Application of the Butler-Volmer Equation in Mathematical Modelling of Amperometric Biosensor

Dainius Šimelevičius

Faculty of Mathematics and Informatics
Vilnius University, Didlaukio 47
LT-08303 Vilnius, Lithuania
Email: dainius.simelevicius@mif.vu.lt

Karolis Petrauskas

Faculty of Mathematics and Informatics
Vilnius University, Didlaukio 47
LT-08303 Vilnius, Lithuania
Email: karolis.petrauskas@mif.vu.lt

***Abstract*—A computational model of a multilayered amperometric biosensor is presented in this paper. Models of biosensors usually simplifies the electrochemistry of biosensors considering that all electrochemical reactions have infinite rates. While in most cases such approximations are tolerable, at lower electrode potentials these models would not be accurate enough. The model proposed in this paper models the electrochemistry occurring during the biosensor operation more accurately, using the Butler-Volmer equation. Computational experiments showed that models with the Butler-Volmer equation may be valuable tools aiding the analysis of the electrochemistry of amperometric biosensors.**

Keywords–Modelling; Reaction-diffusion; Biosensor; Amperometric; Butler-Volmer Equation.

I. INTRODUCTION

A biosensor is an electronic measuring device designed for measuring a concentration of some specific substance (analyte) in a solution. Device specificity for a particular substance is achieved by some biological material, usually an enzyme [1], [2], [3]. An amperometric biosensor assesses concentration of the analyte through measurement of a current on a working electrode [4], [5]. Biosensors are widely used in various applications that require fast quantitative analysis [6], [7], [8], [9], [10].

Manufacturing of a novel biosensor may be very expensive, as it may require a lot of experiments in a laboratory. It is wise to conduct computational experiments prior to physical ones. In order to do that, a mathematical model of the biosensor should be built [11], [12]. Mathematical models of biosensors are built for a few decades already [13], [14], [15].

The biosensor modelled in this paper was modelled previously in two papers. A model in paper [16] assumes rate of an electrochemical reaction as infinite and concentration of an electrochemical reaction reactant on the electrode surface as permanently reduced to zero. An experiment was conducted and another model of the same type of biosensor was presented recently in our paper [17]. A model in paper [17] is augmented with equations representing oxidation of the mediator by oxygen when an experiment is conducted in the aerobic conditions. Computational experiments showed that in the case when N-methylphenazonium methyl sulfate is used as a mediator the mediator oxidation by oxygen may be neglected [17]. The model presented in [17] considers that the rate of an electrochemical reaction as infinite too.

This paper is an extension of our research [17]. This time the model targets electrochemical questions. The model of biosensor presented in this paper considers the fact that the rate of the electrochemical reaction is not infinite. The rate of electrochemical reaction is modelled using the Butler-Volmer equation [18]. The model is not superior with respect to models presented in [16] and [17] but rather it is a helpful tool enabling us to analyse the electrochemical aspect of the amperometric biosensor. We demonstrate that at certain situations the assumption of infinite electrochemical reaction rate may not be a suitable approach.

Behaviour of the biosensor was numerically analysed at various values of input parameters of the model. Influence of an electrode potential, as well as of a standard rate constant on the biosensor response were investigated.

II. MATHEMATICAL MODEL

A. Reaction Scheme

The following reactions take place during operation of this amperometric biosensor [19], [20], [21],

$$\mathrm{GDH_{ox}} + \mathrm{glucose} \xrightarrow{k_1} \mathrm{GDH_{red}} + \mathrm{gluconolactone} \quad (1a)$$

$$\mathrm{GDH_{red}} + \mathrm{PMS_{ox}} \xrightarrow{k_2} \mathrm{GDH_{ox}} + \mathrm{PMS_{red}} \quad (1b)$$

$$\mathrm{PMS_{red}} \rightleftharpoons \mathrm{PMS_{ox}} + 2e^- \quad (1c)$$

where GDH is glucose dehydrogenase and PMS is N-methylphenazonium methyl sulfate.

