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Multistage homotopy perturbation method for nonlinear reaction networks

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Abstract In this paper, we present the multistage homotopy perturbation method for finding the solution of the chemical kinetics with nonlinear reactions. We develop a general scheme for finding the analytic solution of chemical reaction networks and apply it to motivating chemical examples such as the enzyme kinetics model and the Brusselator model. We illustrate the numerical result for the models and show the accuracy of the method.

Keywords Homotopy perturbation method · Chemical reactions · Nonlinear reactions

1 Introduction

In a chemical system, chemical species interact with other species through various reaction channels and their concentrations or molecular numbers are changed by the interactions. Generally a reaction is described in the form

$$\sum_i a_{ij} S_i \xrightarrow{k} \sum_i b_{ij} S_i,$$
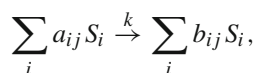
where S_i is the ith species, and a_{ij}, b_{ij} are molar amounts of the ith species as the reactant and the product of the jth reaction, respectively. For example, a reaction $A + B \xrightarrow{k} C + D$ denotes that one mole of a species A and that of B react and produce one mole of C and that of D with the reaction rate constant k. To describe the dynamics of the chemical system, researchers derive a governing equation with the

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system of ordinary differential equations(ODEs), which describes the time evolution of the concentration of species in the system. The general form of the governing equation is

$$\frac{d\mathbf{y}}{dt} = V R(\mathbf{y}),\qquad(1)$$

where $\mathbf{y}(t)$ denotes the vector of concentration of species at time t, V denotes the stoichiometric matrix whose (i, j) component is the stoichiometric amount of the ith species changed by the jth reaction, and $R(\mathbf{y})$ denotes the vector function whose the ith entry is the reaction rate of the ith reaction. The reaction rate function is determined by the mass action kinetics which assumes that the reaction rate is proportional to concentration of reactant species, or other kinetics such as Michaelis–Menten kinetics [1,2]. The system of ODEs has been used as the governing equation in the broad areas of biological sciences such as cell biology, systems biology, physiology and biochemistry. It is well known that the system of ODEs is generally accurate for describing the dynamics of large-scale biological or biochemical networks [3–5]. However, most of the chemical systems include nonlinear reactions whose rate functions are nonlinear and the nonlinearity leads to difficulties in finding the solution of the system of ODEs. The analytic solution of the system of the ODEs have not been known yet for most of chemical systems with nonlinear reactions. Recently several semi-analytic methods such as the differential transform method(DTM) [6–8], homotopy perturbation method(HPM) [9,10]and variational iteration method have been introduced.

Among chemical systems with nonlinear reactions, the enzyme kinetics model is a fundamental and important chemical reaction system. Many important biochemical reactions such as gene transcription, translation and protein-protein interactions can be considered as enzyme kinetics models [11]. Recently an approximate analytic solution of the enzyme kinetics model has been reported with employment of the homotopy perturbation method [9]. The authors claimed the accuracy of their method by comparing the solution curves from the method with numerical solutions from conventional numerical schemes.

In this paper we develop a more accurate and rigorous method for finding the solutions of nonlinear reaction networks based on the multistage homotopy perturbation method (MHPM). We apply our method to the enzyme kinetics model and the Brusselator model, an oscillatory autocatalytic model and illustrate the accuracy of the method. The proposed method can be applied to more complex nonlinear reaction models.

The paper is organized as follows. In Sect. 2, we present a novel multistage homotopy perturbation method. In Sect. 3, we apply the method to two motivating examples such as the enzyme kinetics model and the Brusselator model, and we show detailed analysis on the two models. In Sect. 4, we illustrate the numerical results obtained from our method to show the accuracy and efficiency of our method.

2 Description of multistage homotopy perturbation method

Let us consider a general system in the operator form:

$$L(u_i) + N_i(u_1, u_2, \ldots, u_m) - f_i(t) = 0, \tag{2}$$

subject to the initial conditions $u_i(t_0) = c_{i,0}, i = 1, 2, \ldots, m$, where L is a linear operator and N is a nonlinear operator and f_i are known analytic functions. Homotopy perturbation method(HPM) defines the homotopy $v_i(t, p) : \Omega \times [0, 1] \to \mathbb{R}$ which satisfies

$$\mathcal{H}(v_i, p) = (1 - p)[L(v_i) - L(\hat{v}_i)] + p[L(v_i) + N_i(v_1, v_2, \ldots, v_m) - f_i(t)] = 0, \tag{3}$$

or

$$\mathcal{H}(v_i, p) = L(v_i) - L(\hat{v}_i) + pL(\hat{v}_i) + p[N_i(v_1, u_2, \ldots, v_m) - f_i(t)] = 0, \tag{4}$$

where $p \in [0, 1]$ is the embedding parameter and $\hat{v}_i, i = 1, 2, \ldots, m$ are initial approximations. Then it is easy to see that when $p = 0$, $\mathcal{H}(v_i, p)$ becomes a linear system and when $p = 1$, $\mathcal{H}(v_i, p)$ is the original system (2). Let us consider the embedding parameter p as a small perturbation. Applying the perturbation technique we assume that the solution v_i can be given by a power series in the embedding parameter p

$$v_i = v_{i,0} + pv_{i,1} + p^2 v_{i,2} + \cdots, \tag{5}$$

where $v_{i,j}$ will be determined. Substituting (5) into (4), and arranging the coefficients of the same power of p, we have the system of equations for the function $v_{i,j}$, ($i = 1, 2, \ldots, m, j = 1, 2, \ldots$). Taking inverse operator L^{-1} to the system the function $v_{i,j}$ can be easily obtained. Then we have the approximate solution of (2)

