

## A simplified perturbation solution of Michaelis-Menten kinetics equations in a “total” framework

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**Abstract** A uniformly valid first order perturbation solution of the Michaelis-Menten kinetics equations in a total quasi-steady state setting is derived. This approximate solution has a simpler form than that obtained by Dell’Acqua and Bersani (J Math Chem 50:1136–1148, 2012). We also indicate an inconsistency in the perturbation equations obtained by these authors.

**Keywords** Enzyme kinetics · Asymptotic expansions · Total quasi-steady state approximation

### 1 Introduction

The classical Michaelis-Menten scheme [1] is widely used in biochemistry to describe the reaction between an enzyme  $E$  and substrate  $S$  to give an enzyme-substrate complex  $C$ , which irreversibly yields a product  $P$ :



Applying the law of mass action to kinetic scheme (1), one obtains the following system of differential equations

$$\frac{dS}{dt} = -k_1 (E_T - C) S + k_{-1} C, \quad (2)$$

$$\frac{dC}{dt} = k_1 (E_T - C) S - (k_{-1} + k_2) C, \quad (3)$$

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with conservation laws

$$E_T = E + C, \quad S_T = S + C + P, \quad (4)$$

where  $E_T$  and  $S_T$  are, respectively, the total concentration of the enzyme and the substrate in the system. Usually the following initial conditions are imposed:

$$S(t = 0) = S_T, \quad C(t = 0) = 0. \quad (5)$$

Since Eq. (2)–(3) are not integrable in the general case, approximation schemes have been developed to analyse them, for instance, the standard quasi-steady state approximation (sQSSA) [2–4] and the reverse quasi-steady state approximation (rQSSA) [3,5]. An extension of the validity of the sQSSA was proposed by Borghans, de Boer and Segel [6] by the introduction of a new variable, the total substrate concentration  $\bar{S} = S + C$ , and is known as the total quasi-steady state approximation (tQSSA). Tzafirri [7] rederived the results of Borghans et al. and showed that the tQSSA is always at least roughly valid.

A uniformly valid first order expansion in a total quasi-steady state setting, obtained with respect to the perturbation parameter  $\varepsilon = \frac{K E_T}{(E_T + K_M + S_T)^2}$ , was first found by Dell'Acqua and Bersani [8]. The purpose of the present communication is to show an inconsistency in the perturbation equations obtained by these authors. Then, we derive a simplified uniformly valid first order solution that can be expressed in an analytic and closed form.

## 2 Asymptotic expansions

We shall adopt the same notation as used in [8]. In terms of the total substrate concentration  $\bar{S} = S + C$  and  $C$ , Eqs. (2)–(3) become

$$\frac{d\bar{S}}{dt} = -k_2 C, \quad (6)$$

$$\frac{dC}{dt} = k_1 C^2 - (k_1 E_T + k_{-1} + k_2) C - k_1 \bar{S} C + k_1 E_T \bar{S}. \quad (7)$$

To obtain the inner equations, Dell'Acqua and Bersani [8] introduced the following nondimensional variables and parameters

$$\begin{aligned} \bar{s} &= \frac{\bar{S}}{S_T}, \quad c = \frac{(E_T + K_M + S_T)}{E_T S_T} C, \quad \tau = t k_1 (E_T + K_M + S_T), \\ \sigma &= \frac{S_T}{E_T + K_M + S_T}, \quad \eta = \frac{E_T}{E_T + K_M + S_T}, \quad \kappa_M = \frac{K_M}{E_T + K_M + S_T}, \\ \varepsilon &= \frac{K E_T}{(E_T + K_M + S_T)^2}, \end{aligned} \quad (8)$$

where  $K_M = \frac{k_{-1}+k_2}{k_1}$  is the Michaelis constant and  $K = \frac{k_2}{k_1}$  is the van Slyke–Cullen constant [9]. From the definitions in (8), we have the identity

$$\sigma + \eta + \kappa_M = 1. \tag{9}$$

In terms of these quantities, Eqs. (6)–(7) take the form

$$\frac{d\bar{s}}{d\tau} = -\varepsilon c, \tag{10}$$

$$\frac{dc}{d\tau} = \sigma \eta c^2 - (\eta + \kappa_M) c - \sigma \bar{s} c + \bar{s}, \tag{11}$$

with initial conditions  $\bar{s}(0) = 1$  and  $c(0) = 0$ .

