Chapter 2

Mathematical Modeling and Simulation of Nonlinear Process in Enzyme Kinetics

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Abstract

A deep and analytical understanding of the enzyme kinetics has attracted a great attention of scientists from biology, medicine, chemistry, and pharmacy. Mathematical models of enzyme kinetics offer several advances for this deep and analytical understanding due to their in compensable potential in predicting kinetic processes and anticipating appropriate interventions when required. This chapter concerns mathematical modeling analysis and simulation of enzyme kinetics. Experimental data and available knowledge on enzyme mechanics are used in constituting a mathematical model. The models are either in the form of linear or nonlinear ordinary differential equations or partial differential equations. These equations are composed of kinetic parameters such as kinetic rate constants, initial rates, and concentrations of enzymes. The nonlinear nature of enzymatic reactions and a large number of parameters have caused major issues with regard to efficient simulation of those reactions. In this work, an enzymatic system that includes Michaelis-Menten and Ping Pong kinetics is modeled in the form of differential equations. These equations are solved numerically in which the system parameters are estimated. The numerical results are compared with the results from an existing work in literature.

Keywords: mathematical modeling, enzyme kinetics, chemical kinetics, nonlinear reaction-diffusion equation, amperometric, cyclic voltammetry, chronoamperometric

1. Introduction

Enzyme kinetics is a challenging research field nowadays incorporating modern applied mathematics into biotechnology, engineering science, and pharmacy. Moreover, in medical studies, scientists work on human metabolism to improve the capabilities of some metabolites or enzymes in metabolic pathways. In industrial applications, kinetics methods are also widely used to

develop certain methods for improving functionality of some molecules in a cell. Many problems in theoretical and experimental biology/chemistry involve the solution of the steady-state reaction diffusion equation with nonlinear chemical kinetics. Such problems also arise in the formulation of substrate and product material balances for enzymes immobilized within particles [1, 2], in the description of substrate transport into microbial cells [3–5], in membrane transport, in the transfer of oxygen to respiring tissue [6, 7], and in the analysis of any artificial kidney system [8].

To impose the functionality of some molecules in a cell, a mathematical model of such metabolic systems must be constructed and simulated. Most of the dynamical systems can be approximated by various types of differential and integral equations involving finite number of variables and parameters. Thus, the future behavior of the system can be predicted if model kinetics parameters and initial states of the variables are available. In particular, ordinary and partial differential equations (ODEs and PDEs) are popular in modeling of the metabolic pathways or enzyme kinetics.

Releasing enzyme-substrate reactions under single-molecule kinetics was reported by Shlomi et al. [9]. An integral equation method with Michaelis-Menten kinetics to solve nonlinear diffusion problems in spherical coordinates was stated by Tosaka and Miyale [10]. Maalmi et al. [11] reported numerical and semianalytical solutions of nonlinear equations, which covered diffusivity, size, bulk concentration of reactant, binding constant of Michaelis-Menten kinetics, and site reactivity values. Merchant [12] stated the M-M decay reaction terms and the Gray-Scott scheme along with the semianalytical method to nonlinear reaction-diffusion systems. Indira and Rajendran [13] described a homotopy perturbation method to obtain substrate and product concentrations within the enzymatic layers. Removal of substrate from Michaelis-Menten kinetics governed the extravascular partition in which the analytical solution for the steady-state condition was investigated by Bucolo and Tripathi [14]. Dang Do and Greenfield [15] utilized the finite integral transform method to elucidate the problem based on the nonlinear reaction diffusion coupled with the chemical kinetics of a general shape solid. Chapwanya et al. [16] conveyed an epidemiological model with the Michaelis-Menten contact rate formulation to investigate variations in the enzyme kinetics with a simple susceptible infected recovered (SIR) model. Napper [17] proposed the Michaelis-Menten kinetics model to investigate the oxygen transport to heart tissue. Regalbuto et al. [18] presented an analytical methodology for obtaining solutions based on the maximum principle to nonlinear reaction-diffusion boundary value problems.

