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Analytical Solutions of a Simple Enzyme Kinetic Problem by a Perturbative Procedure

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Abstract. A systematic perturbative procedure (the method of singular perturbation) is developed to follow the time evolution of an enzyme catalyzed reaction with one intermediate product over the entire time domain of interest. The perturbation parameter is the ratio of the enzyme concentration to the Michaelis-Menten constant. The treatment leads to a meaningful definition of the so-called quasi-steady state often invoked in the description of enzyme catalyzed reactions. The legitimacy and the domain of validity of this assumption are examined in the context of both the reversible and irreversible Michaelis-Menten kinetics.

Key words: Michaelis-Menten kinetics – Singular perturbation – Quasi-steady state – One intermediate product.

1. Introduction

Consider the enzyme catalyzed chemical reaction

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E + P\,, \tag{1}$$

where ES is the enzyme-substrate complex. Let e, s, x, and p stand for the concentrations of the enzyme, the substrate, the enzyme-substrate complex and the product respectively. If the system is *closed*, there are two conservation requirements:

$$s + p + x = s_0; \quad e + x = e_0\,. \tag{2}$$

It suffices therefore to consider the rates of change of s and x:

$$\frac{ds}{dt} = k_{-1}x - k_1es = k_{-1}x - k_1s(e_0 - x) \tag{3a}$$

$$\begin{aligned}\frac{dx}{dt} &= k_1es - (k_{-1} + k_2)x + k_{-2}ep \\ &= k_1s(e_0 - x) - (k_{-1} + k_2)x + k_{-2}(e_0 - x)(s_0 - s - x)\,.\end{aligned} \tag{3b}$$

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We use the initial conditions

$$s(0) = s_0 \text{ and } x(0) = 0\,. \tag{4}$$

Following Reich and Sel'kov (1974), it is convenient to cast these equations in the so-called canonical form (in terms of dimensionless variables). Define the dimensionless parameters

$$\varepsilon = \frac{e_0}{K_m}, \quad \xi_{-1} = \frac{k_{-1}}{k_{-1} + k_2}, \quad \beta = \frac{k_{-2}}{k_1} \tag{5a}$$

and the dimensionless variables

$$S = \frac{s}{K_m}, \quad X = \frac{x}{e_0}, \quad \tau = k_1 e_0 t \tag{5b}$$

where $K_m = (k_{-1} + k_2)/k_1$ is the Michaelis-Menten constant. The canonical equations now read

$$\frac{dS}{d\tau} = \xi_{-1} X - S(1 - X) \tag{6a}$$

$$\varepsilon \frac{dX}{d\tau} = S(1 - X) - X + \beta(S_0 - S - \varepsilon X)(1 - X)\,. \tag{6b}$$

Eq. (4) can now be rewritten as

$$S(0) = \frac{s_0}{K_m} = S_0 \text{ and } X(0) = 0\,. \tag{7}$$

Although Eqs. (6) look deceptively simple, their analytical solutions have remained elusive. In fact, closed solutions of Eqs. (6) are known only in the special case of $\beta = 1$. There have been, however, numerous attempts (Hommes, 1962a, b; Walter and Morales, 1964; Wong, 1965; Walter, 1966, 1974; Stayton and Fromm, 1979; Schauer and Heinrich, 1979) to determine the domain of parameters for which the quasi-steady state assumption may hold, or conversely to find if it may not hold for some special values of one or more of the parameters (the rate constants). Thus, it has been suggested (Walter, 1974) that for $\beta > 1$, the use of this assumption could lead to errors.

In this paper, we seek to develop a systematic perturbative procedure to find analytical solutions for the kinetic Eqs. (6). At least for those enzyme systems characterized by a small enzyme concentration, the use of ε [defined in Eq. (5a)] as a perturbation parameter suggests itself. A naive application of such a perturbation development in powers of ε leads to an apparent violation of the conservation requirements Eq. (7). It is easily verified that on setting $\varepsilon = 0$, Eq. (6b) yields

$$S(\tau) = \frac{X(\tau) - \beta S_0[1 - X(\tau)]}{[1 - X(\tau)](1 - \beta)}\,.$$

It now follows that (since $X(0) = 0$)

$$S_0 = S(0) = \frac{\beta}{(\beta - 1)} S_0 \neq S_0 ,$$

which is clearly absurd. This necessitates formulation of the perturbation procedure along more sophisticated lines and we do so in the following sections.

