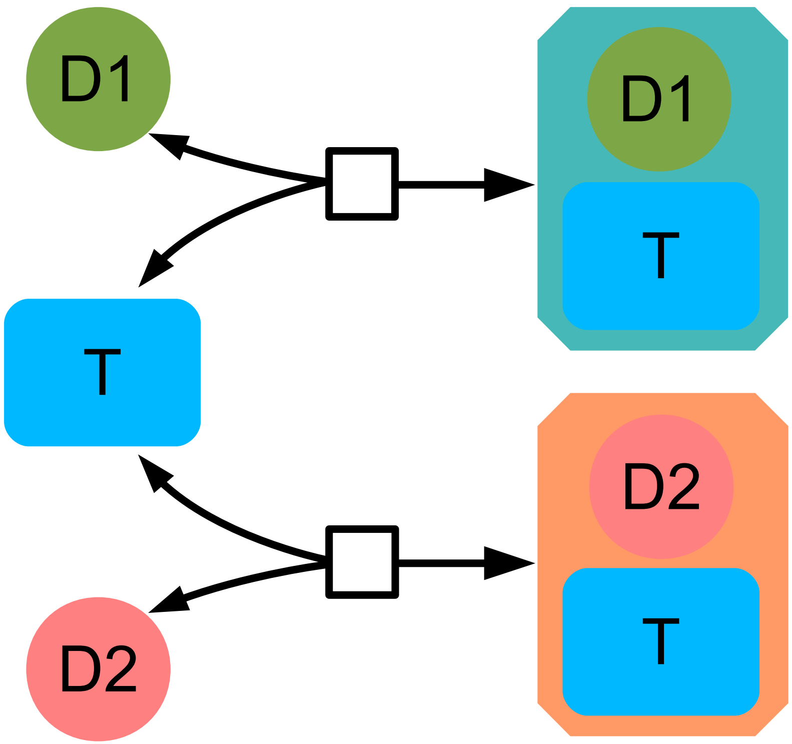



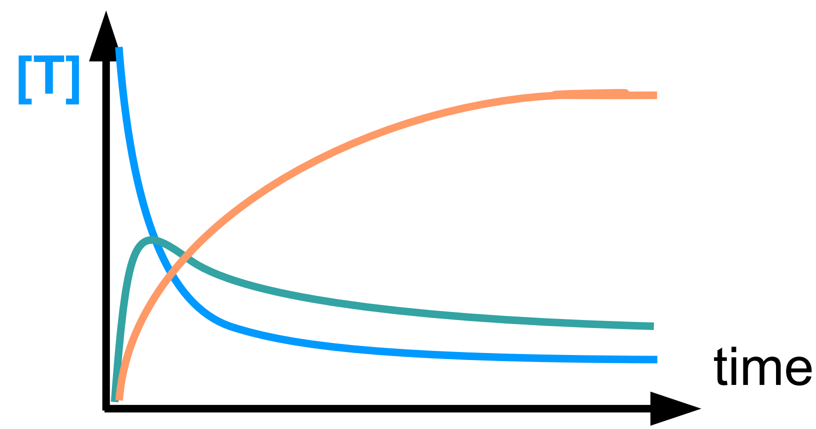

$$\frac{d[T]}{dt} = -k2 \times [T] \times [D2]$$



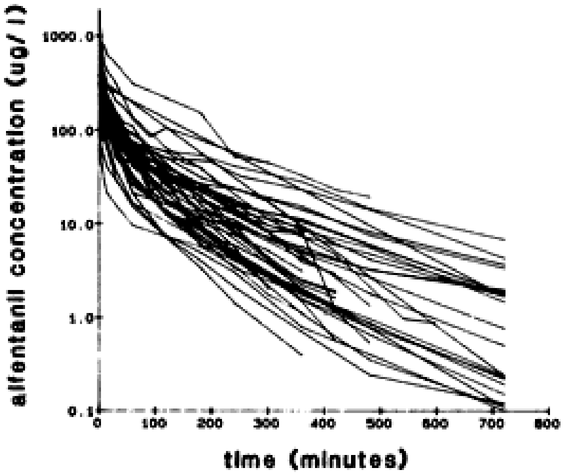
# Systems modelling

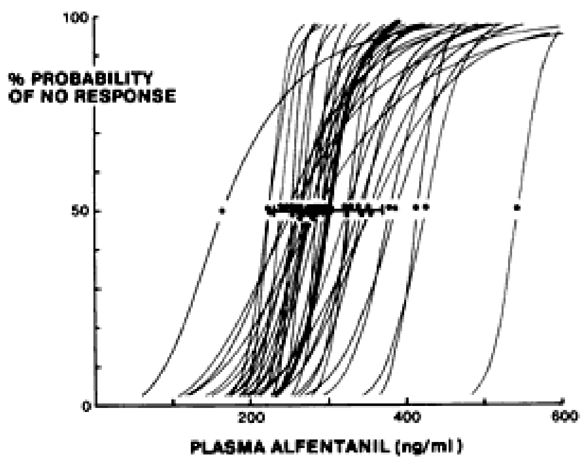