Rajendran and Saravanakumar [19] discussed mediated bioelectrocatalysis in order to build bioreactors, bio fuel cells, and biosensors.

Due to the difficulties in solving nonlinear differential equations in enzyme kinetics, some recent advanced analytical and numerical simulation techniques are used to solve the problems in chemical kinetics. Thus, in this review, all analytical and numerical works in enzyme kinetics are summarized.

2. Reaction diffusion systems

Reaction diffusion system is a mathematical model based on how the concentration of substances/products is disseminated over space changes under the influence of diffusion and a local

chemical reaction. The substances are transformed into each other in local chemical reaction, whereas the substances are spread out over a surface in space in diffusion. Reaction-diffusion (RD) systems arise in many branches of physics, chemistry, biology, ecology, etc. Reviews of the theory and applications of reaction-diffusion systems can be found in books and numerous articles (see, for example [20–23]). These arise in a large variety of application areas, such as flow in porous media [24], heat conduction in plasma [25], combustion problems [26], liquid evaporation [27], and of more recent interest, image processing [28]. A great effort is being made in the development of the mathematical theory of nonlinear diffusion equations and to obtain exact solutions for special cases. Their significance not only relies on the huge number of their applications but also on the fact that they provide with a rather general class of linear and nonlinear differential operators. In mathematical analysis, it has shown to be a milestone for the development of applied, abstract, and numerical analysis as well as for algebra, geometry, and topology.

3. Nonlinear phenomena

The modern theory of the nonlinear reaction diffusion process is an important field in today's science. The nonlinear system and coherent structures represent an interdisciplinary area with many nonlinear applications in various fields. Those applications can be divided into six disciplines: chemistry (autocatalytic chemical and enzyme reactions), physics (nonlinear optics and electric circuits, plasmas and states of solid, condensed atomic gases, hydrodynamics, galaxy dynamics and cosmology, fluid dynamics, and celestial mechanics), general relativity, biology (biofuel cell, bioreactor and biosensor, atmosphere and oceans, and animal dispersal), random media, and modern telecommunications. A great variety of phenomena in physics, chemistry, or biology can be described by nonlinear ODE/PDEs and particularly by reaction-diffusion equations. For these reasons, the theory of the analytical solutions of the reaction-diffusion equations is considered.

In reaction diffusion systems, nonlinear phenomena play a crucial role in applied mathematics and chemistry. Exact (closed-form) solution of nonlinear reaction diffusion equations plays an important role in the proper understanding of qualitative features of many phenomena and processes in various areas of natural science. The main result obtained from reaction and diffusion systems is that nonlinear phenomena include diversity of stationary and spatio-temporary dissipative patterns, oscillations, different types of waves, excitability, biostability, etc. But it is difficult for us to obtain the exact solution for these problems. The investigation of exact solution of nonlinear equation is interesting and important. In general, this results in the need to solve linear and nonlinear reaction diffusion equations with complex boundary conditions. The enzyme kinetics in biochemical systems have usually been modeled by differential equations, which are based only on reaction without spatial dependence of the various concentrations. The dimensionless nonlinear reaction diffusion equations are described below:

$$\frac{\partial S}{\partial \tau} = \nabla^2 S - f(R, \tau, S, P) \tag{1}$$

$$\frac{\partial P}{\partial \tau} = \nabla^2 P + g(R, \tau, S, P) \tag{2}$$

where S and P represent the dimensionless concentrations of substrate and product, τ represents the dimensionless time, and R is the dimensionless radial co-ordinate of the particle. The first term on the right-hand side of the above equation accounts for active species (substrate or product) diffusion, whereas the second term $f(R, \tau, S, P)$ and $g(R, \tau, S, P)$ represents the homogeneous reaction term (nonlinear term), generally polynomial in the concentrations and time.