Further in this paper we use an abstract notation of the chemical species. Glucose is called the substrate S and gluconolactone is called the product P. $\mathrm{E_{ox}}$ is $\mathrm{GDH_{ox}}$, $\mathrm{E_{red}}$ is

Copyright (c) IARIA, 2014. ISBN: 978-1-61208-371-1

GDH_{red}, M_{ox} denotes PMS_{ox} and M_{red} denotes PMS_{red}.

$$E_{ox} + S \xrightarrow{k_1} E_{red} + P \quad (2a)$$

$$E_{red} + M_{ox} \xrightarrow{k_2} E_{ox} + M_{red} \quad (2b)$$

$$M_{red} \rightleftharpoons M_{ox} + 2e^- \quad (2c)$$

B. Biosensor Principal Structure

The biosensor is comprised of three layers (compartments). Mediums of these layers are made of different materials and so are diffusion properties of species in these layers. The mathematical model includes these three layers plus additional layer which is called the diffusion layer. The diffusion layer is part of a solution in which concentrations of species are different compared to the bulk solution. We use the Nernst model of a diffusion layer. By the definition of this model, the diffusion front is stopped by the convection at a certain distance from the electrode and this distance is equal to the thickness of the diffusion layer [22], [23].

Starting from the electrode surface, layers of the biosensor go in the following order: the enzyme layer, the PVA layer, the terylene membrane layer and the diffusion layer. Thicknesses of these layers are defined d_1, d_2, d_3 and d_4, respectively. Distances between the electrode surface and boundaries of biosensor layers are denoted as a_1, a_2, a_3 and a_4 (see Figure 1).

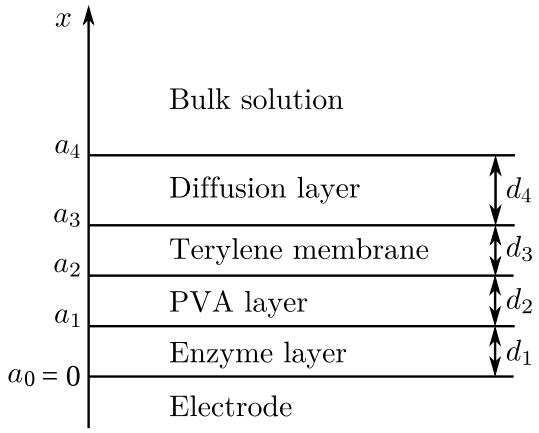

Figure 1. The principal structure of the biosensor.

Enzyme molecules are present in enzyme layer only. As a result biochemical reactions take place in the enzyme layer only. Diffusion of species take place in all four layers of the biosensor. However, enzyme molecules are large and considered as immobile (not influenced by diffusion).

C. Governing Equations

In our model governing equations consist of two parts: kinetics and diffusion. Kinetics is defined according to the law of mass action [24], [15] and diffusion is defined according to the Fick's second law [18] ($0 < x < a_1$, $t > 0$):

$$\frac{\partial e_{ox}}{\partial t} = -k_1 e_{ox} s_1 + k_2 e_{red} m_{ox,1}, \quad (3)$$

$$\frac{\partial e_{red}}{\partial t} = k_1 e_{ox} s_1 - k_2 e_{red} m_{ox,1}, \quad (4)$$

$$\frac{\partial s_1}{\partial t} = D_{S,1} \frac{\partial^2 s_1}{\partial x^2} - k_1 e_{ox} s_1, \quad (5)$$

$$\frac{\partial m_{ox,1}}{\partial t} = D_{M_{ox},1} \frac{\partial^2 m_{ox,1}}{\partial x^2} - k_2 e_{red} m_{ox,1}, \quad (6)$$

$$\frac{\partial m_{red,1}}{\partial t} = D_{M_{red},1} \frac{\partial^2 m_{red,1}}{\partial x^2} + k_2 e_{red} m_{ox,1}, \quad (7)$$

where x is the distance from the electrode surface, t is time from the beginning of an experiment, $e_{ox}(x,t)$ and $e_{red}(x,t)$ are concentrations of the oxidized (E_{ox}) and the reduced (E_{red}) enzyme molecules, respectively; $s_1(x,t)$ is a concentration of the substrate in the enzyme layer; $m_{ox,1}(x,t)$ and $m_{red,1}(x,t)$ are concentrations of the oxidized (M_{ox}) and the reduced (M_{red}) forms of the mediator in the enzyme layer and $D_{S,1}$, $D_{M_{ox},1}$, $D_{M_{red},1}$ are diffusion coefficients of the corresponding species defined by subscripts. Last numeric subscripts in definitions of concentrations and diffusion coefficients show the number of the biosensor layer, i.e., 1 is the enzyme layer. Equations corresponding to enzyme concentrations, lack diffusion term as enzyme molecules are considered immobile. There is no equation corresponding to the product P, because its concentration does not influence other processes defined by the model.

