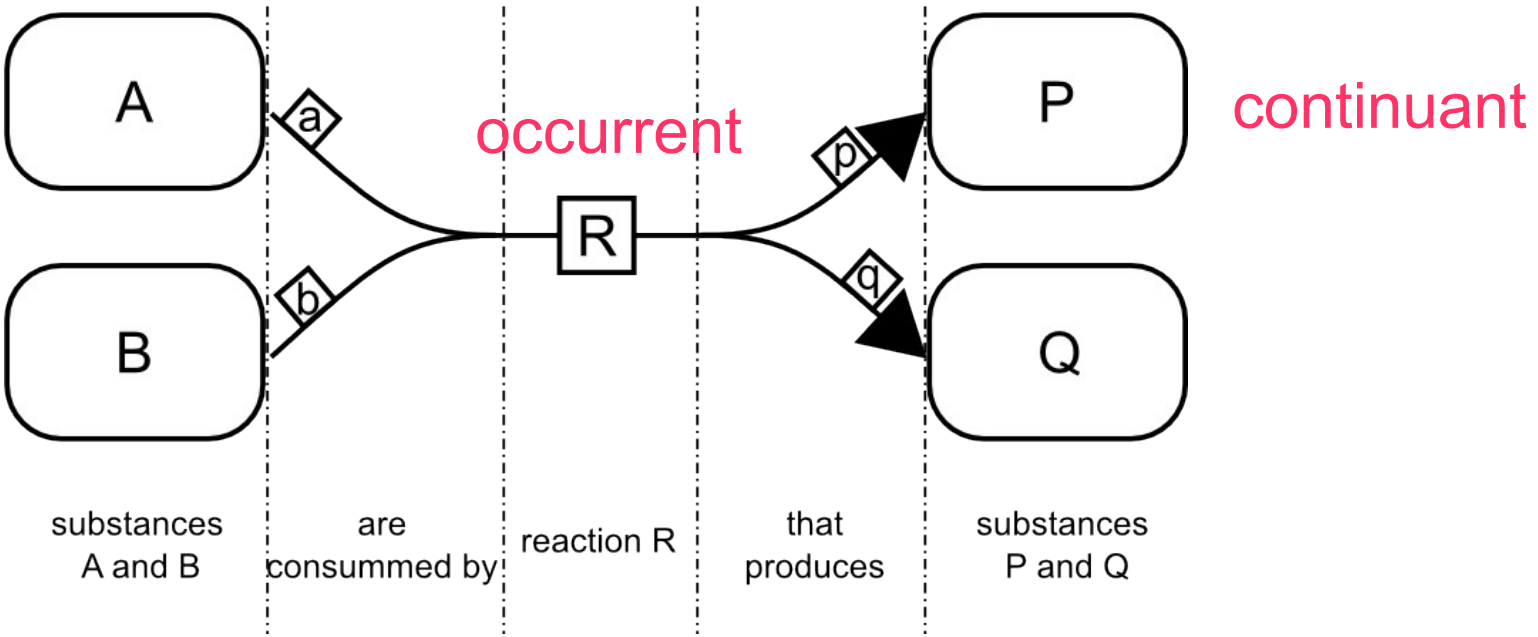
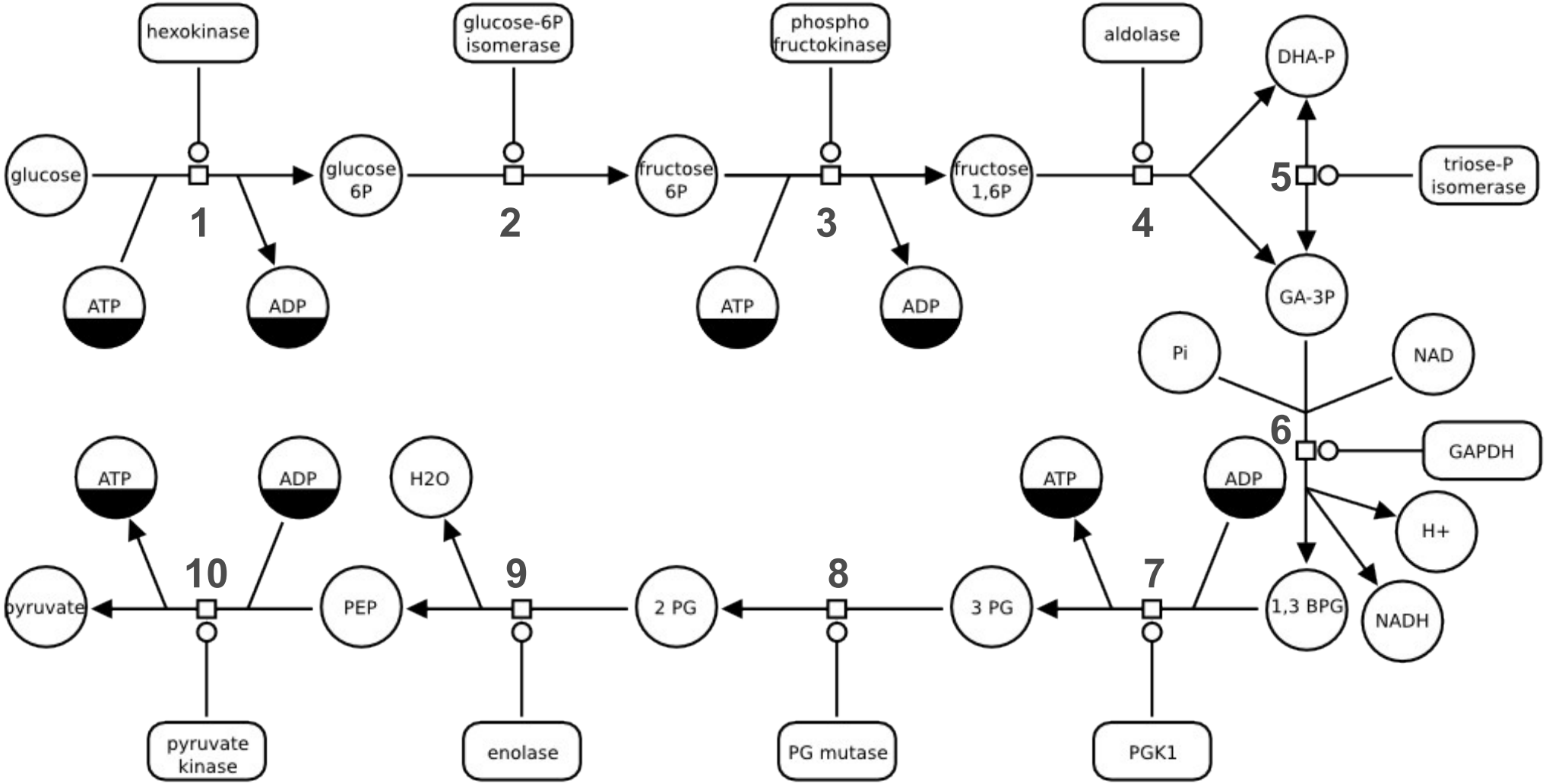
Modelling chemical kinetics

