Investigation of the Mathematical Model of the Biosensor for the Measurement of α-Chaconine Based on the Impulsive Differential System

Alexander Nakonechnyi[a], Vasyl Martsenyuk[b], Andriy Sverstiuk[c], Valentyna Arkhypova[d] and Sergei Dzyadevych[d]

[a] *Taras Shevchenko National University of Kyiv, Volodymyrska St., 60, Kyiv, 01033, Ukraine*
[b] *University of Bielsko-Biala, Willowa St., 2, Bielsko-Biala, 43-300, Poland*
[c] *I. Horbachevsky Ternopil National Medical University, maidan Voli, 1, Ternopil, 46002, Ukraine*
[d] *Institute of Molecular Biology and Genetics NAS of Ukraine, Academica Zabolotnogo St., 150, Kyiv, 03680, Ukraine*

Abstract

Mathematical modeling plays an important role in adjusting the parameters to achieve the desired characteristics of electrochemical biosensors. The investigation of a mathematical model of a potentiometric biosensor for the measurement of a-chaconine is carried out. The mathematical model of the investigation biosensor is presented in the form of a system of impulsive differential equations describing the dynamics of biochemical reactions when the concentration of a-chaconine is measured. In the model of the biosensor, each of the differential equations describes the concentrations of enzyme, substrate, inhibitor, enzyme-substrate, enzyme-inhibitor, enzyme-substrate-inhibitory complexes, as well as product depending on time simulation of mathematical model of biosensor for measurement of a-chaconine using R package is performed. The impulsive values of the system are the initial concentrations of the enzyme in the form of butyrylcholinesterase, the substrate in the form of butyryl choline chloride and a-chaconine as inhibitors. An existing potentiometric biosensor based on immobilized butyrylcholinesterase was used to verify the model and compare it with the experimental response. Conditions of local asymptotical stability for the inhibition stage in terms of corresponding eigenvalues is obtained. Nontrivial steady state of the model of biosensor for the measurement of a-chaconine can be numerically calculated as a positive solution of the system of nonlinear algebraic equations. The absolute value of the error between the experimental and simulated biosensor reactions for measuring α-haconin, which does not exceed 5.7 μA, was calculated. The root mean square error between the experimental and simulated biosensor reactions for measuring α-haconin is 1.6 μA, which corresponds to 5.33%. Based on the results of numerical simulations of the biosensor allows to adequately determine all major components of the compartment components of biochemical reactions when measuring a-chaconine concentration. The use of numerical simulation results will further minimize laboratory experiments with toxic and costly substances to select optimal concentrations of biosensor components to determine a-chaconine.

Keywords

mathematical model, impulsive differential equations, biosensor, α-chaconine, enzymatic kinetics, numerical modeling

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EMAIL: a.nakonechnyi@gmail.com (A. Nakonechnyi); vmartsenyuk@ath.bielsko.pl (V. Martsenyuk); sverstyuk@tdmu.edu.ua (A. Sverstiuk); avalka@yahoo.com (V. Arkhypova); dzyad@yahoo.com (S. Dzyadevych)
ORCID: 0000-0002-8705-3070 (A. Nakonechnyi); 0000-0001-5622-1038 (V. Martsenyuk); 0000-0001-8644-0776 (A. Sverstiuk); 0000-0002-4009-1539 (V. Arkhypova); 0000-0003-2915-716X (S. Dzyadevych)

1. Introduction

Application of the results of mathematical and numerical simulation based on differential equations is a useful tool both for understanding biochemical processes and for making extensive use of optimization analytical characteristics of biosensors in their design. Over the last fifty years, many mathematical models have been developed and applied to optimize the performance of various biosensors [1–3].