Governing equations in other three layers are simpler as there are diffusion terms only in these equations ($a_{i-1} < x < a_i$, $t > 0$, $i = 2, 3, 4$):

$$\frac{\partial s_i}{\partial t} = D_{S,i} \frac{\partial^2 s_i}{\partial x^2}, \quad (8)$$

$$\frac{\partial m_{ox,i}}{\partial t} = D_{M_{ox},i} \frac{\partial^2 m_{ox,i}}{\partial x^2}, \quad (9)$$

$$\frac{\partial m_{red,i}}{\partial t} = D_{M_{red},i} \frac{\partial^2 m_{red,i}}{\partial x^2}, \quad (10)$$

where $i = 2$ corresponds to the PVA layer, $i = 3$ corresponds to the terylene membrane layer and $i = 4$ corresponds to the diffusion layer.

D. Initial Conditions

We model the case when the biosensor is immersed into a solution which lacks the substrate and the mediator prior to experiment. We assume that experiment starts when the substrate and the mediator appear in the bulk solution. This is defined by the initial conditions ($t = 0$),

$$e_{red}(x,0) = 0, \quad e_{ox}(x,0) = e_0, \quad 0 < x < a_1, \quad (11)$$

$$s_i(x,0) = 0, \quad a_{i-1} \le x \le a_i, \quad i = 1,2,3, \quad (12)$$

$$m_{ox,i}(x,0) = 0, \quad a_{i-1} \le x \le a_i, \quad i = 1,2,3, \quad (13)$$

$$m_{red,i}(x,0) = 0, \quad a_{i-1} \le x \le a_i, \quad i = 1,2,3, \quad (14)$$

$$s_4(x,0) = m_{ox,4}(x,0) = 0, \quad a_3 \le x < a_4, \quad (15)$$

$$m_{red,4}(x,0) = 0, \quad a_3 \le x \le a_4, \quad (16)$$

$$s_4(a_4,0) = s_0, \quad m_{ox,4}(a_4,0) = m_0, \quad (17)$$

Copyright (c) IARIA, 2014. ISBN: 978-1-61208-371-1

where e_0 is the total concentration of the enzyme ($e_0 = e_{\mathrm{ox}}(x,t) + e_{\mathrm{red}}(x,t), \forall x,t : x \in (0,a_1), t > 0$), s_0 is the substrate concentration and m_0 is the concentration of the oxidized form of the mediator in the bulk solution.

E. Matching Conditions

Species have different diffusion coefficients in different layers of the biosensor, thus matching conditions have to be defined ($t > 0$, $i = 1, 2, 3$) [22], [23],

$$D_{\mathrm{S},i} \left.\frac{\partial s_i}{\partial x}\right|_{x=a_i} = D_{\mathrm{S},i+1} \left.\frac{\partial s_{i+1}}{\partial x}\right|_{x=a_i}, \quad (18)$$

$$s_i(a_i,t) = s_{i+1}(a_i,t), \quad (19)$$

$$D_{\mathrm{M_{ox}},i} \left.\frac{\partial m_{\mathrm{ox},i}}{\partial x}\right|_{x=a_i} = D_{\mathrm{M_{ox}},i+1} \left.\frac{\partial m_{\mathrm{ox},i+1}}{\partial x}\right|_{x=a_i}, \quad (20)$$

$$m_{\mathrm{ox},i}(a_i,t) = m_{\mathrm{ox},i+1}(a_i,t), \quad (21)$$

$$D_{\mathrm{M_{red}},i} \left.\frac{\partial m_{\mathrm{red},i}}{\partial x}\right|_{x=a_i} = D_{\mathrm{M_{ox}},i+1} \left.\frac{\partial m_{\mathrm{red},i+1}}{\partial x}\right|_{x=a_i}, \quad (22)$$

$$m_{\mathrm{red},i}(a_i,t) = m_{\mathrm{red},i+1}(a_i,t), \quad (23)$$

where $i = 1$ corresponds to the boundary between the enzyme layer and the PVA layer, $i = 2$ corresponds to the boundary between the PVA layer and the terylene membrane layer, whereas $i = 3$ corresponds to the boundary between the terylene membrane layer and the diffusion layer.

