J Math Chem (2013) 51:826–842
DOI 10.1007/s10910-012-0121-8

ORIGINAL PAPER

On approximate analytical solutions of differential equations in enzyme kinetics using homotopy perturbation method

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Received: 4 October 2012 / Accepted: 23 November 2012 / Published online: 4 December 2012

Abstract Homotopy perturbation method is used to extend the approximate analytical solutions of non-linear reaction equations describing enzyme kinetics for combinations of parameters for which solutions obtained in previous works are not valid. Also, by constructing a new homotopy, alternative approximate analytical expressions for substrate, substrate-enzyme complex and product concentrations are found. These first-order approximate solutions give more accurate results than the second-order approximations derived in previous works.

Keywords Homotopy perturbation method · Non-linear reaction equations · Enzyme kinetics

1 Introduction

Enzymes are biological catalysts that are fundamental in many chemical reactions that take place in living organisms. They are very efficient and specific catalysts, as they can speed up reactions by a factor of millions, usually reacting with only one particular substrate or closely related substrates.

One of the most basic enzymatic reactions was first proposed by Michaelis and Menten in [1]. In their reaction scheme, the enzyme E combines with an substrate S to form a substrate-enzyme complex SE. The complex then breaks down into the product P and the free enzyme. This mechanism is usually represented by

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

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where k_1, k_{-1} and k_2 are parameters associated with the rates of reaction. The reaction equations for the mechanism (1) are difficult to solve, so approximate analytical descriptions were developed. One of the most important is the quasi-steady-state approximation, first proposed by Briggs and Haldane [2] in 1925. Laidler [3] found that the condition for validity of the quasi-steady-state approximation is that the initial substrate concentration $[S_0]$ should be much larger than the initial concentration of the enzyme $[E_0]$, i.e., $[E_0]/[S_0] \ll 1$. Later, Segel [4] and Segel and Slemrod [5] showed that a more general condition for the validity of the quasi-steady-state approximation is

$$\frac{[E_0]}{[S_0] + K_M} \ll 1,$$

where $K_M = (k_{-1} + k_2)/k_1$ is called the Michaelis constant. On the other hand, using the reverse quasi-steady-state assumption, Schnell and Maini [6] analysed the case when the enzyme is in excess, i.e., $[S_0]/[E_0] \ll 1$. The existence of a small parameter allows the use of asymptotic methods, like singular perturbation analysis, to obtain approximate solutions of the enzyme kinetics equations [7,8].

In recent years, a new asymptotic technique known as homotopy perturbation method [9] has been used to derive new approximate solutions to reaction differential equations in enzyme kinetics [10–14]. An advantage of the homotopy perturbation method is that it does not depend on a small parameter to be effective.

In this work, we discuss the application of the homotopy perturbation technique to the differential equations that describe the time evolution of the enzyme reaction (1). We derive new analytical expressions for substrate concentration, enzyme-substrate complex concentration and product concentration for special combinations of the parameters for which the approximate expressions obtained in earlier works are not valid. This is done in Sect. 3. In Sect. 4, we propose a modification in the procedure used in the homotopy perturbation method to find alternative analytical approximations of the enzyme kinetics equations. We show that these expressions provide more accurate results than those obtained by other authors. The similarities and differences between our approach and the Simple Iteration Method of [12] is also presented. Finally, Sect. 5 is devoted to the discussion of the results.

2 Basic enzyme kinetics equations

The Law of Mass Action applied to Eq. (1) results in the following system of non-linear reaction equations

$$\frac{d[S]}{dt} = -k_1[E][S] + k_{-1}[SE], \tag{2}$$

$$\frac{d[E]}{dt} = -k_1[E][S] + (k_{-1} + k_2)[SE], \tag{3}$$

$$\frac{d[SE]}{dt} = k_1[E][S] - (k_{-1} + k_2)[SE], \tag{4}$$

$$\frac{d[P]}{dt} = k_2[SE], \tag{5}$$

where [ ] denotes concentration. The initial conditions are

$$[S_0] = s_0, [E_0] = e_0, [SE_0] = [P_0] = 0, \tag{6}$$

where s_0 and e_0 denote the initial concentrations of substrate and enzyme, respectively. Adding Eqs. (3)–(4) we get

$$\frac{d[E]}{dt} + \frac{d[SE]}{dt} = 0 \Rightarrow [E] + [SE] = e_0, \tag{7}$$

which is the conservation law for the enzyme. Another conservation law is obtained by adding Eqs. (2), (4) and (5)

$$\frac{d[S]}{dt} + \frac{d[SE]}{dt} + \frac{d[P]}{dt} = 0 \Rightarrow [S] + [SE] + [P] = s_0. \tag{8}$$

Using Eq. (7) in Eqs. (2) and (4) to eliminate $[E]$, we have the reduced system

$$\frac{d[S]}{dt} = -k_1 e_0 [S] + (k_1 [S] + k_{-1}) [SE], \tag{9}$$

$$\frac{d[SE]}{dt} = k_1 e_0 [S] - (k_1 [S] + k_{-1} + k_2) [SE]. \tag{10}$$

To nondimensionalise the system of Eqs. (9)–(10), we introduce dimensionless variables

$$s(\tau) = \frac{[S]}{s_0}, c(\tau) = \frac{[SE]}{e_0}, E(\tau) = \frac{[E]}{e_0}, P(\tau) = \frac{[P]}{s_0}, \tag{11}$$

$$\varepsilon = \frac{e_0}{s_0}, \lambda = \frac{k_{-1}}{k_1 s_0}, K = \frac{k_{-1} + k_2}{k_1 s_0}, \tau = \frac{k_1 e_0 t}{\varepsilon}. \tag{12}$$

