KOMPIUTERINIS MODELIAVIMAS

A Computational Investigation of the Optical Biosensor by a Dimensionless Model

Evelina Gaidamauskaitė

Vilniaus universiteto Matematikos ir informatikos fakulteto doktorantė
Vilnius University, Faculty of Mathematics and Informatics, PhD student
Naugarduko g. 24, LT-03225 Vilnius
Tel. (+370 5) 219 30 64
El. paštas: evelina.gaidamauskaite@mif.vu.lt

Romas Baronas

Vilniaus universiteto Matematikos ir informatikos fakulteto profesorius, dr.
Vilnius University, Faculty of Mathematics and Informatics, Professor, PhD
Naugarduko g. 24, LT-03225 Vilnius
Tel. (+370 5) 219 30 64
Faks. (+370 5) 215 15 85
El. paštas: romas.baronas@mif.vu.lt

In order to determine the main governing parameters, a dimensionless mathematical model of a peroxidase-based optical biosensor is derived. The mathematical model of the biosensor is based on a system of non-linear reaction-diffusion equations. The modelled biosensor comprises two compartments, an enzyme layer and an outer diffusion layer. The influence of the dimensionless diffusion modulus on the biosensor response and the sensitivity is investigated. The digital simulation was carried out using a finite difference method.

Biosensors are sensing devices made up of a combination of a biological entity, usually an enzyme that recognizes a specific analyte, and a transducer that translates the biorecognition event into an electrical signal (Turner et al., 1987). Biosensors are known to be reliable, cheap and highly sensitive for environment, clinical and industrial purposes (Wollenberger et al., 1997). The biosensors are classified according to the nature of the physical transducer. Optical biosensors are based on the measurement of absorbed or emitted light resulting from a biochemical reaction (Ligler, Taitt, 2002; Choi, 2004; Bosch et al., 2007).

A mathematical model of a peroxidase-based optical biosensor has been recently developed (Baronas et al., 2007). This accurate model involves a comparatively large amount of parameters. In the present work, in order to define the main governing parameters, the corresponding dimensionless mathematical model of the peroxidase-based optical biosensor was derived and investigated. The resulting model was used to simulate the behaviour of the optical biosensor.

Mathematical model

We consider the same reaction scheme in which hydrogen peroxide (H_2O_2) reacts with enzyme peroxidase (E) to form compound I (cmpI) and water (H_2O) with the constant reaction rate k_1 (Baronas et al., 2007). Compound I interacts with the substrate (S) to form product (P) and free enzyme (E) assuming the constant reaction rate k_2,

$$E + H_2O_2 \xrightarrow{k_1} cmpI + H_2O,$$

$$cmpI + S \xrightarrow{k_2} E + P$$

Product (P) absorbs light and therefore the response of the biosensor increases during the reaction as the product is forming. The concentration of analyte (S) can be directly determined from the absorbance of product (P) (Vo-Dinh, 2003; Harvey, 2000).

Dimensionless model

A detailed mathematical model of peroxidase-based optical biosensor has been presented in the previous work (Baronas et al., 2007). In order to define the main governing terms and to reduce the number of the model parameters, the corresponding dimensionless mathematical model was derived. The model is based on the parameters listed in Table 1.

In the enzyme layer, the mass transport and reaction kinetics in a dimensionless form are written as follows:

$$\frac{\partial \hat{S}_e}{\partial \hat{T}} = \frac{\partial^2 \hat{S}_e}{\partial \hat{X}^2} - \alpha_2 \hat{C}\hat{S}_e,$$

$$\frac{\partial \hat{P}_e}{\partial \hat{T}} = \frac{D_{Pe}}{D_{Se}} \frac{\partial^2 \hat{P}_e}{\partial \hat{X}^2} + \alpha_2 \hat{C}\hat{S}_e,$$

$$\frac{\partial \hat{H}_e}{\partial \hat{T}} = \frac{D_{He}}{D_{Se}} \frac{\partial^2 \hat{H}_e}{\partial \hat{X}^2} - \alpha_1 \hat{E}\hat{H}_e,$$

$$\frac{\partial \hat{E}}{\partial \hat{T}} = -\alpha_1 \hat{E}\hat{H}_e + \alpha_2 \hat{C}\hat{S}_e, \quad \frac{\partial \hat{C}}{\partial \hat{T}} = \alpha_1 \hat{E}\hat{H}_e - \alpha_2 \hat{C}\hat{S}_e,$$