The matching conditions define that fluxes of the species exiting the layer are equal to the fluxes entering the neighbouring layer of the biosensor. Additionally, concentrations of species on the surface of one layer are assumed to be equal to concentrations on the surface of the neighbouring layer.

F. Boundary Conditions

Concentrations of the species in the bulk solution are kept constant ($t > 0$),

$$s_4(a_4,t) = s_0, \quad (24)$$

$$m_{\mathrm{ox},4}(a_4,t) = m_0, \quad (25)$$

$$m_{\mathrm{red},4}(a_4,t) = 0. \quad (26)$$

$\mathrm{M_{red}}$ is the reactant of the electrochemical reaction (2c) while $\mathrm{M_{ox}}$ is the product. Stoichiometry of the reaction (2c) suggests that the amount of $\mathrm{M_{red}}$ consumed is equal to the amount of $\mathrm{M_{ox}}$ produced. Thus, the flux of $\mathrm{M_{red}}$ on the electrode surface is equal to the flux of $\mathrm{M_{ox}}$, but in the opposite direction. Also, according to the Faraday's Law the flux is proportional to the current. These relations are expressed by the following boundary condition ($t > 0$),

$$An_eFD_{\mathrm{M_{red}},1} \left.\frac{\partial m_{\mathrm{red},1}}{\partial x}\right|_{x=0} = - An_eFD_{\mathrm{M_{ox}},1} \left.\frac{\partial m_{\mathrm{ox},1}}{\partial x}\right|_{x=0} = i(t). \quad (27)$$

The flux of the substrate on the electrode is equal to zero, as the substrate does not take part in any electrochemical reaction ($t > 0$),

$$D_{\mathrm{S},1} \left.\frac{\partial s_1}{\partial x}\right|_{x=0} = 0. \quad (28)$$

G. Biosensor Response

The measured current is usually assumed as the response of an amperometric biosensor in physical experiments. At pH = 5–9 the electrochemical reaction (2c) is reversible. Two electrons are transferred during the charge transfer [21]. The biosensor current $i(t)$ at time t was expressed by the Butler-Volmer equation [18], [25],

$$i(t) = An_eFk^0 \left[M_{red}(0,t)e^{(1-\alpha)n_e f(E-E_0)} - M_{ox}(0,t)e^{-\alpha n_e f(E-E_0)}\right], \quad (29)$$

where $i(t)$ is the faradaic current generated by the electrochemical reaction (2c), A is the electrode surface, n_e is the number of electrons involved in a charge transfer at the electrode surface, k^0 is the standard rate constant, E_0 is the standard potential, α is the transfer coefficient, E is the electrode potential, $f = F/RT$; F is the Faraday constant, $F = 96\,486\,\mathrm{C/mol}$, R is the gas constant, $R = 8.314\,\mathrm{J\ mol^{-1}\ K^{-1}}$, T is the absolute temperature.

We assume that the system approaches a steady state as $t \to \infty$,

$$i_{\mathrm{st}} = \lim_{t\to\infty} i(t), \quad (30)$$

where i_{st} is the steady-state biosensor current.

III. Numerical Simulation

There is no known analytical solution for the problem (3)–(29). Therefore, the problem was solved numerically, using the finite difference technique [26], [27]. An implicit finite difference scheme was built on a uniform discrete grid with 50 points in the space direction for each modelled layer corresponding to a certain time moment. The simulator has been programmed by the authors in C++ programming language [28].

In the numerical simulation, the biosensor response time was assumed as the time when the change of the biosensor current remains very small during a relatively long term. A special dimensionless decay rate, ε, was used,

$$t_{\mathrm{r}} = \min_{i(t)>0} \left\{ t : \frac{t}{i(t)} \left|\frac{\mathrm{d}i(t)}{\mathrm{d}t}\right| < \varepsilon \right\}, \quad i(t_{\mathrm{r}}) \approx i_{\mathrm{st}}, \quad (31)$$

where t_{r} is the biosensor response time. The decay rate value $\varepsilon = 10^{-2}$ was used in the calculations.