$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1] - k2 \times [T] \times [D2]$$

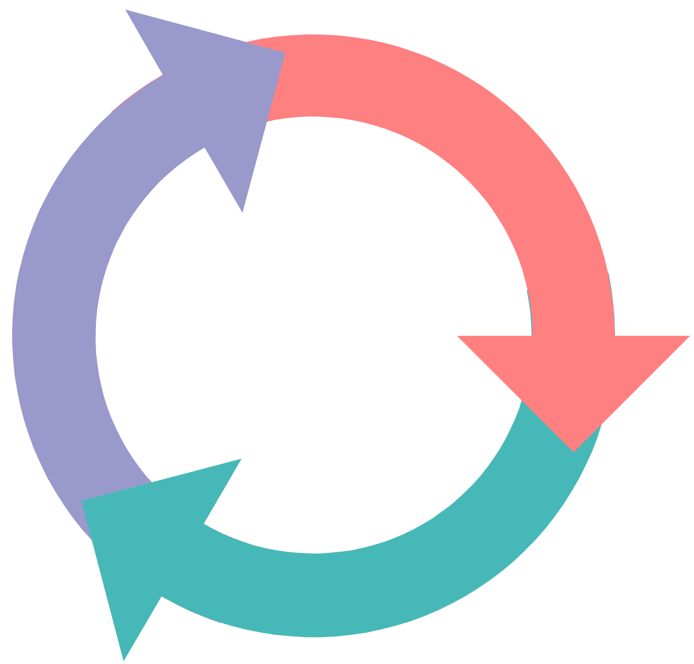


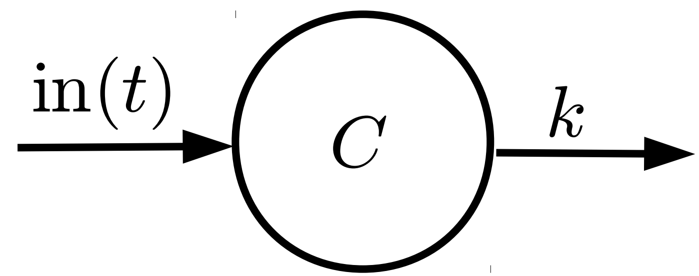



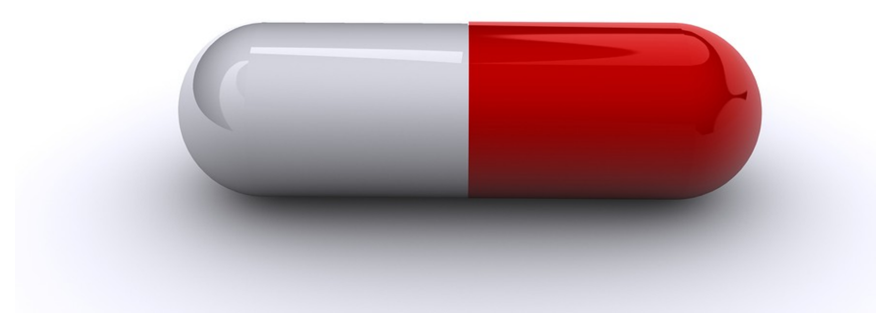
# Drug discovery and pharmacometrics models