In [4, 5], mathematical models for an ammetric electrode with an immobilized enzyme based on nonlinear differential equations are proposed, which describe Michaelis-Menten kinetics and diffusion, as well as a mathematical model of amperometric and potentiometric biosensors [6]. In these models, the homotopy perturbation method is used to solve the system of equations under stationary conditions. The works [7, 8] presented mathematical models of ammetric biosensors, which improved the sensitivity of the developed biosensors by changing the input parameters (reagent concentrations, kinetic constants, and membrane thickness). In these models, the finite-difference method is used to solve the equation system under both steady-state and non-steady-state conditions. The vast majority of mathematical models developed describe enzyme biosensors for direct substrate measurement. In addition, in recent years there has been a tendency to increase the development of biosensors based on inhibitory analysis [9, 10]. To a greater extent, such biosensors are used in environmental monitoring for the detection of toxic substances such as pesticides, heavy metal ions, aflatoxins [11, 12]. To date, quite a few mathematical models of biosensors of this type have been developed. Of these, one can distinguish a mathematical model of the glucose oxidase biosensor for the measurement of mercury ions [13]. In this model, a system of equations describing diffusion and enzymatic nonlinear reactions is related to Michaelis-Menten kinetics, which have been refined to account for irreversible inhibition.

This paper is devoted to the development of a mathematical model and the study of the stability of a previously developed butyrylcholinesterase biosensor based on ion-selective field-effect transistors (ISFET) for inhibitory measurement of α-chaconine [14].

The question is very urgent, given that α-chaconine is a very interesting biological object because of its toxicity and its concentration in potatoes as a food through which potatoes have a bitter taste. Measurement of the content of α-chaconine in potatoes is performed when new varieties with reduced content are removed. In recent years, scientific research has been carried out, which results in the conclusion that mechanisms of resistance of potatoes to disease and insect action depend on the level of α-chaconine. Other factors that affect the level of α-chaconine and can cause a significant increase in its primary concentration are climatic changes, light effects, mechanical damage during potato harvesting and storage [15]. Methods developed to determine total α-chaconine content are based on the use of colorimetry, high performance liquid chromatography, thin layer and gas chromatography, radioimmunological analysis. These methods are characterized by high cost, long duration and complexity of sample preparation techniques. In order to optimize and modify existing methods for the analysis of harmful substances in potatoes, it is appropriate to create simple, inexpensive, highly sensitive methods for the measurement of α-chaconine based on biosensors. At the same time, in order to save time and raw material resources (enzymes, substrates and inhibitors), it is advisable and economically advantageous to create and study adequate mathematical models of biosensors for the measurement of α-chaconine with the possibility of numerical simulation.

2. Materials and Methods

For numerical simulation of mathematical model in the work we used previously developed biosensor for measurement of α-chaconine [14].

As the bioselective element of the biosensor used the enzyme butyrylcholinesterase (BuChE). In a real experiment, 10^{-3} mol butyricoline chloride (BuChCl) was used for working substrate concentration. As potentiometric transducers a pair of identical ion-selective p-type field-effect transistors with a sensitivity of 35-40 μA/pH placed on a single crystal has been used.

3. Modeling of Mathematical Model of Biosensor for Measurement of A-chaconin Baed on the Impulsive Differential System

The impulsive differential equation system, which describes the mathematical model of the functioning of the biosensor for the measurement of α-chaconin, was solved by the R package.

The program also built model responses from biosensors that are comparable to experimental data.

Using the literature data [14] for the inhibitory measurement of α-chaconine using a BuChE-biosensor based on ion-selective field-effect transistors, the measurement process of the biosensor is attributed to a mixed type of inhibition, which can be schematically depicted in Fig.1.

In Fig. 1 k_s and k_{-s} are the constants of the rate of forward and reverse reaction of the formation of the complex (ES), k_p is the constant of the rate υ_p of formation of the product (P), k_i and k_{-i} are the rate constants of the direct and reverse reaction of the formation of the complex (EI).