In all numerical experiments the following values were kept

constant if not stated otherwise [17], [29], [30], [31], [21]:

$$
\begin{aligned}
&d_1 = 5 \times 10^{-6}\,\mathrm{m}, \quad d_2 = 1 \times 10^{-6}\,\mathrm{m},\\
&d_3 = 1.2 \times 10^{-5}\,\mathrm{m}, \quad d_4 = 1.5 \times 10^{-4}\,\mathrm{m},\\
&D_{\mathrm{S},1} = D_{\mathrm{M_{ox}},1} = D_{\mathrm{M_{red}},1} = 1.5 \times 10^{-10}\,\mathrm{m^2/s},\\
&D_{\mathrm{S},2} = D_{\mathrm{M_{ox}},2} = D_{\mathrm{M_{red}},2} = 4.2 \times 10^{-10}\,\mathrm{m^2/s},\\
&D_{\mathrm{S},3} = D_{\mathrm{M_{ox}},3} = D_{\mathrm{M_{red}},3} = 3.75 \times 10^{-10}\,\mathrm{m^2/s},\\
&D_{\mathrm{S},4} = 6.77 \times 10^{-10}\,\mathrm{m^2/s},\\
&D_{\mathrm{M_{ox}},4} = D_{\mathrm{M_{red}},4} = 4.57 \times 10^{-10}\,\mathrm{m^2/s},\\
&e_0 = 1 \times 10^{-3}\,\mathrm{mol/m^3}, \quad m_0 = 5 \times 10^{-2}\,\mathrm{mol/m^3},\\
&s_0 = 4.98\,\mathrm{mol/m^3}, \quad k_1 = 8.1 \times 10^{2}\,\mathrm{m^3\,mol^{-1}\,s^{-1}},\\
&k_2 = 6.7 \times 10^{4}\,\mathrm{m^3\,mol^{-1}\,s^{-1}}, \quad n_\mathrm{e} = 2,\\
&k^0 = 10^{-5}\,\mathrm{m/s}, \quad \alpha = 0.5,\\
&A = 4.5 \times 10^{-6}\,\mathrm{m^2}, \quad T = 293\,\mathrm{K}.
\end{aligned}
\tag{32}
$$

IV. Results and Discussion

A. Model Validation

Experimental calibration curve was compared with simulated calibration curves. Results are depicted in Figure 2.

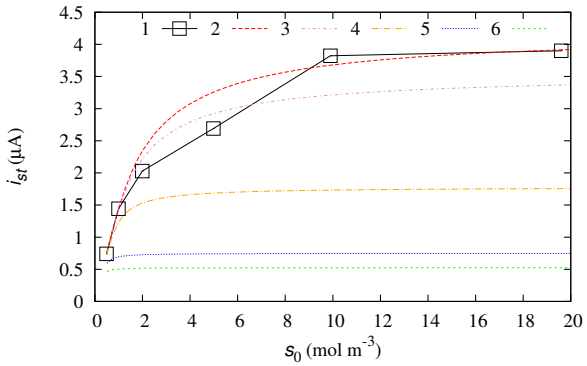

Figure 2. The dependence of the steady-state current on the substrate concentration during physical experiment (1), simulated with the infinite rate of electrochemical reaction (2), simulated at certain electrode potential $(E - E_0)$: 0.1 V (3), 0.05 V (4), 0.02 V (5), 0.01 V (6).

Physical experiments were carried out at potentiostatic conditions, the potential of the working electrode E was set at 0.4 V *vs.* $Ag/AgCl$ [17]. Standard potential E_0 of redox pair M_{red}/M_{ox} is -0.005 V *vs.* $Ag/AgCl$ [32], thus $(E - E_0) = 0.405$ V. In this case the forward electrochemical reaction becomes very fast and the rate of it may be modelled as infinite [17]. The model from paper [17] at anaerobic conditions was used to simulate the biosensor operation with infinite electrochemical reaction rate as depicted by the curve 2.

Using the finite difference technique with the model (3)-(29) becomes impractical at high potential values because modelling very high electrochemical reaction rate requires very small step in time which tremendously increases demand for a computational power. However the model (3)-(29) allows the modelling of lower potentials. Biosensor operation was modelled at potential values $(E - E_0)$ from 0.01 V to 0.1 V. As one can observe from Figure 2 the biosensor response is higher at higher potential values which is consistent with the chemical logic. The model cannot be directly validated with the experimental data but it is evident from Figure 2 that with the higher potential, biosensor response approaches the one observed experimentally.

