Enzyme kinetics

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Reaction and basic model

We consider a reaction where an *enzyme* acts on a *substrate* to form a *product*. The reaction goes via a *complex*, which may either revert to substrate plus enzyme, or to product plus enzyme. In particular, the enzyme is not used up in the process, though some of it will at any time be bound up in the complex. The reaction looks like this:

$$s + e \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} c \xrightarrow{k_2} p + e.$$

This leads to the model

$$\begin{aligned}
\frac{\mathrm{d}s}{\mathrm{d}t} &= -k_1 se + k_{-1} c, \\
\frac{\mathrm{d}c}{\mathrm{d}t} &= k_1 se - k_{-1} c - k_2 c, \\
\frac{\mathrm{d}e}{\mathrm{d}t} &= -k_1 se + k_{-1} c + k_2 c, \\
\frac{\mathrm{d}p}{\mathrm{d}t} &= k_2 c,
\end{aligned}$$

where s, c, e, and p are the concentrations of the various substances. We shall use the initial conditions

$$s(0) = \bar{s}, \quad c(0) = 0, \quad e(0) = \bar{e}, \quad p(0) = 0.$$

Immediate consequences. We get $c + e = \bar{e}$ and $s + c + p = \bar{s}$. Hence we need only solve for s and c. Substitute $e = \bar{e} - c$ into the first two equations and get

our final, non-scaled model:

$$\frac{ds}{dt} = -k_1\bar{e}s + (k_1 s + k_{-1})c, \tag{1}$$

$$\frac{dc}{dt} = \quad k_1\bar{e}s - (k_1 s + k_{-1} + k_2)c, \tag{2}$$

$$s(0) = \bar{s}, \quad c(0) = 0. \tag{3}$$

Scaling

In their treatment of this problem, Lin & Segel were led to a scaling which works in many cases. However, an improved scaling was introduced by Segel & Slemrod (see the References, below). We shall ignore the original Lin & Segel scaling, and move directly to the better scaling.

It is frequently noted that the reactions $s + e \rightleftarrows c$ tend to be *much* faster than the reaction $c \to p + e$. Thus there is an initial, fast transient during which c rapidly increases from 0 to some value at which the first reaction pair are nearly at equilibrium. This is then called a *quasi-steady state* (QSS), and is characterized by dc/dt being very small. To a lowest order approximation, then, we put the righthand side of (2) equal to zero (an *algebraic* equation), solve for c, and replace c by the solution in (1). The resulting single first order equation is known as the *Michaelis–Menten kinetics* for the system.

More precisely, in the quasi-steady state $dc/dt \approx 0$. Assuming this is exact, we solve (2) for c to get

$$c = \frac{s}{s+K}\bar{e}, \qquad \text{where } K = \frac{k_{-1} + k_2}{k_1}.$$

Substitute into (1) and simplify, to get the Michaelis–Menten equation

$$\frac{ds}{dt} = -\frac{k_2\bar{e}s}{s+K}$$

(which is easily solved, but never mind that for now).

Segel & Slemrod use this to find the proper *time scale* for the quasi-steady state.

Clearly the maximal value of s is $\bar{s}$, so we will use this to scale s. One good way to get a time scale is

$$t_{\text{slow}} = \frac{\max|s|}{\max\left|\frac{ds}{dt}\right|} = \frac{\bar{s}}{\frac{k_2\bar{e}\bar{s}}{\bar{s}+K}} = \frac{\bar{s}+K}{k_2\bar{e}}. \tag{4}$$

This is the *long time scale* of the problem.

On the other hand, during the initial transient $s \approx \bar{s}$ and so (2) becomes

$$\frac{\mathrm{d}c}{\mathrm{d}t} \approx k_1 \bar{e}\bar{s} - k_1(\bar{s}+K)c.$$

The equilibrium of this equation is at

$$c = \frac{\bar{e}\bar{s}}{\bar{s}+K},$$

so this value is actually a good scale for c. Moreover, the approach to this equilibrium is exponential with a time constant

$$t_{\mathsf{fast}} = \frac{1}{k_1(\bar{s}+K)}. \tag{5}$$

This is the appropriate choice of the *short time scale*. The ratio between the two time scales is

$$\frac{t_{\mathsf{fast}}}{t_{\mathsf{slow}}} = \frac{k_2\bar{e}}{k_1(\bar{s}+K)^2}.$$

We must have $t_{\mathsf{fast}} \ll t_{\mathsf{slow}}$, or else our assumptions of very different time scales is wrong, and our analysis becomes suspect.

