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 XXth 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

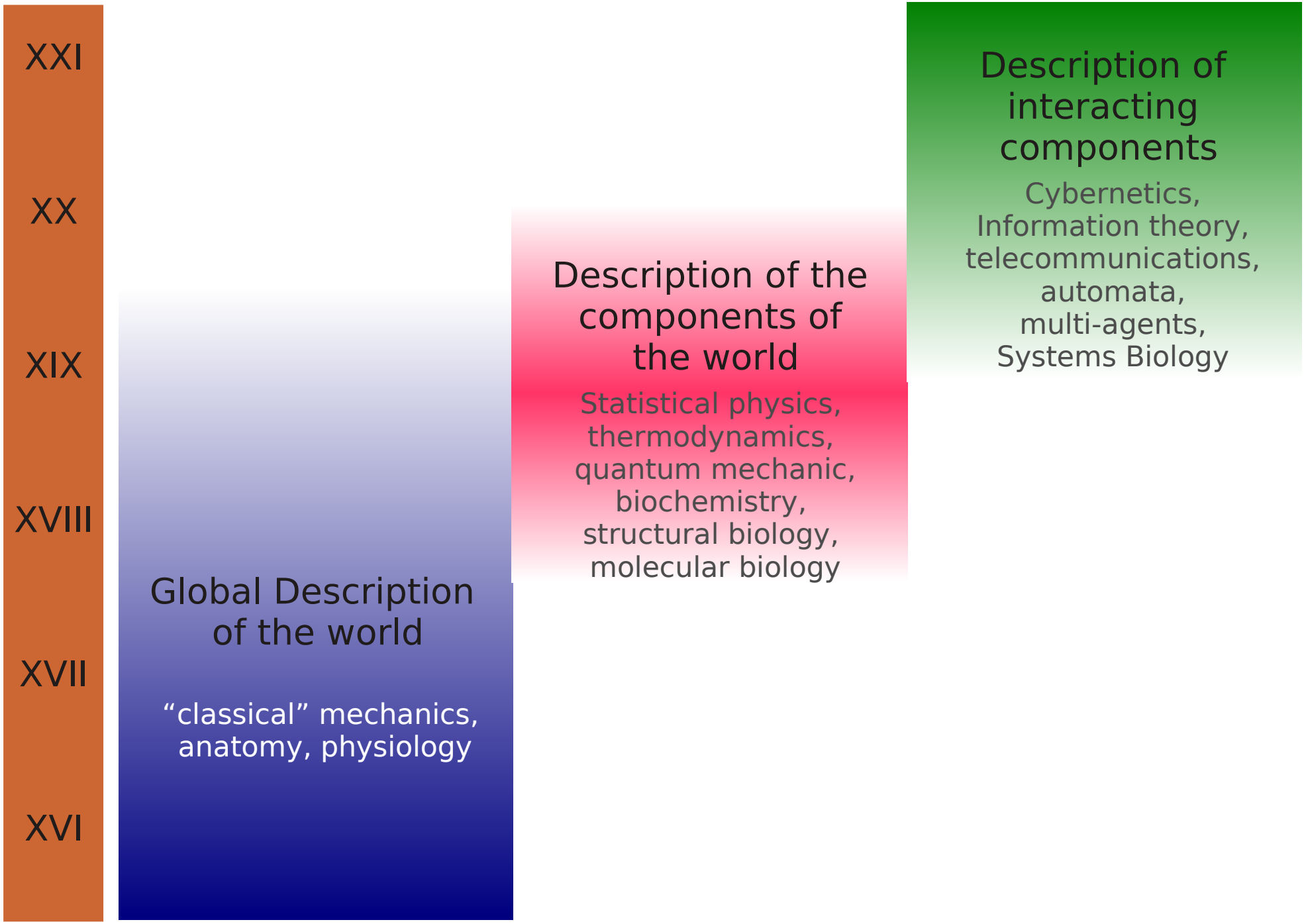
New Generation Computing, 18(2000)199-216
Ohmsha, Ltd. and Springer-Verlag

Invited Paper

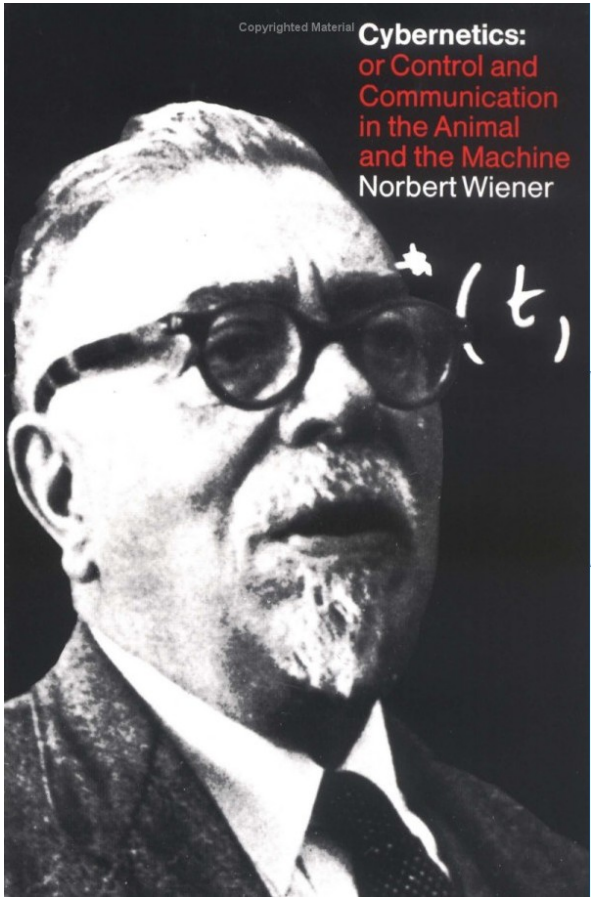
Perspectives on Systems Biology

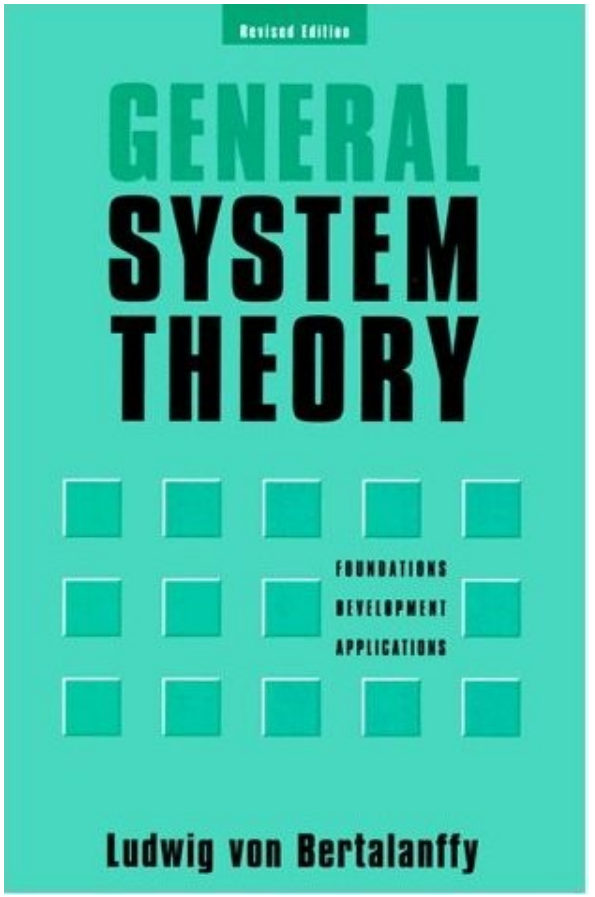
Hiroaki KITANO
Sony Computer Science Laboratories, Inc.

Emergence of the notion of system



Systems are formalised mid-XXth





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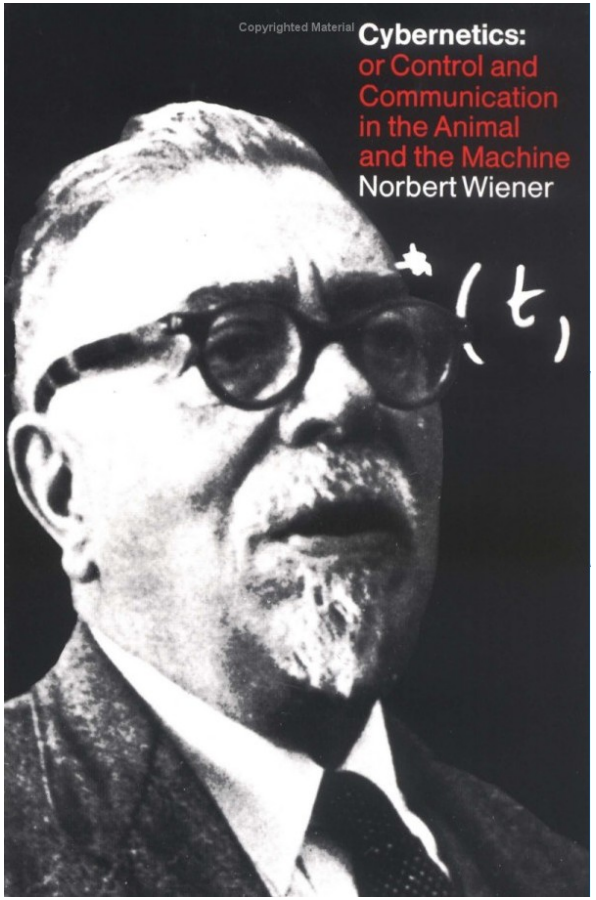
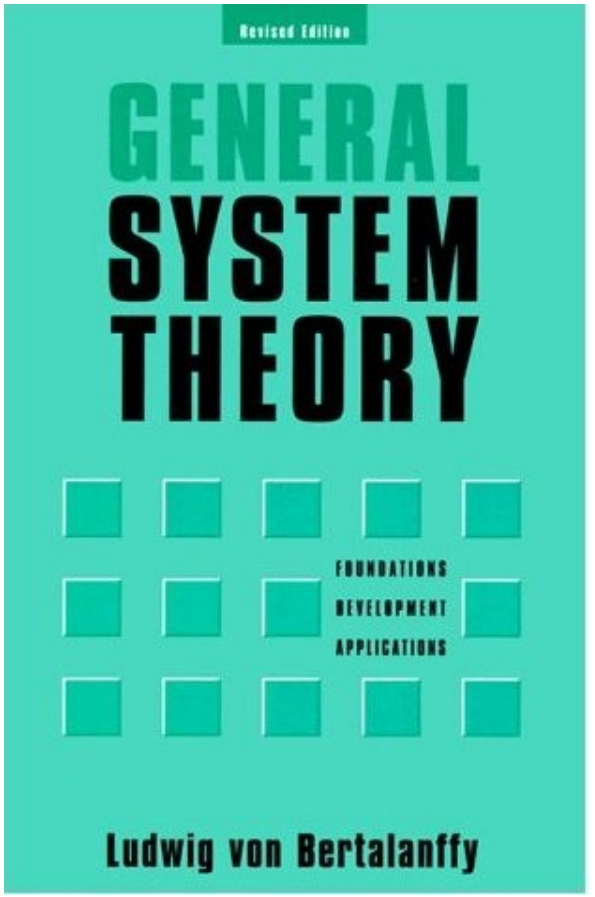
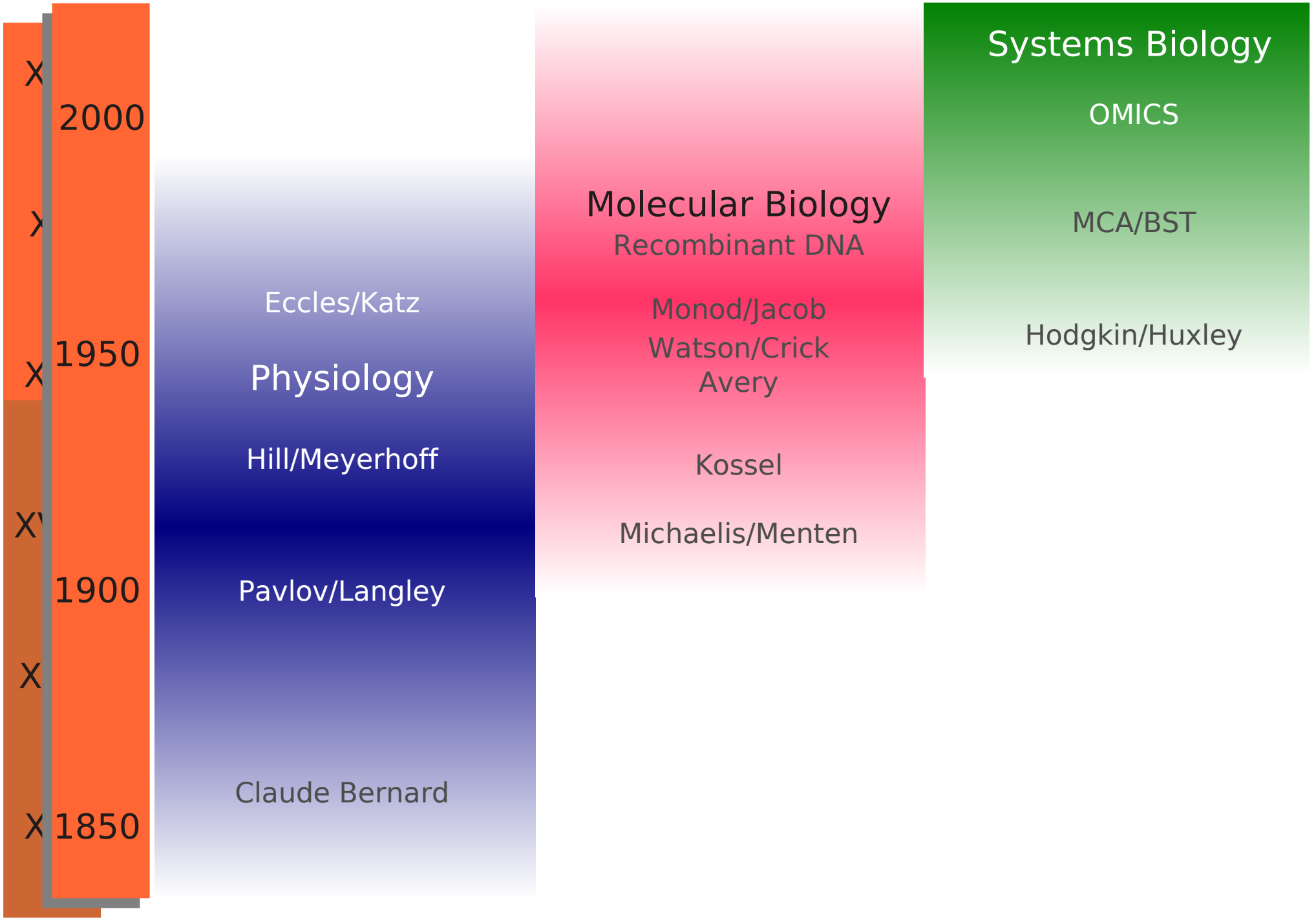




"[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems"
Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

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

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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

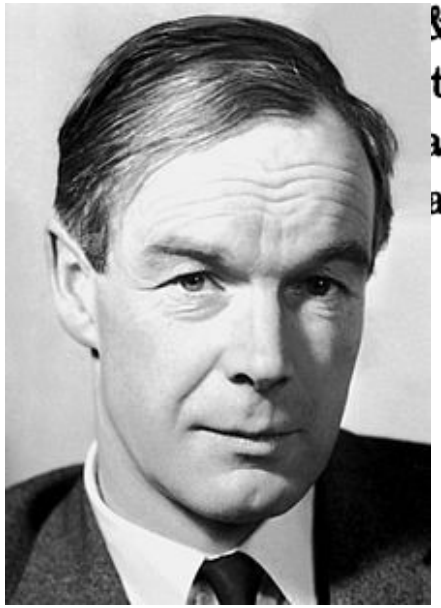
A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

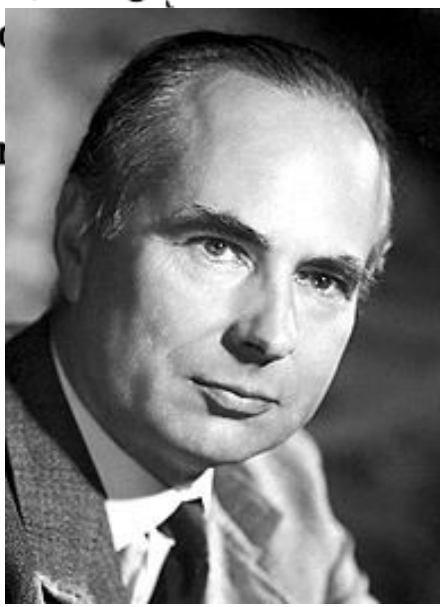
By A. L. HODGKIN and A. F. HUXLEY

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, & 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).



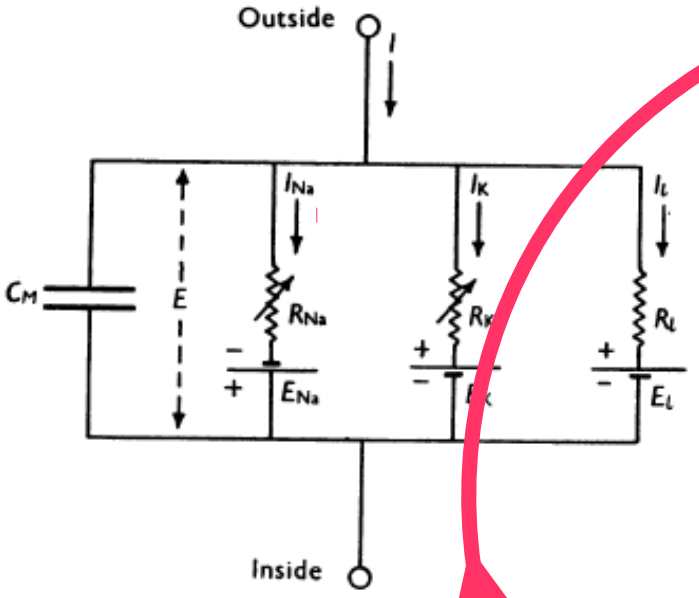


R.I.P. 30 May 2012
Cambridge

The Computational Systems Biology loop

"biological" model

mathematical model



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

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

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

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

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

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

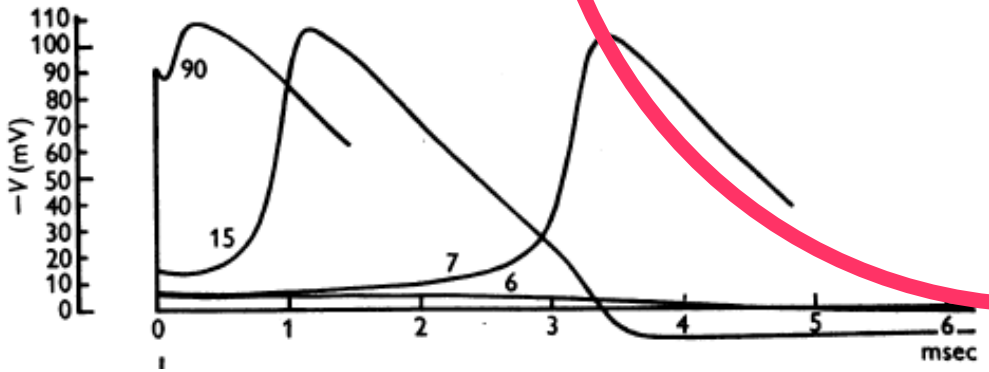
$$\alpha_m = 0{\cdot}1\,(V + 25) \Big/ \left(\exp \frac{V + 25}{10} - 1\right),$$

