



Systems Biology

Nicolas Le Novère, EMBL-EBI



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

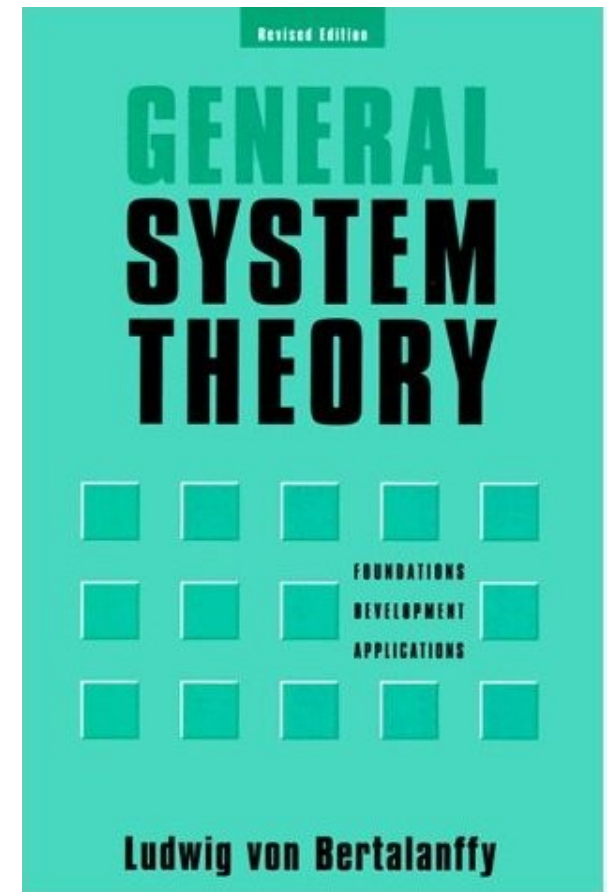
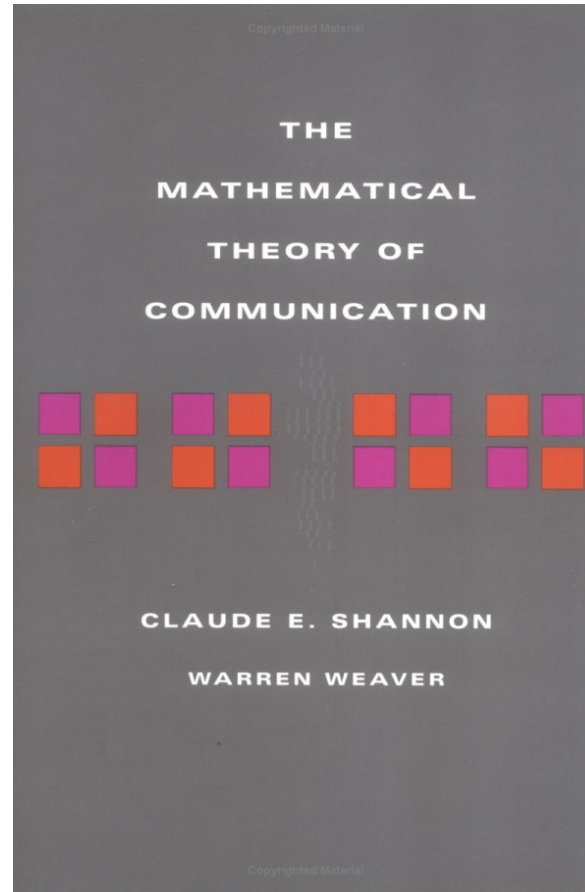
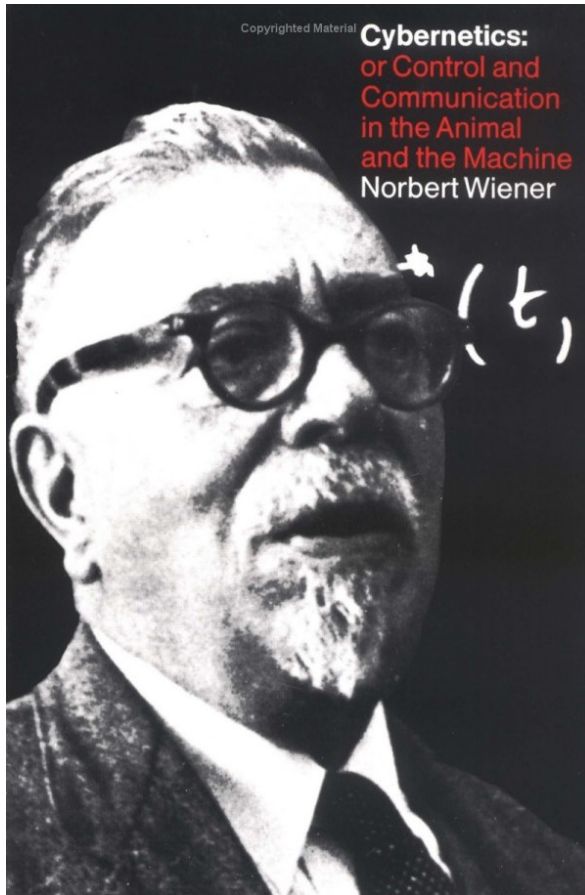
Statistical physics, thermodynamics, quantum mechanic, biochemistry, structural biology, molecular biology

