

## Research Article

# An Analytical Approximate Solution for the Quasi-Steady State Michaelis-Menten Problem

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This article utilizes perturbation method (PM) to find an analytical approximate solution for the Quasi-Steady-State Michaelis-Menten problem. From the comparison of Figures and absolute error values, between approximate and numerical solutions, it is shown that the obtained solutions are accurate, and therefore, they explain the general behaviour of the Michaelis-Menten mechanism.

## 1. Introduction

The Michaelis-Menten mechanism is employed to model the kinetics of enzyme-catalyzed reactions in cases where the concentration of substrate is greater than the concentration of enzyme. The importance of such reactions relies on the fact that the majority of cell processes require enzymes to get a significant rate [1, 2].

Enzymes are protein molecules that act as catalysts with the purpose to accelerate chemical reactions in living organisms. These enzymes work on specific molecules denominated substrates. Without the existence of enzymes, most chemical reactions that keep living organisms alive would be slow to sustain life [2].

Thus, haemoglobin in red blood cells is an enzyme, while the oxygen is the substrate with which it combines. Other example would be the case of oxidation of glucose; this process provides water, carbon dioxide, and energy; nevertheless, it is extremely slow when it is carried out exposed just to open air and there is no appreciable oxidation after years of exposure [1, 2].

Enzymes play a significant role in the regulation of biological processes; they work as activators or inhibitors in a reaction. To comprehend their role in the rate of reactions, the study of enzyme kinetics is necessary; its study consists fundamentally in understanding the temporary behaviour of the several reactions and the conditions that influence them [1]. This article proposes a study of the Michaelis-Menten mechanism, which describes one of the most basic enzymatic reactions starting from perturbation method technique.

The classical perturbation method (PM) is a pioneer technique to solve some cases of nonlinear differential equations. PM was proposed by S. D. Poisson and later extended by J. H. Poincare. Even though PM appeared in the early 19th century, the application of this method to analyse nonlinear problems was not performed until later on that century. The most important application of this method was in the subject of fluid mechanics, celestial mechanics, and aerodynamics [3, 4].

In general, we will suppose that a differential equation can be expressed as the sum of two parts, one linear and one

nonlinear. The nonlinear part is considered as a small perturbation through a small perturbation parameter. As a matter of fact, this last assumption is considered as a disadvantage of PM. As a consequence, other methods have emerged to study the problem of finding approximate solutions for some nonlinear problems such as variational approaches [5, 6], tanh method [7], exp-function [8, 9], Adomian's decomposition method [10, 11], parameter expansion [12], homotopy perturbation method [13–17], homotopy analysis method [18, 19], Boubaker Polynomials Expansion Scheme (BPES) [20, 21], among many others.

Although PM provides, generally, better results for small perturbation parameters  $\varepsilon \ll 1$ , we will see that our approximate solution is handy and has good precision even for relatively large values of the perturbative parameter, such as what was reported in [22–24]. This work will employ PM with the purpose to get an approximate solution for the Michaelis-Menten mechanism previously mentioned.

The rest of this work is presented as follows. Section 2 introduces the basic idea of PM method. In Section 3, we will present the basic enzyme reaction proposed by Michaelis and Menten. Section 4 provides an analytical approximate solution for a Quasi-Steady State Approximation Michaelis-Menten problem. Section 5 discusses the results obtained. A brief conclusion is given in Section 6.

## 2. Basic Idea of Perturbation Method

Let the differential equation of one dimensional nonlinear system be in the form

$$L(x) + \varepsilon N(x) = 0, \quad (1)$$

where we assume that  $x$  is a function of one variable  $x = x(t)$ ;  $L(x)$  is a linear operator which, in general, contains derivatives with respect to  $t$ ;  $N(x)$  is a nonlinear operator; and  $\varepsilon$  is a small parameter.

Assuming that the nonlinear term in (1) is a small perturbation and that the solution for (1) can be written as a power series in terms of the perturbative parameter  $\varepsilon$ :

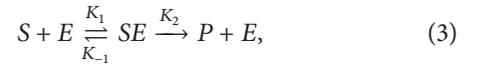
$$x(t) = x_0(t) + \varepsilon x_1(t) + \varepsilon^2 x_2(t) + \dots \quad (2)$$

Then, by substituting (2) into (1) and equating terms having identical powers of  $\varepsilon$ , we obtain a number of differential equations that can be integrated, recursively, to find the functions:  $x_0(t), x_1(t), x_2(t) \dots$

## 3. Michaelis-Menten Enzyme Kinetics

One of the most important enzyme reactions was proposed by Leonor Michaelis and Maud Leonora Menten [1, 25]. It involves a substrate  $S$ , reacting with an enzyme  $E$  to form an enzyme-substrate complex  $SE$ . It is a reversible reaction with forward and backward rate constants  $k_1$  and  $k_{-1}$ , respectively (see below).

