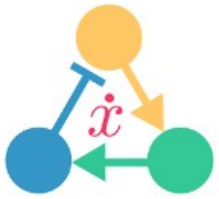
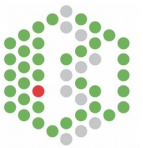


What is Systems Biology? Where does it come from ? What are the challenges ahead?

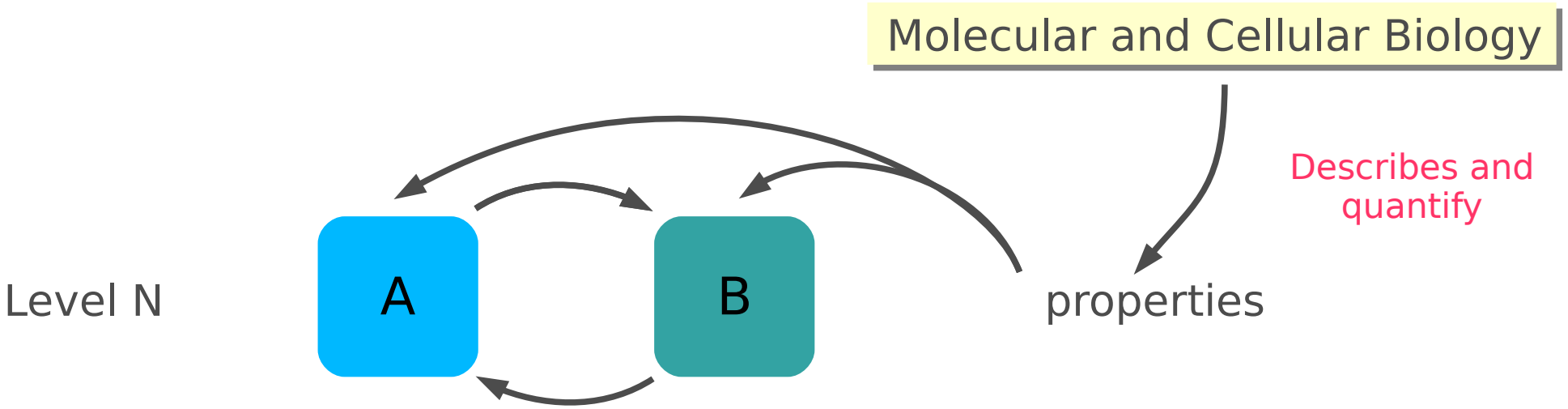
Nicolas Le Novère, Babraham Institute, EMBL-EBI

Babraham Institute

EMBL-EBI



What is Systems Biology



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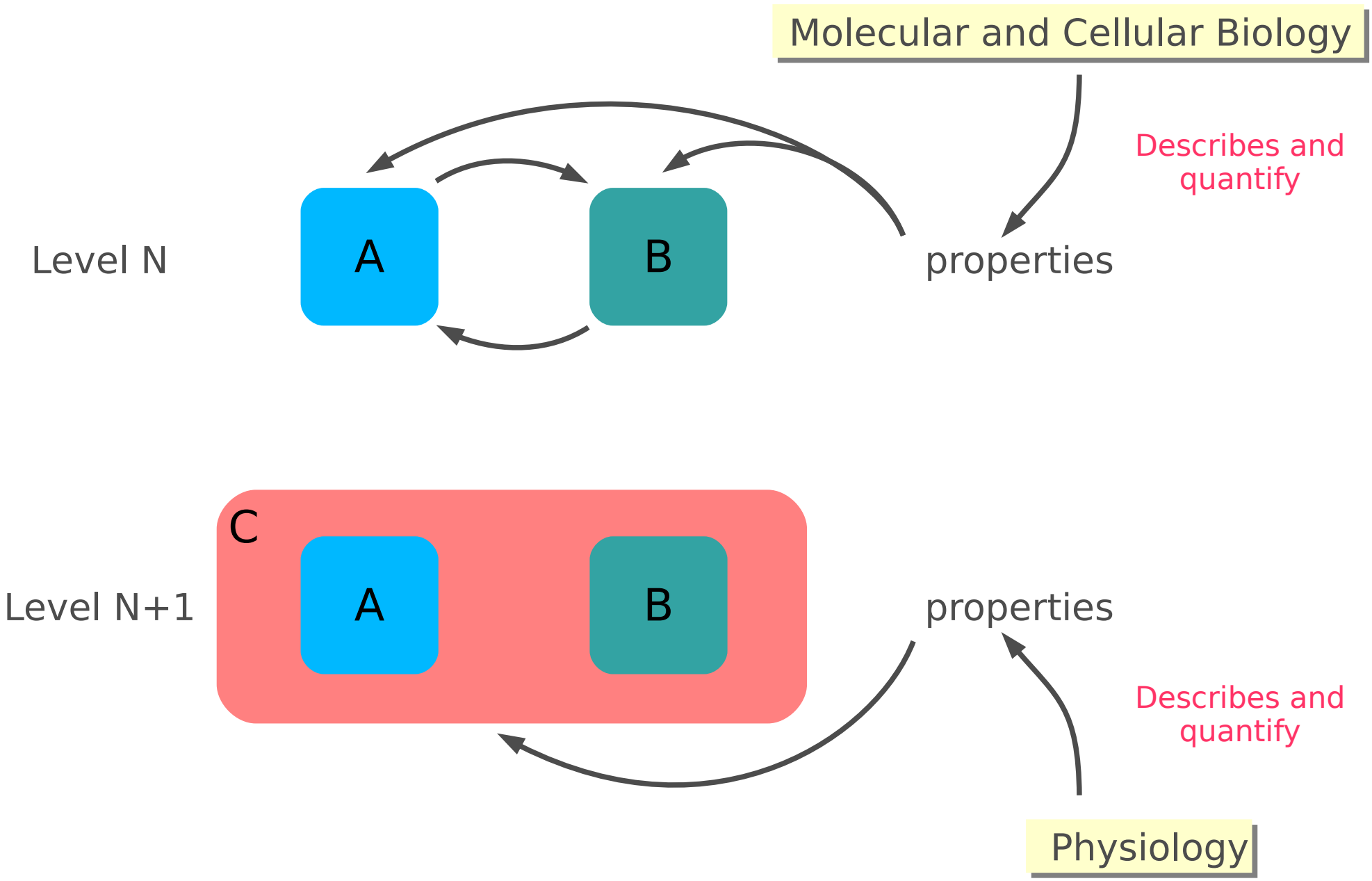

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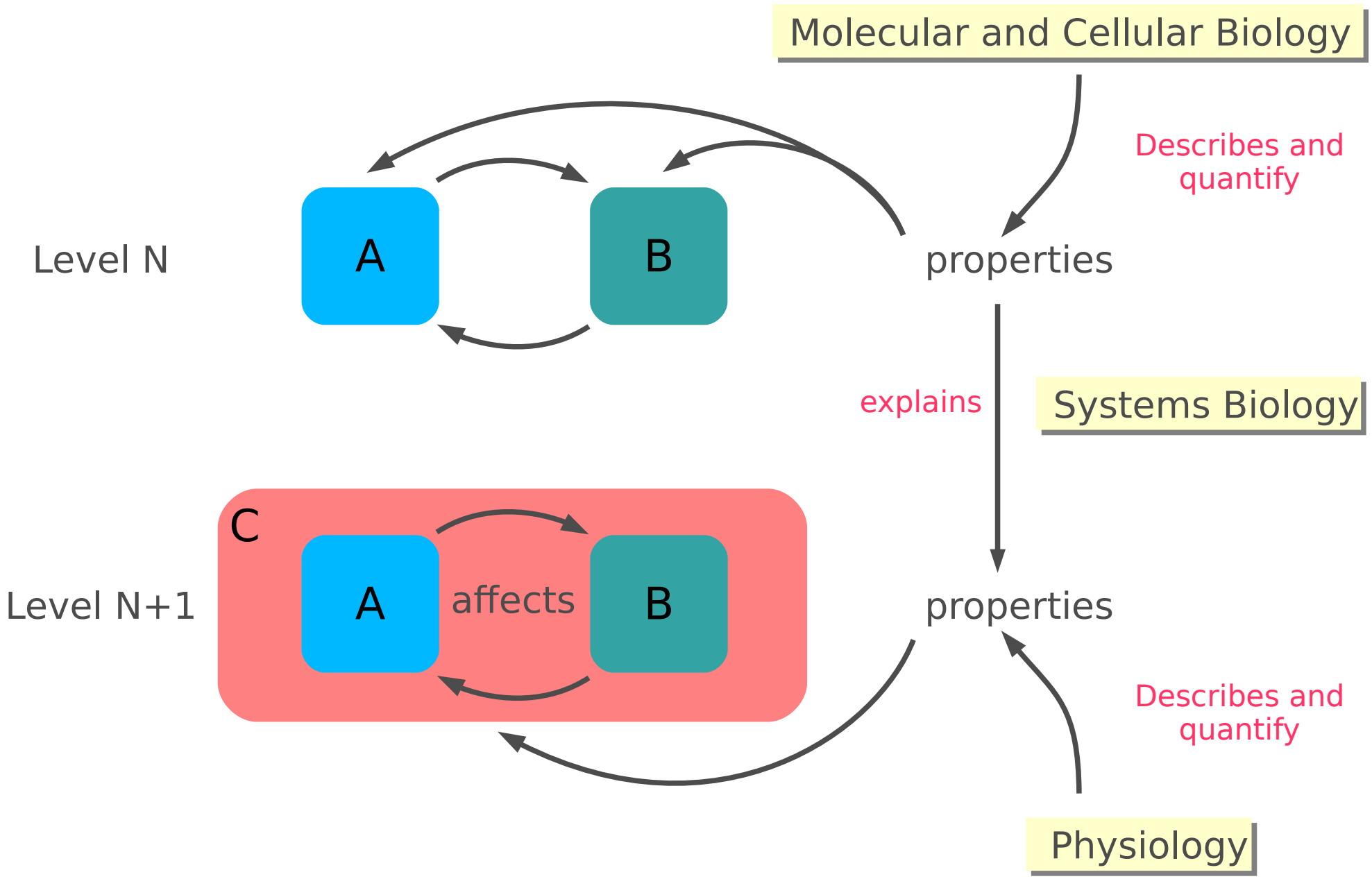

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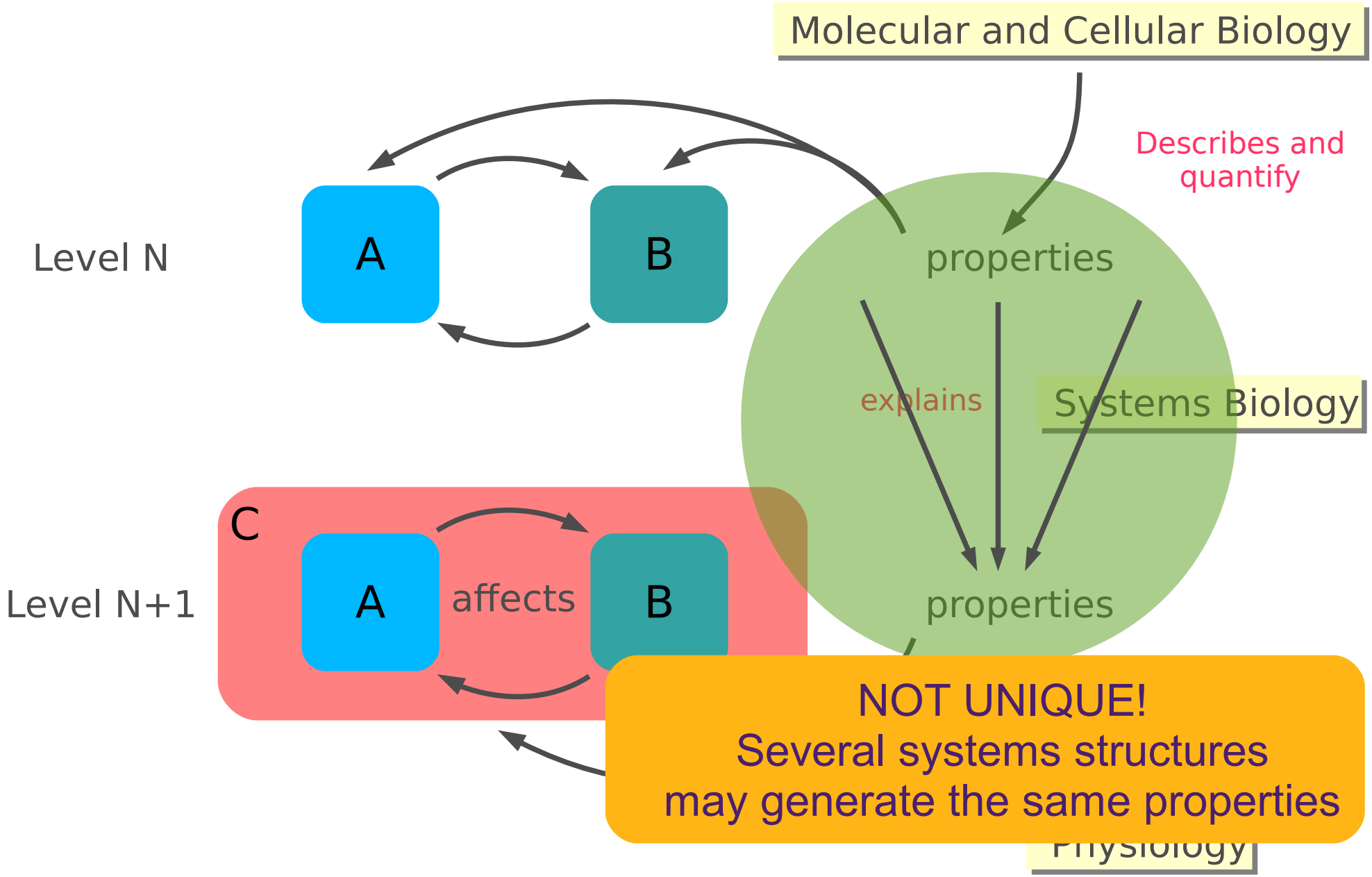

What Systems Biology is not!

Purely theoretical: Most systems biologists are actually experimental biologists

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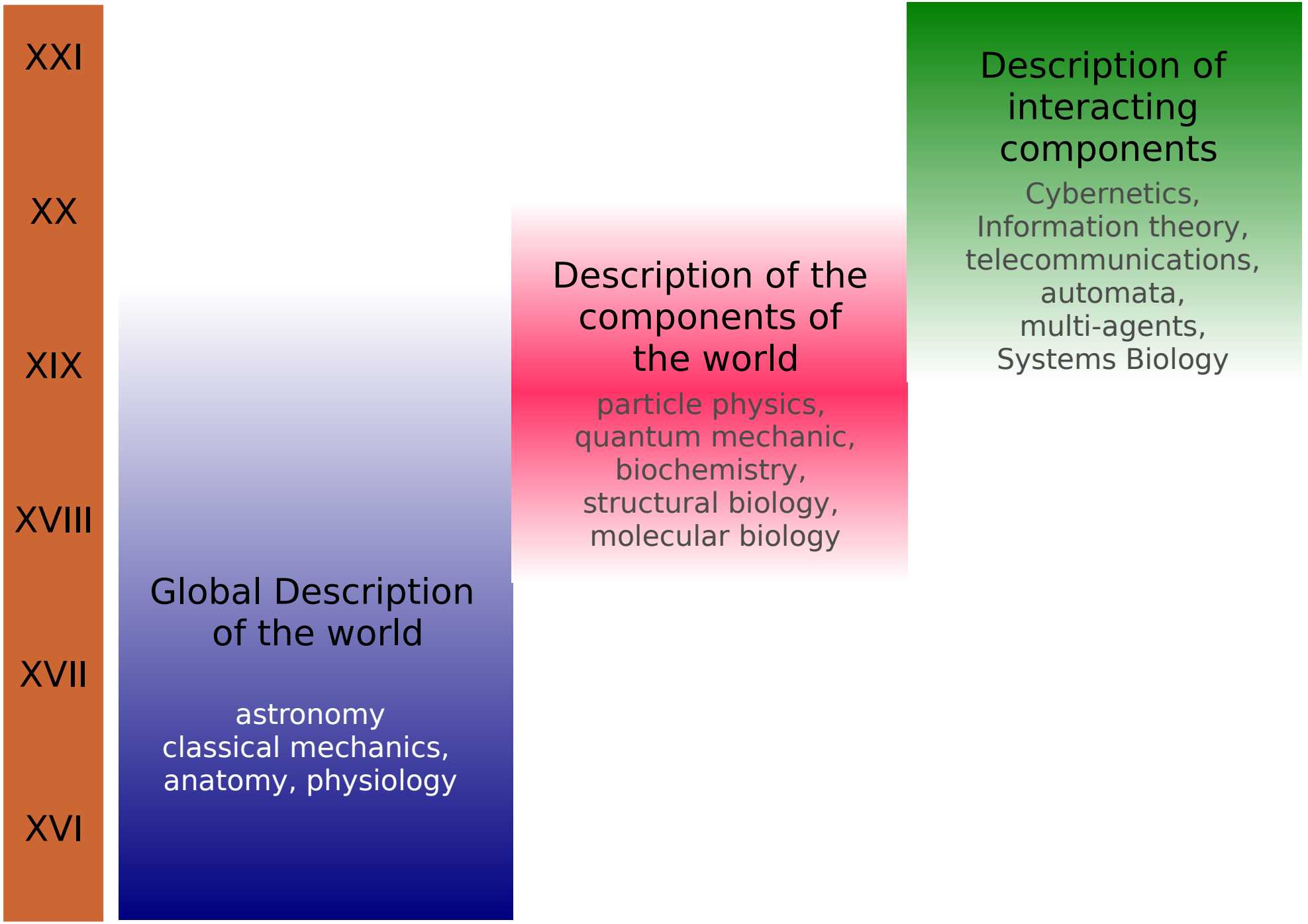
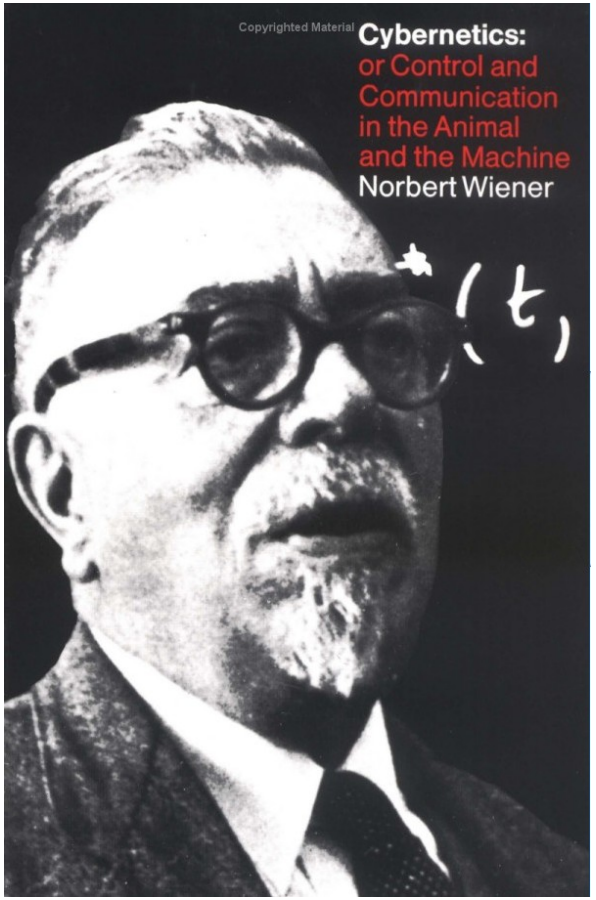
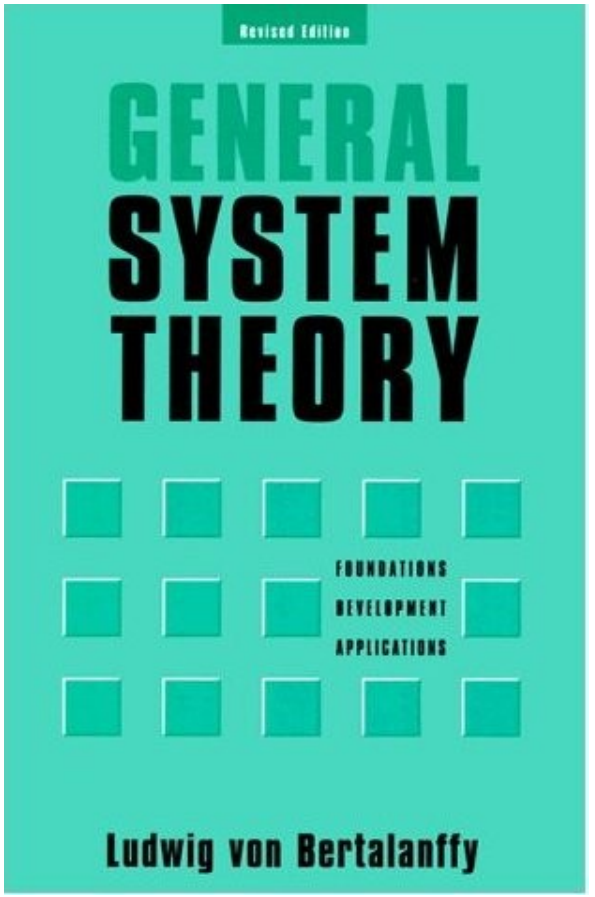
Systems Biology is the study of the ***emerging*** properties of a biological system, taking into account all the ***necessary*** constituents, their ***relationships*** and their ***dynamics***