Description of interacting components

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

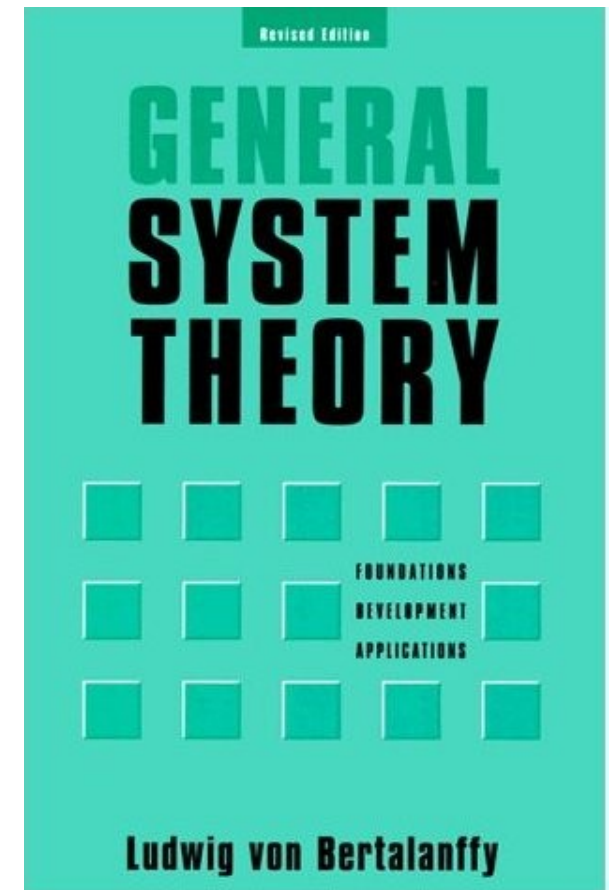
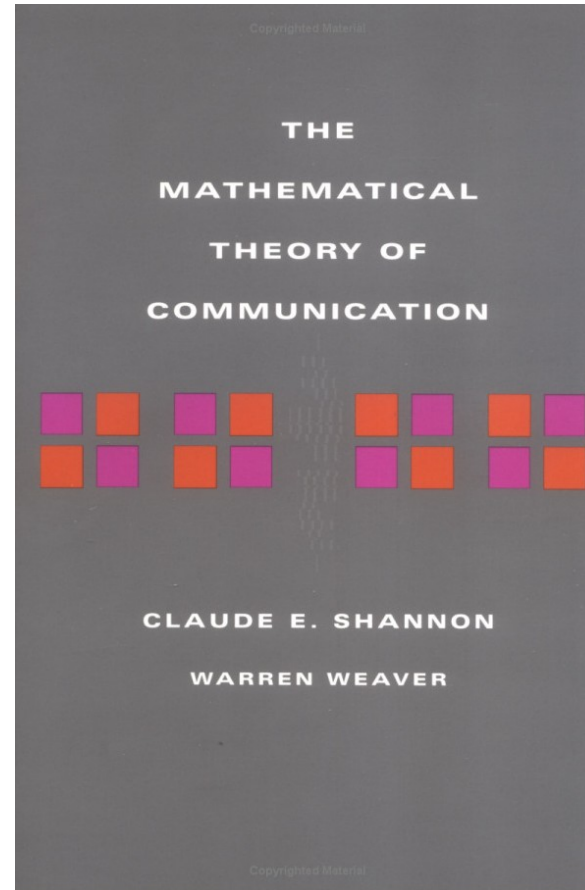
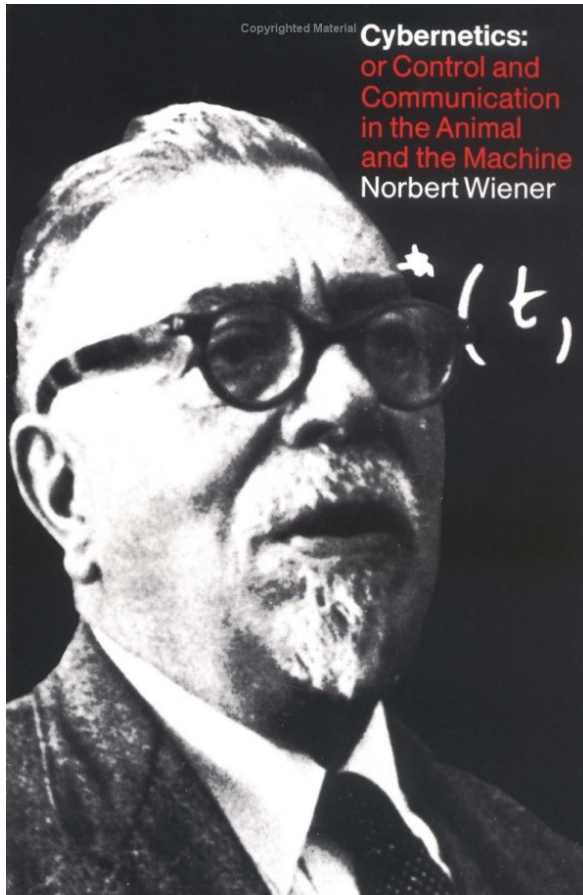


