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.

NEW GENERATION COMPUTING
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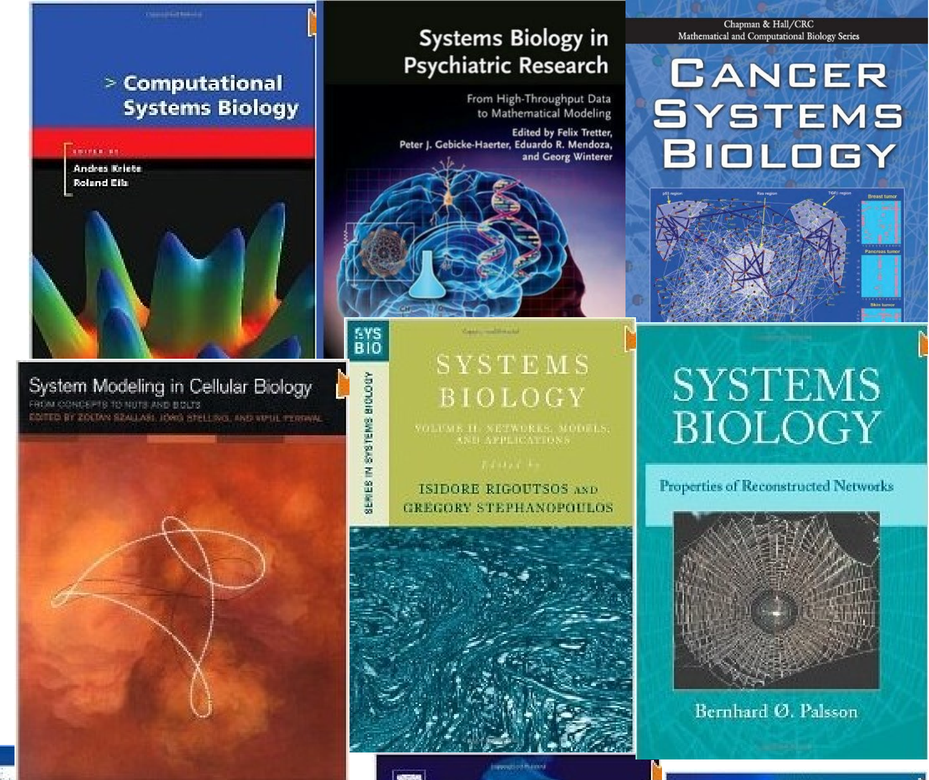
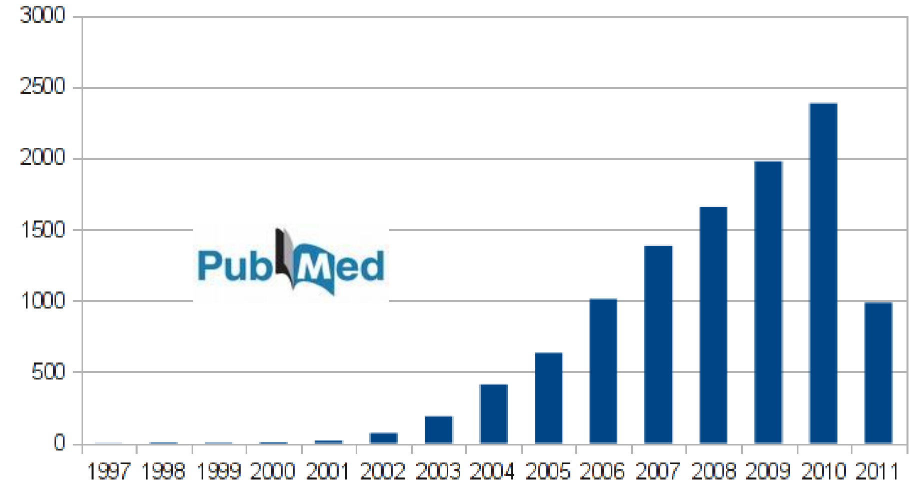


What is Systems Biology?



- 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)

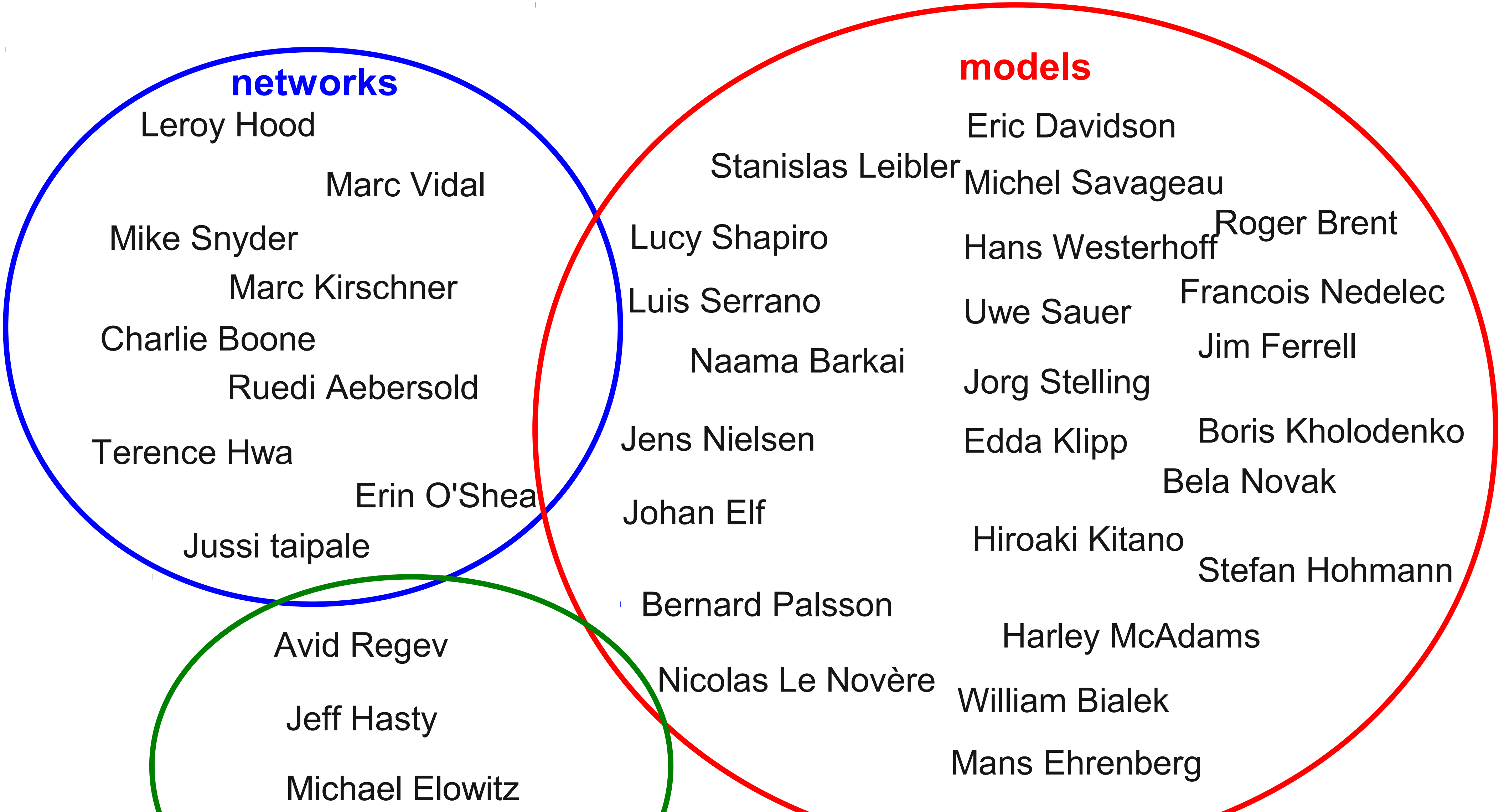
networks

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

Nobel Symposium on Systems Biology (June 2009)



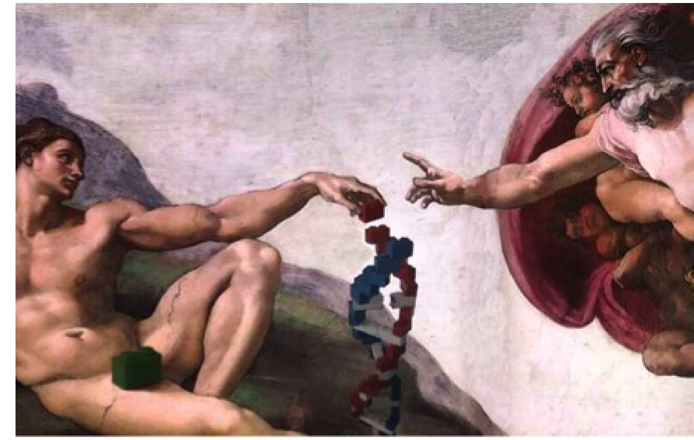
What happened to biology at the end of XX^th^ century?

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

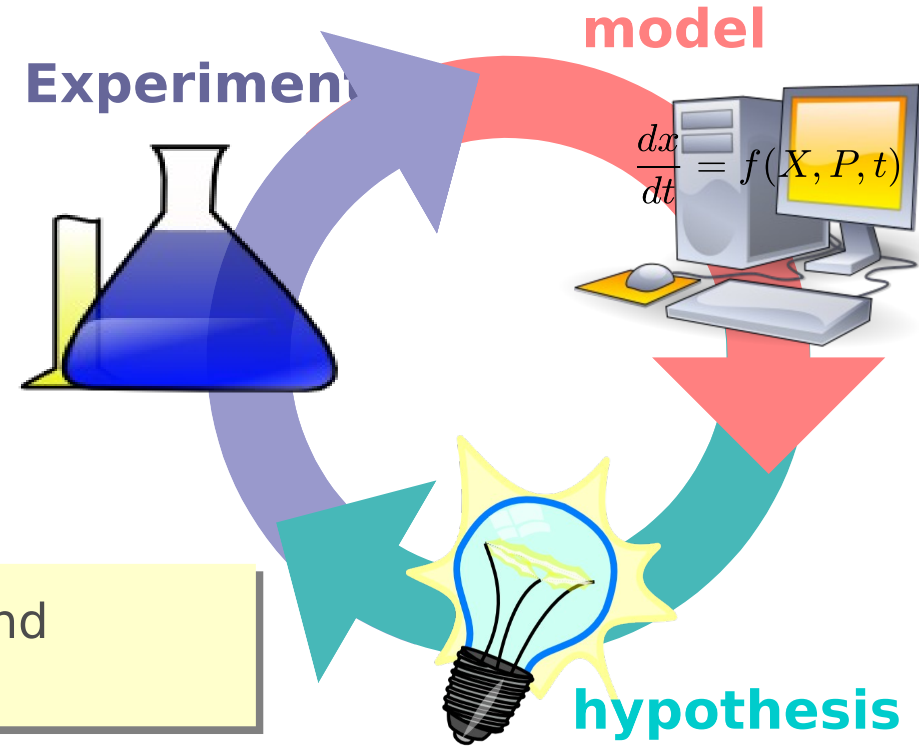
NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com

