INFORMATICA, 2011, Vol. 22, No. 4, 589–600

Optimization-Based Evaluation of Concentrations in Modeling the Biosensor-Aided Measurement

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Received: September 2011; accepted: December 2011

Abstract. The concentration of a substrate in a solution can be measured using amperometric signals of biosensors: in fact the maximum (steady state) current is measured which is calibrated in the units of concentration. Such a simple method is not applicable in the case of several substrates. In the present paper, the problem of evaluation of concentrations of several substrates is tackled by minimizing the discrepancy between the observed and modeled transition processes of the amperometric signal.

Keywords: optimization, modeling, biosensor, concentration measurement.

1. Introduction

We are interested in the establishment of the quantitative structure of a mixture, using observations of its properties and the known properties of its components. The problem is related to the measurement of concentrations of several known substrates in a solution, and can also be formulated as a problem of the evaluation of indirectly observable parameters (see, e.g., Baronas *et al.*, 2004, 2007).

We assume that the structure of the function $z(t,x)$ is known: $z(t,x)=\sum_{j=1}^{k} y_j(t,x_j)$, $0 \leqslant t \leqslant t_{\max}$, $x=(x_1,\ldots,x_k) \in X$ where functions $y_j(t,x_j)$ are supposed to be given. The parameter vector x should be evaluated using the observed values $w_i = z(t_i,x)$, $0 \leqslant t_i \leqslant t_{\max}$, $i = 1,\ldots,n$. A large variety of subproblems of the general problem stated can be specified, and different methods can be appropriate for the solution of concrete subproblems. We focus on the problem related to the evaluation of concentrations of k substrates (components) in a mixture using a recorded signal of the biosensor $w_i,\ i=1,\ldots,n$, and records of similar signals of the biosensor $y_j(t,x_j)$ applied to the liquid that contains only a single known substrate.

Biosensors are analytical devices made of a biologically active substance, usually an enzyme, and a physico-chemical transducer that converts the biochemical reaction result to a measurable quantity (Gutfreund, 1995; Turner *et al.*, 1987; Scheller and Schubert, 1992). Amperometric biosensors measure the current change on the working electrode

due to the direct oxidation or reduction of chemical reaction products. Such biosensors are relatively cheap, sensitive and reliable devices for clinical diagnostics, drug detection, food analysis and environment monitoring (Wollenberger *et al.*, 1997; Rapp *et al.*; Viswanathan *et al.*; Wanekaya *et al.*, 2008).

Mathematical models of biosensor action are very helpful for designing new biosensors and optimizing their characteristics (Amatore *et al.*, 2006; Liu, 2010; Lyons, 2006; Mell and Maloy, 1975; Kulys, 1981; Bartlett and Whitaker, 1987). A comprehensive review of modelling amperometric biosensors has been presented in Schulmeister (1990) and more recently in Baronas *et al.* (2010).

This model is briefly described in the next section to facilitate the references for the readers who are experts in biochemistry. Other readers, who are interested in general problems of evaluation of the quantitative structure of a mixture of the known components, can consider the model being a slightly transparent "black box".

This paper is devoted to commemorate the 80th anniversary of Professor Jonas Mockus.

2. Mathematical Model

The amperometric biosensor is an electrode with a relatively thin layer of enzymes (multi-enzyme membrane) applied onto the electrode surface. The enzyme-catalyzed reaction occurs in the enzyme layer of a biosensor. We consider a mixture of substrates (components) participating in the biochemical reaction network

$$\mathrm{S}_j \xrightarrow{\mathrm{E}_j} \mathrm{P}_j, \quad j = 1, \ldots, k, \tag{1}$$

where the substrate (S_j, combines with the enzyme (E_j) to issue the product (P_j), $j = 1, \ldots, k$) (Gutfreund, 1995; Scheller and Schubert, 1992). The rate of growth of the amount of the product is called the rate of reaction. No interaction between separate enzyme reactions is considered. The reactions in the biosensor are described by Flick's law which leads to the following equations:

