Systems Biology: Where it comes from, what it is, and what it does

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

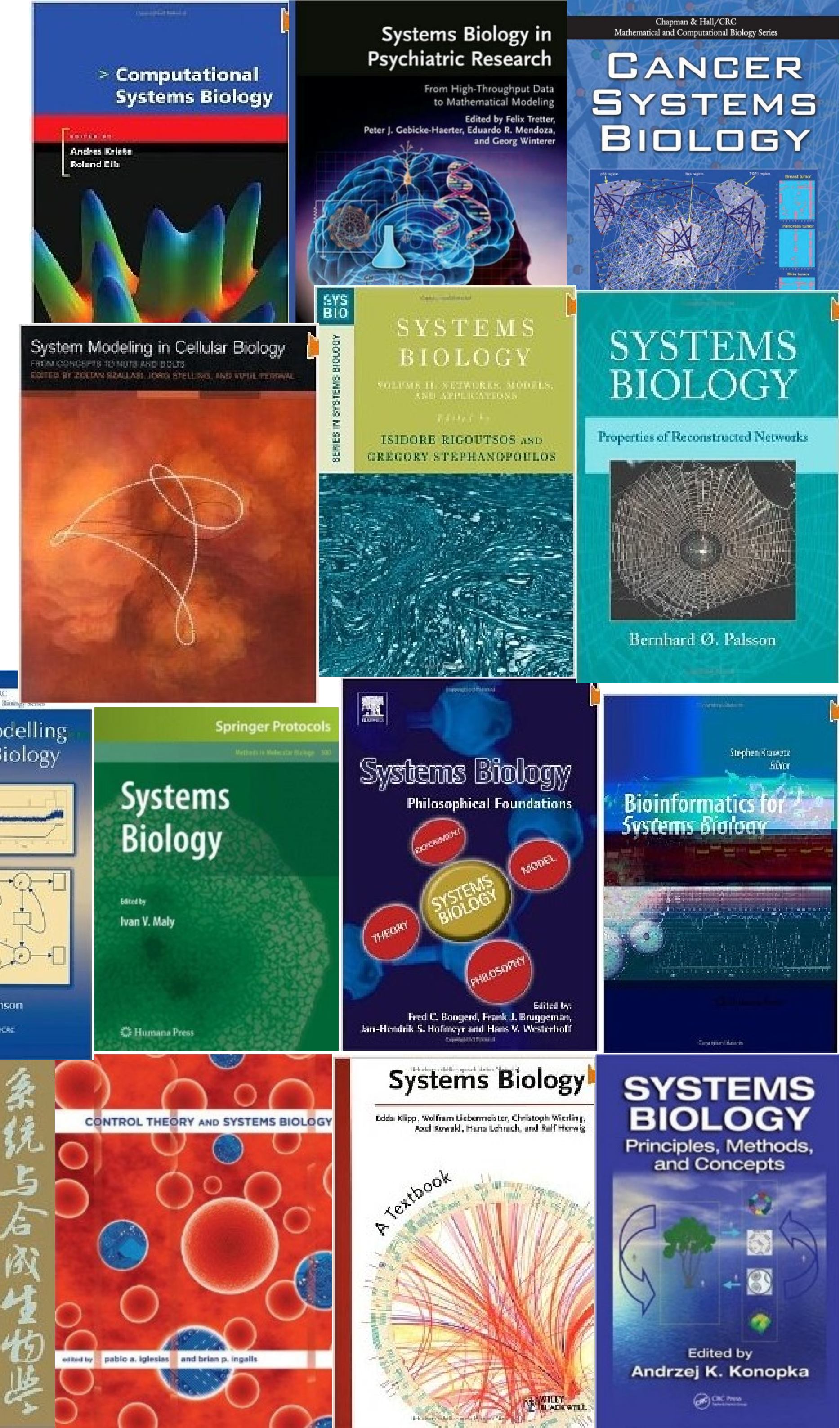
Trey Ideker[1,2], Timothy Galitski[1], and Leroy Hood[1,2,3,4,5]
Institute for Systems Biology[1], Seattle, Washington 98105; Departments of

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

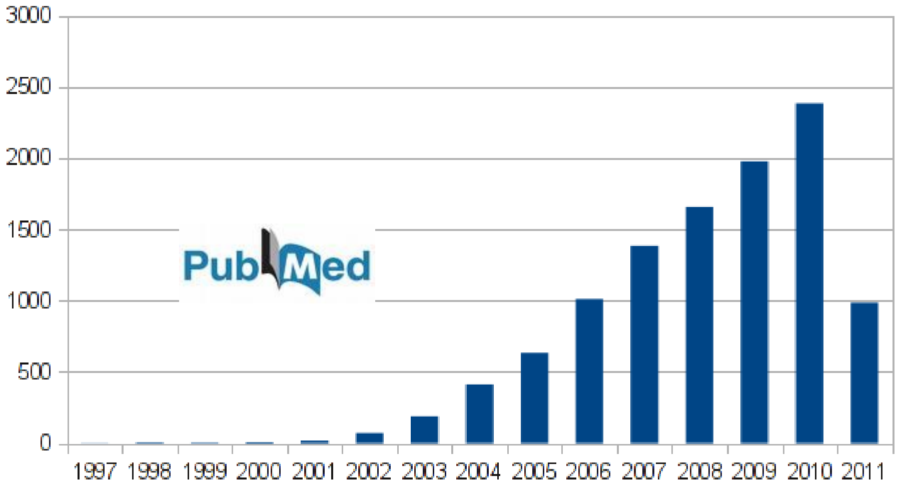
Invited Paper

Perspectives on Systems Biology

Hiroaki KITANO
Sony Computer Science Laboratories, Inc.



What is Systems Biology?



- First mention of the term: 1928 (L Von Bertallanfy)
- Modern revival of the term: 1998 (L Hood, H Kitano)

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

Systems-wide analysis (omics)

- Born: 1990s
- Technologies: high-throughput, statistics
- People's background: molecular biologists, mathematicians
- Key lesson: the selection of a phenotype is done at the level of the system, not of the component (gene expression puzzle)

Application of systems-theory

- Born: 1960s
- Technologies: quantitative measurements, modelling
- People's background: biochemists, engineers
- Key lesson: the properties at a certain level are emerging from the dynamic interaction of components at a lower level

Nobel Symposium on Systems Biology (June 2009)

networks

Leroy Hood
Marc Vidal
Mike Snyder
Marc Kirschner
Charlie Boone
Ruedi Aebersold
Terence Hwa
Erin O'Shea
Jussi taipale

models

Eric Davidson
Stanislas Leibler
Michel Savageau
Roger Brent
Lucy Shapiro
Hans Westerhoff
Francois Nedelec
Luis Serrano
Uwe Sauer
Jim Ferrell
Naama Barkai
Jorg Stelling
Jens Nielsen
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Boris Kholodenko
Bela Novak
Johan Elf
Hiroaki Kitano
Stefan Hohmann
Bernard Palsson
Harley McAdams
Nicolas Le Novère
William Bialek
Mans Ehrenberg

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Nicolas Le Novère
William Bialek
Mans Ehrenberg

Avid Regev
Jeff Hasty
Michael Elowitz
Yoshihide Hayashizaki
Richard Young

synthetic biology
cell reprogramming

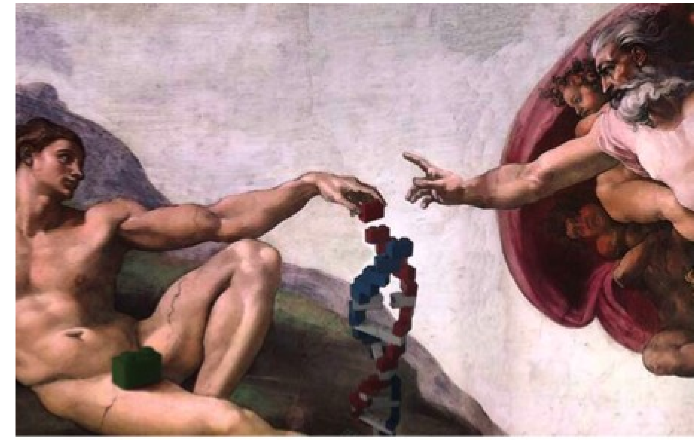
What happened to biology at the end of XXth century?

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

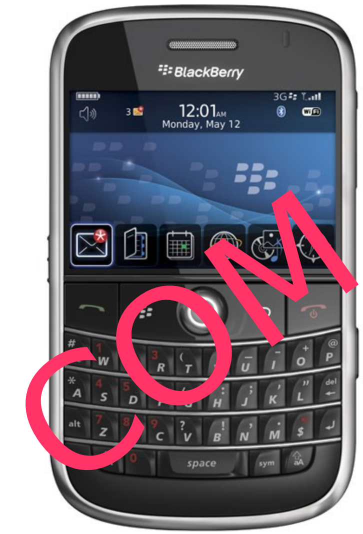
NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com

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 engineering bring?