$$0 < \hat{X} < 1, \quad \hat{T} > 0.$$

Table 1. ***Dimensionless parameters and reduced model terms***

Dimensionless parameters	Expression
Distance from the electrode	$\hat{X} = \frac{x}{d}$
Time	$\hat{T} = \frac{tD_{Se}}{d^2}$
Thickness of the diffusion layer	$\hat{\Delta} = \frac{\delta}{d}$
Thickness of the enzyme membrane	$\hat{L} = \frac{d}{d} = 1$
Substrate concentration	$\hat{S}_e = \frac{S_e}{E_0}, \quad \hat{S}_b = \frac{S_b}{E_0}, \quad \hat{S}_0 = \frac{S_0}{E_0}$
Product concentration	$\hat{P}_e = \frac{P_e}{E_0}, \quad \hat{P}_b = \frac{P_b}{E_0}$
Hydrogen peroxide concentration	$\hat{H}_e = \frac{H_e}{E_0}, \quad \hat{H}_b = \frac{H_b}{E_0}, \quad \hat{H}_0 = \frac{H_0}{E_0}$
Enzyme peroxidase concentration	$\hat{E} = \frac{E}{E_0}, \quad \hat{E}_0 = \frac{E_0}{E_0} = 1$
Compound I concentration	$\hat{C} = \frac{C}{E_0}$

The dimensionless quantities α_1 and α_2 are known as a diffusion modulus or Damkohler number (Aris, 1975),

$$\alpha_1 = \frac{k_1 E_0 d^2}{D_{Se}}, \ \alpha_1 = \frac{k_1 E_0 d^2}{D_{Se}},$$

The diffusion modulus is the ratio of the rate of biochemical reaction to the rate of the mass transport by diffusion. If the diffusion modulus is significantly higher than unity, then the enzyme kinetics predominates in the biosensor response (Turner et al., 1987).

The diffusive flux of the substrate, the product and the hydrogen peroxide in the diffusion layer can be expressed as follows:

$$\frac{\partial \hat{S}_b}{\partial \hat{T}} = \frac{D_{Sb}}{D_{Se}} \frac{\partial^2 \hat{S}_b}{\partial \hat{X}^2}, \qquad \frac{\partial \hat{P}_b}{\partial \hat{T}} = \frac{D_{Pb}}{D_{Se}} \frac{\partial^2 \hat{P}_b}{\partial \hat{X}^2},$$

$$\frac{\partial \hat{H}_b}{\partial \hat{T}} = \frac{D_{Hb}}{D_{Se}} \frac{\partial^2 \hat{H}_b}{\partial \hat{X}^2}, \ 1 < \hat{X} < 1 + \hat{\Delta}, \quad \hat{T} > 0.$$

The initial conditions are chosen to indicate that the biosensor operation starts when some substrate and hydrogen peroxide appear in the bulk solution ($\hat{T} = 0$),

$$\hat{S}_e(\hat{X},0) = \hat{P}_e(\hat{X},0) = \hat{C}(\hat{X},0) = 0,$$

$$\hat{H}_e(\hat{X},0) = \hat{H}_0, \quad \hat{E}(\hat{X},0) = 1, \quad 0 \le \hat{X} \le 1,$$

$$\hat{P}_b(\hat{X},0) = 0, \quad \hat{H}_b(\hat{X},0) = \hat{H}_0, \quad 1 \le \hat{X} \le 1 + \hat{\Delta},$$

$$\hat{S}_b(\hat{X},0) = \begin{cases} 0, & 1 \le \hat{X} < 1 + \hat{\Delta}, \\ \hat{S}_0, & \hat{X} = 1 + \hat{\Delta}. \end{cases}$$

In the bulk solution the concentrations of the substrate, the product and the hydrogen peroxide remain constant. Assuming the impenetrable and unreactive plate surface, the mass flux of the species must vanish at this boundary. On the boundary between two regions having different diffusivities, we define the matching conditions ($\hat{T} > 0$),

$$\hat{S}_b(1 + \hat{\Delta}, \hat{T}) = \hat{S}_0, \ \hat{P}_b(1 + \hat{\Delta}, \hat{T}) = 0,$$

$$\hat{H}_b(1 + \hat{\Delta}, \hat{T}) = \hat{H}_0,$$

$$\left.\frac{\partial \hat{S}_e}{\partial \hat{X}}\right|_{\hat{X}=0} = \left.\frac{\partial \hat{P}_e}{\partial \hat{X}}\right|_{\hat{X}=0} = \left.\frac{\partial \hat{H}_e}{\partial \hat{X}}\right|_{\hat{X}=0} = 0,$$