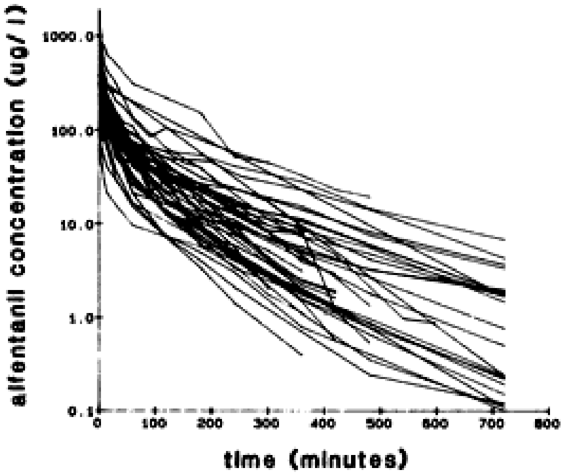



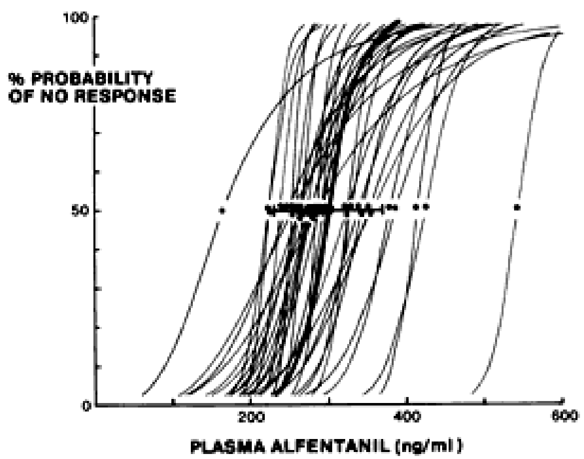



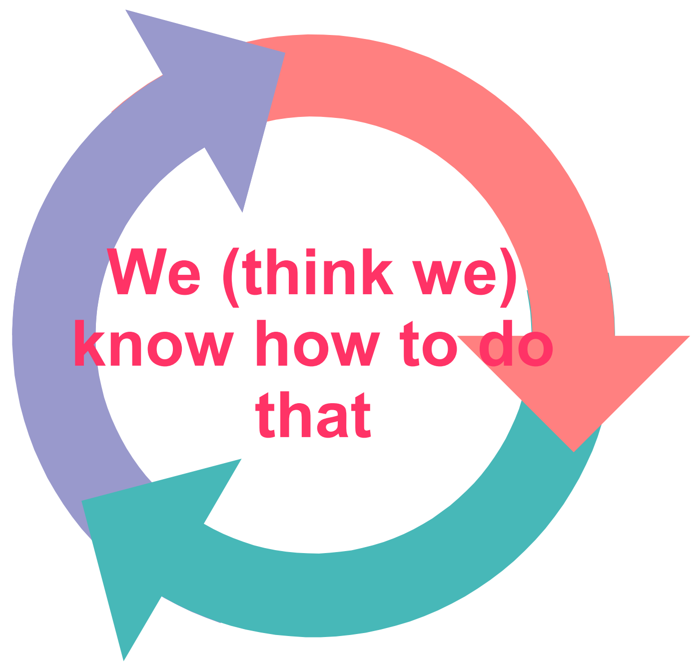


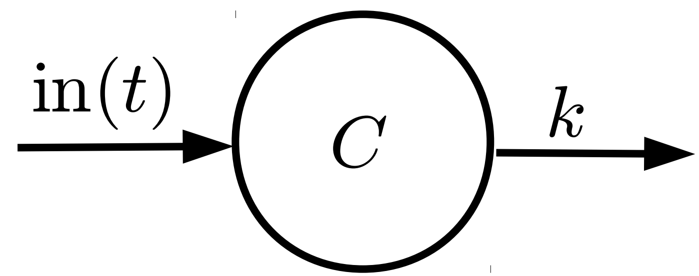



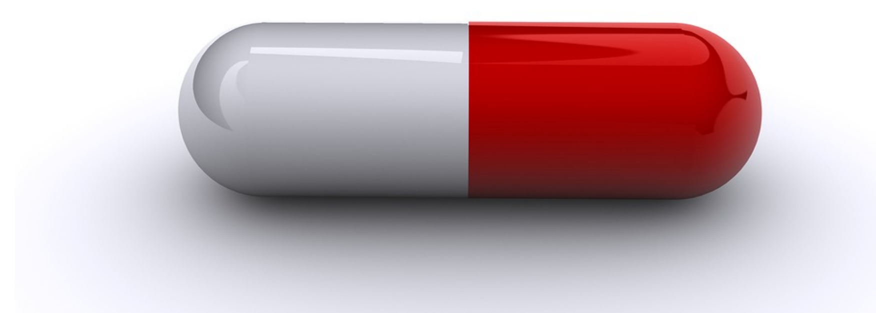
# Drug discovery and pharmacometrics models