Our key observation is that the product  $\sigma \eta$  in Eq. (11) can be expressed as

$$\sigma \eta = \varepsilon \frac{S_T}{K}. \tag{12}$$

Note that relation (12) is exact. Thus, we replace Eq. (11) by

$$\frac{dc}{d\tau} = \varepsilon \frac{S_T}{K} c^2 - (\eta + \kappa_M) c - \sigma \bar{s} c + \bar{s}. \tag{13}$$

Now, we expand the functions  $\bar{s}(\tau)$  and  $c(\tau)$  in the form

$$\bar{s} = \Sigma_0 + \varepsilon \Sigma_1 + \dots, \quad c = \Gamma_0 + \varepsilon \Gamma_1 + \dots. \tag{14}$$

Substituting (14) in Eqs. (10) and (13), and equating terms of like powers of  $\varepsilon$  to zero, we find, at order 0,

$$\Sigma_0 = 1, \tag{15}$$

$$\frac{d\Gamma_0}{d\tau} = 1 - \Gamma_0, \tag{16}$$

where the solution (15) satisfies the initial condition for the total substrate concentration. Note that, because of the relation (12), Eq. (16) has one term less than the corresponding differential equation for  $\Gamma_0$  derived by Dell’Acqua and Bersani [8]. Thus, the approximations they have obtained are inconsistent in the sense that their sequence of differential equations include a contribution of higher order perturbation terms. The solution of Eq. (16) with initial condition  $\Gamma_0(0) = 0$  reads

$$\Gamma_0 = 1 - e^{-\tau}. \tag{17}$$

At order 1 we have

$$\frac{d\Sigma_1}{d\tau} = -\Gamma_0, \tag{18}$$

$$\frac{d\Gamma_1}{d\tau} = \frac{S_T}{K} \Gamma_0^2 - \Gamma_1 - \sigma \Sigma_1 \Gamma_0 + \Sigma_1. \quad (19)$$

The solution of Eqs. (18)–(19) is given by

$$\Sigma_1 = 1 - \tau - e^{-\tau}, \quad (20)$$

$$\Gamma_1 = \frac{S_T}{K} + 2(1 - \sigma) + (\sigma - 1)\tau + (\sigma - 2)e^{-\tau} + \left(2\sigma - 2\frac{S_T}{K} - 1\right)\tau e^{-\tau} - \frac{\sigma}{2}\tau^2 e^{-\tau} + \left(\sigma - \frac{S_T}{K}\right)e^{-2\tau}. \quad (21)$$

The outer equations are obtained by changing the dimensionless time from  $\tau$  to  $T = \varepsilon\tau$ . Thus, Eqs. (10) and (13) transform into

$$\frac{d\bar{s}}{dT} = -c, \quad (22)$$

$$\varepsilon \frac{dc}{dT} = \varepsilon \frac{S_T}{K} c^2 - (\eta + \kappa_M)c - \sigma \bar{s}c + \bar{s}. \quad (23)$$

Now we expand the outer solutions in the form

$$\bar{s} = \bar{s}_0 + \varepsilon \bar{s}_1 + \dots, \quad c = c_0 + \varepsilon c_1 + \dots. \quad (24)$$

After substitution in Eqs. (22)–(23), we get, at order 0,

$$\frac{d\bar{s}_0}{dT} = -c_0, \quad (25)$$

$$\bar{s}_0 - \sigma \bar{s}_0 c_0 - (1 - \sigma)c_0 = 0. \quad (26)$$

The solutions of Eqs. (25)–(26) are, respectively,

$$(1 - \sigma) \ln \bar{s}_0 + \sigma (\bar{s}_0 - 1) = -T, \quad (27)$$

$$c_0 = \frac{\bar{s}_0}{1 - \sigma + \sigma \bar{s}_0}, \quad (28)$$

where the initial condition for  $\bar{s}_0$  was obtained by the matching condition  $\bar{s}_0(T = 0) = \lim_{\tau \rightarrow \infty} \Sigma_0 = 1$ . From Eq. (28), it follows that  $c(T = 0) = 1$ , which is consistent with the matching condition  $c_0(T = 0) = \lim_{\tau \rightarrow \infty} \Gamma_0 = 1$ .