We thus end up with the following scalings, for the outer solution:

$$s' = \bar{s}s, \quad c' = \frac{\bar{e}\bar{s}}{\bar{s}+K}c, \quad t' = t_{\mathsf{slow}}t = \frac{\bar{s}+K}{k_2\bar{e}}t. \tag{6}$$

For the inner solution the rescaled dimensionless time τ is given by

$$t = t_{\mathsf{fast}}\tau = \frac{\tau}{k_1(\bar{s}+K)}.$$

We now need to investigate whether and under what circumstances the inner solution will be valid. We assumed that s did not decrease much during the initial time t_{fast}. So now we *estimate* the decrease in s: Note that we cannot use the QSS assumption here, but insert $c \approx 0$ and $s \approx \bar{s}$ in (1) to get $\mathrm{d}s/\mathrm{d}t \approx -k_1\bar{e}\bar{s}$, from which we get the change

$$\Delta s \approx -k_1\bar{e}\bar{s}t_{\mathsf{fast}} = -\frac{\bar{e}\bar{s}}{\bar{s}+K}.$$

We need $|\Delta s/\bar{s}| \ll 1$, or

$$\varepsilon \stackrel{\mathrm{def}}{=} \frac{\bar{e}}{\bar{s}+K} \ll 1.$$

There are enough parameters in this problem that the most convenient choice of non-dimensional parameters is far from obvious. Following Segel & Slemrod, we choose

$$\sigma = \frac{\bar{s}}{K}, \quad \eta = \frac{\bar{e}}{K}, \quad \kappa = \frac{k_{-1}}{k_2} \tag{7}$$

where K is defined above. Note that

$$\varepsilon = \frac{\eta}{\sigma + 1}.$$

It also turns out useful to insert $k_{-1} = \kappa k_2$ into the definition of K to obtain

$$k_2 = \frac{K k_1}{\kappa + 1}.$$

For example, this leads to a different expression for the ratio of the two time scales in terms of the other dimensionless quantitites:

$$\frac{t_{\mathsf{fast}}}{t_{\mathsf{slow}}} = \frac{\varepsilon}{(\kappa+1)(\sigma+1)}.$$

Thus, if $\varepsilon \ll 1$ then clearly $t_{\mathsf{fast}} \ll t_{\mathsf{slow}}$, since $(\kappa+1)(\sigma+1) > 1$.

Now, applying the scalings (6) to (1)–(3), substituting the above value for k_2 wherever it appears, and simplifying, we finally get the scaled equations (after dropping the primes) on the form

$$\frac{1}{(\kappa+1)(\sigma+1)} \frac{\mathrm{d}s}{\mathrm{d}t} = -s + \Big(\frac{\sigma}{\sigma+1} s + \frac{\kappa}{(\kappa+1)(\sigma+1)} \Big) c, \tag{8}$$

$$\frac{\varepsilon}{(\kappa+1)(\sigma+1)} \frac{\mathrm{d}c}{\mathrm{d}t} = s - \frac{\sigma s + 1}{\sigma + 1} c, \tag{9}$$

$$s(0) = 1, \quad c(0) = 0. \tag{10}$$

Some principles

Segel & Slemrod used these general principles to derive their scaling:

1. Dependent variables (s and c in our example) should be scaled according to their maximal value, so that their dimensionless versions vary between 0 and 1.

2. Independent variables (t in our example) should be scaled so that the dependent variables vary considerably over the chosen scale. In other words, the derivatives of the dependent variables ought to have a maximum value of 1 in the scaled model.