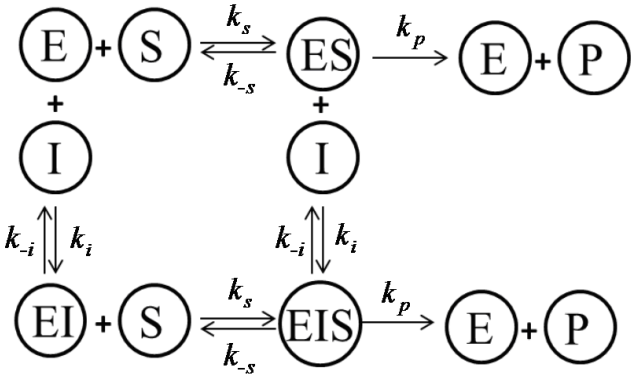


Figure 1: Schematic representation of the enzymatic reaction in a potentiometric biosensor based on BuChE-ISFET in the inhibitory measurement of α-chaconine (E – enzyme, S – substrate, I – inhibitor)

Therefore, measuring with the help of such type of biosensor includes three stages related to the injection of different substances. Namely, the "rest" stage ($t \in [0, t_s)$), when only some amount of enzyme is injected; enzyme reaction ($t \in [t_s, t_i)$), when some amount of substruct is injected; the reaction of enzyme inhibition ($t \in [t_i, t_f]$). Here $0 < t_s < t_i < t_f$ are the corresponding instances of time.

At $t > 0$, $t \notin \{t_s, t_i\}$ this system can be described by the following system of differential equations:

$$\frac{dn_e(t)}{dt} = -k_s n_e(t) n_s(t) - k_i n_e(t) n_i(t) + k_{-s} n_{es}(t) + k_{-i} n_{ei}(t) + k_p n_{es}(t) \quad (1)$$

$$\frac{dn_s(t)}{dt} = -k_s n_e(t) n_s(t) - \alpha k_s n_{ei}(t) n_s(t) + k_{-s} n_{es}(t) + \alpha k_{-s} n_{esi}(t) \quad (2)$$

$$\frac{dn_{es}(t)}{dt} = k_s n_e(t) n_s(t) - k_{-s} n_{es}(t) - \alpha k_i n_{es}(t) n_i(t) + \alpha k_{-i} n_{esi}(t) - k_p n_{es}(t) \quad (3)$$

$$\frac{dn_i(t)}{dt} = -k_i n_e(t) n_i(t) - \alpha k_i n_{es}(t) n_i(t) + k_{-i} n_{ei}(t) + \alpha k_{-i} n_{esi}(t) \quad (4)$$

$$\frac{dn_{ei}(t)}{dt} = k_i n_e(t) n_i(t) - k_{-i} n_{ei}(t) - \alpha k_s n_{ei}(t) n_s(t) + \alpha k_{-s} n_{esi}(t) \quad (5)$$

$$\frac{dn_{esi}(t)}{dt} = \alpha k_i n_{es}(t) n_i(t) - \alpha k_{-i} n_{esi}(t) + \alpha k_s n_{ei}(t) n_s(t) - \alpha k_{-s} n_{esi}(t) \quad (6)$$

$$\frac{dn_p(t)}{dt} = k_p n_{es}(t) - k_w n_p(t) \quad (7)$$

where k_s, k_{-s}, k_i, k_{-i} and k_p are the corresponding rate constants of the reactions of complex formation; k_w is washout constant; α is a constant whose numerical value determines the inhibition or activation of the enzyme; $n_e(t)$, $n_s(t)$, $n_i(t)$, $n_p(t)$, $n_{es}(t)$, $n_{ei}(t)$, $n_{esi}(t)$ are concentrations of

enzyme, substrate, inhibitor, product, as well as enzyme-substrate, enzyme-inhibitory and enzyme-substrate-inhibitory complexes, which change over time. The change in product concentration $n_p(t)$ time is directly proportional to the response of the biosensor.

