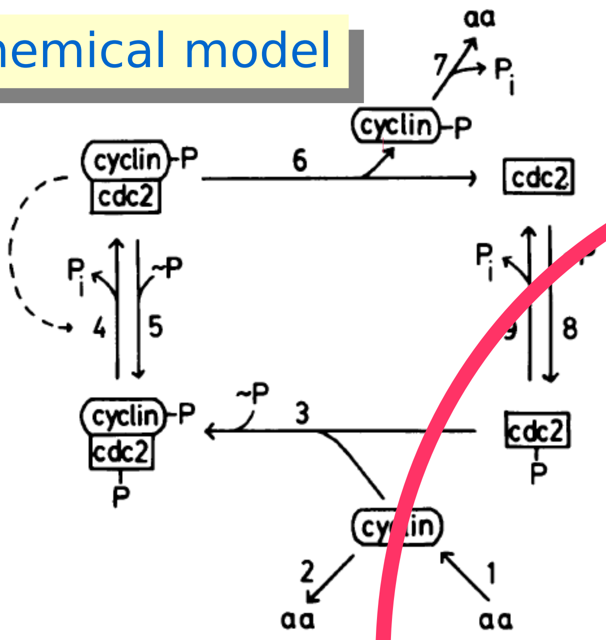
Modeling chemical kinetics

The Computational Systems Biology loop

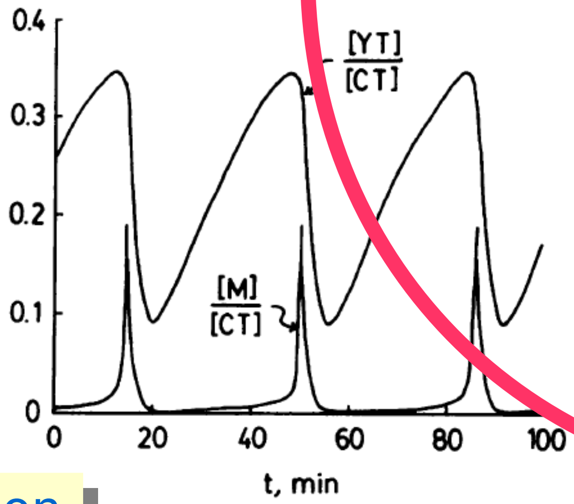
biochemical model



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



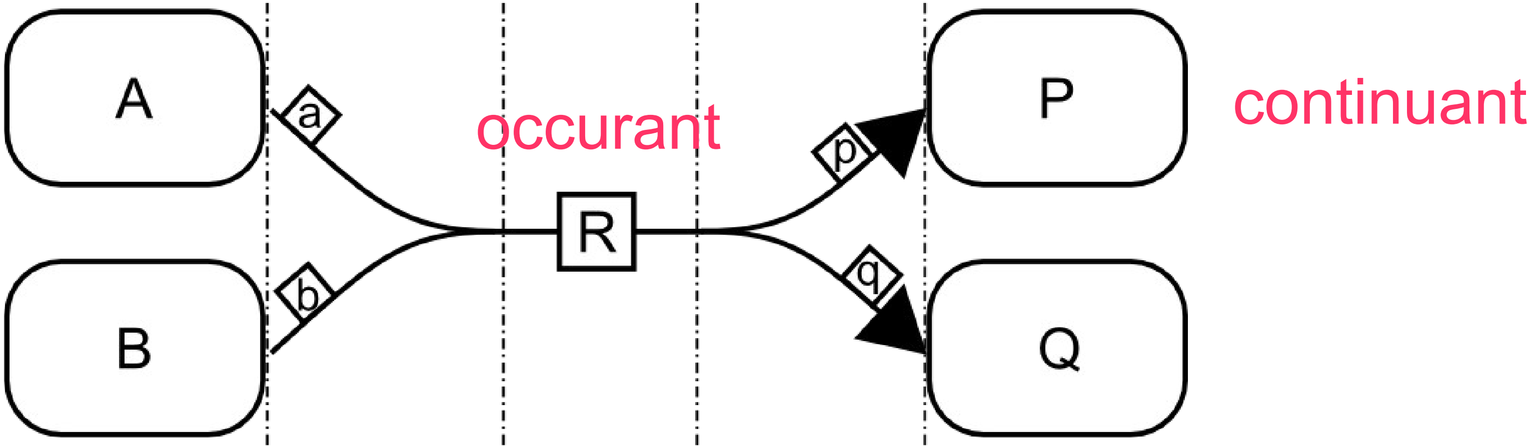
simulation

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

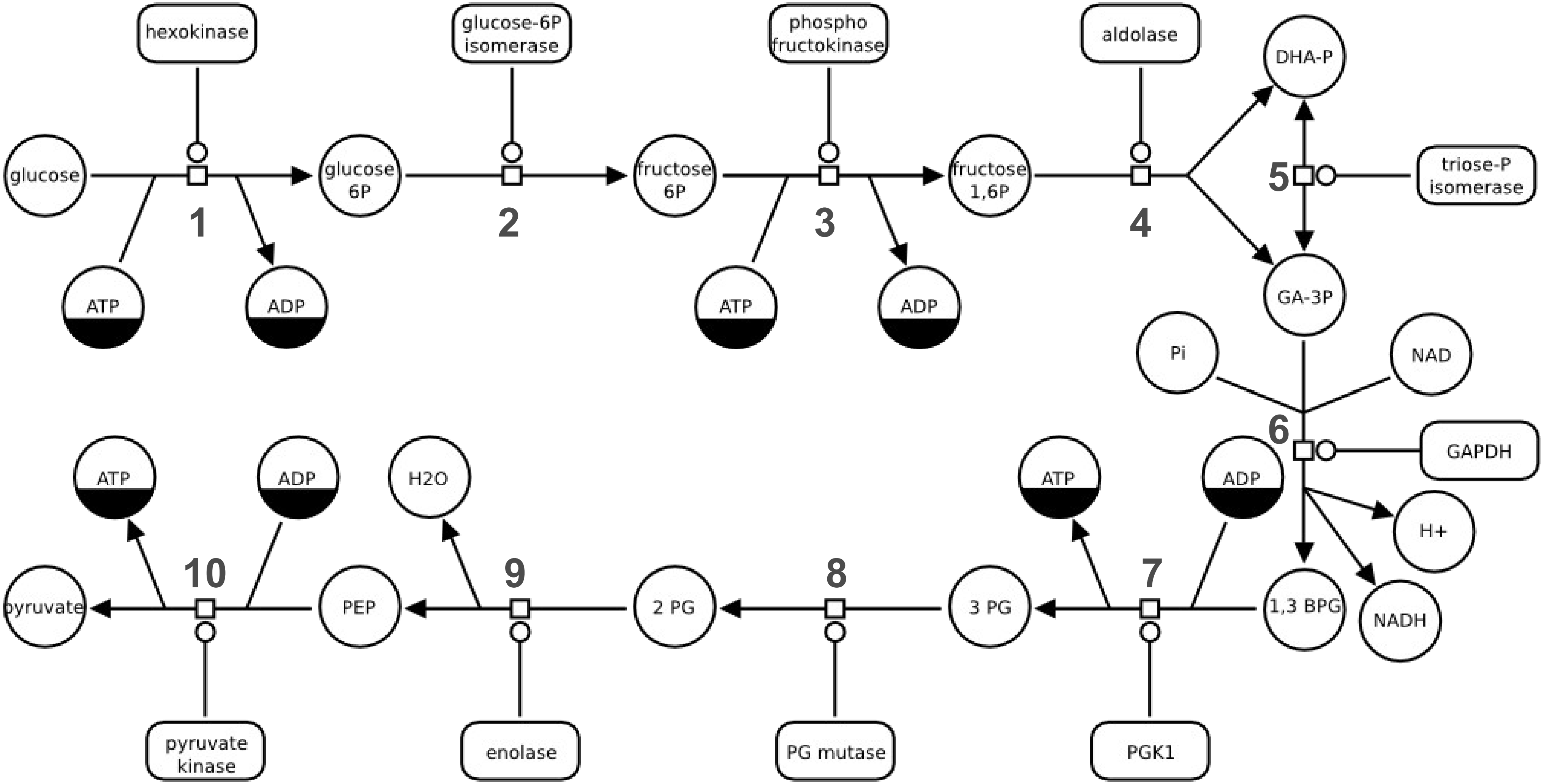
computational model

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

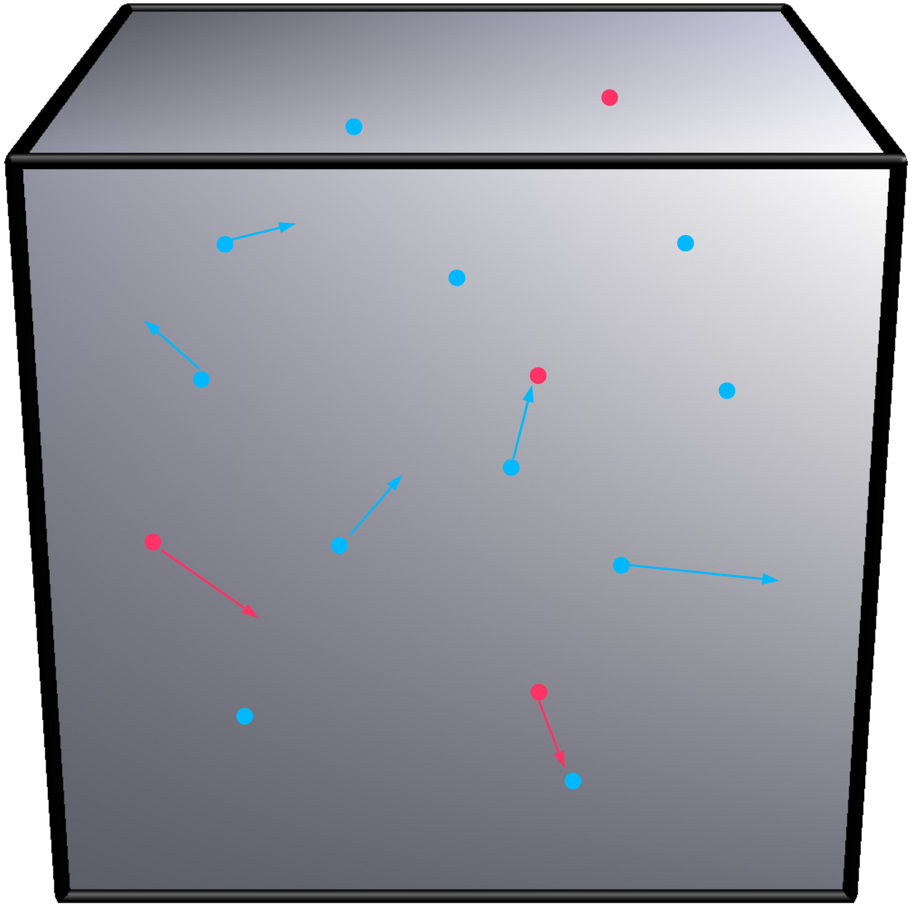


	substances A and B	are consummed by	reaction R	that produces	substances P and Q
SBO	SBO:0000240 material entity	SBO:0000394 consumption	SBO:0000375 process	SBO:0000393 production	SBO:0000240 material entity
SBML	Species	Species Reference	Kinetic Law	Species Reference	Species