Systems Biology models ≠ ODE models

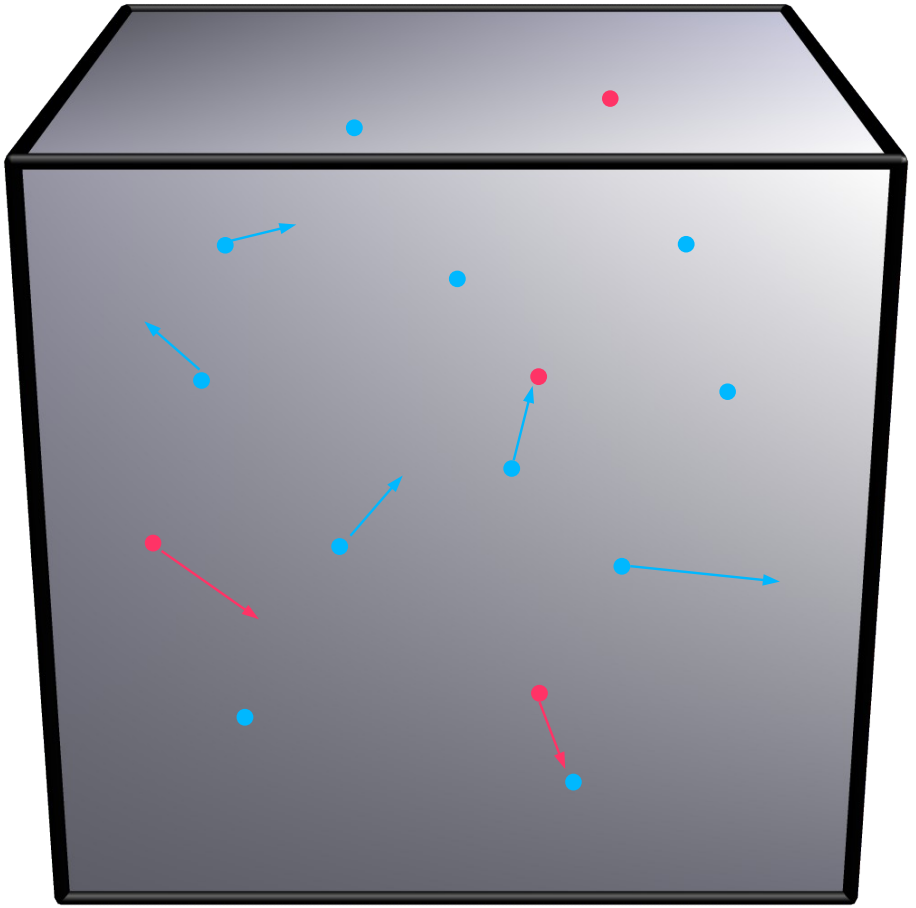
- Reconstruction of state variable evolution from process description:
  - Processes can be combined in ODEs (for deterministic simulations); transformed in propensities (for stochastic simulations)
  - Systems can be reconfigured quickly by adding or removing a process





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

Statistical physics and chemical reaction



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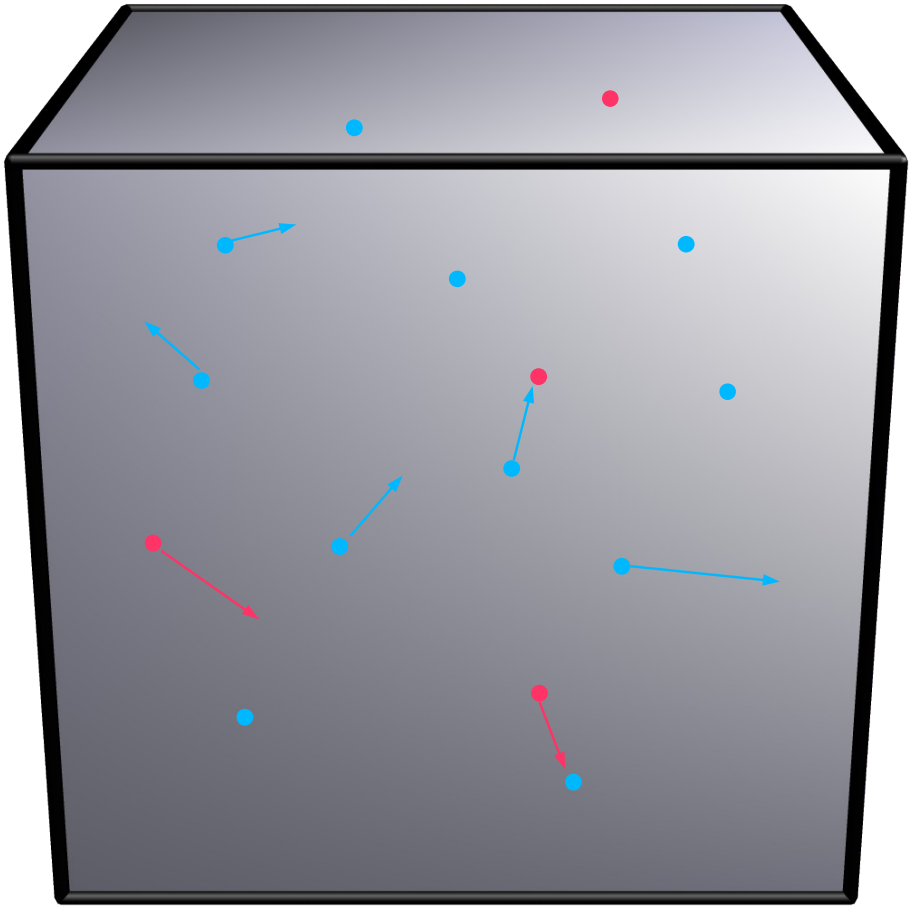
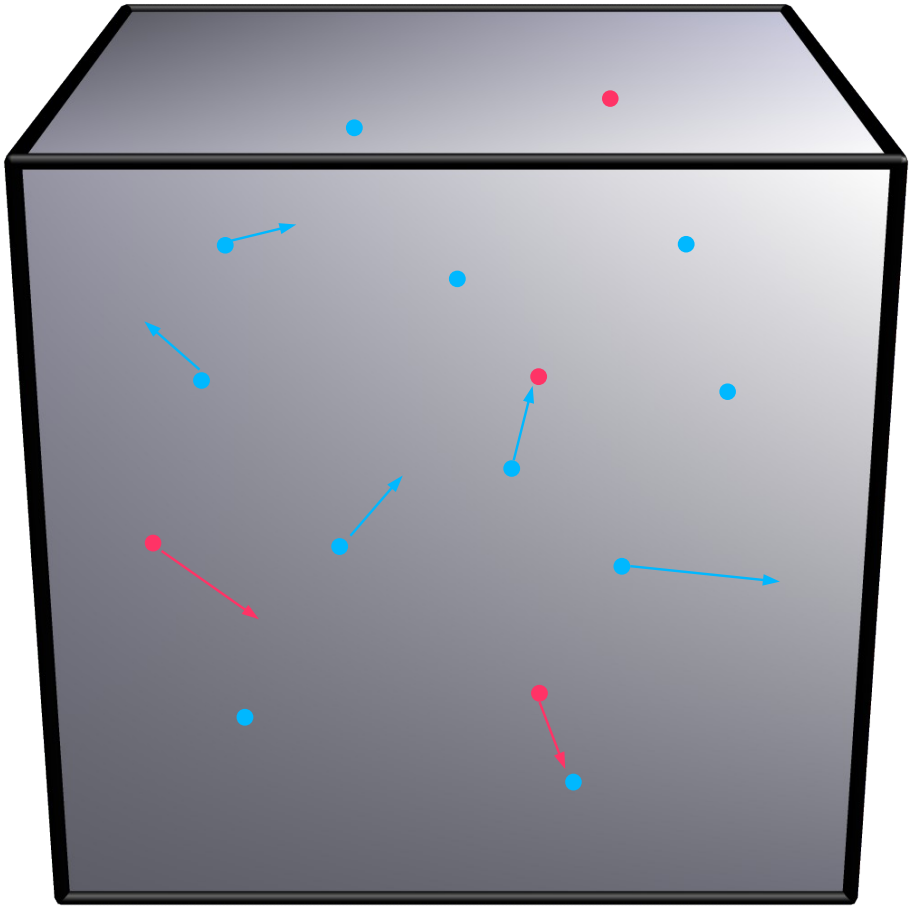