$$u_i = \lim_{p \to 1} v_i = v_{i,0} + v_{i,1} + v_{i,2} + \cdots. \tag{6}$$

Since $u_i(t_0) = c_{i,0}$, we assume that $v_{i,0}(t_0) = c_{i,0}$ and $v_{i,j}(t_0) = 0, j = 1, 2, \ldots$. Let $\phi_{i,n}$ be the n-term approximation of u_i defined by

$$\phi_{i,n} = \sum_{j=0}^{n} v_{i,j}. \tag{7}$$

Since the HPM is based on the perturbation with the initial approximation, $v_{i,0}$ with $v_{i,0}(t_0) = c_{i,0}$, the n-term approximation $\phi_{i,n}$ is a good agreement of the solution u_i in a neighborhood of $t = t_0$. However, the HPM could fail to obtain an accurate approximation $\phi_{i,n}$ in a large domain Ω. To overcome this difficulty the new modification of HPM which is called the multistage HPM (MHPM) has been introduced [12]. In MHPM the domain $\Omega = (0, t_f)$ can be divided into a sequence of subintervals $(t_0, t_1), (t_1, t_2), \ldots, (t_{l-1}, t_l)$, where $t_0 = 0, t_l = t_f$. For the simplicity we assume the equalspaced points t_k with $\Delta t = t_{k+1} - t_k, k = 1, 2, \ldots, l - 1$. In each

subinterval $\Omega_k = (t_k, t_{k+1})$ the MHPM employs the standard HPM. Let us denote $u_i^k = u_i|_{\Omega_k}$, $v_{i,j}^k = v_{i,j}|_{\Omega_k}$ and $\phi_{i,n}^k = \phi_{i,n}|_{\Omega_k}$. To apply the HPM in each subinterval Ω_k, it is necessary to know the values of initial conditions at t_k. That is, $v_{i,0}^k$. Here we impose the value of initial condition as $v_{i,0}^k \approx \phi_{i,n}^{k-1}(t_k)$, $k = 0, 1, \ldots, l-1$.

3 Applications of multistage homotopy perturbation method

In the following, we apply the multistage homotopy perturbation method to two motivating models, enzyme-substrate model and Brusselator model and show the effectiveness of the proposed method.

3.1 Enzyme-substrate reaction model

The enzyme kinetics model is a chemical model which includes a nonlinear reaction. The model consists of the binding/unbinding of enzyme and substrate, and production of the product. The model mechanism is described as follows;

$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \overset{k_2}{\rightarrow} \mathrm{E} + \mathrm{P}, \tag{8}$$

where E, S, ES and P denote enzyme, substrate, enzyme-substrate complex and product, respectively, and k_1, k_{-1} and k_2 denote the rates of reactions. If we denote the concentrations of E, S, ES, P by y_1, y_2, y_3, y_4, respectively, and $\mathbf{y} = (y_1, y_2, y_3, y_4)^T$, we write the governing equation as

$$\frac{d\mathbf{y}}{dt} = \begin{bmatrix} -1 & 1 & 1 \\ -1 & 1 & 0 \\ 1 & -1 & -1 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} k_1 y_1 y_2 \\ k_{-1} y_3 \\ k_2 y_3 \end{bmatrix} = \begin{pmatrix} -k_1 y_1 y_2 + k_{-1} y_3 + k_2 y_3 \\ -k_1 y_1 y_2 + k_{-1} y_3 \\ k_1 y_1 y_2 - k_{-1} y_3 - k_2 y_3 \\ k_2 y_3 \end{pmatrix}, \tag{9}$$

We assume a typical initial condition $(y_1, y_2, y_3, y_4) = (e_0, s_0, 0, 0)$. Since the substrate is exhausted and it produces the product P at the equilibrium, the equilibrium of the model can be founded easily as $(y_1, y_2, y_3, y_4) = (e_0, 0, 0, s_0)$. Since the conserved quantities for the model are $y_1 + y_3 + y_4 = s_0$ and $y_2 + y_3 = e_0$, one can reduce the above system (9) into

$$\begin{aligned} \frac{dy_1}{dt} &= -k_1 e_0 y_1 + k_1 y_1 y_3 + k_{-1} y_3 \\ \frac{dy_3}{dt} &= k_1 e_0 y_1 - k_1 y_1 y_3 - (k_{-1} + k_2) y_3 \end{aligned} \tag{10}$$

with the initial condition $(y_1, y_3) = (s_0, 0)$.

As in [9], to obtain the system of the nondimensional variables from the above system (10) we define the following variables.

$$u(\tau) = \frac{y_1(t)}{s_0}, \, v(\tau) = \frac{(s_0 + K_m)y_3(t)}{e_0 s_0}, \, \tau = k_1(s_0 + K_m)t,$$

$$K_m = \frac{k_{-1} + k_2}{k_1}, \, \rho = \frac{k_{-1}}{k_2}, \, \epsilon = \frac{e_0}{s_0 + K_m}, \, \sigma = \frac{s_0}{K_m} \tag{11}$$

and

$$T = \epsilon(1 + \rho)k_2 t = \frac{\epsilon(1 + \rho)k_2}{(s_0 + K_m)k_1}\tau.$$