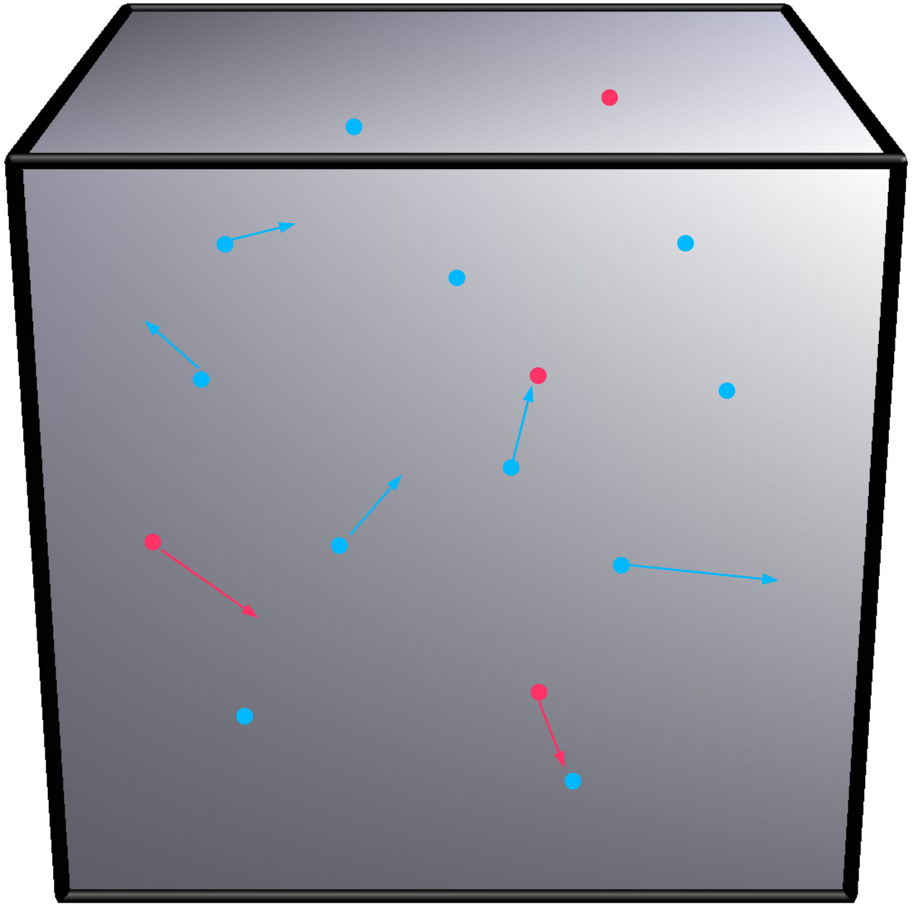


ATP is consumed by processes 1 and 3, and produced by processes 7 and 10

Statistical physics and chemical reaction

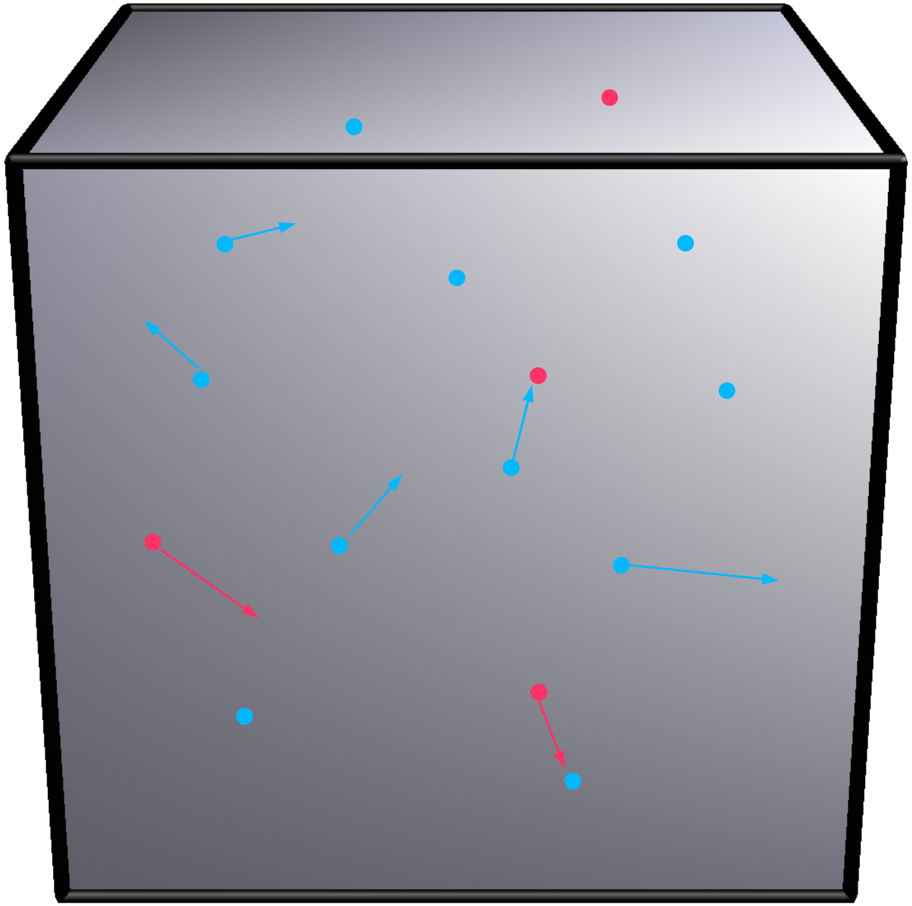


Statistical physics and chemical reaction



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

Statistical physics and chemical reaction



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

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

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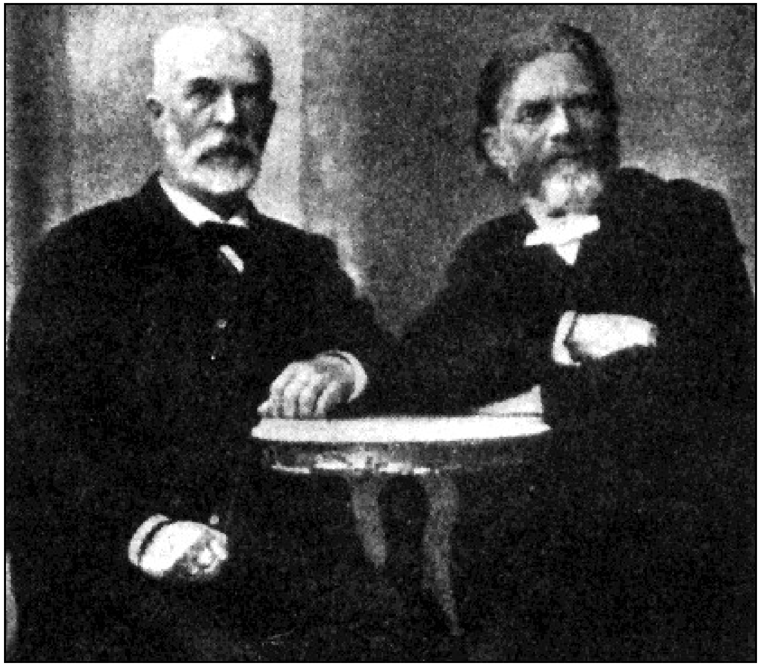
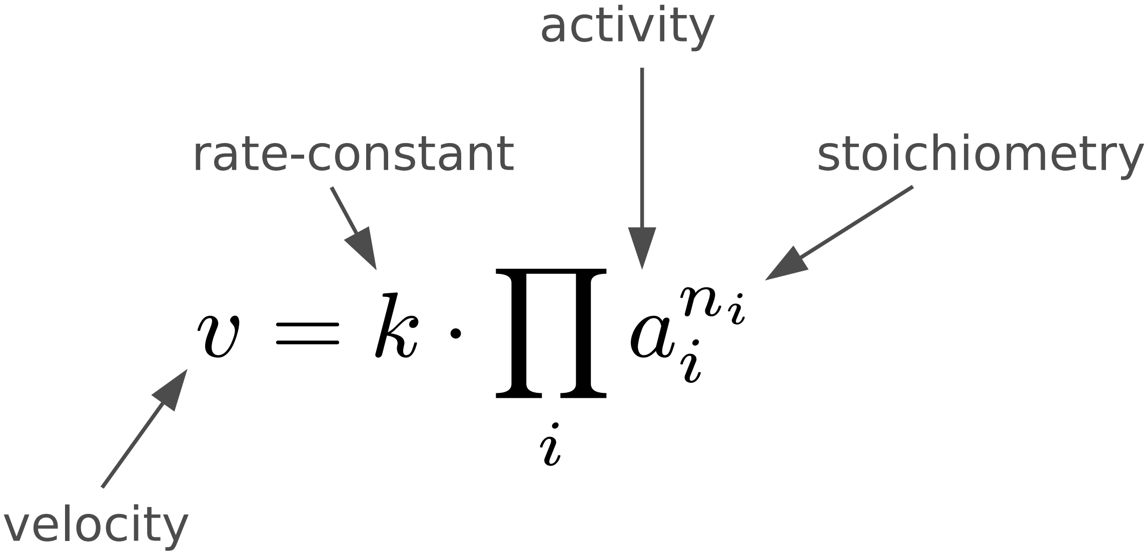
Law of Mass Action

Waage and Guldberg (1864)





activity

rate-constant

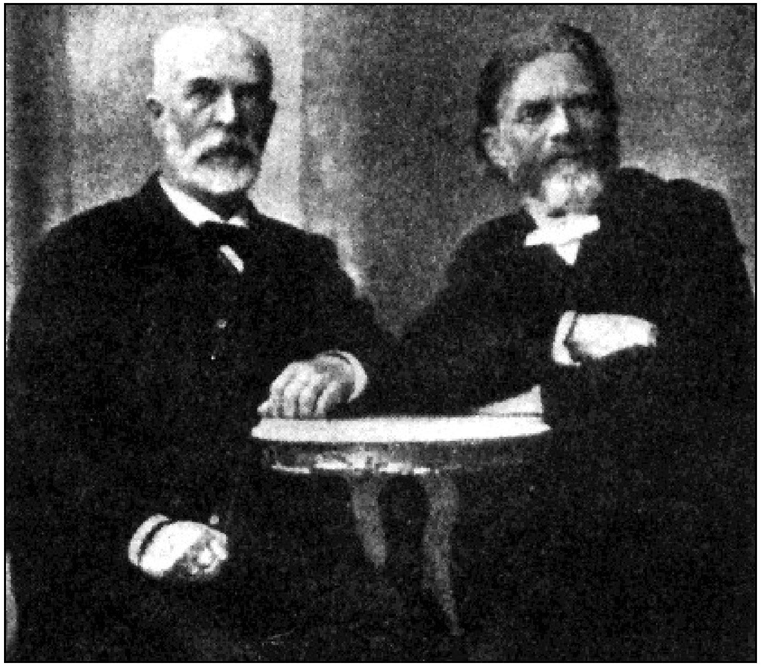
stoichiometry

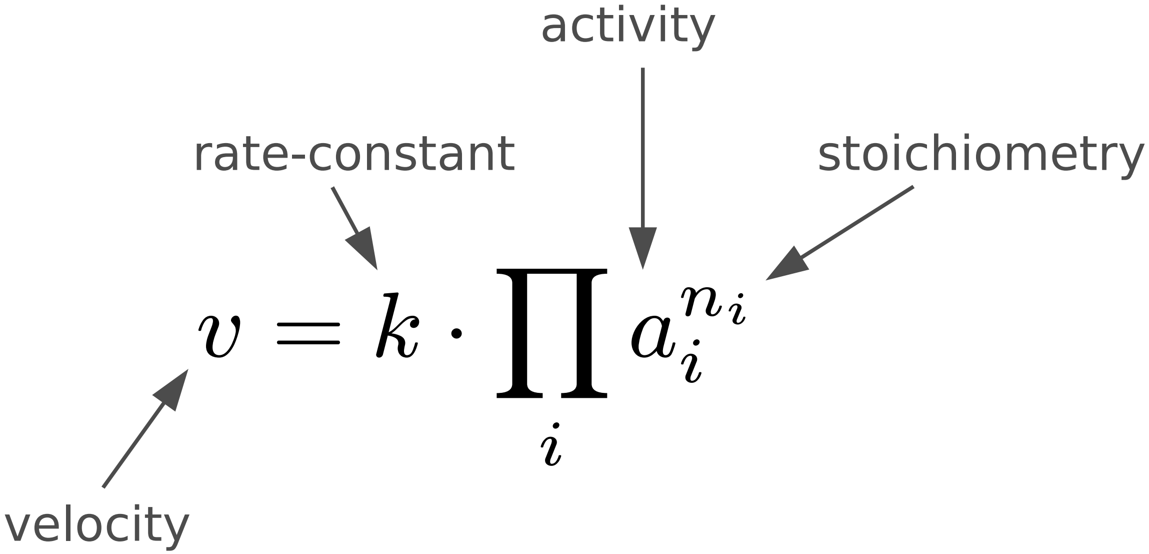
$$v = k \cdot \prod_i a_i^{n_i}$$

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 $x \xrightarrow{k} y$

