What is Systems Biology? Where does it come from?

Nicolas Le Novère, The Babraham Institute

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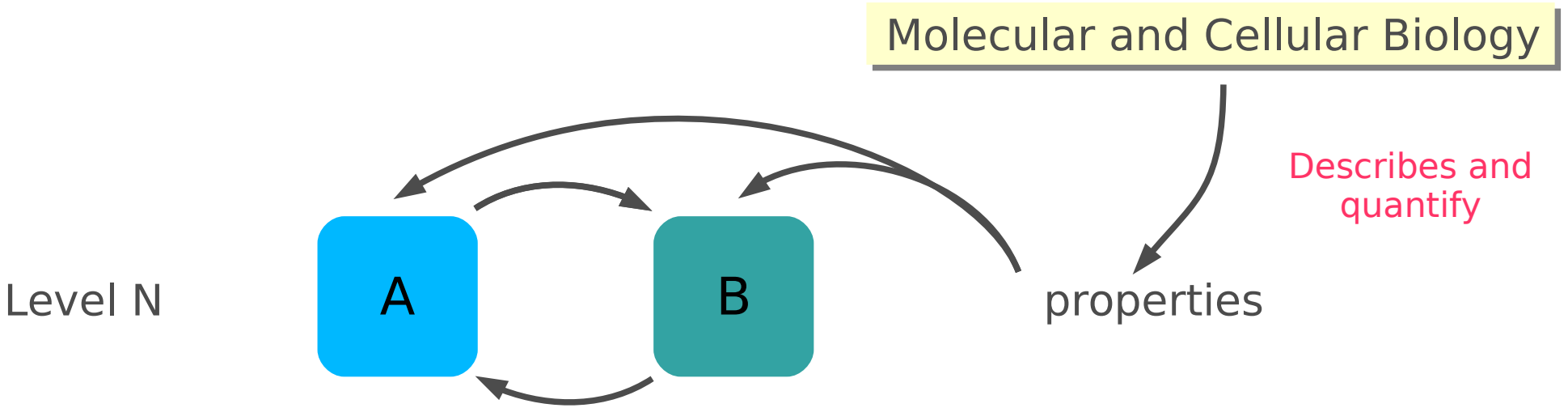
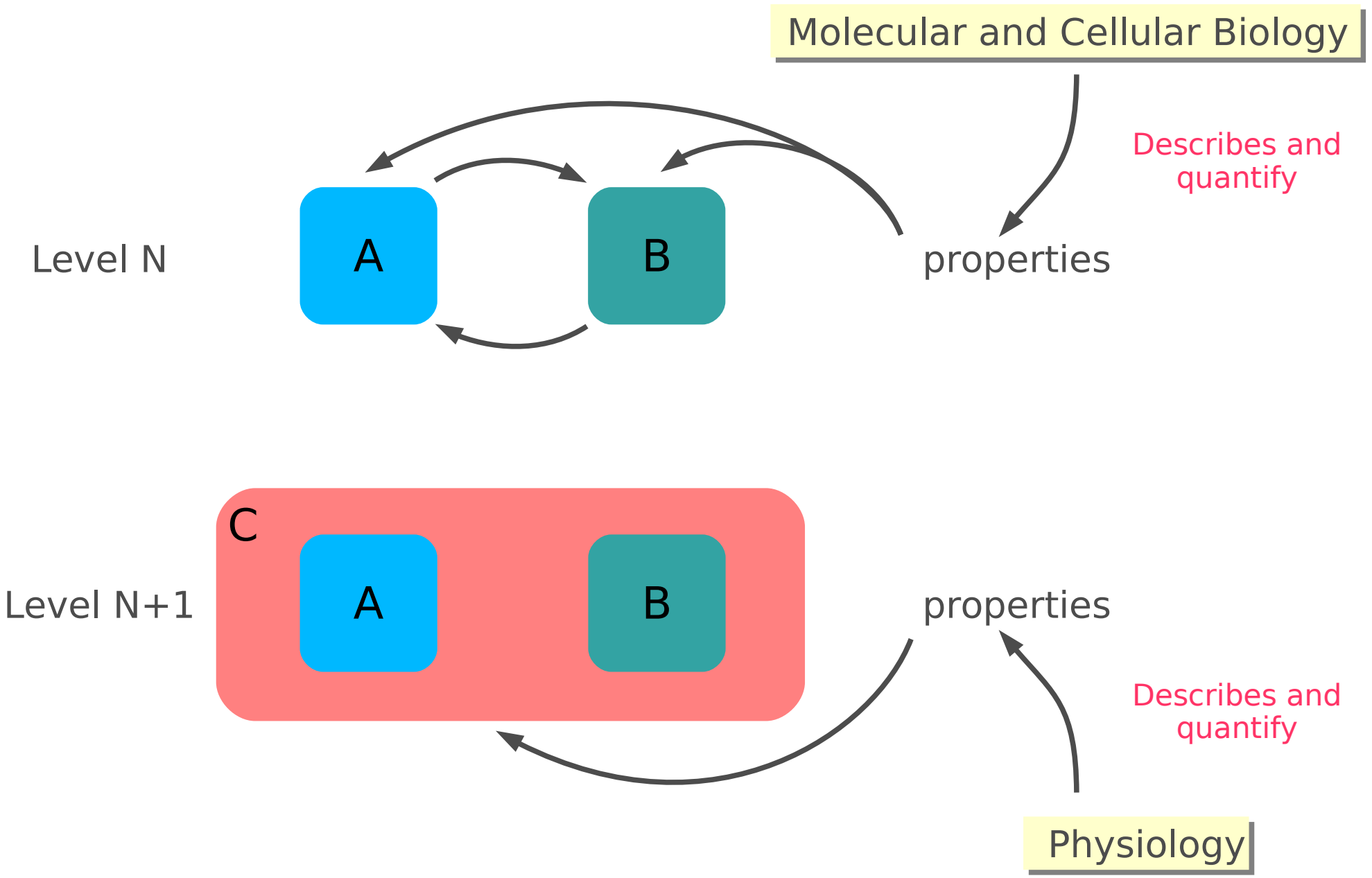