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

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

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

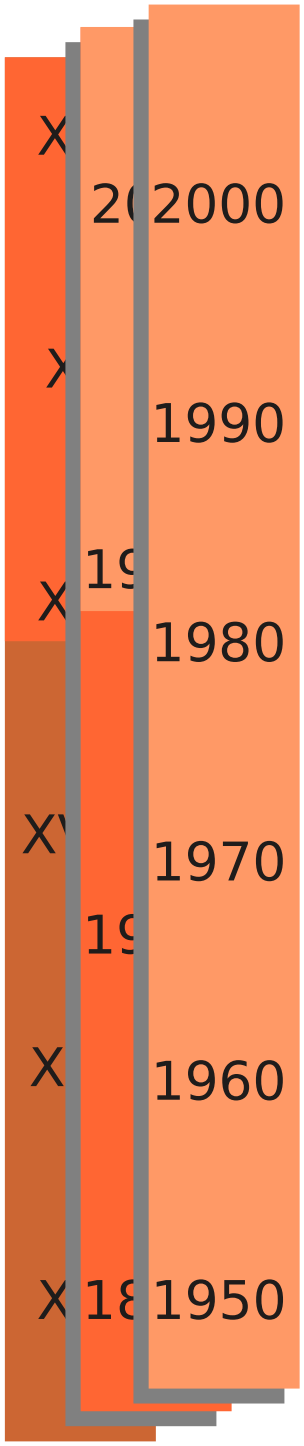
Constant (1)	Value chosen (2)	Experimental values: Mean (3)	Experimental values: Range (4)
C_M (μF/cm^2)	1·0	0·91	0·8 to 1·5
V_{Na} (mV)	−115	−109	−95 to −119
V_K (mV)	+ 12	+ 11	+ 9 to + 14
V_l (mV)	−10·613	− 11	− 4 to − 22
$\bar{g}_{Na}$ (m.mho/cm^2)	120	80 160	65 to 90 120 to 260
$\bar{g}_K$ (m.mho/cm^2)	36	34	26 to 49
$\bar{g}_l$ (m.mho/cm^2)	0·3	0·26	0·13 to 0·50



simulation

computational model

Towards Systems Biology



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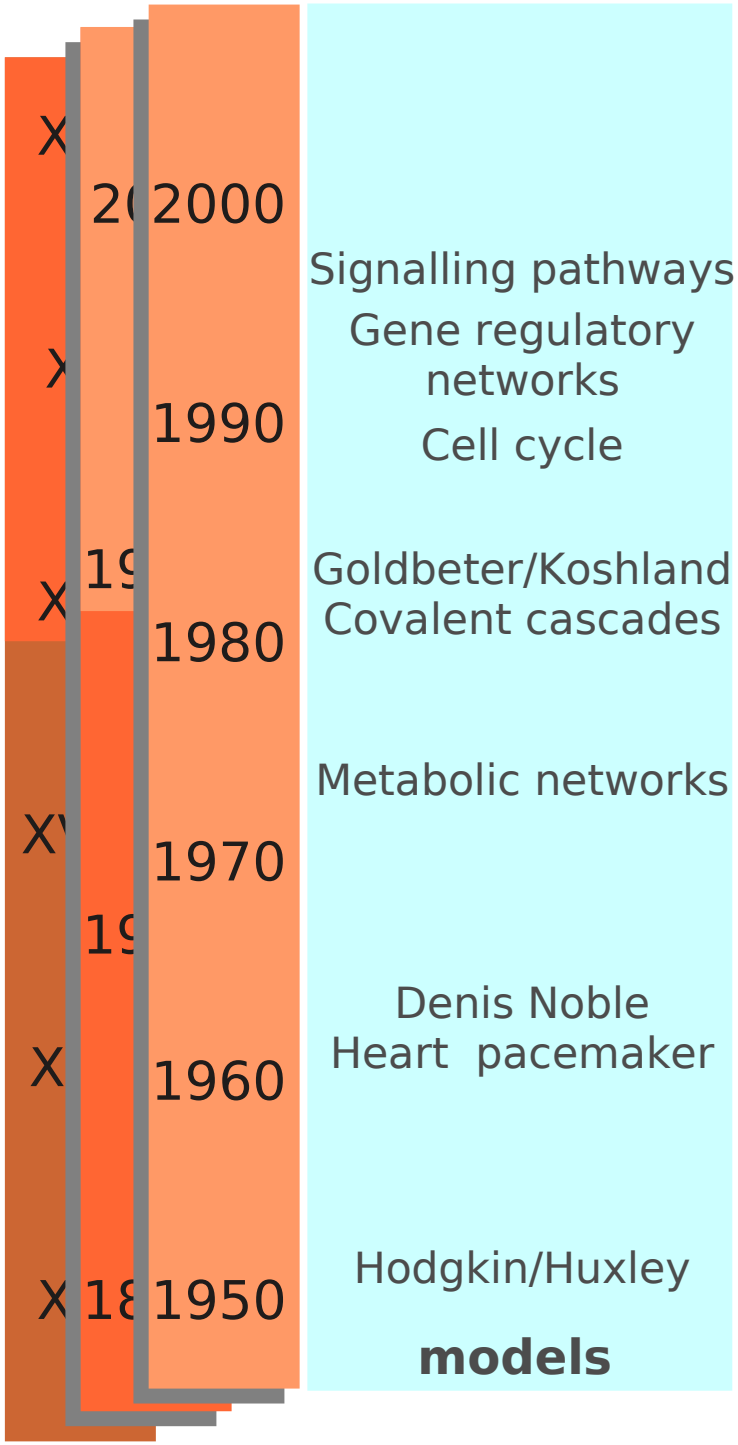

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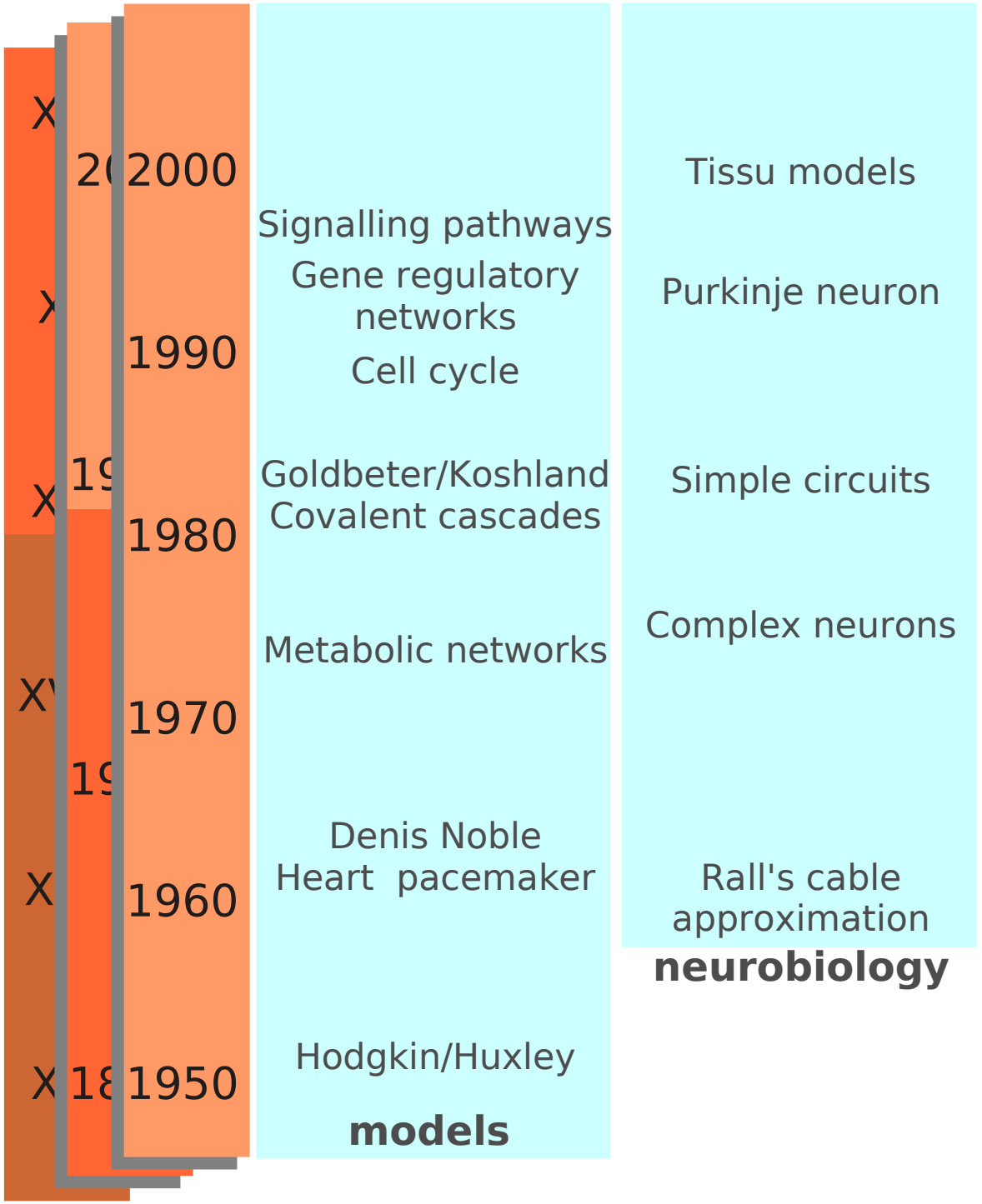
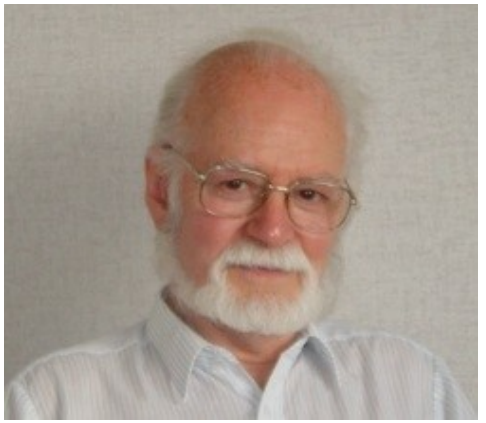


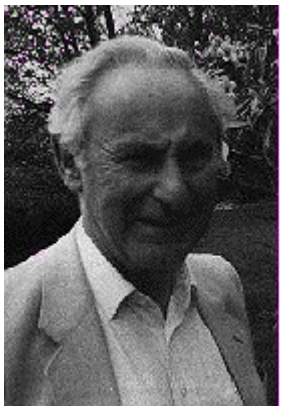
60s and 70s

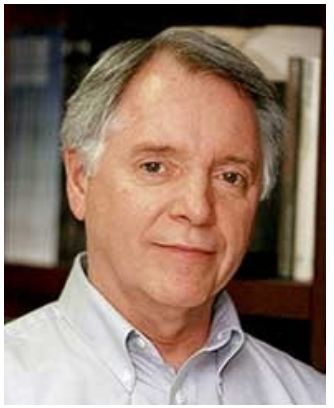
- Mihajlo Mesarovic: 1966 Symposium "general systems theory and biology

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



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





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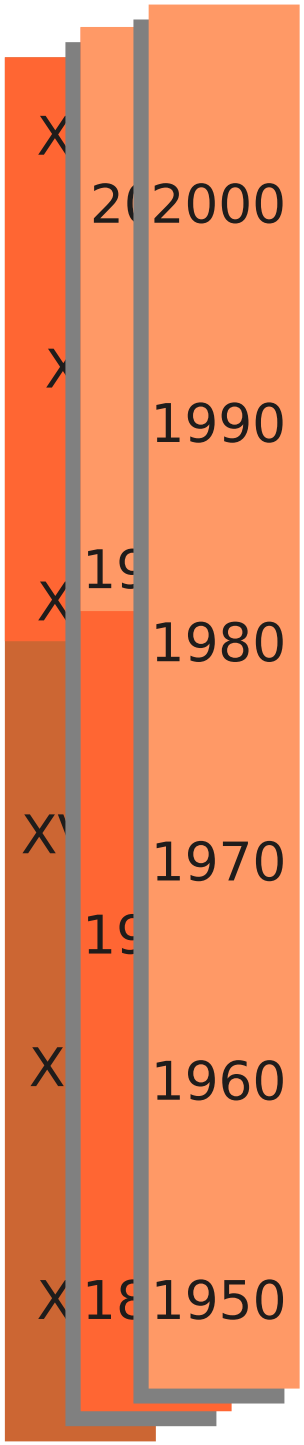


2000
1990
1980
1970
1960
1950

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

models

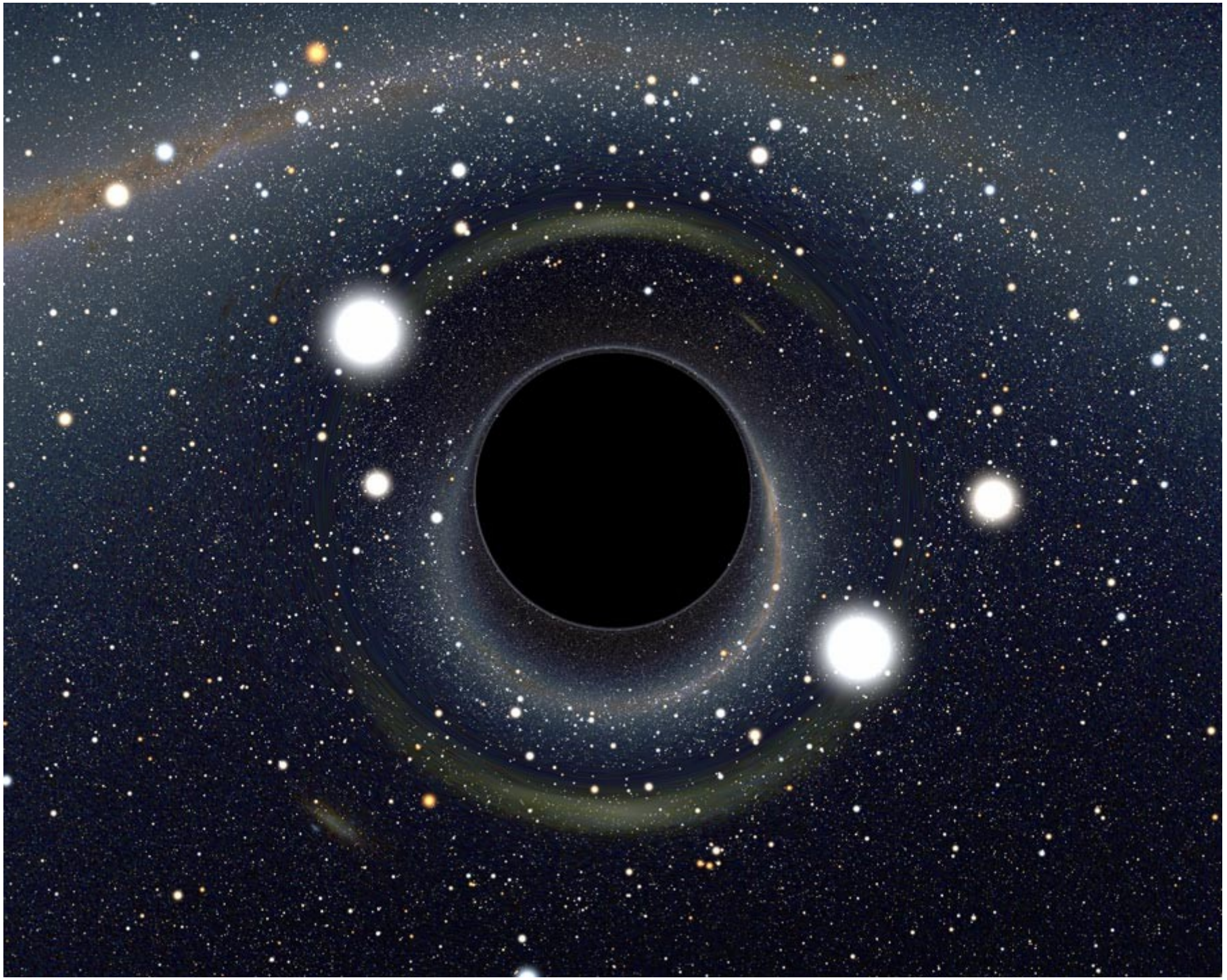
Tissu models
Purkinje neuron
Simple circuits
Complex neurons
Rall's cable approximation

neurobiology

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

methods

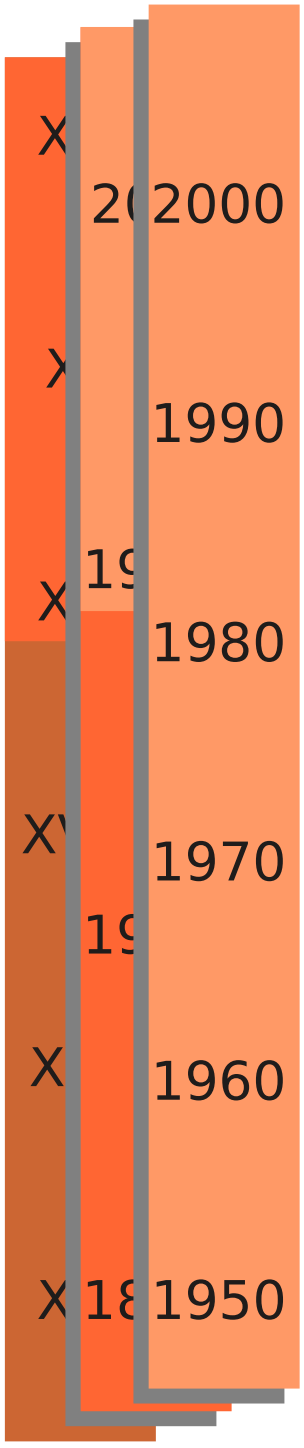
80s: The reign of Molecular Biology



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



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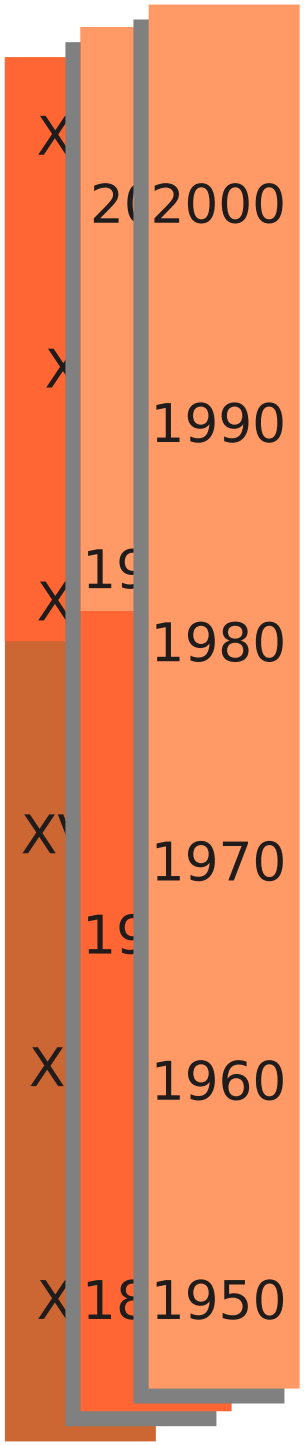
Barabasi