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

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

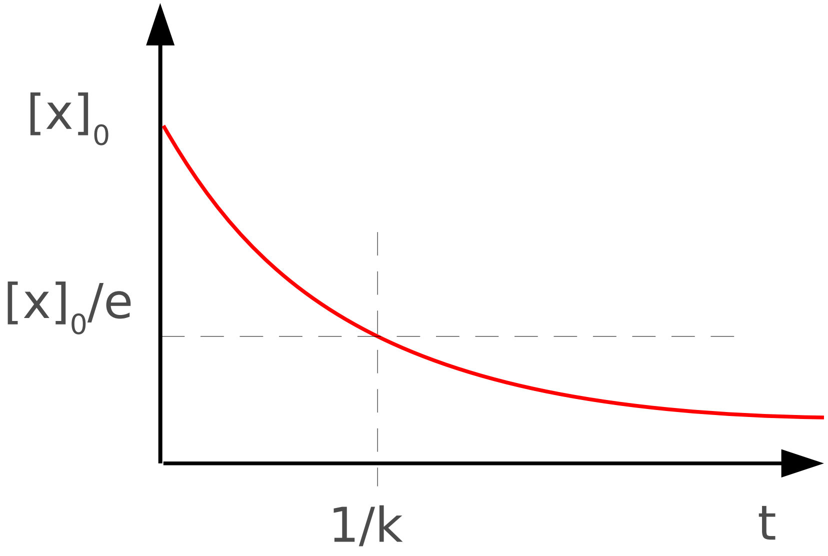
Evolution of a reactant

- 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

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

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

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

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

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

Example of an enzymatic reaction

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

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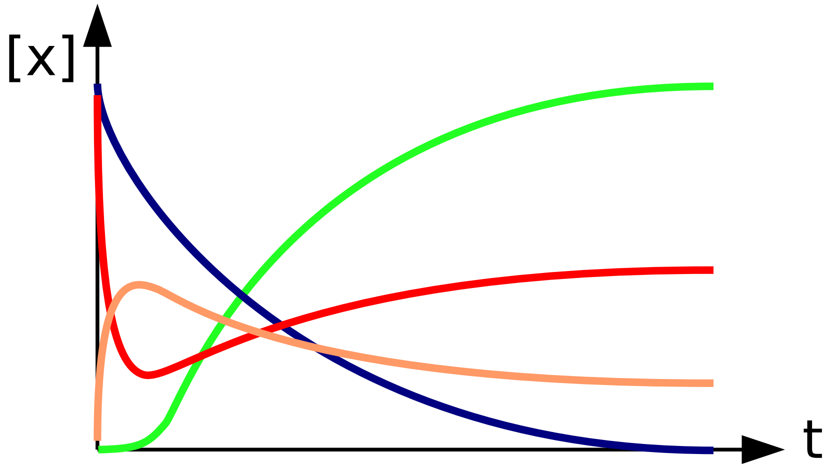
$$\begin{aligned}
d[S]/dt &= -k_1[E][S] & +k_2[ES] & \\
d[P]/dt &= & & +k_3[ES] \\
d[E]/dt &= -k_1[E][S] & +k_2[ES] & +k_3[ES] \\
d[ES]/dt &= +k_1[E][S] & -k_2[ES] & -k_3[ES]
\end{aligned}$$