Emergence of the notion of system



Systems are formalised mid-XXth





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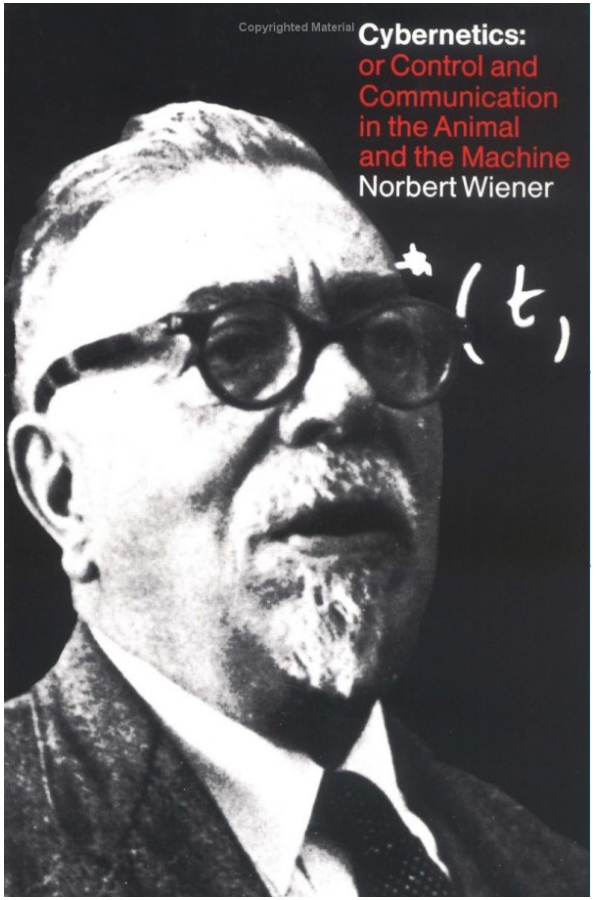
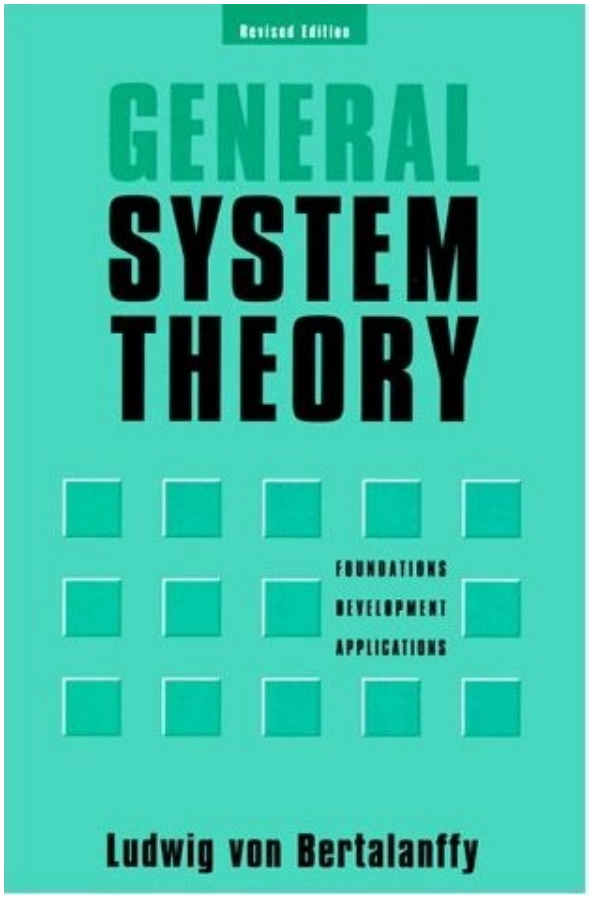
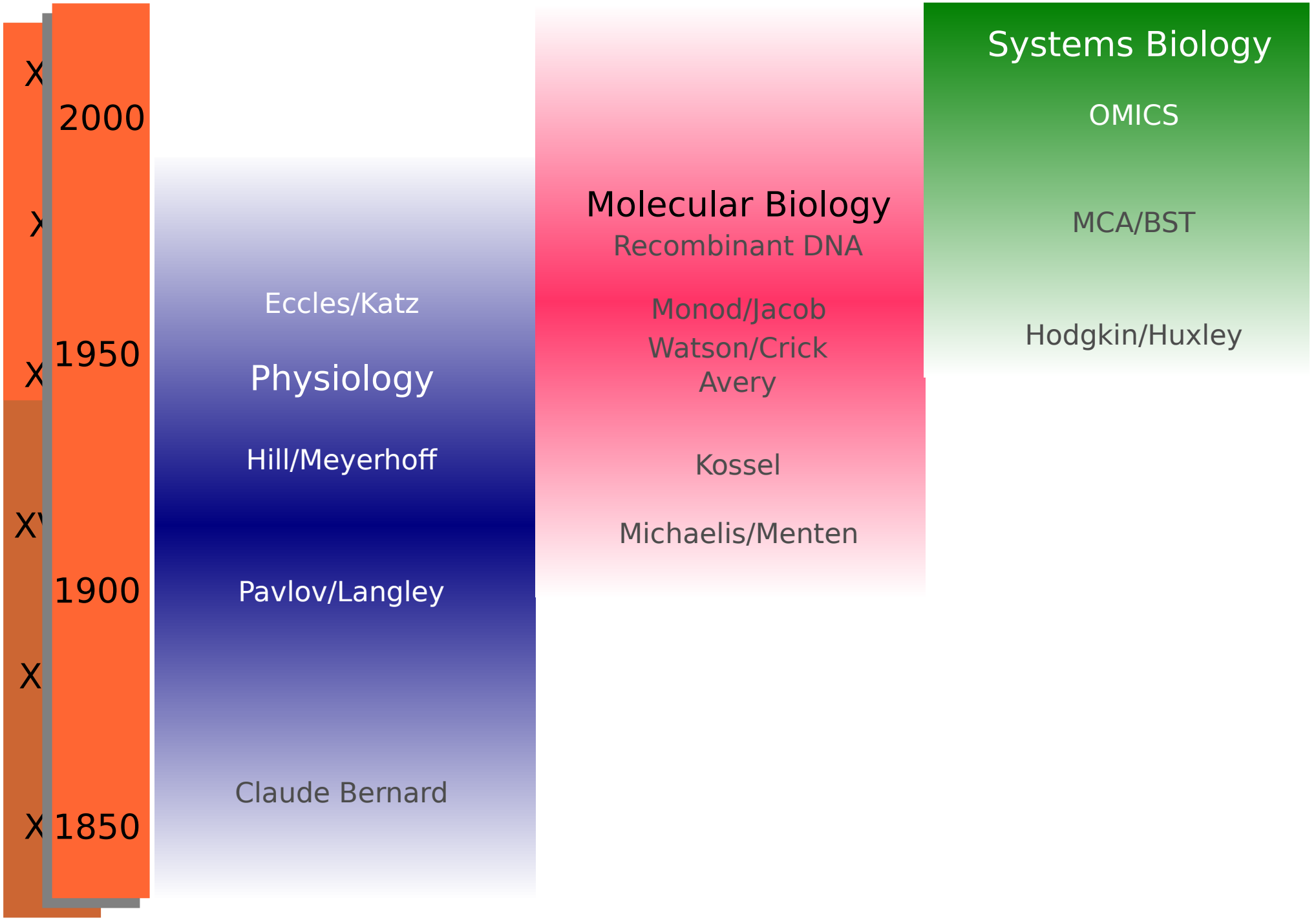


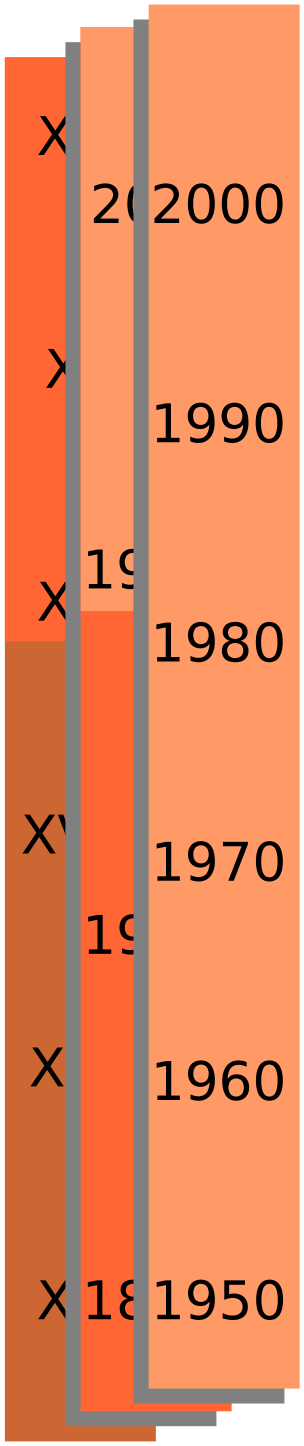


"[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems"
Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

The three paradigms of Biology



Towards Systems Biology



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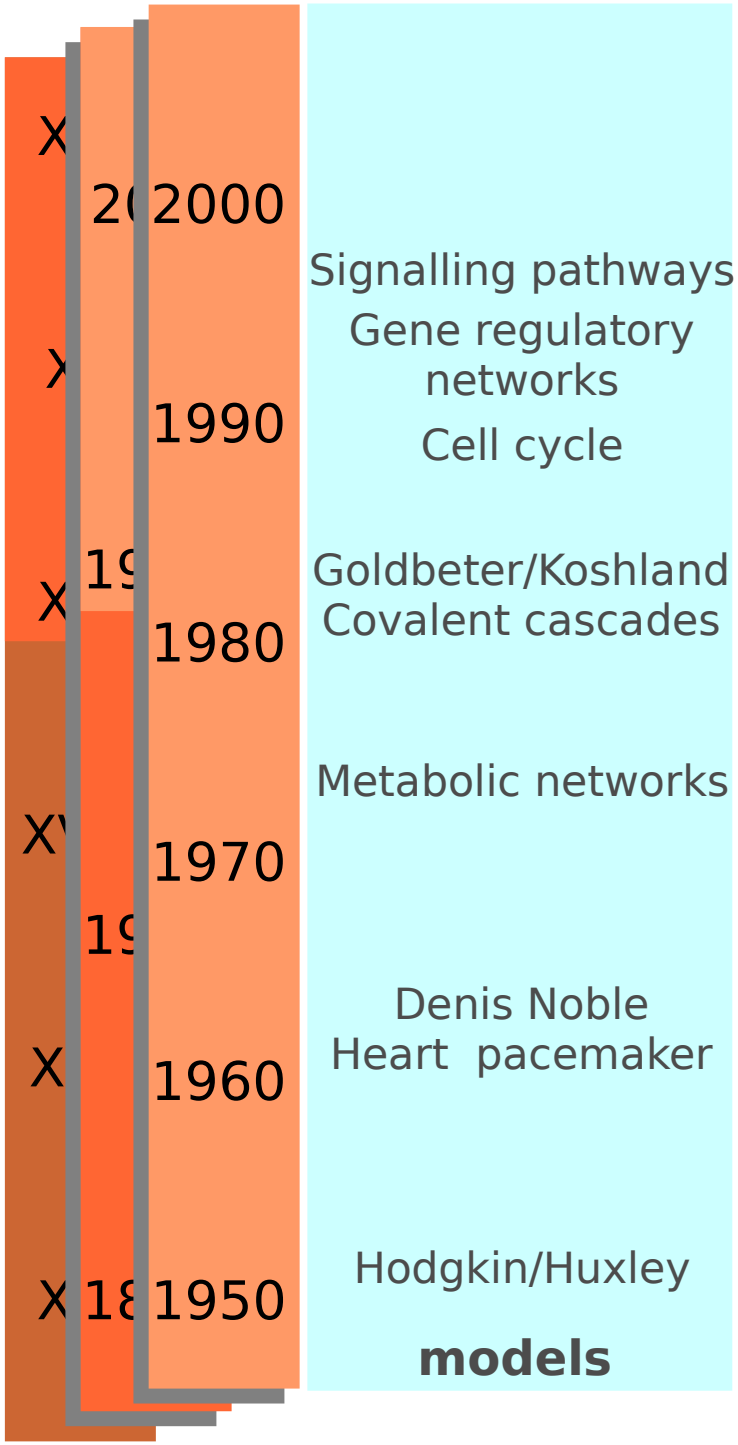

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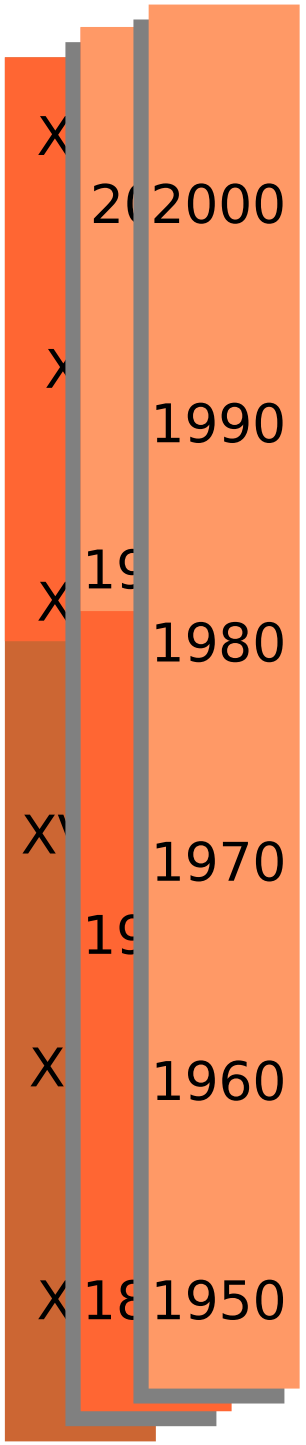

2000

1990

1980

1970

1960

1950

Organ level

Tissue models

Signalling pathways

Gene regulatory networks

Purkinje neuron

Cell cycle

Goldbeter/Koshland
Covalent cascades

Simple circuits

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Heart pacemaker

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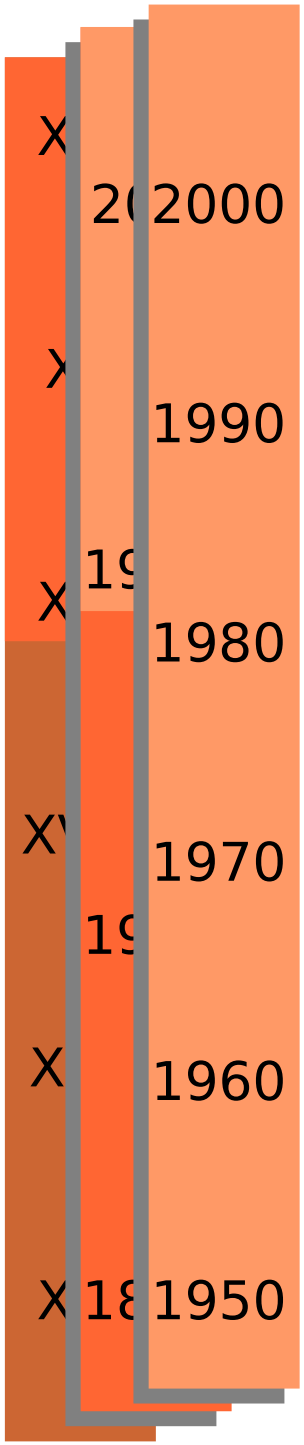

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Stochastic algorithms

MCA/BST

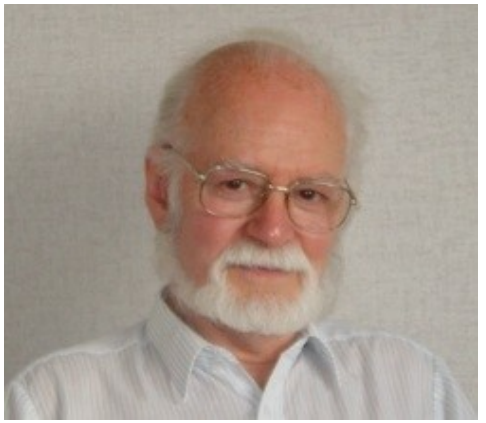
Boolean networks

methods

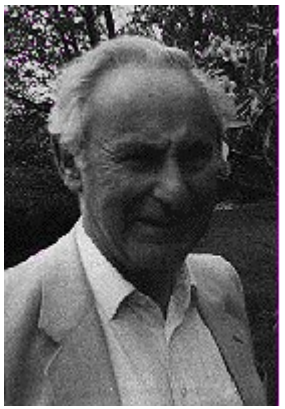
60s and 70s

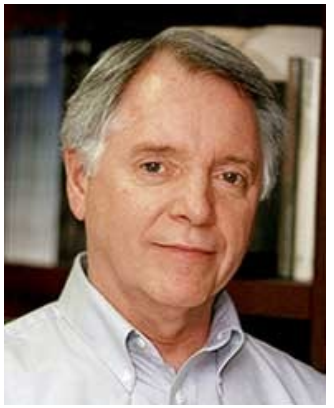
- Mihajlo Mesarovic: 1966 Symposium "general systems theory and biology

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

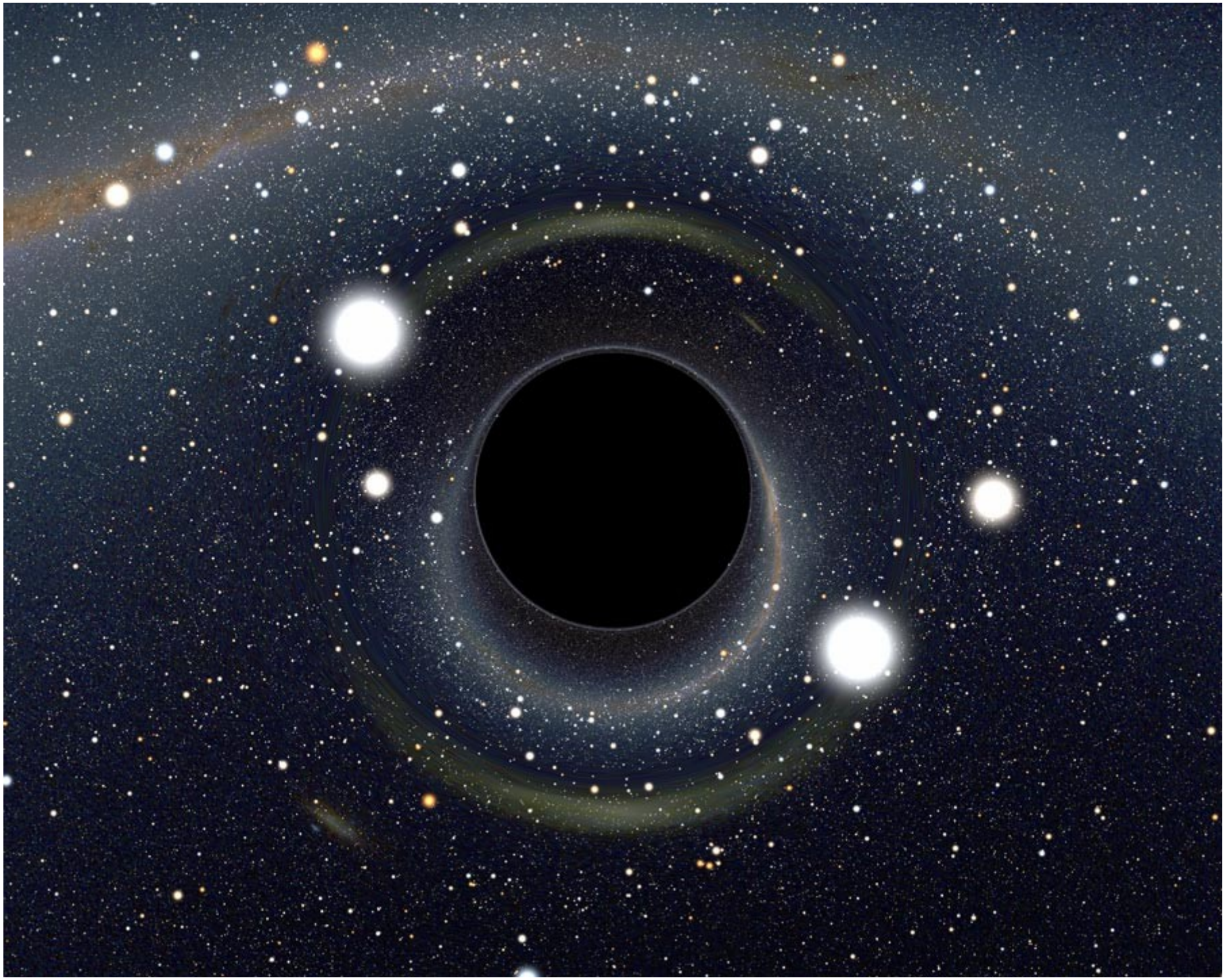


- Henri Kacser: Metabolic control analysis, Michel Savageau: Biochemical Systems Theory





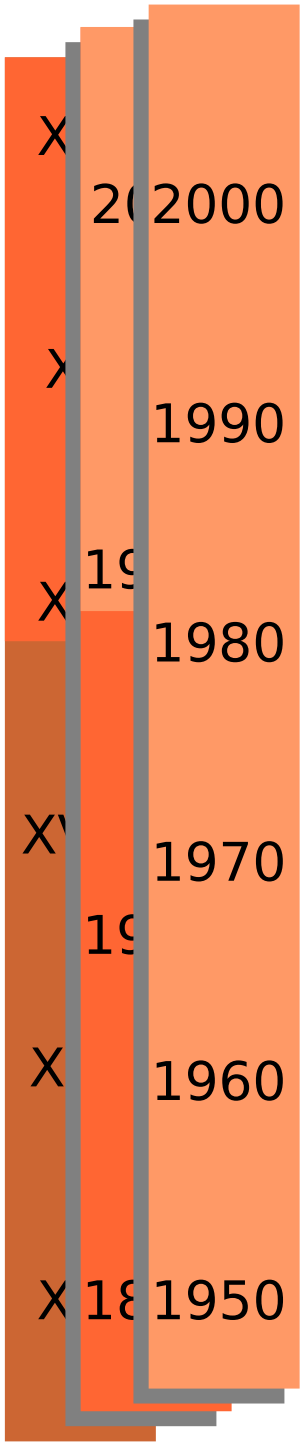
80s: The reign of Molecular Biology



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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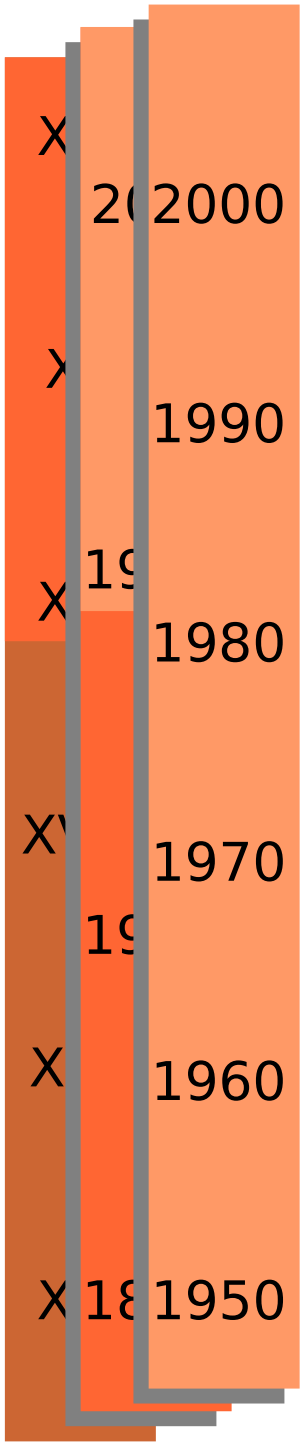
Repressilator
Barabasi

Towards Systems Biology



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methods

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

Two kinds of Systems Biology?