page discussion view source history teams

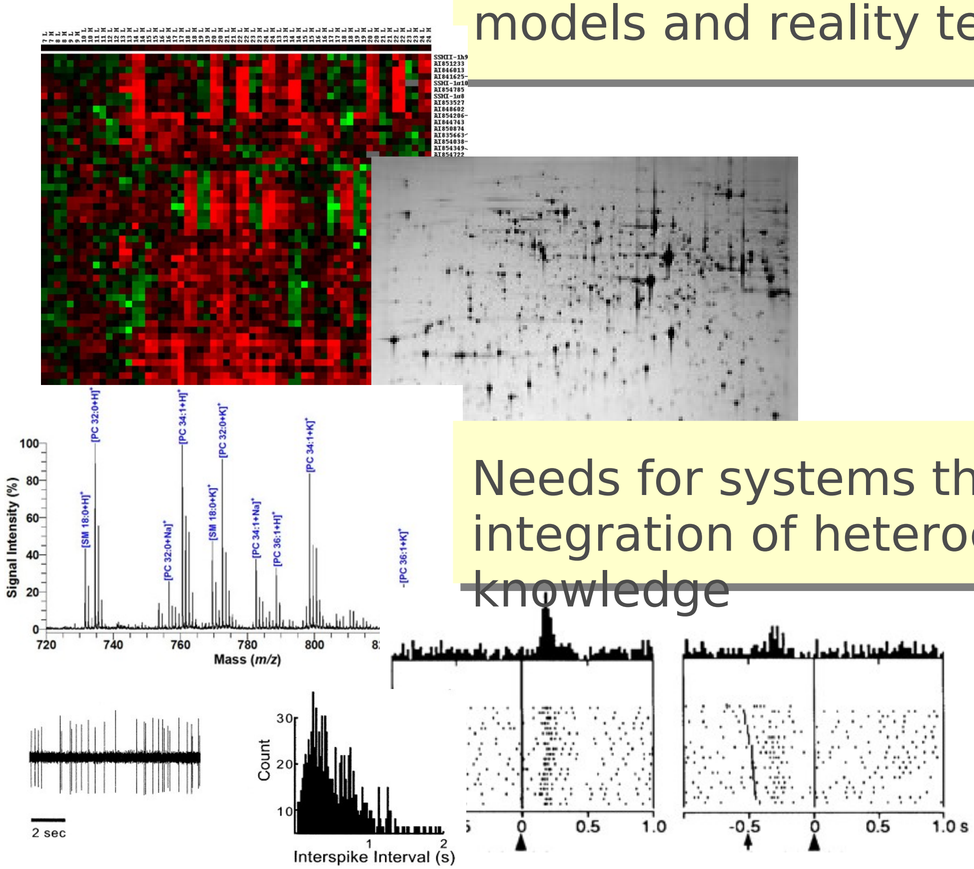
About

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

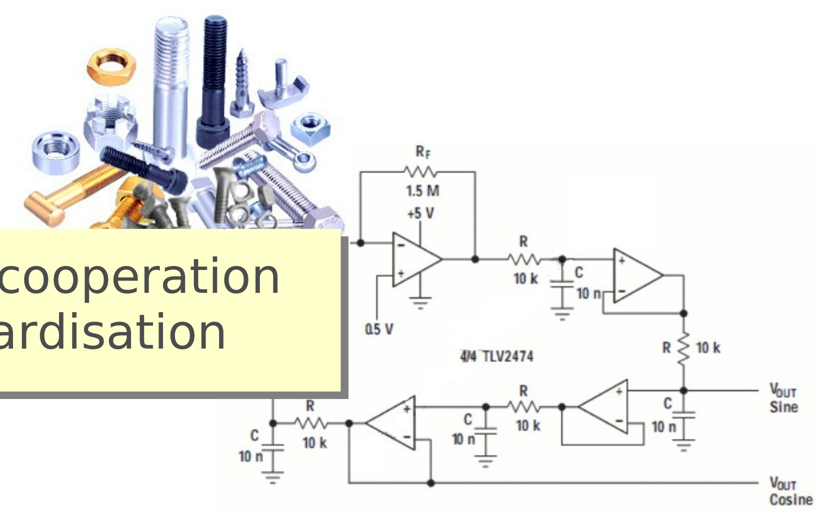
New way of doing biomedical research



Needs for interplay between models and reality tests



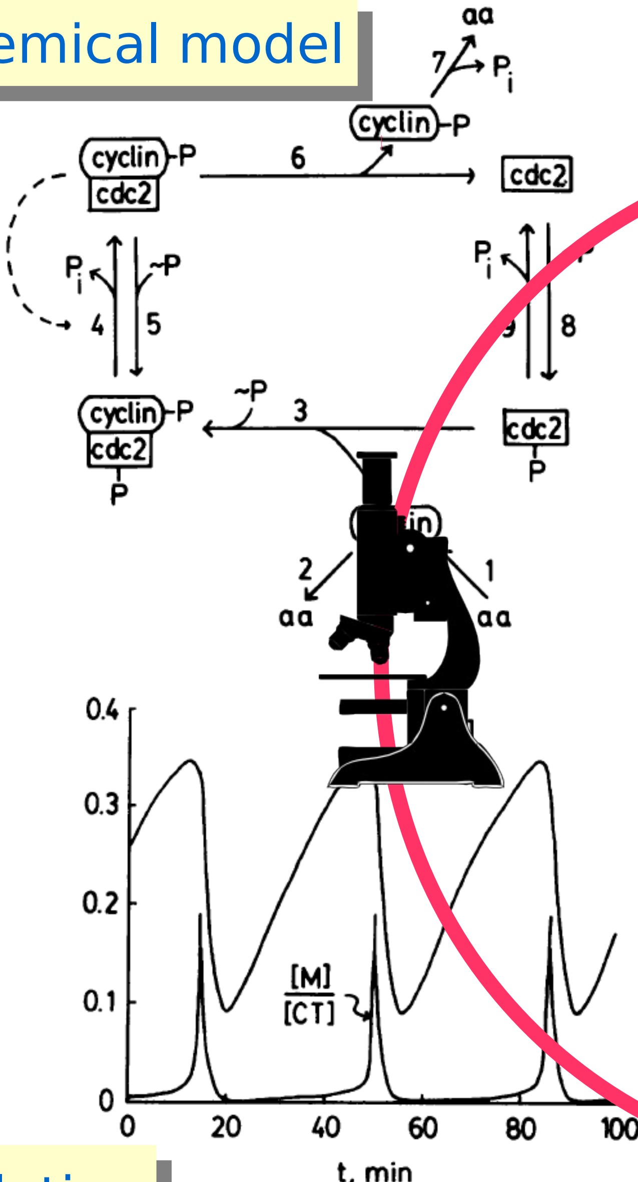
Needs for systems thinking and integration of heterogeneous knowledge



Needs for cooperation and standardisation

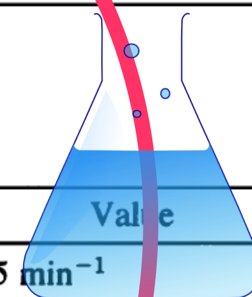
The models I am talking about

biochemical model



mathematical model

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



Parameter	Value	Notes
$k_1[\mathrm{aa}]/[\mathrm{CT}]$	0.015 min^{-1}	*
k_2	0	†
$k_3[\mathrm{CT}]$	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	$>> k_6$	§

