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MATHEMATICAL MODELING OF AN AMPEROMETRIC GLUCOSE SENSOR: THE EFFECT OF MEMBRANE PERMEABILITY AND SELECTIVITY ON PERFORMANCE

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Abstract. Interference from electro-active chemicals such as ascorbic acid, uric acid and acetaminophen can be a problem for peroxide based glucose biosensors. Most works focused on the employment of a perm-selective membrane sandwiched between the electrode and the active component of the sensor to overcome this problem. In this work, a mathematical model has been developed to study the effect of membrane permeability and selectivity on peroxide based glucose biosensor performance. Digital simulation was carried out using the finite difference method. As expected, membrane selectivity to peroxide played a major role in interference reduction. However, interestingly, the model also suggested that the manipulation of the transport properties of the protective outer layer would also result in acceptable interference reduction.

Keywords: Glucose biosensors; mathematical modeling; acetaminophen; interferents; transport properties

Abstrak. Gangguan dari bahan kimia elektro-aktif seperti asid askorbik, asid urik dan asetaminofen adalah merupakan satu masalah bagi biosensor glukosa berasaskan peroksid. Kebanyakan kerja penyelidikan memfokuskan kepada penggunaan membran yang perm-selektif di antara elektrod dan komponen aktif sensor untuk menghilangkan masalah ini. Dalam kerja penyelidikan ini, satu model matematik telah dibina untuk mengkaji kesan kebolehtelapan dan kememilihan bagi prestasi biosensor glukosa berasaskan peroksid. Simulasi digital telah dijalankan menggunakan kaedah pembezaan terhingga. Seperti yang dijangka, kememilihan membran kepada peroksid memainkan peranan besar dalam mengurangkan gangguan. Namun begitu, model juga mencadangkan yang manipulasi sifat pengangkutan lapisan pelindung luar boleh juga menghasilkan keputusan yang memberangsangkan dalam mengurangkan gangguan.

Kata kunci: Biosensor glukosa; model matematik; asetaminofen; pengganggu; sifat pengangkutan

1.0 INTRODUCTION

For many years, considerable effort has been devoted to the research and development of glucose biosensors. Along with the groundwork and the realization of the actual sensor, the development and analysis of a mathematical model that aids in the understanding of the behavior of the sensor is also crucial. Insights into the workings

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of a sensor will assist researchers in identifying key information needed to improve sensor design.

The most well researched method of glucose sensing is the amperometric technique. Glucose oxidase, which catalyzes the reaction between glucose and oxygen to produce gluconolactone and hydrogen peroxide, is immobilized in a membrane and is coupled to the working electrode. The increase in peroxide concentration or the decrease in oxygen concentration can then be monitored amperometrically. The current will be proportional to glucose concentration in the bulk solution.

Given the popularity of the method, it is hardly surprising that most of the mathematical models reported in literature are based on amperometric glucose sensors. Iliev *et al*. [1] described the influence of enzyme layer position and the ratio of the effective diffusion coefficients of the substrate and the products on the transient behavior of the sensor. In their model, the thickness of the enzyme layer is assumed to be negligibly small compared to other thickness and is treated as a point. Tse and Gough [2] analyzed the transient behavior of an enzymatic glucose sensor in response to substrate concentration changes. Sudoh *et al*. [3] compared the output linearity between oxygen detection and hydrogen peroxide detection for amperometric glucose sensors. Sakamoto [4] examined the effect of enzyme concentration on the dynamic behavior of a membrane-bound enzyme system. Krishnan *et al*. [5] modeled the behavior of an amperometric enzyme electrode based on a porous matrix of Stober glass beads. Kurnik *et al*. [6] presented mathematical modeling for a combined iontophoretic device and amperometric enzyme electrode. Baronas *et al*. [7] developed a mathematical model that described the influence of the enzyme membrane thickness on the response of amperometric biosensors. The model could be used for selection of appropriate membrane thickness to ensure stable biosensor response. Csoka *et al*. [8] developed a mathematical model that described the concentration profiles of reactants and products inside the reaction layer of a biosensor. The results were compared to experimentations carried out using scanning electrochemical microscopy with amperometric or potentiometric measuring tips.

Many of the amperometric glucose biosensors are based on the detection of hydrogen peroxide due its simple configuration, as unlike oxygen, hydrogen peroxide is not present in the sample to be analyzed. However, this type of glucose sensor is affected by interference from readily oxidizable species such as ascorbic acid, uric acid and acetaminophen [9]. A number of perm-selective membranes have been employed to reduce the interferences [10–14]. In most cases, effective but incomplete rejection has been reported.

In this work, the major problem that plagues peroxide-based glucose sensor, namely electrochemical interference, was highlighted. Due to its uncharged nature acetaminophen is more prone to produce a larger bias to sensor response than other interferents as most selective membranes that are employed for interference elimination are designed to repel interferents on the basis of their charged nature. Thus,

acetaminophen was used as a representative interferent in this model. Unlike previous mathematical models, this work aimed to mathematically model the influence of acetaminophen on the performance of a peroxide-based amperometric glucose biosensor. The effect of membrane permeability and selectivity on interference elimination of acetaminophen was studied.

2.0 MATHEMATICAL MODEL

A typical glucose biosensor configuration consists of three layers on the electrode surface (Figure 2). The inner layer (layer 3), which is in contact with the electrode serves as the selective membrane that retards the interferents to some extent while allowing the diffusion of H_2O_2. The middle layer (layer 2) is the immobilized enzyme layer, within which glucose is depleted and converted to H_2O_2. The outer layer (layer 1) must be able to serve the dual purpose of providing biocompatibility and allowing maximum passage of oxygen compared to glucose in order to ensure a glucose diffusion controlled process.