In terms of these variables, Eqs. (9)–(10) and Eq. (5) can be represented as

$$\frac{ds}{d\tau} = -\varepsilon s + \varepsilon s c + \lambda \varepsilon c, \tag{13}$$

$$\frac{dc}{d\tau} = -K c + s - s c, \tag{14}$$

$$\frac{dP}{d\tau} = (K - \lambda)\varepsilon c, \tag{15}$$

and the conservation Eqs. (7) and (8) take the form

$$E + c = 1, \tag{16}$$

$$s + \varepsilon c + P = 1. \tag{17}$$

3 Approximate solution by homotopy perturbation method

Because of the non-linearity of Eqs. (13)–(14), it is difficult to find exact solutions, and no such solutions for arbitrary values of the parameters have been found so far. Thus, approximate analytical methods are a valuable tool in these cases. In recent years, homotopy perturbation method [9] has been used as an alternative approach to traditional perturbation methods to find approximate solutions of non-linear equations in engineering and physical science problems (see, for instance, [15] and references therein). In the particular case of enzyme kinetics, Uma Maheswari and Rajendran [10], and Varadharajan and Rajendran [11] used homotopy perturbation technique to find closed analytical expressions for substrate, substrate-enzyme complex, and product for the reaction scheme (1), while Khoshnaw [12] extended their analysis for reversible kinetics. Also, Varadharajan and Rajendran [13] applied the homotopy perturbation method to enzyme kinetics equations with non-mechanism-based enzyme inactivation, and Pandi and Rajendran [14] obtained approximate analytical expressions for enzyme reaction with cooperative behaviour.

To illustrate the basic idea of homotopy perturbation method, we consider a non-linear differential equation in the form [15]

$$L(u) + N(u) - f(r) = 0, \quad r \in \Omega, \tag{18}$$

with boundary conditions

$$B(u, \partial u/\partial n) = 0, \quad r \in \Gamma, \tag{19}$$

where L and N are, respectively, a linear and a non-linear differential operator, $f(r)$ is a known analytic function, B is a boundary operator and Γ is the boundary of the domain Ω.

We construct a homotopy $v(r, p) : \Omega \times [0, 1] \to \mathbb{R}$, which satisfies

$$H(v, p) = (1 - p)\,[L(v) - L(u_0)] + p\,[L(v) + N(v) - f(r)] = 0, \tag{20}$$

or

$$H(v, p) = L(v) - L(u_0) + pL(u_0) + p\,[N(v) - f(r)] = 0, \tag{21}$$

where $p \in [0, 1]$ is an embedding parameter, while u_0 is an initial approximation of Eq. (18), which satisfies the boundary conditions. From Eq. (20) or (21) we have

$$H(v, 0) = L(v) - L(u_0) = 0, \tag{22}$$

$$H(v, 1) = L(v) + N(v) - f(r) = 0. \tag{23}$$

Thus, when $p = 0$, Eq. (20) or (21) becomes a linear equation, and when $p = 1$ it becomes the original non-linear equation (18). As the parameter p increases from 0 to 1, the problem $L(v) - L(u_0) = 0$ (which is supposedly easy to solve) is continuously deformed to the (difficult) problem $L(v) + N(v) - f(r) = 0$.

According to the homotopy perturbation method, the solution of Eq. (20) or (21) can be written as a power series in p

$$v = v_0 + pv_1 + p^2 v_2 + \cdots. \tag{24}$$

Setting $p = 1$ results in the approximate solution of Eq. (18),

$$u = \lim_{p\to 1} v = v_0 + v_1 + v_2 + \cdots. \tag{25}$$

To apply the preceding formalism to Eqs. (13)–(14), the following homotopy has been constructed [10–12]

$$(1-p)\left(\frac{ds}{d\tau} + \varepsilon s\right) + p\left(\frac{ds}{d\tau} + \varepsilon s - \varepsilon sc - \lambda\varepsilon c\right) = 0, \tag{26}$$

$$(1-p)\left(\frac{dc}{d\tau} + Kc\right) + p\left(\frac{dc}{d\tau} + Kc - s + sc\right) = 0, \tag{27}$$

or equivalently,

$$\frac{ds}{d\tau} + \varepsilon s + p\left(-\varepsilon sc - \lambda\varepsilon c\right) = 0, \tag{28}$$

$$\frac{dc}{d\tau} + Kc + p\left(-s + sc\right) = 0, \tag{29}$$

with initial conditions $s(0) = 1$, $c(0) = 0$. Also, the functions $s(\tau)$ and $c(\tau)$ are approximated by

$$s = s_0 + ps_1 + p^2 s_2 + \cdots, \tag{30}$$

$$c = c_0 + pc_1 + p^2 c_2 + \cdots, \tag{31}$$

Substituting Eqs. (30)–(31) into Eqs. (28)–(29) and comparing the coefficients of like powers of p, we obtain the system of differential equations

$$p^0 : \frac{ds_0}{d\tau} + \varepsilon s_0 = 0, \tag{32}$$

$$p^1 : \frac{ds_1}{d\tau} + \varepsilon s_1 - \varepsilon s_0 c_0 - \lambda\varepsilon c_0 = 0, \tag{33}$$

$$p^2 : \frac{ds_2}{d\tau} + \varepsilon s_2 - \varepsilon s_0 c_1 - \varepsilon s_1 c_0 - \lambda\varepsilon c_1 = 0, \tag{34}$$

and

$$p^0 : \frac{dc_0}{d\tau} + Kc_0 = 0, \tag{35}$$

$$p^1 : \frac{dc_1}{d\tau} + Kc_1 - s_0 + s_0c_0 = 0, \tag{36}$$

$$p^2 : \frac{dc_2}{d\tau} + Kc_2 - s_1 + s_0c_1 + s_1c_0 = 0, \tag{37}$$

with initial conditions

$$s_0(0) = 1, c_0(0) = 0, s_i(0) = 0, c_i(0) = 0, i = 1, 2, \ldots. \tag{38}$$

Solving Eqs. (32)–(37) with the initial conditions (38), we find

$$s_0(\tau) = e^{-\varepsilon\tau}, \quad s_1(\tau) = 0, \tag{39}$$

$$s_2(\tau) = \left[\frac{1}{K} - \frac{\lambda\varepsilon}{(K-\varepsilon)^2}\right]e^{-\varepsilon\tau} + \frac{\lambda\varepsilon}{K-\varepsilon}\tau e^{-\varepsilon\tau} - \frac{e^{-2\varepsilon\tau}}{K-\varepsilon} + \frac{\varepsilon}{K(K-\varepsilon)}e^{-(K+\varepsilon)\tau} + \frac{\lambda\varepsilon}{(K-\varepsilon)^2}e^{-K\tau}, \tag{40}$$