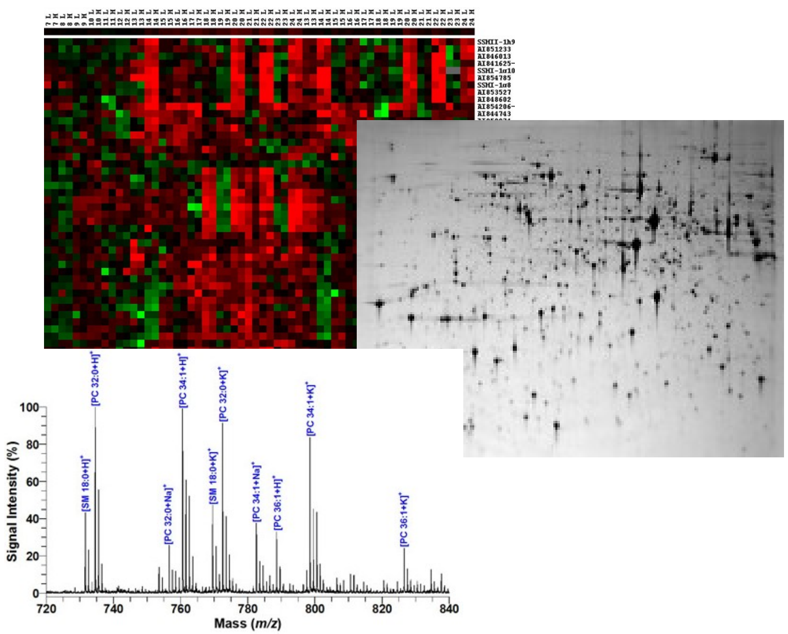



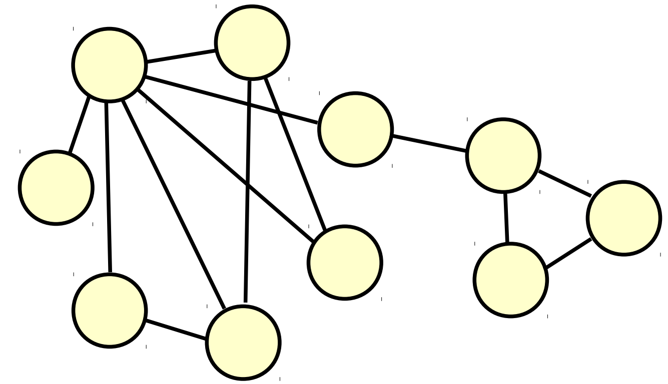



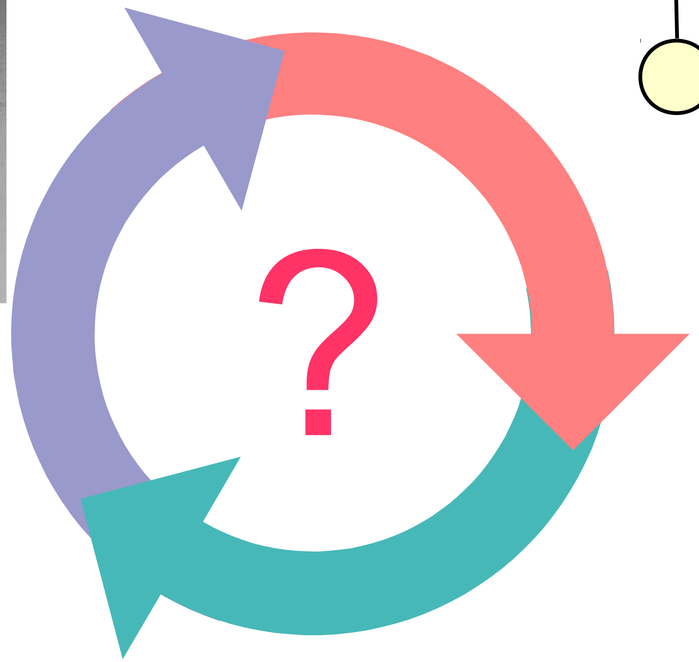



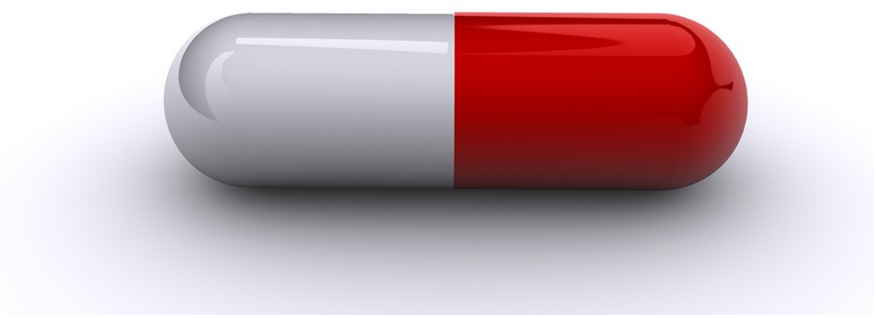



