

New Solution of Substrate Concentration in the Biosensor Response by Discrete Homotopy Analysis Method

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ABSTRACT

In this article, Discrete Homotopy Analysis Method (DHAM), as a new numerical method, is employed to investigate amperometric biosensor at mixed enzyme kinetics and diffusion limitation. Mathematical modeling of the problem is developed utilizing non-Michaelis-Menten kinetics of the enzymatic reaction. Different results are obtained for different values of the dimensionless parameters described in the paper. The presented solution is then compared with the available actual and simulated results.

Keywords: Discrete Homotopy Analysis Method; Amperometric Biosensor; Mathematical Modeling; Non-Michaelis-Menten Kinetics

1. Introduction

Biosensor is a device which measures biologically relevant information such as oxygen electrodes, neutral interfaces, etc. [1]. It is also utilized as a component of the transduction mechanisms [1]. Furthermore, it has been applied as a transducer, mapping the change in biomolecules into electrical signals [2]. Biosensors produce a signal indicative of the concentration of the measured analyte. As such, they are used in many industrial, environmental, food safety [3], and medical applications. Examples of such use are detection of pathogens [4], toxic metabolites such as mycotoxins [5], and pesticides and water contaminants such as heavy metal ions [6]. These applications showcase the wide usage and studies of biosensors and highlight the requirement of low detection limits and quicker analysis with high specificity for biosensors [2]. Mathematical modeling is widely used as an important tool to investigate and optimize the analytical characteristics of biosensors [9]. Investigative monolayer membrane contained in the model biosensors are used to study the biochemical treatment of biosensors [7,8]. The mathematical model developed is based on reaction-diffusion equations including none-linear terms that relate to non-Michaelis-Menten kinetics of the enzymatic reaction [9,10].

In addition to several numerical methods employed for

solving linear and nonlinear differential equations, there exists some analytical methods such as perturbation method [11], δ -expansion method [12], Adomian decomposition method (ADM) [13,14], and Homotopy perturbation method (HPM) [15,16]. All of the above mentioned methods including the numerical methods have certain restrictions, such as necessity for existence of small parameters, incapability of determining convergence regions, etc. One of the analytical methods proposed in the last couple of decades is homotopy analysis method (HAM) in which many of these restrictions have been omitted. In 1992, Liao introduced homotopy analysis method (HAM) for solving strongly nonlinear differential equations [17]. Using the linear property of homotopy, one can transform a nonlinear problem into an infinite number of linear sub-problems regardless of the existence of small parameters in the original non-linear problem. HAM is a powerful mathematical technique and has already been applied to several nonlinear problems [16-22].

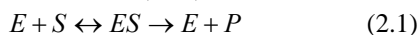
Since HAM has many advantages in comparison to other analytical methods, it is employed to solve continuous problems. Hence, after the discrete ADM method [23], discrete Homotopy analysis method (DHAM) was introduced in 2010 by Zhu *et al.* [24]. This method can be applied to complex problems containing discontinuity

in fluid characteristics and the geometry of the problem. In addition, it needs little computational cost as a numerical method in comparison to HAM as an analytical approach. DHAM has similar advantages to continuous HAM. For instance, by means of introducing an auxiliary parameter one can adjust and control the convergence region of the solution series. This method should be employed for solving various differential equations to highlight its high capabilities in comparison with other numerical methods.

The main focus of this paper is on amperometric biosensor at mixed enzyme kinetics and diffusion limitation by utilizing DHAM as a powerful method. Non-Michaelis-Menten kinetics of the enzymatic reaction is used to obtain the constitutive equation of the problem. Several non-dimensional parameters are defined to the dimensionless equation. The obtained non-dimensional equation is used to procure the m^{th} -order deformation equation as an important step towards obtaining the solution. The h -curves obtained for several cases are illustrated in this paper to clarify the convergence region of the solution. Finally, the obtained solution is analyzed to investigate the effects of varying each dimensionless parameter in the procured equation of the problem. In addition, some of the results are compared with the actual and simulated results available in the literature [25].