and

$$c_0(\tau) = 0, \quad c_1(\tau) = \frac{e^{-\varepsilon\tau} - e^{-K\tau}}{K-\varepsilon}, \tag{41}$$

$$c_2(\tau) = \frac{e^{-K\tau}}{\varepsilon(K-2\varepsilon)} - \frac{e^{-2\varepsilon\tau}}{(K-\varepsilon)(K-2\varepsilon)} - \frac{e^{-(K+\varepsilon)\tau}}{\varepsilon(K-\varepsilon)}. \tag{42}$$

According to the homotopy perturbation method, we have

$$s(\tau) = \lim_{p\to 1} s_0 + ps_1 + p^2s_2 = s_0 + s_1 + s_2, \tag{43}$$

$$c(\tau) = \lim_{p\to 1} c_0 + pc_1 + p^2c_2 = c_0 + c_1 + c_2. \tag{44}$$

Using Eqs. (39)–(42) we can express the approximate solutions for the concentrations of the substrate and of the enzyme-substrate complex as

$$s(\tau) = \left[1 + \frac{1}{K} - \frac{\lambda\varepsilon}{(K-\varepsilon)^2}\right]e^{-\varepsilon\tau} + \frac{\lambda\varepsilon}{K-\varepsilon}\tau e^{-\varepsilon\tau} - \frac{e^{-2\varepsilon\tau}}{K-\varepsilon} + \frac{\varepsilon}{K(K-\varepsilon)}e^{-(K+\varepsilon)\tau} + \frac{\lambda\varepsilon}{(K-\varepsilon)^2}e^{-K\tau}, \tag{45}$$

$$c(\tau) = \frac{e^{-\varepsilon\tau}}{K-\varepsilon} - \frac{e^{-2\varepsilon\tau}}{(K-\varepsilon)(K-2\varepsilon)} + \left[\frac{1}{\varepsilon(K-2\varepsilon)} - \frac{1}{K-\varepsilon}\right]e^{-K\tau} - \frac{e^{-(K+\varepsilon)\tau}}{\varepsilon(K-\varepsilon)}. \tag{46}$$

The enzyme and product concentrations can be found using the conservation Eqs. (16)–(17), respectively. The final expression for the product concentration reads

$$P(\tau) = 1 - \left[\frac{1}{K} + \frac{K}{K-\varepsilon} - \frac{\lambda\varepsilon}{(K-\varepsilon)^2}\right] e^{-\varepsilon\tau} - \frac{\lambda\varepsilon}{K-\varepsilon}\tau e^{-\varepsilon\tau} + \frac{e^{-2\varepsilon\tau}}{K-2\varepsilon} - \left[\frac{\lambda\varepsilon}{(K-\varepsilon)^2} + \frac{1}{(K-2\varepsilon)} - \frac{\varepsilon}{K-\varepsilon}\right] e^{-K\tau} + \frac{e^{-(K+\varepsilon)\tau}}{K}. \quad (47)$$

At this point we should note that, if we calculate the product concentration using Eq. (15), we obtain a different result, namely [11]

$$P(\tau) = (K-\lambda)\varepsilon \int_0^\tau c(u)\,\mathrm{d}u = \frac{(K-\lambda)\left(1-e^{-\varepsilon\tau}\right)}{K-\varepsilon} + \frac{(K-\lambda)\left(e^{-2\varepsilon\tau}-1\right)}{2\,(K-\varepsilon)\,(K-2\varepsilon)} + \frac{(K-\lambda)\left(1-e^{-K\tau}\right)}{K\,(K-2\varepsilon)} + \frac{\varepsilon(K-\lambda)\left(e^{-K\tau}-1\right)}{K\,(K-\varepsilon)} + \frac{(K-\lambda)\left[e^{-(K+\varepsilon)\tau}\right]}{K^2-\varepsilon^2}. \quad (48)$$

From Eq. (48) we have

$$\lim_{\tau\to\infty} P(\tau) = \frac{(K-\lambda)(2K+2\varepsilon-1)}{2K(K+\varepsilon)} \neq 1, \quad (49)$$

so the expression (48) is not consistent with the conservation Eq. (17), since

$$\lim_{\tau\to\infty} s(\tau) = 0, \text{ and } \lim_{\tau\to\infty} c(\tau) = 0. \quad (50)$$

In Fig. 1 we display the curves of s, c, E and P, obtained from the numerical solution of the system of Eqs. (13)–(15), while the dots were computed with the approximate solutions (45)–(47). The values of the parameters are $\varepsilon = 4.8$, $K = 4.0$ and $\lambda = 0$. These are the same values that were used in Fig. 3 of [11] ($k = \lambda = 4.0$ in their nondimensionalisation, since they defined $\lambda = k_2/(k_1 s_0)$). It is seen that in this case, the approximations obtained with the homotopy perturbation method are very close to the numerical solutions. Also, in Fig. 1, the circles represent the product concentration calculated with Eq. (48). It is clear that the product concentration obtained from the conservation equation (17) represents a better approximation than the solution (48).