Systems have been formalised for a while





Systems have been formalised for a while



"[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 Bertalanffy, Kritische Theorie der Formbildung, 1928



The three paradigms of Biology

1850

1900

1950

2000

Physiology

Claude Bernard

Pavlov
Langley

Hill
Meyerhof

Eccles
Katz

Molecular Biology

Michaelis
Menten

Kossel
Avery

Watson/Crick
Monod/Jacob

recombinant
DNA

Systems Biology

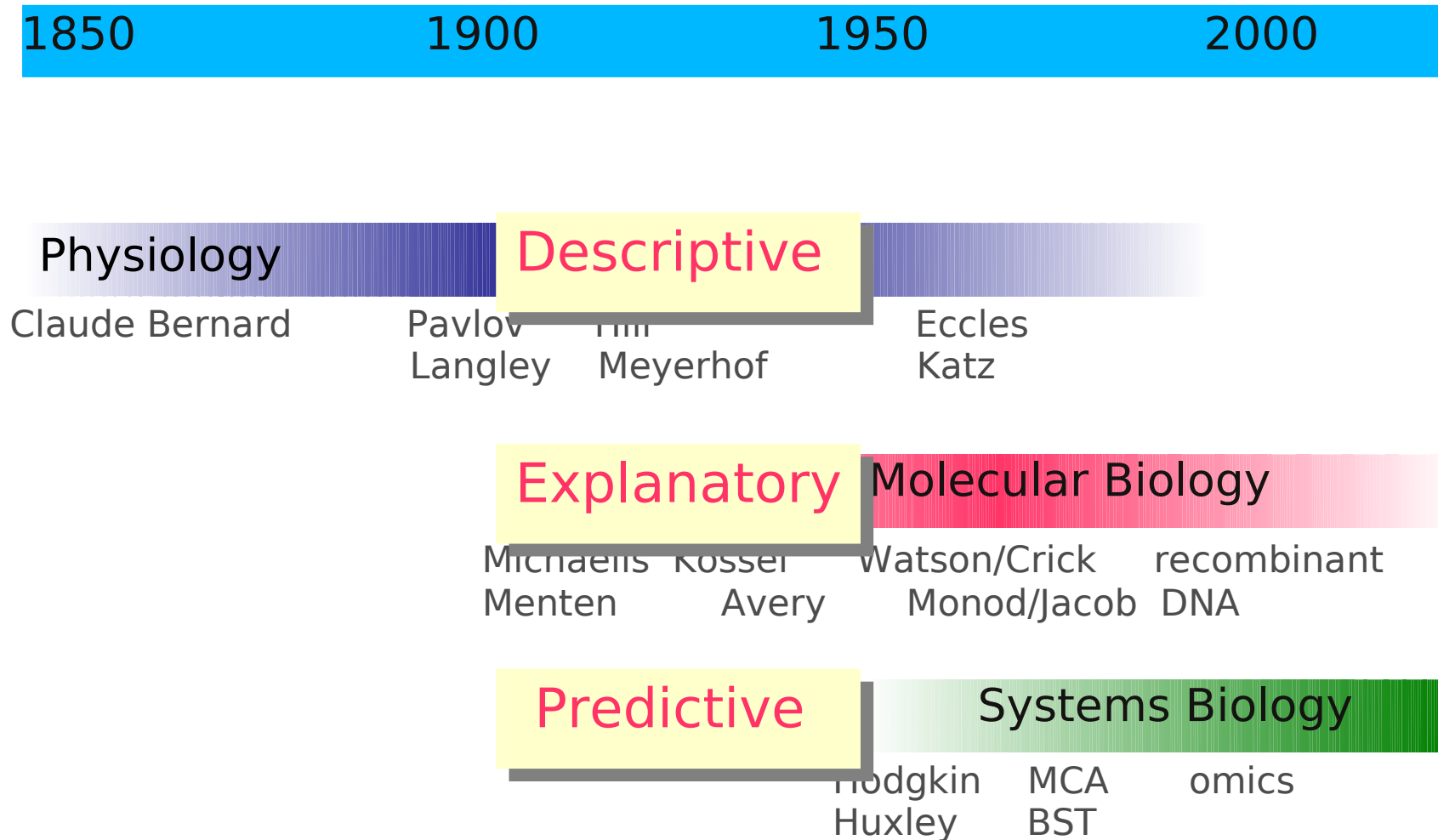
Hodgkin
Huxley

MCA
BST

omics



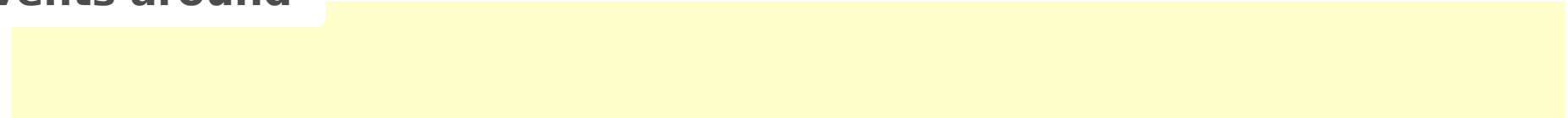
The three paradigms of Biology





Towards Systems Biology

Events around



Hodgkin-Huxley

models



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

[37]

THE CHEMICAL BASIS OF MORPHOGENESIS

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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, 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