$$\left.\frac{\partial \hat{S}_e}{\partial \hat{X}}\right|_{\hat{X}=1} = \frac{D_{Sb}}{D_{Se}} \left.\frac{\partial \hat{S}_b}{\partial \hat{X}}\right|_{\hat{X}=1}, \quad \hat{S}_e(1,\hat{T}) = \hat{S}_b(1,\hat{T}),$$

$$\left.\frac{\partial \hat{P}_e}{\partial \hat{X}}\right|_{\hat{X}=1} = \frac{D_{Pb}}{D_{Pe}} \left.\frac{\partial \hat{P}_b}{\partial \hat{X}}\right|_{\hat{X}=1}, \quad \hat{P}_e(1,\hat{T}) = \hat{P}_b(1,\hat{T}),$$

$$\left.\frac{\partial \hat{H}_e}{\partial \hat{X}}\right|_{\hat{X}=1} = \frac{D_{Hb}}{D_{He}} \left.\frac{\partial \hat{H}_b}{\partial \hat{X}}\right|_{\hat{X}=1}, \quad \hat{H}_e(1,\hat{T}) = \hat{H}_b(1,\hat{T}).$$

The light absorbance was assumed as the response of the optical biosensor. The dimensionless light absorbance $\hat{A}(\hat{T})$ is given by

$$\hat{A}(\hat{T}) = \hat{l}_{ef} \hat{P}_{avg} = \frac{A(t)}{E_0 \varepsilon_P d}, \quad \hat{l}_{ef} = 1 + \hat{\Delta},$$

$$\hat{P}_{avg} = \frac{1}{1 + \hat{\Delta}} \left(\int_0^1 \hat{P}_e(\hat{X},\hat{T}) d\hat{X} + \int_1^{1+\hat{\Delta}} \hat{P}_b(\hat{X},\hat{T}) d\hat{X} \right).$$

The dimensionless stationary absorbance $\hat{A}_\infty$ is defined as follows:

$$\hat{A}_\infty = \lim_{\hat{T} \to \infty} \hat{A}(\hat{T}).$$

Numerical solution

Because of the nonlinearity of the problem, no analytical solutions are possible. Hence numerical simulation was used. We applied a uniform discrete grid to simulate the biosensor using the implicit finite difference method (Samarskii, 2001). The program was implemented in the Java programming language.

The biosensor response $\hat{A}_R$ calculated at the moment $\hat{T}_R$ was assumed as the steady state response,

$$\hat{A}_R = \hat{A}(\hat{T}_R) \approx \hat{A}_\infty, \ \hat{T}_R = \min_{j>0, \hat{A}_j > 0} \left\{ t_j : \frac{\hat{A}_j - \hat{A}_{j-1}}{\hat{A}_j} < \varepsilon \right\}.$$

We used $\varepsilon = 10^{-3}$ for calculations.

The sensitivity of the biosensor is defined as a gradient of the steady state absorbance with respect to the substrate concentration (Turner et al., 1987),

$$\hat{B}_S(\hat{S}_0) = \frac{\hat{S}_0}{\hat{A}_R(\hat{S}_0)}\left(\frac{d\hat{A}_R(\hat{S}_0)}{d\hat{S}_0}\right).$$

The values of the model parameters employed in all the numerical experiments were the same as in the previous work (Baronas et al., 2007).

The impact of the diffusion modulus

Fig. 1a shows the dependence of the steady state dimensionless absorbance $\hat{A}_R$ on the diffusion modulus α_1. The diffusion modulus α_1 is directly proportional to the square of thickness of the enzyme layer *d*, therefore the resulting observations might be explained by the variation of the thickness of the enzyme layer. As the thickness of the enzyme layer grows, the absolute amount of the enzyme also increases. Thus, the increase and the following steady level of absorption $\hat{A}_R$ is a result of the enzyme build-up. The absorbance approaches the steady state when the quantity of the enzyme is so large that the substrate concentration reaches a rate-limiting value. Apparently, the response increases if the concentration of substrate is higher (Fig. 1a, compare curves 1, 2, and 3).

The dependence of the dimensionless sensitivity $\hat{B}_S$ on the parameter α_1 is depicted in Fig 1b. The sensitivity highly depends on the outer substrate concentration S_0: the increase of the latter corresponds to the lower values of the sensitivity. However, the increase in the substrate concentration can be counterbalanced by thickening the diffusion layer (see curve 2).

Conclusions

The dimensionless mathematical model of a peroxidase-based optical biosensor can be used for digital simulation and investigation of the biosensor response. It has been shown that the dimensionless absorbance $\hat{A}_R$ and the dimensionless sensitivity $\hat{B}_S$ depend on the diffusion modulus α_1 (Fig. 1). The simulation results were explained by the relation of the reaction velocity to the concentration of the substrate or enzyme. This unambiguously shows the model's usefulness in predicting the response of the modelled biosensor. The dimensionless approach allows omitting some of the parameters, which make the accurate model rather complicated. To prove the conclusions drawn, the experiments are running using peroxidase-based optical biosensors with different dimensionless parameters.

