J Math Chem (2012) 50:1136–1148
DOI 10.1007/s10910-011-9957-6

ORIGINAL PAPER

A perturbation solution of Michaelis–Menten kinetics in a "total" framework

Guido Dell'Acqua · Alberto Maria Bersani

Received: 26 September 2011 / Accepted: 11 December 2011 / Published online: 20 December 2011
© Springer Science+Business Media, LLC 2011

Abstract In this paper we expand the equations governing Michaelis–Menten kinetics in a total quasi-steady state setting, finding the first order uniform expansions. Our results improve previous approximations and work well especially in presence of an enzyme excess.

Keywords Michaelis–Menten kinetics · Quasi-steady state approximations · Asymptotic expansions

1 Introduction

Since the pioneering papers by Bodenstein and Underhill [1] and Chapman [2] in 1913 the quasi-steady state approximation (QSSA) has represented a very important tool in the mathematical modeling of biochemical reactions. It brings to a simplification of the model and allows the qualitative analysis of the reaction, in terms of time scales separation, asymptotic behavior etc., which any numerical analysis could not, in general, capture.

In enzyme kinetics, the standard QSSA (sQSSA), or Michaelis–Menten–Briggs–Haldane approximation [3,4] was introduced in order to describe the phase after the

G. Dell'Acqua (✉) · A. M. Bersani
Dipartimento di Scienze di Base e Applicate per l'Ingegneria (S.B.A.I.),
"Sapienza" University, Via A. Scarpa 16, 00161 Rome, Italy
e-mail: guido.dellacqua@sbai.uniroma1.it

A. M. Bersani
International Research Center for Mathematics and Mechanics of Complex System (M&MoCS), Cisterna di Latina, Italy
e-mail: alberto.bersani@sbai.uniroma1.it

short transient, where the catalytic enzyme and the substrate rapidly form complexes at high concentrations.

From the Sixties of the last century, mathematicians have interpreted the QSSA in terms of leading order in asymptotic expansions with respect to an appropriate parameter ε, which must be supposed sufficiently small. Heineken et al. [5] use $\varepsilon = \frac{E_T}{S_T}$, where E_T and S_T are respectively the total catalyst concentrations and the substrate concentrations; Segel and Slemrod [6] use $\varepsilon = \frac{E_T}{S_T+K_M}$, where K_M is the *Michaelis constant* or *affinity constant*, showing that the sQSSA is valid in a more extended parameter range than the one supposed by biochemists.

The technique of singular perturbations allows us to mathematically reproduce the boundary layer in the temporal evolution of the complex concentrations and the separation between the two characteristic time scales, related to the rapid complex formation and to the substrate depletion.

Laidler in 1955 [7], Swoboda in 1957 [8,9], Schauer and Heinrich in 1979 [10] and Borghans, deBoer and Segel in 1996 [11] have approached enzyme kinetics from a different point of view, which is now known as total QSSA (tQSSA) and is valid in a wider range of parameters (see also [12]). The tQSSA has been applied to several enzyme reactions [13–18] even in a stochastic framework [19].

In the papers [8–12,17] the tQSSA has been approached requiring some conditions which simplify equations, without any formal tool in terms of asymptotic expansions. In 2002 Schnell and Maini [20] studied the tQSSA by means of aggregation or lumping techniques, which reduce the number of differential equations describing the system [21]. They nondimensionalized the system of differential equations governing the reaction and introduced the perturbation parameter $\varepsilon = \frac{KE_T}{(K_M+E_T+S_T)^2}$, where K is the van Slyke–Cullen constant [22]. They consider a more general form of the total substrate $\bar{s}$ introduced by Swoboda. However, the leading order term of their expansion unexpectedly reproduces the sQSSA, instead of the tQSSA. In 2008 Dingee and Anton [23] developed a two-parameter singular perturbation analysis which curiously, at the leading order, does not reproduce the approximated solutions given by Laidler, Schauer and Heinrich and Borghans, deBoer and Segel, but the zero-order approximation of the tQSSA, obtained by Tzafriri [12] with respect to the parameter

$$\varepsilon = \frac{K}{2S_T}\left(\frac{E_T + K_M + S_T}{\sqrt{(E_T + K_M + S_T)^2 - 4E_T\, S_T}} - 1\right)$$

which is valid in a more restricted range of parameters.

In this paper we find, as far as we know for the first time, the tQSSA as the leading order of an asymptotic expansion, obtained with respect to the parameter $\varepsilon = \frac{KE_T}{(K_M+E_T+S_T)^2}$, we find the first order corrections of the inner and the outer solutions (reproducing, respectively, the transient and the QSSA phase) and finally the uniform approximations.

