Mathematical and Computer Simulation of the Response of a Potentiometric Biosensor for the Determination of α-chaconine

Vasyl Martsenyuk[a], Oksana Bahrii-Zaiats[b] , Andriy Sverstiuk[b] , Sergei Dzyadevych[c], Borys Shelestovskyi [d]

[a] *University of Bielsko-Biala, Willowa St. 2, Bielsko-Biala, 43-300, Poland*
[b] *I. Horbachevsky Ternopil National Medical University, 12 Rus'ka St., Ternopil, 46001, Ukraine*
[c] *Institute of Molecular Biology and Genetics National Academy of Sciences of Ukraine, Kyiv, Ukraine*
[d] *Ternopil Ivan Puluj National Technical University, Ternopil, Ukraine*

Abstract

The article is devoted to the problem of developing a mathematical model of the response of a potentiometric biosensor for the determination of α-chaconine in the form of a system of seven differential equations that describe the dynamics of biochemical reactions during the full cycle of α-chaconine concentration measurement. At the same time, each of the differential equations establishes the concentration dependence of substrate, enzyme, inhibitor, enzyme-substrate, product, enzyme-inhibitor, enzyme-substrate-inhibitor complexes as a function of time. The mathematical model of the biosensor for the determination of α-chaconine was solved numerically in the R package. The input parameters of the system were used, namely, the concentrations of the enzyme, substrate, and inhibitor (5.8×10^{-4} M butyrylcholinesterase, 1×10^{-3} M butyrylcholine chloride, and 1×10^{-6}; 2×10^{-6}; 5×10^{-6}; 10×10^{-6} M of α-chaconine, respectively), which are measured during experiments. To verify the model and compare it with the experimental response a potentiometric biosensor based on immobilized butyrylcholine chloride was used. Selection of direct and inverse rate constants of enzymatic reactions was carried out in such a way that the result of numerical modeling corresponded as much as possible to the experimental response of the studied biosensor. A comparative analysis of the experimental and simulated responses of the biosensor for the determination of α-chaconine was established. It was found that the absolute error does not exceed 0.045 units. As a result of computer simullation, it was concluded that the developed kinetic model of the potentiometric biosensor makes it possible to identify all the main components that were measured this study.

Keywords 1

Mathematical model, biosensor, α-chaconine, butyrylcholinesterase, inhibitory analysis, enzymatic kinetics, numerical modeling

1. Introduction

The development of science and technology requires the emergence of new detection methods. Therefore, interest in biosensors is growing in science and industry. Biosensors are an alternative to commonly used methods, which are characterized by poor selectivity, high cost, poor stability, low response and can mostly be used only by highly experienced personnel. Biosensors are a new generation of sensors that use biological materials in their design, which provide high selectivity, selectivity, accuracy, and enable quick and simple measurements [1, 2]. Biosensors are characterized by high efficiency and are widely used in the food industry [3, 4, 5], in environmental protection [6], in the defense industry [7], but are most often used in medicine as a tool for making diagnoses: to control the

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EMAIL: vmartsenyuk@ath.bielsko.pl (A. 1); bagrijzayats@tdmu.edu.ua (A. 2) sverstyuk@tdmu.edu.ua (A. 3); dzyad@yahoo.com (A. 4); kaf_vm@tu.edu.te.ua (A.5)
ORCID: 0000-0001-5622-1038 (A. 1); 0000-0002-5533-3561 (A. 2); 0000-0001-8644-0776 (A. 3); 0000-0003-2915-716X (A. 4); 0000-0002-5606-6290 (A. 5)

level of glucose [8, 9], the level of hemoglobin [10], detection of oncological diseases [11, 12], pathogenic bacteria [13]. In general, the family of biosensors is divided into two parts. The first is related to the level of the receptor for the biological material used in its structure. Receptors can be enzyme, protein, porphyrin, antigen or antibody. The second part of biosensors is limited to the conductor layer, where the biological effect is transformed into a measurement signal, which can be electrochemical [14, 15], piezoelectric [16, 17], amperometric [18], impedancemetric [19], optical [20] and others.

It is known that the theory of differential equations is one of the most powerful tools for learning about the world around us. The use of mathematical modeling based on differential equations can be a useful tool for a better understanding of biochemical processes and the widespread use of optimization of analytical characteristics of biosensors. Starting from the seventies and up to today, various mathematical and computer models have been developed and effectively improved to optimize the operation of biosensors [21-23].

