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

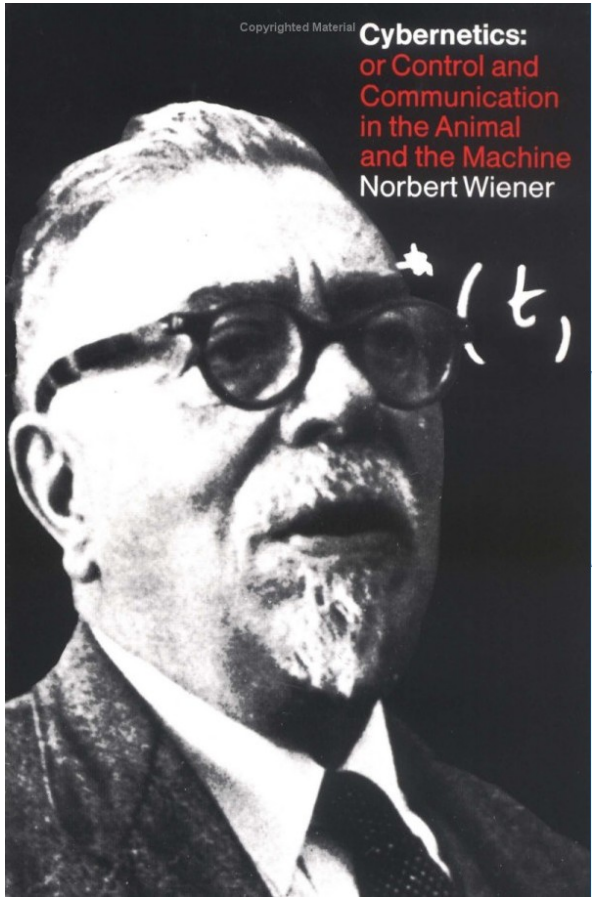
Description of the components of the world

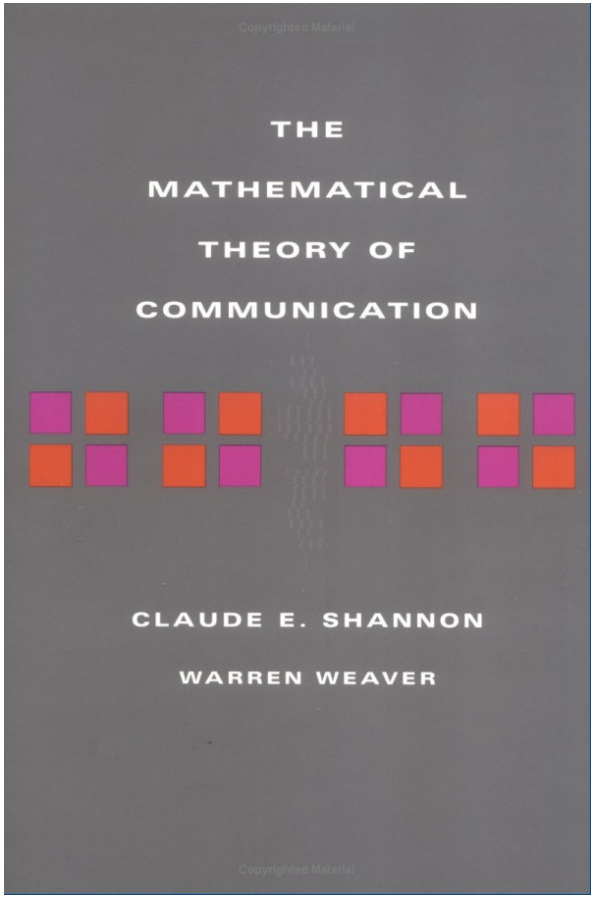
Statistical physics, thermodynamics, quantum mechanic, biochemistry, structural biology, molecular biology

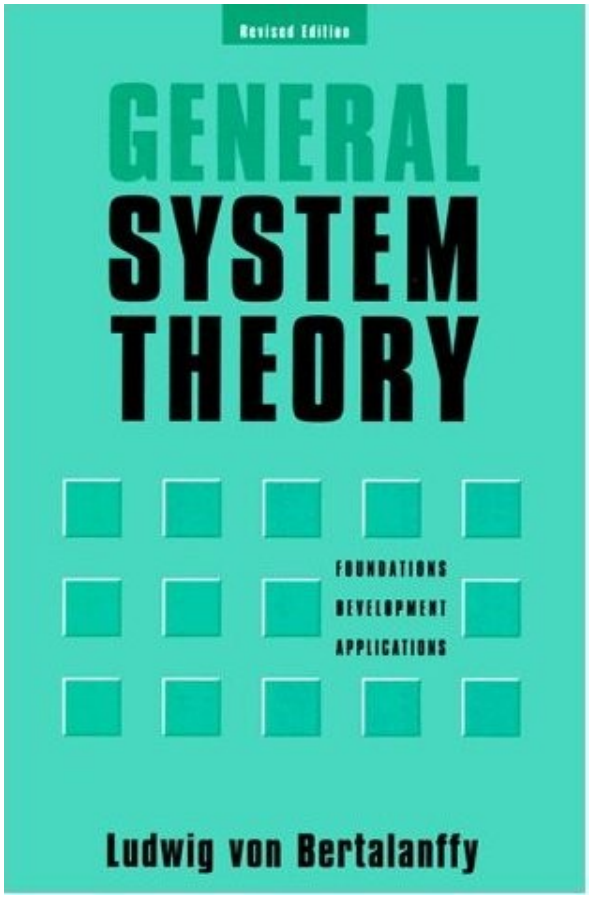
Description of interacting components

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

Systems have been formalised for a while







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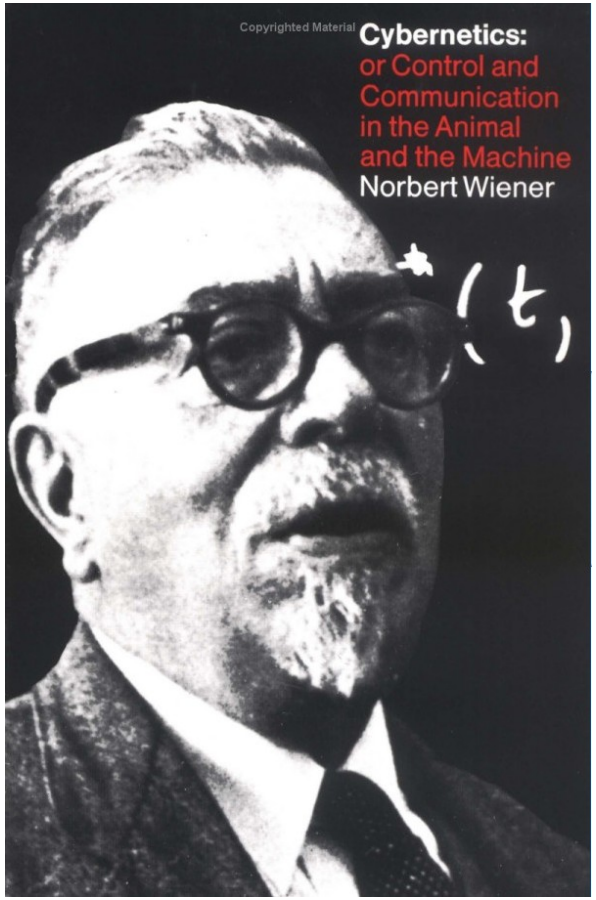
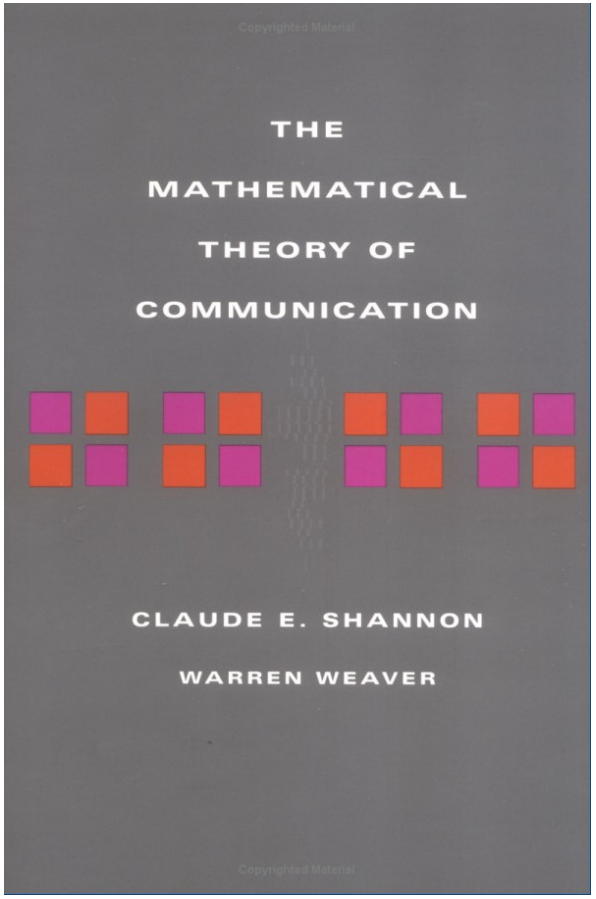
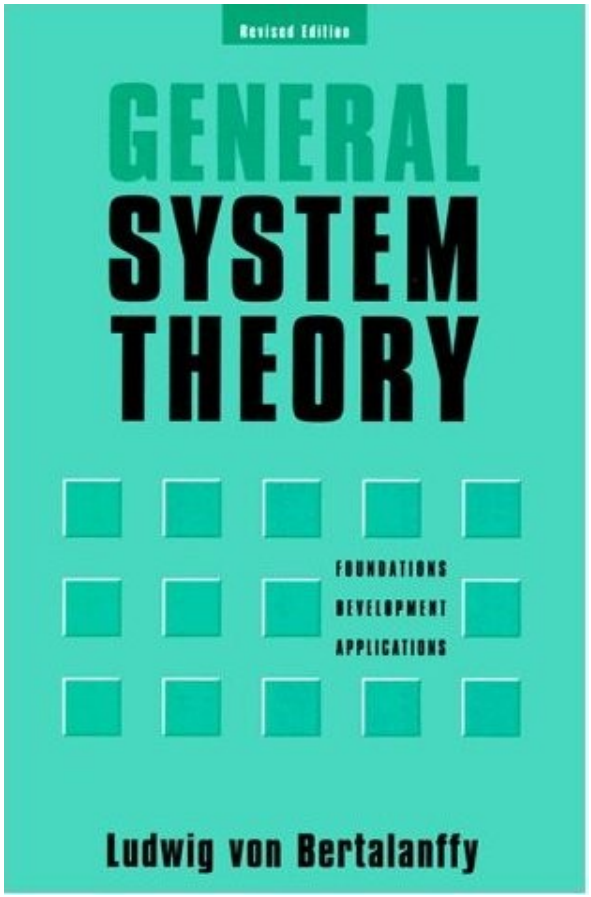
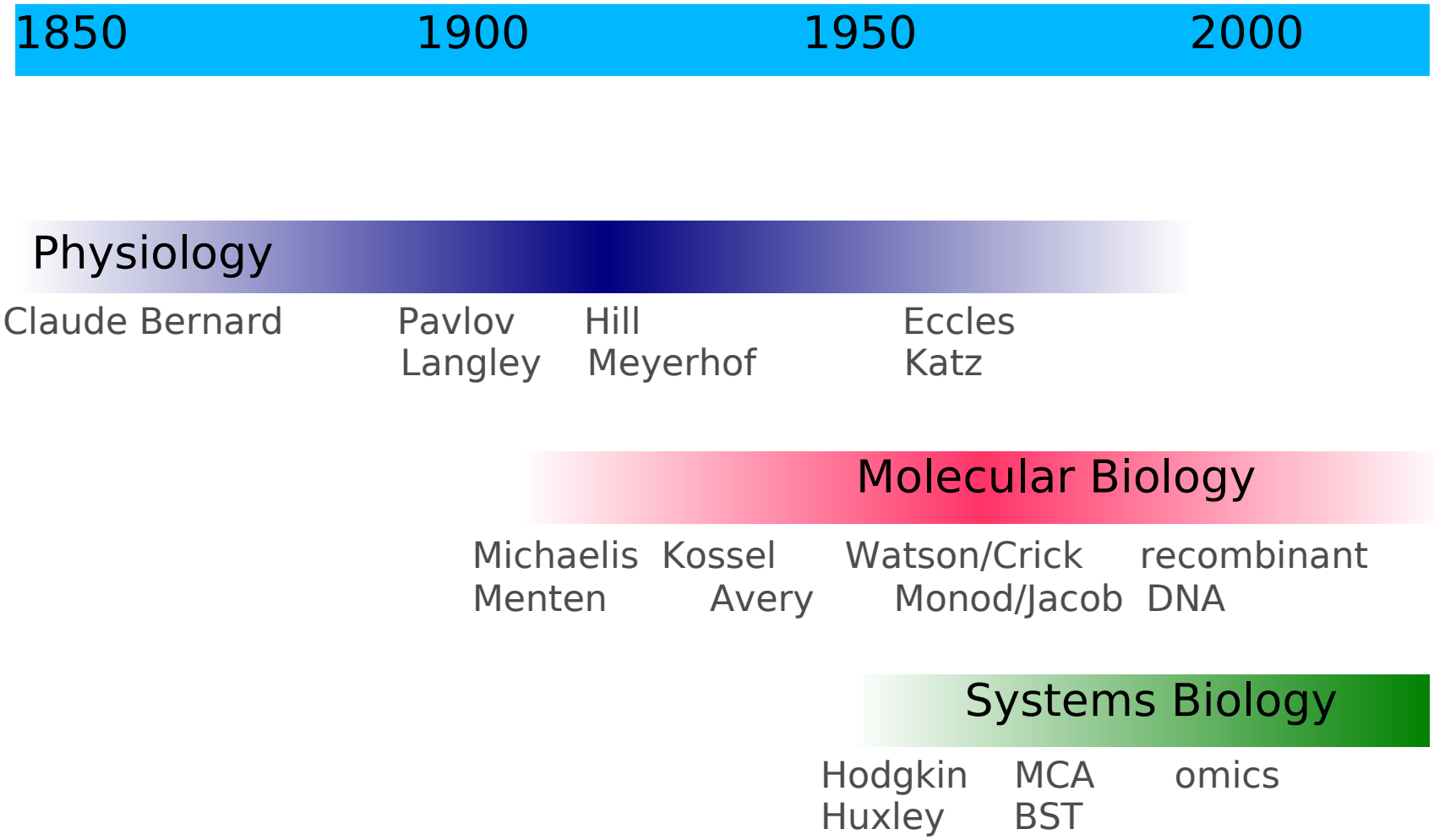




