

# Mathematical Modelling and Transient Analytical Solution of a Glucose Sensitive Composite Membrane for Closed-Loop Insulin Delivery Using He's Variational Iteration Method

R. Angel Joy, L. Rajendran

**Abstract** – A mathematical modelling of an enzymatic reaction and diffusion of reactants and product inside glucose sensitive composite membrane is discussed. The model is based on time- and position-dependent diffusivity of species and involves the system of non-linear reaction diffusion equations. He's variational iteration method is used to obtain approximate and analytical solutions of the system. A comparison of the analytical approximation and numerical simulation is also presented. **Copyright © 2012 Praise Worthy Prize S.r.l. - All rights reserved.**

**Keywords:** Enzymatic Reaction, Nonlinear Partial Differential Equations, He's Variational Iteration Method, Boundary Value Problem, Glucose Sensitive Composite Membrane

## Nomenclature

$C_g$	Concentration of glucose (mol/cm <sup>3</sup> )
$C_{OX}$	Concentration of oxygen (mol/cm <sup>3</sup> )
$C_a$	Concentration of gluconic acid (mol/cm <sup>3</sup> )
$D_g$	Diffusion coefficient of glucose (cm <sup>2</sup> /s)
$D_{OX}$	Diffusion coefficient of oxygen (cm <sup>2</sup> /s)
$D_a$	Diffusion coefficient of gluconic acid (cm <sup>2</sup> /s)
$K_g$	Michaelis-Menten constant for glucose (mol/cm <sup>3</sup> )
$K_{OX}$	Michaelis-Menten constant for glucose oxidase (mol/cm <sup>3</sup> )
$v_{max}$	Maximal reaction rate (mol s <sup>-1</sup> cm <sup>-3</sup> )
$x$	Distance (mm)
$t$	Time (s)
$C_g^*$	Concentration of glucose in the external solution (mol/cm <sup>3</sup> )
$C_{OX}^*$	Concentration of glucose in the oxygen solution (mol/cm <sup>3</sup> )
$l$	Half thickness of the membrane (mm)
$u$	Dimensionless concentration of glucose (none)
$v$	Dimensionless concentration of oxygen (none)
$w$	Dimensionless concentration of gluconic acid (none)
$X$	Dimensionless distance (none)
$\tau$	Dimensionless time (none)
$\gamma_{E1}, \gamma_{S1}, \alpha, \beta$	Dimensionless reaction diffusion parameters (none)
$\eta, \mu$	Ratio of diffusion coefficients (none)

## I. Introduction

Nearly 5% of the present world's population is suffering by the common, serious disease diabetes [1].

The diabetes which is called Insulin dependent diabetes mellitus (IDDM) requires treatment with insulin delivered by injection several times a day or by a pump to control glucose levels. Hence researches are going on the various types of insulin delivery systems containing a glucose sensitive membrane for the past three decades.

Some of these delivery systems contains immobilized glucose oxidase and catalase in a pH response polymeric hydrogen [2]-[7]. In this system an increase in the external glucose concentration brings more gluconic acid as a product of glucose oxidation. This causes changes in the hydrogen swelling and hence the insulin permeability

The pH-sensitive hydrogels may be classified as cationic or anionic according to the nature of the charges present in the network. Cationic hydrogels, consisting of amino groups, swells as pH decreases at higher glucose levels, while anionic hydrogels shrink due to protonization of acidic groups. The external stimuli such as pH changes can alter the structure and physical properties of ionic hydrogels. Hence these can be used for stimulus responsive drug delivery. The extensive use of homogeneous hydrogels is limited because of its weak mechanical polymers are developed to overcome this problem. Thus the composite materials provide a well-controlled and efficient drug release and have good mechanical properties.

The percolation theory [8],[9] describes the transport through composite materials. Here the release of drug is governed either by diffusion or swelling kinetics.

Though there is a lot of experimental investigation on glucose sensitive membranes, only a few studies

consider their mathematical model. In this work a mathematical model, based on the above description was developed to describe a dynamic process of diffusion of reactants and product couples with an enzymatic reaction inside a glucose sensitive composite membrane containing anionic nano particles glucose oxidase and catalase embedded in a hydrophobic polymer.

The Mathematical modelling of the glucose sensitive composite membrane for closed loop insulin delivery results in a system of nonlinear partial differential equation of second order.

The solution of non-linear equations can be obtained using Homotopy Perturbation method[10], Adomian decomposition method [11]-[13], parameter expansion method [14]-[16] and variational iteration method (VIM) etc. The VIM was first proposed by He[17] and was successfully applied to the systems obtained from various fields. In this method the solution procedure is by means of variational theory. The purpose of this work is to derive concentration profile for glucose, oxygen and gluconic acid. A comparison of the analytical approximation and numerical simulation is also presented for small values of time.

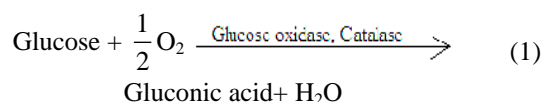
## II. Mathematical Formulation of the Problem

This model involves an enzymatic reaction and diffusion of reactants and product inside a glucose sensitive composite membrane.