One more interesting dependence may be observed from Figure 2, the lower the potential, the shorter the range of substrate concentrations in which biosensor may operate. The biosensor is almost entirely insensitive to the change in substrate concentration when the potential is the lowest (0.02 V and 0.01 V). This possibly indicates that the charge transfer is the slowest (limiting) process in this situation.

B. Biosensor Response vs. Electrode Potential

It is important to understand the dependence of the biosensor response on the electrode potential. Thus this dependence was more thoroughly investigated at three different substrate concentrations. Results are depicted in Figure 3.

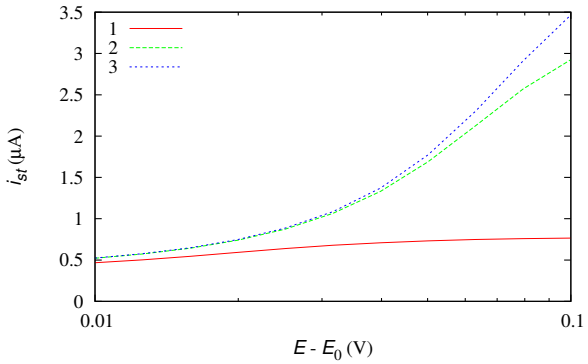

Figure 3. The dependence of the steady-state current on the electrode potential $(E - E_0)$ at different substrate concentrations s_0: 0.5 mol/m^3 (1), 5 mol/m^3 (2), 50 mol/m^3 (3).

At low substrate concentration (curve 1) the biosensor response dependence on the electrode potential is little pronounced. This indicates that in this case the charge transfer is not a limiting process. At higher substrate concentrations (curves 2 and 3), the biosensor response shows stronger dependence on the electrode potential. At these two concentrations charge transfer is possibly a limiting process at lower part of investigated potential range because in this part of the range the curves 2 and 3 coincide. At higher potentials biosensor shows dependence on both the electrode potential and substrate concentration.

C. Biosensor Response vs. Standard Rate Constant

Standard rate constant k^0 is the constant defining the kinetics of electrochemical reaction (2c). This constant shows whether electrochemical reaction reaches equilibrium fast or slow. The value of the constant may range from 10^{-11} m/s for very slugish kinetics to 0.1 m/s for very fast electron-transfer processes [18]. It is important to investigate how standard rate constant of $\mathrm{M_{red}}/\mathrm{M_{ox}}$ redox couple affects the biosensor response. This dependence was investigated at several values of substrate concentration. Results are depicted in Figure 4.

Copyright (c) IARIA, 2014. ISBN: 978-1-61208-371-1

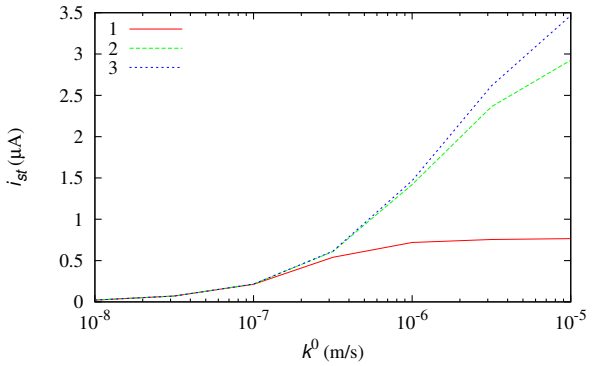

Figure 4. The dependence of the steady-state current on the standard rate constant at different substrate concentrations s_0: 0.5 mol/m^3 (1), 5 mol/m^3 (2), 50 mol/m^3 (3); $E - E_0 = 0.1$ V.

Slugish electron-transfer is not desirable in amperometric biosensor because in such a case the electrochemical reaction may be the slowest (limiting) process and solely determine the biosensor response. This is possibly the case when $k^0 \in [10^{-8}\,\text{m/s}..10^{-7}\,\text{m/s}]$ because the biosensor response is not dependent on the substrate concentration even though it is varied by two orders of magnitude (see Figure 4). The biosensor response is dependent on the substrate concentration in the range $[10^{-7}\,\text{m/s}..10^{-6}\,\text{m/s}]$ when concentration is relatively low. Biosensor is not responsive to the change in substrate concentration at higher concentrations though. When $k^0 \in [10^{-6}\,\text{m/s}..10^{-5}\,\text{m/s}]$ the charge transfer is not limiting process, biosensor response is different at all three values of substrate concentration.