Towards Systems Biology



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Synthetic Biology

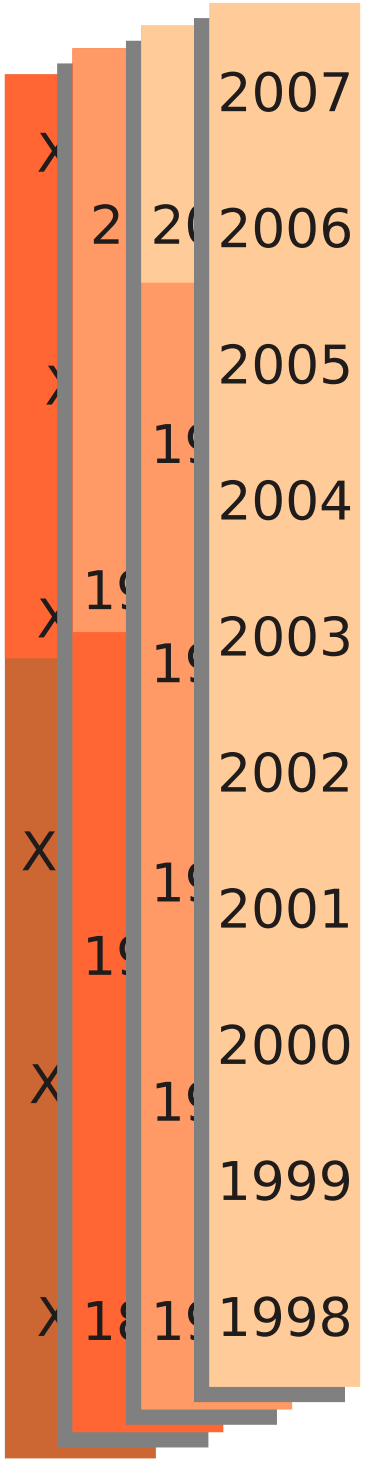
Repressilator
Barabasi

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



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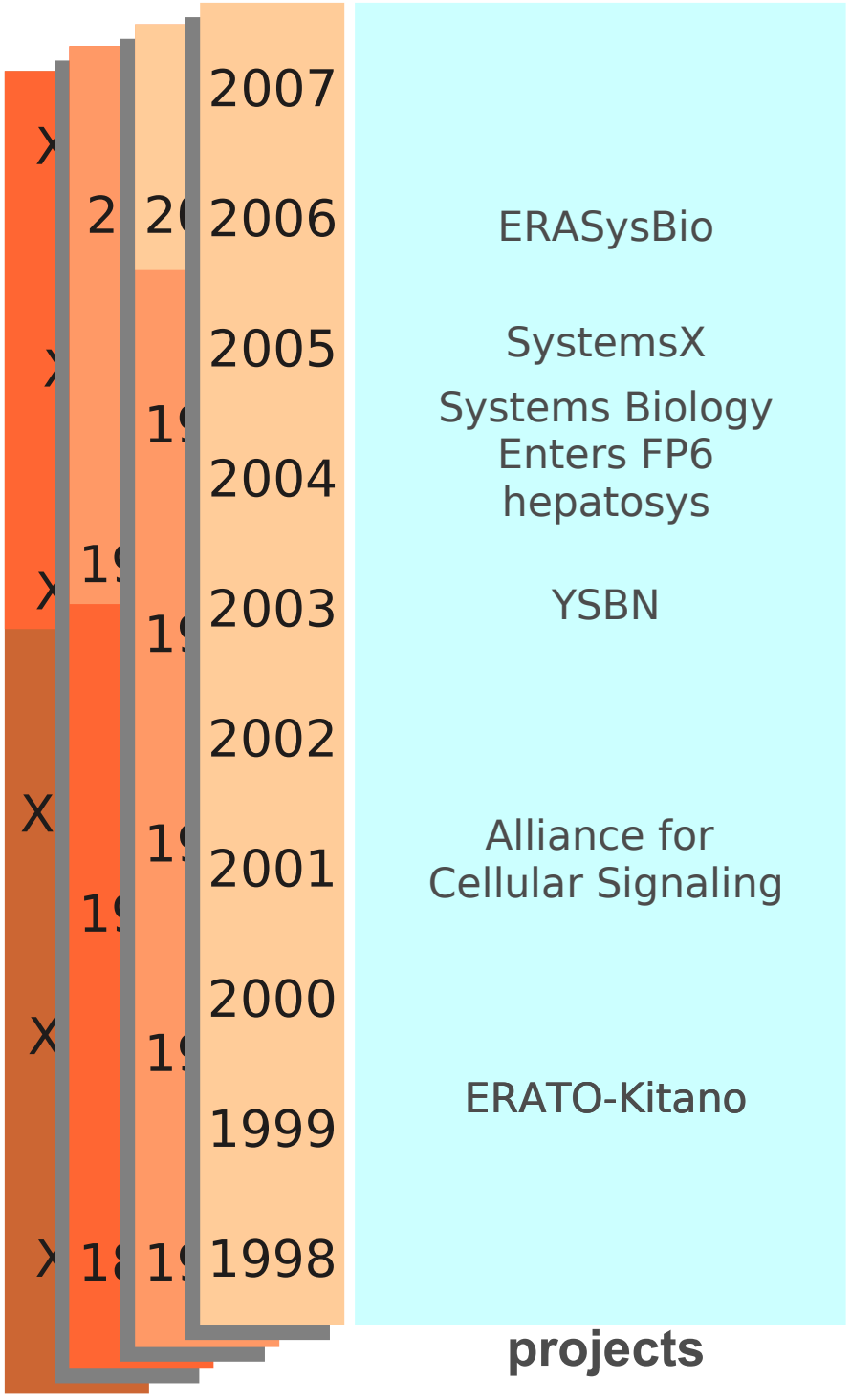

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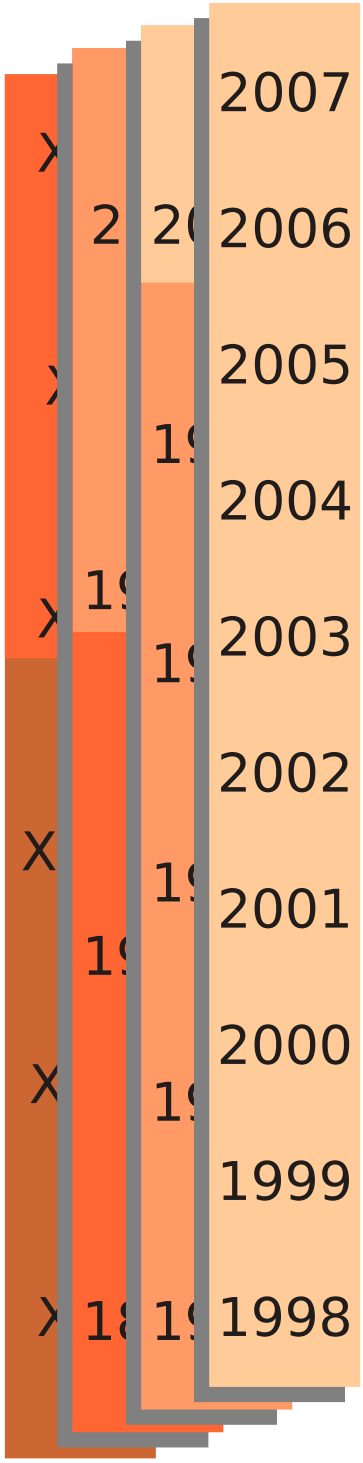
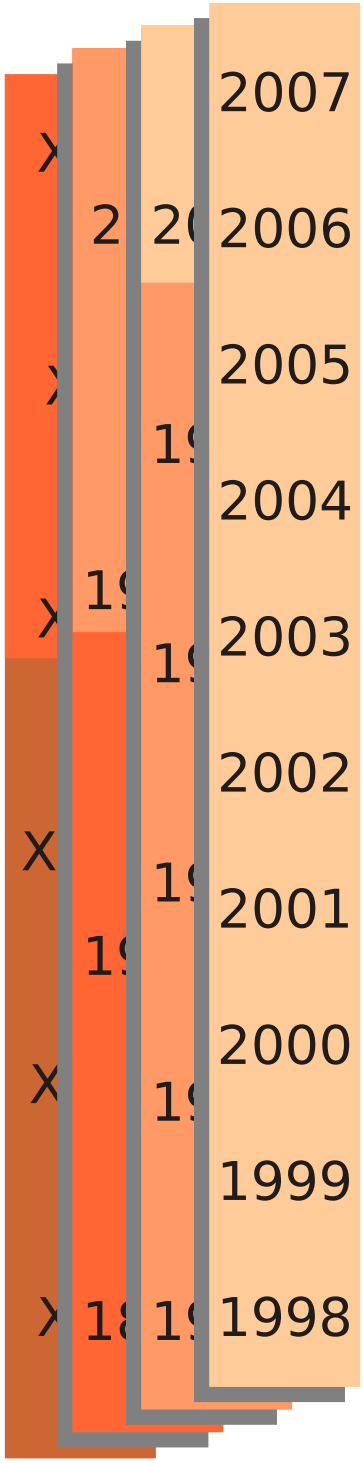


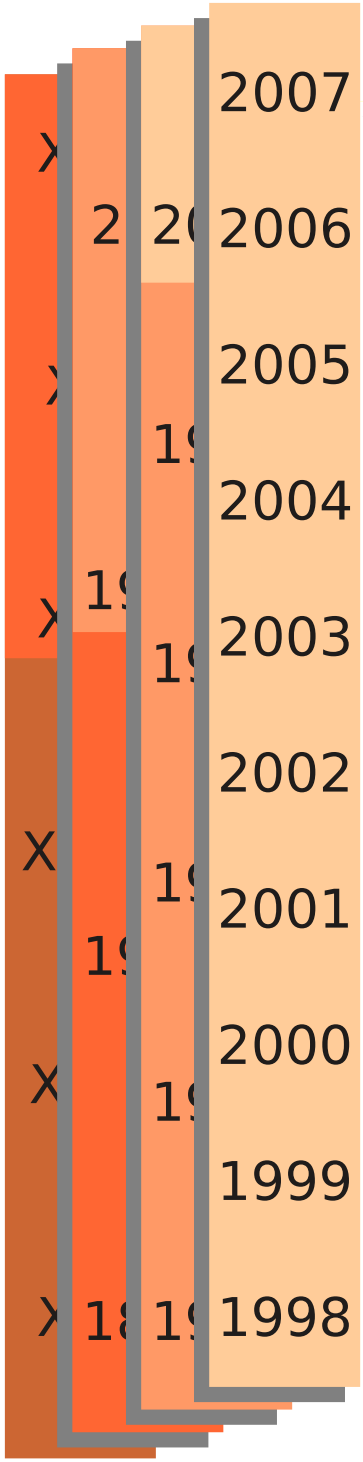
	projects	publications
2007		Choi Boogerd Grierson Palsson
2006	ERASysBio	BMC Sys Bio Alon Szallasi Kriete MSB
2005	SystemsX	Klipp Kaneko
2004	Systems Biology Enters FP6 hepatosys	IEE Sys Bio
2003	YSBN	SBML
2002		*Science* special issue
2001	Alliance for Cellular Signaling	“Foundations of Systems Biology” Ideker/Hood
2000		Von Dassow “Computational Cell Biology”
1999	ERATO-Kitano	
1998		ECell

Rise of Systems Biology as a paradigm



projects	publications	Institutes
ERASysBio	Choi Boogerd Grierson Palsson BMC Sys Bio Alon Szallasi Kriete MSB Klipp Kaneko	6 BBSRC centres
SystemsX	IEE Sys Bio	BioQuant
Systems Biology Enters FP6 hepatosys	SBML	
YSBN	*Science* special issue	
Alliance for Cellular Signaling	"Foundations of Systems Biology" Ideker/Hood	Tokyo Systems Biology Institute
ERATO-Kitano	Von Dassow "Computational Cell Biology"	Seattle Institute for Systems Biology
	ECell	

Rise of Systems Biology as a paradigm



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Alliance for Cellular Signaling

ERATO-Kitano

End of BBSRC Systems Biology calls

6 BBSRC centres

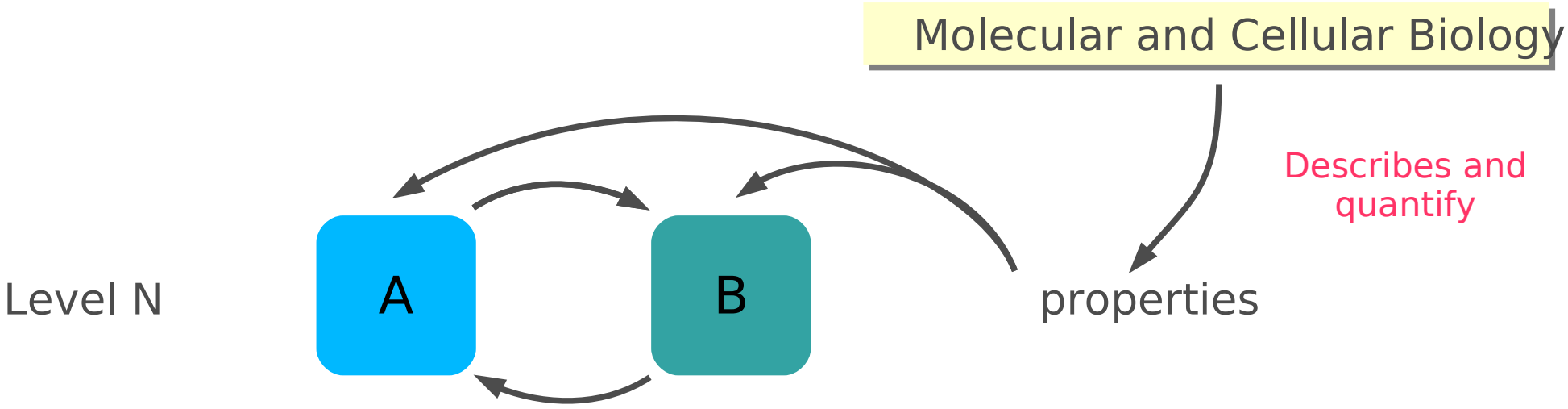
BioQuant

Tokyo Systems Biology Institute

Seattle Institute for Systems Biology

projects **publications** **Institutes**

But what is Systems Biology???



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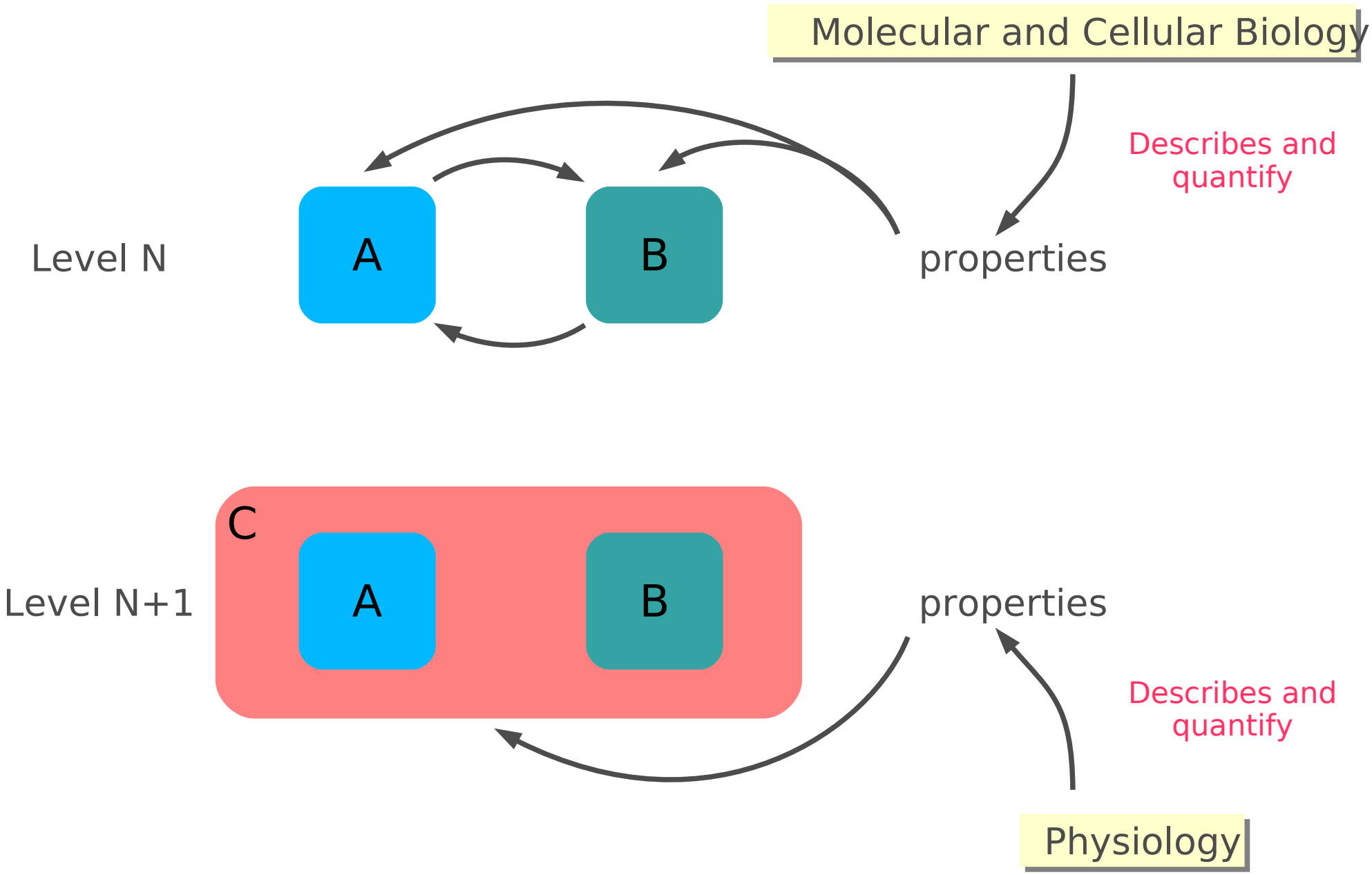

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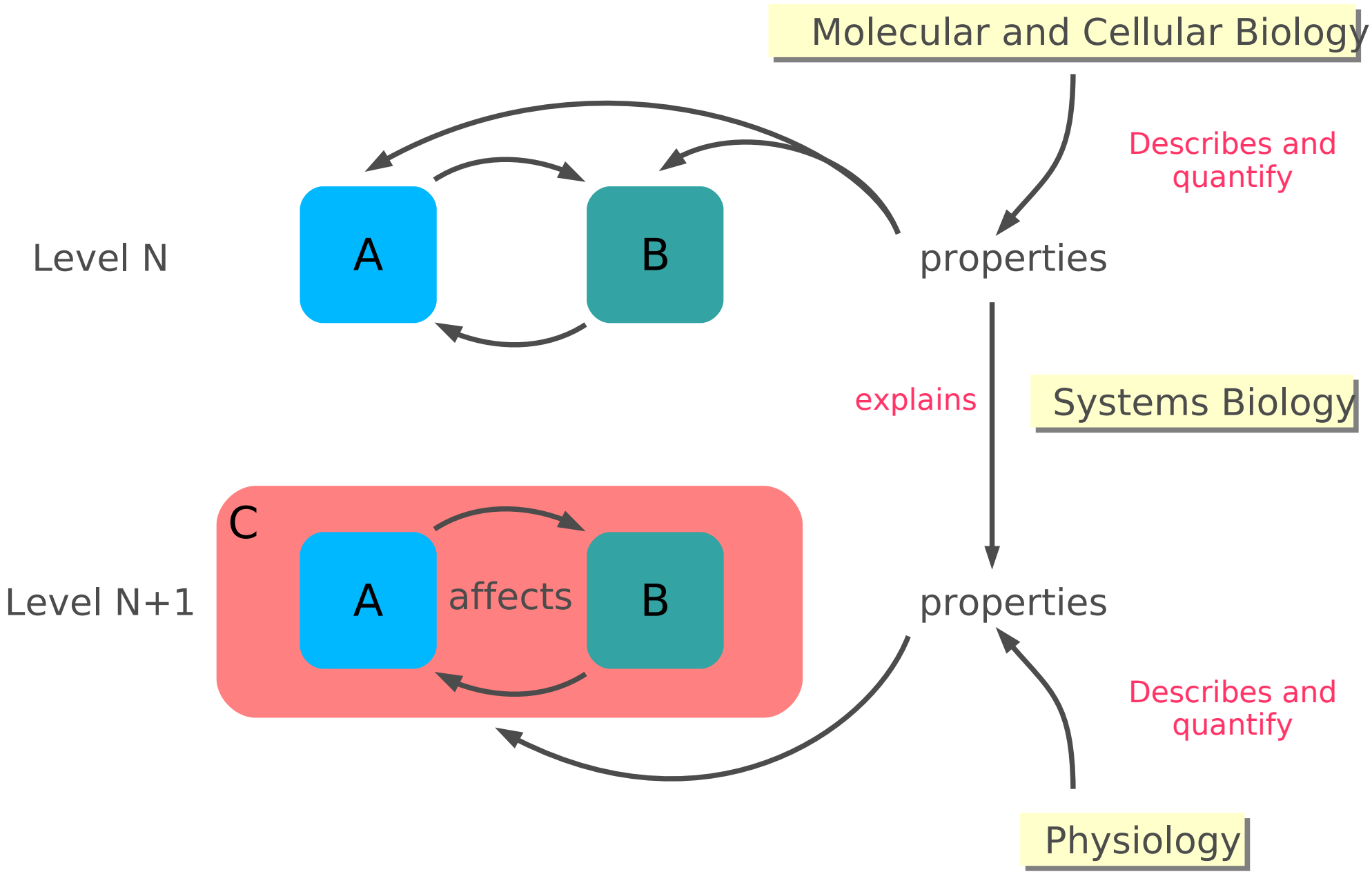

