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Mathematical modelling of an enzyme-based biosensor

Abstract

The behavior of biosensors lies on a well-defined physical, chemical and biological reactions, which are specified by nonlinear differential equations. These biosensors have plethora of applications in diverse fields; hence mathematical modeling of the same is highly desirable. This can help in prefiguring its various characteristics. A mathematical model is proposed which studies the cyclic conversion of substrate in an amperometric biosensor. The governing parameters for the Michaelis-Menten kinetics of enzymatic reactions are the enzyme kinetic rate and the diffusion rate across the enzymatic layer. The mathematical model was analytically and numerically solved and simulated in MATLAB® v2016b software using partial differential equation solver pdepe function. . The non-dimensional mathematical model of the amperometric biosensor can be successfully used to investigate the response of biosensors with cyclic substrate conversion. The analytical results are compared with numerically simulated results for various conditions to validate the model parameters. Relative influence of these parameters is decided by a non dimensional number called Damkohler number, which is a ratio of the rate of enzymatic reaction to the rate of diffusion. The effect of Damkohler number on the current density, substrate concentration, and product concentration has been studied. It has been observed that when the Damkohler number is low then enzyme kinetics controls the biosensor response whereas when it is high (of the order of 1) the response is under control of diffusion rate. The current density is found to increase with the decrease in Damkohler number and vice versa.

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Introduction

Biosensors are compact analytical devices, made up of a combination of a specific biological element, mainly an enzyme which recognizes a specific analyte (substrate) and the transducer which translates this biorecognition signal into an appropriate electrical signal.[1,2] Amperometric biosensor is a type of biosensor which measure the current that arises on a working indicator electrode by direct electrochemical oxidation or reduction of the biochemical reaction product. These biosensors are widely used in clinical diagnostics, environment monitoring, food analysis, drug detection and industrial purposes because they are reliable, highly sensitive and comparatively cheap.[3] The development of these biosensing systems depends greatly on a quantitative measurement of the enzyme activity before and after exposure to a target substrate.[4] In recent days amperometric based electrochemical biosensors are highly used for fast and accurate detection.[5,6] The operations of electrochemical sensors are very simple and never affect the host material.[7,8] These biosensors, produces the output current based on the sensing materials on the working electrode act as a catalyst and catalyze the redox reaction. During measurement, the electrode potential is kept constant while the current is monitored. Optimization of biosensor is the time consuming process, for that mathematical modeling is used to reduce the optimization time, cost and optimize the analytical characteristics of actual biosensor.[9–11]

The proposed one-dimensional-in-space (1-D) mathematical model does not consider the geometry of the enzymatic membrane and it also includes efficient diffusion coefficients. The quantitative value of diffusion coefficients is limited for one dimensional model. Recently, a two-dimensional-in-space (2-D) mathematical model has been proposed considering the perforation geometry.[12] However, a simulation of the biosensor based on the 2-D model is much more time-consuming than a simulation based on the corresponding 1-D model. This is more important when we investigate numerical peculiarities of the biosensor response in extensive ranges of catalytic and geometrical parameters. The multifold numerical simulation of the biosensor response based on the 1-D model is much more efficient than the simulation based on the corresponding 2-D model. The detection limit of the enzyme electrodes depends on the sensitivity of the amperometric system. The sensitivity of the enzyme electrode can be increased by the cyclic conversion of the substrate.[13] The electrode cyclic conversion of the substrate is carried out by conjugation of the enzymatic reaction with the electrochemical process. The goal of this work is to make a model by which we can measure the biosensor response utilizing the amplification done by conjugated electrochemical and enzymatic substrate conversion. The developed model is based on non-stationary diffusion equation containing a non-linear term related to the enzymatic reaction. Here, we modeled an amperometric biosensor and numerically analyzed it to detect the dependence of current density, substrate concentration and product concentration on Damkohler number.

Mathematical modelling

The amperometric biosensor was constructed as an electrode and a relatively thin layer of an enzyme which is applied onto the electrode surface. The model involves enzyme layer where the enzymatic reaction as well as the mass transport by diffusion takes place where the analyte concentration is maintained constant.[14] Consider the scheme of substrate (S) electrochemical conversion to a product (P) following catalyzed with enzyme (E) product conversion to substrate, ES is a transitory complex assumed to be at a steady concentration:

$$S + E \underset{k_{-1}}{\overset{k_1}{\longleftrightarrow}} \{ES\} \xrightarrow{k_2} E + P \qquad (1)$$

