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Solution method for the transformed time-dependent Michaelis–Menten enzymatic reaction model

Ronald Li · Robert A. Van Gorder · Kristina Mallory · Kuppalappalle Vajravelu

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Abstract The dynamic form of the Michaelis–Menten enzymatic reaction equations provides a time-dependent model in which a substrate S reacts with an enzyme E to form a complex C which is in turn converted into a product P and the enzyme E. In the recent paper [Mallory and Van Gorder in J Math Chem 52: 222–230, 2014], it was shown that this system of four nonlinear equations can be reduced to a single nonlinear differential equation, which is simpler to solve numerically than the system of four equations. Qualitative properties of solutions were discussed, and stability results were given. In the present paper, we apply the optimal homotopy analysis method to the solution of this problem in order to obtain quantitative results. To do so, we transform the governing equation into a form that is more amenable to analysis. From the homotopy solutions, we are then able to study the effects of the model parameters on the solutions to the dynamic Michaelis–Menten enzymatic reaction equations. The results demonstrate the accuracy and efficiency of the approach, with residual errors of 10^{-6}–10^{-10} by considering relatively few iterations of the method. Therefore, the optimal homotopy analysis method is shown to be a rather useful tool for constructing analytical solutions to the dynamic Michaelis–Menten enzymatic reaction equations.

Keywords Dynamic Michaelis–Menten model · Nonlinear dynamics · Stability · Enzyme reactions

R. Li · R. A. Van Gorder (✉) · K. Mallory · K. Vajravelu
Department of Mathematics, University of Central Florida, Orlando, FL 32816-1364, USA
e-mail: rav@knights.ucf.edu

1 Introduction

The dynamic form of the Michaelis–Menten enzymatic reaction model [1] reads

$$\begin{aligned}\frac{dS}{dt} &= -k_1 ES + k_{-1} C\,,\\ \frac{dE}{dt} &= -k_1 ES + (k_{-1} + k_2) C\,,\\ \frac{dC}{dt} &= k_1 ES - (k_{-1} + k_2) C\,,\\ \frac{dP}{dt} &= k_2 C\,,\end{aligned} \tag{1.1}$$

where $S(t)$ is the concentration of a substrate, $E(t)$ is the concentration of an enzyme, $C(t)$ is the concentration of the resulting complex, and $P(t)$ is the concentration of the resulting product. This is the time-dependent form of the model originally proposed by Michaelis and Menten [1], which is used to study enzyme kinetic reactions. Under this framework, a substrate S reacts with an enzyme E to form a complex C which is in turn converted into a product P and the enzyme E; the schematic is $E + S \rightleftharpoons C \rightarrow E + P$. Note that:

(i) $k_1 > 0$ is the rate of reaction governing the production of the complex from the substrate and the enzyme;
(ii) $k_{-1} > 0$ is the rate of reaction governing decomposition of the complex to the substrate and enzyme, and;
(iii) $k_2 > 0$ is the rate of reaction governing the breakdown of the complex into the product and the enzyme.

Let us label the initial conditions as $S(0) = S_0,\ E(0) = E_0,\ C(0) = 0$, and $P(0) = 0$. One can always introduce scaling of the functions and parameters so that the system (1.1) is non-dimensional.

A variety of solutions and solution methods have been brought to bear on the Michaelis–Menten enzymatic reaction model. Much of what is considered in the literature is either static or quasi-static solutions. Many authors have considered a quasi-steady state assumption [2–5]. Golicnik [6] presented solutions to a Michaelis–Menten model in terms of the Lambert $W(x)$ function. Later, the time-dependent problem was also considered by Golicnik [7]. Abu-Reesh [8] derived analytical equations for the optimal design of a number of membrane reactors in series performing enzyme catalyzed reactions described by Michaelis–Menten kinetics with competitive product inhibition.

