I. BRIGGS-HALDANE AND BEYOND: BASICS

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This is the first pat of our sequence of papers on *enzyme Kinetics* giving an algebro-geometric view, by making use of the geometry of surfaces in space which arise from our point of view. The new geometry will be exposed in the second part.

Introduction

1. The basic differential equations

If X is a substance, we will use $[X]$ for its molar concentration in gram moles per liter. It is customary in Chemistry to write (X), but we will not use it here since we want to be able to write $f(X)$ to mean a function of X.

S: Substrate
E: Enzyme
ES: Intermediate complex
P: Product
t: Time
v: $\frac{d[P]}{dt}$
V: k_3E^*
S^*: Initial concentration of Substrate = value of $[S]$ at $t = 0$
E^*: Initial concentration of Enzyme
$(ES)^*$: Initial concentration of the intermediate complex
P^*: Initial concentration of Product

We have the following *Reaction Kinetic Scheme*:

$$S + E \xrightarrow{k_1} ES \xrightarrow{k_3} P + E$$
$$S + E \xleftarrow{k_2} ES$$

To conform to the notation used in Chemistry, we write $[S], [E], [ES], [P]$ to denote the functions of t defined by S, E, ES, P.

Hypothesis: $\frac{d[S]}{dt} < 0$, for all positive t.

So $[S]$ is a strictly decreasing function, and it goes from S^* to 0. In particular, it is one-to-one as a function of t and admits an inverse. Consequently, we may view all the basic quantities, which are a priori functions of t, as functions of $[S]$.

Assuming the *Law of Mass Action*, we obtain the following four inter-related, inhomogeneous differential equations

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

$$\frac{d[ES]}{dt} = k_1[S][E] - (k_2+k_3)[ES] \tag{2}$$

(Note that $\frac{d[ES]}{dt}$ would be > 0 if k_3 were zero, since then $\frac{d[ES]}{dt}$ would equal $-\frac{d[S]}{dt}$.)

$$\frac{d[E]}{dt} = -k_1[S][E] + (k_2+k_3)[ES] \tag{3}$$

$$v = \frac{d[P]}{dt} = k_3[ES] \tag{4}$$

Adding (2) and (3) and integrating, we get

$$[ES] = (ES)^* + E^* - [E], \tag{5}$$

while adding (1), (2) and (4), followed by integration, leads to

$$[S] + [ES] + [P] = S^* + (ES)^* + P^*. \tag{6}$$

Consequently, given all the initial parameters, the four quantities $[S], [E], [ES], [P]$ are all determined by just the knowledge of any two of them.

Thanks to (4) and (5), we see that v is 0 at the start, i.e., when $[S] = S^*$, and it is again zero at the end, i.e., when $[S] = 0$. Thus the maximum value of v occurs in $(0, S^*)$

Put

S_p: the value of $[S]$ where the absolute maximum value of v occurs.

We will see later (see Lemma 2.1) that S_p is unique.

Lemma 1.1 *At any critical point of v as a function of $[S]$ in $(0, S^*)$, we have*

$$[S] = \left(\frac{k_2+k_3}{k_1}\right)\left(\frac{(ES)^* + E^* - [E]}{[E]}\right).$$

In particular, this happens at S_p.

Proof. As $v = \frac{d[P]}{dt}$, we have

$$\frac{dv}{d[S]} = \frac{dt}{d[S]}\frac{d}{dt}\frac{d[P]}{dt}.$$

Recall that by our hypothesis, $\frac{d[S]}{dt}$ is strictly negative, so $\frac{dt}{d[S]}$ is well defined and non-zero (outside the end points). So we see that the critical points occur exactly when

$$\frac{dv}{dt} = \frac{d^2[P]}{dt^2} = 0.$$

Applying (4), since $k_3 > 0$, we have to solve

$$\frac{d[ES]}{dt} = 0.$$

Thanks to (2), this condition becomes

$$k_1[S][E] - (k_2 + k_3)[ES] \,=\, 0.$$

Because of (5), the critical point for v occurs at $[S]$ if and only if we have

$$k_1[S][E] - (k_2 + k_3)((ES)^* + E^* - [E]) \,=\, 0.$$

The Lemma now follows easily. □

We have implicitly assumed that $E^* - [E]$ is positive except possibly at the end points, which is a reasonable hypothesis.