The complex  $SE$  undergoes unimolecular decomposition to form irreversibly a product  $P$  and the enzyme  $E$ . This autocatalytic reaction is expressed as



and this equation says that one molecule of  $S$  combines with one molecule of  $E$ , to form one molecule of  $SE$ , which produces one molecule of  $P$  and one molecule of  $E$  again.

Next, we will apply to (3) the law of mass action, which says that the rate of reaction is proportional to the product of the concentrations of the reactants [1, 2].

For the sake of simplicity, we will use the same symbols to denote the concentrations; thus

$$\begin{aligned} S &= [S], \\ E &= [E], \\ C &= [SE], \\ P &= [P], \end{aligned} \quad (4)$$

where  $[\ ]$  denotes concentration.

The law of mass action applied to (3) leads to one equation for each reactant; thus, the relevant chemical reaction equations are

$$\begin{aligned} \dot{S} &= -k_1 ES + k_{-1} C, \\ \dot{E} &= -k_1 ES + (k_{-1} + k_2) C, \\ \dot{C} &= k_1 ES - (k_{-1} + k_2) C, \\ \dot{P} &= k_2 C, \end{aligned} \quad (5)$$

where the dot denotes differentiation with respect to  $t$ . The initial values of concentrations are

$$\begin{aligned} S(0) &= S_0, \\ E(0) &= E_0, \\ C(0) &= 0, \\ P(0) &= 0. \end{aligned} \quad (6)$$

The  $k$ 's, called rate constants, are constants of proportionality in the application of the law of mass action.

In order to show that system (5) can be reduced to two coupled ordinary differential equations (ODES) for  $S(t)$  and  $C(t)$ , we add the second and third equations of (5), to obtain

$$\dot{E} + \dot{C} = 0, \quad (7)$$

and after integrating (7) we get,

$$E(t) + C(t) = E_0, \quad (8)$$

or

$$E(t) = -C(t) + E_0. \quad (9)$$

The above equation denotes a conservation law for  $E(t)$ . It is expected that since  $E$  is a catalyst and it only facilitates the reaction, therefore, its concentration has to be constant.

By substituting (9) into the first and third equations of (5), we get the following system:

$$\begin{aligned}\dot{S} &= -k_1 E_0 S + (k_1 S + k_{-1}) C, \\ \dot{C} &= k_1 E_0 S - (k_1 S + k_{-1} + k_2) C.\end{aligned}\quad (10)$$

We note that the last equation of (5) is uncoupled from other three and can be expressed as follows:

$$P(t) = k_2 \int_0^t C(t') dt'. \quad (11)$$

Equation (11) determines  $P(t)$ , once  $C(t)$  is known.

Next, we will obtain a dimensionless form of (10), by introducing the quantities [1, 2]

$$\begin{aligned}\tau &= k_1 E_0 t, \\ x(\tau) &= \frac{S(\tau)}{S_0}, \\ y(\tau) &= \frac{C(\tau)}{E_0}, \\ \lambda &= \frac{k_2}{k_1 S_0}, \\ K &= \frac{k_{-1} + k_2}{k_1 S_0} \equiv \frac{K_M}{S_0}, \\ \varepsilon &= \frac{E_0}{S_0}.\end{aligned}\quad (12)$$

After substituting (12) into (10), we get the dimensionless system

$$\begin{aligned}\dot{x}(\tau) &= -x + (K - \lambda) y + xy, \quad x(0) = 1, \\ \varepsilon \dot{y}(\tau) &= x - Ky - xy, \quad y(0) = 0,\end{aligned}\quad (13)$$

where  $K_M$  is called the Michaelis constant [1, 2] and the dot denotes differentiation with respect to  $\tau$ . It is relevant to note that (12) implies the inequality  $K - \lambda > 0$ .

Although (13) does not have an exact analytical solution there exists a useful approximation for this system, noting that in many biological process [1, 2] a very small amount of enzyme is required in a reaction, in comparison to the amount of substrate. This implies that  $\varepsilon \ll 1$  (see (12)), so that, neglecting the term  $\varepsilon \dot{y}(\tau)$  of (13), we get  $y$  in terms of  $x$  as follows:

$$y = \frac{x}{K + x}. \quad (14)$$

Substituting (14) into the first equation of (13) yields

$$\dot{x} = -\frac{\lambda x}{K + x}. \quad (15)$$

Equations (14) and (15) define the Quasi-Steady State Approximation (QSSA).