For the time-dependent dynamic models, closed-form solutions are not possible, and therefore numerical or approximation methods are needed. The homotopy perturbation method has been applied to the study of enzyme reaction models [9,10]. However, such solutions may or may not converge since the homotopy perturbation method permits no way to control the error inherent in the approximations (see, for instance [11,12], for examples of when the homotopy perturbation method does not converge). Some limitations were discussed in [10], and it was shown that the homo-

topy perturbation method solutions are good for some parameter regimes and poor for others. On the other hand, the homotopy analysis method often can be made to converge, since it includes a type of convergence control parameter. Recently, Motsa et al. [13] considered this approach, and obtained homotopy analysis solutions through a hybrid spectral approach. However, no comprehensive error analysis was conducted on how to best select the convergence control parameter, h.

In a recent paper, Mallory and Van Gorder [14] were able to reduce the nonlinear differential equation system (1.1) into a single nonlinear ordinary differential equation. Using this equation, they were able to succinctly study solutions of (1.1) qualitatively. They were also able to determine stability properties of solutions to (1.1), demonstrating that such solutions tend toward equilibirum values (for large time) and that such solutions are globally asymptotically stable.

The focus of the present paper is to conduct a more quantitative analysis of the system qualitatively studied in [14]. To do so, we apply the homotopy analysis method (see [15–20]). This method has proven useful for describing analytical solutions to a number of interesting problems: some specific examples include nonlinear equations arising in heat transfer [21–24], fluid mechanics [25–32], solitons and integrable models [33–36], nanofluids [37,38] and the Lane–Emden equation which appears in stellar astrophysics [39–42], to name a few areas. One modern development on the method would be the use of the convergence control parameter in order to minimize the error inherent in the approximate analytical solutions. This method is referred to as the *optimal* homotopy analysis method, and this approach has recently been used to find error-minimizing approximate solutions to a variety of nonlinear equations (see [43–48]). Using this approach, we shall be able to obtain analytical approximations with minimal error. Often, the residual error can be reduced to between order 10^{-6} and order 10^{-10} after relatively few iterations of the method.

The paper is organized as follows. In Sect. 2, we give a background discussion and derivation of the single ODE we are interested in solving. We shall put the equation derived in Mallory and Van Gorder [14] into a specific form which will aid in our computational approach. Then, in Sect. 3, we obtain accurate approximate solutions via the optimal homotopy analysis method. These solutions are shown to have minimal residual errors even after relatively few terms are calculated. Therefore, the computational approach is both accurate and efficient for solving the problem. In Sect. 4, we give some concluding remarks.

2 Background and derivation of the governing equation

Consider Eq. (2.5) in Mallory and Van Gorder [14], which puts the system (1.1) into a single second order nonlinear ordinary differential equation. For completeness, we include the equation here:

$$\frac{dE}{dt} = (k_1 E(t) + k_{-1} + k_2)(E_0 - E(t)) - k_1 S_0 E(t) + k_1 k_2 E(t) \int_0^t (E_0 - E(\tau)) d\tau. \tag{2.1}$$

This is an equation with a derivative and an integral in the unknown function $E(t)$. To remove the non-locality inherent in having an integral term, we may define

$$G(t) = \int_0^t (E_0 - E(\tau))d\tau \,. \tag{2.2}$$

Then, $G'(t) = E_0 - E(t)$ and $G''(t) = -E'(t)$, so Eq. (2.5) of Mallory and Van Gorder [14] reduces to an equation of the form

$$\frac{1}{k_1}G'' + (E_0 + S_0 + K_m)G' + k_1k_2E_0G - k_1G'^2 - k_1k_2GG' = k_1E_0S_0\,, \tag{2.3}$$

where

$$K_m = \frac{k_{-1} + k_2}{k_1} \tag{2.4}$$

is the Michaelis constant. Making the change of variables

$$G(t) = \frac{g(T)}{k_1}, \quad T = k_1t\,, \tag{2.5}$$

we have

$$g'' + (E_0 + S_0 + K_m)g' + \frac{k_2E_0}{k_1}g - g'^2 - \frac{k_2}{k_1}gg' = E_0S_0\,. \tag{2.6}$$