2. Convexity of $v = \frac{d[P]}{dt}$ as a function of $[S]$

Recall that S_p is, by definition, where v attains its absolute maximum. Since v is a differentiable function of $[S]$, it attains its maximum at a critical point. On the other hand, by Lemma 1.1, there is a unique critical point of v, which gives part (i) of the following:

Lemma 2.1 *We have*

(i) *S_p is the unique critical point of $v = \frac{d[P]}{dt}$ on the open interval $(0, S^*)$;*

(ii) *$\frac{d^2v}{d[S]^2}$ is everywhere negative, hence the graph of v as a function of $[S]$ is entirely bell-shaped (convex).*

Proof. We need to prove only part (ii). Again, since by our hypothesis, $d[S]/dt$ is everywhere negative on $(0, S^*)$, and as k_3 is positive, we are left (by equation (4) of section 1) to prove that

$$\frac{d}{dt}\left(\frac{d[ES]}{d[S]}\right) \,>\, 0.$$

Applying equations (1) and (2) of section 1, we obtain

$$\frac{d[ES]}{d[S]} \,=\, \frac{[ES]'}{[S]'} \,=\, \frac{k_1[S][E] - (k_2 + k_3)[ES]}{-k_1[S][E] + k_2[ES]},$$

where $[S]'$, resp. $[ES]'$, denotes $\frac{d[S]}{dt}$, resp. $\frac{d[ES]}{dt}$. Comparing (1) and (2), we have

$$[ES]' \,=\, -[S]' - k_3[ES],$$

which yields

$$\frac{d[ES]}{d[S]} \,=\, -1 - k_3\frac{[ES]}{[S]'}.$$

Taking derivatives with respect to t and multiplying both sides by $-k_3^{-1}([S]')^2$, we obtain

$$-k_3^{-1}([S]')^2\frac{d}{dt}\left(\frac{d[ES]}{d[S]}\right) \,=\, [S]'[ES]' - [S]''[ES].$$

Now we *claim* that on the open interval $(0, S^*)$,

$$\frac{d}{dt}\left(\frac{d[ES]}{d[S]}\right) \,\neq\, 0.$$

Indeed, the left hand side can be zero if and only if we have

$$[S]'[ES]' - [S]''[ES] \,=\, 0.$$

In other words,
$$\frac{[S]''}{[S]'} = \frac{[ES]'}{[ES]},$$
which integrates to give
$$\log[S]' = \log[ES] + c,$$
for a real constant c. Exponentiating, we obtain
$$[S]' = e^c[ES].$$
Since $e^c > 0$ for any real number c, we deduce that, if the claim were false, $[S]'$ and $[ES]$ must, in particular, have the same sign in $(0, S^*)$. This is patently false as $[S]'$ is negative and $[ES]$ is ≥ 0. Hence the Claim.

Consequently, to prove the Proposition, we need only show that
$$[S]'[ES]' - [S]''[ES] < 0, \text{ for some } [S].$$
This is because the expression on the left is continuous (since $[ES], [S]$ are repeatedly differentiable) and non-zero (by the claim above), and thanks to the intermediate value theorem, once it is positive somewhere, it will be so everywhere.

Since $[S]' < 0$ and $[ES] \geq 0$, it suffices to prove that
$$\exists\, [S] \text{ such that } [ES]' > 0 \text{ and } [S]'' > 0.$$

We know that $[ES]'$ is negative when t is small, i.e., when $[S]$ is near S^*. Moreover, differentiating (1) (with respect to t) yields
$$[S]'' = -k_1[S]'[E] - k_1[S][E]' + k_2[ES]'.$$
From (2) and (3), we see that $[E]' = -[ES]'$, implying
$$[S]'' = -k_1[S]'[E] + (k_1[S] + k_2)[ES]',$$
which is positive when $[ES]' > 0$, since $[S]' < 0$, while $[E], [S], k_1, k_2$ are positive.

This finishes the proof of the Proposition.

□

3. The Briggs-Haldane model

Now suppose we make (just in this section) the following **stationary state assumption**:

$$\frac{d[ES]}{dt} = 0, \tag{7}$$

or equivalently (by (2)):

$$k_1[S][E] = (k_2 + k_3)[ES]. \tag{7$'$}$$

Proposition 3.1 (Briggs-Haldane) *Under the steady state assumption above, we have*
$$v = \frac{V[S]}{K_m + [S]}, \text{ where } V = k_3E^*,\ K_m = (k_2 + k_3)/k_1.$$
In particular, in this model, $v = \frac{d[P]}{dt}$ goes to zero as $[S] \to 0$, i.e., as $t \to \infty$. Moreover, at the peak point $[S] = S_p$, this curve meets the actual curve defining v.