The initial conditions are:

$$\begin{gathered} n_e(0) = n_e^0,\ n_s(0) = 0, \\ n_i(0) = 0,\ \ n_p(0) = 0, \\ n_{es}(0) = 0,\ \ n_{ei}(0) = 0,\ \ n_{esi}(0) = 0, \end{gathered} \tag{8}$$

whereas impulsive influences are:

$$\begin{gathered} n_e(t_s^+) = n_e(t_s^-),\ n_s(t_s^+) = n_s(t_s^-) + n_s^0, \\ n_i(t_s^+) = n_i(t_s^-),\ \ n_p(t_s^+) = n_p(t_s), \\ n_{es}(t_s^+) = n_{es}(t_s^-),\ \ n_{ei}(t_s^+) = n_{ei}(t_s^-),\ \ n_{esi}(t_s^+) = n_{esi}(t_s^-), \end{gathered} \tag{9}$$

and

$$\begin{gathered} n_e(t_i^+) = n_e(t_i^-),\ n_s(t_i^+) = n_s(t_i^-), \\ n_i(t_i^+) = n_i(t_i^-) + n_i^0,\ \ n_p(t_i^+) = n_p(t_i^-), \\ n_{es}(t_i^+) = n_{es}(t_i^-),\ \ n_{ei}(t_i^+) = n_{ei}(t_i^-),\ \ n_{esi}(t_i^+) = n_{esi}(t_i^-) \end{gathered} \tag{10}$$

Note that since the right-hand sides of (1-7) are locally Lipschitz continuous with respect to initial conditions and impulses at fixed times t_s and t_i, there is a unique solution of the initial value problem (1–10).

4. Investigation of Steady States of the Biosensor Model

Steady states of the system (1-10) can be found as a solution of the algebraic system:

$$-k_s n_e^* n_s^* - k_i n_e^* n_i^* + k_{-s} n_{es}^* + k_{-i} n_{ei}^* + k_p n_{es}^* = 0 \tag{11}$$

$$-k_s n_e^* n_s^* - \alpha k_s n_{ei}^* n_s^* + k_{-s} n_{es}^* + \alpha k_{-s} n_{esi}^* = 0 \tag{12}$$

$$k_s n_e^* n_s^* - k_{-s} n_{es}^* - \alpha k_i n_{es}^* n_i^* + \alpha k_{-i} n_{esi}^* - k_p n_{es}^* = 0 \tag{13}$$

$$-k_i n_e^* n_i^* - \alpha k_i n_{es}^* n_i^* + k_{-i} n_{ei}^* + \alpha k_{-i} n_{esi}^* = 0 \tag{14}$$

$$k_i n_e^* n_i^* - k_{-i} n_{ei}^* - \alpha k_s n_{ei}^* n_s^* + \alpha k_{-s} n_{esi}^* = 0 \tag{15}$$

$$\alpha k_i n_{es}^* n_i^* - \alpha k_{-i} n_{esi}^* + \alpha k_s n_{ei}^* n_s^* - \alpha k_{-s} n_{esi}^* = 0 \tag{16}$$

$$k_p n_{es}^* - k_w n_p^* = 0 \tag{17}$$

Clearly, the system (11–17) has trivial solution $(0, 0, 0, 0, 0, 0, 0)^T$. Nontrivial solutions $n^* = (n_s^*, n_{es}^*, n_i^*, n_{ei}^*, n_{esi}^*, n_p^*)^T$ can be calculated numerically. Rate parameters and initial values of the model (1-10) are presented in Table 1.

Table 1

Rate parameters and initial values of the model of biosensor for the measurement of α-chaconine

Model parameters	Numerical value	Unit of measurement
k_s	$5*10^4$	L/(mol*s)
k_i	$2*10^4$	L/(mol*s)
k_{-s}	25	1/s
k_{-i}	0.0187	1/s
k_p	0.05	1/s
k_w	1.42	1/s
α	20	-
n_e^0	$2*10^{-5}$	mol/L
n_s^0	$4*10^{-3}$	mol/L
n_i^0	$3.2*10^{-6}$	mol/L

Further stability research is restricted to the stage of inhibition $t \geq t_i$. For the parameter values of Table 1 we get the steady state of the model (1–7) presented in the form of Table 2.

Table 2

Steady state of the model biosensor for the measurement of α -chaconine.