4. Common geometries and nonlinear reaction

Most commonly used electrodes/microelectrodes consist of a conducting metal/glassy carbon or semiconducting surface embedded in an insulating wall. When the conducting surface is a rectangle or disc of a few millimeters, this is known as a "planar" electrode. Diffusion to this surface is effectively planar (the effects of the edges are negligible), hence the nonlinear one-dimensional reaction diffusion equation is given by:

$$\frac{\partial[C]}{\partial t} = D\frac{\partial^2[C]}{\partial x^2} + f([C]) \tag{3}$$

Two other electrode geometries where diffusion occurs in only one spatial dimension are the hemispherical and hemicylindrical electrodes. The nonlinear two-dimensional (hemispherical or spherical) reaction diffusion equation is:

$$\frac{\partial[C]}{\partial t} = D\left(\frac{\partial^2[C]}{\partial x^2} + \frac{2}{r}\frac{\partial[C]}{\partial r}\right) + f([C]) \tag{4}$$

and for the latter is:

$$\frac{\partial[C]}{\partial t} = D\left(\frac{\partial^2[C]}{\partial x^2} + \frac{1}{r}\frac{\partial[C]}{\partial r}\right) + f([C]) \tag{5}$$

The hemisphere can be achieved experimentally via a small drop of mercury positioned over a smaller conducting disc. A soft polymer, rubber, or other similar materials are usually employed to fabricate a hemicylinder. The electrodes are usually employed in theoretical studies due to the low dimensionality of the mass-transport equation. Additional terms such as diffusion and nonlinear reaction allow the equation to be solved analytically. Furthermore, the electrodes are not accurately or easily fabricated for practical geometries.

The corresponding nonlinear reaction-diffusion issues in enzyme kinetics are focused on the mathematical resolution. **Table 1** shows the response of particular electrodes with special emphasis on earlier theoretical works in the field.

Example 1: Michaelis-Menten kinetics and microcylinder electrodes

The model is written for an enzyme reaction to generate an electro-active product (e.g., hydrogen peroxide from an oxidase enzyme) that reacts at an immobilization matrix, which

Author	Reference	Experimental technique	Enzymatic scheme	Modeling method
		Analytical solutions		
G. Rahamathunissa et al.	Journal of theoretical and Computational Chemistry, 7(1)(2008)113–138	Amperometric	$S + C \overset{K_M}{\rightarrow} [SC] \rightarrow \left[PC^{'}\right] \overset{k_c}{\rightarrow} P + CC^{'} \overset{k_E^{'}}{\rightarrow} C$	Danckwort's expression
R. Senthamarai et al.	Electrochemical Acta 53(2008)3566–3578	Chronoamperometric	$A + e \rightarrow B$ $B + Z \overset{k}{\rightarrow} A + product$	Analytical
G. Rahamathunissa L. Rajendran	Journal Mathematical Chemistry 44(2008)849–801	Amperometric	$E + S \overset{K_M}{\leftrightarrow} ES \overset{K_2}{\rightarrow} E + P$	Variation iteration method (VIM)
A. Meena et al.	Journal Mathematical Chemistry, 48(2010)179–186	Amperometric	$E + S \underset{K_{-1}}{\overset{K_1}{\rightarrow}} ES \rightarrow E + P$	He's variation iteration method
A. Eswari, L. Rajendran	Journal of Electroanalytical Chemistry 641(2010) 35–44	Amperometric	$S + E_1 \underset{K_2}{\overset{K_1}{\leftrightarrow}} [E_1S] \overset{K_{cat}}{\rightarrow} P + E_2$	Homotopy perturbation method (HPM)
P. Manimozhi et al.	Sensors and Actuators B 147(2010)290–297	Amperometric	$E + S \underset{k_{-1}}{\overset{k_1}{\rightarrow}} ES \overset{k_c}{\rightarrow} E + P$ $ES + S \leftrightarrow ES_3$	Variational iteration and homotopy perturbation method (VIM & HPM)
S. Logambal, L. Rajendran	Electrochemical Acta 55(2010)5230–5238	Amperometric	$A + E_2 \overset{K_A}{\rightarrow} B + E_1$ $E_1 + S \overset{K_E}{\rightarrow} E_2 + P$	Homotopy perturbation method (HPM)
A. Meena, L. Rajendran	Journal of Electroanalytical Chemistry, 6411 (2010)50–59	Amperometric and Potentiometric	$E + S \leftrightarrow [ES] \rightarrow E + P$	Homotopy perturbation method (HPM)
S. Anitha, L. Rajendran	Journal of Physical Chemistry 114(2010)7030–7037	Amperometric	$B \overset{D_E}{\rightarrow} B + S \overset{K}{\rightarrow} A + Z \rightarrow A \rightarrow B$	Reduction of order method
P. Manimozhi, L. Rajendran	Journal of Electroanalytical Chemistry 647(2010) 87–92	Amperometric	$S + E \underset{K_a}{\overset{K_a}{\leftrightarrow}} ES$ $ES \overset{K_{cat}}{\rightarrow} S^{'} + E$	Analytical
A. Eswari, L. Rajendran	Journal of Electroanalytical Chemistry 648(2010) 36–46	Amperometric	$S + E_1 \underset{K_{-1}}{\overset{K_1}{\leftrightarrow}} [E_1S] \rightarrow P + E_2$	Homotopy perturbation method (HPM)
A. Eswari, L. Rajendran	Russian Journal of Electroanalytical Chemistry 47(2011)195–204	Cyclic voltammetry	$EA + e \leftrightarrow B$ $CB \overset{k_1}{\rightarrow}$ Products	Laplace Transformation
A. Eswari, L. Rajendran	Russian Journal of Electroanalytical Chemistry 47(2011)205–212	Cyclic voltammetry	$EA + e \leftrightarrow B$ $C_2\ B + B \overset{k_1}{\rightarrow}$ Products	Homotopy perturbation method (HPM)