Results show that from this point of view the mediator for the biosensor was chosen very successfully as the standard rate constant for the redox couple $\text{M}_{\text{red}}/\text{M}_{\text{ox}}$ is quite high ($k^0 = 10^{-5}$ m/s) [30].

V. Conclusion

The Butler-Volmer equation may be used in mathematical models of amperometric biosensors. Models with the Butler-Volmer equation may provide valuable information about biosensor behaviour at different values of electrochemical parameters. However numerical simulation using finite difference technique is impractical in cases when electrode potential is high. In such cases models assuming infinite rate of electrochemical reaction should be used.

The models of amperometric biosensors with the Butler-Volmer equation may be useful in the design phase of a biosensor by providing information about the minimum electrode potential at which biosensor may be successfully operated. Also such models may provide insight into which species may be used as mediators prior to the biosensor manufacture.

Acknowledgment

This research was funded by the European Social Fund under the Global Grant Measure, Project No. VP1-3.1-ŠMM-07-K-01-073/MTDS-110000-583.

References

[1] A. P. F. Turner, I. Karube, and G. S. Wilson, Biosensors: Fundamentals and Applications. Oxford: Oxford University Press, 1987.

[2] F. W. Scheller and F. Schubert, Biosensors, ser. Techniques and Instrumentation in Analytical Chemistry. Amsterdam: Elsevier, 1992, vol. 11.

[3] B. D. Malhotra and A. Chaubey, "Biosensors for clinical diagnostics industry," Sens. Actuators B, vol. 91, no. 1-3, 2003, pp. 117–127.

[4] A. Chaubey and B. Malhotra, "Mediated biosensors," Biosens. Bioelectron., vol. 17, no. 6-7, 2002, pp. 441–456.

[5] N. J. Ronkainen, H. B. Halsall, and W. R. Heineman, "Electrochemical biosensors," Chem. Soc. Rev., vol. 39, no. 5, 2010, pp. 1747–1763.

[6] K. R. Rogers, "Biosensors for environmental applications," Biosens. Bioelectron., vol. 10, no. 6-7, 1995, pp. 533–541.

[7] F. W. Scheller, F. Schubert, and J. Fedrowitz, Practical Applications, ser. Frontiers in Biosensorics. Basel: Birkhäuser, 1997, vol. 2.

[8] J. F. Liang, Y. T. Li, and V. C. Yang, "Biomedical application of immobilized enzymes," J. Pharm. Sci., vol. 89, no. 8, 2000, pp. 979–990.

[9] D. Yu, B. Blankert, J.-C. Virè, and J.-M. Kauffmann, "Biosensors in drug discovery and drug analysis," Anal. Lett., vol. 38, no. 11, 2005, pp. 1687–1701.

[10] E.-H. Yoo and S.-Y. Lee, "Glucose biosensors: an overview of use in clinical practice," Sensors, vol. 10, no. 5, 2010, pp. 4558–4576.

[11] J. I. Reyes De Corcuera, R. P. Cavalieri, J. R. Powers, and J. Tang, "Amperometric enzyme biosensor optimization using mathematical modeling," in Proceedings of the 2004 ASAE / Csae Annual International Meeting. Ottawa, Ontario: American Society of Agricultural Engineers, 8 2004.

[12] C. Amatore, A. Oleinick, I. Svir, N. da Mota, and L. Thouin, "Theoretical modeling and optimization of the detection performance: a new concept for electrochemical detection of proteins in microfluidic channels," Nonlinear Anal. Model. Control, vol. 11, no. 4, 2006, pp. 345–365.

[13] L. D. Mell and J. T. Maloy, "A model for the amperometric enzyme electrode obtained through digital simulation and applied to the immobilized glucose oxidase system," Anal. Chem., vol. 47, no. 2, 1975, pp. 299–307.

[14] J.-P. Kernevez, Enzyme Mathematics, ser. Studies in Mathematics and its Applications, J. L. Lions, G. Papanicolaou, and R. T. Rockafellar, Eds. Amsterdam: North-Holland Publishing Company, 1980, vol. 10.

[15] P. N. Bartlett and R. G. Whitaker, "Electrochemical imobilisation of enzymes: Part I. Theory," J. Electroanal. Chem., vol. 224, no. 1-2, 1987, pp. 27–35.