$$\begin{aligned} \frac{\partial s_j}{\partial t} &= D_{\mathrm{S_j}} \frac{\partial^2 s_j}{\partial \tau^2} - \frac{V_j s_j}{K_j + s_j}, \\ \frac{\partial p_j}{\partial t} &= D_{\mathrm{P_j}} \frac{\partial^2 p_j}{\partial \tau^2} + \frac{V_j s_j}{K_j + s_j}, \quad 0 < \tau < d,\ 0 < t \leqslant t_{\max},\ j = 1, \ldots, k, \end{aligned} \tag{2}$$

where $s_j(\tau, t)$ and $p_j(\tau, t)$ are the substrate and product concentrations in the enzyme layer, D_{S_j}, D_{P_j} are substrate and product diffusion coefficients respectively, V_j, is the maximal enzymatic rate attainable with that amount of enzyme completely saturated with the substrate S_j, $j = 1, \ldots, k$. K_j ($j = 1, \ldots, k$) is the Michaelis constant, t is time, $t_{\max}$ is the duration of the time interval in which the biosensor is analyzed, d is the thickness of the enzyme layer. During the substrates interaction with the biosensor the mass transport

by diffusion takes place, and the biochemical reactions start when the substrates appear on the enzyme layer because of the diffusion. Initial conditions ($t = 0$) in the biosensor model are defined as follows:

$$s_j(\tau, 0) = \begin{cases} 0, & 0 \leqslant \tau < d, \\ S_0 \cdot x_j, & \tau = d, \end{cases}$$
$$p_j(\tau, 0) = 0, \quad 0 \leqslant \tau \leqslant d,\ j = 1, \ldots, k, \tag{3}$$

where $S_0 \cdot x_j$ is the concentration of substrate S_j, $S_0 = 10^{-8}\ \mathrm{mol/cm^3}$. During the experiment the diffusion layer is constantly contiguous to the substrate solution; this fact in the batch mode is expressed by the following boundary conditions ($0 < t \leqslant t_{\max}$) :

$$\left.\frac{\partial s_j}{\partial \tau}\right|_{\tau=0} = 0, \tag{4}$$
$$s_j(d, t) = S_0 \cdot x_j, \quad t \leqslant t_{\max}, \tag{5}$$
$$p_j(0, t) = p_j(d, t) = 0, \quad j = 1, \ldots, k. \tag{6}$$

In the injection mode the substrate appears in the bulk solutions only for short period of time, known as injection time (T_F). Later the substrate concentration is set to zero. Boundary conditions in the injection mode are defined as follows:

$$\left.\frac{\partial s_j}{\partial \tau}\right|_{\tau=0} = 0, \tag{7}$$
$$s_j(d, t) = \begin{cases} S_0 \cdot x_j, & t \leqslant T_F, \\ 0, & t > T_F, \end{cases} \tag{8}$$
$$p_j(0, t) = p_j(d, t) = 0, \quad j = 1, \ldots, k. \tag{9}$$

The current, measured as a result of a physical experiment, is proportional to the gradient of the reaction product concentration at the electrode surface, i.e., on the border $x = 0$. The density $y_j(t, x_j)$ of the biosensor current at time t can be obtained explicitly from Faraday's and Fick's laws (Schulmeister, 1990),

$$y_j(t, x_j) = n_e F D_{P_j} \left.\frac{\partial p_j}{\partial \tau}\right|_{\tau=0}, \quad j = 1, \ldots, k, \tag{10}$$

where n_e is the number of electrons involved in the charge transfer, and F is the Faraday constant.

We assume that the system reaches the equilibrium as $t \to \infty$. The steady-state current is the main characteristic in commercial amperometric biosensors acting in the batch mode (Gutfreund, 1995; Turner *et al.*, 1987; Scheller and Schubert, 1992). The entire biosensor response $z(t, x)$ is the sum of individual biosensor currents $y_j(t, x_j)$, $j = 1, \ldots, k$.