By the actual curve, we mean the one obtained without the steady state assumption. Later on, we will denote the approximate expression for v given by Briggs-Haldane by v_{BH}.

Proof of Proposition 3.1 Write $[ES]'$ for $\frac{d[ES]}{dt}$, etc. From equation (5) of section 1, we see that $[E]' = -[ES]'$ (since $[ES] = (ES)^* + E^* - [E]$), so the steady state hypothesis gives, thanks to equation (3) (of section 1),

$$k_1(E^* - [ES])[S] \,=\, (k_2 + k_3)[ES],$$

which yields

$$(k_1[S] + k_2 + k_3)[ES] \,=\, k_1 E^*,$$

or equivalently,

$$[ES] \,=\, \frac{V[S]}{K_m + [S]},$$

with K_m, V as in the statement of the Proposition. (The subscript m usually stands for Michaelis.)

Now substituting this in the equation (4) gives us the assertion on $v = \frac{d[P]}{dt}$ under the steady state assumption.

It is left to prove that the Briggs-Haldane approximation v_{BH}, as denoted from here on, equals the actual function v at $[S] = S_p$. For this recall that in section 2 we proved, with no hypothesis, that S_p is the unique critical point of v in $(0, S^*)$. Since $v = [P]'$ equals $k_3[ES]$ by equation (4),

$$\frac{dv}{d[S]} \,=\, k_3 \frac{[ES]'}{[S]'},$$

which vanishes at the unique critical point, and since $[S]'$ is non-zero in $(0, S^*)$, we see that

$$\frac{d[ES]}{dt} \,=\, 0 \;\text{ at }\; [S] = S_p.$$

Since this vanishing is the starting point ("steady state") for the Briggs-Haldane model, we get

$$v \,=\, v_{BH} \;\text{ at }\; [S] = S_p.$$

In other words, the graphs of v and v_{BH} as functions of $[S]$ meet at the peak point $[S] = S_p$. (This point is not the peak for v_{BH}, however.)

□

4. A new approach

As S approaches 0 (corresponding to $t \to \infty$), so does $v = \frac{d[P]}{dt}$ as long as there is no back reaction between $[P] + [E]$ and $[ES]$, which we will assume to be the case. Thanks to equation (4), $[ES]$ 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 $[S] = S^*$. 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 $[ES]$ and $[P]$, respectively, are zero.

Step 1: Start with $[ES] = 0$, which happens at $[S] = 0$. (It also happens at $[S] = S^*$ if $[ES]^* = 0$.)

Then equation (1) becomes

$$[S]' \,=\, -k_1 E^*[S],$$

resulting in the unique solution

$$[S] \;=\; S^* e^{-k_1 E^* t}. \tag{8}$$

Moreover, equation (6) then yields $[P] = S^* - [S]$, i.e.,

$$[P] \;=\; S^*(1 - e^{-k_1 E^* t}).$$

Hence $v = [P]'$ equals $k_1 E^* S^* e^{-k_1 E^* t}$. Combining this with (8), we get

$$v \;=\; \frac{V}{k_3/k_1}[S], \tag{9}$$

where $V = k_3 E^*$. 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 $[ES]$ 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

$$v = m_1[S], \;\text{ with }\; m_1 := k_1 E^*,$$

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

$$[ES] \;=\; \frac{k_1 E^*}{k_3}[S]. \tag{10a}$$

Differentiating this with respect to t, we get

$$[ES]' \;=\; \frac{k_1 E^*}{k_3}[S]'. \tag{10b}$$

To make use of this equation, we have to first calculate $[S]'$. Using equation (1)), we obtain

$$[S]' \;=\; -\frac{k_1 E^*}{k_3}(k_3 - k_2)[S] + \frac{k_1^2 E^*}{k_3}[S]^2. \tag{11}$$

Recall that by adding equations (1), (2) and (4),

$$v + [S]' + [ES]' \;=\; 0. \tag{12}$$

Hence by (10b),

$$v \;=\; -(1 + \frac{k_1}{k_3}E^*)[S]'.$$

Substituting for $[S]'$ from (11) yields

$$v \;=\; (1 + \frac{k_1}{k_3}E^*)\left(\frac{k_1 E^*}{k_3}(k_3 - k_2)[S] - \frac{k_1^2 E^*}{k_3}[S]^2\right). \tag{13}$$

If we put

$$m_2 \;=\; (1 + \frac{k_1}{k_3}E^*)\left(\frac{k_1 E^*}{k_3}(k_3 - k_2)\right),$$

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, (13) 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 (13):

$$v = v_n = \sum_{j=1}^{n} c_j(n)[S]^j, \tag{14}$$

for suitable constants $c_j(n)$, with $c_1(n) = m_n$. This gives an expression for $[ES]$ (via (4)), and also one for $[S]'$ by using (1). Then we find $[ES]'$ by differentiating, and using the expression for $[S]'$. Now, equation (12) 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 (14), 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 supply a proof of this result later.