[16] D. Baronas, A. Žilinskas, and F. Ivanauskas, "Computational modelling and validation of a multilayer amperometric biosensor," in Proceedings of the XVIII International Master and PhD Students Conference Information Society and University Studies (IVUS 2013). Kaunas: Vytautas Magnus University, 4 2013, pp. 22–26.

[17] D. Šimelevičius, K. Petrauskas, R. Baronas, and J. Razumienė, "Computational modeling of mediator oxidation by oxygen in an amperometric glucose biosensor," Sensors, vol. 14, no. 2, 2014, pp. 2578–2594.

[18] A. J. Bard and L. R. Faulkner, Electrochemical Methods: Fundamentals and Applications, 2nd ed. New York: John Wiley & Sons, Inc., 2001.

[19] J. Razumiene, A. Vilkanauskyte, V. Gureviciene, J. Barkauskas, R. Meskys, and V. Laurinavicius, "Direct electron transfer between PQQ dependent glucose dehydrogenases and carbon electrodes: An approach for electrochemical biosensors," Electrochim. Acta, vol. 51, no. 24, 2006, pp. 5150–5156.

[20] V. Laurinavicius, B. Kurtinaitiene, V. Liauksminas, A. Ramanavicius, R. Meskys, R. Rudomanskis, T. Skotheim, and L. Boguslavsky, "Oxygen insensitive glucose biosensor based on PQQ-dependent glucose dehydrogenase," Anal. Lett., vol. 32, no. 2, 1999, pp. 299–316.

[21] J. Kulys and A. Malinauskas, "Electrochemical reduction-oxidation of phenazine methosulfate," Lietuvos TSR Mokslu Akademijos darbai, vol. B4, 1979, pp. 41–47.

[22] T. Schulmeister, "Mathematical modelling of the dynamic behaviour of amperometric enzyme electrodes," Sel. Electrode Rev., vol. 12, 1990, pp. 203–260.

Copyright (c) IARIA, 2014. ISBN: 978-1-61208-371-1

[23] R. Baronas, F. Ivanauskas, and J. Kulys, Mathematical Modeling of Biosensors, ser. Springer Series on Chemical Sensors and Biosensors, G. Urban, Ed. Dordrecht: Springer, 2010, vol. 9.

[24] H. Gutfreund, Kinetics for the Life Sciences: Receptors, Transmitters and Catalysts. Cambridge: Cambridge University Press, 1995.

[25] K. J. Vetter, Electrochemical Kinetics: Theoretical and Experimental Aspects. Academic Press, 1967.

[26] D. Britz, Digital Simulation in Electrochemistry, 3rd ed., ser. Lecture Notes in Physics. Berlin Heidelberg: Springer, 2005, vol. 666.

[27] A. A. Samarskii, The Theory of Difference Schemes. New York-Basel: Marcel Dekker, 2001.

[28] W. H. Press, S. A. Teukolsky, W. T. Vetterling, and B. P. Flannery, Numerical Recipes in C++: The Art of Scientific Computing, 3rd ed. Cambridge: Cambridge University Press, 2002.

[29] A. C. F. Ribeiro, O. Ortona, S. M. N. Simões, C. I. A. V. Santos, P. M. R. A. Prazeres, A. J. M. Valente, V. M. M. Lobo, and H. D. Burrows, "Binary mutual diffusion coefficients of aqueous solutions of sucrose, lactose, glucose, and fructose in the temperature range from (298.15 to 328.15) K," J. Chem. Eng. Data, vol. 51, no. 5, 2006, pp. 1836–1840.

[30] B. Strehlitz, B. Gründig, W. Schumacher, P. M. H. Kroneck, K.-D. Vorlop, and H. Kotte, "A nitrite sensor based on a highly sensitive nitrite reductase mediator-coupled amperometric detection," Anal. Chem., vol. 68, no. 5, 1996, pp. 807–816.

[31] J. Kulys, L. Tetianec, and I. Bratkovskaja, "Pyrroloquinoline quinone-dependent carbohydrate dehydrogenase: activity enhancement and the role of artificial electron acceptors," Biotechnol. J., vol. 5, no. 8, 2010, pp. 822–828.

[32] C. D. Jaeger and A. J. Bard, "Electrochemical behavior of donor-tetracyanoquinodimethane electrodes in aqueous media," Journal of the American Chemical Society, vol. 102, no. 17, 1980, pp. 5435–5442.

Copyright (c) IARIA, 2014. ISBN: 978-1-61208-371-1