For the initial conditions, note that

$$G(0) = \int_0^0 (E_0 - E(\tau))d\tau = 0 \tag{2.7}$$

and

$$G'(0) = E_0 - E(0) = E_0 - E_0 = 0\,, \tag{2.8}$$

therefore, $g(0) = 0$ and $g'(0) = 0$. Hence we shall solve the initial value problem

$$\begin{aligned} &g'' + (E_0 + S_0 + K_m)g' + \frac{k_2E_0}{k_1}g - g'^2 - \frac{k_2}{k_1}gg' = E_0S_0\,,\\ &g(0) = 0\,,\ g'(0) = 0\,. \end{aligned} \tag{2.9}$$

Regarding the homotopy treatment, we should define the nonlinear operator by

$$N[g] = g'' + (E_0 + S_0 + K_m)g' + \frac{k_2E_0}{k_1}g - g'^2 - \frac{k_2}{k_1}gg' - E_0S_0\,. \tag{2.10}$$

The auxiliary linear operator should be chosen so that solutions decay as $T \to \infty$.

One may recover the meaningful solution by

$$E(t) = E_0 - G'(t) = E_0 - \frac{d}{dt}\frac{g(k_1 t)}{k_1} = E_0 - g'(k_1 t)\,. \tag{2.11}$$

Note that $E(0) = E_0$ ($g'(0) = 0$) and $E(t) \to E_0$ as $t \to \infty$ (if $g' \to 0$ as $T \to \infty$). For reasonable parametric values, the function g' should attain a maximal value, and then decay back to zero for large T. This is consistent with the numerical results in the literature.

Once g is found, we can recover the other quantities of interest, which can be found by

$$C(t) = g'(k_1 t)\,, \tag{2.12}$$

$$S(t) = S_0 - g'(k_1 t) + \frac{k_2}{k_1} g(k_1 t)\,, \tag{2.13}$$

$$P(t) = \frac{k_2}{k_1} g(k_1 t)\,. \tag{2.14}$$

From these solutions, we have the relation

$$S(t) + C(t) = S_0 + P(t)\,. \tag{2.15}$$

3 Solutions via homotopy analysis method

In order to solve Eq. (2.9), we turn to the homotopy analysis method (HAM) [15–20]. The main idea governing HAM is that the solution to a nonlinear equation can be expressed as an infinite sum of solutions to several linear sub-problems, where each sub-problem is associated with a specific deformation equation. This greatly aids in our ability to compute solutions to such problems.

We define the nonlinear operator N as

$$N[g(T)] = \frac{d^2 g}{dT^2} + (E_0 + S_0 + K_m)\frac{dg}{dT} + \frac{k_2 E_0}{k_1} g - \frac{dg}{dT}^2 - \frac{k_2}{k_1} g \frac{dg}{dT} - E_0 S_0\,, \tag{3.1}$$

which is just the nonlinear problem (2.9) we are interested in. Using the embedding parameter $q \in [0, 1]$, a linear homotpy is constructed between the two operators L and N, such that

$$(1 - q)L[\hat{g}(T; q) - g_0(T)] - qhN[\hat{g}(T; q)] = 0, \tag{3.2}$$

where L is an auxiliary linear operator of our choosing, $h \neq 0$ is an auxiliary parameter, g_0 is an initial guess, and $\hat{g}(T; q)$ is defined by

$$\hat{g}(T;q) = g_0(T) + \sum_{n=1}^{\infty} g_n(T) q^n. \tag{3.3}$$

Notice, at $q = 0$ and $q = 1$, we have $\hat{g}(T;0) = g_0(T)$ and $\hat{g}(T;1) = g(T)$, respectively. As q increases from 0 to 1, the solution $\hat{g}(T;q)$ varies continuously from the initial guess, $g_0(T)$, to the exact solution, $g(T)$. Therefore, the HAM solution which satisfies (2.9) takes the form

$$g(T) = g_0(T) + \sum_{n=1}^{\infty} g_n(T). \tag{3.4}$$

For our problem, we may select the auxiliary linear operator L as

$$L[g(T)] = \frac{d^2 g}{dT^2} + (E_0 + S_0 + K_m)\frac{dg}{dT} + \frac{k_2 E_0}{k_1} g, \tag{3.5}$$