Molecular and Cellular Biology
Describes and quantify
Level N
A
B
properties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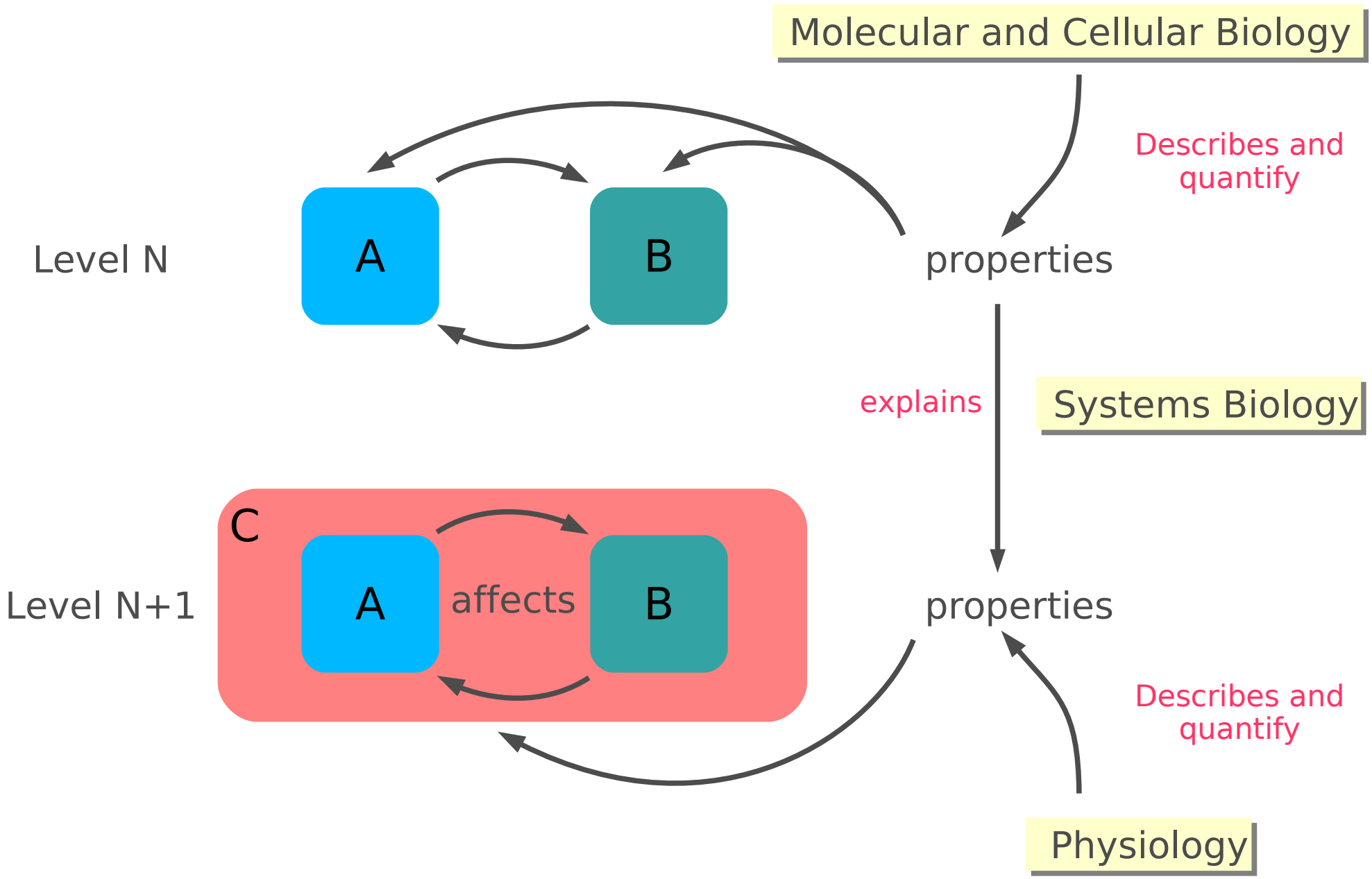
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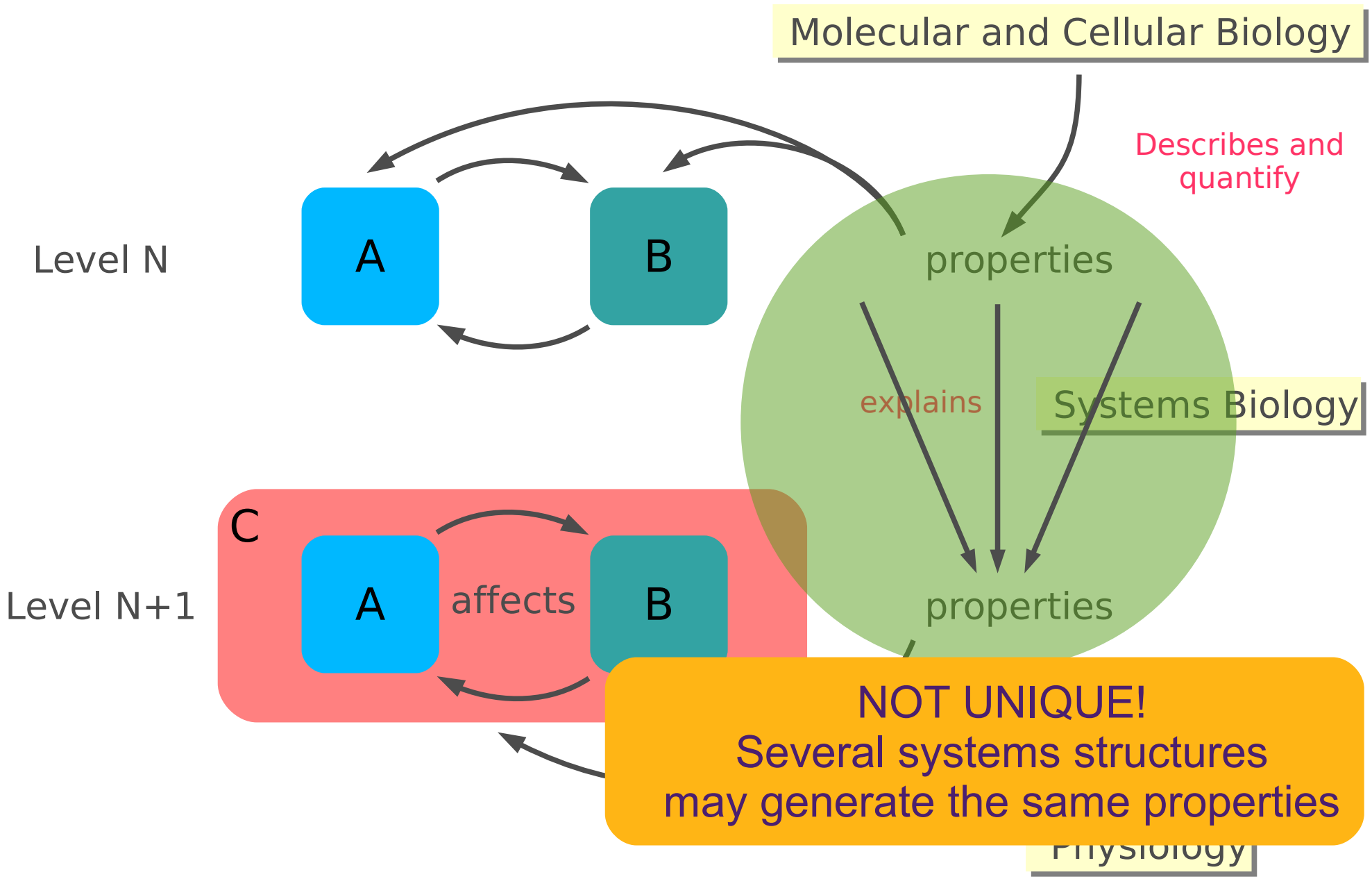
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NOT UNIQUE!
Several systems structures
may generate the same properties
Physiology

What Systems Biology is not!