biological model

mathematical model

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

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h,$$

$$\alpha_n = 0.01 (V + 10) / \left(\exp \frac{V + 10}{10} - 1 \right),$$

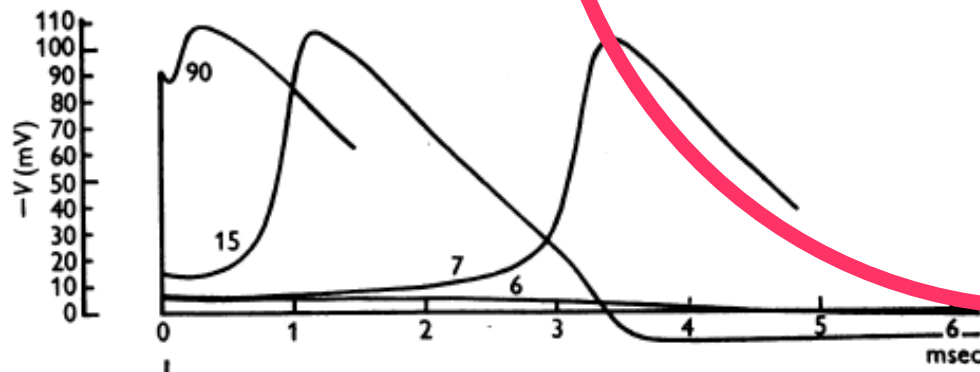
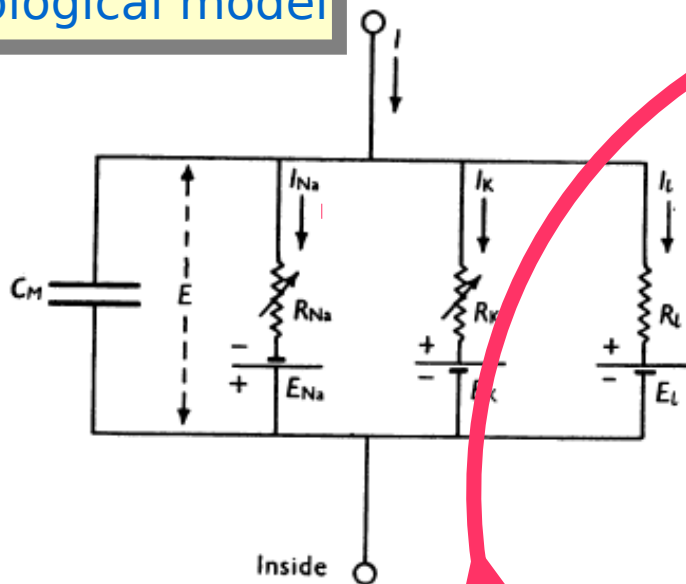
$$\beta_n = 0.125 \exp (V/80),$$

$$\alpha_m = 0.1 (V + 25) / \left(\exp \frac{V + 25}{10} - 1 \right),$$

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

$$\alpha_h = 0.07 \exp (V/20),$$

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



simulation

computational model

Constant
(1)

C_M ($\mu\text{F}/\text{cm}^2$)

V_{Na} (mV)

V_K (mV)

V_l (mV)