2. Mathematical Modeling

Spatial dependency of enzyme kinetics on biochemical systems has recently attracted much attention by considering the effect of diffusion in these processes [9,10]. The simplest scheme of non-Michaelis-Menten kinetics may for instance be described by adding to the Michaelis-Menten scheme (2.1) the relationship of the interaction of the enzyme substrate complex (ES) with another substrate molecule (S) (2.2) followed by the generation of non-active complex (ES_2) as



The reaction is sometimes said to display Michaelis-Menten kinetics in which the relationship between the rate of an enzyme catalyzed reaction and the substrate concentration takes the form

$$v = \frac{V_{\max} [S]}{K_M + [S]} \quad (2.3)$$

where v and V_{\max} are the so-called "initial reaction velocity" and maximum velocity respectively.

In addition, K_M is known as Michaelis constant for S . K_M and V_{\max} are constants at a given temperature and a given enzyme concentration.

The reactions exhibit non-Michaelis-Menten kinetics, in which the kinetic behavior does not obey the Equation

(2.3). The velocity function v for the simple reaction process without competitive inhibition is given by Pao [26] and Baronas *et al.* [27], which is based on the non-Michaelis-Menten hypothesis,

$$v = \frac{k_c [E]_0 [S]}{K_M + [S] + [S]^2 / K_i} = \frac{V_{\max} [S]}{K_M + [S] + [S]^2 / K_i} \quad (2.4)$$

where the constants $V_{\max} = k_c [E]_0$, K_M and K_i are Michaelis-Menten and inhibition constants respectively. The Equation (2.4) conforms to Equation (2.3) for large values of K_i with respect to K_M . On the basis of Equation (2.4), the rate is maximized by increasing the concentration. It is then said to be inhibited by the substrate. In addition, the constant K_i (which has the dimension of a concentration) is called the substrate inhibition constant. For obtaining the rate of change of substrate concentration $S = S(\eta, t)$ at time t and position $\eta \in \Omega$ throughout the domain, the following equation given by Pao [26] is used.

$$\frac{\partial S}{\partial t} = D_s \nabla \cdot (\nabla S) - v(\eta, t) \quad (2.5)$$

D_s is the substrate diffusion coefficient and ∇S is the gradient operation. On the basis of non-Michaelis-Menten kinetics, Equation (2.5) becomes

$$\frac{\partial S}{\partial t} = D_s \frac{\partial^2 S}{\partial \eta^2} - \frac{KS}{1 + S/K_M + S^2/K_i K_M} \quad (2.6)$$

in which $K = K_c E_0 / K_M$.

In this paper, the steady state condition is accounted for and hence, Equation (2.6) is changed to the non-dimensional form [25] using the following non-dimensional parameters

$$D_s \frac{\partial^2 S}{\partial \eta^2} - \frac{KS}{1 + S/K_M + S^2/K_i K_M} \quad (2.7)$$

$$u = \frac{S}{ks^\infty}, \quad x = \frac{\eta}{L}, \quad K = \frac{kL^2}{D_s} = \phi^2, \quad \alpha = \frac{ks^\infty}{K_M}, \quad \beta = \frac{ks^\infty}{K_i K_M}$$

This results in the following non-dimensional differential equation

$$\frac{\partial^2 u}{\partial x^2} - \frac{Ku}{1 + \alpha u + \beta u^2} = 0, \quad 0 < u \leq 1 \quad (2.8)$$

Equation (2.8) must be solved such that it satisfies the following boundary conditions

$$\begin{aligned} u &= 1 & \text{at } x &= 1 \\ \frac{\partial u}{\partial x} &= 0 & \text{at } x &= 0 \end{aligned} \quad (2.9)$$

