Simulating Plant Metabolic Pathways with Enzyme-Kinetic Models Using a New Approach to Homotopy Perturbation Method

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Abstract

The mathematical models of plant metabolic pathways are discussed. Kinetic modeling is the most detailed mathematical description of a metabolic network and constitutes an important branch in the growing fields of systems biology. This model is based on non-stationary diffusion equations containing a nonlinear term related to the Michaelis-Menten kinetics. An analytical expression of metabolic concentration was obtained for all values of parameters using the new approach to Homotopy perturbation method. Our analytical results were compared with simulation results. Satisfactory agreement with simulation data is noted.

Keywords: Nonlinear equations; New homotopy perturbation method; Mathematical modeling; Michaelis-menten kinetics

Introduction

A Mathematical model is a description of a system using mathematical concepts and language. The process of developing a mathematical model is termed mathematical modeling. Mathematical models are used not only in the natural sciences, but also in the social sciences (e.g., economics, psychology, sociology, and political science). Mathematical models can take many forms, including but not limited to dynamical systems, statistical models, differential equations, or game theoretic models. Mathematical modeling of metabolism is usually closely associated with changes in compound concentrations that are described in terms of rates of biochemical reactions [1].

Various aspects of plant physiology have been analyzed extensively with kinetic models, and the field has a history going back for more than two decades. Detailed surveys of these models, the pathways they address, and the techniques used can be found in [2,3]. A recent review was devoted to a quantitative comparison and ranking of all the kinetic models that have been published on the Calvin-Benson cycle [4]. This information will not be repeated here; instead, the purpose of this section is 2-fold. First, a summary of recent plant kinetic models that have been published since the last comprehensive review by is presented [3].

Kinetic modeling is the most detailed and complex mathematical description of a metabolic network and constitutes an important branch in the growing fields of systems biology. Kinetics modeling is to express the stoichiometries and regulatory interactions in quantitative terms. The dynamics of metabolic networks are predominated by the activity of enzymes – proteins that have evolved to catalyze specific biochemical transformations. The activity and specificity of all enzymes are described in terms of rates of biochemical reactions [1].

Mathematical Formulation of Problems and Analysis

During an enzyme-kinetic model [8]

\[
D_{s} \frac{d^{2}S}{dx^{2}} + R_{i} - 2R_{f} = D_{s} \frac{d^{2}S}{dx^{2}} + k_{i} - 2 \left( \frac{S}{K_{ii} + S} \right) = 0
\]

(1)

\[
D_{s} \frac{d^{2}P}{dx^{2}} + R_{f} = D_{s} \frac{d^{2}P}{dx^{2}} + 2 \left( \frac{S}{K_{ii} + S} \right) - k_{i}S_{2} = 0
\]

(2)

Where \( S \) is imported into the modeled system by \( R_{i} \) converted to \( P \) by \( R_{f} \) and finally taken out of the system by \( R_{i} \), where \( K_{i} \) and \( K_{f} \) indicate the velocities of the reactions, \( S \) and \( P \) are the concentrations of the two metabolites. \( R_{f} \) carries a constant flux, while \( R_{i} \) and \( R_{f} \) follow mass action kinetics; in case of \( R_{i} \) the product \( P \) is acting as an activator of the reaction. At this point it is important to account for reversibility as well as inhibition or activation of an enzyme, since omitting these effects is a common cause of unrealistic behavior [6].

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A general scheme (Figure 1) that represents the change in metabolite concentration is shown below: The differential equations for the metabolites can be established from Eq. (1) and Eq. (2) respectively.

\[ D_1 \frac{d^2 S}{dx^2} + k_1 - 2 V_{max} \frac{P}{K_a + P} = 0 \]  
(3)

\[ D_2 \frac{d^2 P}{dx^2} + 2 V_{max} \frac{P}{K_a + P} - k_1 P = 0 \]  
(4)

where \( S \) and \( P \) are the concentrations of the two metabolites, \( D_1 \) and \( D_2 \) are the diffusion coefficients, \( V_{max} \) are the maximal velocity of the enzymatic reaction, \( K_a \) are the Michaelis- menten constant, \( K_a \) \( K_c \) are parameters indicating the velocities of the reactions. In the above equations the initial and boundary conditions are given by

\[ X = 0: S = 0, \frac{dP}{dx} = 0 \]  
(5)

\[ X = L: S = 0, P = P_0 \]  
(6)

