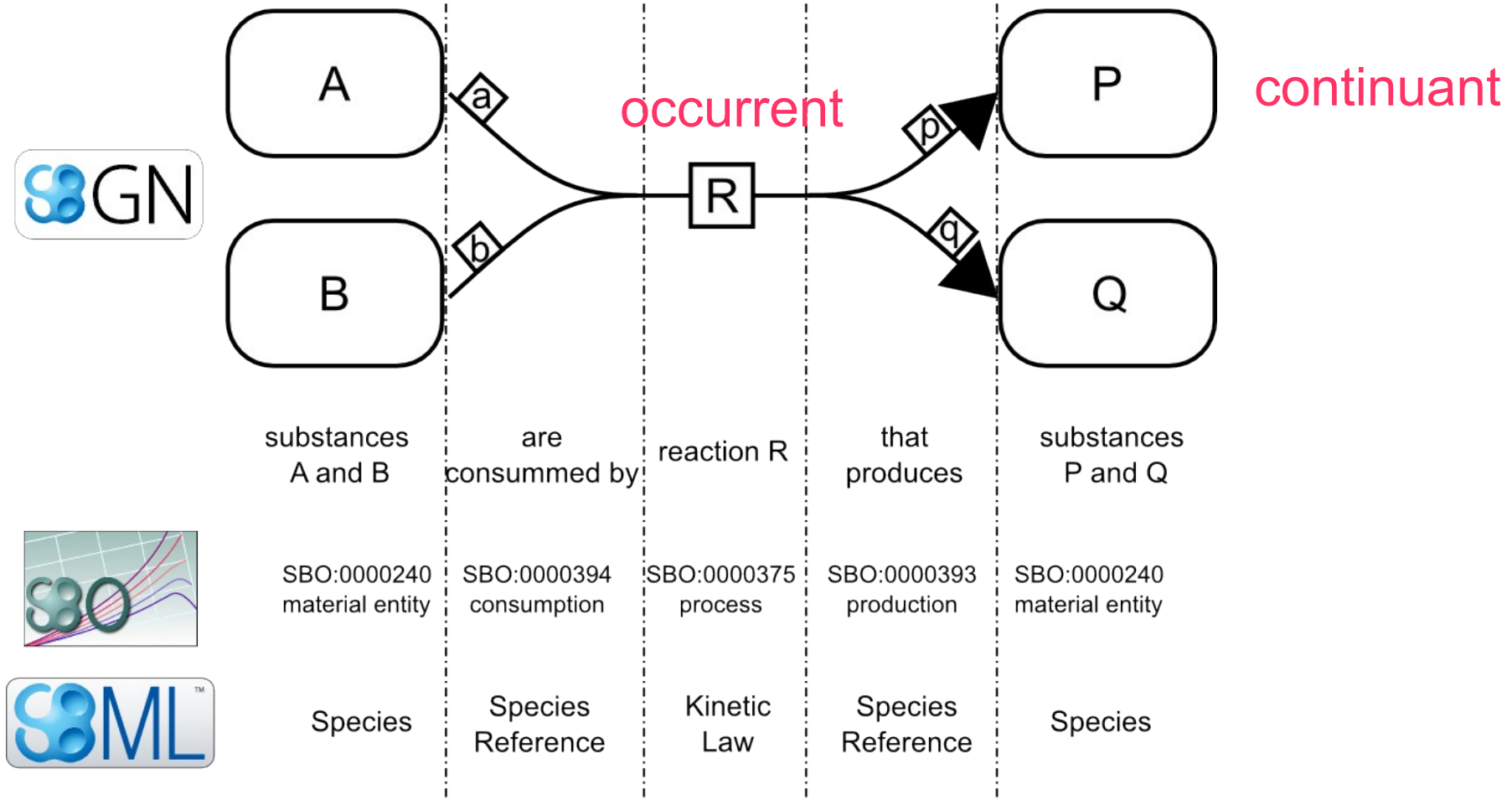
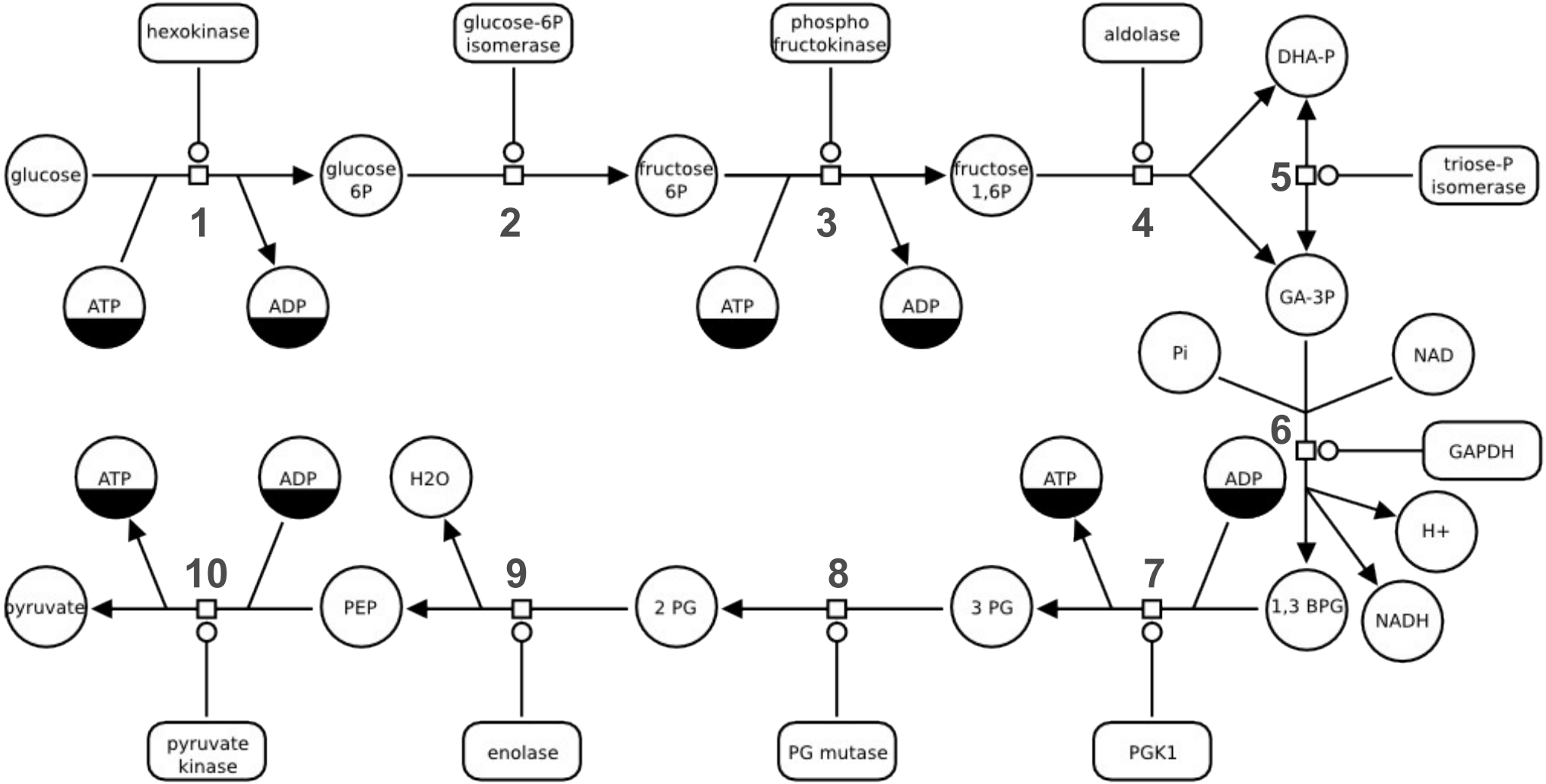
Modelling chemical kinetics