In the last ten years, mathematical models for an amperometric electrode with an immobilized enzyme based on Michaelis-Menten kinetics using nonlinear differential equations and diffusion [24, 25]. Particulary for potentiometric and amperometric biosensors a mathematical models [26] have been used. In these models, the method of homotopy perturbations is used to solve the system of equations under conditions of stationarity. Mathematical models of amperometric biosensors are described in works [27, 28], in which, by changing the input parameters (such as the concentration of reagents, kinetic constants, and membrane thickness), the sensitivity of the developed biosensors is improved. In these models, the finite difference method was used to solve the system of equations under stationary and non-stationary conditions. For direct determination of the substrate during development of enzyme biosensors, most of the considered mathematical models are used. In recent decades there has been paid more attention to development of biosensors based on the direct and reverse inhibitory process [29, 30]. The most common field of use of such biosensors is environmental monitoring, as example for measuring toxic substances such as heavy metal ions, pesticides, aflatoxins, etc. [31, 32]. Nowadays a very small number of mathematical models of the operation of biosensors of this type have been developed. A mathematical model of the operation of the glucose oxidase biosensor for the determination of mercury ions can be distinguished from them [33]. In this model, the system of equations describing enzymatic nonlinear reactions based on Michaelis-Menten kinetics and diffusion is modified taking into account irreversible inhibition.

This article is devoted to the investigation of a mathematical model of butyrylcholinesterase biosensor based on ion-selective field-effect transistors (ISFET) for the inhibitory determination of α-chaconine [34]. The question is extremely relevant, given that α-chaconine is a very interesting object from a biological point of view due to its toxicity and the determination of its concentration in potatoes, as a food product, due to which potatoes acquire a bitter taste. Measurement of the content of α-chaconine in potatoes is carried out when new varieties with reduced content are bred. In recent years, scientific research has been conducted, based on the results of which it can be concluded that the mechanisms of resistance of potatoes to diseases and the effects of insects depend on the level of α-chaconine. Among other factors that affect the level of α-chaconine and can cause a significant increase in its initial concentration, it should be noted climatic changes, the effect of light, mechanical damage during harvesting and storage of potatoes [35]. The currently developed methods for determining the total content of α-chaconine are based on the use of colorimetry, high-performance liquid chromatography, thin-layer and gas chromatography, and radioimmunological analysis. The listed methods are characterized by high cost, long duration and complexity of sample preparation methods. In order to optimize and modify the existing methods of analyzing harmful substances in potatoes, it is advisable to create simple, cheap, highly sensitive methods for determining α-chaconine based on biosensors. At the same time, in order to save time and raw materials (enzymes, substrates, and inhibitors), it is expedient and economically beneficial to create and research adequate mathematical models of biosensors for the determination of α-chaconine with the possibility of verifying the simulated response, as well as estimating the amount of error relative to experimental data.

The use of mathematical modeling to optimize the analytical characteristics of the biosensor for the determination of α-chaconine will allow to minimize laboratory experiments with toxic and expensive substances in order to select optimal concentrations of components.

2. Materials and methods

2.1. Potentiometric biosensor based on butyrylcholinesterase

For the production of a bioselective membrane, the enzyme butyrylcholinesterase (BuChE) of horse blood serum with an activity of 13 units act/mg of Sigma-Aldrich Chemie (Germany), bovine serum albumin (BSA, fraction V) (Sigma-Aldrich Chemie, Germany), 50% aqueous solution of glutaraldehyde (HA) ("n.d.a."Sigma- Aldrich Chemie, Germany), glycerol (purity 99%, Sigma-Aldrich Chemie, Germany) were used.

Butyrylcholine chloride (BuChCl, purity 99%) from Sigma-Aldrich Chemie (Germany) was used as a substrate. Crystalline glycoalkaloid α-chaconine (95% pure), manufactured by Sigma-Aldrich Chemie GmbH (Steinheim, Germany), was used as an inhibitor.

The phosphate buffer was made from potassium dihydrogen orthophosphate (KH_2PO_4) (purity 98.5%, Helicon) and sodium hydroxide (NaOH) (purity 99%, Helicon).