Then the system of (10) can be represented in dimensionless form as follows:

$$\frac{du}{dt} = -(1 + \sigma)u + \sigma u v + \frac{\rho}{1 + \rho}v,$$

$$\epsilon \frac{dv}{dt} = (1 + \sigma)u - \sigma u v - v,$$

subject to an appropriate initial condition $u(0) = c_0$ and $v(0) = d_0$ determined by (11). In order to apply the MHPM we consider a subinterval $\Omega_i = (t_i, t_{i+1})$ with an equalspaced point $t_i = \Delta t \times i, i = 0, 1, 2, \ldots$. Let $u_i = u|_{\Omega_i}$ and $v_i = v|_{\Omega_i}$. Then u_i and v_i satisfy the following system in Ω_i

$$\frac{du_i}{dt} = -(1 + \sigma)u_i + \sigma u_i v_i + \frac{\rho}{1 + \rho}v_i,$$

$$\epsilon \frac{dv_i}{dt} = (1 + \sigma)u_i - \sigma u_i v_i - v_i, \tag{12}$$

Applying the HPM to (12) we can construct the homotopy which satisfies the following relations:

$$(1 - p)\left[\frac{du_i}{dt} + (1 + \sigma)u_i\right] + p\left[\frac{du_i}{dt} + (1 + \sigma)u_i - \sigma u_i v_i - \frac{\rho}{1 + \rho}v_i\right] = 0,$$

$$(1 - p)\left[\epsilon \frac{dv_i}{dt} + v_i\right] + p\left[\epsilon \frac{dv_i}{dt} - (1 + \sigma)u_i + \sigma u_i v_i + v_i\right] = 0. \tag{13}$$

Let u_i and v_i be given by a power series with respect to the embedding parameter p as follows:

$$u_i = u_{i,0} + p u_{i,1} + p^2 u_{i,2} + p^3 u_{i,3} + \cdots,$$

$$v_i = v_{i,0} + p v_{i,1} + p^2 v_{i,2} + p^3 v_{i,3} + \cdots. \tag{14}$$

Substituting (14) into (13) and collecting terms with the same powers of p, we have a few corresponding equations for $u_{i,j}$ and $v_{i,j}$ as follows:

$$p^0 : \frac{du_{i,0}}{dt} + (1+\sigma)u_{i,0} = 0,$$

$$p^1 : \frac{du_{i,1}}{dt} + (1+\sigma)u_{i,1} - \sigma u_{i,0}v_{i,0} - \left(\frac{\rho}{1+\rho}\right) = 0,$$

$$p^2 : \frac{du_{i,2}}{dt} + (1+\sigma)u_{i,2} + \sigma u_{i,0}v_{i,1} + \sigma u_{i,1}v_{i,0} - \left(\frac{\rho}{1+\rho}\right)v_{i,1} = 0,$$

$$\vdots \tag{15}$$

and

$$p^0 : \epsilon\frac{dv_{i,0}}{dt} + v_{i,0} = 0,$$

$$p^1 : \epsilon\frac{dv_{i,1}}{dt} - (1+\sigma)u_{i,1} + v_{i,1} + \sigma u_{i,0}v_{i,0} = 0,$$

$$p^2 : \epsilon\frac{dv_{i,2}}{dt} - (1+\sigma)u_{i,1} + v_{i,2} + \sigma u_{i,1}v_{i,0} + \sigma u_{i,0}v_{i,1} = 0,$$

$$\vdots \tag{16}$$

Let $s_{u_i,m}$ and $s_{v_i,m}$ be the m-partial sums of u_i and v_i defined by

$$s_{u_i,m} = \sum_{j=0}^{m} u_{i,j}, \quad s_{v_i,m} = \sum_{j=0}^{m} v_{i,j}. \tag{17}$$

In order to obtain $u_{i,j}$, $v_{i,j}$, $i, j = 0, 1, 2, \ldots$, it is necessary to impose initial conditions $u_{i,j}(t_i)$ and $v_{i,j}(t_i)$. From the initial condition $u(0) = c_0$, $v(0) = d_0$ we have $u_{0,0}(t_0) = c_0$ and $v_{0,0}(t_0) = d_0$. For $i \geq 1$ we assume $u_{i,0}(t_i) = s_{u_{i-1},m}(t_i) \equiv c_i$, $v_{i,0}(t_i) = s_{v_{i-1},m}(t_i) \equiv d_i$, and $u_{i,j}(t_i) = v_{i,j}(t_i) = 0$ for $j \geq 1$. Using these initial conditions the solutions of $u_{i,j}$ and $v_{i,j}$ in (15), (16) can be solved. Since the solutions $u_{i,j}$, $v_{i,j}$, $j \geq 2$ are very complicated we only list the first two solutions of $u_{i,j}$ and $v_{i,j}$, $j = 0, 1$ as follows:

$$u_{i,0}(t) = c_i e^{(t_i-t)(1+\sigma)}$$

$$u_{i,1}(t) = \frac{d_i\epsilon}{(1+\rho)(-1+\epsilon+\epsilon\sigma)}e^{-t(1+\epsilon+\epsilon\sigma)/\epsilon}$$
$$[e^{t+t_i/\epsilon+t\sigma}\rho - c_i e^{t_i(1+1/\epsilon+\sigma)}(1+\rho)\sigma(-1+\epsilon+\epsilon\sigma)$$
$$+ e^{t_i+t/\epsilon+t_i\sigma}\{c_i\sigma(-1+\epsilon+\epsilon\sigma) + \rho(-1+c_i\sigma(-1+\epsilon+\epsilon\sigma))\}]], \tag{18}$$

and

$$v_{i,0}(t) = d_i e^{(t_i-t)/\epsilon}$$

$$v_{i,1}(t) = [c_i e^{-t/\epsilon} - e^{t/\epsilon+(t_i-t)(1+\sigma)}\epsilon(1+\sigma)^2 + d_i e^{-t(1+\sigma)+t_i(1+1/\epsilon+\sigma)}$$
$$\sigma(-1+\epsilon+\epsilon\sigma) + e^{t_i/\epsilon}\{d_i\sigma - \epsilon(1+\sigma)(-1+(-1+d_i)\sigma)\}]$$
$$/(\epsilon(1+\sigma)(-1+\epsilon+\epsilon\sigma)). \tag{19}$$

