CHAPTER – I

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1.1 Mathematical modeling

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 can take many forms, including but not limited to dynamical systems, statistical models, differential equations, or game theoretic models. These and other types of models can overlap, with a given model involving a variety of abstract structures. In general, mathematical models may include logical models, as far as logic is taken as a part of mathematics. In many cases, the quality of a scientific field depends on how well the mathematical models developed on the theoretical side agree with results of repeatable experiments. Lack of agreement between theoretical mathematical models and experimental measurements often leads to important advances as better theories are developed.

If all the operators in a mathematical model exhibit linearity, the resulting mathematical model is defined as linear. A model is considered to be nonlinear otherwise. The definition of linearity and nonlinearity is dependent on context, and linear models may have nonlinear expressions in them. For example, in a statistical linear model, it is assumed that a relationship is linear in the parameters, but it may be nonlinear in the predictor variables. Similarly, a differential equation is said to be linear if it can be written with linear differential operators, but it can still have nonlinear expressions in it. In a mathematical programming model, if the objective functions and constraints are represented entirely by linear equations, then the model is regarded as a linear model. If one or more of the objective functions or constraints are represented with a nonlinear equation, then the model is known as a nonlinear model.
Nonlinearity, even in fairly simple systems, is often associated with phenomena such as chaos and irreversibility. Although there are exceptions, nonlinear systems and models tend to be more difficult to study than linear ones. A common approach to nonlinear problems is linearization, but this can be problematic if one is trying to study aspects such as irreversibility, which are strongly tied to nonlinearity.

One can think of mathematical modeling as an activity or process that allows a mathematician to be a bio-chemical, an ecologist, an economist, a physiologist. Instead of undertaking experiments in the real world, a modeler undertakes experiments on mathematical representations of the real world. Analytical models are mathematical models that have a closed form solution, i.e. the solution to the differential equations used to describe changes in a system can be expressed as a mathematical analytic function.

1.2 Boundary value problems

In mathematics, in the field of differential equations, a boundary value problem is a differential equation together with a set of additional restraints, called the boundary conditions. A solution to a boundary value problem is a solution to the differential equation which also satisfies the boundary conditions.

Boundary value problems arise in several branches of physics and chemistry. Problems involving the diffusion or heat equation such as the determination of normal modes, are often stated as boundary value problems. A large class of important boundary value problems is the Sturm–Liouville problems. The analysis of these problems involves the eigen functions of a differential operator. To be useful in applications, a boundary value problem should be well posed. This means that given the input to the problem there exists a unique solution, which depends continuously on the input. Much theoretical work in the field of partial differential
equations is devoted to proving that boundary value problems arising from scientific and engineering applications are in fact well-posed.

### 1.3 Biochemical systems

Mathematical modeling in biochemical system is based on ordinary differential equations (ODE) or partial differential equations (PDE). Biochemical processes are represented using power-law expansions in the variables of the system. This framework, which became known as Biochemical systems Theory, has been developed since the 1960s by Michael Savageau and others for the systems analysis of biochemical processes [1,2]. According to Cornish-Bowden they "regarded this as a general theory of metabolic control, which includes both metabolic control analysis and flux-oriented theory as special cases [3]. The dynamics of a species is represented by a differential equation with the structure:

\[
\frac{dX_i}{dt} = \sum_{j} \mu_j \gamma_j \prod_{k} X_k^{\gamma_k}
\]

where \(X_i\) represents one of the \(n_d\) variables of the model (metabolite concentrations, protein concentrations or levels of gene expression). \(j\) represents the \(n_t\) biochemical processes affecting the dynamics of the species. On the other hand, \(\mu_j\) (stoichiometric coefficient), \(\gamma_j\) (rate constants) and \(f_k\) (kinetic orders) are two different kinds of parameters defining the dynamics of the system.