In the present paper, the mathematical model described above was used to model real-world processes corresponding to the following parameters: $10^{-10}\ \mathrm{mol/(cm^3\ s)} \leqslant V_j \leqslant$

10^{-7} mol/(cm^3 s), $K_j = 10^{-7}$ mol/cm^3, $0 \leqslant t \leqslant 300$ s, 0.01 cm $\leqslant d \leqslant 0.03$ cm, and $0 \leqslant S_0 \cdot x_j \leqslant 64 \times 10^{-8}$ mol/cm^3, $j = 1, \ldots, k$, $k = 4$. The data for modeling are chosen the same as in Baronas *et al.* (2004, 2007) where further details can be found.

3. A Prerequisite for the Statement of a Numerically Tractable Problem

Biosensors are successfully applied to measure the concentration of a single known substrate in a presented liquid. The signal of the biosensor is measured in the steady state (i.e., for large enough t) for different specified concentrations, and the signal values are calibrated in units of concentration. A linear dependency between the concentration and the value of the signal is desirable, and for many important applications biosensors with linear characteristics are available. When the presented liquid contains a mixture of substrates, the concentration measurement problem is more complicated since the linearity of that characteristic for the all considered substrates in the ranges of the concentrations of interest normally is difficult (or even impossible) to achieve. The same value of the signal in the steady state can be observed for different concentrations of substrates. Therefore the measurement of the signal value at the steady state only is not sufficient to establish concentrations for the mixture of components. We intend here to extract the information on concentrations from the observations over the transition process of the signal, i.e., during the time interval which starts from the moment when the biosensor contacts with the liquid of interest, and finishes at the steady state.

Let w_i, $i = 1, \ldots, n$, be a sequence of the recorded values of the biosensor signal at discrete time moments; technically the electric current, defined by (10), is recorded. Using the software implementation of the mathematical model of reactions in the biosensor, the signal $z(t, x)$ can be modeled in the form of a of time $t \in T$ function, and of concentrations $x = (x_1, \ldots, x_k)$, where T is the set of time moments t_i when the biosensor signal was recorded. If the measurements were precise, the model were ideally adequate, and the substrate concentrations in the model were the same as in the experiment, then w_i and $z(t_i, x)$ would be coincident. A natural idea is to evaluate unknown concentrations by fitting w_i with $z(t_i, x)$, $t_i \in T$, i.e., to accept the minimizer in the following problem as an estimate

$$\tilde{x} = \arg\min_{x \in X} f\big(W, Z(x)\big), \tag{11}$$

where $f(\cdot)$ denotes a measure of difference between $W = (w_1, \ldots, w_n)$ and $Z(x) = (z(t_1, x), \ldots, z(t_n, x))$. The following expression could be considered, for example, as a possible measure of difference

$$f_2\big(W, Z(x)\big) = \sum_{i=1}^{n} \big(w_i - z(t_i, x)\big)^2. \tag{12}$$

The structure of minimization problem (11) corresponds to that of problems of nonlinear regression (Seber and Wild, 2003). However, the formulated minimization prob-

lem is difficult to analyze, since analytical properties of $z(t,x)$ are not known; moreover, computation of $z(t,x)$ is time consuming. The most serious difficulty here may be caused by the multimodality of the objective function. Another potential challenge is non-differentiability of $z(\cdot,x)$. In the least favorable case, where the functions $z(t,x)$ can coalesce for some different x, any method (not only optimization-based) for evaluating concentrations, using information on $z(t,x)$, would be challenged by the multiplicity of solutions. The problem should be considered as ill-defined if, for considerably different $x^{(1)}$, $x^{(2)}$, ($||x^{(1)} - x^{(2)}|| > \Delta$), $z(\cdot,x^{(1)})$ and $z(\cdot,x^{(2)})$ would either coincide or differ but insignificantly. Doe to these properties, (11) is a difficult global optimization problem. For the general discussion on global optimization we refer to Törn and Žilinskas (1989), and for the global optimization methods in nonlinear regression we refer to Křivý *et al.* (2000), Žilinskas (2011), Žilinskas and Žilinskas (2010).