3. Analytical and Numerical Solutions

DHAM Solution

The discrete form of the nonlinear differential equation

(Equation (2.8)) is obtained as the first step of DHAM’s procedure of the solution

$$N[\varphi_i(q)] = \left(1 + \alpha\varphi_i(q) + \beta(\varphi_i(q))^2\right) \frac{\varphi_{i-1}(q) - 2\varphi_i(q) + \varphi_{i+1}(q)}{\Delta x^2} - K\varphi_i(q) \tag{3.1}$$

where i is the node number, N is the nonlinear operator, and the function $\varphi_i(q)$ is defined as

$$\lim_{q \rightarrow 0} \varphi_i(q) = u_{0,i}(X),$$

$$\lim_{q \rightarrow 1} \varphi_i(q) = u_i$$

where u_i is the unknown field variable at node number i , $q \in (0,1)$ is the embedding parameter, and $u_{0,i}$ is the initial guess which is employed to meet the requirements of the boundary conditions. Here, $U_{0,i}$ is valued at “1” satisfying all the boundary conditions stated in Equation (2.9).

Through the generalizing concept of DHAM, the so-called zero-order deformation equation can be written as

$$(1-q)L[\varphi_i(q) - u_{0,i}] = qhH_iN[\varphi_i(q)]$$

where $h \neq 0$ is the non-zero auxiliary parameter, H_i is the auxiliary function, and L is the auxiliary linear operator which is chosen here as

$$\mathcal{L}(f_i) = \frac{f_{i-1} - 2f_i + f_{i+1}}{\Delta x^2} \tag{3.2}$$

Expanding $\varphi_i(q)$ in Taylor series with respect to the embedding parameter q , one obtains

$$\varphi_i(q) = u_{0,i} + \sum_{m=1}^{\infty} u_{m,i} q^m$$

$$u_{m,i} = \frac{1}{m!} \left. \frac{\partial^m \varphi_i(q)}{\partial q^m} \right|_{q=0}$$

With due attention to the procedure of DHAM [27], $u_{m,i}$ should be chosen so as the following equation is satisfied

$$\frac{3u_{m,0} - 4u_{m,i} + u_{m,i}}{2\Delta x} = u_m(1) = 0 \tag{3.3}$$

If the series $\varphi_i(q)$ converges at $q=1$, then the series solution is

$$\varphi_i(1) = u_{0,i} + \sum_{m=1}^{\infty} u_{m,i}$$

where $u_{m,i}$ could be obtained by the so-called high-order deformation equation. For obtaining the m^{th} -order deformation equation, the following vector is defined as

$$\mathbf{u}_n = \{u_{0,i}, u_{1,i}, \dots, u_{n,i}\}$$

Differentiating both sides of the zero-order equation m

times with respect to q and then setting $q=0$, the so-called m^{th} -order deformation equation can be obtained as

$$L[u_{m,i} - \chi_m u_{m-1,i}] = hH_i R_{m,i}(\mathbf{u}_{m-1})$$

where

$$\chi_m = \begin{cases} 0, & m \leq 1 \\ 1, & \text{otherwise} \end{cases}$$

$$R_{m,i}(\mathbf{u}_{m-1}) = \frac{1}{(m-1)!} \left. \frac{\partial^{m-1} N[\varphi_i(q)]}{\partial q^{m-1}} \right|_{q=0}$$

Therefore, the following relation is obtained

$$R_{m,i}(\mathbf{u}_{m-1}) = u_{m-1}'' + \alpha \sum_{j=0}^{m-1} u_j u_{m-1-j}'' + \beta \sum_{j=0}^{m-1} u_{m-1-j} \sum_{k=0}^j u_k u_{j-k}'' - K u_{m-1}$$

We are free to choose the auxiliary parameter h , the auxiliary function H_i , the initial guess $u_{0,i}$, and the auxiliary linear operator L so that the validity and flexibility of the DHAM solution to control the convergence region is proven. Due to the rule of solution expression [27], the auxiliary function is chosen as follows

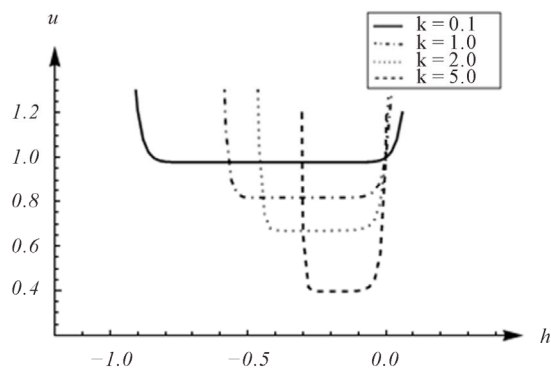
$$H_i = 1$$

According to the DHAM, the valid region of the auxiliary parameter h for convergence of the solution series is the flat regions of h -curves. To see the proper values of h , the h -curves are plotted for different values of dimensionless parameters α , β and K in **Figure 1** for obtaining the valid results for the considered conditions.