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Author	Reference	Experimental technique	Enzymatic scheme	Modeling method
A. Eswari, L. Rajendran	Journal of Electroanalytical Chemistry 651(2011) 173–184	Chronoamperometric	$O + ne^- \leftrightarrow R$ $R + Z \overset{k}{\rightarrow} O + \text{Products}$	Homotopy perturbation method (HPM)
G. Rahamathunissa et al.	Journal of Mathematical Chemistry 9(2011)457–474	Chronoamperometric	$S + E \underset{}{\overset{k_M}{\leftrightarrow}} ES \overset{k_2}{\rightarrow} E + P$	VIM
S. Logambal, L. Rajendran	Journal of Membrane Sciences 373(2011)20–28	Amperometric	$E_{OX} + S \underset{k_M}{\overset{k_{-1}}{\leftrightarrow}} ES \overset{k_2}{\rightarrow} E_{red} + P$ $E_{red} + O_2 \overset{k_3}{\rightarrow} E_{OX} + H_2O_2$	Homotopy perturbation method (HPM)
S. Anitha et al.	Electrochimica Acta 56(2011)3345–3352	Amperometric	$S + E_1 \overset{K_M}{\leftrightarrow} [E_1S] \overset{k_{cat}}{\rightarrow} P + E_2A \rightarrow B$	Homotopy perturbation method (HPM)
K. Indra, L. Rajendran	Electrochimica Acta 56(2011)6411–6419	Chronoamperometric	$S_1 + O_2 \overset{PPO}{\rightarrow} P_2 + H_2O\ V_1$ $P_2 + 2e^- + 2H^+ \underset{k_r}{\overset{k_0}{\leftrightarrow}} S_2\ E^0$ $S_2 + \frac{1}{2}O_2 \overset{PPO}{\rightarrow} P_2 + H_2O\ V_2$	Homotopy perturbation method (HPM)
S. Thiagarajan et al.	Journal of Mathematical Chemistry DOI: 10.1007/s10919-011-9854-z	Chronoamperometric	$S + M_{ox} \overset{k_M}{\leftrightarrow} SM_{ox} \overset{k_{cat}}{\rightarrow} P + M_{red}$	Homotopy perturbation method (HPM)
M. Uma Maheswari, L. Rajendran	Journal of Mathematical Chemistry DOI: 10.1007/s10919-011-9853-0	Chronoamperometric	$E + S \overset{K_1}{\leftrightarrow}_{k-1} ES \overset{k_2}{\rightarrow} E + P$	Homotopy perturbation method (HPM)
P. Rijiravanich et al.	Electroanalytical Chemistry 589(2006)249	Amperometric	$O_2 + 2catechol \rightarrow 2o - quinone + 2H_2O$ $o - quinone + 2H^+ + 2e^- \rightarrow catechol$	Theory and experiment
A. Eswari, L. Rajendran	Journal of Electroanalytical Chemistry 660(2011) 200–208	Amperometric	$O_2 + 2catechol \rightarrow 2o - quinone + 2H_2O$ $o - quinone + 2H^+ + 2e^- \rightarrow catechol$	VIM
G. Varatharajan, L. Rajendran	Applied Mathematics 2(2011)1140–1147	Amperometric	$S + E \underset{k-1}{\overset{K_1}{\leftrightarrow}} C \overset{k_{cat}}{\rightarrow} P + E$ $E \overset{k_3}{\rightarrow} E_i$	Homotopy perturbation method (HPM)
K. Venugopal et al.	Journal of Biomedical Science and Engineering 4 (2011)631–641	Chronoamperometric	$O_2 + 2catechol \rightarrow 2o - quinone + 2H_2O$ $o - quinone + 2H^+ + 2e^- \rightarrow catechol$	Homotopy perturbation method (HPM)
K. Indra, L. Rajendran	Journal of Mathematical Chemistry DOI: 10.1007/s10910-011-9968-3	Chronoamperometric	$A \leftrightarrow B + C$ $B \pm e^- \rightarrow products$	Homotopy perturbation method (HPM)
V. Margret Ponrani, L. Rajendran	Journal of Mathematical Chemistry DOI: 10.1007/s10910-011-9973-6	Amperometric	$G + E \underset{K_1}{\overset{k_{-1}}{\leftrightarrow}} X \overset{k_{-2}}{\underset{k_2}{\rightarrow}} F + E$	Homotopy perturbation method (HPM)