To state the considered practical problem in the form of an optimization problem which was numerically tractable, the establishment of favorable properties of the objective function is crucial. Because of difficulties in the application of analytical methods to analyze the solutions of (2)–(10), in the present paper the properties of $z(t,x)$ are investigated experimentally, using software implementation of the mathematical model developed in Baronas *et al.* (2010). The measurements of the biosensor signal are substituted by those modeled. The errors of measurements are not taken into account, and computations are assumed ideally precise. The investigation of the influence of measurement errors and of the precision of computations would follow, if the results obtained in the idealized case were promising. By the replacement of experimental data with that generated according to a mathematical model we somewhat ignore the complexities of the original real-world problem. But that seems inevitable since such a replacement enables us to generate large amounts of data with desirable characteristics which would be impossible to collect experimentally because of the expensiveness and duration of experiments.

4. Analysis of the Properties of the Mathematical Model

Let us start from a graphical illustration of signals of the biosensor modeled in both measurement modes: batch and injection; we refer to Baronas *et al.* (2004, 2007) for details. The graphs of the biosensor signals in both modes are presented in Fig. 1 for four substrates with parameter V_j equal to 10^{-6-j}, $j = 1,\ldots,4$, $d = 0.02$ cm, and of the maximum concentration ($x_j = 64$) .

From the left graphs in Fig. 1 it is obvious that the evaluation of concentrations in the batch mode is difficult (no matter which method would be used) because of two reasons at least: the scale similarity between the signals (especially corresponding to $V_1 = 10^{-7}$ and $V_2 = 10^{-8}$), and relatively small values of the biosensor signal corresponding to $V_4 = 10^{-10}$ (the ratio of the signal values corresponding to $V_1 = 10^{-10}$ and $V_1 = 10^{-7}$ at $t = 300$ is equal to 8.8934×10^{-4}). The latter difficulty, caused by potentially negligible influence of the fourth substrate, can also challenge the evaluation of concentration in the injection mode. However, the scale similarity in this case is not so evident.

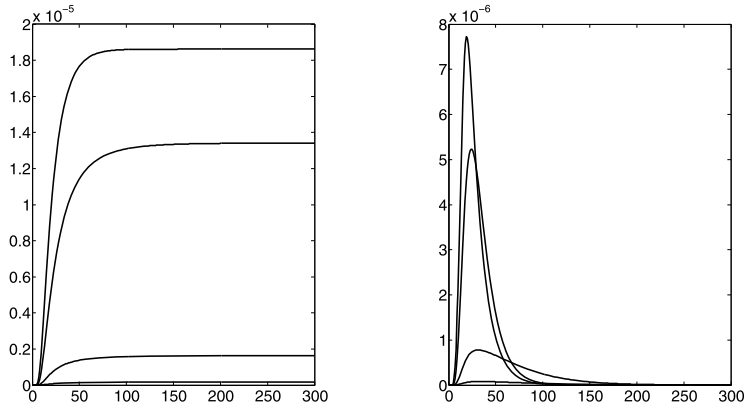

Fig. 1. Signals of the biosensor in the batch mode on the left, and in the injection mode on the right. Each curve represents a measurement for a single substrate with $V_j = 10^{-6-j}$, and $x_j = 64$, $j = 1, \ldots, 4$.

