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IDENTIFICATION OF PARAMETERS AND INVESTIGATION OF STABILITY OF THE MATHEMATICAL MODEL BIOSENSOR FOR MEASURING A-CHACONINE

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Summary. *The article is devoted to the problem of improving the existing mathematical and computational tools for obtaining and analyzing the results of numerical modeling in the design of biosensors. Parameters are identified in the work, stability is investigated and mathematical model is verified of a potentiometric biosensor based on the inverse inhibition of butyricolinesterase to determine α-chaconin is substantiated. The mathematical model of the biosensor under study is represented by a system of seven linear differential equations that describe the dynamics of biochemical reactions during a complete cycle of measurement of α-chaconine concentration. In this case, each of the differential equations describes the concentration of enzyme, substrate, inhibitor, product, enzyme-substrate, enzyme-inhibitory, enzyme-substrate-inhibitory complexes depending on time. A mathematical model of the biosensor for the determination of α-chaconine is numerically solved using Wolfram Mathematica software. The initial parameters of the system are the initial concentrations of the enzyme, substrate and inhibitor (5.8×10^{-4} M butyricholinesterase, 1×10^{-3} M butyrylcholine chloride and 1×10^{-6}; 2×10^{-6}; 5×10^{-6}; 10×10^{-6} M α-chaconine, respectively), which are experimentally calculated. An existing potentiometric biosensor based on immobilized butyrylcholinesterase was used to verify the model and compare it with the experimental response. The forward and reverse rate constants of the enzymatic reactions are chosen so that the result of the numerical simulation is as consistent as possible with the experimental response of the biosensor under study. According to the results of the comparative analysis, the dependence of the deviation of the simulated and experimental responses of the biosensor to determine α-chaconine is established. It is found that the absolute error does not exceed 0.045 conventional units. Based on the results of numerical simulation, it is concluded that the developed kinetic model of the potentiometric biosensor allows to adequately determine all the main components of the compartment components of biochemical reactions when measuring the concentration of α-chaconine*

Key words*: mathematical model, biosensor, investigation of stability, α-chaconine, numerical modeling*

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Problem statement. 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.

Analysis of known research results. In recent years, much attention has been paid to the development and use of biosensors by researchers [1–10]. In [5–10], the main tasks related to the study of stability in biosensors are formulated. Over the last fifty years, many mathematical models have been developed and applied to optimize the performance of various biosensors [11–13]. In [14, 15], 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 [16]. In these models, the homotopy perturbation method is used to solve the system of equations under stationary conditions. [17, 18] presented mathematical

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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 [19, 20]. To a greater extent, such biosensors are used in environmental monitoring for the detection of toxic substances such as pesticides, heavy metal ions, aflatoxins [21, 22]. 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 [23]. 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 [24].

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 [25].

The goal of the work. The goal of the work is to ground, investigation of stability and verification of the mathematical model of the potentiometric biosensor for determination of α-chaconine.

Setting objectives. 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.

Results of the research.

Mathematical model of a potentiometric biosensor for determine α-chaconin.

For numerical simulation of mathematical model in the work we used previously developed biosensor for measurement of α-chaconine [24].

As the bioselective element of the biosensor used the enzyme butyrylcholinesterase (BuChE). In a real experiment, 10^{-3} M 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.

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

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

Using the literature data [24] 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 Figure 1.

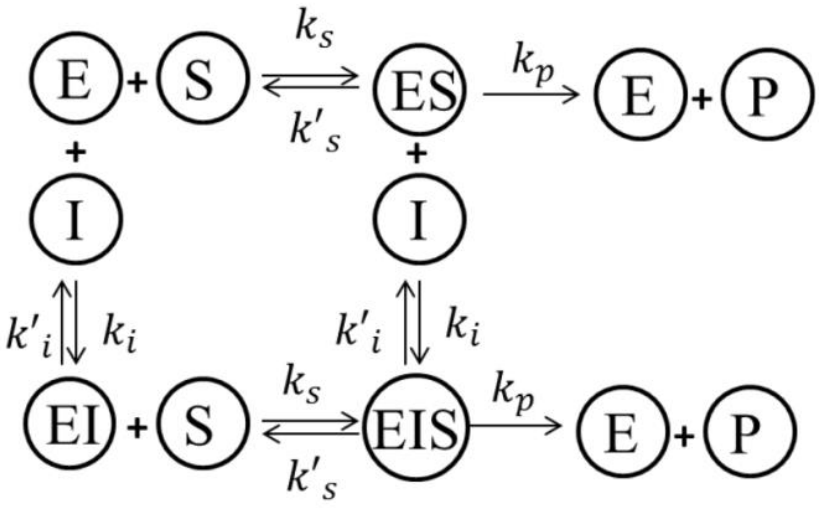

Figure 1. Schematic representation of the enzymatic reaction in a potentiometric biosensor based on BuChE-ISFET in the inhibitory measurement of α-chaconine (E – enzyme, S – substrate, I – inhibitor)