simulation

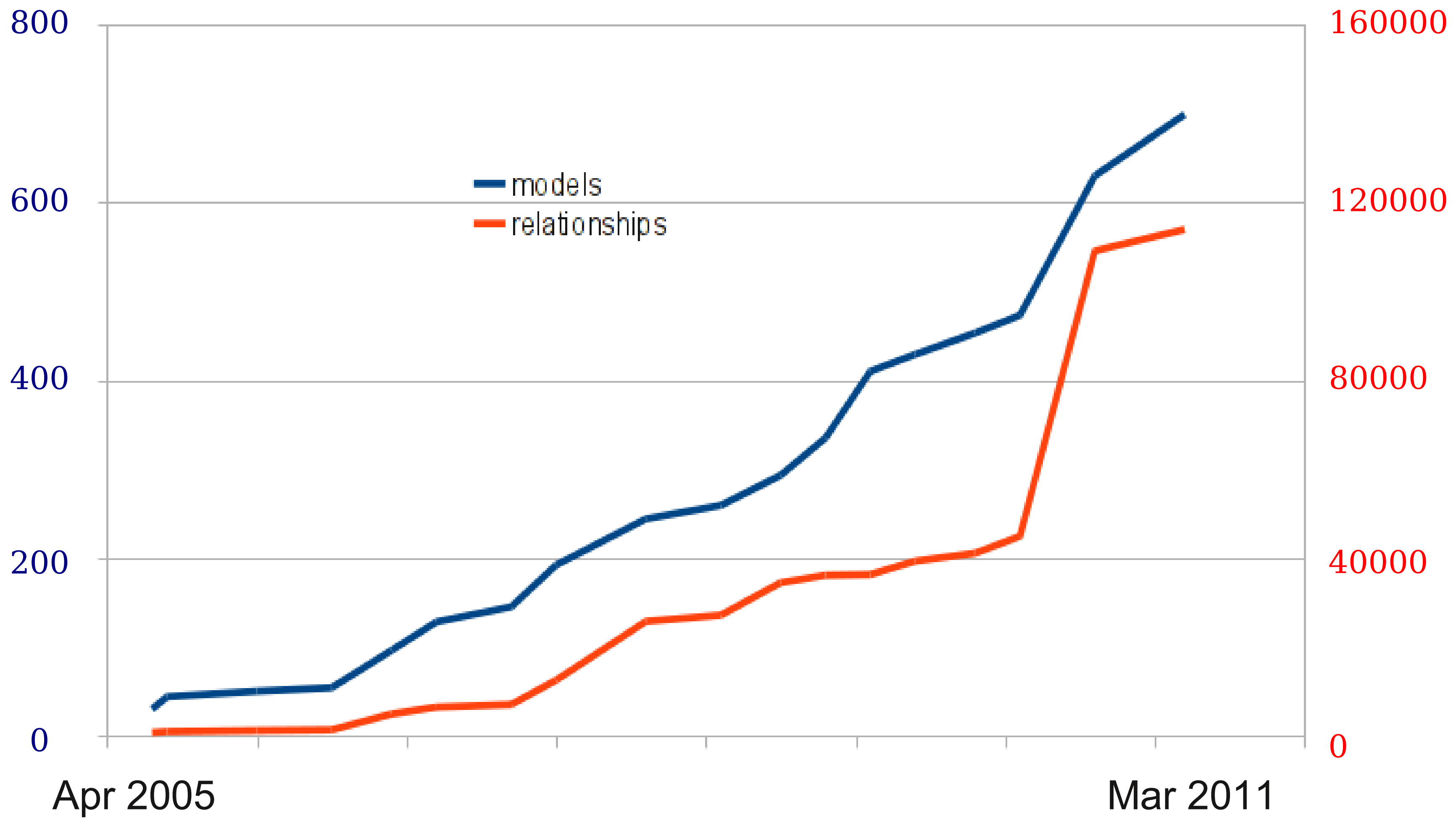
Tyson et al (1991) PNAS 88(1):7328-32

computational model

Computational modelling left the niches

- Metabolic networks Fung et al. A synthetic gene-metabolic oscillator. ***Nature*** 2005; Herrgård et al. A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. ***Nat Biotechnol*** 2008
- Signalling pathways Bray et al. Receptor clustering as a cellular mechanism to control sensitivity. ***Nature*** 1998; Bhalla ad Iyengar. Emergent properties of signaling pathways. ***Science*** 1998; Schoeberl et al. Computational modeling of the dynamics of the MAP kinase cascade activated by surface and internalized EGF receptors. ***Nat Biotechnol*** 2002; Hoffmann et. The IκB-NF-κB signaling module: temporal control and selective gene activation. ***Science*** 2002; Smith et al. Systems analysis of Ran transport. ***Science*** 2002; Bhalla et al. MAP kinase phosphatase as a locus of flexibility in a mitogen-activated protein kinase signaling network. ***Science*** 2002; Nelson et al. Oscillations in NF-κB Signaling Control the Dynamics of Gene Expression. ***Science*** 2004; Werner et al. Stimulus specificity of gene expression programs determined by temporal control of IKK activity. ***Science*** 2005; Sasagawa et al. Prediction and validation of the distinct dynamics of transient and sustained ERK activation. ***Nat Cell Biol*** 2005; Basak et al. A fourth IkappaB protein within the NF-κB signaling module. ***Cell*** 2007; McLean et al. Cross-talk and decision making in MAP kinase pathways. ***Nat Genet*** 2007; Ashall et al. Pulsatile Stimulation Determines Timing and Specificity of NF-κB-Dependent Transcription. ***Science*** 2009; Becker et al. Covering a broad dynamic range: information processing at the erythropoietin receptor. ***Science*** 2010
- Gene regulatory networks McAdams and Shapiro. Circuit simulation of genetic networks. ***Science*** 1995; Yue et al. Genomic cis-regulatory logic: Experimental and computational analysis of a sea urchin gene. ***Science*** 1998; Von Dassow et al. The segment polarity network is a robust developmental module. ***Nature*** 2000; Elowitz and Leibler. A synthetic oscillatory network of transcriptional regulators. ***Nature*** 2000; Shen-Orr et al, Network motifs in the transcriptional regulation network of Escherichia coli. ***Nat Genet*** 2002; Yao et al. A bistable Rb-E2F switch underlies the restriction point. ***Nat Cell Biol*** 2008; Friedland. Synthetic gene networks that count. ***Science*** 2009
- Pharmacometrics models Labrijn et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. ***Nat Biotechnol*** 2009
- Physiological models Noble. Modeling the heart from genes to cells to the whole organ. ***Science*** 2002; Izhikevich and Edelman. Large-scale model of mammalian thalamocortical systems. ***PNAS*** 2008
- Infectious diseases Perelson et al. HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. ***Science*** 1996; Nowak. Population dynamics of immune responses to persistent viruses. ***Science*** 1996; Neumann et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. ***Science*** 1998

Computational models on the rise

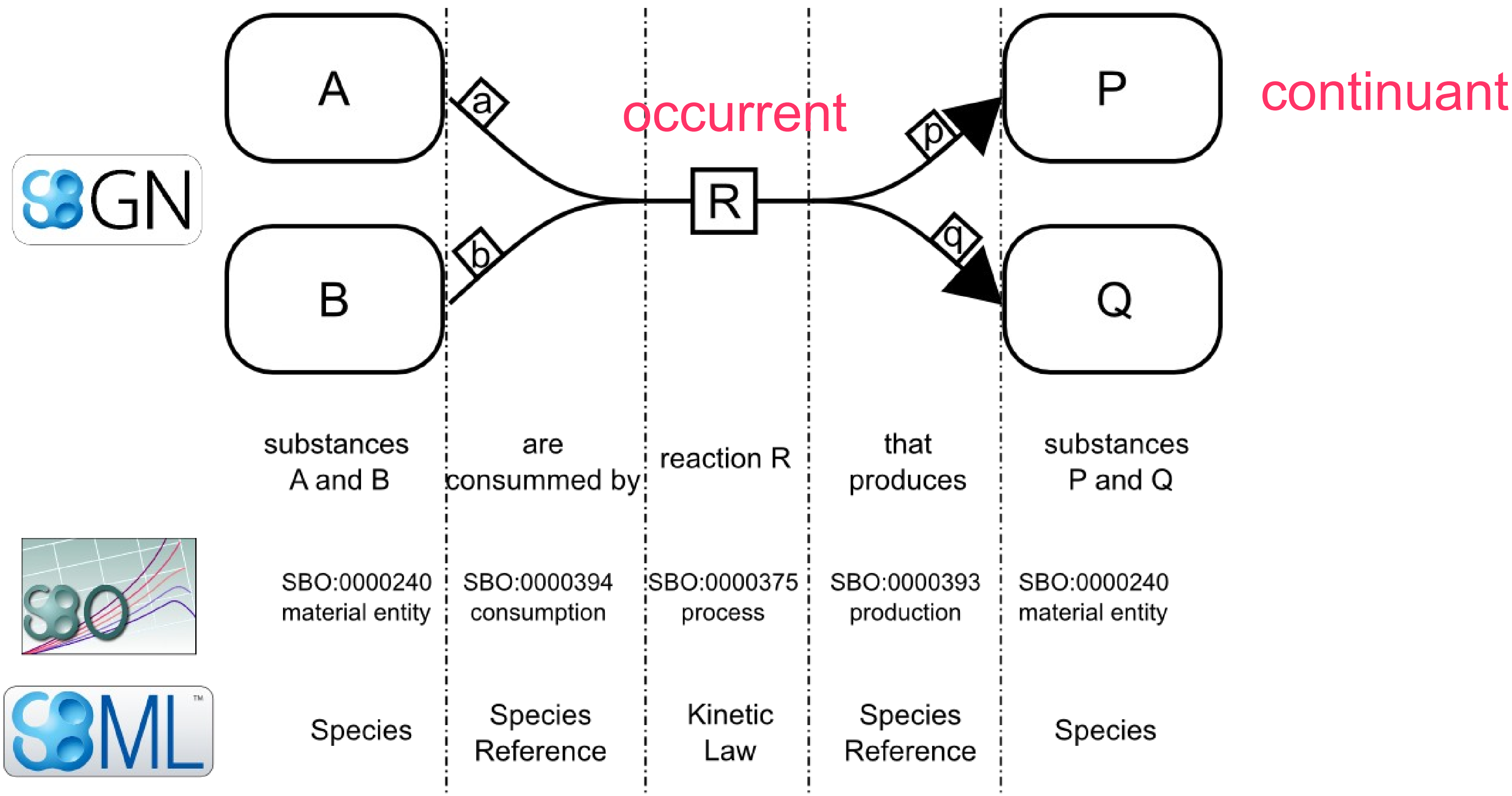


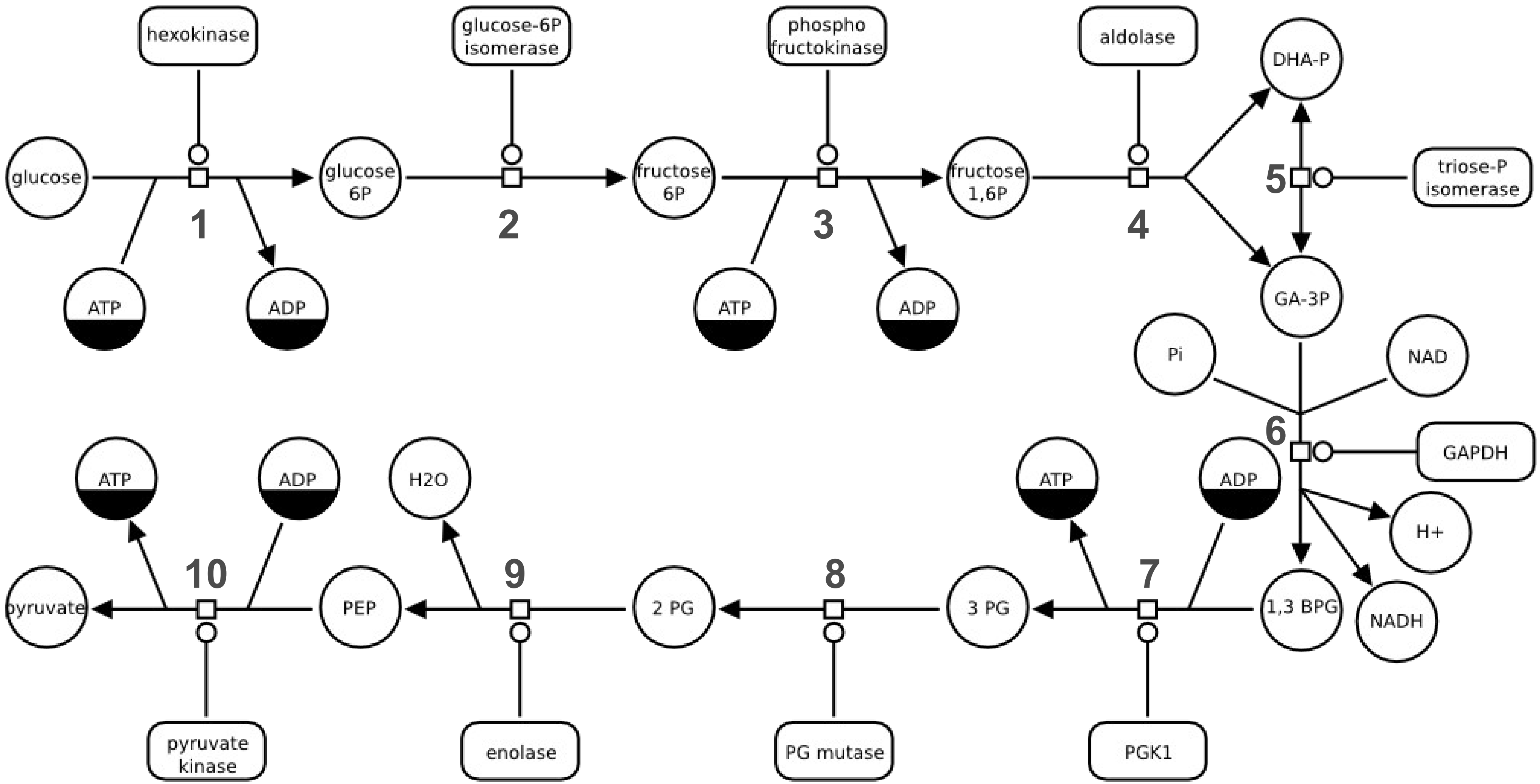
Growth of BioModels Database since its creation