2.1. The Method of Singular Perturbation

Physically there exist two characteristic time scales in the system: a "short-time" scale characterizing the rapid evolution of the intermediate complex to the quasi-steady state during which the substrate concentration remains virtually unaltered and a "long-time" scale over which both the substrate and the intermediate complex concentrations evolve to their equilibrium values. The perturbation procedure employed exploits the existence of these two time scales. Figure 1 shows the essential ingredients of our approach at a glance. The time evolution of the system is broken up into two parts, a short-time and a long-time evolution. Two sets of kinetic equations are written down, one for each description. The short-time solutions satisfy the prescribed initial conditions, but have the wrong asymptotic behaviour (do not yield the equilibrium). The long-time solutions, on the other hand, yield the equilibrium, but violate the initial conditions. Both solutions have a region of overlap over an intermediate time domain, which we term the "matching region". The solutions are matched (*in each order* of the perturbation in ε) by means of the matching principle which will be explained in a subsequent section.

2.2. The Short-Time Evolution

The time evolution immediately following the commencement of the reaction is described on the short-time scale. Following the recipe of the method of singular

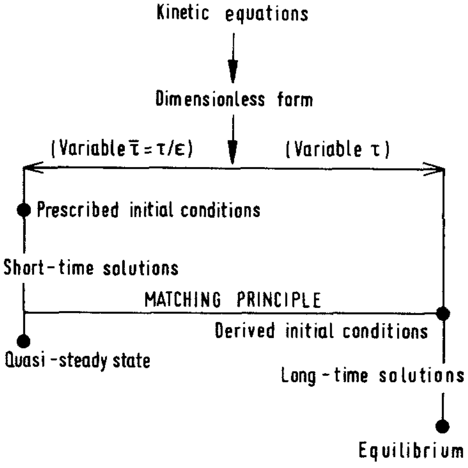

Fig. 1. The basic ingredients of the singular perturbation procedure

perturbation (Van Dyke, 1975), we define the "strained variable"

$$\bar{\tau} = \frac{\tau}{\varepsilon} = (k_{-1} + k_2)\, t\,. \tag{8}$$

It must be emphasized that no matter how small ε is, $\bar{\tau} = O(1)$ by proper choice of τ. This serves to define roughly the extent of the short-time domain. Eqs. (6) can now be transformed to the form

$$\frac{d\bar{S}}{d\bar{\tau}} = \varepsilon[\xi_{-1}\bar{X} - \bar{S}(1 - \bar{X})] \tag{9a}$$

$$\frac{d\bar{X}}{d\bar{\tau}} = \bar{S}(1 - \bar{X}) - \bar{X} \tag{9b}$$

for the irreversible reaction scheme ($\beta = 0$, i.e., the product formation is irreversible) and

$$\frac{d\bar{S}}{d\bar{\tau}} = \varepsilon[\xi_{-1}\bar{X} - \bar{S}(1 - \bar{X})] \tag{9a}$$

$$\frac{d\bar{X}}{d\bar{\tau}} = \bar{S}(1 - \bar{X}) - \bar{X} + \beta(S_0 - \bar{S} - \varepsilon\bar{X})(1 - \bar{X}) \tag{9c}$$

for the reversible reaction scheme ($\beta \neq 0$).
For both schemes, the initial conditions are

$$\bar{S}(0) = S_0; \quad \bar{X}(0) = 0\,.$$

All variables referred to the short-time scale carry bars over them as in Eqs. (9). We refer to Eqs. (9) as the short-time kinetic equations and note in passing that this terminology is meaningful only in the context of a perturbation expansion in ε. We deal with systems in which ε may be regarded small. Accordingly we make perturbation expansions in ε:

$$\bar{S}(\bar{\tau}) = \bar{S}^0(\bar{\tau}) + \varepsilon\bar{S}^1(\bar{\tau}) + \cdots \tag{10a}$$

$$\bar{X}(\bar{\tau}) = \bar{X}^0(\bar{\tau}) + \varepsilon\bar{X}^1(\bar{\tau}) + \cdots \tag{10b}$$