The considered problem has been tackled in Baronas *et al.* (2004, 2007) by approximating the straightforward mapping

$$\Phi\colon (w_1, \ldots, w_n) \to x. \tag{13}$$

An approximation of $\Phi(\cdot)$ was constructed as the inverse of the mapping $x \to (w_1, \ldots, w_n)$. The latter was defined according to (2)–(10) for $x \in C$ where C was a four-dimensional cubic mesh based on the following set of values of the components of x: $C = \{1, 2, 4, 8, 12, 16, 32, 64\}$. The set of 4096 biosensor signals was considered, where the signals were modeled for the mixtures of four substrates with concentrations defined by $x_j \in C$. Let us analyze the batch mode signals. If it were known a priori that $x_j \in C$, and were possible to measure the values of the signal $w_i = z(t_i, x)$ precisely, then x could be traced from the observation of a single value w_{300}. Such a conclusion is implied by the fact that the difference between the values w_{300}, corresponding to different x, is no less than 2.1×10^{-13}. However, to distinguish between these values, a super-precise equipment is needed with the measurement error no larger than $6.8 \times 10^{-6}\%$. In the case of measurement precision 0.1%, there are 374 indistinguishable pairs of signals, i.e., there exist 374 pairs $x^{(m)} \in C^4$, $x^{(r)} \in C^4$ such that

$$\max_{i=1,\ldots,300} \frac{|z(t_i, x^{(m)}) - z(t_i, x^{(r)})|}{\min\{z(t_{300}, x^{(m)}),\ z(t_{300}, x^{(r)})\}} < 0.001. \tag{14}$$

For example, two graphs of the signals, corresponding to the concentration vectors $x = (2, 64, 16, 32)$ and $x = (1, 64, 32, 12)$, practically coalesce; see the left graph of Fig. 2. However, if the signals are modeled for the same concentrations in the injection mode, they are still distinguishable as seen from the right graph of Fig. 2.

The set of 4096 biosensor signals in Baronas *et al.* (2004, 2007) was randomly bisected, and one part was used to train an artificial neural network which was used as

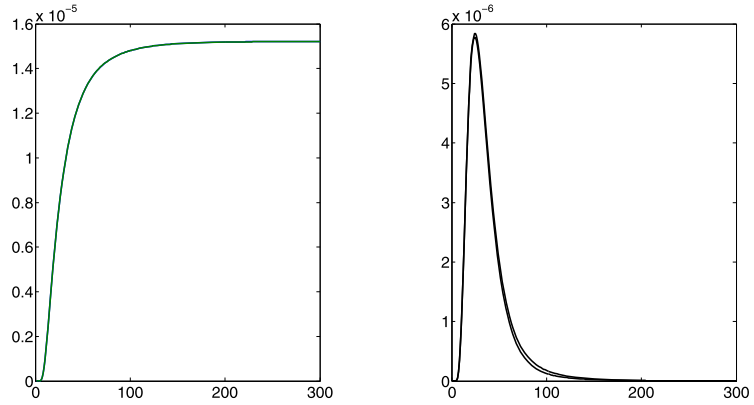

Fig. 2. Two signals, modeled in the batch mode, coalesce, but can be vaguely distinguished if modeled in the injection mode.

an approximant of (13). The second part was used as an examination set. Several experiments have been done with different model parameters, corresponding to the various conditions of measurement, and some conclusions have been drawn about the precision of evaluations of x for the data related to $x \in C^4$. A qualitative conclusions in Baronas *et al.* (2004, 2007) can be briefly formulated as follows: concentrations can be evaluated more precisely in the injection mode than in the batch mode, and the precision increases with increasing d. The quantitative estimates obtained for the data corresponding to C^4, which is rather a rough discretization of X, are not necessarily applicable to the biosensor signals corresponding to arbitrary $x \in X$. It would be of interest to see whether the evaluations in Baronas *et al.* (2004, 2007) failed for the data similar to illustrated in Fig. 2, however the authors of these papers have not commented the cases of failures. A disadvantage of the artificial neural network-based method is in the implicit tackling of the difficulties mentioned above, since an optimization algorithm is hidden in the training procedure.