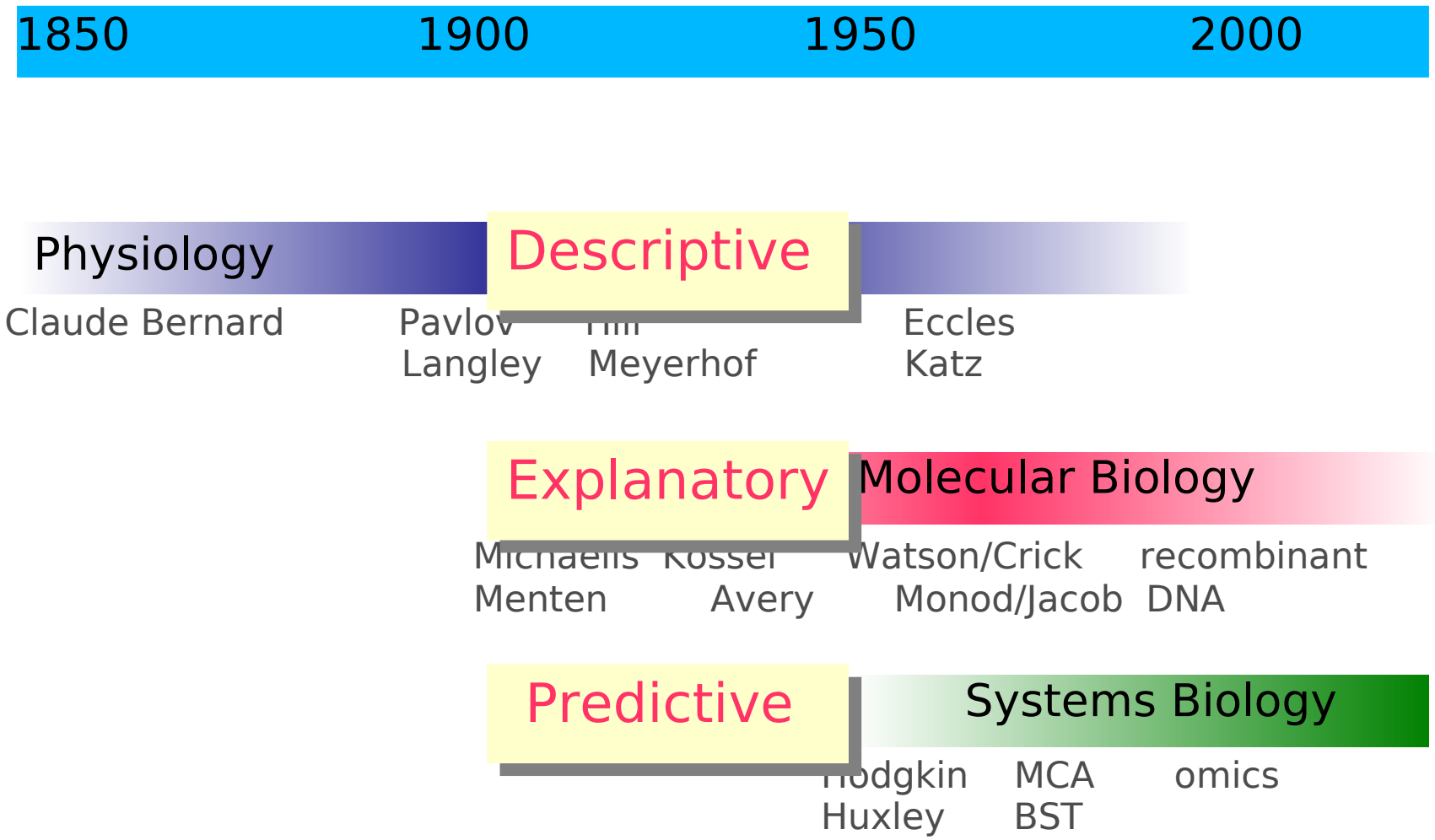


"[A system consists of] a dynamic order of parts and processes standing in mutual interaction. [...] The fundamental task of biology [is] the discovery of the laws of biological systems"
Ludwig von Bertalanfy, Kritische Theorie der Formbildung, 1928

The three paradigms of Biology



The three paradigms of Biology



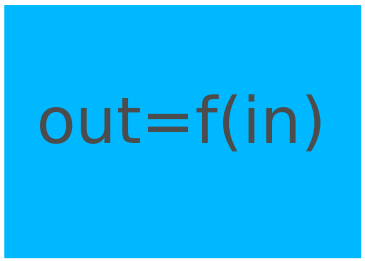
What Systems Biology is not ... only

- Modelling: This is Mathematical (or Theoretical) Biology
- High-throughput data generation: This is Functional Genomics
- Quantitative data measurement: That should always be the case in life science ... shouldn't it?

  Those are techniques. Systems Biology is a scientific paradigm, a way of thinking life

  (Molecular Biology is not defined by the use of restriction enzymes ... or is it?)

Systems Biology is REALLY NOT



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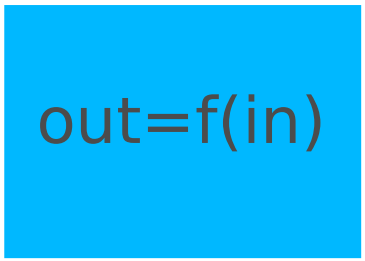
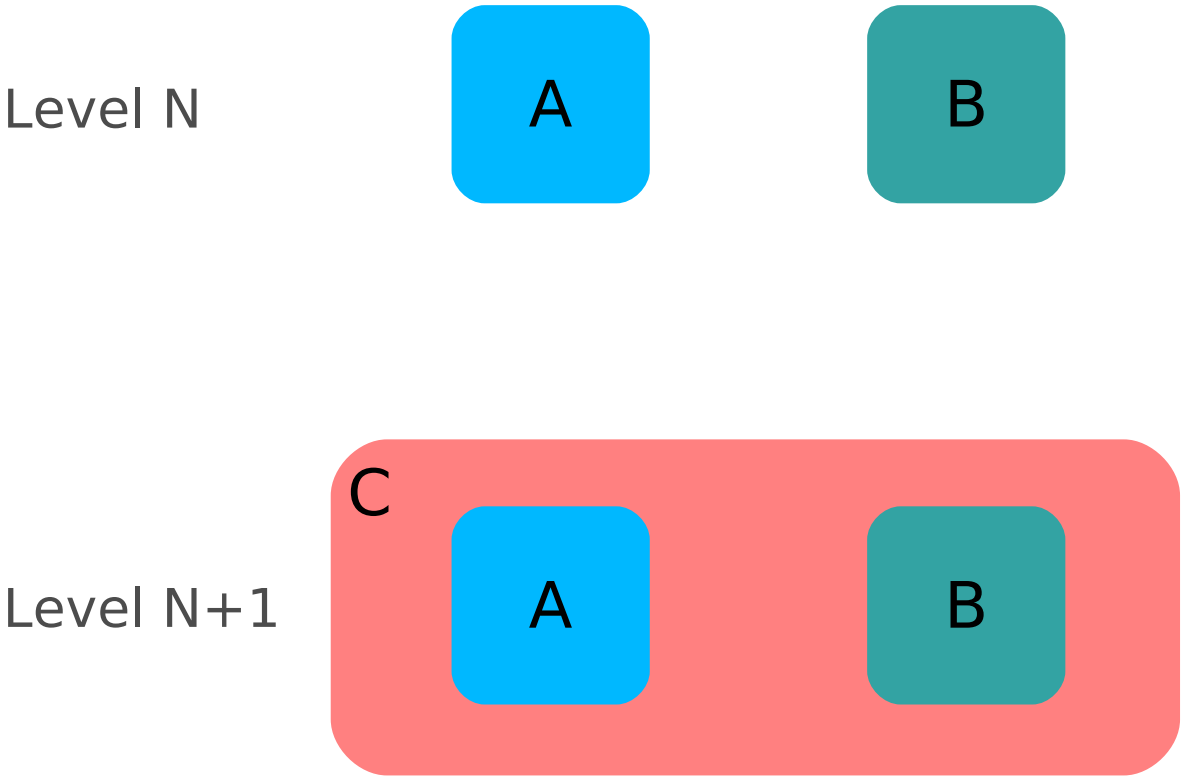


This is physiology!

What is Systems Biology?

Level N

What is Systems Biology?



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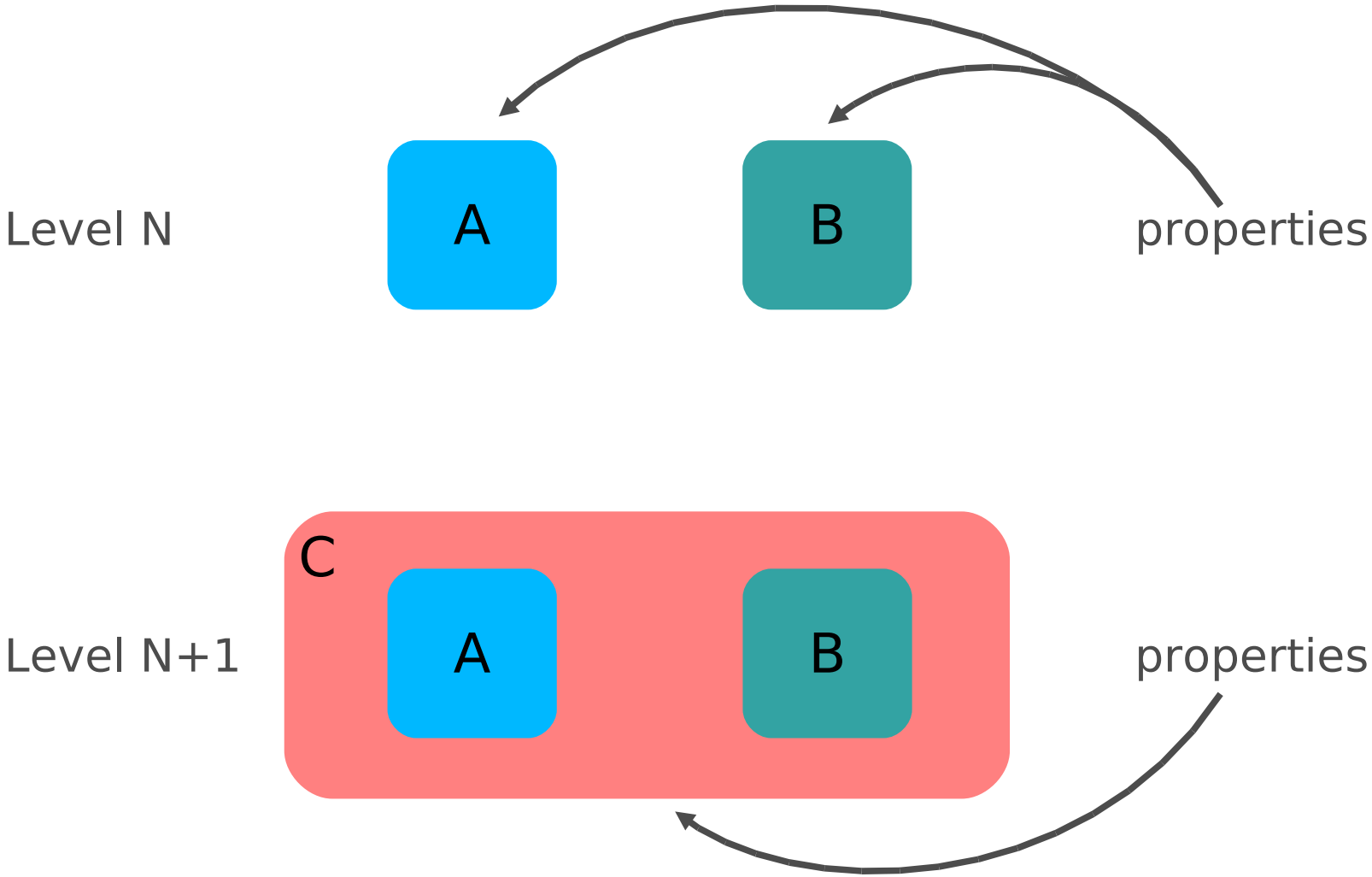

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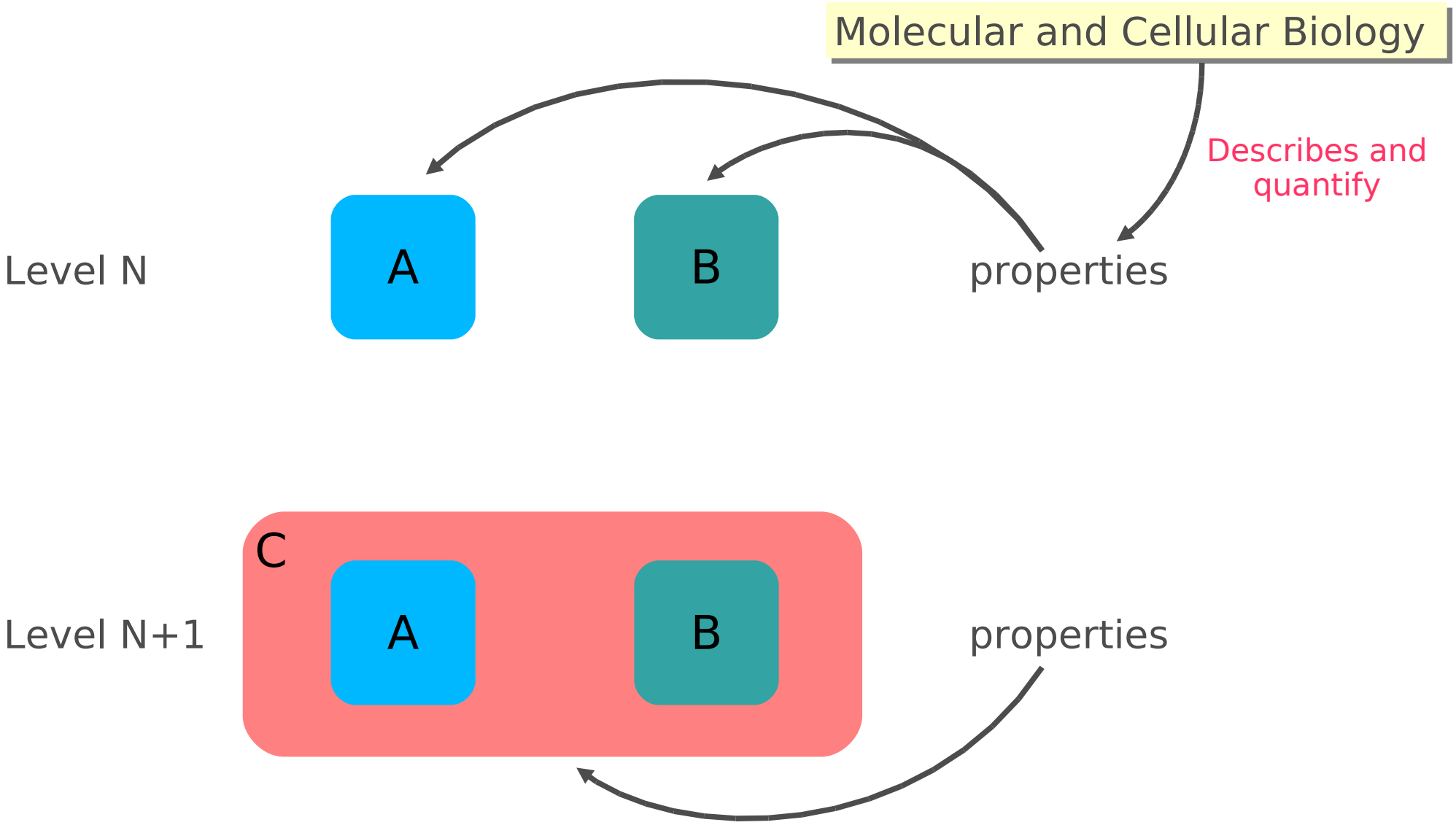