Modelling chemical kinetics

Systems Biology models ≠ ODE models

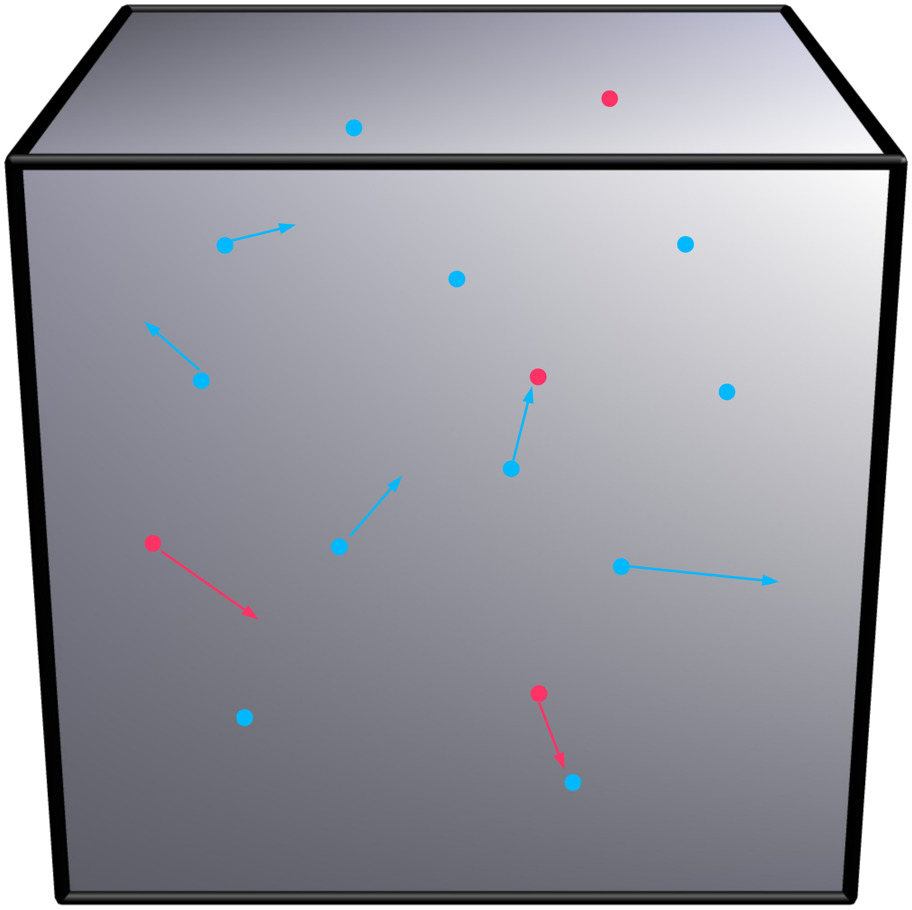
- Reconstruction of state variable evolution from process description:
  - Processes can be combined in ODEs (for deterministic simulations); transformed in propensities (for stochastic simulations)
  - Systems can be reconfigured quickly by adding or removing a process



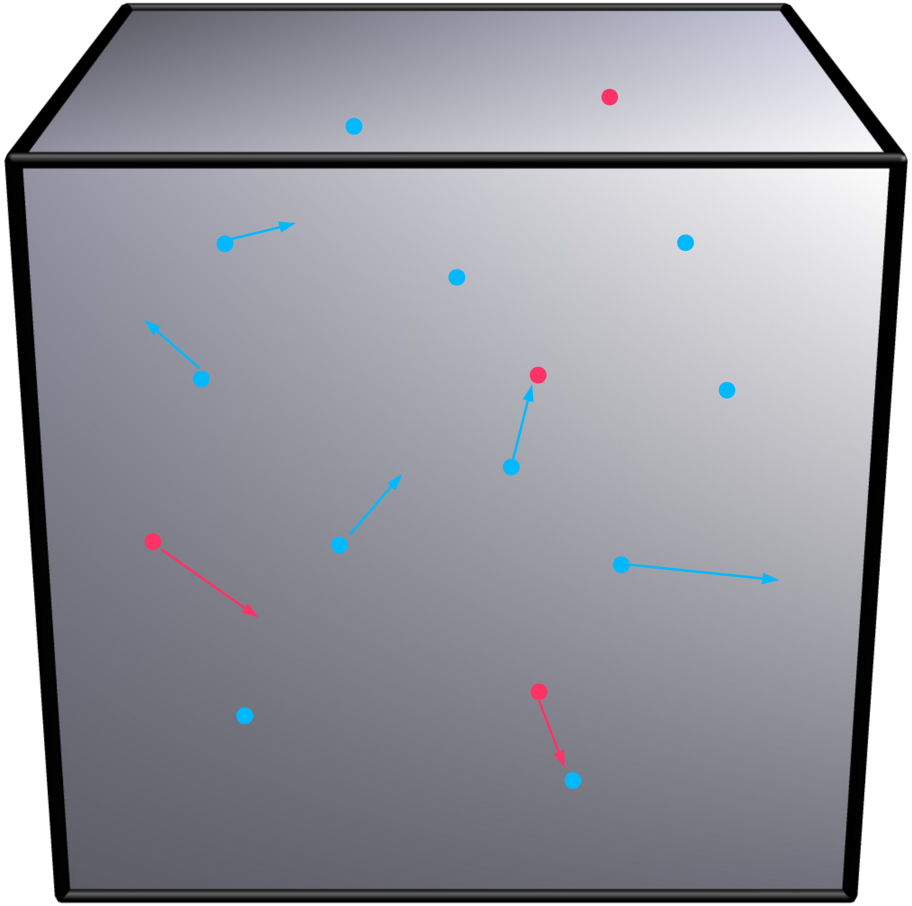


ATP is consumed by processes 1 and 3, and produced by processes 7 and 10

Statistical physics and chemical reaction



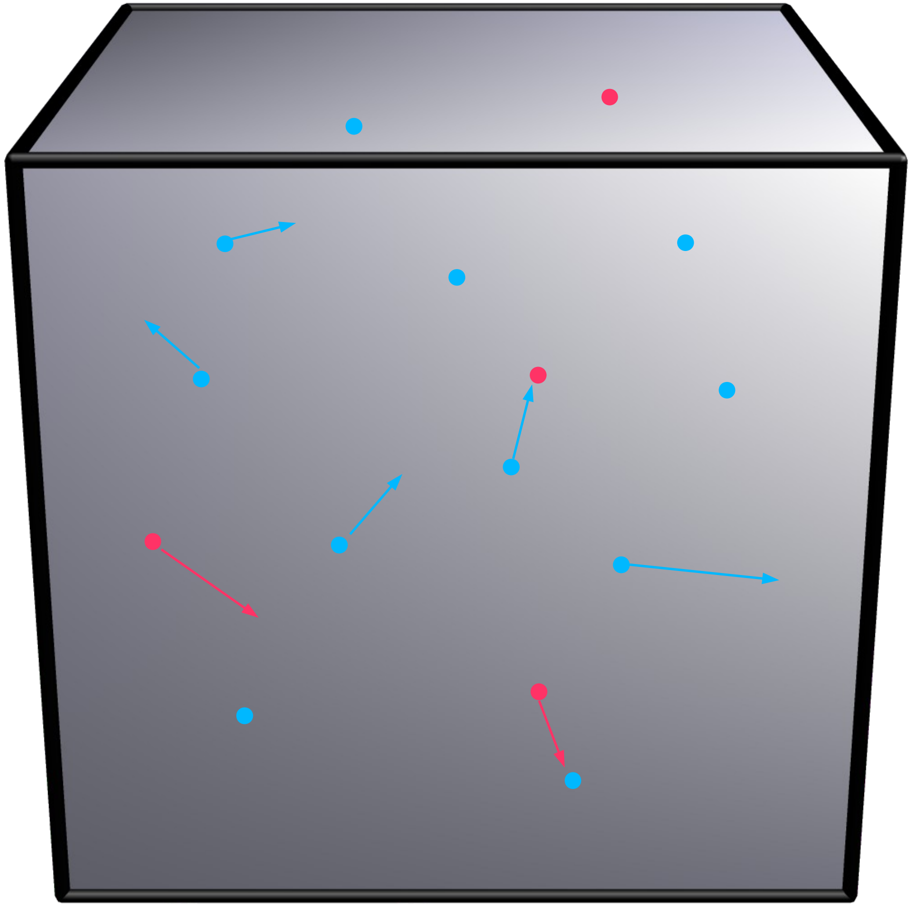
Statistical physics and chemical reaction



Probability to find an object in a container within an interval of time

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

Statistical physics and chemical reaction



Probability to find an object in a container within an interval of time

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

$$P(\text{reaction}\,\textcolor{cyan}{\bullet} + \textcolor{red}{\bullet}) = P(\textcolor{cyan}{\bullet}) \times P(\textcolor{red}{\bullet}) \times P(\textcolor{cyan}{\bullet}\ \text{reacts with}\ \textcolor{red}{\bullet})$$

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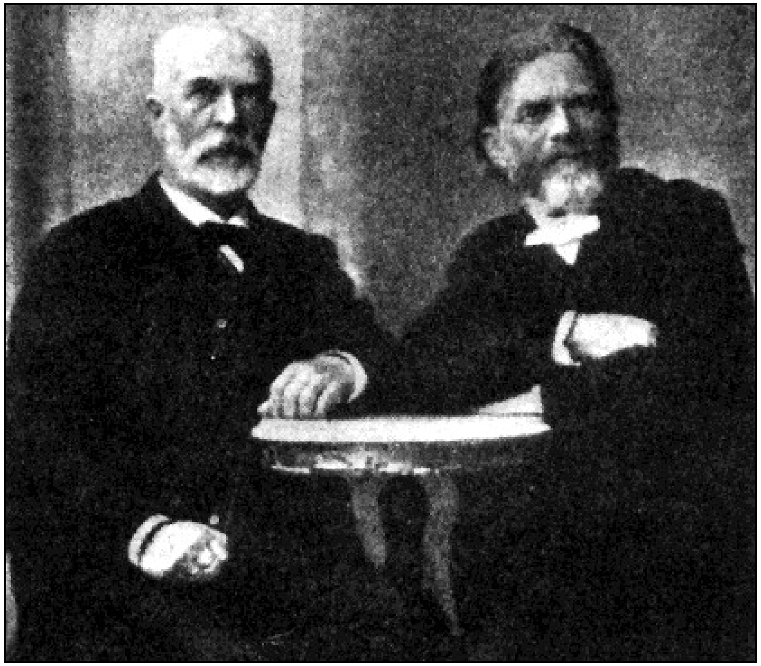
Law of Mass Action

Waage and Guldberg (1864)



activity

rate-constant

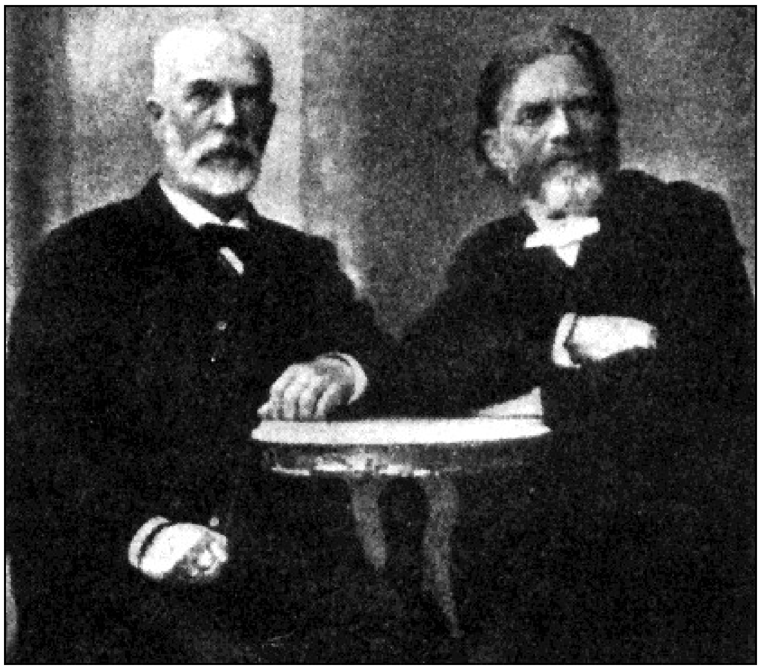
stoichiometry

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

velocity

Law of Mass Action

Waage and Guldberg (1864)