Emergence of the notion of system

XVI XVII XVIII XIX XX XXI

Global Description of the world

“classical” mechanic, anatomy, physiology

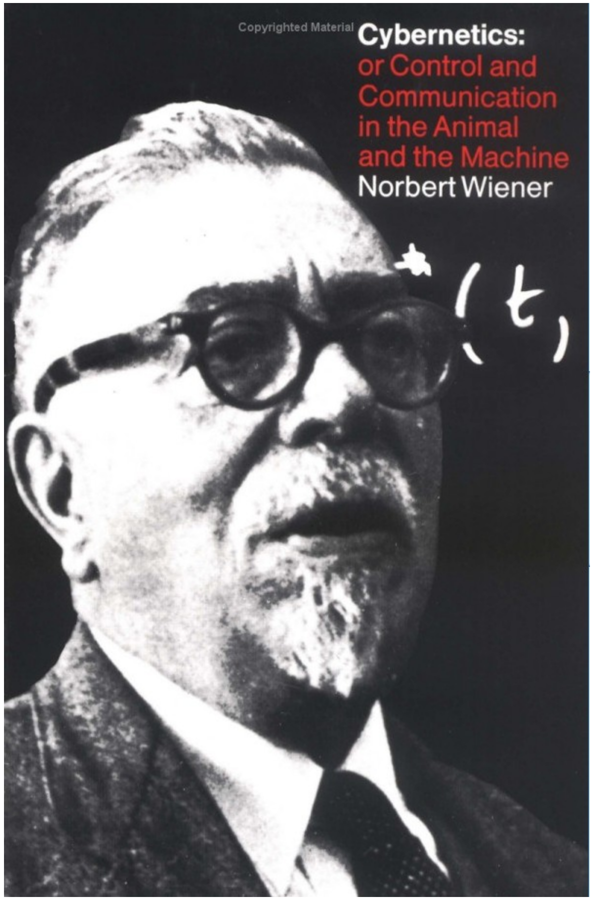
Description of the components of the world

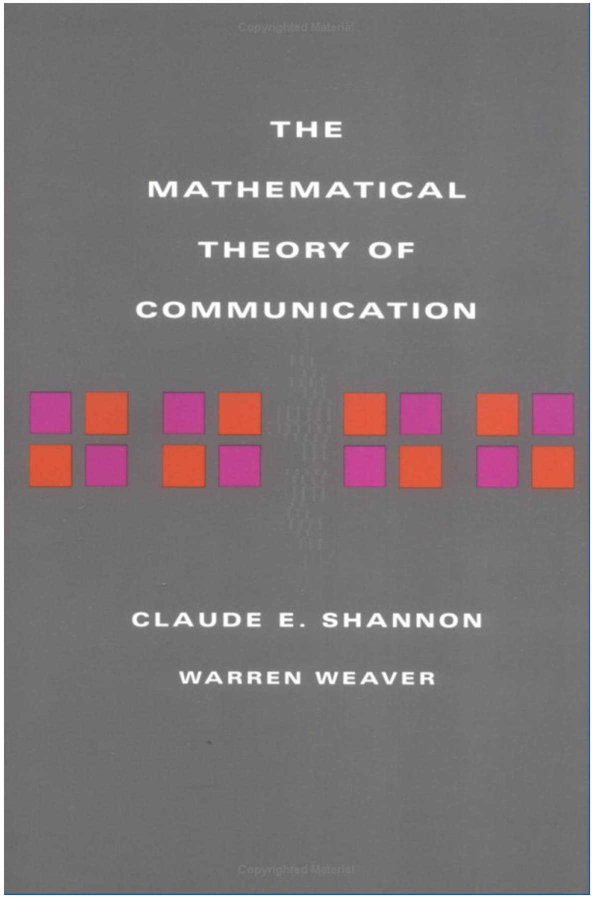
Statistical physics, thermodynamics, quantum mechanic,
biochemistry, structural biology, molecular biology

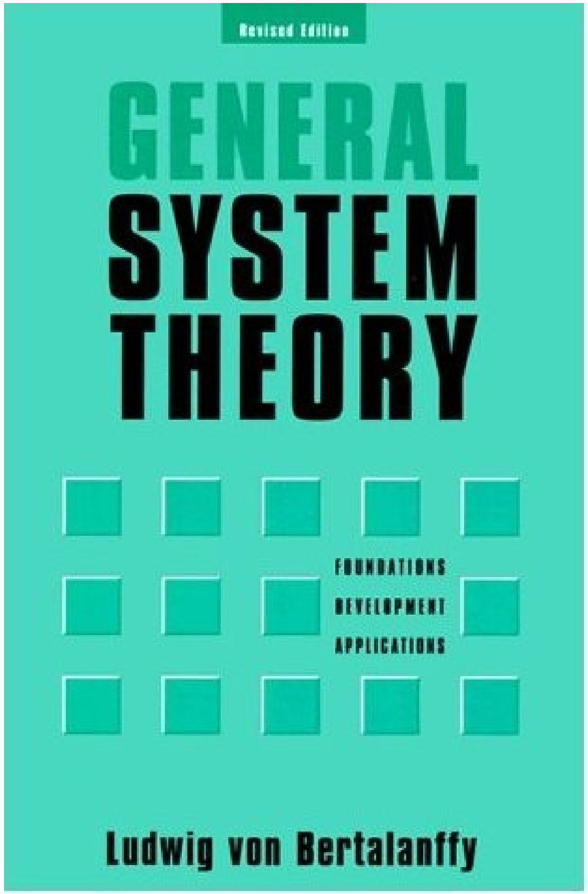
Description of interacting components

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

Systems have been formalised for a while







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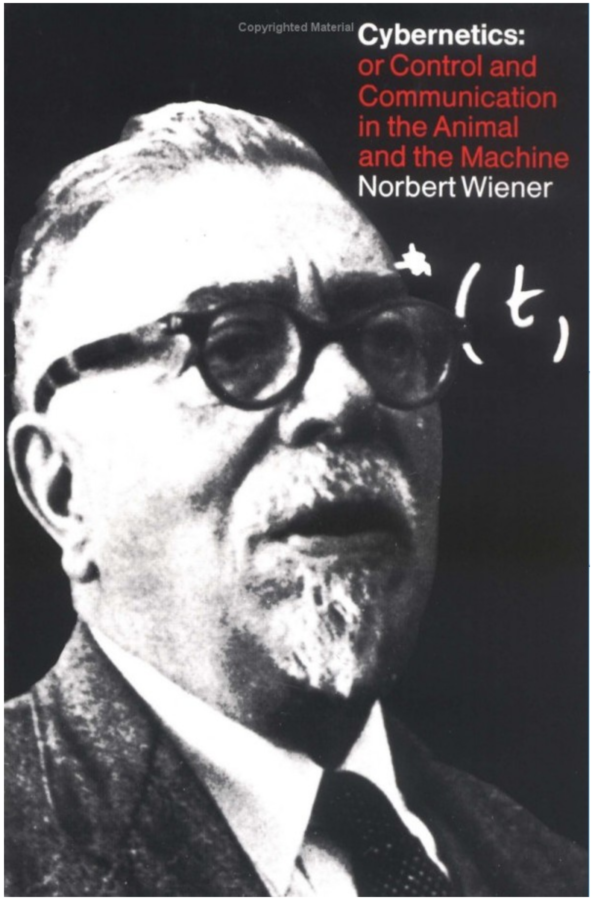
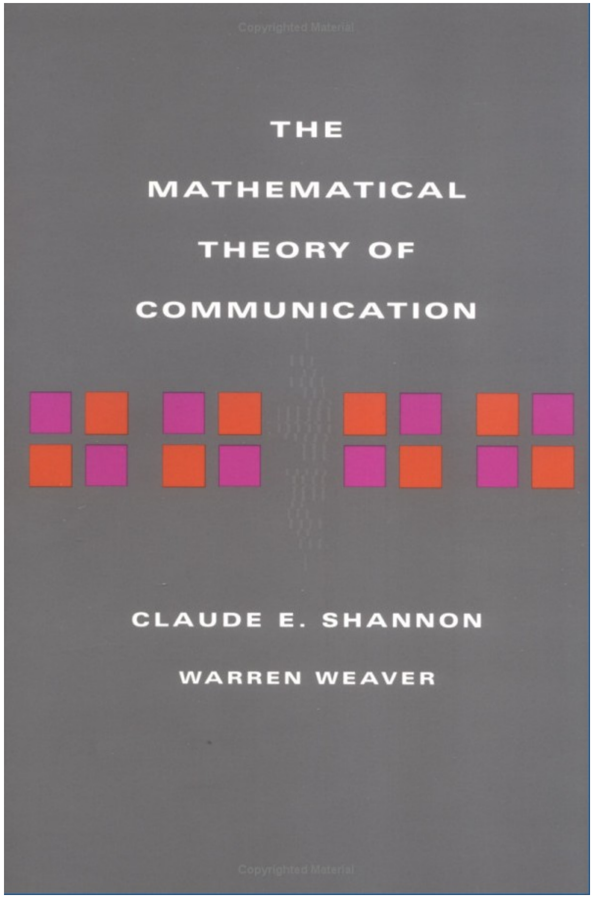
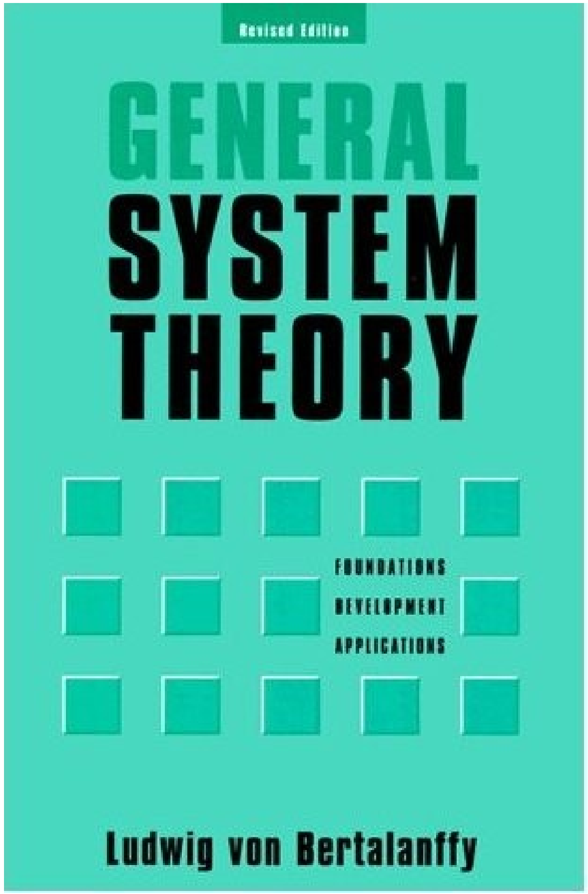
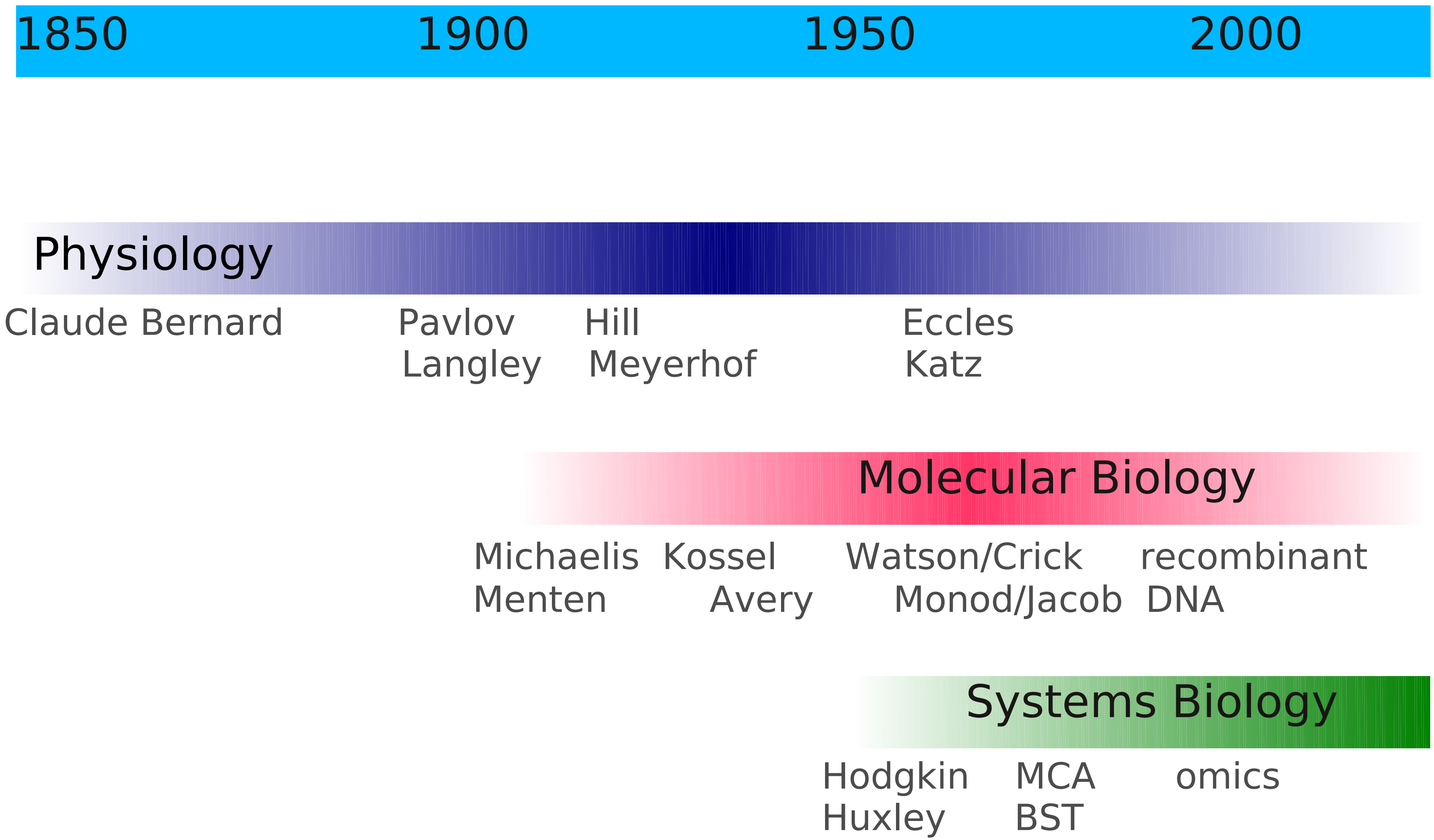