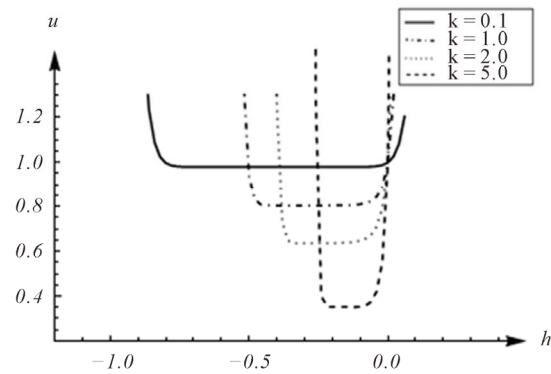
4. Results and Discussion

The procedure for solving the non-dimensional equation of enzyme reaction (Equation (2.8)) which is based on the non-Michaelis-Menten kinetics theory utilizing DHAM is described in the Section 3. It is mentioned there that the m^{th} -order deformation equation should be employed to solve the problem. As the first step towards the solution, the diagrams for variation of non-dimensional parameter $u(X)$ versus auxiliary parameter h for different investigated cases are illustrated in **Figure 1**. Then, the flat region of h -curves in each case is obtained from these diagrams.

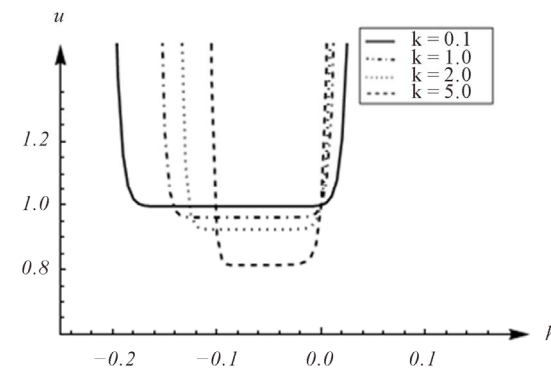
On the basis of the chosen values of auxiliary parameter h in the flat regions of h -curves (**Figure 1**), some useful diagrams including variations of $u(X)$ versus X (**Figure 2**) are procured to clarify the dependency of these variations on different non-dimensional parameters defined in Equation (2.8). It is shown in **Figure 2** that the effect of variation of non-dimensional parameter K on the profiles of $u(X)$ is substantial. Values of $u(X)$ at



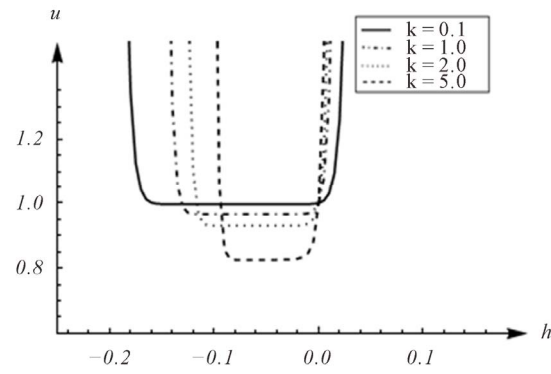
(a)



(b)

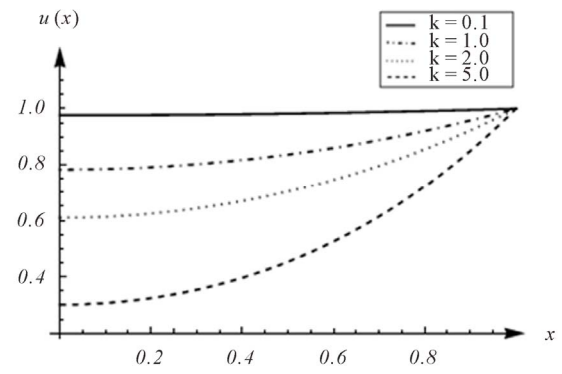


(c)