activity

rate-constant

stoichiometry

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

velocity

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

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

Evolution of a reactant

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

Evolution of a reactant

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

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

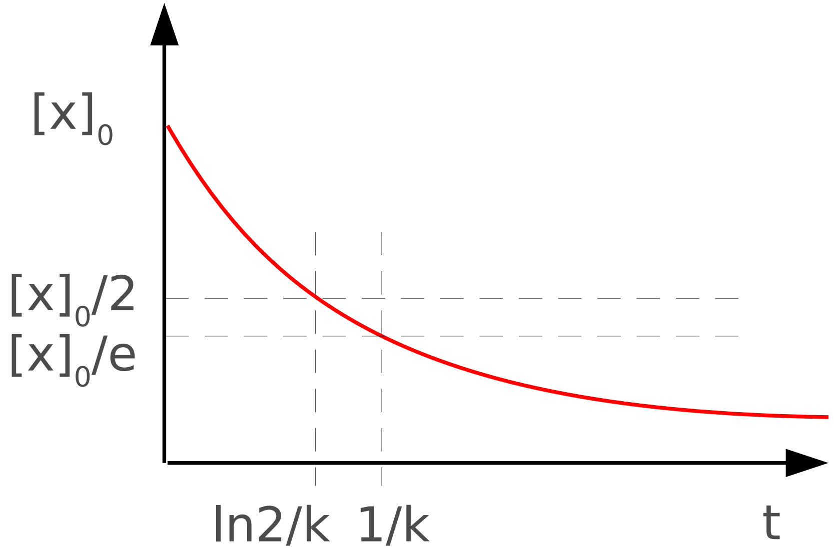
Evolution of a reactant

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

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

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

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



Reversible reaction

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

is equivalent to

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

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

Reversible reaction

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is equivalent to

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

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

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

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

Example of an enzymatic reaction

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

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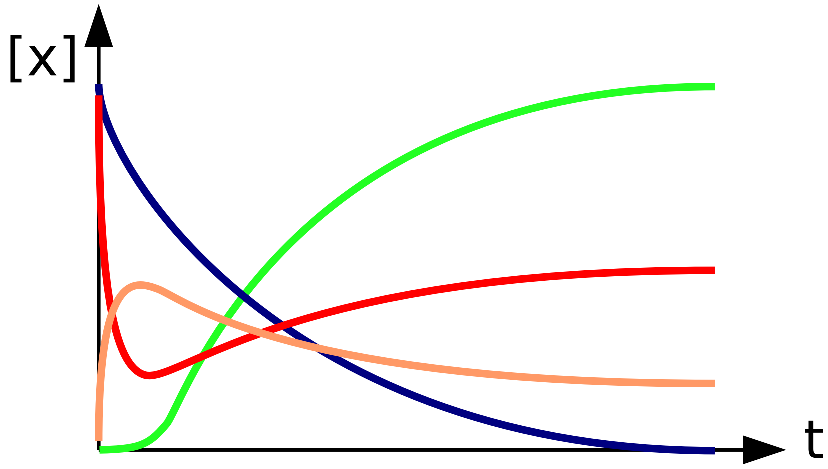
$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

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

Example of an enzymatic reaction

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

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



Not feasible in general

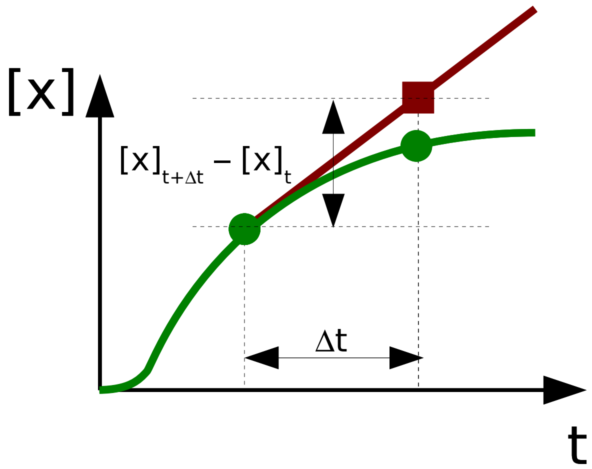
→ Numerical integration

Numerical integration

Euler method:

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

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



Numerical integration

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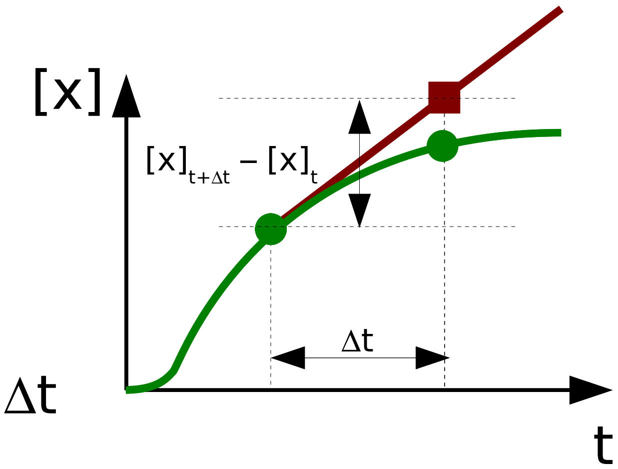

$$[P]_{t+\Delta t} = [P]_t + k_3[ES]_t \,.\, \Delta t$$

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

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

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

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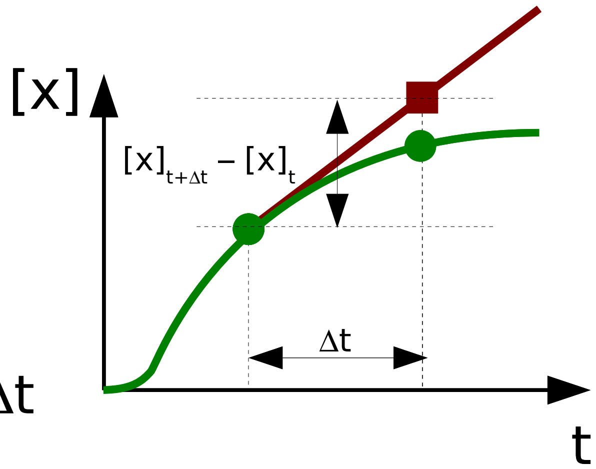

$$[P]_{t+\Delta t} = [P]_t + k_3[ES]_t \,.\, \Delta t$$

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

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

4^{th} order Runge-Kutta:

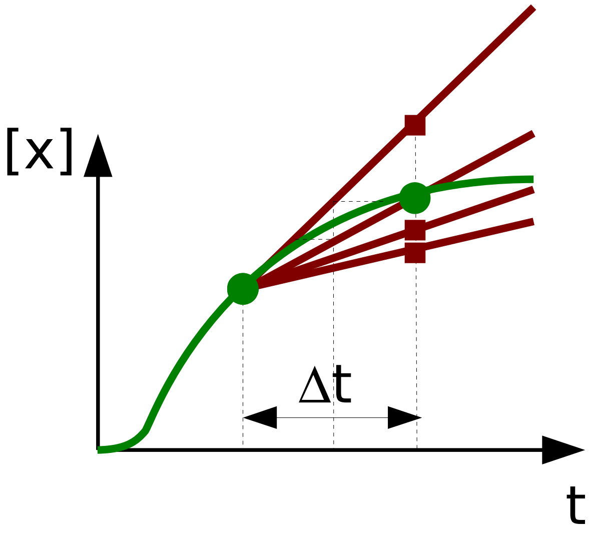
$$[x]_{t+\Delta t} = [x]_t + (F_1+2F_2+2F_3+F_4)/6 \,.\, \Delta t$$

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

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

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

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

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$$E+S \underset{ksd}{\overset{ksa}{\leftrightarrows}} ES \xrightarrow{kcat} E+P$$

product is consumed
before rebinding

Choose the right formalism

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

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catalysis irreversible

$$E+S \underset{ksd}{\overset{ksa}{\rightleftharpoons}} ES \xrightarrow{kcat} E+P$$

product is consumed before rebinding

$$S \xrightarrow{E} P$$

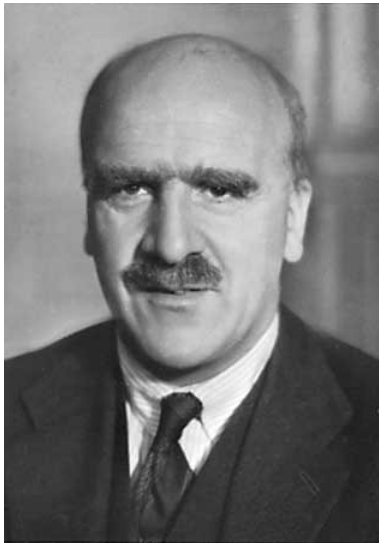
steady-state

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

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

$$\boxed{E + S \underset{k_{-1}}{\overset{k\,1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P}$$

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

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

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

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

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

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

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

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

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

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

Briggs-Haldane on Henri-Michaelis-Menten

$$\boxed{E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P}$$

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

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

steady-state!!!

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

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

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

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

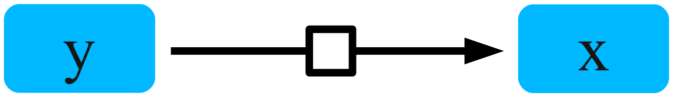
$$K_m = \frac{k_{-1} + k_2}{k_1}$$

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

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

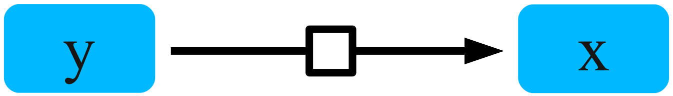
$$\frac{d[P]}{dt} = k_2[E_0]\frac{[S]}{K_m + [S]} = \boxed{V_{max}\frac{[S]}{K_m + [S]}}$$

Generalisation of modulation



$$\frac{d[x]}{dt} = v(= k \cdot [y])$$

Generalisation: activators



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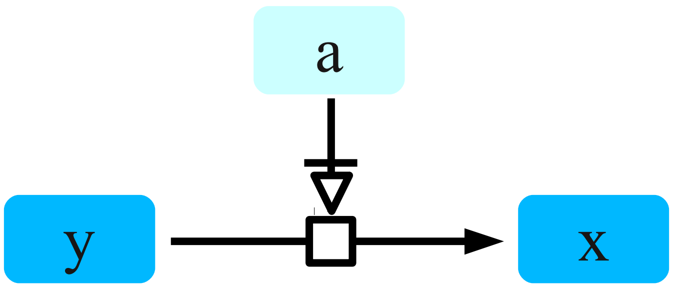
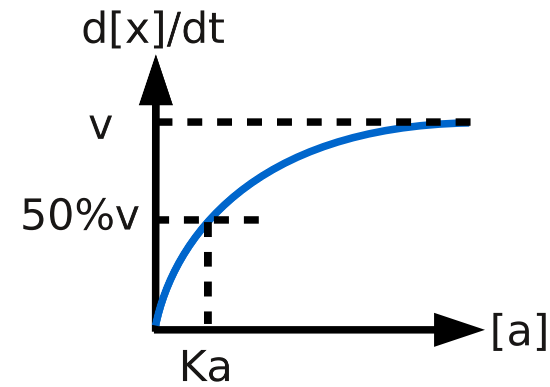
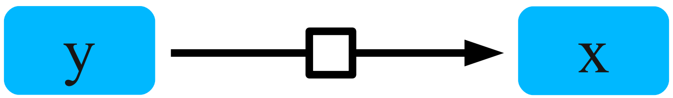


$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$



Generalisation: activators



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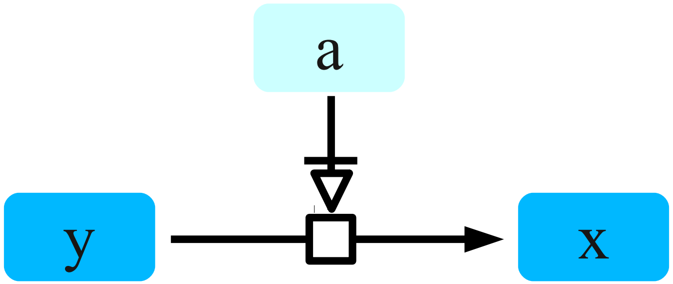

