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Optimal design of amperometric biosensors applying multi-objective optimization and decision visualization

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ABSTRACT

This paper presents a method combining mathematical modeling, multi-objective optimization and multi-dimensional visualization intended for the design and optimization of amperometric biosensors. An approach for optimizing the biosensor parameters is based on the availability of mathematical model of a catalytic biosensor (bioelectrode). A multi-objective visualization of trade-off solutions and Pareto optimal decisions is applied for the selection of the most favorable decision by a human expert when designing the biosensor. The proposed method is applied to the industrially relevant optimization of a glucose dehydrogenase-based amperometric biosensor utilizing the synergistic substrates conversion. The following three objectives were optimized: the apparent Michaelis constant, the output current and the enzyme amount.

1. Introduction

Catalytic biosensors are based on enzyme-catalyzed conversion of analytes [1]. The output current of amperometric biosensors is produced by means of oxidation or reduction of enzymatic reaction products. The abundance of enzymatic catalytic processes permits to construct lots of schemes of bioelectrocatalysis. Combining the biocatalytic and chemical processes as well as applying different semi-permeable membranes permit to build new bioelectrocatalytic systems. The prediction of both, geometric and catalytic parameters, is of crucial importance for the development of novel biosensors.

With the aid of computer tools, the efforts for the design and optimization of biosensors can be remarkably reduced [2]. Moreover, these tools often allow to observe processes inside the devices which are not accessible by the measurement technology. The multi-objective optimization of biochemical processes and systems has been successfully performed in different applications, particularly, for the technological improvement of biochemical systems [3,4], for increasing the productivity and yield of a multi-enzymatic system [5], for the optimal design of a pressure swing adsorption system [6]. The importance of the multi-objective optimization in chemical and biochemical engineering permanently increases due to the development of new methods sustained by increased computational resources [4].

Multi-objective optimization tools provide a mechanism to obtain a certain number of trade-off solutions, largely known as Pareto optimal solutions. Establishing an efficient approach to find a set of solutions with good trade-off among different objectives has a great practical significance, as these allow engineers to gain insight into the key characteristics of potentially good designs before moving on to more detailed simulations and pilot plant tests. Trade-off curves as a visualisation of trade-off solutions are widely used for learning and making decisions when designing products [7].

The computer based design of industrial analytical systems is still a challenging task due to not only multiple often conflicting objectives, but also to a combination of factors with complex nonlinear mathematical models [2,4,6]. The action of catalytic biosensors is associated with the substrates diffusion from a bulk solution into a biocatalytic membrane and an enzyme-catalyzed substrates conversion to products [8,9]. The action can be mathematically described by partial differential equations of the reaction-diffusion type [9,10].

This paper demonstrates the potential of mathematical modelling, multi-objective optimization and multi-dimensional visualization for the design and optimization of biosensors. An approach for optimizing the biosensor parameters with the prior knowledge of mathematical model of the biosensor is proposed. The approach is demonstrated by applying it to a biosensor utilizing a synergistic scheme, in which an enzyme catalyses parallel

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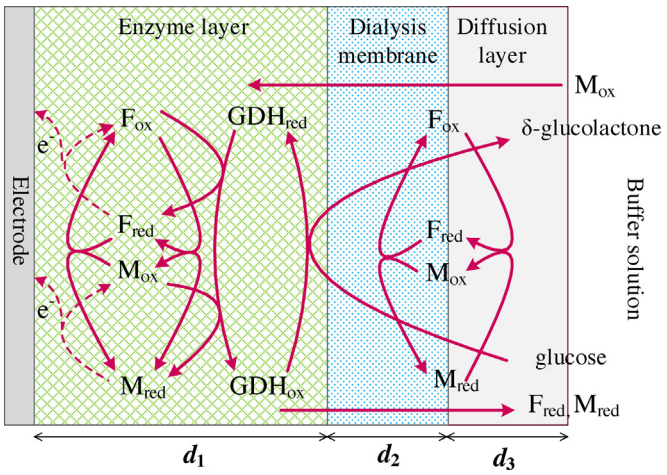

Fig. 1. The schematic view of the GDH biosensor and the reaction network (1).

conversion of substrates followed by chemical cross reaction of the products [11,12]. The synergistic schemes of the substrates conversion are of particular interest due to applying them to producing highly sensitive bioelectrodes [12,13] and powerful biofuel cells [14,15].

2. Mathematical modelling

2.1. The modelling biosensor

The glucose dehydrogenase (GDH)-based amperometric biosensor is a particular case of biosensors utilising the synergistic substrates conversion used for glucose measurement in blood [12]. The GDH biosensor being modelled is assumed to be composed of a graphite electrode covered with an enzyme (GDH) layer [12]. The enzyme layer is separated from the bulk solution by means of the inert dialysis membrane. The schematic view of the modelled biosensor is presented in Fig. 1 [16].