We introduce the following set of dimensionless variables:

\[ \frac{x}{L} = \frac{X}{L}, \frac{u}{L} = \frac{S}{K_a}, \frac{k}{P_0} = \frac{P}{P_0}, \alpha = 2V_{max} \frac{L}{D_1}, \beta = \frac{D_2}{D_1} \]

(7)

The above non-linear differential equations are expressed in the following dimensionless form:

\[ \frac{d^2 u}{dx^2} + m - \frac{\alpha v}{1 + \beta v} = 0 \]  
(8)

\[ \frac{d^2 v}{dx^2} + m v + \frac{\alpha v}{1 + \beta v} = 0 \]  
(9)

Where \( \alpha \), \( \alpha_1 \), and \( \beta \) are the saturation parameters, \( x \) is the dimensionless distance, \( m \) and \( m_1 \) are diffusion parameters, \( u \) and \( v \) are the dimensionless concentration. The boundary conditions in non-dimensional form for the studied cases are:

\[ x = 0: u = 0, \frac{dv}{dx} = 0 \]  
(10)

\[ x = 1: u = 0, v = 1 \]  
(11)

**Analytical Expression of the Concentration Using the New Homotopy Perturbation Method**

Recently, many authors have applied the Homotopy perturbation method to various problems and demonstrated the efficiency of the Homotopy perturbation method for handling non-linear structures and solving various physics and engineering problems [9-12]. This method is a combination of Homotopy in topology and classic perturbation techniques. Ji-Huan He used the HPM to solve the Lighthill equation, the duffing equation and Blasius equation [13-15]. The idea has been used to solve nonlinear boundary value problems, integral equations and many other problems [16,17]. The HPM is unique in its applicability, accuracy and efficiency. The HPM uses the imbedding parameter \( P \) as a small parameter and only a few iterations are needed to search for an asymptotic solution. Using this method (Appendix A), we can obtain the following solution to Eqs. 8 and 9 (Appendix B).

\[ u(x) = m \left[ 1 - \frac{1}{1 + \beta} \left( x - \frac{1}{1 + \beta} \right) \right] \]  
(12)

\[ v(x) = m \left[ 1 + \frac{1}{1 + \beta} \left( x - \frac{1}{1 + \beta} \right) \right] \]  
(13)

Eq. (12) and Eq. (13) represent the new simple analytical expression of the concentrations for all values of parameters \( m, \alpha, \alpha_1, \beta \).

**Discussion**

Eqs. (3) and (4) represents the approximation analytical expression of concentrations of substrate \( S \) and product \( P \). The non linear Eqs. (8)-(9) are also solved by numerical methods. Our analytical results for the numerical concentration of substrate is compared with simulation results in Figure 2. (a)-(c) for various values parameter \( m, \alpha, \alpha_1, \beta \). Also the value of concentration of substrate \( u(x) \) is equal to zero when \( x=0 \) and \( L \). From the Figure 2a, it is observed that the substrate concentration \( u(x) \) is slowly increases when \( x \) increases for small value of other parameters. Also the numerical concentration of substrate \( S \) and product \( P \). The non linear Eqs. (3) and (4) represents the approximation analytical expression of concentrations of substrate \( S \) and product \( P \). The non linear Eqs. (8)-(9) are also solved by numerical methods. Our analytical results for the numerical concentration of substrate is compared with simulation results in Figure 2. (a)-(c) for various values parameter \( m, \alpha, \alpha_1, \beta \). Also the value of concentration of substrate \( u(x) \) is equal to zero when \( x=0 \) and \( L \). From the Figure 2a, it is observed that the substrate concentration \( u(x) \) is slowly increases when \( x \) increases for small value of other parameters. Also the numerical concentration of substrate \( S \) and product \( P \). The non linear Eqs. (8)-(9) are also solved by numerical methods. Our analytical results for the numerical concentration of substrate is compared with simulation results in Figure 2. (a)-(c) for various values parameter \( m, \alpha, \alpha_1, \beta \). Also the value of concentration of substrate \( u(x) \) is equal to zero when \( x=0 \) and \( L \). From the Figure 2a, it is observed that the substrate concentration \( u(x) \) is slowly increases when \( x \) increases for small value of other parameters. Also the numerical concentration of substrate \( S \) and product \( P \). The non linear Eqs. (8)-(9) are also solved by numerical methods. Our analytical results for the numerical concentration of substrate is compared with simulation results in Figure 2. (a)-(c) for various values parameter \( m, \alpha, \alpha_1, \beta \). Also the value of concentration of substrate \( u(x) \) is equal to zero when \( x=0 \) and \( L \). From the Figure 2a, it is observed that the substrate concentration \( u(x) \) is slowly increases when \( x \) increases for small value of other parameters. Also the numerical concentration of substrate \( S \) and product \( P \). The non linear Eqs. (8)-(9) are also solved by numerical methods. Our analytical results for the numerical concentration of substrate is compared with simulation results in Figure 2. (a)-(c) for various values parameter \( m, \alpha, \alpha_1, \beta \). Also the value of concentration of substrate \( u(x) \) is equal to zero when \( x=0 \) and \( L \). From the Figure 2a, it is observed that the substrate concentration \( u(x) \) is slowly increases when \( x \) increases for small value of other parameters. Also