The analysis of biosensor signals corresponding to the rough discretization of X indicates that the considered problem is likely to be ill-defined. An other serious difficulty is caused by the time consuming computations needed to model a biosensor signal; it takes approximately 56 seconds for HP Compaq 6710 with Intel(R) Core(TM) Duo CPU/2.20 GHz/2.00 GB.

5. Statement of the Relevant Optimization Problem

The minimization of $f(W, Z(x))$, where $Z(x)$ were modeled in every call of the subroutine of computation of an objective function value, would be very time-consuming as indicated above. Therefore the computation of $y(\cdot)$ is replaced by the computation of interpolant $\tilde{y}(\cdot)$, where the value $\tilde{y}_j(t_i, x_j)$ is obtained by interpolation of values $y_j(t_i, k)$, $k = 1, 2, \ldots, 64$ using a cubic spline. The values of $\tilde{y}(\cdot)$ are computed by a subroutine which uses the coefficients of splines evaluated in advance. For the latter evaluation, a set of 264 biosensor signals was modeled: $y_j(t_i, k)$, $j \in \{1, 2, 3, 4\}$,

$t_i \in T,\ k = 1, 2, \ldots, 64$. The approximation precision has been evaluated statistically: 1000 vectors x were generated randomly with a uniform distribution over X and a relative error of approximating $y(\cdot)$ by $\tilde{y}(\cdot)$ was computed similarly to (14). The mean value of the relative error (computed as by a formula simila r to (14)) was equal to 6.1158×10^{-7}, and its standard deviation was equal to 5.3274×10^{-6}.

The quadratic measure of difference (12) seems to be suited for application of gradient local descent methods. However, some experimentation has shown that for such an objective function the well recognized local descent algorithm from the MATLAB Optimization toolbox terminates not necessarily close to the solution. Since in these experiments the first-order necessary optimality conditions have been satisfied with a high precision, the objective function should be recognized as multimodal. The results of some experiments with local non-differentiable minimization algorithms for the objective function, defined as the measure of difference corresponding to the Chebyshev norm, were also not promising. Therefore, a global optimization method is needed for the considered problem.

The minimization problem (11)–(12), where the summands of $z(\cdot, x)$ are approximated by cubic polynomials, seems favorable to apply an interval arithmetic-based global optimization methods. However, the solution time for this type of problems is exceedingly high as shown in Žilinskas and Žilinskas (2010).

In this paper, we do not have intention to select the global optimization algorithm most suitable for the minimization problem considered. Our goal is to investigate the suitability of the optimization-based approach to evaluate the concentrations of components of a mixture, and to establish the properties of the optimization problem that could be important in a further real-world implementation in the form of an embedded system. The experimental investigation of properties of the objective function has shown that its hypersurface can be characterized as a deep valley with a flat bottom, where first-order optimality conditions are fulfilled with rather a high precision. Therefore a simple combination of the global random search with a local descent seems promising to find a point at the bottom of the valley with the objective function value close to the global minimum.

A global search algorithm was developed taking into account the experimentally established features of $z(t, x)$. The first summand, $y_1(t, \kappa)$ is linear with respect to the concentration variable κ during the entire transition process; see the left side of Fig. 3 where 64 graphs of $y_1(t, \kappa)/\kappa,\ \kappa = 1, \ldots, 64$ are presented which, however, all coincide. The forth summand $y_4(t, \kappa)$ is highly nonlinear with respect to κ, and the range of $y_4(t, \kappa)$ is a small fraction of the range of $y_1(t, \kappa)$; see the right side of Fig. 3. The linearity of $y_1(t, \kappa)$ can be exploited to simplify the minimization of (12):

$$\begin{aligned} \arg\min_{x_1} f_2\big(W, \tilde{Z}(x)\big) &= \arg\min_{x_1} \sum_{i=1}^{300} \left(w_i - x_1 \tilde{y_1}(t_i, 1) - \sum_{j=2}^{4} \tilde{y}_j(t_i, x_j) \right)^2 \\ &= \frac{\sum_{i=1}^{300} (w_i - \sum_{j=2}^{4} \tilde{y}_j(t_i, x_j)) \cdot \tilde{y_1}(t_i, 1)}{\sum_{i=1}^{300} \tilde{y}_1^2(t_i, 1)}. \end{aligned} \tag{15}$$