and the initial guess to be the solution to $L[g(T)] = 0$, namely $g_0(T) = 0$. To obtain higher order equations of our HAM solution, we recursively solve the so called mth-order deformation equation

$$L[g_m(T) - \chi_m g_{m-1}(T)] = \frac{h}{(m-1)!}\left[\frac{d^{m-1} N[\hat{g}(T;q)]}{dq^{m-1}}\right]_{q=0}, \tag{3.6}$$

subject to the conditions $g_m(0) = 0$ and $g_m'(0) = 0$, where χ_m is defined by

$$\chi_m = \begin{cases} 0, & m \leqslant 1 \\ 1, & m > 1. \end{cases} \tag{3.7}$$

Finally, an Mth-order approximate solution can be obtained by the partial sum

$$g(T) \approx g_M(T) = g_0(T) + \sum_{n=1}^{M} g_n(T). \tag{3.8}$$

By applying Eqs. (3.6) and (3.7), the first few terms of the HAM solution to (2.9) are

$$g_1(T) = -h\frac{S_0 k_1}{k_2} \times \left[1 - \frac{(\alpha \cosh(\tfrac{1}{2}\alpha T) + (E_0 + S_0 + K_m)\sinh(\tfrac{1}{2}\alpha T))e^{-\frac{1}{2}(E_0+S_0+K_m)T}}{\alpha}\right] \tag{3.9}$$

$$g_2(T) = -(h^2 + h)\frac{S_0 k_1}{E_0 k_2} \times \left[1 - \frac{(\alpha \cosh(\tfrac{1}{2}\alpha T) + (E_0 + S_0 + K_m)\sinh(\tfrac{1}{2}\alpha T))e^{-\frac{1}{2}(E_0+S_0+K_m)T}}{\alpha}\right] \tag{3.10}$$

where α denotes the composite parameter

$$\alpha = \sqrt{(E_0 + S_0 + K_m)^2 - \frac{4k_2 E_0}{k_1}}\,. \tag{3.11}$$

Higher order terms of the series in (3.4) can be easily obtained by means of computer algebra system. For computational purposes, we utilize the Mathematica package BVPh 2.0, developed by Liao. For a more detailed description of the BVPh 2.0 package, the reader is referred to Liao [17].

3.1 Minimization of residual error

In treating $q \in [0, 1]$ as a small parameter, $\hat{g}(T; q)$ can be expanded in a Taylor series about q to obtain (3.3). The convergence of this series is dependent on the auxiliary parameter h. Although h has no physical meaning in the frame of the problem, it has been shown by Liao [18] that careful selection of h can control the region and rate of convergence of the HAM solution (3.4). The power of HAM lies in the flexibility of choosing the auxiliary parameters so as to guarantee convergence of the HAM solution. Recall that if (3.3) is convergent at $q = 1$, then we recover the solution to the original Eq. (2.9).

A straightforward way to select the optimal auxiliary parameter h is to examine the squared residual error. Recall in the previous section, we truncate our HAM solution up to some Mth term. Let

$$\epsilon_M(T^*) = |N[g_M(T)]|\Big|_{T*}, \tag{3.12}$$

denote the residual error of our Mth-order approximate HAM solution, taken at some time T^* in the domain. Then the sum of the residual error taken over the whole domain is

$$R_\epsilon(T) = \int_0^\infty |N[g_M(T)]| dT. \tag{3.13}$$

Is it often the case that the integration in (3.13) is too CPU intensive to compute, even for low order approximations. In practice, we evaluate the sum of the squared residual given by

$$E_M(h) = \int_0^{T^*} (N[g_M(T)])^2 dT, \tag{3.14}$$

taken up to some stopping time T^*. Therefore, the minimum of the squared residual E_M corresponds to the optimal choice for the auxiliary paramter h and thus the optimal approximate HAM solution. For a more in depth look at the squared residual error technique, the reader is referred to [20,47,48].