We have assumed the symmetrical geometry of the electrode and homogeneous distribution of immobilized enzyme in the enzyme membrane. The $k_1,\ k_{-1},\ and\ k_2$ are the reaction rate constants. Coupling of the enzyme-catalyzed reaction in the enzyme layer with the one-dimensional-in-space diffusion, described by Fick's law, leads to the following equations:

$$\frac{\partial S}{\partial x} = Ds\frac{\partial^2 S}{\partial x^2} + \frac{V_{\max} P}{K_M + P},\ 0 < x < d,\ 0 < t \le T \tag{2}$$

$$\frac{\partial P}{\partial x} = D_P\frac{\partial^2 P}{\partial x^2} + \frac{V_{\max} P}{K_M + P},\ 0 < x < d,\ 0 < t \le T \tag{3}$$

Where x and t stand for space and time, respectively; S(x, t) and P(x, t) denote the concentration functions of the substrate and reaction product, respectively, V_{max} is the maximum enzymatic rate attainable when the enzyme is fully saturated with substrate, K_M the Michaelis-Menten constant, d the thickness of the enzyme layer, Ds and Dp are the diffusion coefficients of the substrate and product, respectively, T is the full time of biosensor operation to be analyzed. Electrode surface is represented by x=0 plane while x=d represents the bulk solution/membrane interface. The operation of the biosensor starts when some substrate appears on the surface of the enzyme layer. This is used in the initial conditions (t = 0):

$$S\left(x,0\right) = 0, S\left(d,0\right) = S_0,\ 0 \le \mathrm{x} < d, \tag{4}$$

$$P\left(x,0\right) = 0,\ \ 0 \le \mathrm{x} \le d, \tag{5}$$

Where S_0 is the concentration of substrate in the bulk solution. During electrochemical conversion, the product is produced at the electrode. The rate of the product formation at the electrode is proportional to the rate of conversion of the substrate. When the substrate is well-stirred outside the membrane, then the thickness of the diffusion layer remains constant $\left(0 < x < d\right)$. Consequently, the concentration of substrate as well as the product over the enzyme surface (bulk solution/membrane interface) remains constant while the biosensor interacts with the solution of substrate. This is used in the boundary conditions $\left(0 < t \le T\right)$ given by:

$$S\left(0,t\right) = 0;\ \ S\left(d,t\right) = S_0;$$
$$Dp\frac{\partial P}{\partial x_{x=0}} = -Ds\frac{\partial S}{\partial x_{x=0}} \tag{6}$$

The current is measured as a response of the biosensor and the density I(T) can be obtained explicitly from Faraday's law and Fick's law using the flux of the concentration S at the surface of the electrode:

$$I\left(T\right) = n_e FD_s\frac{\partial S}{\partial x_{x=0}} \tag{7}$$

Non-dimensional form

The following parameters are used to convert the above Equations 2 and 3 into normalized form.

$$S^* = \frac{S}{K_M},\ P^* = \frac{P}{K_M},\ x^* = \frac{x}{d},\ t^* = \frac{D_S t}{d^2},\ R = \frac{D_P}{D_S} \tag{8}$$

Using the above normalizing parameters, the equation for depletion rate of substrate can be written as:

$$\frac{\partial s^*}{\partial t^*} = \frac{\partial^2 s^*}{\partial x^{*2}} + \sigma^2\left(\frac{P^*}{1+P^*}\right) \tag{9}$$

$$\sigma^2 = \frac{V_{\max} d^2}{D_S K_M} \tag{10}$$

Where σ^2 is the Damkohler number (Da).

Damkohler number is also termed as diffusion modulus which is used to compare the rate of enzyme reaction $\left(\frac{V_{max}}{K_M}\right)$ with the rate of diffusion through the enzymatic layer $\left(\frac{D_S}{d^2}\right)$. In this whole procedure, if Damkohler number is less than 1 then the enzyme kinetics controls the biosensor response. And, if the Damkohler number is greater than 1 then the diffusion rate controls the biosensor response.