The membrane is structured as a porous media where the pores are filled with a weakly acidic gel and water. Here the pH inside the membrane influences the swelling of the anionic gel and hence accelerate solute permeability. This exhibits the pH profile as a function of internal concentration of gluconic acid.

The concentration of glucose, the permeability of the reactants and products, and the rate of enzymatic reaction determine the internal concentration of gluconic acid.

This mathematical model describes the enzymatic reaction, kinetics of diffusion, temporal and spatial distribution of the reactants and products, and resultant membrane porosity and permeability. The glucose sensitive enzymatic reaction is expressed as:



The increase in glucose concentration increases the extent of accumulation of gluconic acid and the degree of shrinkage in particle depends on this. Applying the conservation law of mass and Fick's second law of diffusion, the equation for diffusion and reaction is:

$$\frac{\partial C_i}{\partial t} = \frac{\partial}{\partial x} \left( D_i \frac{\partial C_i}{\partial x} \right) + \nu_i R \quad (2)$$

where  $i$  represents individual species, e.g.  $i=g$  for glucose,  $i=ox$  for oxygen, and  $i=a$  for gluconic acid; the stoichiometric coefficient,  $\nu_i$ , are:  $\nu_g = -1$ ,  $\nu_{ox} = -1/2$  and  $\nu_a = 1$ ;  $C$  is the concentration function of time and position,  $D$  is the diffusion coefficient in the membrane and  $x$  is the length parameter, and  $R$  is the overall reaction rate that can be written in the following form [18]-[20]:

$$R = \frac{\nu_{max} C_g C_{ox}}{C_{ox} (K_g + C_g) + C_g K_{ox}} \quad (3)$$

where  $K_g$  and  $K_{ox}$  are respectively the Michaelis-Menton constants for glucose and glucose oxidase, and  $\nu_{max}$  is the maximal reaction velocity that is proportional to the concentration of enzyme ( $C_{enz}$ ) in the membrane. Assuming that the membrane is immersed in a well-stirred external medium of large volume with a constant concentration of each species, the initial and boundary conditions are:

$$t = 0, C_g = C_g^* \frac{\cosh\left(\frac{x}{l}\right)}{\cosh(1)} \quad (4)$$

$$C_{ox} = C_{ox}^* \frac{\cosh\left(\frac{x}{l}\right)}{\cosh(1)} \quad (4)$$

$$C_a = \frac{C_{ox}^*}{\cosh(1)} \left[ 1 - \cosh\left(\frac{x}{l}\right) \right]$$

$$x = 0, \frac{\partial C_g}{\partial x} = 0; \frac{\partial C_{ox}}{\partial x} = 0; \frac{\partial C_a}{\partial x} = 0 \quad (5)$$

$$x = l, C_g = C_g^*; C_{ox} = C_{ox}^*; C_a = 0 \quad (6)$$

where  $l$  is half thickness of the membrane,  $x=0$  is the centre of the membrane, and  $C_{ox}^*$  and  $C_g^*$  are the concentrations of oxygen and glucose in the external solution, respectively.

We introduce the following set of dimensionless variables:

$$\begin{aligned} u &= \frac{C_g}{C_g^*}; v = \frac{C_{ox}}{C_{ox}^*}; w = \frac{C_a}{C_{ox}^*}; X = \frac{x}{l} \\ \tau &= \frac{D_g t}{l^2}; \gamma_{E1} = \frac{l^2 \nu_{max}}{D_g C_g^*}; \gamma_{S1} = \frac{l^2 \nu_{max}}{D_g C_{ox}^*} \\ \alpha &= \frac{C_g^*}{K_g}; \beta = \frac{C_{ox}^*}{K_{ox}}; \eta = \frac{D_{ox}}{D_g}; \mu = \frac{D_a}{D_g} \end{aligned} \quad (7)$$

By using these variables, Eq. (2) for  $i=g, ox, a$  can be cast into the following dimensionless form:

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial X^2} - \gamma_{E1} uv \left[ uv + \frac{v}{\alpha} + \frac{u}{\beta} \right]^{-1} \quad (8)$$

$$\frac{\partial v}{\partial \tau} = \eta \frac{\partial^2 v}{\partial X^2} - \frac{\gamma_{S1} uv}{2} \left[ uv + \frac{v}{\alpha} + \frac{u}{\beta} \right]^{-1} \quad (9)$$

$$\frac{\partial w}{\partial \tau} = \mu \frac{\partial^2 w}{\partial X^2} + \gamma_{S1} uv \left[ uv + \frac{v}{\alpha} + \frac{u}{\beta} \right]^{-1} \quad (10)$$

Here  $u$ ,  $v$  and  $w$  are the dimensionless concentration of glucose, oxygen and gluconic acid, and  $\gamma_{E1}$ ,  $\gamma_{S1}$  are the corresponding Thiele modulus.  $\alpha$  and  $\beta$  are the dimensionless rate constant.