Solution by perturbation

Outer solution. First, put $\varepsilon = 0$ in the differential equations (and add a subscript zero to s and c). Then (9) becomes the algebraic equation

$$c_0 = \frac{(\sigma+1)s_0}{\sigma s_0 + 1}.$$

We substitute this into (8), which simplifies into

$$\frac{1}{\sigma+1}\frac{\mathrm{d}s_0}{\mathrm{d}t} = -\frac{s_0}{\sigma s_0 + 1}.$$

This separable equation has the general solution

$$\sigma s_0 + \ln s_0 = Q - (\sigma+1)t. \tag{11}$$

The integration constant Q can be determined by using $s_0(0) = 1$, so $Q = \sigma$. (This is consistent with our assumptions, but should really have been obtained by matching.) The other initial condition ($c_0(0) = 0$) is not satisified, but this was not to be expected in the outer solution.

Inner solution. In the inner solution, we use t_{fast} as a time scale. Thus the *inner dimensionless time* τ is written in terms of (outer) dimensionless time t (should be t', but we *have* dropped the primes) by

$$t = \frac{t_{\mathsf{fast}}}{t_{\mathsf{slow}}}\tau = \frac{\varepsilon}{(\kappa+1)(\sigma+1)}\tau.$$

Plugging this into (8), (9), (10) (and using S, C for the inner solution) we get

$$\frac{1}{\varepsilon}\frac{\mathrm{d}S}{\mathrm{d}\tau} = -S + \Big(\frac{\sigma}{\sigma+1}S + \frac{\kappa}{(\kappa+1)(\sigma+1)}\Big)C \tag{12}$$

$$\frac{\mathrm{d}C}{\mathrm{d}\tau} = S - \frac{\sigma S + 1}{\sigma+1}C \tag{13}$$

$$S(0) = 1, \quad C(0) = 0. \tag{14}$$

We set $\varepsilon = 0$ and add subscripts zero to the functions. Then (12) becomes $S_0 =$ constant, which together with the first initial condition in (14) implies $S_0 = 1$. We plug this into the second equation and get

$$\frac{\mathrm{d}C_0}{\mathrm{d}\tau} = 1 - C_0$$

which together with the second initial condition in (14) has the solution

$$C_0 = 1 - e^{-\tau}.$$

Matching and uniform approximation. To this order, we can match inner and outer solutions by simply requiring that $\lim_{\tau\to\infty} S_0(\tau) = \lim_{t\to 0} s_0(t)$. This yields $Q = \sigma$, as we guessed before.

The similar equation $\lim_{\tau\to\infty} C_0(\tau) = \lim_{t\to 0} c_0(t)$ turns out to be automatically satisfied.

To get a uniformly valid approximation (we hope), we join together inner and outer solutions by simply adding them together and subtracting the common part (which is the constant 1 both in case of (s_0, S_0) and (c_0,C_0)). Thus the lowest order approximation to s is quite simply

$$s(t) \approx s_0(t) + S_0(\tau) - 1 = s_0(t),$$

while that for c is

$$c(t) \approx c_0(t) + C_0(\tau) - 1 = \frac{(\sigma+1)s_0(t)}{\sigma s_0(t) + 1} - \exp\Big(-\frac{(\kappa+1)(\sigma+1)}{\varepsilon}\, t\Big).$$

Unfortunately, we can give no simple formula for $s_0(t)$. It has to be found by solving the trancendental equation (11).[1]

References

C.C LIN & L.A. SEGEL: *Mathematics applied to deterministic problems in the natural sciences*. ISBN 0898712297. Chapter 10 (pp. 302–320).

LEE A. SEGEL & MARSHALL SLEMROD: The quasi-steady state assumption: A case study in perturbation. *SIAM Review* **31** #3 (1989), pp. 446-477. Available at the mathematics library, and also from JSTOR: `http://www.jstor.org/`. Follow the links marked *browse*, then *mathematics* (you need to be within the network of NTNU, or another institution which subscribes to JSTOR).

[1] It can be exressed in terms of Lambert's W function: $W(z)$ is defined as a solution w of $we^w = z$. Maple knows about this function, under the name W.