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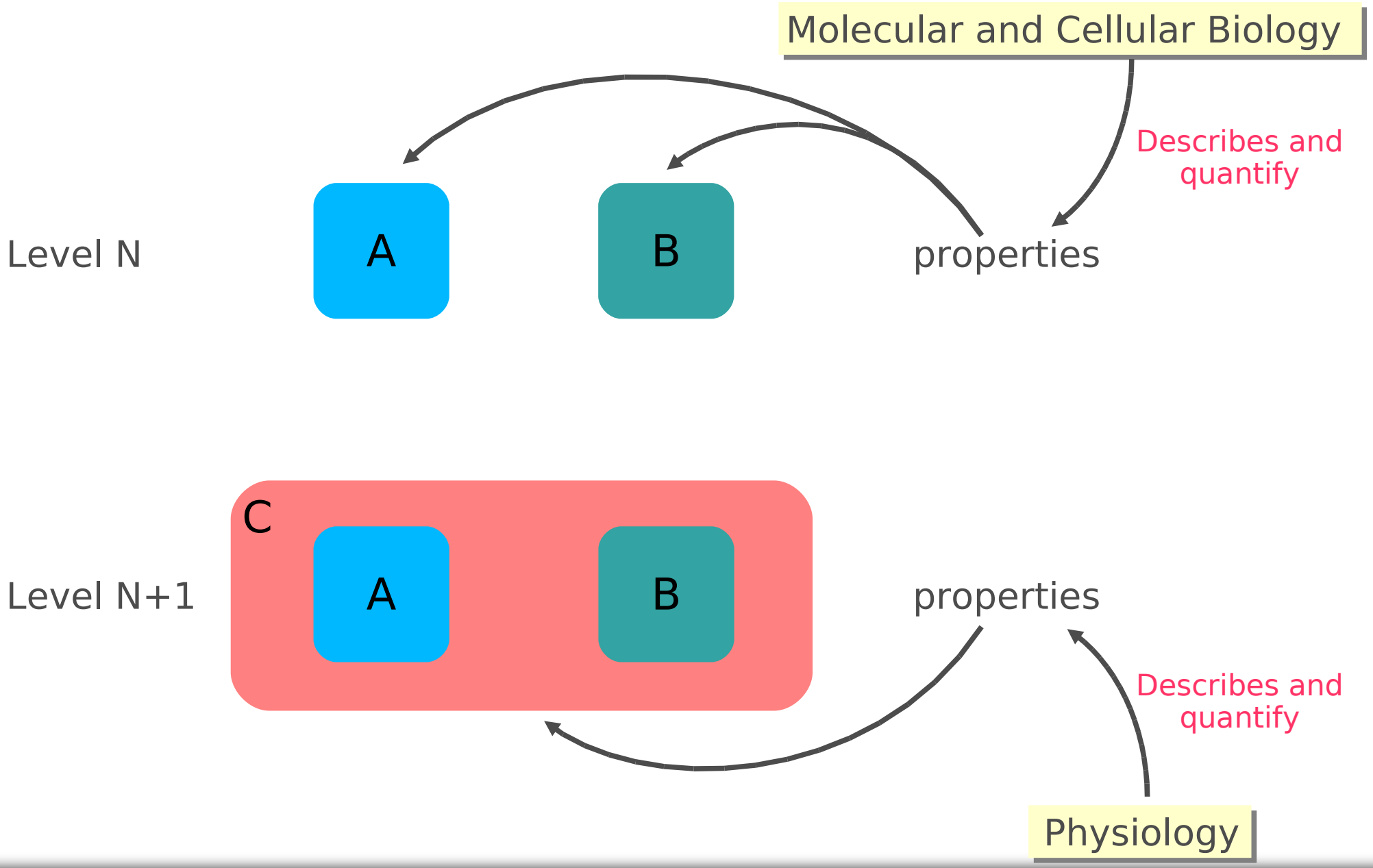
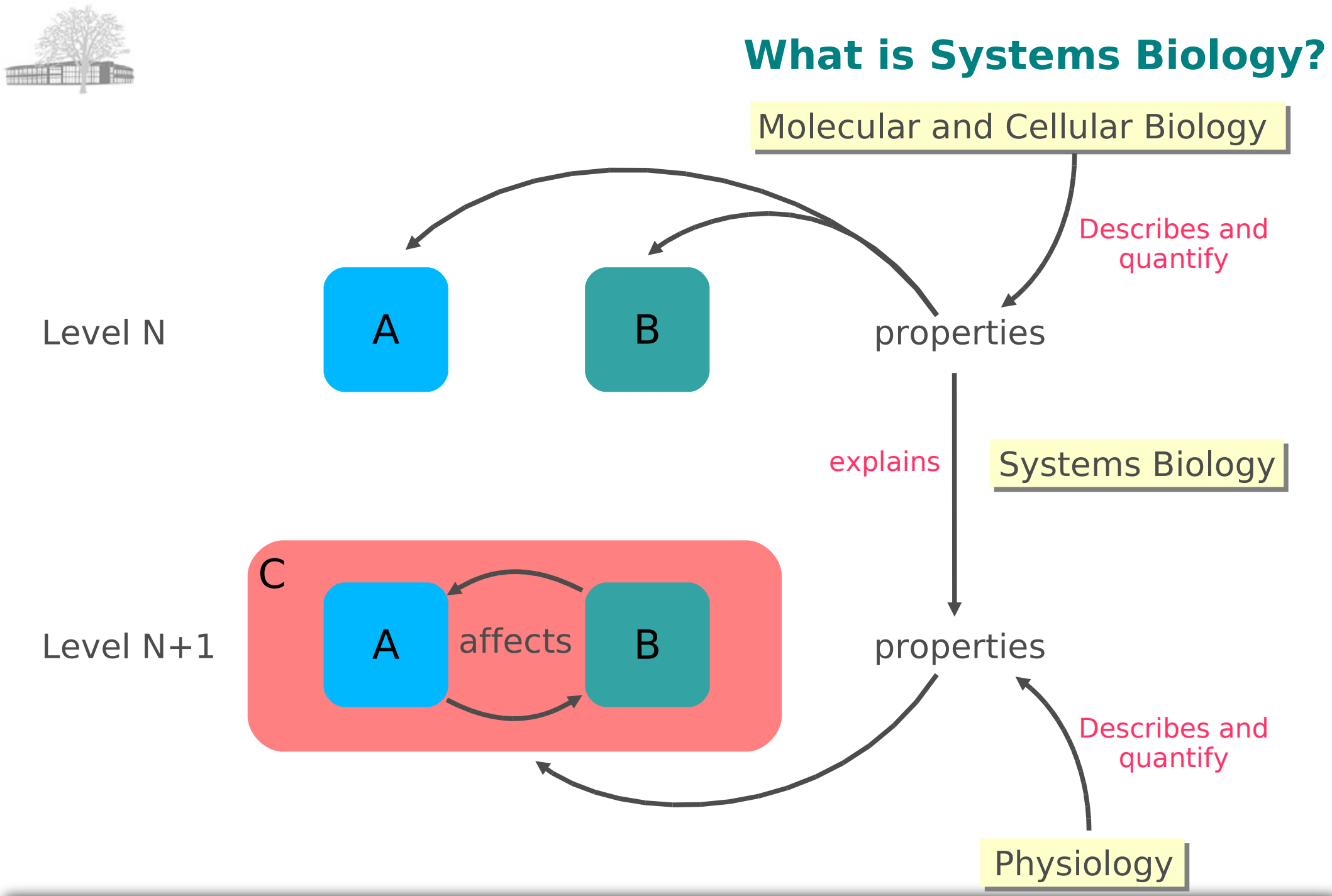


What is Systems Biology?



History of Systems Biology

Events around

First computers
PDB
EMBLbank
PC
Genomes
Interactomes

1950 1960 1970 1980 1990 2000

models

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

neurobiology

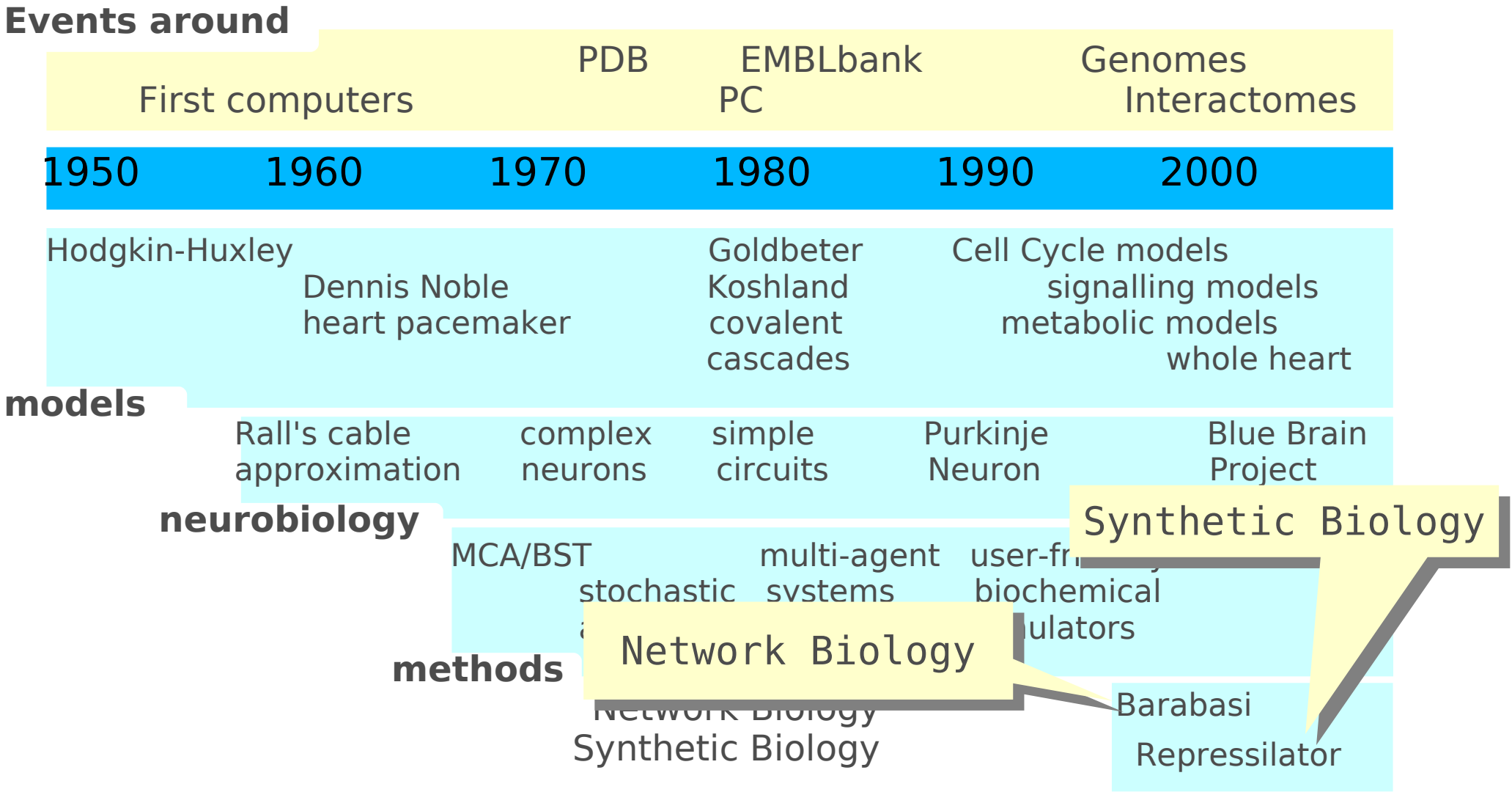
Rall's cable approximation
complex neurons
simple circuits
Purkinje Neuron
Blue Brain Project

methods

MCA/BST
stochastic algorithms
multi-agent systems
user-friendly biochemical simulators
SBML

Network Biology
Synthetic Biology
Barabasi
Repressilator

History of Systems Biology



Rise of Systems Biology as a paradigm

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
projects	ERATO-Kitano			Alliance for Cellular Signaling			HepatoSys	SystemsX		
						YSBN	SysBio enters FP6		ERASysBio	
publications	ECell		Von Dassow	*Annual Review Science* Ideker/Hood special issue		SBML	“Foundations of Systems Biology”	Klipp Kriete	Alon Palsson	Choi Boogerd
							“Computational Cell Biology”	Kaneko	Szallasi	Grierson
							IEE Sys Bio	MSB	BMC Sys Bio	
Institutes			Tokyo Systems Biology Institute							
			Seattle Institute for Systems Biology					6 BBSRC centres		
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End of BBSRC Systems Biology calls

The “two” Systems Biology

What	■ **Reconstructions of systems** kinetic modelling, simulation, numerical analysis. Mainly metabolic networks and signalling pathways	■ **Systems-wide analysis** Genome-wide analysis, interactomes, regulatory networks, boolean models. Mainly gene regulatory networks
Who	■ Originate from Biochemistry, Physics and Engineering *Arkin, Bhalla, Bray, Fell, Ferrell, Hunter, Kell, Kholodenko, Kitano, Leibler, Noble, Palsson, Tyson, Westerhoff* International Society for Systems Biology	■ Originate from Functional Genomics, Bioinformatics and Mathematics *Birney, Bork, Brunak, Hood, Ideker, Snyder, Vidal* International Society of Computational Biology
When	■ International Conference on Systems Biology	■ Intelligent Systems in Molecular Biology, International Conference on Pathways, Networks, and Systems Medicine
Where	■ Biochemical journals, BMC Systems Biology, IET Systems Biology, Molecular Systems Biology	■ Bioinformatics, PloS Computational Biology