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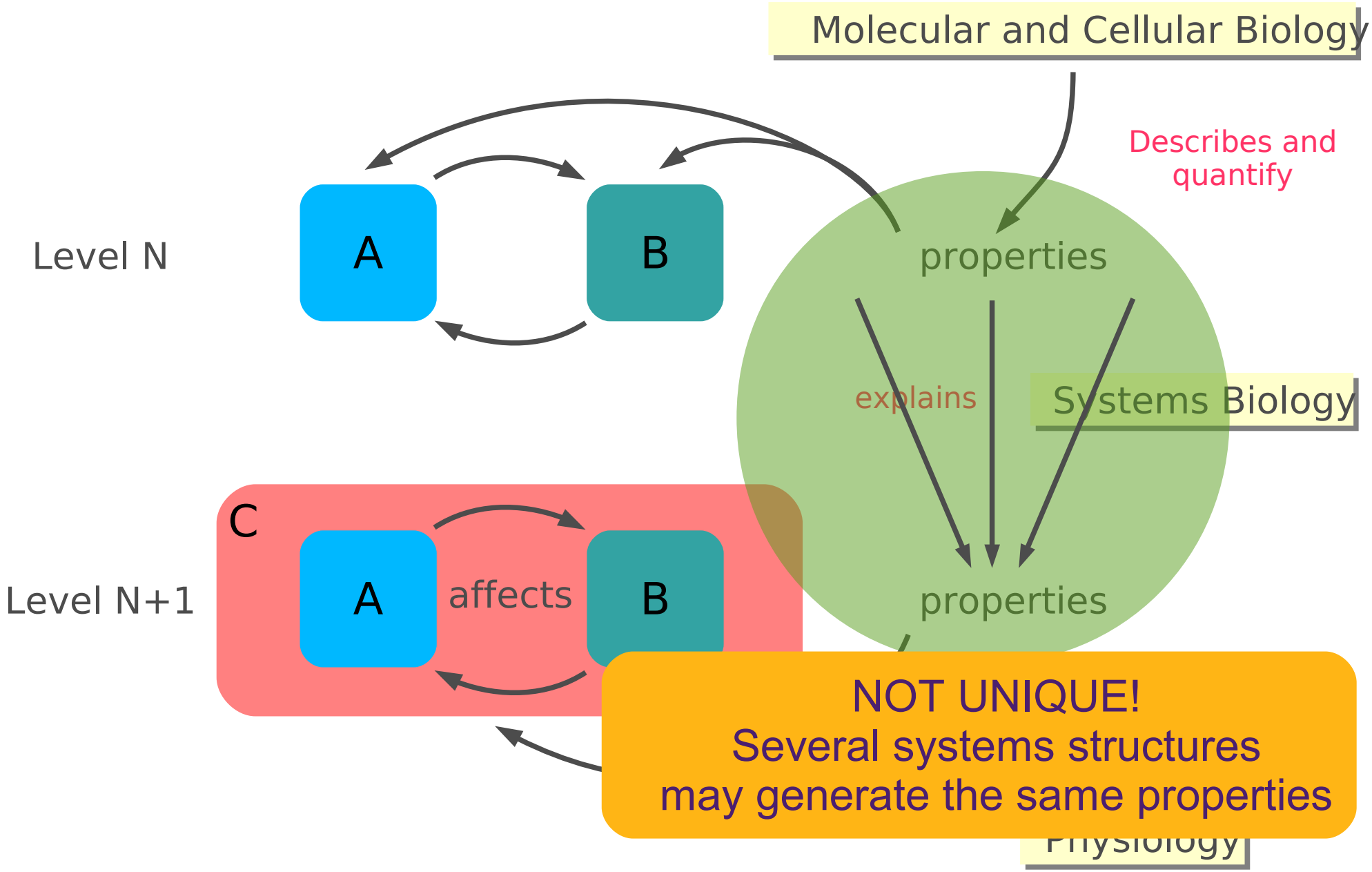

What Systems Biology is not!

Purely theoretical: Most systems biologists are actually experimental biologists

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

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

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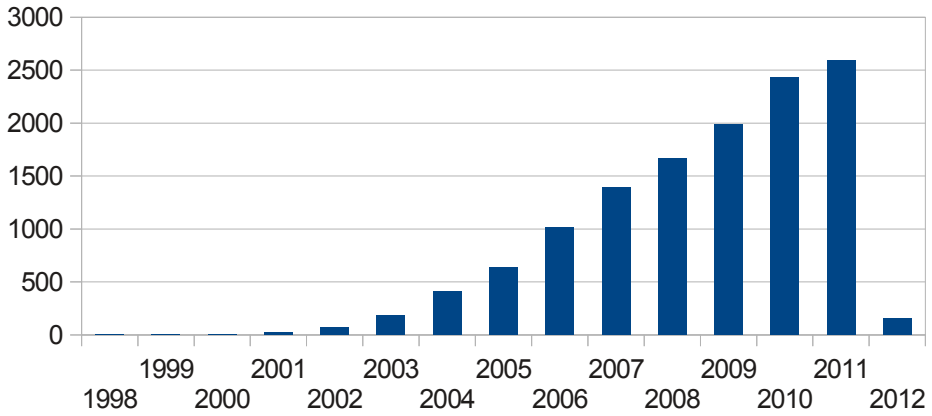
Systems Biology is the study of the ***emerging*** properties of a biological system, taking into account all the ***necessary*** constituents, their ***relationships*** and their ***dynamics***

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

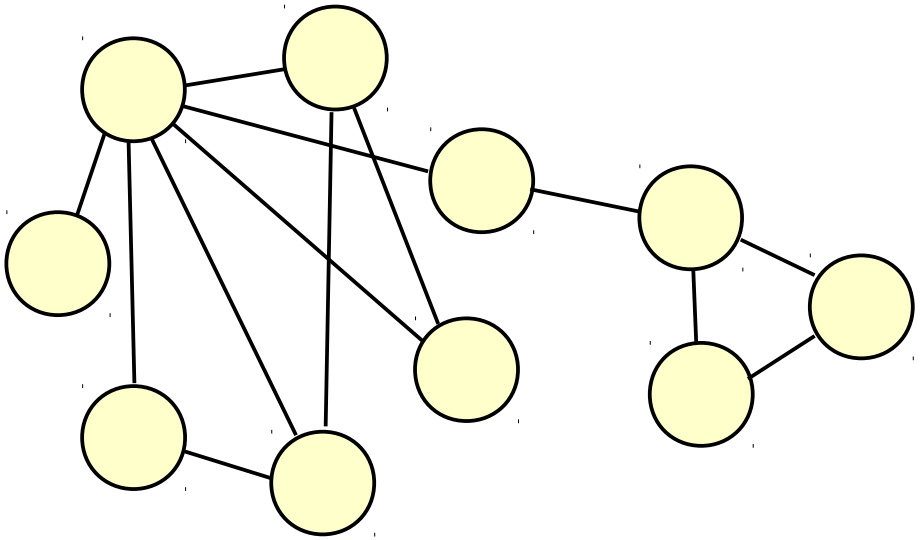
Types of representation

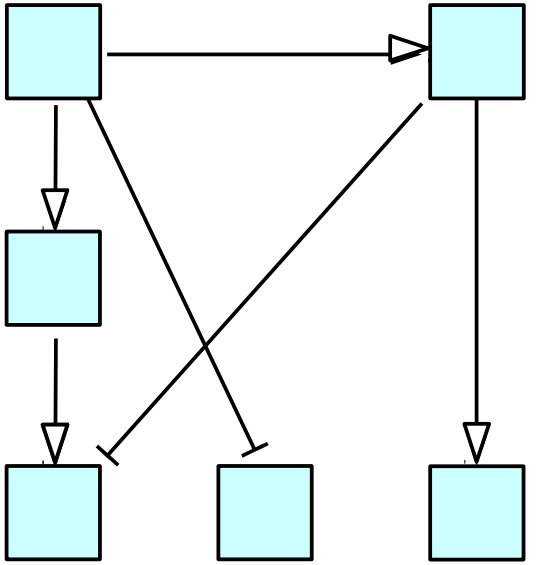
Scales and the mesoscopic gap

Genotype-system-phenotype problem

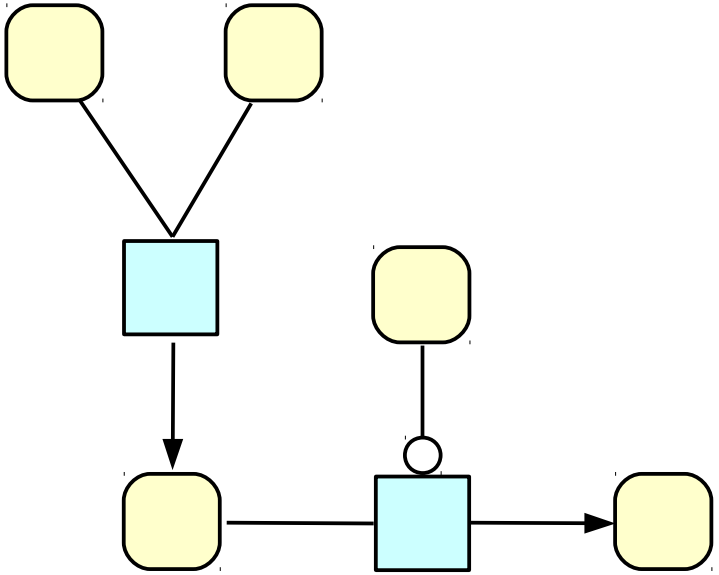
Drug discovery models
Vs systems modelling

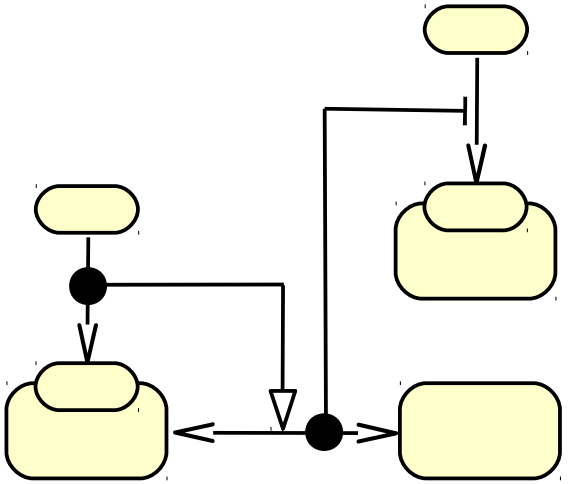
Drug discovery models
Vs “omics” data



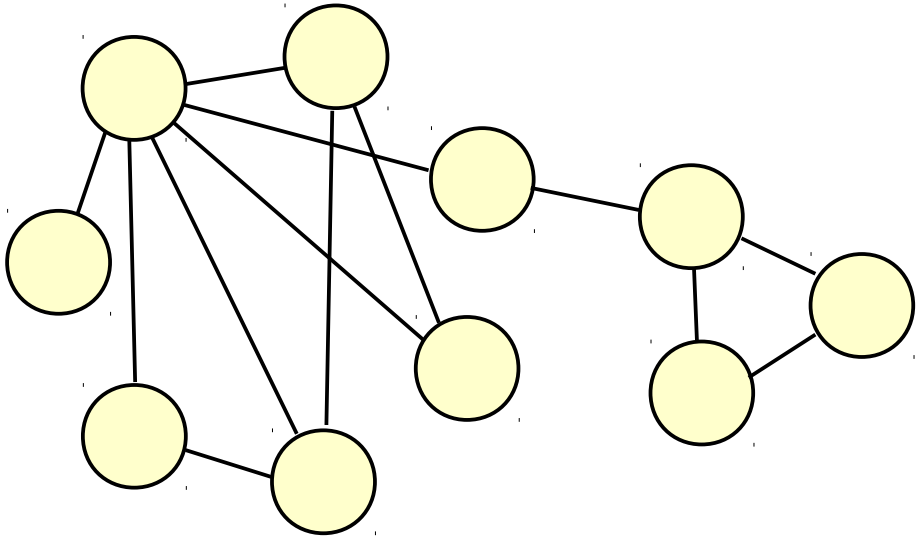


The four views of systems biology



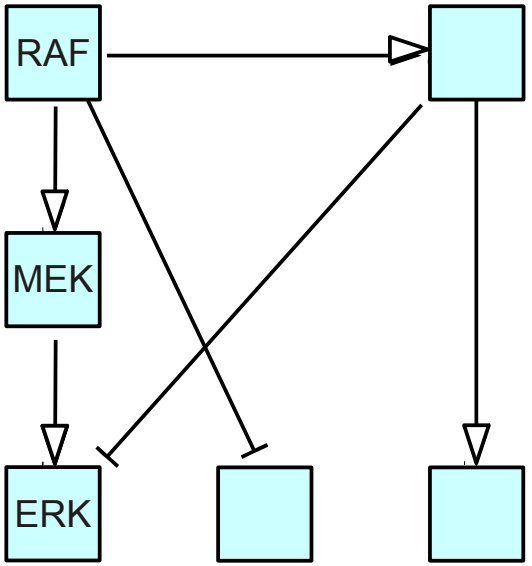


Interaction networks



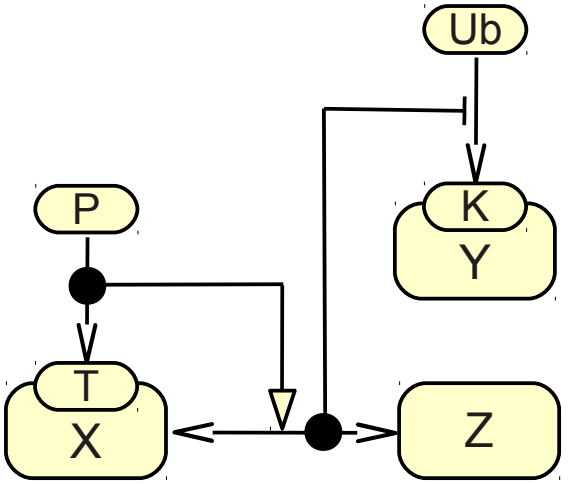
- Non-directional
- Non-sequential
- Non-mechanistic
- Statistical modelling
- Functional genomics
- IntAct, DIP, String

Activity-Flows



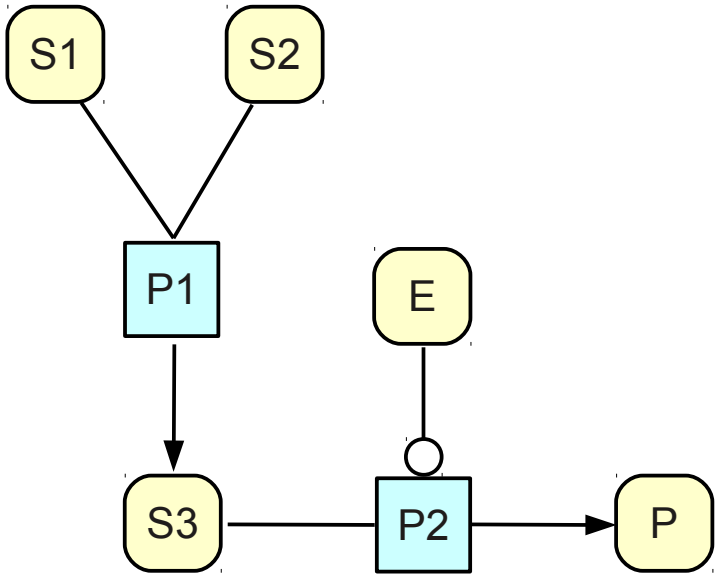
- Directional
- Sequential
- Non-mechanistic
- Logical modelling
- Signalling pathways, gene regulatory networks
- KEGG, STKEs

Entity Relationships

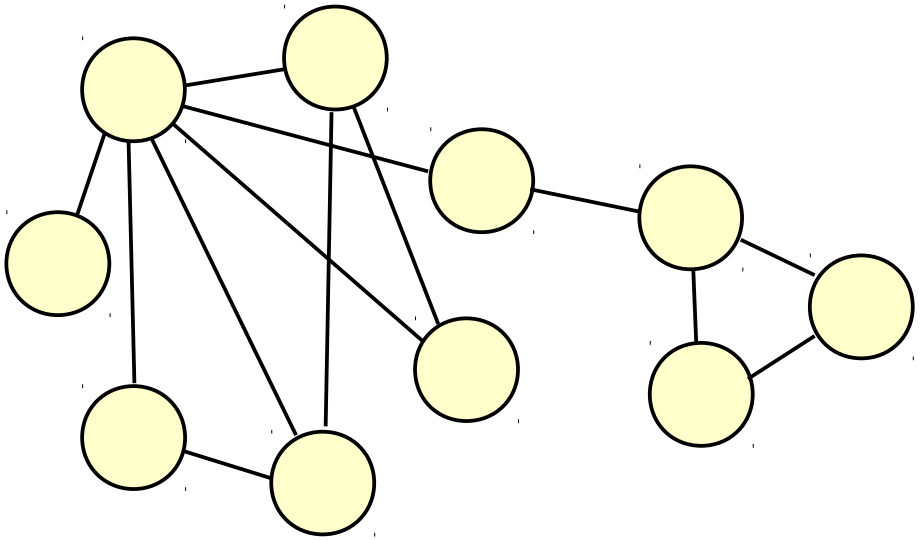


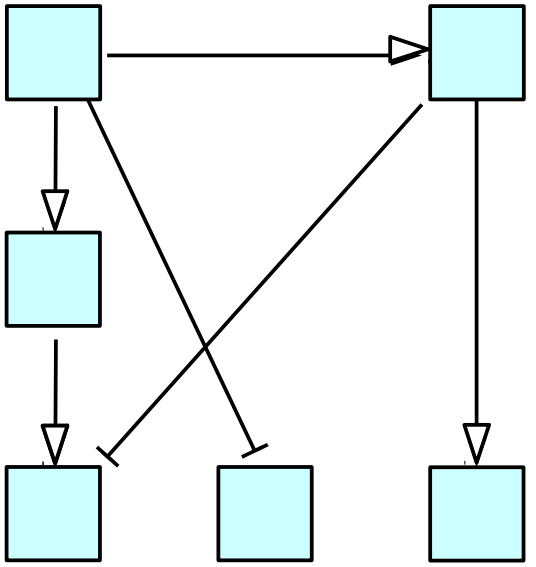
- Directional
- Non-sequential
- Mechanistic
- Independent rules: no explosion
- Rule-based modelling
- Molecular Biology
- MIM