In Figure 1 k_s and k'_s – the constants of the rate of forward and reverse reaction of the formation of the complex (ES), k_p – the constant of the rate υ_p of formation of the product (P), k_i and k'_i – the rate constants of the direct and reverse reaction of the formation of the complex (EI).

Mathematical model of a potentiometric biosensor based on the inverse inhibition of butyricolinesterase to determine α-chaconin 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 – the corresponding rate constants of the reactions of complex formation; k_w – washout constant; α – a constant whose numerical value determines the inhibition or activation of the enzyme; $n_e(t)$, $n_s(t)$, $n_i(t)$, $n_p(t)$, $n_{es}(t)$, $n_{ei}(t)$, $n_{esi}(t)$ – 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 equations (1–7) describe the biochemical reactions taking place for concentrations of enzyme, substrate, inhibitor, product, enzyme-substrate, enzyme-inhibitory and enzyme-substrate-inhibitory. The first equation is considered for enzyme concentration $n_e(t)$. The first term on the right-hand side, $-k_s n_e(t) n_s(t)$, represents change of enzyme concentration $n_e(t)$ due to the reaction $\mathrm{E} + \mathrm{S} \rightarrow \mathrm{ES}$ going with a rate of k_s. The rate of this reaction is proportional to the enzyme concentration $n_e(t)$ and to the substrate concentration $n_s(t)$. The negative sign in this differential equation means that the process of ES formation results a decrease in the concentration of the enzyme $n_e(t)$.

The next term, $-k_i n_e(t) n_i(t)$, similarly to the first term, accounts for the reaction $\mathrm{E} + \mathrm{I} \rightarrow \mathrm{EI}$. The formation rate of EI complexes is proportional to the concentration of free (available) enzymes ne(t) and available inhibitors ni(t), and it leads to a decrease of ne(t), so it goes in negative. Dissociation of ES and EI molecules increases concentration of enzymes. It is taken into account by adding terms $+k_s' n_{es}(t)$ and $+k_i' n_{ei}(t)$. Formation of product also releases enzyme molecules as $+k_p n_{es}(t)$. All the other equations (2–7) are composed according to the following reactions in Figure 1.

Investigation of Steady States of the Biosensor Model.

Steady states of the system (1–7) can be found as a solution of the algebraic system:

$$-k_s n_e^* n_s^* - k_i n_e^* n_i^* + k_s' n_{es}^* + k_i' n_{ei}^* + k_p n_{es}^* = 0 \quad (8)$$

$$-k_s n_e^* n_s^* - \alpha k_s n_{ei}^* n_s^* + k_s' n_{es}^* + \alpha k_s' n_{esi}^* = 0 \quad (9)$$

$$k_s n_e^* n_s^* - k_s' n_{es}^* - \alpha k_i n_{es}^* n_i^* + \alpha k_i' n_{esi}^* - k_p n_{es}^* = 0 \quad (10)$$

$$-k_i n_e^* n_i^* - \alpha k_i n_{es}^* n_i^* + k_i' n_{ei}^* + \alpha k_i' n_{esi}^* = 0 \quad (11)$$

$$k_i n_e^* n_i^* - k_i' n_{ei}^* - \alpha k_s n_{ei}^* n_s^* + \alpha k_s' n_{esi}^* = 0 \quad (12)$$

$$\alpha k_i n_{es}^* n_i^* - \alpha k_i' n_{esi}^* + \alpha k_s n_{ei}^* n_s^* - \alpha k_s' n_{esi}^* = 0 \tag{13}$$

$$k_p n_{es}^* - k_w n_p^* = 0 \tag{14}$$

Clearly, the system (8–14) has trivial solution $(0, 0, 0, 0, 0, 0, 0)^{\mathrm{T}}$. Nontrivial solutions $n^* \equiv (n_e^*, n_s^*, n_{es}^*, n_i^*, n_{ei}^*, n_{esi}^*, n_p^*)^{\mathrm{T}}$ can be calculated numerically.