Modeling and encoding chemical kinetics

Nicolas Le Novère, EMBL-EBI

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

[37]

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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.*

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

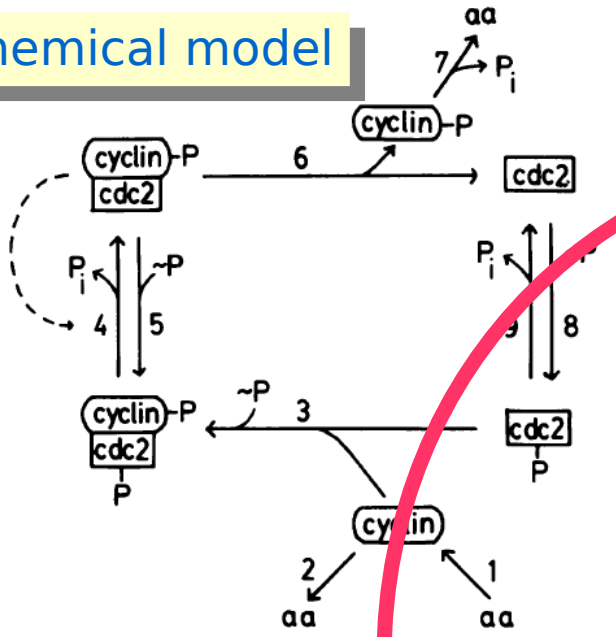
From the Physiological Laboratory, University of Cambridge

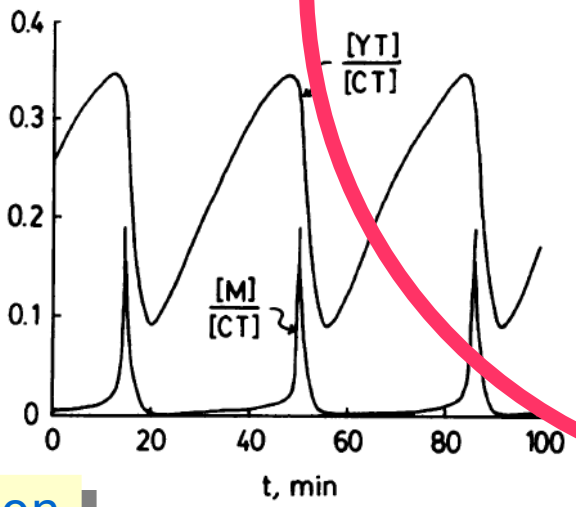
(*Received* 10 *March* 1952)

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

biochemical model





simulation

mathematical model

$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$
$$d[CP]/dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP]$$
$$d[pM]/dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M]$$
$$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$$
$$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$$
$$d[YP]/dt = k_6[M] - k_7[YP]$$

Parameter	Value	Notes
$k_1[aa]/[CT]$	0.015 min^{-1}	*
k_2	0	†
$k_3[CT]$	200 min^{-1}	*
k_4	10–1000 min^{-1} (adjustable)	
k_4'	0.018 min^{-1}	
$k_5[\sim P]$	0	‡
k_6	0.1–10 min^{-1} (adjustable)	
k_7	0.6 min^{-1}	†
$k_8[\sim P]$	$>>k_9$	§
k_9	$>>k_6$	§

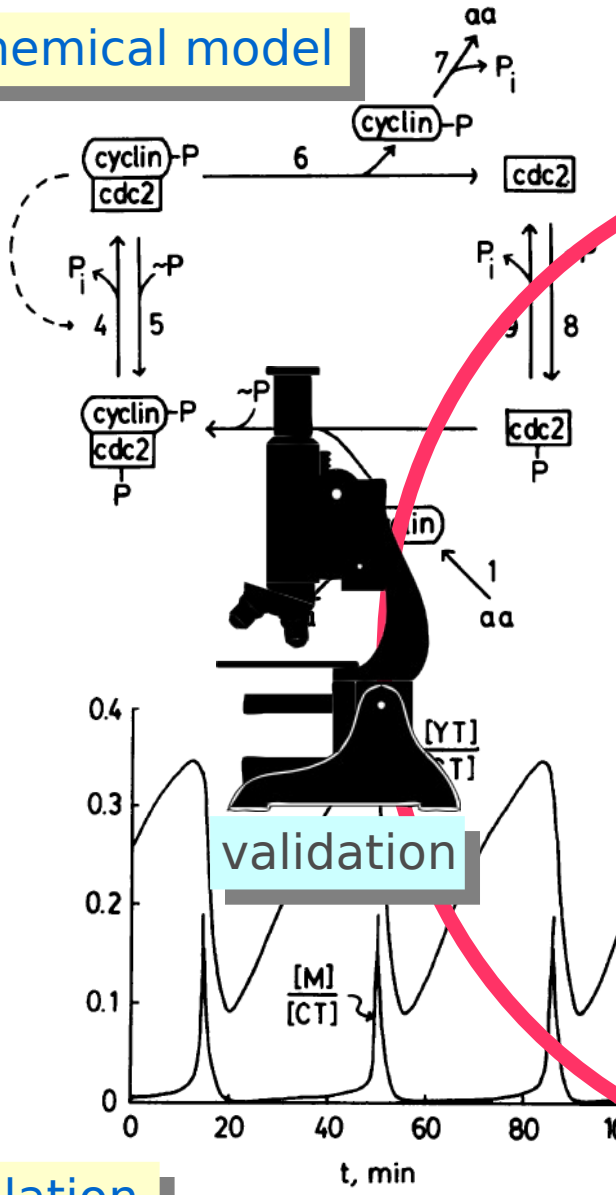
computational model

Tyson et al (1991) PNAS 88(1):7328-32

The Computational Systems Biology loop

biochemical model

mathematical model



validation

parameterisation

$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$

$d[CP]/dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP]$

$d[pM]/dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M]$

$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$

$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$

$d[YP]/dt = k_6[M] - k_9[YP]$

Parameter	Value	Notes
$k_1[aa]/[CT]$	0. min^{-1}	*
k_2	0	†
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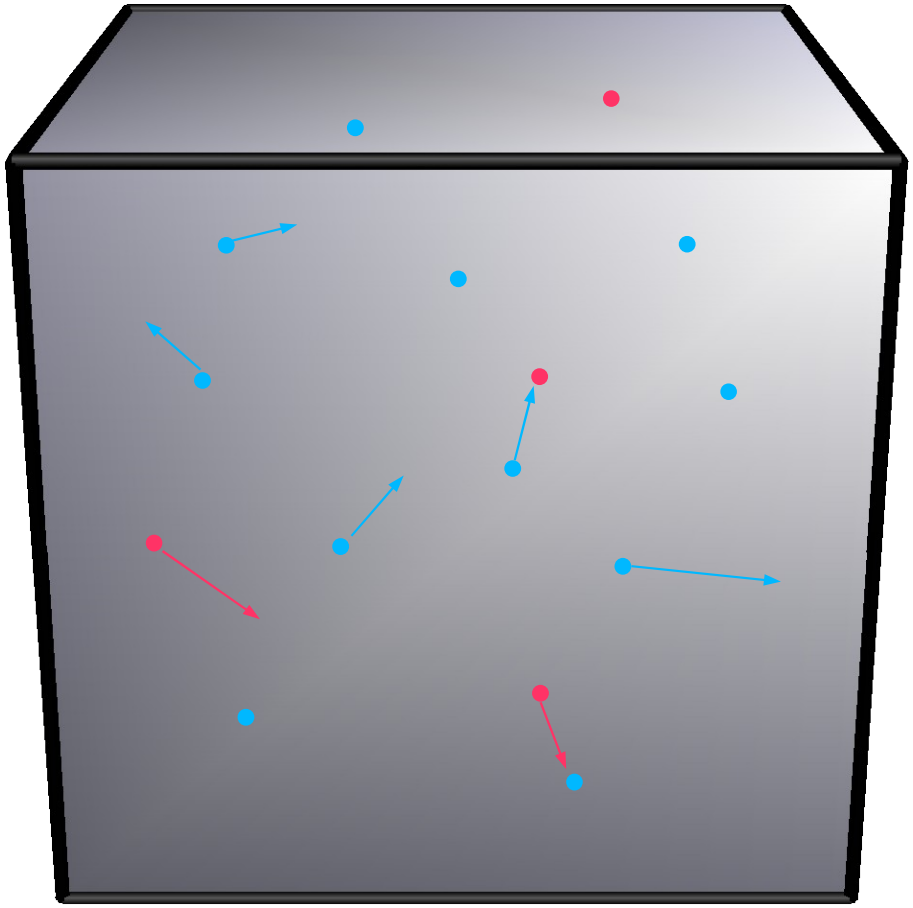
k_4		
k_4'		
$k_5[\sim P]$	0	‡
k_6	0.1–10 m n^{-1} (adjustable)	
k_7	0.6 mi n^{-1}	†
$k_8[\sim P]$	>> k_9	§
k_9	> k_6	§

simulation

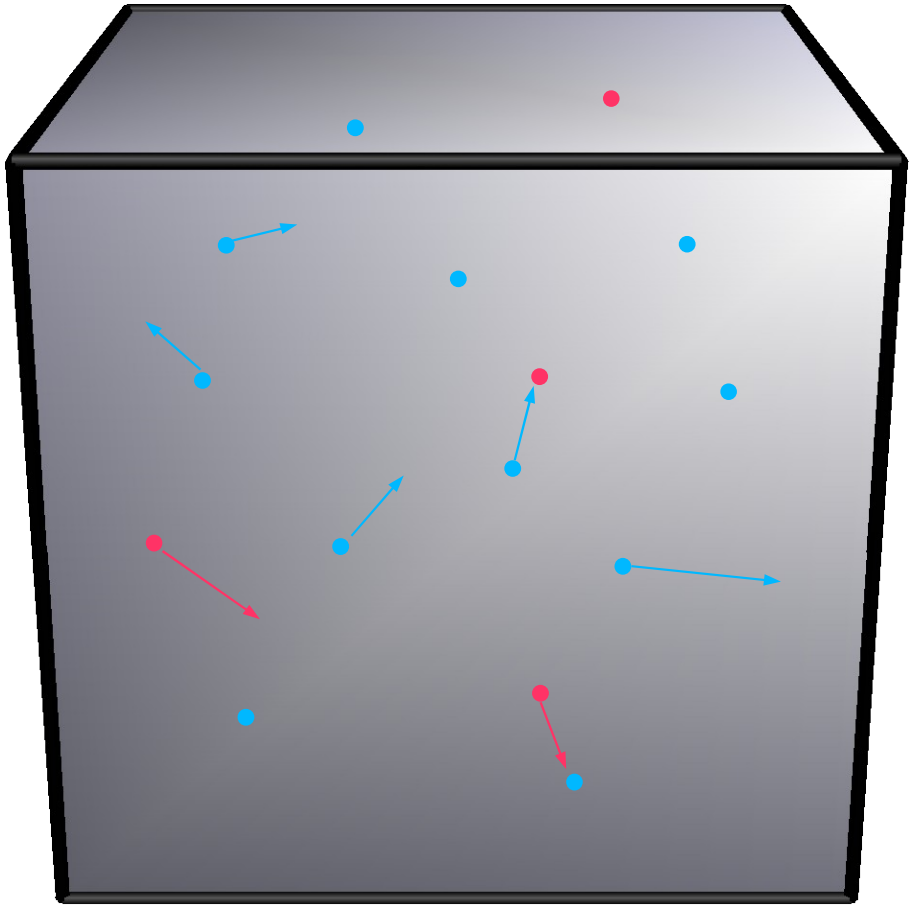
computational model

Tyson et al (1991) PNAS 88(1):7328-32

Statistical physics and chemical reaction

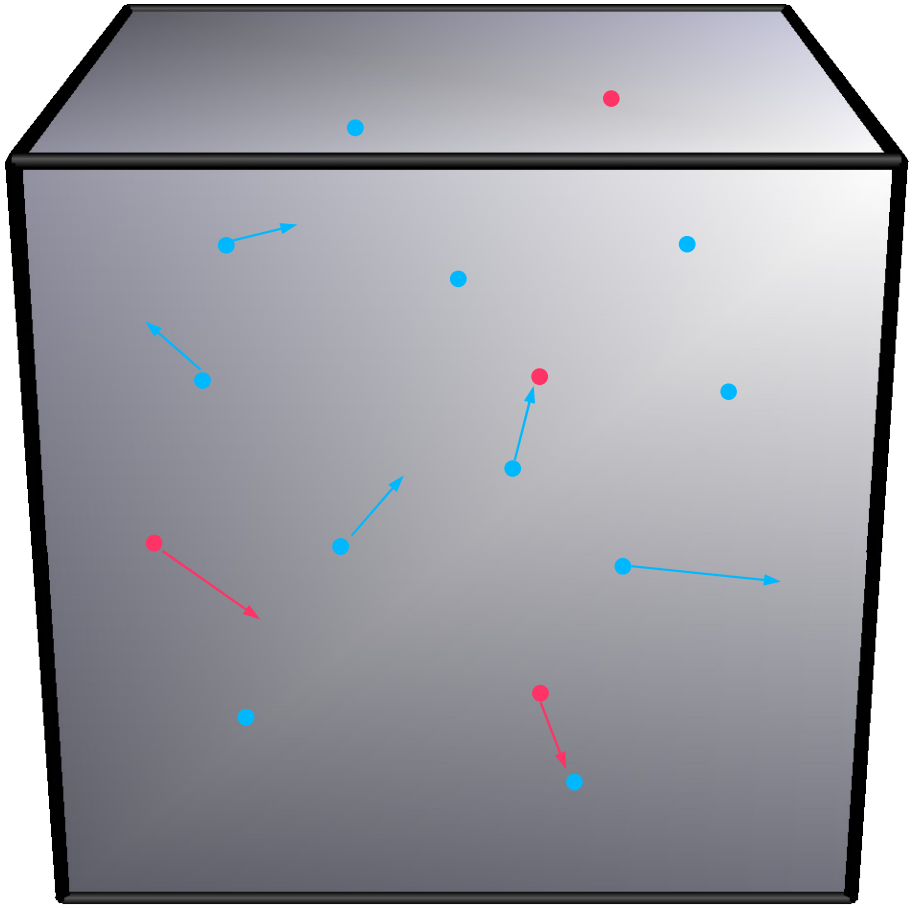


Statistical physics and chemical reaction



$$P(\bullet) \propto \frac{n(\bullet)}{V} = [\bullet]$$

Statistical physics and chemical reaction



$$P(\bullet) \propto \frac{n(\bullet)}{V} = [\bullet]$$

$$P(\text{reaction } \bullet + \bullet) = P(\bullet) \times P(\bullet) \times P(\bullet \text{ reacts with } \bullet)$$