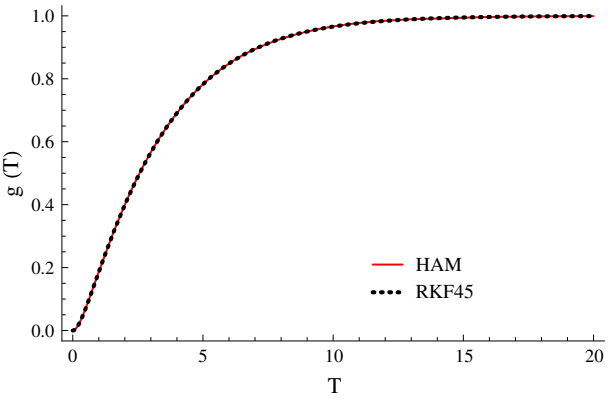

Fig. 1 Comparison of the HAM and numeric solutions for the case where $k_{-1} = k_1 = k_2 = 1$ and $E_0 = S_0 = 1$

3.2 Physically relevant numerical examples

In order to demonstrate the usefulness of the homotopy analysis method for solving the nonlinear equation (2.9), we shall give several specific examples. The system (1.1) can be scaled so that the initial quantities S_0 and E_0 may be taken to equal unity. Therefore, the parameters of interest are k_{-1}, k_1 and k_2, so we shall focus on these three parameters.

In Fig. 1, we provide a comparison of the HAM solution to a numerical solution obtained via the Runge–Kutta–Felhberg 4–5 method (denoted RKF45, see [49]), for the case where $k_{-1} = k_1 = k_2 = 1$ and $E_0 = S_0 = 1$. A plot of the corresponding residual error is given in Fig. 2, and this plot demonstrates that the error inherent in the approximation sharply decreases as additional terms are added to the analytical approximation. HAM solutions are plotted in Figs. 3, 4, and 5 to study the effects of varying the reaction rate parameter k. The residual error curves are included in Figs. 6 and 7 in order to illustrate the effect of addition additional terms in the HAM solutions. Optimal values of the convergence control parameter are given in Table 1, along with values of the minimized sum of squared residual errors. For all plots considered, we take the domain $0 \leq T \leq 20$. The maximal time value $T^* = 20$ is used for calculating the residual errors.

From the numerous examples considered here, we see that the optimal homotopy analysis method allows us to construct rather accurate solutions with relatively few iterations. While we have solved the problem (2.9), note that a solution g to this problem encodes all of the information needed to recover the solutions $S(t)$, $E(t)$, $C(t)$ and $P(t)$ for (1.1). Indeed, g can be used in equations (2.11)–(2.14), respectively, in order to obtain each of these functions.

4 Conclusions

We have solved the nonlinear equation (2.9) governing the transformed dynamic form of the Michaelis–Menten model by applying the optimal homotopy analysis method.

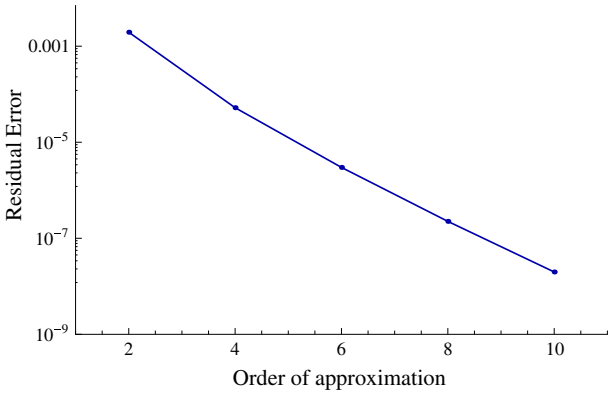

Fig. 2 Plot of the squared residual error versus order of approximation for the case where $k_{-1} = k_1 = k_2 = 1$ and $E_0 = S_0 = 1$

