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BRIEF COMMUNICATION

On the appropriate use of asymptotic expansions in enzyme kinetics

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Abstract In this short note we address the paper (Vogt in J Math Chem 51:2257–2263, 2013) where Vogt claimed to have found errors and inconsistencies in Dell'Acqua and Bersani (J Math Chem 50:1136–1148, 2012). After a critical review, we show also numerical evidence of the inconsistency of the main point of Vogt (J Math Chem 51:2257–2263, 2013).

Keywords Asymptotic expansions · Systems biology · Enzyme kinetics

Mathematics Subject Classification 34E05 · 92C42 · 92C45

1 Introduction

Enzyme kinetics deals with the dynamics of enzymes and substrates in a variety of scenarios, whose common features are the different time scales involved in the two-step mechanism of the substrate catalysis. This is why this subject is often used in textbooks (see, for example, [6]) as a nice application of singular perturbation theory, whereas it allows to catch the relevant time scales and to perform a detailed study of each step.

In [4] the authors studied the well known standard Quasi-Steady State Approximation (sQSSA), or Michaelis–Menten–Briggs–Haldane approximation [3,7], in a

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“total” framework, that is to say, “total” variables (as introduced in [2]) were used to nondimensionalize the resulting “total” differential equations and to find the appropriate scaling quantities (including time scales). The resulting first order expansion turned out to be very accurate, even compared with the expansions obtained by other authors [1,2,5,8]. Anyway, in [9] Vogt found a simplification of our argument and claimed to have found an inconsistency in our results.

The subject of this short note is to show that the main inconsistency is in the fact that the simplification made by Vogt is just a particular case of our argument and, in general, does not give reliable results as it lies in an oversimplification of the differential equations, that changes the premises upon which the perturbative equations are built.

The paper is organized as follows. In Sect. 2 we recall briefly the model equations and the results obtained in [4]. In Sect. 3 we summarize the results obtained in [9] by Vogt and discuss the weakness of his argument, showing numerical simulations that support our analysis. Finally, in Sect. 4 we state our conclusions.

2 Model equations and “total” results

Let us consider the classical Michaelis–Menten kinetics scheme:

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

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). Applying the law of mass action and using the same symbols to denote the reactants and their concentrations, 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

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

Nondimensionalizing these latter equations it is possible to find all the scaling quantities and, more importantly, the slow time scale and the fast one (for the details see [4]). We obtain therefore the inner differential equations for the inner nondimensional variables $\overline{s}$ and c as:

$$\begin{aligned} \frac{d\overline{s}}{d\tau} &= -\varepsilon\, c \\ \frac{dc}{d\tau} &= \sigma\, \eta c^2 - (\eta + \kappa_M)\, c - \sigma\, \overline{s}\, c + \overline{s} \end{aligned} \tag{8}$$

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

$$\varepsilon = \frac{K\, E_T}{(K_M + E_T + S_T)^2} \tag{9}$$

where $K = \frac{k_2}{k_1}$ is the Van Slyke–Cullen constant. Expanding the solutions of (8) in the form

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

it is easy to find (see again [4] for details) that

$$\Sigma_0 = const = 1 \tag{10}$$

$$\Sigma_1 = \frac{1}{\sigma\, \eta} \log\left(\frac{\Gamma_0^+ \exp(\sqrt{1 - 4\sigma\, \eta}\; \tau) - \Gamma_0^-}{\Gamma_0^+ - \Gamma_0^-} \right) - \Gamma_0^+\, \tau\,; \tag{11}$$

$$\Gamma_0(\tau) = \frac{\exp(\sqrt{1 - 4\sigma\, \eta}\; \tau) - 1}{\sigma\, \eta\, [\Gamma_0^+ \exp(\sqrt{1 - 4\sigma\, \eta}\; \tau) - \Gamma_0^-]} \tag{12}$$