Process Descriptions

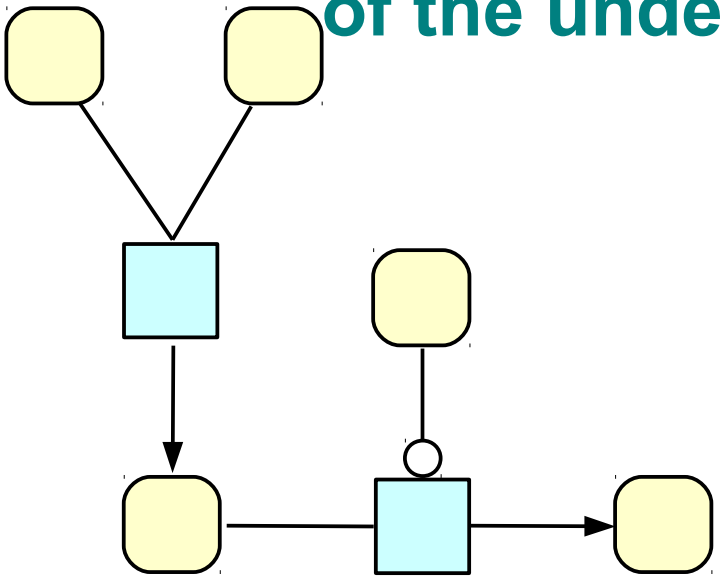


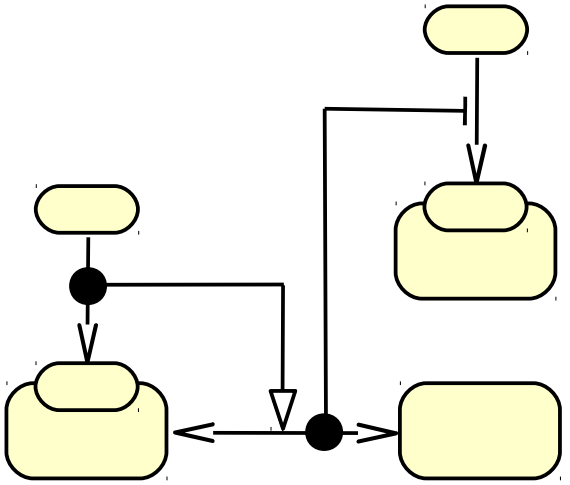
- Directional
- Sequential
- Mechanistic
- Subjected to combinatorial explosion
- Process modelling
- Biochemistry, Metabolic networks
- KEGG, Reactome

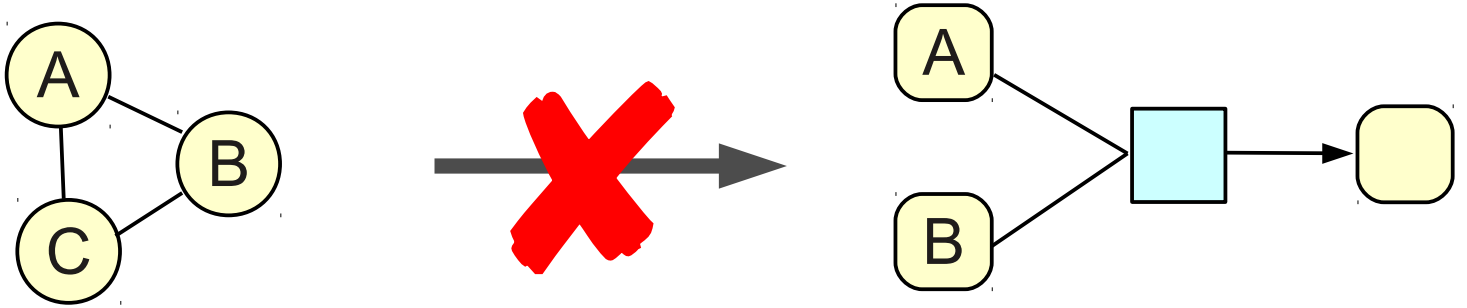




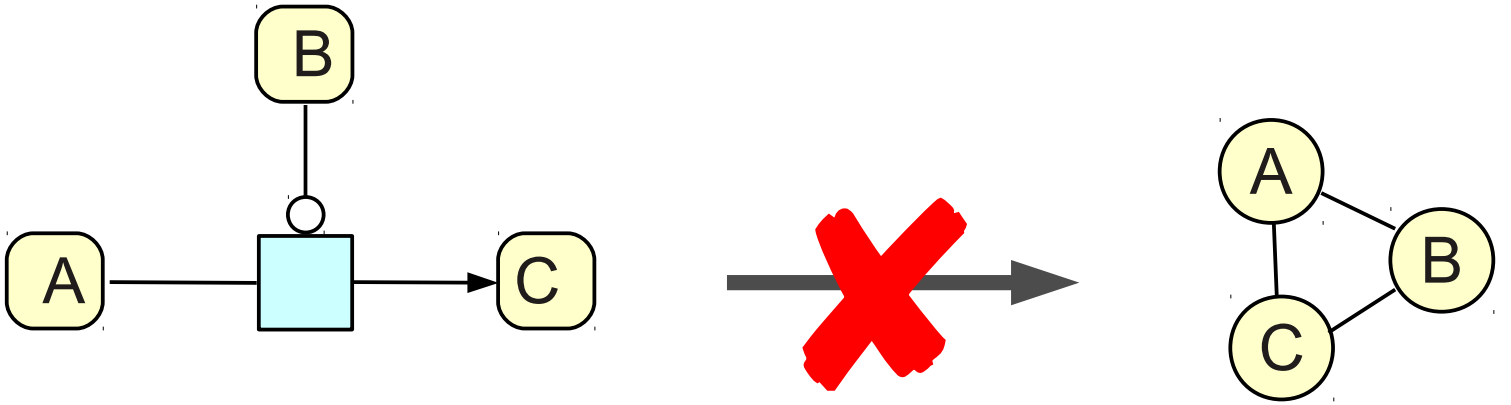
The four views are orthogonal projections of the underlying biological phenomena





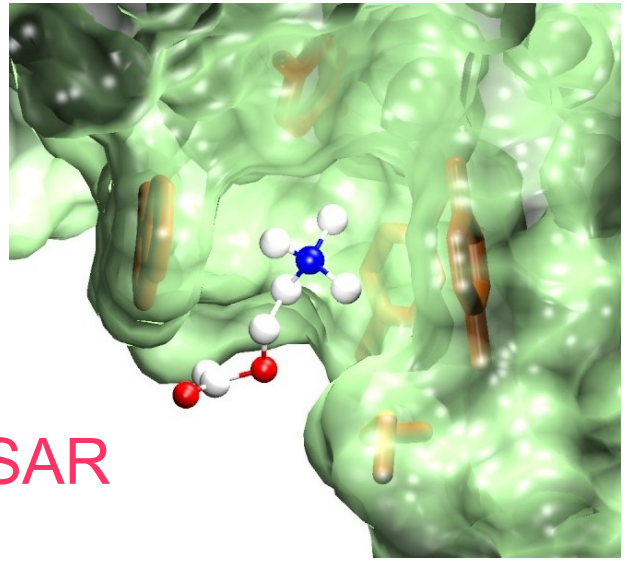


Think scaffolding proteins

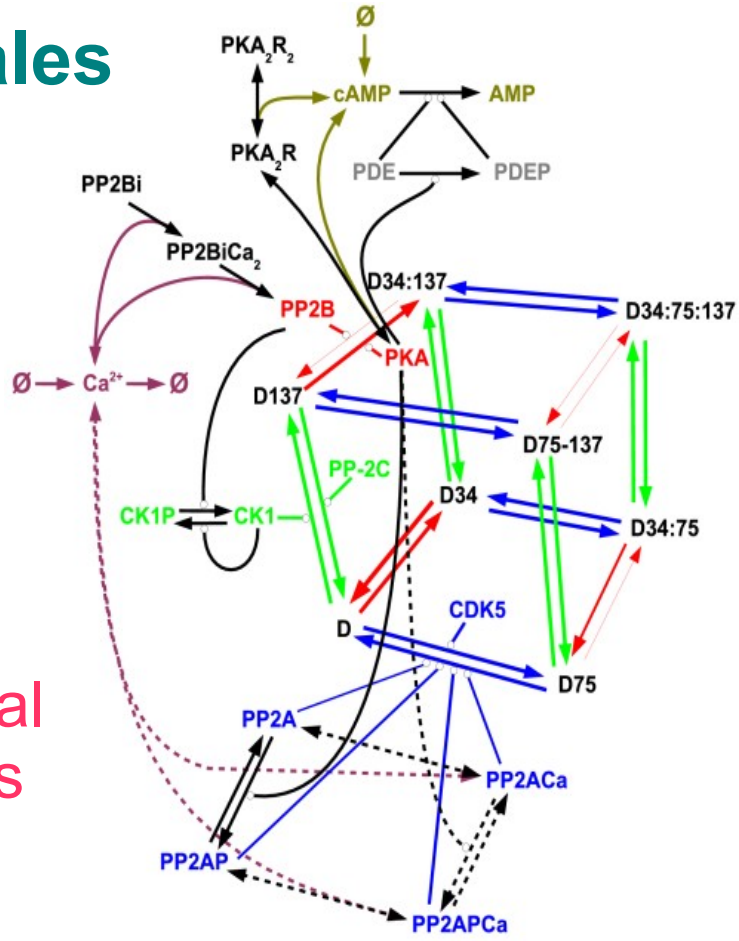


Think phosphorylated signals

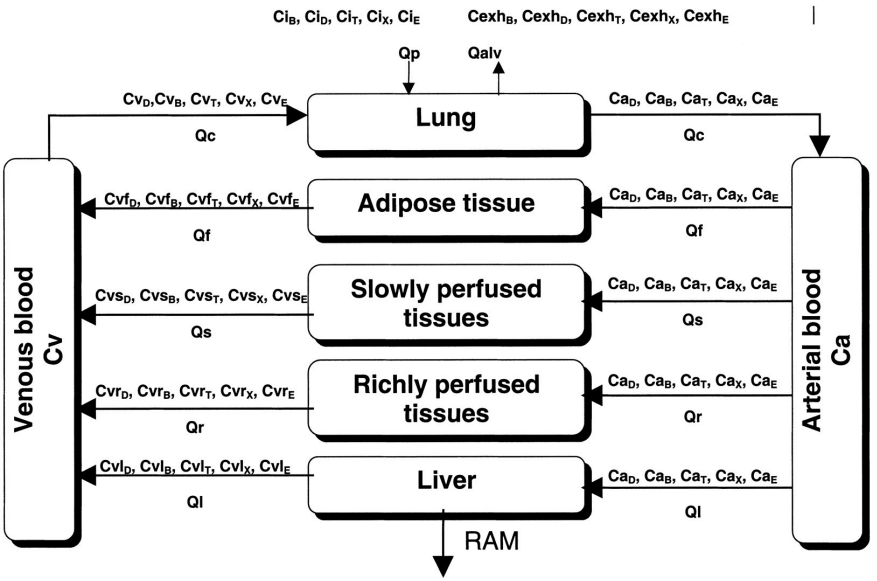
The problem of scales



QSAR



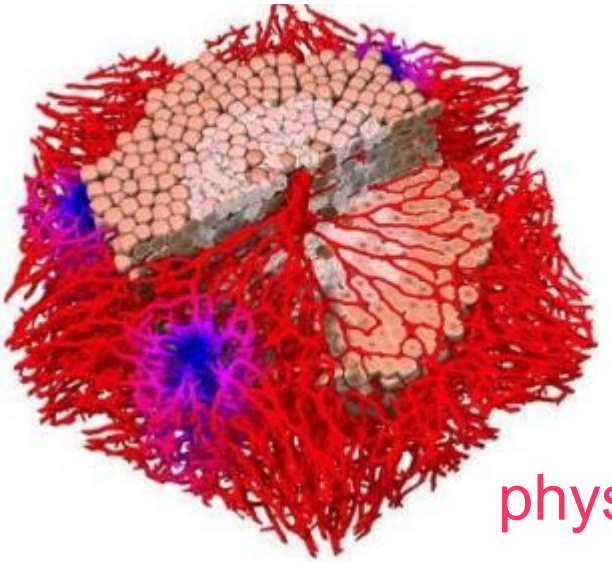
chemical kinetics



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

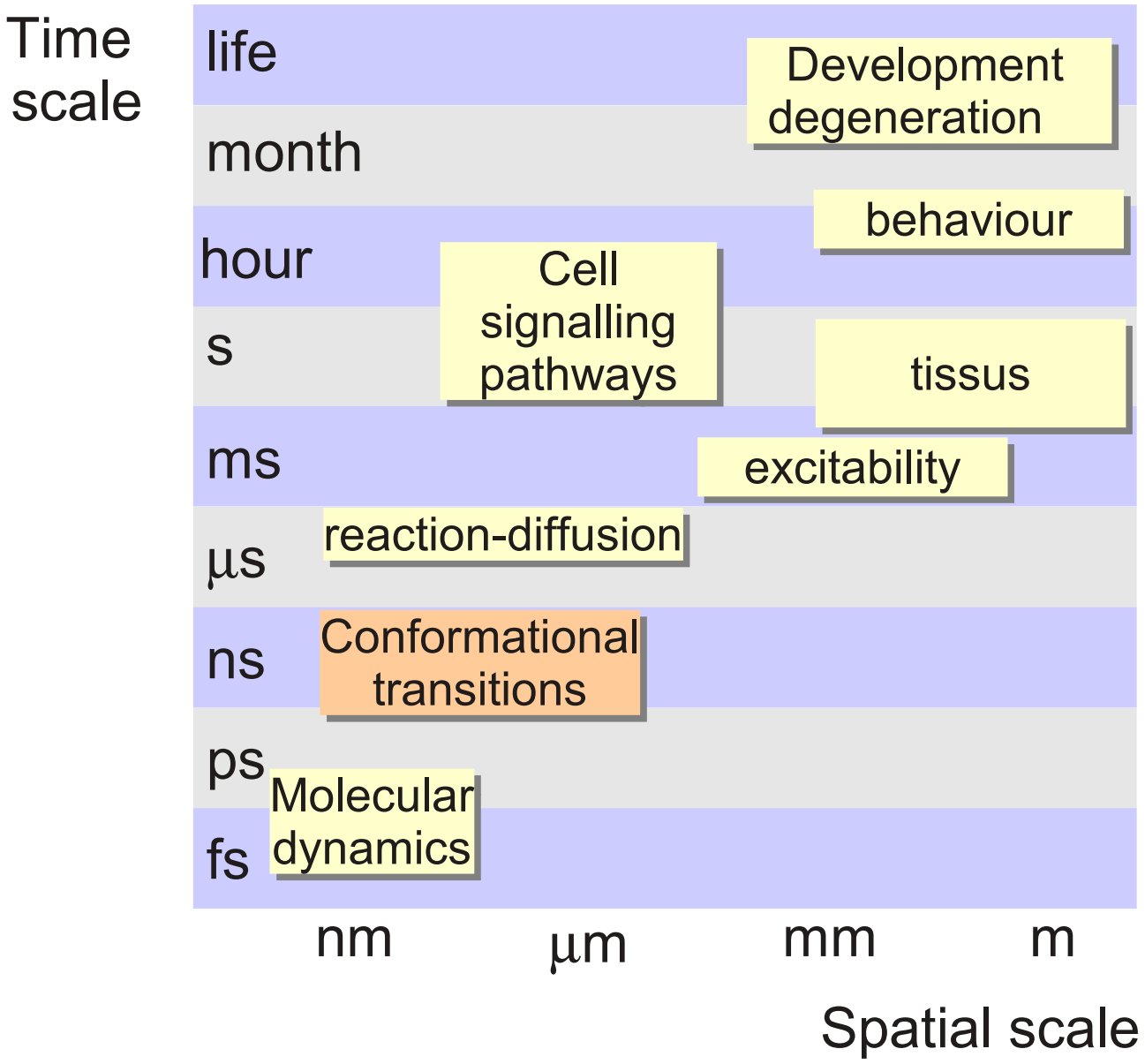
$$RAM_B = \frac{Vmax_B \; Cvl_B}{Km_B\left(1+\frac{Cvl_D}{Ki_{DB}}+\frac{Cvl_T}{Ki_{TB}}+\frac{Cvl_E}{Ki_{EB}}+\frac{Cvl_X}{Ki_{XB}}\right)+Cvl_B}$$