Systems Biology models ≠ ODE models

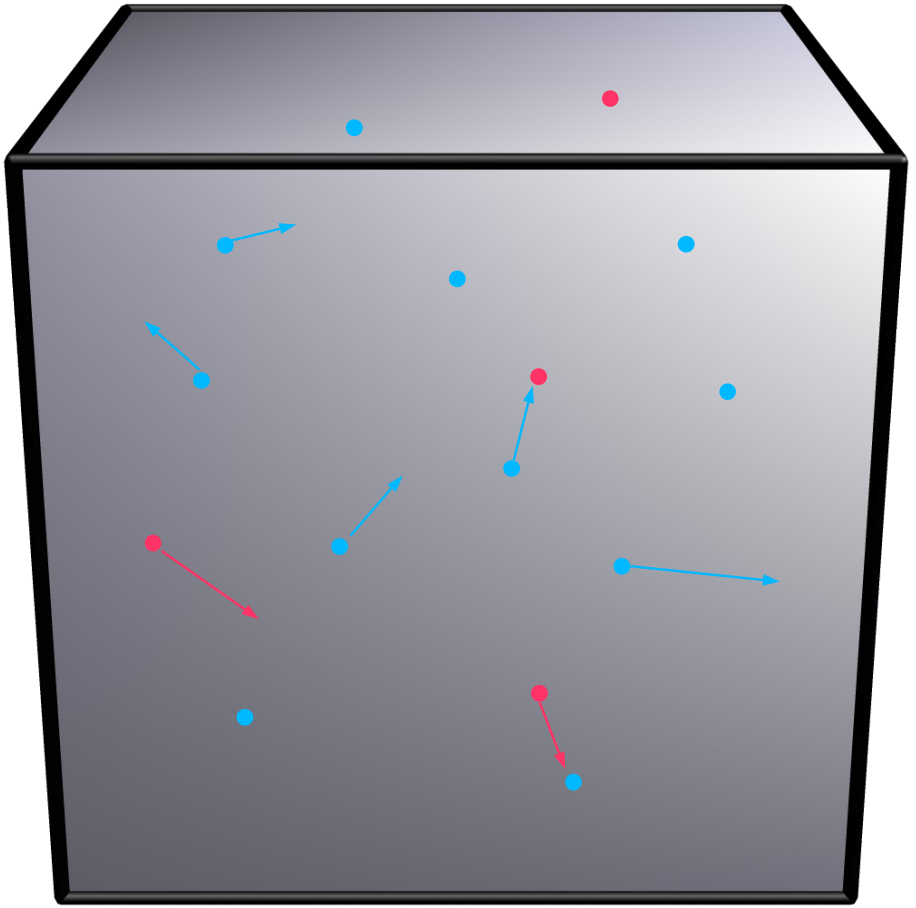
- Reconstruction of state variable evolution from process description:
  - Processes can be combined in ODEs (for deterministic simulations); transformed in propensities (for stochastic simulations)
  - Systems can be reconfigured quickly by adding or removing a process





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

Statistical physics and chemical reaction



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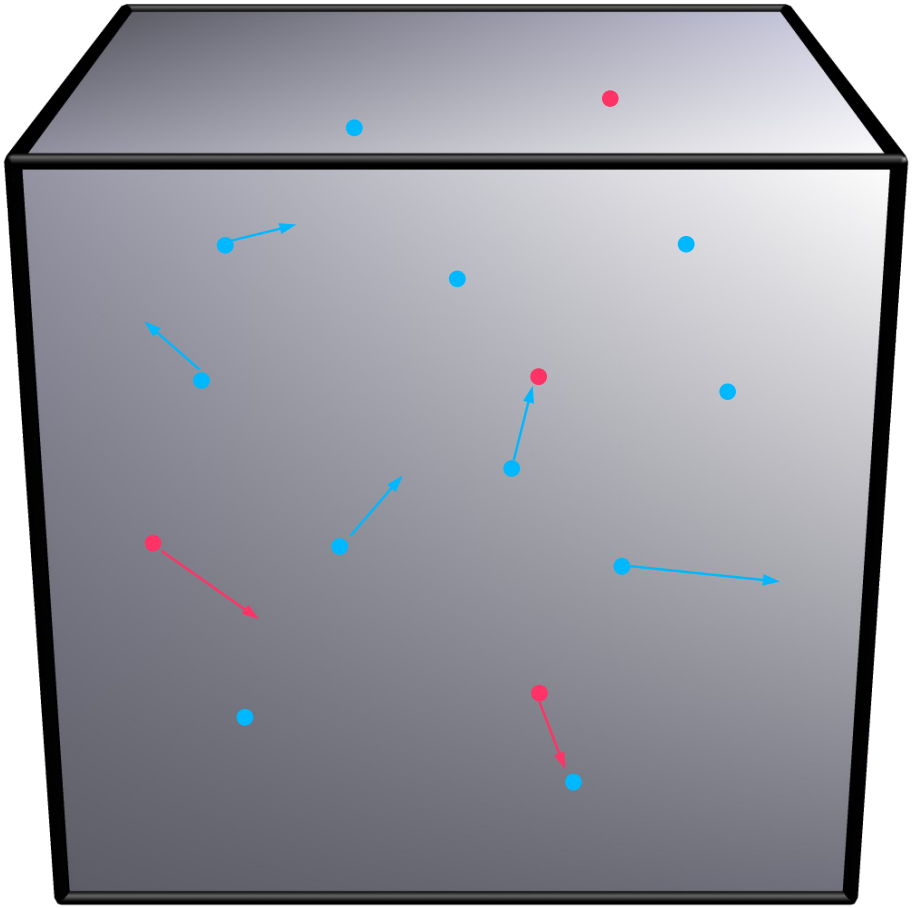
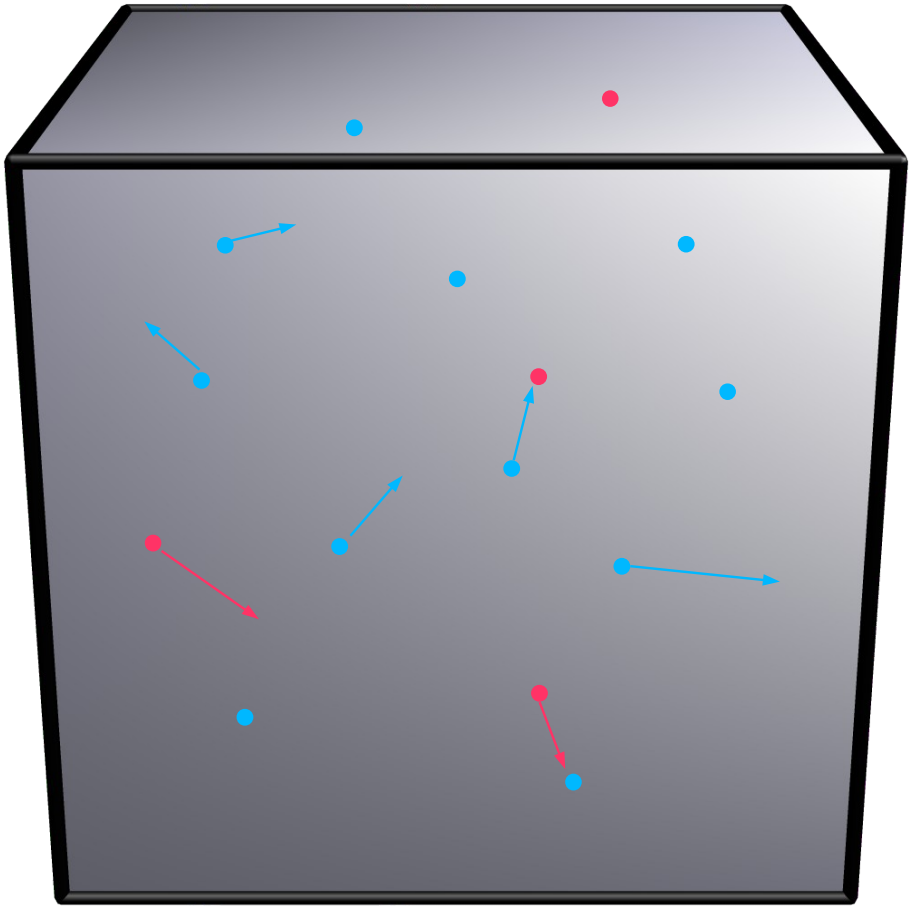