Purely theoretical: Most systems biologists are actually experimental biologists

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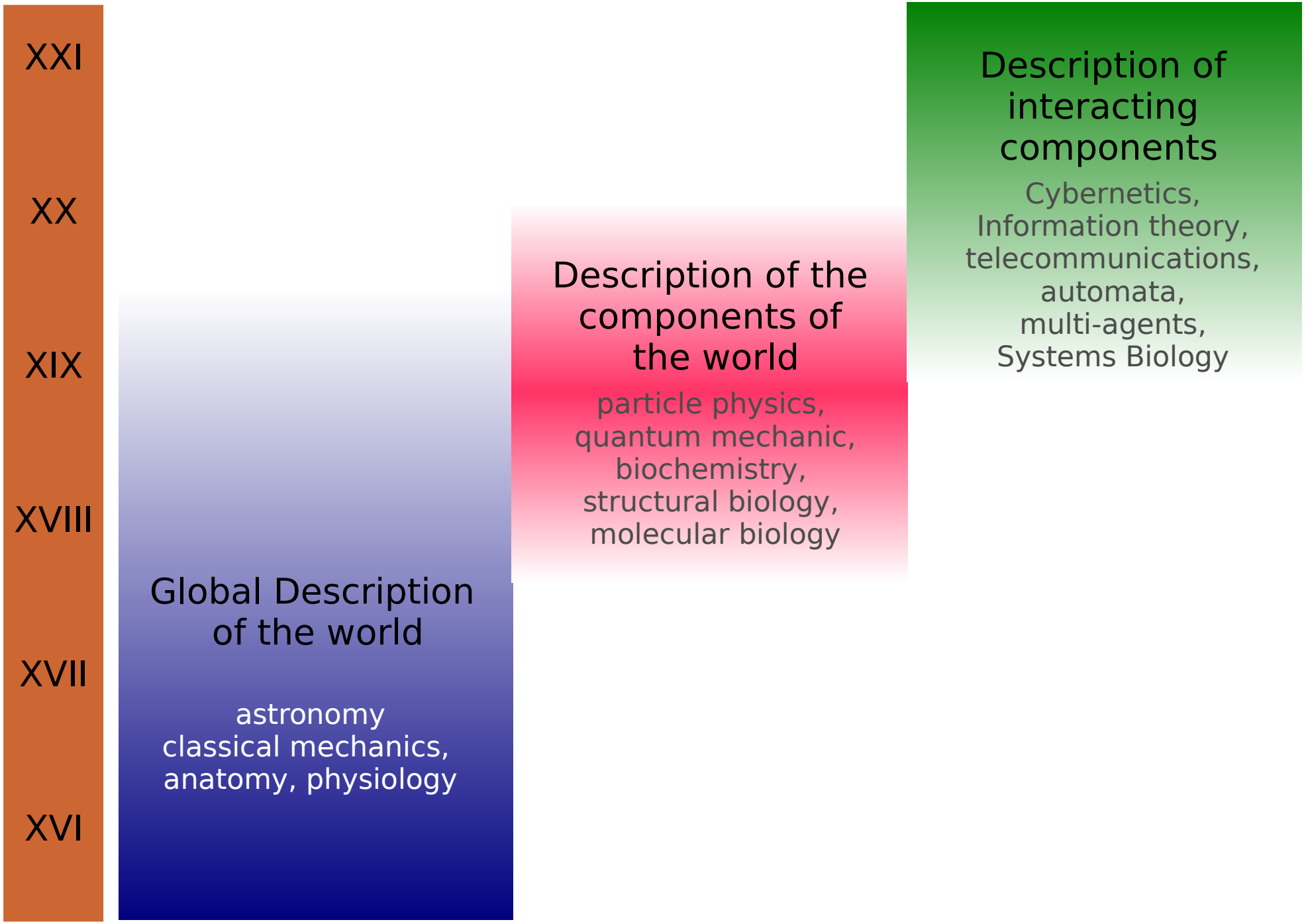
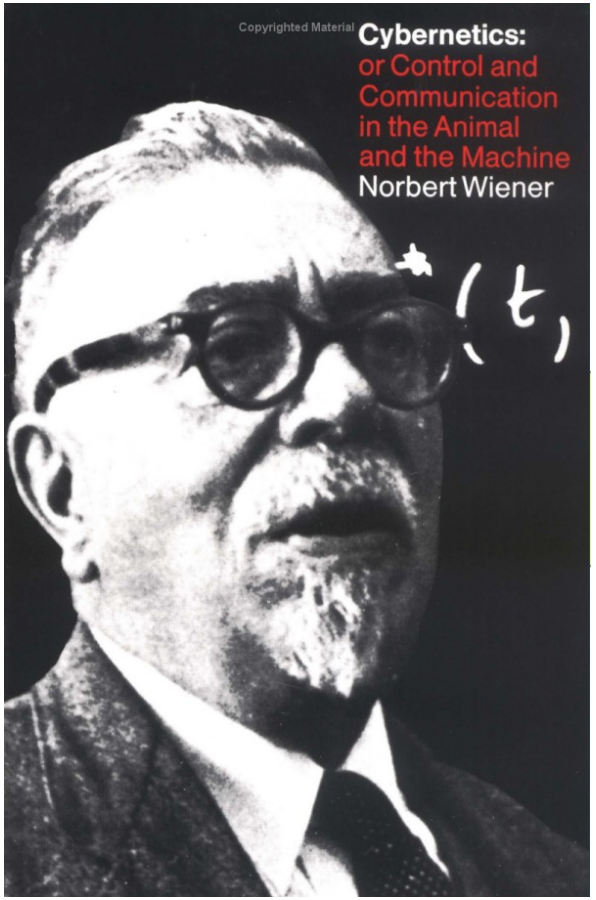
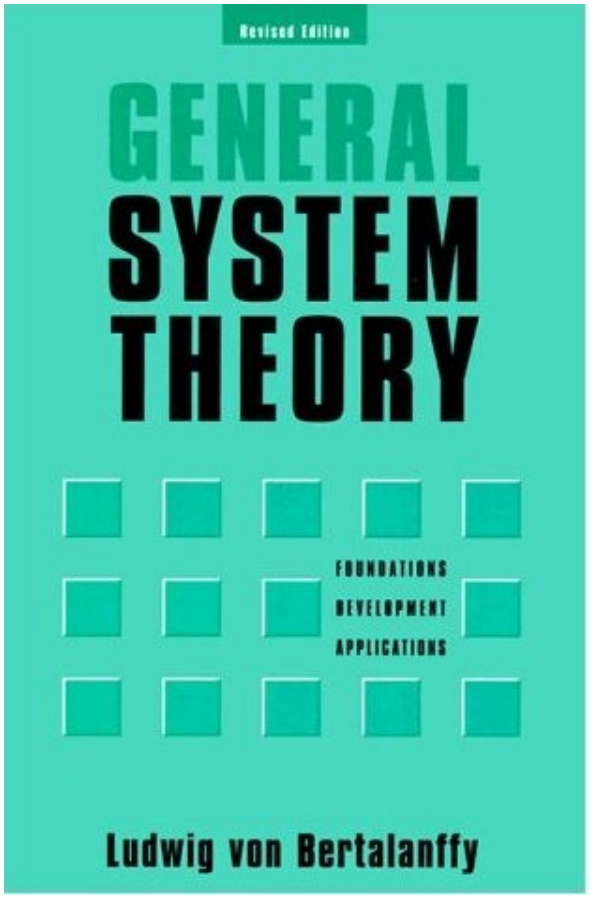
Systems Biology is the study of the ***emerging*** properties of a biological system, taking into account all the ***necessary*** constituents, their ***relationships*** and their ***dynamics***