Potentiometric transducers were produced at the V. E. Lashkaryov Institute of Semiconductor Physics NAS of Ukraine. The sensor consists of two identical pairs of p-channel type transistors (SiO_2/Si_3N_4-ISFETs), located on a monocrystalline silicon substrate with a total area of 8×8 mm. One transistor is the working electrode, and the other is used as the reference electrode. The sensor elements used in the work showed a pH sensitivity of approximately 40 mV/pH, thereby providing a pH sensitivity of the current in the transistor channel of approximately 15-20 μA/pH. The threshold voltage of the pH-PT was about 2.5 V. The measurements were carried out with an initial value of the current in the channel of about 500 μA, the drain-to-drain voltage was about 2 V.

Measurements were carried out using a portable device developed and manufactured at the V. E. Lashkaryov Institute of Semiconductor Physics NAS of Ukraine. The device works by measuring the surface potential on the gate of the transistor using a measuring circuit with negative feedback, which maintains a constant magnitude of the current in the field-effect transistor channel of 0.3 mA at a constant drain-to-drain voltage of about 2 V. The output signal corresponds to the gate potential. The information from the sensors is imported into the computer and processed using the MSW_32 software (V.Y. Lashkarev Institute of Semiconductor Physics of the NAS of Ukraine).

Potentiometric measurements were carried out after placing the transducers in a measuring cell filled with 5 mM phosphate buffer, pH 7.0. The solution was constantly stirred. All experiments were performed in two or three series of repetitions. Nonspecific changes in the output signal associated with fluctuations in temperature, pH of the environment and other factors were eliminated by using the differential measurement mode.

After stabilization of the differential output signal, a certain aliquot of a concentrated solution of the substrate was added to the measuring cell, and after stabilization of the response to the substrate, the necessary volumes of concentrated solutions of α-chaconine were introduced and the level of inhibition was measured.

A pair of identical p-type ion-selective field-effect transistors with a sensitivity of 35-40 μA/pH, which are placed on one crystal, were used as potentiometric converters.

2.2. Mathematical modeling of a biosensor for the determination of α-chaconine

The system of differential equations, which describes the mathematical model of the functioning of the developed biosensor for the determination of α-chaconine, was solved numerically using the software Wolfram Mathematica 10. Model responses of the biosensor were also built in this program, which were compared with experimental data.

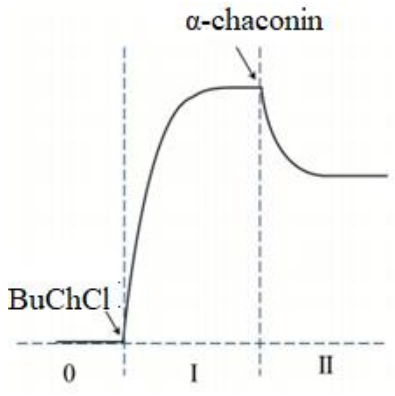
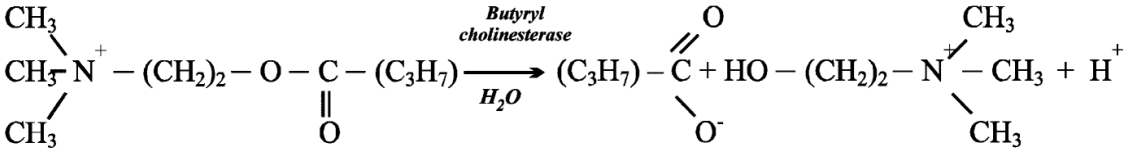


Figure 1: Schematic representation of the operation of the BuChCl biosensor based on ISFET in the inhibitory determination of α-chaconine

When α-chaconine is determined as inhibitory by means of a BuChE biosensor based on ion-selective field-effect transistors, the functioning of the biosensor can be conventionally divided into the following stages (Fig. 1): obtaining a baseline (0), response to the working concentration of BuChCl as a substrate (I), and response to α-chaconine as an inhibitor (II).

The functioning of the BuChE biosensor is based on an enzymatic reaction that takes place in a bioselective membrane and can be presented in the following form. The basis of the work of biosensors based on butyrylcholinesterase is the following enzymatic reaction:



During the chemical reaction, protons are generated, which leads to a change in the pH inside the membrane, so it is advisable to use a potentiometric biosensor based on pH-sensitive field-effect transistors.