A detail about the analytical expressions derived above and that was not mentioned in earlier works, is that Eqs. (45)–(47) apparently are not valid when $K = \varepsilon$, and so Eqs. (46)–(47) when $K = 2\varepsilon$. Since the numerical solutions for these particular combinations of parameters are well-behaved (see below), something must have been missed when solving the differential Eqs. (32)–(37). In fact, the differential equations have the form

$$\frac{dx}{d\tau} + ax = \sum_i k_i e^{-b_i\tau}, \quad (51)$$

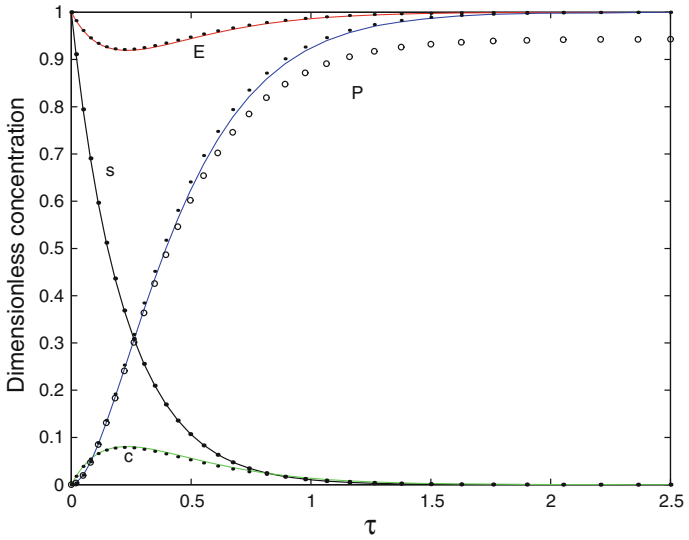

Fig. 1 Curves of the substrate concentration s (*black*), enzyme-substrate complex concentration c (*green*), enzyme concentration E (*red*) and product concentration P (*blue*), for parameters $\varepsilon = 4.8$, $K = 4.0$ and $\lambda = 0$. The *curves* represent the numerical solution of Eqs. (13)–(15), while dots were computed with Eqs. (45)–(47). The circles represent the product concentration calculated with Eq. (48)

where $a > 0, b_i > 0$ and k_i are constants. As usual, to solve this equation, we multiply it by the integrating factor $e^{a\tau}$

$$\frac{d}{d\tau}\left(xe^{a\tau}\right) = \sum_i k_i e^{(a-b_i)\tau} \Rightarrow x(\tau) = ce^{-a\tau} + \sum_i \frac{k_i}{a-b_i} e^{-b_i\tau}, \tag{52}$$

where c is a constant. However, if $b_j = a$, we have

$$\frac{d}{d\tau}\left(xe^{a\tau}\right) = k_j + \sum_{i\neq j} k_i e^{(a-b_i)\tau} \Rightarrow x(\tau) = ce^{-a\tau} + k_j\tau e^{-a\tau} + \sum_{i\neq j} \frac{k_i}{a-b_i} e^{-b_i\tau}. \tag{53}$$

As an example, consider the differential equation (36)

$$\frac{dc_1}{d\tau} + Kc_1 = e^{-\varepsilon\tau}, \tag{54}$$

whose solution is given by (41) if $K \neq \varepsilon$. However, when $K = \varepsilon$, we obtain

$$c_1(\tau) = \tau e^{-\varepsilon\tau}. \tag{55}$$

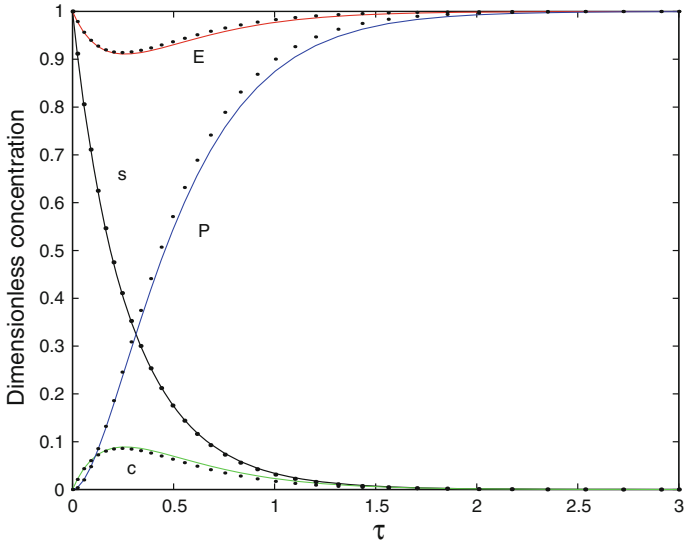

Fig. 2 Curves of the substrate concentration s (*black*), enzyme-substrate complex concentration c (*green*), enzyme concentration E (*red*) and product concentration P (*blue*), for parameters $K = \varepsilon = 4$ and $\lambda = 0.25$. The *curves* represent the numerical solution of Eqs. (13)–(15), while dots were calculated with Eqs. (56)–(58)

Proceeding in this way, we obtain following results for the concentrations of s, c and P, if $K = \varepsilon$

$$s(\tau) = \frac{(1+\varepsilon)}{\varepsilon} e^{-\varepsilon\tau} + \frac{\lambda\varepsilon}{2}\tau^2 e^{-\varepsilon\tau} - \frac{e^{-2\varepsilon\tau}}{\varepsilon} - \tau e^{-2\varepsilon\tau}, \tag{56}$$

$$c(\tau) = -\frac{e^{-\varepsilon\tau}}{\varepsilon^2} + \tau e^{-\varepsilon\tau} + \frac{e^{-2\varepsilon\tau}}{\varepsilon^2} + \frac{\tau e^{-2\varepsilon\tau}}{\varepsilon}, \tag{57}$$

$$P(\tau) = 1 - e^{-\varepsilon\tau} - \varepsilon\tau e^{-\varepsilon\tau} - \frac{\lambda\varepsilon}{2}\tau^2 e^{-\varepsilon\tau}, \tag{58}$$

and, if $K = 2\varepsilon$

$$s(\tau) = \frac{[1+2(\varepsilon-\lambda)]}{2\varepsilon} e^{-\varepsilon\tau} + \lambda\tau e^{-\varepsilon\tau} + \frac{(\lambda-1)}{\varepsilon} e^{-2\varepsilon\tau} + \frac{e^{-3\varepsilon\tau}}{2\varepsilon}, \tag{59}$$

$$c(\tau) = \frac{e^{-\varepsilon\tau}}{\varepsilon} + \frac{(1-\varepsilon)}{\varepsilon^2} e^{-2\varepsilon\tau} - \frac{\tau e^{-2\varepsilon\tau}}{\varepsilon} - \frac{e^{-3\varepsilon\tau}}{\varepsilon^2}, \tag{60}$$

$$P(\tau) = 1 - \frac{[1+2(\varepsilon-\lambda)]}{2\varepsilon} e^{-\varepsilon\tau} - \lambda\tau e^{-\varepsilon\tau} + \frac{(\varepsilon-\lambda)}{\varepsilon} e^{-2\varepsilon\tau} + \tau e^{-2\varepsilon\tau} + \frac{e^{-3\varepsilon\tau}}{2\varepsilon}. \tag{61}$$