Probability to find an object in a container within an interval of time

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

Statistical physics and chemical reaction



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

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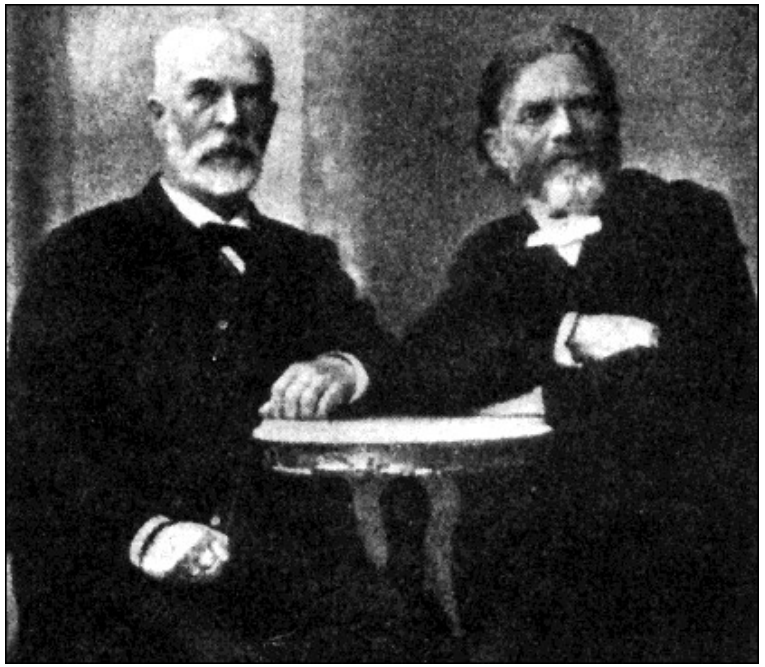
Law of Mass Action

Waage and Guldberg (1864)



activity

rate-constant

stoichiometry

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

velocity

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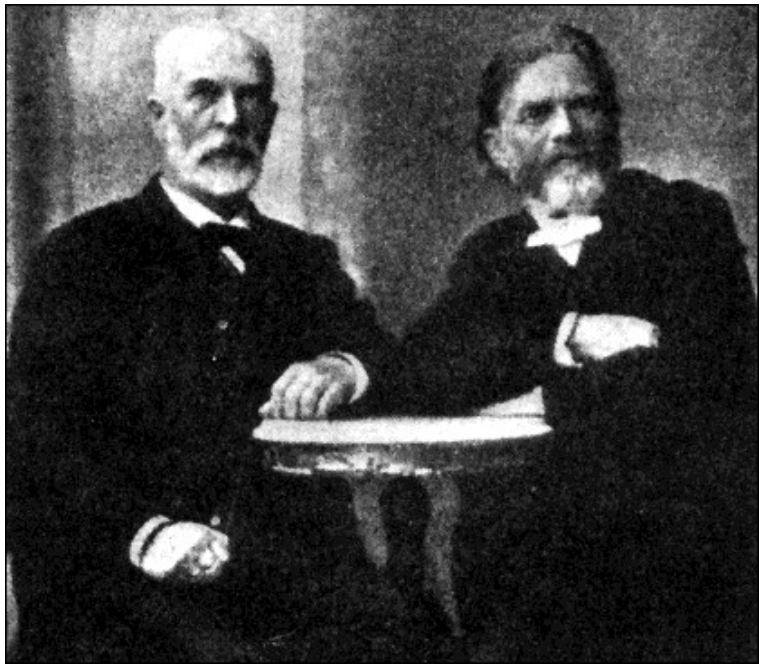

activity

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 $x \xrightarrow{k} y$

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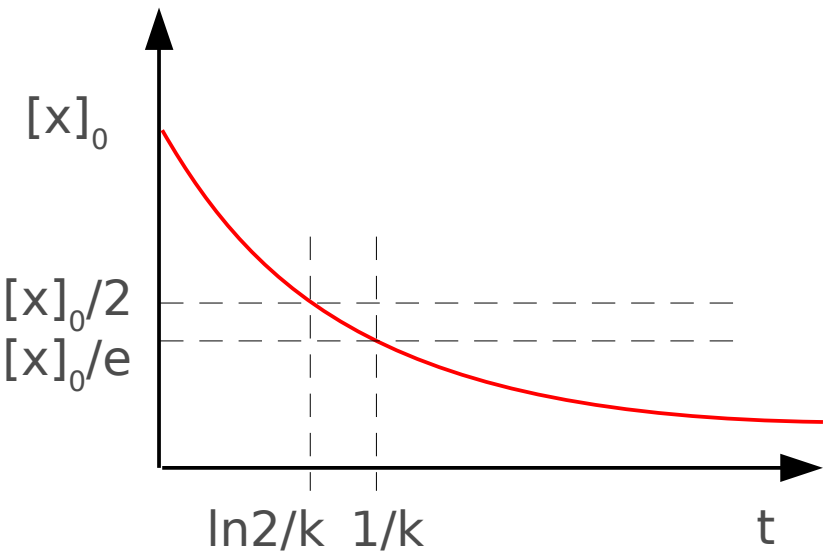
$$x(t) = [x]_0 \cdot e^{-kt}$$



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

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

Example of an enzymatic reaction

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

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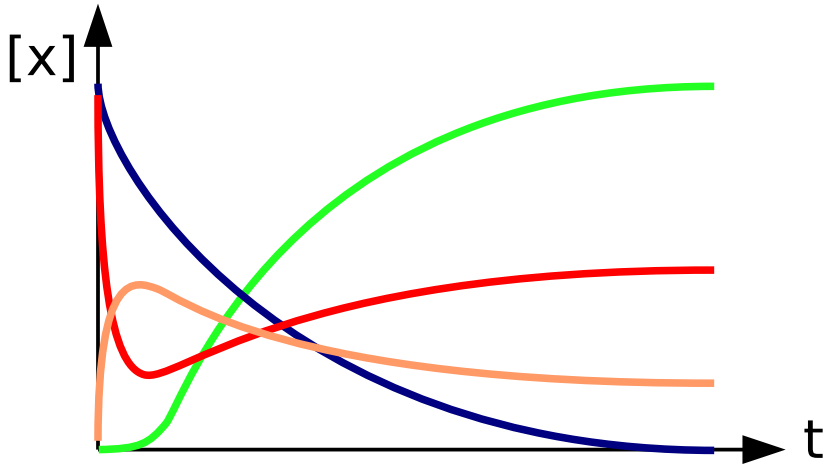


Not feasible in general

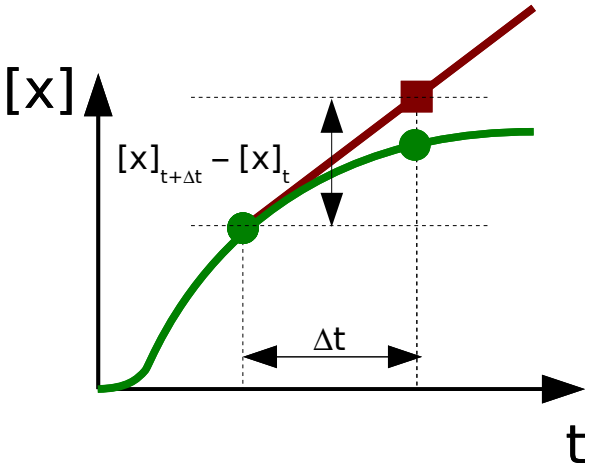
→ Numerical integration

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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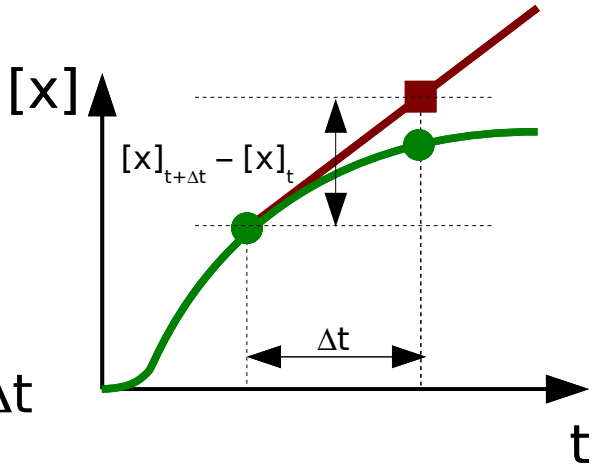

$$[P]_{t+\Delta t} = [P]_t + k_3[ES]_t \,.\, \Delta t$$

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

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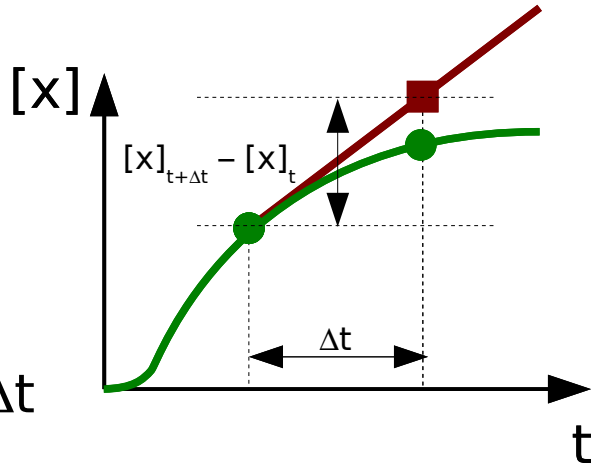