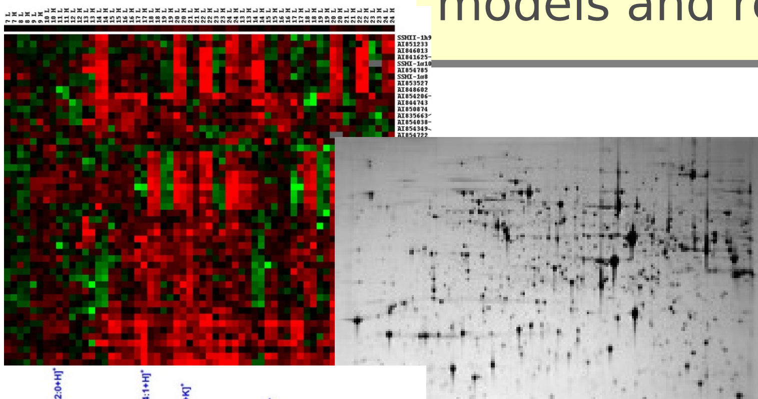
"[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems"
Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

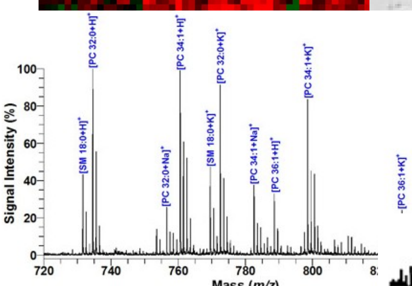
The three paradigms of Biology



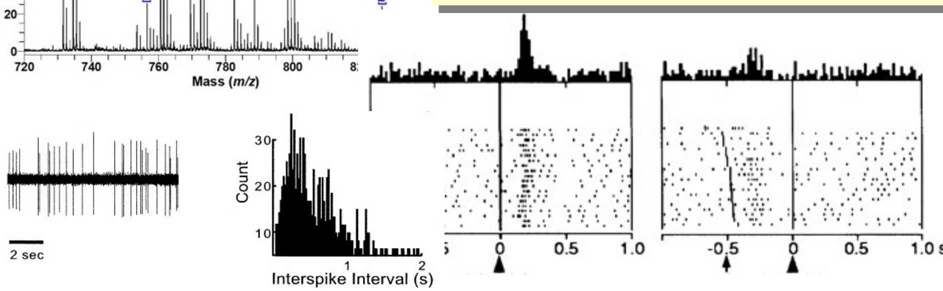
New way of doing biomedical research

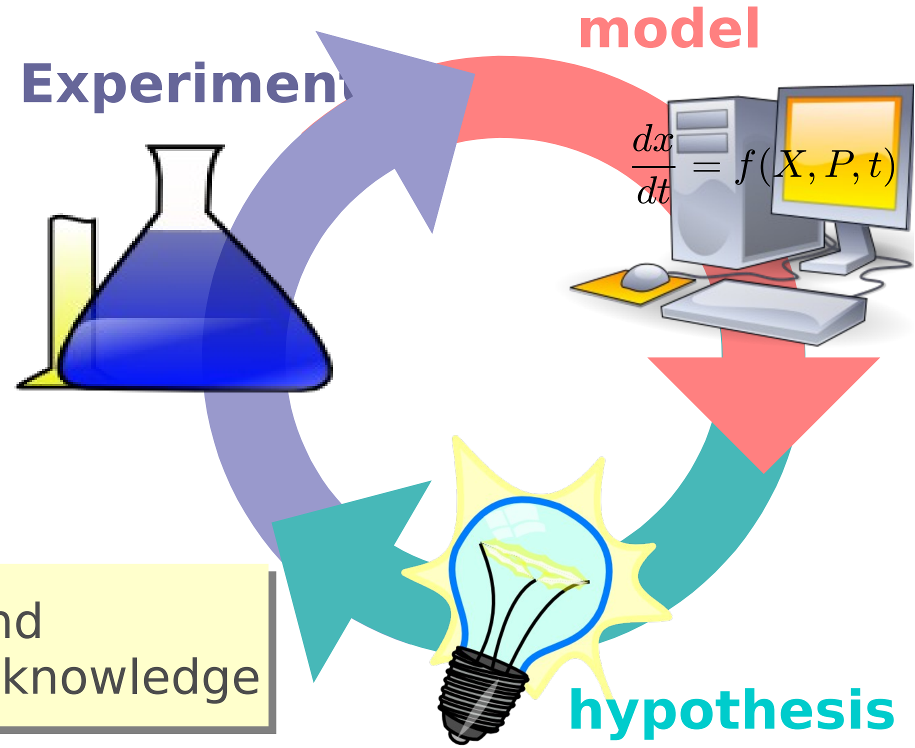
Needs for interplay between models and reality tests

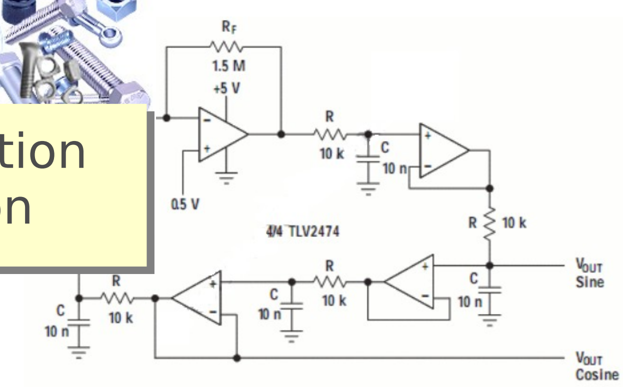




Needs for systems thinking and integration of heterogeneous knowledge







Needs for cooperation and standardisation

Computer simulations Vs. mathematical models

[37]

THE CHEMICAL BASIS OF MORPHOGENESIS

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

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

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

Computer simulations Vs. mathematical models

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

Birth of Computational Systems Biology

J. Physiol. (1952) 117, 500–544

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

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

From the Physiological Laboratory, University of Cambridge

(*Received* 10 *March* 1952)