Emergence of the notion of system



Systems are conceptualised mid-XXth





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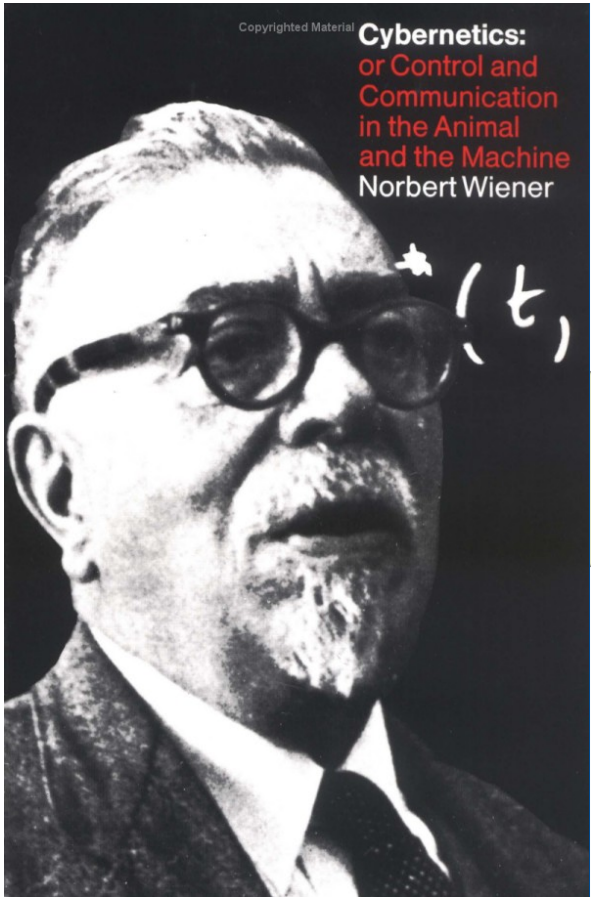
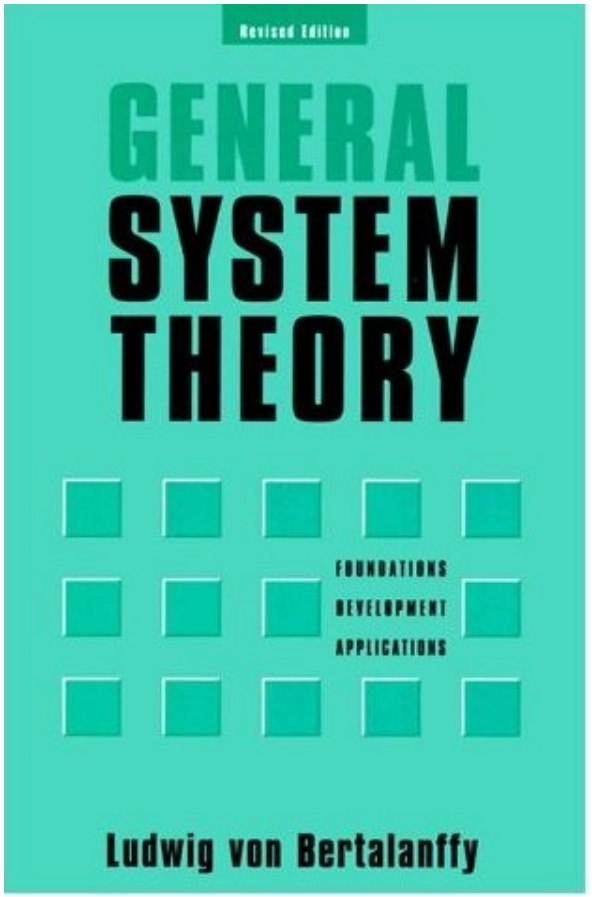
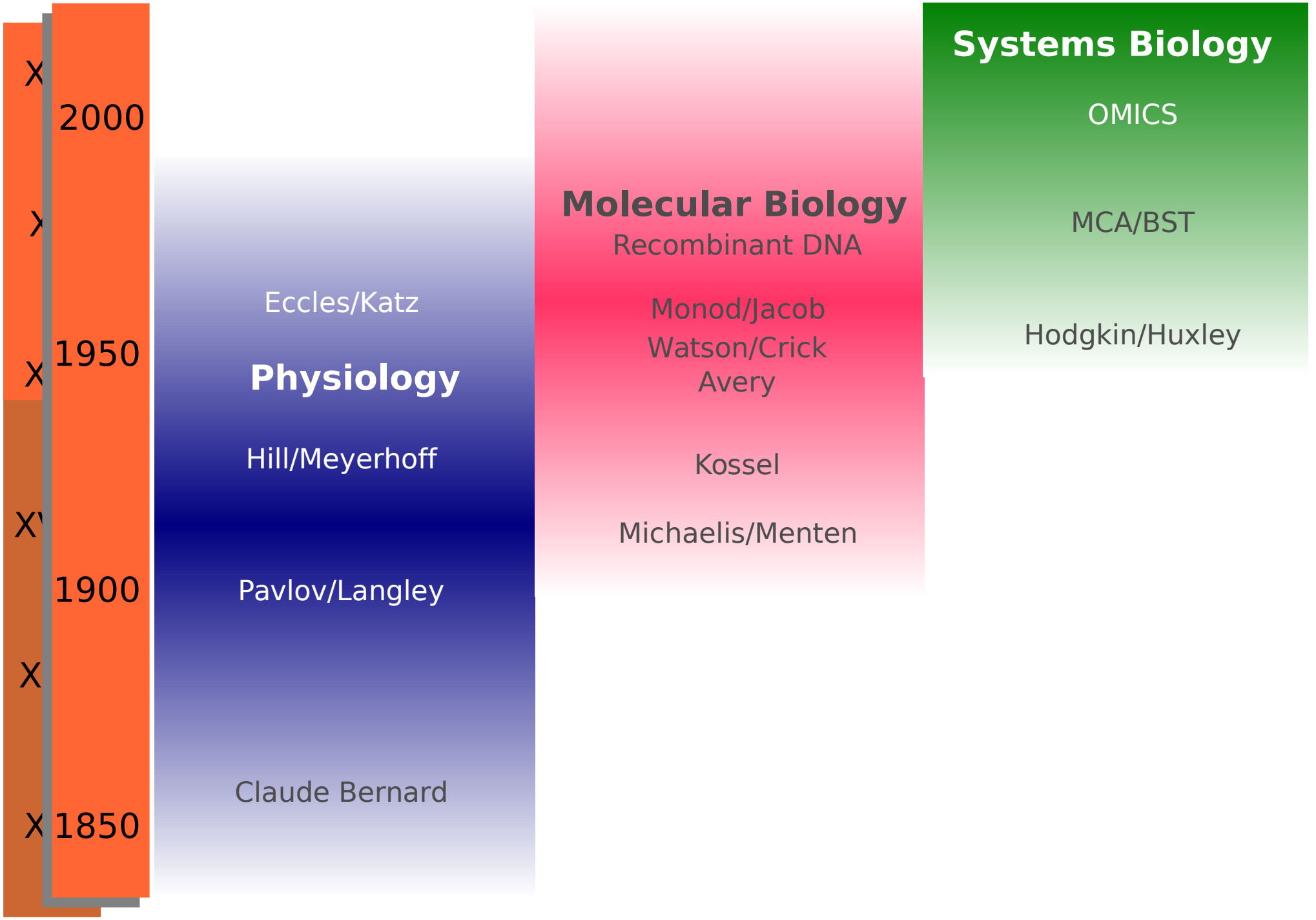


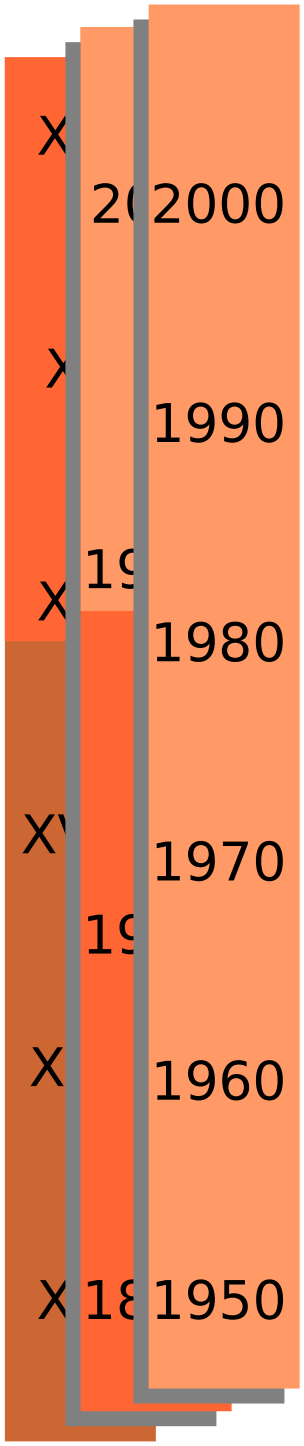


"[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems"
Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