Example of an enzymatic reaction

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

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



Not feasible in general

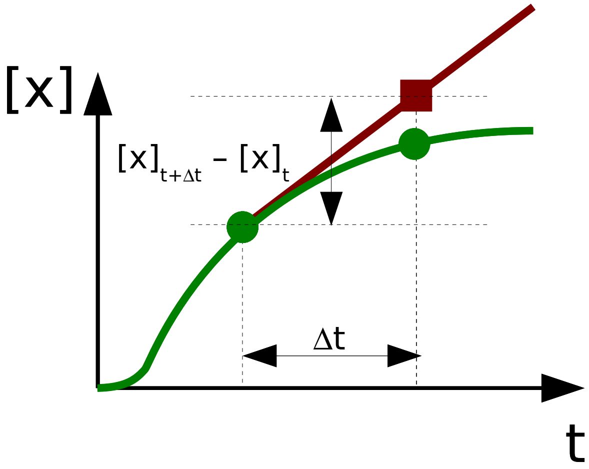
→ Numerical integration

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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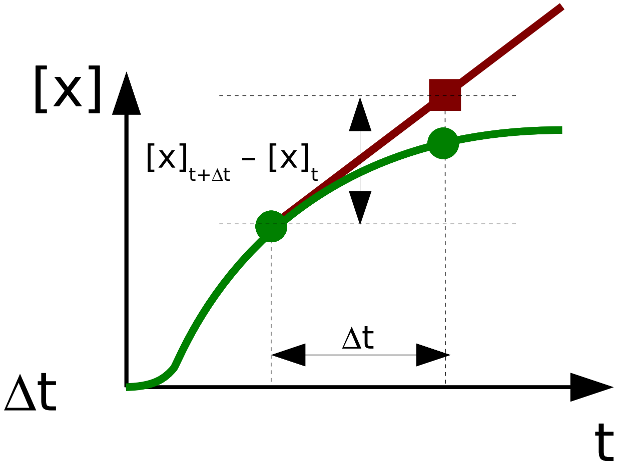

$$[P]_{t+\Delta t} = [P]_t + k_3[ES]_t \;.\; \Delta t$$

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

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

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

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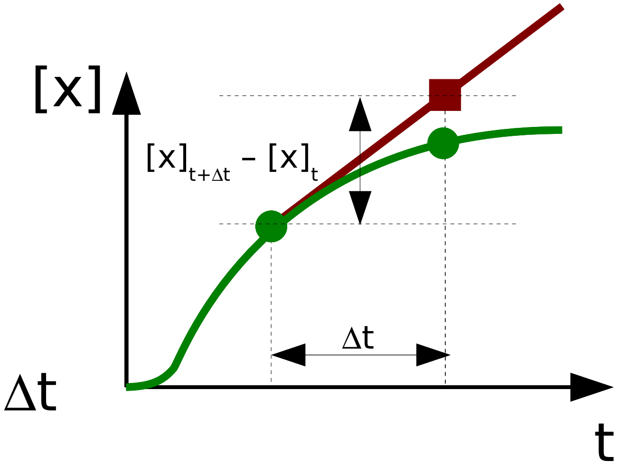

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$$[ES]_{t+\Delta t} = [S]_t + (k_1[E]_t[S]_t - (k_2+k_3)[ES]_t) \,.\, \Delta t$$

4th order Runge-Kutta:

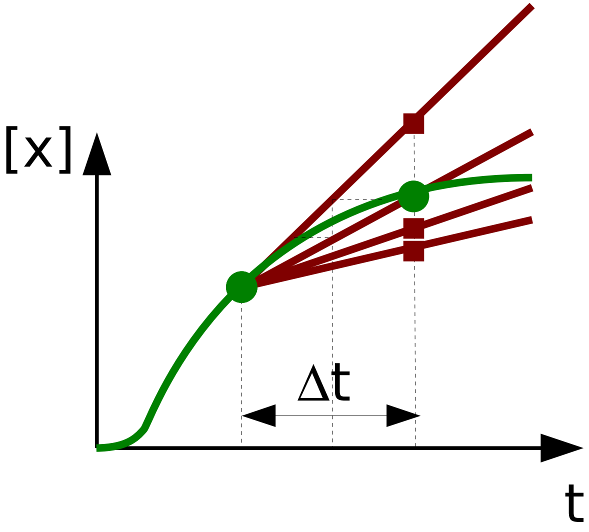
$$[x]_{t+\Delta t} = [x]_t + (F_1+2F_2+2F_3+F_4)/6 \,.\, \Delta t$$

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

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

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

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



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

catalysis irreversible

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catalysis irreversible

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

product is consumed
before rebinding

Choose the right formalism

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

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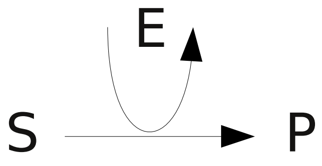
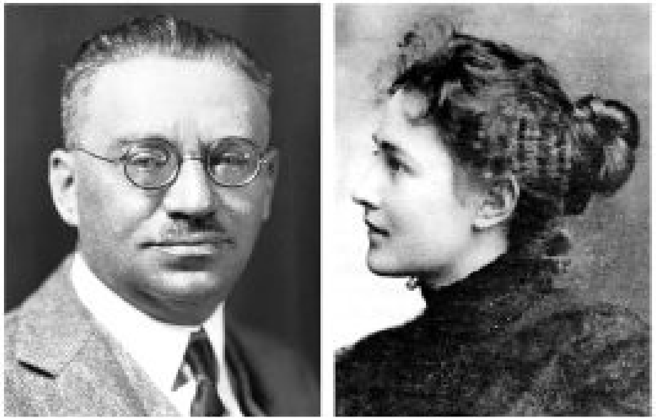


steady-state

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

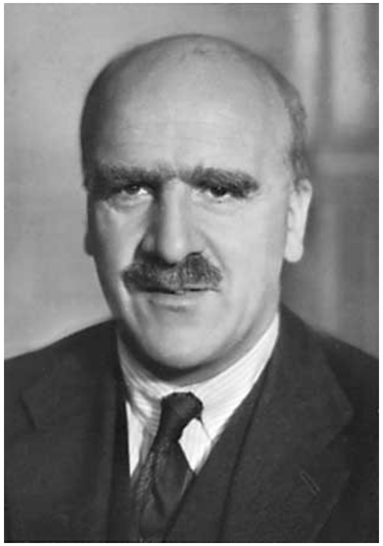
Enzyme kinetics

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

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

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

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

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

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

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

$$[E]=[E_0]\text{-}[ES]$$

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

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

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

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

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steady-state!!!

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

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

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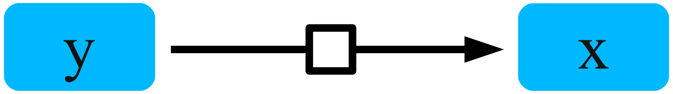
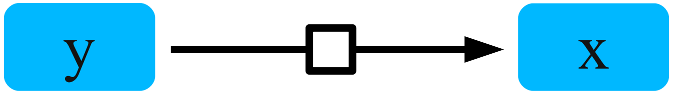
Generalisation of modulation



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

Generalisation: activators



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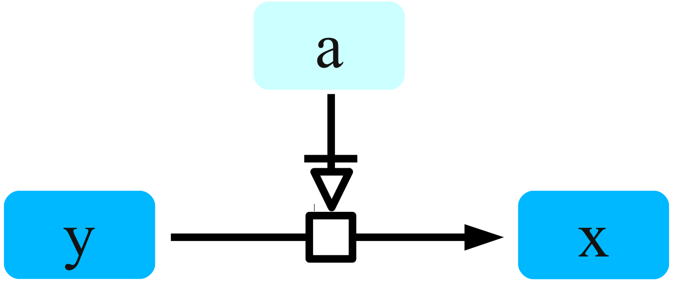
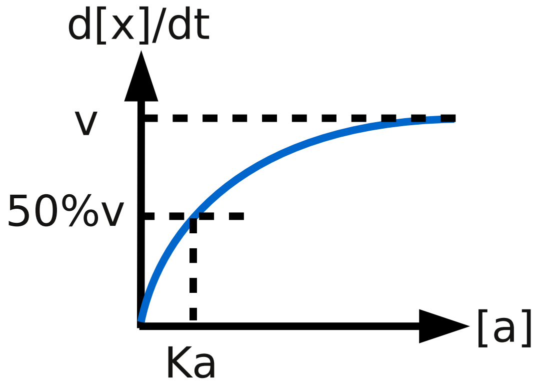


$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$



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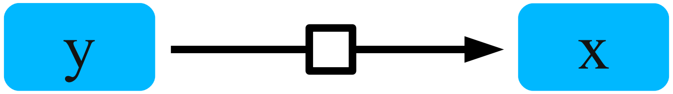

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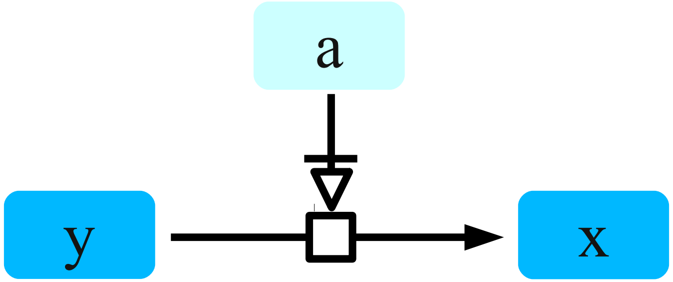