We compare our results with those ones given by [11,23] and with similar ones obtained in the case $E_T \gg S_T$ [24] in a *standard* framework. Due to the first order corrections to their formulas, the parameter range of validity of our results improves that one obtained by Borghans, deBoer and Segel. We also compute the errors of the

different approximations here considered with respect to the numerical solutions of the full system of equations. The results show that the expansion obtained in this paper is in a very good agreement with the numerical solutions for a wide range of parameters.

2 Model equations and nondimensionalization

Let us consider the classical Michelis–Menten kinetics

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} E + P, \tag{1}$$

where E, S, C, P represent respectively the catalytic enzyme, its substrate, the enzyme–substrate complex and the final product (i.e., the activated substrate). Using the law of mass action this scheme can be translated into the following system of (dimensional) differential equations:

$$\begin{aligned} \frac{dS}{dt} &= -k_1(E_T - C)S + k_{-1}\,C \\ \frac{dC}{dt} &= k_1(E_T - C)S - (k_{-1} + k_2)C\ , \end{aligned} \tag{2}$$

with initial conditions

$$S(0) = S_T, \quad C(0) = 0, \tag{3}$$

and conservation laws

$$E + C = E_T, \quad S + C + P = S_T. \tag{4}$$

Introducing the total substrate $\overline{S} = S + C$, we obtain

$$\begin{aligned} \frac{d\overline{S}}{dt} &= -k_2\,C, \\ \frac{dC}{dt} &= k_1\left[C^2 - (E_T + \overline{S} + K_M)\,C + E_T\,\overline{S}\right] \end{aligned} \tag{5}$$

with initial conditions

$$\overline{S}(0) = S_T, \quad C(0) = 0, \tag{6}$$

and conservation laws

$$E + C = E_T, \quad \overline{S} + P = S_T. \tag{7}$$

If we adopt the change of variables

$$\overline{S} = \alpha\,\overline{s}\,, \quad C = \beta\,c\,, \quad t = \gamma\,\tau$$

we find that Eq(s). (5) become

$$\begin{aligned} \frac{\alpha}{\gamma}\frac{d\overline{s}}{d\tau} &= -k_2\beta\,c \\ \frac{\beta}{\gamma}\frac{dc}{d\tau} &= k_1\left[\beta^2\,c^2 - (E_T + K_M + \alpha\,\overline{s})\beta\,c + E_T\,\alpha\overline{s}\right] \end{aligned} \tag{8}$$

We should first scale the inner variables, since they are supplemented by the initial conditions (6) that give us, when they are nonzero, information about the magnitude of the variables involved. Thus it follows immediately that $\alpha = S_T$. Therefore the second equation of (8) becomes

$$\frac{\beta}{\gamma}\frac{dc}{d\tau} = k_1\left[\beta^2\,c^2 - (E_T + K_M + S_T\,\overline{s})\beta\,c + E_T\,S_T\overline{s}\right] \tag{9}$$

Now we attempt to ensure that all the terms on the right hand side of (9) are of the same magnitude, supposing that both c and $\overline{s}$ are $O(1)$. Proceeding as in [6] and [11], neglecting the term in c^2 and then setting for scaling purposes $\overline{s} = 1$ and $c = 1$, we find

$$(E_T + K_M + S_T)\,\beta = E_T\,S_T\,, \quad \text{i.e.,} \quad \beta = \frac{E_T\,S_T}{E_T + K_M + S_T} \tag{10}$$

while γ is determined by requiring that the left hand side of (9) is of the same magnitude as the right hand side, i.e.,

$$\gamma = \frac{\beta}{k_1 E_T S_T} = \frac{1}{k_1(E_T + K_M + S_T)} \tag{11}$$

The parameter γ corresponds to the time scale t_c of the complex formation [11,23].

3 Asymptotic expansions

Substituting in (8) the values obtained for α, β and γ, we have the inner equations:

$$\begin{aligned} \frac{d\overline{s}}{d\tau} &= -\varepsilon\,c \\ \frac{dc}{d\tau} &= \sigma\,\eta c^2 - (\eta + \kappa_M)\,c - \sigma\,\overline{s}\,c + \overline{s} \end{aligned} \tag{12}$$

with initial conditions $\overline{s}(0) = 1$ and $c(0) = 0$, where

$$\sigma = \frac{S_T}{K_M + E_T + S_T}\,, \quad \eta = \frac{E_T}{K_M + E_T + S_T}\,, \quad \kappa_M = \frac{K_M}{K_M + E_T + S_T}$$

and

$$\varepsilon = \frac{KE_T}{(K_M + E_T + S_T)^2} \tag{13}$$

where $K = \frac{k_2}{k_1}$ is the Van Slyke–Cullen constant.