Input parameters of the model (1–7), which were used in the experiment, are presented in the form of Table 1.

Table 1

Input parameters of the model biosensor for the measurement of α-chaconine

Model parameters	Numerical value	Unit of measurement
k_s	1670	L/(mol*s)
k_i	167000	L/(mol*s)
k_s'	0.4	1/s
k_i'	0.0003	1/s
k_p	0.0008	1/s
k_w	0.02	1/s
α	0.2	-
$n_e(0)$	$5.8*10^{-6}$	mol/L
$n_s(0)$	0.001	mol/L
$n_i(0)$	$4*10^{-6}$	mol/L

For the parameter values of Table 1 we get the steady n^* 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

Model parameters	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 fulfilled based on the linear model

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

where $J(x(t))$ is the Jacobian of the system (1)–(7). Namely,

$$J(n(t)) = \begin{bmatrix} -k_s n_s(t) - k_i n_i(t) & -k_s n_e(t) & k_s' + k_p & -k_i n_e(t) & k_i' & 0 & 0 \\ -k_s n_s(t) & -k_s n_e(t) - ak_s n_{ei}(t) & k_s' & 0 & -ak_s n_s(t) & ak_s' & 0 \\ k_s n_s(t) & k_s n_e(t) & -k_s' - ak_i n_i(t) - k_p & ak_i n_{es}(t) & 0 & ak_i' & 0 \\ -k_i n_i(t) & 0 & -ak_i n_i(t) & -k_i n_e(t) - ak_i n_{es}(t) & k_i' & ak_i' & 0 \\ k_i n_i(t) & -ak_s n_{ei}(t) & 0 & k_i n_e(t) & -k_i' - ak_s n_s(t) & ak_s' & 0 \\ 0 & ak_s n_{ei}(t) & ak_i n_i(t) & ak_i n_{es}(t) & ak_s n_s(t) & -ak_i' - ak_s' & 0 \\ 0 & 0 & k_p & 0 & 0 & 0 & -k_w \end{bmatrix}$$

For the parameter values in Table 1 we get

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

Hence, we get all eigenvalues of $J(n(t))\big|_{n(t)\equiv n^*}$ with negative real part, namely: $\lambda_1 = -1.759682e+02$, $\lambda_2 = -3.517811e+01$, $\lambda_3 = -1.420000e-01$, $\lambda_4 = -1.116629e-01$, $\lambda_5 = -9.815916e-04$, $\lambda_6 = -3.437626e-05$, $\lambda_7 = -3.865944e-15$.

Hence, using Hartman-Grobman theorem [26], we can conclude that the steady state n^* of the system (1)–(7) at parameter values from Table 1 is locally asymptotically stable.

Numeric modeling of mathematical model of biosensor for measurement of α-chakonin.

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 Figure 2.