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

The Computational Systems Biology loop

mathematical model

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

$$\mathrm{d}n/\mathrm{d}t = \alpha_n(1-n) - \beta_n n,$$

$$\mathrm{d}m/\mathrm{d}t = \alpha_m(1-m) - \beta_m m,$$

$$\mathrm{d}h/\mathrm{d}t = \alpha_h(1-h) - \beta_h h,$$

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

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

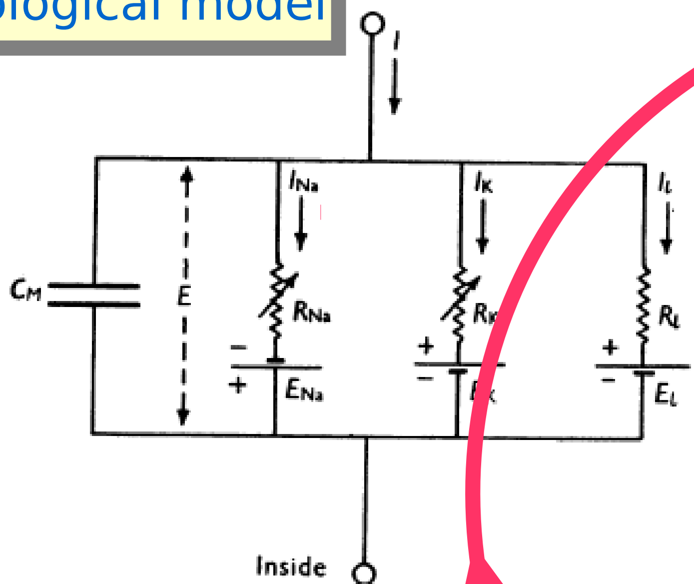
$$\alpha_m = 0{\cdot}1\,(V+25) \Big/ \left(\exp\frac{V+25}{10} - 1\right),$$

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

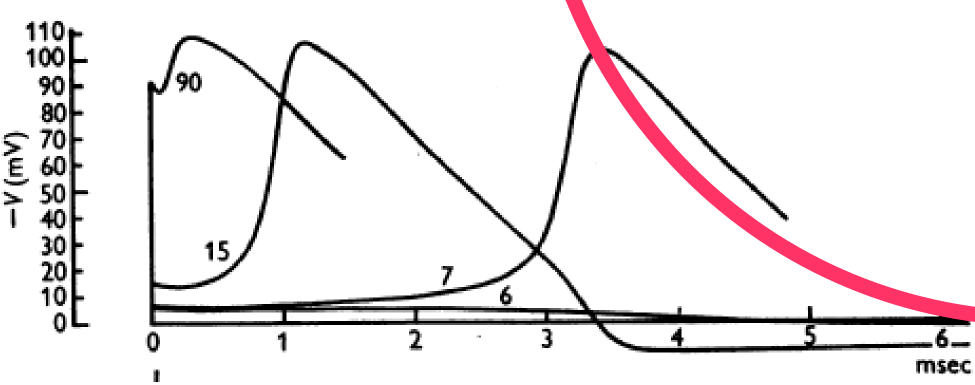
$$\alpha_h = 0{\cdot}07 \exp(V/20),$$

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

biological model



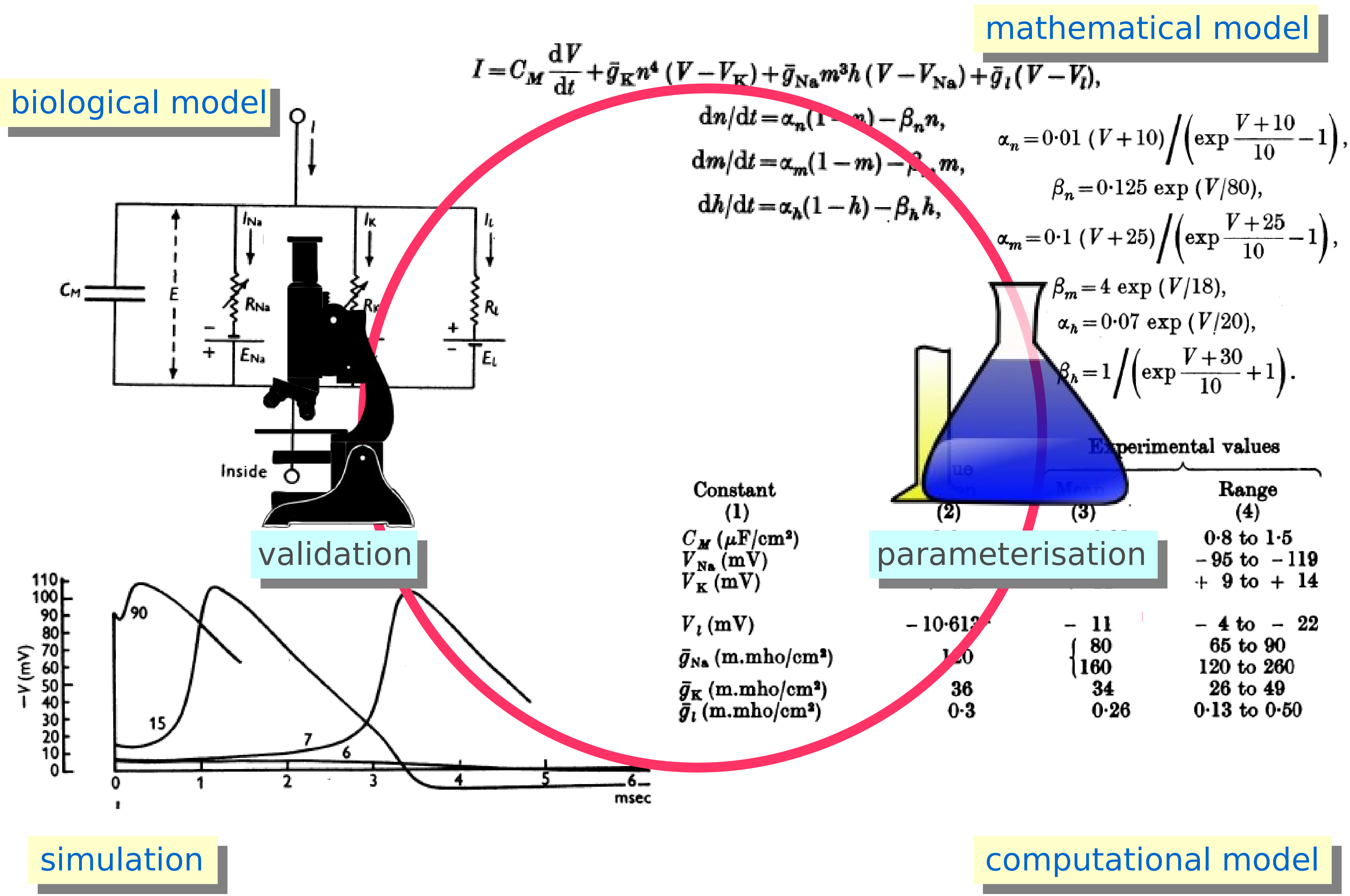
Constant (1)	Value chosen (2)	Experimental values: Mean (3)	Experimental values: Range (4)
C_M (μF/cm²)	1·0	0·91	0·8 to 1·5
V_{Na} (mV)	−115	−109	−95 to −119
V_K (mV)	+ 12	+ 11	+ 9 to + 14
V_l (mV)	−10·613	− 11	− 4 to − 22
$\bar{g}_{Na}$ (m.mho/cm²)	120	80 160	65 to 90 120 to 260
$\bar{g}_K$ (m.mho/cm²)	36	34	26 to 49
$\bar{g}_l$ (m.mho/cm²)	0·3	0·26	0·13 to 0·50



simulation

computational model

The Computational Systems Biology loop



Towards Systems Biology

Events around

		PDB	EMBLbank		Genomes
First computers			PC		Interactomes
1950	1960	1970	1980	1990	2000

Towards Systems Biology

Events around

PDB EMBLbank Genomes

First computers PC Interactomes

1950 1960 1970 1980 1990 2000

Hodgkin-Huxley Goldbeter Cell Cycle models

Dennis Noble Koshland signalling models

heart pacemaker covalent metabolic models

cascades models of gene reg

whole heart

models

Towards Systems Biology

	1950	1960	1970	1980	1990	2000
Events around		First computers	PDB	EMBLbank, PC		Genomes, Interactomes
models	Hodgkin-Huxley	Dennis Noble heart pacemaker		Goldbeter Koshland covalent cascades	Cell Cycle models, signalling models, metabolic models, models of gene reg	whole heart
neurobiology		Rall's cable approximation	complex neurons	simple circuits	Purkinje Neuron	Blue Brain Project