where

$$\Gamma_0^{\pm} = \frac{1 \pm \sqrt{1 - 4\,\sigma\, \eta}}{2\,\sigma\, \eta} \tag{13}$$

and the corresponding Γ_1, which has a more complicated formula. The same treatment is to be used with the outer differential equations, for the outer nondimensional variables $\overline{s}$ and c, obtained choosing the fast timescale in such a way that the perturbative parameter ε equals the ratio of the slow timescale over the fast one:

$$\begin{aligned} \frac{d\overline{s}}{dT} &= -c \\ \varepsilon \frac{dc}{dT} &= \sigma\, \eta c^2 - (\eta + \kappa_M)\, c - \sigma\, \overline{s}\, c + \overline{s} \end{aligned} \tag{14}$$

Setting

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

we find

$$c_0 = \frac{\eta + \kappa_M + \sigma\, \overline{s}_0 \pm \sqrt{(\eta + \kappa_M + \sigma\, \overline{s}_0)^2 - 4\sigma\, \eta \overline{s}_0}}{2\, \sigma \eta} \tag{15}$$

while s_0 is given by

$$\frac{d\overline{s}_0}{dT} = -c_0 \tag{16}$$

with the initial condition given by the matching condition $\overline{s}_0(0) = \lim_{\tau\to\infty} \Sigma_0(\tau) = 1$. From (14) it is found that the first correction terms in the outer solutions are given by

$$\frac{d\overline{s}_1}{dT} = -c_1 \tag{17}$$

$$c_1 = \frac{c_0' + \overline{s}_1\, (\sigma\, c_0 - 1)}{2\, \eta\, \sigma\, c_0 - \sigma\, \overline{s}_0 - \eta - \kappa_M}. \tag{18}$$

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

$$c^{un}(\tau) = c_0^{un}(\varepsilon\tau) + \varepsilon c_1^{un}(\tau); \qquad \overline{s}^{un}(\tau) = \overline{s}_0^{un}(\varepsilon\tau) + \varepsilon \overline{s}_1^{un}(\tau) \tag{19}$$

where, following [6], we obtain the uniform approximations adding the inner and outer solutions and subtracting their common part, i.e.,

$$\begin{aligned} c_0^{un}(\tau) &= c_0(\varepsilon\tau) + \Gamma_0(\tau) - \Gamma_0^- \\ \overline{s}_0^{un}(\tau) &= \overline{s}_0(\varepsilon\tau) + \Sigma_0(\tau) - 1 = \Sigma_0(\tau) \\ c_1^{un}(\tau) &= c_1(\varepsilon\tau) + \Gamma_1(\tau) - m\tau - q \\ \overline{s}_1^{un}(\tau) &= \overline{s}_1(\varepsilon\tau) + \Sigma_1(\tau) - \tfrac{1}{\sigma\eta} \log \tfrac{\Gamma_0^+}{\Gamma_0^+ - \Gamma_0^-} + \Gamma_0^-\, \tau \end{aligned} \tag{20}$$

where m and q are found using appropriate matching conditions (see [4] for details).

3 A critical review of [9]

The main point of [9] deals with the second equation of (8). Substituting in it the equality

$$\sigma\,\eta = \varepsilon\frac{S_T}{K} \tag{21}$$

Eq. (8) becomes

$$\frac{dc}{d\tau} = \varepsilon\frac{S_T}{K}c^2 - (\eta + \kappa_M)\,c - \sigma\,\bar{s}\,c + \bar{s} \tag{22}$$

Looking now for leading order solutions, the first term on the right hand side of (22) disappears and therefore the leading order solutions are simpler than the ones obtained in [4]. As a consequence, in [9] the author is able to find a nice, closed form of the first order expansions of all variables. Neverthless this argument is, in general, not valid. In fact, the introduction of (21) in (8) changes the inner nondimensionality of the equation, because it reintroduces the dimensional quantity S_T that, in general, may not be of order unity. In the simulations shown in [9] (where, surprisingly, the comparison is not with the numerical solution of the full system of differential equations but with the first order expansions given in [4]) the "simplified" solutions are in good agreement with the "not–simplified" ones, but this is only because in those simulations S_T is of order unity.