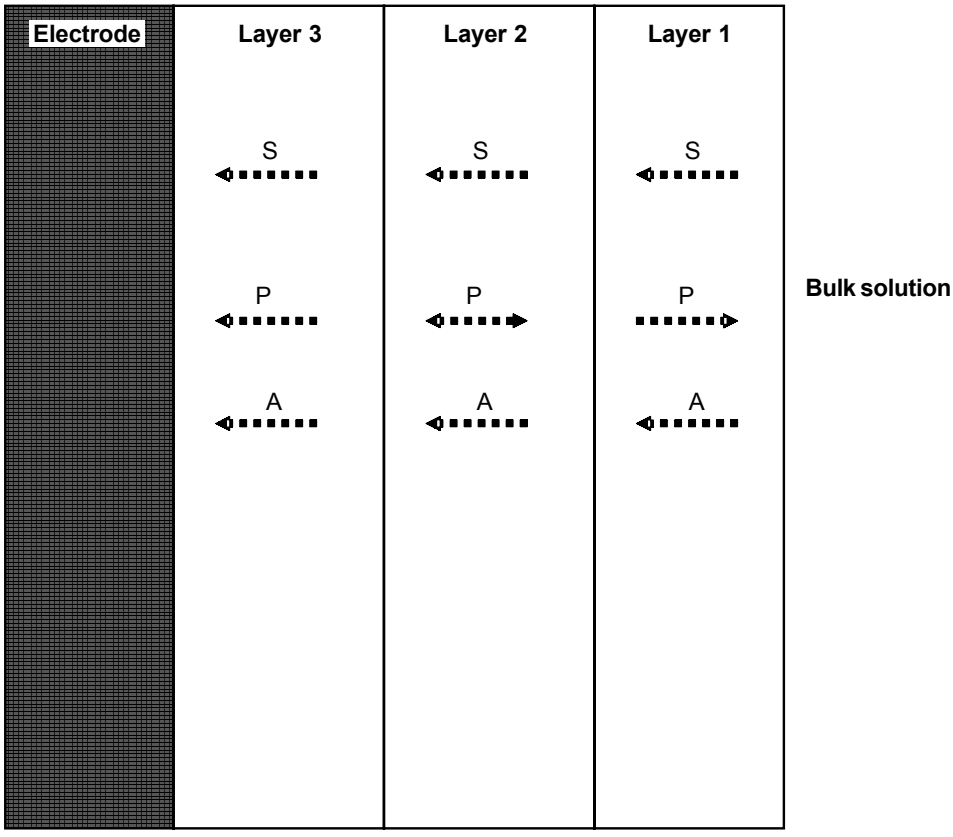

Figure 1 One-dimensional schematic diagram of the sensor configuration. Note: S:substrate=glucose, P:product=H_2O_2, A: acetaminophen

The following describes the system that was modeled. In the bulk solution, the concentration of H_2O_2 is set equal to zero as it was assumed to be diluted instantaneously. In layer 3, glucose, H_2O_2 and acetaminophen diffuse towards the electrode. Both H_2O_2 and acetaminophen are instantaneously oxidized at the electrode surface resulting in $[P] = 0$ and $[A] = 0$.

In layers 1, 3 and fibrotic capsule (fc) no reaction occurrs. Glucose, H_2O_2 and acetaminophen simply diffuse through the membranes. The transient behavior of the concentration distribution of the said species is described by:

$$\begin{aligned}\frac{\partial[S]}{\partial t} &= D_{Si}\frac{\partial^2[S]}{\partial x^2}\\ \frac{\partial[P]}{\partial t} &= D_{Pi}\frac{\partial^2[P]}{\partial x^2}\\ \frac{\partial[A]}{\partial t} &= D_{Ai}\frac{\partial^2[A]}{\partial x^2} \quad ;i=1,3,fc\end{aligned} \tag{1}$$

The enzymatic reaction that occurs in layer 2 was simplified such that it followed the Michaelis-Menten kinetics:

$$E + S \underset{k_{-1}}{\overset{k_1}{\longleftrightarrow}} E - S \xrightarrow{k_2} E + P \tag{2}$$

The system was assumed not to be limited by oxygen supply. Since all enzyme is either 'free' or complexed:

$$[E_0] = [E-S] + [E] \tag{3}$$

where $[E_0]$ is the initial concentration of the enzyme (which was assumed to be 1.25×10^{-07} mmol/mm^3 of matrix [15]), $[E–S]$ is the concentration of the complexed enzyme and [E] is the concentration of the 'free' enzyme.

The following equations describe the behavior of the system in this layer:

$$\begin{aligned}\frac{\partial[S]}{\partial t} &= D_{S2}\frac{\partial^2[S]}{\partial x^2} - k_1[E_0][S] + k_{-1}[E-S] + k_1[S][E-S]\\ \frac{\partial[E-S]}{\partial t} &= k_1[E_0][S] - k_{-1}[E-S] - k_2[E-S] - k_1[S][E-S]\\ \frac{\partial[P]}{\partial t} &= D_{P2}\frac{\partial^2[P]}{\partial x^2} + k_2[E-S]\\ \frac{\partial[A]}{\partial t} &= D_{A2}\frac{\partial^2[A]}{\partial x^2}\end{aligned} \tag{4}$$

For the mathematical solution to these equations, the following initial conditions and boundary conditions (*BC*) were employed.

$$[S] = [P] = [A] = 0 \text{ in all layers, } [E] = [E_0] \text{ in layer 2, } [E\text{–}S] = 0 \tag{5}$$

BC at each iteration: $[P] = 0$, $[S] = \alpha_{S1}[S_0(t)]$ and $[A] = \alpha_{A1}[A_0(t)]$ at the interface between layer 1 or *fc* and bulk solution; $[P] = 0$, $[A] = 0$ and $\partial[S]/\partial x = 0$ (flux = 0) at the electrode surface; $D_{Si}\,\partial[S]/\partial x = D_{Si+1}\,\partial[S]/\partial x$, $D_{Pi}\,\partial[P]/\partial x = D_{Pi+1}\,\partial[P]/\partial$x and D_{Ai}

$\partial[A]/\partial x = D_{Ai+1}\,\partial[A]/\partial x$ at other interfaces (where $i = 1, 2$). (6)

For the enzyme layer, the continuity equation for the substrate (glucose) can also be written as:

$$\frac{\partial[S]}{\partial t} = D_{S2}\frac{\partial^2[S]}{\partial x^2} - \frac{k_2[E_0][S]}{[S]+[K_m]} \tag{7}$$

where K_m is the Michaelis constant given by

$$K_m = \frac{k_{-1} + k_2}{k_1} \tag{8}$$

It was assumed that the Michaelis constant, K_m, was 20 mM [16]. The kinetic constants that made up K_m were $k_2 = 735\ s^{-1}$ [17] and $k_{-1} / k_1 = 0.6$ mM.