$\bar{g}_{Na}$ (m.mho/ cm^2)

$\bar{g}_K$ (m.mho/ cm^2)

$\bar{g}_l$ (m.mho/ cm^2)

Value
chosen
(2)

1.0

-115

+12

-10.612

120

36

0.3

Experimental values

Mean
(3)

0.91

-109

+11

-11

{ 80

{ 160

0.26

Range
(4)

0.8 to 1.5

-95 to -119

+9 to +14

-4 to -22

65 to 90

120 to 260

26 to 49

0.13 to 0.50



The Computational Systems Biology loop

biological model

mathematical model

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

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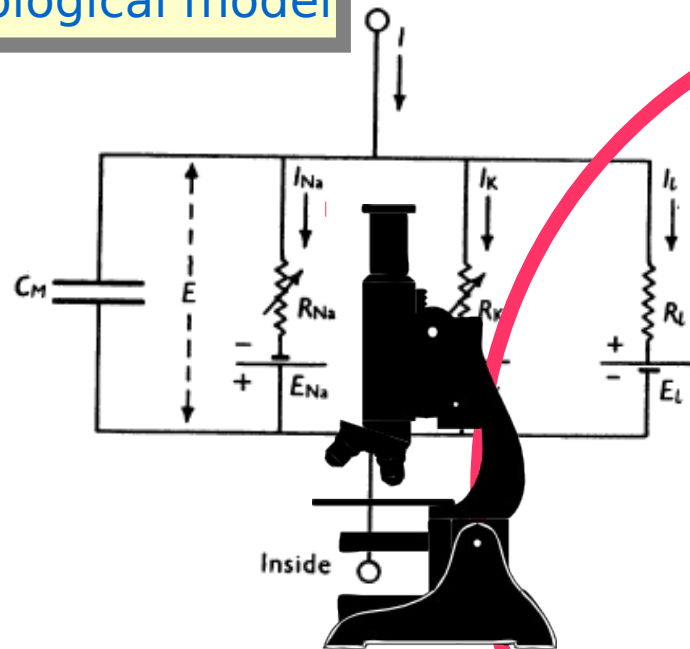
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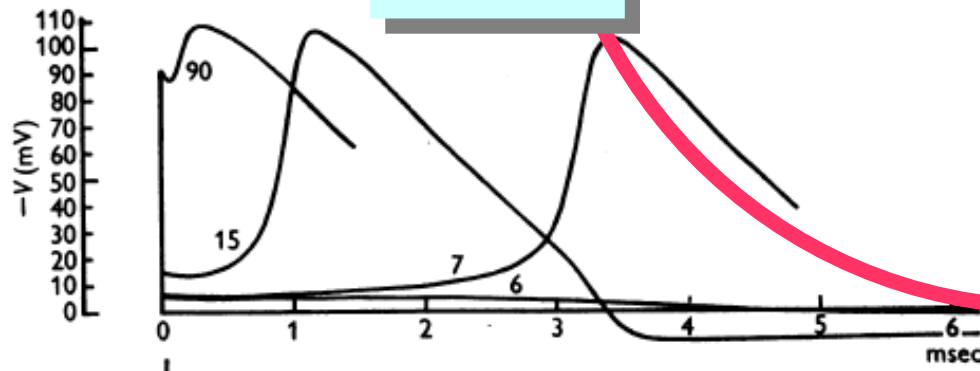
$$\beta_m = 4 \exp (V/18),$$