Zeroth Order: We substitute the above perturbation expansions in Eqs. (9) and equate terms of the same order in ε. Eq. (9a) now yields

$$\frac{d\bar{S}^0}{d\bar{\tau}} = 0 \text{ or } \bar{S}^0(\bar{\tau}) = S_0 \tag{11a}$$

for both the reversible and irreversible schemes. In fact, the reversible and irreversible schemes are indistinguishable in the zeroth order, as both Eqs. (9b) and (9c) lead to

$$\frac{d\bar{X}^0}{d\bar{\tau}} = S_0(1 - \bar{X}^0) - \bar{X}^0 ,$$

whose solution is

$$\bar{X}^0(\bar{\tau}) = \frac{S_0}{(1 + S_0)}\{1 - \exp[-(1 + S_0)\bar{\tau}]\} . \tag{11b}$$

It may be mentioned that use has been made of the initial conditions

$$\bar{S}^0(0) = S_0 \quad (\bar{S}^j(0) = 0 \text{ for } j > 0)$$

and

$$\bar{X}^0(0) = 0 \quad (\bar{X}^j(0) = 0 \text{ for } j > 0)$$

in the derivation of the above. Here j denotes the order of the perturbation. In other words, the zeroth order solutions satisfy the prescribed initial conditions, while all the higher order solutions are identically zero at the initial time.

First Order: From Eqs. (9a) and (10), we obtain for both the reversible and irreversible schemes

$$\frac{d\bar{S}^1}{d\bar{\tau}} = \xi_{-1}\bar{X}^0 - S_0(1 - \bar{X}^0) \text{ with } \bar{S}^1(0) = 0 . \tag{12}$$

Thus

$$\bar{S}^1(\bar{\tau}) = -\frac{(\xi_{-1} + S_0)S_0}{(1 + S_0)^2} - \bar{\tau}\,\frac{(1 - \xi_{-1})S_0}{(1 + S_0)} + \frac{(\xi_{-1} + S_0)S_0}{(1 + S_0)^2}\exp[-(1 + S_0)\bar{\tau}] , \tag{13a}$$

which has the following asymptotic form for large $\bar{\tau}$:

$$\lim_{\bar{\tau} \to \infty} \bar{S}^1(\bar{\tau}) = -\frac{(\xi_{-1} + S_0)S_0}{(1 + S_0)^2} - \bar{\tau}\,\frac{(1 - \xi_{-1})S_0}{(1 + S_0)} \tag{13b}$$

One obtains from Eq. (9c) for the reversible scheme

$$\frac{d\bar{X}^1}{d\bar{\tau}} + (1 + S_0)\bar{X}^1 = \bar{S}^1 - \bar{X}^0\bar{S}^1 + \beta(\bar{X}^{0^2} + \bar{X}^0\bar{S}^1 - \bar{S}^1 - \bar{X}^0) ,$$

whose solution is

$$\begin{aligned}
\bar{X}^1(\bar{\tau}) = S_0 \Bigg[& -\frac{S_0 + 2\,\xi_{-1} - 1}{(1+S_0)^4} - \frac{(1-\xi_{-1})}{(1+S_0)^3}\,\bar{\tau} \\
& + \left\{ \frac{(\xi_{-1}+S_0)\,(S_0+2) - (1+S_0)}{(1+S_0)^4} + \frac{(\xi_{-1}+S_0)\,(1-S_0)}{(1+S_0)^3}\,\bar{\tau} \right. \\
& \left. - \frac{S_0(1-\xi_{-1})}{2\,(1+S_0)^2}\,\bar{\tau}^2 \right\} \exp\left[-(1+S_0)\bar{\tau}\right] \\
& - \frac{(\xi_{-1}+S_0)S_0}{(1+S_0)^4} \exp\left[-2\,(1+S_0)\bar{\tau}\right] \Bigg] \\
& + \beta S_0 \Bigg[-\frac{2\,(1-\xi_{-1})}{(1+S_0)^4} + \frac{(1-\xi_{-1})}{(1+S_0)^3}\,\bar{\tau} \\
& + \left\{ \frac{(1-\xi_{-1})(S_0+2)}{(1+S_0)^4} + \frac{(1-\xi_{-1})(1-S_0)}{(1+S_0)^3}\,\bar{\tau} \right. \\
& \left. + \frac{S_0(1-\xi_{-1})}{2\,(1+S_0)^2}\,\bar{\tau}^2 \right\} \exp\left[-(1+S_0)\bar{\tau}\right] \\
& - \frac{(1-\xi_{-1})S_0}{(1+S_0)^4} \exp\left[-2\,(1+S_0)\bar{\tau}\right] \Bigg] .
\end{aligned} \tag{13c}$$