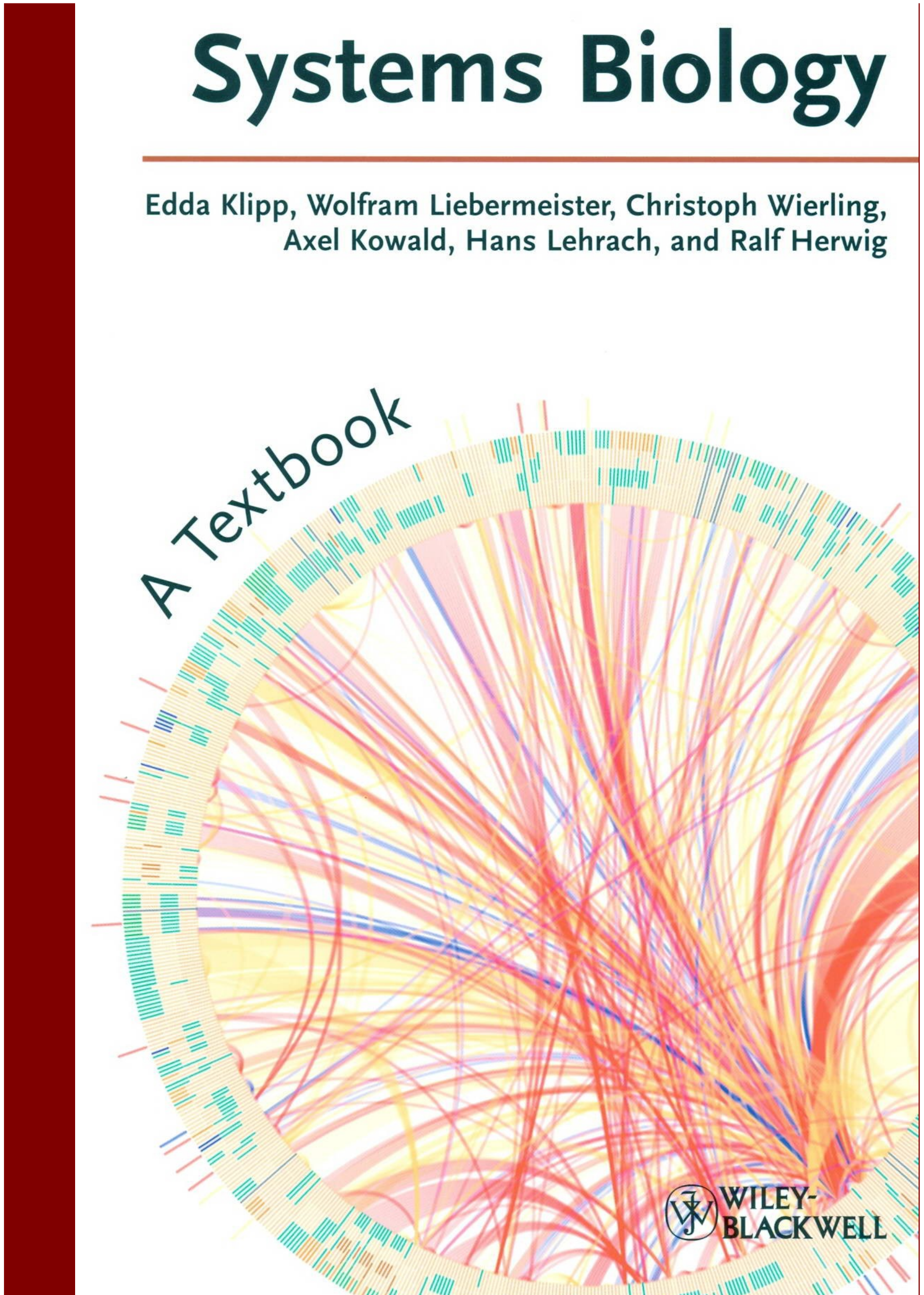
# Drug discovery and omics

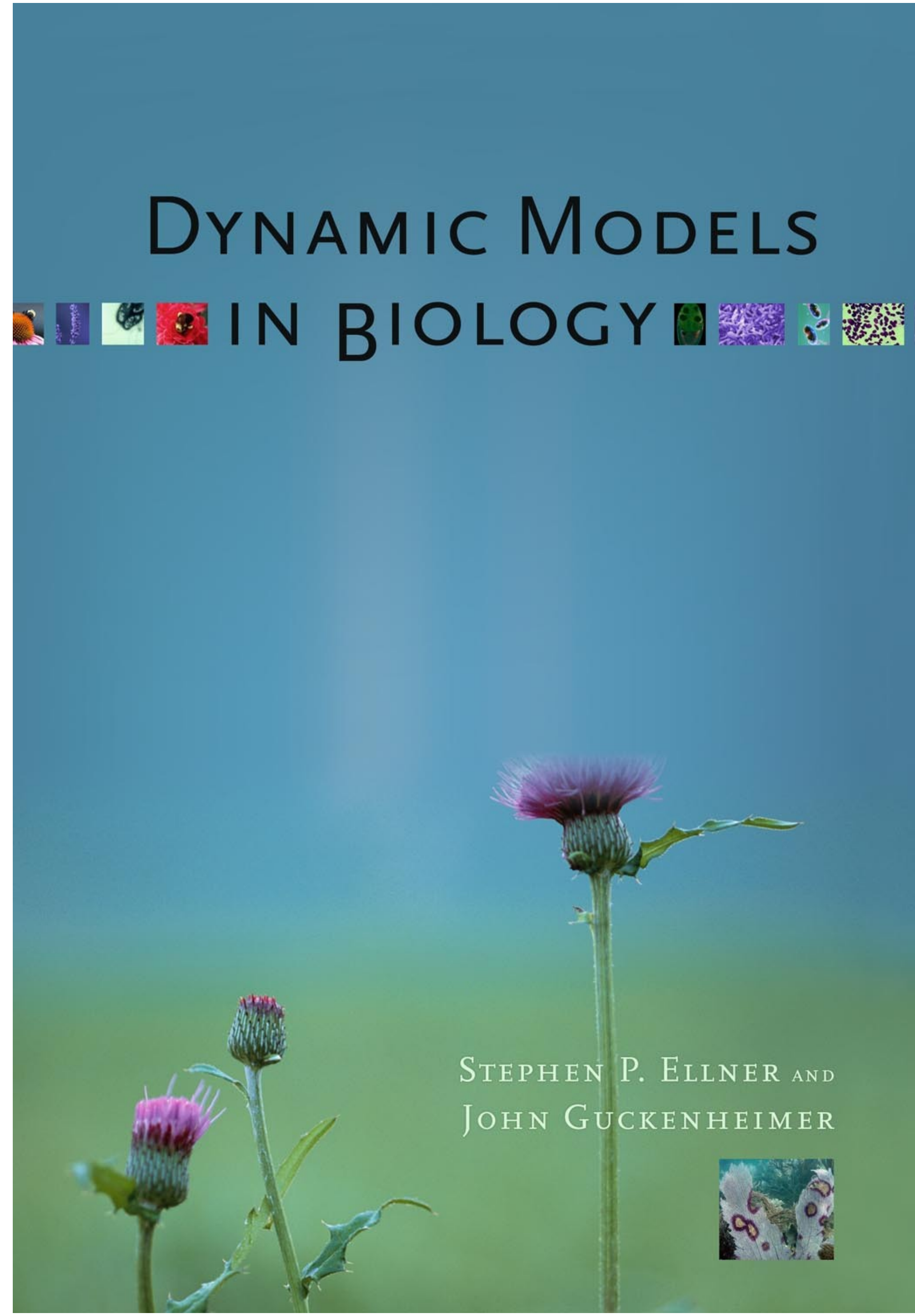





Systems Biology
Edda Klipp, Wolfram Liebermeister, Christoph Wierling,
Axel Kowald, Hans Lehrach, and Ralf Herwig
A Textbook
WILEY-BLACKWELL


DYNAMIC MODELS
IN BIOLOGY
STEPHEN P. ELLNER AND
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