The principal difference of power-law models with respect to other ODE models used in biochemical systems is that the kinetic orders can be non-integer numbers. A kinetic order can have even negative value when inhibition is modelled. In this way, power-law models have a higher flexibility to reproduce the non-linearity of biochemical systems. Modelling and Simulating networks of biochemical reactions are an active research field today.
In general, using matrix notation, one can always write down the rate laws for a system of biochemical reactions on the following form:

\[ N_j = \frac{dS_j}{dt} \]  

(1.2)

where \( S \) is a vector of concentrations, \( j \) is a vector of reaction fluxes, and \( N \) denotes the stoichiometric matrix. The resulting system of ordinary differential equations can be solved using some suitable numerical or analytical method. In this thesis some of the following nonlinear bio-chemical problems are solved analytically and numerically.

1.4 Concentrations inside the cationic glucose sensitive membrane

In spite of extensive experimental investigations, only a few studies concerned mathematical modelling of such systems [4-8]. Albin et al. [9] developed a mathematical model to describe the steady state behaviour of a cationic glucose-sensitive membrane. Gough and co-workers [6-8] modelled the steady state behaviour and transient response of a cylindrical glucose sensor. Wuet al. [9] derived a mathematical model with consideration of oxygen limitation to describe the glucose sensitivity of a cationic membrane at the steady state conditions. The reaction scheme in a glucose-sensitive membrane can be written as follows:

\[
\text{Glucose} + O_2 \xrightarrow{\text{Glucooxidase}} \text{Gluconic acid} + H_2O_2
\]  

(1.3)

The catalase catalyzes the conversion of hydrogen peroxide to oxygen and water:

\[
H_2O_2 \xrightarrow{\text{catalase}} H_2O + \frac{1}{2}O_2
\]  

(1.4)

If an excess of catalase is immobilized with glucose oxidase, all hydrogen peroxide is reduced. Thus, the overall reaction becomes:
Glucose $+ O_2 / 2 \rightarrow$ Gluconic acid

The corresponding governing system of non-linear differential equation in planar co-
ordinates inside the cationic glucose sensitive membrane may be written as [10]:

\[
D_{OX} \frac{\partial^2 C_{OX}}{\partial x^2} - \frac{1}{2} \frac{v_{max} C_g C_{OX}}{C_{OX} (k_g + C_g) + C_g k_{OX}} = 0
\]

(1.6)

\[
D_g \frac{\partial^2 C_g}{\partial x^2} - \frac{v_{max} C_g C_{OX}}{C_{OX} (k_g + C_g) + C_g k_{OX}} = 0
\]

(1.7)

\[
D_a \frac{\partial^2 C_a}{\partial x^2} + \frac{v_{max} C_g C_{OX}}{C_{OX} (k_g + C_g) + C_g k_{OX}} = 0
\]

(1.8)

where $C_{OX}$, $C_g$ and $C_a$ denote the concentration of the oxygen, glucose and gluconic acid respectively. $D_g$, $D_{ox}$ and $D_a$ are the corresponding diffusion coefficients. $x$ is the spatial coordinate and $v_{max}$ is the maximum reaction rate. $k_g$ and $k_{ox}$ are Michaelis-Menten constant for the glucose and glucose oxidase respectively. Equations (1.6) - (1.8) are solved for the following boundary conditions by assuming that the membrane is immersed in a well stirred external medium with a constant concentration of each species due to continuous flow of a fresh medium.

\[
C_{OX} = C_{OX}^* ; \quad C_g = C_g^* ; \quad C_a = 0 \quad \text{at} \quad x = 0, x = l
\]

(1.9)

where $l$ is the thickness of the membrane and $C_{OX}^*$ and $C_g^*$ are the concentrations of oxygen and glucose in the external solution, respectively. In this thesis, the above problem was solved analytically for all values of the parameters using the Homotopy analysis method.
1.5 Immobilized enzymes system with reversible Michaelis-Menten Kinetics