Noting that  $x(0) = 1$ , it is clear from (14) that  $y$  does not satisfy the initial condition  $y(0) = 0$ , for which, it is expected that (14) results in a good approximation only for times not so close to initial  $\tau = 0$ .

Nevertheless, it results that there exists a more general condition for which QSSA is valid. This condition is expressed in terms of Michaelis constant  $K_M$  as follows [1]:

$$\frac{E_0}{S_0 + K_M} \cdot \frac{1}{1 + (k_{-1}/k_2) + (S_0 k_1/k_2)} \ll 1. \quad (16)$$

From this condition, we see that, even for a case, such that  $\varepsilon = E_0/S_0 = O(1)$ , (16) could be still satisfied, if  $K_M$  is large, such as it occurs in many reactions [1].

An alternative way to express (16), useful for this study, is in terms of some parameters defined by (12).

$$\frac{\varepsilon}{1 + K} \cdot \frac{1}{1 + (k_{-1}/k_2) + (S_0 k_1/k_2)} \ll 1. \quad (17)$$

Thus, the condition that  $K_M$  is large is also equivalent to  $K$  large values ( $K \gg 1$ ).

Despite its simple appearance, the nonlinear equation (15) does not admit an explicit exact solution. In order to obtain information, numerical methods are used, which require the integration of (15) to obtain an implicit solution for  $x(\tau)$ , as follows:

$$x(\tau) + K \ln x(\tau) = 1 - \lambda \tau. \quad (18)$$

Next, information is obtained, integrating (18) numerically for different values of time  $\tau$ .

From the above it is clear that the mathematical description of QSSA is just numerical until this point.

#### 4. An Analytical Approximate Solution for the Quasi-Steady State Approximation

Next, we will show that PM provides an efficient tool in order to get a good approximation for QSSA problem.

We will see that despite the approximated origin of (15), its solutions will have the required accuracy to be considered as one of the solutions for (13). As a matter of fact, we will see that it is also possible to employ these same solutions with the purpose of obtaining an approximate solution  $y = y(\tau)$ , from the solution of a linear equation.

In order to obtain an approximate solution to (15), we will start from the general hypothesis, on the validity of QSSA (16) (or (17)).

We begin rewriting (15) as

$$\dot{x} = -\frac{kx}{1 + \alpha x} = -kx(1 + \alpha x)^{-1}, \quad (19)$$

where we have defined

$$\begin{aligned}k &= \frac{\lambda}{K}, \\ \alpha &= \frac{1}{K}.\end{aligned}\quad (20)$$

Although this work assumes small  $\varepsilon$  values, QSSA requires, preferentially, large values of  $K$  and in this limit;  $\alpha$  can be employed as an adequate perturbation parameter (see (20)).

Employing the Newton's binomial formula, (19) gets the simpler form

$$\dot{x} + kx - \alpha kx^2 = 0, \quad (21)$$

where, for the sake of simplicity, we kept only the first order power of  $\alpha$ , since the rest of the terms contain higher powers of the mentioned perturbation parameter. Of course, in general, to get more accurate solutions it is necessary considering more terms of (19).

Identifying  $\alpha$  with the PM parameter, we assume a solution for (21) in the form

$$\begin{aligned} x(\tau) = & x_0(\tau) + \alpha x_1(\tau) + \alpha^2 x_2(\tau) + \alpha^3 x_3(\tau) \\ & + \alpha^4 x_4(\tau) + \dots \end{aligned} \quad (22)$$

(see (2)).

After substituting (22) into (21) and equating the terms with identical powers of  $\alpha$ , it can be solved for  $x_0(\tau), x_1(\tau), x_2(\tau), x_3(\tau), \dots$ , and so on. Later it will be seen that a precise handy result is obtained by keeping up to fourth order approximation.

$$\alpha^0) \dot{x}_0 + kx_0 = 0, \quad x_0(0) = 1, \quad (23)$$

$$\alpha^1) \dot{x}_1 + kx_1 - kx_0^2 = 0, \quad x_1(0) = 0, \quad (24)$$

$$\alpha^2) \dot{x}_2 + kx_2 - 2kx_0x_1 = 0, \quad x_2(0) = 0, \quad (25)$$

$y(\tau)$

$$= \left[ \frac{e^{-k\tau} + \alpha(e^{-k\tau} - e^{-2k\tau}) + \alpha^2(e^{-k\tau} - 2e^{-2k\tau} + e^{-3k\tau}) + \alpha^3(e^{-k\tau} - 3e^{-2k\tau} + 3e^{-3k\tau} - e^{-4k\tau}) + \alpha^4(3e^{-k\tau} - 4e^{-2k\tau} + 6e^{-3k\tau} - 4e^{-4k\tau})}{K + e^{-k\tau} + \alpha(e^{-k\tau} - e^{-2k\tau}) + \alpha^2(e^{-k\tau} - 2e^{-2k\tau} + e^{-3k\tau}) + \alpha^3(e^{-k\tau} - 3e^{-2k\tau} + 3e^{-3k\tau} - e^{-4k\tau}) + \alpha^4(3e^{-k\tau} - 4e^{-2k\tau} + 6e^{-3k\tau} - 4e^{-4k\tau})} \right] \quad (36)$$