At order 1 we have

$$\frac{d\bar{s}_1}{dT} = -c_1, \quad (29)$$

$$\frac{dc_0}{dT} = \frac{S_T}{K} c_0^2 - (\eta + \kappa_M)c_1 - \sigma (\bar{s}_1 c_0 + \bar{s}_0 c_1) + \bar{s}_1. \quad (30)$$

Using Eqs. (25) and (28), Eq. (30) can be expressed as

$$c_1 = \frac{(1 - \sigma) \bar{s}_0}{(1 - \sigma + \sigma \bar{s}_0)^4} + \frac{S_T \bar{s}_0^2}{K (1 - \sigma + \sigma \bar{s}_0)^3} + \frac{(1 - \sigma) \bar{s}_1}{(1 - \sigma + \sigma \bar{s}_0)^2}. \tag{31}$$

We can use this relation to express  $\bar{s}_1$  as a function of  $\bar{s}_0$ . With a change of variables, Eq. (29) can be rewritten as

$$\frac{d\bar{s}_1}{d\bar{s}_0} = \frac{c_1}{c_0}. \tag{32}$$

Using (31), this differential equation can be solved in closed form,

$$\begin{aligned} \bar{s}_1 = & \frac{\bar{s}_0}{(1 - \sigma + \sigma \bar{s}_0)^2} + \frac{\bar{s}_0}{(1 - \sigma) (1 - \sigma + \sigma \bar{s}_0)} \ln \left( \frac{\bar{s}_0}{1 - \sigma + \sigma \bar{s}_0} \right) \\ & + \frac{S_T \bar{s}_0}{K \sigma (1 - \sigma + \sigma \bar{s}_0)} \ln (1 - \sigma + \sigma \bar{s}_0), \end{aligned} \tag{33}$$

with  $\bar{s}_1(\bar{s}_0 = 1) = 1$ . To obtain this initial condition, we first note that  $\Sigma_1$  behaves asymptotically as  $\Sigma_1 \sim 1 - \tau$ , for  $\tau \rightarrow \infty$ . Thus, from the matching condition between the inner and the outer solutions, we should have  $\bar{s}_1(T = 0) = \Sigma_1(\tau = 0) = 1$ . Since  $\bar{s}_0(T = 0) = 1$ , we have the result.

The asymptotic behaviour of the function  $\Gamma_1$ , Eq. (21), is given by

$$\lim_{\tau \rightarrow \infty} \Gamma_1(\tau) \sim \frac{S_T}{K} + 2(1 - \sigma) + (\sigma - 1) \tau. \tag{34}$$

One can easily check, using Eq. (31), that  $c_1(T = 0) = S_T/K + 2(1 - \sigma)$ , thus satisfying the matching condition with the inner solution  $\Gamma_1$ .

To obtain the uniformly valid approximations, we add the corresponding inner and the outer solutions, and subtract their common part,

$$\bar{s}_0^{un.} = \Sigma_0(\tau) + \bar{s}_0(\varepsilon\tau) - 1 = \bar{s}_0(\varepsilon\tau), \tag{35}$$

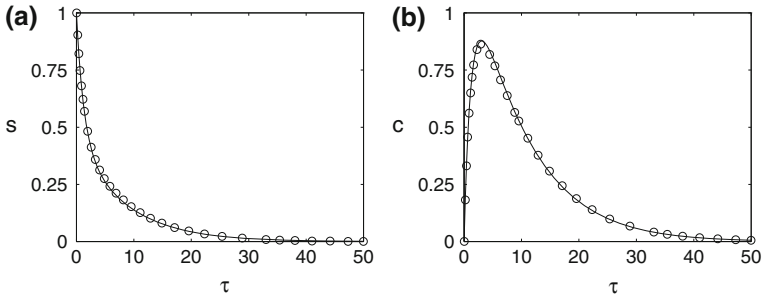
$$c_0^{un.} = \Gamma_0(\tau) + c_0(\varepsilon\tau) - 1 = c_0(\varepsilon\tau) - e^{-\tau}, \tag{36}$$

$$\bar{s}_1^{un.} = \Sigma_1(\tau) + \bar{s}_1(\varepsilon\tau) - 1 + \tau = \bar{s}_1(\varepsilon\tau) - e^{-\tau}, \tag{37}$$