The parameter ε, appearing in the right hand side of the first equation (12), arises as the natural perturbation parameter of our asymptotic expansion.

Let us remark that, with our scaling argumentation, we obtain the same perturbation parameter as in [20,23]. Moreover, for any set of kinetic parameters and initial conditions, $\varepsilon \leq \frac{1}{4}$ [23].

Observe that

$$\sigma + \kappa_M + \eta = 1 \tag{14}$$

Let us expand the solutions of (12) in the form

$$\overline{s} = \Sigma_0 + \varepsilon\, \Sigma_1 + o(\varepsilon)\,, \quad c = \Gamma_0 + \varepsilon\, \Gamma_1 + o(\varepsilon).$$

Substituting in (12) and taking into account the initial conditions, we find at order 0 that $\Sigma_0 = const = 1$ and

$$\frac{d\Gamma_0}{d\tau} = \sigma\, \eta\, \Gamma_0^2 - \Gamma_0 + 1 \tag{15}$$

whose solution, complying with (6), is easily found as

$$\Gamma_0(\tau) = \frac{\exp(\sqrt{1 - 4\sigma\, \eta}\, \tau) - 1}{\sigma\, \eta\, [\Gamma_0^+\, \exp(\sqrt{1 - 4\sigma\, \eta}\, \tau) - \Gamma_0^-]} \tag{16}$$

where $\Gamma_0^{\pm} = \dfrac{1 \pm \sqrt{1 - 4\,\sigma\, \eta}}{2\,\sigma\, \eta}$.

Let us observe that in the classical treatment of the transient phase, in order to simplify equations, one of the most commonly accepted assumptions is that, mostly when $S_T \gg E_T$, S can be considered constant, i. e., $\frac{dS}{dt} = 0$. Actually, taking into account the initial conditions, we have $\frac{dS}{dt}(0) = -k_1 E_T S_T$, which is clearly in contrast with the previous assumption, especially when $E_T\, S_T$ is high. On the contrary, using the total substrate, from (5) we have $\frac{d\overline{S}}{dt}(0) = 0$, which is much more realistic, since it mathematically reproduces the fact that, in the transient phase, the sum of S and C can be considered constant, because the product P has not been substantially created yet. The leading order approximation $\Sigma_0 = const. = 1$ is thus consistent with this assumption.

Note that

$$\frac{1}{\Gamma_0^{\pm}} = \sigma \eta \Gamma_0^{\mp}$$

and

$$\Gamma_0^+ \cdot \Gamma_0^- = \frac{1}{\sigma\eta}.$$

Moreover,

$$\lim_{\tau\to\infty} \Gamma_0(\tau) = \frac{1}{\sigma\eta\Gamma_0^+} = \Gamma_0^-.$$

At order 1 we have

$$\frac{d\Sigma_1}{d\tau} = -\Gamma_0 \tag{17}$$

$$\frac{d\Gamma_1}{d\tau} = \Gamma_1\,(2\sigma\,\eta\,\Gamma_0 - 1) - \sigma\,\Sigma_1\,\Gamma_0 + \Sigma_1 \tag{18}$$

with homogeneous initial conditions, which give

$$\Sigma_1 = \frac{1}{\sigma\,\eta}\log\left(\frac{\Gamma_0^+\,\exp(\sqrt{1-4\sigma\,\eta}\,\tau) - \Gamma_0^-}{\Gamma_0^+ - \Gamma_0^-}\right) - \Gamma_0^+\,\tau \tag{19}$$

and the corresponding Γ_1. Details for this latter function are given in the Appendix (A).

Now we turn our attention to the outer solutions of (8). We only need to change the timescale γ; to this aim let us focus on the first equation of (8). In the slow, quasi-steady state phase the total variable $\overline{s}$ cannot anymore be considered roughly constant: it decreases monotonically from S_T to zero. Hence, to balance the left hand side with the right one we set

$$\gamma = \frac{\alpha}{k_2\,\beta} = \frac{E_T + K_M + S_T}{v_{max}} \tag{20}$$

where $v_{max} = k_2\,E_T$ is the maximal reaction velocity. In this case, γ represents the time scale $t_{\overline{s}}$, related to the total substrate depletion [11,23]. Note that, having denoted by t_c the time scale in the fast, pre-steady phase and by $t_{\overline{s}}$ the time scale in the slow, quasi-steady phase, we get

$$\frac{t_c}{t_{\overline{s}}} = \varepsilon. \tag{21}$$

Thus ε represents a measure of the separation between the two time scales.