pharmacometrics

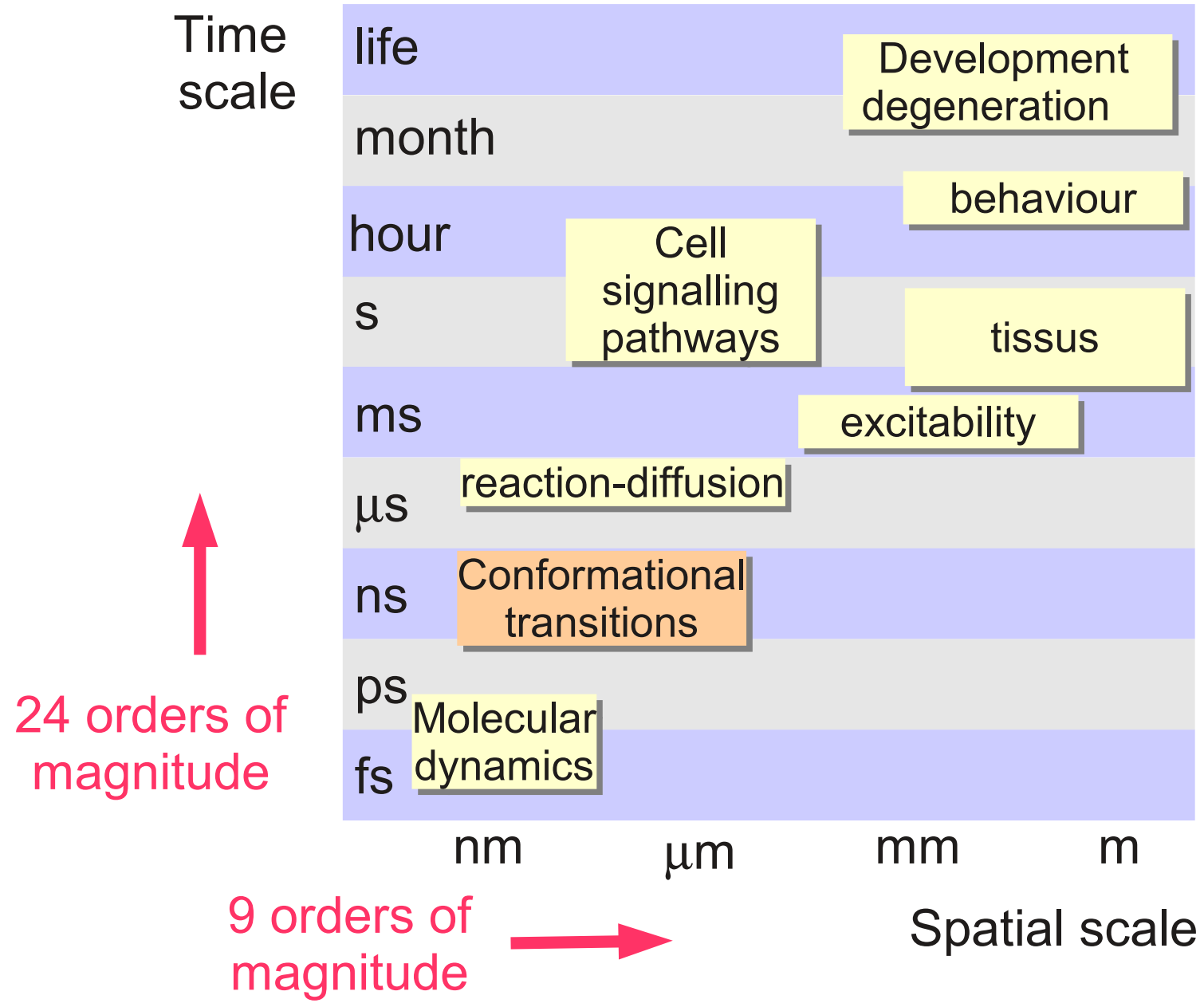


physiology

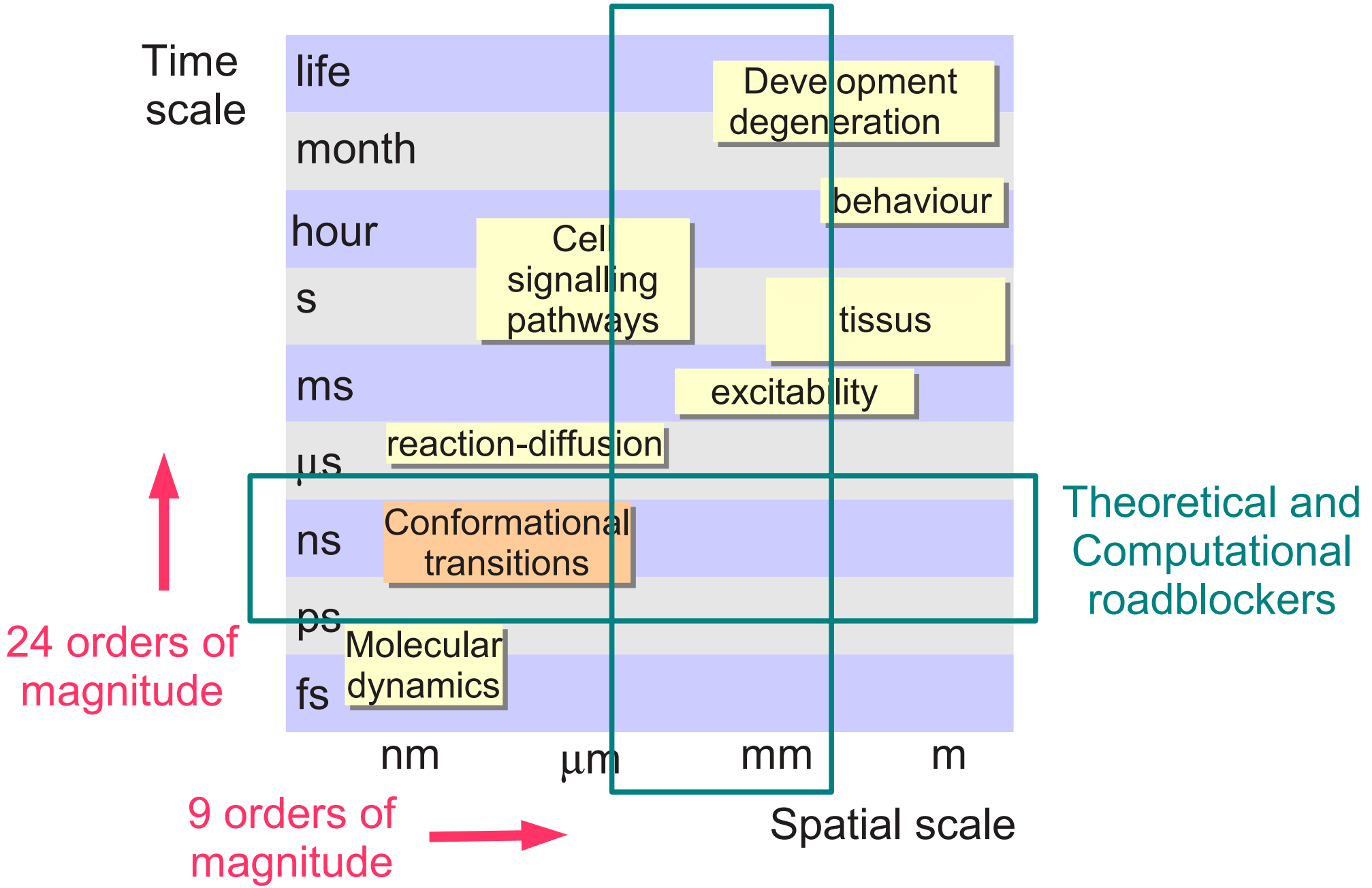
The mesoscopic gap



The mesoscopic gap



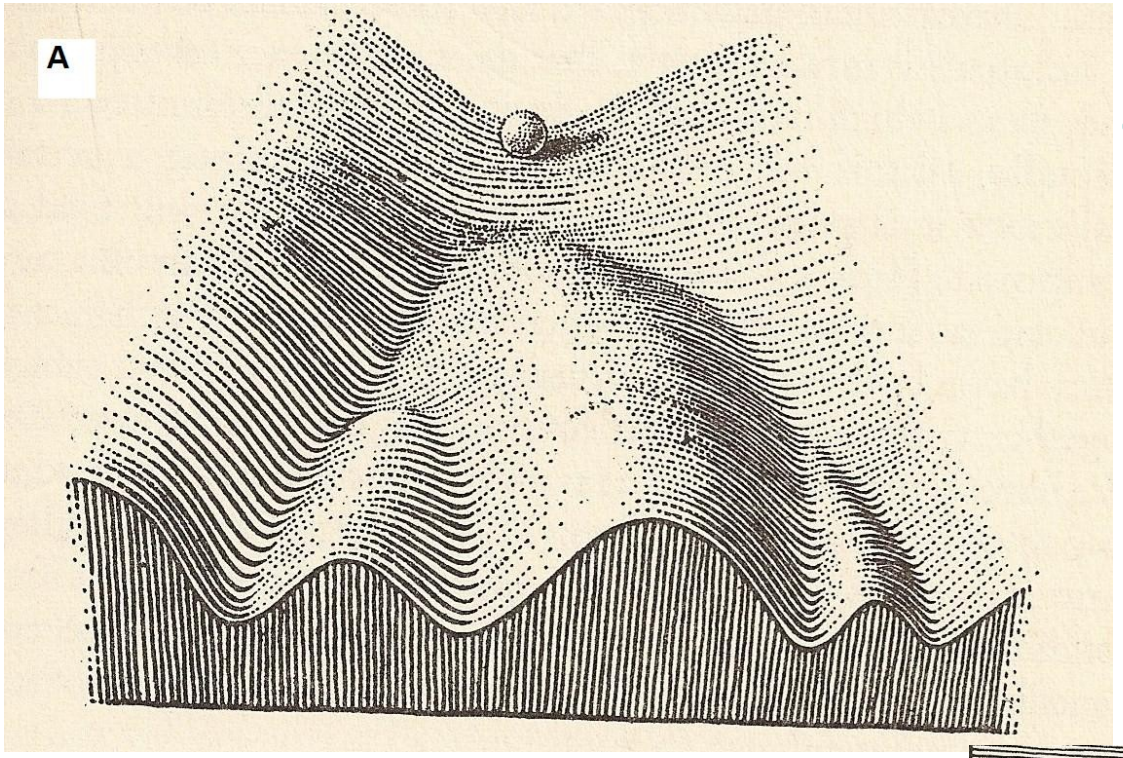
The mesoscopic gap



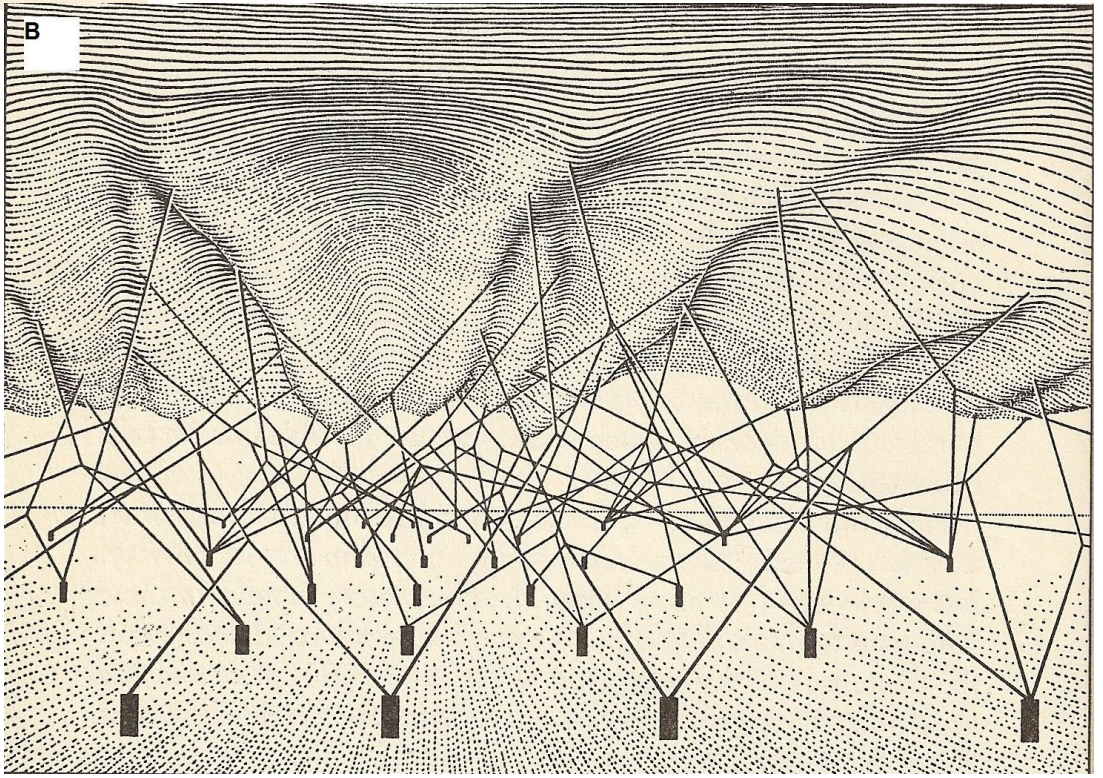
Multi-scale does not mean fine scale plus massive power

- 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.

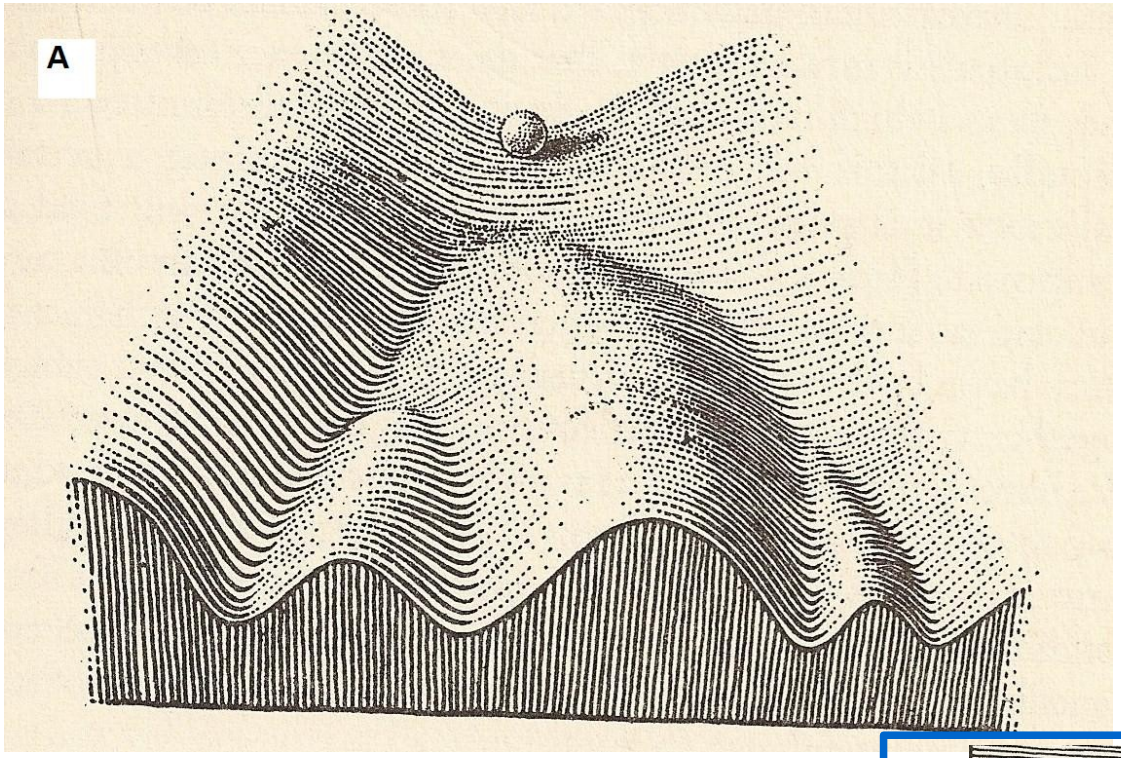
Emergent properties and the gene-system-phenotype puzzle



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



Emergent properties and the gene-system-phenotype puzzle



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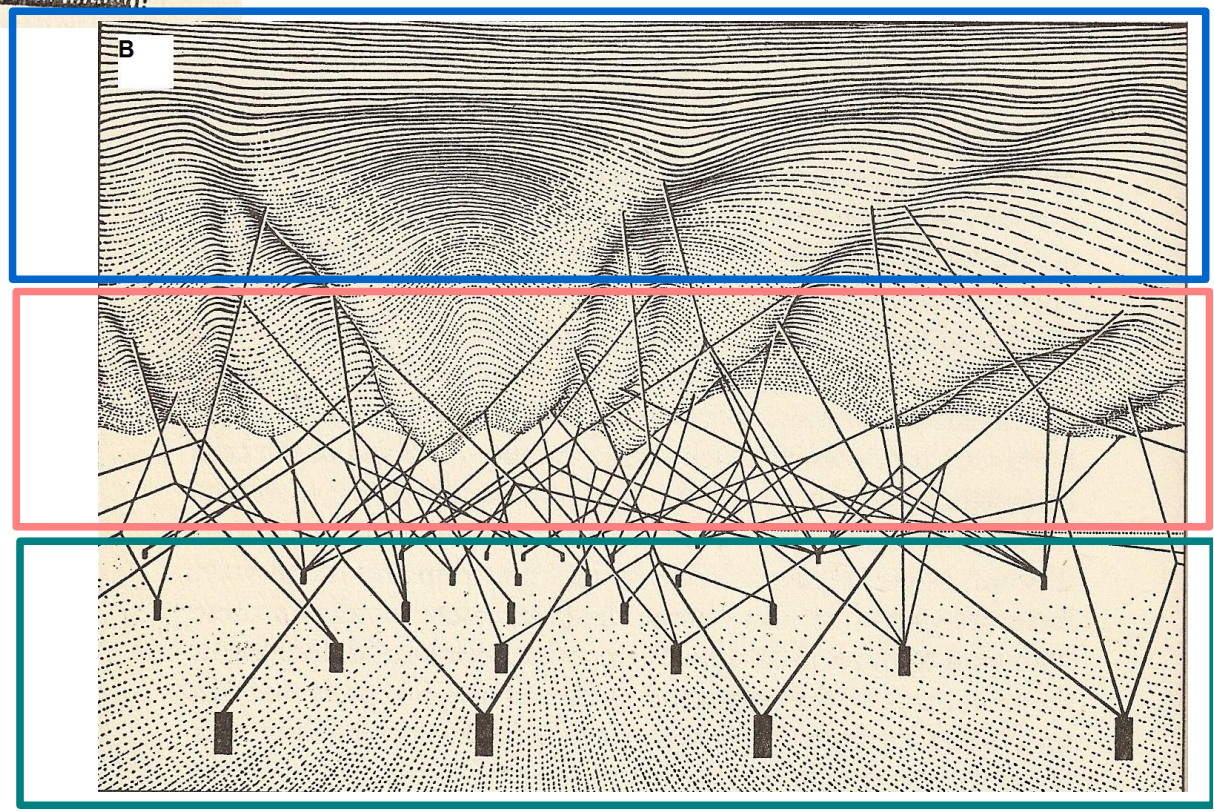
George Allen & Unwin