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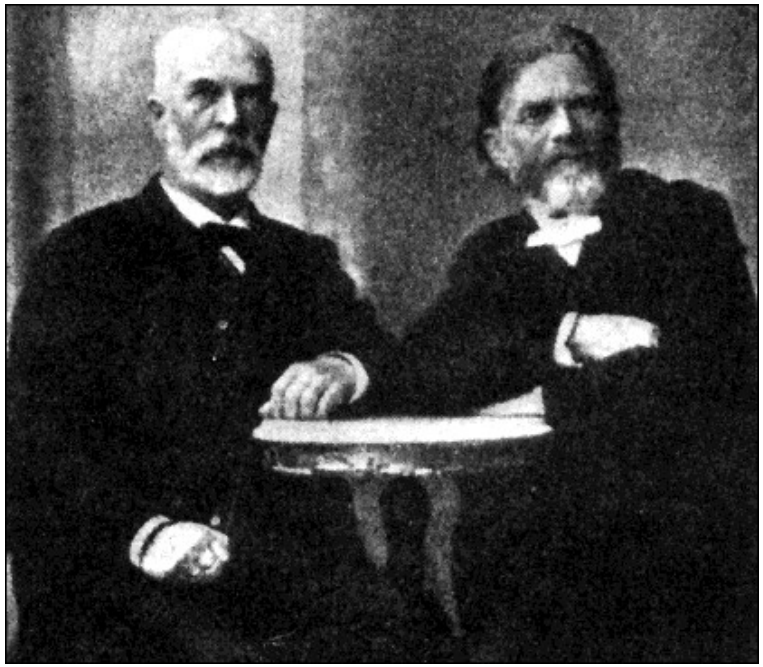
Law of Mass Action

Waage and Guldberg (1864)



activity

rate-constant

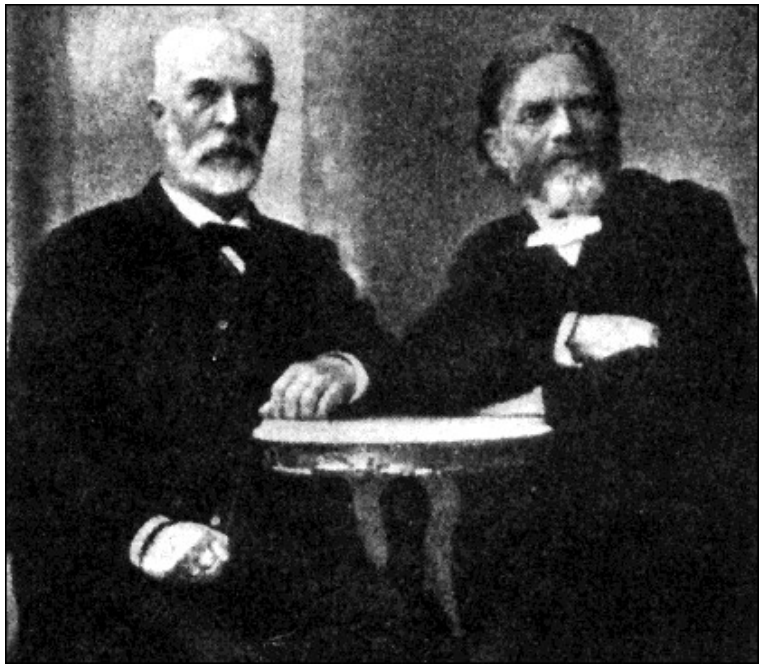
stoichiometry

$$v = k \cdot \prod_i a_i^{n_i}$$

velocity

Law of Mass Action

Waage and Guldberg (1864)



activity

rate-constant

stoichiometry

$$v = k \cdot \prod_i a_i^{n_i}$$

velocity

$$v = k \cdot \prod_i P_i^{n_i}$$

velocity in reaction events per unit of time

$$v = k \cdot \prod_i [X_i]^{n_i}$$

Evolution of a reactant

- Velocity multiplied by stoichiometry
- negative if consumption, positive if production
- Example of a unimolecular reaction $x \xrightarrow{k} y$

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$$\frac{d[x]}{dt} = -1 \cdot v = -1 \cdot k \cdot [x]$$

$$\frac{d[y]}{dt} = +1 \cdot v = +1 \cdot k \cdot [x]$$

Evolution of a reactant

- Velocity multiplied by stoichiometry
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- Example of a unimolecular reaction $x \xrightarrow{k} y$

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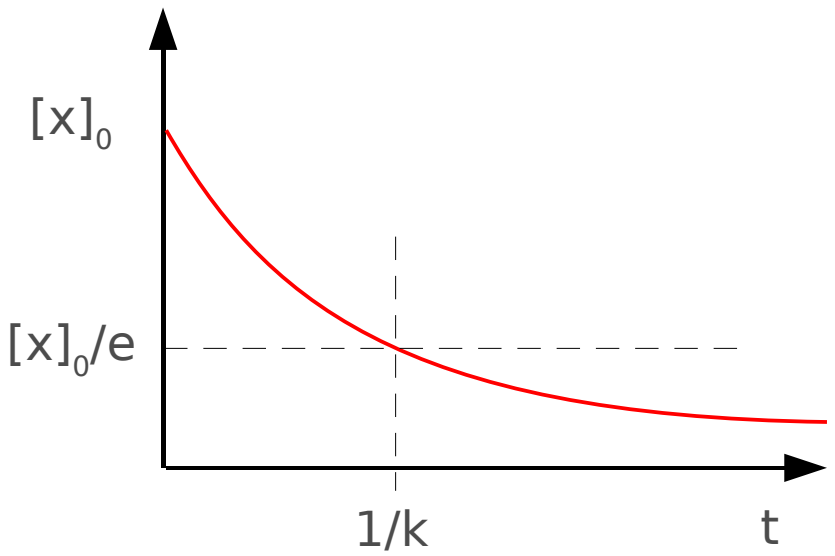
$$\frac{d[y]}{dt} = +1 \cdot v = +1 \cdot k \cdot [x]$$

$$x(t) = [x]_0 \cdot e^{-kt}$$



Reversible reaction

$$2x \underset{k2}{\overset{k1}{\rightleftharpoons}} y$$ is equivalent to

$$2x \rightarrow y; v1 = k1 \cdot [x]^2$$

$$y \rightarrow 2x; v2 = k2 \cdot [y]$$

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$$2x \rightarrow y; v1 = k1 \cdot [x]^2$$

$$y \rightarrow 2x; v2 = k2 \cdot [y]$$

$$\frac{d[x]}{dt} = -2 \cdot v1 + 2 \cdot v2 = -2 \cdot k1 \cdot [x]^2 + 2 \cdot k2 \cdot [y]$$

$$\frac{d[y]}{dt} = +1 \cdot v1 - 1 \cdot v2 = +1 \cdot k1 \cdot [x]^2 - 1 \cdot k2 \cdot [y]$$

General expression

$$\frac{d[x]}{dt} = \sum_j (n_j \cdot k_j \cdot \prod_i [x_i]^{n_{ij}})$$

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$$\frac{d[x]}{dt} = \sum_j (n_j \cdot k_j \cdot \prod_i [x_i]^{n_{ij}})$$

$$\dot{X} = N \cdot V$$

V: vector of velocities, N: matrix of stoichiometries

Example of an enzymatic reaction

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

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$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

$$\begin{aligned}
d[S]/dt &= -k_1[E][S] + k_2[ES] \\
d[P]/dt &= +k_3[ES] \\
d[E]/dt &= -k_1[E][S] + k_2[ES] + k_3[ES] \\
d[ES]/dt &= +k_1[E][S] - k_2[ES] - k_3[ES]
\end{aligned}$$

Example of an enzymatic reaction

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d[E]/dt &= -k_1[E][S] + k_2[ES] + k_3[ES] \\
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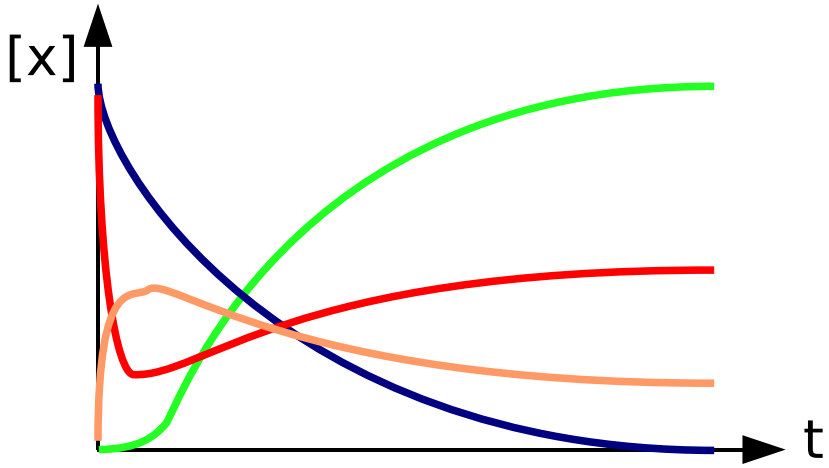
\end{aligned}$$



Not feasible in general

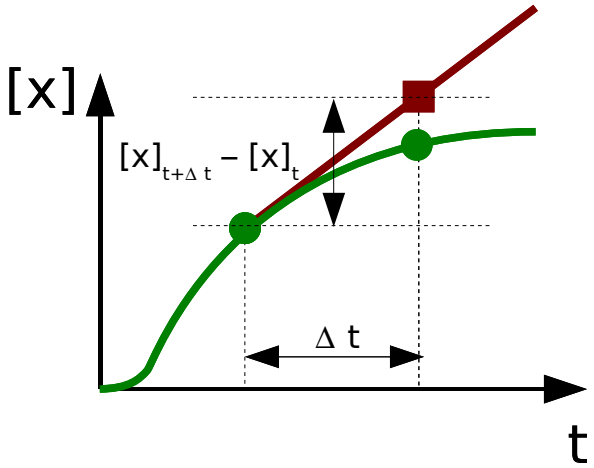
→ Numerical integration

Numerical integration

Euler method:

$$d[x]/dt \approx ([x]_{t+\Delta t} - [x]_t) / \Delta t$$

$$[x]_{t+\Delta t} \approx [x]_t + d[x]/dt \,.\, \Delta t$$



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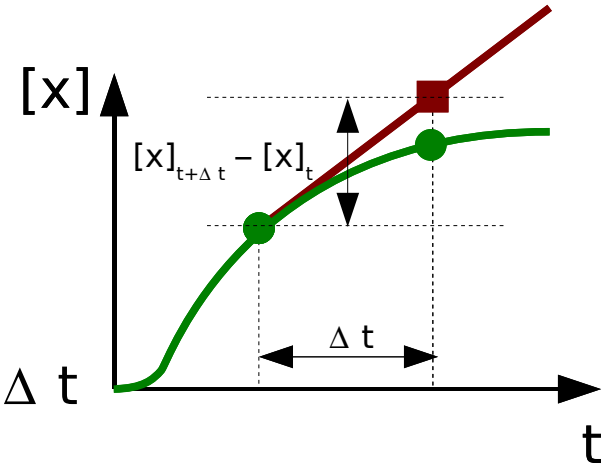


$$[P]_{t+\Delta t} = [P]_t + k_3[ES]_t \,.\, \Delta t$$

$$[E]_{t+\Delta t} = [E]_t + ((k_2 + k_3)[ES]_t - k_1[E]_t[S]_t) \,.\, \Delta t$$

$$[S]_{t+\Delta t} = [S]_t + (k_2[ES]_t - k_1[E]_t[S]_t) \,.\, \Delta t$$

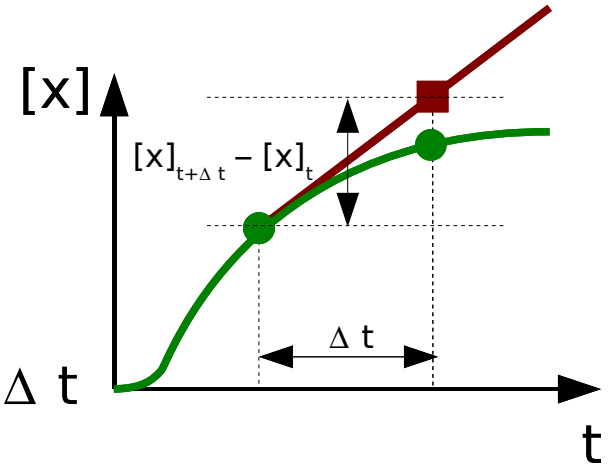
$$[ES]_{t+\Delta t} = [S]_t + (k_1[E]_t[S]_t - (k_2+k_3)[ES]_t) \,.\, \Delta t$$

Numerical integration

Euler method:

$$d[x]/dt \approx ([x]_{t+\Delta t} - [x]_t) / \Delta t$$

$$[x]_{t+\Delta t} \approx [x]_t + d[x]/dt \,.\, \Delta t$$



$$[P]_{t+\Delta t} = [P]_t + k_3[ES]_t \,.\, \Delta t$$

$$[E]_{t+\Delta t} = [E]_t + ((k_2 + k_3)[ES]_t - k_1[E]_t[S]_t) \,.\, \Delta t$$

$$[S]_{t+\Delta t} = [S]_t + (k_2[ES]_t - k_1[E]_t[S]_t) \,.\, \Delta t$$

$$[ES]_{t+\Delta t} = [S]_t + (k_1[E]_t[S]_t - (k_2+k_3)[ES]_t) \,.\, \Delta t$$

4^{th} order Runge-Kutta:

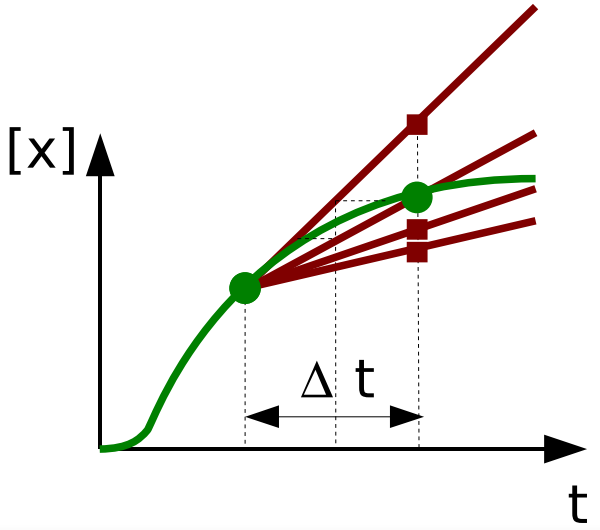
$$[x]_{t+\Delta t} = [x]_t + (F_1+2F_2+2F_3+F_4)/6 \,.\, \Delta t$$

with $F_1 = d[x]/dt = f([x], t)$

$F_2 = f([x]_t + \Delta t/2 \,.\, F_1, t + \Delta t/2)$

$F_3 = f([x]_t + \Delta t/2 \,.\, F_2, t + \Delta t/2)$

$F_4 = f([x]_t + \Delta t \,.\, F_3, t + \Delta t)$



Choose the right formalism

$$E + S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \underset{kcat'}{\overset{kcat}{\rightleftharpoons}} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E + P \qquad \frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