3.2 Brusselator model

The Brusselator model is an autocatalytic and oscillatory chemical model, which was proposed by Prigogine and his collaborators [13]. The autocatalytic reaction is a common nonlinear reaction in which a reactant species interacts with other species to increase its production rate. The mechanism of the Brusselator model is described as

$$A \xrightarrow{k_1} X, \, 2X + Y \xrightarrow{k_2} 3X,$$
$$B + X \xrightarrow{k_3} Y + D, \, X \xrightarrow{k_4} E \tag{20}$$
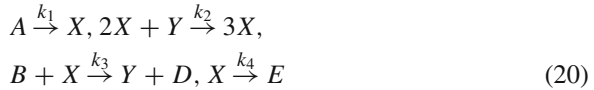
Here X and Y are the autocatalytic species and A, B, D and E are constant species. If we denote the concentration of species X, Y, A, B, D, E by x, y, A, B, D, E, respectively. we writhe the governing equation as

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 & 1 & -1 & -1 \\ 0 & -1 & 1 & 0 \end{bmatrix} \begin{bmatrix} k_1 A \\ k_2 x^2 y \\ k_3 B x \\ k_4 x \end{bmatrix}$$

To find the equilibrium points, we set

$$k_1 A + k_2 x^2 y - k_3 B x - k_4 x = 0, \quad -k_2 x^2 y + k_3 B x = 0.$$

It gives the unique equilibrium point (x_e, y_e), where

$$x_e = \frac{k_1 A}{k_4}, \, y_e = \frac{k_3 k_4 B}{k_1 k_2 A}.$$

For a stability analysis at the equilibrium point, we find the Jacobian

$$J = \begin{pmatrix} 2k_2 x_e y_e - k_3 B - k_4 & k_2 x_e^2 \\ -2k_2 x_e y_e + k_3 B & -k_2 x_e^2 \end{pmatrix} = \begin{pmatrix} k_3 B - k_4 & k_2 x_e^2 \\ -k_3 B & -k_2 x_e^2 \end{pmatrix},$$

and its characteristic equation is

$$|J - \lambda I| = \begin{vmatrix} k_3 B - k_4 - \lambda & k_2 x_e^2 \\ -k_3 B & -k_2 x_e^2 - \lambda \end{vmatrix} = \lambda^2 - (k_3 B - k_4 - k_2 x_e^2)\lambda + k_2 k_4 x_e^2 = 0.$$

From the basic theory of the stability analysis, we see that since $k_2 k_4 x_e^2 > 0$, the equilibrium point is unstable if $trace(J - \lambda I) = (k_3 B - k_4 - k_2 x_e^2) > 0$ and stable if $(k_3 B - k_4 - k_2 x_e^2) < 0$.

Without loss of generality, if we assume $k_1 = k_2 = k_3 = k_4 = 1$, we find that if $B > 1 + A^2$, the equilibrium point is unstable and if $B < 1 + A^2$, then it is stable. This model has different dynamical behaviors for different values of A and B. Especially, if $B > 1 + A^2$, the solution trajectory shows oscillations. We will show that our method can capture this notable property accurately.

To present the method for the model, we first rewrite the governing equation of (20) under the assumption $k_1 = k_2 = k_3 = k_4 = 1$ as follows;

$$\frac{dx}{dt} = A + x^2 y - Bx - x,$$
$$\frac{dy}{dt} = -x^2 y + Bx, \tag{21}$$

subject to the initial condition $x(0) = c_0$ and $y(0) = d_0$. Let us consider a subinterval $\Omega_i = (t_i, t_{i+1})$ with $t_i = \Delta t \times i$, $i = 0, 1, 2, \ldots$. Define $x_i = x|_{\Omega_i}$ and $y_i = y|_{\Omega_i}$, $i = 0, 1, 2, \ldots$. Then we have

$$\frac{dx_i}{dt} = A + x_i^2 y_i - Bx_i - x_i,$$
$$\frac{dy_i}{dt} = -x_i^2 y_i + Bx_i, \tag{22}$$

In order to apply the HPM to (22) we can construct the homotopy as follows:

$$(1 - p)\left[\frac{dx_i}{dt}\right] + p\left[\frac{dx_i}{dt} - A - x_i^2 y_i + Bx_i + x_i\right] = 0,$$
$$(1 - p)\left[\frac{dy_i}{dt}\right] + p\left[\frac{dy_i}{dt} + x_i^2 y_i - Bx_i\right] = 0. \tag{23}$$

Suppose that the solutions x_i and y_i can be represented as a power series with respect to the embedding parameter p

$$x_i = x_{i,0} + p x_{i,1} + p^2 x_{i,2} + p^3 x_{i,3} + \cdots,$$
$$y_i = y_{i,0} + p y_{i,1} + p^2 y_{i,2} + p^3 y_{i,3} + \cdots \tag{24}$$