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4^{th} order Runge-Kutta:

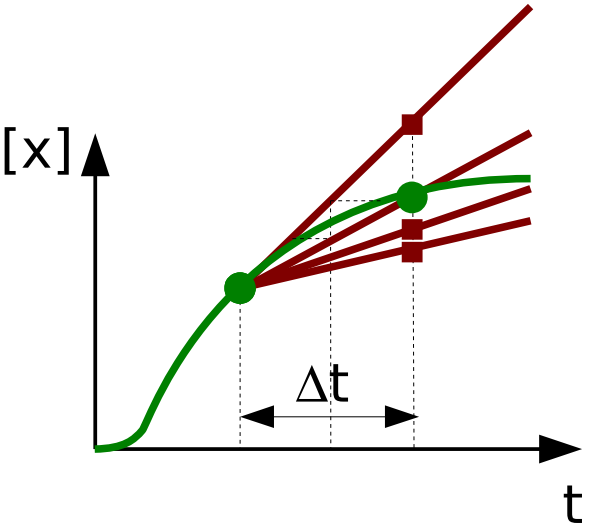
$$[x]_{t+\Delta t} = [x]_t + (F_1 + 2F_2 + 2F_3 + F_4)/6 \,.\, \Delta t$$

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

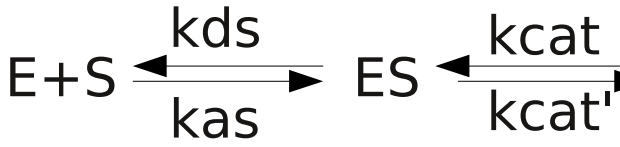
$F_2 = f([x]_t + \Delta t/2 \,.\, F_1, t + \Delta t/2)$

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

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



Choose the right formalism



$$\frac{d[P]}{dt} = k_{dp}[EP] - k_{ap}[E][P]$$

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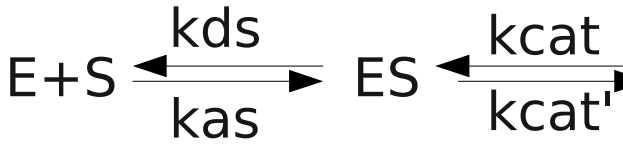

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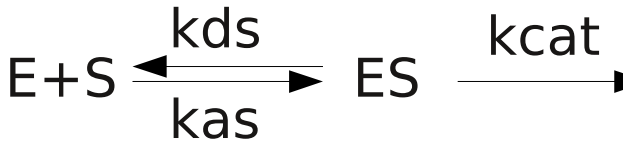

catalysis irreversible

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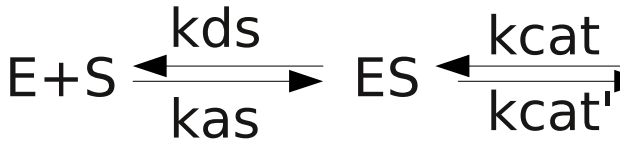

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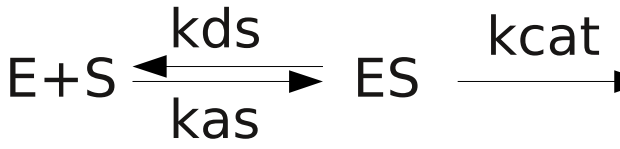

catalysis irreversible

product is consumed
before rebinding

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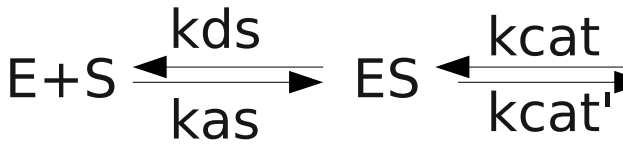

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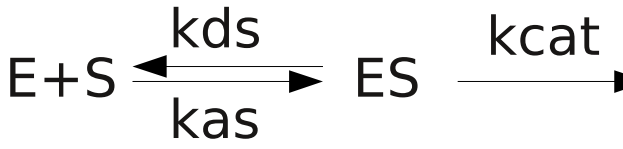

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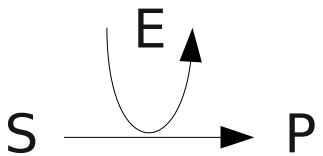


steady-state

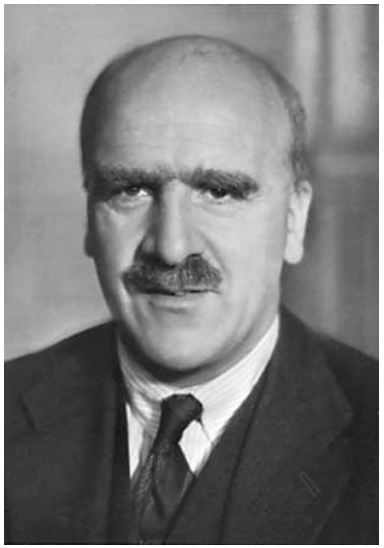
$$\frac{d[P]}{dt} = [E]k_{\text{cat}}\frac{[S]}{K_m + [S]}$$

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

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

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

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

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

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

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

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

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

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

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

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steady-state!!!

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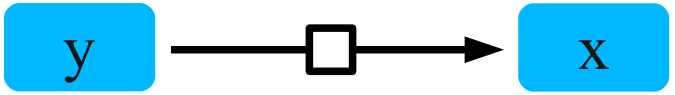
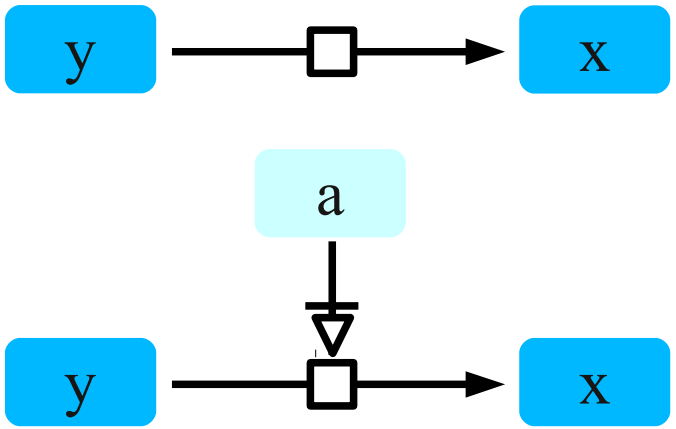
Generalisation of modulation