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validation



simulation

parameterisation

Constant
(1)

C_M ($\mu\text{F}/\text{cm}^2$)

V_{Na} (mV)

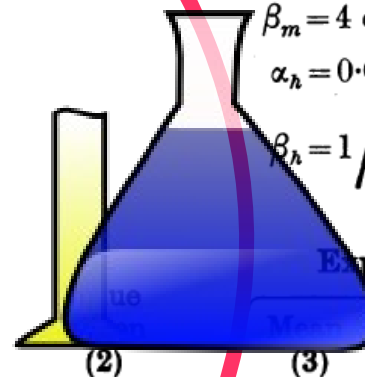
V_K (mV)

V_l (mV)

$\bar{g}_{Na}$ (m.mho/cm²)

$\bar{g}_K$ (m.mho/cm²)

$\bar{g}_l$ (m.mho/cm²)



Experimental values

Range
(4)

0.8 to 1.5

-95 to -119

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0.13 to 0.50

computational model



Towards Systems Biology

Events around

First computers		PDB	EMBLbank PC	Genomes Interactomes	
1950	1960	1970	1980	1990	2000
Hodgkin-Huxley		Goldbeter Koshland covalent cascades		Cell Cycle models signalling models metabolic models models of gene reg whole heart	
Rall's cable approximation		complex neurons	simple circuits	Purkinje Neuron	Blue Brain Project
		MCA/BST stochastic algorithms	multi-agent systems	user-friendly biochemical simulators	SBML
					Barabasi Repressilator

models

neurobiology

methods



Towards Systems Biology

Events around

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

Hodgkin-Huxley	Dennis Noble heart pacemaker		Goldbeter Koshland covalent cascades	Cell Cycle models signalling models metabolic models models of gene reg whole heart	
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models

Rall's cable approximation	complex neurons	simple circuits	Purkinje Neuron	Blue Brain Project
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neurobiology

MCA/BST	multi-agent stochastic svstems	user-fr biochemical ulators	Synthetic Biology
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methods

Network Biology

Barabasi
Repressilator



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; Perelson et al. HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. *Science* 1996; 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 creation 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: L 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



The “two” Systems Biology

What

- **Reconstructions of systems**
kinetic modelling, simulation, numerical analysis. Mainly metabolic networks and signalling pathways

Who

- Originates from Biochemistry, Physics and Engineering
Arkin, Bhalla, Bray, Fell, Ferrell, Hunter, Kell, Kholodenko, Kitano, Leibler, Noble, Palsson, Tyson, Westerhoff ...
International Society for Systems Biology

When

- International Conference on Systems Biology

Where

- Biochemical journals, BMC Systems Biology, IET Systems Biology, Molecular Systems Biology

- **Systems-wide analysis**

Genome-wide analysis, interactomes, regulatory networks, boolean models. Mainly gene regulatory networks

- Originates from Functional Genomics, Bioinformatics and Mathematics
Bork, Brunak, Kirschner, Hood, Ideker, Snyder, Vidal ...
International Society of Computational Biology

- Intelligent Systems in Molecular Biology, International Conference on Pathways, Networks, and Systems Medicine