The corresponding initial and boundary conditions (4) - (6) become:

$$u = \frac{\cosh(X)}{\cosh(1)} \\ v = \frac{\cosh(X)}{\cosh(1)} \quad \text{when } t = 0 \quad (11)$$

$$w = 1 - \frac{\cosh(X)}{\cosh(1)}$$

$$\frac{\partial u}{\partial X} = 0; \quad \frac{\partial v}{\partial X} = 0; \quad \frac{\partial w}{\partial X} = 0 \quad \text{when } X = 0 \quad (12)$$

$$u = 1; \quad v = 1; \quad w = 0 \quad \text{when } X = 1 \quad (13)$$

In order to solve the boundary value problem (8)-(13) we have used the He's Variational iteration method [17], [21]. The basic principle of this method and detailed derivations of the dimensionless concentrations  $u$ ,  $v$  and  $w$  of glucose, oxygen and gluconic acid are described in Appendix A. As a result, we have obtained:

$$u(X, \tau) = \frac{\cosh(X)}{\cosh(1)} \left[ 1 + \left( 1 - \frac{\gamma_{E1} \alpha \beta}{\alpha \beta \frac{\cosh(X)}{\cosh(1)} + \alpha + \beta} \right) \tau \right] \quad (14a)$$

$$v(X, \tau) = \frac{\cosh(X)}{\cosh(1)} \left[ 1 + \left( \eta - \frac{\gamma_{S1} \alpha \beta}{2 \left( \alpha \beta \frac{\cosh(X)}{\cosh(1)} + \alpha + \beta \right)} \right) \tau \right] \quad (14b)$$

$$w(X, \tau) = 1 + \frac{\cosh(X)}{\cosh(1)} \left[ 1 + \left( \mu - \frac{\gamma_{S1} \alpha \beta}{\alpha \beta \frac{\cosh(X)}{\cosh(1)} + \alpha + \beta} \right) \tau \right] \quad (14c)$$

### III. Numerical Simulation

The non-linear differential Eqs (8)-(10) with the boundary conditions (12) and (13) are solved by numerical methods. The function `pdex4` in SCILAB software [22] which is a function of solving the boundary value problem for differential equation is used to solve this equation.

Its numerical solution is compared with variational iteration method in Figs. 1-5 and it gives satisfactory results for short time. The SCILAB program is also given in Appendix B.

### IV. Results and Discussion

Eqs. (14a)-(14c) represent the analytical expressions for the dimensionless concentration of glucose  $u(X, \tau)$ , oxygen  $v(X, \tau)$  and gluconic acid  $w(X, \tau)$  valid for short time and all values of parameters  $\gamma_{E1}$ ,  $\gamma_{S1}$ ,  $\alpha$ ,  $\beta$ ,  $\eta$  and  $\mu$  considered in this study. The Thiele modulus  $\gamma_{E1}$  and  $\gamma_{S1}$  can be varied by changing either the thickness of the membrane or the concentration of oxygen and glucose in the external solution. This parameter describes the relative importance of diffusion and reaction in the enzyme layer.

When it is small, the kinetics are the dominant resistance; the overall uptake of glucose, oxygen and gluconic acid in the enzyme matrix is kinetically controlled. Under these conditions, the glucose concentration profile across the membrane is essentially uniform. The overall kinetics are determined by the maximal reaction rate. In contrast, when the Thiele modulus is large, diffusion limitations are the principal determining factor.

Figs. 1-3 present the dimensionless concentration of glucose  $u(X, \tau)$  for some fixed values of parameters. From the figures, it is evident that the value of the concentration of glucose increases when thickness of the membrane increases. Also the value of  $u(X, \tau)$  is maximum at  $X=1$ . The value of the dimensionless concentration of oxygen  $v(X, \tau)$  versus the dimensionless distance for the fixed value of dimensionless time  $\tau = 0.1$  is plotted in figure 4. From this figure, it is inferred that the value of the concentration of oxygen increases when thickness of the membrane increases.

Fig. 5 presents the concentration of gluconic acid  $w(X, \tau)$  as a function of  $X$  and  $\tau = 0.3$ . From this figure, it is obvious that the value of the concentration of gluconic acid  $w(X, \tau)$  decreases with increasing  $X$ , approaching zero at  $X=1$ . The normalized concentration of glucose, oxygen and gluconic acid is compared with numerical values for short time in the Tables I-III.

TABLE I  
COMPARISON OF NORMALIZED ANALYTICAL CONCENTRATION OF GLUCOSE  $u$  WITH NUMERICAL RESULTS FOR VARIOUS VALUES OF  $X$  &  $\tau$  AND FOR SOME FIXED VALUES OF PARAMETER  $\alpha = 0.1, \beta = 0.01, \gamma_{E1} = 100, \gamma_{S1} = 0.01, \eta = 0.1$

X	Concentration of glucose $u$											
	$u$ (when $\tau = 0.01$ )			$u$ (when $\tau = 0.1$ )			$u$ (when $\tau = 0.3$ )			$u$ (when $\tau = 0.5$ )		
	<i>analytica</i> <i>l</i>	numerical	% error	<i>analytica</i> <i>l</i>	numerical	% error	<i>analytica</i> <i>l</i>	numerical	% error	<i>analytica</i> <i>l</i>	numerical	%error
0	0.6487	0.6481	0.06	0.6543	0.6524	0.19	0.6668	0.6531	1.37	0.6792	0.6641	1.51
0.2	0.6617	0.6611	0.06	0.6674	0.6655	0.19	0.6802	0.661	1.41	0.6929	0.6766	1.63
0.4	0.7013	0.7006	0.07	0.7074	0.7050	0.24	0.7209	0.7055	1.54	0.7345	0.7146	1.99
0.6	0.7690	0.7682	0.08	0.7757	0.7724	0.33	0.7907	0.7727	1.80	0.8056	0.7795	2.61
0.8	0.8676	0.8667	0.09	0.8752	0.8698	0.54	0.8922	0.8699	2.23	0.9092	0.8736	3.56
1	1.0010	1.0000	0.10	1.0099	1.0000	0.99	1.0297	1.0000	2.97	1.0495	1.0000	4.95