Replacing x_1 by its optimal value $x_{1\mathrm{opt}}$ we reduce the four-dimensional optimization problem to a three-dimensional one. The global search was performed by generating

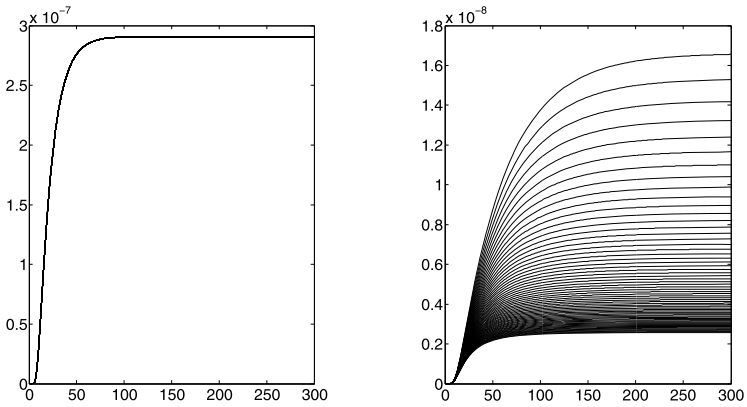

Fig. 3. Graphs of normalized biosensor signals $y_j(t,\kappa)/\kappa$ ($j = 1$ on the left side, and $j = 4$ on the right side) drawn for $\kappa = 1,\ldots,64,\ t = 0,\ldots,300$. These graphs show that $y_1(t,\kappa)$,, is linear with respect to the concentration κ during the whole transition time interval, while the signal $y_4(t,\kappa)$ is nonlinear

N_g random vectors (x_2, x_3, x_4) with a uniform distribution over the three-dimensional feasible region, and selecting g best points $(x_{1\mathrm{opt}}, x_2, x_3, x_4)$. The latter were used as the starting points for local descent. As seen in Fig. 3, the influence of $y_4(t,\kappa)$ to the objective function values can be relatively weak, therefore termination conditions of the local descent should be set sufficient to guarantee the computation of a local minimizer with a high accuracy.

6. Numerical Experiments

To investigate the precision of evaluation of concentrations, the biosensor signals were modeled under the conditions discussed above. The mixture contained four substrates characterized by $V_j = 10^{-6-j}$, $j \in \{1,2,3,4\}$. The concentration of each substrate could vary in the interval $1 \leqslant x_j \leqslant 64$, and for each experiment below 1000 random vectors x with a uniform distribution over that region were generated to model the biosensor signals.

The first experiment was performed to investigate the precision of the concentration evaluation in the batch mode. The global search was performed with the following parameters of the algorithm: $N_g = 1000,\ g = 5$. For the local minimization, the MATLAB subroutine *fmincon* was used with a user supplied gradient. Termination condition was defined by the tolerances *TolFun* $= 10^{-4}$ for the values of objective function (12) multiplied by 10^7 (to accommodate the scale of the function values and the scale of the parameters of the algorithm), and by *TolX* $= 0.005$. The results are presented in Table 1, where Δx_j denotes the difference between the actual x_j and its evaluated value, and $f_{\min}$ denotes the relative approximation error computed as in (14). The precision of the evaluation of the concentrations of the first two substrates are quite good, but the evaluation of the accuracy of the last two substrates is insufficient. The low accuracy obtained fo r the latter two substrates can be explained by their insignificant input

Table 1

Precision of the evaluation of concentrations in the batch mode for the biosensor with the layer $d = 0.02$ cm wide

	$f_{\min}$	Δx_1	Δx_2	Δx_3	Δx_4
Mean	2.5520×10^{-4}	0.6304	0.5139	9.3593	19.4844
Std.	4.0538×10^{-4}	0.9354	0.6951	15.1093	15.3593