5. The slope at $[S] = 0$

Put

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

Let $V = k_3E^*$ as before. In our recursive method, $[ES]$, 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 (14), with $v_1 = b_1V[S]$. So $[ES]$ is given by $[ES]_n := v_n/k_3$, and this leads to expressions for $[S]'_n$ and also $[ES]'_n$.Then our procedure gives

$$v_{n+1} = -[S]'_n - [ES]'_n, \tag{15}$$

which is the key recursive formula.

If we now use the fact that $v_n = m_n[S] + O([S]^2)$, we get by (15),

$$m_{n+1} = -\left(1 + \frac{m_n}{k_3}\right)(b_1V - b_2m_n). \tag{16}$$

Put (formally)

$$m := \lim_{n\to\infty} m_n. \tag{17}$$

Then (16) 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

$$b_2m^2 - (b_1V - (b_2+1)k_3)m - b_1V = 0. \tag{18}$$

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

$$D = (b_1V - (b_2+1)k_3)^2 + 4b_1b_2V, \tag{19a}$$

then

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

There is a unique positive solution, given by

$$m = \frac{b_1 V - (k_2 + k_3)}{2b_2} + \frac{\sqrt{D}}{2b_2}. \tag{19b}$$

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 $[S] = 0$:*

$$m = \frac{1}{2k_2}\left(k_1 V - (k_2 + k_3)k_3 + \sqrt{(k_1 V - (k_2 + k_3)k_3)^2 + 4k_1 k_2 V}\right).$$

6. Comparison of m with m_{BH} and m_{MM}

Let m denote the slope at $[S] = 0$ obtained in the section above. Put

$$m_{BH} := \frac{k_1 V}{k_2 + k_3}, \tag{20a}$$

which is the slope in the Briggs-Haldane model, and

$$m_{MM} := \frac{k_1 V}{k_2}, \tag{20b}$$

the slope coming from the Michaelis-Menton model.

Proposition *We have*

$$m_{BH} \le m \le m_{MM}.$$

7. A quadratic approximation for small $[S]$

We explicated the linear term of our method in the previous sections and compared it to the Briggs-Haldane and Michaelis-Menton approaches. Our approach can go much further and give an approximation of any order desired (for small $[S]$). In the next section we will in fact give an exact infinite series expansion, from which approximations of any order can be deduced. Now let us delineate the quadratic case. We will preserve the earlier notations involving $v_n, [ES]_n$, etc., denoting the values of $v, [ES]$, etc., at the n-th stage of the recursion. Let us write

$$v_n = m_n[S] + q_n[S]^2 + O([S]^3), \tag{21}$$

where m_n is the slope at the n-th stage, and q_n the coefficient controlling the quadratic term. As usual, $O([S]^r)$ denotes, for any $r > 0$, a sum of terms of order at least $[S]^r$. It follows by differentiation that

$$[v]'_n = m_n[S]' + 2q_n[S][S]' + [S]'O([S]^2) + O([S]^3). \tag{22}$$

Since $v = k_3[ES]$, we get from (21),

$$k_2[ES]_n = \frac{k_2}{k_3} m_n[S] + \frac{k_2}{k_3} q_n[S]^2 + O([S]^3), \tag{23a}$$

and

$$k_1[S][ES]_n = \frac{k_1}{k_3} m_n[S]^2 + O([S]^3). \tag{23b}$$

These give, thanks to (1) and (5), at stage n,

$$[S]', = \left(\frac{k_2}{k_3}m_n - \frac{k_1}{k_3}V\right)[S] + \frac{(k_1 m_n + k_2 q_n)}{k_3}[S]^2 O([S]^3). \tag{24}$$

In particular, $[S]'$ is $O([S])$, and

$$[S][S]' \;=\; \left(\frac{k_2}{k_3}m_n - \frac{k_1}{k_3}V\right)[S]^2 + O([S]^3).$$