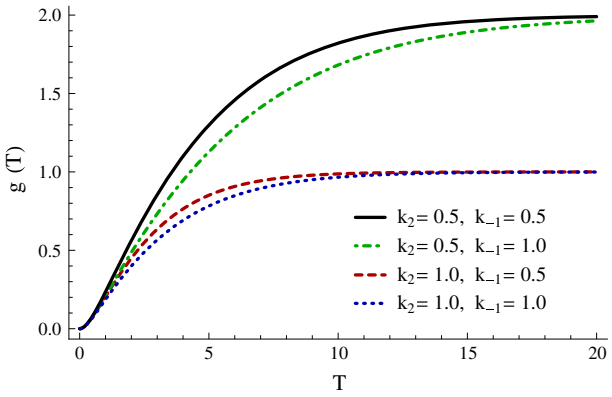

Fig. 3 Variations of the HAM solutions to Eq. (2.9) for different values of k_2 and k_{-1}. We fix the parameter value $k_1 = 1$ and $E_0 = S_0 = 1$

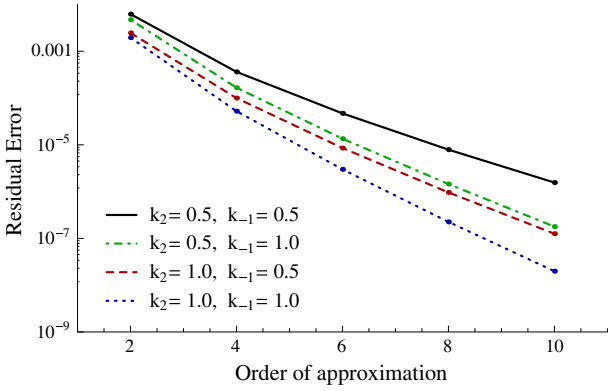

Fig. 4 Plot of the squared residual error versus order of approximation for various values of k_2 and k_{-1}. We fix the parameter value $k_1 = 1$ and $E_0 = S_0 = 1$

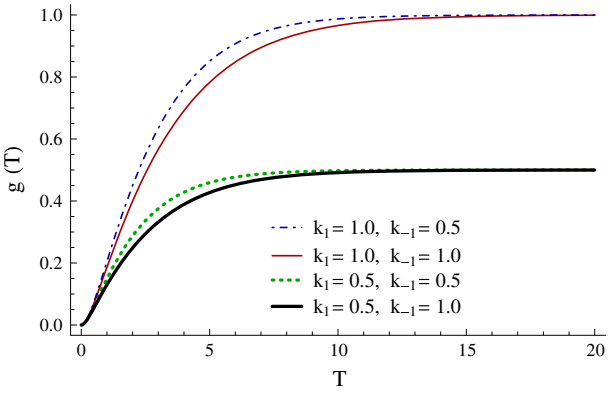

Fig. 5 Variations of the HAM solutions to Eq. (2.9) for different values of k_1 and k_{-1}. We fix the parameter value $k_2 = 1$ and $E_0 = S_0 = 1$

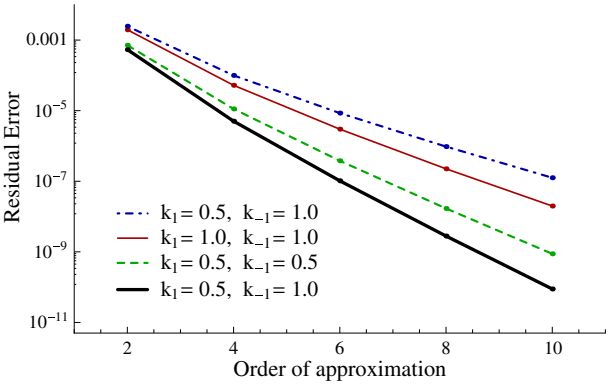

Fig. 6 Plot of the squared residual error versus order of approximation for various values of k_1 and k_{-1}. We fix the parameter value $k_2 = 1$ and $E_0 = S_0 = 1$