TABLE II  
COMPARISON OF NORMALIZED ANALYTICAL CONCENTRATION OF OXYGEN  $v$  WITH NUMERICAL RESULTS FOR VARIOUS VALUES OF  $X$  &  $\tau$  AND FOR SOME FIXED VALUES OF  $\alpha = 0.1, \beta = 0.01, \gamma_{E1} = 100, \gamma_{S1} = 0.01, \eta = 0.1$

X	Concentration of oxygen $v$											
	$v$ (when $\tau = 0.01$ )			$v$ (when $\tau = 0.1$ )			$v$ (when $\tau = 0.3$ )			$v$ (when $\tau = 0.5$ )		
	<i>analytica</i> <i>l</i>	numerical	% error	<i>analytica</i> <i>l</i>	numerical	% error	<i>analytica</i> <i>l</i>	numerical	% error	<i>analytica</i> <i>l</i>	numerical	%error
0	0.6487	0.6481	0.06	0.6545	0.6546	0.01	0.6675	0.6679	0.04	0.6804	0.6806	0.02
0.2	0.6617	0.6611	0.06	0.6677	0.6677	0.00	0.6809	0.6812	0.03	0.6941	0.6941	0.00
0.4	0.7013	0.7006	0.07	0.7076	0.7077	0.01	0.7216	0.7217	0.01	0.7356	0.7347	0.09
0.6	0.7690	0.7682	0.08	0.7759	0.7758	0.01	0.7913	0.7901	0.12	0.8066	0.8022	0.44
0.8	0.8676	0.8667	0.09	0.8754	0.8742	0.12	0.8927	0.8854	0.73	0.9100	0.8936	1.64
1	1.0010	1.0000	0.10	1.0100	1.0000	1.00	1.0300	1.0000	3.00	1.0500	1.0000	5.00

TABLE III  
COMPARISON OF NORMALIZED ANALYTICAL CONCENTRATION OF GLUCONIC ACID  $w$  WITH NUMERICAL RESULTS FOR VARIOUS VALUES OF  $X$  &  $\tau$  AND FOR SOME FIXED VALUES OF  $\alpha = 0.1, \beta = 0.01, \gamma_{E1} = 100, \gamma_{S1} = 0.01, \mu = 0.1$

X	Concentration of gluconic acid $w$											
	$w$ (when $\tau = 0.01$ )			$w$ (when $\tau = 0.1$ )			$w$ (when $\tau = 0.3$ )			$w$ (when $\tau = 0.5$ )		
	<i>analytica</i> <i>l</i>	numerical	% error	<i>analytica</i> <i>l</i>	numerical	% error	<i>analytica</i> <i>l</i>	numerical	% error	<i>analytica</i> <i>l</i>	numerical	%error
0	0.3513	0.3519	0.06	0.3455	0.3461	0.06	0.3325	0.3328	0.03	0.3196	0.3194	0.02
0.2	0.3383	0.3389	0.06	0.3323	0.3329	0.06	0.3191	0.3195	0.04	0.3059	0.3059	0.00
0.4	0.2987	0.2994	0.07	0.2924	0.2931	0.07	0.2784	0.8790	0.06	0.2644	0.2653	0.09
0.6	0.2310	0.2318	0.08	0.2241	0.2249	0.08	0.2087	0.2105	0.18	0.1934	0.1978	0.44
0.8	0.1324	0.1333	0.09	0.1246	0.1265	0.19	0.1073	0.1150	0.77	0.0900	0.1065	1.65
1	-0.0010	0.0000	0.10	-0.0100	0.0000	1.00	-0.0300	0.0000	3.00	-0.0500	0.0000	5.00

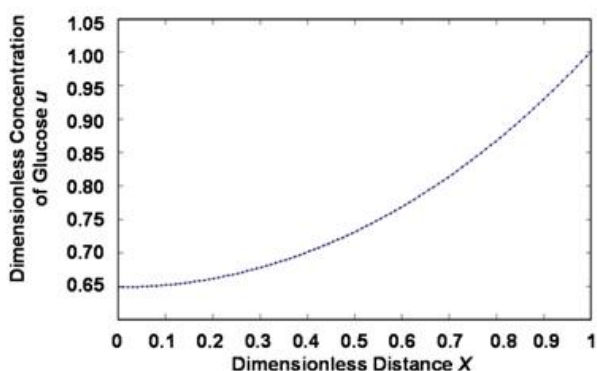


Fig. 1. Dimensionless concentration of glucose vs. dimensionless distance  $X$  calculated for  $\alpha = 0.1, \beta = 0.01, \gamma_{E1} = 100$  and  $\tau = 0.01$ . Solid line represents the analytical solution presented in this work (Eq. (14a)) and the dotted line the numerical solution