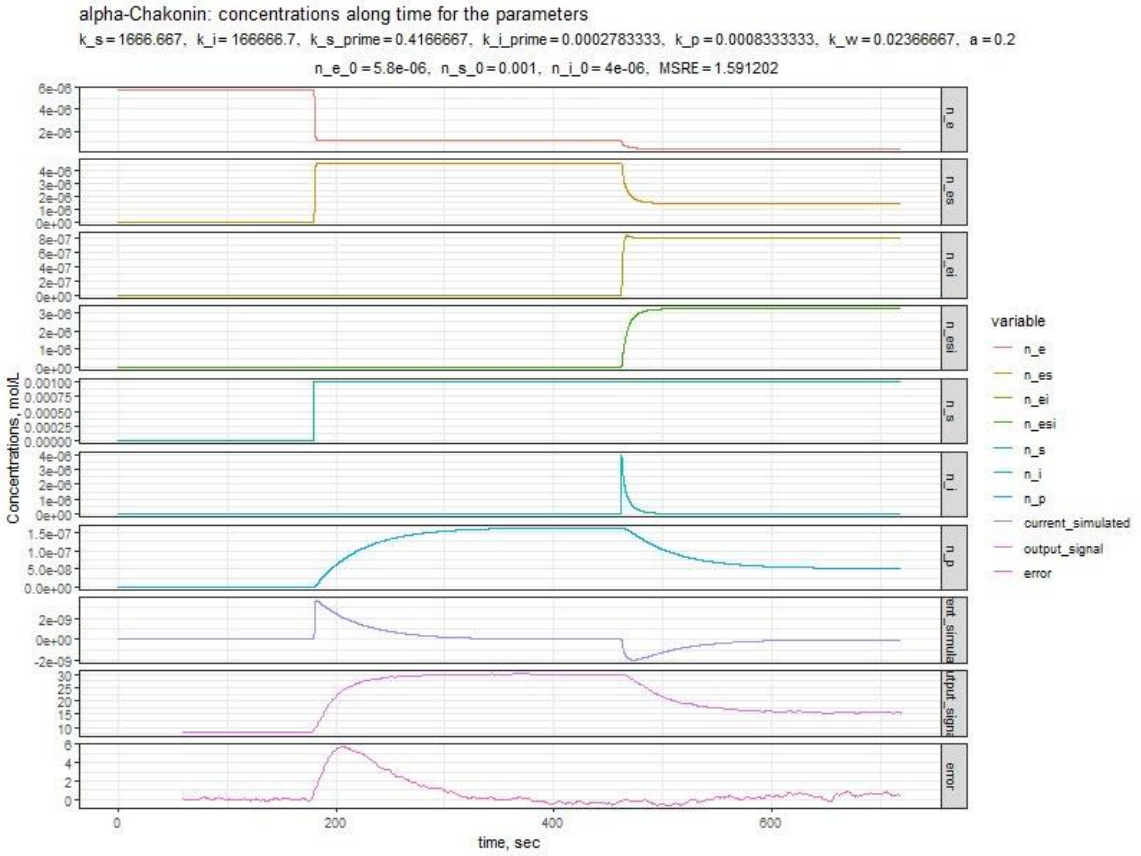

Figure 2. Numerical simulationof the enzymatic reaction in the BuCHE-ISFET membrane of the biosensor using kinetic equations (1–7) and the parameters presented in table 1 (n_e, n_es, n_ei, n_esi, n_s, n_i, n_p – concentrations of enzyme, enzyme-substrate, enzyme-inhibitory, enzyme-substrate-inhibitory complexes, substrate, inhibitor, product, which change over time)

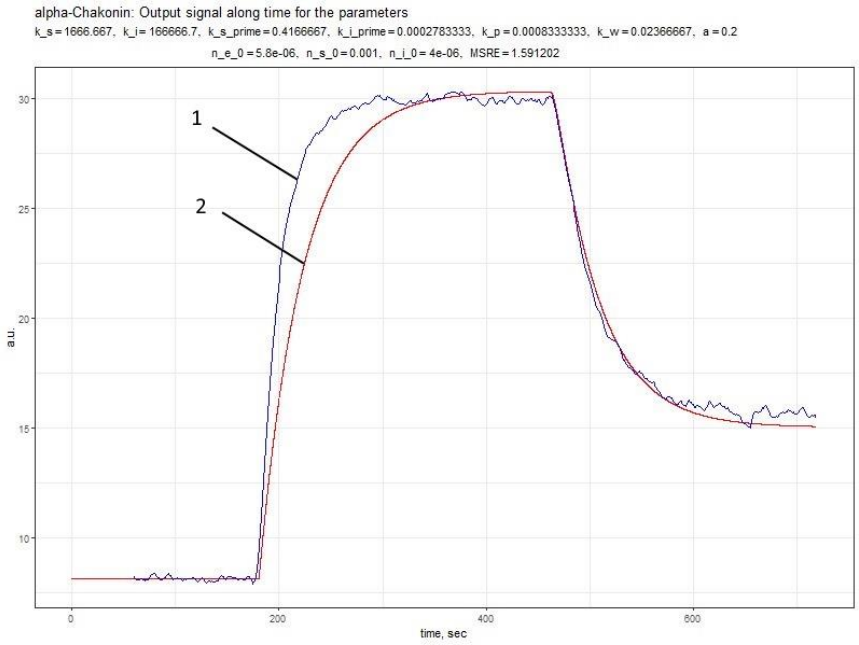

Figure 3. BuCHE-ISFET biosensor response: 1 – experimental; 2 – numerical simulation of the system (1–7)

The squared error between experimental and simulated responses (Figure 3) of biosensor for measurement of α-chaconine is 1.6 a.u.