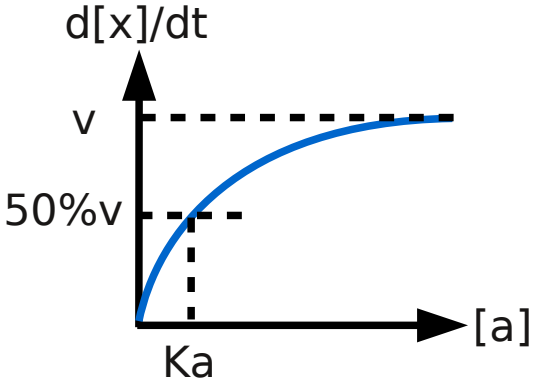
$$\frac{d[x]}{dt} = v(= k \cdot [y])$$

Generalisation: activators



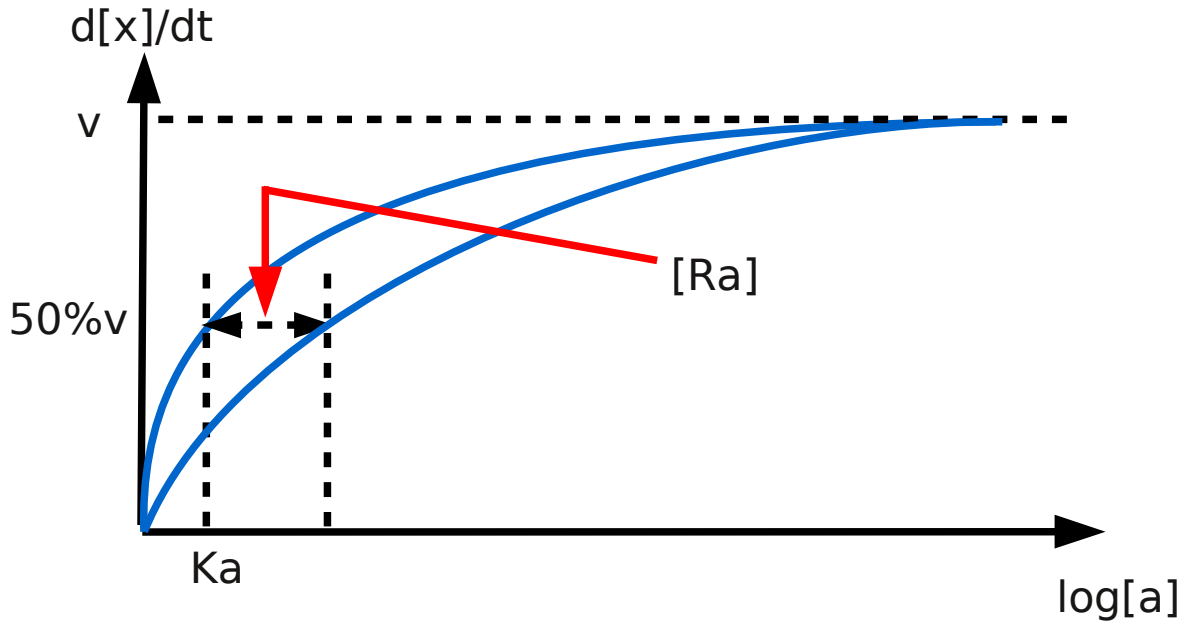
$$\frac{d[x]}{dt} = v(= k \cdot [y])$$

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



Beware of the ligand depletion!

- [a] is the concentration of FREE activator. In the dose-response experiment, the x-axis most often represent the TOTAL concentration (initial concentration). The two are equal only if the concentration of sensor (receptor, enzyme etc.) is much lower than the Ka.



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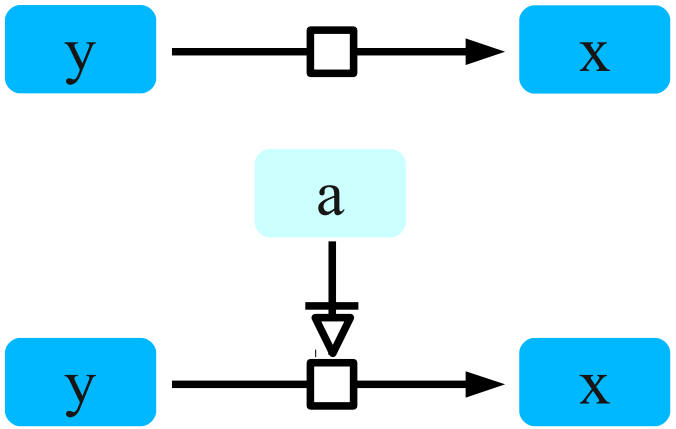

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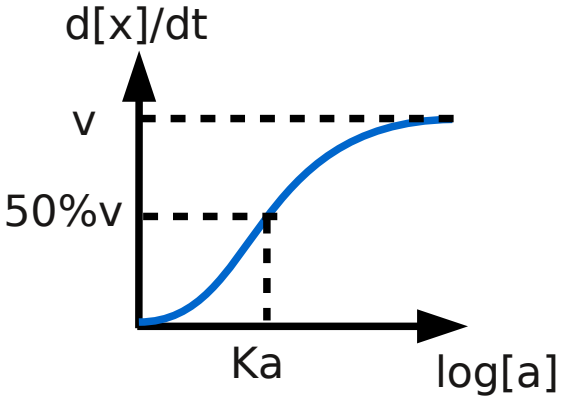
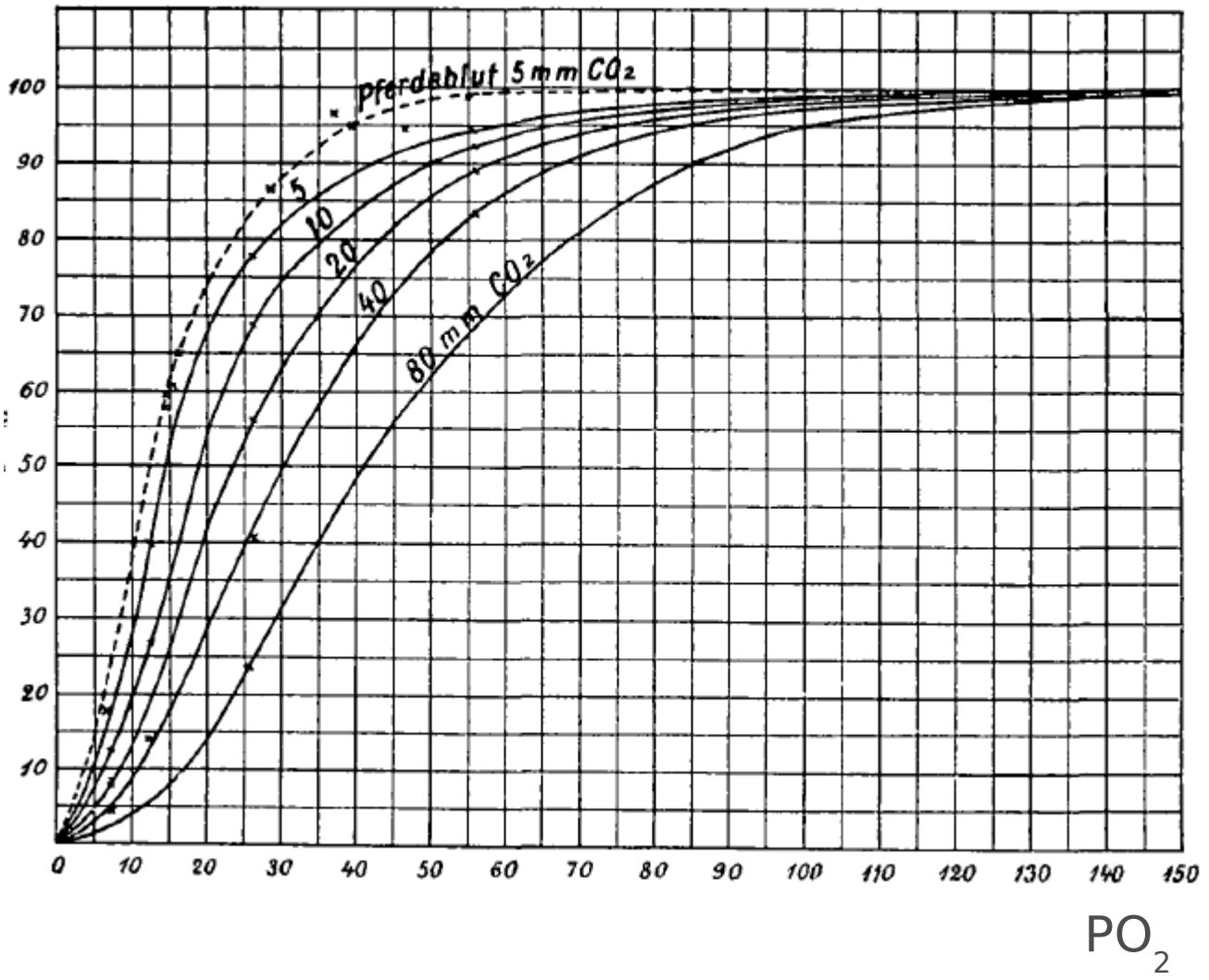


Origins of ultrasensitivity: Bohr



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

$$\mathrm{Hb} + \mathrm{O_2} \rightleftarrows \mathrm{HbO_2},$$
$$\mathrm{Hb}_n + n\mathrm{O_2} \rightleftarrows \mathrm{Hb}_n\mathrm{O}_{2n},$$

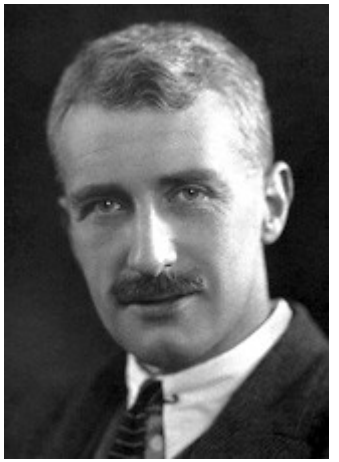
where Hb_n represents the aggregate of n molecules of Hb. I have supposed that in every solution there are many different sized aggregates, corresponding to many values of n.