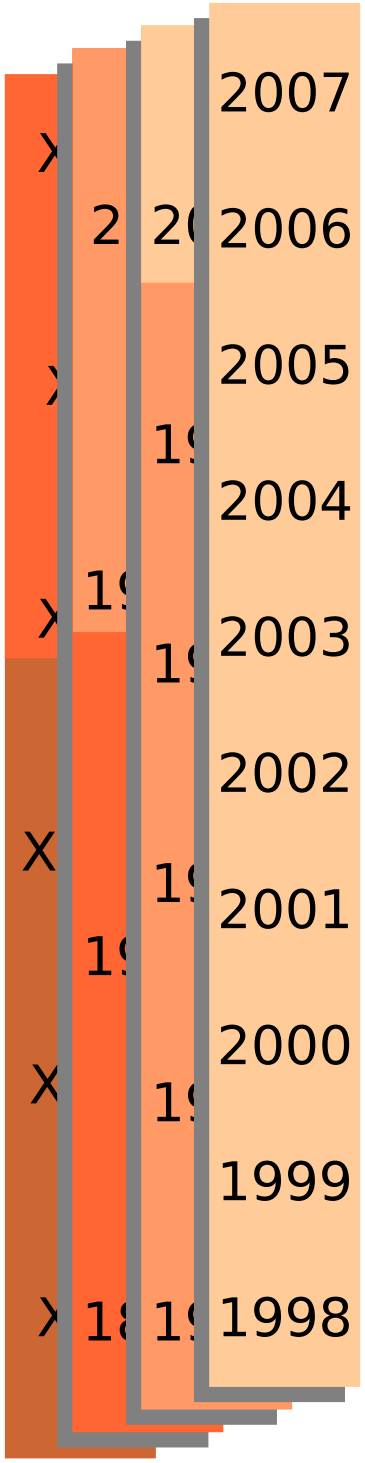
Systems-wide analysis (omics)

- 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)

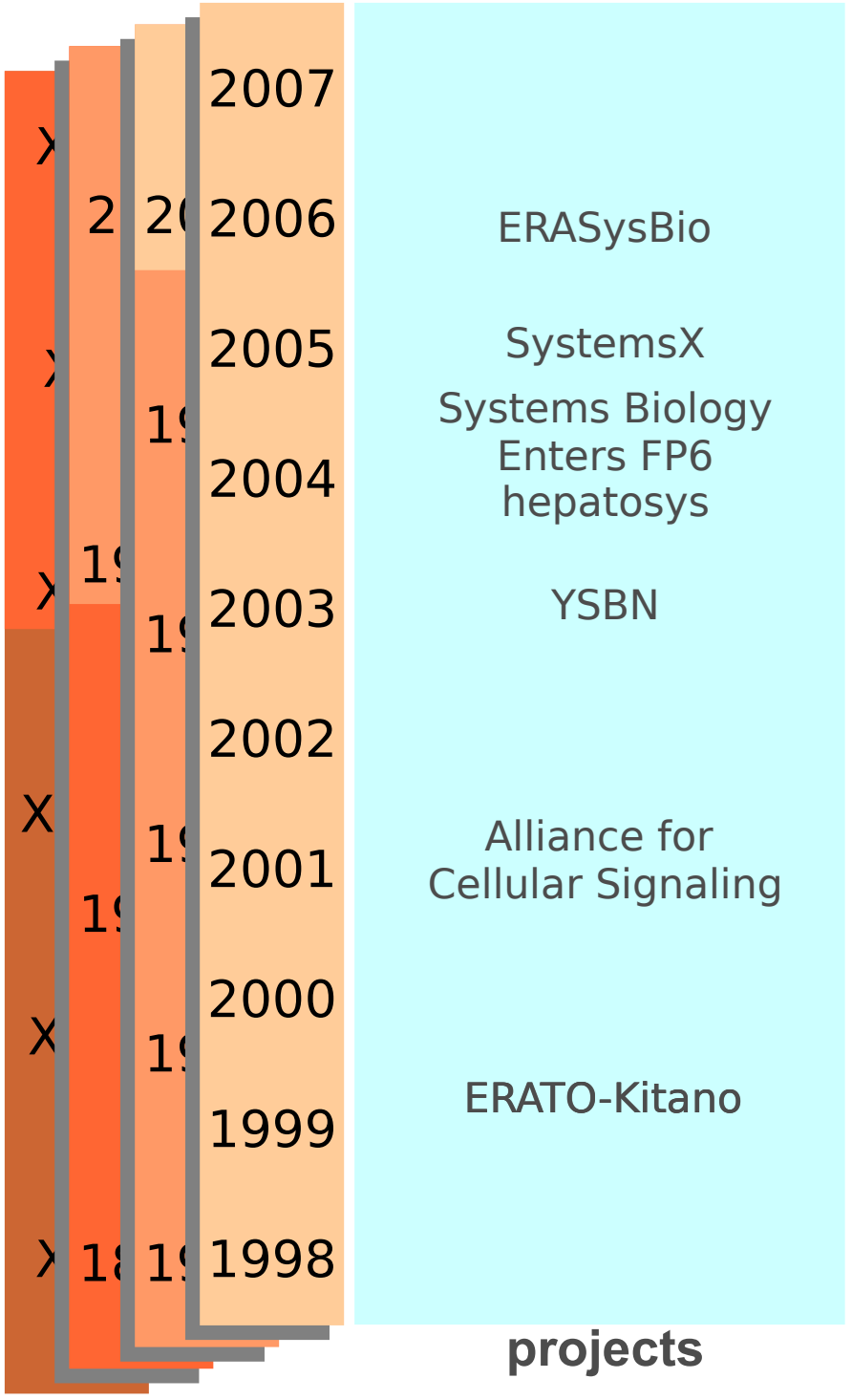
Application of systems-theory

- 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

Rise of Systems Biology as a paradigm



Rise of Systems Biology as a paradigm



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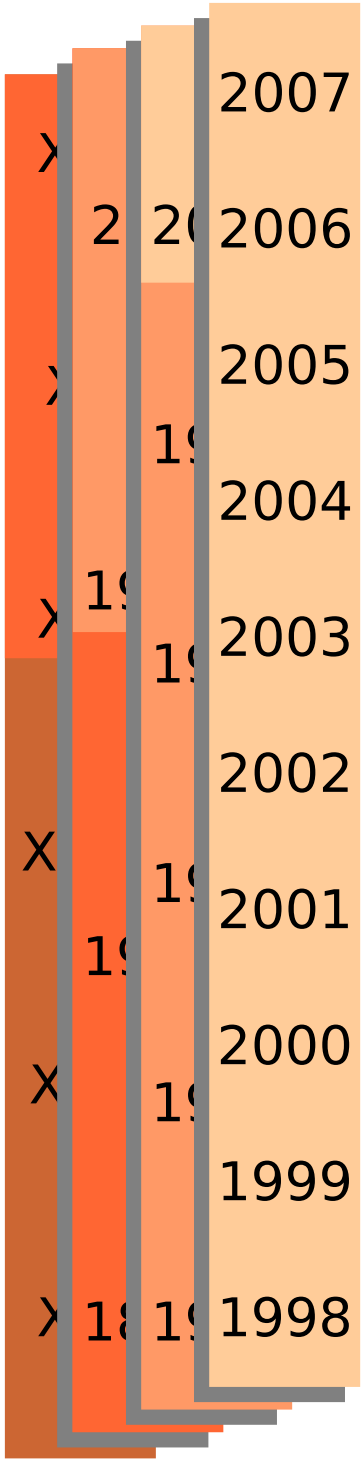
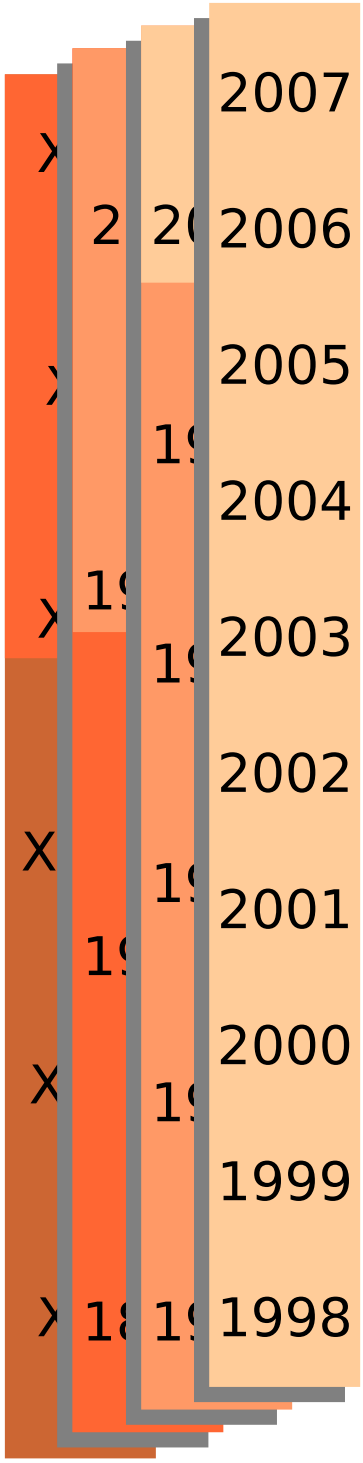


	projects	publications
2007		Choi Boogerd Grierson Palsson
2006	ERASysBio	BMC Sys Bio Alon Szallasi Kriete MSB
2005	SystemsX	Klipp Kaneko
2004	Systems Biology Enters FP6 hepatosys	IEE Sys Bio
2003	YSBN	SBML
2002		*Science* special issue
2001	Alliance for Cellular Signaling	“Foundations of Systems Biology” 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	
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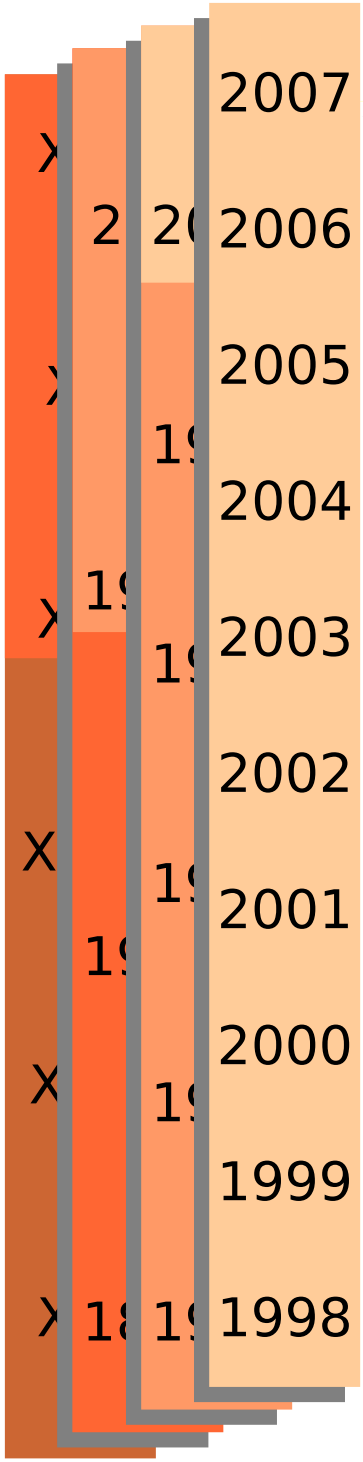
	ECell	

Rise of Systems Biology as a paradigm



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End of BBSRC Systems Biology calls

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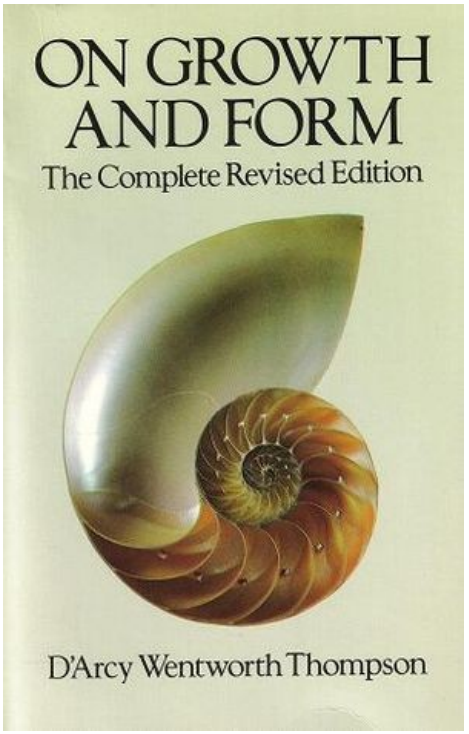
	ECell	

Procedure does not depend on directionality

	Bottom-up	Top-down
Build the system	literature	network inference
Put numbers	biochemistry	“omics”
Parametrise	parameter search	not (always) relevant
Analyse	Simulation	structural analysis, steady-state analysis
perturb	Inhibition, stimulation, suppression, overexpression	

Why using mathematical models?

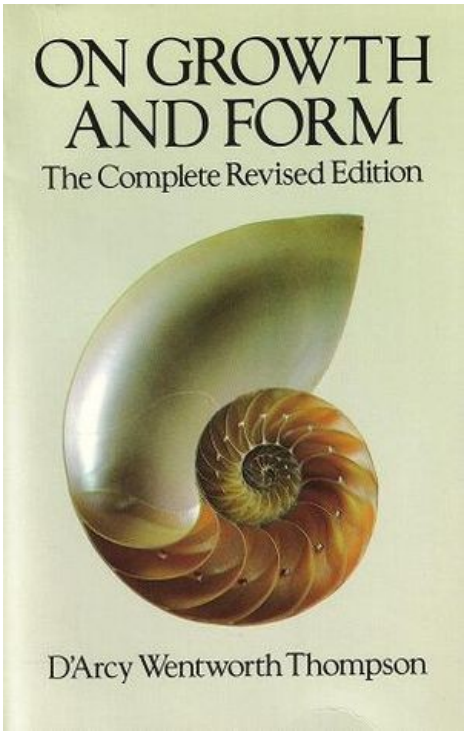
Describe



1917

Why using mathematical models?

Describe	Explain



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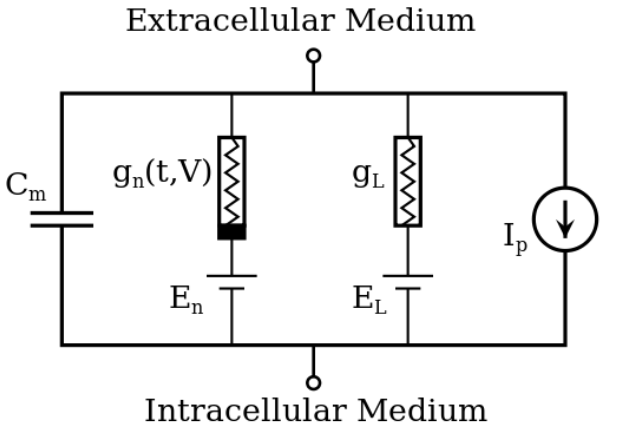
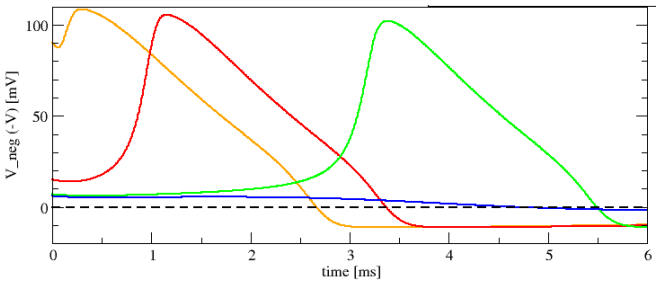
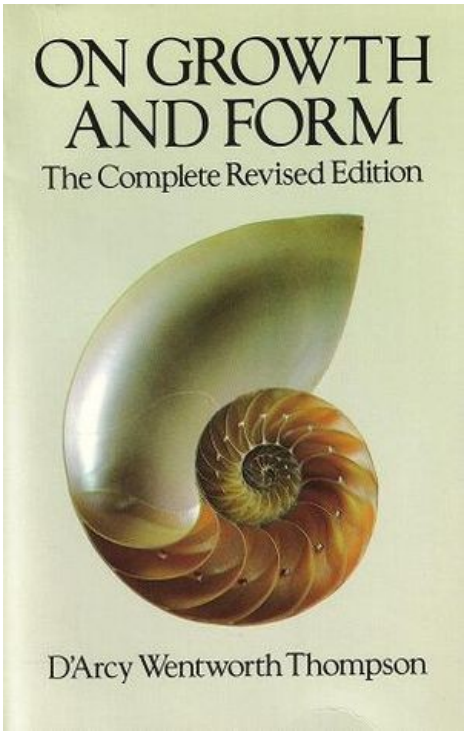


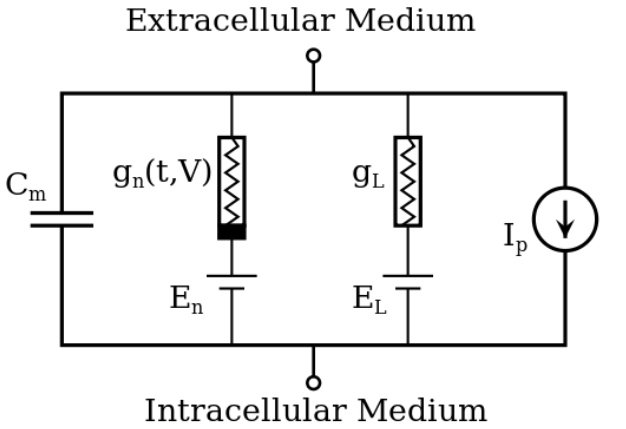


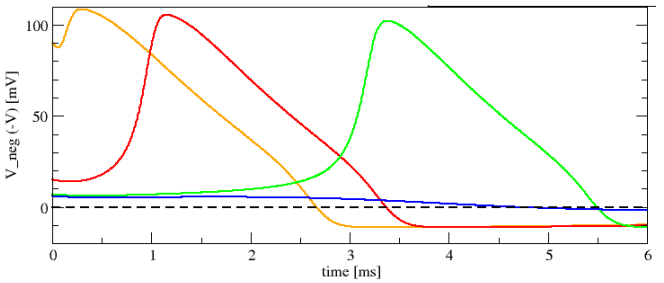
1952

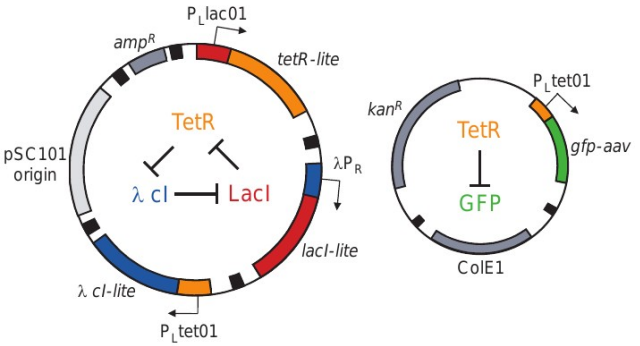
Why using mathematical models?

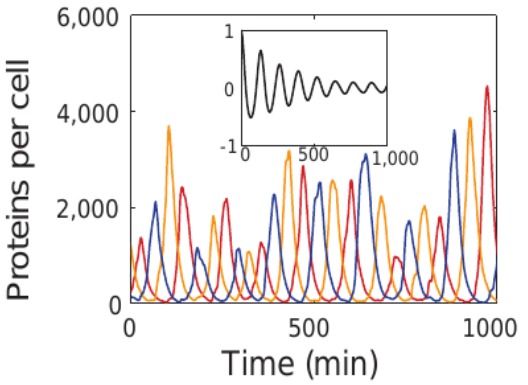
Describe	Explain	Predict











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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variables

[x]

Vmax

Kd

EC_{50}

length

$t_{1/2}$

What we want to know or compare with experiments

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relationships

$$K_d = \frac{[A] \cdot [B]}{[AB]}$$

$$d[X]/dt = k \cdot [Y]^2$$

$$\sum_i [X]_i - F(t) = 0$$

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

If $\text{mass}_t > \text{threshold}$

then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$

What we already know or want to test

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constraints

[x]>0

Energy conservation

Boundary conditions
(v < upper limit)

Objective functions
(maximise ATP)

Initial conditions

The context or what we want to ignore

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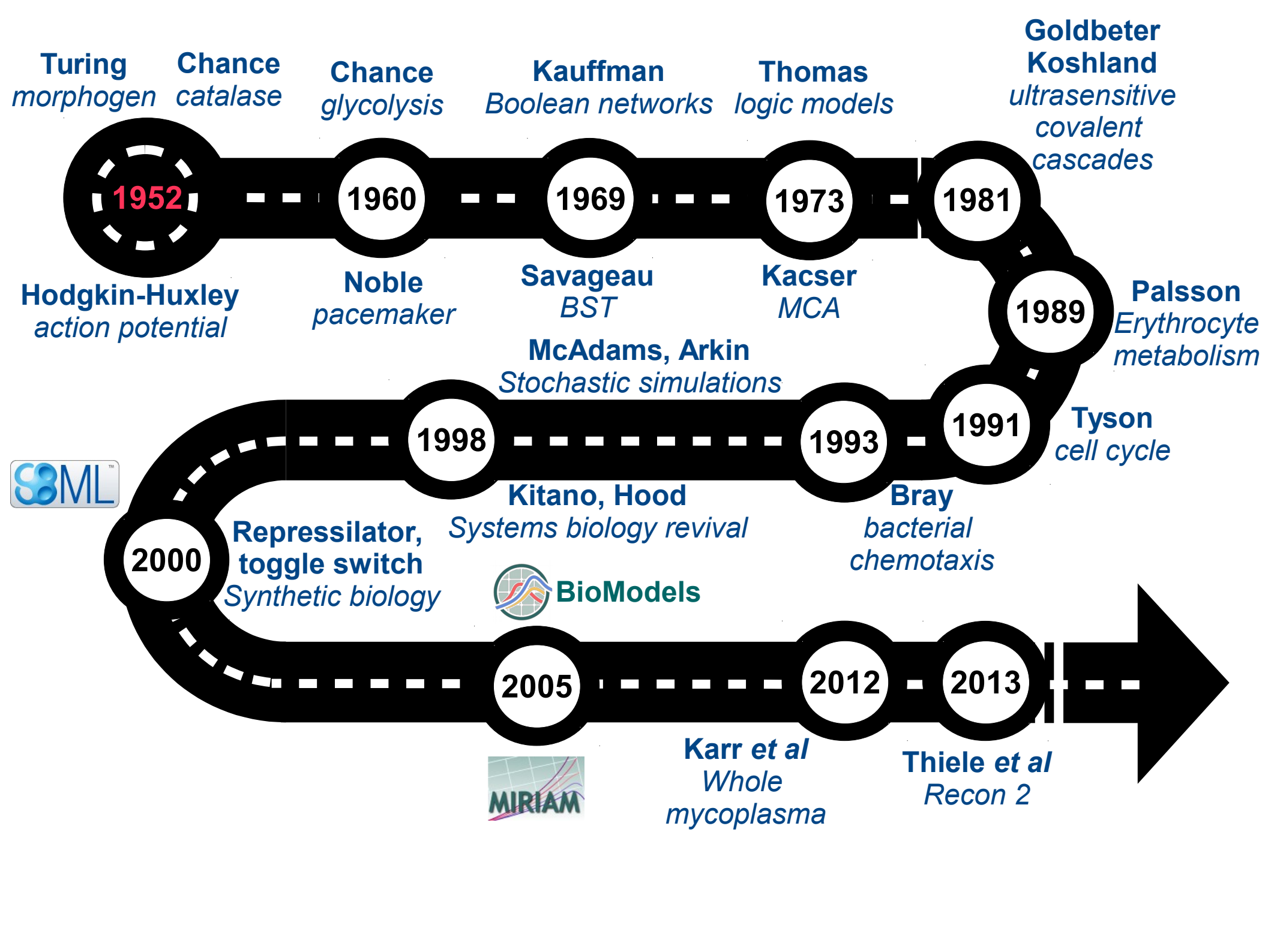
Different types: Dynamical models, logical models, rule-based models, multi-agent models, statistical models, etc.