Towards Systems Biology

Events around

PDB EMBLbank Genomes

First computers PC Interactomes

1950 1960 1970 1980 1990 2000

Hodgkin-Huxley

Dennis Noble
heart pacemaker

Goldbeter
Koshland
covalent
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Cell Cycle models
signalling models
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whole heart

models

Rall's cable
approximation

complex
neurons

simple
circuits

Purkinje
Neuron

Blue Brain
Project

neurobiology

MCA/BST

stochastic
algorithms

multi-agent
systems

user-friendly
biochemical
simulators

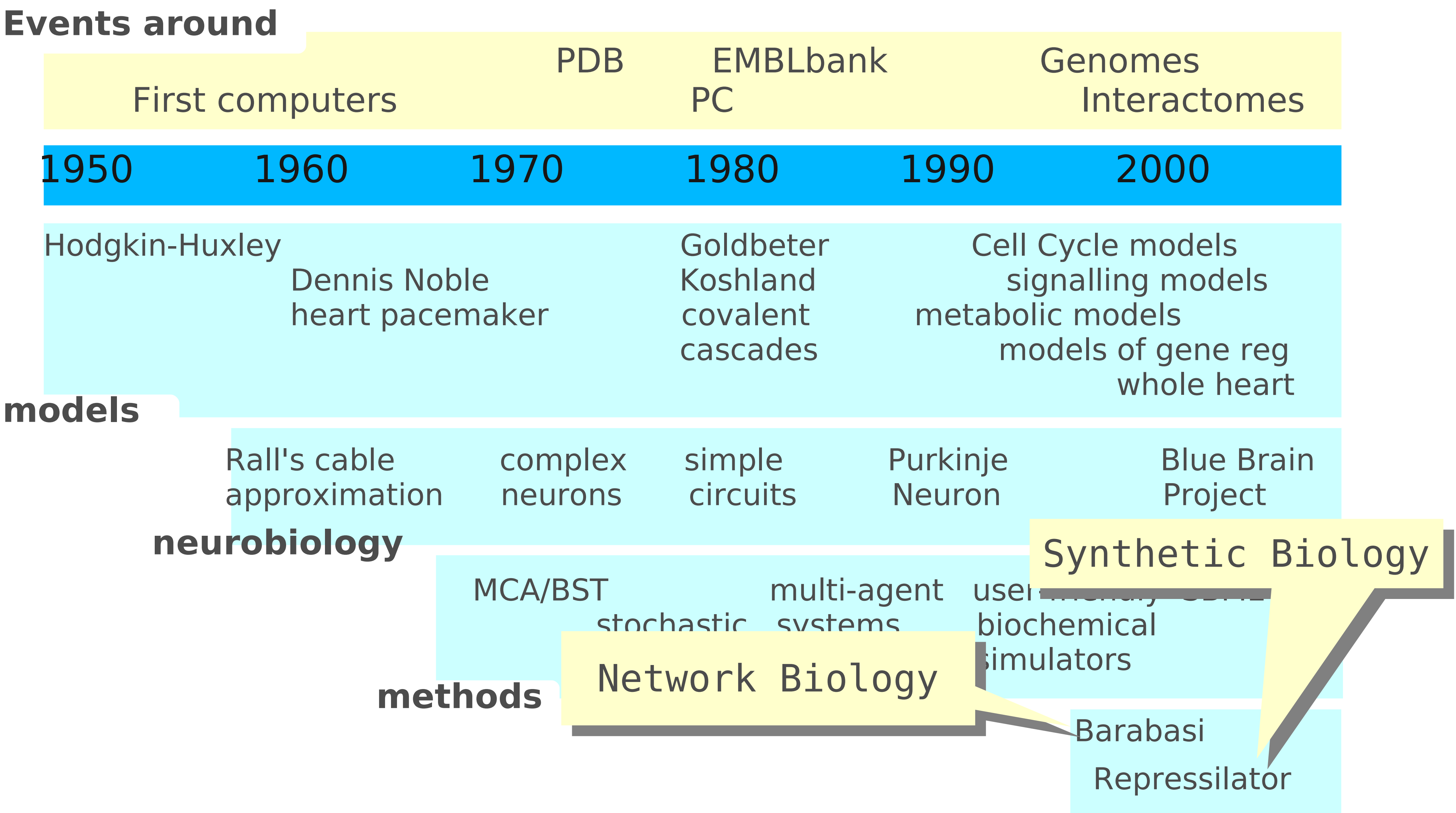
SBML

methods

Barabasi

Repressilator

Towards Systems Biology



90s: maturation of the community

- Publication of modelling work in high visibility journals, e.g.:
    - Tyson. modeling the cell-division cycle - cdc2 and cyclin interactions. *PNAS* 1991; McAdams and Shapiro. Circuit simulation of genetic networks. *Science* 1995; Barkai and Leibler. Robustness in simple biochemical networks. *Nature* 1997; Neuman et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. *Science* 1998; Yue et al. Genomic cis-regulatory logic: Experimental and computational analysis of a sea urchin gene . *Science* 1998; Bray et al. Receptor clustering as a cellular mechanism to control sensitivity. *Nature* 1998
- Structuration of the community modelling metabolism
- Large-scale simulation projects
    - E-Cell project 1996; The Virtual Cell 1998
- Availability of high-throughput data on parts and interactions
    - Two-hybrids (1989); microarrays (1995) etc.
- Large-scale funding for wet+dry studies of biological systems
    - Alliance For Cellular Signalling (http://www.afcs.org/). First of the NIH “glue grants”. 1998

Formal revival of Systems Biology

- “Modelling” Systems Biology
  - 1998 - Hiroaki Kitano founds the Systems Biology Institute in Tokyo
  - First appearance: Kyoda, Kitano. Virtual Drosophila project: Simulation of drosophila leg formation. *Genome Informatics Series* (1998)
  - Kitano, H. Perspectives on systems biology. *New Generation Computing* Volume 18, Issue 3, 2000, Pages 199-216
- “Network” Systems Biology
  - First appearance: Leroy Hood. Systems biology: new opportunities arising from genomics, proteomics and beyond. *Experimental Hematology*. Volume 26, Issue 8, 1998, Page 681
  - Schwikowski B, Uetz P, Fields S. A network of protein-protein interactions in yeast. *Nat Biotechnol*. 2000 Dec;18(12):1257-61.
  - 2000 - Leroy Hood founds the Systems Biology Institute in Seattle

Rise of Systems Biology as a paradigm

1998	1999	2000	2001	2002	2003	2004	2005	2006	2007

Rise of Systems Biology as a paradigm

1998	1999	2000	2001	2002	2003	2004	2005	2006	2007

ERATO-Kitano

SystemsX

Alliance for Cellular Signaling

HepatoSys

projects

SysBio enters FP6

YSBN

ERASysBio

Rise of Systems Biology as a paradigm

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

ERATO-Kitano
SystemsX
Alliance for Cellular Signaling
HepatoSys
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YSBN
ERASysBio

ECell
Von Dassow
SBML
Klipp
Alon
Choi
Annual Review
Science
Kriete
Palsson
Ideker/Hood
special issue
Boogerd
publications
“Foundations of Systems Biology”
Kaneko
Szallasi
Grierson
Computational Cell Biology”
IEE Sys Bio
MSB
BMC Sys Bio

Rise of Systems Biology as a paradigm

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

Rise of Systems Biology as a paradigm

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

projects

ERATO-Kitano
Alliance for Cellular Signaling
SystemsX
HepatoSy
Sy
YSBN

End of BBSRC Systems Biology calls

publications

ECell
Von Dassow
Annual Review
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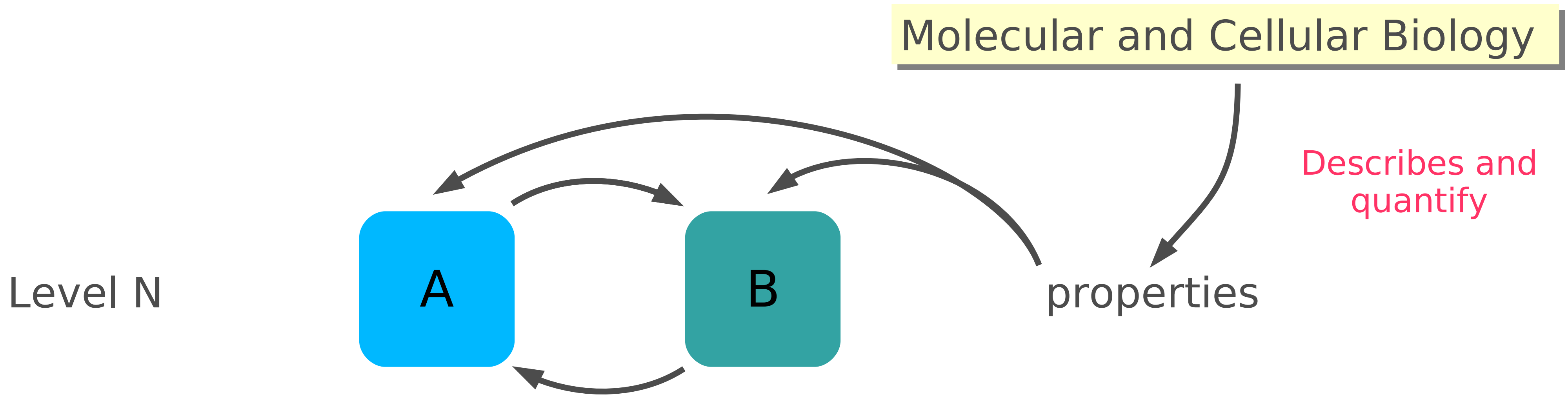
What is Systems Biology?