In Fig. 2, we compare the curves of s, c, E and P, calculated numerically, with the approximations (56)–(58), represented by dots, for parameters $K = \varepsilon = 4$ and $\lambda = 0.25$. In Fig. 3, the same quantities are shown, the dots represent Eqs. (59)–(61),

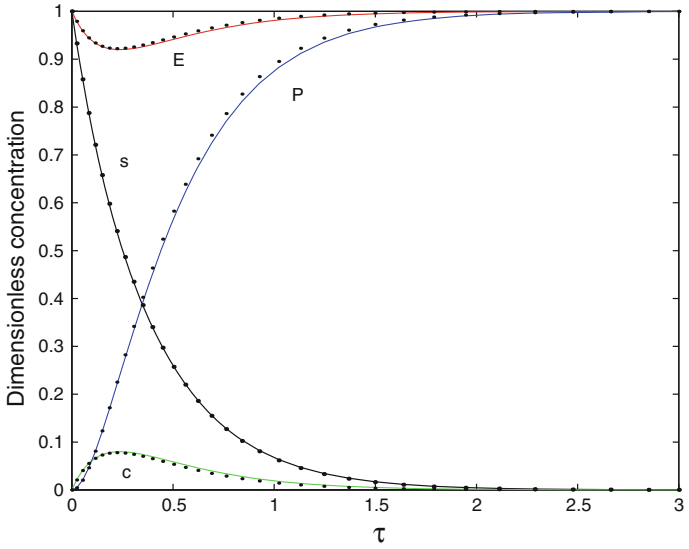

Fig. 3 Curves of the substrate concentration s (*black*), enzyme-substrate complex concentration c (*green*), enzyme concentration E (*red*) and product concentration P (*blue*), for parameters $K = 6$, $\varepsilon = 3$ and $\lambda = 0.25$. The *curves* represent the numerical solution of Eqs. (13)–(15), while dots were calculated with Eqs. (59)–(61)

and the parameters have values $K = 6$, $\varepsilon = 3$ and $\lambda = 0.25$. In both examples, the analytical expressions are close to the numerical solutions.

Although the approximations derived with the homotopy perturbation method were in good agreement with the numerical solutions in the examples presented so far, they have a limited applicability. As an example, in Fig. 4 we display the numerical solution and the analytical expressions of s, c, E and P for parameters $\varepsilon = 2$, $K = 1.5$ and $\lambda = 0.5$. For times $\tau \gtrapprox 0.5$, we observe a poor agreement.

4 An alternative approximate solution using homotopy perturbation method

In this Section, we propose a small modification in the procedure used in the homotopy perturbation method and find alternative analytical approximations of the enzyme kinetics equations. The modification is somewhat similar to the Simple Iteration Method proposed by Khoshnaw [12].

Instead of using the homotopy given by Eqs. (28)–(29), we propose

$$\frac{ds}{d\tau} + \varepsilon s - \lambda\varepsilon c - p\varepsilon sc = 0, \tag{62}$$

$$\frac{dc}{d\tau} + Kc - s + psc = 0, \tag{63}$$

With this homotopy, we retain all linear terms that appear in the differential equations (13)–(14) when $p = 0$. Substituting equations (30)–(31) into (62)–(63) and comparing

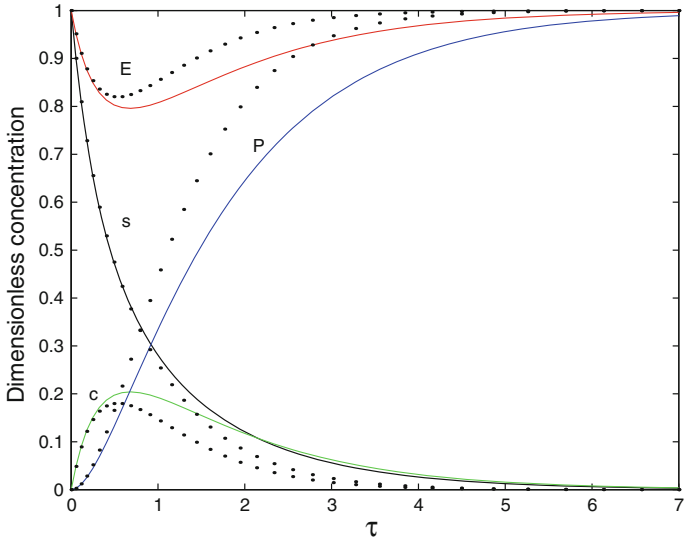

Fig. 4 Curves of the substrate concentration s (*black*), enzyme-substrate complex concentration c (*green*), enzyme concentration E (*red*) and product concentration P (*blue*), for parameters $\varepsilon = 2$, $K = 1.5$ and $\lambda = 0.5$. The *curves* represent the numerical solution of Eqs. (13)–(15), while dots were calculated with Eqs. (45)–(47)

the coefficients of like powers of p, we obtain for the coefficient p^0

$$\frac{ds_0}{d\tau} + \varepsilon s_0 - \lambda\varepsilon c_0 = 0, \tag{64}$$

$$\frac{dc_0}{d\tau} + K c_0 - s_0 = 0, \tag{65}$$

For convenience, we rewrite the system (64)–(65) as a second order ODE

$$\frac{d^2c_0}{d\tau^2} + (\varepsilon + K)\frac{dc_0}{d\tau} + \varepsilon(K - \lambda)c_0 = 0, \tag{66}$$

with initial conditions

$$c_0(0) = 0, \frac{dc_0(0)}{d\tau} = s_0(0) - K c_0(0) = 1. \tag{67}$$

The solution is

$$c_0(\tau) = \frac{e^{\alpha_1\tau} - e^{\alpha_2\tau}}{A}, \tag{68}$$

with

$$\alpha_{1,2} = -\frac{\varepsilon + K}{2} \pm \frac{A}{2}, \quad A = \sqrt{(\varepsilon - K)^2 + 4\varepsilon\lambda}. \tag{69}$$