Probability to find an object in a container within an interval of time

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

Statistical physics and chemical reaction



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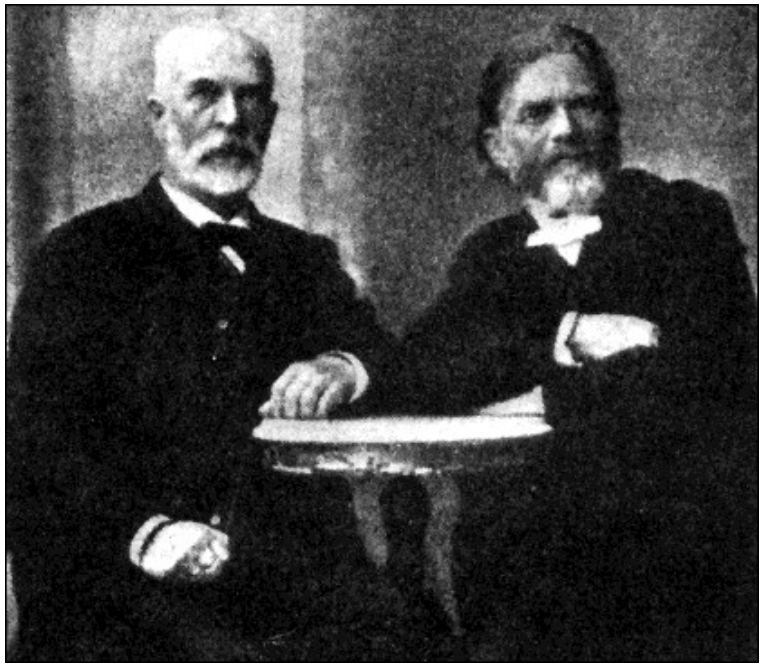
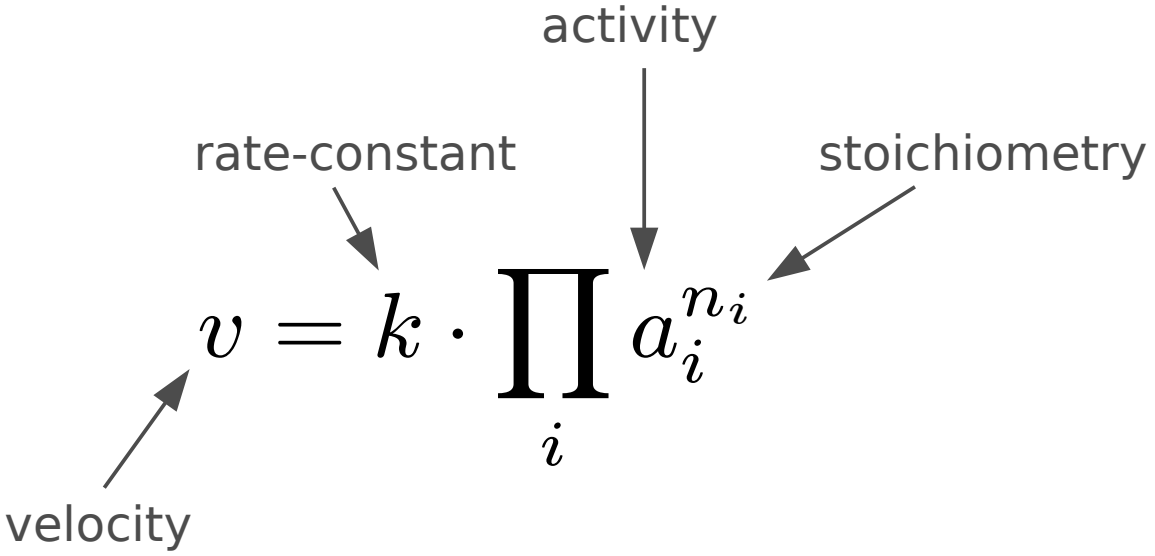
Law of Mass Action

Waage and Guldberg (1864)





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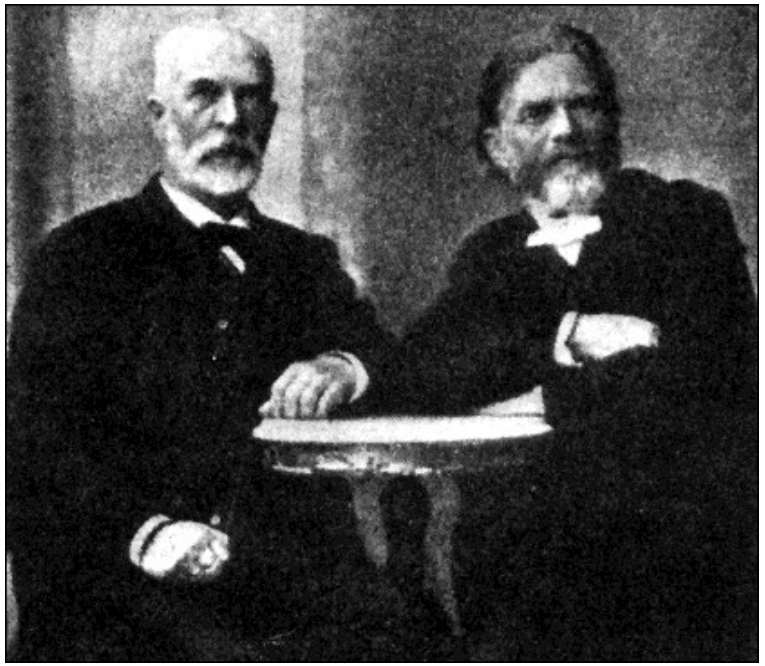

activity

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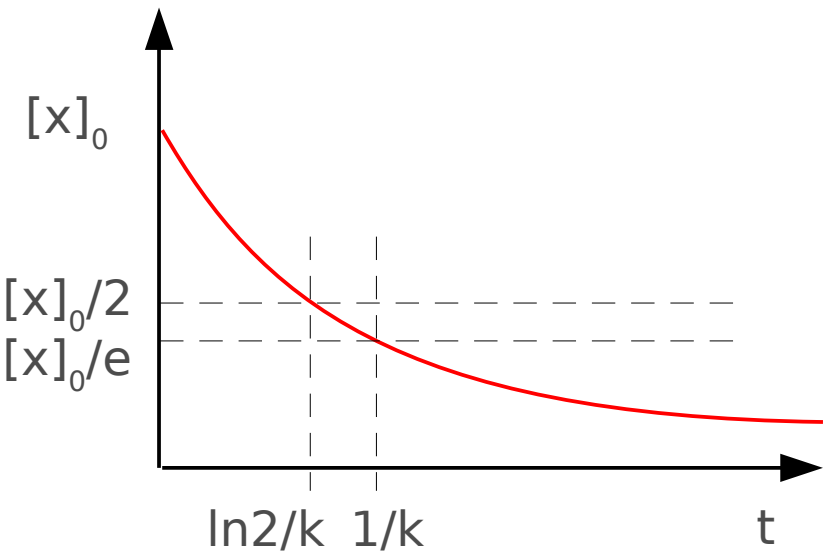
$$x(t) = [x]_0 \cdot e^{-kt}$$