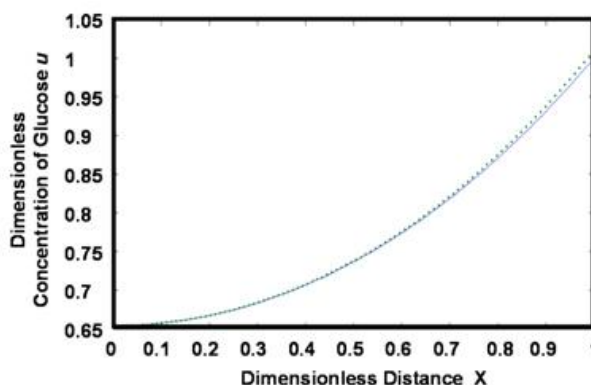


Fig. 2. Dimensionless concentration of glucose vs. dimensionless distance  $X$  calculated for  $\alpha = 0.1, \beta = 0.01, \gamma_{E1} = 100$  and  $\tau = 0.1$ . Solid line represents the analytical solution presented in this work (Eq. (14a)) and the dotted line the numerical solution

From the tables it is inferred that, the concentrations of glucose and oxygen increases when time increases whereas that of gluconic acid decreases when time increases.

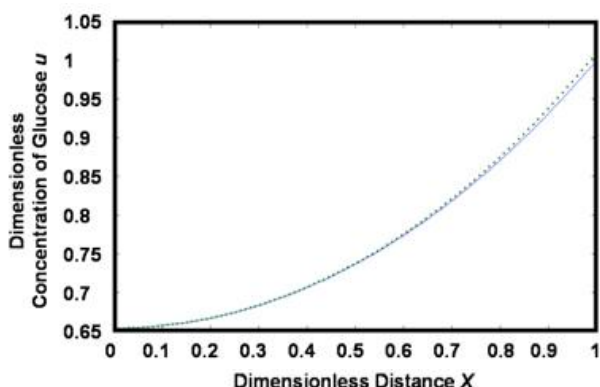


Fig. 3. Dimensionless concentration of glucose vs. dimensionless distance X calculated for  $\alpha = 0.1, \beta = 0.01, \gamma_{E1} = 100$  and  $\tau = 0.3$ . Solid line represents the analytical solution presented in this work (Eq. (14a)) and the dotted line the numerical solution

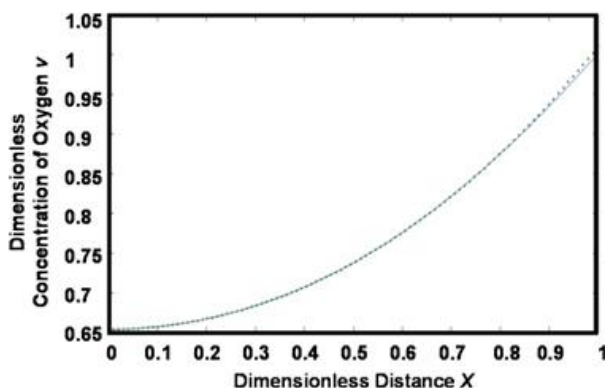


Fig. 4. Dimensionless concentration of oxygen vs. dimensionless distance X calculated for  $\alpha = 0.1, \beta = 0.01, \gamma_{S1} = 0.01, \eta = 0.1$  and  $\tau = 0.1$ . Solid line represents the analytical solution presented in this work (Eq. (14b)) and the dotted line the numerical solution

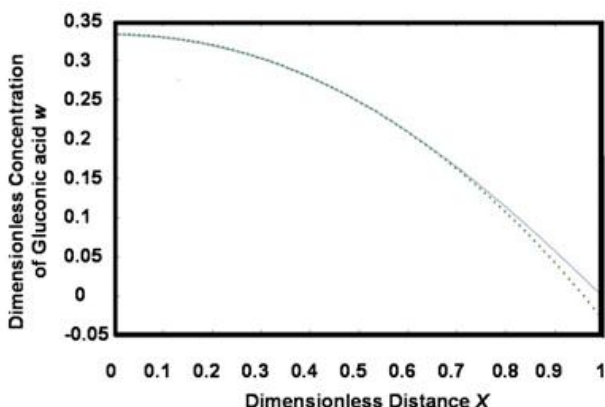


Fig. 5. Dimensionless concentration of gluconic acid vs. dimensionless distance X calculated for  $\alpha = 0.1, \beta = 0.01, \gamma_{S1} = 0.01, \eta = 0.1$  and  $\tau = 0.3$ . Solid line represent the analytical solution presented in this work (Eq. (14c)) and the dotted line the numerical solution

## V. Conclusion

We have analysed the theoretical ancient model describing the process of reaction and diffusion in glucose-responsive composite membranes, previously described in [2].

The system of non-linear, non steady state reaction-diffusion equations of the model has been solved analytically. The accuracy of the approximate analytical solutions has been verified by comparison with numerical solutions. The analytical results obtained can be employed to analyze effects of membrane formulation such as enzyme loading, the type of buffer in the external solution and for the optimization of the design of glucose sensitive membranes.

## Acknowledgements

The authors gratefully acknowledged financial support from the University Grants Commission (F. No. 39-58/2010(SR)), New Delhi, India. The authors are thankful to The Principal, The Madura College, Madurai and The Principal, Sri G. V. G. Visalakshi College for women, Udumalpet for their encouragement.