The solution for s_0 can be found from Eq. (65)

$$s_0(\tau) = \frac{(K-\varepsilon+A)}{2A}e^{\alpha_1\tau} - \frac{(K-\varepsilon-A)}{2A}e^{\alpha_2\tau}. \tag{70}$$

For the coefficient p^1 we have the equations

$$\frac{ds_1}{d\tau} + \varepsilon s_1 - \lambda\varepsilon c_1 = \varepsilon s_0 c_0, \tag{71}$$

$$\frac{dc_1}{d\tau} + Kc_1 - s_1 = -s_0 c_0, \tag{72}$$

which are equivalent to the non-homogeneous second order ODE

$$\frac{d^2c_1}{d\tau^2} + (\varepsilon+K)\frac{dc_1}{d\tau} + \varepsilon(K-\lambda)c_1 = (\varepsilon+K)s_0c_0 - \varepsilon\lambda c_0^2 - s_0^2, \tag{73}$$

with initial conditions

$$c_1(0) = 0, \frac{dc_1(0)}{d\tau} = -Kc_1(0) + s_1(0) - s_0(0)c_0(0) = 0. \tag{74}$$

The solution for c_1 reads

$$\begin{aligned} c_1(\tau) = {} & \frac{[(K-\varepsilon)(K+\varepsilon-A)+2\varepsilon(K-\lambda)]}{\varepsilon A(K-\lambda)(K+\varepsilon+3A)}e^{\alpha_1\tau} \\ & -\frac{[(K-\varepsilon)(K+\varepsilon+A)+2\varepsilon(K-\lambda)]}{\varepsilon A(K-\lambda)(K+\varepsilon-3A)}e^{\alpha_2\tau} + \frac{2(K-\varepsilon+A)}{A^2(K+\varepsilon-3A)}e^{2\alpha_1\tau} \\ & +\frac{2(K-\varepsilon-A)}{A^2(K+\varepsilon+3A)}e^{2\alpha_2\tau} + \frac{(\varepsilon^2-K^2)}{\varepsilon A^2(K-\lambda)}e^{-(K+\varepsilon)\tau}, \end{aligned} \tag{75}$$

and from Eq. (72) we get s_1

$$\begin{aligned} s_1(\tau) = {} & \frac{[(K-\varepsilon)(2K-\varepsilon-3\lambda+A)+A(K-\lambda)]}{A(K-\lambda)(K+\varepsilon+3A)}e^{\alpha_1\tau} \\ & -\frac{[(K-\varepsilon)(2K-\varepsilon-3\lambda-A)-A(K-\lambda)]}{A(K-\lambda)(K+\varepsilon-3A)}e^{\alpha_2\tau} \\ & +\frac{[(K-2\varepsilon)(K-\varepsilon+A)+2\varepsilon\lambda]}{A^2(K+\varepsilon-3A)}e^{2\alpha_1\tau} + \frac{[(K-2\varepsilon)(K-\varepsilon-A)+2\varepsilon\lambda]}{A^2(K+\varepsilon+3A)}e^{2\alpha_2\tau} \\ & +\frac{(\varepsilon+\lambda)(K-\varepsilon)}{A^2(K-\lambda)}e^{-(K+\varepsilon)\tau}. \end{aligned} \tag{76}$$

Taking the limit $p \to 1$, we obtain

$$
\begin{aligned}
s(\tau) &= s_0 + s_1 \\
&= \left[\frac{K-\varepsilon+A}{2} + \frac{(K-\varepsilon)(2K-\varepsilon-3\lambda+A)+A(K-\lambda)}{(K-\lambda)(K+\varepsilon+3A)}\right]\frac{e^{\alpha_1\tau}}{A} \\
&\quad - \left[\frac{K-\varepsilon-A}{2} + \frac{(K-\varepsilon)(2K-\varepsilon-3\lambda-A)-A(K-\lambda)}{(K-\lambda)(K+\varepsilon-3A)}\right]\frac{e^{\alpha_2\tau}}{A} \\
&\quad + \frac{[(K-2\varepsilon)(K-\varepsilon+A)+2\varepsilon\lambda]}{A^2(K+\varepsilon-3A)}e^{2\alpha_1\tau} + \frac{[(K-2\varepsilon)(K-\varepsilon-A)+2\varepsilon\lambda]}{A^2(K+\varepsilon+3A)}e^{2\alpha_2\tau} \\
&\quad + \frac{(\varepsilon+\lambda)(K-\varepsilon)}{A^2(K-\lambda)}e^{-(K+\varepsilon)\tau},
\end{aligned} \tag{77}
$$

and

$$
\begin{aligned}
c(\tau) = c_0 + c_1 &= \left[1 + \frac{(K-\varepsilon)(K+\varepsilon-A)+2\varepsilon(K-\lambda)}{\varepsilon(K-\lambda)(K+\varepsilon+3A)}\right]\frac{e^{\alpha_1\tau}}{A} \\
&\quad - \left[1 + \frac{(K-\varepsilon)(K+\varepsilon+A)+2\varepsilon(K-\lambda)}{\varepsilon(K-\lambda)(K+\varepsilon-3A)}\right]\frac{e^{\alpha_2\tau}}{A} \\
&\quad + \frac{2(K-\varepsilon+A)}{A^2(K+\varepsilon-3A)}e^{2\alpha_1\tau} + \frac{2(K-\varepsilon-A)}{A^2(K+\varepsilon+3A)}e^{2\alpha_2\tau} \\
&\quad + \frac{(\varepsilon^2-K^2)}{\varepsilon A^2(K-\lambda)}e^{-(K+\varepsilon)\tau}.
\end{aligned} \tag{78}
$$