Next, we consider, as a case study, the value of the parameters  $\lambda = 0.1, K = 8, \varepsilon = 0.1$  ( $\alpha = 0.125, k = 0.0125$ ) in such way that (35) and (36) get the form

$$x(\tau) = -0.001953125e^{-0.05\tau} + 0.021484375e^{-0.0375\tau} - 0.162109375e^{-0.025\tau} + 1.142578125e^{-0.0125\tau} \quad (37)$$

$$y(\tau) = \left[ \frac{-0.001953125e^{-0.050\tau} + 0.021484375e^{-0.0375\tau} - 0.162109375e^{-0.0250\tau} + 1.142578125e^{-0.01250\tau}}{8 - 0.001953125e^{-0.050\tau} + 0.021484375e^{-0.03750\tau} - 0.162109375e^{-0.0250\tau} + 1.142578125e^{-0.01250\tau}} \right] \quad (38)$$

From Figure 1 it is clear that the numerical solution and analytical approximate solution (37) and (38) are in good agreement, but  $y(\tau)$  given by (38) does not satisfy the initial

$$\alpha^3) \dot{x}_3 + kx_3 - 2kx_0x_2 - kx_1^2 = 0, \quad x_3(0) = 0, \quad (26)$$

$$\alpha^4) \dot{x}_4 + kx_4 - 2kx_0x_3 - 2kx_1x_2 = 0, \quad x_4(0) = 0, \quad (27)$$

$$\vdots \quad (28)$$

Thus, after solving iteratively (23)–(27) we get

$$x_0(\tau) = e^{-k\tau}, \quad (29)$$

$$x_1(\tau) = e^{-k\tau} - e^{-2k\tau}, \quad (30)$$

$$x_2(\tau) = e^{-k\tau} - 2e^{-2k\tau} + e^{-3k\tau}, \quad (31)$$

$$x_3(\tau) = e^{-k\tau} - 3e^{-2k\tau} + 3e^{-3k\tau} - e^{-4k\tau}, \quad (32)$$

$$x_4(\tau) = 3e^{-k\tau} - 4e^{-2k\tau} + 6e^{-3k\tau} - 4e^{-4k\tau} - e^{-5k\tau}, \quad (33)$$

$$\vdots \quad (34)$$

By substituting (29)–(33) into (22) we obtain a handy fourth order approximation for the solution of (21), as it is shown

$$\begin{aligned} x(\tau) &= e^{-k\tau} + \alpha(e^{-k\tau} - e^{-2k\tau}) \\ &+ \alpha^2(e^{-k\tau} - 2e^{-2k\tau} + e^{-3k\tau}) \\ &+ \alpha^3(e^{-k\tau} - 3e^{-2k\tau} + 3e^{-3k\tau} - e^{-4k\tau}) \\ &+ \alpha^4(3e^{-k\tau} - 4e^{-2k\tau} + 6e^{-3k\tau} - 4e^{-4k\tau} - e^{-5k\tau}). \end{aligned} \quad (35)$$

The corresponding value of  $y(\tau)$  is obtained by substituting (35) into (14)

condition  $y(0) = 0$ ; therefore we will provide a way to improve it.

After directly adding the two equations (13), we obtain

$$\varepsilon \dot{y}(\tau) + \lambda y = -\dot{x}(\tau), \tag{39}$$

unlike (21), we note that (39) was obtained without employing any kind of approximated process.

Since the proposed solution (37) for  $x(\tau)$  provided a good accuracy, next we propose to substitute (35) into (39), in order obtain to a linear differential equation for  $y(\tau)$ . (We would expect good results considering adequate values of  $\varepsilon$  and  $K$ .)

$$\begin{aligned} \varepsilon \dot{y}(\tau) + \lambda y &= ke^{-k\tau} + \alpha k(e^{-k\tau} - 2e^{-2k\tau}) \\ &+ \alpha^2 k(e^{-k\tau} - 4e^{-2k\tau} + 3e^{-3k\tau}) \\ &+ \alpha^3 k(e^{-k\tau} - 6e^{-2k\tau} + 9e^{-3k\tau} - 4e^{-4k\tau}). \end{aligned} \tag{40}$$