Set $\beta = 0$ for the irreversible case. Further,

$$\begin{aligned}
\lim_{\bar{\tau}\to\infty} \bar{X}^1(\bar{\tau}) = & - \left[\frac{(S_0 + 2\,\xi_{-1} - 1)S_0}{(1+S_0)^4} - \bar{\tau}\,\frac{(1-\xi_{-1})S_0}{(1+S_0)^3} \right] \\
& - \beta \left[\frac{2\,(1-\xi_{-1})S_0}{(1+S_0)^4} - \bar{\tau}\,\frac{(1-\xi_{-1})S_0}{(1+S_0)^3} \right] .
\end{aligned} \tag{13d}$$

2.3. The Long-Time Evolution

The time evolution subsequent to the attainment of the quasi-steady state is best described on the long-time scale

$$\tau = k_1 e_0 t \, .$$

Eqs. (6) may be taken over as they stand for the long-time description. Expansions similar to those in Eqs. (10) can again be made:

$$S(\tau) = S^0(\tau) + \varepsilon S^1(\tau) + \cdots\cdots \tag{14a}$$

$$X(\tau) = X^0(\tau) + \varepsilon X^1(\tau) + \cdots\cdots . \tag{14b}$$

It must be stressed again that the initial conditions for the long-time description are not the prescribed initial conditions. Instead, the quantities $S^j(0)$ and $X^j(0)$ ($j \geqslant 0$) must be regarded as integration constants to be determined. Their actual determination calls for a knowledge of the asymptotic forms of the short-time solutions. A discussion of this point will be deferred to the next section.

Zeroth Order: Eq. (6a) yields in the zeroth order

$$\frac{dS^0}{d\tau} = \xi_{-1}X^0 - S^0(1 - X^0) \tag{15a}$$

for both the reversible and irreversible schemes, while

$$0 = S^0(1 - X^0) - X^0 \tag{15b}$$

and

$$0 = S^0(1 - X^0) - X^0 + \beta(S_0 - S^0)(1 - X^0) \tag{15c}$$

follow from Eq. (6b) for the irreversible and reversible schemes respectively. Solving for $X^0(\tau)$ from Eq. (15c),

$$X^0(\tau) = \frac{S^0(\tau) + \beta[S_0 - S^0(\tau)]}{1 + S^0(\tau) + \beta[S_0 - S^0(\tau)]} . \tag{16}$$

(Set $\beta = 0$ for the irreversible scheme). On substituting this expression in Eq. (15a), the following transcendental equation results for $S^0(\tau)$:

$$\frac{(1 - \xi_{-1} + \xi_{-1}\beta) + \beta S_0}{(1 - \xi_{-1} + \xi_{-1}\beta)^2} \ln (S^0 - S^0_{\text{eq}}) + \frac{(1 - \beta)}{(1 - \xi_{-1} + \xi_{-1}\beta)} S^0 = -\tau + h . \tag{17a}$$

For the irreversible scheme, Eq.(17a) simplifies to the form

$$\ln S^0 + S^0 = -(1 - \xi_{-1})(\tau - h) . \tag{17b}$$

In Eqs. (17), S^0_{eq} is the equilibrium substrate concentration evaluated at $\varepsilon = 0$; h is an integration constant. The appendix lists the explicit forms of the equilibrium concentrations. Although, neither of the transcendental equations above can be solved in closed form for $S^0(\tau)$, nevertheless, their solution can be reduced to purely an algebraic operation by essentially inverting the relationship between S^0 and τ. In other words, we specify an S^0 such that $S_0 \geqslant S^0 \geqslant S^0_{\mathrm{eq}}$ and determine the corresponding τ from Eq. (17a).