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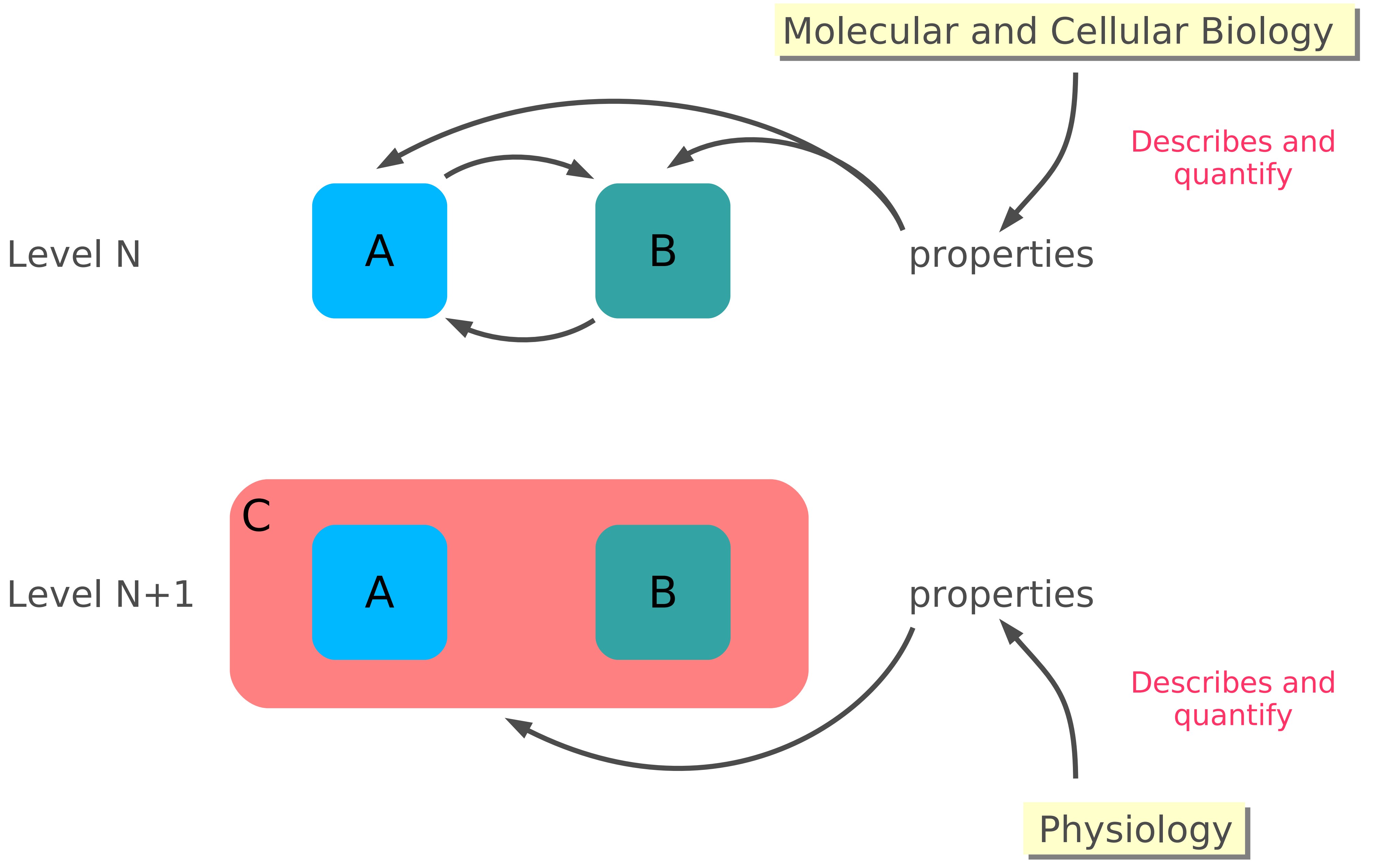

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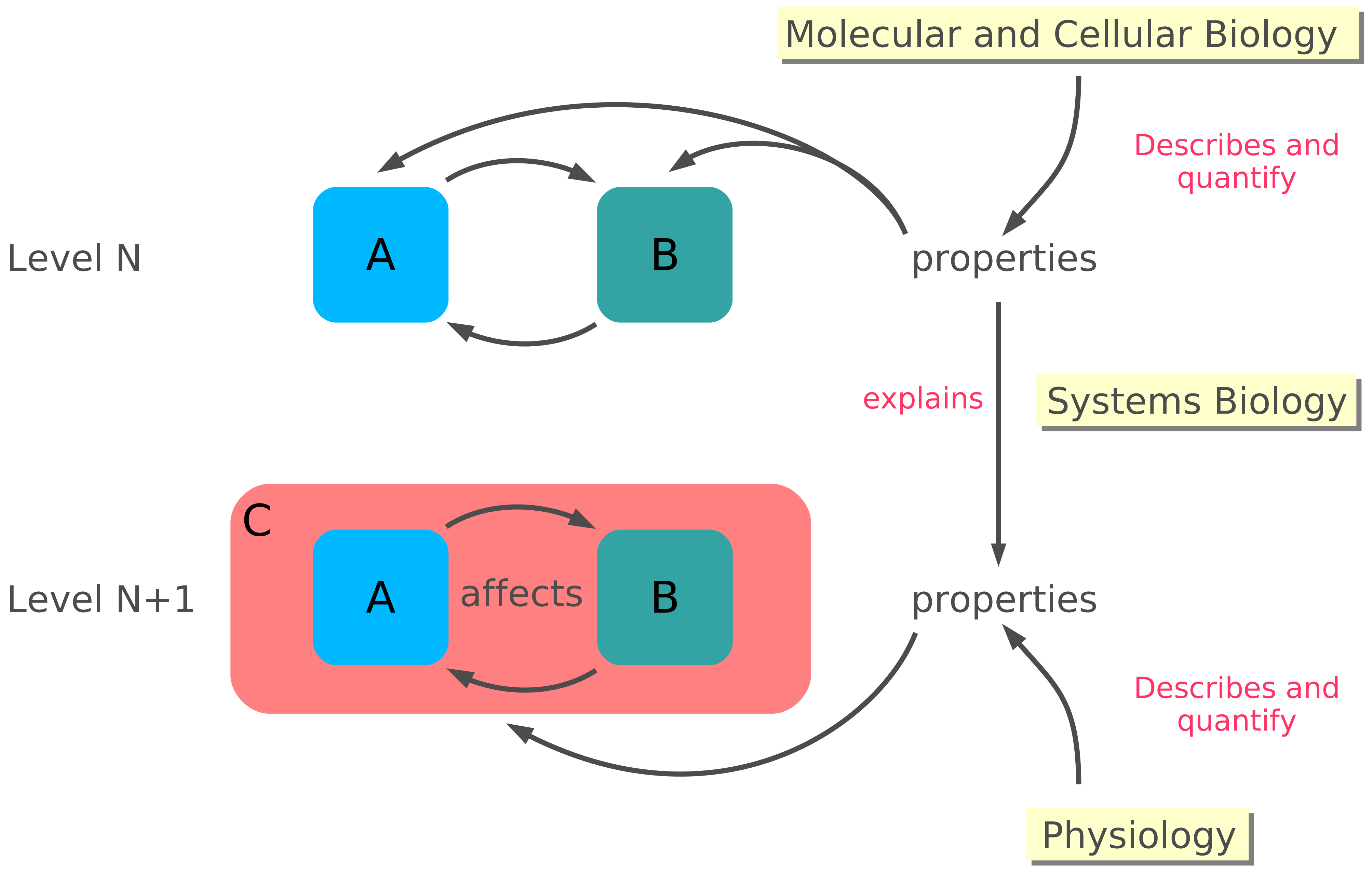

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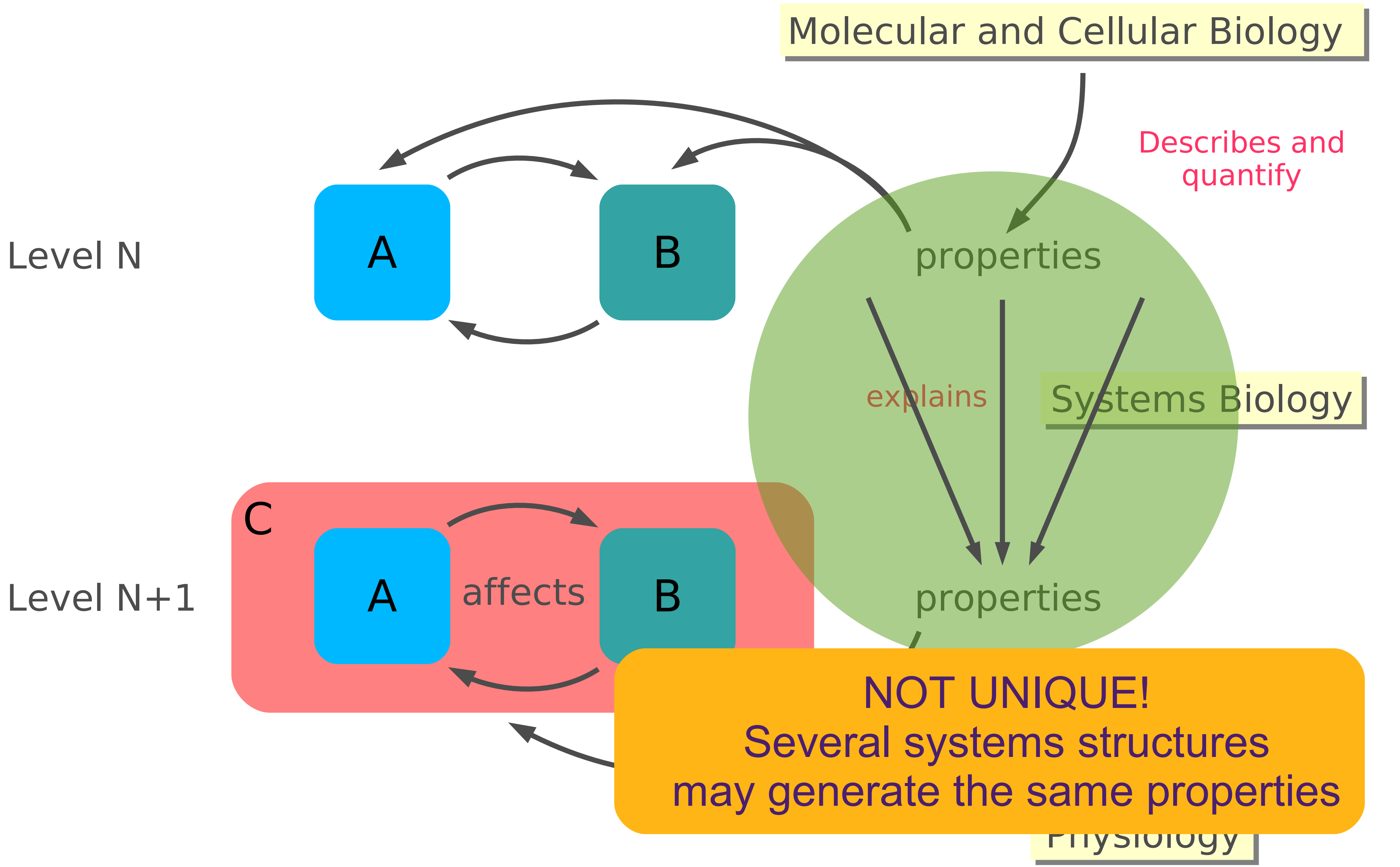