The three paradigms of Biology



Towards Systems Biology



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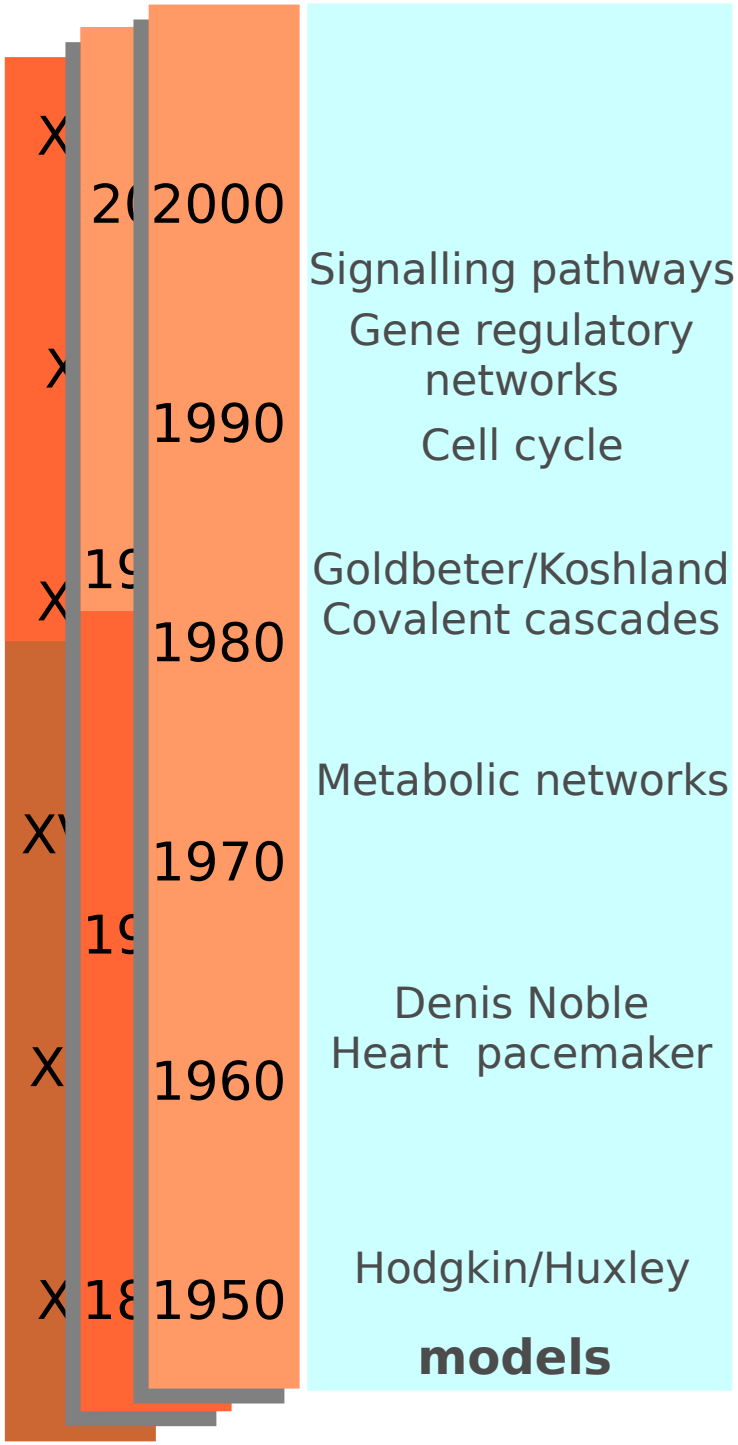

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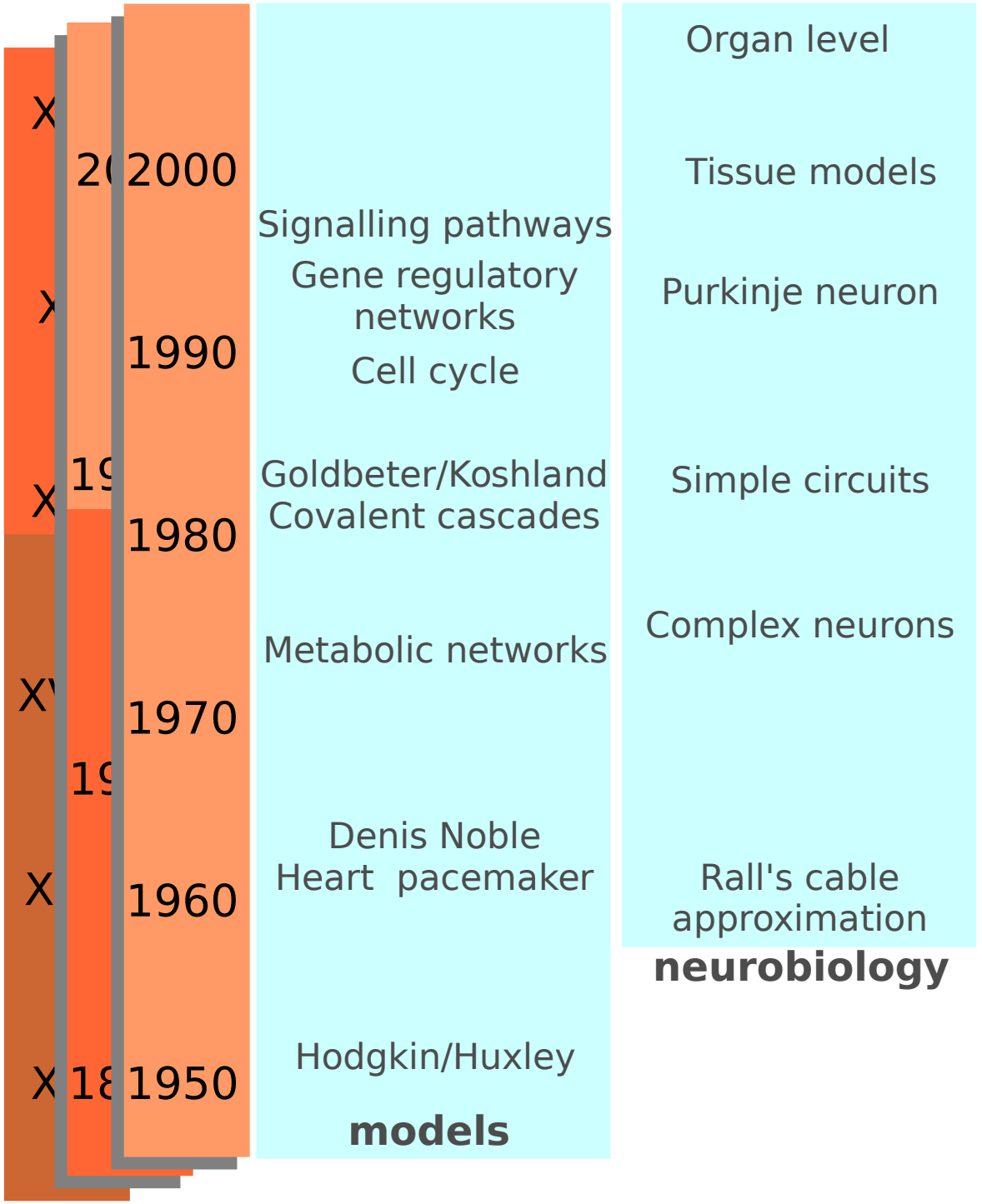
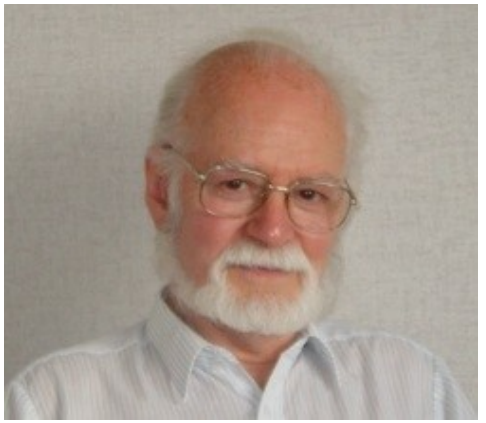


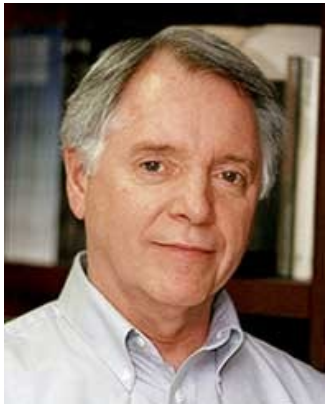
1960s and 1970s

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

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



- Henrik Kacser: Metabolic control analysis, Michael Savageau: Biochemical Systems Theory