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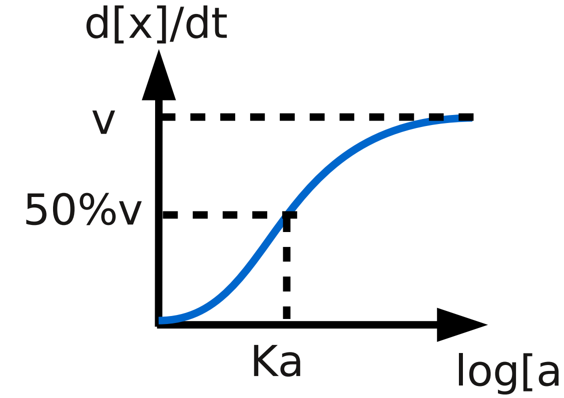
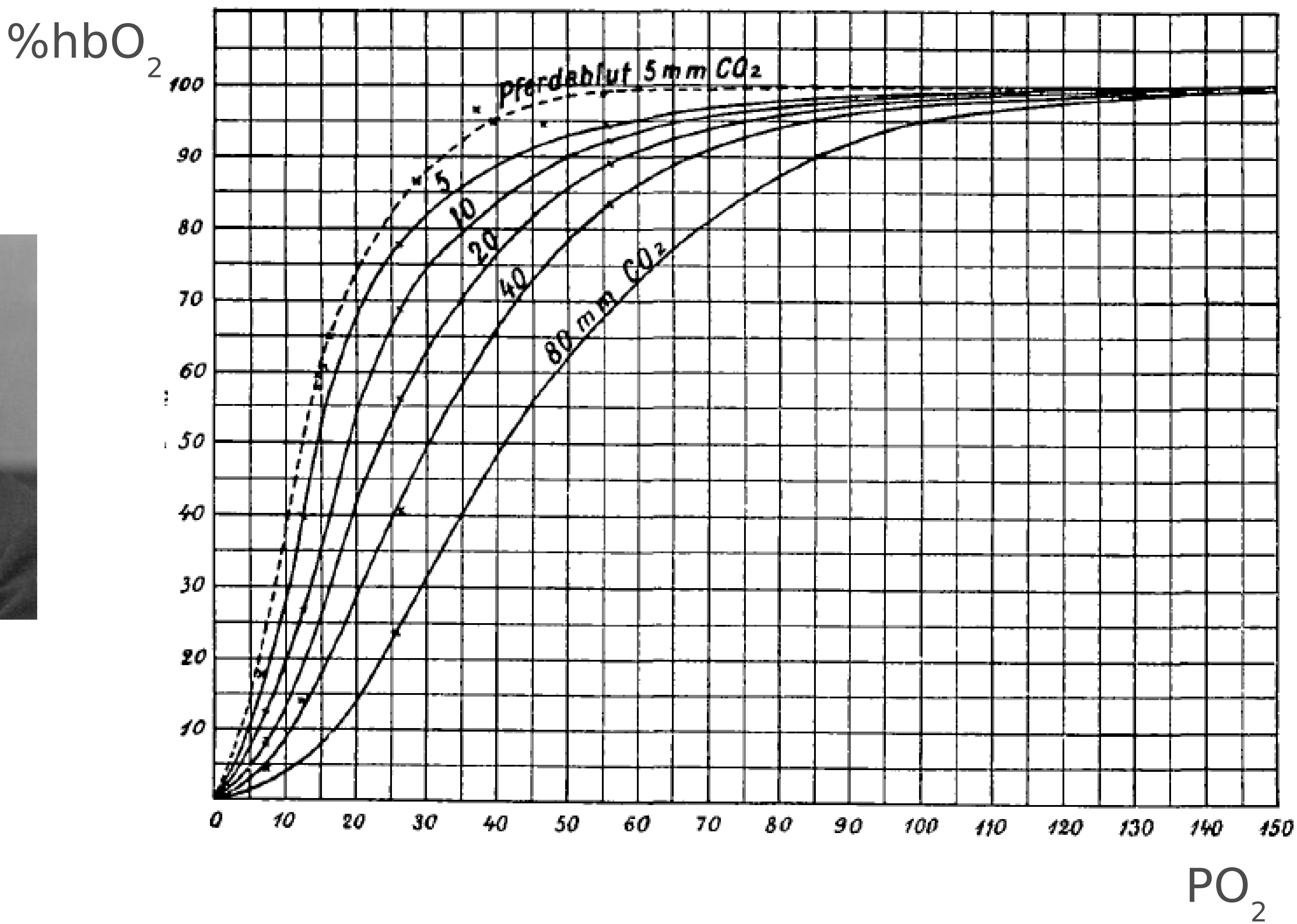


Origins of ultrasensitivity: Bohr



Bohr C (1903) Theoretische behandlung der quantitativen verhältnisse bei der sauerstoff aufnahme des hämoglobins *Zentralbl Physiol* 17: 682

Origins of ultrasensitivity: Hill

The possible effects of the aggregation of the molecules of hæmoglobin on its dissociation curves. By A. V. HILL.

In a previous communication Barcroft and I gave evidence which seemed to us to prove conclusively that dialysed hæmoglobin consists simply of molecules containing each one atom of iron. The molecular weight is therefore Hb = 16,660. These experiments have not been published yet, but I shall assume the results.

Other observers (Reid, Roaf, Hüfner and Gansser) working on different solutions have obtained divergent results. The method used by all of them was the direct estimation of the osmotic pressure, by means of a membrane permeable to salts, but not to hæmoglobin. The method involves a relatively large error, because the quantity measured is small. It is doubtful however whether this can explain the discordant results.

Our work led me to believe that the divergence between the results of different observers was due to an aggregation of the hæmoglobin molecules by the salts present in the solution, a consequent lowering of the number of molecules, and an increase in the average molecular weight as observed by the osmotic pressure method. To test this hypothesis I have applied it to several of the dissociation curves obtained by Barcroft and Camis with hæmoglobin in solutions of various salts, and with hæmoglobin prepared by Bohr's method.

The equation for the reaction would be

$$Hb + O_2 \rightleftarrows HbO_2,$$
$$Hb_n + nO_2 \rightleftarrows Hb_nO_{2n},$$

where Hb_n represents the aggregate of n molecules of Hb. I have supposed that in every solution there are many different sized aggregates, corresponding to many values of n.

If there were in the solution only Hb and Hb_2 the dissociation curve would be

$$y = \lambda \frac{K'x^2}{1 + K'x^2} + (100 - \lambda)\frac{Kx}{1 + Kx} \quad \text{..............(A)},$$

where λ % is as Hb_2, $(100 - \lambda)$ % as Hb, K' is the equilibrium constant of the reaction $Hb_2 + 2O_2 \rightleftarrows Hb_2O_4$ and K that of $Hb + O_2 \rightleftarrows HbO_2$: K has the value ·125 (Barcroft and Roberts).

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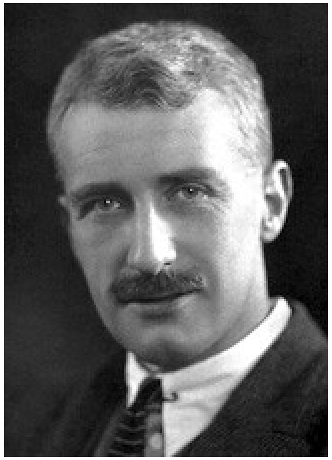

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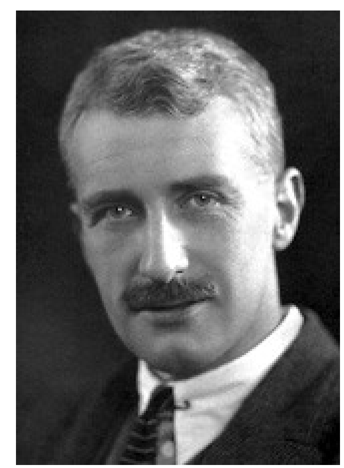
Now it is unlikely that in either of these cases there is only Hb and Hb_2: and as the calculation of the constants in these equations is very tedious I decided to try whether the equation

$$y = 100\frac{Kx^n}{1+Kx^n} \quad \text{...........................(B)}$$

would satisfy the observations.



Origins of ultrasensitivity: Hill

iv PROCEEDINGS OF THE PHYSIOLOGICAL

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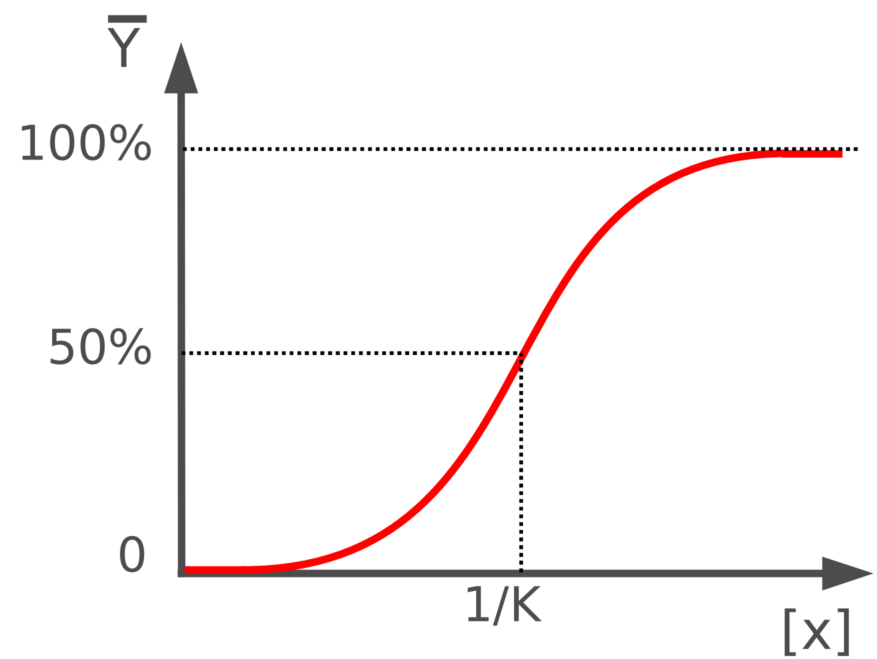
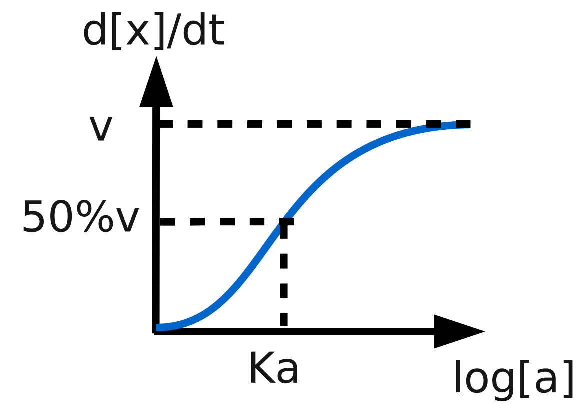