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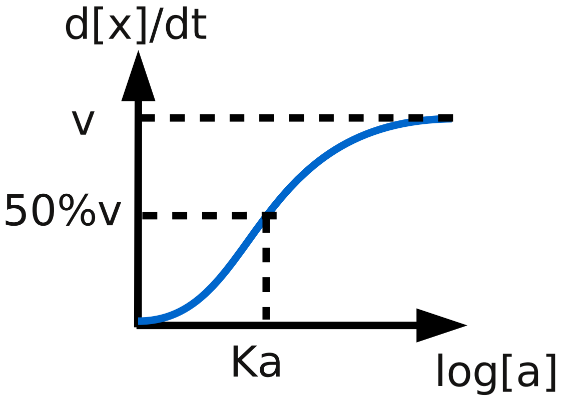
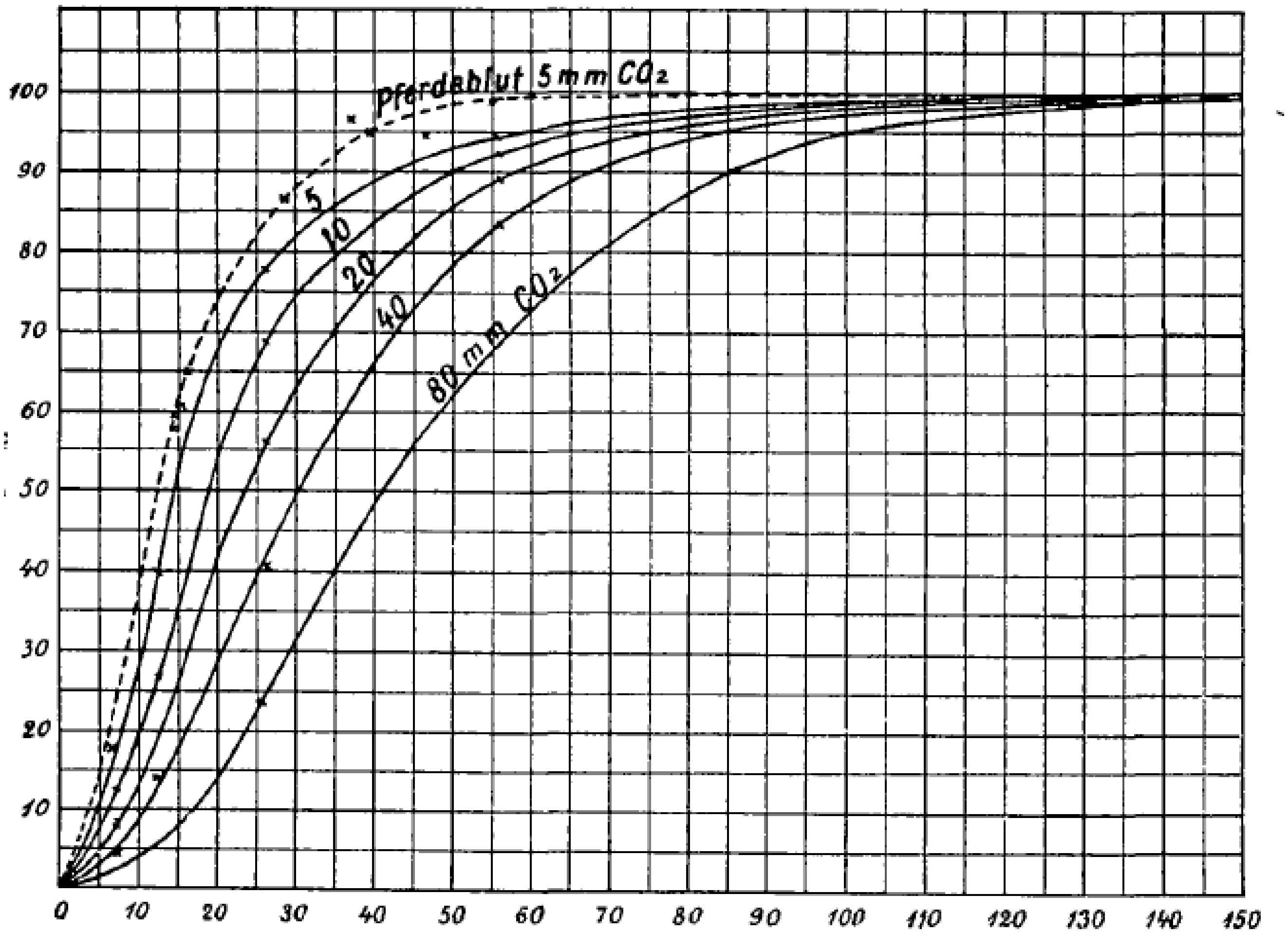


Origins of cooperativity: Bohr

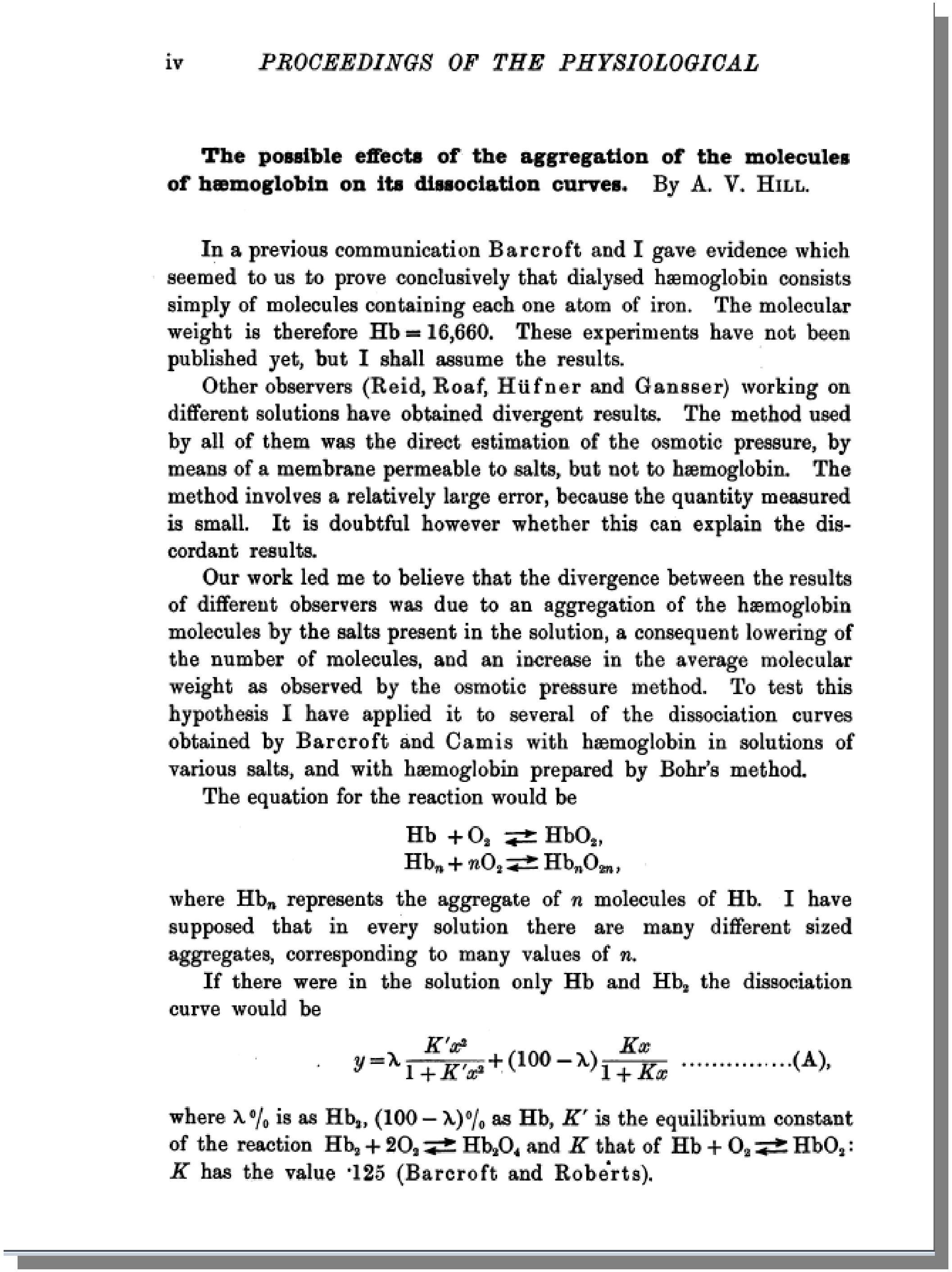
%hbO$_2$



PO$_2$

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

Origins of cooperativity: Hill



iv *PROCEEDINGS OF THE PHYSIOLOGICAL*

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

$$\begin{aligned} \mathrm{Hb} + \mathrm{O}_2 &\rightleftarrows \mathrm{HbO}_2, \\ \mathrm{Hb}_n + n\mathrm{O}_2 &\rightleftarrows \mathrm{Hb}_n\mathrm{O}_{2n}, \end{aligned}$$

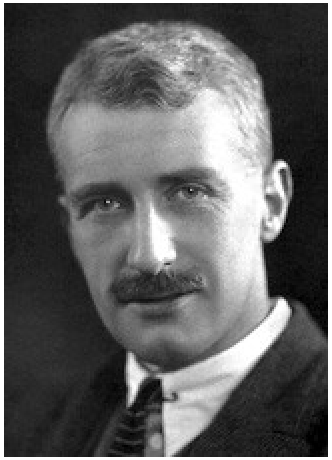
where Hb_n represents the aggregate of n molecules of Hb. I have supposed that in every solution there are many different sized aggregates, corresponding to many values of n.