Turing
morphogen
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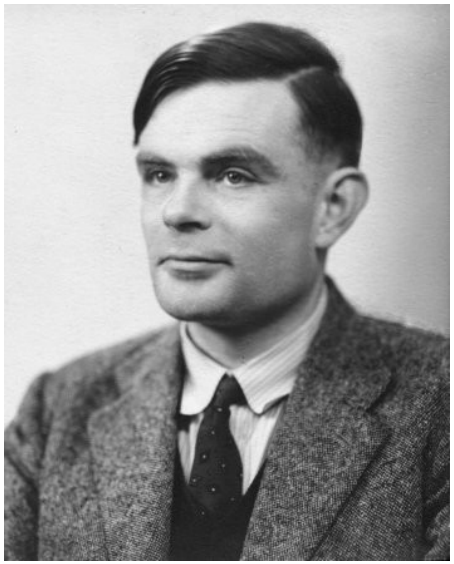
Recon 2

Computer simulations Vs. mathematical models



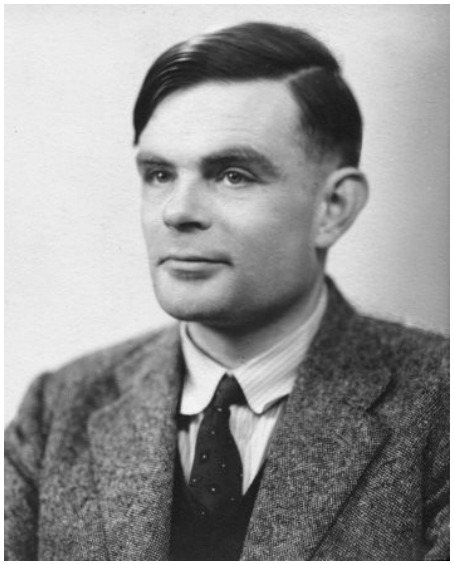
THE CHEMICAL BASIS OF MORPHOGENESIS

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

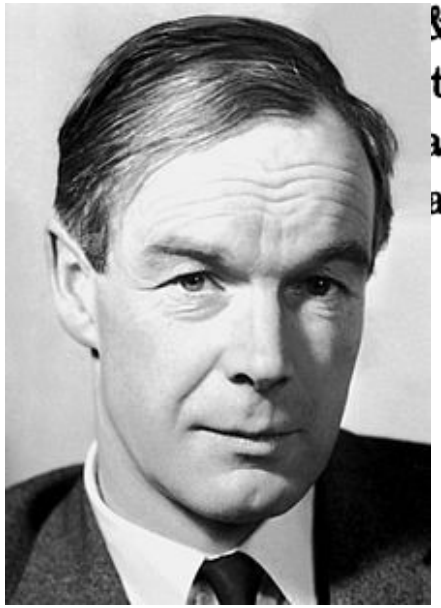
A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

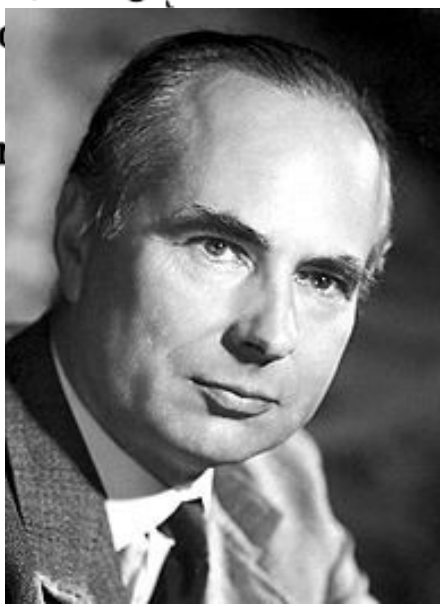
By A. L. HODGKIN and A. F. HUXLEY

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

Birth of Computational Systems Biology

The Mechanism of Catalase Action. [1]

II. Electric Analog Computer Studies

Britton Chance, David S. Greenstein, Joseph Higgins and C. C. Yang

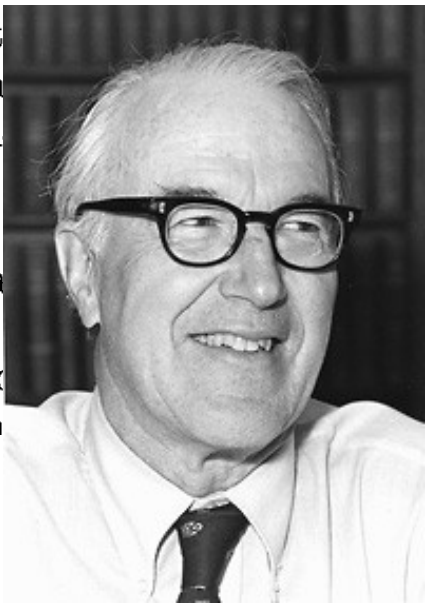
From the Johnson Research Foundation, University of Pennsylvania, Philadelphia, Pennsylvania

Received October 26, 1951

Introduction

In early studies of enzyme reactions only the disappearance of substrate could be measured and only the steady-state operation of the enzyme could be studied. We can now study directly the formation and disappearance of compounds of enzyme and substrate by sensit spectrophotometric methods. Thus not only the steady-state but a the transient portions of the enzyme action are revealed. And th transient portions are very sensitive indicators of the mechanism which the enzyme acts.

Differential equations representing the transient formation a disappearance of an enzyme-substrate complex can readily be set for enzyme reactions that follow the law of mass action, and solutic of these equations are readily obtained for the special and often un



The Computational Systems Biology loop

"biological" model

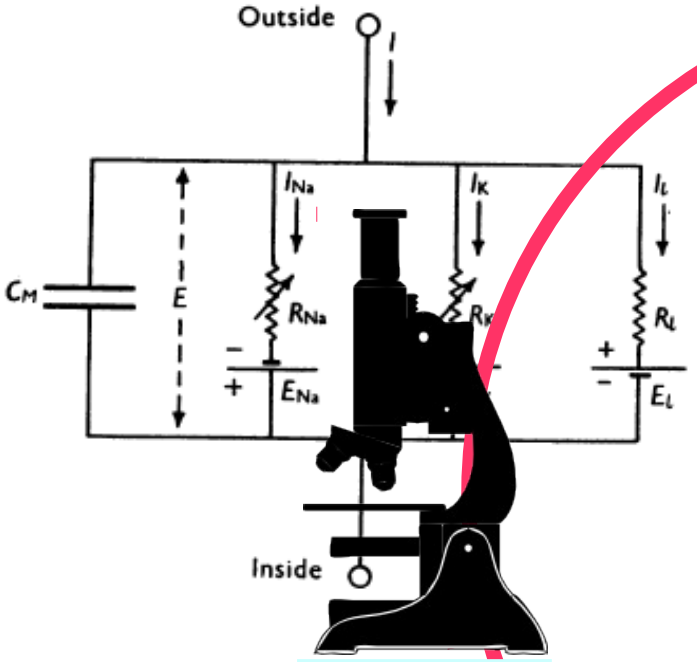
mathematical model

validation

parameterisation

simulation

computational model



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

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

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

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

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

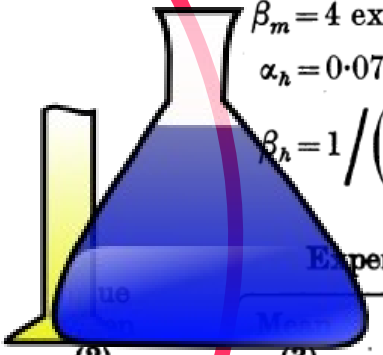
$$\beta_n = 0{\cdot}125 \exp (V/80),$$

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

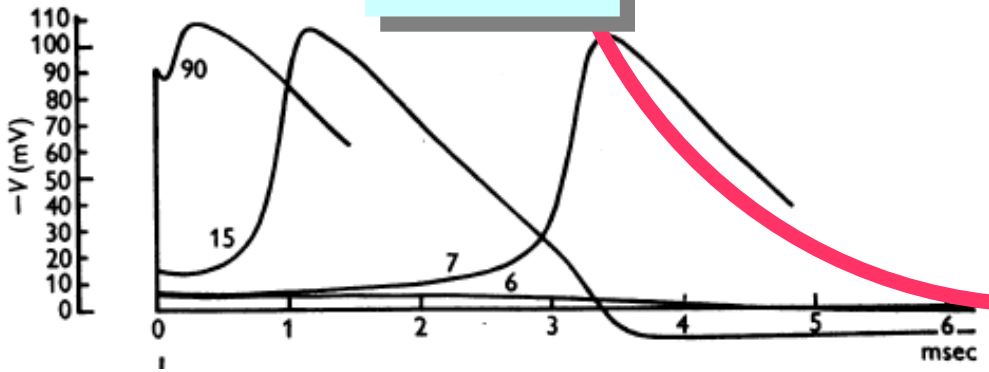
$$\beta_m = 4 \exp (V/18),$$

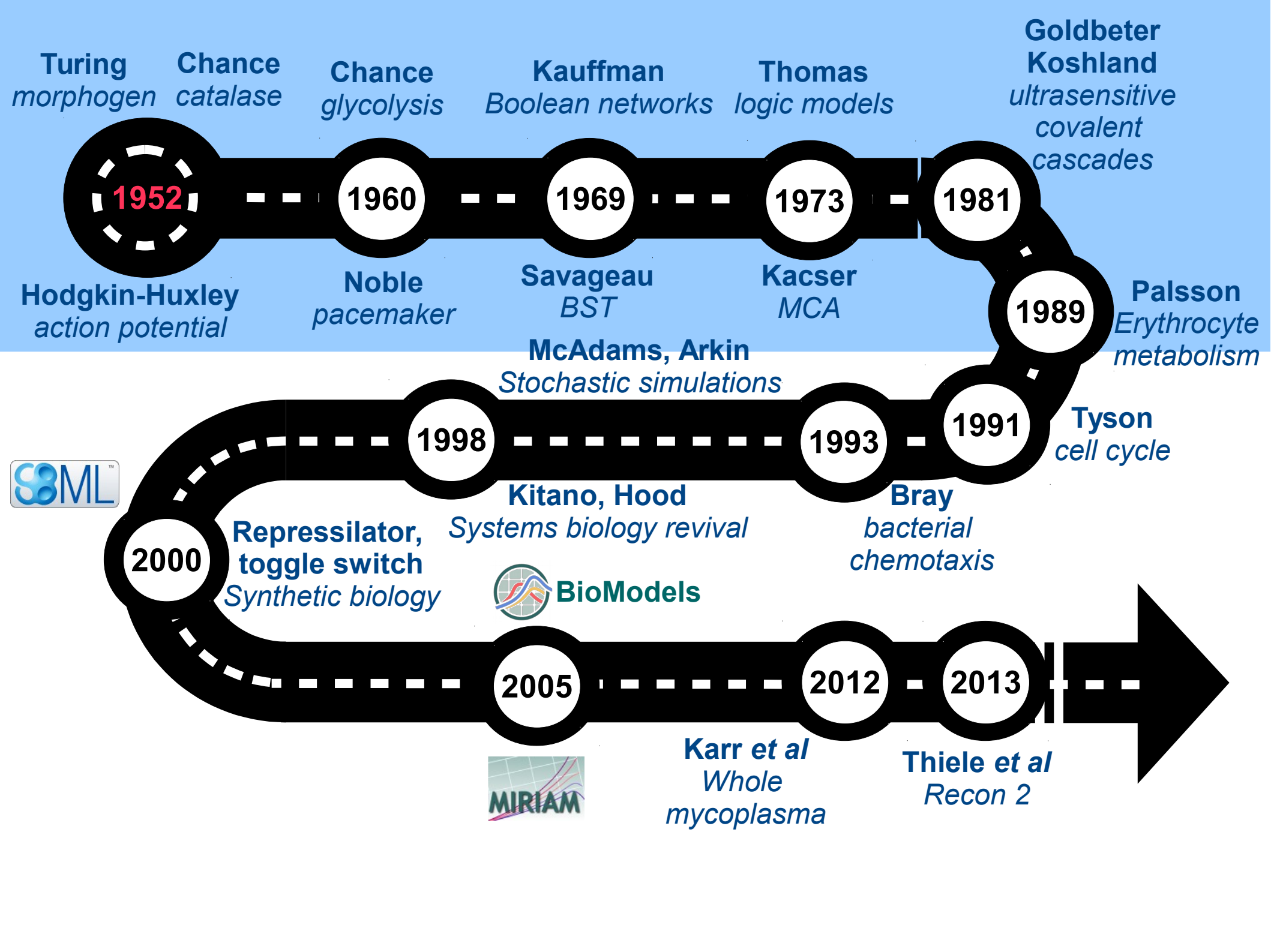
$$\alpha_h = 0{\cdot}07 \exp (V/20),$$

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



Constant (1)	(2)	Experimental values (3)	Range (4)
C_M (μF/cm^2)			0·8 to 1·5
V_{Na} (mV)			− 95 to − 119
V_K (mV)			+ 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

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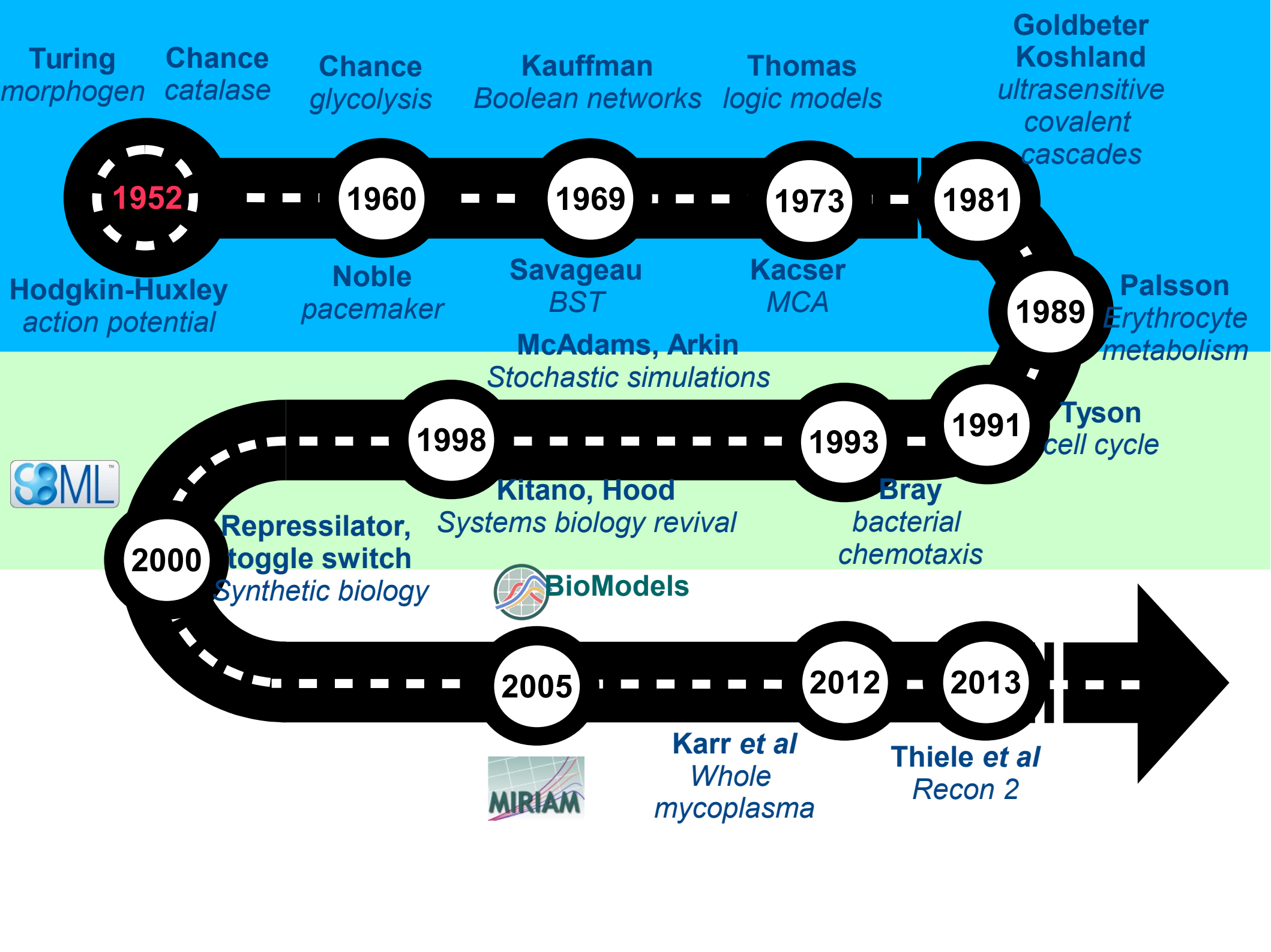
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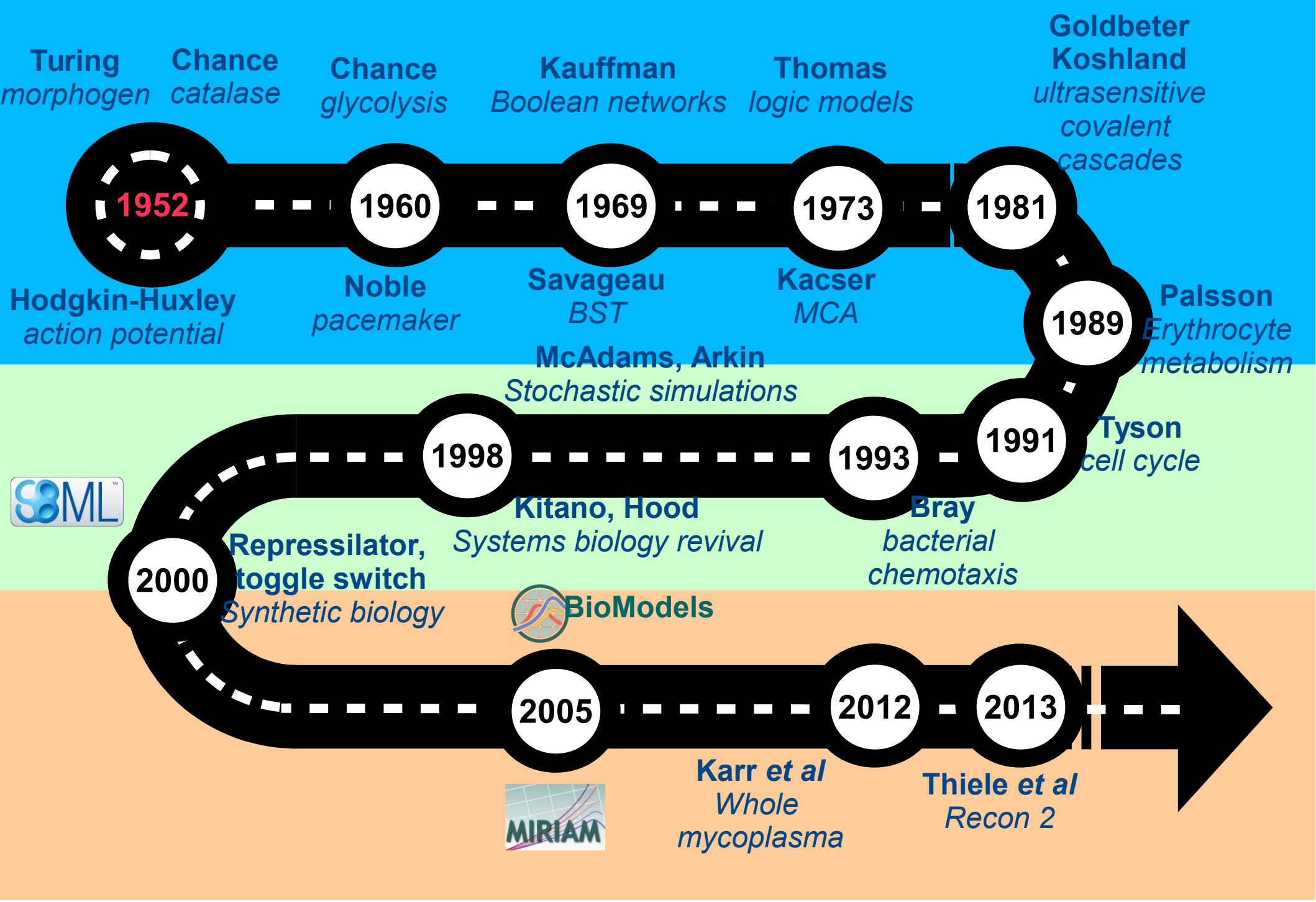
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The challenges ahead