The dimensionless form of Equation 7 is normalized using $I_0 = FV_{\max} d$, to give:

$$I^*\left(T^*\right) = \frac{I\left(T\right)}{I_0} = \frac{n_e FD_s\dfrac{\partial S}{\partial x_{x=0}}}{FV_{\max} d} = \frac{n_e D_s K_M}{V_{\max} d^2}.\frac{\partial s^*}{\partial x^*}_{x^*=0} \tag{11}$$

The Equations 3 and 4 reduce to the following dimensionless form

$$\frac{\partial s^*}{\partial t^*} = \frac{\partial^2 s^*}{\partial x^{*2}} + \sigma^2\left(\frac{P^*}{1+P^*}\right) \tag{12}$$

$$\frac{\partial P^*}{\partial t^*} = \frac{\partial^2 P^*}{\partial x^{*2}} - \sigma^2\left(\frac{P^*}{1+P^*}\right) \tag{13}$$

If Damkohler less than one, then the enzyme kinetics controls the biosensor response. The dimensionless initial and boundary conditions are:

$$S^*\left(x^*,0\right) = 0;\ \ S^*\left(1,0\right) = S^*;\ \ P^*\left(x^*,0\right) = 0$$

$$S^*\left(0,t^*\right) = 0;\ \ S^*\left(1,t^*\right) = S^*_0$$
$$D_p\frac{\partial P}{\partial x_{x=0}} = -D_s\frac{\partial S}{\partial x_{x=0}} \tag{14}$$

$$P^*\left(1,t^*\right) = 0$$

Numerical simulation

The Equations 12 and 13, for the corresponding initial and boundary conditions are solved numerically using pdepe function in MATLAB software.[15] The partial differential equations are solved using finite difference schemes. Numerical solutions are obtained for various parameters such as initial substrate concentrations, ration of

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reaction diffusion, and sigma for every value of time and space vector (Figures 1 & Figure 2).

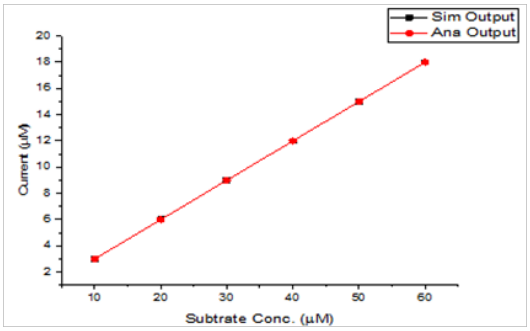

Figure 1 Output current with respect to substrate concentration.

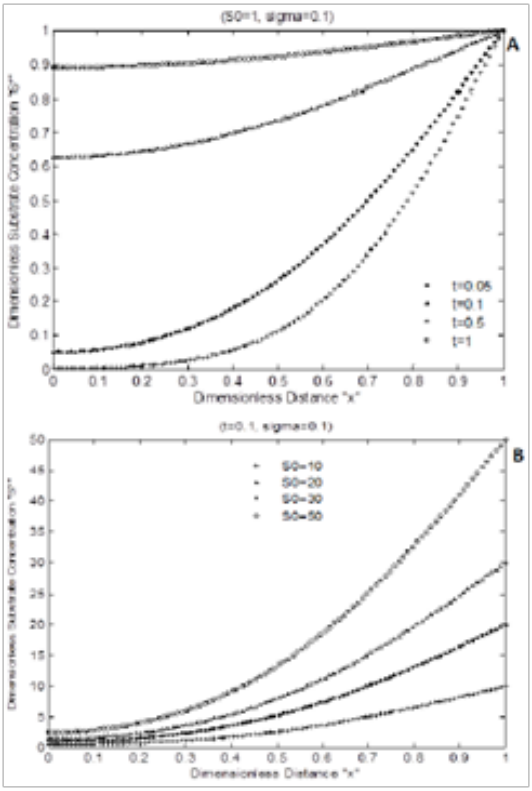

Figure 2 Substrate concentration with respect to distance for various time t, initial substrate concentration S_0, σ.

Result and discussion

Validation

The present numerical model is validated against the published result of.[16] They considered a case of an amperometric biosensor with initial substrate concentration of 20nmol/cm^3 and the thickness of enzyme layer was 0.02 cm. They considered the case of cyclic conversion of substrate. The results are obtained for variation of substrate and product concentrations with time. From Figure 3, it can be noticed that our numerical prediction matches quite well with the result obtained by.[16] Using numerical simulation, pecularities of the biosensor action has been investigated for different values of the model parameters. The biosensor current density as well as substrate concentration along with product formation is dependent on its enzyme interface. A mathematical model was used to study the effect of Damkohler number on the response of the biosensor to know whether it is a diffusion rate driven or enzyme kinetic rate driven. Using computer simulation we have investigated the dependence of non-dimensional current density, product concentration, substrate concentration on Damkohler number.

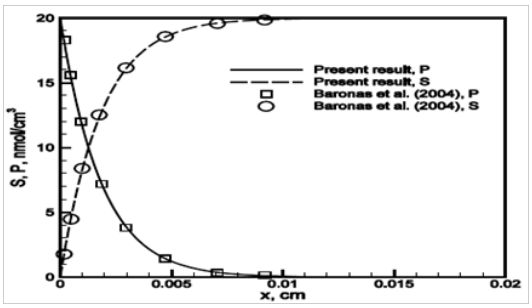

Figure 3 Validation of the present numerical model.