Phenomenological ultrasensitivity

$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$



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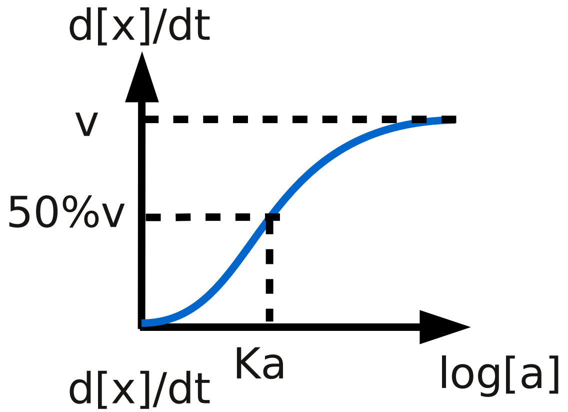
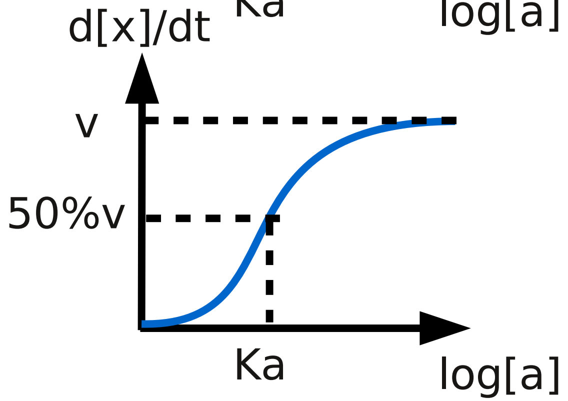


$$\frac{d[x]}{dt} = v \cdot \frac{[a]^2}{Ka^2 + [a]^2}$$

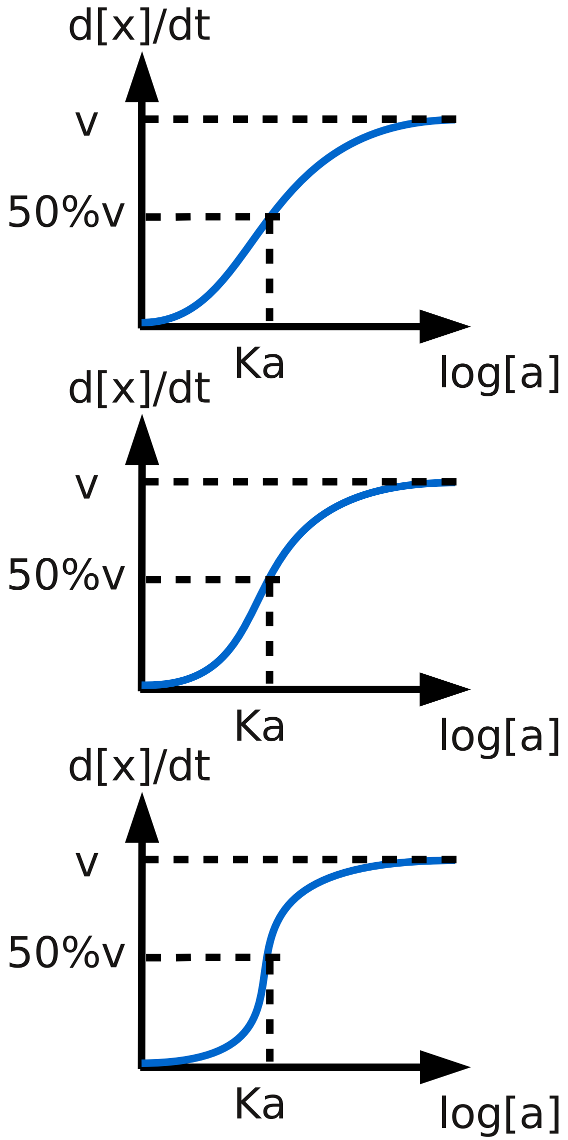


Phenomenological ultrasensitivity

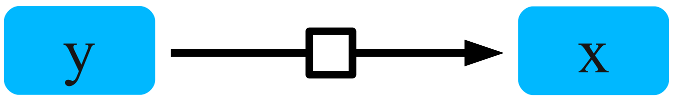
$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$

$$\frac{d[x]}{dt} = v \cdot \frac{[a]^2}{Ka^2 + [a]^2}$$

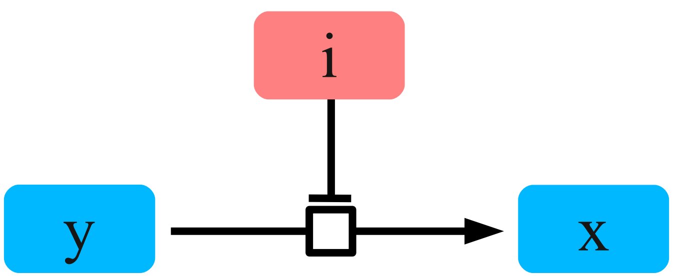
$$\frac{d[x]}{dt} = v \cdot \frac{[a]^n}{Ka^n + [a]^n}$$



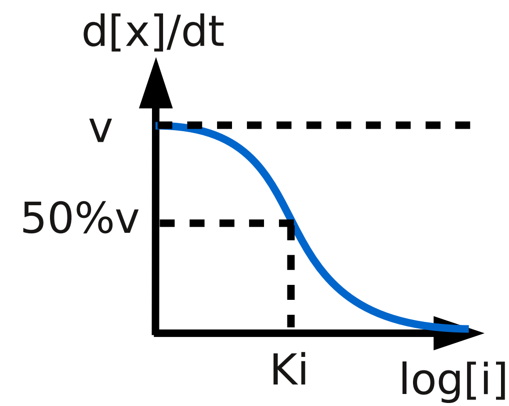
Generalisation: inhibitors



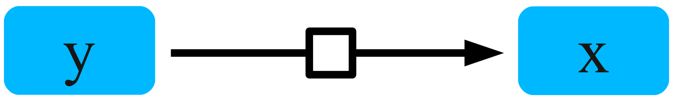
$$\frac{d[x]}{dt} = v(= k \cdot [y])$$



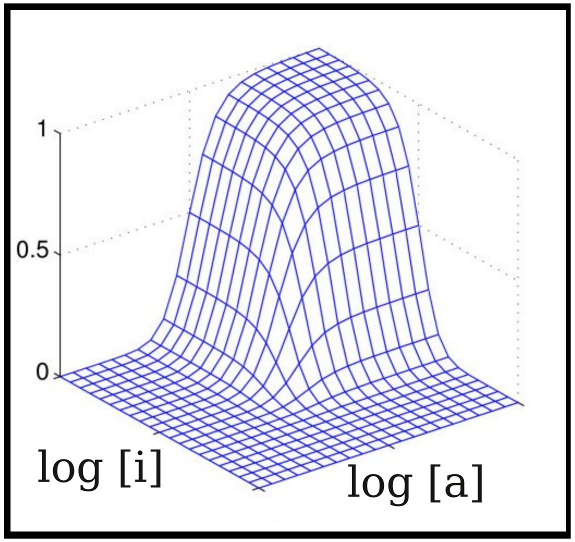
$$\frac{d[x]}{dt} = v \cdot \frac{Ki^m}{Ki^m + [i]^m}$$

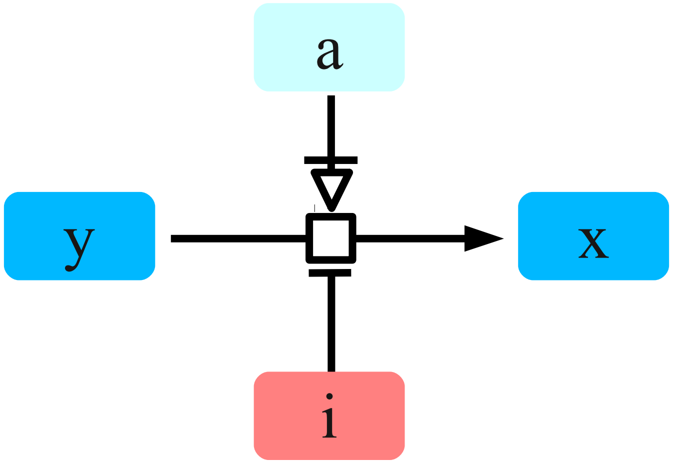


Generalisation: activators and inhibitors



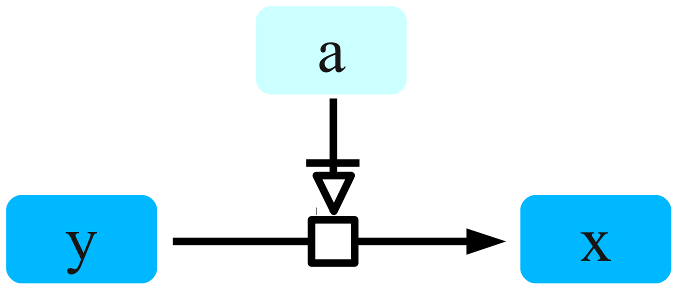
$$\frac{d[x]}{dt} = v (= k \cdot [y])$$





$$\frac{d[x]}{dt} = v \cdot \frac{[a]^n}{Ka^n + [a]^n} \cdot \frac{Ki^m}{Ki^m + [i]^m}$$

absolute Vs relative activators



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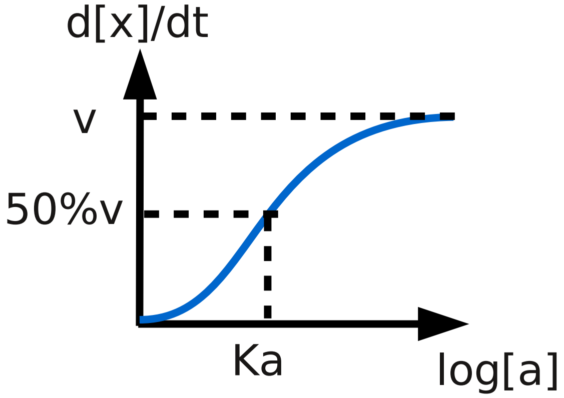

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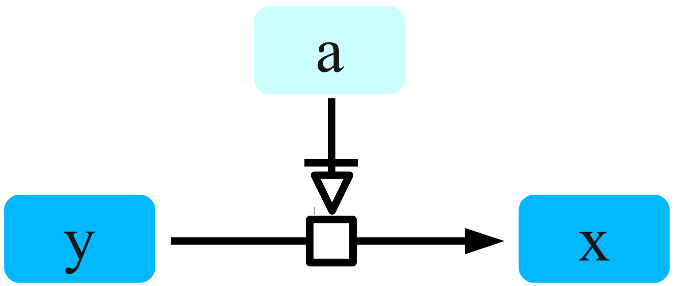