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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d[P]/dt &= +k_3[ES] \\
d[E]/dt &= -k_1[E][S] + k_2[ES] + k_3[ES] \\
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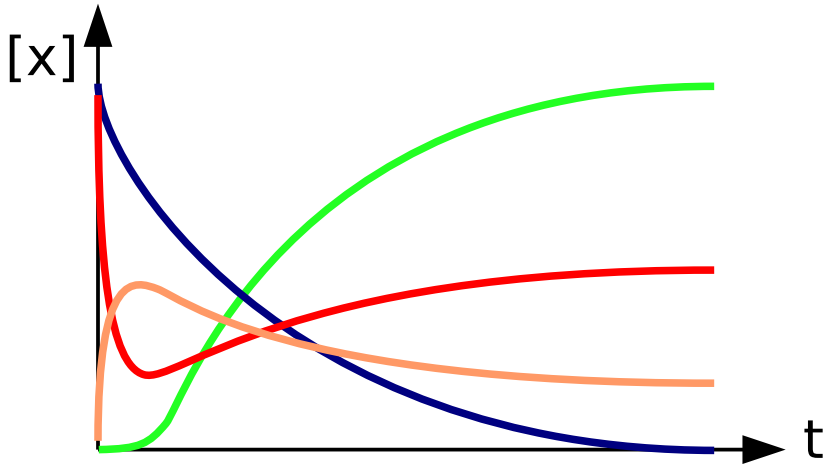


Not feasible in general

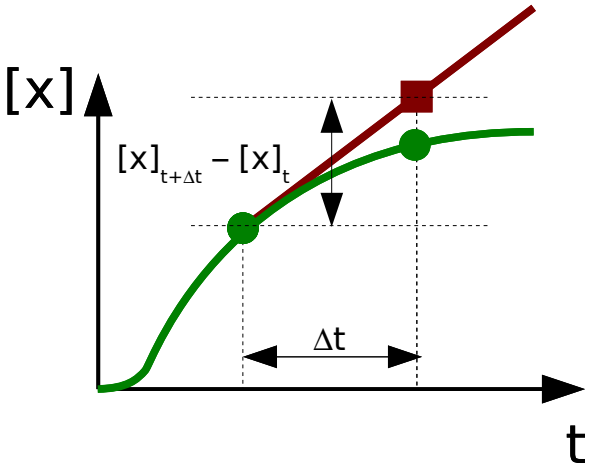
→ Numerical integration

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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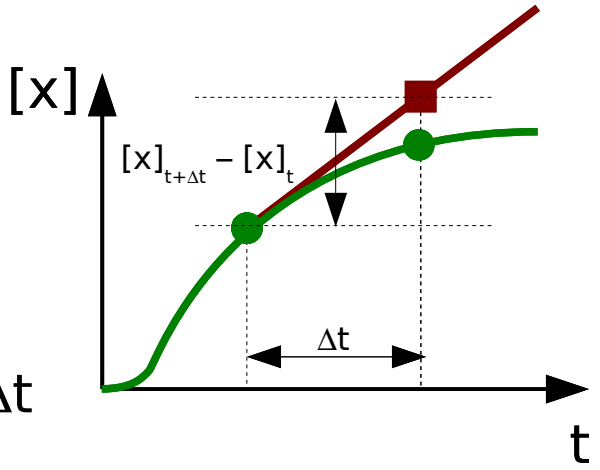

$$[P]_{t+\Delta t} = [P]_t + k_3[ES]_t \,.\, \Delta t$$

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

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

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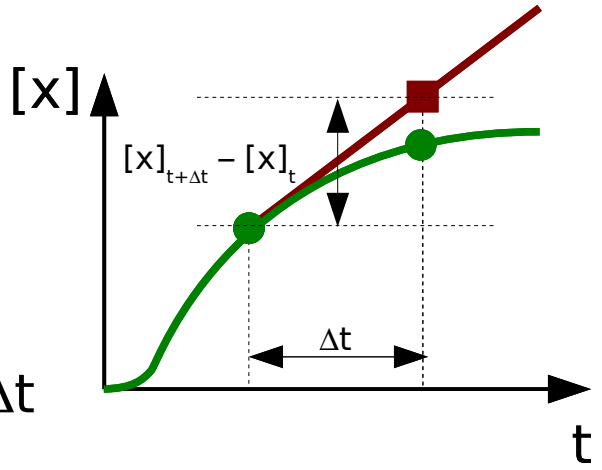

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4th order Runge-Kutta:

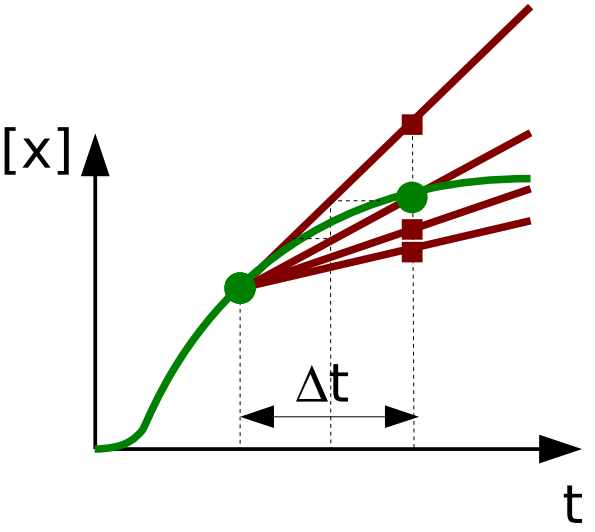
$$[x]_{t+\Delta t} = [x]_t + (F_1 + 2F_2 + 2F_3 + F_4)/6 \,.\, \Delta t$$

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

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

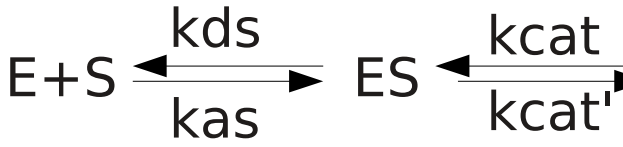
$F_3 = f([x]_t + \Delta t/2 \,.\, F_2, t + \Delta t/2)$

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



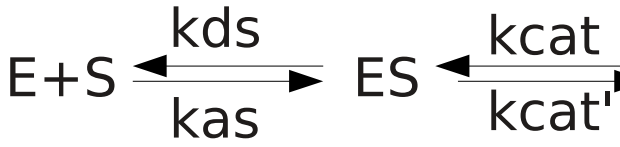
Pause

Choose the right formalism



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

Choose the right formalism



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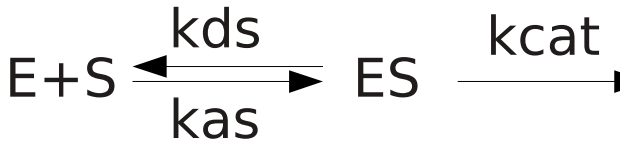
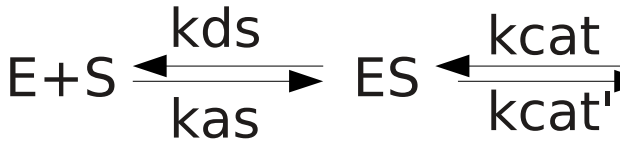


catalysis irreversible

Choose the right formalism



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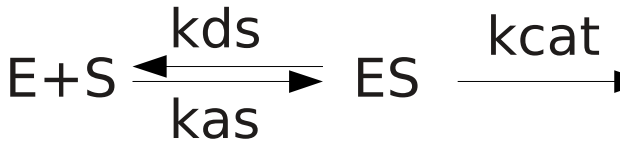
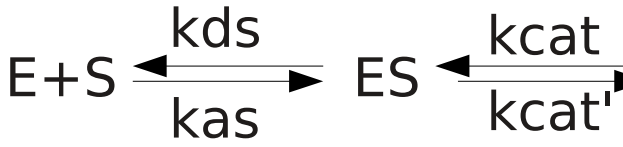


catalysis irreversible

product is consumed
before rebinding

Choose the right formalism



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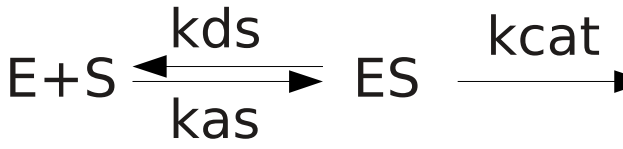

