Enzyme kinetics ala Lin & Segel

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Reaction and basic model

The reaction looks like:

$$s^* + e^* \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} c^* \to p^* + e^*$$

which leads to the model

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

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:

$$\frac{\mathrm{d}s^*}{\mathrm{d}t^*} = -k_1 \bar{e} s^* + (k_1 s^* + k_{-1}) c^* \tag{1}$$

$$\frac{\mathrm{d}c^*}{\mathrm{d}t^*} = \quad k_1 \bar{e} s^* - (k_1 s^* + k_{-1} + k_2) c^* \tag{2}$$

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

Scaling

Put

$$s^* = \bar{s}s, \quad c^* = \bar{e}c, \quad t^* = \frac{t}{k_1 \bar{e}}$$

and, with the nondimensional parameters

$$\kappa = \frac{k_{-1} + k_2}{k_1 \bar{s}}, \quad \lambda = \frac{k_2}{k_1 \bar{s}}, \quad \varepsilon = \frac{\bar{e}}{\bar{s}}$$

we have the problem on its non-dimensional form:

$$\begin{aligned}\dot{s} &= -s + (s + \kappa - \lambda)c \\ \varepsilon\dot{c} &= \quad s - (s + \kappa)c \\ s(0) &= 1, \quad c(0) = 0\end{aligned}$$

For later reference, it will be useful to remember that $0 < \lambda < \kappa$, and we shall assume $0 < \varepsilon \ll 1$.

Solution by perturbation

Outer solution. First, put $\varepsilon = 0$ in the differential equations. The second equation becomes the algebraic equation $s - (s + \kappa)c = 0$. We solve this for c and substitute in the first equation, which becomes $\dot{s} = -\lambda s/(s + \kappa)$. We call the solution (s_0, c_0):

$$s_0 + \kappa \ln s_0 = Q - \lambda t, \quad c_0 = \frac{s_0}{s_0 + \kappa} \tag{4}$$

The integration constant Q might be determined by using $s_0(0) = 1$, so $Q = 1$. But then the other initial condition is not satisified, and so we are not quite sure whether even the first one is satisfied. So presumably, Q must be determined by matching.

Inner solution. Initially we expect $s \approx 1$, in which case $\varepsilon\dot{c} \approx 1 - (1+\kappa)c$. Thus c seems to tend towards 1 with a time constant $\varepsilon/(1+\kappa)$. Introduce this time constant as a new time scale, and define the *inner dimensionless time* τ by[1]

$$t = \frac{\varepsilon}{1 + \kappa}\tau$$

[1] Here we depart from Lin & Segel in a small way. It simplifies a few formulae, but changes nothing important.

With $s(t) = S(\tau)$ and $c(t) = C(\tau)$ the equations become

$$(1+\kappa)S' = \varepsilon\big(-S + (S+\kappa-\lambda)C\big)$$
$$(1+\kappa)C' = S - (S+\kappa)C$$

and, of course, we can use the intial conditions as well, so $S(0) = 1$ and $C(0) = 0$.

With $\varepsilon = 0$ we get $S' = 0$, so the initial conditions imply $S = 1$. We plug that into the second equation and get $C' = \frac{1}{1+\kappa} - C$, which is easy to solve with the initial condition $C = 0$. Renaming this solution (S_0, C_0) we thus have

$$S_0(\tau) = 1, \quad C_0(\tau) = \frac{1-e^{-\tau}}{1+\kappa}$$

Matching. To this order, we can match inner and outer solutions by simply requiring that $\lim_{\tau\to\infty} S(\tau) = \lim_{t\to 0} s(t)$. Thus $Q = 1$, as we guessed before. The similar equation $\lim_{\tau\to\infty} C(\tau) = \lim_{t\to 0} c(t)$ turns out to be automatically satisfied.

To the next order. We try to substitute power series $S = S_0 + \varepsilon S_1 + \cdots$, $C = C_0 + \varepsilon C_1 + \cdots$, $s = s_0 + \varepsilon s_1 + \cdots$, and $c = c_0 + \varepsilon c_1 + \cdots$ into the inner and outer equations. For S_0, C_0, s_0 and c_0 we find the equations and solutions we have already discovered. Next, we find

$$S_1 = -\frac{1}{(1+\kappa)^2}\big(\lambda\tau + (1+\kappa-\lambda)(1-e^{-\tau})\big)$$
$$C_1 = -\frac{1}{(1+\kappa)^4}\Big(\lambda\kappa\tau + \kappa(1+\kappa-2\lambda) + (1+\kappa-\lambda)e^{-2\tau}$$
$$+ \Big[\frac{1}{2}\lambda\tau^2 + (1+\kappa-\lambda)(1-\kappa)\tau - ((1+\kappa)^2 - \lambda - 2\kappa\lambda)\Big]e^{-\tau}\Big)$$