Variable	Numerical values	Unit of measurement
n_e^*	$1{,}415 * 10^{-7}$	mol/L
n_s^*	$4 * 10^{-3}$	mol/L
n_{es}^*	$1{,}129 * 10^{-6}$	mol/L
n_i^*	$1{,}27 * 10^{-6}$	mol/L
n_{ei}^*	$2{,}146 * 10^{-7}$	mol/L
n_{esi}^*	$1{,}715 * 10^{-6}$	mol/L
n_p^*	$3{,}977 * 10^{-8}$	mol/L

Stability research is based on the linear model

$$\frac{dx(t)}{dt} = J(x(t))\big|_{x(t)\equiv n^*} x(t),\ x(t) \in R^7,\ t \geq 0,$$

where $J(x(t))$ is Jacobian of the system (1) – (7), which can be presented in the form

$$J(n(t)) = \begin{bmatrix} -k_s n_s(t) - k_i n_i(t) & -k_s n_e(t) & k_{-s} + k_p & -k_i n_e(t) & k_{-i} & 0 & 0 \\ -k_s n_s(t) & -k_s n_e(t) - ak_s n_{ei}(t) & k_{-s} & 0 & -ak_s n_s(t) & ak_{-s} & 0 \\ k_s n_s(t) & k_s n_e(t) & -k_{-s} - ak_i n_i(t) - k_p & ak_i n_{es}(t) & 0 & ak_{-i} & 0 \\ -k_i n_i(t) & 0 & -ak_i n_i(t) & -k_i n_e(t) - ak_i n_{es}(t) & k_{-i} & ak_{-i} & 0 \\ k_i n_i(t) & -ak_s n_{ei}(t) & 0 & k_i n_e(t) & -k_{-i} - ak_s n_s(t) & ak_{-s} & 0 \\ 0 & ak_s n_{ei}(t) & ak_i n_i(t) & ak_i n_{es}(t) & ak_s n_s(t) & -ak_{-i} - ak_{-s} & 0 \\ 0 & 0 & k_p & 0 & 0 & 0 & -k_w \end{bmatrix}$$

For the values of parameters in Table 1 and steady state in Table 2 we get the following matrix

$$J(n(t))\big|_{n(t)\equiv n^*} = \begin{bmatrix} -1.507978e+02 & -0.120773074 & 2.505000e+01 & -0.04830923 & 0.01670 & 0.00000 & 0.000 \\ -1.507948e+02 & -0.125109570 & 2.500000e+01 & 0.00000000 & -30.15896 & 5.00000 & 0.000 \\ 1.507948e+02 & 0.120773074 & -2.505060e+01 & 0.05816714 & 0.00000 & 0.00334 & 0.000 \\ -3.001462e-03 & 0.000000000 & -6.002924e-04 & -0.10647636 & 0.01670 & 0.00334 & 0.000 \\ 3.001462e-03 & -0.004336496 & 0.000000e+00 & 0.04830923 & -30.17566 & 5.00000 & 0.000 \\ 0.000000e+00 & 0.004336496 & 6.002924e-04 & 0.05816714 & 30.15896 & -5.00334 & 0.000 \\ 0.000000e+00 & 0.000000000 & 5.000000e-02 & 0.00000000 & 0.00000 & 0.00000 & -0.142 \end{bmatrix}$$

We get all eigenvalues of $J(n(t))\big|_{n(t)\equiv n^*}$ as the numbers with negative real part, namely:

$\lambda_1 = -1.759682e+02$, $\lambda_2 = -3.517811e+01$, $\lambda_3 = -1.420000e-01$, $\lambda_4 = -1.116629e-01$, $\lambda_5 = -9.815916e-04$, $\lambda_6 = -3.437626e-05$, $\lambda_7 = -3.865944e-15$.

Thus, using Hartman–Grobman theorem [16], we conclude that the stationary state n^* of the system (1)–(7) at the rate parameters' values from the Table 1 is locally asymptotically stable at the inhibition stage $t \geq t_i$.

It is also taken into account that the system maintains a constant total concentration of the enzyme E_0, so at any given time the sum of the concentrations of free (E) and bound (ES), (EI), (ESI) enzyme is equal to $(E) + (ES) + (EI) + (ESI) = E_0$. To simulate the operation of the biosensor, the system described above was decoupled using package R.