**Figure 2:** Normalized concentration profiles of substrate \( u(x) \) from Eq. (12), for different values of \( m, \alpha, \alpha_1 \) and \( \beta \) when (a) \( \alpha_1 = 0.1, \alpha = 0.1, \beta = 0.1, m_1 = 0.1 \) (b) \( \alpha_1 = 3, \alpha = 3, m_1 = 3 \) (c) \( \alpha_1 = 3, \beta = 3, m_1 = 3 \). Solid lines represent the analytical solution obtained in this work; dotted lines represent the numerical solution.
value of concentration substrate \( u(x) \) increases when \( \alpha \) decreases for large value of other parameters (Figure 2c).

Figure 3(a)-(c) represents the comparison of analytical expression of concentration of product with simulation results from the Figure 3a it is inferred that the concentration of product \( v(x) \) is slowly increases when small values of \( m_1 \). In Figure 3b the product concentration \( v(x) \) is increases when \( \beta \) decreases for large value of \( \alpha_1 \) and \( m_1 \). Also value of concentration of product \( v(x) \) increases when \( \alpha_1 \) increases for different value of saturation parameter \( \beta \) and diffusion parameter \( m_1 \) (Figure 3c).

**Figure 3**: Normalized concentration profiles of product \( v(x) \) from Eq. (13), for different values of \( m_1, \alpha_1 \) and \( \beta \) when (a) \( \alpha_1 = 0.001, \beta = 0.01 \) (b) \( \alpha_1 = 65, m_1 = 65 \) (c) \( \beta = 0.01, m_1 = 65 \). Solid lines represent the analytical solution obtained in this work; dotted lines represent the numerical solution.

**Conclusion**

The time independent, non-linear reaction/diffusion equation has been formulated and solved analytically. An approximate analytical expression for the concentration of substrate and product are obtained by using the Homotopy perturbation method. The primary result of this work is simple approximate calculation of concentration for all possible values of parameters. This method can be easily extended to find the solution of all other non-linear reaction diffusion equations in metabolic modeling for various complex boundary conditions.

**References**

Appendix A

Approximate analytical solution of the concentration of the substrate and concentration of the product using new Homotopy perturbation method. In this appendix, solution of non-linear system of equations Eq. (8) and Eq. (9) is derived using the new Homotopy perturbation method.

\[
(1 - p) \left\{ \frac{d^2 u}{dx^2} + m - \frac{\alpha v}{1 + \beta v(x = 1)} \right\} + p \{ (1 + \beta v)(\frac{d^2 u}{dx^2} + m) - \alpha v \} = 0 \quad (A.1)
\]

\[
(1 - p) \left\{ \frac{d^2 v}{dx^2} - m_1 + \frac{\alpha_i v}{1 + \beta_i v(x = 1)} \right\} + p \{ (1 + \beta v)(\frac{d^2 v}{dx^2} - m_1) + \alpha_i v \} = 0 \quad (A.2)
\]

Supposing the approximate solutions of Eq.(A.1) and Eq.(A.2) have the form

\[
\begin{align*}
\left\{ u = u_0 + p u_1 + p^2 u_2 + \ldots \\
v = v + p v_1 + p^2 v_2 + \ldots
\end{align*}
\]

(A.3)