- Bioinformatics, PloS Computational Biology



Rise of Systems Biology as a paradigm

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

ERATO-Kitano
Alliance for Cellular Signaling

SystemsX

projects

HepatoSys

SysBio enters FP6

YSBN

ERASysBio

ECell

Von Dassow

SBML

Klipp

Alon

Choi

Annual Review

Science

Kriete

Palsson

Boogerd

publications

Ideker/Hood

special issue

“Foundations of Systems Biology”

Kaneko

Szallasi

Grierson

Computational Cell Biology”

IEE Sys Bio

MSB

BMC Sys Bio

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

ERATO-Kitano
Alliance for Cellular Signaling

projects

SystemsX

HepatoS
Sy

YSBN

End of BBSRC
Systems Biology
calls

ECell

Von Dassow

SBML

Klipp

Alon

Choi

Annual Review

Science

Kriete

Palsson

Boogerd

publications

Ideker/Hood

special issue

"Foundations of Systems Biology"

Kaneko

Szallasi

Grierson

"Molecular Cell Biology"

IEE Sys Bio

MSB

BMC Sys Bio

Tokyo Systems Biology Institute

Seattle Institute for Systems Biology

6 BBSRC centres

Institutes

BioQuant



Merging communities

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



Merging communities

Nobel Symposium on Systems Biology (June 2009)

networks

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models

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Roger Brent
Francois Nedelec
Jim Ferrell
Uwe Sauer
Jorg Stelling
Edda Klipp
Boris Kholodenko
Bela Novak
Hiroaki Kitano
Stefan Hohmann
Harley McAdams
William Bialek
Mans Ehrenberg

synthetic biology cell reprogramming

Avid Regev
Jeff Hasty
Michael Elowitz
Yoshihide Hayashizaki
Richard Young

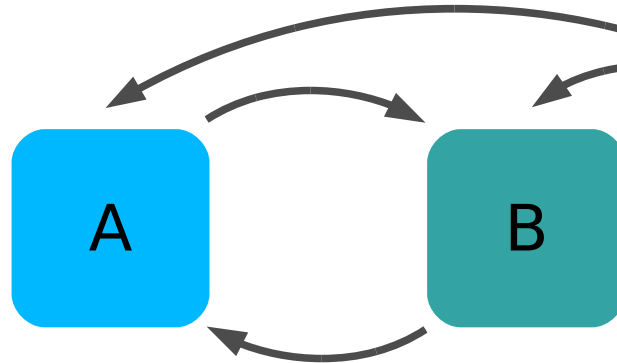


What is Systems Biology?

Molecular and Cellular Biology

Describes and quantify

Level N

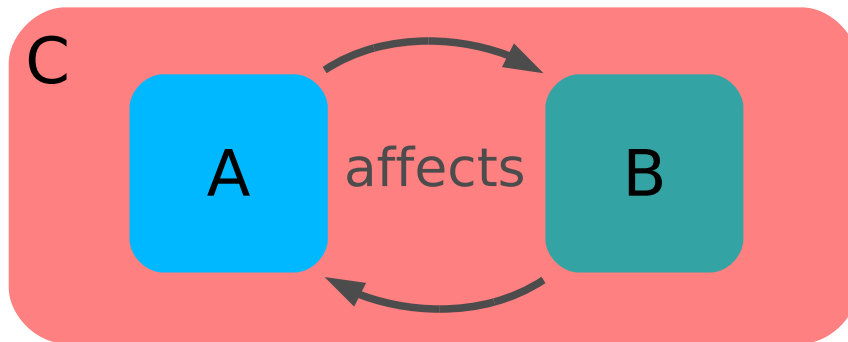


properties

explains

Systems Biology

Level N+1



properties

Describes and quantify

Physiology



Systems Biology is the study of a biological system, taking into account all its constituents, their relationships and their evolution



Au travail !



Programme of the course

- Day 1: Current achievements: Scientific presentations by some of the trainers
- Day 2 – 4: Training. Technical presentation and hands-on
 - Day 2: Reconstructing Networks – How to use large-scale OMICS data to generate relationships.
 - Day 3: Analysing Networks – What to do with those relationships graphs
 - Day 4: Modelling Networks – The next step, linking observation and mechanisms