

On the allosteric and related kinetics

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Abstract

The Michaelis-Menten law and the Monod-Wyman-Changeux model for allosteric kinetics are derived by means of the general relaxation (decay) laws.

Michaelis-Menten law. In a classic paper[1] it was shown that the reaction



where E is an enzyme, S is a "substrate", P is a product of reaction and $k_{1,2,3}$ are reaction constants, obeys approximately the Michaelis-Menten law

$$\frac{dp}{dt} = \text{const} \frac{s}{\text{const} + s} , \quad (2)$$

where s , p are the concentrations of the substrate S and, respectively, product P and t is the time. The derivation goes as follows:

$$\begin{aligned} de/dt &= -k_1 e \cdot s + k_2(es) + k_3(es) , \\ ds/dt &= -k_1 e \cdot s + k_2(es) , \\ d(es)/dt &= k_1 e \cdot s - k_2(es) - k_3(es) , \\ dp/dt &= k_3(es) , \end{aligned} \quad (3)$$

where e and (es) are the concentration of the enzyme E and, respectively, the complex enzyme-substrate ES ; from the first and the third equations (3) we get $e + (es) = \text{const}$, which expresses the conservation of the enzyme concentration; assuming the equilibrium $k_1 e \cdot s = k_2(es)$ ($ds/dt = 0$) we get $e + (k_1/k_2)e \cdot s = \text{const}$ from the conservation law, or $e = \text{const}/(\text{const} + s)$ and $dp/dt = \text{const} \cdot s/(\text{const} + s)$ from the last equation (3); this is the Michaelis-Menten law.

It is easy to see that this derivation and the kinetic equations (3) have several drawbacks; the kinetic equations imply the law of mass action, based usually on (low-dilution, high-mobility) diffusion, which is rather unrealistic in enzymatic reactions; the final rate k_3 must be much smaller than the rate k_2 , in order to have equilibrium in the first step of the reaction; this implies a low concentration of enzyme; it would be more reasonably to write the equilibrium as $k_1 e \cdot s =$

$k_2(es) + k_3(es)$, which leads to the same Michaelis-Menten law,[2] or to admit the reversibility in the last step of the kinetic equations, *i.e.* to write the reaction as



In any case, the underlying mechanism of the Michaelis-Menten law is questionable, though the law with its saturation-like character seems to be valid in practice; some versions of the law imply often an inflexion point (a sigmoid curve), which is validated by practice.

Kinetic laws. The problem consists in estimating the reaction product as a function of the concentration of one reactants, say the substrate, at equilibrium for a general reaction written as $(E, S) \rightleftharpoons (E, P)$. We denote by f the concentration of the product and by x the concentration of the substrate. Increasing x by dx will increase the product by df ; the simplest law for this process is $df = B\lambda dx$, where B and λ are constants. The product disappears also, with the simplest (decaying, relaxing) law $df = -\lambda f dx$. Combining the two contributions we get the kinetic equation

$$\frac{df}{dx} + \lambda f = B\lambda ; \quad (5)$$

the solution is

$$f = B + Ce^{-\lambda x} , \quad (6)$$

where C is a constant; for a vanishing product at the initial $x = 0$, we get $B + C = 0$ and

$$f = B(1 - e^{-\lambda x}) ; \quad (7)$$

the product is generated initially with the rate $B\lambda$, as obtained either from equation (7) for small x ($f \simeq B\lambda x$) or from equation (5) by neglecting the small term λf ; and for larger x it saturates at $f = B$ (equation (7)), *i.e.* its slope is vanishing in equation (5) which gives indeed $f = B$.

The processes described above can be complicated by including a cooperative aspect; instead of $df = B\lambda dx$ we may have $df = 2B\lambda x dx$ and instead of $df = -\lambda f dx$ we may have $df = -2\lambda x f dx$, leading to the equation

$$\frac{df}{dx} + 2\lambda x f = 2B\lambda x ; \quad (8)$$

whose solution is

$$f = B + Ce^{-\lambda x^2} , \quad (9)$$

or

$$f = B(1 - e^{-\lambda x^2}) \quad (10)$$

for $f(x = 0) = 0$. This solution has an inflexion point.

Similarly, we can consider the equation

$$\frac{df}{dx} + \lambda \alpha x^{\alpha-1} f = B\lambda \alpha x^{\alpha-1} \quad (11)$$

with $\alpha > 1$ and get a generalized solution

$$f = B(1 - e^{-\lambda x^\alpha}) . \quad (12)$$

Monod-Wyman-Changeux model.[3, 4] First we note that equation (7) can also be written as

$$f = B \frac{e^{\lambda x} - 1}{e^{\lambda x}} \simeq B \frac{\lambda x}{1 + \lambda x} = \text{const} \frac{x}{\text{const} + x} , \quad (13)$$

which is the Michaelis-Menten law. Similarly, using equation (10) or equation (12), we get $f \simeq \text{const} \cdot x^2 / (\text{const} + x^2)$ or $f \simeq \text{const} \cdot x^\alpha / (\text{const} + x^\alpha)$, which is a generalization of the Michaelis-Menten law.

The relaxation equation (6) suggests a decaying law, which, written for two populations (two channels, allosteric activity), reads

$$N_1 = N_{01}e^{-\lambda_1 x}, \quad N_2 = N_{02}e^{-\lambda_2 x} = N_{01}e^{-\lambda_2 x}/L, \quad (14)$$

where $L = N_{01}/N_{02}$; it is worth noting that

$$\begin{aligned} \frac{e^{\lambda_1 x}}{e^{\lambda_1 x} + Le^{\lambda_2 x}} &= \frac{N_{01}/N_1}{N_{01}/N_1 + N_{01}/N_2} = \frac{N_2}{N_1 + N_2}, \\ \frac{Le^{\lambda_2 x}}{e^{\lambda_1 x} + Le^{\lambda_2 x}} &= \frac{N_{01}/N_2}{N_{01}/N_1 + N_{01}/N_2} = \frac{N_1}{N_1 + N_2}, \end{aligned} \quad (15)$$

so that $e^{\lambda_1 x}$ and $Le^{\lambda_2 x}$ can be used as statistical weights. We may write also

$$\frac{e^{\lambda_1 x}}{e^{\lambda_1 x} + Le^{\lambda_2 x}} \simeq \frac{(1 + \lambda_1 x/n)^n}{(1 + \lambda_1 x/n)^n + L(1 + \lambda_2 x/n)^n} \quad (16)$$

or, redefining $\lambda_1 x/n \rightarrow x$ and denoting $\lambda_2 = c\lambda_1$,

$$\frac{e^{\lambda_1 x}}{e^{\lambda_1 x} + Le^{\lambda_2 x}} \simeq \frac{(1 + \lambda_1 x/n)^n}{(1 + \lambda_1 x/n)^n + L(1 + \lambda_2 x/n)^n} = \frac{(1 + x)^n}{(1 + x)^n + L(1 + cx)^n}; \quad (17)$$

this is the Monod-Wyman-Changeux model. We can see that $(1 + x)^n$ has the aspect of a sum of multiple states with weights 1 and x , so we can define the mean of the x -state

$$Y = \frac{\frac{x}{1+x}(1+x)^n + \frac{cx}{1+cx}L(1+cx)^n}{(1+x)^n + L(1+cx)^n} = \frac{x(1+x)^{n-1} + Lcx(1+cx)^{n-1}}{(1+x)^n + L(1+cx)^n}, \quad (18)$$

which is the so-called saturation function (it exhibits saturation and inflexions). By equation (12) we may replace x by x^α in equation (18), which is a generalization of the saturation law.

References

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