If there were in the solution only Hb and $\mathrm{Hb_2}$ the dissociation curve would be

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

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

Hill AV (1910) The possible effects of the aggregation of the molecules of hæmoglobin on its dissociation curves. *J Physiol* 40: iv-vii.



Origins of ultrasensitivity: Hill

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

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The equation for the reaction would be

$$\mathrm{Hb} + \mathrm{O_2} \rightleftarrows \mathrm{HbO_2},$$
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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.

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

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

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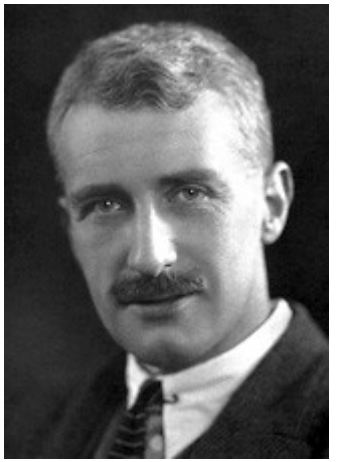

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iv PROCEEDINGS OF THE PHYSIOLOGICAL

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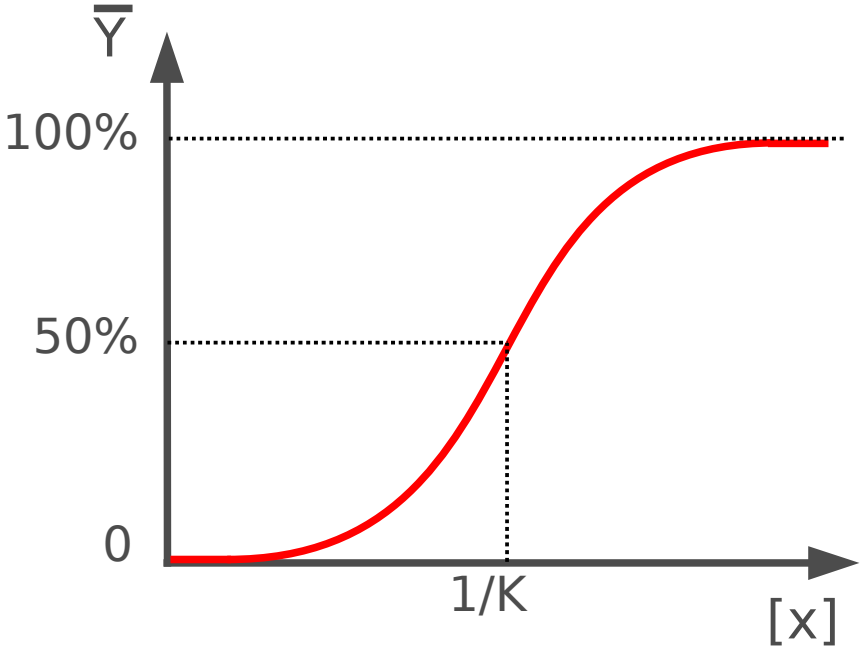
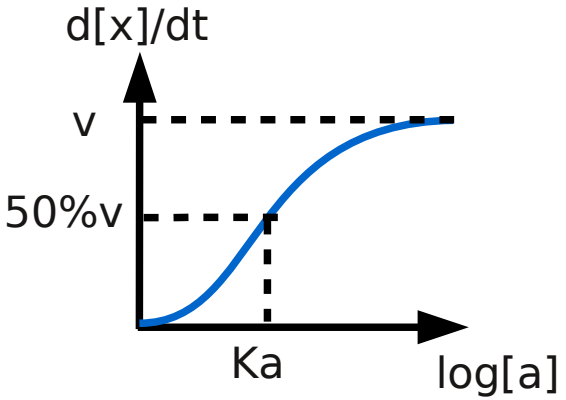


Phenomenological ultrasensitivity

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



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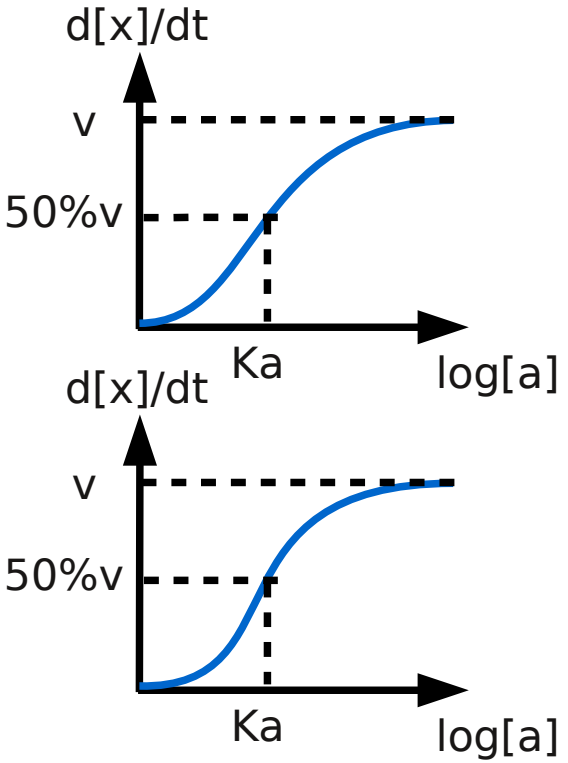

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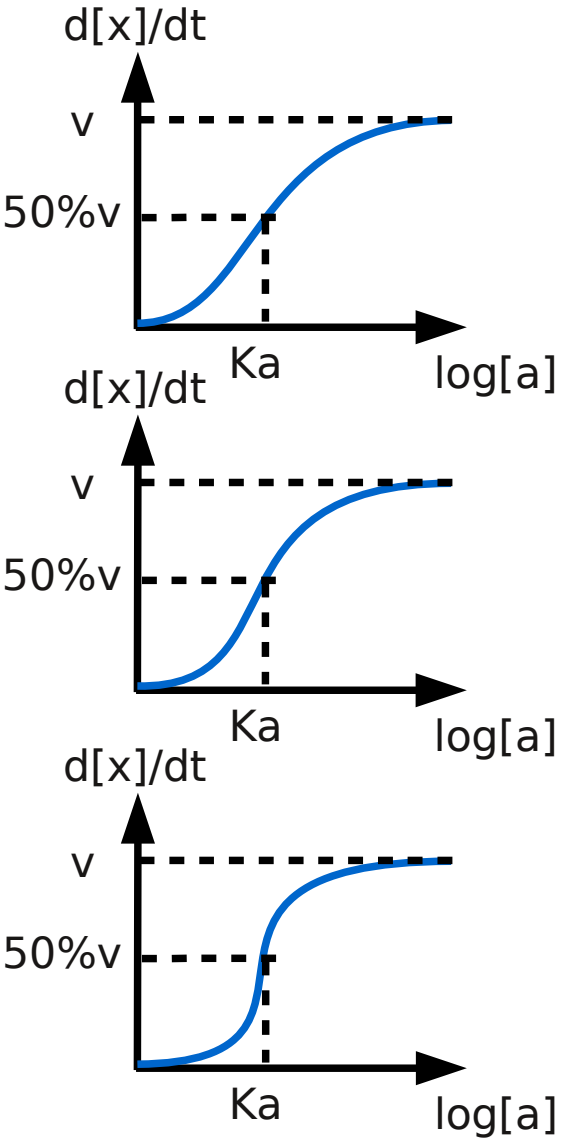
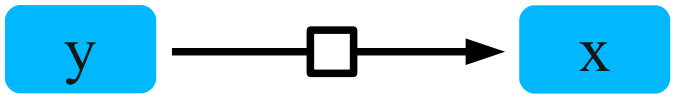
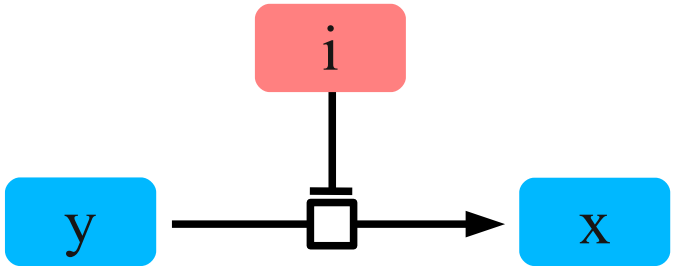