Next, we will get approximate solutions for  $x$  and  $y$  by substituting, for instance, the following sets of parameters:

$$\begin{aligned} x(\tau) &= -0.14052755e^{-0.22222\tau} + 0.0173754e^{-0.33333\tau} - 0.00198140e^{-0.44444\tau} - 0.00015241e^{-0.55555\tau} \\ &+ 1.12528577e^{-0.11111\tau} \\ y(\tau) &= -0.00005897 \left( \begin{aligned} &-2130.75563672e^{22.11111\tau} + 534.87165124x10^{-7}e^{22\tau} \\ &-99.70426444e^{21.88888\tau} + 15.23705819e^{21.77777\tau} \\ &+ 1.47261509e^{21.66666} + 1678.87857663 \end{aligned} \right) e^{-22.22222\tau}. \end{aligned} \tag{41}$$

and for the second set

$$\begin{aligned} x(\tau) &= -0.3104e^{-0.52\tau} + 0.0736e^{-0.78\tau} - 0.0144e^{-1.04\tau} - 0.0016e^{-1.3\tau} + 1.2528e^{-0.26\tau}; \\ y(\tau) &= -0.000039528 \left( \begin{aligned} &-6396.29648664e^{28.62888\tau} + 3198.60577169e^{28.36888\tau} \\ &-1148.17140038e^{28.10888\tau} + 302.31935032e^{27.84888\tau} \\ &+ 42.38450461e^{27.58888\tau} + 4001.15826039 \end{aligned} \right) e^{-28.88888\tau}. \end{aligned} \tag{42}$$

### 5. Discussion

The aim of this study was to explore the possibility of finding analytical approximate solutions for the Michaelis-Menten enzyme kinetics problem. The study of this problem is relevant, because it involves enzyme reactions, and the most of the cell processes require enzymes to obtain a significant rate. Because the nonlinear system (13) has no exact analytical solution, we proposed PM method in order to get a perturbative solution for QSSA (see (14) and (15)).

In order to test the potentiality of PM to describe QSSA, we considered as case study the values of the parameters  $\lambda = 0.1$ ,  $K = 8$ , and  $\varepsilon = 0.1$  ( $\alpha = 0.125$ ,  $k = 0.0125$ ) (note that the condition  $K > \lambda$  is satisfied and  $\varepsilon$  small). Although

$$\begin{aligned} \lambda &= 1, \\ K &= 9, \end{aligned} \tag{41}$$

$$\begin{aligned} \varepsilon &= 0.045 \left( \alpha = \frac{1}{9}, k = \frac{1}{9} \right), \\ \lambda &= 1.3, \\ K &= 5, \end{aligned} \tag{42}$$

$$\varepsilon = 0.045 \left( \alpha = \frac{2}{3}, k = \frac{13}{50} \right)$$

(where we have taken into account the perturbative character of  $\varepsilon$ ).

The unknown function,  $x$ , is determined for each case, by substituting the above parameters into (35), while the corresponding  $y$  is obtained, by solving (40) through elementary methods.

The solutions for the first set of parameters (41) are given by

we obtained a handy accurate approximate solution in almost the entire domain of  $\tau$  (see Figure 1), (38) does not satisfy the initial condition  $y(0) = 0$  and its precision is subject, in principle, for times not too close to  $\tau = 0$ .

Although (38) failed, which was assumed from the beginning for QSSA (since we adopted the approximate result (14)), we employed the approximate solution (35) for  $x$ , as starting point to obtain a better analytical approximation for  $y$  (in fact, since (21) was obtained after keeping only first order power of  $\alpha$  from Newton's binomial formula applied to (19), we considered as case studies values of  $\alpha$  less than one, so that good approximations were expected for  $x$ , since (unlike  $y$ ) the solution (35) for the ODE (21) satisfies the correct initial condition  $x(0) = 1$ ). With this purpose, we substituted (35)