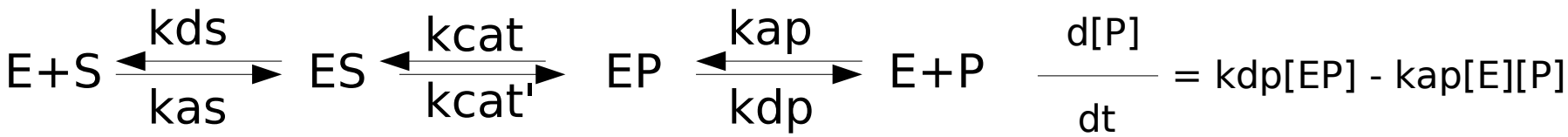
Choose the right formalism

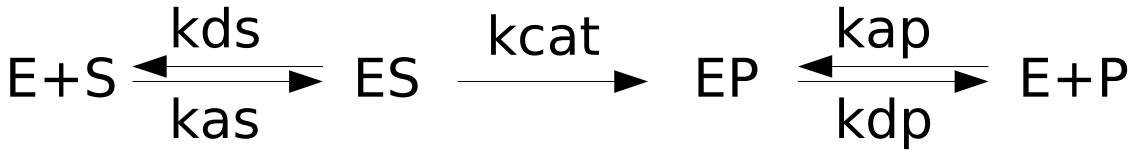
$$E+S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \underset{kcat'}{\overset{kcat}{\rightleftharpoons}} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E+P \qquad \frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

$$E+S \underset{kas}{\overset{kds}{\rightleftharpoons}} ES \xrightarrow{kcat} EP \underset{kdp}{\overset{kap}{\rightleftharpoons}} E+P$$

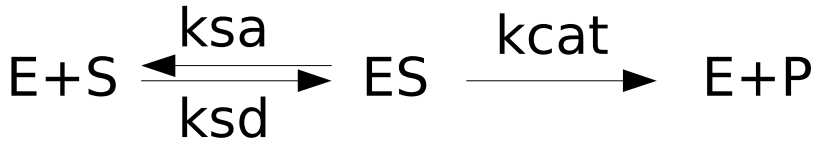
catalysis irreversible

Choose the right formalism



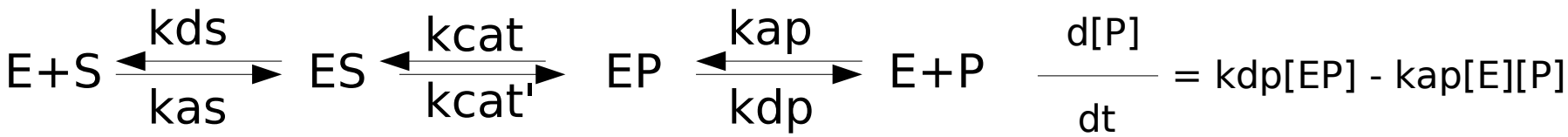


catalysis irreversible

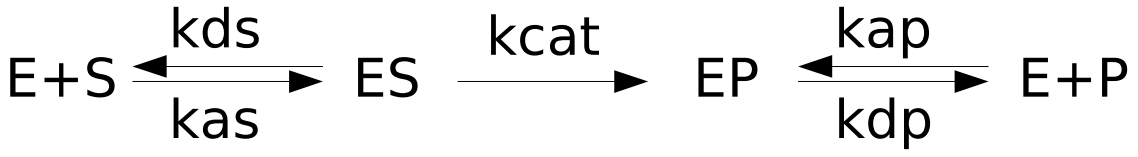


product is consumed
before rebinding

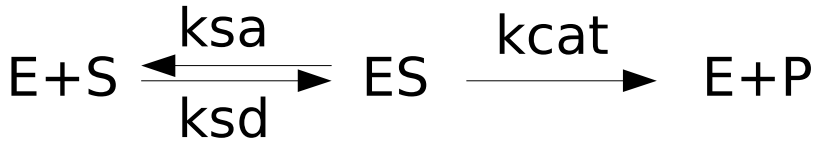
Choose the right formalism



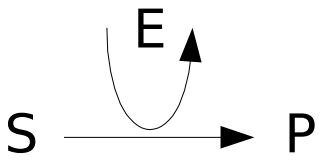
$$\frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$



catalysis irreversible



product is consumed before rebinding



steady-state

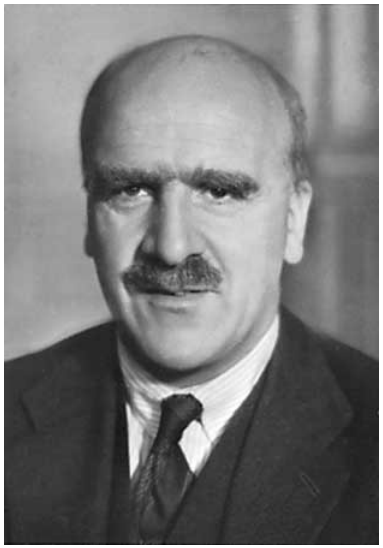
$$\frac{d[P]}{dt} = \frac{[E]\,kcat}{1 + \frac{Km}{[S]}}$$

Enzyme kinetics

Victor Henri (1903) Lois Générales de l'Action des Diastases. Paris, Hermann.

Leonor Michaelis, Maud Menten (1913). Die Kinetik der Invertinwirkung, Biochem. Z. 49:333-369

George Edward Briggs and John Burdon Sanderson Haldane (1925) A note on the kinetics of enzyme action, Biochem. J., 19: 338-339



Briggs-Haldane on Henri-Michaelis-Menten

$$E + S \underset{k_{-1}}{\overset{k1}{\rightleftharpoons}} ES \overset{k_2}{\rightarrow} E + P$$

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0$$

$$[ES] = \frac{k_1[E][S]}{k_{-1} + k_2}$$

$$K_m = \frac{k_{-1} + k_2}{k_1}$$

$$[ES] = \frac{[E][S]}{K_m}$$

$$\frac{d[P]}{dt} = k_2[ES]$$

$$[E] = [E_0] - [ES]$$

$$[ES]\frac{K_m}{[S]} = [E_0] - [ES]$$

$$[ES](1 + \frac{K_m}{[S]}) = [E_0]$$

$$[ES] = [E_0]\frac{1}{1 + \frac{K_m}{[S]}}$$

$$\frac{d[P]}{dt} = k_2[E_0]\frac{[S]}{K_m + [S]} = V_{max}\frac{[S]}{K_m + [S]}$$

Briggs-Haldane on Henri-Michaelis-Menten

$$E + S \underset{k_{-1}}{\overset{k1}{\rightleftharpoons}} ES \overset{k_2}{\rightarrow} E + P$$

$$\frac{d[P]}{dt} = k_2[ES]$$

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0$$

$$[E]=[E_0]-[ES]$$

steady-state!!!

$$[ES]\frac{K_m}{[S]} = [E_0] - [ES]$$

$$[ES] = \frac{k_1[E][S]}{k_{-1} + k_2}$$

$$[ES](1 + \frac{K_m}{[S]}) = [E_0]$$

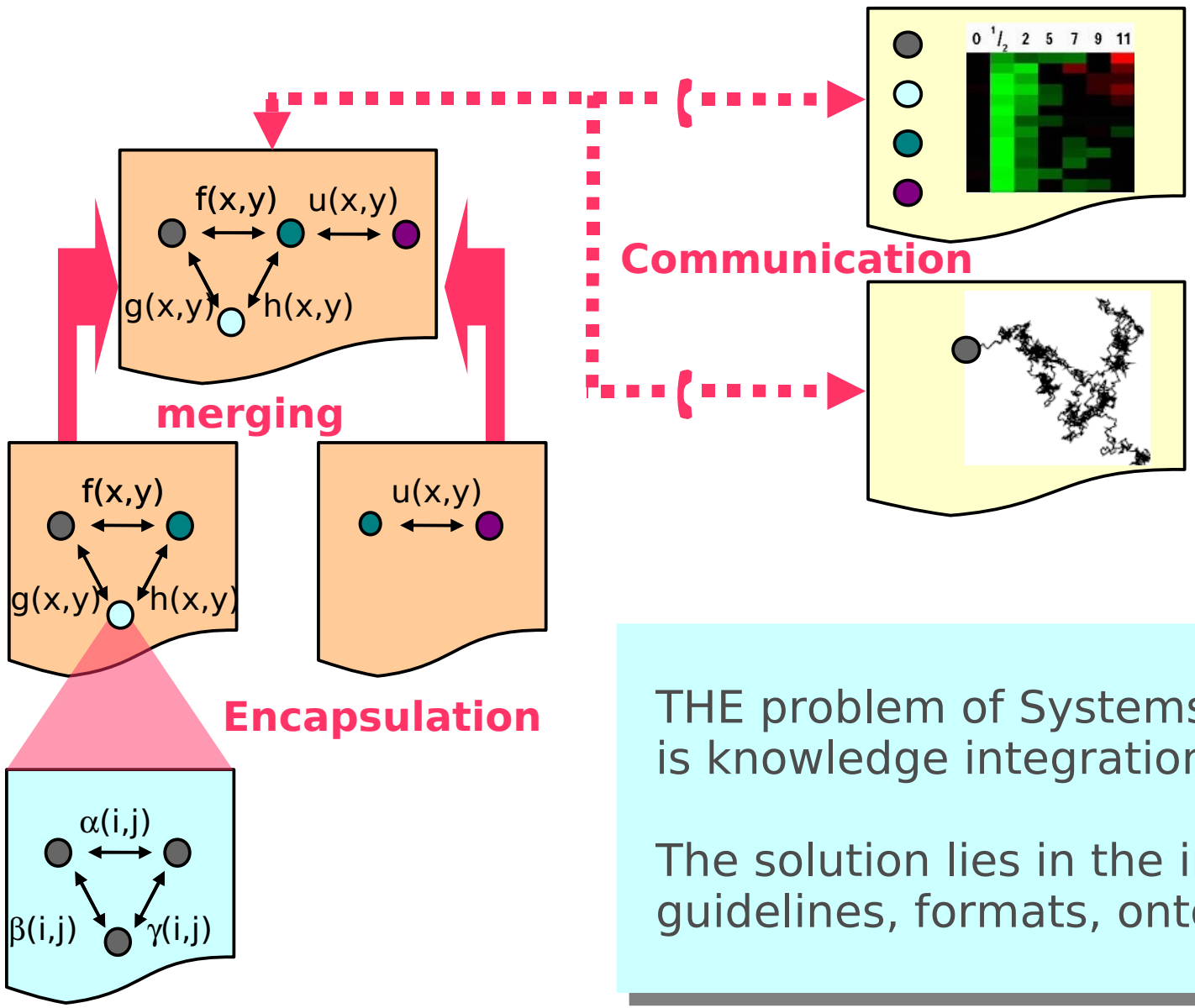
$$K_m = \frac{k_{-1} + k_2}{k_1}$$

$$[ES] = [E_0]\frac{1}{1 + \frac{K_m}{[S]}}$$

$$[ES] = \frac{[E][S]}{K_m}$$

$$\frac{d[P]}{dt} = k_2[E_0]\frac{[S]}{K_m + [S]} = V_{max}\frac{[S]}{K_m + [S]}$$

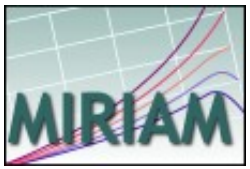
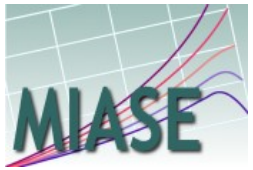
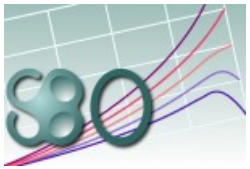
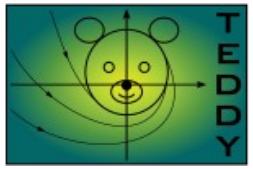
Integrative Systems Biology



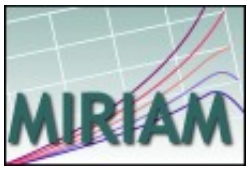
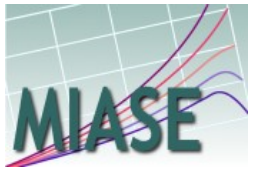
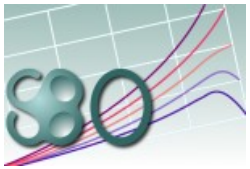
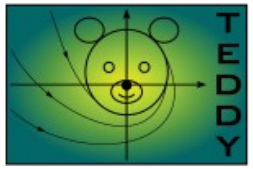
THE problem of Systems Biology is knowledge integration