Types of representation

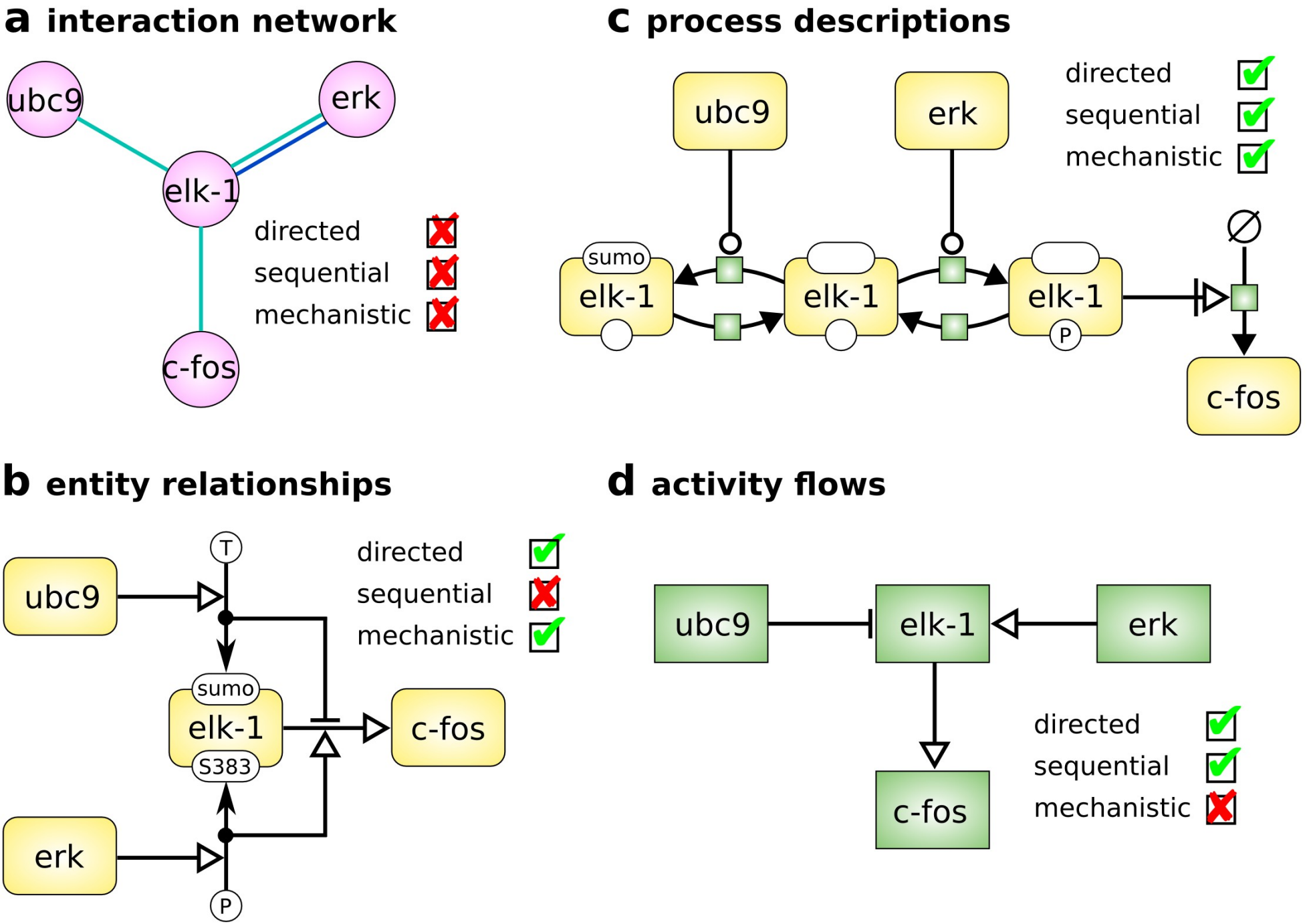
Scales and the mesoscopic gap

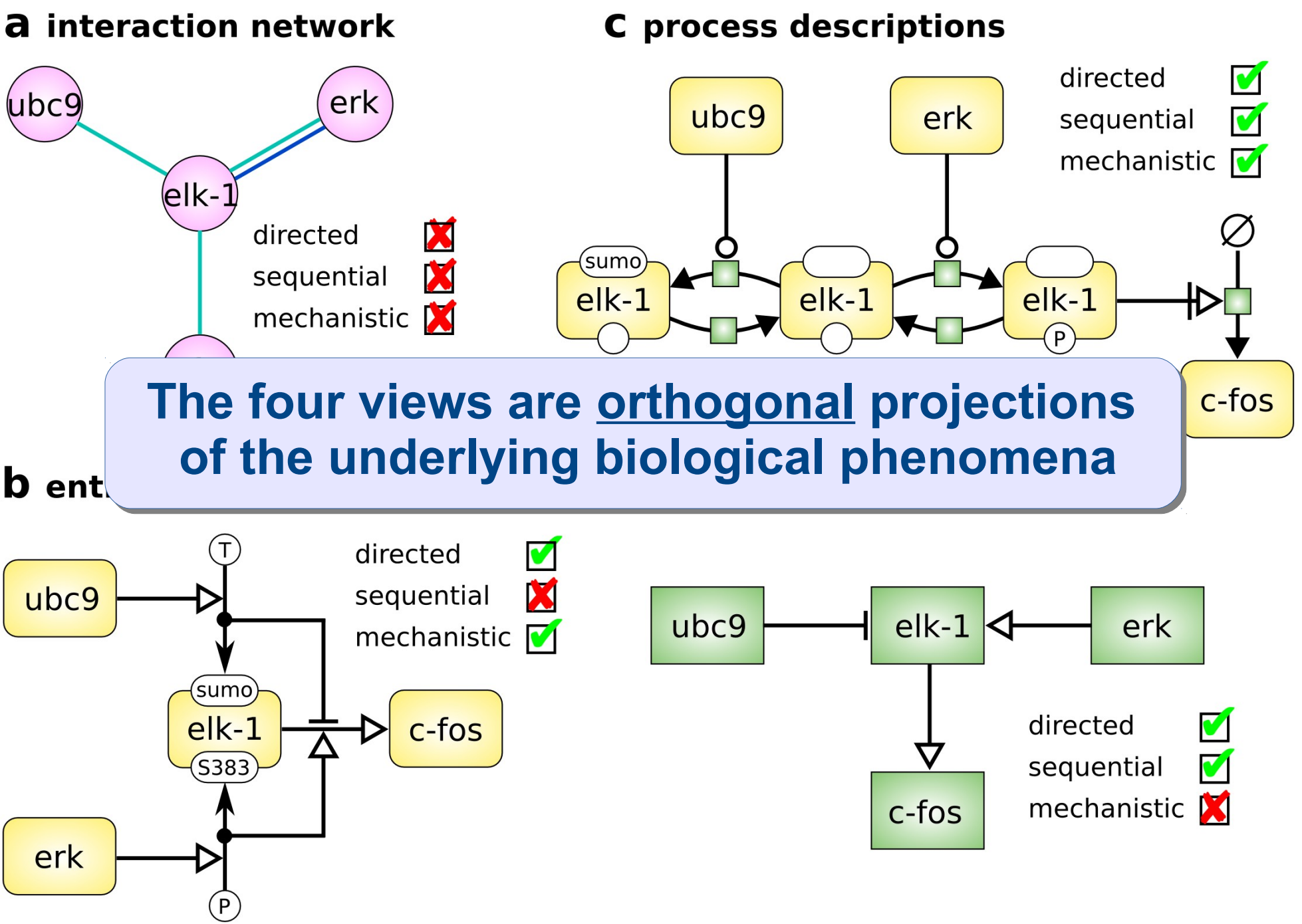
Genotype-system-phenotype problem

Drug discovery models
Vs systems modelling

Drug discovery models
Vs “omics” data

The four views of systems biology




a interaction network
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mechanistic
c process descriptions
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The four views are orthogonal projections of the underlying biological phenomena
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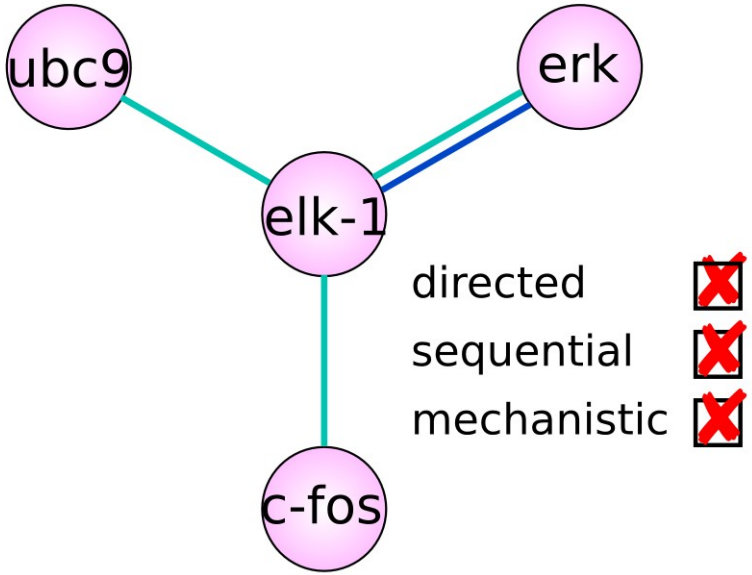
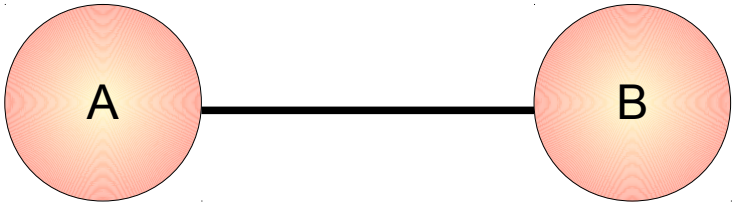
Interaction networks



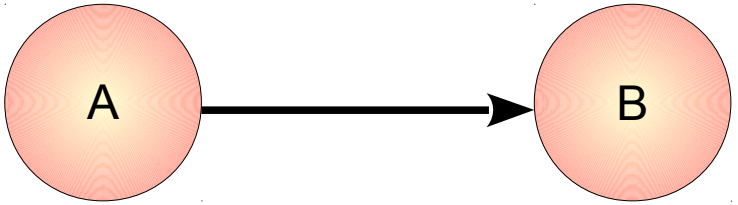
- Statistical modelling
- Functional genomics
- IntAct, DIP, String

Undirected, directed, signed



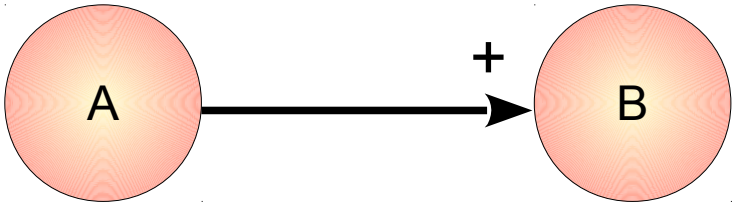
Undirected

"A interacts with B"



directed

"A influences B"

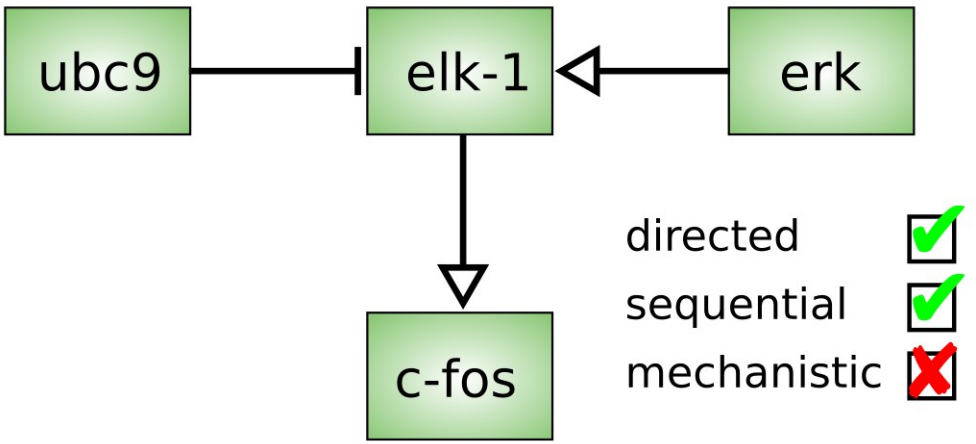


Signed

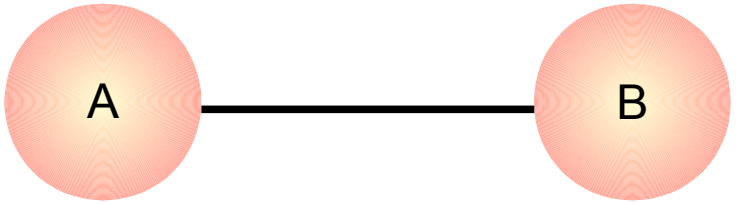
A influences positively B

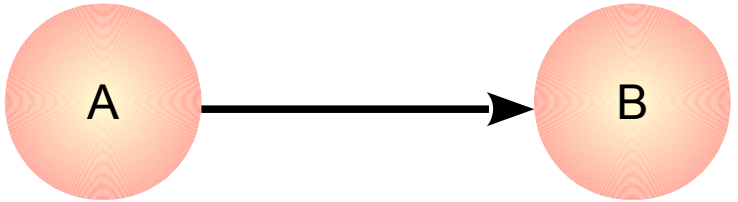
Activity Flows

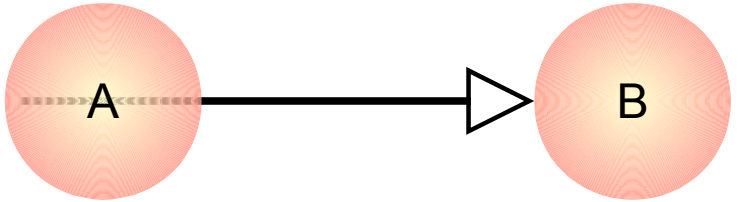
- Logical modelling
- Signalling pathways, gene regulatory networks
- KEGG non-metabolic, STKE



Undirected, directed, signed

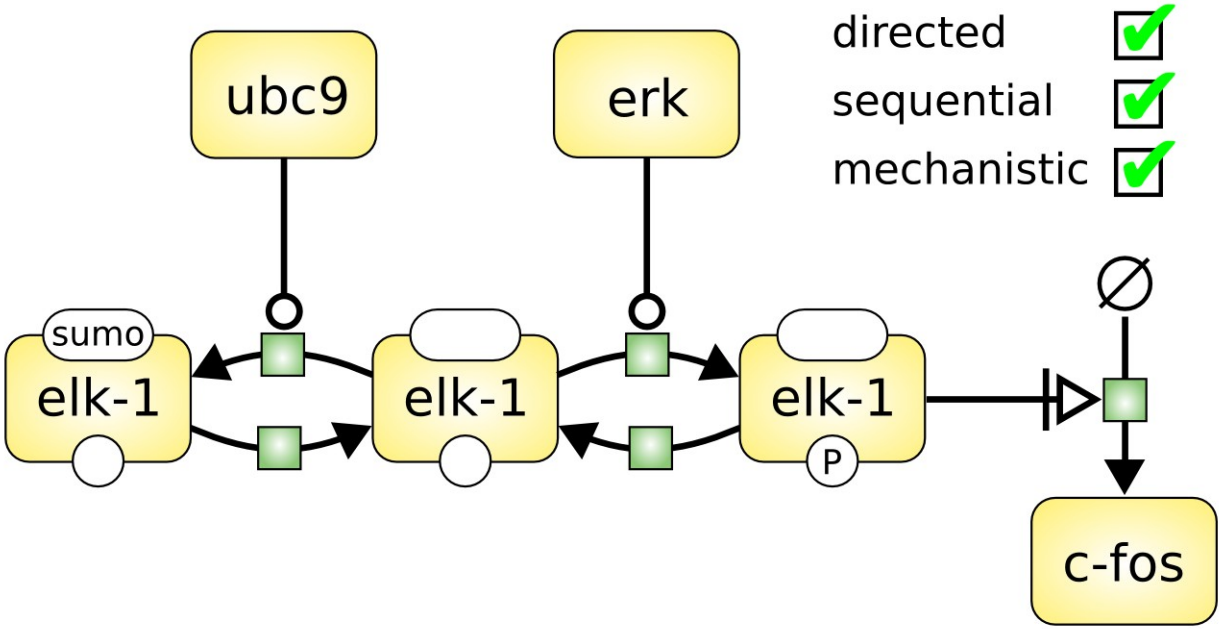






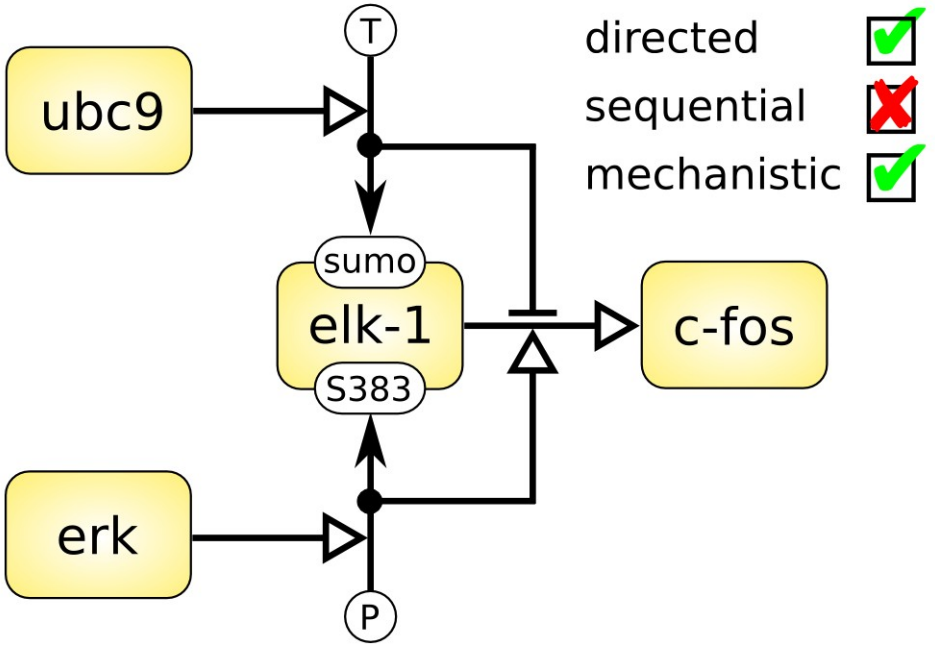
A signed interaction network
is equivalent to an activity flow

Process Descriptions



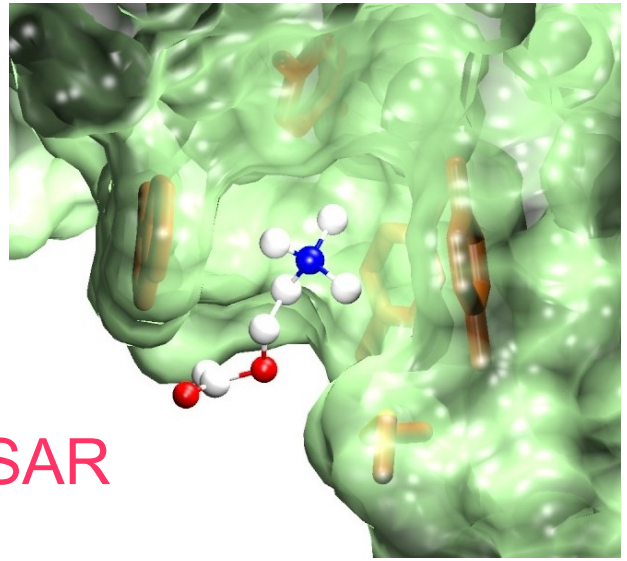
- Process modelling
- Biochemistry, Metabolic networks
- Generally within “closed world”
- Subjected to combinatorial explosion
- KEGG metabolic, Reactome

Entity Relationships

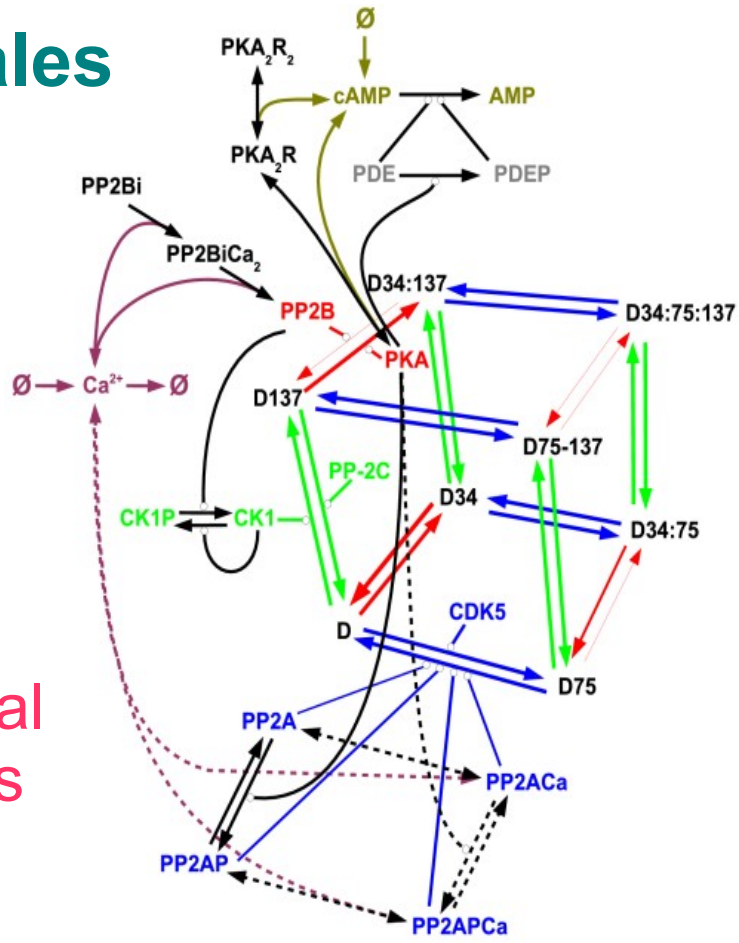


- Rule-based modelling
- Molecular Biology
- “Open world”
- Independent rules: no explosion
- Molecular Interaction Maps

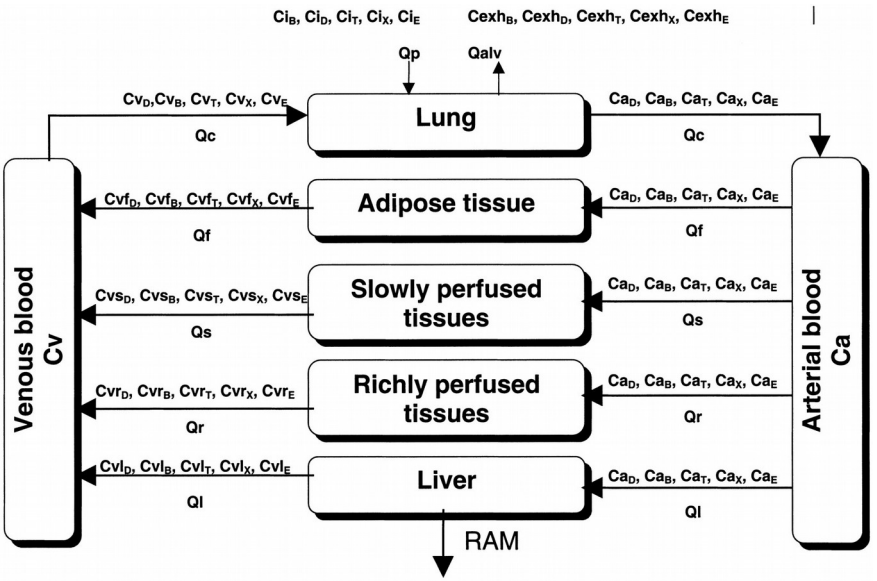
The problem of scales



QSAR



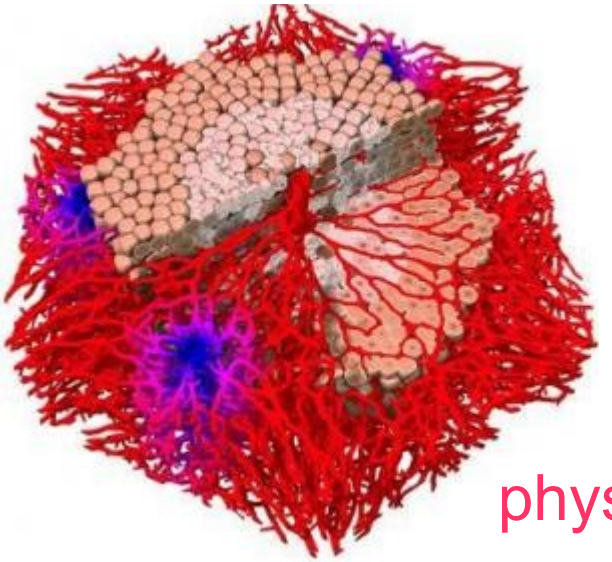
chemical kinetics



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

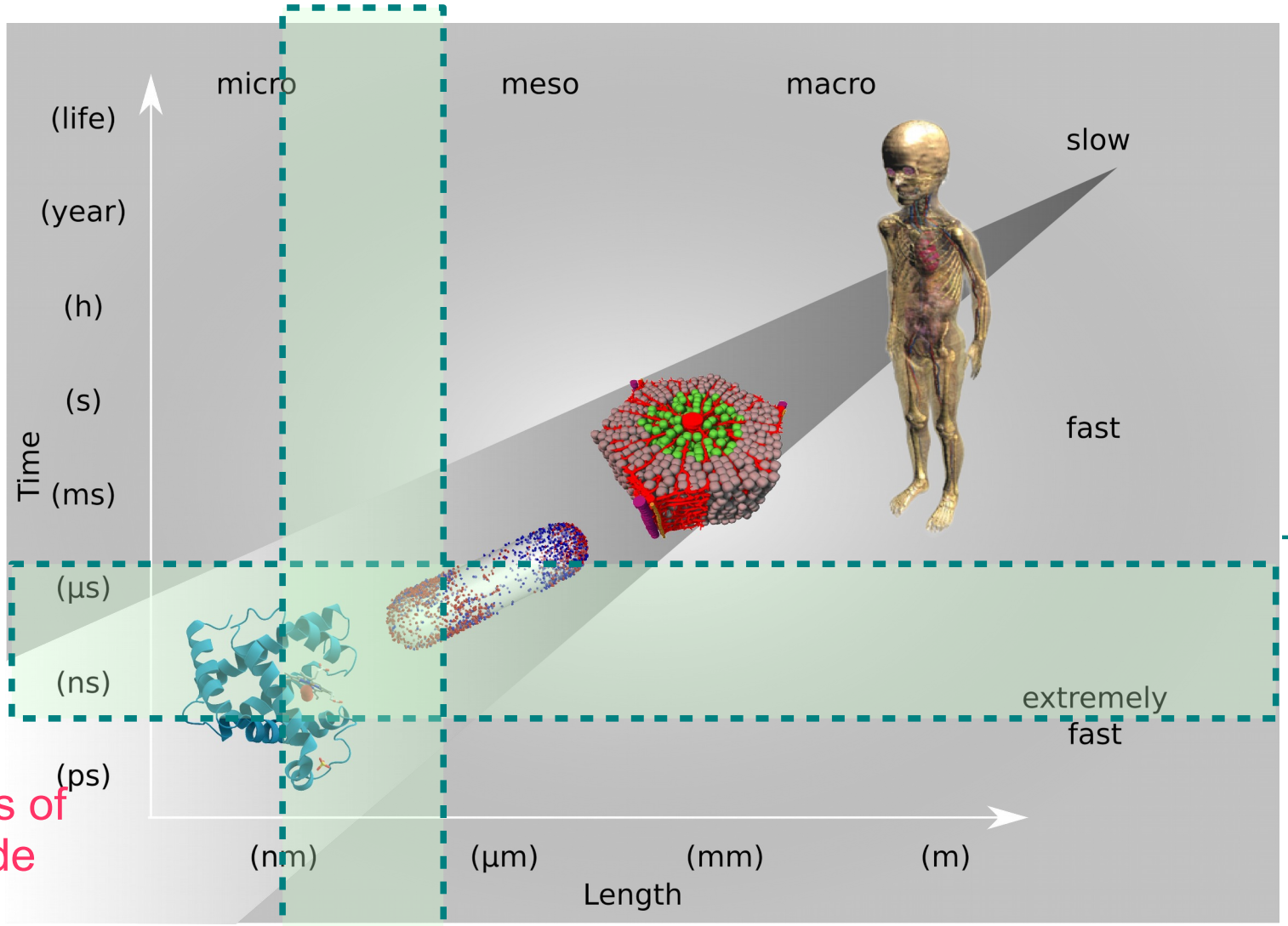
$$RAM_B = \frac{Vmax_B \; Cvl_B}{Km_B\left(1+\frac{Cvl_D}{Ki_{DB}}+\frac{Cvl_T}{Ki_{TB}}+\frac{Cvl_E}{Ki_{EB}}+\frac{Cvl_X}{Ki_{XB}}\right)+Cvl_B}$$