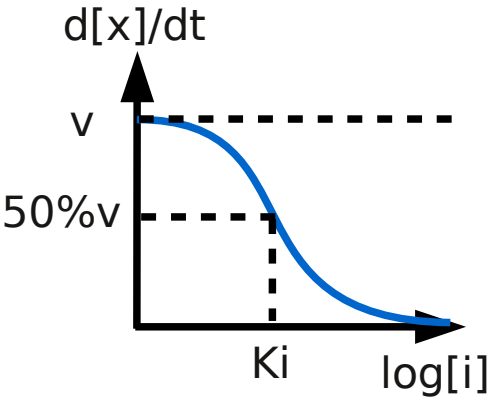
Generalisation: inhibitors



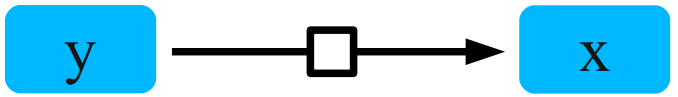
$$\frac{d[x]}{dt} = v(= k \cdot [y])$$



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



Generalisation: activators and inhibitors



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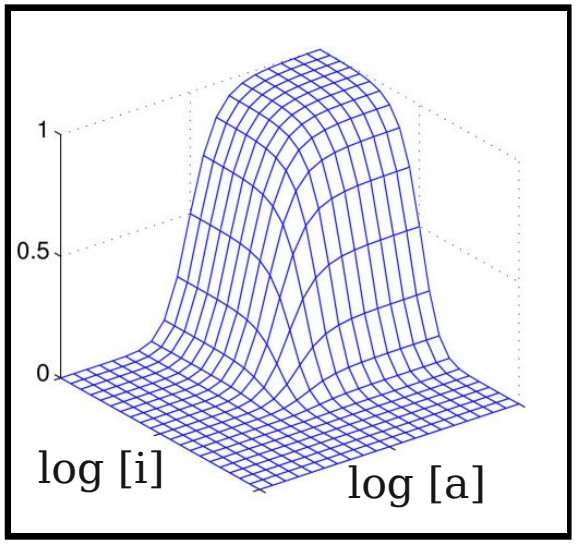
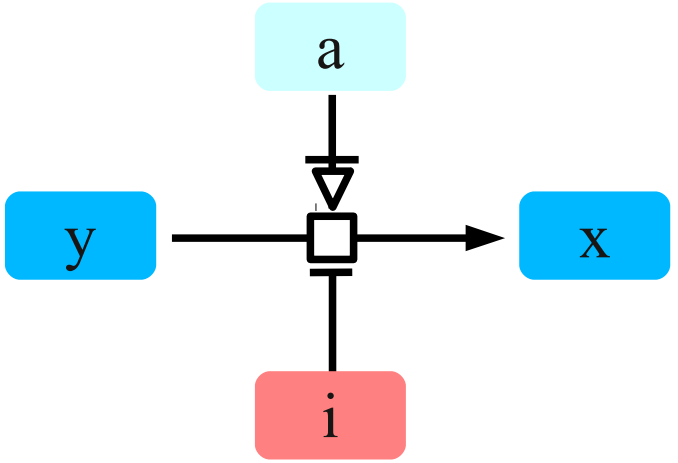
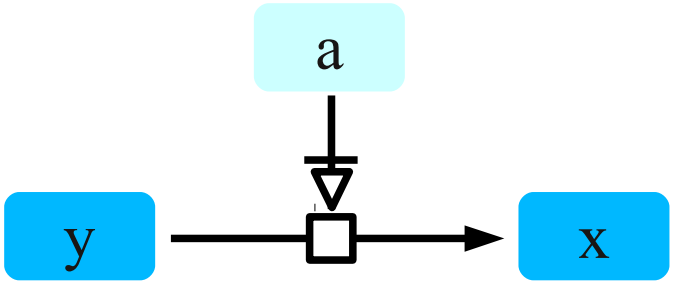




$$\frac{d[x]}{dt} = v \cdot \frac{[a]^n}{Ka^n + [a]^n} \cdot \frac{Ki^m}{Ki^m + [i]^m}$$

absolute Vs relative activators



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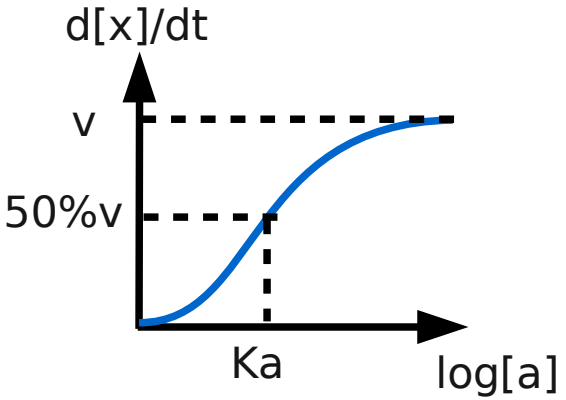

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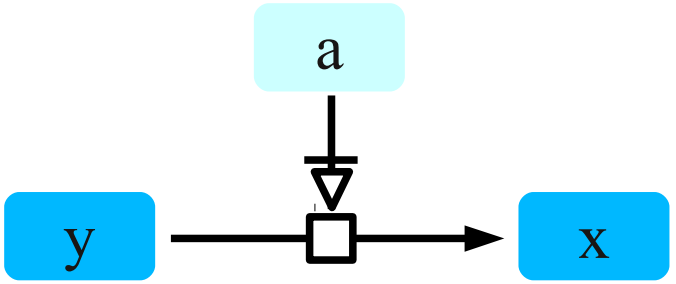

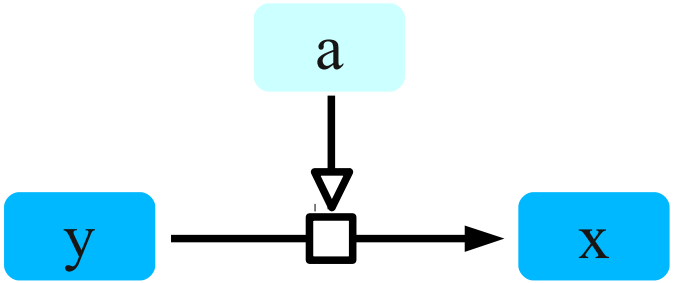

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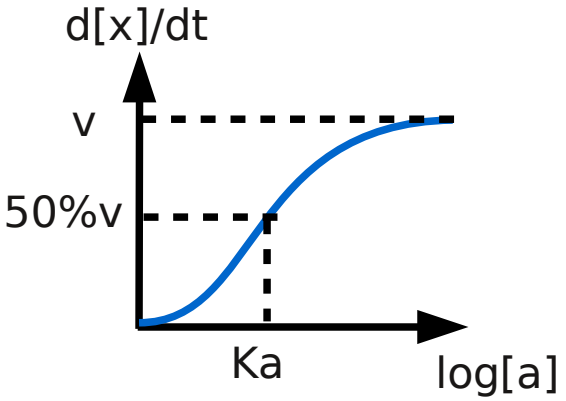

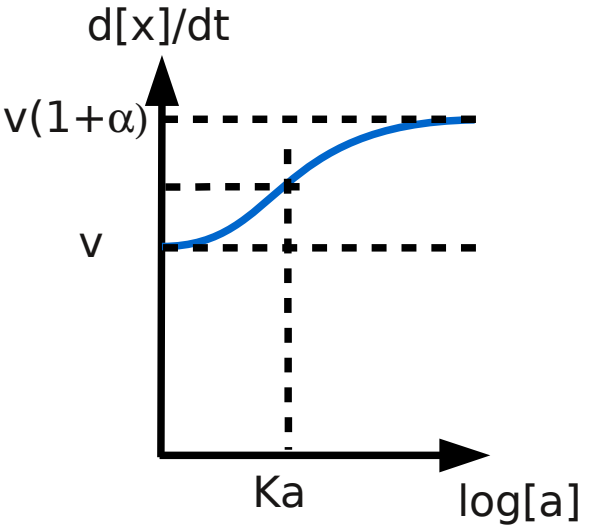

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How can-we maintain a stable level with a dynamic system?