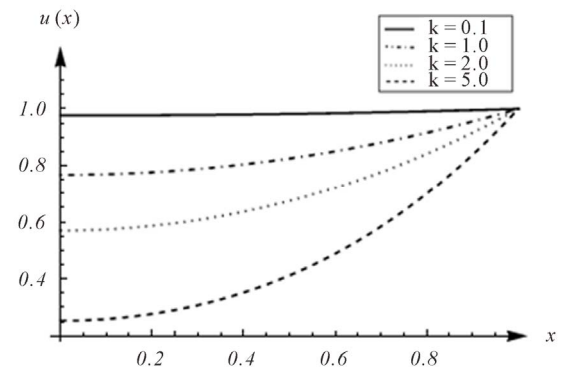


(d)

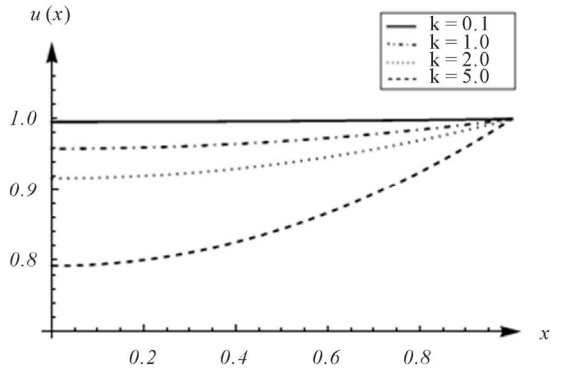
Figure 1. Variations of $u(X)$ versus non-dimensional parameter X for (a) $\alpha = 1.0, \beta = 0.1$, (b) $\alpha = 0.1, \beta = 1.0$, (c) $\alpha = 10.0, \beta = 0.1$ and (d) $\alpha = 10.0, \beta = 1.0$.



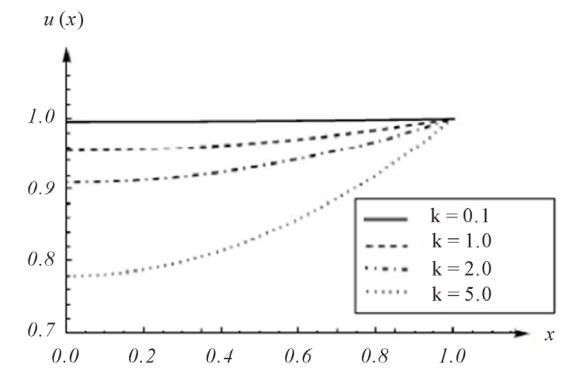
(a)



(b)



(c)



(d)

Figure 2. Variations of $u(X)$ versus auxiliary parameter h for (a) $\alpha = 1.0, \beta = 0.1$, (b) $\alpha = 0.1, \beta = 1.0$, (c) $\alpha = 10.0, \beta = 0.1$ and (d) $\alpha = 10.0, \beta = 1.0$.

different locations are presented in **Tables 1** and **2** for better clarifying the effects of K , as well as other non-dimensional parameter (α, β) . It is clearly shown that the values of variable for lower value of α are lower than the higher ones. In addition, the spatial variation of variables which is also shown in **Figure 2** is clarified.

Verification of the Solution

The results of the problem obtained by employing DHAM and the results procured by simulation and actual results [25] are compared in **Table 3** to show the accuracy of the presented solution. As such, the presented result in this paper can be utilized as promising data for investigating the behavior of the enzyme reaction in the considered conditions.