At the zero stage, when the bioselective membrane is in contact only with the working buffer, no reactions occur in the membrane, and the biosensor signal reflects the "baseline" (Fig. 1, stage 0). At the first stage, an enzymatic reaction takes place with the participation of the substrate, which is added to the working cell. As a result of this reaction, a product (proton) is formed, as a result of which the local concentration of ions in the near-electrode region changes, which is registered by a potentiometric transducer. This change is visualized in the form of a response to the substrate (Fig. 1, stage I). At the second stage of the biosensor operation, when α-chaconine, which is a reverse BuChE inhibitor, is added to the measuring cell, an enzyme inhibition reaction occurs. According to literature data [35], the mechanism of BuChE inhibition by α-chaconine belongs to the mixed type of inhibition, which can be schematically depicted in Fig. 2:

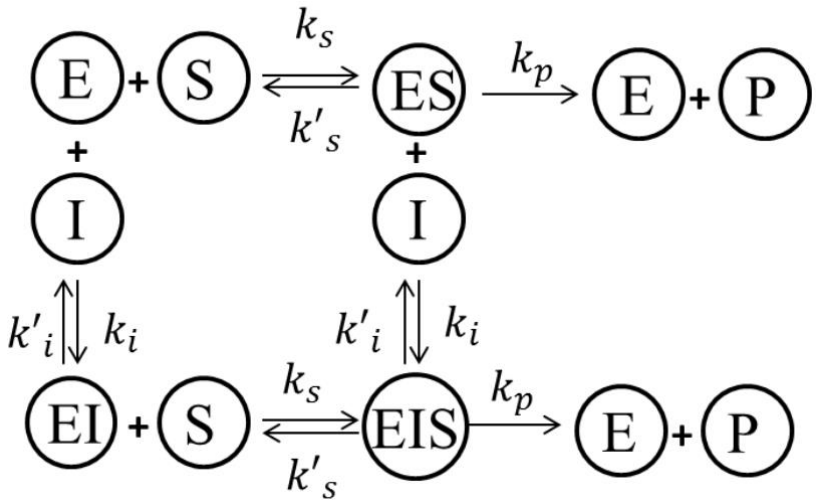


Figure 2: Reaction scheme for the inhibitory determination of α-chaconine based on the enzymatic reaction in a potentiometric biosensor (E – enzyme, I – inhibitor, S – substrate)

In Fig. 2 k_s and k_s' are the rate constants of the direct and reverse reaction of complex formation (ES), k_p is the rate constant υ_p of product formation (P), k_i and k_i' are the rate constants of the direct and reverse reaction of complex formation (EI).

For a potentiometric biosensor based on BuChE-ISFET the mathematical model of the enzymatic reaction in in the inhibitory determination of α-chaconine 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' are the corresponding reaction rate constants for the formation of complexes; k_w – leaching constant; α – constant, the numerical value of which determines enzyme inhibition or activation; $n_e(t)$, $n_s(t)$, $n_i(t)$, $n_p(t)$, $n_{es}(t)$, $n_{ei}(t)$, $n_{esi}(t)$ – respectively concentrations of enzyme, substrate, inhibitor, product, as well as enzyme-substrate, enzyme-inhibitor and enzyme-substrate-inhibitor complexes, respectively, which change over time. The change in product concentration over time $n_p(t)$is directly proportional to the response of the biosensor.

It is also taken into account that the system maintains a constant total concentration of the enzyme E_0, so at any moment in time the sum of the concentrations of free (E) and bound $(ES), (EI), (ESI)$ enzyme is equal to $(E) + (ES) + (EI) + (ESI) = 0$.

3. Results and discussion

According to the results of the experiment, the response of the biosensor for the determination of α-chaconine was obtained, which is shown in Fig. 3. This experimental response was obtained at concentrations of enzyme 5.8×10^{-4} mol/l, substrate 1×10^{-3} mol/l, inhibitor 10×10^{-6} mol/l.