The approximate expression for the product concentration reads

$$
\begin{aligned}
P = 1 - s - \varepsilon c &= 1 - \frac{[(K+\varepsilon+A)(K+\varepsilon+3A)+2(3K-\varepsilon+A)]}{2A(K+\varepsilon+3A)}e^{\alpha_1\tau} \\
&\quad + \frac{[(K+\varepsilon-A)(K+\varepsilon-3A)+2(3K-\varepsilon-A)]}{2A(K+\varepsilon-3A)}e^{\alpha_2\tau} \\
&\quad - \frac{[K(K-\varepsilon+A)+2\varepsilon\lambda]}{A^2(K+\varepsilon-3A)}e^{2\alpha_1\tau} - \frac{[K(K-\varepsilon-A)+2\varepsilon\lambda]}{A^2(K+\varepsilon+3A)}e^{2\alpha_2\tau} \\
&\quad + \frac{(K-\varepsilon)}{A^2}e^{-(K+\varepsilon)\tau}.
\end{aligned} \tag{79}
$$

In Fig. 5a–d we show the numerical solution (solid curves) and the analytical expressions of s, c, E and P for parameters $\varepsilon = 2$, $K = 1.5$ and $\lambda = 0.5$ (the same values as were used in Fig. 4). The dots were calculated with Eqs. (77)–(79), and the dashed curves represent the approximate expressions (45)–(47). It is seen that, unlike the solutions calculated in Sect. 3, the analytical results obtained with our modified homotopy agree well with the numerics. Is is also important to note that the approximations (77)–(79) are first-order solutions with respect to the embedding parameter p, while solutions (45)–(47) are second-order approximations.

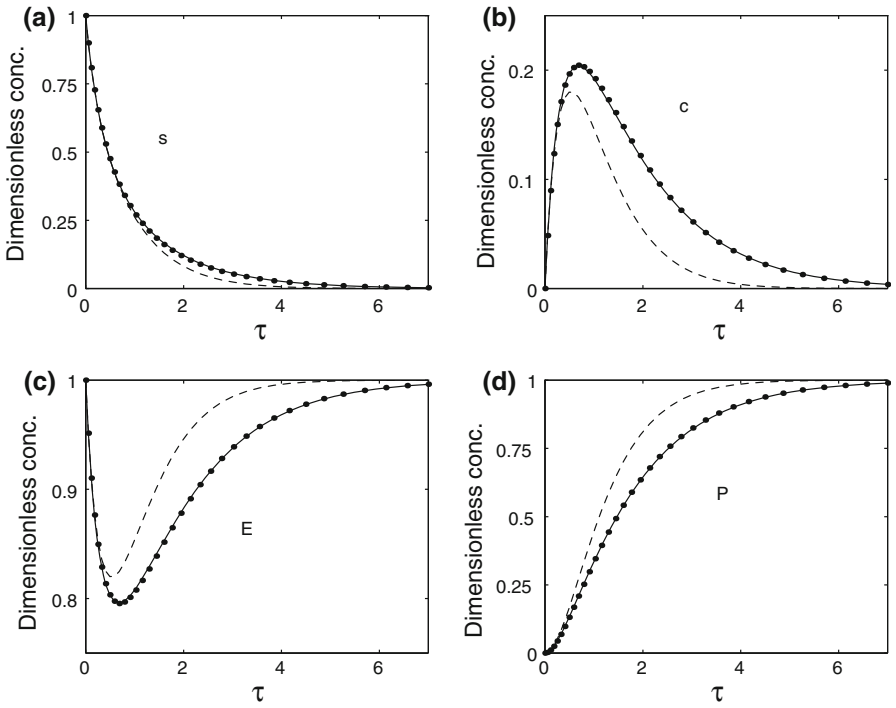

Fig. 5 Curves of **a** the substrate concentration s, **b** enzyme-substrate complex concentration c, **c** enzyme concentration E and **d** product concentration P, for parameters $\varepsilon = 2$, $K = 1.5$ and $\lambda = 0.5$. The *solid curves* represent the numerical solution of Eqs. (13)–(15), *dots* were calculated with solutions (77)–(79), while the *dashed curves* represent the approximations (45)–(47)

We must consider separately the case $A = 0$, which only happens if $K = \varepsilon$ *and* $\lambda = 0$. In this case, the general solution of the ODE (66) with initial conditions (67) is

$$c_0(\tau) = \tau e^{-\varepsilon\tau}. \tag{80}$$

Repeating the calculations for $s_0(\tau)$, $c_1(\tau)$ and $s_1(\tau)$, we arrive at the following results

$$s(\tau) = \frac{1+\varepsilon}{\varepsilon}e^{-\varepsilon\tau} - \frac{e^{-2\varepsilon\tau}}{\varepsilon} - \tau e^{-2\varepsilon\tau}, \tag{81}$$

$$c(\tau) = -\frac{3}{\varepsilon^2}e^{-\varepsilon\tau} + \frac{1+\varepsilon}{\varepsilon}\tau e^{-\varepsilon\tau} + \frac{3}{\varepsilon^2}e^{-2\varepsilon\tau} + \frac{2}{\varepsilon}\tau e^{-2\varepsilon\tau}, \tag{82}$$

$$P(\tau) = 1 + \frac{2-\varepsilon}{\varepsilon}e^{-\varepsilon\tau} - (1+\varepsilon)\tau e^{-\varepsilon\tau} - \frac{2}{\varepsilon}e^{-2\varepsilon\tau} - \tau e^{-2\varepsilon\tau}. \tag{83}$$

The solution for $s(\tau)$ is the same as Eq. (56) with $\lambda = 0$.