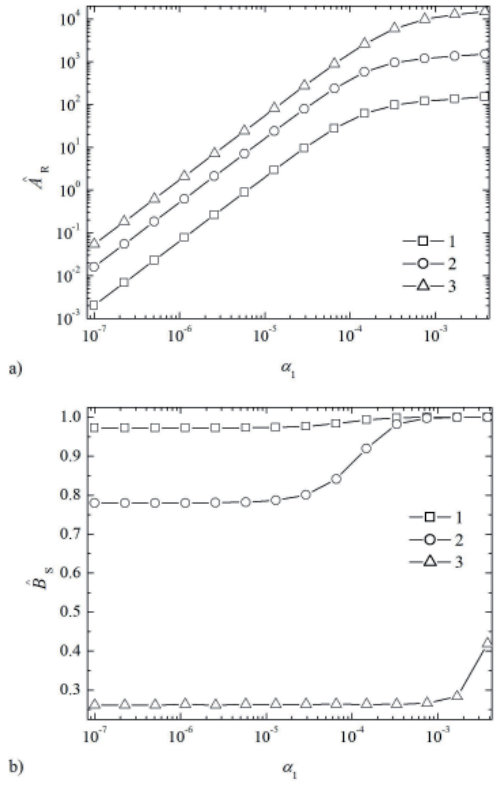

Figure 1. ***The dependence of the dimensionless absorbance $\hat{A}_R$ (a) and the dimensionless sensitivity $\hat{B}_S$ (b) on the diffusion modulus α_1 changing the thickness d of the enzyme layer at three initial concentrations S_0 of the substrate: 10(1), 100(2), 1000(3) μM***

REFERENCES

ARIS, R. (1975). *The Mathematical Theory of Diffusion and Reaction in Permeable Catalysts. The Theory of the Steady State*. Oxford: Clarendon Press.

BARONAS, R.; GAIDAMAUSKAITĖ, E.; KULYS, J. (2007). Modelling a peroxidase-based optical biosensor. *Sensors*, vol. 11, p. 2723–2740.

BOSCH, M. E.; SANCHEZ, A. J. R.; ROJAS, F. S.; OJEDA, C. B. (2007). Recent development in optical fiber biosensors. *Sensors*, vol. 7, p. 797–859.

CHOI, M. M. F. (2004). Progress in enzyme-based biosensors using optical transducers. *Microchimica Acta*, vol. 148, p. 107–132.

HARVEY, D. (2000). *Modern Analytical Chemistry*. McGraw-Hill Higher Education.

LIGLER, F. S.; TAITT, C. R. (2002). *Optical Biosensors: Present and Future*. Amsterdam: Elsevier Science.

SAMARSKII, A. A. (2001). *The Theory of Difference Schemes*. New York-Basel: Marcel Dekker.

TURNER, A. P. F.; KARUBE, I.; WILSON, G. S. (1987). *Biosensors: Fundamentals and Applications*. Oxford: Oxford University Press.

VO-DINH, T. (2003). *Biomedical Photonics Handbook*. New York: CRC Press LLC.

WOLLENBERGER, U.; LISDAT, F.; SCHELLER, F. W. (1997). *Frontiers in Biosensorics 2. Practical Applications*. Basel: Birkhauser Verlag.

KOMPIUTERINIS OPTINIO BIOJUTIKLIO SAVYBIŲ TYRIMAS TAIKANT BEDIMENSĮ MODELĮ

Evelina Gaidamauskaitė, Romas Baronas

Santrauka

Šiame darbe, siekiant nustatyti pagrindinius kinetinius peroksidazinio optinio biojutiklio matematinio modelio parametrus, buvo sudarytas bedimensis modelis. Biojutikliui taikomos reakcijos-difuzijos lygtys su netiesiniu nariu, aprašančiu fermentinę reakciją. Biojutiklio veikimas modeliuojamas fermento ir difuzijos sluoksniuose. Ištirta biojutiklio atsako ir jautrio priklausomybė nuo bedimensio biojutiklio modulio. Suformuluotas uždavinys sprendžiamas baigtinių skirtumų metodu. Gauti rezultatai pagrindžia šio modelio pritaikomumą. Atliekami peroksidazinio optinio biojutiklio eksperimentiniai tyrimai leis nustatyti modelio taikymo ribas.