Dependence of substrate concentration on damkohler number

The Figure 4 shows the variation of substrate concentration (S*) with the enzyme layer thickness (X*). It can be seen that as the Damkohler number decreases the substrate concentration increases with the increase in enzyme layer thickness and when the Damkohler number is less than 1, the enzyme diffusion rate dominates which is reflected by almost a straight line passing through the origin. The variation loses its linearity for lower values of Damkohler number, which shows the dominance of enzyme kinetic rate over the enzyme diffusion rate. It is also interesting to observe that an instant of maximum substrate concentration corresponds to an instant of minimum product formation throughout the enzyme layer, which is the result of cyclic conversion of substrate.

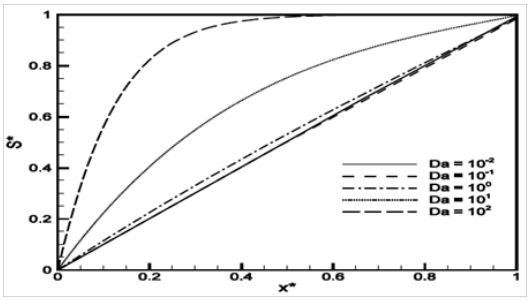

Figure 4 Substrate concentration Versus Enzyme layer.

Dependence of current density on damkohler number

In the numerical simulation the Damkohler number is changed from 10^{-2} to 10^2 by a factor of 10 and the change in the nature of the non-dimensional current density is measured. It can be easily observed from Figure 5 that with decrease in the Damkohler number there is an increase in the non-dimensional current density. Hence, it can be concluded from here that with the decrease in Damkohler number, the process is governed by diffusion controlled reaction which in turn results in an increase in the current density. In this we get an increase in the non-dimensional current density whereas whenever the process is enzymatic controlled rate driven, the current density in non-dimensional form decreases in comparison to diffusion controlled rate driven process.

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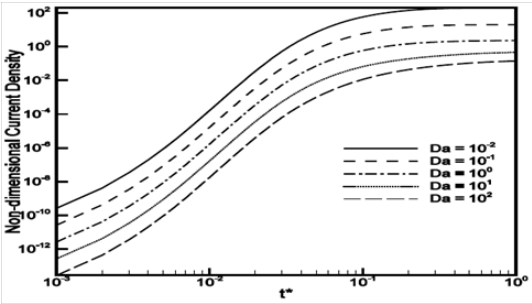

Figure 5 Non-dimensional current density vs. the time.

Dependence of product concentration on damkohler number

Now the product concentration that is formed depends on the enzymatic layer and the diffusion rate of the enzyme. From Figure 6, it is concluded that when the Damkohler number is less than 1, the enzyme diffusion dominates and it penetrates deeper into the substrate, and the product concentration varies linearly. The enzyme catalytic reaction rate dominates the product formation when the Damkohler number is greater than 1. The nature of variation of product is quite different than the case when the reaction is governed by enzymatic diffusion. Now, the product concentration first decreases rapidly up to a certain point of enzyme layer thickness and then it decreases gradually with increase in the enzyme layer thickness.

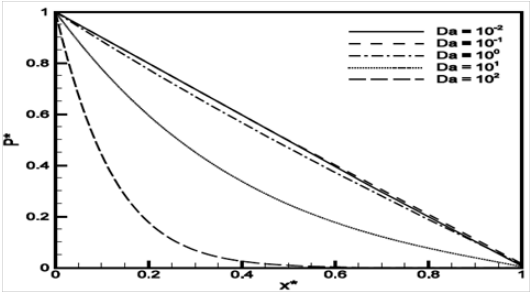

Figure 6 Non-dimensional Product concentration versus Length of the Enzyme layer.

Conclusion

The non-dimensional mathematical model of an amperometric biosensor can be successfully used to investigate the response of biosensors with cyclic substrate conversion and it is also been used to determine the dependence of non-dimensional current intensity, substrate concentration, and the product concentration upon the Damkohler number. The Damkohler number states that whether the reaction rate is diffusion rate driven or enzyme kinematic rate driven. It has been found that the current density increases with the decrease in Damkohler number and vice-versa. Also, an instant of maximum substrate concentration corresponds to an instant of minimum product formation throughout the enzyme layer.

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Conflict of interest

The author declares no conflict of interest.

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