Substituting Eq. (A.3) into Eq. (A.1) and Eq. (A.3) into Eq. (A.2) (respectively), and equate the terms with the identical powers of $p$, we obtain

\[
p^0 = \frac{d^2 u_0}{dx^2} + m - \frac{\alpha v_0}{1 + \beta} \quad \text{(A.4)}
\]

\[
p^1 : \frac{d^2 u_1}{dx^2} + \frac{\alpha v_1}{1 + \beta} - \alpha \alpha_i (v_0 + \beta v_0^2) = 0
\]

and

\[
p^0 \ : \frac{d^2 v_0}{dx^2} - m_1 + \frac{\alpha v_0}{1 + \beta} = 0 \quad \text{(A.6)}
\]

\[
p^1 : \frac{d^2 v_1}{dx^2} + \frac{\alpha v_1}{1 + \beta} - m_1 + \alpha v_0 \left( \frac{2 + \beta + \beta v_0}{1 + \beta} \right) = 0 \quad \text{(A.7)}
\]

The initial conditions are as follows:

\[
u_0(x = 0) = 0; u_0(x = 1) = 0 \quad \text{(A.8)}
\]

\[
dv_0(x = 0)/dx = 0; v_0(x = 1) = 1 \quad \text{(A.9)}
\]

and

\[
u_i(x = 0) = 0; u_i(x = 1) = 0 \quad \text{for all } i = 1, 2, 3, \ldots \quad \text{(A.10)}
\]

\[
dv_i(x = 0)/dx = 0; v_i(x = 1) = 1 \quad \text{for all } i = 1, 2, 3, \ldots \quad \text{(A.11)}
\]

Solving the Eq.(A.4) and Eq.(A.6) and using the boundary conditions Eq.(A.8) and Eq.(A.9), we get

\[
u(x) = \frac{x}{2(m + m_0 + \alpha)} \left\{ \frac{1}{\cosh \left( \frac{m - m_0 x}{1 + \beta} \right)} \right\} - \frac{1}{2(m + m_0 + \alpha)} \left\{ \frac{1}{\cosh \left( \frac{m - m_0 x}{1 + \beta} \right)} \right\} \left( \frac{x}{2(m + m_0 + \alpha)} \right)^{1 - (1 + \beta) x} \sum_{i=0}^{\infty} \frac{(-1)^i}{\cosh \left( \frac{m - m_0 x}{1 + \beta} \right)^i} \left( \frac{x}{2(m + m_0 + \alpha)} \right)^i \quad \text{(A.12)}
\]
\[ v_0(x) = \sec h \left( \sqrt{\frac{m_1 - \frac{\alpha_1}{1 + \beta}}{1 + \beta}} x \right) \] (A.13)

Substituting the values of \( u_0(x) \) in the Eq. (A.5) and solving the equations, using the boundary conditions Eq. (A.10) and Eq. (A.11), we can obtain the value of \( u(x) \). Similarly we can get the value of \( v_1(x) \) by solving the Eq. (A.7). When \( p=1 \), the approximate solution Eq. (A.3) becomes

\[ u_0(x) = u_0 + u_1 \approx u_0 \] (A.14)

\[ v_0(x) = v_0 + v_1 \approx v_0 \] (A.15)

Using the above equations, we get Eq. (12) and Eq. (13) in the next.

**Appendix B**

Matlab/Scilab program to find the numerical solution of equations (8)-(9).

```matlab
function pdex4
m = 0;
x = linspace(0,1);
t = linspace(0,1);
sol = pdepe(m,@pdex4pde,@pdex4ic,@pdex4bc,x,t);
u1 = sol(:,:,1);
u2 = sol(:,:,2);
figure
plot(x,u1(end,:))
title('u1(x,t)')
xlabel('Distance x')
ylabel('u1(x,2)')
figure
plot(x,u2(end,:))
title('u2(x,t)')
xlabel('Distance x')
ylabel('u2(x,2)')

function [c,f,s] = pdex4pde(x,t,u,DuDx);
c = [1;1];
f = [1;1].*DuDx;
m2=3;
m1=3;
alpha=3;
beta=.01;
alpha1=.0001;
F1=m2-((alpha*u(2))/(1+beta*u(2)));```

```
F2=-m1*u(2)+((alpha1*u(2))/(1+beta*u(2)));  s=[F1;F2];
% --------------------------------------------------------------
function u0 = pdex4ic(x);
    u0 = [0;0];
% --------------------------------------------------------------
function [pl,ql,pr,qr]=pdex4bc(xl,ul,xr,ur,t)
    pl=[ul(1)-0;0];
    ql=[0;1];
    pr=[ur(1)-0;ur(2)-1];
    qr =[0;0];