pharmacometrics



physiology

The problem of scales



Coupled multi-scale models

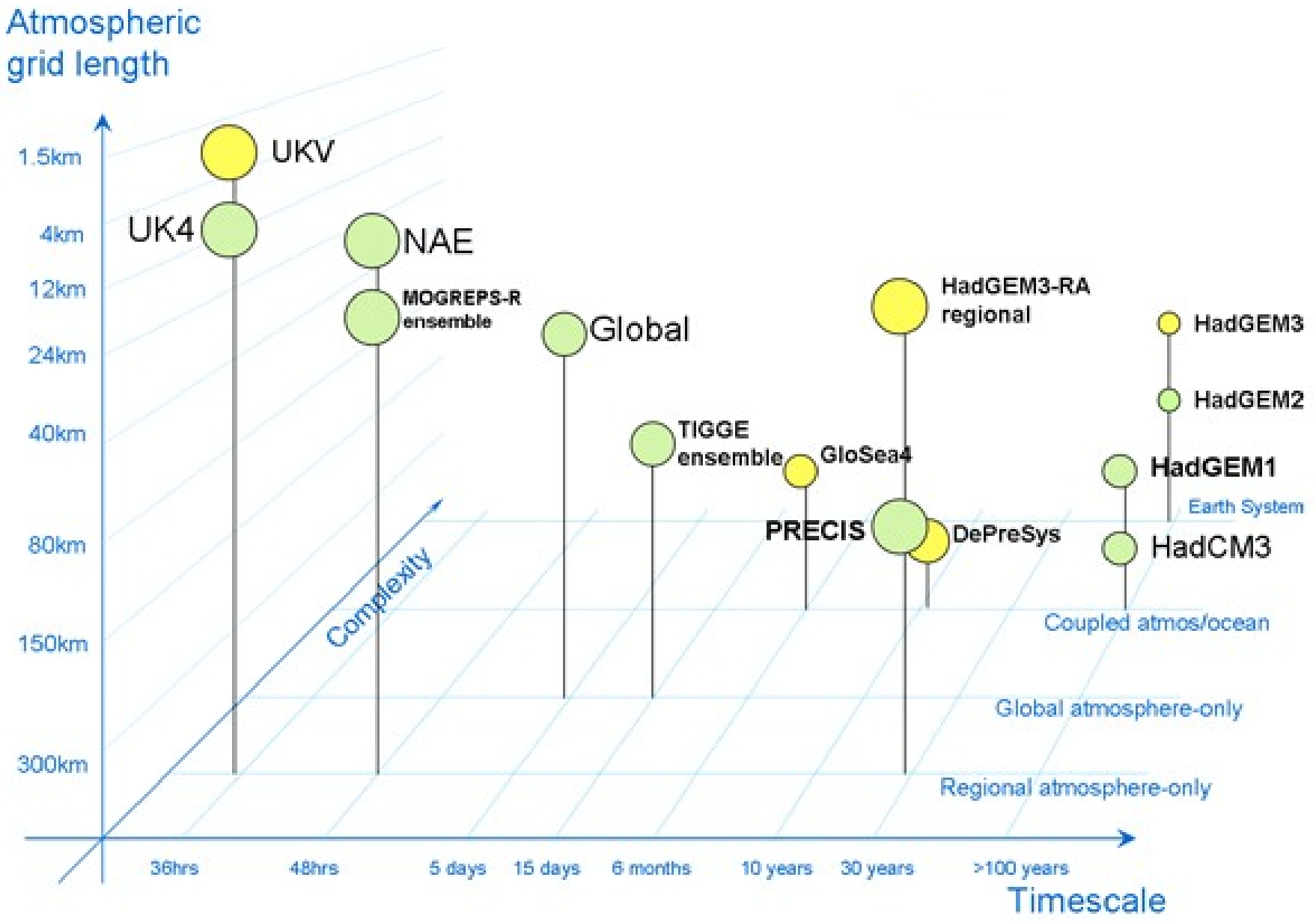
Theoretical and Computational roadblockers

24 orders of magnitude

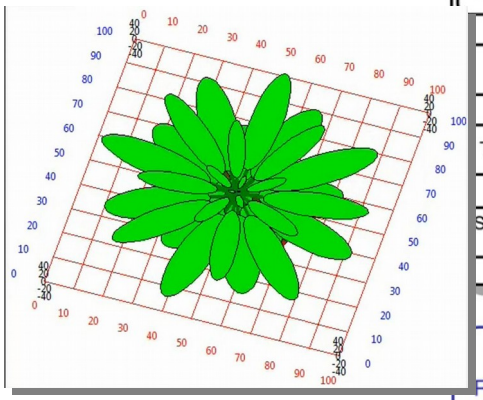
9 orders of magnitude

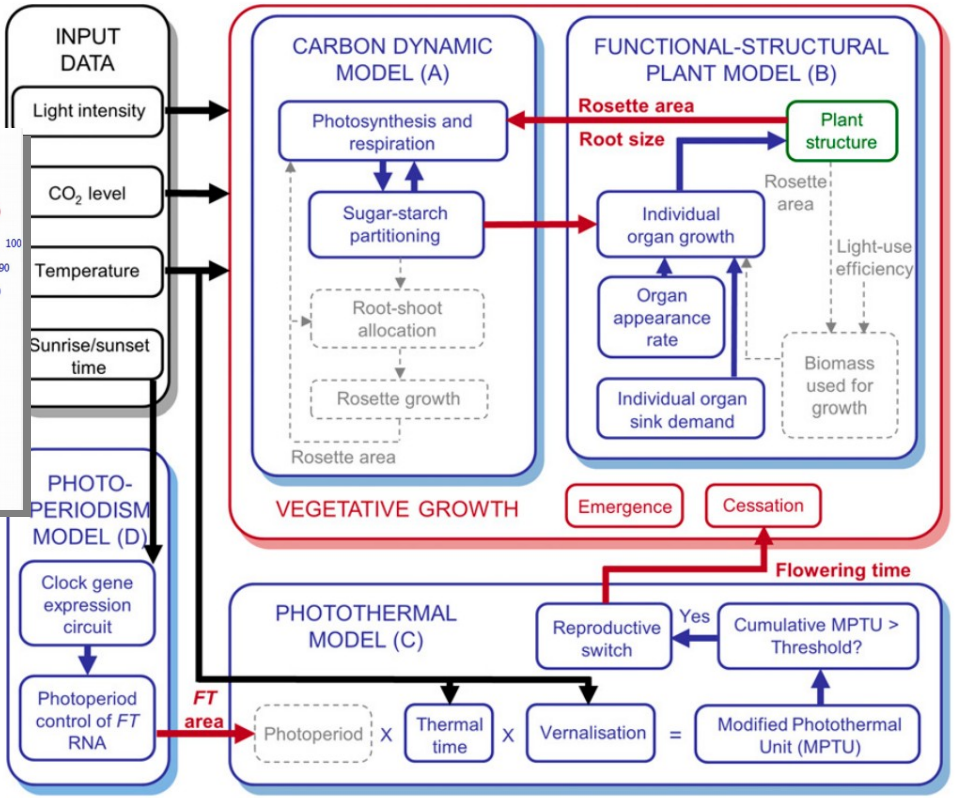
Adapted from Castiglione *et al.* (2014)

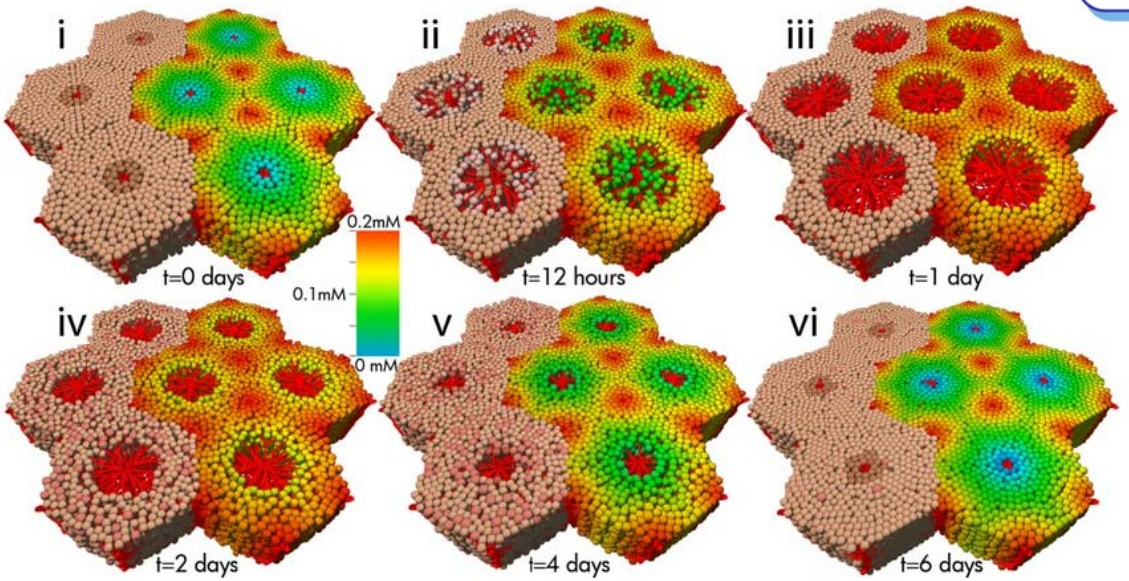
Met Office Seamless Unified Model



Chew *et al.* (2014)

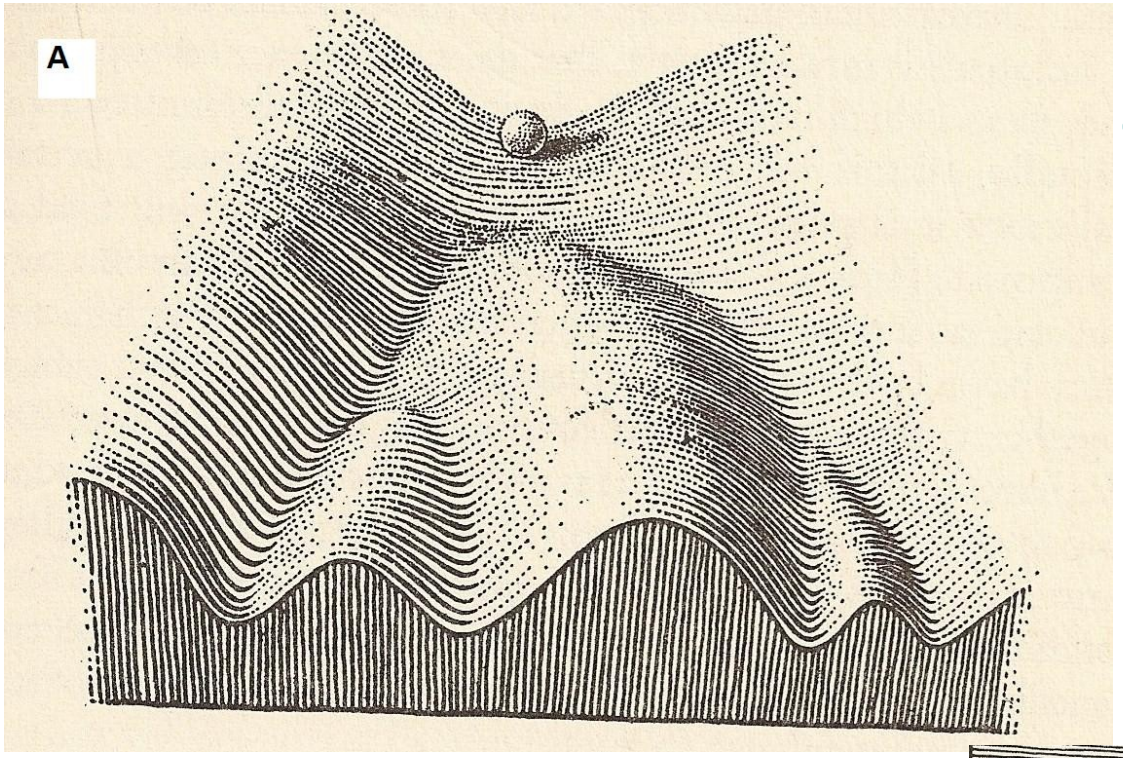




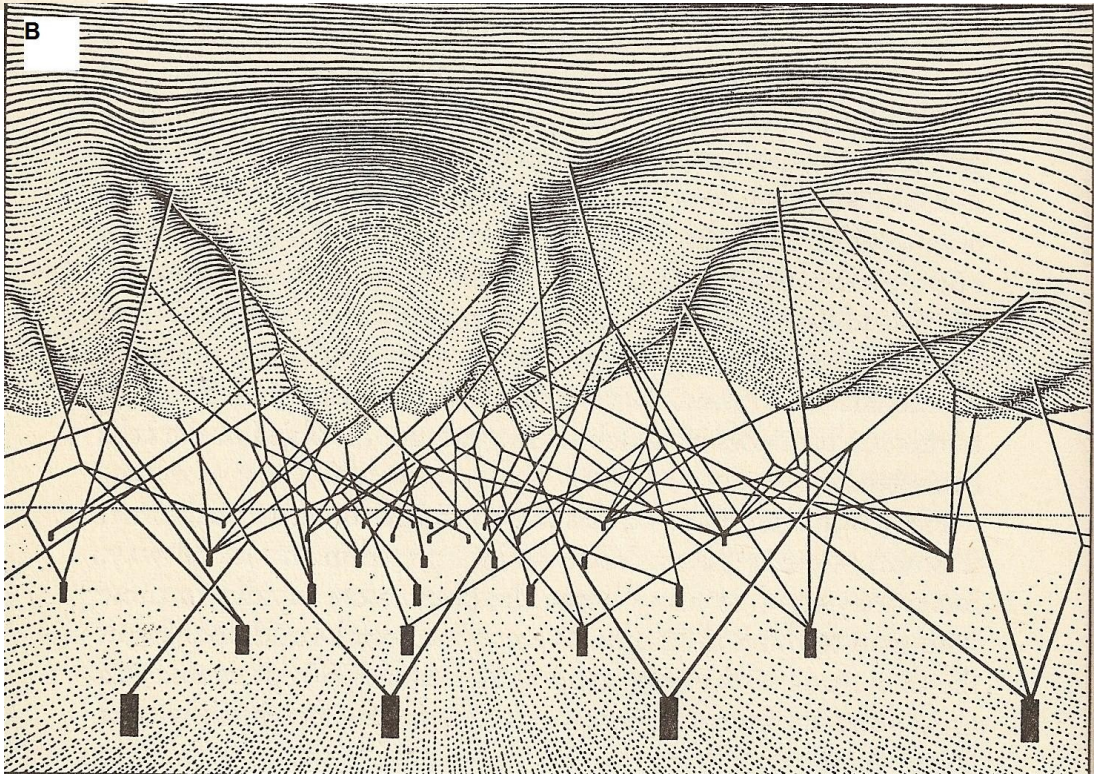


Schliess *et al.* (2014)

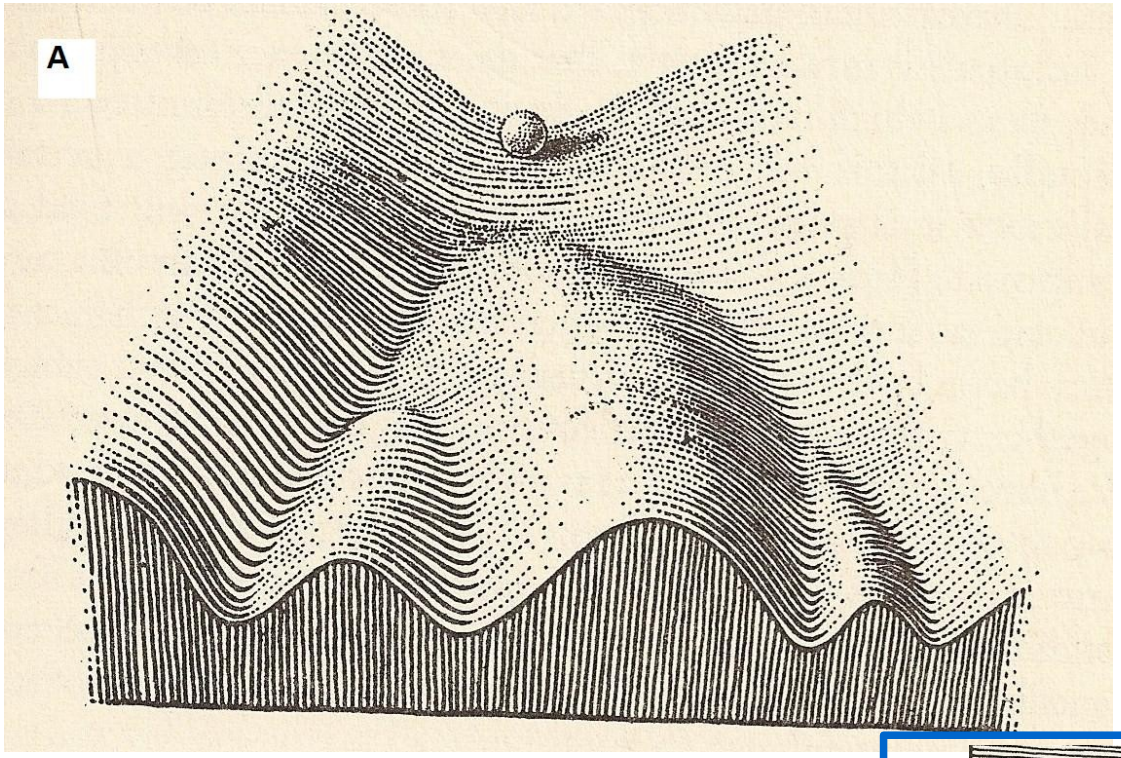
Emergent properties and the gene-system-phenotype puzzle