Peak acetaminophen concentrations in plasma of 0.1–0.2 mM, corresponding to the maximum therapeutic dose of 1000 mg, have been reported [18]. The peak concentration occurred approximately 20–50 minutes after ingestion. To simulate the maximum possible interference, a step change from 0 to 0.2 mM was introduced to the system once the sensor had reached equilibrium after being exposed to a glucose resting concentration of 5 mM.

The transient current produced would be proportional to the flux of H_2O_2 and acetaminophen and is given by:

$$\begin{aligned} i(t) &= nFA_e J(t) \\ &= nFA_e\left[D_{P3}\frac{\partial[P]}{\partial x} + D_{A3}\frac{\partial[A]}{\partial x}\right]_{\text{electrode surface, } t} \end{aligned} \tag{9}$$

where n is the number of electrons involved in the electrochemical reaction, F is the Faraday constant and A_e is the electrode area, which was 0.1963 cm^2 in this study.

Solutions to these differential equations were obtained numerically using an explicit finite difference method. The equations were discretized using forward difference in time and central difference in space approximations [19]. Boundary conditions at the interface between the membranes were discretized using central differences. These equations were solved by means of a computer program developed in Fortran 90 language.

The sensor layers were assumed to be poly(vinyl alcohol) (PVA), a non-toxic, water-soluble synthetic material that has good film forming properties and results in hydrophilic yet strong membranes. As such, all the transport properties used in the modeling were based on published values for PVA.

Assumptions for the partitioning behavior of the solutes into the sensor were based on the work of Matsuyama *et al.* [20], where the partition coefficient was defined as the probability of a diffusing species finding a mesh size with a volume equal to or greater than the solute size. They reported that the partition coefficient decreased with an increase in solute size, depended on the hydrophilicity of the solute, and was affected by the degree of cross-linking for large molecules. The partition coefficient of theophylline (MW 180) in lightly cross-linked PVA was determined to be approximately 0.86.

For this work, the molecular weights of the solutes were assumed to be small enough that the probability of the solutes finding a mesh size of at least the solute size remained unchanged with the degree of cross-linking, or in other words, the partition coefficients were not affected by the degree of cross-linking. As glucose is more hydrophilic than acetaminophen, its partition coefficient should be higher than that of acetaminophen. For partitioning between membranes, partition coefficients for glucose were assumed to be 1.0. Taking into account all the assumptions made, the following values of partition coefficients were used in the modeling: $\alpha_{s1} = 0.9$; $\alpha_{s2} = \alpha_{s3} = 1.0$; $\alpha_{p1} = \alpha_{p3} = 1.0$; $\alpha_{A1} = 0.85$; $\alpha_{A2} = \alpha_{A3} = 1.0$.

The values for the diffusion coefficients used in the model were based on the work of Dai and Barbari for homogeneously cross-linked PVA [21]. They reported values of approximately 1.25 to 4.0×10^{-06} cm^2/s for the effective diffusion coefficient of creatinine in cross-linked PVA containing 60% to 80% water content, respectively. Diffusion coefficients for creatinine were assumed to be similar to those for acetaminophen and glucose. As a conservative estimate, the effective diffusion coefficient of peroxide was assumed to be twice that of acetaminophen, i.e the same ratio as that in buffer [22]. Thus, the values of the effective diffusion coefficient of peroxide were taken to be between 2.5 and $8.0 \times 10^{-06} cm^2/s$. Since partition coefficients of small solutes in PVA are close to 1.0, the actual diffusion coefficients of peroxide in the model were taken to be within this range, except for when it was necessary to demonstrate the effect of extreme values on sensor performance.

Selectivity (σ) in the outer and inner layers was based on the ratio of the permeability of peroxide to that of acetaminophen:

$$\sigma = \frac{\alpha_{\text{peroxide}} D_{\text{peroxide}}}{\alpha_{\text{acetaminophen}} D_{\text{acetaminophen}}} \tag{10}$$

Meanwhile, selectivity in the enzyme layer was based on the ratio of the diffusion coefficient of peroxide to the permeability of acetaminophen since peroxide was generated in this layer:

$$\sigma = \frac{\alpha_{\text{peroxide}}}{\alpha_{\text{acetaminophen}} D_{\text{acetaminophen}}} \tag{11}$$

With respect to enzyme activity, only 1% of the enzyme was considered active after the immobilization process. This is consistent with the studies of Castner and Wingard [23] and Mell and Maloy [24].

3.0 RESULTS AND DISCUSSION

The simulation was performed for a sensor with either two or three layers of membrane on the electrode. In the case of an implantable sensor, the model was also used to evaluate the effect of fibrotic capsule on sensor performance. The model was challenged with a host of different parameters to investigate their effects on sensor performance, namely the response time and the percent of interference. Response time was defined as the time to reach 90% of the steady-state current value.