As may readily be verified from Eq. (16),

$$\frac{dX^0}{d\tau} = (1-\beta)\frac{dS^0}{d\tau}\frac{1}{[1+S^0+\beta(S_0-S^0)]^2}\,. \tag{18}$$

Inspection of Eq. (18) shows that (since $dS^0/d\tau \leqslant 0$) $X^0(\tau)$ increases or decreases monotonically from its quasi-steady state value $X^0(0)$ to its equilibrium value X^0_{eq} according as whether $\beta > 1$ or $\beta < 1$.

First Order: Eqs. (6) yield in the first order

$$\frac{dS^1}{d\tau} = (\xi_{-1}+S^0)X^1 - S^1(1-X^0) \tag{19a}$$

$$\begin{aligned}\frac{dX^0}{d\tau} = &-[1+S^0+\beta(S_0-S^0)]X^1 + (1-X^0)(1-\beta)S^1\\ &-\beta X^0(1-X^0)\,.\end{aligned} \tag{19b}$$

Eliminating X^1 between these equations and solving for $S^1(\tau)$, one obtains

$$\begin{aligned}S^1(\tau) = {}& G\frac{cS^0+d}{aS^0+b} + \frac{cS^0+d}{aS^0+b}\left[\frac{1-a}{c^2}\ln(cS^0+d)\right.\\ &\left.+\frac{(1-a)(b-1+c)+(1-c)c-ad}{(1-c-b)^2}\ln\frac{aS^0+b}{cS^0+d}\right]\\ &+\frac{cS^0+d}{(aS^0+b)^2}+\frac{(ad-c+c^2)(1-a)(b-1)}{ac^2(c+b-1)(aS^0+b)}\,.\end{aligned} \tag{20}$$

Here G is an integration constant and a, b, c, and d are given by

$$\begin{aligned}&a=(1-\beta);\quad b=1+\beta S_0;\\ &c=1+\xi_{-1}(\beta-1);\quad d=-\xi_{-1}\beta S_0\,.\end{aligned} \tag{20a}$$

Substituting in Eq. (19b) the above expression for $S^1(\tau)$, $X^1(\tau)$ may be obtained. We shall not reproduce here this expression.

2.4. The Matching Principle

As mentioned earlier, the initial values $S^j(0)$ and $X^j(0)$ remain to be determined. These are determined by appealing to the principle of "asymptotic matching" (Van Dyke, 1975). Stated in simple terms, this principle asserts that the "long-time limit" of the short-time solutions must coincide with the "short-time limit" of the long-time solutions. Formulated in mathematical terms, this implies for the zeroth and the first orders of perturbation

$$\lim_{\bar{\tau}\to\infty} \{\bar{S}^0(\bar{\tau}) - S^0(0)\} = 0 \tag{21a}$$

and

$$\lim_{\bar{\tau}\to\infty} \left\{\bar{S}^1(\bar{\tau}) - S^1(0) - \bar{\tau}\left(\frac{dS^0}{d\tau}\right)_{\tau=0}\right\} = 0\,. \tag{21b}$$

Eqs. (11a) and (21a) taken together imply that $S^0(0) = S_0$. Setting $\tau = 0$ in Eqs. (17), the integration constant h may be determined. Further, it follows from Eq. (16) that

$$X^0(0) = \frac{S_0}{1 + S_0}, \tag{22}$$

which is precisely the asymptotic limit of $\bar{X}^0(\bar{\tau})$ as $\bar{\tau} \to \infty$ [see Eq. (11b)]. Note that $X^0(0) \neq 0$! Using the known asymptotic form for $\bar{S}^1(\bar{\tau})$ [Eq. (13b)] in Eq. (21b), it turns out that

$$S^1(0) = -\frac{(\xi_{-1} + S_0)S_0}{(1 + S_0)^2}; \tag{23}$$

incidentally, use has been made of Eq.(15a). Putting in this value of $S^1(0)$ in Eq. (20), the integration constant G may be determined. $X^1(0)$ may be determined by proceeding along the same lines.