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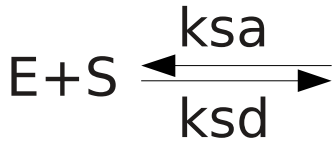

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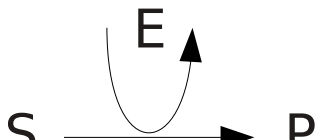


steady-state

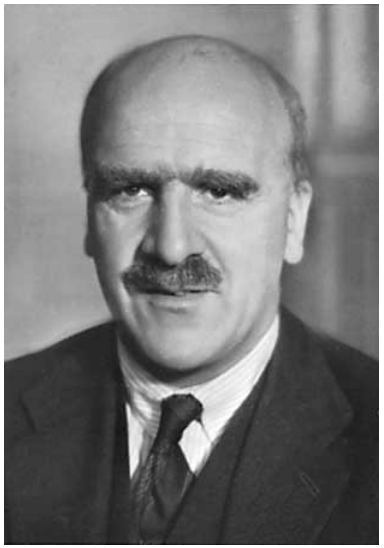
$$\frac{d[P]}{dt} = [E]k_{\text{cat}}\frac{[S]}{K_m + [S]}$$

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

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

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

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

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

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

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

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

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

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

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

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

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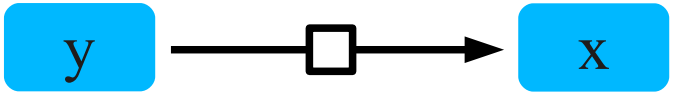
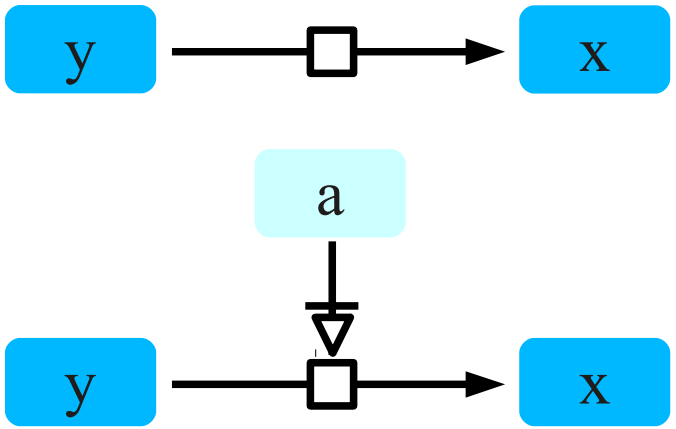
Generalisation of modulation



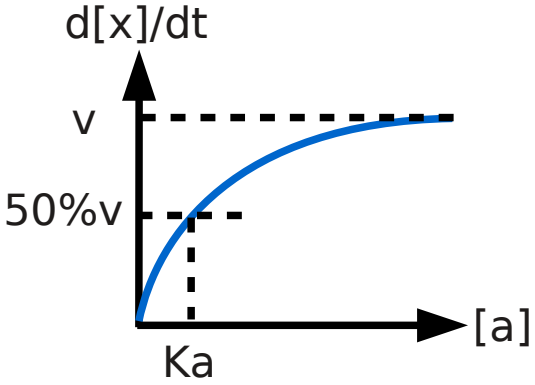
$$\frac{d[x]}{dt} = v(= k \cdot [y])$$

Generalisation: activators



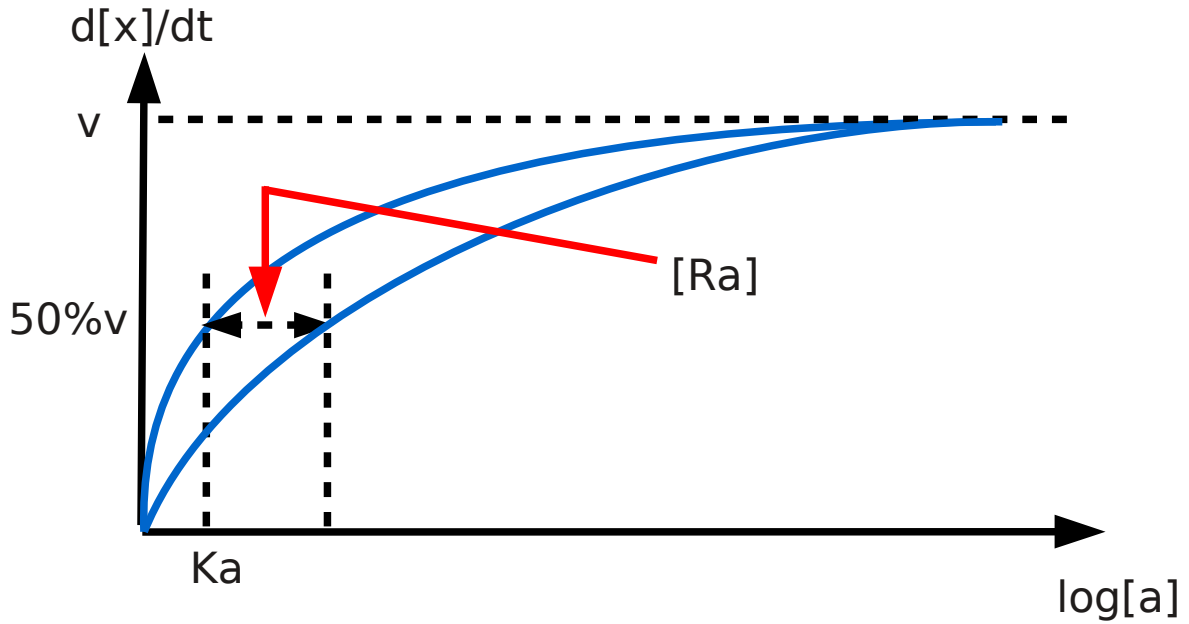
$$\frac{d[x]}{dt} = v(= k \cdot [y])$$

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



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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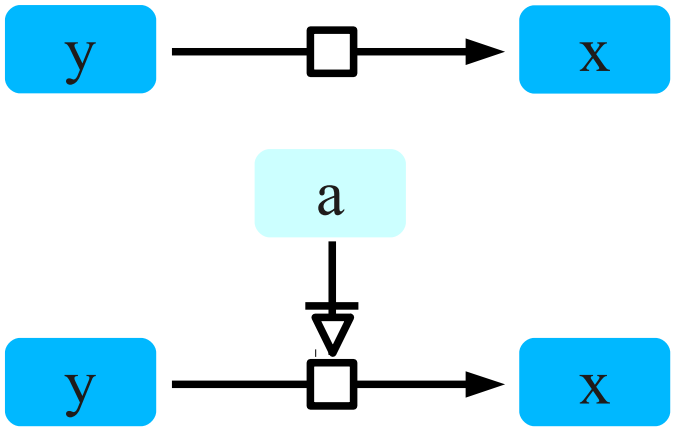