Figure 2 shows the effect of challenging a two layer sensor (outer and enzyme) with 0.2 mM acetaminophen, 5 mM glucose and 20 mM glucose at different peroxide diffusivity through the sensor. Both layers of the sensor have the same transport

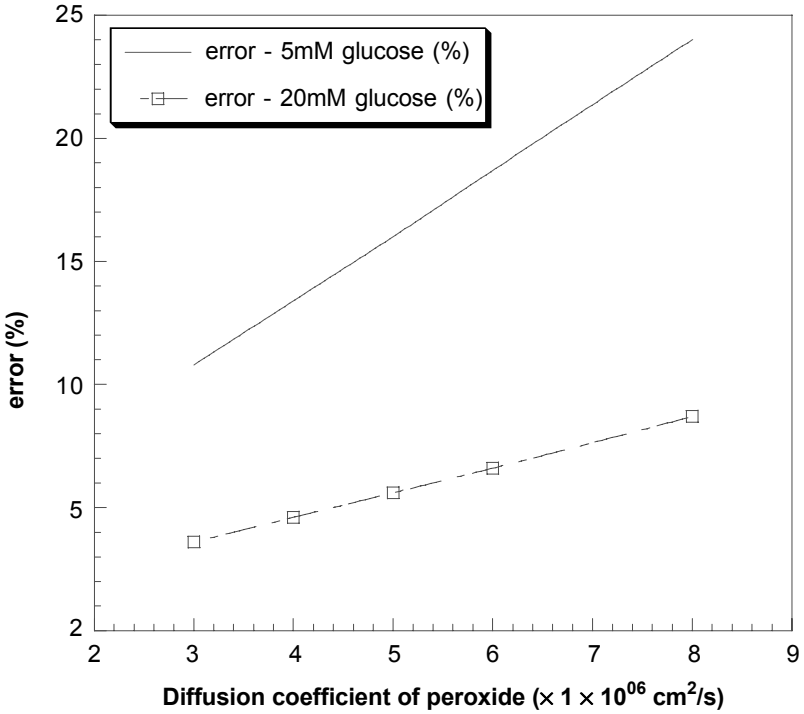

Figure 2 Dependence of error on peroxide diffusivity through the sensor at 5 and 20 mM glucose. Sensor was modeled as having two layers (outer and enzyme) with the same material used for both layers. Both layers have a selectivity of 2

properties i.e the diffusion of peroxide through the layers is at the same rate. The interference from 0.2 mM acetaminophen during the oxidation of 5 mM glucose (resting glucose concentration) was more pronounced than that of a higher glucose concentration. Thus, unless otherwise noted, interference was defined as the error that results from the increase in current due to the oxidation of acetaminophen with respect to the current that would be generated in the presence of 5 mM glucose.

3.1 The Effect of Varying Membrane Permeability and Selectivity on Sensor Performance

To study the effect of permeability and selectivity on performance, the sensor was modeled as having two layers: the outer and enzyme layers or the enzyme and inner layers. The enzyme was assumed to be immobilized in PVA with a moderate cross-linking density. The moderate cross-linking density would not only ensure that loss of active enzyme through leakage would be minimal, but also provide an acceptable environment wherein the activity of the enzyme would not be too greatly compromised.

The following parameters were used to investigate the effect of membrane permeability on the sensor response:

For the enzyme layer: $D_{P2} = 5.0 \times 10^{-06}$ cm^2/s; $D_{A2} = D_{S2}$; $\sigma = 2$; thickness = 50 μ.
For the outer or inner layer: D_{P1} or D_{p3} varied from 0.16 D_{P2} to 1.6 D_{P2}; $\sigma = 2$ for either layer; thickness = 20 μ.

Figure 3 shows the effect of membrane permeability on sensor response time and the ability to cope with electrochemical interference. Varying the permeability of the inner layer did not significantly decrease the percent error (Figure 3(b)). An order of magnitude decrease in D_{P3}, only resulted in an approximately 8% decrease in error in this case. This can be attributed to the fact that peroxide can diffuse in both directions. Therefore, decreasing the permeability of the inner layer would force most of the peroxide formed in the enzyme layer to diffuse into the bulk solution, and thus reduce the current response of the sensor to glucose. On the other hand, decreasing the permeability of the outer layer could significantly improve percent error (Figure 3(a)). An order of magnitude reduction in D_{P1} resulted in approximately 60% decrease in error. Even though decreasing the peroxide permeability of the outer layer at constant α decreases the permeability of acetaminophen and glucose as well, the lower permeability of the outer layer keeps most of the peroxide generated inside the sensor and thus maintains the response of the sensor to glucose at an acceptable value. From this result, it can be concluded that another function of the outer layer is to reduce the amount of peroxide that can diffuse out into the bulk solution.

Varying the diffusion coefficient of the outer layer and the inner layer between 0.6 and 1.6 times the value of D_{P2} decreased the response time to nearly the same degree. However, a further reduction in the diffusion coefficient of the outer layer to 0.16 of