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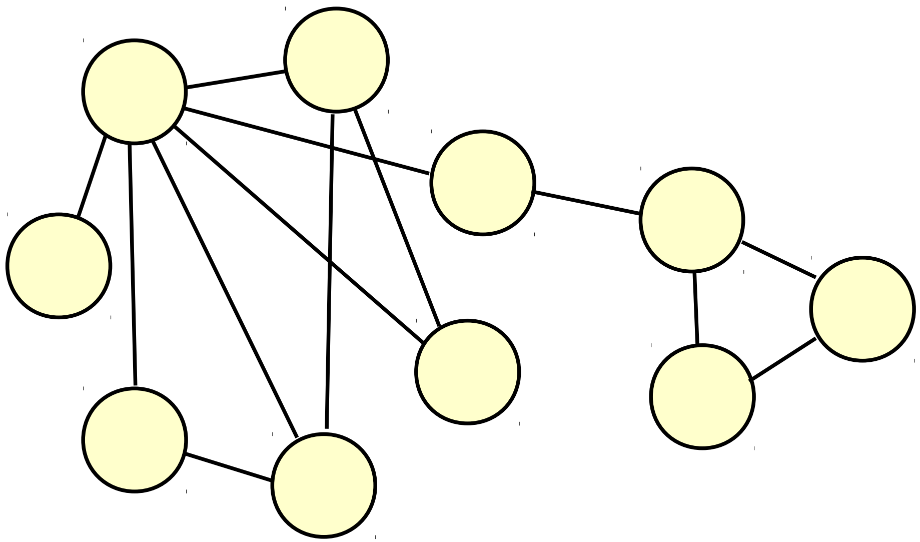
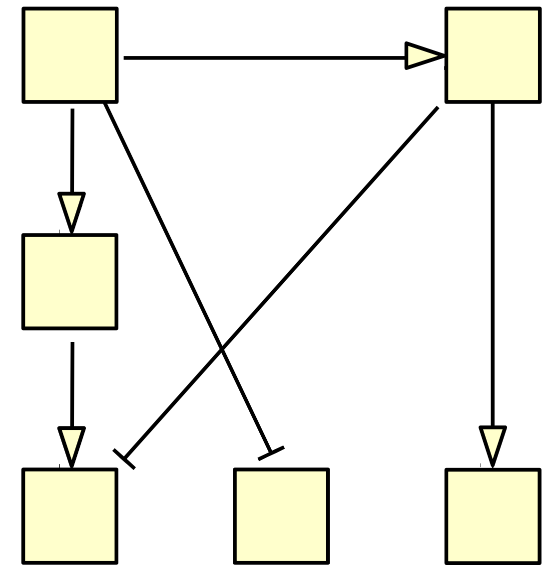
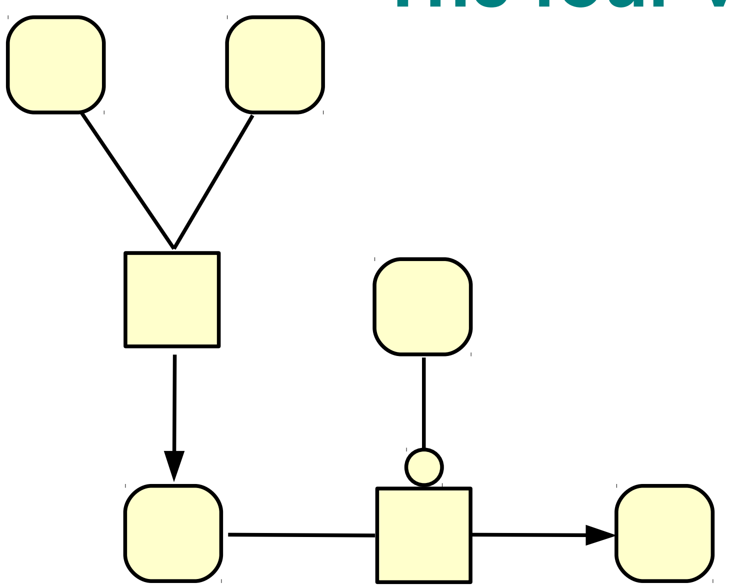
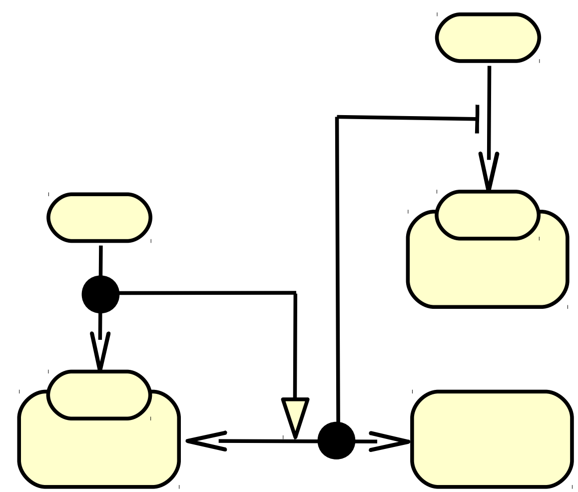


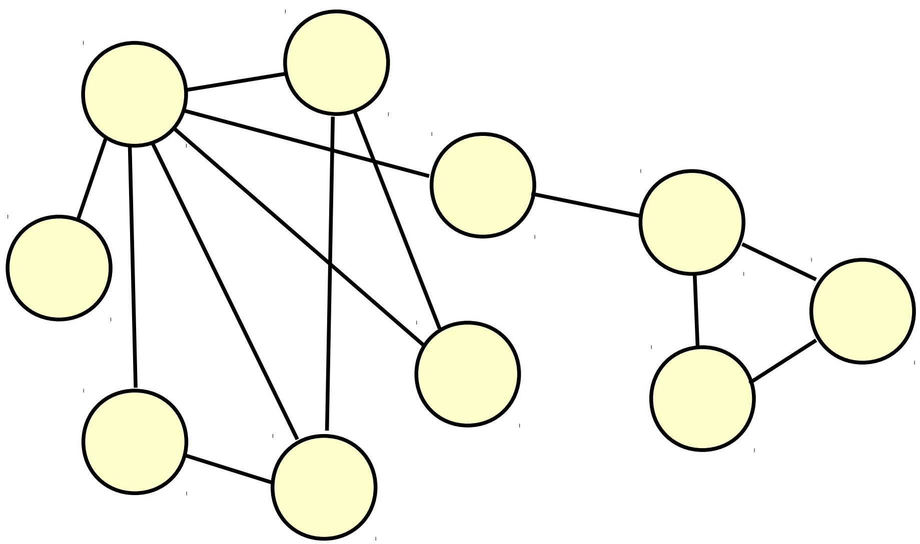


The four views of systems biology



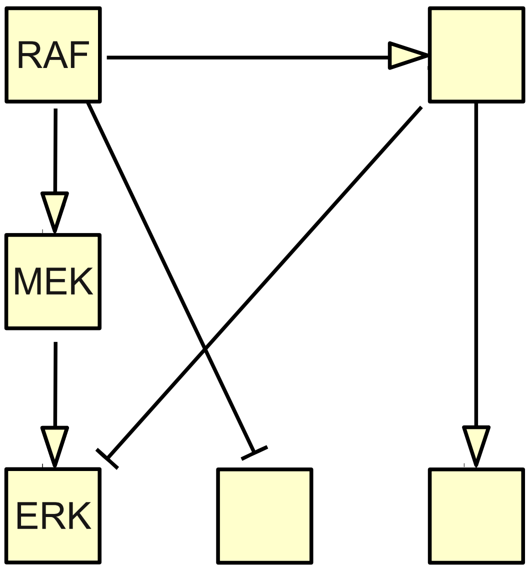


Interaction networks



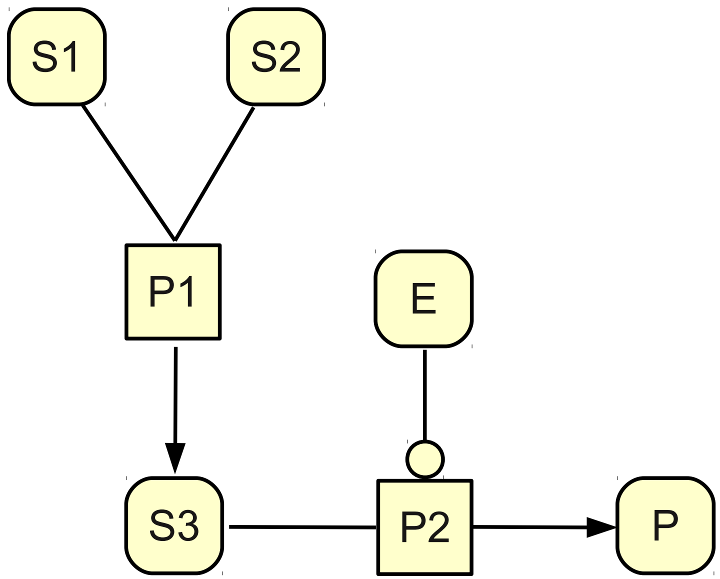
- Non-directional
- Non-sequential
- Non-mechanistic
- Statistical modelling
- Functional genomics
- IntAct, DIP, String