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.

The response to the inhibitor is simulated by substituting the previous solutions and the concentration of the inhibitor known under the conditions of the experiment (Figure 4).

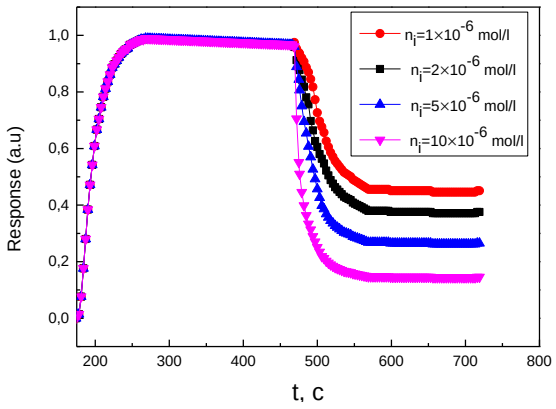

Figure 4. Numerical simulation of the response of the biosensor at different values of the concentration of inhibitor

In Figure 4 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-chaconin. Analyzing the results of numerical simulation obtained in Figure 4 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.

Conclusions. 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 parameters of the model of the investigation biosensor are identified in the paper. The stability is investigated and mathematical model is verified of a potentiometric biosensor based on the inverse inhibition of butyricolinesterase to determine α-chaconin is substantiated. 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. Numerical simulation was performed at initial concentrations of enzyme, substrate and inhibitor used in the experimental studies in the package R. The physical content of the constants of the rate of formation of complexes was studied, on the basis of which the corresponding constants were selected so that the simulated response coincided as much as possible with the experimental response of the biosensor. The selected constants were used to model the responses of the biosensor to the addition of substrates and inhibitors. The results of numerical simulation are especially relevant when developing new biosensors and when dealing with toxic substance.

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ІДЕНТИФІКАЦІЯ ПАРАМЕТРІВ ТА ДОСЛІДЖЕННЯ СТІЙКОСТІ МАТЕМАТИЧНОЇ МОДЕЛІ БІОСЕНСОРУ ДЛЯ ВИЗНАЧЕННЯ α-ЧАКОНІНУ

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Резюме. *Присвячено проблемі вдосконалення існуючих математичних і обчислювальних засобів для отримання та аналізу результатів чисельного моделювання при проектуванні біосенсорів. Ідентифіковано параметри, досліджено стійкість та проведено верифікацію математичної моделі потенціометричного біосенсору на основі зворотного інгібування бутирихолінестерази для визначення α-чаконіну. Математична модель досліджуваного біосенсору представлена системою семи лінійних диференціальних рівнянь, які описують динаміку біохімічних реакцій під час повного циклу вимірювання концентрації α-чаконіну. При цьому кожне із диференціальних рівнянь описує концентрації ферменту, субстрату, інгібітора, продукту, фермент-субстратного, фермент-інгібіторного, фермент-субстрат-інгібіторного комплексів залежно від часу. Математична модель біосенсора для визначення α-чаконіну розв'язана чисельно за допомогою пакета R. Вхідними параметрами системи є початкові концентрації ферменту, субстрату та інгібітора (5,8×10^{-4} М бутирихолінестерази, 1×10^{-3} М бутирихолін хлориду та 1×10^{-6}; 2×10^{-6}; 5×10^{-6}; 10×10^{-6} М α-чаконіну відповідно), які експериментально розраховані. Для верифікації моделі та порівняння з експериментальним відгуком використано існуючий потенціометричний біосенсор на основі іммобілізованої бутирихолінестерази. Прямі та зворотні константи швидкостей ферментативних реакцій підібрані таким чином, щоб результат чисельного моделювання максимально відповідав експериментальному відгуку досліджуваного біосенсора. За результатами порівняльного аналізу встановлено залежність відхилення змодельованого та експериментального відгуків біосенсора для визначення α-чаконіну. Встановлено, що абсолютна похибка не перевищує 0,045 ум.од. На основі отриманих результатів чисельного моделювання зроблено висновок, що розроблена кінетична модель потенціометричного біосенсора дає змогу адекватно визначати усі основні складові компартментних компонент біохімічних реакцій при вимірюванні концентрації α-чаконіну.*

Ключові слова: *математична модель, біосенсор, дослідження стійкості α-чаконін, чисельне моделювання.*

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