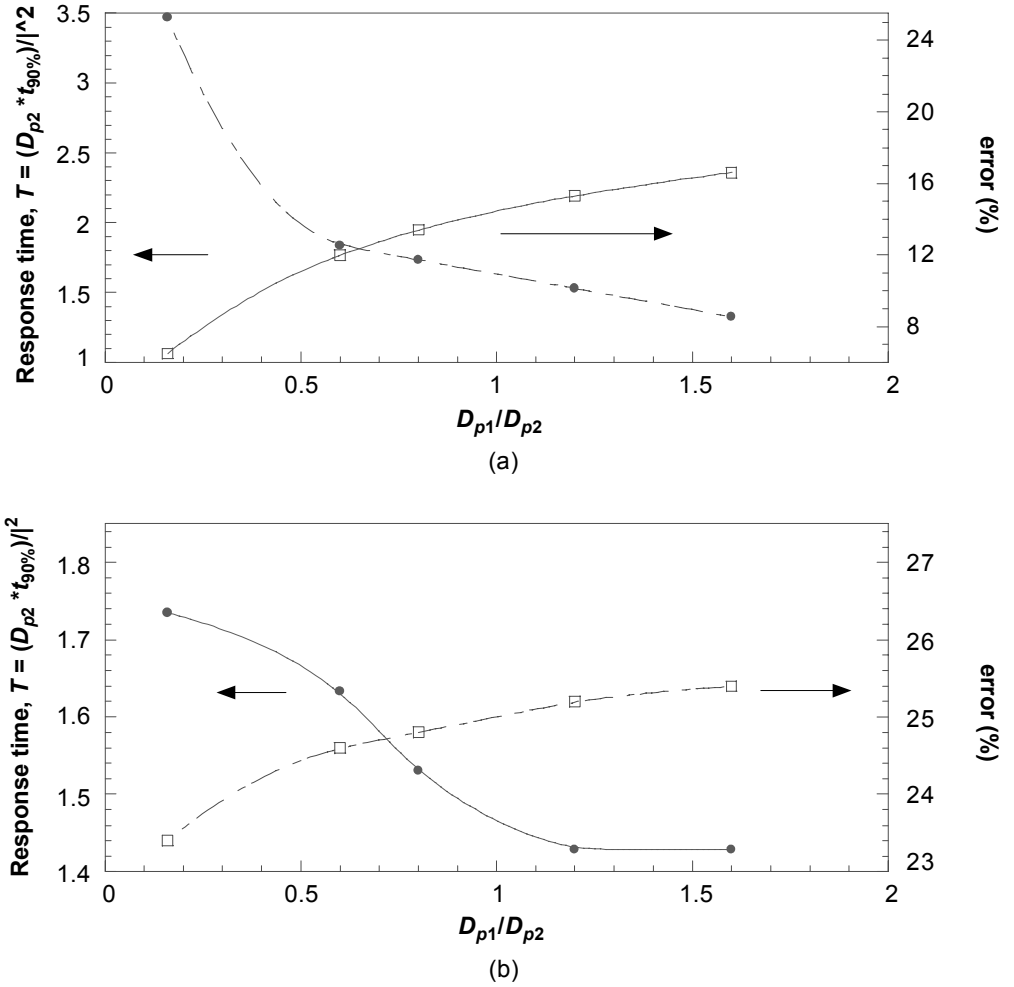

Figure 3 The effect of membrane permeability on the performance of a two-layer sensor. (a) outer and enzyme layers (b) inner and enzyme layers. For reference, a value of $T = 2$, corresponds to $t_{90\%}$ of approximately 20 seconds

D_{P2} increased the response time sharply, probably due to the decrease in the accessibility of glucose to the reaction area (Figure 3(a)). The same decrease in the diffusion coefficient of the inner layer did not result in the same effect on sensor response time (Figure 3(b)).

The following parameters were used to investigate the effect of membrane selectivity on sensor performance:

For the enzyme layer: $D_{P2} = 5.0 \times 10^{-06}$ cm^2/s; $D_{A2} = D_{S2}$; $\sigma = 2$; thickness: 50μ.
For the outer or inner layer: $D_{P1} = D_{P3} = 4.0 \times 10^{-06}$ cm^2/s; σ varied from 2 to 20; thickness = 20μ.

Figure 4 shows the effect of membrane selectivity on the sensor response. Increasing the selectivity of either the inner or outer layer of a two-layer sensor reduces the percent error. Increasing the selectivity of the outer membrane from 2 to 10 (Figure 4(a)) results in a smaller percent error compared to increasing the selectivity of the inner membrane from 2 to 10 (Figure 4(b)). However, a membrane with a very good selectivity for peroxide (e.g. a selectivity of 15 or 20) would be better off employed as an inner layer (Figure 4(b)) rather than an outer layer (Figure 4(a)). This is because the current generated in response to glucose would be quite low due to the combined effect of low diffusion coefficient of glucose and the relatively high diffusion coefficient of peroxide in the outer layer, thus lowering the ability of the sensor to reduce interference.

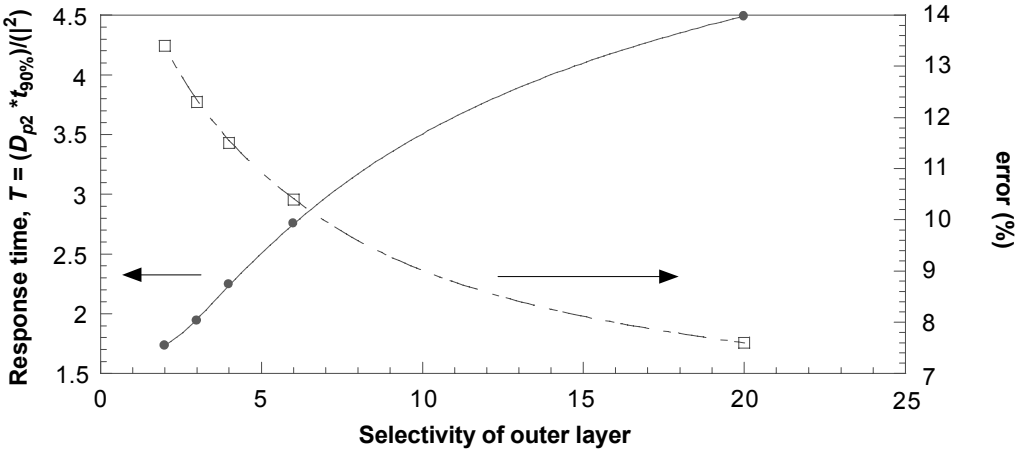

Figure 4 The effect of membrane selectivity on the performance of a two-layer sensor. (a) outer and enzyme layers (b) inner and enzyme layers

Increasing the selectivity of the outer layer increased response time, as the diffusion coefficient of glucose would be decreased along with that of acetaminophen and hence reduce the accessibility of glucose to the reaction area (Figure 4(a)). Increasing the selectivity of the inner layer did not affect response time as the rate at which peroxide reached the electrode surface remained constant.

3.2 The Effect of an Additional Layer on Sensor Performance

In this section, the effect of adding another layer to the previous two-layer sensor is described. As before, the investigation is centered on sensor performance when membrane permeability and selectivity are varied.

The following parameters were used to examine the effect of membrane permeability on the response of a three-layer sensor:

For the enzyme layer: $D_{P2} = 5.0 \times 10^{-06}$ cm^2/s; $D_{A2} = D_{S2}$; $\sigma = 2$; thickness = 50μ.
For the outer and inner layers: D_{P1} or D_{P3} was varied from 0.16 to 1.6 that of D_{P2}; $\sigma = 2$ for both layers; when D_{P1} was varied, $D_{P3} = D_{P2}$ and when D_{P3} was varied, $D_{P1} = D_{P2}$; thickness = 20μ for both layers.