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 $\mathrm{Hb}_2 + 2\mathrm{O}_2 \rightleftarrows \mathrm{Hb}_2\mathrm{O}_4$ 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 cooperativity: Hill

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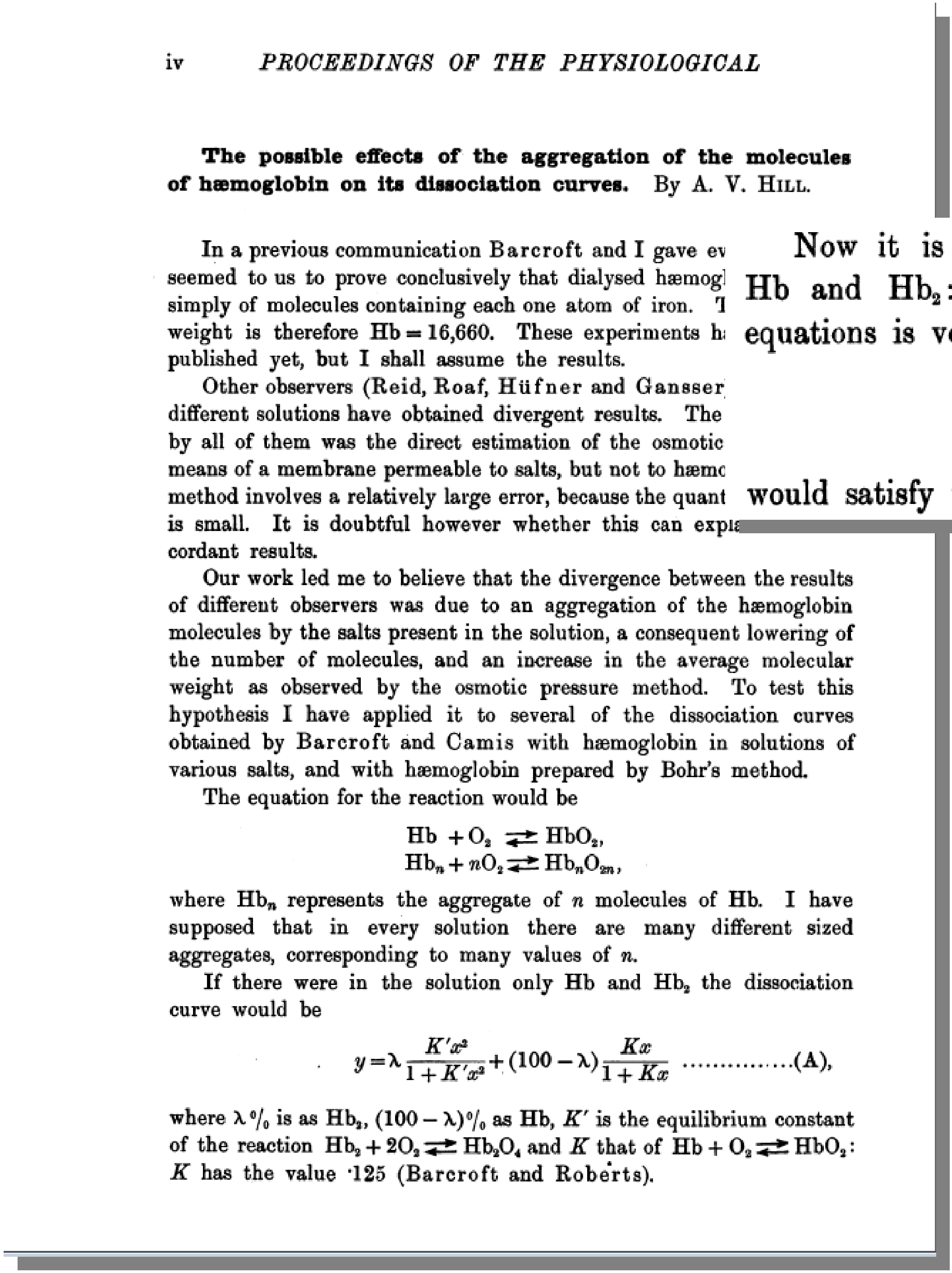

iv *PROCEEDINGS OF THE PHYSIOLOGICAL*

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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

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

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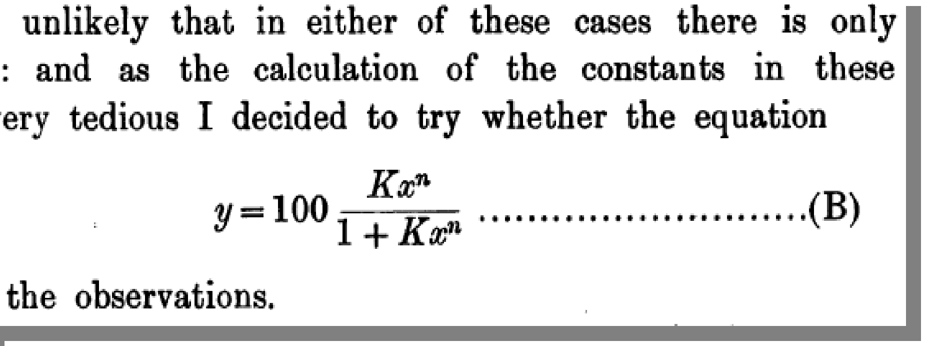
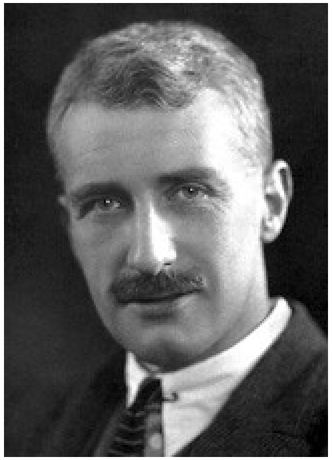


Now it is unlikely that in either of these cases there is only Hb and $\mathrm{Hb_2}$: and as the calculation of the constants in these equations is very tedious I decided to try whether the equation

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

would satisfy the observations.



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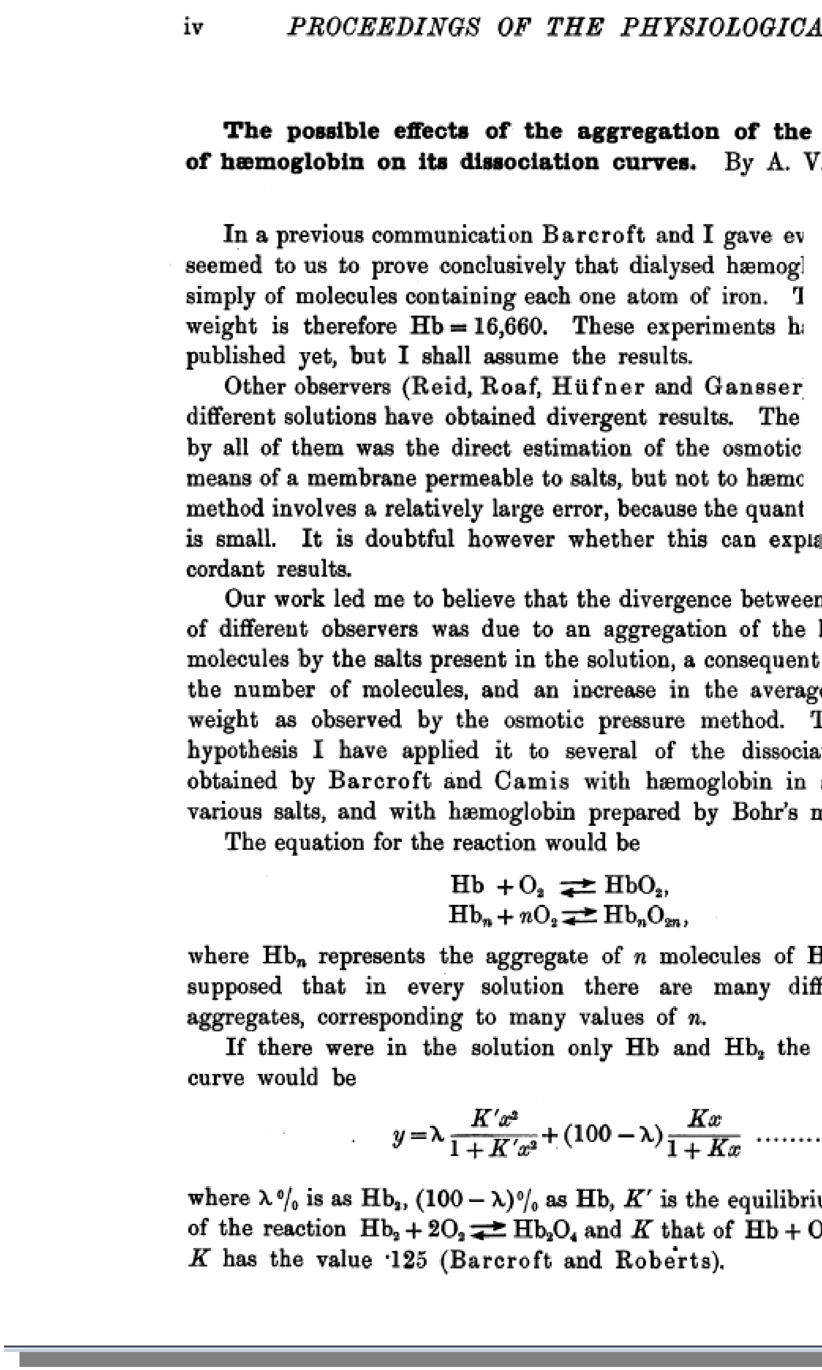