Setting $T = \gamma\,t$ and substituting (20) in (8) we obtain

$$\begin{aligned} \frac{d\overline{s}}{dT} &= -c \\ \varepsilon\frac{dc}{dT} &= \sigma\,\eta c^2 - (\eta + \kappa_M)\,c - \sigma\,\overline{s}\,c + \overline{s} \end{aligned} \tag{22}$$

Since ε multiplies the highest derivative, we expect a boundary layer effect in the time evolution of c.

Let us expand the solutions of (22) in the form

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

Upon substitution in (22) we find, at leading order,

$$\begin{aligned} &\frac{d\bar{s}_0}{dT} = -c_0 \\ &\sigma\, \eta c_0^2 - (\eta + \kappa_M + \sigma\, \bar{s}_0)\, c_0 + \bar{s}_0 = 0 \end{aligned} \tag{23}$$

which correspond to the equations obtained in the tQSSA [10,11].

The second equation above is algebraic in c_0 with solutions

$$c_0^{\pm} = \frac{\eta + \kappa_M + \sigma\, \bar{s}_0 \pm \sqrt{(\eta + \kappa_M + \sigma\, \bar{s}_0)^2 - 4\sigma\, \eta \bar{s}_0}}{2\,\sigma\,\eta} \tag{24}$$

and it is easy to see that only c_0^- is admissible.

Because of (24), the first equation in (23) becomes

$$\frac{d\bar{s}_0}{dT} = -c_0^-. \tag{25}$$

with the initial condition given by the matching condition $\bar{s}_0(0) = \lim_{\tau\to\infty} \Sigma_0(\tau) = 1$ for the leading order terms in the inner and outer expansions of $\bar{s}$; thus we have automatically that $c_0(0) = c_0^-(0) = \Gamma_0^-$.

From (22) it is found that the first correction terms in the outer solutions are given by

$$\frac{d\bar{s}_1}{dT} = -c_1 \tag{26}$$

$$c_1 = \frac{c_0' + \bar{s}_1\,(\sigma\, c_0 - 1)}{2\,\eta\,\sigma\, c_0 - \sigma\, \bar{s}_0 - \eta - \kappa_M}. \tag{27}$$

Note that, since for $\tau \to \infty$ we get

$$\Sigma_1(\tau) \sim \frac{1}{\sigma\,\eta} \log \frac{\Gamma_0^+}{\Gamma_0^+ - \Gamma_0^-} - \Gamma_0^-\, \tau\,, \tag{28}$$

then the matching condition for the first order corrections of $\bar{s}$ gives the appropriate initial condition to solve numerically the first equation in (26), i.e.,

$$\bar{s}_1(0) = \frac{1}{\sigma\,\eta} \log \frac{\Gamma_0^+}{\Gamma_0^+ - \Gamma_0^-}. \tag{29}$$

It only remains to find the matching condition for the first order correction of the complex concentration c. To this aim, we observe that Γ_1, given by (42), behaves asymptotically as a straight line of the form $y = m\tau + q$, whose slope is

$$m = \frac{\Gamma_0^- \left(\sigma \Gamma_0^- - 1\right)}{\sqrt{1 - 4\sigma\eta}} \tag{30}$$

and whose y-intercept must be equal to the y-intercept of the outer solution c_1, that is $q = c_1(0)$, where the latter quantity is found using (42) or, equivalently, (27) and (24), as

$$q = \frac{1}{\eta\sqrt{1 - 4\sigma\eta}} \left[\frac{\Gamma_0^-}{2} \left(1 - \frac{1 - 2\eta}{\sqrt{1 - 4\sigma\eta}} \right) + \frac{1 - \sigma\Gamma_0^-}{\sigma} \log\left(\frac{\Gamma_0^+}{\Gamma_0^+ - \Gamma_0^-} \right) \right] \tag{31}$$

In conclusion, we can write the (nondimensional) uniform expansions as

$$c^{un}(\tau) = c_0^{un}(\varepsilon\tau) + \varepsilon c_1^{un}(\tau) \quad ; \quad \bar{s}^{un}(\tau) = \bar{s}_0^{un}(\varepsilon\tau) + \varepsilon \bar{s}_1^{un}(\tau) \tag{32}$$

where, following [25], we obtain the uniform approximations adding the inner and outer solutions and subtracting their common part, i.e.,

$$\begin{aligned}
c_0^{un}(\tau) &= c_0(\varepsilon\tau) + \Gamma_0(\tau) - \Gamma_0^- \\
\bar{s}_0^{un}(\tau) &= \bar{s}_0(\varepsilon\tau) + \Sigma_0(\tau) - 1 = \Sigma_0(\tau) \\
c_1^{un}(\tau) &= c_1(\varepsilon\tau) + \Gamma_1(\tau) - m\tau - q \\
\bar{s}_1^{un}(\tau) &= \bar{s}_1(\varepsilon\tau) + \Sigma_1(\tau) - \tfrac{1}{\sigma\eta} \log \tfrac{\Gamma_0^+}{\Gamma_0^+ - \Gamma_0^-} + \Gamma_0^- \tau
\end{aligned} \tag{33}$$

where m and q are given by (30) and (31).