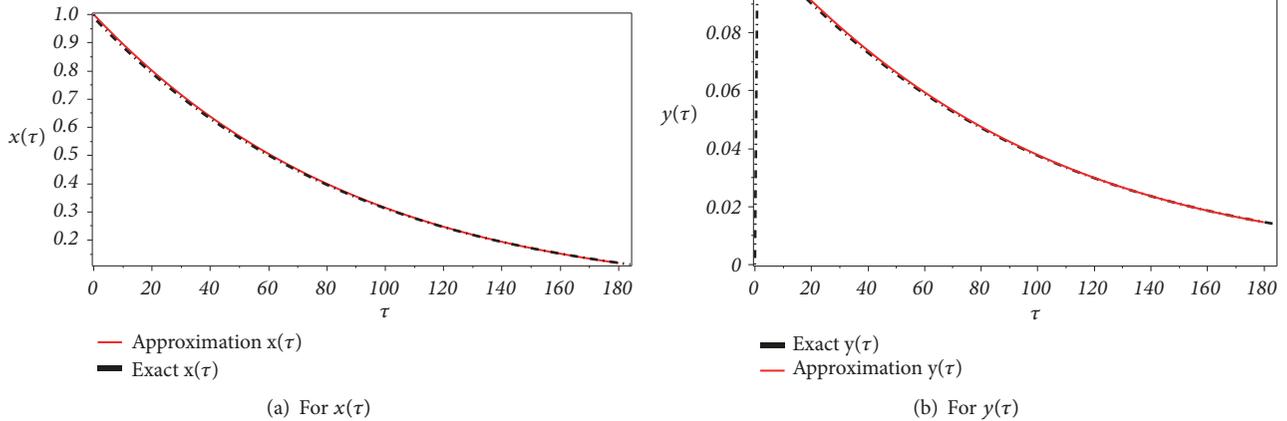


FIGURE 1: Comparison between numerical solutions and approximations (37) and (38).

into (39) (obtained without employing approximations) to give rise the linear differential equation (40).

Figures 2 and 3 show the comparison between numerical and approximate solutions for parameter sets (41) and (42), respectively, for which the condition  $K > \lambda$  was satisfied.

Although it is clear from the figures mentioned that the proposed approximate solutions have good precision, it is necessary to provide a more analytical criterion to ensure the accuracy of our solutions. For this purpose, Figures 4 and 5 show the absolute errors that result from using the approximations proposed in this paper. Thus, for the first set of parameters (41) we note that the absolute maximum errors committed by using  $x$  and  $y$ , respectively (see (43)), are of the order of 0.0045 and 0.01, while for the second set (42), the absolute errors for  $x$  and  $y$  (see (44)) reach maximum values of 0.012 and 0.0155. From all the mentioned above, the most complicated region to model just right at the beginning seems natural, especially for the case of (43) and (44) for the variable  $y$  (see Figures 4 and 5). However, it is worth noting that our procedure provides flexibility to get more accuracy if necessary, adding more terms to (21) and increasing higher order terms in the approximate solution (35), which makes it useful for practical applications. Thus, from Figures 2-5 we deduced that our approximations (43) and (44) have good precision and they explain the general behaviour of Michaelis-Menten mechanism in the limit studied.

A relevant fact to mention is that although the first case (41) belongs to the domain of validity ( $\alpha$  small), (42) corresponds to  $\alpha \cong 0.67$ , which cannot be considered small at all and any way we got an analytical approximation with good precision, which provides a certain additional margin of applicability to our proposed solutions. Therefore, the coupled system of differential equations (21) and (39) preserves a lot of the chemical information content in the nonlinear system (13) (for QSSA approximation).

Equations (44), for instance, correctly describe the asymptotic final state  $x \rightarrow 0$  and  $y \rightarrow 0$  as  $\tau \rightarrow \infty$ ; this implies that both substrate and the substrate-enzyme

complex concentrations tend to zero in this limit. This is expected, because reaction (3) converts S into a product P.

A brief qualitative description based on [1] is as follows: from (21), it is clear that, in the limit  $\tau \rightarrow 0$ ,  $dx/d\tau < 0$  (because  $x(0) = 1$  and  $|\alpha| < 1$ ); thus,  $x$  begins to decrease from its initial value  $x(0) = 1$ . On the other hand, since  $-dx/d\tau > 0$  near  $\tau \cong 0$ ,  $\varepsilon > 0$  and  $y(0) = 0$ ; then, (39) implies that  $dy/d\tau > 0$ . What is more,  $y$  increases from its initial value  $y(0) = 0$  until a maximum value, which corresponds to the condition  $dy/d\tau = 0$ ; from (39)  $y = -\dot{x}/\lambda$  is obtained. Even further, in accordance with the second equation of (13), this value is given also by  $y = x/(K + x)$ .

Besides, from conservation law (9) and, for instance, of  $y(\tau)$  in (44), we can describe the general behaviour for  $E(t)$ . Enzyme concentration decreases from its initial value  $E_0$ , while the one of  $C$  is increased to its maximum value. From this moment,  $C$  decreases and  $E$  asymptotically approaches again to its initial value (see (9)).

From all the above, it is highlighted that the first order ordinary differential equations system, composed by (21) and (39) besides providing many information of the phenomenon under study, is simpler than (13) and very useful in the search for approximate solutions in the domain of QSAA.