Activity-Flows



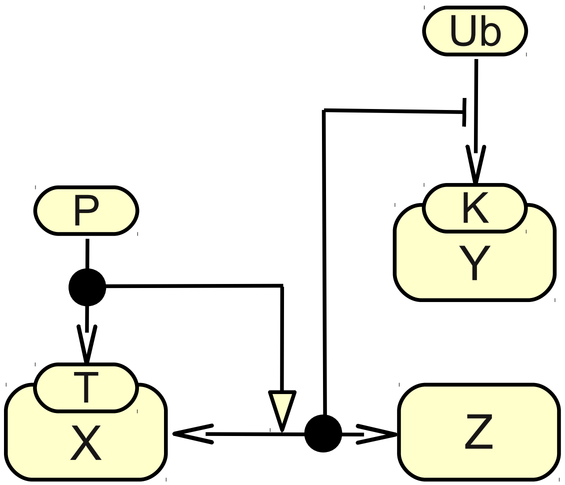
- Directional
- Sequential
- Non-mechanistic
- Logical modelling
- Signalling pathways, gene regulatory networks
- KEGG, STKEs

Process Descriptions

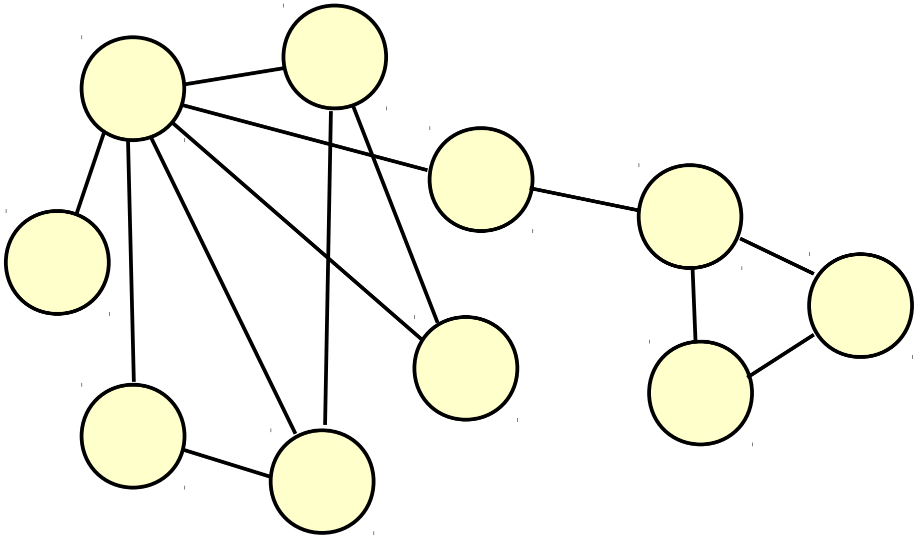


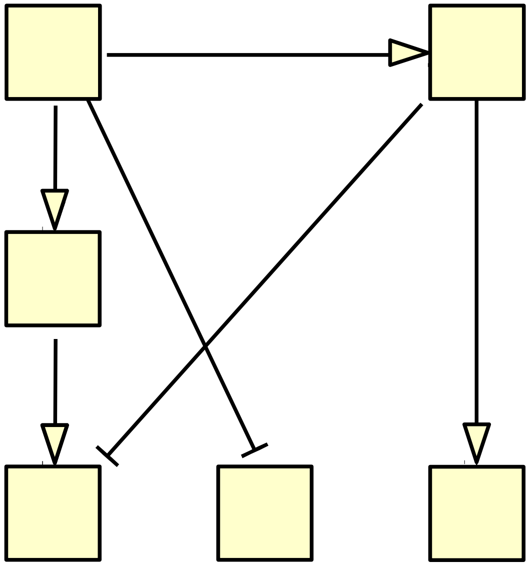
- Directional
- Sequential
- Mechanistic
- Subjected to combinatorial explosion
- Process modelling
- Biochemistry, Metabolic networks
- KEGG, Reactome

Entity Relationships

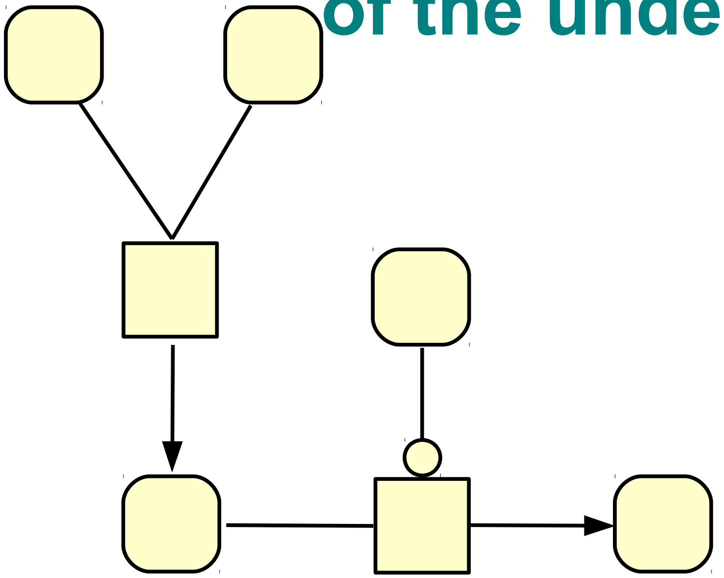


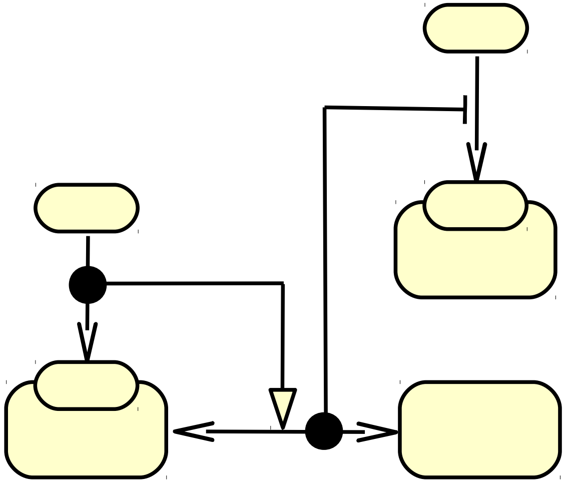
- Directional
- Non-sequential
- Mechanistic
- Independent rules: no explosion
- Rule-based modelling
- Molecular Biology
- MIM





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





What to do?

- Build the system
- Put numbers
- Parametrise
- Analyse
- perturb

What to do?

	bottom-up
▪ Build the system	literature
▪ Put numbers	biochemistry
▪ Parametrise	parameter search
▪ Analyse	Simulation
▪ perturb	Inhibition, stimulation, suppression, overexpression

What to do?

	bottom-up	top-down
Build the system	literature	“pathway” database
Put numbers	biochemistry	lipid/metabol/prote/ transcript“omics”
Parametrise	parameter search	hmm....
Analyse	Simulation	structural analysis, steady-state analysis
perturb	Inhibition, stimulation, suppression, overexpression	

What to do?

	bottom-up	top-down
Build the system	literature	“pathway” database
Put numbers	biochemistry	lipid/metabol/prote/ transcript“omics”
Parametrise	parameter search	hmm....
Analyse	Simulation	structural analysis, steady state analysis
perturb	Inhibition, stimulation, suppression, overexpression	

biochemistry

Bioinformatics

high-throughput

Modelling

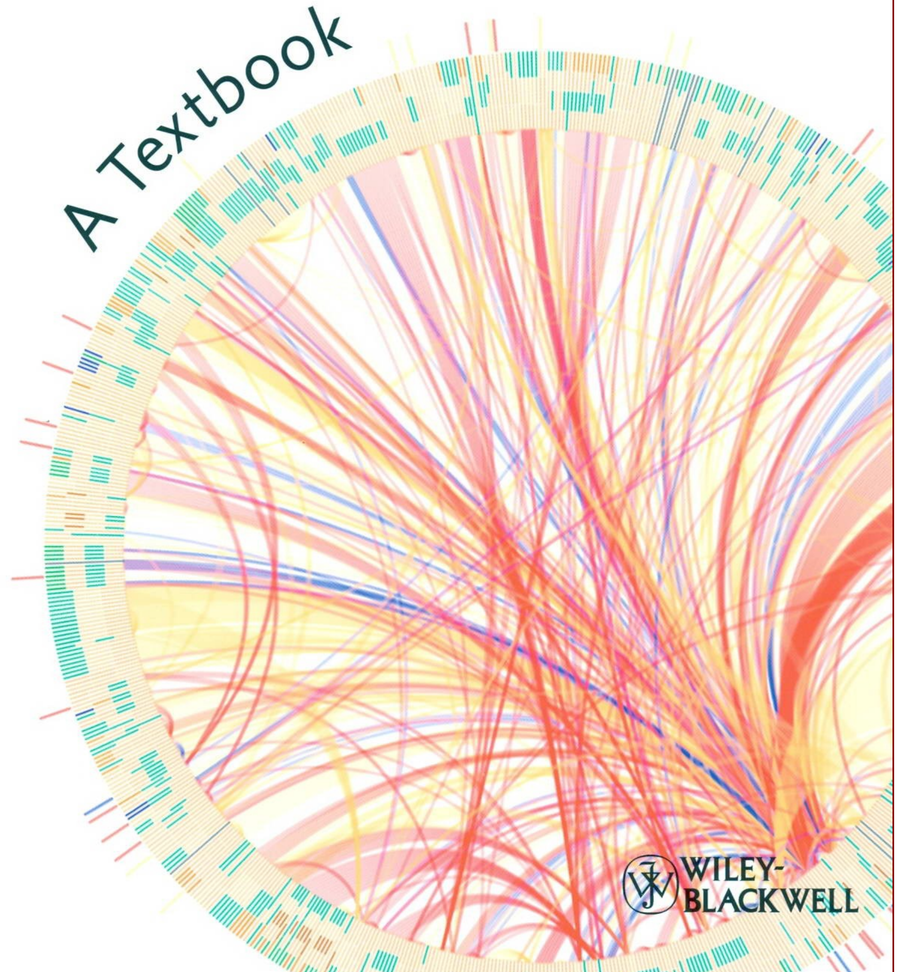
Molecular biology

pharmacology

Systems Biology

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

A Textbook



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