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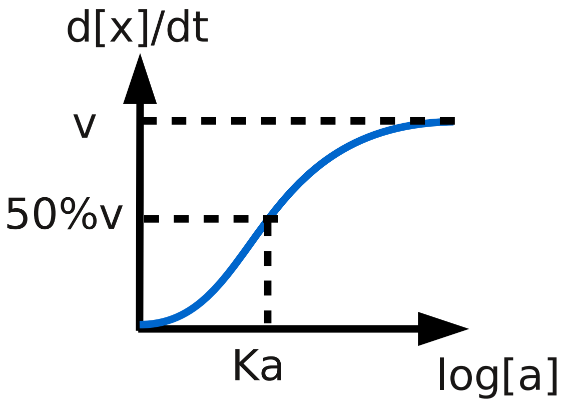
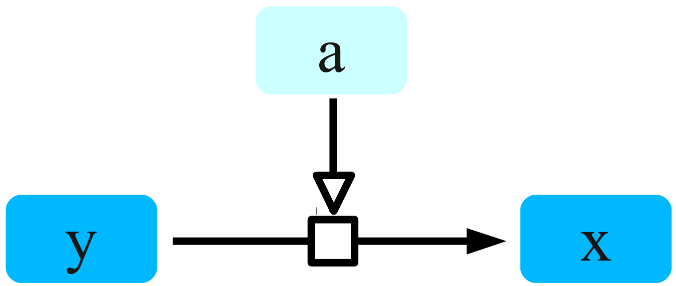
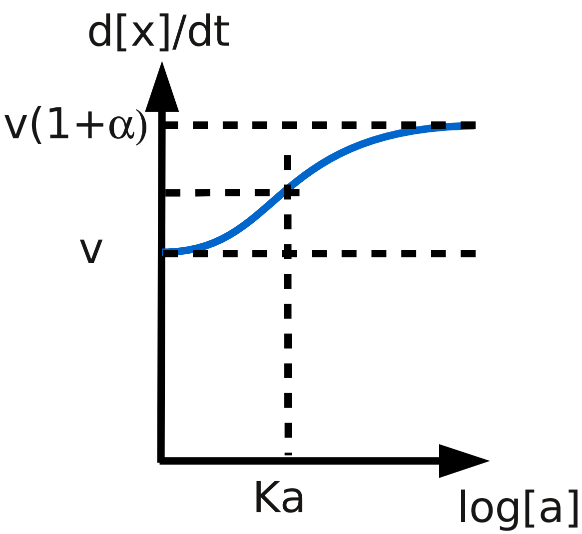


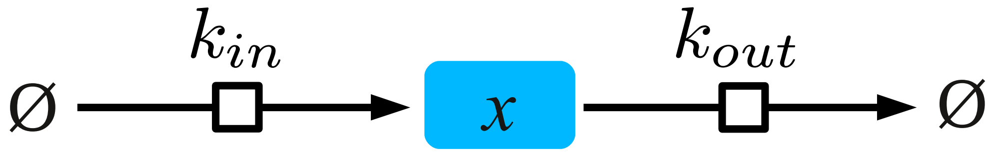


$$\frac{d[x]}{dt} = v \cdot (1 + \alpha \cdot \frac{[a]}{Ka + [a]})$$



Homeostasis

How can-we maintain a stable level with a dynamic system?



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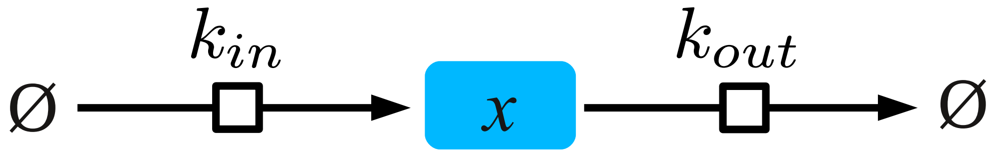


$$\frac{d[x]}{dt} = k_{in} - k_{out} \cdot [x]$$

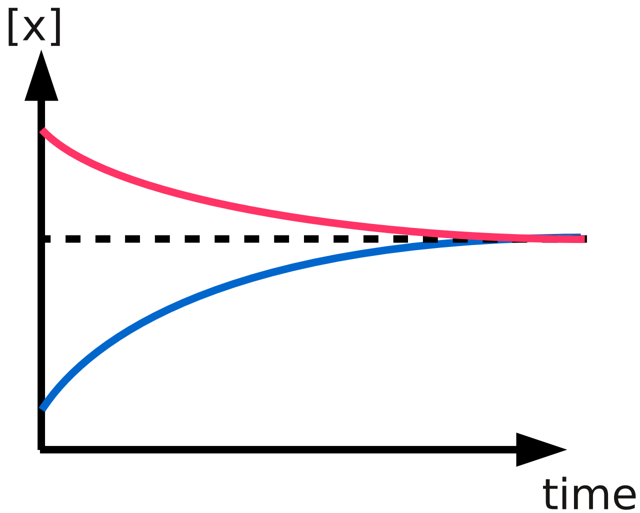
Homeostasis

How can-we maintain a stable level with a dynamic system?

$$\emptyset \xrightarrow{k_{in}} x \xrightarrow{k_{out}} \emptyset$$

$$\frac{d[x]}{dt} = k_{in} - k_{out} \cdot [x]$$

$$[x]_{eq} = \frac{k_{in}}{k_{out}}$$



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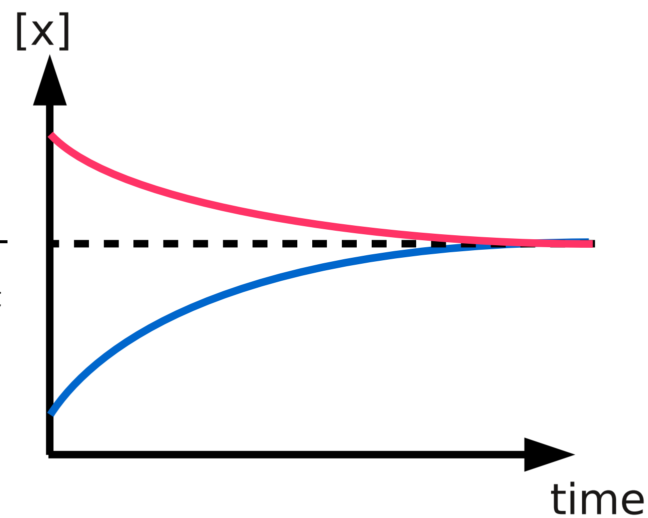
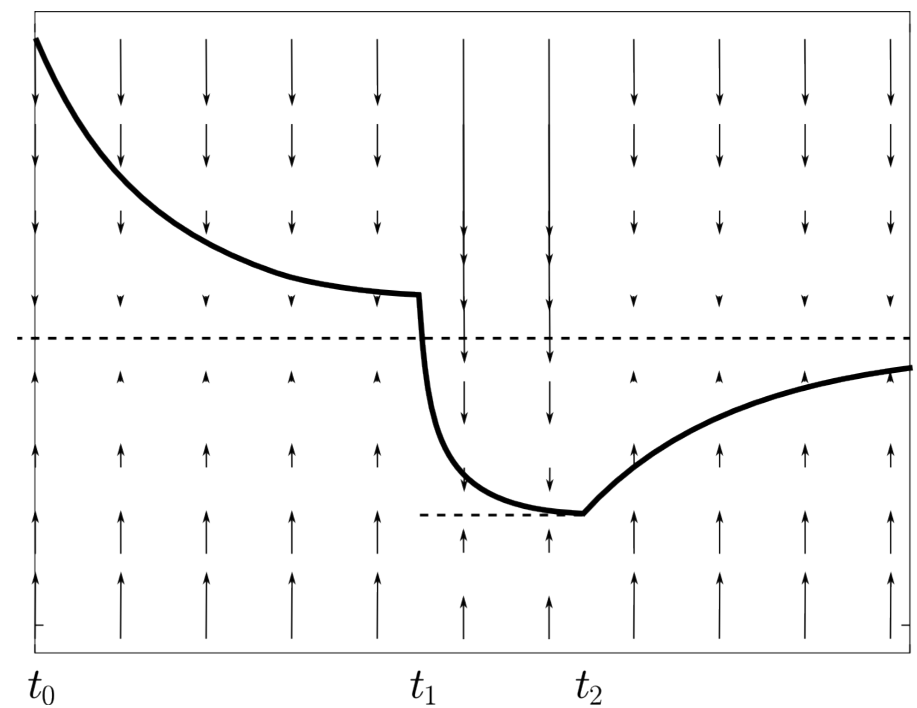
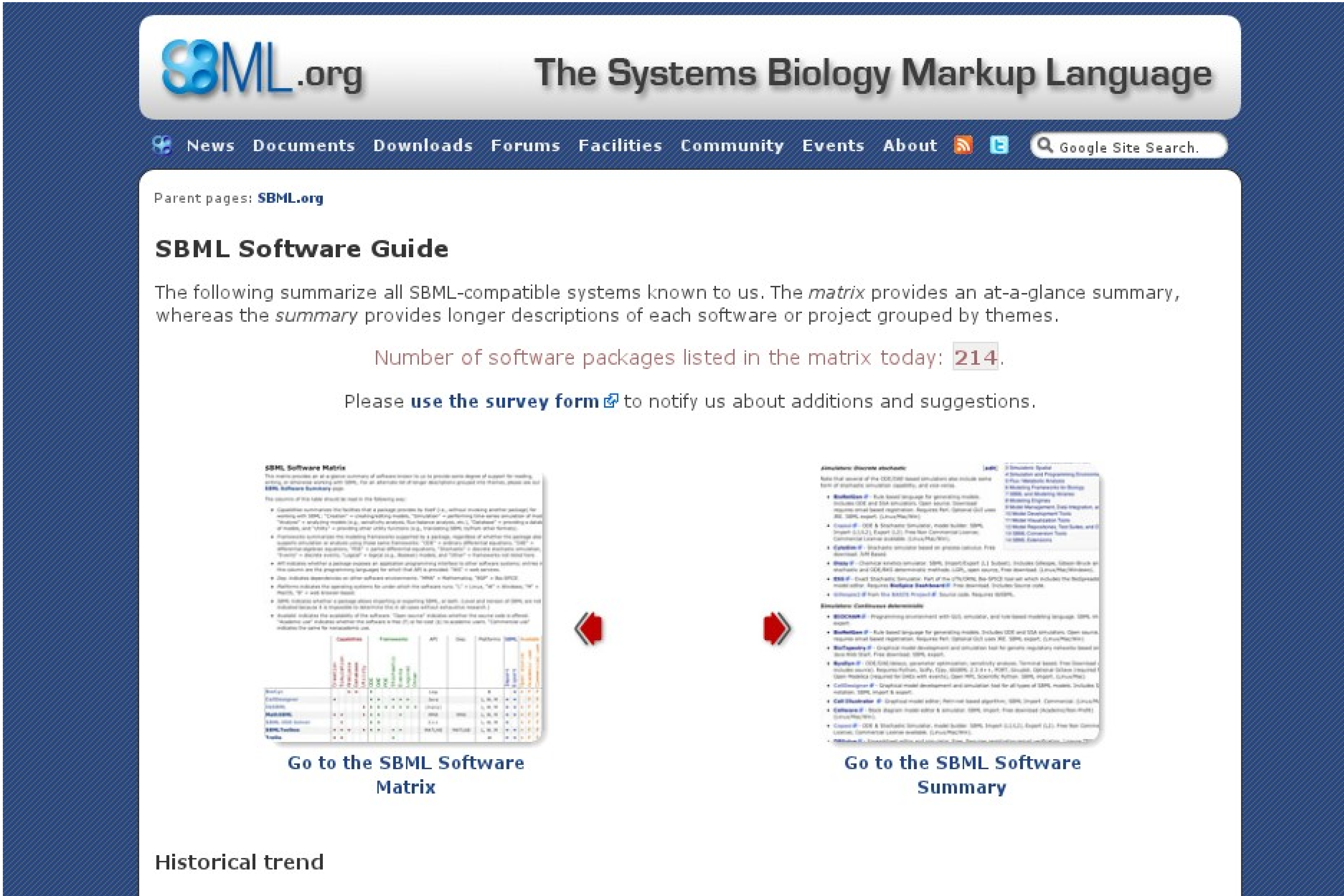




Many many software exist



Your turn!

COPASI