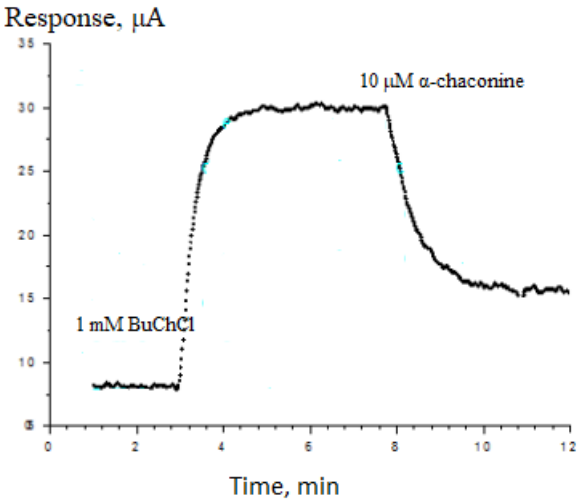


Figure 3: Experimental response of a potentiometric biosensor for the determination of α-chaconine

To simulate the operation of the biosensor, system (1-7) was solved using the Wolfram Mathematica software and the built-in NDSolve algorithm.

Important input parameters for modeling the biosensor's operation are the concentration of the substrate, inhibitor, and enzyme in the bioselective membrane of the biosensor. These initial concentrations are obtained from experimental data (Table 1). In the real experiment, $1x10^{-3}$ M butyricholin chloride (BuChCl) was used as the working concentration of the substrate. The model concentrations of the inhibitor - α-chaconine were 1×10^{-6} M, 2×10^{-6} M, 5×10^{-6} M, 10×10^{-6} M. The concentration of the enzyme butyrylcholinesterase (BuChE) in the bioselective membrane of the biosensor was also estimated. The volume of one biosensor membrane is approximately 0.05 μl, which corresponds to 0.05 mg. Taking into account the fact that the membrane contains 5% BuChE, it is possible to calculate the mass of the enzyme in the membrane, which was 2.5×10^{-6} g. The molar mass of BuChE was 85 kDa, or 85×10^{3} g/mol (1 Da = 1 g/mol). Knowing the mass and molar mass of the enzyme, the amount of enzyme substance is calculated, which is 2.9×10^{-11} mol. If this value is divided by the known volume of the membrane, the molar concentration is obtained, which is used for modeling. Thus, the approximate molar concentration of the enzyme in the membrane is about 5.8×10^{-4} M.

At the zero stage of modeling, the following initial conditions are set, that is, when there is no substrate and inhibitor in the system, but only the initial concentration of the enzyme is introduced in the working membrane of the biosensor. Given the given initial conditions and given parameters, there are solutions of the system.

At the first stage, the system is solved under the initial conditions $n_s(0) = n_i(0) = n_{es}(0) = n_{ei}(0) = n_{esi}(0) = n_p(0) = 0$, which are given by the solutions of the zero-stage system, and the initial concentration of the substrate added to the working cell is also set.

At the second stage, the response to the inhibitor is simulated, by substituting the previous solutions and the initial concentrations of the inhibitor 1×10^{-6} mol/l, 2×10^{-6} mol/l, 5×10^{-6} mol/l, 10×10^{-6} mol/l, which are known according to the experimental conditions.

Table 1 shows the parameters of the mathematical model of the biosensor for the of α-chaconine, which were used in numerical modeling using the system of differential equations (1-7).

Table 1
Parameters of the mathematical model as a result of experiment for the measurement of α-chaconine, which were used for its numerical simulation

Designation	Numerical values	Units of measurement
n_e	$5{,}8\times10^{-4}$	mol/l
n_s	1×10^{-3}	mol/l
n_{i_1}	1×10^{-6}	mol/l
n_{i_2}	2×10^{-6}	mol/l
n_{i_3}	5×10^{-6}	mol/l
n_{i_4}	10×10^{-6}	mol/l
k_s	600	l/(mol*s)
k_i	1.3×10^{2}	l/(mol*s)
k_s'	20.23	1/s
k_i'	0.0167	1/s
k_p	0.05	1/s
k_w	0.168	1/s
α	0.3	-

The results of numerical modeling of the response of the biosensor for the determination of α-chaconine based on the parameters of Table 1 at different concentrations of the inhibitor are shown in Figure 4.