4 Figures and discussion

We have solved numerically (2) and we have compared the results with our uniform approximations. This is shown in Figs. 1, 2, where we have changed only two kinetic parameters, in order to have different values of ε. In both cases our uniform expansion shows an excellent agreement with the numerical solution of the full system (2).

In Fig. 2 we observe a less accurate approximation, since in this case the value of $\varepsilon = 0.1856$ is close to the bound $\frac{1}{4}$.

Observe that we have chosen values for S_T and E_T such that the sQSSA approximates the dynamics with very low accuracy. In fact this latter approximation, in general, works well when there is a substrate excess, or when $K_M \gg E_T$ [5,6]. When there is an enzyme excess, as in our case, the perturbation techniques rely on the

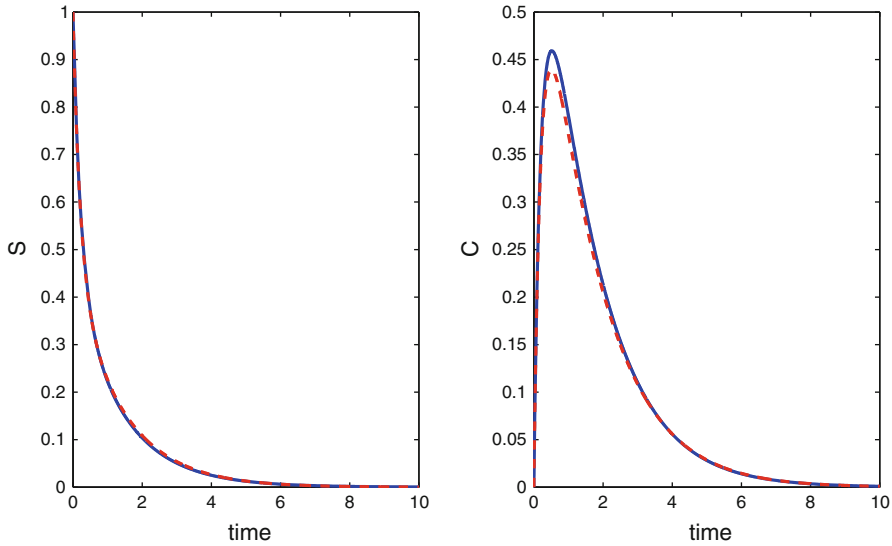

Fig. 1 Dynamics of S (*left panel*) and of C (*right panel*): full system (*solid*), uniform approximation (*dashed*). Kinetic parameters: $E_T = 3$, $S_T = 1$, $k_1 = 1$, $k_{-1} = 1$, $k_2 = 1$

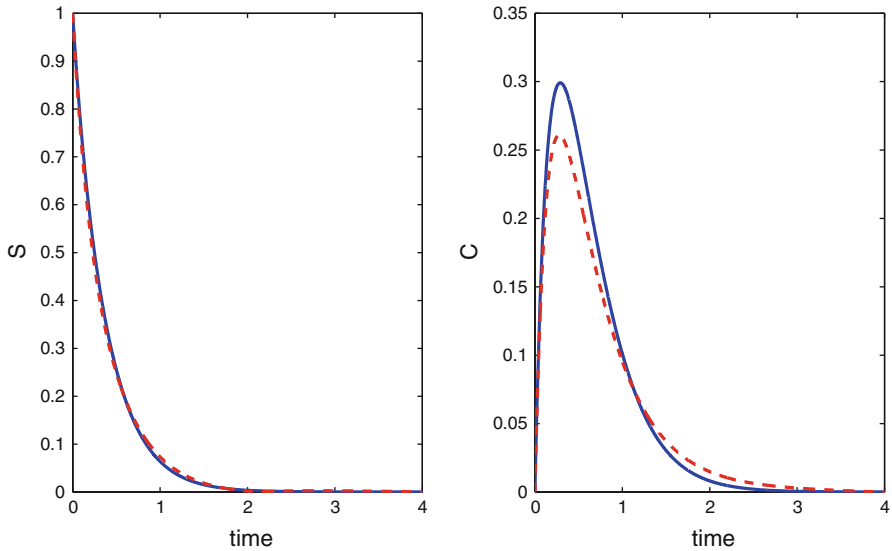

Fig. 2 Dynamics of S (*left panel*) and of C (*right panel*): full system (*solid*), uniform approximation (*dashed*). Kinetic parameters: $E_T = 3$, $S_T = 1$, $k_1 = 1$, $k_{-1} = 0.04$, $k_2 = 4$