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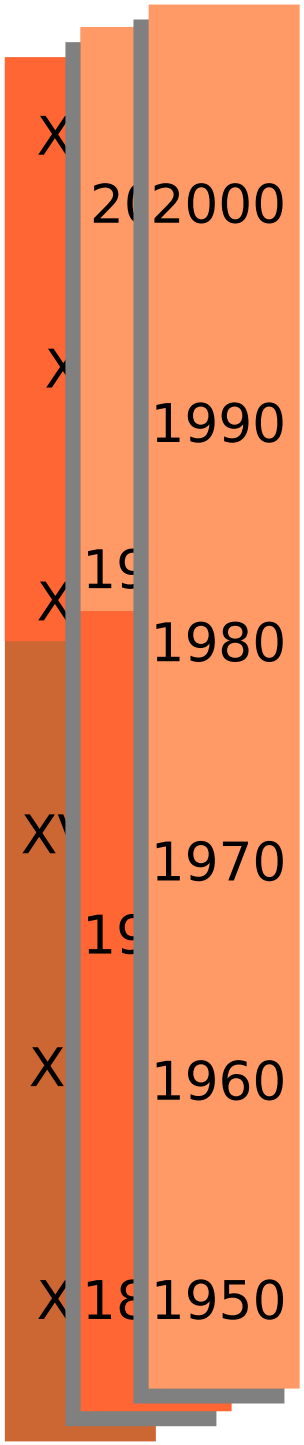

2000

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

Organ level

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Purkinje neuron

Simple circuits

Complex neurons

Rall's cable approximation

neurobiology

SBML

User-friendly simulators

Multi-agent systems

Stochastic algorithms

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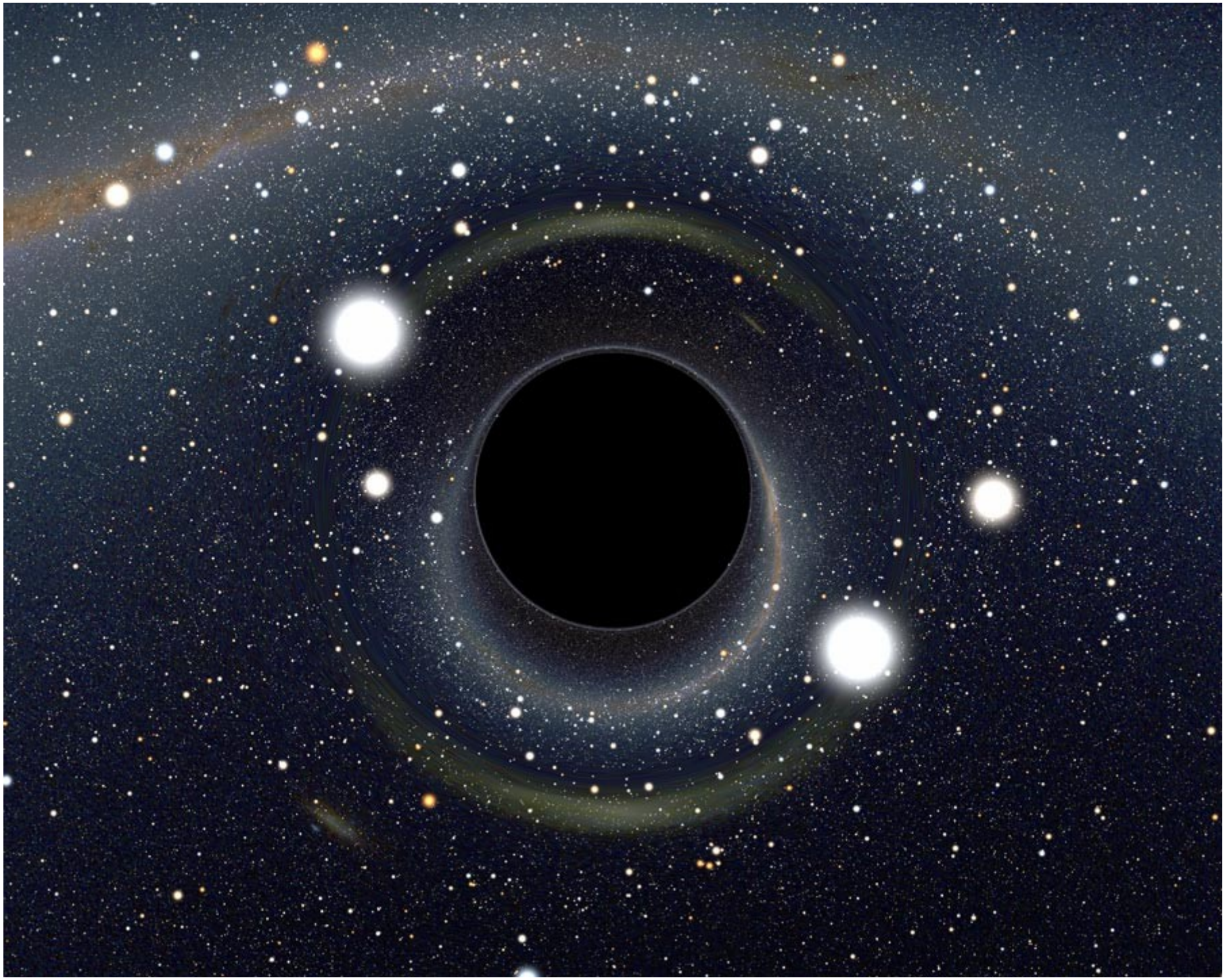
Boolean networks

methods

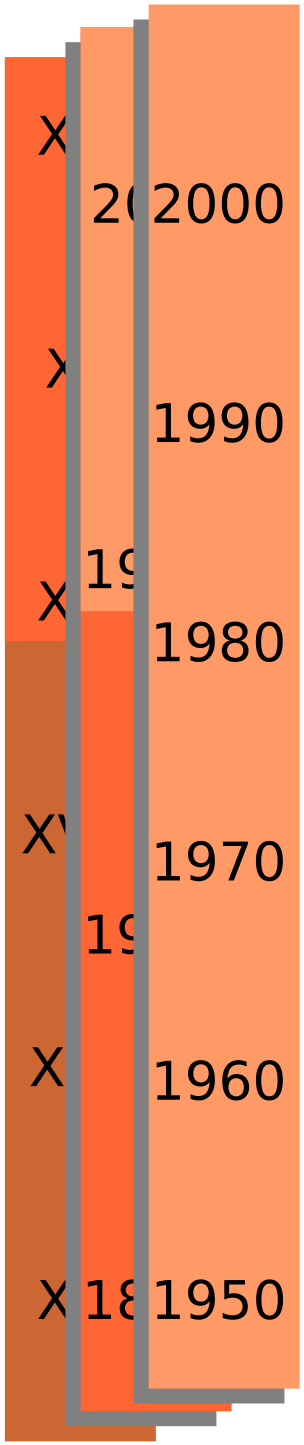
80s: The reign of Molecular Biology



1990s: the community matures

- 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 that models 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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Hodgkin/Huxley

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Heart pacemaker

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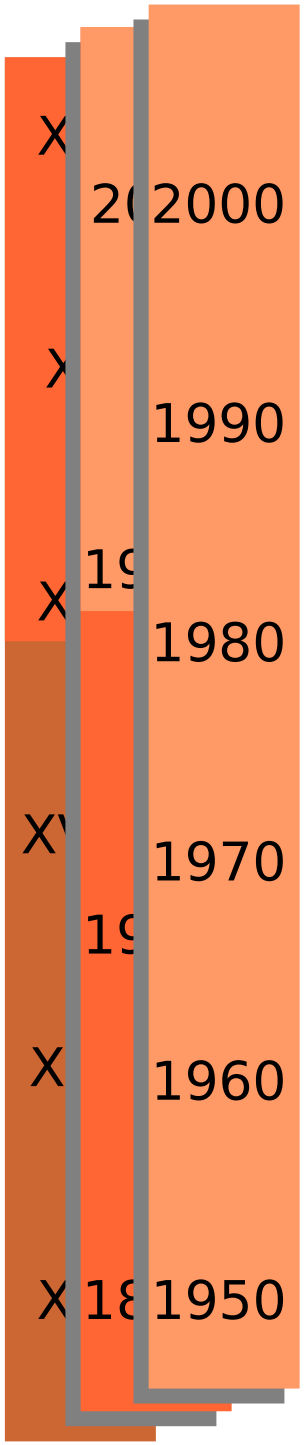