Table 2

Precision of the evaluation of concentrations in the injection mode for the biosensor with the layer $d = 0.02$ cm wide

	$f_{\min}$	Δx_1	Δx_2	Δx_3	Δx_4
Mean	2.8495×10^{-5}	0.0041	0.0108	0.0408	0.0464
Std.	3.1573×10^{-4}	0.0388	0.1663	0.8404	0.9755

Table 3

Precision of evaluation of concentrations in the injection mode for the biosensors with the layer width $d = 0.01$ cm and $d = 0.03$ cm wide

	$d = 0.01$				
	$f_{\min}$	Δx_1	Δx_2	Δx_3	Δx_4
Mean	6.2751×10^{-5}	0.0024	0.0553	0.4929	0.4498
Std.	2.2811×10^{-4}	0.0123	0.2489	2.0472	1.8462
	$d = 0.03$				
	$f_{\min}$	Δx_1	Δx_2	Δx_3	Δx_4
Mean	1.8358×10^{-4}	0.0945	0.1133	0.1106	0.3823
Std.	6.2409×10^{-4}	0.3029	0.3506	0.3945	1.2043

to the biosensor signal; for the discussion about the significance of the inputs of the considered substrates to the signal of a biosensor we refer to Section 3. This diversity in precision is well illustrated also by the following example: the relative discrepancy between two signals, corresponding to $x = (44.5764, 62.3342, 16.0006, 38.7044)$ and to $x = 43.0724, 63.1362, 35.9738, 15.8452)$, computed according to (14) is negligible since equal to 3.7361×10^{-4}.

The second experiment was performed in the same conditions as above but in the injection measurement mode. The results presented in Table 2 show that the accuracy of this evaluation method is quite acceptable in the praxis. Similar conclusion can be drawn from the results of the experiments presented in Table 3 where the constructive parameter of the biosensor d is varied around the basic value.

The optimization-based evaluation of concentrations under general conditions of the modeled experiment yields the results of acceptable to the praxis precision. Note that a

very simple optimization algorithm has been used. The optimization precision could be enhanced, but it does not seem reasonable because of an inevitably restricted precision of the modeling algorithm. From the point of view of real-world applications, a further investigation of the problem is urgent, taking into account the interaction between separate enzyme reactions, and measurement errors. Optimization in the presence of noise is considerably more difficult than that without noise. On the other hand, in practical problems optimization can possibly be facilitated by narrower intervals of the model parameters (which define the measurement conditions) than that in the present paper. Selection of the most suitable optimization algorithm is of especial interest taking into account the requirements of the potential i mplementation in an embedded measurement system.

7. Conclusions

In the mathematical modeling setting the optimization-based approach is efficient to evaluate concentrations of several substrates in a liquid where the available data is modeled as an amperometric signal of a biosensor. An urgent problem of further research is extension of the obtained results to the case where the interaction between separate enzyme reactions is taken into account as well as complications caused by collecting data of real-world experiments.

Acknowledgments. The research of A. Žilinskas is supported by the European Social Fund under Global Grant measure VP1-3.1-ŠMM-07-K. The authors thank participants of the seminar of Vilnius University "Biomoda" for valuable remarks.

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Optimizacija pagrįstas koncentracijų vertinimas biosensorinio matavimo modeliavime

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Esant tirpale vienam substratui, jo koncentracija lengvai matuojama amperometriniais biosensoriais: matuojama srovė, kurios dydis yra kalibruotas srovės vienetais. Tačiau taip paprastai išmatuoti kelių substratų, esančių tirpale koncentracijas nėra galimybės. Šiame straipsnyje koncentracijų nustatymo uždavinys sprendžiamas panaudojant optimizavimo metodus, kuriais minimizuojamas skirtumas tarp matuojamo ir modeliuojamo biosensoriaus signalo.