Author	Reference	Experimental technique	Enzymatic scheme	Modeling method
S. Sevukaperumal et al.	Applied Mathematics 3(2012)373–381	Chronoamperometric	$Glucose + O_2 \overset{Glucoseoxidase}{\rightarrow} gluconicacid + H_2O_2$ $H_2O_2 \overset{Catalase}{\rightarrow} H_2O_2 + \frac{1}{2}O_2$	Homotopy analysis method (HPM)
		Numerical solution		
R. Baronas et al.	Biosensors and Bioelectronics 19(2004)915–922	Amperometric	$S \rightarrow P \overset{E}{\rightarrow} S$	Finite-difference technique
R. Baronas	Electrochimica Acta 240(2017)399–407	Amperometric biosensor	$S + E \leftrightarrow_{k_{-1}}^{k_1} ES \rightarrow P + E$ $S \overset{E}{\rightarrow} P$	Numerical simulation and analytical solution
V. Ašerisa et al.	Journal of Electroanalytical Chemistry 685(2012) 63–71	Amperometricparallel substrates conversion	$S_1 \overset{E_1}{\rightarrow} \frac{1}{2}P_1$ $S_1 + S_2 \overset{E_2}{\rightarrow} P_2$	Digital simulation-finite-difference technique
V. Flexer et al.	Bioelectrochemistry 74(2008)201–209	Cyclic voltammetry	$S + E_{OX} \leftrightarrow_{k_{-1}}^{k_1} ES \overset{k_{cat}}{\rightarrow} P + E_{red}$	Numerical simulation
R. Baronas et al.	Chemometrics and Intelligent Laboratory Systems 126(2013)108–116	Amperometric	$E + S_i k_{1_i} \leftrightarrow ES_i \overset{k_{2_i}}{\rightarrow} E + P_i, i = 1, \ldots, k$	Numerical
R. Baronas	Nonlinear Analysis: Modeling and Control 9(3) (2004)203–218	Amperometric	$S \overset{E}{\rightarrow} P$	Digital simulation-finite-difference technique.
R. Baronas et al.	Sensors 12(2012)9146–9160	Amperometric	$E_{OX} + S \overset{k_1}{\rightarrow} E_{red} + P$ $E_{red} \overset{k_2}{\rightarrow} E_{OX} + n_e e^-$	Finite-difference
R. Baronas et al.	J. Mathematical Chemistry 32 (2)(2002)225–237	Amperometric	$S \overset{E}{\rightarrow} P$	Numerical simulation
R. Baronas et al.	Mathematical Modeling of Biosensors, Springer Series on chemical sensors and biosensors (2009)	Amperometric	All enzyme reactions	Analytical and numerical methods
L. Rajendran	Biosensor: Modeling and Simulation of Diffusion-Limited Process, Chemical Sensors: Simulation and Modeling, GhenadiiKorotcenkov (Ed.), Electrochemical Sensors, Vol. 5, Momentum Press, LLC, New York (2013)	Amperometric	All enzyme reactions	Analytical, HPM&HAM, VIM,ADM, etc.