3. Discussion

The principal result of this paper is that it presents for the first time analytical solutions of a simple problem in enzyme kinetics, albeit by a perturbative procedure. Figures 2, 3, and 4 display the results graphically for $\beta < 1, \beta = 1$, and $\beta > 1$ respectively. Note that the concentration of the intermediate complex and the dimensionless quantity plotted in these figures are related by $x^0 + \varepsilon x^1 = e_0(X^0 + \varepsilon X^1)$. We use the HP-9815 A calculator together with the plotter HP-9872 A to facilitate the evaluation of the complicated formulae derived in this paper. One observes in both Figs. 2 and 4 a well-defined plateau-like region, which we term the quasi-steady state region. Note that these are semi-log plots. During this phase of the evolution, the concentration of the intermediate complex is apparently time independent. We may term the "width" of the plateau-like region as the "life-time" of the quasi-steady state. Prior to the attainment of the quasi-steady state, the enzyme-substrate complex evolves very rapidly and this evo-

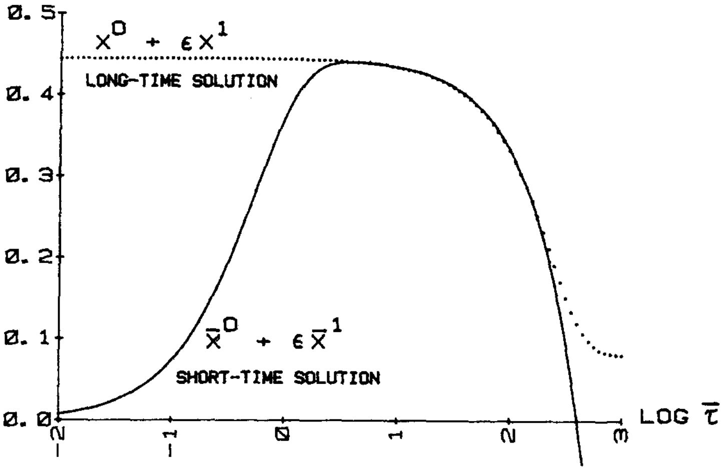

Fig. 2. Time evolution of the enzyme-substrate complex (the sum of zeroth and first order terms in dimensionless units) for $\beta < 1$ ($\beta = 0.1$). ——— Short-time solution. - - - - - - - Long-time solution. The region of overlap of both solutions is the matching region. $\bar{\tau} = (k_{-1} + k_2)t$. Parameters: $S_0 = 0.8$, $\xi_{-1} = 0.1$, $\varepsilon = 0.01$

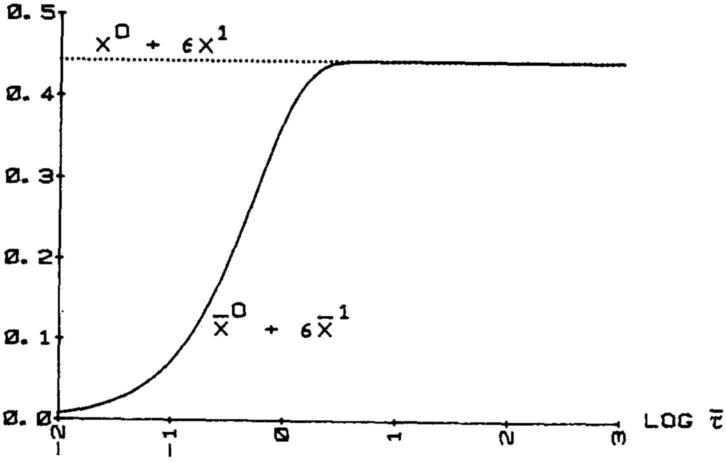

Fig. 3. Time evolution of the enzyme-substrate complex for $\beta = 1$. (S_0, ξ_{-1}, ε as in Fig. 2)

lution is described on the short-time scale. Following the attainment of the quasi-steady state, the evolution is relatively slow and tapers off to the equilibrium.