Finally we note that the loss of information assumed, by using (14) and (15) instead of system (13), is partly reduced, for the case of large values of  $K$ , because the incorrect initial condition resulting from (14),  $y(0) = 1/K + 1$  (since  $x(0) = 1$ ), differs less from the real value  $y(0) = 0$  as  $K$  increases. These considerations and the fact that (14) has the correct asymptotic behaviour undoubtedly contributed to the accuracy of the proposed results.

## 6. Conclusions

The main contribution of this work was the proposal to employ the pair of differential equations (21) and (39), which provided handy analytical approximate solutions, for the QSSA Michaelis-Menten mechanism, through the whole

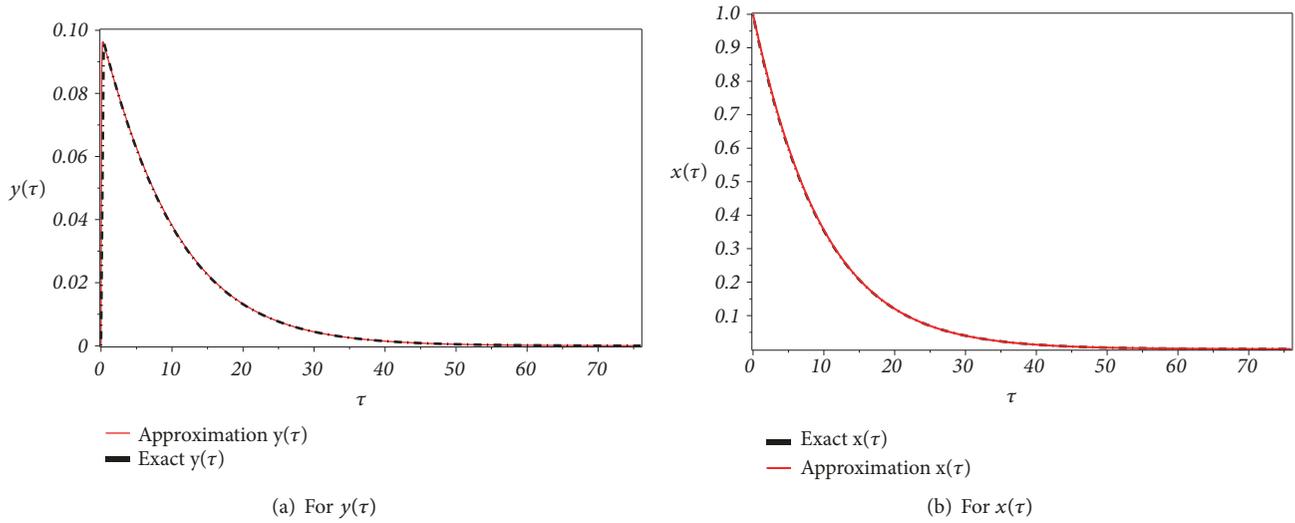


FIGURE 2: Comparison between numerical solutions and approximations (43).

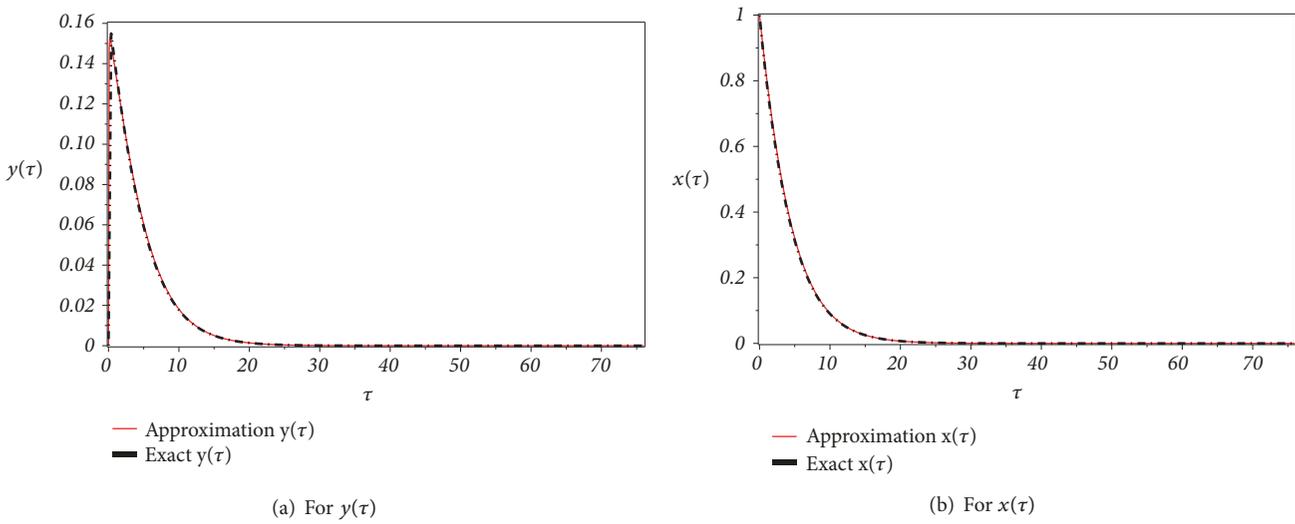


FIGURE 3: Comparison between numerical solutions and approximations (44).