Table 1. Contributions to the theoretical modeling of enzymatic electrodes.

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is metallically conducting sites/particles. The reaction within the film under the Michaelis-Menten kinetics may be written as follows:

$$S + E_1 \underset{k_{-1}}{\overset{k_1}{\Leftrightarrow}} [E_1 S] \xrightarrow{k_{cat}} P + E_2 \tag{6}$$

The consumption rate of S is given by $k_1 c_S c_E - k_{-1} c_{ES}$, where c_i denotes the concentration of species i. The rate is equivalent to $(k_{cat}/K_M)\, c_S c_E$, where K_M is the Michaelis constant, defined as $K_M = (k_{-1} + k_{cat})/k_1$. The consumption rate of S in the film is compensated by diffusion. If the solution is stirred uniformly, so that S is constantly supplied to the film, the mass balance for S can be written in cylindrical coordinates:

$$\frac{D_S}{r}\frac{d}{dr}\left(r\frac{dc_S}{dr}\right) - \frac{k_{cat} c_E c_S}{c_S + K_M} = 0 \tag{7}$$

where c_S is the concentration profile of substrate, c_E is the concentration profile of enzyme, D_S is its diffusion coefficient, and K_M is the Michaelis constant. The rate of consumption will be $v(r) = k\ c_H$, where k is the rate constant for the hydrogen peroxide reaction and c_H is the peroxide concentration. Then, the equation of continuum for hydrogen peroxide is generally expressed in the steady-state by

$$\frac{D_H}{r}\frac{d}{dr}\left(r\frac{dc_H}{dr}\right) + \frac{k_{cat} c_E c_S}{c_S + K_M} - v(r) = 0 \tag{8}$$

At the electrode surface (r_0) and at the film surface (r_1), the boundary conditions are [29]:

$$\begin{aligned} r = r_0 : &\quad \frac{dc_S}{dr} = 0, \quad c_H = 0 \\ r = r_1 : &\quad c_S = c_S^*, \quad c_H = 0 \end{aligned} \tag{9}$$

where c_S^* is the bulk concentration of S scaled by the partition coefficient of the film. The current is provided by the consumption rate at each site. Thus, the total current at an electrode of length L is expressed by [29]

$$I/nF = 2\pi L \int_{r_0}^{r_1} rv\, dr \tag{10}$$

The analytical results of the problem are discussed by Eswari and Rajendran [30].