same parameter ε given in (13), but in a QSSA setting [24,26]. To highlight the accuracy of our expansions, we have compared our approximations with the ones given in [11,20,23,24] computing the mean absolute percentage error (MAPE) for each approximation and each set of kinetic parameters (see Tables 1, 2). It turns out that the

Table 1 Perturbation parameters ε and MAPEs for the substrate S in the approximations (33) and in the ones given in [11,20,23,24], respectively

Figures	ε	err_{un}	err_{BD}	err_{BdBS}	err_{DA}	err_{SM}
1	0.0833	0.0396	0.6064	0.4330	0.0578	1.6150
2	0.1856	0.2676	0.3103	1.2842	0.2815	0.0202

Table 2 Perturbation parameters ε and MAPEs for the complex C in the approximations (33) and in the ones given in [11,20,23,24], respectively

Figures	ε	err_{un}	err_{BD}	err_{BdBS}	err_{DA}	err_{SM}
1	0.0833	0.0287	0.5112	0.1199	0.0407	1.8380
2	0.1856	0.1324	1.3117	0.2836	0.1311	0.2370

MAPEs of our approximations have the same order of magnitude of the perturbation parameter, as in the approximation given in [23]. Anyway, this latter result rely on a double-parameters perturbation technique and is much more involved than ours. On the other hand, as expected, the results given in [11] give bigger MAPEs (they are our leading order terms), as for the results given in [24]. These latter ones were found, anyway, in a *standard* setting. Surprisingly, the results given in [20] are consistently worse than ours, in all cases but one. Maybe this is due to the fact that in [20] the inner expansion is carried out in detail, while the outer is almost missing.

Acknowledgments Alberto Bersani gratefully acknowledges the financial support of the "Fondazione Tullio Levi-Civita di Cisterna di Latina".

Appendix A: Solution of Eq. (18)

Let us set $R = \sqrt{1 - 4\eta\sigma}$.

The equation for the term Γ_1 is

$$\frac{d\Gamma_1}{d\tau} = (2\sigma\eta\Gamma_0 - 1)\Gamma_1 + (1 - \sigma\Gamma_0)\Sigma_1 \tag{34}$$

i.e.

$$\frac{d\Gamma_1}{d\tau} + \left\{1 + 2\left[\frac{1 - e^{R\tau}}{\Gamma_0^+ e^{R\tau} - \Gamma_0^-}\right]\right\}\Gamma_1 = \left\{\frac{1}{\sigma\eta}\log\left[\frac{\Gamma_0^+ e^{R\tau} - \Gamma_0^-}{\Gamma_0^+ - \Gamma_0^-}\right] - \Gamma_0^+\tau\right\}\left\{1 + \left[\frac{1 - e^{R\tau}}{\eta\left(\Gamma_0^+ e^{R\tau} - \Gamma_0^-\right)}\right]\right\} \tag{35}$$

whose formal solution is

$$\Gamma_1(\tau) = e^{-A(\tau)} \cdot \int_0^\tau \left\{ \frac{1}{\sigma\eta} \log\left[\frac{\Gamma_0^+ e^{Rw} - \Gamma_0^-}{\Gamma_0^+ - \Gamma_0^-} \right] - \Gamma_0^+ w \right\} \left\{ 1 + \left[\frac{1 - e^{Rw}}{\eta\left(\Gamma_0^+ e^{Rw} - \Gamma_0^-\right)} \right] \right\} e^{A(w)} dw \tag{36}$$

where

$$e^{A(\tau)} = exp\left(\int_0^\tau \left\{ 1 + 2\left[\frac{1 - e^{Rw}}{\Gamma_0^+ e^{Rw} - \Gamma_0^-} \right] \right\} dw \right) = \left[\frac{\Gamma_0^+ e^{R\tau} - \Gamma_0^-}{\Gamma_0^+ - \Gamma_0^-} \right]^2 \cdot e^{-R\tau}. \tag{37}$$