Substituting (24) into (23) and collecting terms with the same powers of p, we have a few corresponding equations for $x_{i,j}$ and $y_{i,j}$ as follows:

$$p^0 : \frac{dx_{i,0}}{dt} = 0,$$
$$p^1 : \frac{dx_{i,1}}{dt} - A + x_{i,0} + Bx_{i,0} - x_{i,0}^2 y_{i,0} = 0,$$
$$p^2 : \frac{dx_{i,2}}{dt} + x_{i,1} + Bx_{i,1} - 2x_{i,0}x_{i,1}y_{i,0} - x_{i,0}^2 y_{i,1} = 0, \tag{25}$$

and

$$p^0 : \frac{dy_{i,0}}{dt} = 0,$$
$$p^1 : \frac{dy_{i,1}}{dt} - Bx_{i,0} + x_{i,0}^2 y_{i,0} = 0,$$
$$p^2 : \frac{dy_{i,2}}{dt} - Bx_{i,1} + 2x_{i,0}x_{i,1}y_{i,0} + x_{i,0}^2 y_{i,1} = 0. \tag{26}$$

The initial conditions $x(0) = c_0, y(0) = d_0$ give $x_{0,0}(t_0) = c_0, y_{0,0}(t_0) = d_0$. We assume $x_{i,0}(t_i) = s_{i-1,m}(t_i) \equiv c_i, y_{i,0}(t_i) = s_{i-1,m}(t_i) \equiv d_i$ for $i \geq 1$, and $x_{i,j}(t_i) = y_{i,j}(t_i) = 0$ for $i, j \geq 1$. Here $s_{x_i,m}$ and $s_{y_i,m}$ are the m-partial sums of x_i and y_i, defined by

$$s_{x_i,m} = \sum_{j=0}^{m} x_{i,j}, \quad s_{y_i,m} = \sum_{j=0}^{m} y_{i,j}.$$

Solving the systems (25) and (26) combined with the imposed initial conditions we can obtain the solutions $x_{i,j}$ and $y_{i,j}$. The first three solutions of $u_{i,j}$ and $v_{i,j}$, $j = 0, 1, 2$ are given as follows:

$$\begin{aligned}
x_{i,0}(t) &= c_i, \\
x_{i,1}(t) &= (A + c_i(-1 - B + c_i d_i))(t - t_i), \\
x_{i,2}(t) &= -1/2[A(1 + B - 2c_i d_i) + c_i(-1 - B^2 + 3c_i d_i + c_i^3 d_i \\
&\quad -2c_i^2 d_i^2 - B(2 + c_i^2 - 3c_i d_i))](t - t_i)^2,
\end{aligned} \tag{27}$$

and

$$\begin{aligned}
y_{i,0}(t) &= d_i, \\
y_{i,1}(t) &= c_i(B - c_i d_i)(t - t_i), \\
y_{i,2}(t) &= 1/2[A(B - 2c_i d_i) + c_i(-B^2 - B(1 + c_i^2 - 3c_i d_i) \\
&\quad +c_i d_i(2 + c_i^2 - 2c_i d_i))](t - t_i)^2.
\end{aligned} \tag{28}$$

4 Results and discussions

4.1 Enzyme-substrate reaction model

To show the performance of the MHPM to (12) we employ the m-partial sums of u_i, v_i in each subinterval Ω_i

$$s_{u_i,m} = \sum_{j=0}^{m} u_{i,j}, \quad s_{v_i,m} = \sum_{j=0}^{m} v_{i,j},$$

where $u_{i,j}$ and $v_{i,j}$ are the solutions in (18) and (19), respectively. Let us define $s_{u,m}, s_{v,m}$ by the m-partial sums of u, v in whole domain Ω

$$s_{u,m} = \sum_{i=0}^{n} s_{u_i,m} \chi_i, \quad s_{v,m} = \sum_{i=0}^{n} s_{v_i,m} \chi_i,$$

where χ_i is a characteristic function defined by $\chi_i(t) = 1, t \in \Omega_i$ and $\chi_i(t) = 0$, otherwise. For all numerical tests the initial conditions are set by $c_0 = 1$ and $d_0 = 0$.
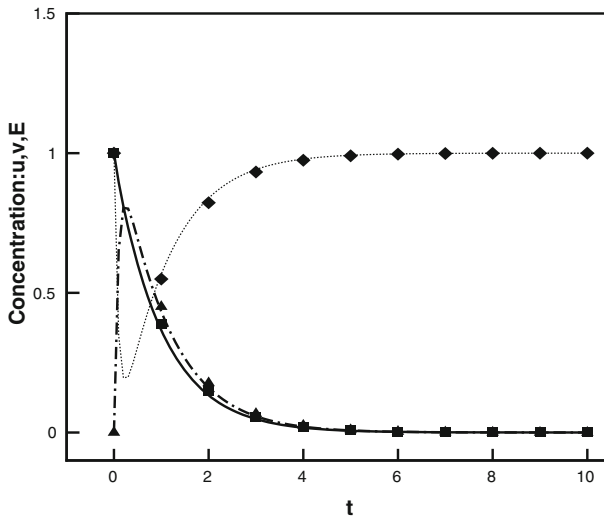
Fig. 1 Profile of the normalized concentrations of the substrate u (*solid line*), enzyme-substrate complex v (*dash-dot line*) and enzyme E (*dotted line*) for $\epsilon = 0.1$, $\sigma = 0.1$, $\rho = 0.1$. The *curves* represent the numerical solutions by the MHPM and the symbols by the RK4

In Figs. 1, 2 and 3, the numerical results by the MHPM and the fourth-order Runge–Kutta(RK4) are plotted. Here the parameters are set by $\sigma = \rho = 0.1$ and the ϵ is varying from 0.1 to 10. In MHPM the two-term approximations $s_{u,1}$ and $s_{v,1}$ are employed with the step size of time $h = 0.1$ and the RK4 uses $h = 0.001$ as the step size of time. It is worth noting that all results obtained by the MHPM with less computational work are in a good agreement with the ones by the RK4. In [9] authors showed various results by the standard HPM with different parameters. The dynamics of the concentrations u and v are agreed with our results. However, the behavior of the concentration of u is different. It is easy to see from (12) that the concentration of u should be decreasing at $t = 0$ because of $u(0) = 1$, $v(0) = 0$ and the positive parameters. The results in [9] showed that the concentration u is increasing at $t = 0$.