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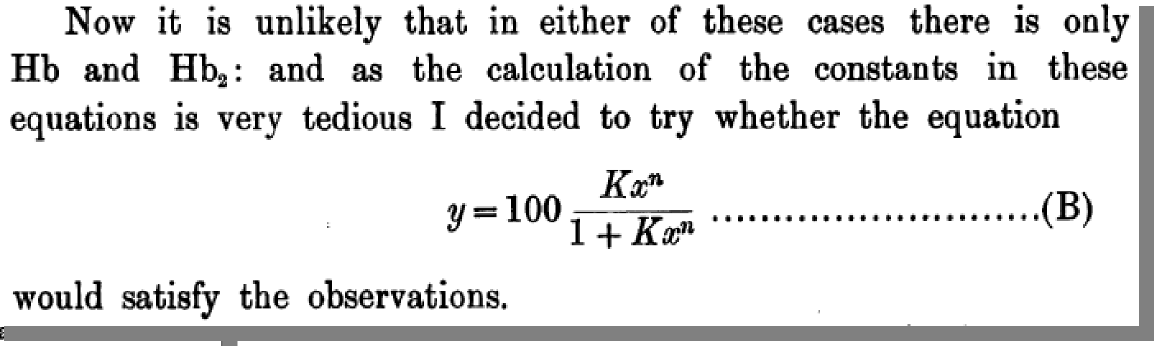

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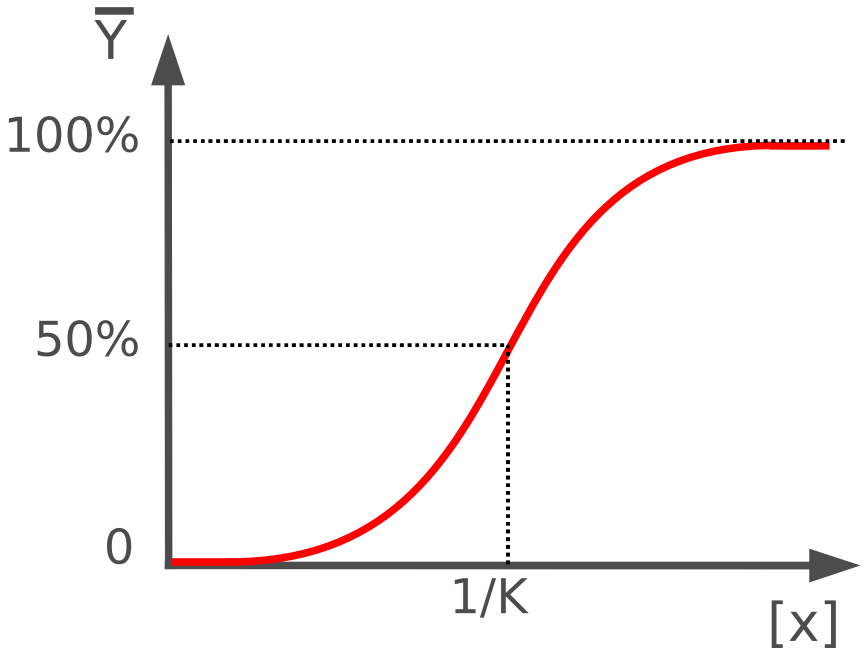
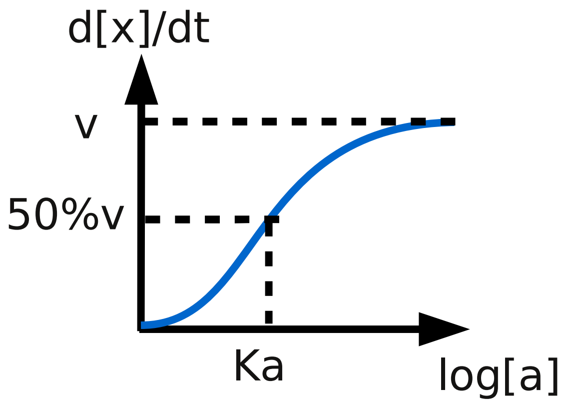


Ultrasensitivity

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



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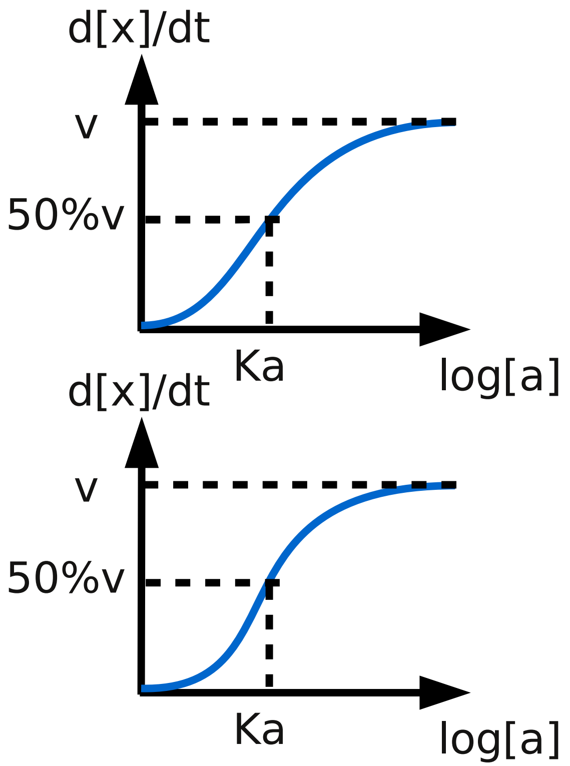

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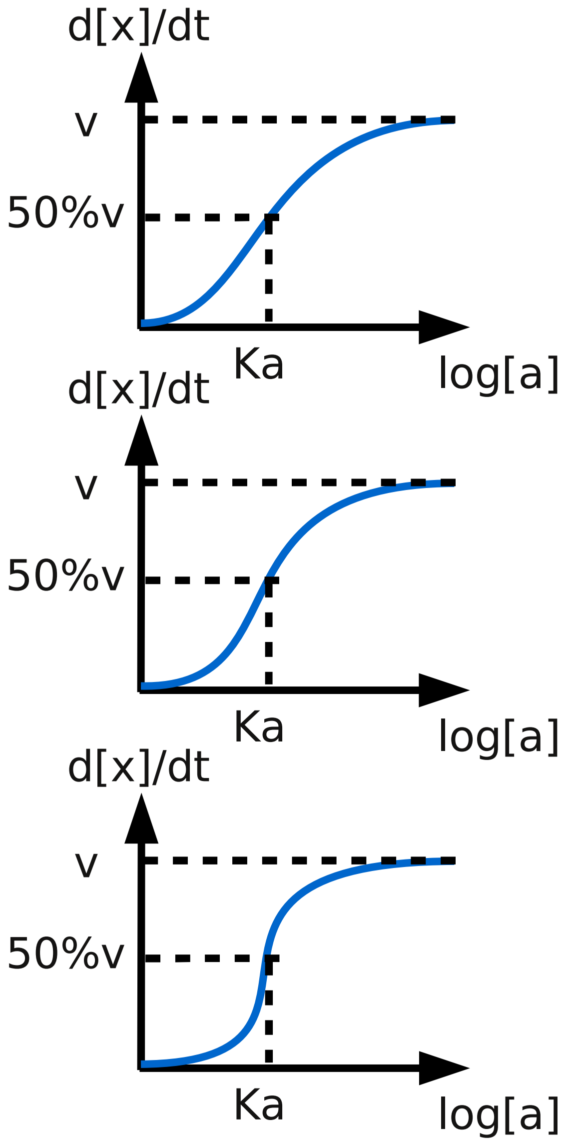
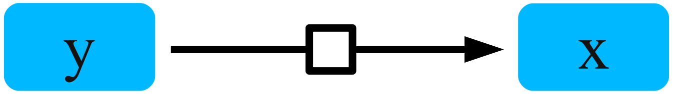
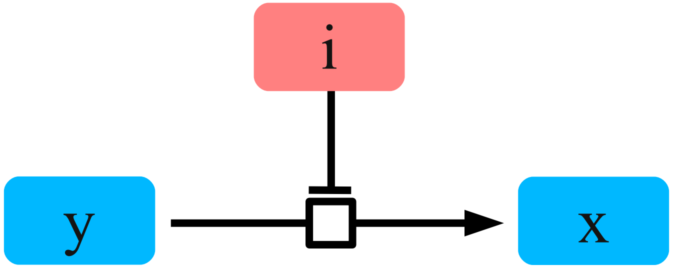