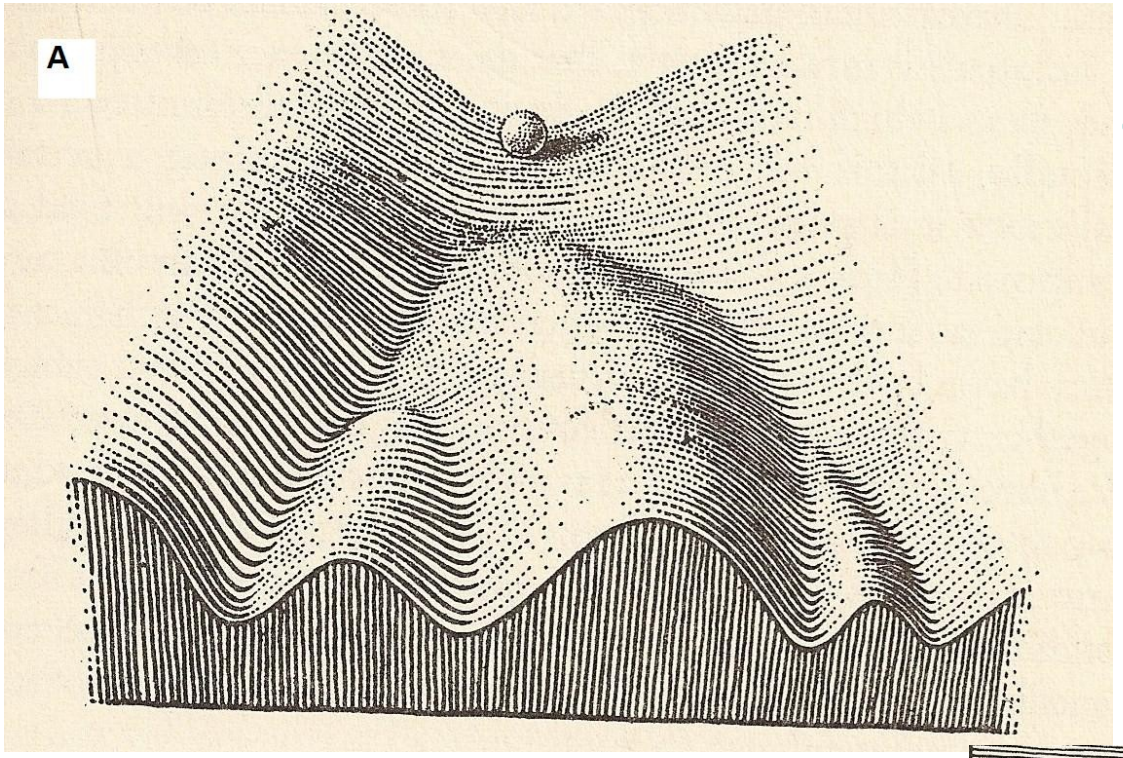
physiology ← phenotype

systems biology ← system

genetics ← genotype



Emergent properties and the gene-system-phenotype puzzle



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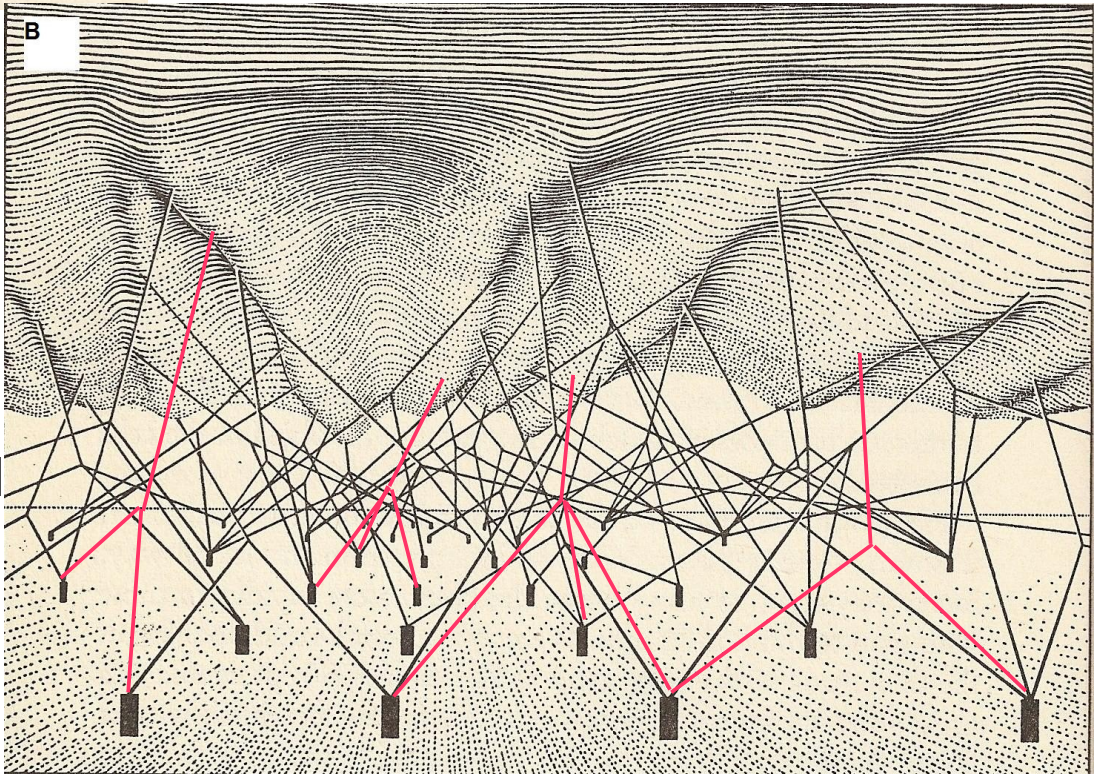
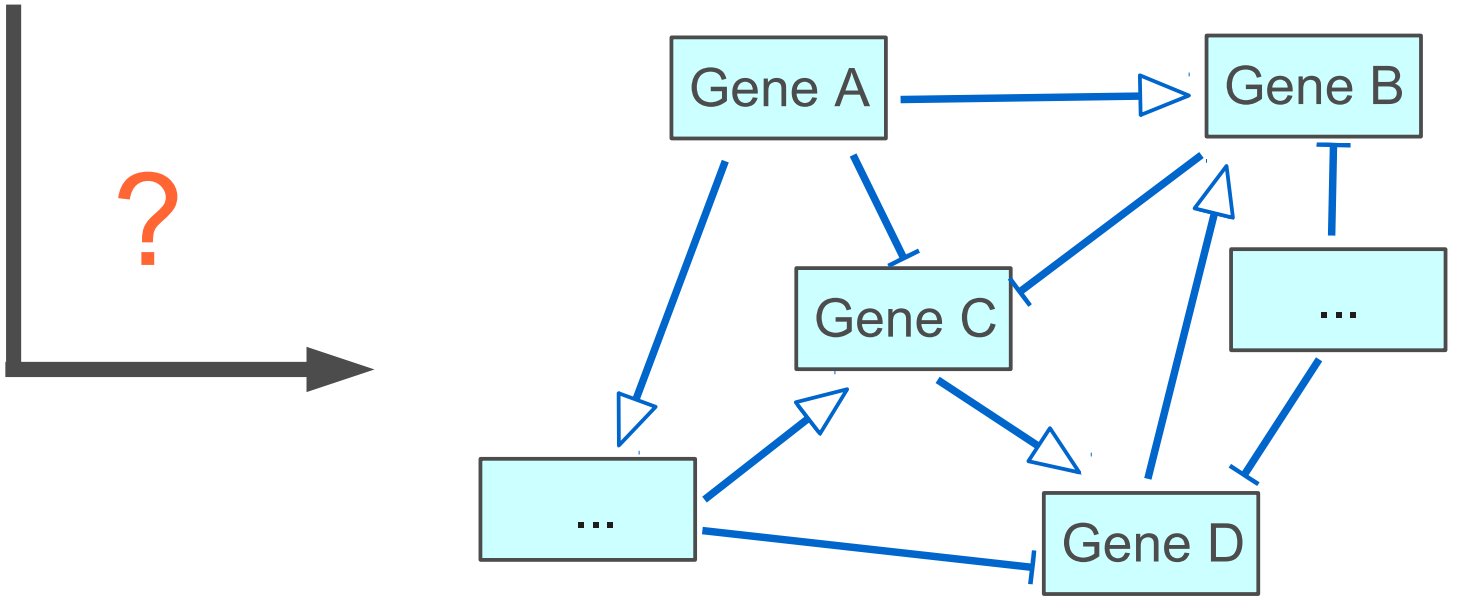
Many networks can theoretically generate the same phenotype, and this happens, in a synchronous (sister cells with same phenotype but different transcript/prote/metabol/omes) and diachronous manner (*omes of a cell changes over time but same phenotype).

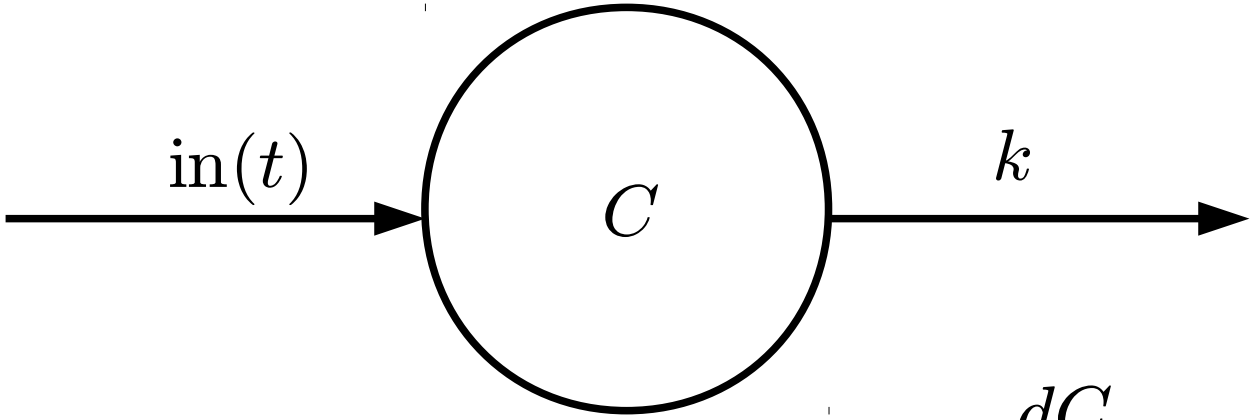


Reverse engineering is hard ...

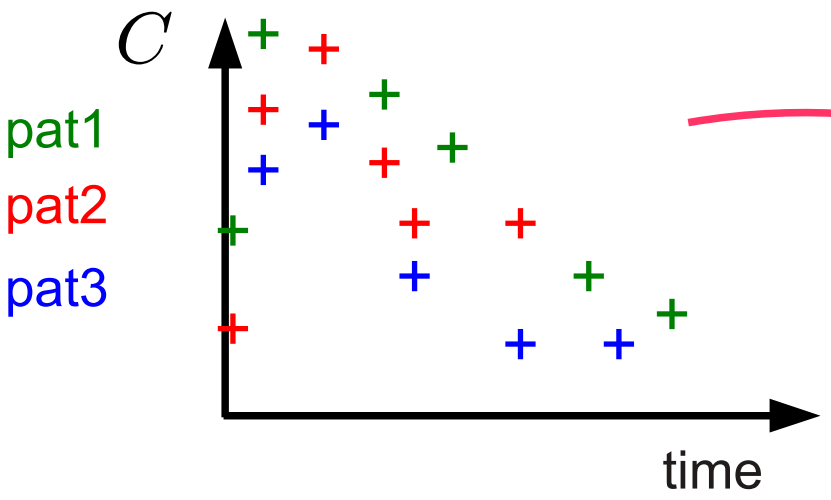
	Gene A	Gene B	Gene C	Gene D	...
Phenotype X	✔	✘	✔	✘	
Phenotype Y	✔	✘	✘	✔	
Phenotype Z	✘	✔	✔	✘	
...					

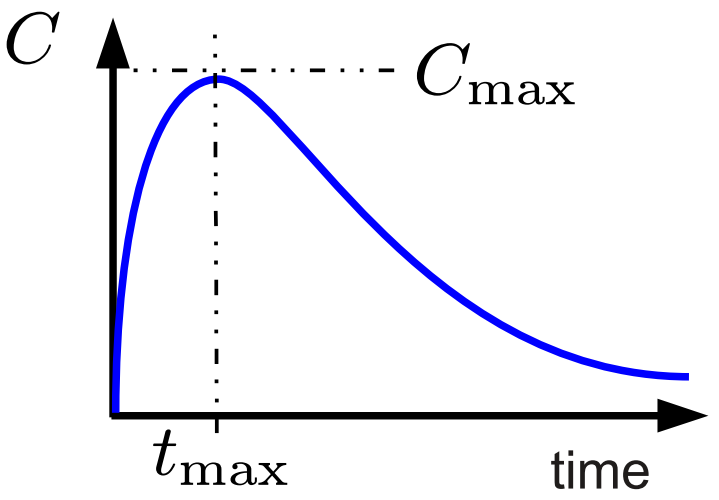


Drug discovery modelling: pharmacometrics

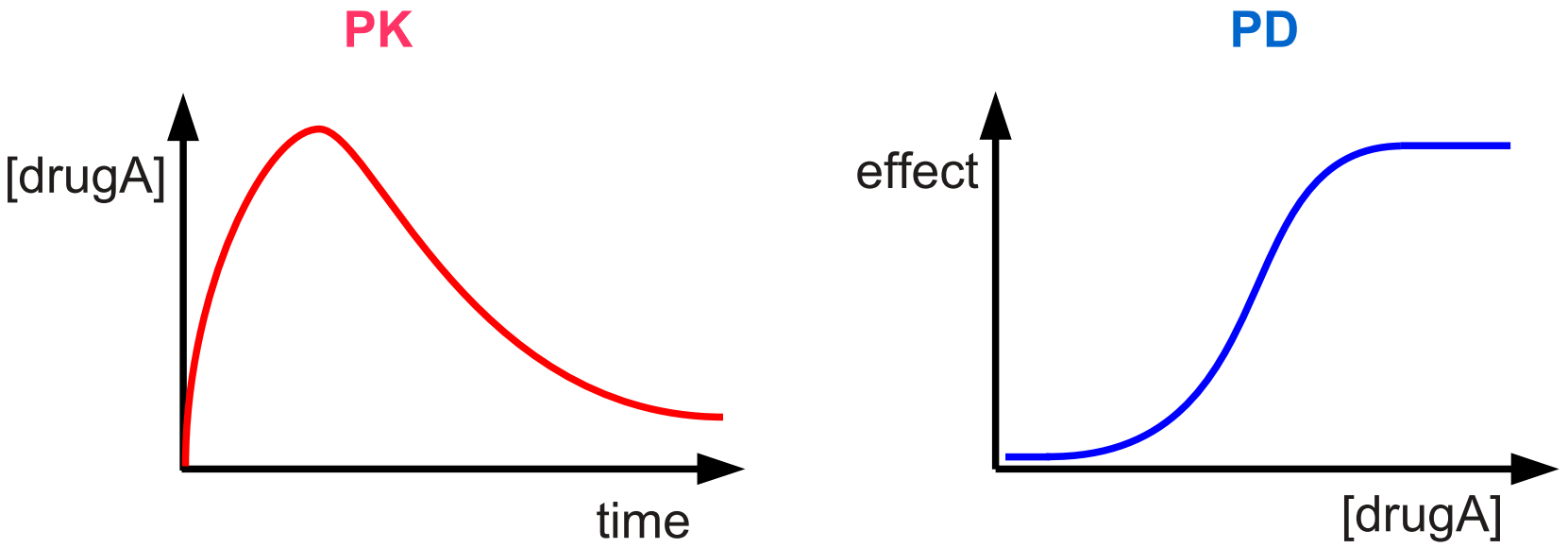


$$\frac{dC}{dt} = \text{in}(t) - k \times C$$

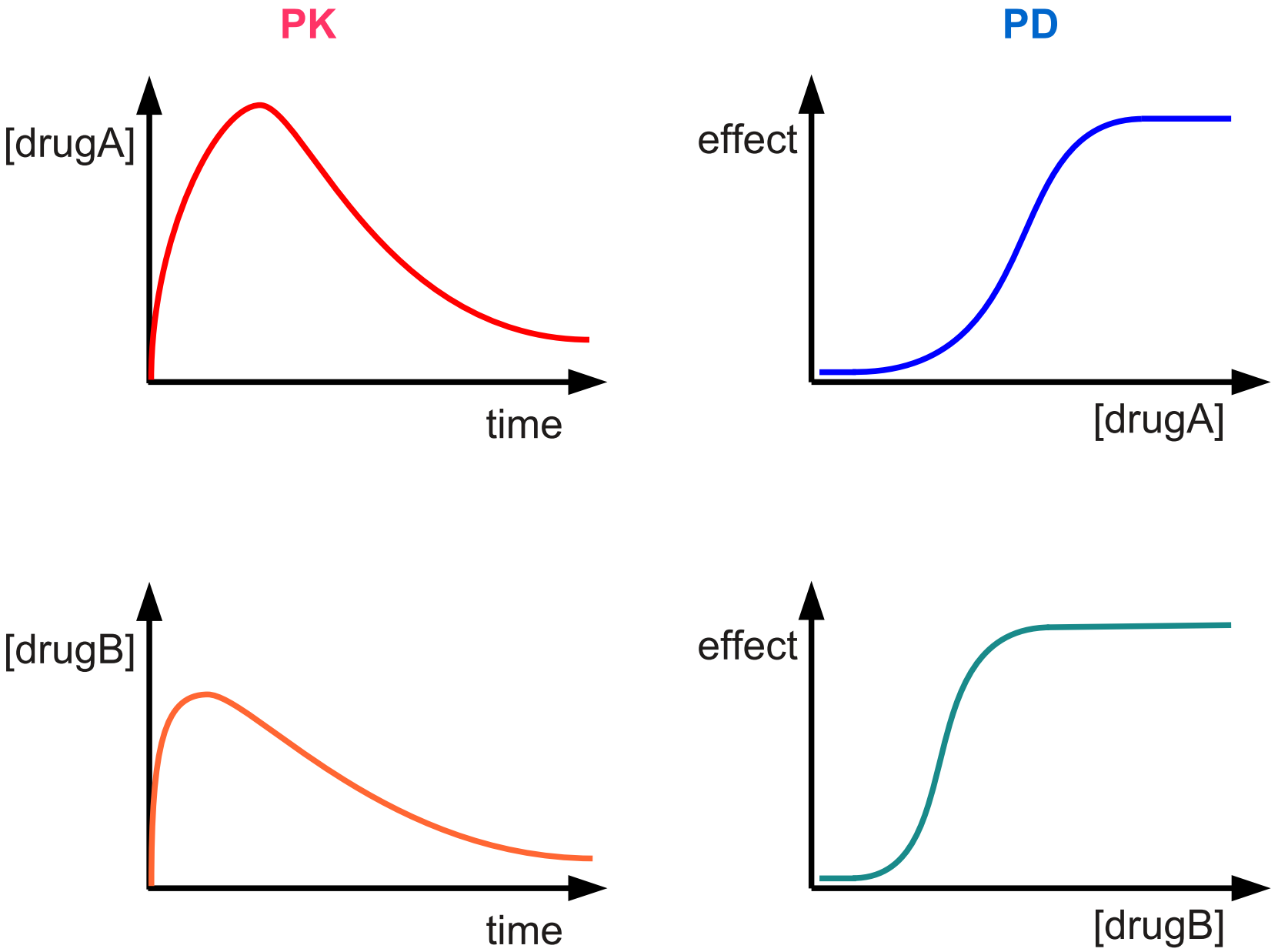




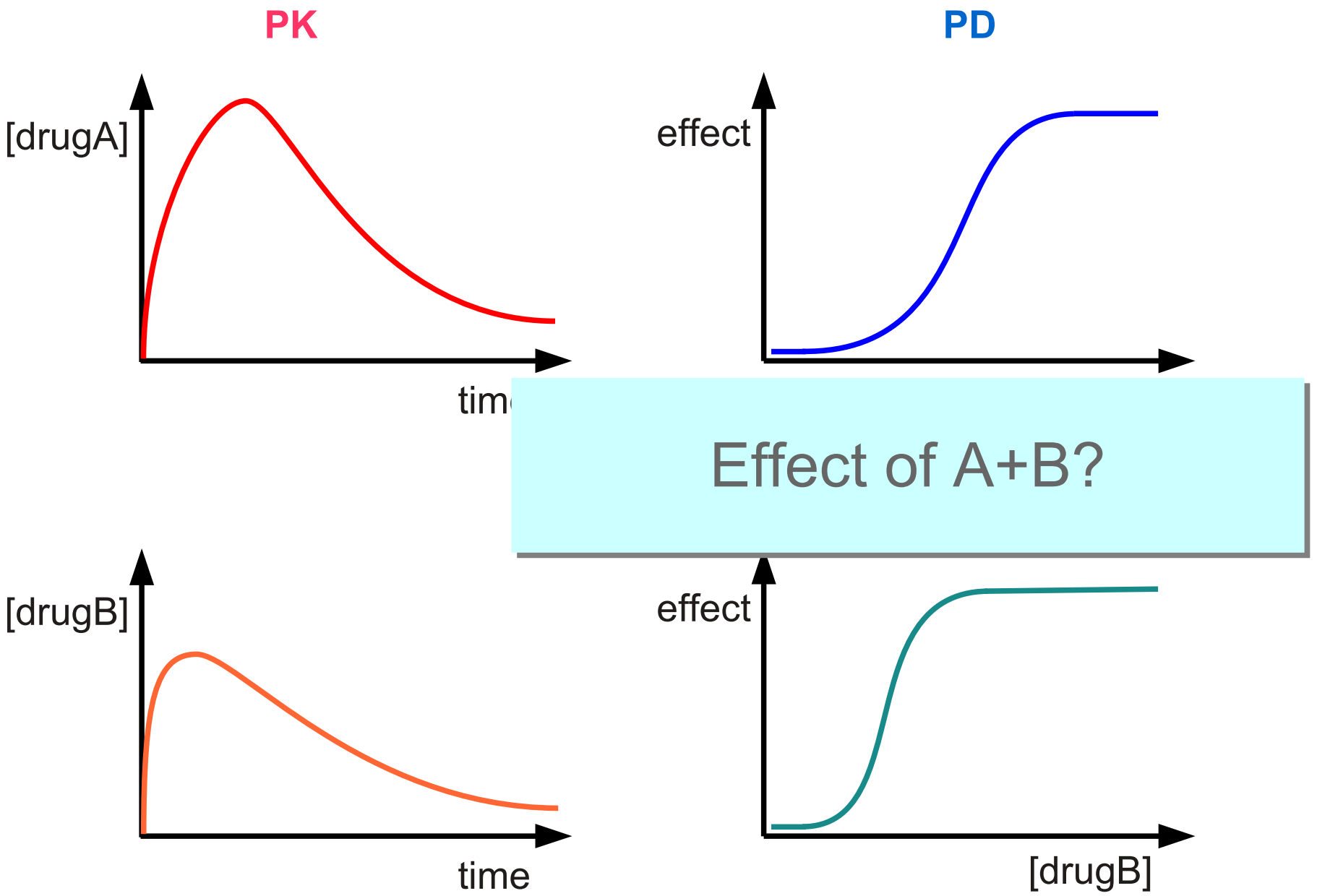
Drug discovery modelling: pharmacometrics



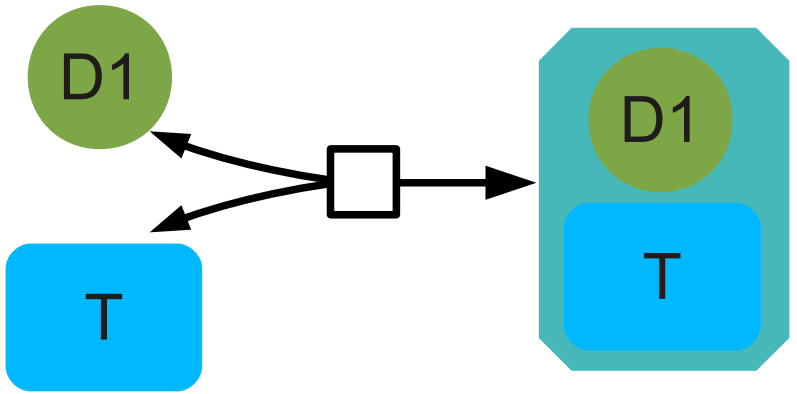
Drug discovery modelling: pharmacometrics