## Appendix A

*The variational iteration method of solving non-linear differential equation[21].*

Here we can solve the system of non-linear equations (8)-(13) analytically using variational iteration method [21] in the following way. Let us consider the following system:

$$L[u(x,t)] + R[u(x,t)] + N[u(x,t)] = g(x,t) \quad (1-A)$$

where  $L = \frac{\partial}{\partial t}$ ,  $R$  is a linear operator which has partial derivatives with respect to  $x$ ,  $N[u(x,t)]$  is a non-linear term and  $g(x,t)$  is an inhomogeneous term. According to the variational iteration method, we can construct the following iteration formula:

$$u_{n+1}(x,t) = u_n(x,t) + \int_0^t \lambda \left[ Lu_n(x,\xi) + R\widetilde{u}_n(x,\xi) + N\widetilde{u}_n(x,\xi) - g(x,\xi) \right] d\xi \quad (2-A)$$

where  $\lambda$  is called a general Lagrange multiplier which can be identified optimally via variational theory,  $\widetilde{R u}_n$  and  $\widetilde{N u}_n$  are considered as restricted variation.

In this method a trial function (an initial solution) is chosen which satisfies given boundary conditions.

Using above variational iteration method we can write the correct functional of (8)-(10) as follows:

$$u_{n+1}(X, \tau) = u_n(X, \tau) + \int_0^\tau \lambda_1 \left[ \frac{\partial u_n(X, \xi)}{\partial \xi} - \frac{\partial^2 \tilde{u}_n(X, \xi)}{\partial X^2} + \frac{\gamma_{E1} \tilde{u}_n v_n \alpha \beta}{\alpha \beta u_n v_n + \beta v_n + \alpha u_n} \right] d\xi \quad (3-A)$$

$$v_{n+1}(X, \tau) = v_n(X, \tau) + \int_0^\tau \lambda_2 \left[ \frac{\partial v_n(X, \xi)}{\partial \xi} - \eta \frac{\partial^2 \tilde{v}_n(X, \xi)}{\partial X^2} + \frac{\gamma_{S1} \tilde{u}_n v_n \alpha \beta}{2(\alpha \beta u_n v_n + \beta v_n + \alpha u_n)} \right] d\xi \quad (4-A)$$

$$w_{n+1}(X, \tau) = w_n(X, \tau) + \int_0^\tau \lambda_3 \left[ \frac{\partial w_n(X, \xi)}{\partial \xi} - \mu \frac{\partial^2 \tilde{w}_n(X, \xi)}{\partial X^2} + \frac{\gamma_{S1} \tilde{u}_n v_n \alpha \beta}{(\alpha \beta u_n v_n + \beta v_n + \alpha u_n)} \right] d\xi \quad (5-A)$$

where  $\lambda_1$ ,  $\lambda_2$  and  $\lambda_3$  are Lagrange multipliers. Here it is to be mentioned that for linear problems, using variational iteration method, its exact solution can be obtained by only one iteration.

But for non-linear problems, its accurate solution can be obtained by two or three iterations.

Considering the variation with respect to  $u_n$ ,  $v_n$  and  $w_n$ , we have:

$$\delta u_{n+1}(X, \tau) = \delta u_n(X, \tau) + \int_0^\tau \lambda_1 \left[ \frac{\partial u_n(X, \xi)}{\partial \xi} - \frac{\partial^2 \tilde{u}_n(X, \xi)}{\partial X^2} + \frac{\gamma_{E1} \tilde{u}_n v_n \alpha \beta}{\alpha \beta u_n v_n + \beta v_n + \alpha u_n} \right] d\xi \quad (6-A)$$

$$\delta v_{n+1}(X, \tau) = \delta v_n(X, \tau) + \int_0^\tau \lambda_2 \left[ \frac{\partial v_n(X, \xi)}{\partial \xi} - \eta \frac{\partial^2 \tilde{v}_n(X, \xi)}{\partial X^2} + \frac{\gamma_{S1} \tilde{u}_n v_n \alpha \beta}{2(\alpha \beta u_n v_n + \beta v_n + \alpha u_n)} \right] d\xi \quad (7-A)$$

$$\delta w_{n+1}(X, \tau) = \delta w_n(X, \tau) + \int_0^\tau \lambda_3 \left[ \frac{\partial w_n(X, \xi)}{\partial \xi} - \eta \frac{\partial^2 \tilde{w}_n(X, \xi)}{\partial X^2} + \frac{\gamma_{S1} \tilde{u}_n v_n \alpha \beta}{(\alpha \beta u_n v_n + \beta v_n + \alpha u_n)} \right] d\xi \quad (8-A)$$

Here  $\frac{\partial^2 \tilde{u}_n}{\partial X^2}$ ,  $\tilde{u}_n v_n$ ,  $\frac{\partial^2 \tilde{v}_n}{\partial X^2}$ ,  $\frac{\partial^2 \tilde{w}_n}{\partial X^2}$  are considered as restricted variations. Under this consideration the stationary conditions of the above correction functional ((6-A), (7-A), (8-A)) can be expressed as follows:

$$\delta u_n : 1 + \lambda_1(\xi) \Big|_{\xi=\tau} = 0; \quad \delta u_n : \lambda_1'(\tau) = 0 \quad (9-A)$$

$$\delta v_n : 1 + \lambda_2(\xi) \Big|_{\xi=\tau} = 0; \quad \delta v_n : \lambda_2'(\tau) = 0 \quad (10-A)$$

$$\delta w_n : 1 + \lambda_3(\xi) \Big|_{\xi=\tau} = 0; \quad \delta w_n : \lambda_3'(\tau) = 0 \quad (11-A)$$