To show the accuracy of the MHPM the comparisons of the maximum errors $||s_{u,m} - u_h||_\infty$, $||s_{v,m} - v_h||_\infty$, $m = 1, 2$ are demonstrated in Tables 1 and 2. Here u_h and v_h are the numerical approximations by the RK4. Also the rates of convergence are listed in the same tables. It has been shown that the rate of convergence is of linear order with respect to the number of term. Let us remark that even though the approximation by the standard HPM gives a similar dynamic behavior, the MHPM yields a more accurate approximation.

4.2 Brusselator model

As presented in the previous section we consider the m-partial sums $s_{x_i,m}$ and $s_{y_i,m}$ of x_i and y_i in (22) to demonstrate effectiveness of the proposed method. That is,
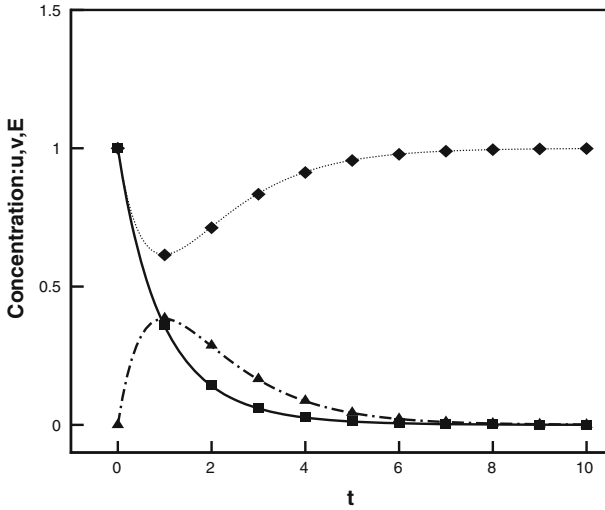
Fig. 2 Profile of the normalized concentrations of the substrate u (*solid line*), enzyme-substrate complex v (*dash-dot line*) and enzyme E (*dotted line*) for $\epsilon = 1.0, \sigma = 0.1, \rho = 0.1$. The *curves* represent the numerical solutions by the MHPM and the symbols by the RK4

Fig. 3 Profile of the normalized concentrations of the substrate u (*solid line*), enzyme-substrate complex v (*dash-dot line*) and enzyme E (*dotted line*) for $\epsilon = 10, \sigma = 0.1, \rho = 0.1$. The *curves* represent the numerical solutions by the MHPM and the symbols by the RK4
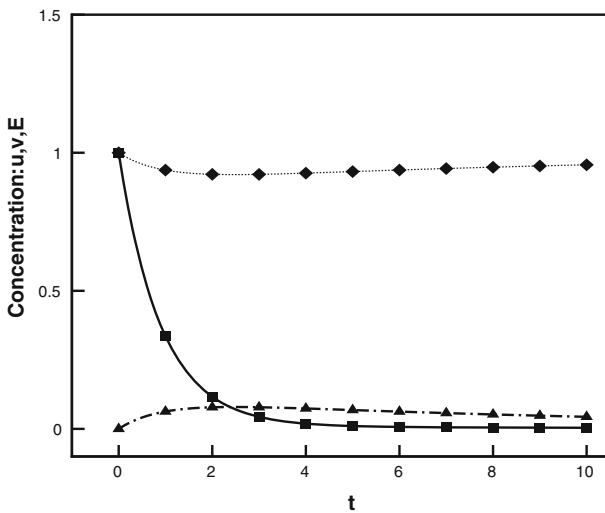
$$s_{x_i,n} = \sum_{j=0}^{n} x_{i,j}, \quad s_{y_i,n} = \sum_{j=0}^{n} y_{i,j},$$

where $x_{i,j}$ and $y_{i,j}$ are the solutions in (27) and (28), respectively. In a similar way we define $s_{x,m}, s_{y,m}$ by the m-partial sums of x, y in a whole domain. For all numerical

Table 1 Maximum errors and convergence rates for the approximation $s_{u,m}$, $m = 1, 2$ with $\epsilon = 1.0$, $\sigma = 0.1$, $\rho = 0.1$

h	$||s_{u,1} - u_h||_\infty$	Rate	$||s_{u,2} - u_h||_\infty$	Rate
0.32	9.03529(−3)		1.61093(−4)	
0.16	4.63788(−3)	0.96211	4.53692(−5)	1.82811
0.08	2.34792(−3)	0.98208	1.20118(−5)	1.91726
0.04	1.18126(−3)	0.99105	3.08000(−6)	1.96345
0.02	5.92591(−4)	0.99522	7.82900(−7)	1.97603
0.01	2.96779(−4)	0.99765	1.97093(−7)	1.98995

Table 2 Maximum errors and convergence rates for the approximation $s_{v,m}$, $m = 1, 2$ with $\epsilon = 1.0$, $\sigma = 0.1$, $\rho = 0.1$