In fact, the situation changes dramatically if we set $S_T \gg 1$ (see Figs. 1, 2), where we have compared the (dimensional) first order expansion of C (the results for the

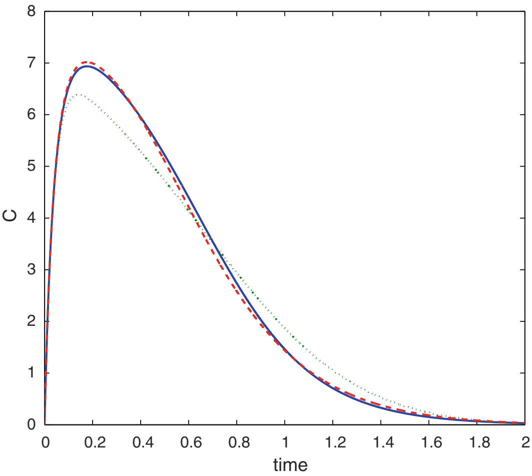

Fig. 1 Dynamics of C: full system (*solid*), first order expansion from [9] (*dotted*), first order expansion from [4](*dashed*). Kinetic parameters: $E_T = 10,\ S_T = 20,$ $k_1 = 1,\ k_{-1} = 0.04,\ k_2 = 4$

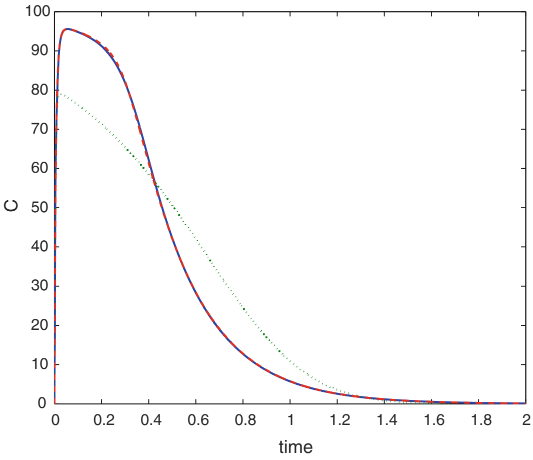

Fig. 2 Dynamics of C: full system (*solid*), first order expansion from [9] (*dotted*), first order expansion from [4](*dashed*). Kinetic parameters: $E_T = 100,\ S_T = 200,$ $k_1 = 1,\ k_{-1} = 0.04,\ k_2 = 4$

variable S is analogous) given in [9] with the numerical solution of (2) and with the first order expansion given in [4]. As expected, the expansions given in [9] are far from being accurate, while ours are in good agreement with the numerical solution of (2). This happens especially in Fig. 2, where the numerical solution and the expansion given by [4] are almost undistinguishable, while the expansion given by [9] misses largely its target.

4 Conclusions

Singular perturbation methods are powerful techniques that allow the reconstruction of approximate solutions of differential equations with great accuracy. The procedure to use such methods is in some way arbitrary, in the sense that it requires some choices (and therefore some expertise), depending on the result that you are looking for. Anyway, once you have chosen to follow a way, the "philosophy" of the choice must be respected and preserved. In [9], after nondimensionalizing the differential equations, it makes no sense to reintroduce dimensional quantities without a strong justification such as, e.g., the discussion of a particular case.

In fact, the author could have discussed the case treated in [9] as an application of the argument used in [4] to obtain better and simpler results, when the total substrate S_T is of order unity or, at least, when it is of the same order of the Van Slyke–Cullen constant $K = \frac{k_2}{k_1}$. However, it is not possible to generalize his results to all combinations of kinetics parameters, as shown by our argument and simulations.

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