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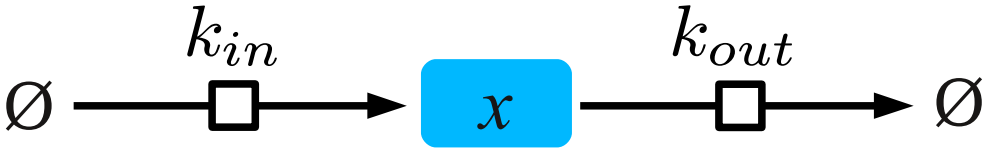

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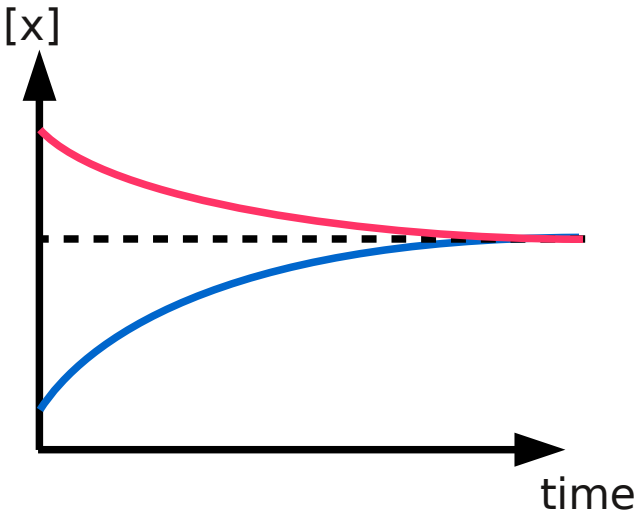

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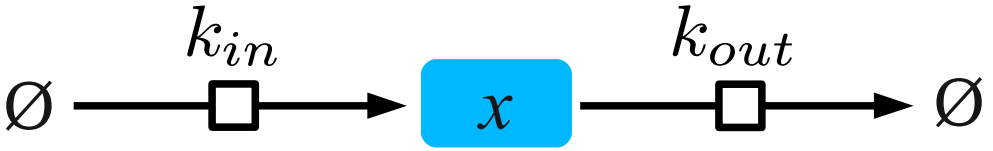

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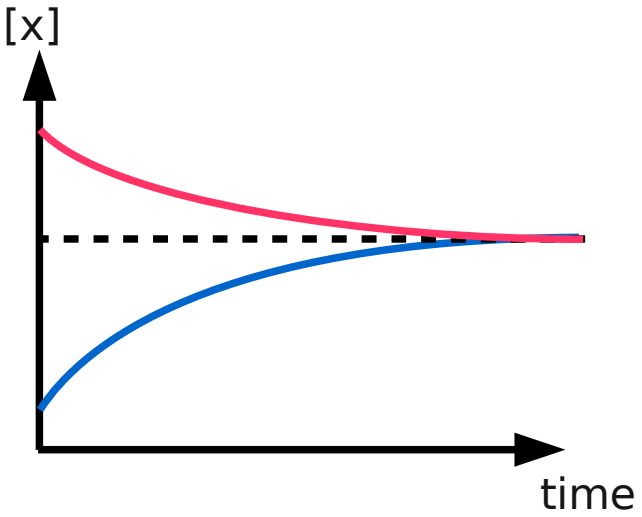
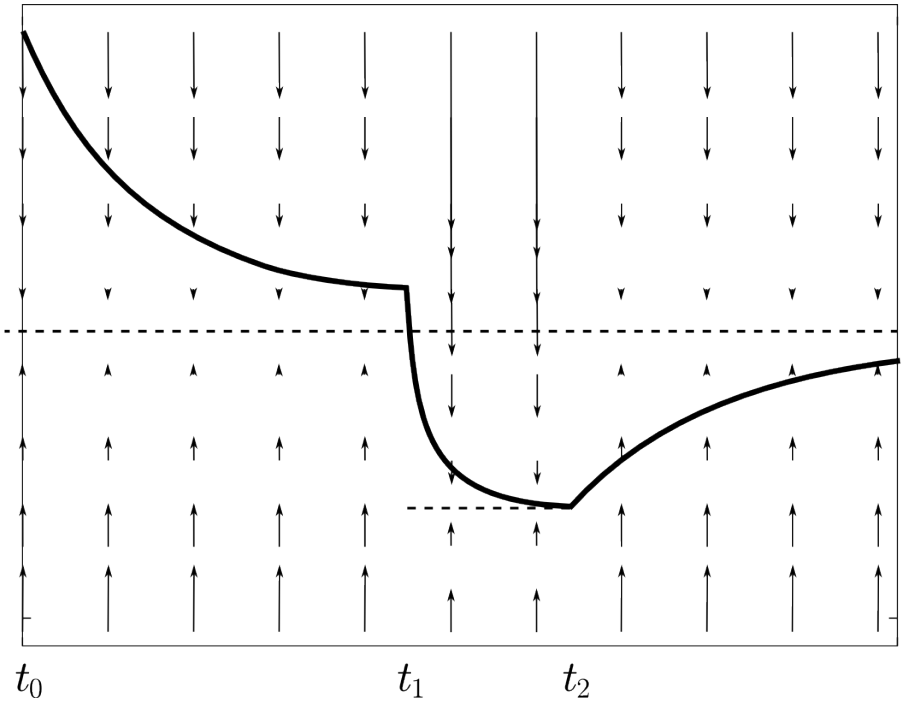




Much software exist

SBML.org The Systems Biology Markup Language

News Documents Downloads Forums Facilities Community Events About Google Site Search.

Parent pages: SBML.org

SBML Software Guide

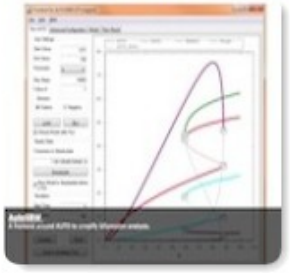
The following pages describe SBML-compatible software packages known to us. We offer different ways of viewing the information, all drawn from the same underlying data collected from the systems' developers via our **software survey**. The *Matrix* provides a table listing all known software and a variety of their features; the *Summary* provides general descriptions of most of the software; and the *Showcase* provides a sequential slideshow of a subset of the software.

Number of software packages listed in the matrix today: 230.

Go to the SBML Software Matrix

Go to the SBML Software Summary

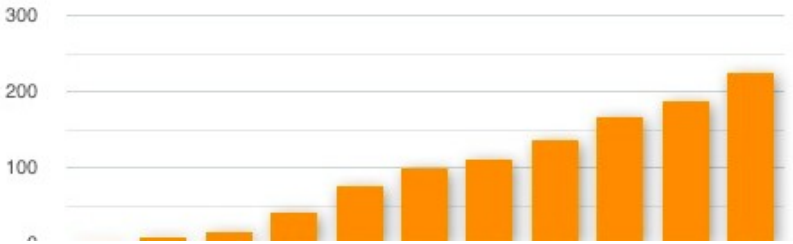
Go to the SBML Software Showcase



Please **use the survey form** to notify us about additions and suggestions.

Historical trend

The following graph shows the total number of known SBML-compatible software packages each year, as counted by the SBML Team. The counts shown are for approximately the middle of each year.



Your turn tomorrow!

- You will need:
  - COPASI stable version 4.7 (Build 34 from):

    http://www.copasi.org/tiki-index.php?page=downloadnoncommercial#stable
  - **CellDesigner**:

    http://www.celldesigner.org
  - Access to the network, and in particular:

    http://www.ebi.ac.uk/~lenov/SystemsX2011/

    http://www.ebi.ac.uk/biomodels/