From the above equations, the Lagrange multipliers can be identified as:

$$\lambda_1(\tau) = -1, \lambda_2(\tau) = -1, \lambda_3(\tau) = -1 \quad (12-A)$$

Using (12-A) and taking  $n=0$  in the iteration formula ((3-A)-(5-A)) we have:

$$u_1(X, \tau) = u_0 + \int_0^\tau \left[ \frac{\partial u_0}{\partial \xi} - \frac{\partial^2 u_0}{\partial X^2} + \frac{\gamma_{E1} u_0 v_0 \alpha \beta}{\alpha \beta u_0 v_0 + \beta v_0 + \alpha u_0} \right] d\xi \quad (13-A)$$

$$v_1(X, \tau) = v_0 + \int_0^\tau \left[ \frac{\partial v_0}{\partial \xi} - \eta \frac{\partial^2 v_0}{\partial X^2} + \frac{\gamma_{S1} u_0 v_0 \alpha \beta}{2(\alpha \beta u_0 v_0 + \beta v_0 + \alpha u_0)} \right] d\xi \quad (14-A)$$

$$w_1(X, \tau) = w_0 + \int_0^\tau \left[ \frac{\partial w_0}{\partial \xi} - \mu \frac{\partial^2 w_0}{\partial X^2} + \frac{\gamma_{S1} u_0 v_0 \alpha \beta}{(\alpha \beta u_0 v_0 + \beta v_0 + \alpha u_0)} \right] d\xi \quad (15-A)$$

We now consider the initial approximate solution satisfying ((12),(13)) as:



$$u = \frac{\cosh(X)}{\cosh(1)}; \quad v = \frac{\cosh(X)}{\cosh(1)} \quad (16-A)$$

$$w = 1 - \frac{\cosh(X)}{\cosh(1)}$$

By the iteration formula ((13-A)-(15-A)) we obtain the equations (14) in the text.

## Appendix B

A SCILAB/MATLAB program [22] for the numerical solution of the system of non linear second order differential Eqs. (8)-(10) for the glucose composite membrane is given below:

```
function pdex4
m = 0;
x = [0,0.2,0.4,0.6,0.8,1];
t=[0.01,0.1,0.3,0.5];
sol = pdepe(m,@pdex4pde,@pdex4ic,@pdex4bc,x,t);
u1 = sol(:,:,1);
u2 = sol(:,:,2);
u3 = sol(:,:,3);
figure
surf(x,t,u1)
title('u1(x,t)')
xlabel('Distance x')
ylabel('time t')
zlabel('u1(x,2)')
figure
surf(x,t,u2)
title('u2(x,t)')
xlabel('Distance x')
ylabel('time t')
zlabel('u2(x,2)')
figure
surf(x,t,u3)
title('u3(x,t)')
xlabel('Distance x')
ylabel('time t')
zlabel('u3(x,2)')
function [c,f,s] = pdex4pde(x,t,u,DuDx)
c = [1; 1; 1];
eta=0.1;
mue=0.1;
f = [1; eta; mue] * DuDx;
alpha=0.1;
beta=0.01;
y = (u(1)* u(2))/(u(1) * u(2)+(u(2)/alpha)+(u(1)/beta));
gamma=100;
gamma1=0.01;
F =(-gamma*y);
F2 =(gamma1*y);
F1 =(-(1/2)*gamma1*y);
s=[F;F1;F2];
function u0 = pdex4ic(x)
```

```
u0 = [(cosh(x)/cosh(1));(cosh(x)/cosh(1));1-
(cosh(x)/cosh(1))];
function [pl,ql,pr,qr]=pdex4bc(xl,u1,xr,ur,t)
pl = [0; 0 ;0];
ql = [1; 1 ;1];
pr = [ur(1)-1; ur(2)-1;ur(3)];
qr = [0; 0;0];
```