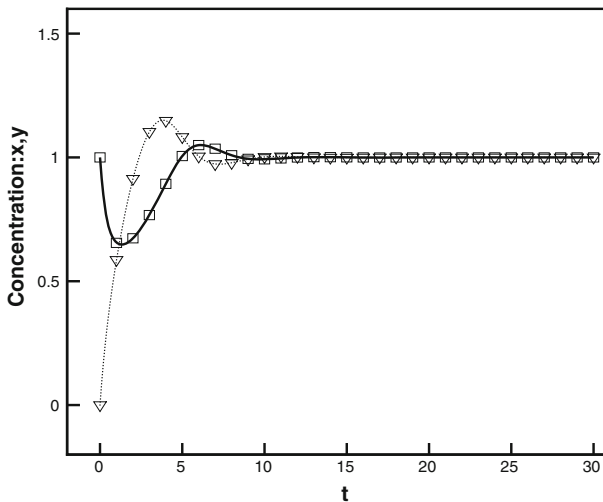| h	$||s_{v,1} - v_h||_\infty$	Rate	$||s_{v,2} - v_h||_\infty$	Rate
0.32	9.53380(−3)		1.06277(−3)	
0.16	5.13533(−3)	0.89259	2.67272(−4)	1.99145
0.08	2.67213(−3)	0.94246	6.71800(−5)	1.99221
0.04	1.36236(−3)	0.97188	1.68177(−5)	1.99805
0.02	6.87856(−4)	0.98593	4.20900(−6)	1.99843
0.01	3.45612(−4)	0.99295	1.05226(−6)	1.99999

Fig. 4 Profile of the concentrations of species x (*solid line*) and y (*dotted line*) for $A = 1.0$, $B = 1.0$. The *curves* represent the numerical solutions by the MHPM and the symbols by the RK4

tests the initial conditions are set to be $c_0 = 1$ and $d_0 = 0$ and the parameter A is fixed by $A = 1$ and B is varying from 1.0 to 2.5. It has been known that the phase of $x(t)$ and $y(t)$ is highly oscillating as the parameter B is increasing. For all parameters B numerical results by the MHPM are in a good agreement with the results by the RK4 in Figs. 4, 5, 6 and 7. Here the step sizes of time in MHPM and RK4 are $h = 0.1$ and $h = 0.001$, respectively. The three-term approximations $s_{x,2}$ and $s_{y,2}$ are employed in MHPM. To demonstrate of the accuracy of MHPM the maximum errors between MHPM and RK4 are shown in Tables 3, 4, 5 and 6 as the number of
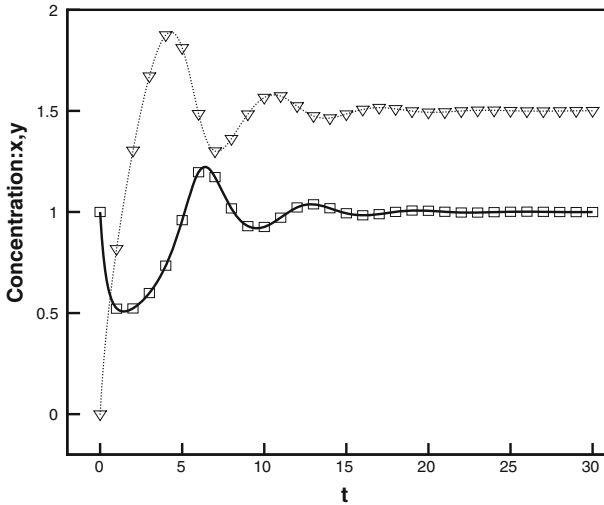
Fig. 5 Profile of the concentrations of species x (*solid line*) and y (*dotted line*) for $A = 1.0$, $B = 1.5$. The *curves* represent the numerical solutions by the MHPM and the symbols by the RK4
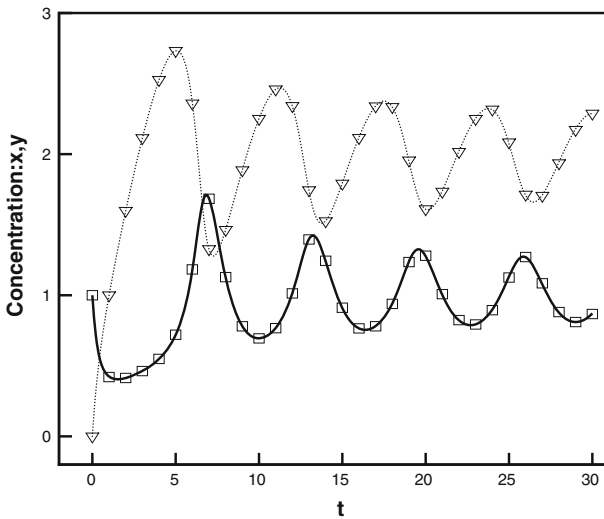

Fig. 6 Profile of the concentrations of species x (*solid line*) and y (*dotted line*) for $A = 1.0$, $B = 2.0$. The *curves* represent the numerical solutions by the MHPM and the symbols by the RK4

term n is increasing from $n = 2$ to $n = 6$. The results show that the proposed method is of linear rate of convergence with respect to the number of term. For the large number of term $m = 6$ the approximations $s_{x,m}$, $s_{y,m}$ do not follow the linear order because of very small errors. Let us note that the standard HPM yields all approximations which are blowing up exponentially in a short time as the parameter B is increasing.
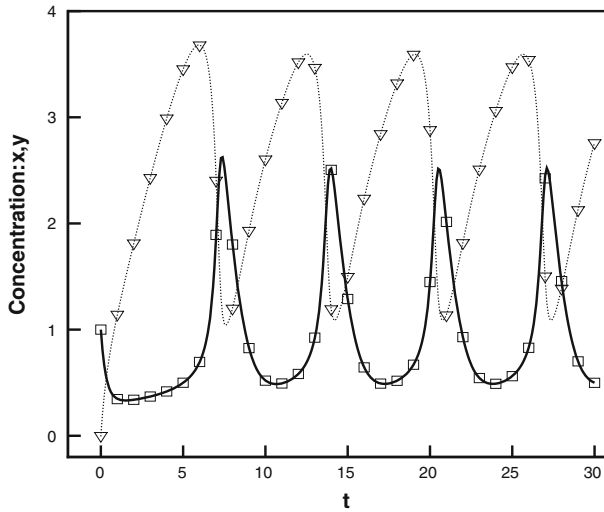
Fig. 7 Profile of the concentrations of species x (*solid line*) and y (*dotted line*) for $A = 1.0$, $B = 2.5$. The *curves* represent the numerical solutions by the MHPM and the symbols by the RK4