The numerical simulation results are shown in Fig. 2.

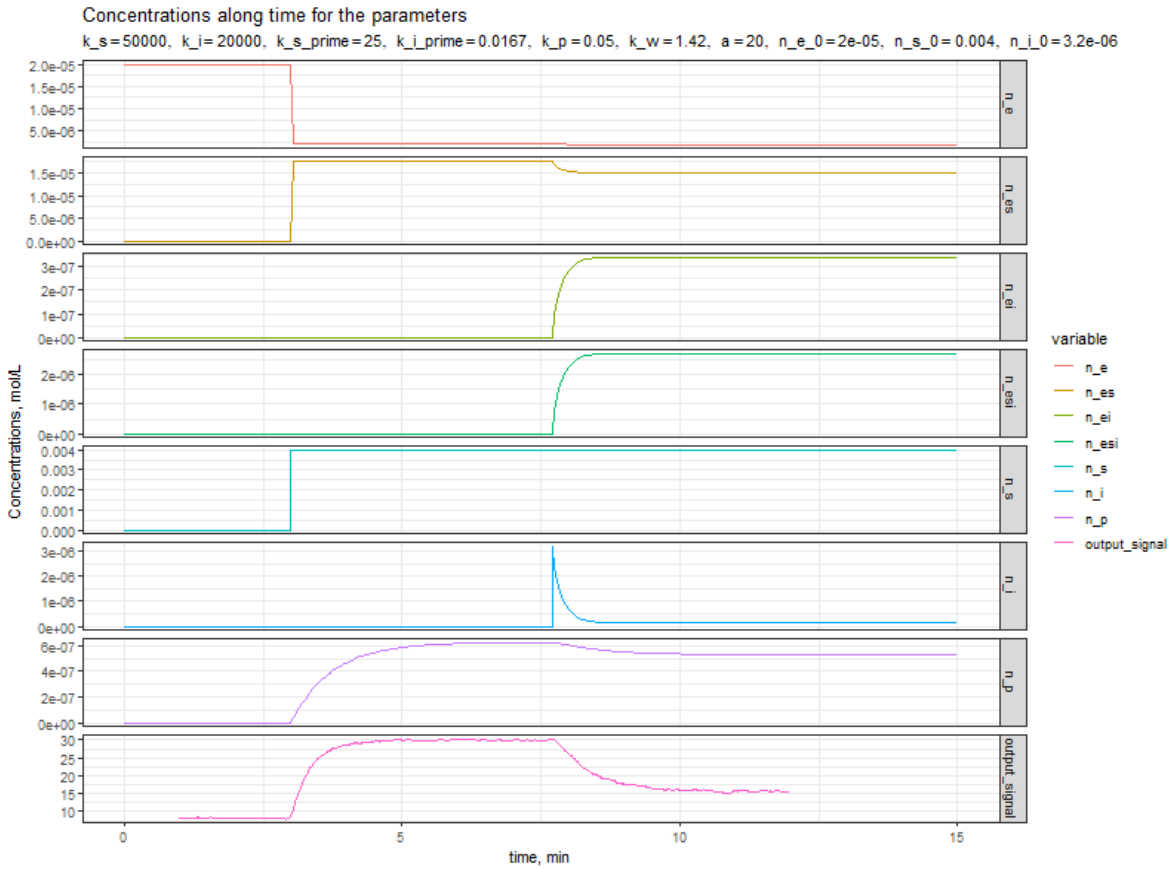


Figure 2: Numerical simulation of the enzymatic reaction in the BuCHE-ISFET membrane of the biosensor using kinetic equations (1–7) and the parameters presented in table 1

At the zero stage of the simulation, the following initial conditions are set $n_s(0) = n_i(0) = n_{es}(0) = n_{ei}(0) = n_{esi}(0) = n_p(0) = 0$, that is, when there is no substrate and inhibitor in the system, but only the initial enzyme concentration in the working membrane of the biosensor is entered. Under the given initial conditions and given parameters, there are solutions of the system. In the first stage, the system is decoupled under the initial conditions given by the zero-phase system junctions and the initial substrate concentration is added to the working cell.