## References

- [1] Diabetes Atlas, 5<sup>th</sup> ed. *International Diabetes Federation*, 2011.
- [2] M. J. Abdekhodaie, X.Y. Wu, Modelling of a glucose sensitive composite membrane for closed-loop insulin delivery, *J. Membr sci* 335 (2009) 21-31.
- [3] M. J. Abdekhodaie, X.Y. Wu, Modelling of a cationic glucose sensitive membrane with consideration of oxygen limitation, *J. Membr.Sci.* 245 (2005) 119-27.
- [4] G. Albin, T. A. Horbett, B. D. Ratner, Glucose sensitive membranes for controlled deliver of insulin, in: J.Kost (Ed.), *Pulsed and Self - regulated Drug Delivery*, CRC Press, Boca Ration, FL, 1990, pp. 159-185.
- [5] T.Traitel, Y.Cohen, J.Kost, Characterization of glucose sensitive insulin release system in simulated in vivo conditions, *Biomaterials* 21 (2000) 1679-1687.
- [6] K.Podual, F.J.Doyle III, N.A.Peppas, Glucose sensitivity of glucose oxidase containing cationic copolymer hydrogels having poly(ethylene glycol) grafts, *J. Controlled Release* 67 (2000) 9-17.
- [7] K.Zhang, X, Y.Wu, Modulated insulin permeation across a glucose sensitive polymeric composite membrane, *J.Controlled Release* 80 (2002) 169-181.
- [8] R.A.Siegel, Modelling of drug release from porous polymers. In: M.Rosoff {Ed}, *Controlled Release of Drugs: Polymers and Aggregate Systems*. VCH, NY, 1989, pp.1-51.
- [9] X.Y.Wu, P.I.Lee, Synthesis and characterization of thermal and pH-sensitive nanosphers, *Pharm. Res.*10 (1993) 1544-1547.()
- [10] J.H. He, Homotopy perturbation technique, *Comput. Methods Appl Mech.Eng.* 178 (3-4) (1998) 257-262.
- [11] G. Adomian, Convergent series solution of nonlinear equations, *J. Comp. Appl. Math.* 11 (1984) 2 25-230.
- [12] G.Adomian, M. Witten, Computation of solutions to the generalized Michaelis-Menten equation, *Appl. Math.Lett.*7 (1994) 45-48.
- [13] S.Z. Rida, Approximate analytical solutions of generalized linear and nonlinear reaction-diffusion equations in an infinite domain, *Phys. Lett. A* 374 (2010) 829-835
- [14] J.H. He, some asymptotic methods for strongly non-linear equations, *Int.J.Mod.Phys B* 20( 10)(2006) 1141-1199.
- [15] Shou.D.H et. al, *Application* oif parameter-expanding method to strongly non-linear oscillators, *Int J. Non-linear Sci Numer simul* 8(2007) 113-116.
- [16] J.H.He, Modified Lindsedt-Poincare methods for some strongly non-linear oscillations, Part I: Expansion of a constant. *Int J Nonlinear Mech* 37(2002) 309-14
- [17] J.H. He, Variational iteration method- a kind of non-linear analytical technique, *Int. J Non-linear Mech*34(4)(1999)699-708.
- [18] G.W.Albin, T.A.Albin, T.A.Horbett, S.R.Miller, N.L.Ricker, Theoretical and experimental studies of glucose sensitive membranes, *J.Controlled Release* 6(1987) 267-291.
- [19] L.A.Klumb, T.A.Horbett, Design of insulin delivery device based on glucose , sensitive membranes, *J.Controlled release* 6(1987) 267- 291.
- [20] P.H.S. Tse.J.K.Leyboldt, D.A.Gough, Determination of the intrinsic kinetic constants of immobilized glucose oxidase and catalase, *Biotechnol. Bioeng.* XXIX (1987) 696-704.
- [21] Tamer A.Abassy, Magdy A.El-Tawil, H.El Zoheiry, Toward a modified variational iteration method, *J.Comput.Appl. Math.*207 (2007) 137-147.
- [22] MATLAB 6.1, The MathWorks Inc., Natick, MA, 2000; [www.scilab-enterprises.com](http://www.scilab-enterprises.com)

## Authors' information



**R. Angel Joy** born at Valparai, Coimbatore, Tamil Nadu, India on 19.11.1968. Obtained her M.Sc. in Mathematics from Bharathiar University, Coimbatore, Tamil Nadu, India during 1990, and then received her M. Phil. in Mathematics from Madras University, Tamil Nadu, India in the year 1991. Also she is doing her Ph.D. in “Analysis, Computation and

Mathematical modelling of reaction diffusion processes” at Bharathiyar University under the guidance of Dr. L.Rajendiren, Assistant Professor in Mathematics, Madura College, Madurai, Tamil Nadu India. She has 15 years of teaching experience and one year of research experience. She has published one article in Peer-reviewed journal.

E-mail: [angeljoy\\_ruban@yahoo.com](mailto:angeljoy_ruban@yahoo.com)



**Dr. L. Rajendran** born on 04/01/1957. He received his M.Sc. in Mathematics in 1981 from Presidency College, Chennai, TN, India. He obtained his Ph.D. in Applied Mathematics from Alagappa University, Karaikudi, TN, India during 2000. At present, he is an Assistant Professor in Mathematics at Madura College, Madurai, TN, India. Before this position (1986–

2007), he was working as a Post Graduate Assistant in Mathematics at SMSV Higher Secondary School, Karaikudi, TN, India. He has 20 years teaching experience and 15 years research experience. He has authored and coauthor over 100 research publications including about 80 scholarly articles in peer-reviewed journals. He visited institute fur Organische Chemie, University at Tubingen, Germany in year 2003 under INSA and DFG Postdoctoral Research Fellowship. He also visited Polish Academy of Sciences, Krakow, Poland in the year 2011. Currently he has three research projects from DST, CSIR and UGC. His current research interests include mathematical and computational modeling of electrochemical biosensor.

E-mails: [raj\\_sms@rediffmail.com](mailto:raj_sms@rediffmail.com)

[dr.rajendran.l@gmail.com](mailto:dr.rajendran.l@gmail.com)