Example 2: enzyme catalysis reaction

The reactions without spatial dependence on various concentrations have modeled the enzyme kinetics in biochemical systems. Nonlinear systems of ordinary differential equations are solely based on that. Michaelis and Menten were pioneers in explaining the enzyme reaction model. In addition, they also reported the free enzyme binding to the reactant, which

produced an enzyme-reactant complex. Eq. (11) illustrates the Michaelis-Menten kinetics, in which the enzyme-substrate complex is formed after the enzyme is combined with the substrate.

$$E + S \underset{k_{-1}}{\overset{k_1}{\leftrightarrow}} ES \overset{k2}{\rightarrow} E + P \tag{11}$$

As can be seen from Eq. (11), the product P is released by the binding of substrate S with enzyme E. The product released is not reversible; however, the substrate binding is reversible. The reactants' concentrations in Eq. (11) are represented by the following letters:

$$s = [S], \quad e = [E], \quad c = [SE], \quad p = [P] \tag{12}$$

The law of mass action leads to the system of following nonlinear reaction equations [31],

$$\frac{ds}{dt} = -k_1 es + k_{-1} c \tag{13a}$$

$$\frac{de}{dt} = -k_1 es + (k_{-1} + k_2) c \tag{13b}$$

$$\frac{dc}{dt} = k_1 es - (k_{-1} + k_2) c \tag{13c}$$

$$\frac{dp}{dt} = k_2 c \tag{13d}$$

where k_1 is the forward rate of ES complex formation and k_{-1} is the backward rate constant. The above problem is discussed theoretically by Meena et al. [32].

Example 3: Michaelis-Menten mechanism for co-substrate and substrate

Figure 1 illustrates Michaelis-Menten reaction kinetics scheme for co-substrate and substrate. Limoges et al. [33] reported for a redox enzymatic homogenous system along with one-dimensional mass transport equation a concise discussion and derivation.

When the enzyme is being solubilized, the electrochemical signal that is produced during the reaction is governed by the following set of nonlinear partial differential equations.

$$\frac{\partial [Q]}{\partial t} = D_P \frac{\partial^2 [Q]}{\partial x^2} - \frac{C_E^0}{\frac{1}{k_1 [S]} + \frac{1}{k_{1,2}} + \frac{1}{k_{2,2}} + \frac{1}{k_2 [Q]}} \tag{14}$$

$$\frac{\partial [S]}{\partial t} = D_S \frac{\partial^2 [S]}{\partial x^2} - \frac{C_E^0}{\frac{1}{k_1 [S]} + \frac{1}{k_{1,2}} + \frac{1}{k_{2,2}} + \frac{1}{k_2 [Q]}} \tag{15}$$

where D_P, D_S are the diffusion coefficients of co-substrate and substrate, respectively; Q, S are the concentrations of co-substrate and substrate, respectively; x is the distance from the

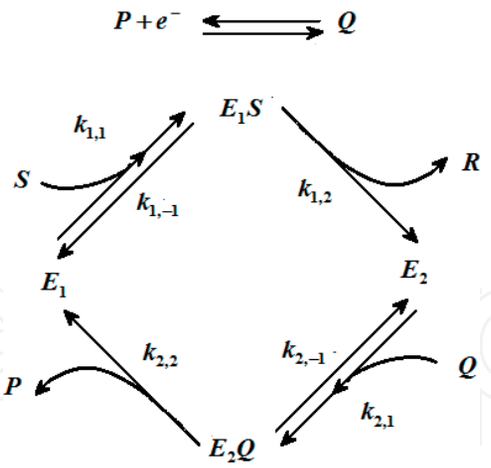

Figure 1. Reaction scheme for substrate and co-substrate.