5. Conclusions

Solution to the amperometric biosensor at mixed enzyme kinetics and diffusion limitation is presented utilizing

DHAM as a new numerical method. Dimensionless equation of the problem is obtained using the mathematical modeling presented in this paper, which is based on non-Michaelis-Menten kinetics of the enzymatic reaction. Solution procedure of the non-dimensional equation of enzyme reaction is described and m^{th} -order deformation equation is obtained on the basis of the non-dimensional enzyme reaction equation presented in this paper. Several h -curves are depicted to show the convergence region of the solution. Results of the solution are presented for different quantities of the dimensionless parameters used to non-dimensionalize the enzyme reaction equation. It is shown that the most effective parameter in the reaction and local dependency of the dependent variable of the problem $u(X)$ is K . Available results in the literature are used conclusively to prove the high accuracy of the presented solution.

On the basis of the presented solution for the considered problem in the area of enzyme kinetics, it can be concluded that DHAM can be employed to solve differ-

Table 1. Values of non-dimensional variable $u(X)$ at different locations for $\alpha = 1.0, \beta = 0.1$ and $\alpha = 0.1, \beta = 1.0$ for different values of non-dimensional parameter K .

x	$\alpha = 1.0, \beta = 0.1$				$\alpha = 0.1, \beta = 1.0$			
	$K = 0.1$	$K = 1.0$	$K = 2.0$	$K = 5.0$	$K = 0.1$	$K = 1.0$	$K = 2.0$	$K = 5.0$
0	0.9764	0.7831	0.6097	0.3012	0.9762	0.7675	0.5694	0.2532
0.2	0.9773	0.7916	0.6246	0.3244	0.9771	0.7767	0.5860	0.2770
0.4	0.9802	0.8172	0.6695	0.3967	0.9800	0.8044	0.6360	0.3521
0.6	0.9849	0.8601	0.7457	0.5255	0.9848	0.8507	0.7207	0.4884
0.8	0.9915	0.9209	0.8551	0.7221	0.9914	0.9159	0.8416	0.7000
1.0	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000

Table 2. Values of non-dimensional variable $u(X)$ at different locations for $\alpha = 10.0, \beta = 0.1$ and $\alpha = 10.0, \beta = 1.0$ for different values of non-dimensional parameter K .

x	$\alpha = 10.0, \beta = 0.1$				$\alpha = 10.0, \beta = 1.0$			
	$K = 0.1$	$K = 1.0$	$K = 2.0$	$K = 5.0$	$K = 0.1$	$K = 1.0$	$K = 2.0$	$K = 5.0$
0	0.9955	0.9551	0.9105	0.7790	0.9958	0.9583	0.9167	0.7924
0.2	0.9957	0.9569	0.9141	0.7878	0.9960	0.9600	0.9200	0.8007
0.4	0.9962	0.9623	0.9248	0.8142	0.9965	0.9650	0.9300	0.8255
0.6	0.9971	0.9712	0.9427	0.8583	0.9973	0.9733	0.9467	0.8670
0.8	0.9984	0.9838	0.9678	0.9202	0.9985	0.9850	0.9700	0.9252
1.0	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000

Table 3. Comparison of results of the DHAM with simulation and actual results of the problem at different location and for different values of non-dimensional parameter K .

x	$K = 0.1$			$K = 1.0$			$K = 5.0$		
	Simulation	DHAM	Actual	Simulation	DHAM	Actual	Simulation	DHAM	Actual
0	0.9500	0.9520	0.9520	0.6500	0.6481	0.6481	0.2100	0.2113	0.2113
0.25	0.9529	0.9550	0.9550	0.6666	0.6684	0.6684	0.2502	0.2452	0.2452
0.50	0.9618	0.9639	0.9639	0.7295	0.7308	0.7308	0.3585	0.3578	0.3578
0.75	0.9767	0.9789	0.9789	0.8386	0.8390	0.8390	0.5893	0.5851	0.5851
1.0	0.9976	1.0000	1.0000	0.9940	1.0000	1.0000	0.9970	1.0000	1.0000

ent nonlinear ordinary differential equations used to model different problems in Engineering and Science. The accuracy is clearly shown and the ability of the approach to control the convergence of the solution is obviously shown. Therefore, the employed method not only can be used to solve different complicated nonlinear problems but also can be considered as a promising numerical technique.

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