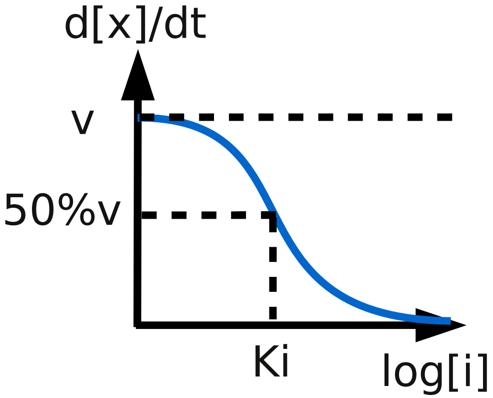
Generalisation: inhibitors



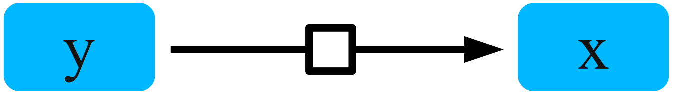
$$\frac{d[x]}{dt} = v(= k \cdot [y])$$



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



Generalisation: activators and inhibitors



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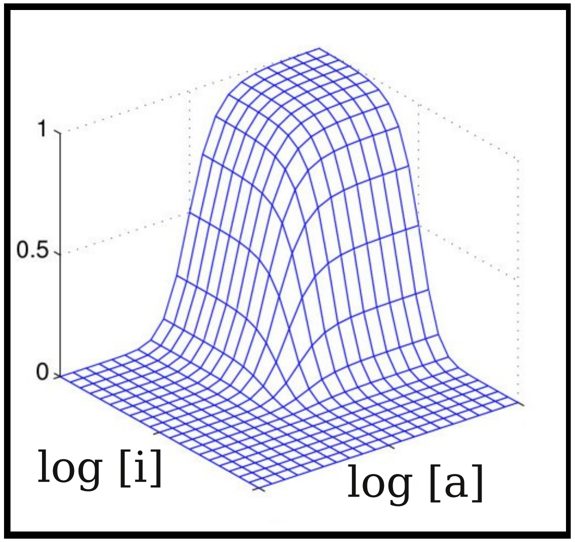
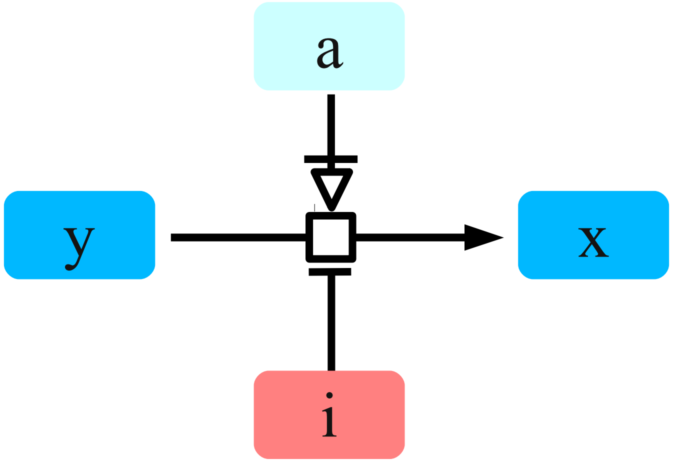
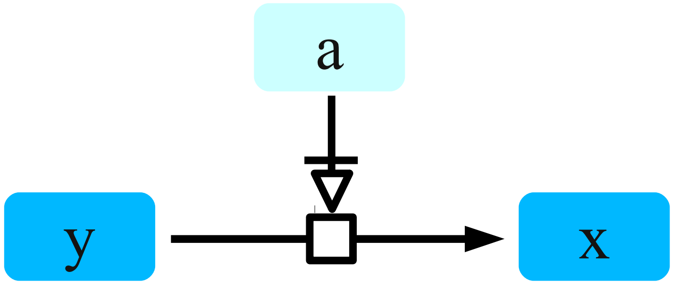




$$\frac{d[x]}{dt} = v \cdot \frac{[a]^n}{Ka^n + [a]^n} \cdot \frac{Ki^m}{Ki^m + [i]^m}$$

absolute Vs relative activators

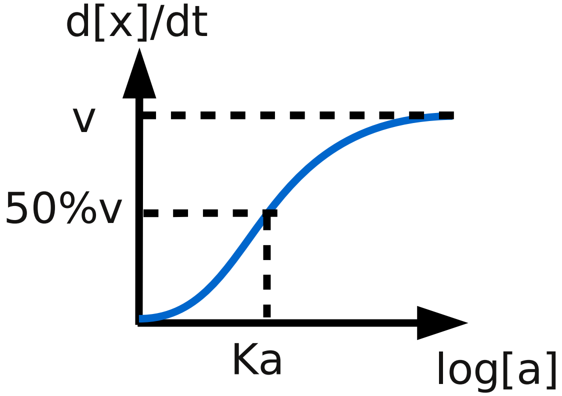


a

y

x

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



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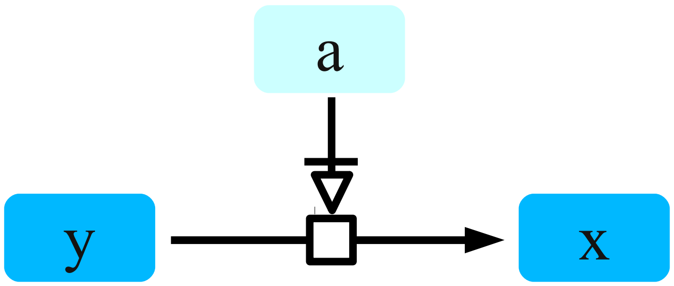

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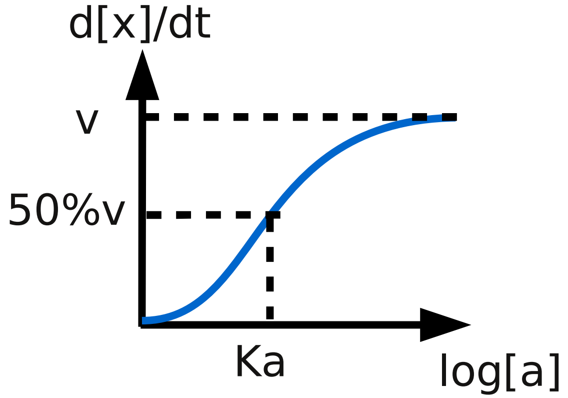
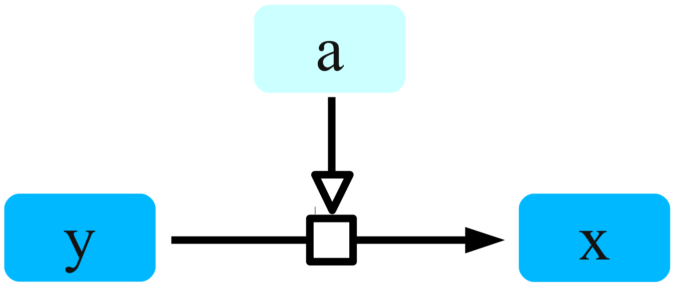
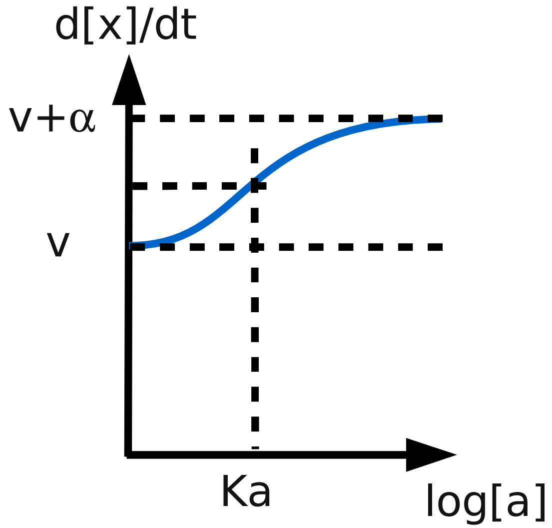


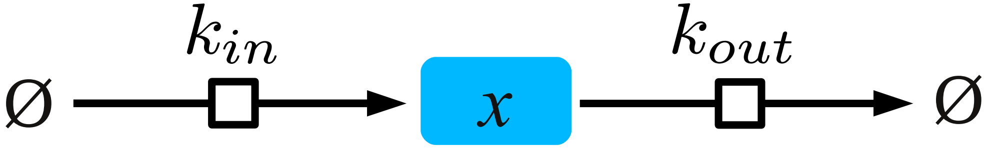


$$\frac{d[x]}{dt} = v \cdot (1 + \alpha \cdot \frac{[a]}{Ka + [a]})$$



Homeostasis

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



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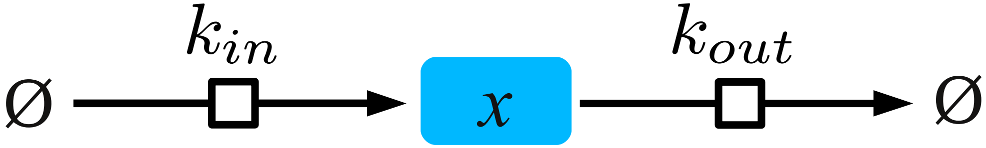

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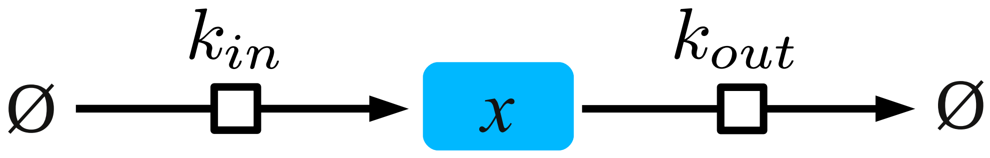

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