electrode surface; C_S^0 is the bulk concentration of substrate; C_E^0 is the total concentration of enzyme; k_1, $k_{2,2}$, and k_2 are the reaction rate constants; and t is the time. The initial and boundary conditions for Eqs. (14) and (15) are given by:

$$t = 0, x \geq 0, \text{and } x = \infty, x \geq 0, [Q] = 0, [S] = C_S^0 \tag{16}$$

$$x = 0, t \geq 0 : [Q] = \frac{C_P^0}{1 + \exp\left[\frac{F}{RT}\left(E - E_{PQ}^0\right)\right]}, \frac{\partial[S]}{\partial x} = 0 \tag{17}$$

$$x = \infty, \partial[Q]/\partial x = 0 \tag{18}$$

The analytical expressions corresponding to the concentration of co-substrate for steady and nonsteady state conditions have been obtained by solving the above nonlinear equation using a new approach to homotopy perturbation method (HPM). Analytical expressions of the plateau current are also presented for steady and nonsteady state conditions:

$$i = FSD_P\left(\frac{\partial[Q]}{\partial x}\right)_{x=0} \tag{19}$$

where E is the electrode potential, E_{PQ}^0 is the standard potential of the P/Q couple, F is the Faraday constant, and S is the surface area of the electrode. The above problem is discussed theoretically by Rasi et al. [34].

5. Analytical solutions

To study many of the physical phenomena, the exact solutions of nonlinear partial or ordinary differential equations play an important role. In order to understand the mechanism of complicated dynamical processes and physical phenomena modeled by nonlinear differential equations, the existence of approximate analytical and exact solutions is very important. In

addition, nonlinear differential equations can also assist to investigate the stability of these solutions as well as checking the simulation analysis. Nonlinear partial differential equations govern a significant variety of phenomena including physical, chemical, and biological. The development of techniques aimed at exact solutions of nonlinear differential equations with nonsteady and steady state [35] has been one of the most exciting advances of nonlinear science and theoretical physics/chemistry. An important role in nonlinear science is played by exact solutions of differential equations. Furthermore, this can be especially observed in nonlinear physical chemistry science. This can be attributed to the provision of physical information as well as more insight into the physical aspects of the problem, which could lead to further applications. Over the past few decades, different methods have been reported to solve analytical solutions such as Tanh-sech [36], extended tanh [37], Jacobi elliptic function expansion [39], hyperbolic function [38], F-expansion [40], and the First integral [41]. To solve different types of nonlinear systems of PDEs, the sine-cosine method [42] has been employed. A variety of powerful analytical methods such as homotopy perturbation method [43–45], homotopy analysis method [46, 47], Adomian decomposition method [48, 49], wavelet transform method [50], etc. are applied to solve the nonlinear problems (e.g., Eqs. (8) and (13)–(15)) in chemical kinetics [51].

6. Numerical solutions

Many differential equations cannot be solved analytically. For practical purpose, however, such as in physical engineering sciences, a numerical approximation to the solution is often sufficient. The numerical method is mainly to solve complex problem physically or geometrically. It is also used to validate the experimental results. Some of the nonlinear equations in chemical kinetics were solved using numerical methods [52–56].

7. Summary

Most mathematical models of enzyme kinetics are based on reaction diffusion equations or rate equations containing nonlinear terms related to the kinetics of the enzyme reaction. Powerful and accurate analytical (HPM, HAM, ADM, etc.) and numerical mathematical methods have been employed for their resolution under steady and nonsteady state conditions. The theoretical results provide very useful insight into the effects on the performance of the thickness and structure of the enzymatic film, the loading of the different species, the diffusivity of the mediator, etc. Also, the theoretical modeling and simulation of these systems enable us to characterize the enzymatic reactions (i.e., rate constant, turnover rate, and Michaelis-Menten constants).

In spite of the above-mentioned benefits, there are only limited theoretical studies addressing kinetics of enzyme reaction and most of them include a number of simplifying assumptions mainly related to the mass and charge transport inside and outside the biocatalyst film, the enzymatic kinetic scheme, and the electrode morphology. Experimental validation of proposed

models is even more seldom. Therefore, more effort in the future research is needed in this direction in order to develop more detailed models and accurate simulations that can assist the rational development and optimization of enzyme electrodes.

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