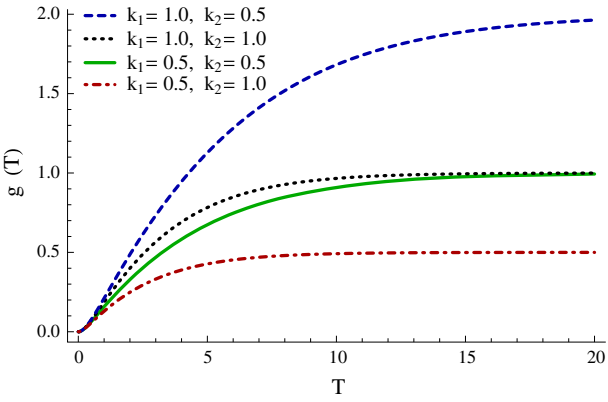

Fig. 7 Variations of the HAM solutions to Eq. (2.9) for different values of k_1 and k_2. We fix the parameter value $k_{-1} = 1$ and $E_0 = S_0 = 1$

Table 1 Optimal value of the convergence control parameter h^* and minimum squared residual E_M on the domain $0 \leq T \leq 20$ for different values of k

k_1	k_2	k_{-1}	h^*	E_{10}
1.0	0.5	0.5	−1.05997	1.560×10^{-6}
1.0	0.5	1.0	−1.04993	1.785×10^{-7}
1.0	1.0	0.5	−1.04689	1.257×10^{-7}
1.0	1.0	1.0	−1.03853	1.988×10^{-8}
1.0	1.0	0.5	−1.04689	1.257×10^{-7}
1.0	1.0	1.0	−1.03853	1.988×10^{-8}
0.5	1.0	0.5	−1.02919	8.801×10^{-10}
0.5	1.0	1.0	−1.02251	8.876×10^{-11}
1.0	0.5	1.0	−1.04993	1.785×10^{-7}
1.0	1.0	1.0	−1.03853	1.988×10^{-8}
0.5	0.5	1.0	−1.02835	1.100×10^{-9}
0.5	1.0	1.0	−1.02251	8.876×10^{-11}

From the results shown here, we find that the resulting analytical solutions have rather low residual errors after relatively few terms are computed, highlighting the accuracy and efficiency of the technique. Using the homotopy solutions g to Eq. (2.9), we may recover physical solutions for each of the quantities of interest using Eqs. (2.11)–(2.14). From the stability results of [14], these solutions will be asymptotically stable.

Unlike other methods used to solve the dynamic Michaelis–Menten model, the optimal homotopy analysis method allows one to control the residual error inherent in the approximating solutions to the dynamic Michaelis–Menten model. To this end, we have included a subsection outlining the error analysis for the method. For all parametric values considered, the accuracy of the method improves by a factor between 5 and 10 on each iteration. Therefore, by adding additional terms to our expansion, and by picking the convergence control parameter, h, so that residual error is minimized, we are able to construct rather accurate solutions.

Since we are only working with a single nonlinear ordinary differential equation, we only need to minimize the residual errors for one equation. If one were to attempt to solve (1.1) directly, one would need to construct four homotopies with four distinct convergence control parameters, making the minimization of error much more challenging (see [46] for a demonstration of this point). This in turn lends validity to the approach of [14], where a single equation was derived to represent the dynamic Michaelis–Menten model. Indeed, considering such a transformed form of the model enables us to more accurately construct analytical solutions. As mentioned before, once constructed, the solution $g(T)$ can then easily be mapped into solutions for the unknown functions $S(t)$, $E(t)$, $C(t)$ and $P(t)$.

The methods employed here are rather useful for solving the nonlinear equation (2.9) governing the transformed dynamic form of the Michaelis–Menten model analytically. However, the methods are certainly not specific to this model and could prove useful in other areas of mathematical chemistry. Already, this optimal homotopy

approach has been applied to many problems in mathematical physics, fluid dynamics, and engineering. Further application of the optimal homotopy analysis method in various areas of mathematical chemistry could shed light on various biochemical processes which are governed by complicated systems of equations for which no closed-form exact solutions can be found.

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