while s_1 and c_1 are given by

$$\dot{s}_1 = (c_0 - 1)s_1 + (\kappa - \lambda + s_0)c_1, \quad \dot{c}_0 = s_1(1-c_0) - (\kappa + s_0)c_1$$

which requires an initial condition for s_1.[2] So we introduce the intermediate time scale Ψ, put $t = \Psi\tau_i$, and note that

$$\tau = \frac{1+\kappa}{\varepsilon}t = \frac{(1+\kappa)\Psi}{\varepsilon}\tau_i$$

[2] At this stage, we do not need an initial condition for c_1, as this is system is actually just one differential equation and one algebraic equation, c_0 being a known function.

We get, therefore

$$S(\tau) = S_0\Big(\frac{(1+\kappa)\Psi}{\varepsilon}\tau_i\Big) + \varepsilon S_1\Big(\frac{(1+\kappa)\Psi}{\varepsilon}\tau_i\Big) + \cdots$$
$$= 1 - \frac{\lambda\tau_i\Psi}{1+\kappa} - \frac{(1+\kappa-\lambda)\varepsilon}{(1+\kappa)^2} + \mathrm{TST} + \cdots$$

which needs to be matched to $s(t) = s_0(t) + \varepsilon s_1(t) + \cdots$ with $t = \Psi\tau_i$.

Thus we need a power series representation for s_0 in terms of t: Write $s_0(t) = 1 + \gamma t + \cdots$ and insert into the first part of (4): $1 + \gamma t + \kappa\gamma t + \cdots = 1 - \lambda t$, so $\gamma = -\lambda/(1+\kappa)$, and we can write

$$s(t) = s_0(\tau_i\Psi) + \varepsilon s_1(\tau_i\Psi) + \cdots = 1 - \frac{\lambda\tau_i\Psi}{1+\kappa} + s_1(0)\varepsilon + \cdots$$

and we see that the required matching implies

$$s_1(0) = -\frac{(1+\kappa-\lambda)\varepsilon}{(1+\kappa)^2}.$$

Note: the next term in the approximation for $s(t)$ would contain a factor Ψ^2. In order for our argument to remain valid, we need $\Psi^2 \ll \varepsilon$ as $\varepsilon \to 0$; thus we must have

$$\lim_{\varepsilon\to 0}\frac{\Psi}{\varepsilon} = \infty, \quad \lim_{\varepsilon\to 0}\frac{\Psi}{\sqrt{\varepsilon}} = 0.$$

A better scaling

The above analysis is due to Lin & Segel. An improved scaling was introduced by Segel & Slemrod (see References, below).

They find the proper *time scales* first. (The choice of $\bar{s}$ as the scale for s^* is pretty obvious even at this stage, though.)

After the initial transient, in the quasi-steady state $\mathrm{d}c^*/\mathrm{d}t^* \approx 0$. 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

$$\frac{\mathrm{d}s^*}{\mathrm{d}t^*} = -\frac{k_2\bar{e}s^*}{s^*+K}$$

(which is easily solved, but never mind that for now). Clearly the maximal value of s^* is $\bar{s}$, and one good way to get a time scale is

$$T = \frac{\max|s^*|}{\max\left|\frac{\mathrm{d}s^*}{\mathrm{d}t^*}\right|} = \frac{\bar{s}}{\frac{k_2\bar{e}\bar{s}}{\bar{s}+K}} = \frac{\bar{s}+K}{k_2\bar{e}}. \tag{5}$$

This, then 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

$$\varepsilon T = \frac{1}{k_1(\bar{s}+K)}.$$

This is the appropriate choice of the *short time constant*. The ratio between the two time constants is

$$\varepsilon = \frac{k_2\bar{e}}{k_1(\bar{s}+K)^2}.$$

We must have $\varepsilon \ll 1$, or else our assumptions of very different time scales is wrong, and our analysis becomes suspect. (But in practice, we can get surprisingly good results even for $\varepsilon \approx 1$.)

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

$$s^* = \bar{s}s, \quad c^* = \frac{\bar{e}\bar{s}}{\bar{s}+K}c, \quad t^* = \frac{\bar{s}+K}{k_2\bar{e}}t.$$

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

$$t = \varepsilon\tau$$

where ε is given above.

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. (In our example, this was achieved by equation (5).)

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).