In Fig. 6a–d we present the numerical solution (solid curves) and the analytical expressions of s, c, E and P for parameters $K = \varepsilon = 1$ and $\lambda = 0$. The dots were calculated with Eqs. (81)–(83), and the dashed curves represent the approxi-

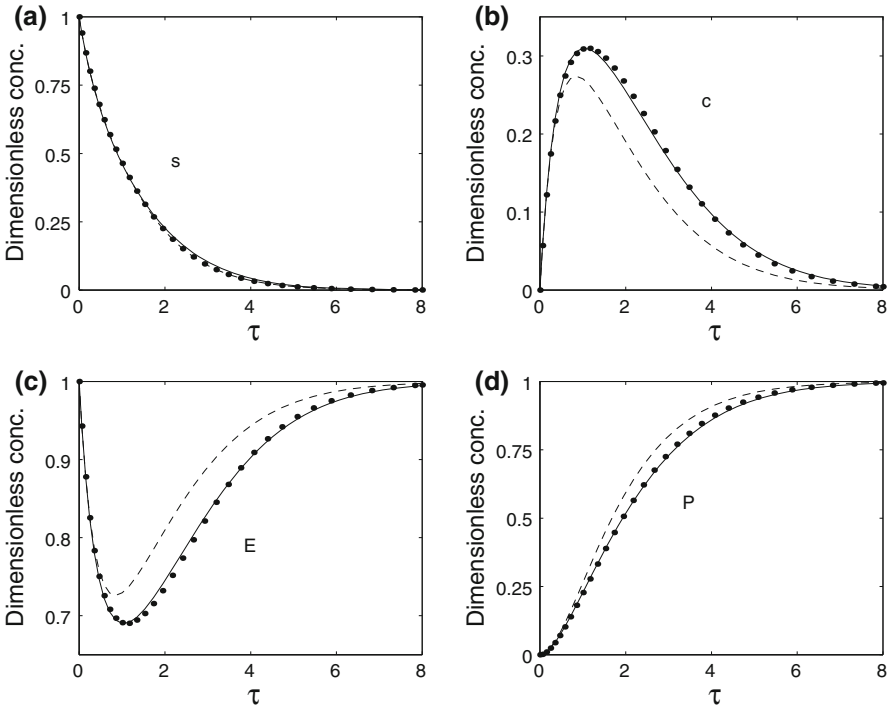

Fig. 6 Curves of **a** the substrate concentration s, **b** enzyme-substrate complex concentration c, **c** enzyme concentration E and **d** product concentration P, for parameters $K = \varepsilon = 1$ and $\lambda = 0$. The *solid curves* represent the numerical solution of Eqs. (13)–(15), *dots* were calculated with solutions (81)–(83), while the *dashed curves* represent the approximations (56)–(58)

mate expressions (56)–(58). Apart from the curves for the substract concentration, our approximate solutions are much more accurate than those from Sect. 3.

Finally, we comment some similarities and differences between our alternative homotopy construction and the Simple Iteration Method proposed by Khoshnaw [12]. In his procedure, which is in fact a method of successive approximations, the solution of the system of Eqs. (13)–(14) is approximated by

$$\frac{ds_{(n+1)}}{d\tau} = -\varepsilon s_{(n+1)} + \lambda\varepsilon c_{(n+1)} + \varepsilon s_{(n)} c_{(n)}, \tag{84}$$

$$\frac{dc_{(n+1)}}{d\tau} = -K c_{(n+1)} + s_{(n+1)} - s_{(n)} c_{(n)}, \tag{85}$$

for $n = 0, 1, 2, \ldots$. In the first step, take $s_{(0)} = 1$, $c_{(0)} = 0$ and solve for $s_{(1)}$, $c_{(1)}$. This results in the same system as Eqs. (64)–(65). In the second step, take $n = 1$ and solve for $s_{(2)}$, $c_{(2)}$ using the solutions of $s_{(1)}$, $c_{(1)}$. This is equivalent to the system of Eqs. (71)–(72). However, there is a crucial difference between both methods. In the Simple Iteration Method, each iteration $s_{(n)}$, $c_{(n)}$ is taken as a better approximation to the true solution, while in our homotopy approximation method, the final approximation is the

sum of the "iterates". Moreover, if we take the coefficients of p^2 in our alternative homotopy, the next system of equations to solve is

$$\frac{ds_2}{d\tau} + \varepsilon s_2 - \lambda\varepsilon c_2 = \varepsilon s_0 c_1 + \varepsilon s_1 c_0, \tag{86}$$

$$\frac{dc_2}{d\tau} + K c_2 - s_2 = -s_0 c_1 - s_1 c_0, \tag{87}$$

which is different from solving the system (84)–(85) for $s_{(3)}$, $c_{(3)}$.

5 Discussion

Using homotopy perturbation method, we extended the approximate analytical solutions of the differential equations describing the time evolution of the enzyme reaction (1) to include cases for which the results of earlier works were not valid. We also proposed a modification of the traditional homotopy equations to derive alternative analytical approximations of the enzyme kinetics equations. These solutions, which are first-order approximations with respect to the embedding parameter p, provide more accurate results than the second-order approximate expressions obtained by other authors for the same values of the parameters. We also commented the similarities and differences between our approach and the Simple Iteration Method proposed by Khoshnaw [12].

Although our alternative approximate solutions give better results, we found that they deviate progressively from the numerical solutions as the value of the parameter ε becomes smaller. Thus, they also have a limited applicability. One may argue that, to obtain better approximations, one only needs to include higher order terms in the homotopy perturbation expansion. However, the amount of calculations and the size of the resulting expressions increases very fast. Ideally, we would like to have an approximate analytical solution that could be, at the same time, simple and accurate for a wide range of values of the parameters. This poses an interesting question: can one construct a non-trivial homotopy for the enzyme kinetics equations (13)–(14) that yield even better approximate solutions and that are simpler than those already found? One may also not forget that we considered only one of the most basic enzymatic reaction mechanisms. In living organisms, much more complex reactions involving enzymes are the rule rather than the exception, and their kinetics is described by more complicated systems of differential equations that are even harder to analyse.

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