So (22) simplifies as

$$k_3[ES]'_n \;=\; m_n[S]' + \left(\frac{k_2}{k_3}m_n - \frac{k_1}{k_3}V\right)[S]^2 + O([S]^3). \tag{25}$$

The recursion is defined in such a way that

$$v_{n+1} \;=\; -[S]'_n - [ES]'_n, \tag{26}$$

where $[S]_n$ denotes the value of $[S]'$ at stage n. Thus, by (25),

$$v_{n+1} \;=\; -\left(1 + \frac{m_n}{k_3}\right)[S]'_n - \left(\frac{k_2}{k_3}m_n - \frac{k_1}{k_3}V\right)[S]^2 + O([S]^3). \tag{27}$$

Plugging in (24), we then get

(28)

$$v_{n+1} \;=\; -\left(1 + \frac{m_n}{k_3}\right)\left(\frac{k_2}{k_3}m_n - \frac{k_1}{k_3}V\right)[S] - \left((1 + \frac{m_n}{k_3})(\frac{(k_1 m_n + k_2 q_n)}{k_3}) - (\frac{k_2}{k_3}m_n - \frac{k_1}{k_3}V)\right).$$

Since this is $m_{n+1}[S] + q_{n+1}[S]^2 + O([S]^3)$, we obtain

$$q_{n+1} \;=\; -\left(1 + \frac{m_n}{k_3}\right)\left(\frac{k_1 m_n + k_2 q_n}{k_3}\right). \tag{29}$$

Now we let n go to infinity, and obtain, for $q = \lim_{n\to\infty} q_n$, the relation

$$q \;=\; -\left(1 + \frac{m}{k_3}\right)\left(\frac{k_1 m + k_2 q}{k_3}\right).$$

This yields

$$q \;=\; -\frac{(1 + \frac{m}{k_3})\frac{k_1 m}{k_3}}{1 + (1 + \frac{m}{k_3})\frac{k_2}{k_3}}. \tag{30}$$

Note that this is independent of $[E]^*$.

Putting $v = \lim_{n\to\infty} v_n$, this gives the expression

$$v \;=\; m[S] - \left(\frac{(k_3 + m)k_1 m}{k_3^2 + (k_3 + m)k_2}\right)[S]^2 + O([S]^3), \tag{31}$$

where m is given by (19b). Consequently,

$$\frac{dv}{d[S]} \;= m - \left(\frac{2(k_3 + m)k_1 m}{k_3^2 + (k_3 + m)k_2}\right)[S] + O([S]^2). \tag{32}$$

If S^* is small, then so is S_p, in which case this quadratic approximation has some validity near it, allowing to deduce that S_p is close to $\frac{k_3^2 + (k_3 + m)k_2}{2(k_3 + m)k_1}$.

8. A quadratic approximation at S^*

This section not delicate as the previous section, since the $[S]$-derivatives of $v\frac{d[P]}{d[S]}$ are all well defined and easily calculated at S^* (unlike at $[S]=0$). Nevertheless, the formulae below are useful in the following section. As before, we will write $[S]'$ for $\frac{d[S]}{dt}$, $[ES]' = \frac{d[ES]}{dt}$, etc.

Lemma *t the point $[S]=S^*$, the following values hold:*

(a) $[S]' = -k_2 S^* E^*$, $[ES]' = k_1 S^* E^*$, *and* $[E]' = k_1 S^* E^*$.
(b) $\frac{dv}{d[S]} \;=\; -k_3$.
(c) $\frac{d^2v}{d[S]^2} \;=\; -\frac{k_3^2}{k_1 S^* E^*}$.

Consequently, the quadratic Taylor approximation to v near $[S]=S^*$ is given by

$$v \;=\; -k_3([S]-S^*) - \frac{k_3^2}{2k_1S^*E^*}([S]-S^*)^2 + O(([S]-S^*)^3).$$

Proof. (a): This follows directly from the basic differential equations by evaluation at S^*.

(b): We saw in the proof of Lemma 2.1 that

$$\frac{d[ES]}{d[S]} \;=\; -1 - k_3\frac{[ES]}{[S]'}.$$

Since $v = k_3[ES]$ and $[ES] = E^* - [E]$ is zero at S^*, we get $\frac{dv}{d[S]} = -k_3$.

(c): Differentiating relative to t,

$$\frac{d}{dt}\left(\frac{d[ES]}{d[S]}\right) \;=\; -k_3\frac{[S]'[ES]' - [S]''[ES]}{([S]')^2}.$$

9. Approximations to S_p

Now that we have expansions for v at 0 and at S^*, we can find a series of approximations $S_{p,n}$ to S_p, which will be good for small S^*, by equating the n-th order terms of the respective expansions.