Figure 5 compares the effect of membrane permeability on the performance of a two-layer (a) and a three-layer sensor (b). Comparing Figure 5(a) and (b), the addition of an extra layer, whether internal or external, increased the response time of the sensor as expected. However, response time was more affected by the reduction of the permeability of the outer layer than that of the inner layer. For the case where an unselective and highly permeable internal membrane was added to a two layer sensor consisting of an outer and enzyme layer, percent error did not improve significantly even when the permeability of the outer layer for the three-layer sensor was reduced significantly (Figure 5(a)(i) and Figure 5(b)(i)). On the other hand, for the case where an unselective and highly permeable external membrane was added to a two-layer sensor consisting of an inner and enzyme layer, percent error improved significantly (Figure 5(a)(ii) and Figure 5(b)(ii)). Percent error was reduced by roughly 40% no matter whether the permeability of the inner layer to peroxide was 1.6 or 0.16 times that of the enzyme layer. The external layer reduced the amount of peroxide that diffused out into the bulk solution and therefore kept response current fairly high.

Comparing the performance of the three-layer sensor where either the permeability of the outer or inner layer was varied, reducing the permeability of the outer layer proved to be more effective in reducing interference than reducing the permeability of the inner layer (Figure 5(b) (i) and (ii)). This indicates that the external layer plays an important role in diminishing the impact of electrochemical interference on sensor response. However, there is a larger penalty with respect to increased response time.

The following parameters were used to determine the effect of membrane selectivity on the response of a three-layer sensor:

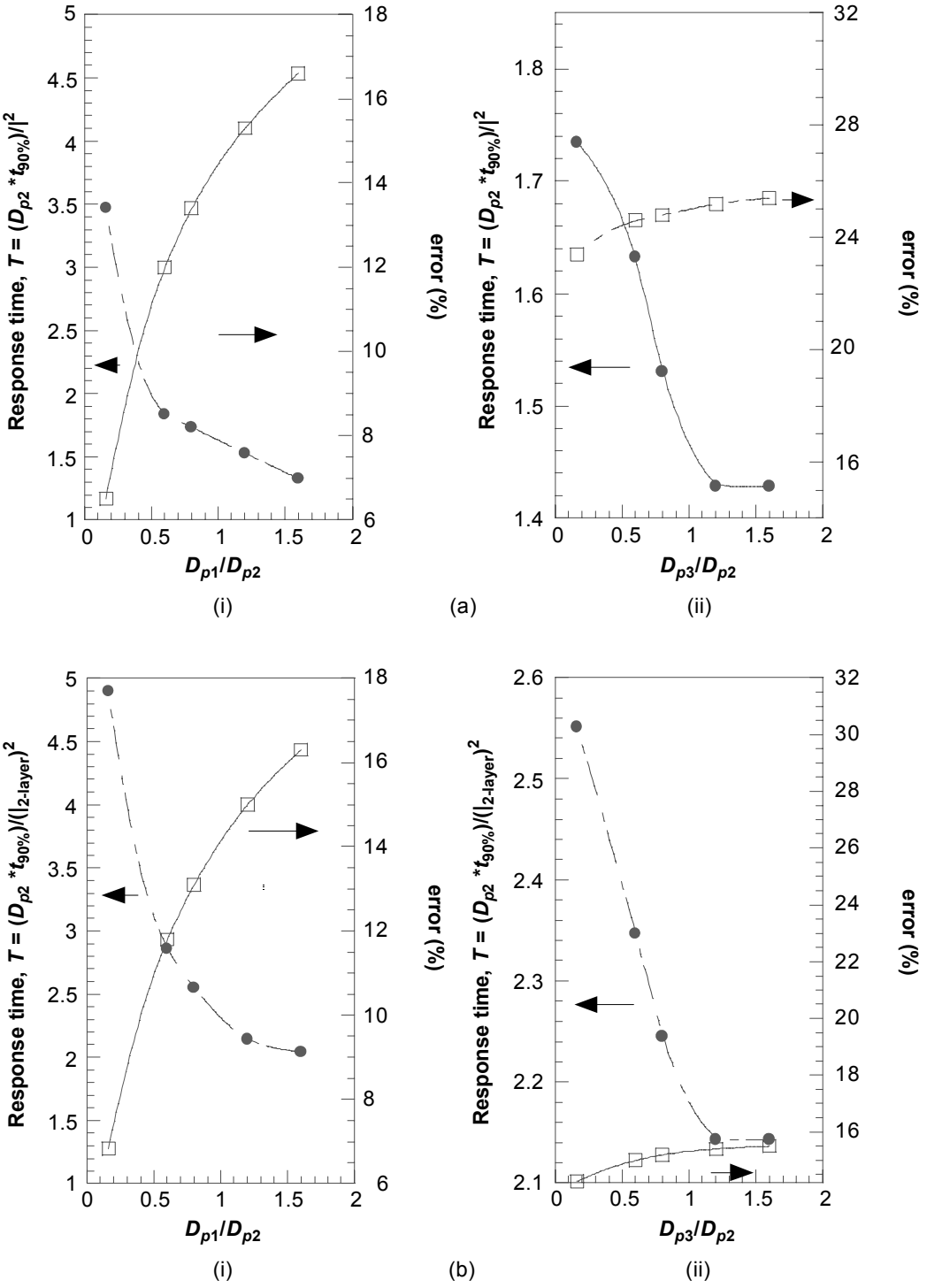

Figure 5 Effect of membrane permeability on the performance of a (a) two-layer and a (b) three-layer sensor