Table 3 Maximum errors and convergence rates for the approximation $s_{x,m}$, $m = 2, 4, 6$ with $A = 1.0$, $B = 1.5$

h	$\|\|s_{x,2} - x_h\|\|_\infty$	Rate	$\|\|s_{x,4} - x_h\|\|_\infty$	Rate	$\|\|s_{x,6} - x_h\|\|_\infty$	Rate
0.32	9.0668(−2)		3.0866(−2)		1.2754(−2)	
0.16	1.0508(−2)	2.58706	1.1963(−3)	4.68931	1.2427(−4)	6.68134
0.08	2.9750(−3)	2.34254	5.1655(−5)	4.53361	1.2120(−6)	6.67995
0.04	6.6565(−4)	2.16007	2.6585(−6)	4.28021	1.4548(−8)	6.38033
0.02	1.5704(−4)	2.08356	1.5095(−7)	4.13846	1.9886(−10)	6.19299
0.01	3.8158(−5)	2.04112	8.9738(−9)	4.07224	2.1782(−11)	3.19053

Table 4 Maximum errors and convergence rates for the approximation $s_{y,m}$, $m = 2, 4, 6$ with $A = 1.0$, $B = 1.5$

h	$\|\|s_{y,2} - y_h\|\|_\infty$	Rate	$\|\|s_{y,4} - y_h\|\|_\infty$	Rate	$\|\|s_{y,6} - y_h\|\|_\infty$	Rate
0.32	6.9831(−2)		2.739(−2)		1.1808(−2)	
0.16	1.2216(−2)	2.51508	1.066(−3)	4.68318	1.1525(−4)	6.67874
0.08	2.4482(−3)	2.31896	4.887(−5)	4.44760	1.1836(−6)	6.60556
0.04	5.4723(−4)	2.16154	2.577(−6)	4.25048	1.4521(−8)	6.34883
0.02	1.2942(−4)	2.08000	1.468(−7)	4.12761	1.9979(−10)	6.18358
0.01	3.1484(−5)	2.03946	8.770(−9)	4.06606	3.6115(−11)	2.46782

Table 5 Maximum errors and convergence rates for the approximation $s_{x,m}, m = 2, 4, 6$, with $A = 1.0, B = 2.5$

h	$\|\|s_{x,2} - x_h\|\|_\infty$	Rate	$\|\|s_{x,4} - x_h\|\|_\infty$	Rate	$\|\|s_{x,6} - x_h\|\|_\infty$	Rate
0.32	3.9234(−1)		1.8491(−1)		1.2704(−1)	
0.16	8.0172(−2)	2.29095	7.0581(−3)	4.68931	1.4430(−3)	6.46005
0.08	1.8889(−2)	2.08553	4.3600(−4)	4.53361	1.8121(−5)	6.31527
0.04	4.5433(−3)	2.05574	2.5523(−5)	4.28021	2.5556(−7)	6.14783
0.02	1.1234(−3)	2.01581	1.5495(−6)	4.13846	3.6707(−9)	6.12149
0.01	2.7925(−4)	2.00829	9.5037(−8)	4.07224	1.7345(−10)	4.40348

Table 6 Maximum errors and convergence rates for the approximation $s_{y,m}, m = 2, 4, 6$ with $A = 1.0, B = 2.5$

h	$\|\|s_{y,2} - y_h\|\|_\infty$	Rate	$\|\|s_{y,4} - y_h\|\|_\infty$	Rate	$\|\|s_{y,6} - y_h\|\|_\infty$	Rate
0.32	5.3609(−1)		2.2791(−1)		1.7955(−1)	
0.16	1.2169(−1)	2.13922	9.4247(−3)	4.59591	1.9065(−3)	6.55728
0.08	2.7652(−2)	2.13780	5.3302(−4)	4.14418	2.4247(−5)	6.29703
0.04	6.7861(−3)	2.02675	3.1559(−5)	4.07806	3.2580(−7)	6.21767
0.02	1.6825(−3)	2.01194	1.8673(−6)	4.07901	4.5776(−9)	6.15325
0.01	4.1937(−4)	2.00435	1.1320(−7)	4.04401	2.5079(−10)	4.19003

5 Conclusion

We presented the multistage homotopy perturbation method for approximating analytic solutions of nonlinear reaction networks. We applied the method to the enzyme-substrate model and the Brusselator model with a rigorous manner and we illustrated the accuracy and efficiency of the method. In the enzyme-substrate model, we compared our results with those by conventional schemes such as fourth-order Runge–Kutta method, and we showed that the numerical solutions from the proposed method are efficient and accurate. In the Brusselator model, we employed the method for various parameters which lead to different dynamical behavior of the model. The solution trajectories for each parameter are found accurately and the method successfully captured highly oscillating behavior of the model as well as dynamics near the equilibrium.

For most of complex reaction networks, the analytic solutions of their governing equations are not obtainable. The method proposed in this paper can be applied for finding the approximate analytic solutions of the complex reaction networks with nonlinear reactions. We expect that the method will be used to investigate the dynamical behavior of large reaction networks such as genetic networks and metabolic networks.

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