Solving the integrals and setting

$$M(\tau) = \frac{e^{R\tau}}{R \cdot \left(\Gamma_0^+ e^{R\tau} - \Gamma_0^-\right)^2}; \quad N(\tau) = -\frac{\Gamma_0^+}{R\eta} M(\tau); \quad Q(\tau) = \frac{1}{\sigma\eta^2} M(\tau) \tag{38}$$

we have

$$\begin{aligned}
\Gamma_1(\tau) = N(\tau) \cdot \Bigg\{ & \left[e^{R\tau}(R\tau - 1) + 1 \right] (\eta\Gamma_0^+ - 1)\Gamma_0^+ + \frac{R^2\tau^2}{2} \left(\Gamma_0^+ + \Gamma_0^- - 2\Gamma_0^+\Gamma_0^-\eta \right) \\
& + \Gamma_0^-(\eta\Gamma_0^- - 1) \cdot \left[-e^{-R\tau}(R\tau + 1) + 1 \right] \Bigg\} \\
& + Q(\tau) \Bigg\{ \Gamma_0^+(\eta\Gamma_0^+ - 1) \left[e^{R\tau} \log\left(\frac{\Gamma_0^+ e^{R\tau} - \Gamma_0^-}{\Gamma_0^+ - \Gamma_0^-} \right) - e^{R\tau} + 1 \right] \\
& + (\Gamma_0^- - \Gamma_0^+) \log\left(\frac{\Gamma_0^+ e^{R\tau} - \Gamma_0^-}{\Gamma_0^+ - \Gamma_0^-} \right) + \Gamma_0^-(\eta\Gamma_0^- - 1) \\
& \left[-e^{-R\tau} \log\left(\frac{\Gamma_0^+ e^{R\tau} - \Gamma_0^-}{\Gamma_0^+ - \Gamma_0^-} \right) - \frac{\Gamma_0^+}{\Gamma_0^-} R\tau \right] \\
& + (\Gamma_0^+ + \Gamma_0^- - 2\eta\Gamma_0^+\Gamma_0^-) \int_1^{e^{R\tau}} \frac{1}{z} \log\left(\frac{\Gamma_0^+ z - \Gamma_0^-}{\Gamma_0^+ - \Gamma_0^-} \right) dz \Bigg\}.
\end{aligned} \tag{39}$$

Though formula (39) does not have a closed form, it can be useful for the study of the asymptotic behavior of Σ_1.

Since, for $\tau \to +\infty$,

$$\int_1^{e^{R\tau}} \frac{1}{z} \log\left(\frac{\Gamma_0^+ z - \Gamma_0^-}{\Gamma_0^+ - \Gamma_0^-}\right) dz \sim \frac{R^2\tau^2}{2} + R\tau \log\left(\frac{\Gamma_0^+}{\Gamma_0^+ - \Gamma_0^-}\right) \tag{40}$$

and

$$N(\tau) \sim \frac{\sigma\Gamma_0^-}{R^2} e^{-R\tau}; \qquad Q(\tau) \sim \frac{\sigma(\Gamma_0^-)^2}{R} e^{-R\tau}, \tag{41}$$

the leading order terms in (39) are given by

$$\begin{aligned}
&\Gamma_1(\tau) \sim_{\tau\to+\infty} (\eta\Gamma_0^+ - 1)\Gamma_0^+ \\
&\quad \left\{\frac{\sigma\Gamma_0^-}{R^2} e^{-R\tau} e^{R\tau}(R\tau - 1) + \frac{\sigma(\Gamma_0^-)^2}{R} e^{-R\tau} e^{R\tau}\left[\log\left(\frac{\Gamma_0^+ e^{R\tau}}{\Gamma_0^+ - \Gamma_0^-}\right) - 1\right]\right\} \\
&\sim \frac{\Gamma_0^-(\sigma\Gamma_0^- - 1)}{R^2}\left[R\tau - 1 - R\Gamma_0^+ \log\left(\frac{\Gamma_0^+}{\Gamma_0^+ - \Gamma_0^-}\right)\right] \\
&\quad = \frac{\Gamma_0^-(\sigma\Gamma_0^- - 1)}{R}\tau + \frac{1}{\eta R}\left[\frac{\Gamma_0^-}{2}\left(1 - \frac{1-2\eta}{R}\right) + \frac{1-\sigma\Gamma_0^-}{\sigma}\log\left(\frac{\Gamma_0^+}{\Gamma_0^+ - \Gamma_0^-}\right)\right].
\end{aligned} \tag{42}$$

This means that Γ_1 behaves asymptotically as a straight line, for $\tau \to +\infty$.