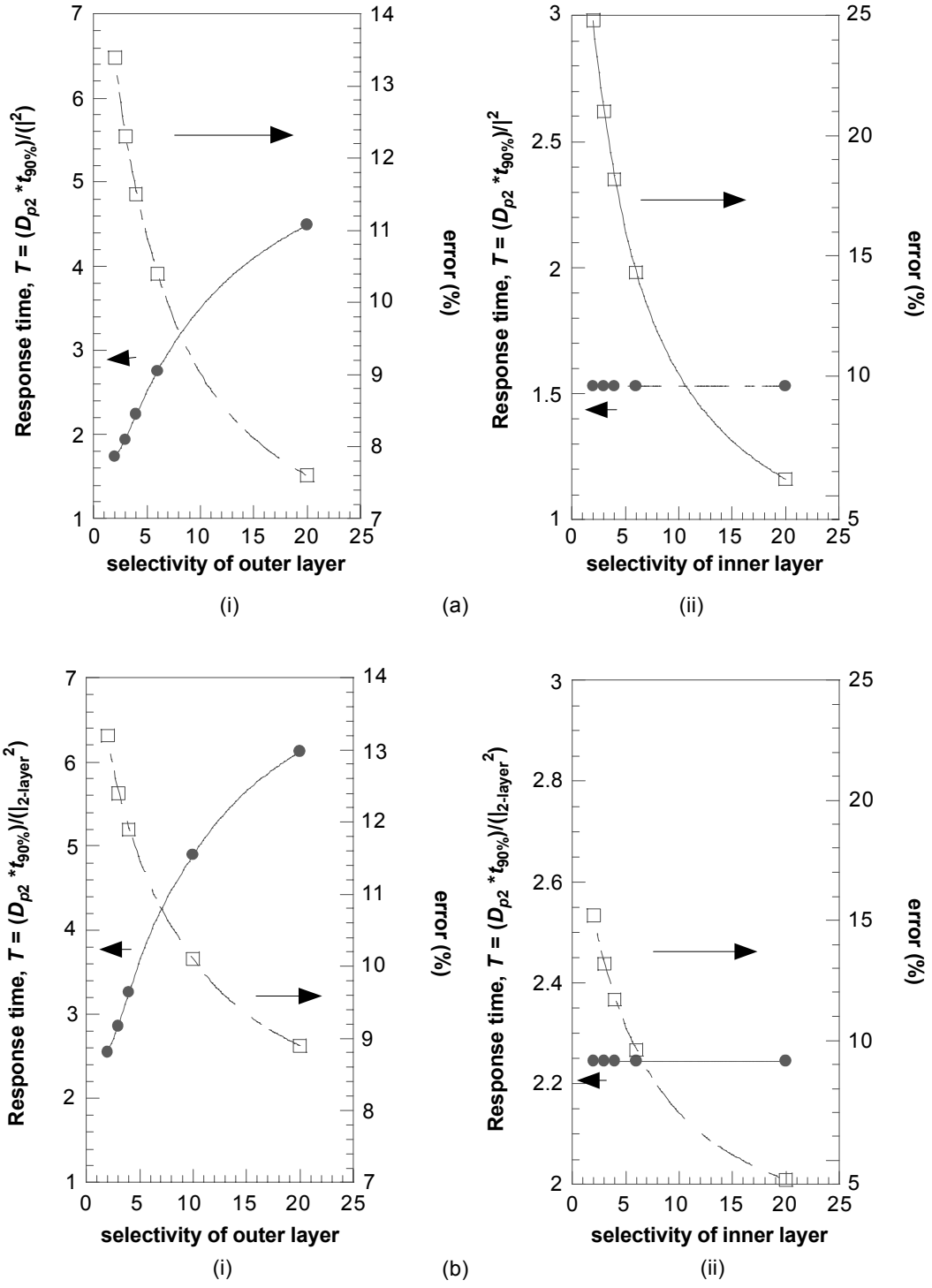

Figure 6 The effect of membrane selectivity on the performance of a (a) two-layer and a (b) three-layer sensor

For the enzyme layer: $D_{P2} = 5.0 \times 10^{-06}$ cm^2/s; $D_{A2} = D_{S2}$; $\sigma = 2$; Thickness = 50μ. For the outer and inner layers: σ was varied from 2 to 20 for either layer and the permeability of that layer was set equal to 4.0×10^{-06} cm^2/s; when σ of outer layer was varied, $D_{P3} = D_{P2}$ and when s of inner layer was varied, $D_{P1} = D_{P2}$; Thickness = 20μ for both layers.

Figure 6 compares the impact of membrane selectivity on the performance of two-layer (a) and three-layer sensors (b). For a two-layer sensor comprising an outer and enzyme layer, adding an unselective and permeable inner layer did not improve the percent error significantly, even when the outer layer was made very selective towards peroxide (Figure 6(a)(i) and Figure 6(b)(i)). In fact, when the selectivity of the outer layer was higher than 4, the performance of the three-layer sensor was worse than that of a two-layer sensor, interference-wise. As indicated in the previous section, this might be due to the combined effects of low permeability to glucose and a relatively high permeability to peroxide in the outer layer that results in a low response current to glucose. This problem was then compounded by the addition of an inner layer. For a two-layer sensor consisting of an enzyme and inner layer, increasing the selectivity of the inner layer improved the ability of the sensor to retard interference, especially if the membrane was made to be highly selective (at least 10) (Figure 6(a)(ii)). Performance would be improved with the addition of an outer layer, even an unselective one (Figure 6(b)(ii)).

Increasing the selectivity of the outer layer had an adverse effect on the response time of three-layer sensor. On the other hand, increasing the selectivity of the inner layer had absolutely no effect on the sensor as D_{P3} was held constant.

3.3 Transient Behavior of an Amperometric Glucose Sensor

The transient behavior of an amperometric glucose sensor can also be examined using the model developed here. A typical current vs. time plot for a three-layer sensor is shown in Figure 7. The sensor was immersed in a stirred solution containing 5 mM glucose at $t = 0$. At a later time, it was subjected to a step-wise increase in glucose concentration to 20 mM, and then was challenged with 0.2 mM acetaminophen.

For a case study, the following parameters were employed for the sensor:

For the enzyme layer: $D_{P2} = 5.0 \times 10^{-06}$ cm^2/s; $D_{A2} = D_{S2}$; $\sigma = 2$; thickness = 50μ. For the outer and inner layer: $D_{P1} = 3.0 \times 10^{-06}$ cm^2/s; $D_{P3} = 4.0 \times 10^{-06}$ cm^2/s; (D_{P3} was chosen to be higher than D_{P1} to favor peroxide transport towards the electrode and to improve response time); $\sigma = 4$ for both layers; thickness = 20μ for both layers.