The scheme of the GDH-based bioelectrocatalytical system involves oxidised GDH (GDH_{ox}) reaction (1a) with glucose followed by the reduced GDH (GDH_{red}) oxidation (1b) with ferricyanide (F_{ox}) and (1c) with the oxidized mediator (M_{ox}) as well as a cross reaction (1d) of the ferricyanide and the reduced mediator (M_{red}) resulting in ferrocyanide (F_{red}) and oxidised mediator [12,16],

$$GDH_{ox} + glucose \xrightarrow{k_1} GDH_{red} + \delta\text{-}glucolactone, \tag{1a}$$

$$GDH_{red} + 2F_{ox} \xrightarrow{k_2} GDH_{ox} + 2F_{red}, \tag{1b}$$

$$GDH_{red} + 2M_{ox} \xrightarrow{k_3} GDH_{ox} + 2M_{red}, \tag{1c}$$

$$F_{ox} + M_{red} \underset{k_5}{\overset{k_4}{\leftrightarrow}} F_{red} + M_{ox}, \tag{1d}$$

where the reaction rate constants k_1, k_2 and k_3 correspond to the respective biocatalytical process, k_4 and k_5 belong to the electron exchange reactions.

On the electrode surface, the electrons are released and the biocatalytical current is produced during the oxidation of the ferrocyanide and the reduced mediator,

$$F_{red} \longrightarrow F_{ox} + e^-, \tag{2a}$$

$$M_{red} \longrightarrow M_{ox} + e^-. \tag{2b}$$

2.2. The mathematical model of the considered biosensor

Optimization based design methods require mathematical models of the analytical system [17]. Assuming the symmetrical geometry of the biosensor and homogeneous distribution of the immobilized enzyme and coupling reactions in the enzyme layer with the one-dimensional-in-space diffusion, described by the Fick's second law, lead to the following equations of the reaction-diffusion type ($0 < z < d_1$, $t > 0$) [10,16]:

$$\frac{\partial E_{red}}{\partial t} = D_{E_{red}} \frac{\partial^2 E_{red}}{\partial z^2} + k_1 E_{ox} G - 2k_2 E_{red} S_1 - 2k_3 E_{red} S_2, \tag{3a}$$

$$\frac{\partial E_{ox}}{\partial t} = D_{E_{ox}} \frac{\partial^2 E_{ox}}{\partial z^2} - k_1 E_{ox} G + 2k_2 E_{red} S_1 + 2k_3 E_{red} S_2, \tag{3b}$$

$$\frac{\partial S_1}{\partial t} = D_{S_1} \frac{\partial^2 S_1}{\partial z^2} - 2k_2 E_{red,1} S_1 - k_4 S_1 P_2 + k_5 P_1 S_2, \tag{3c}$$

$$\frac{\partial S_2}{\partial t} = D_{S_2} \frac{\partial^2 S_2}{\partial z^2} - 2k_3 E_{red} S_2 + k_4 S_1 P_2 - k_5 P_1 S_2, \tag{3d}$$

$$\frac{\partial P_1}{\partial t} = D_{P_1} \frac{\partial^2 P_1}{\partial z^2} + 2k_2 E_{red} S_1 + k_4 S_1 P_2 - k_5 P_1 S_2, \tag{3e}$$

$$\frac{\partial P_2}{\partial t} = D_{P_2} \frac{\partial^2 P_2}{\partial z^2} + 2k_3 E_{red} S_2 - k_4 S_1 P_2 + k_5 P_1 S_2, \tag{3f}$$

$$\frac{\partial G}{\partial t} = D_G \frac{\partial^2 G_1}{\partial z^2} - k_1 E_{ox} G_1, \tag{3g}$$

where z and t stand for space and time, respectively, $E_{red}(z, t)$ and $E_{ox}(z, t)$ are the concentrations of the oxidised (E_{ox}) and reduced (E_{red}) GDH, respectively, $S_1(z, t)$ and $S_2(z, t)$ are the concentrations of the substrates (ferricyanide and oxidised mediator), $P_1(z, t)$ and $P_2(z, t)$ are the concentrations of the reaction products (ferrocyanide and reduced mediator), $G(z, t)$ - the glucose concentration, $D_{E_{red}}$, $D_{E_{ox}}$, D_{S_i}, D_{P_i}, D_G are the corresponding diffusion coefficients in the enzyme layer, and d_1 is the thickness of the enzyme layer, $i = 1, 2$.

No enzymatic reaction takes place outside the enzyme layer ($z > d_1$). The kinetics of the non-enzymatic reactions (1d) as well as the mass transport by the diffusion in the dialysis membrane ($d_1 < z < d_1 + d_2$) and in the external diffusion (Nernst) layer ($d_1 + d_2 < z < d_1 + d_2 + d_3$) were described by similar systems of the reaction-diffusions equations [16].

Initially, the enzyme as well as the substrate S_1 are uniformly distributed in the enzyme layer $0 < z < d_1$. The biosensor operation starts ($t = 0$) when the substrate S_2 as well as the glucose appear on the outer boundary of the diffusion layer ($z = d_1 + d_2 + d_3$).

Governing equations (3) are typical for a class of biosensors used for the synergistic substrates determination [11,18–20].

2.3. Biosensor characteristics

There are several important characteristics of the biosensor response [21]. The measured current is usually accepted as a response of an amperometric biosensor in physical experiments. In the case of the biosensor, schematically shown in Fig. 1, the output current $I(t)$ depends upon the flux of the ferrocyanide and the reduced mediator at the electrode surface and is expressed explicitly from Faraday's and Fick's laws [9],

$$I(t) = AF \left(D_{P_1} \frac{\partial P_1}{\partial z}|_{z=0} + D_{P_2} \frac{\partial P_2}{\partial z}|_{z=0} \right), \tag{4}$$

where F is Faraday's constant, A is area of the electrode surface.