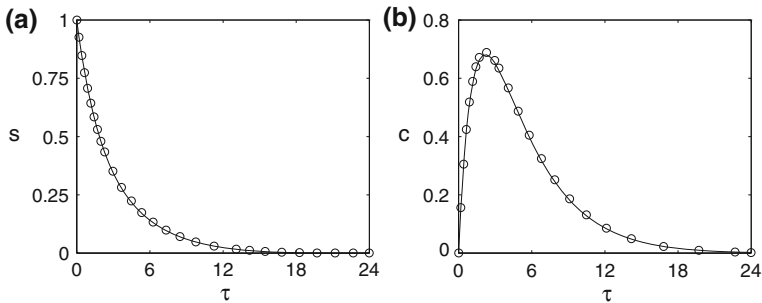
$$\begin{aligned} c_1^{un.} = & \Gamma_1(\tau) + c_1(\varepsilon\tau) - \frac{S_T}{K} - 2(1 - \sigma) - (\sigma - 1) \tau = c_1(\varepsilon\tau) + (\sigma - 2) e^{-\tau} \\ & + \left( 2\sigma - 2\frac{S_T}{K} - 1 \right) \tau e^{-\tau} - \frac{\sigma}{2} \tau^2 e^{-\tau} + \left( \sigma - \frac{S_T}{K} \right) e^{-2\tau}. \end{aligned} \tag{38}$$

The final expressions for our approximate solutions read

$$\bar{s}^{un.} = \bar{s}_0^{un.} + \varepsilon \bar{s}_1^{un.}, \quad c^{un.} = c_0^{un.} + \varepsilon c_1^{un.}. \tag{39}$$



**Fig. 1** **a** The substrate concentration  $s = S/S_T$  and **b** the dimensionless enzyme-substrate complex concentration  $c$ , as function of the time  $\tau$ . The *solid lines* were calculated with the expressions derived in [8], while the *circles* represent the approximations (39). Parameters:  $E_T = 3$ ,  $S_T = 1$ ,  $k_1 = 1$ ,  $k_{-1} = 1$  and  $k_2 = 1$



**Fig. 2** **a** The substrate concentration  $s = S/S_T$  and **b** the dimensionless enzyme-substrate complex concentration  $c$ , as function of the time  $\tau$ . The *solid lines* were calculated with the expressions derived in [8], while the *circles* represent the approximations (39). Parameters:  $E_T = 3$ ,  $S_T = 1$ ,  $k_1 = 1$ ,  $k_{-1} = 0.04$  and  $k_2 = 4$

We have compared our solutions with those obtained by Dell'Acqua and Bersani [8]. In Fig. 1a, b, we display, respectively, the dimensionless substrate concentration  $s = S/S_T$ , and the dimensionless enzyme-substrate complex concentration  $c$ , as function of the time  $\tau$ , for the parameter values  $E_T = 3$ ,  $S_T = 1$ ,  $k_1 = 1$ ,  $k_{-1} = 1$  and  $k_2 = 1$ . The solid lines represent the solutions found in [8], while the circles were calculated with the expressions (39). In Fig. 2a, b, we show the same quantities for the parameter values  $E_T = 3$ ,  $S_T = 1$ ,  $k_1 = 1$ ,  $k_{-1} = 0.04$  and  $k_2 = 4$  (both sets of parameters were used in the examples discussed in [8]). From the figures, we observe a good agreement between the two perturbation solutions; the relative error was found to be  $<5\%$ .

We believe the main advantage of the present perturbation solution over that derived in [8] is that it yields relative simple closed form expressions, and with similar accuracy.

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