The solution lies in the interfaces: guidelines, formats, ontologies

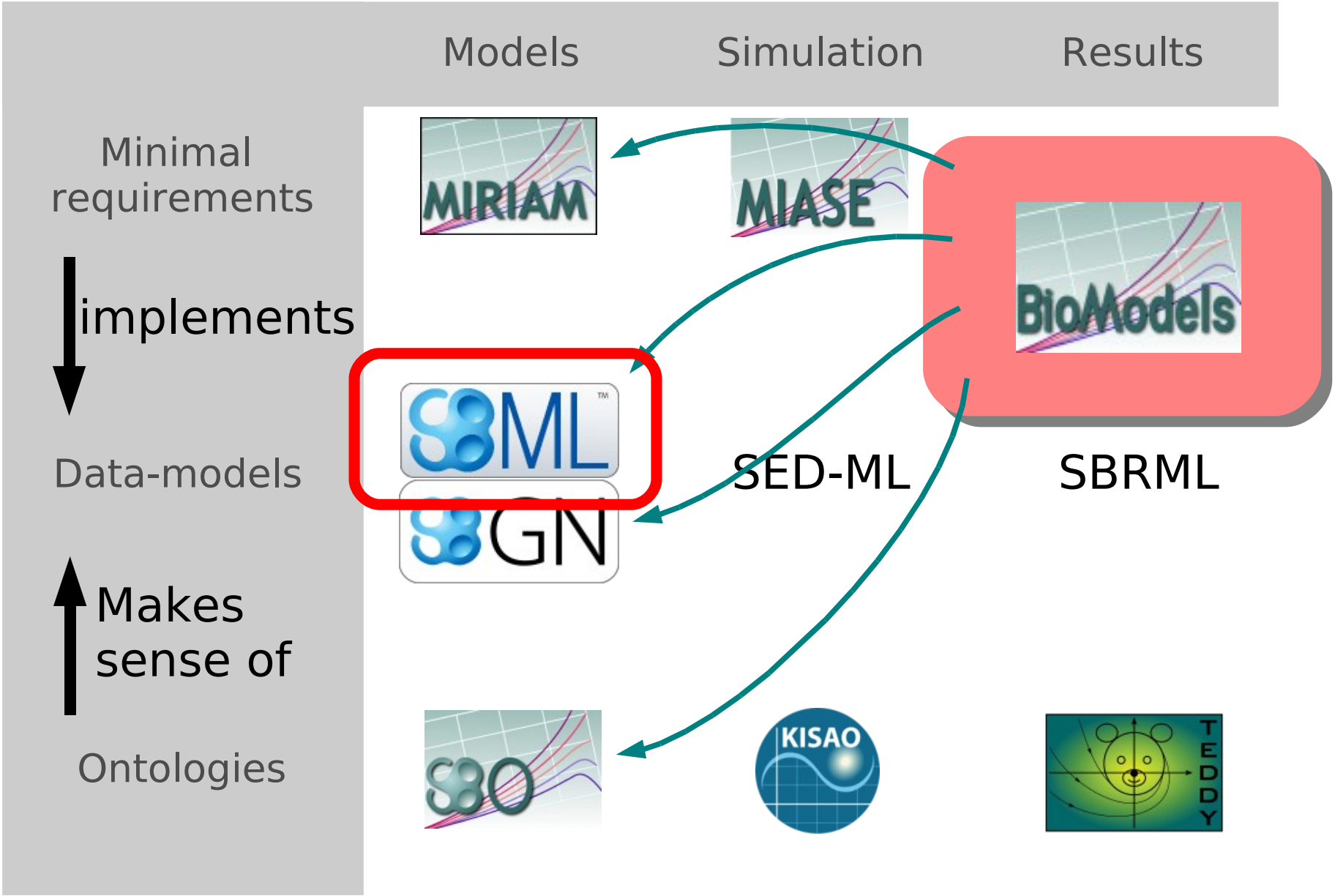
Mosaic of standards for Systems Biology

	Models	Simulation	Results
Minimal requirements			?
implements			
Data-models		SED-ML	SBRML
Makes sense of			
Ontologies			

Mosaic of standards for Systems Biology

	Models	Simulation	Results
Minimal requirements			?
implements			
Data-models		SED-ML	SBRML
Makes sense of			
Ontologies			

Mosaic of standards for Systems Biology



SBML.org — The Systems Biology Markup Language

The **Systems Biology Markup Language** (**SBML**) is a computer-readable format for representing models of biochemical reaction networks in software. It's applicable to models of metabolism, cell-signaling, and many others. SBML has been evolving since mid-2000 thanks to an international community of software developers and users. This website is the portal for the global SBML development effort; here you can find information about all aspects of SBML.

For the curious

What *is* SBML? Read our **basic introduction** and then perhaps browse the **mailing lists** to get a sense for what's currently going on in the world of SBML.

For modelers

Are you looking for ready-to-run software that supports SBML? Take a look at our **SBML Software Guide**. Are you instead looking for ready-to-use models? Visit the **BioModels Database**, where you can find hundreds of tried and tested models.

For software developers

Are you interested in developing SBML support for your software? Read our **basic introduction** and then the **SBML specifications** to understand how to use SBML. After that, you may want to look at **libSBML**, an API library supporting many programming languages.

Whether you use SBML as a modeler or a developer, we invite you to sign up for news updates either through our **RSS feed** or one of the **mailing lists**, and get involved with community efforts to help keep SBML improving. You

SBML News

LibSBML 3.3.2 released!

(3 Mar.'09) **LibSBML** is an API library for SBML. The new release fixes bugs and a memory leak in 3.3.1.

LibSBML 3.3.1 released!

(3 Feb.'09) **LibSBML** is an API library for SBML. The new release fixes a few bugs in 3.3.0, including a potential crasher.

LibSBML 3.3.0 released!

(21 Jan.'09) **LibSBML** is an API library for working with SBML. New features include support for SBML Level 2 Version 4.

Older news ...

Community News

SBW 2.7.9 released

(3 Mar.'09) The **Systems Biology Workbench** is a component-based application framework. This release improves simulator and auto-layout performance, and adds other features.

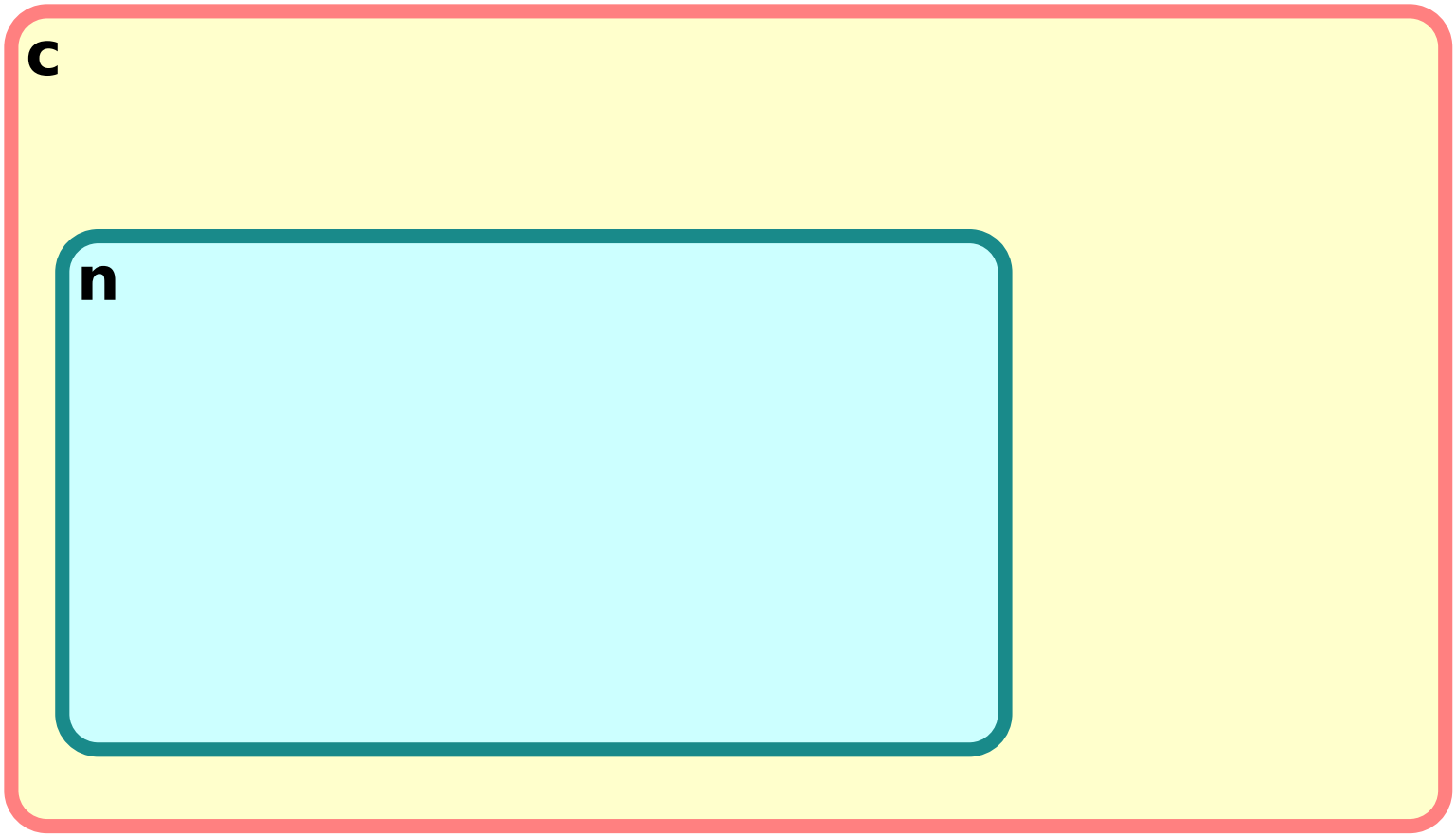
BioModels Database mirror @ Caltech

(26 Feb.'09) **BioModels Database**, a free, public resource, now has a mirror site at Caltech for better load balancing.

New version of SABIO-RK

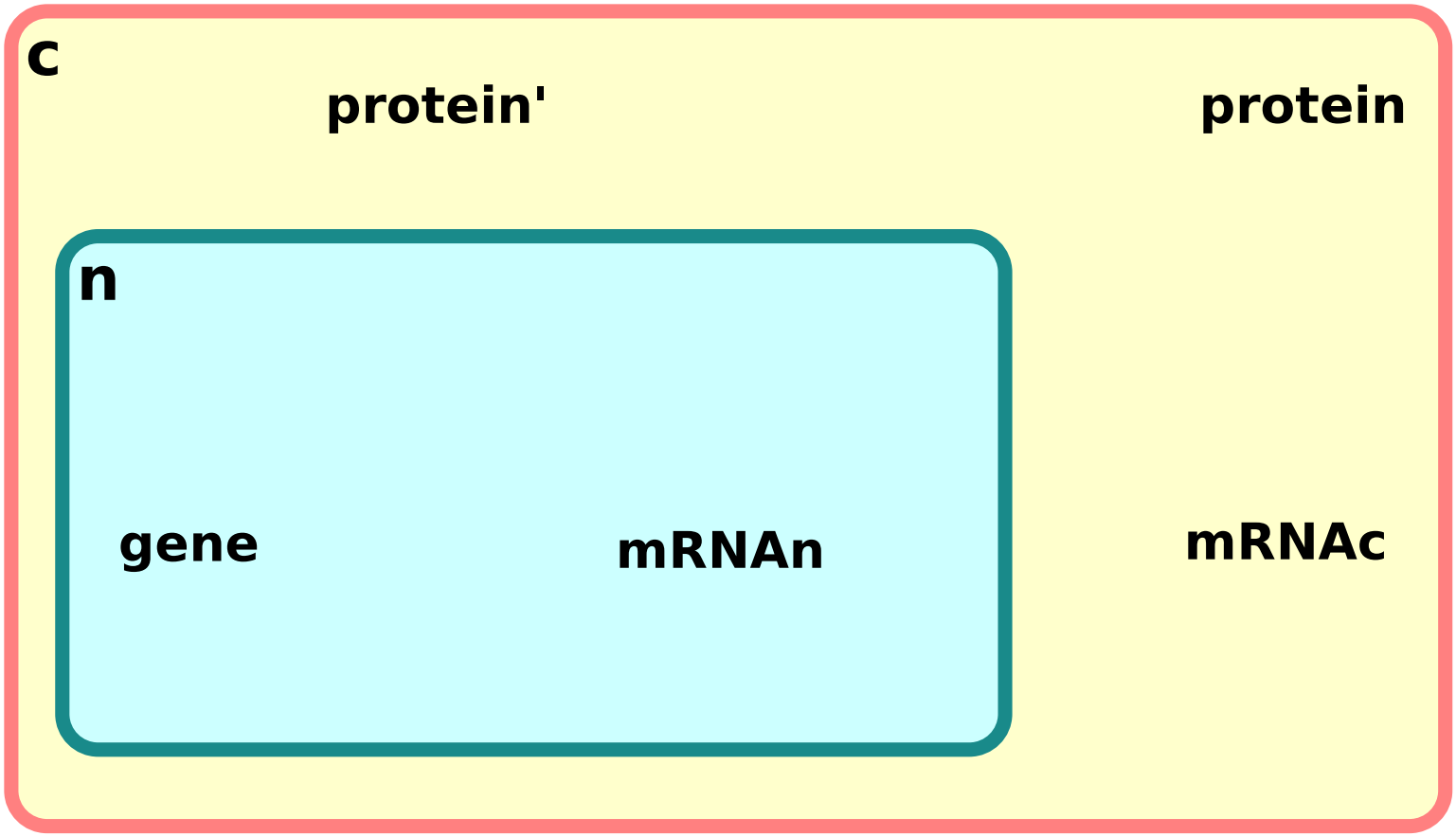
What can we encode in SBML?

containers (compartments)



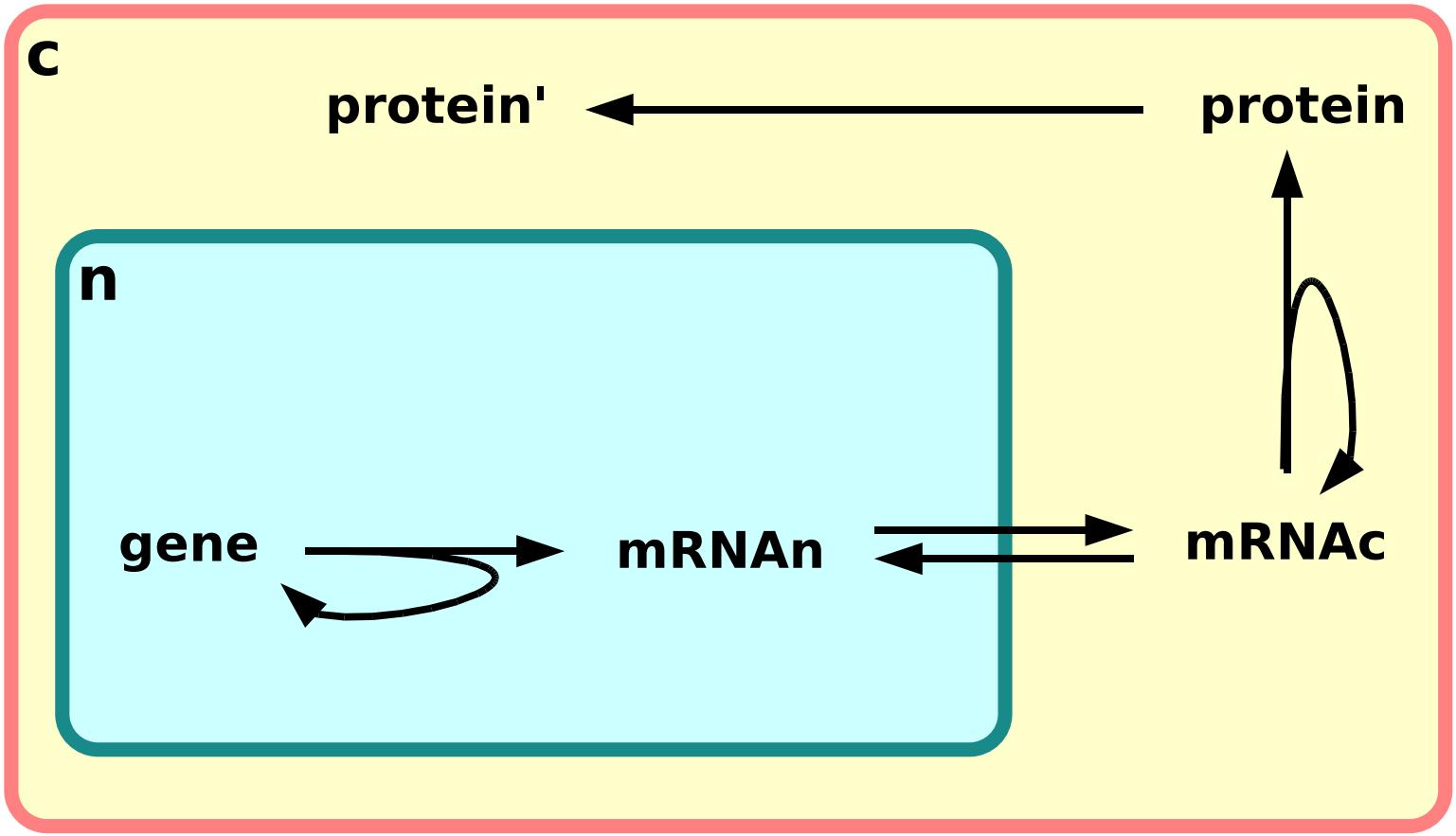
What can we encode in SBML?