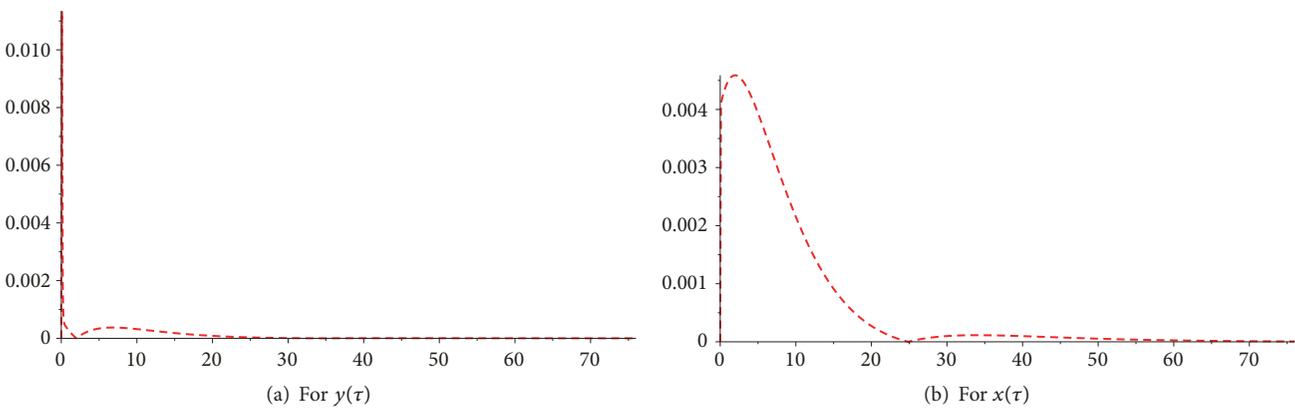


FIGURE 4: Absolute error for solutions (43).

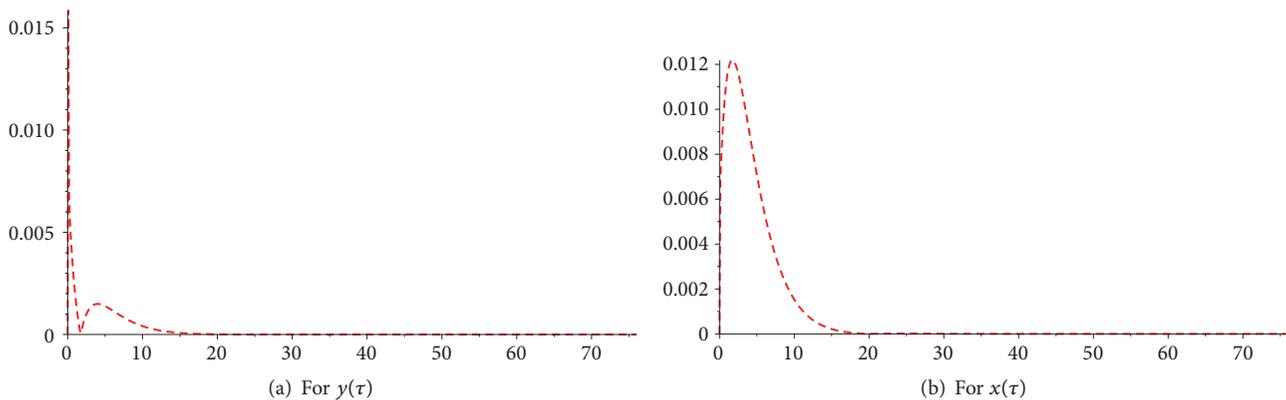


FIGURE 5: Absolute error for solutions (44).

domain of time  $t \geq 0$ . It is worth mentioning the notable roll of PM method, whose application contributed to obtain an accurate analytical approximate solution for (21). Although this work assumed large values of  $K$ , this condition is not so restrictive because this case occurs in many reactions [1]. Besides, our case studies showed the potentiality of (21) and (39), even for values of  $K > 1$ , but not  $K \gg 1$ . Finally, given the flexibility to improve precision if necessary, it is expected that proposal of this article will be useful for practical applications of the studied enzyme reactions.

### Data Availability

All data generated or analysed during this study is included within this research article.

### Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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