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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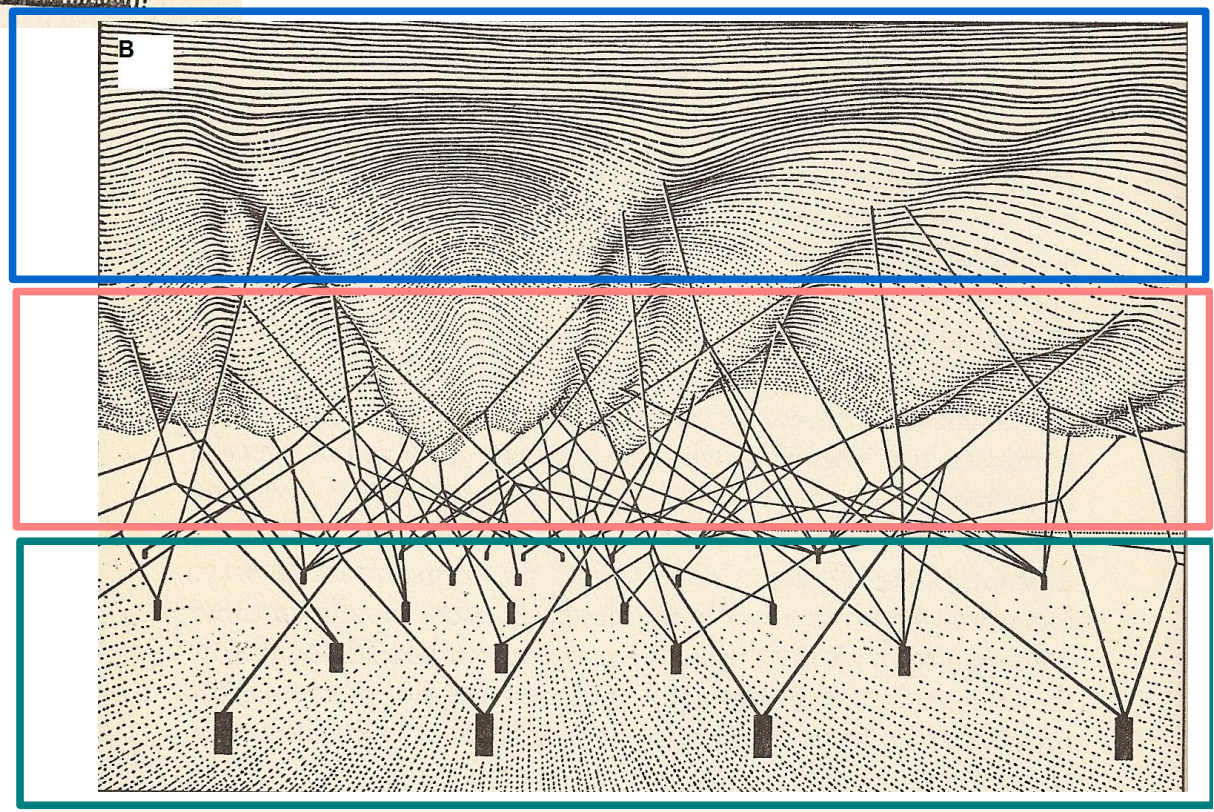
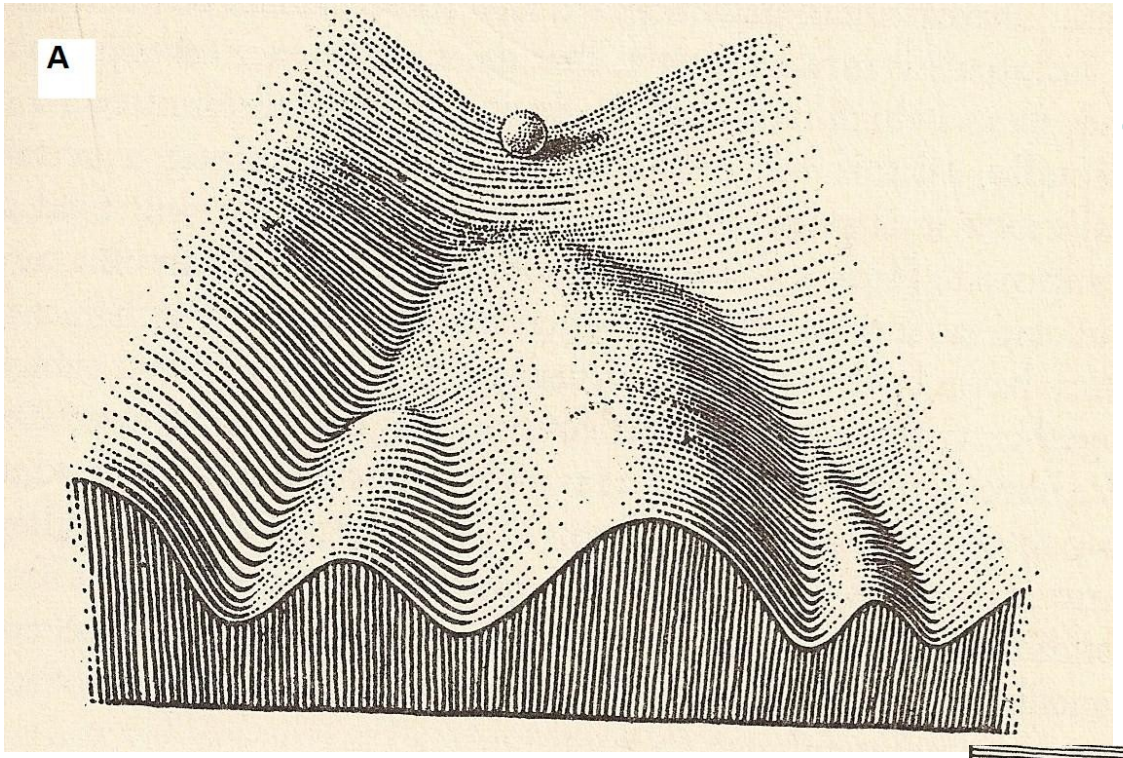
physiology ← phenotype

systems biology ← system

genetics ← genotype

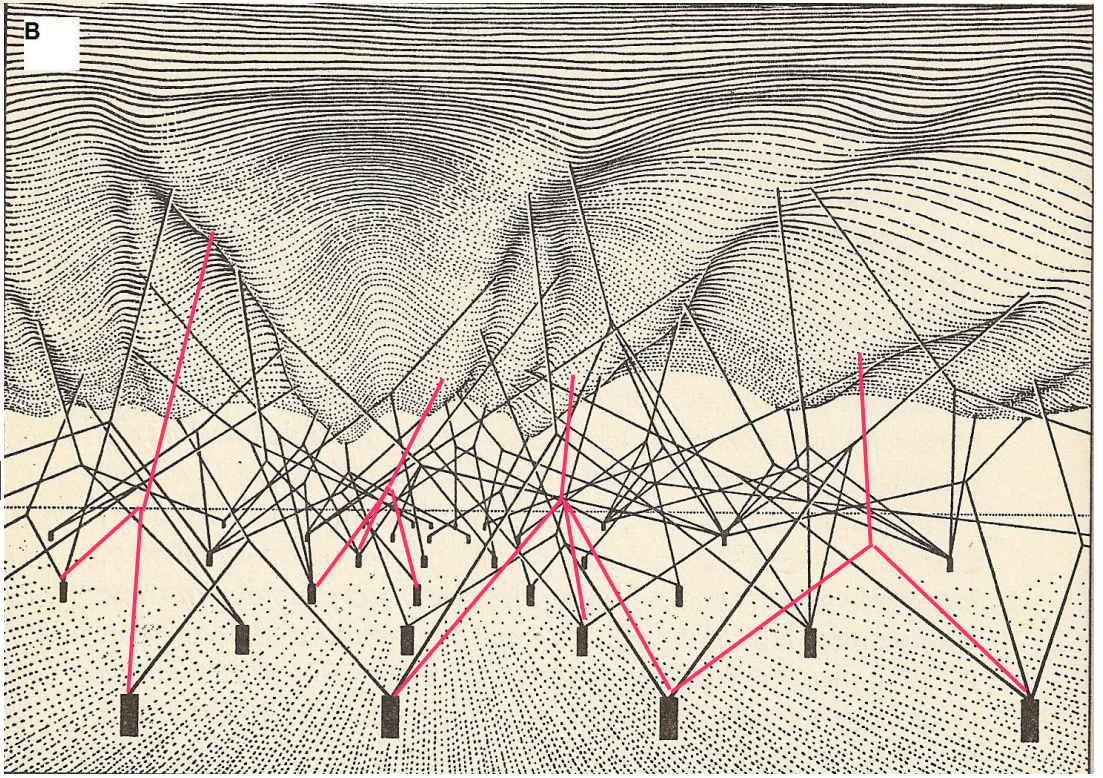


Emergent properties and the gene-system-phenotype puzzle



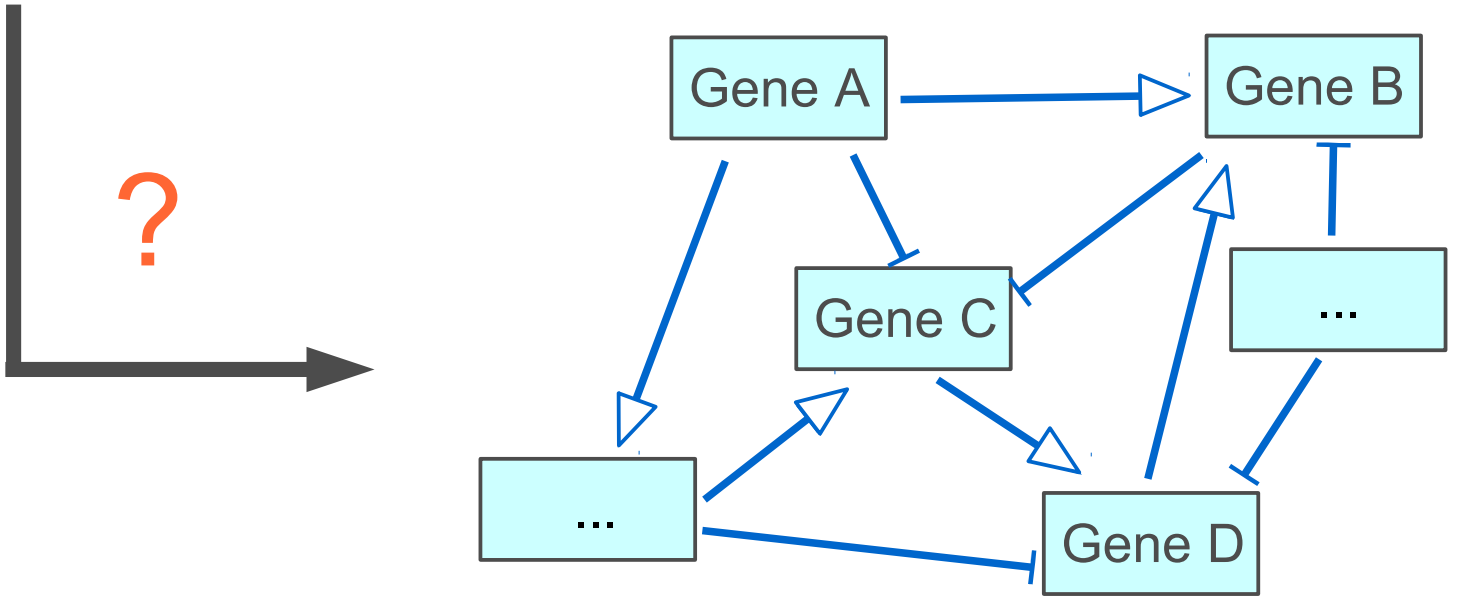
Waddington C.H., Kacser H (1957)
The Strategy of the Genes:
A Discussion of Some Aspects of
Theoretical Biology.
George Allen & Unwin

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).

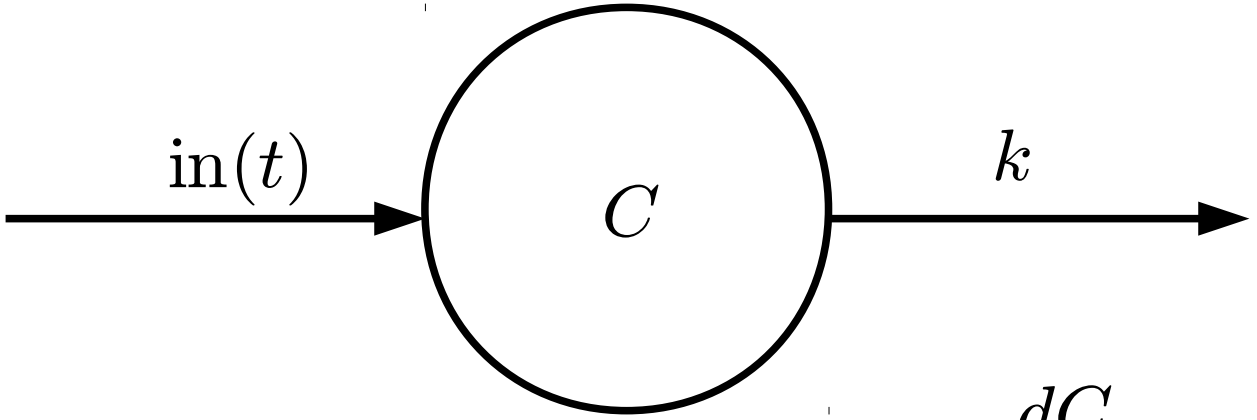


Reverse engineering is hard ...

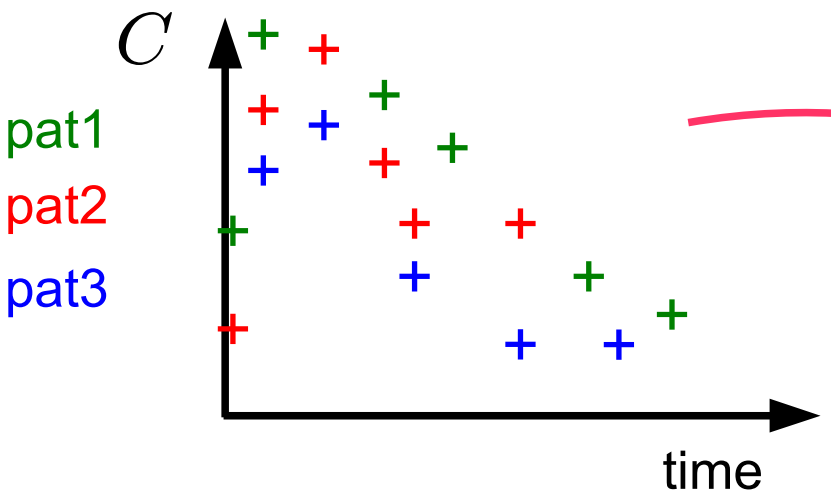
	Gene A	Gene B	Gene C	Gene D	...
Phenotype X	✔	✘	✔	✘	
Phenotype Y	✔	✘	✘	✔	
Phenotype Z	✘	✔	✔	✘	
...					

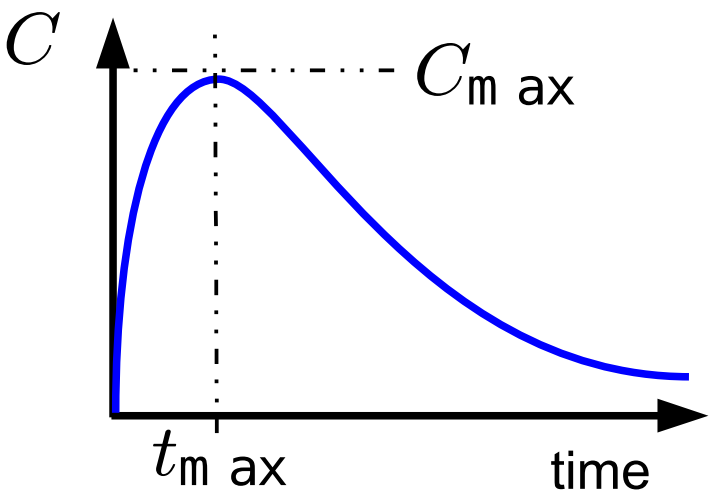


Drug discovery modelling: pharmacometrics

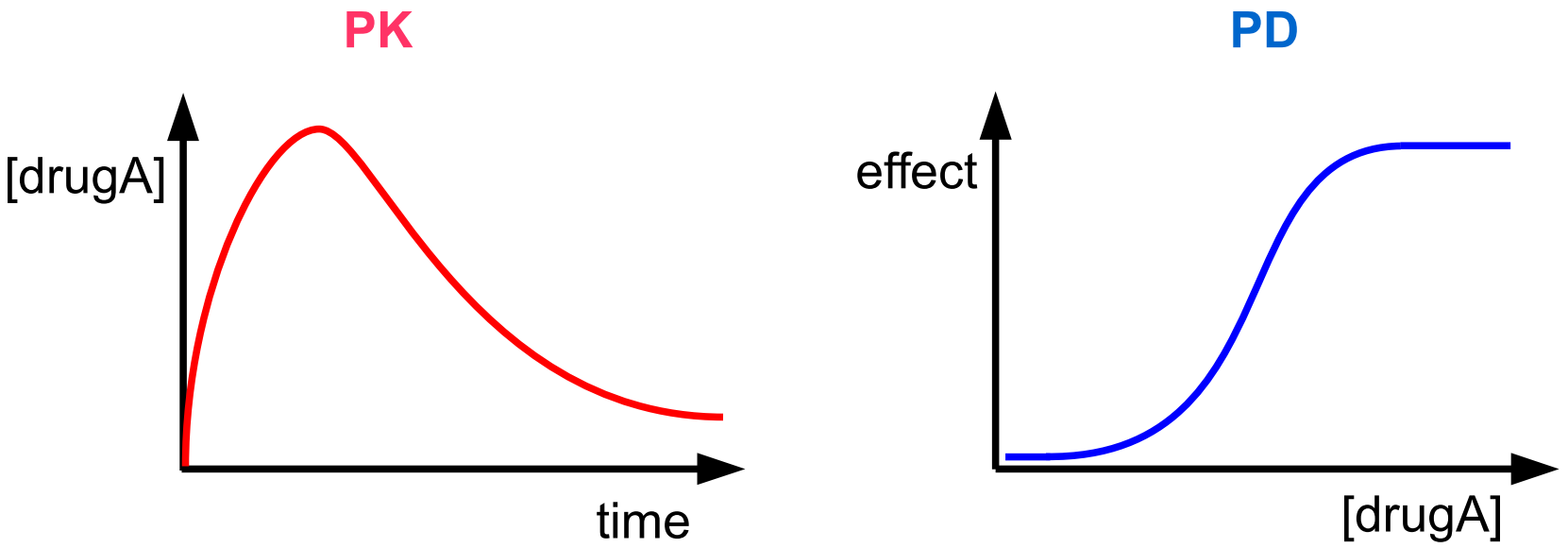


$$\frac{dC}{dt} = \text{in}(t) - k \times C$$

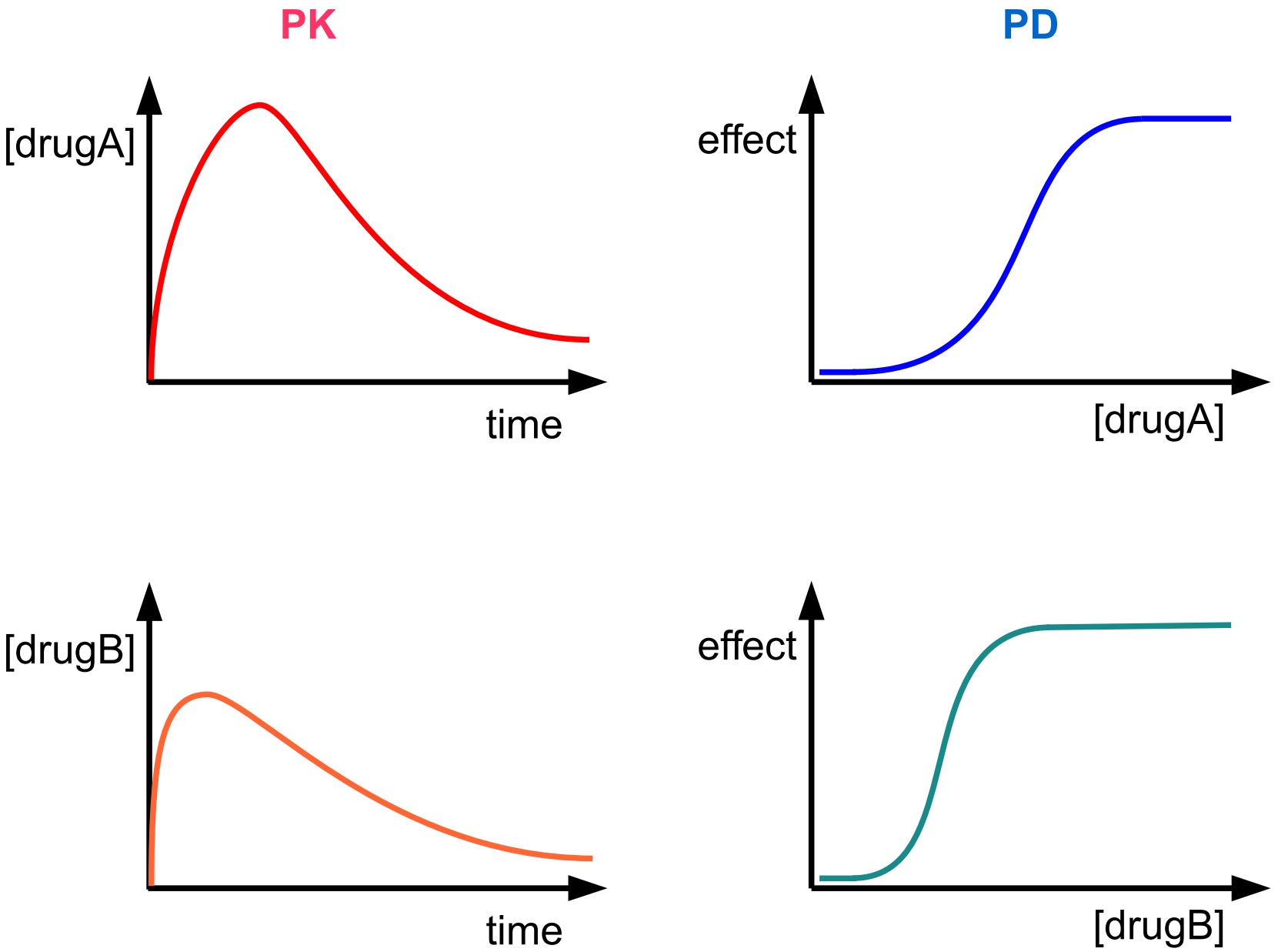




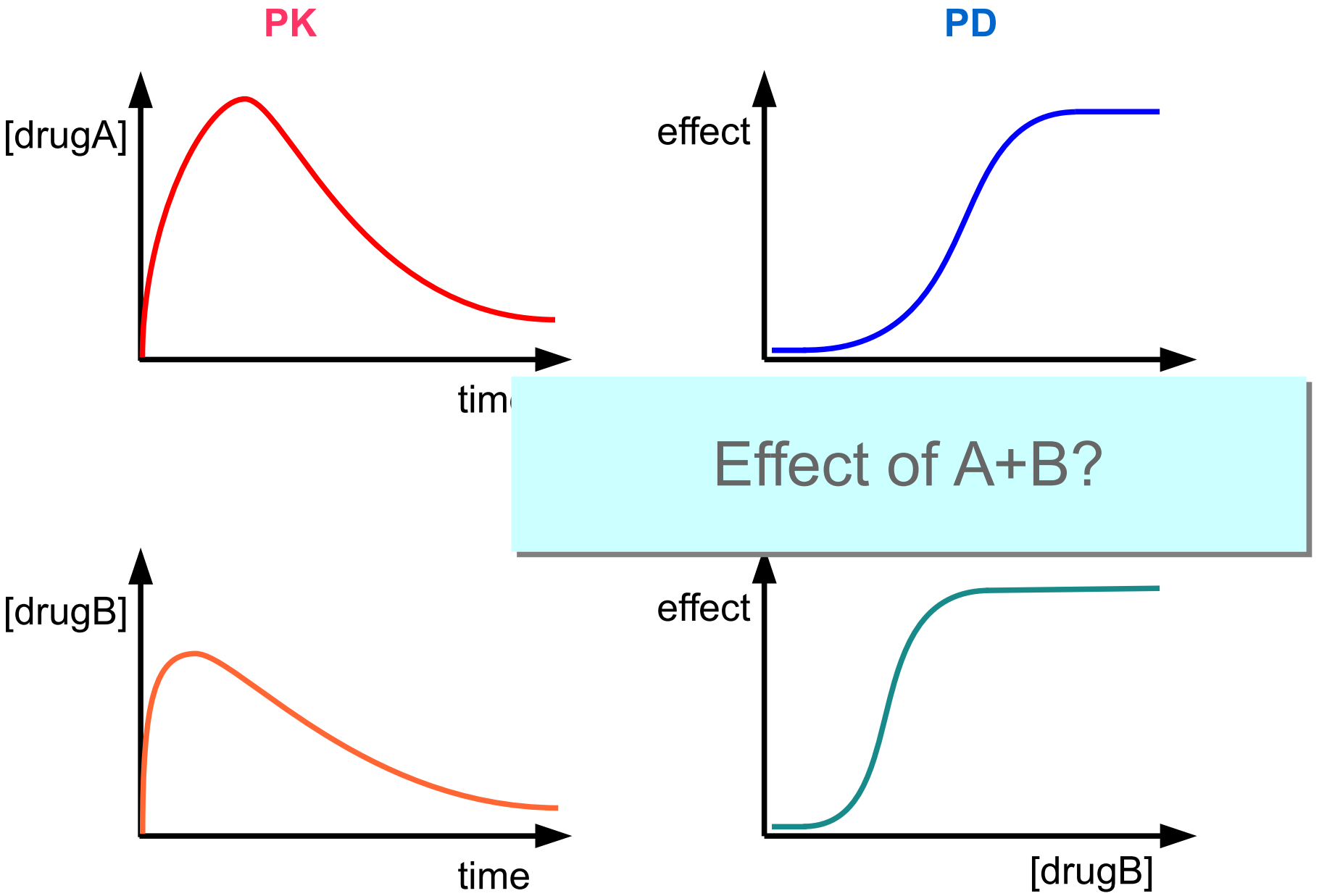
Drug discovery modelling: pharmacometrics