Figure 7 shows the transient electrode current response to glucose and acetaminophen for a 3-layer sensor. The response time of the sensor to 5 mM glucose (time to reach 90% of the steady state current concentration) was 39 s. The oxidation of 0.2 mM

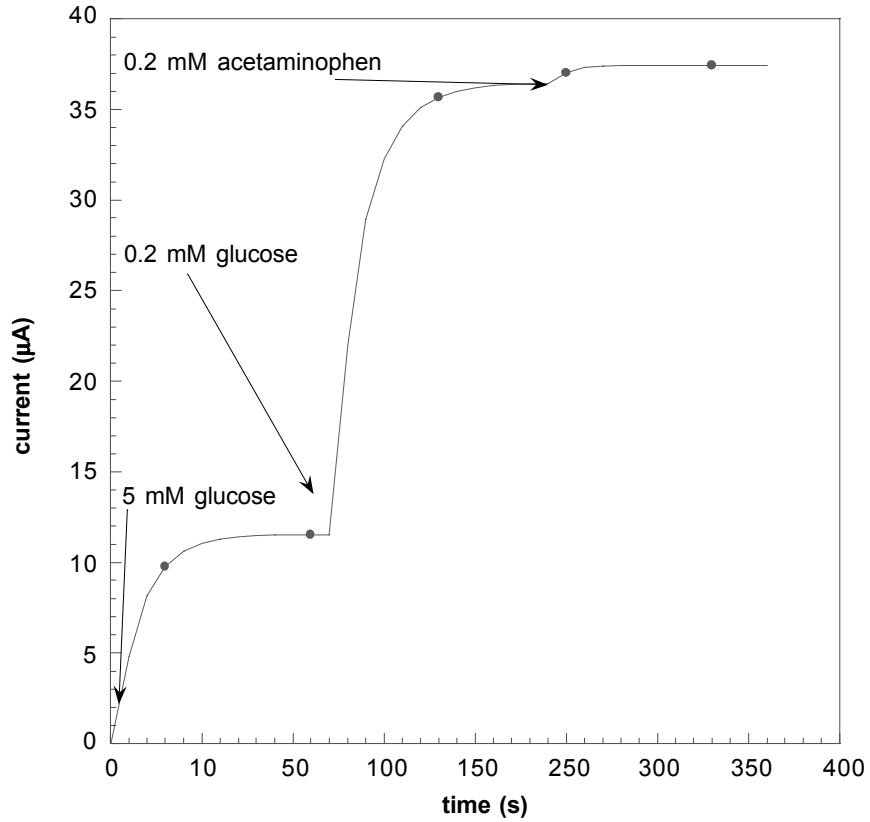

Figure 7 Plot of transient electrode current response to glucose and acetaminophen for a three-layer sensor

acetaminophen gave rise to 8.9% error in the response of the sensor to 5 mM glucose and 1% error in the response of the sensor to 20 mM glucose, respectively. The performance of the sensor can be attributed to the properties selected for the external and internal layers.

The simulation can also provide the transient concentration profiles of the various solutes diffusing through the sensor. A typical plot of the concentration profiles is shown in Figure 8. The plot shows the concentration profile for the previous three-layer sensor, and for clarity only the concentration profiles at steady state (5 mM glucose and 20 mM glucose) are depicted.

The ultimate aim for a glucose biosensor is for implanted purposes so that a close loop system consisting of an implanted biosensor and an insulin pump can be designed and real time monitoring of blood glucose can be done. For implanted glucose sensors, the interaction between the body and the object foreign to the body will ultimately result in the formation of a fibrotic capsule around the foreign object. To investigate the effect of the fibrotic capsule on sensor performance, the model was modified to include another layer. The sensor was assumed to have the same transport characteristics as the previous three-layer sensor.

The following parameters were used to describe the properties of the fibrotic capsule layer:

Partitioning equilibrium was assumed to be similar to PVA membranes used in this work as fibrotic capsules generally contain 75 – 80% water. $D_{glucose}$ = 0.07 – 0.4 × 10^{-06} cm^2/s [25]; thickness = 150 μ [25]; σ = 4; glucose concentration in interstitial fluid is similar to that in blood [26].

Figure 9 shows the transient response of the sensor corresponding to the diffusion coefficient of glucose in the fibrotic capsule of 0.07 and 0.4×10^{-06} cm^2/s, respectively. The presence of the fibrotic capsule was beneficial in the sense that it can further reduce electrochemical interference. Percent error (corresponding to 5 mM glucose) was reduced from 8.9% for a three-layer sensor to 3.8% and 3.5% for a four-layer sensor where $D_{glucose}$ in the fibrotic capsule was 0.4 and 0.07 × 10^{-06} cm^2/s, respectively. However, the advantage in the reduction in interference was offset by the significantly long response time of the sensor. The addition of the fibrotic capsule increased response time of the sensor from 39 s to a value between 5 min and 17.5 min for this case. This is expected as an additional layer will impose added diffusional constraint to the permeability of glucose through the sensor. This shows that real time monitoring of glucose need to take into account the offset due to the increase in the response time.

4.0 CONCLUSION

So far, in tackling the problem of electrochemical interference in peroxide-based amperometric glucose sensors, the focus has always been on the introduction of a selective internal layer to the system. The simulation results show that indeed a selective internal layer proves effective in reducing electrochemical interference; however membrane selectivity to peroxide, as defined in this work, must be at least 10 before significant reduction in interference can be observed. Another advantage of a highly selective inner layer is that, if the diffusion coefficient of peroxide is rather high, a sensor with good resistance to interference and a short response time can be realized. On the other hand, interestingly, the model also suggests another strategy that can be employed in the quest to reduce interference is the manipulation of the transport properties of the outer layer. Lowering the permeability of the external layer or increasing the selectivity of the external layer can also result in a reduction of error to the sensor readings. However, drastic changes in either approach can result in unacceptably long response times. Thus, a careful selection in the transport properties of both the inner and outer layer can result in a sensor with excellent performance even when the selectivity of the inner membrane is less than 10.

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