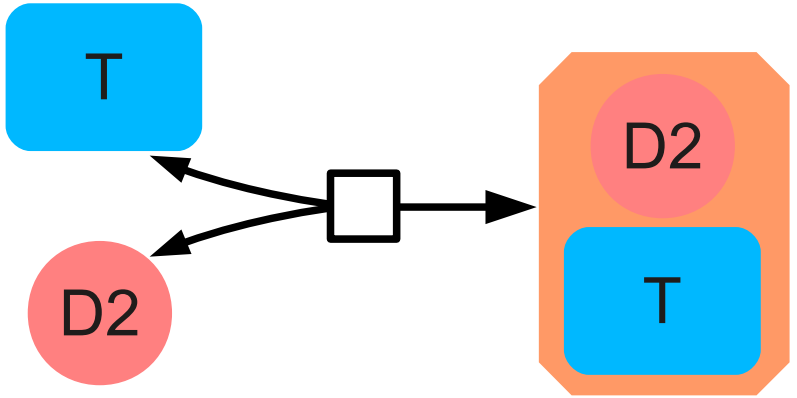
Drug discovery modelling: pharmacometrics



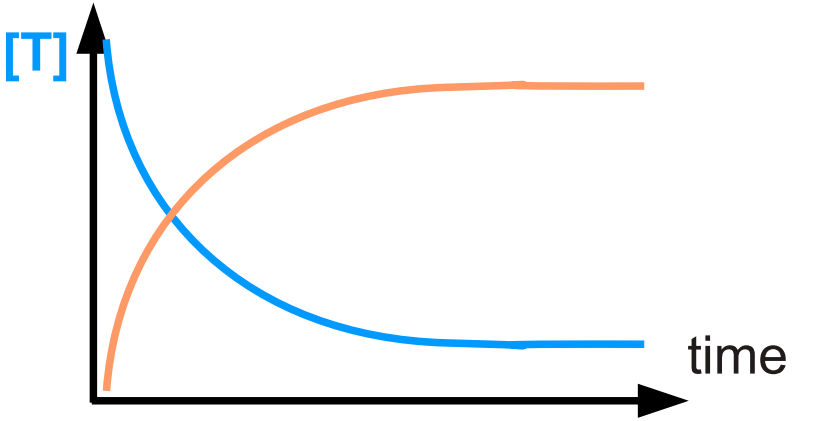
Systems modelling



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

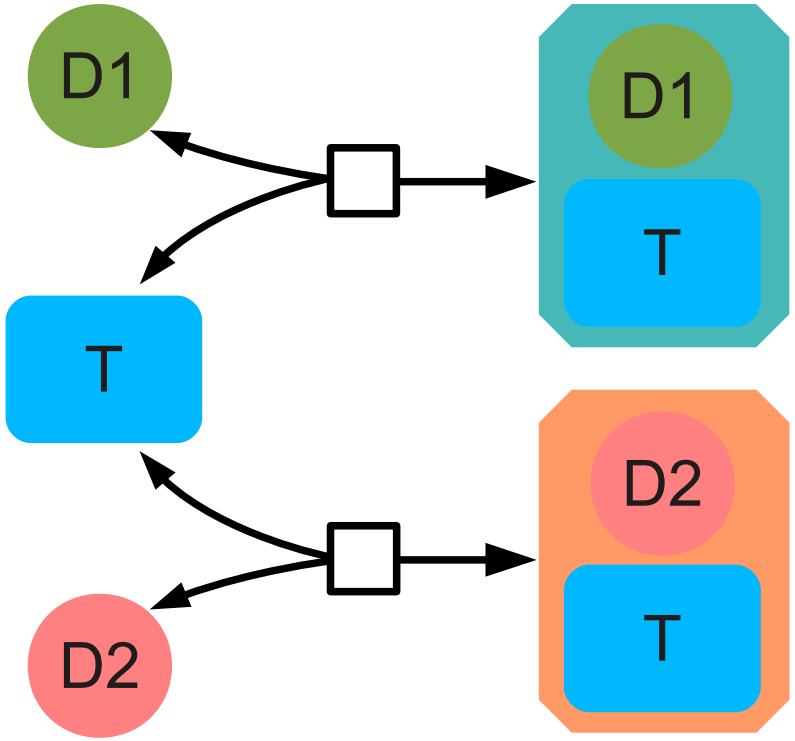


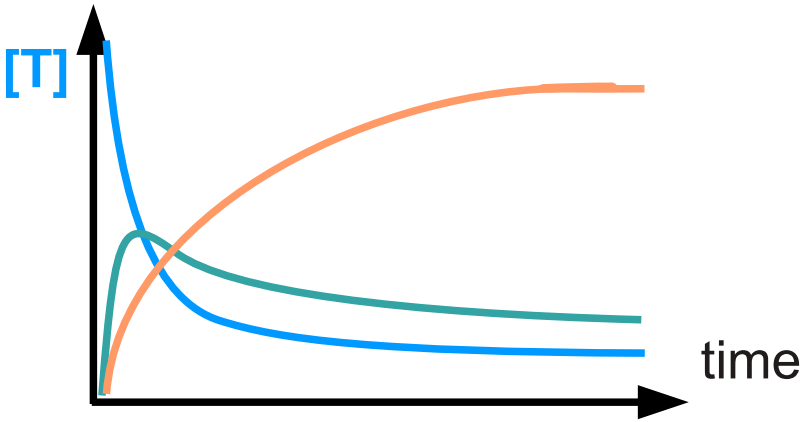
$$\frac{d[T]}{dt} = -k2 \times [T] \times [D2]$$



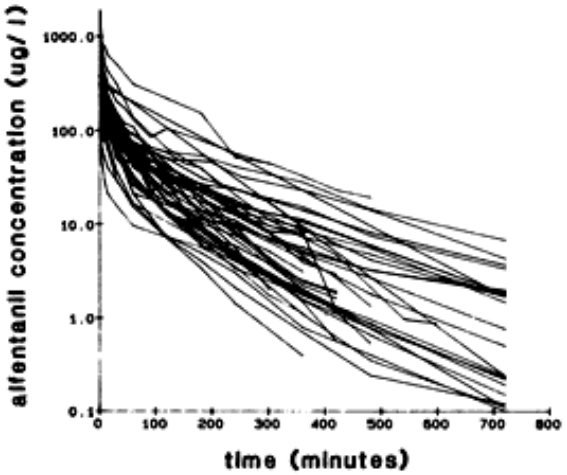
Systems modelling

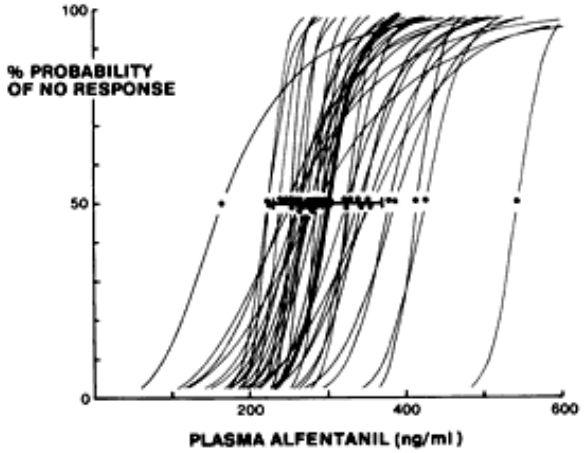
$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1] - k2 \times [T] \times [D2]$$

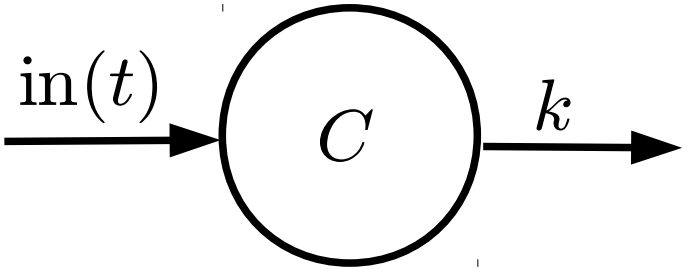


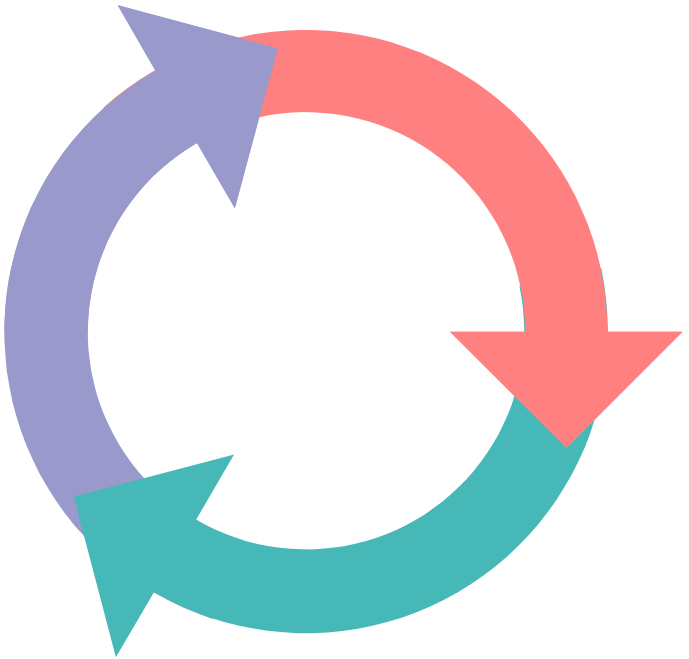


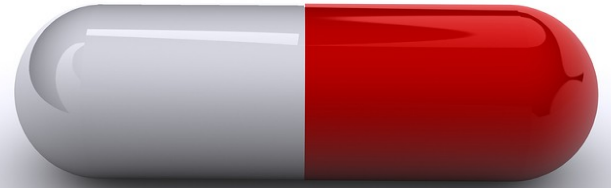
Drug discovery and pharmacometrics models



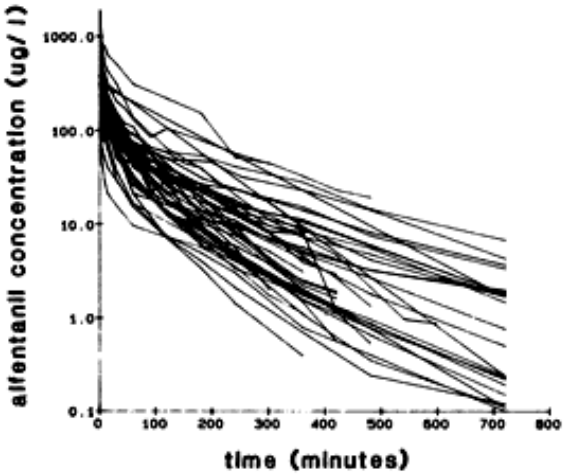


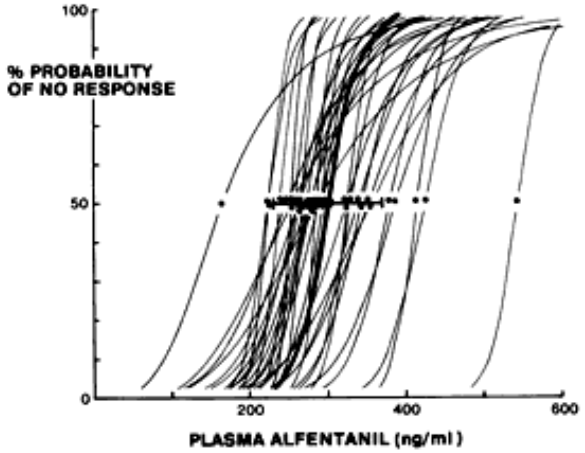


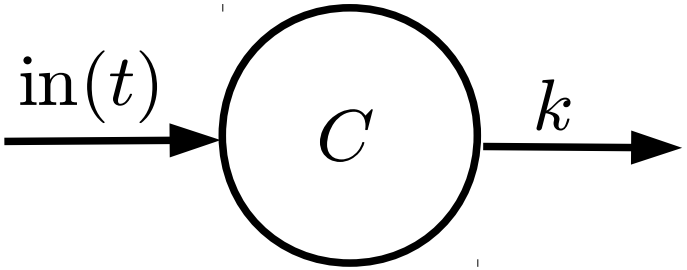


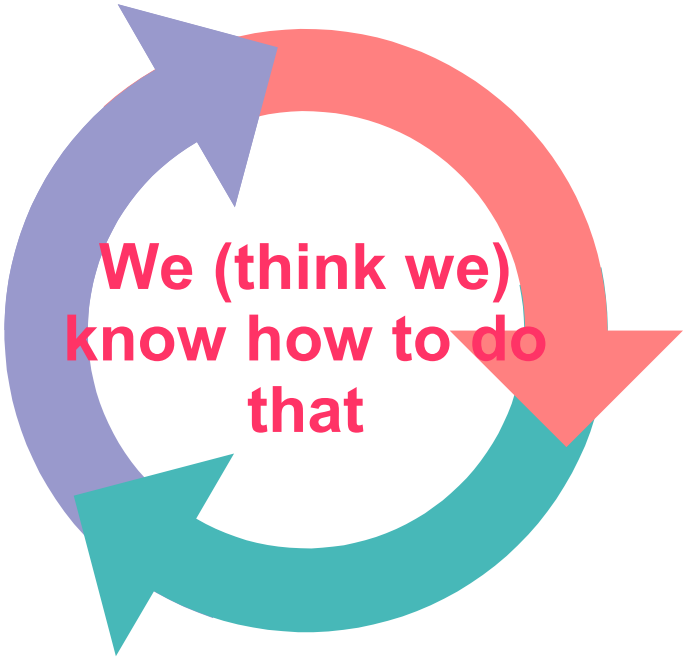


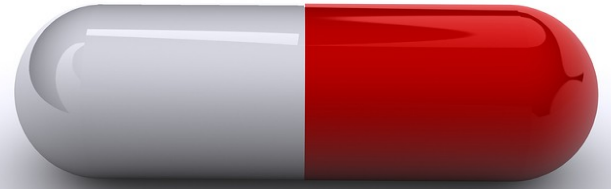
Drug discovery and pharmacometrics models



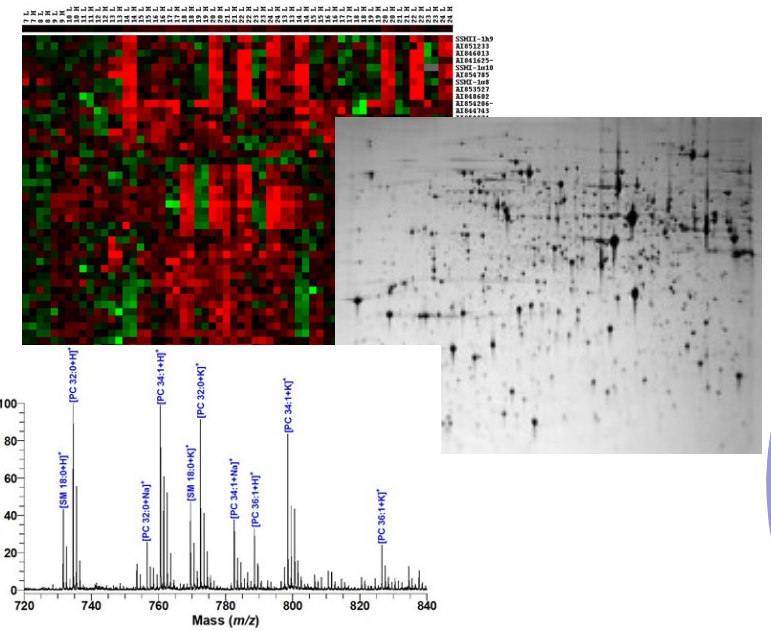


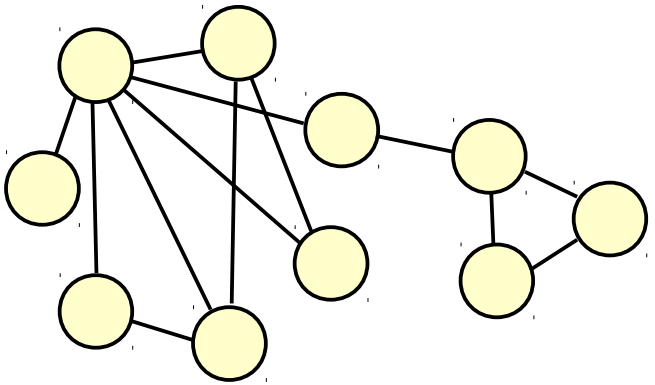


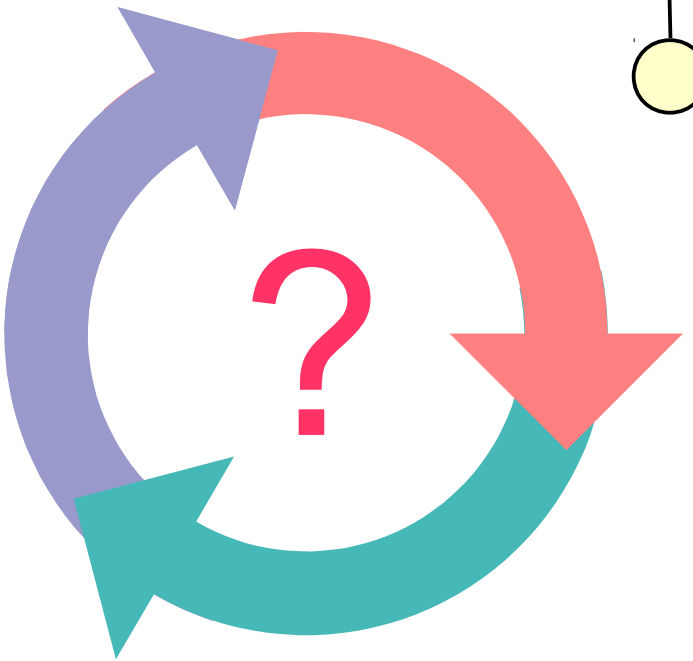


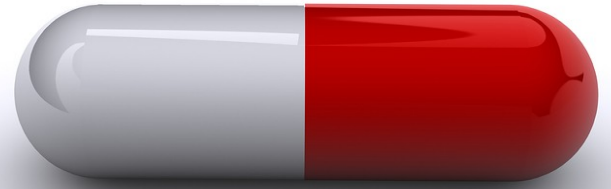


Drug discovery and omics









Systems Biology

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

A Textbook

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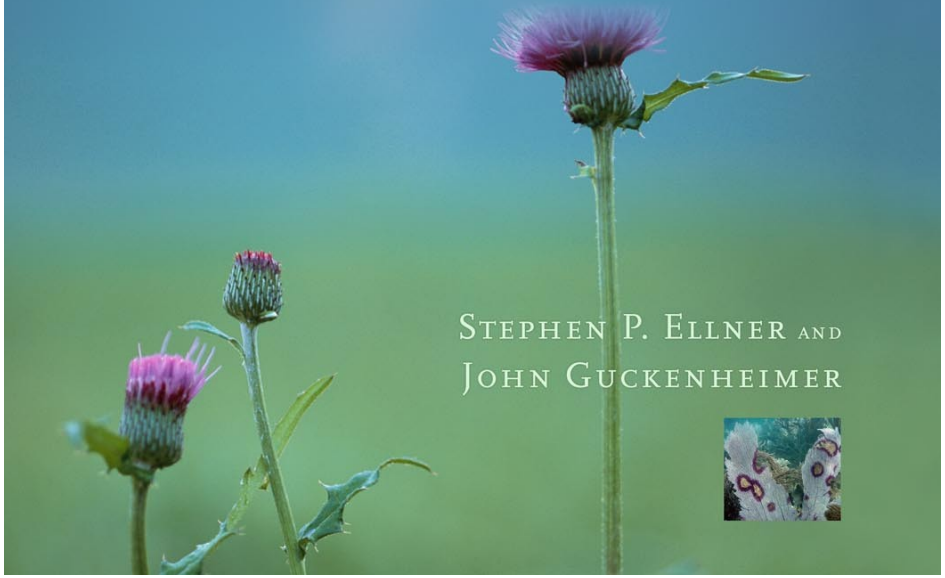
Dynamic Models in Biology



Stephen P. Ellner and
John Guckenheimer