entity pools (species)

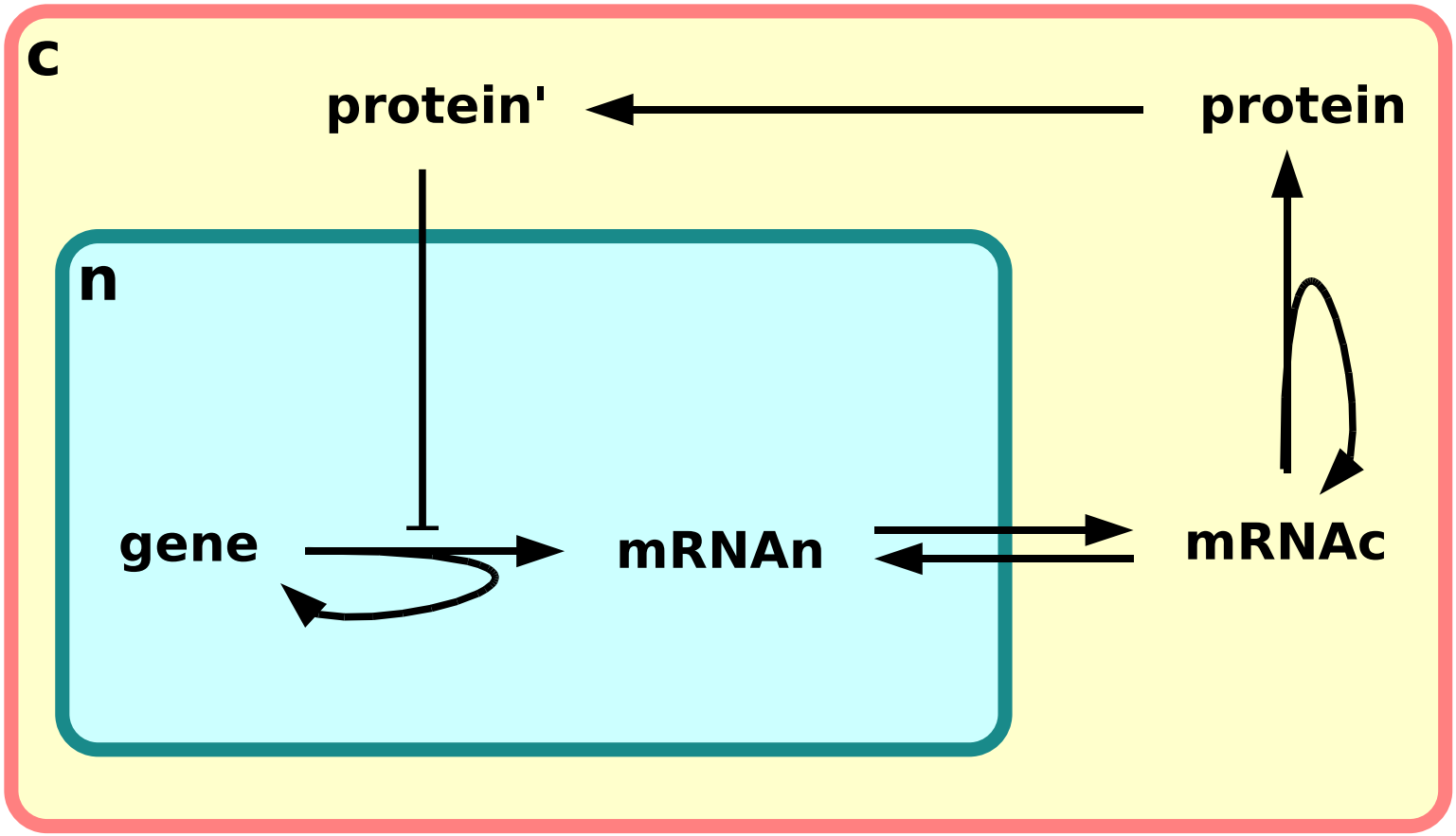


What can we encode in SBML?

reactions

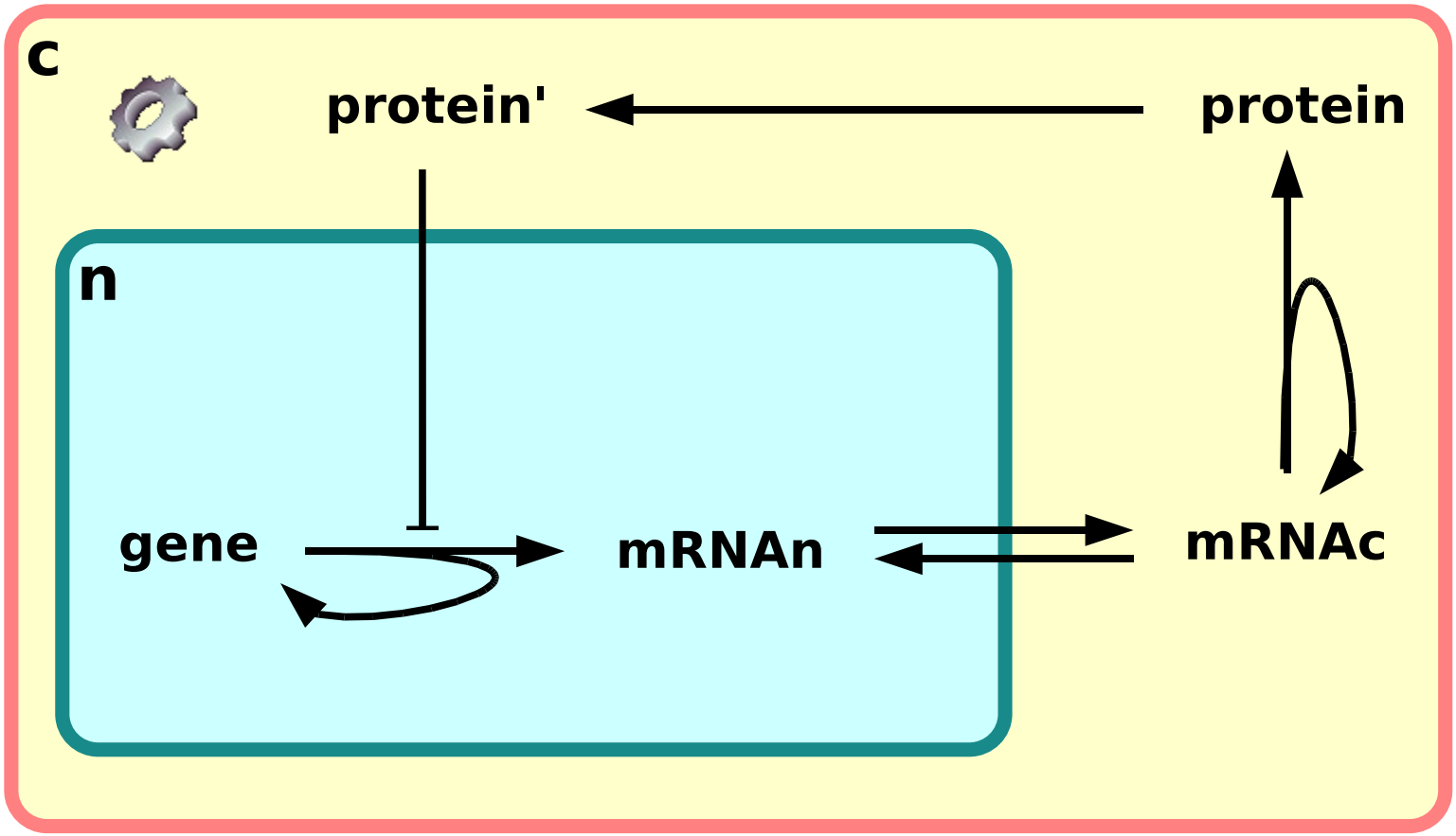


modulations



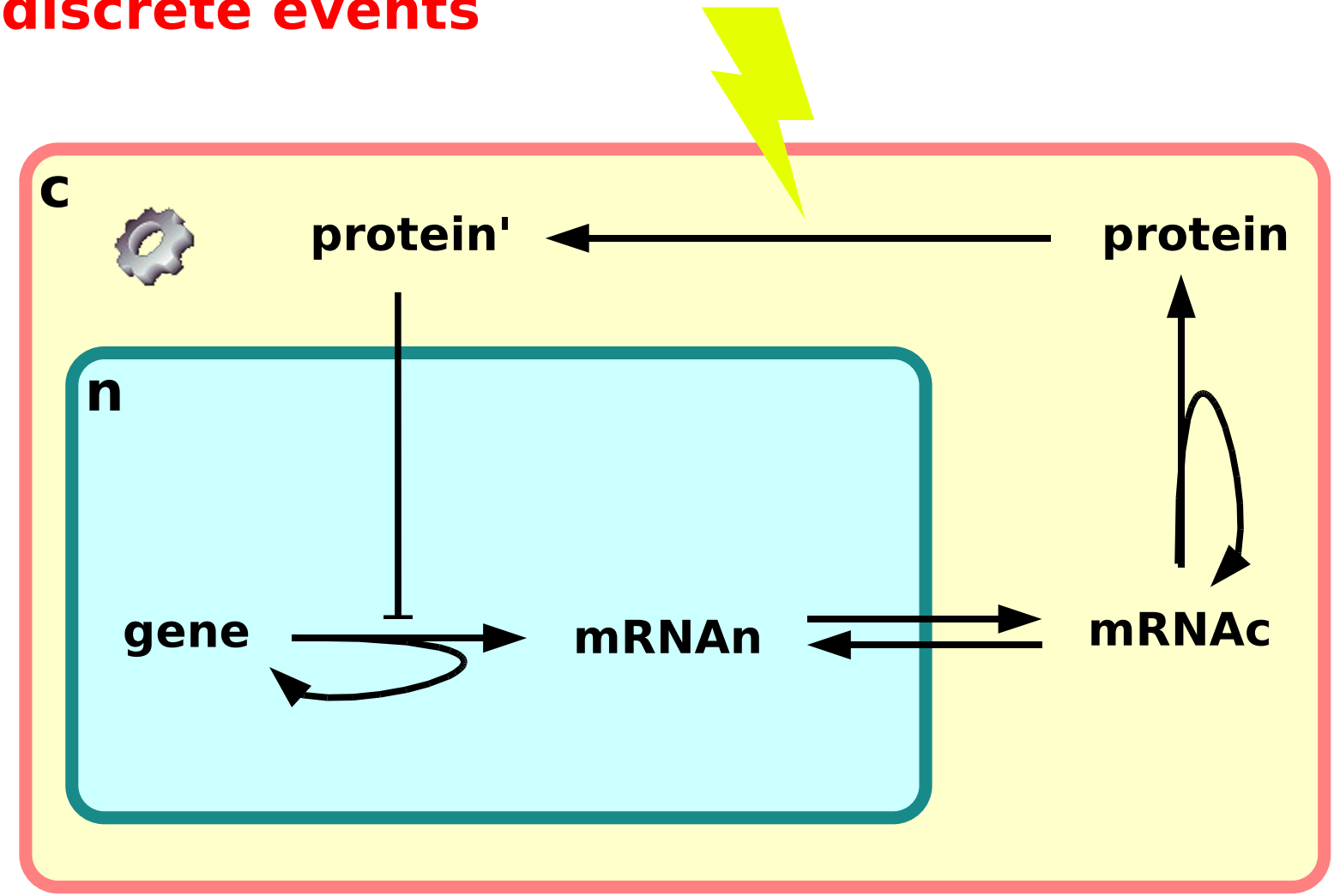
What can we encode in SBML?

arbitratry rules



What can we encode in SBML?

discrete events



A → B

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```


A more realistic example ...

```
<species
    id="A"
    name="α-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX"
    sboTerm="SBO:0000245" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:GO%3A0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```


SBML is not limited to biochemistry!

Rate Rules can describe the temporal evolution of any quantitative parameter, e.g. transmembrane voltage;

Events can describe any discontinuous change, e.g. neurotransmitter release or repolarisation;

A species is an entity participating to a reaction, **not always** a **chemical** entity:

- It can be a molecule
- It can be a cell
- It can be an organ
- It can be an organism

➔ Systems Biology is scale-free!

SBML roadmap

- SBML Levels are supposed to co-exist, last version is the official
  - Level 1 Version 1: 2 March 2001
  - Level 1 Version 2: 28 August 2003
  - Level 2 Version 1: 28 July 2003
  - Level 2 Version 2: 26 September 2006
  - Level 2 Version 3 release 1: 16 June 2007
  - Level 2 Version 4: 22 December 2008

conversion using libSBML

- Backward compatibility within Level
- Unambiguous and bug-free specification requires heavy work ... 166 pages, single spacing, 10pt, small margin.

A glimpse of SBML Level 3

Modular SBML, with core + optional packages

- Core package – specification under discussion
- Graph Layout – specification finalised
- Model composition – specification under discussion
- Complex species – specification under discussion
- Qualitative models – specification under discussion
- Graph rendering – specification proposed
- Distributions and changes - specification proposed
- Arrays and sets – specifications proposed
- Geometry - needed
- Spatial diffusion – needed
- Dynamic structures - needed

???

What is a “paradigm”?

- Thomas Kuhn: Set of practices that define a scientific discipline during a particular period of time
  - *what* is to be observed and scrutinized
  - *which* questions are supposed to be asked and probed for answers in relation to this subject
  - *how* these questions are to be structured
  - *how* the results of scientific investigations should be interpreted
  - *how* is an experiment to be conducted, and what equipment is available to conduct the experiment.