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Synthetic Biology

Repressilator

Barabasi

Network Biology

Formal revival of Systems Biology

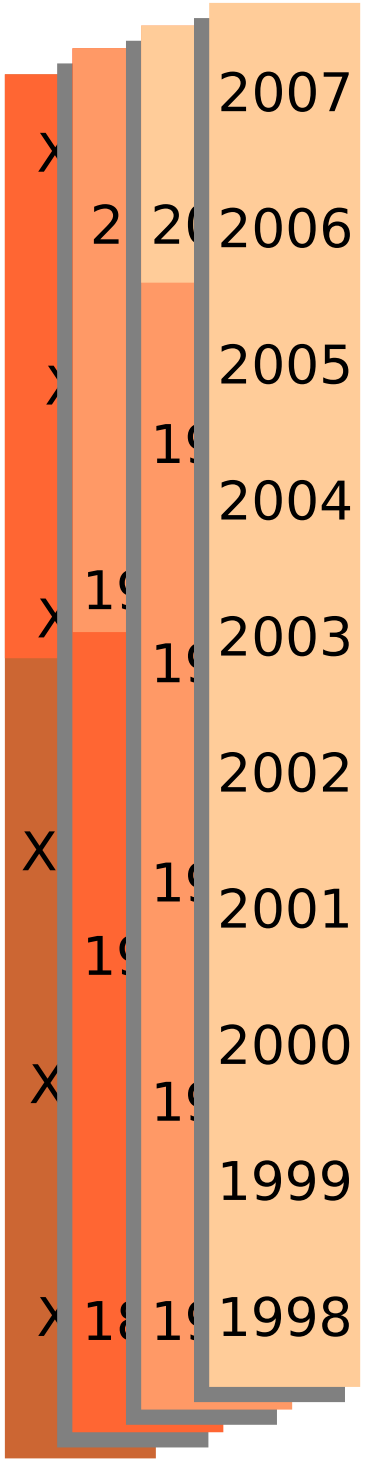
- "Modelling" Systems Biology

  - 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* (2000)

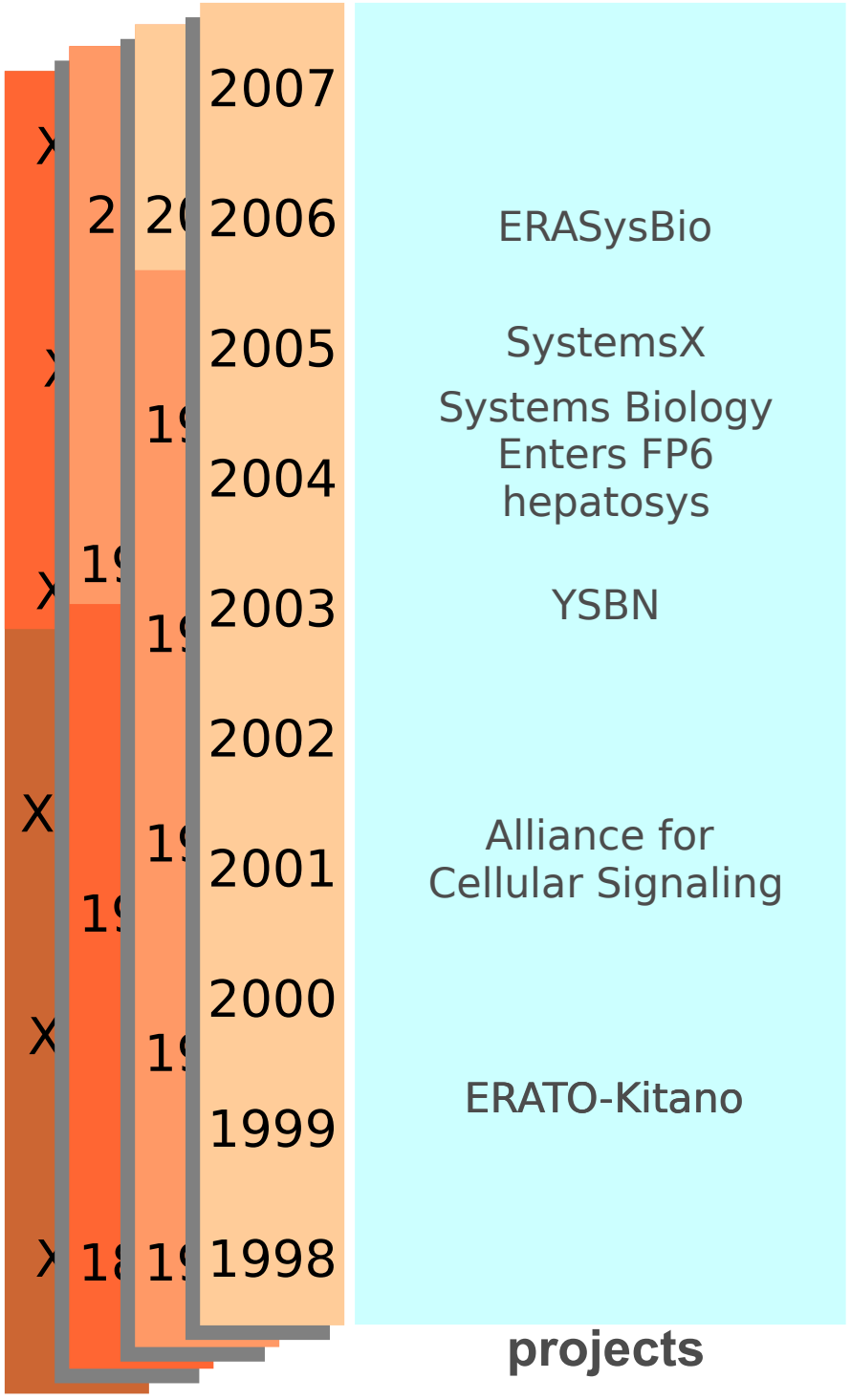
- "Network" Systems Biology

  - First appearance: Leroy Hood. Systems biology: new opportunities arising from genomics, proteomics and beyond. *Experimental Hematology* (1998)
  - Schwikowski B, Uetz P, Fields S. A network of protein-protein interactions in yeast. *Nat Biotechnol*. (2000)
  - 2000 - Leroy Hood founds the Systems Biology Institute in Seattle

Rise of Systems Biology as a paradigm



Rise of Systems Biology as a paradigm



Rise of Systems Biology as a paradigm

2007
2006
2005
2004
2003
2002
2001
2000
1999
1998

ERASysBio

SystemsX

Systems Biology
Enters FP6
hepatosys

YSBN

Alliance for
Cellular Signaling

ERATO-Kitano

projects

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

IEE Sys Bio

SBML

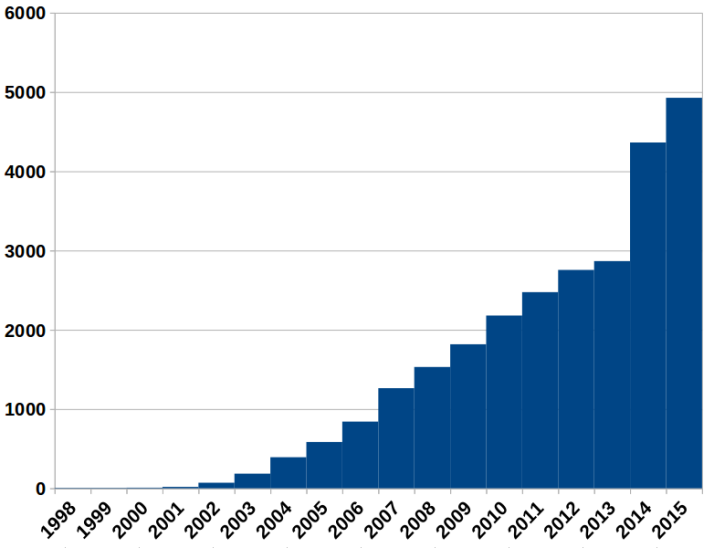
Science special issue

“Foundations of
Systems Biology”
Ideker/Hood

Von Dassow
“Computational
Cell Biology”