A few remarks about the matching principle at this juncture are in order. Despite its abstract character, it has a simple physical meaning: it bridges, as it were, solutions that correspond to two different time domains. It is seen that the "matching region" (the region of overlap of the short and long-time solutions) extends well beyond the plateau or the quasi-steady state region. This vindicates the matching procedure. An increase of either ε or β ($\beta > 1$), however, has been observed to diminish the extent of overlap of the

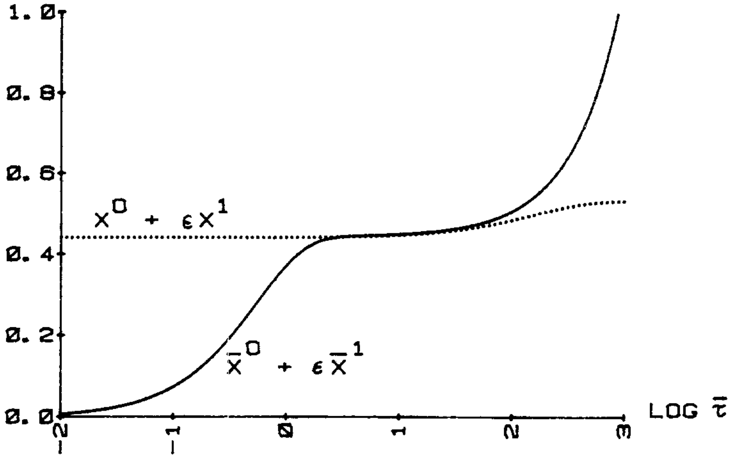

Fig. 4. Time evolution of the enzyme-substrate complex for $\beta > 1$. ($\beta = 1.5$; S_0, ζ_{-1}, ε as in Fig. 2)

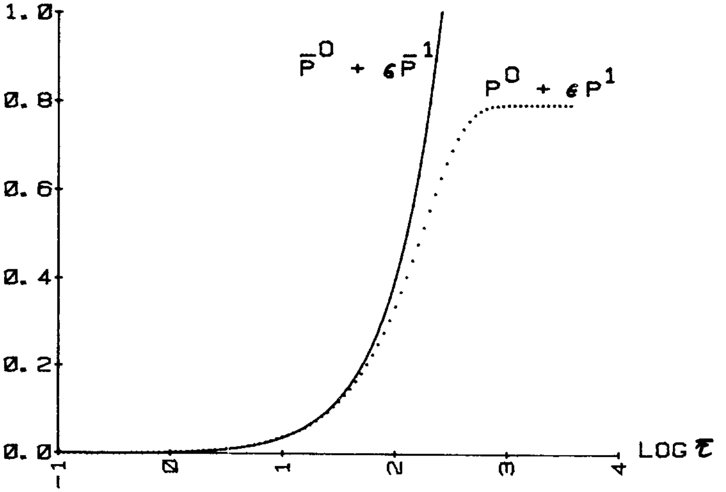

Fig. 5. Time evolution of the product (the sum of zeroth and first order terms in dimensionless units; all parameters as in Fig. 2)

two solutions. In the perturbation development, terms containing the product $\varepsilon\beta$ have been regarded as $O(\varepsilon)$. This would be clearly invalid if, for any given ε, β increases indefinitely. With increasing ε and/or β, the width of the plateau region decreases (Walter, 1974).

The case $\beta = 1$ (Fig. 3) is particularly interesting. Then, as shown by Eq. (18), $X^0(\tau)$ is independent of τ. In fact, it may be shown by induction that $X^j(\tau)$ is independent of τ for all j. This has the immediate consequence that

$$X^{\mathrm{eq}} = \lim_{\bar{\tau} \to \infty} \{\bar{X}^0(\bar{\tau}) + \varepsilon \bar{X}^1(\bar{\tau}) + \cdots\} .$$

For $\beta < 1$, the concentration of the intermediate complex exhibits an extremum, while for $\beta > 1$, it increases monotonically to its equilibrium value. Nevertheless, even in the latter case a well-defined plateau region is noticeable (Fig. 4) provided that β is not too large. $\beta = 1$ marks the transition between these two types of solutions.