Proposition

(a) $S_{p,1} \;=\; \frac{k_3S^*}{m+k_3}$;
(b) $S_{p,2}$ *satisfies a quadratic equation:*

$$AX^2 + BX + C = 0,$$

with

$$A = \left(\frac{k_3^2}{2k_1S^*E^*} - \frac{(k_3+m)k_1m}{k_3^2+k_3+mk_2}\right),$$

$$B = \left(\frac{k_3}{2k_1E^*} - m - k_3\right),$$

and

$$C = \left(\frac{k_3^2}{2k_1E^*} - k_3S^*\right)\left(\frac{k_3}{2k_1S^*E^*} - 1\right).$$

10. A recursive variation on Briggs-Haldane

Here we present a recursive approach to understanding the situation arround the point $[S] = S_p$, starting with the steady state hypothesis of Briggs-Haldane, but which does not hold any more after the first iteration.

For simplicity, we will continue to assume that the initial values $(ES)^*$ and P^* of $[ES]$ and $[P]$, respectively, are zero.

Step 1: Start with $[ES]' = 0$, which happens at $[S] = S_p$. Then by (2):

$$k_1[S](E^* - [ES]) \;=\; (k_2 + k_3)[ES],$$

which gives the Briggs-Haldane formulae

$$[ES]_{BH} \;=\; \frac{E^*[S]}{K_m + [S]} \text{ and } v_{BH} = k_3[ES]_{BH} = \frac{V[S]}{K_m + [S]}. \tag{33}$$

We will write $[ES]_0$ and $v_0 = [P]'_0$ instead to signify that these values are at the zeroth stage.

Using (1), we also get

$$[S]' \;=\; -k_1E^*[S] + (k_2 + k_1[S])([ES]) \;=\; E^*[S]\left(-k_1 + \frac{k_2 + k_1[S]}{K_m + [S]}\right).$$

This simplifies as

$$[S]' \;=\; -\frac{V[S]}{K_m + [S]}. \tag{34}$$

Of course this should have been expected, as at the zeroth stage, $[ES]' = 0$, while the time derivative of equation (6) gives $[ES]' + [P]' + [S]' = 0$, and since $v = [P]'$, we get $0 = [ES]' = -v - [S]'$ (at that stage).

Of course $[ES]'$ will soon become non-zero as we go away from $[S] = S_p$, and the idea is to feed the information we have obtained at the end of this step back into the differential system.

Step 2: Differentiating $[ES]$ using (33), we get

$$[ES]' \;=\; \frac{(E^*(K_m + [S]) - E^*[S])[S]'}{(K_m + [S])^2},$$

which simplifies as

$$[ES]' \;=\; \frac{E^*K_m[S]'}{(K_m + [S])^2}. \tag{35}$$

Since $v + [S]' + [ES]' = 0$, we get from (35),

$$v \;=\; -[S]'\left(1 + \frac{E^*K_m}{(K_m + [S])^2}\right).$$

Substituting for $[S]'$ from (34),

$$v \;=\; \left(\frac{V[S]}{K_m + [S]}\right)\left(1 + \frac{E^*K_m}{(K_m + [S])^2}\right). \tag{36}$$

We call this v_1.

Taking the derivative with respect to $[S]$, we obtain

$$\frac{dv_1}{d[S]} \;=\; \frac{VK_m}{(K_m + [S])^2} + \frac{E^*VK_m(K_m - 2[S])}{(K_m + [S])^4}. \tag{37}$$

Clearly,

$$\frac{dv_1}{d[S]}_{|_{[S]=0}} \;=\; \frac{V}{K_m} + \frac{E^*V}{K_m^2}, \tag{38}$$

and

$$\frac{dv_1}{d[S]} = 0 \;\Leftrightarrow\; ([S] + K_m)^2 - 2E^*([S] + K_m) + 3E^*K_m \;=\; 0.$$

Thus the critical points of v_1 are given by

$$[S] \;=\; -K_m + E^* \pm \sqrt{E^*(E^* - 3K_m)}.$$

Note that

$$\text{If } E^* = 0 \text{ then } \left(\frac{dv_1}{d[S]} = 0 \Leftrightarrow [S] = -K_m\right).$$

This agrees with the Briggs-Haldane limit; of course, in reality, $[S]$ will not be negative.