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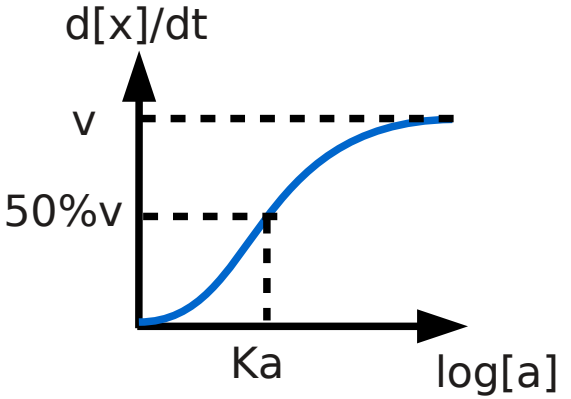
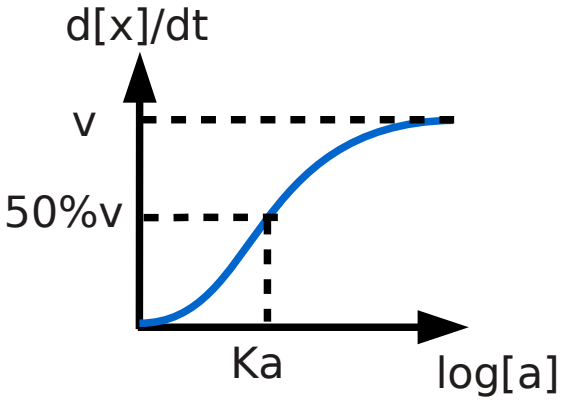


Phenomenological ultrasensitivity

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



Phenomenological ultrasensitivity

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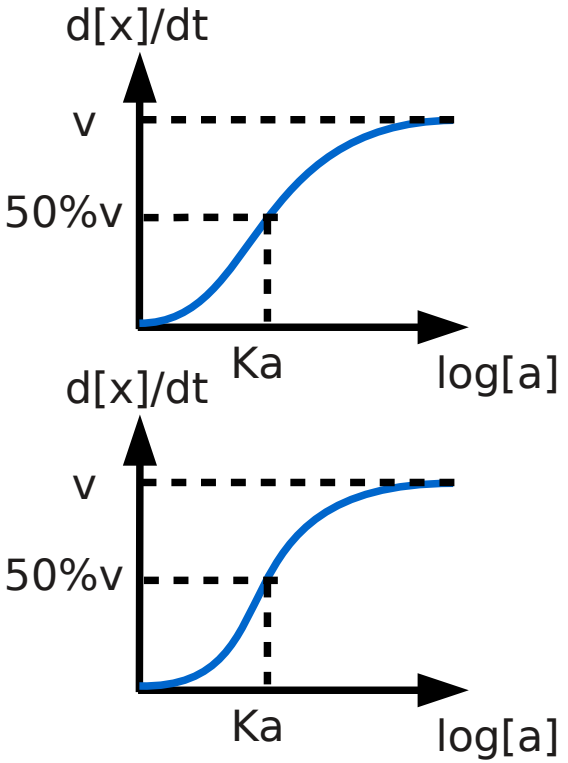

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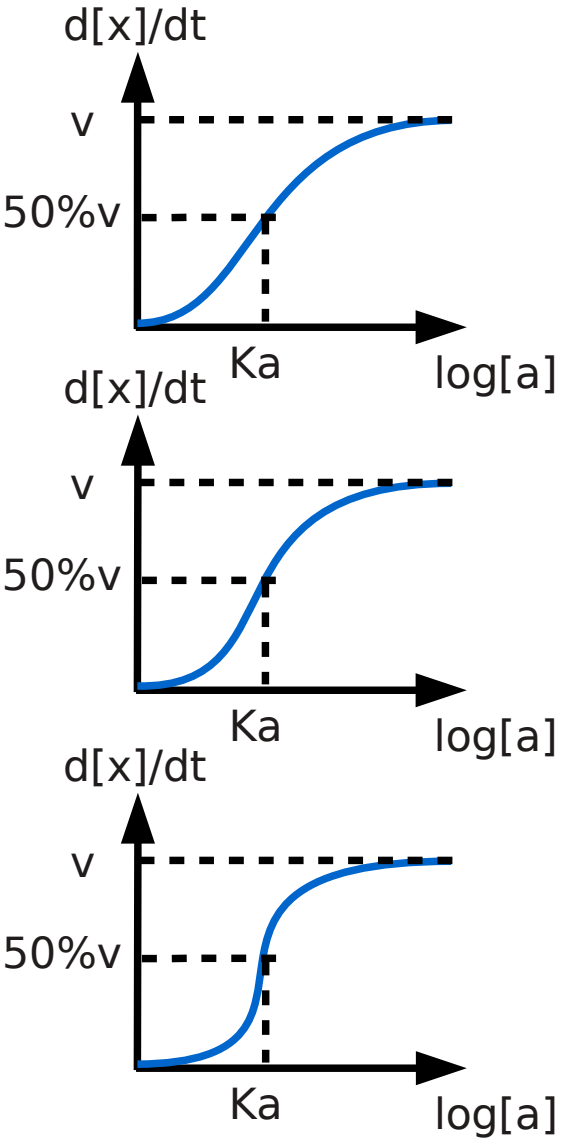
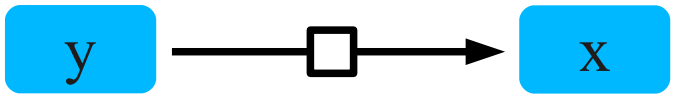


Generalisation: inhibitors



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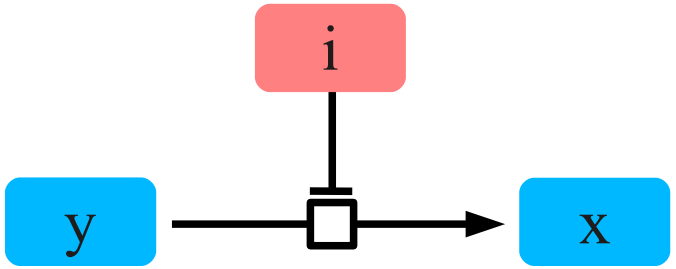
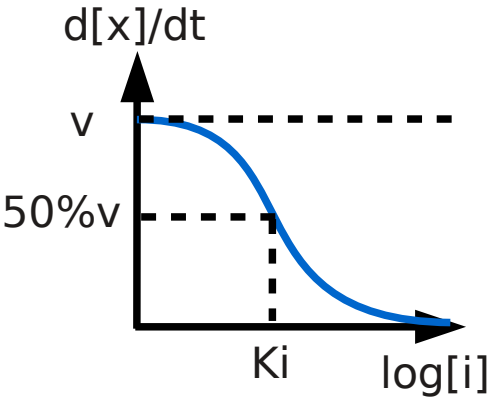
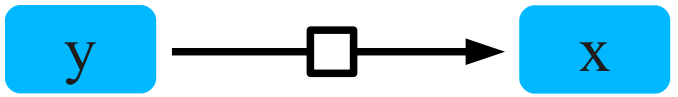


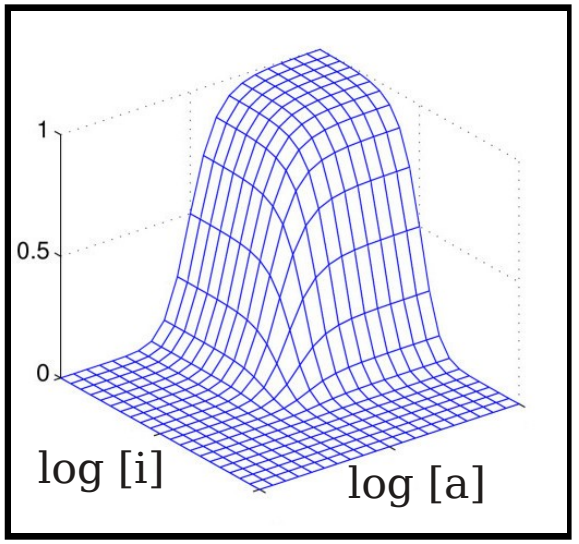
$$\frac{d[x]}{dt} = v \cdot \frac{Ki^m}{Ki^m + [i]^m}$$