From the conservation requirement Eq. (2), one obtains

$$P = p/K_M = S_0 - S - \varepsilon X . \tag{24}$$

Hence,

$$P^0 + \varepsilon P^1 = S_0 - S^0 - \varepsilon S^1 - \varepsilon X^0 \tag{24a}$$

to first order in ε. This enables us to examine the time evolution of the product. On the short-time scale, the barred quantities ($\bar{S}^0$, $\bar{S}^1$, $\bar{X}^0$) are used instead. The product concentration and the dimensionless quantity plotted in Fig. 5 are related by $p^0 + \varepsilon p^1 = K_m(P^0 + \varepsilon P^1)$. The validity of the so-called integrated versions of the Michaelis-Menten equation (Glick et al., 1979; Stayton and Fromm, 1979), may be established by comparing their predictions with the above plot.

Within the scope of our treatment, a small ε appears to ensure the existence of a well-defined quasi-steady state. For $\beta = 1$ or close to 1, the assumption of a quasi-steady state again seems to be well-founded. In biological systems, ε may not necessarily be small. The first order corrections evaluated in this paper may then become sizeable and significant. In the literature, incorrect statements appear (Stayton and Fromm, 1979; Schauer and Heinrich, 1979) with regard to what one must assume to derive the so-called integrated Michaelis-Menten equations. These stem either for want of rigour or because the canonical form of the kinetic equations are not employed. Inspection of Eq. (18) clearly shows that $dX^0/d\tau \neq 0$. *Nevertheless*, the left-hand side of Eq. (6b) can be set equal to zero [since it is of $O(\varepsilon)$] in the zeroth order approximation. Thus, there is no inconsistency between a nonzero $dX^0/d\tau$ and the neglect of $\varepsilon dX/d\tau$ in the zeroth order. For precisely the same reason [see Eqs. (24)], $dP/d\tau$ may be set equal to $-dS/d\tau$ in the zeroth order (except during the short-time evolution).

We would like to conclude with some observations regarding the advantages of our method over numerical integration procedures. In the special case of $\beta = 1$, we have compared our results with the exact analytical solution. They agree remarkably. Secondly, the dependence on the parameters is explicit in our solutions (even if somewhat clumsy), whereas, to extract this information by means of numerical methods, a good deal of computational labour is called for. Thirdly, unlike analytical solutions, numerical techniques cannot yield very limited information such as the values of the concentrations at some specific instant of time or over some specific phase of the evolution, should this be needed. The extension of the present treatment to reactions with multiple intermediate products is straightforward and reveals some very curious features. These will be reported elsewhere.

Appendix

The equilibrium concentrations are given by

$$X_{\mathrm{eq}} = \frac{S_{\mathrm{eq}}}{\xi_{-1} + S_{\mathrm{eq}}} \tag{A1}$$

with

$$S_{\mathrm{eq}} = \frac{\{\xi_{-1}(\xi_{-1} - 1 - \beta\xi_{-1}) + \xi_{-1}\beta S_0 - \varepsilon\beta\xi_{-1}\}}{2\,(1 - \xi_{-1} + \beta\xi_{-1})} + \frac{[\{\xi_{-1}(\xi_{-1} - 1 - \beta\xi_{-1}) + \xi_{-1}\beta S_0 - \varepsilon\beta\xi_{-1}\}^2 + 4\,\xi_{-1}^2\beta S_0(1 - \xi_{-1} + \beta\xi_{-1})]^{1/2}}{2\,(1 - \xi_{-1} + \beta\xi_{-1})}. \tag{A2}$$

$$S_{\mathrm{eq}}^0 = S_{\mathrm{eq}}\,(\varepsilon = 0) = \frac{\xi_{-1}\beta S_0}{(1 - \xi_{-1} + \beta\xi_{-1})}. \tag{A3}$$

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