In the second step, the response to the inhibitor is simulated by substituting the previous solutions and the initial concentration of the inhibitor $n_i(t)$ known under the conditions of the experiment. The results of numerical simulation of the response of the biosensor at different values of the concentration of inhibitor is presented in Fig. 3.

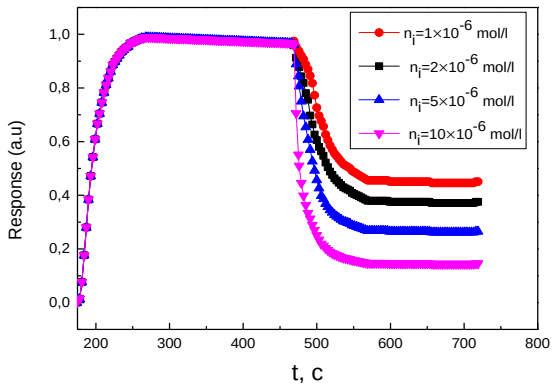
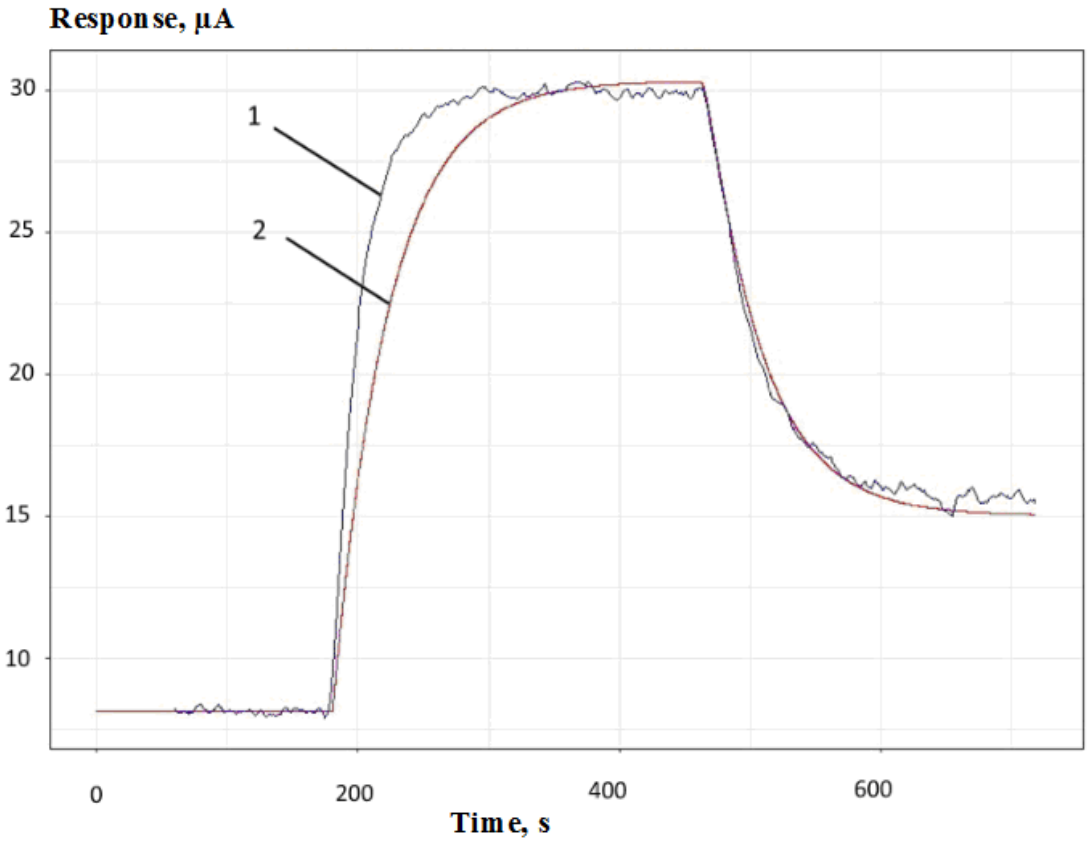
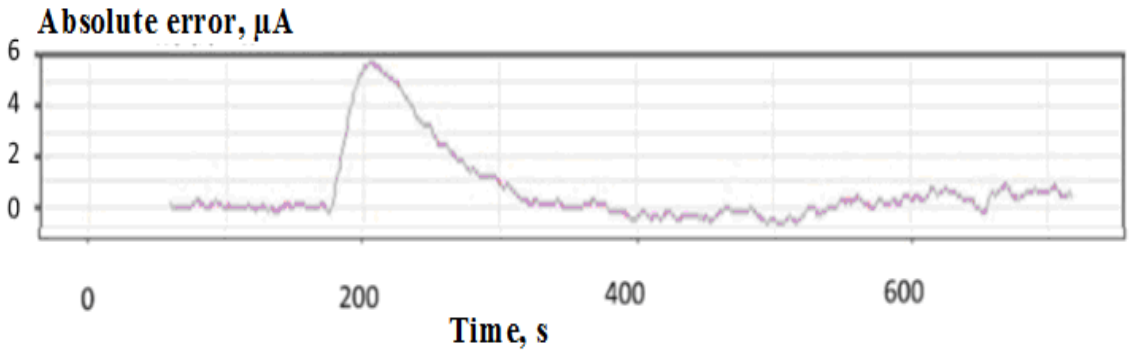


