Lecture 7

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(The odd numbered lectures are given by D. Ramakrishnan, and the even ones by R. Tanner.)

0.1 A new approach

As S approaches 0 (corresponding to $t \to \infty$), so does $v = \frac{dp}{dt}$ as long as there is no backward reaction between $P + E$ and C, which we will assume to be the case. Thanks to equation (4), c goes to zero as well.

Here we present a recursive approach to understanding the situation near the point $s = 0$, which also works at the other boundary point $s = s_0$. It does not make use of any steady state hypothesis, and so is independent of the Briggs-Haldane approach.

For simplicity, we will assume from here on that the initial values $(ES)^*$ and P^* of c and p, respectively, are zero.

Step 1: Start with $c = 0$, which happens at $s = 0$. (It also happens at $s = s_0$ since $c_0 = 0$.)

Then the basic differential equation for ds/dt becomes

$$s' = -k_1 e_0 s,$$

resulting in the unique solution

$$s = s_0 e^{-k_1 e_0 t}. \tag{5.1}$$

Moreover, the equation $p + s + e = s_0$ (from earlier) then yields $p = s_0 - s$, i.e.,

$$p = s_0(1 - e^{-k_1 e_0 t}).$$

Hence $v = p'$ equals $k_1 e_0 s_0 e^{-k_1 e_0 t}$. Combining this with (5.1), we get

$$v = \frac{V}{k_3/k_1} s, \tag{5.2}$$

where $V = k_3 e_0$. This is a different starting point than what one gets in the Briggs-Haldane or the Michaelis-Menton models. In all three cases (including our own, the general form is $v = \frac{V}{K} s$, for suitable K.

Of course c will soon become non-zero as we go away from $s = 0$, and the idea is to feed the information we have obtained at the end of this step back into the differential system.

Step 2: At the end of Step 1, we had

$$v = m_1 s, \text{ with } m_1 := k_1 e_0,$$

where := means definition. (We will denote this value of v at the first stage as v_1.) Since $v = k_3 c$, this gives us the starting point of this step, namely

$$c = \frac{k_1 e_0}{k_3} s. \tag{5.3a}$$

Differentiating this with respect to t, we get

$$c' = \frac{k_1 e_0}{k_3} s'. \tag{5.3b}$$

To make use of this equation, we have to first calculate s'. Using equation (1)), we obtain

$$s' = -\frac{k_1 e_0}{k_3}(k_3 - k_2)s + \frac{k_1^2 e_0}{k_3} s^2. \tag{5.4}$$

Recall that

$$v + s' + c' = 0. \tag{5.5}$$

Hence by (5.3b),

$$v = -(1 + \frac{k_1}{k_3} e_0) s'.$$

Substituting for s' from (5.4) yields

$$v = (1 + \frac{k_1}{k_3} e_0) \left(\frac{k_1 e_0}{k_3}(k_3 - k_2)s - \frac{k_1^2 e_0}{k_3} s^2 \right). \tag{5.6}$$

If we put

$$m_2 = (1 + \frac{k_1}{k_3} e_0) \left(\frac{k_1 e_0}{k_3}(k_3 - k_2) \right),$$

then we have, in particular,

$$v = m_2 s + O(s^2).$$

In other words, when s is small enough so that s^2 is negligible, v is like $m_2 s$ at the end of Step 2. So m_2 gives an approximation, finer than m_1, to the slope of the tangent to the curve v as a function of s at $s = 0$.

Of course, (5.6) gives a more precise formula at this stage, and also allows us to keep track of the quadratic term.

Step $\mathbf{n+1}$: After the n-th step, we get an analogue of (5.6):

$$v = v_n = \sum_{j=1}^{n} c_j(n) s^j, \tag{5.7}$$

for suitable constants $c_j(n)$, with $c_1(n) = m_n$. This gives an expression for c (via (4)), and also one for s' by using (1). Then we find c' by differentiating, and using the expression for s'. Now, equation (5.5) gives a new expression for v as a polynomial of degree n in s with new coefficients $c_j(n+1)$.

Continue this way ad infinitum, and take the limit as $n \to \infty$.

Theorem *For every positive integer n, let v_n denote the expression on the right of (5.7), i.e., the value of v at the end of Step n. Then there exists a positive real number $R > 0$ such that the sequence v_n converges for $s < R$. Moreover, the limit is v near $s = 0$.*

We will not prove this result here.

0.2 The slope at $s = 0$

Put

$$b_j = \frac{k_j}{k_3}, \text{ for } j = 1, 2.$$

Let $V = k_3 e_0$ as before. In our recursive method, c, and hence v, is zero at the zeroth stage; we put $v_0 = 0 = m_0$. After the n-th stage, v is given by v_n as in (5.7), with $v_1 = b_1 V s$. So c is given by $c_n := v_n / k_3$, and this leads to expressions for s'_n and also c'_n.Then our procedure gives

$$v_{n+1} = -s'_n - c'_n, \tag{5.8}$$

which is the key recursive formula.

If we now use the fact that $v_n = m_n s + O(s^2)$, we get by (5.8),

$$m_{n+1} = -\left(1 + \frac{m_n}{k_3}\right)(b_1 V - b_2 m_n). \tag{5.9}$$

Put (formally)

$$m := \lim_{n\to\infty} m_n. \tag{5.10}$$

Then (5.9) implies, by taking limits of both sides,

$$m \;=\; \left(1+\frac{m}{k_3}\right)(b_1V - b_2m).$$

In other words, m satisfies the quadratic equation

(5.11). $$b_2m^2 - (b_1V - (b_2+1)k_3)m - b_1V \;=\; 0.$$

This equation has real solutions, incidentally showing that the limit exists. Indeed, if we look at the discriminant of this quadratic, namely

$$D \;=\; (b_1V - (b_2+1)k_3)^2 + 4b_1b_2V, \tag{5.12a}$$

then

$$D \;>\; (b_1V - (b_2+1)k_3)^2 \;\geq 0.$$

There is a unique positive solution, given by

$$m \;=\; \frac{b_1V - (k_2+k_3)}{2b_2} + \frac{\sqrt{D}}{2b_2}. \tag{5.12b}$$

The positivity of the slope is forced by the convexity (proved in section 2) of v as a function of s.

Let us state the final result for later use:

Proposition *The convex curve describing the graph of $v = \frac{dP}{dt}$ as a function of s, has the following slope at $s = 0$:*

$$m \;=\; \frac{1}{2k_2}\left(k_1V - (k_2+k_3)k_3 + \sqrt{(k_1V - (k_2+k_3)k_3)^2 + 4k_1k_2V}\right).$$