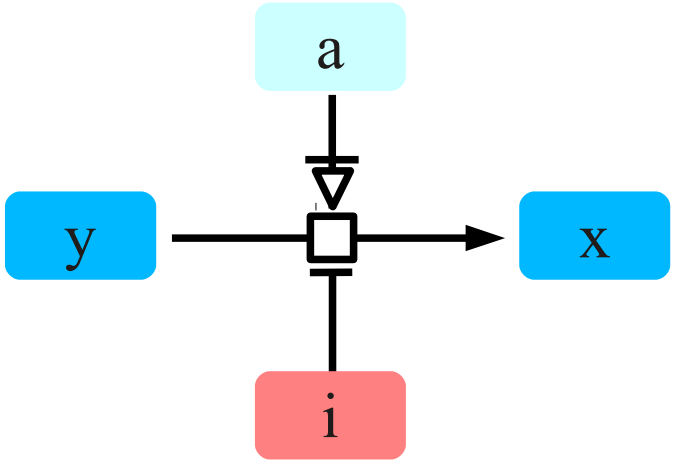


Generalisation: activators and inhibitors



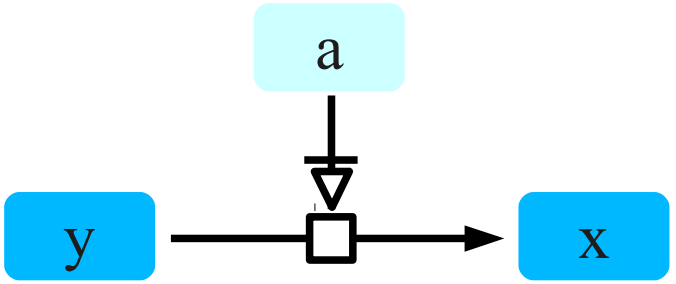
$$\frac{d[x]}{dt} = v(= k \cdot [y])$$



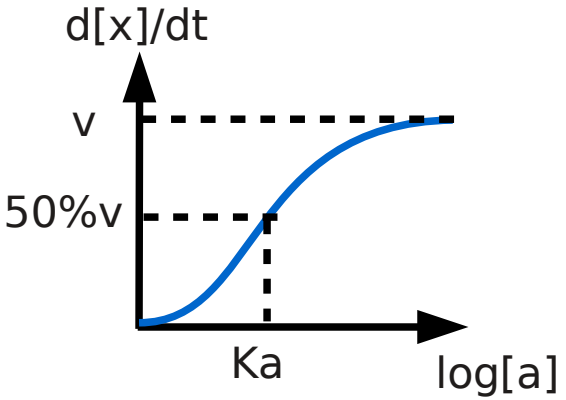


$$\frac{d[x]}{dt} = v \cdot \frac{[a]^n}{Ka^n + [a]^n} \cdot \frac{Ki^m}{Ki^m + [i]^m}$$

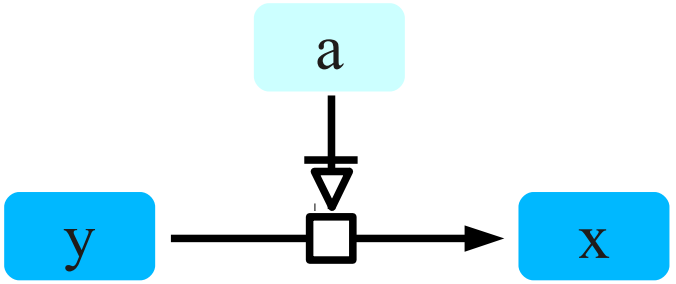
absolute Vs relative activators

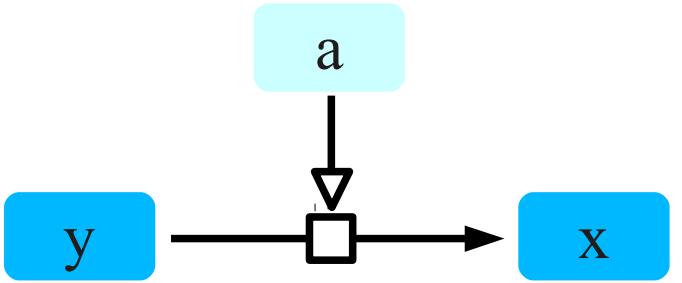


$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$



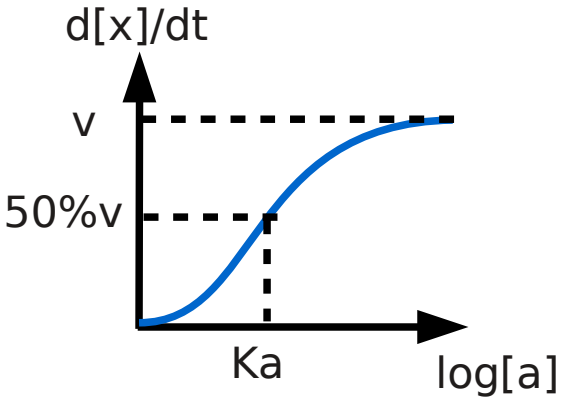
absolute Vs relative activators

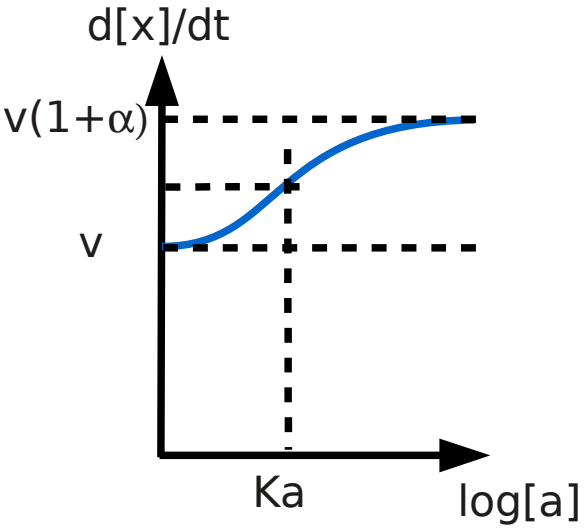




$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$

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





Homeostasis

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

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

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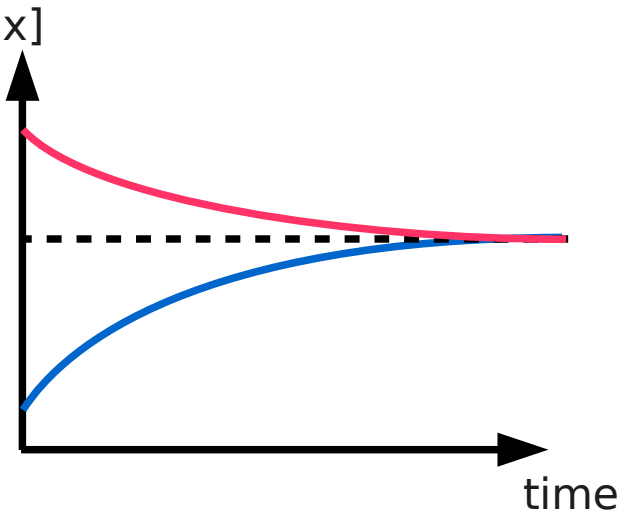
$$\frac{d[x]}{dt} = k_{in} - k_{out} \cdot [x]$$

