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

M. S. Seshadri and G. Fritzsch

Max-Planck Institute for Biophysics, Kennedyallee 70, D-6000 Frankfurt 70, Federal Republic of Germany

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.

I. Introduction

Consider the enzyme catalyzed chemical reaction

\[ E + S \xrightarrow{k_1} ES \xrightarrow{k_2} E + P , \]

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:

\[ s + p + x = s_0; \quad e + x = e_0. \]

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

\[ \frac{ds}{dt} = k_{-1}x - k_1es = k_{-1}x - k_1s(e_0 - x) \]

\[ \frac{dx}{dt} = k_1es - (k_{-1} + k_2)x + k_{-2}ep \]

\[ = k_1s(e_0 - x) - (k_{-1} + k_2)x + k_{-2}(e_0 - x)(s_0 - s - x) . \]
We use the initial conditions
\[ s(0) = s_0 \quad \text{and} \quad x(0) = 0. \] (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

\[ \varepsilon = \frac{e_0}{K_m}, \quad \xi_{-1} = \frac{k_{-1}}{k_{-1} + k_2}, \quad \beta = \frac{k_{-2}}{k_1} \] (5a)

and the dimensionless variables

\[ S = \frac{s}{K_m}, \quad X = \frac{x}{e_0}, \quad \tau = k_1 e_0 t \] (5b)

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

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

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

Eq. (4) can now be rewritten as

\[ S(0) = \frac{s_0}{K_m} = s_0 \quad \text{and} \quad X(0) = 0. \] (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 \( \varepsilon \) [defined in Eq. (5a)] as a perturbation parameter suggests itself. A naive application of such a perturbation development in powers of \( \varepsilon \) leads to an apparent violation of the conservation requirements Eq. (7). It is easily verified that on setting \( \varepsilon = 0 \), Eq. (6b) yields

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