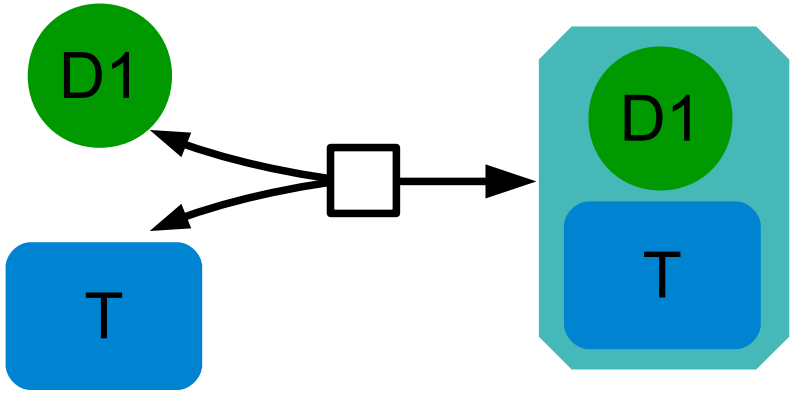
Drug discovery modelling: pharmacometrics



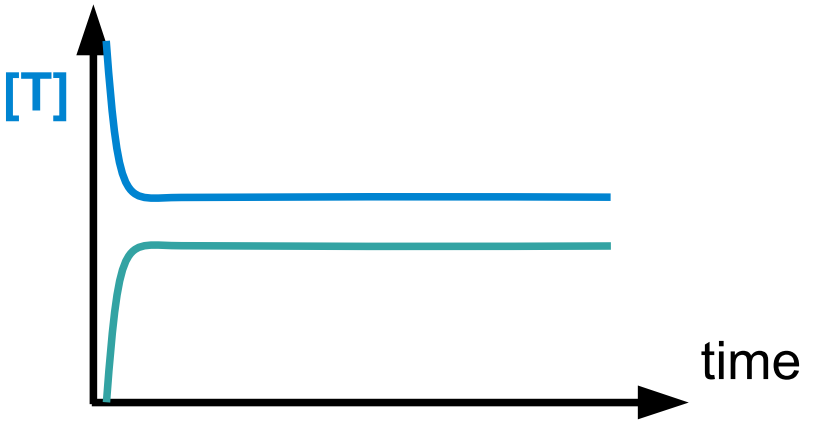
Drug discovery modelling: pharmacometrics

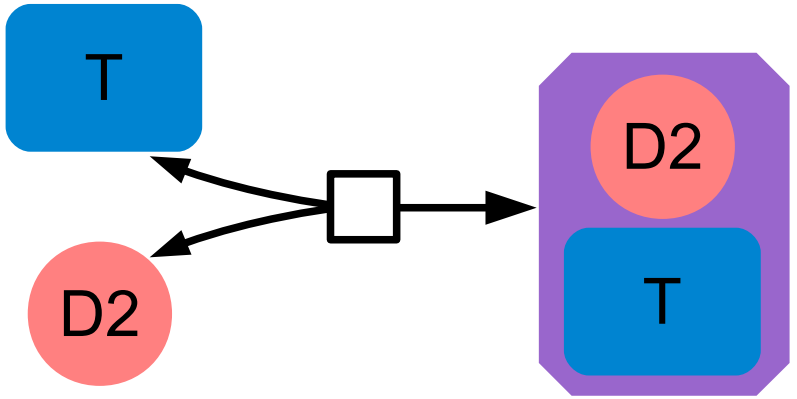


Systems modelling

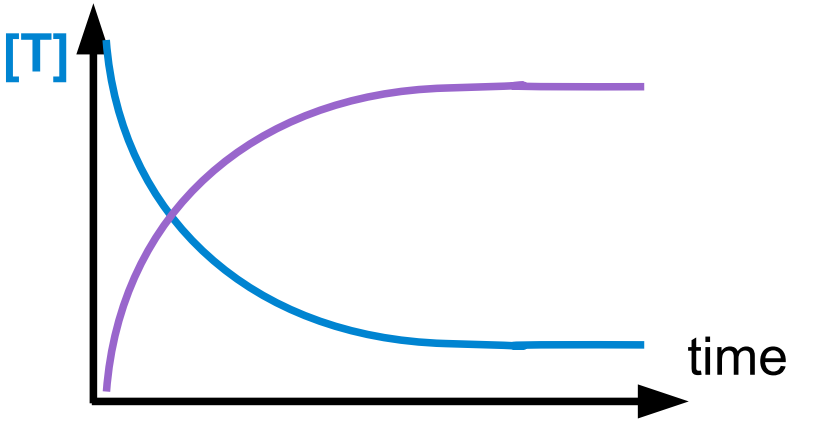


$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1]$$



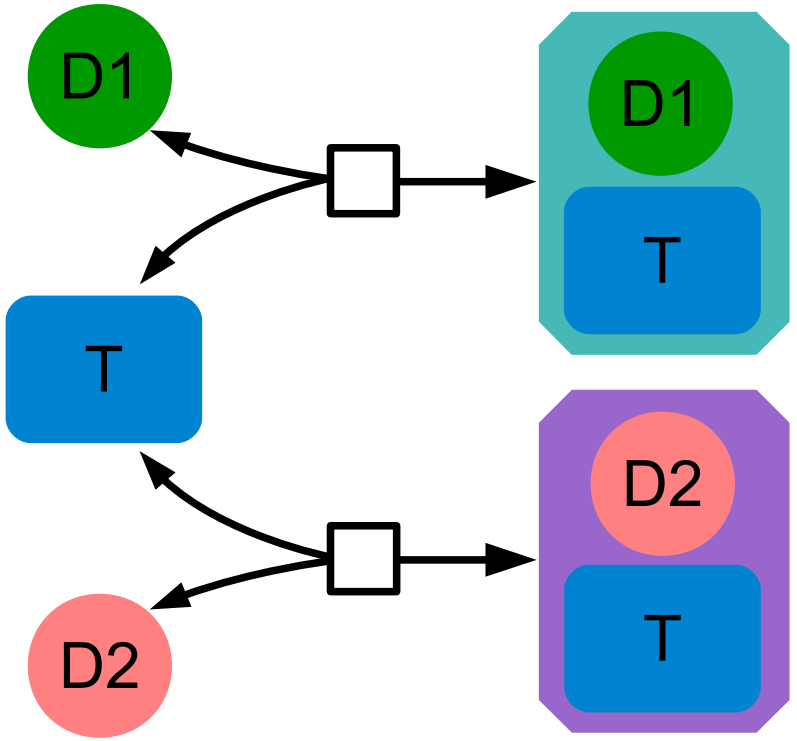


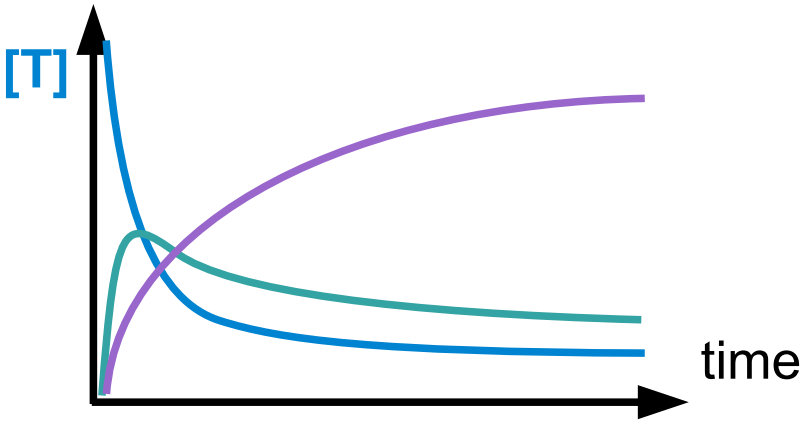
$$\frac{d[T]}{dt} = -k2 \times [T] \times [D2]$$



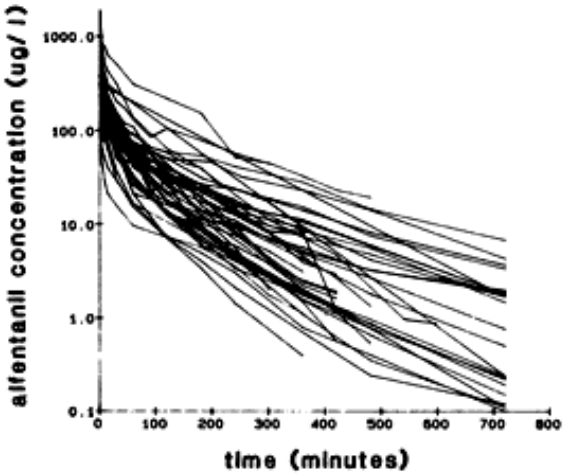
Systems modelling

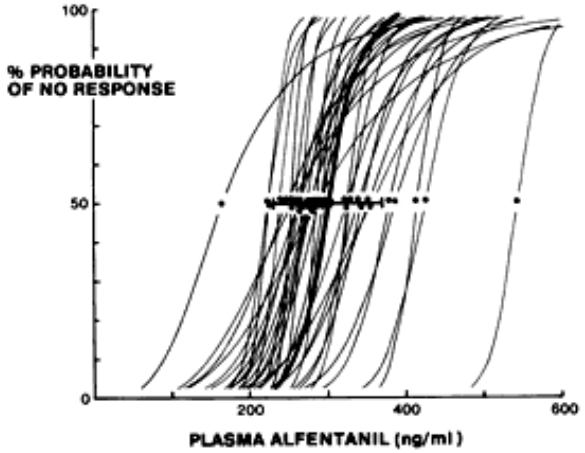
$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1] - k2 \times [T] \times [D2]$$

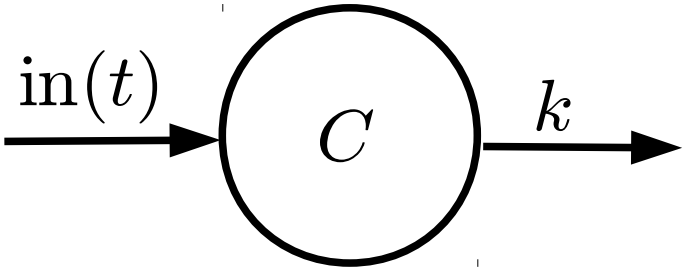


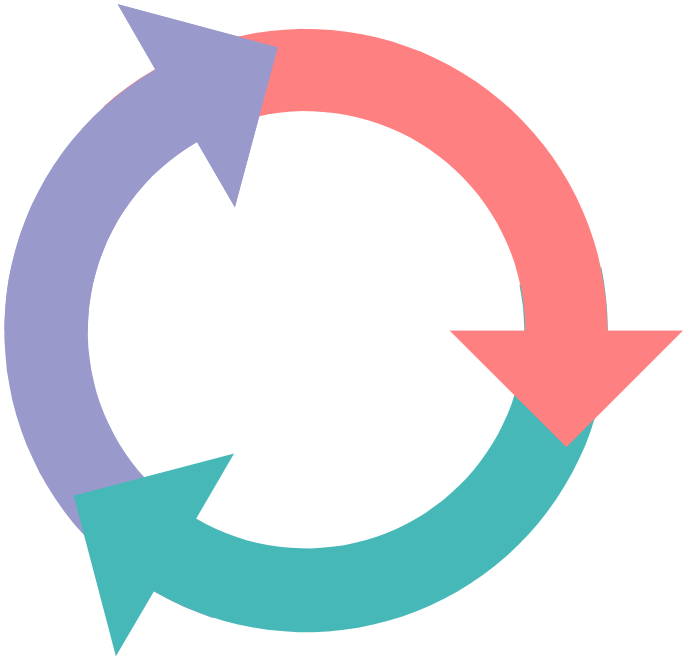


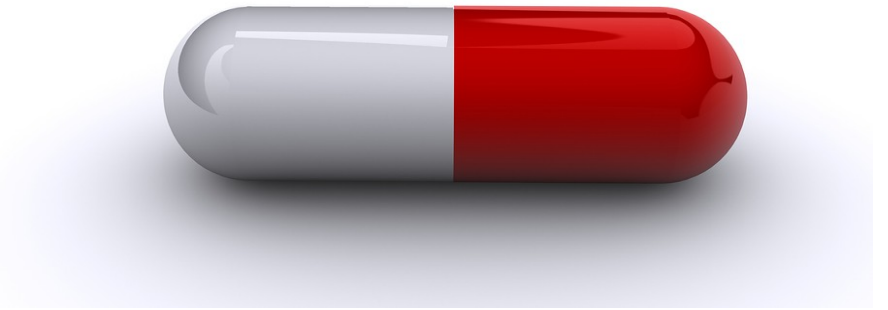
Drug discovery and pharmacometrics models



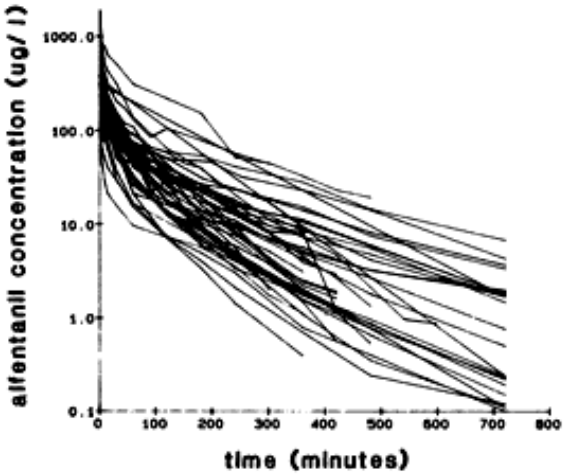


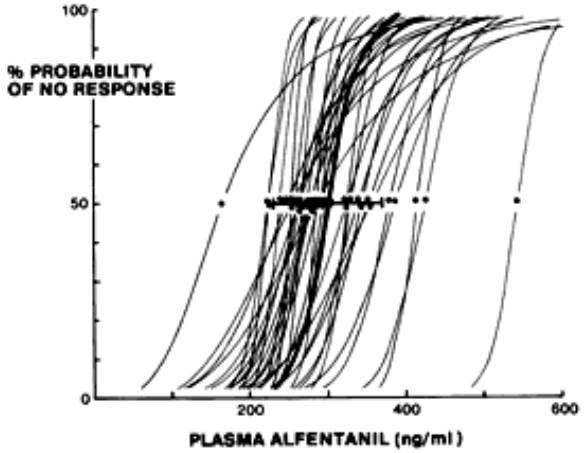


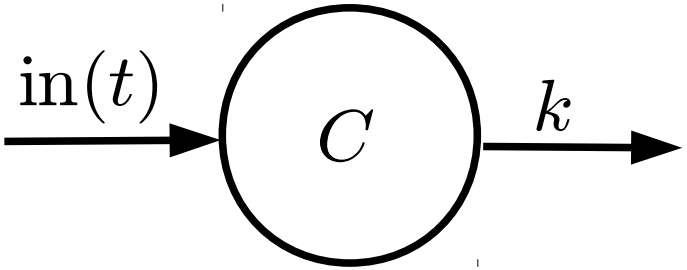


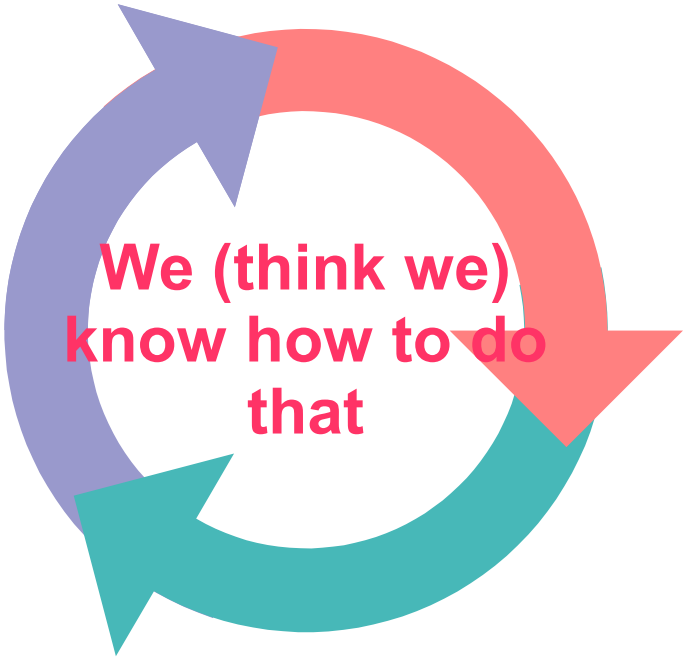


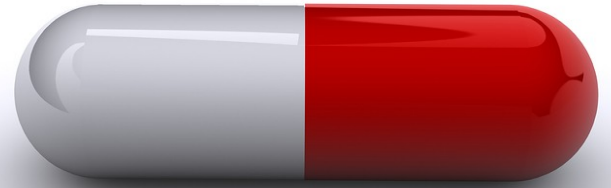
Drug discovery and pharmacometrics models



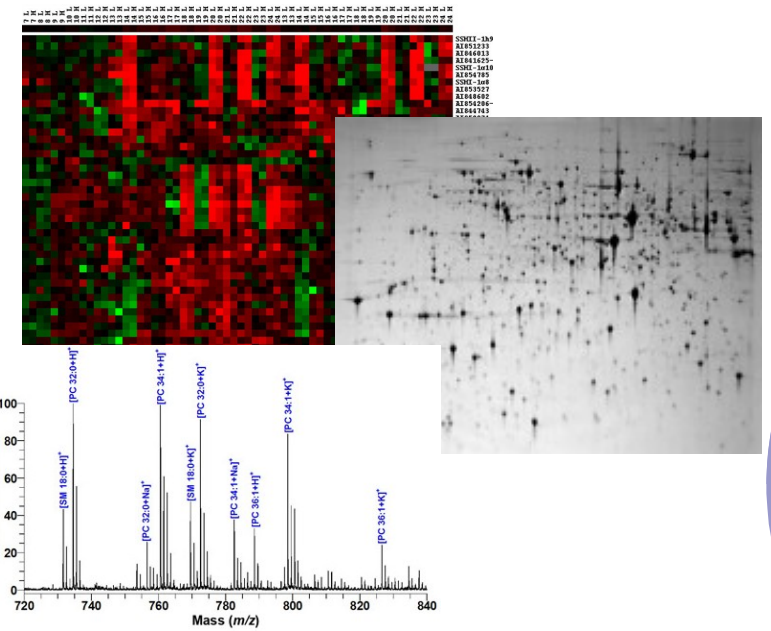


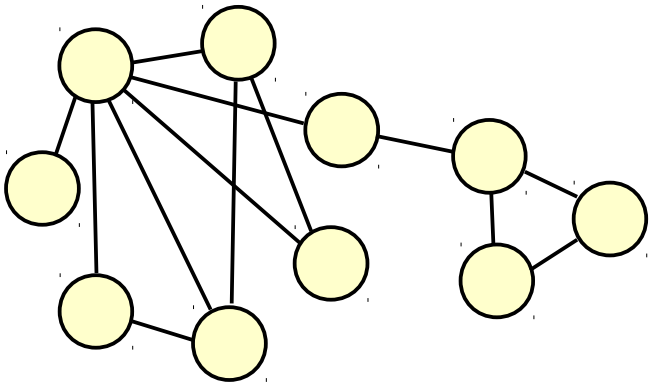


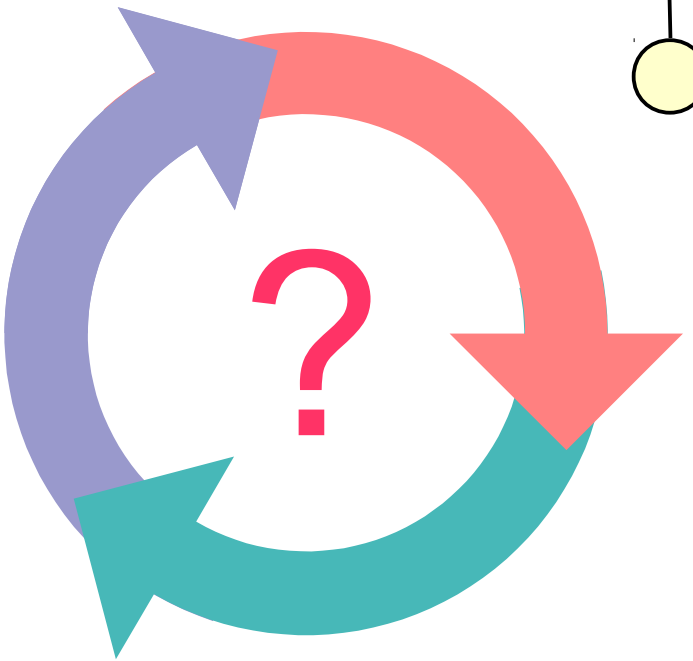


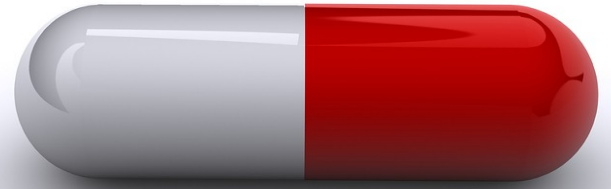


Drug discovery and omics









Systems Biology

Edda Klipp, Wolfram Liebermeister, Christoph Wierling,
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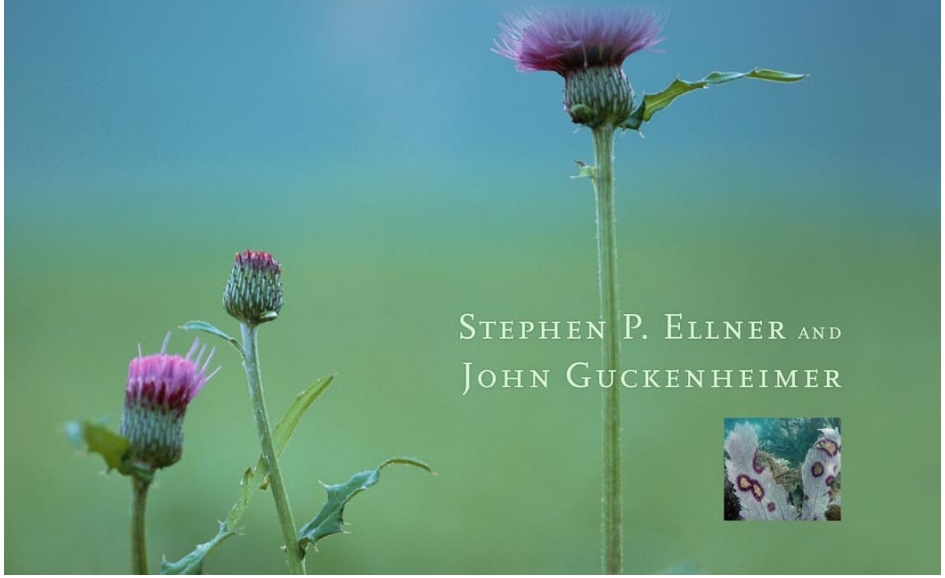

Stephen P. Ellner and
John Guckenheimer