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



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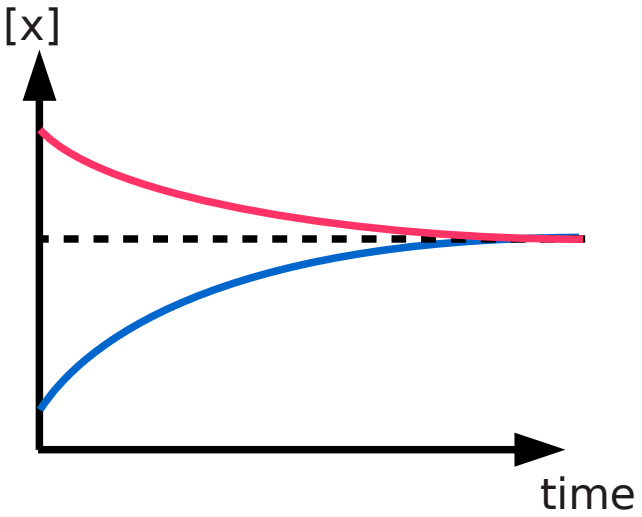
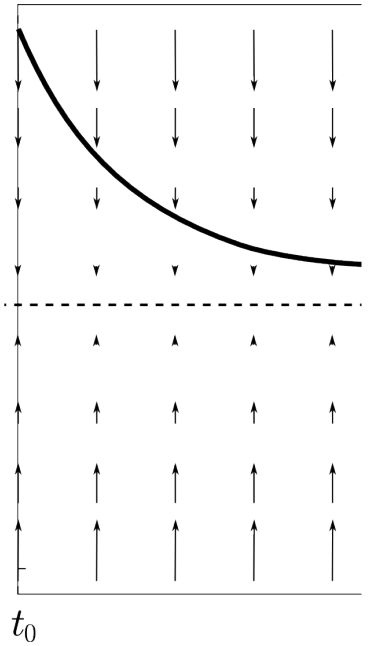
$$\frac{d[x]}{dt} = k_{in} - k_{out} \cdot [x]$$

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





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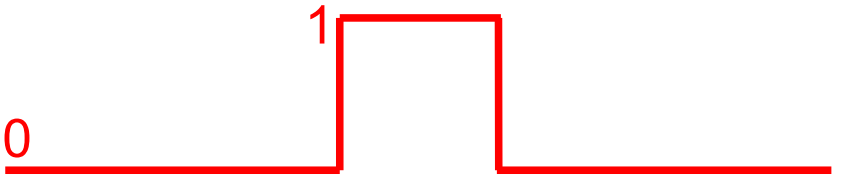
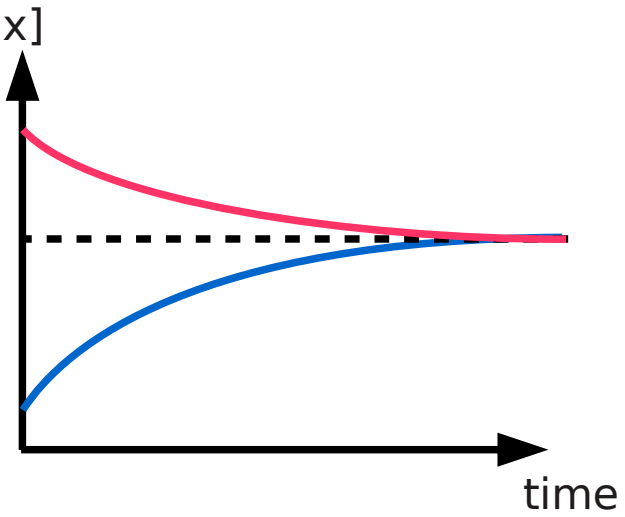
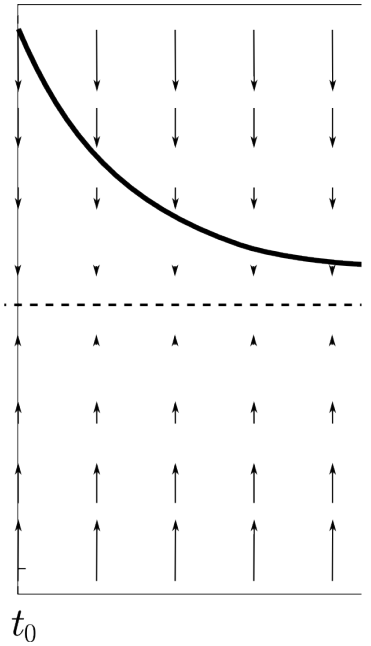
$$\frac{d[x]}{dt} = k_{in} - k_{out} \cdot [x]$$



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

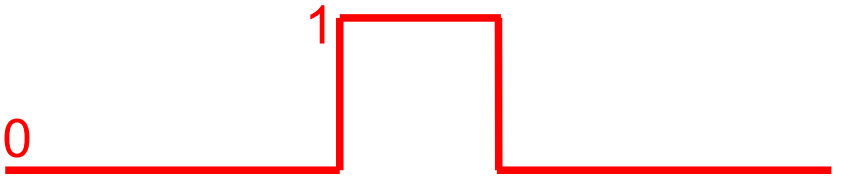




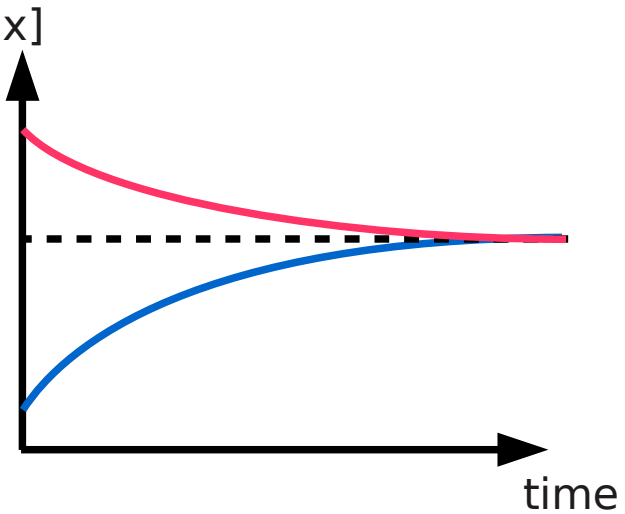
Homeostasis

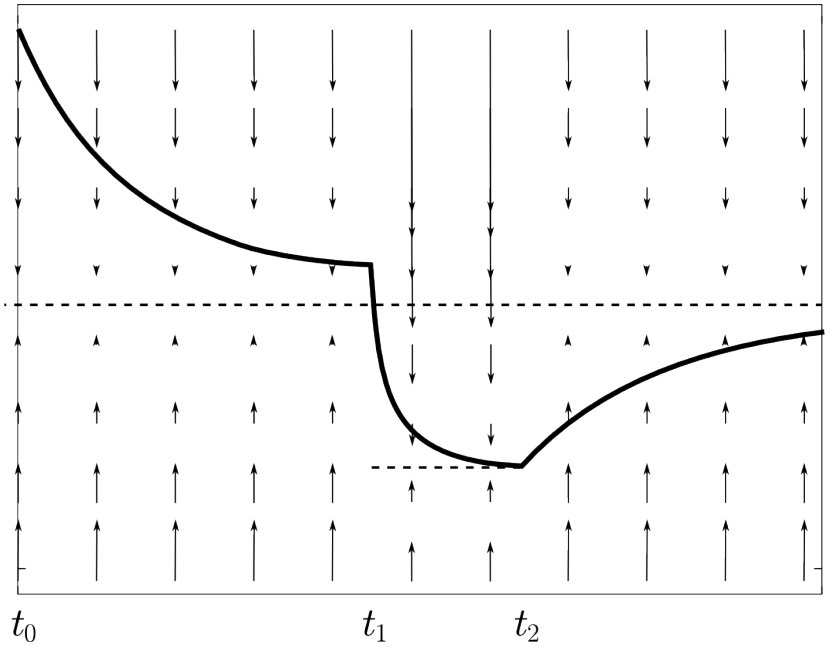
How can-we maintain a stable level with a dynamic system?

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



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





Lunch