Recently, there has been much interest in the development of Immobilized enzyme system are immobilized enzyme system are also analyzed for more complex kinetics: reversible reactions [11], competitive Michaelis-Menten kinetics [12] or two-substrate enzymatic reactions [13]. Under these above assumptions, the differential mass balance equation for substrate and product in spherical co-ordinates are as follows [14]:

\[
D_s \frac{d^2 C_s}{dr^2} + \frac{2D_s}{r} \left( \frac{dC_s}{dr} \right) = V_s \tag{1.10}
\]

\[
D_p \frac{d^2 C_p}{dr^2} + \frac{2D_p}{r} \left( \frac{dC_p}{dr} \right) = -V_s \tag{1.11}
\]

The boundary conditions are

\[
\frac{dC_s}{dr} = 0, \quad \frac{dC_p}{dr} = 0 \quad \text{when} \quad r = 0 \tag{1.12}
\]

\[
C_s = C_{SR} \quad C_p = C_{PR} \quad \text{when} \quad r = R \tag{1.13}
\]

where \( V_s = \frac{V_m (C_s - \frac{C_p}{K_p})}{K_m + C_s + (K_m/K_p)C_p} \) and \( C_s \) and \( C_p \) denote the dimensional substrate and product concentration, \( r \) is the radial co-ordinate. The form of \( V_s \) determines the mathematical method to solve the above equations and its complexity. Most of the already published articles on enzymatic solution were dealt with non-reversible Michaelis-Menten kinetics [15]. In thesis the concentrations were determined by solving the above non linear equation using Homotopy perturbation method.
1.6 Objectives and scope of the present investigation

The objectives of the present investigation are as follows:

- To find the analytical expression of concentrations inside the cationic glucose-sensitive membrane by solving the system of non-linear equations using Homotopy analysis method.
- To derive a general and closed form of an analytical expression pertaining to the substrate concentration profile and effectiveness factor.
- To evaluate the approximate solution of non-linear boundary value problems in immobilized glucoamylase kinetics using asymptotic methods.
- To get the analytical expression of concentration and effectiveness factor of the reactant inside the catalyst pellets using modified Adomain decomposition method.

1.7 Organization of the thesis

This thesis presents the development of mathematical models using Homotopy perturbation method, Homotopy analysis method and Adomian decomposition method are used to predict the theoretical results on solving the system of nonlinear ordinary and partial differential equations. Numerical simulations are also obtained and compared to show the efficiency of the above methods applied.

Chapter one gives a short introduction to mathematical models, their applications in differential equations and some bio-chemical systems.
Chapter two provides a mathematical model of a cationic glucose-sensitive membrane. This model involves the system of non-linear steady-state reaction-diffusion equations. Analytical expressions pertaining to concentration of oxygen, glucose and gluconic acid for all values of parameters are presented. Homotopy analysis method is used to evaluate the approximate analytical solutions of the non-linear boundary value problem. Analytical approximation are compared with numerical simulation results.

Chapter three presents a mathematical model of immobilized enzyme system. The model is based on non-stationary diffusion equation containing a nonlinear term related to reversible Michaelis-Menten kinetics of the enzymatic reaction. He’s Homotopy perturbation method is used to solve the non-linear reaction/diffusion equation in immobilized enzymes system. A general and closed form of an analytical expression pertaining to the substrate concentration profile and effectiveness factor are reported for all possible values of parameters.

Chapter four focuses on theoretical model to describe the enzyme reaction, mass transfer and heat effects in the calorimetric system. The model is based on non-stationary diffusion equation containing a non-linear term related to immobilize liver esterase by flow calorimetry. The complex numerical methods (Adomian decomposition method, Homotopy analysis and perturbation method) is used to solve the non-linear differential equations. Approximate analytical expressions for substrate concentration have been derived for all values of parameters.

In Chapter five, the analytical expression of concentration and effectiveness factor of the reactant inside the catalyst pellets are derived. The approximate analytical expression for the steady state concentration of substrate for all values of parameters $\gamma$ and $\beta$ in a packed bed reactor was obtained using the modified Adomian decomposition method.

Chapter six is the overall conclusion and future enhancements of the thesis.