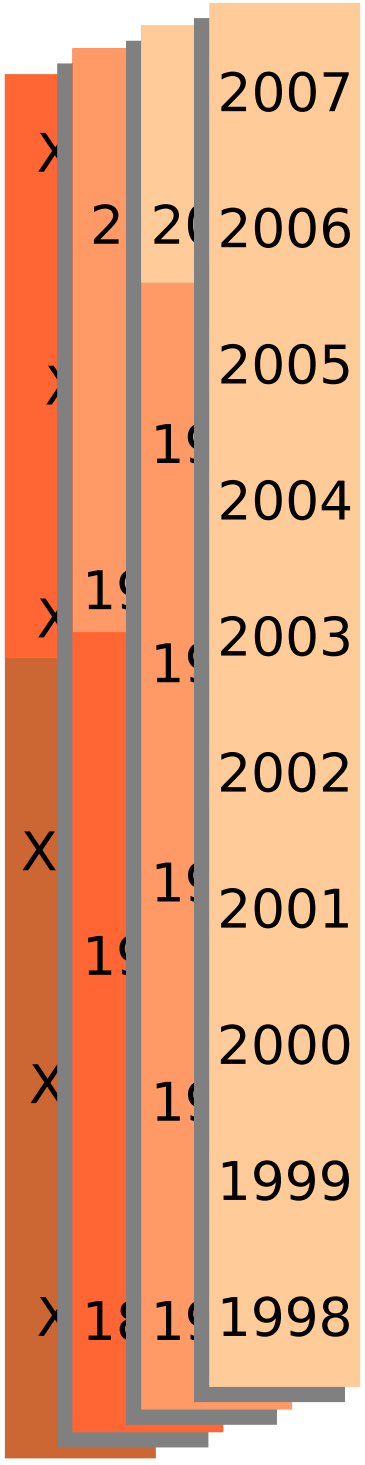
ECell

publications



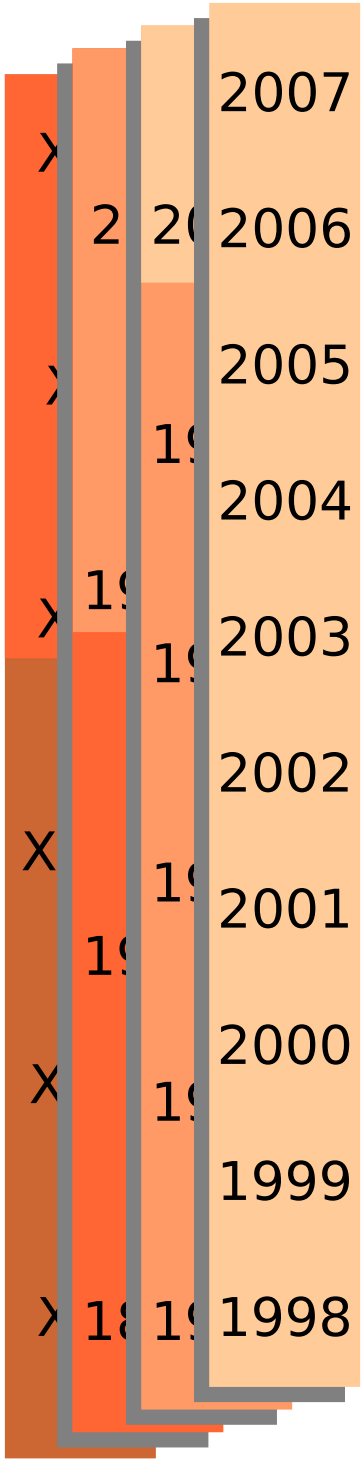
PubMed

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 (Heidelberg)
Systems Biology Enters FP6 hepatosys	SBML	
YSBN	*Science* special issue	
Alliance for Cellular Signaling	"Foundations of Systems Biology" Ideker/Hood	Seattle Institute for Systems Biology
ERATO-Kitano	Von Dassow "Computational Cell Biology"	
	ECell	Tokyo Systems Biology Institute

Rise of Systems Biology as a paradigm



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End of BBSRC Systems Biology calls

6 BBSRC centres

BioQuant (Heidelberg)

Seattle Institute for Systems Biology

Tokyo Systems Biology Institute

projects **publications** **Institutes**

Two kinds of Systems Biology?

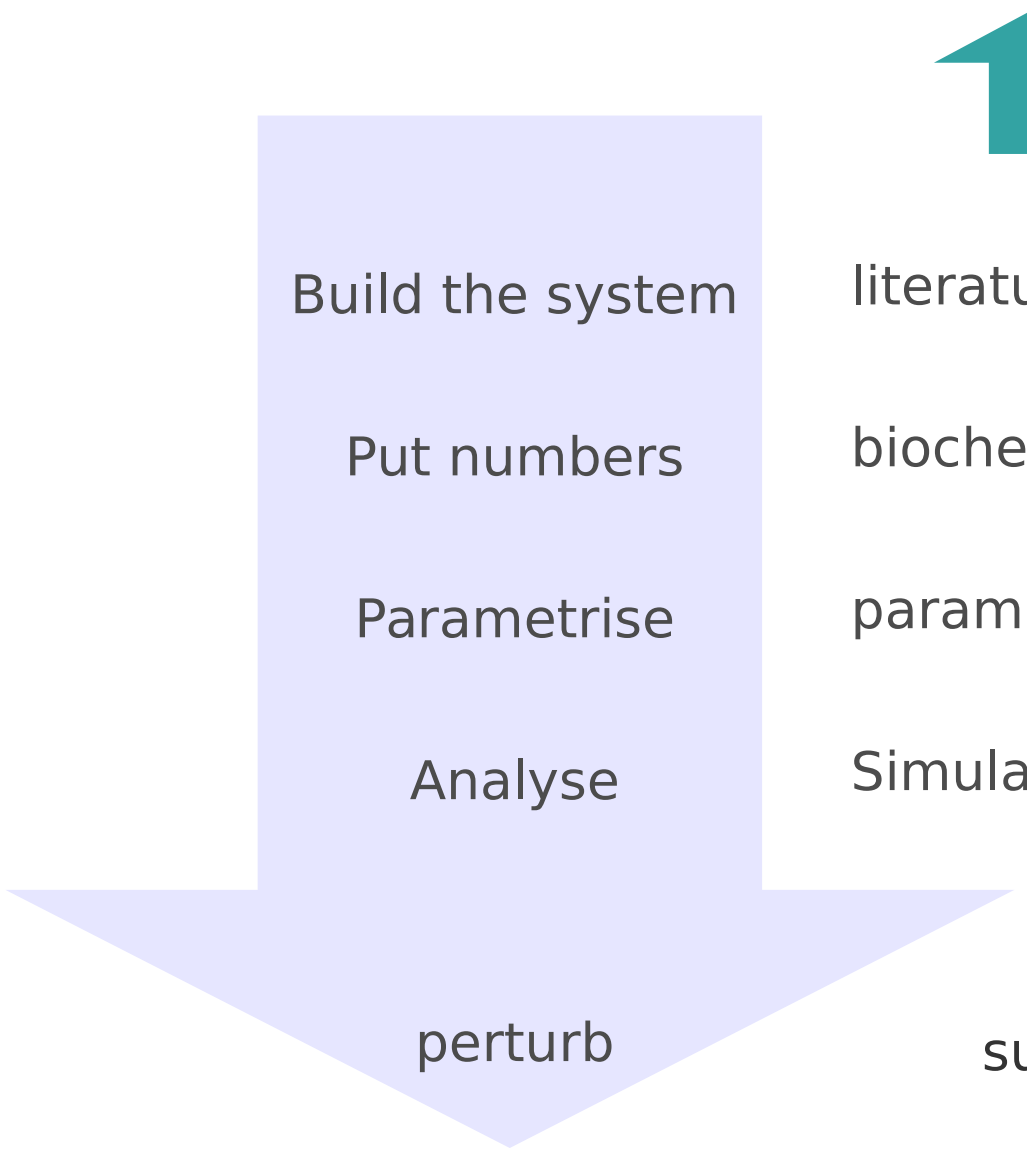
Systems-wide analysis (omics)

- 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

Bottom → up *Vs* 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	