Figure 3: Numerical simulation of the response of the biosensor at different values of the concentration of inhibitor

In Fig. 3 are presented results of numerical simulation of the response of the biosensor for the measurement of α-chaconine at values of the concentration of inhibitor $1*10^{-6}$ mol/L, $2*10^{-6}$ mol/L, $5*10^{-6}$ mol/L, $10*10^{-6}$ mol/L. It should be noted that the concentration of the inhibitor used are measuring levels of α-chaconine. Analyzing the results of numerical simulation obtained in Fig. 3 we can conclude that the higher the concentration of the inhibitor, the smaller the amplitude of the response of the investigation model of the biosensor. The simulated responses of the biosensor at different concentrations of the inhibitor are fully consistent with the principle of inhibition.



a)



b)

Fig. 4. Comparison of biosensor responses for the determination of α-chaconine (1 - experimental response; 2 - simulated system response) (a); absolute value of error between experimental and simulated feedback (b)

In Fig. 4 (b) shows the absolute value of the error between the experimental and simulated responses of biosensor for the measurement of α-chaconine, which does not exceed 5.7 µA. The root mean square error between the experimental and simulated responses of biosensor for measuring α-chaconine is 1.6 µA, which corresponds to 5.33%.

5. Conclusion

As a result of numerical simulation of the functioning of the biosensor, the concentrations of the enzyme, substrate, inhibitor, product, as well as enzyme-substrate, enzyme-inhibitory and enzyme-substrate-inhibitory complexes, which change over time, are obtained to determine α-chaconine.

The results obtained from the study of the stability of the biosensor model for measurement of α-chaconine should be used for the design of new biosensors. The use of numerical simulation results will further minimize laboratory experiments with toxic and costly substances to select optimal concentrations of biosensor components to determine α-chaconine.

The model is the system of impulsive differential equations, where impulsive effects describes injection of substruct and inhibitor. Here we obtained the local stability conditions at the stage of inhibition, which were checked for the developed mathematical model of potentiometric biosensor based on butyrylcholinesterase for inhibitory determination of α -chaconine in accordance with [17, 18]. We evidenced that the nontrivial steady state is locally asymptotically stable at this stage. Stability condition is reduced to analyzing of corresponding eigenvalues. The numerical simulation results of the biosensor model of impulsive differential equations for measurement of α-chaconine should be used in research, design organizations, medical and laboratory centers in the development and testing of cyber-physical systems of medical and biological processes. In further researches for the analysis of numerical modeling intermediate results the cyber-physical system of medico-biological processes with use expert estimation [20, 21] will be developed.

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