References

1. M.Z. Bodenstein, Eine theorie der photochemischen reaktionsgeschwindigkeiten. Z. Phys. Chem. **85**, 329–397 (1913)
2. D.L. Chapman, L.K. Underhill, The interaction of chlorine and hydrogen. The influence of mass. J. Chem. Soc. Trans. **103**, 496–508 (1913)
3. L. Michaelis, M.L. Menten, Die kinetik der invertinwirkung. Biochem. Z. **49**, 333–339 (1913)
4. G. Briggs, J. Haldane, A note on the kinetics of enzyme action. Biochem. J. **19**, 338–339 (1925)
5. F.G. Heineken, H.M. Tsushiya, R. Aris, On the mathematical status of the pseudo-steady state hypothesis of biochemical kinetics. Math. Biosci. **1**, 95–113 (1967)
6. L.A. Segel, M. Slemrod, The quasi steady-state assumption: a case study in perturbation. SIAM Rev. **31**, 446–477 (1989)
7. K.J. Laidler, Theory of the transient phase in kinetics, with special reference to enzyme systems. Can. J. Chem. **33**, 1614–1624 (1955)
8. P.A.T. Swoboda, The kinetics of enzyme action. Biochim. Biophys. Acta **23**, 70–80 (1957)
9. P.A.T. Swoboda, The kinetics of enzyme action, ii. the terminal phase of the reaction. Biochim. Biophys. Acta **25**, 132–135 (1957)
10. M. Schauer, R. Heinrich, Analysis of the quasi-steady-state approximation for an enzymatic one-substrate reaction. J. Theor. Biol. **79**, 425–442 (1979)
11. J. Borghans, R. de Boer, L. Segel, Extending the quasi-steady state approximation by changing variables. Bull. Math. Biol. **58**, 43–63 (1996)
12. A. Tzafriri, Michaelis–Menten kinetics at high enzyme concentrations. Bull. Math. Biol. **65**, 1111–1129 (2003)

13. M.G. Pedersen, A.M. Bersani, E. Bersani, The total quasi steady-state approximation for fully competitive enzyme reactions. Bull. Math. Biol. **69**, 433–457 (2005)
14. M.G. Pedersen, A.M. Bersani, E. Bersani, Steady-state approximations in intracellular signal transduction—a word of caution. J. Math. Chem. **43**, 1318–1344 (2008)
15. M.G. Pedersen, A.M. Bersani, E. Bersani, G. Cortese, The total quasi-steady state approximation for complex enzyme reactions. MATCOM **79**, 1010–1019 (2008)
16. M.G. Pedersen, A.M. Bersani, The total quasi-steady state approximation simplifies theoretical analysis at non-negligible enzyme concentrations: pseudo first-order kinetics and the loss of zero-order ultrasensitivity. J. Math. Biol. **60**, 267–283 (2010)
17. A.R. Tzafriri, E.R. Edelman, The total quasi-steady-state approximation is valid for reversible enzyme kinetics. J. Theor. Biol. **226**, 303–313 (2004)
18. A. Ciliberto, F. Capuani, J.J. Tyson, Modeling networks of coupled anzymatic reactions using the total quasi-steady state approximation. PLoS Comput. Biol. **3**, 463–472 (2007)
19. S. MacNamara, A.M. Bersani, K. Burrage, R.B. Sidje, Stochastic chemical kinetics and the total quasi-steady-state assumption: application to the stochastic simulation algorithm and chemical master equation. J. Chem. Phys. **129**, 1–13 (2008)
20. S. Schnell, P.K. Maini, Enzyme kinetics far from the standard quasi-steady-state and equilibrium approximations. Math. Comput. Model. **35**, 137–144 (2002)
21. J. Wei, J.C.W. Kuo, A lumping analysis in monomolecular reaction systems: analysis of the exactly lumped system. Ind. Eng. Chem. Fundam. **8**, 114–123 (1969)
22. D.D. Van Slyke, G.E. Cullen, The mode of action of urease and of enzymes in general. J. Biol. Chem. **19**, 141–180 (1914)
23. J.W. Dingee, A.B. Anton, A new perturbation solution to the Michaelis-Menten problem. AIChE J. **54**, 1344–1357 (2008)
24. A.M. Bersani, G. Dell'Acqua, Asymptotic expansions in enzyme reactions with high enzyme concentration. Math. Method. Appl. Sci. **34**(16), 1954–1960 (2011)
25. C.C. Lin, L.A. Segel, *Mathematics applied to deterministic problems in the natural sciences* (Society for Industrial and Applied Mathematics (SIAM), Philadelphia, 1988)
26. S. Schnell, P.K. Maini, Enzyme kinetics at high enzyme concentration. Bull. Math. Biol. **62**, 483–499 (2000)