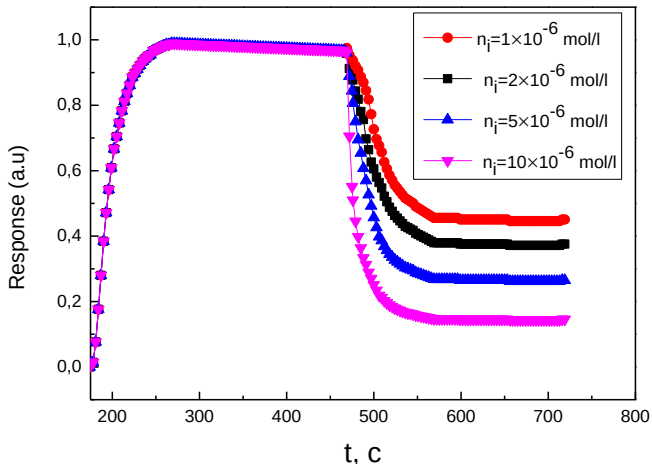


Figure 4: Results of numerical modeling of biosensor response for determination of α-chaconine

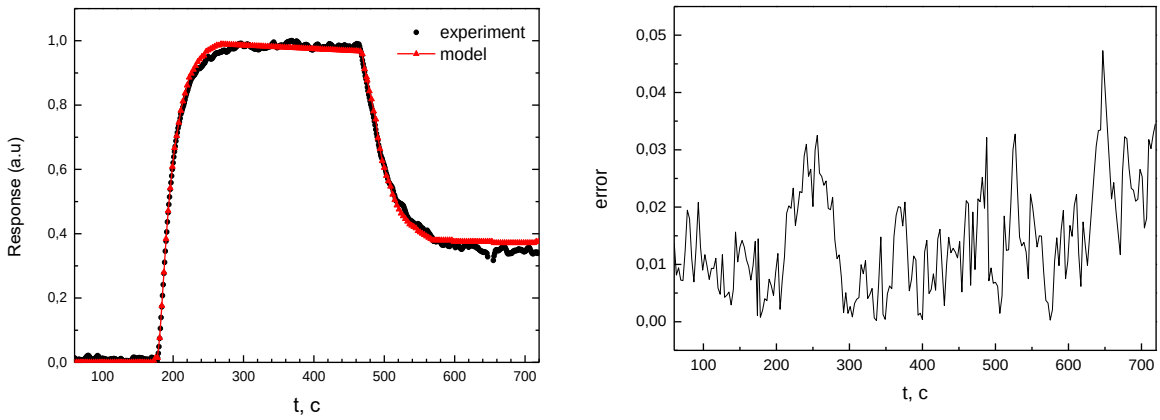
Analyzing the numerical simulation results obtained in Figure 4, it can be concluded that the higher the concentration of the inhibitor, the smaller the response amplitude of the biosensor model under study. The simulated reactions of the biosensor at different concentrations of the inhibitor fully correspond to the principle of inhibition.

4. Study of system input parameters

Biochemical reaction rate constants k are difficult to obtain directly from experiment. In this study, these constants were selected in such a way that the model response coincided with the experimental responses. It was established that the stable operation of the biosensor (given the concentration of the

enzyme, substrate and inhibitor) is achieved with a limited balance between the parameters k. In our case, the interaction of the inhibitor with the enzyme is stronger than the interaction of the substrate with the enzyme by approximately 100 times ($k_i = 100k_s$). The rate of dissociation of complexes (EI) and (ES) is much lower than the rate of their formation ($k_i' = 10^{-4}k_i,\ k_s' = 0.01k_s$).

According to the results of a detailed study of the input parameters of the system, their selection was carried out in such a way that the simulated response of the studied biosensor coincided with the experimental one as much as possible. The numerical values of such modeling are shown in Table 1, and the result of verification of the mathematical model of the biosensor for determining α-chaconine and the modeling error is shown in Figure 5.



a) b)

Figure 5: The result of comparing the simulated and experimental responses of the biosensor for the determination of α-chaconine (a) and the absolute error of the simulation (b)

The maximum verification error is manifested in the area of stabilization of the response of the biosensor to the action of the inhibitor and does not exceed 0.045 con. units.

5. Conclusions

A mathematical model of the potentiometric biosensor based on butyrylcholinesterase for the inhibitory determination of α-chaconine was developed. Analytical aspects of inhibition of immobilized butyrylcholinesterase by α-chaconine were established. Using the new approach "method of the degree of inhibition", the type of inhibition of the immobilized enzyme was experimentally established in the analysis of α-chaconine. The created model describes the biochemical reactions occurring in the biosensor membrane during α-chaconine measurement in the form of a system of differential levels. Numerical calculations was done in1×10^{-6} Wolfram Mathematica software. The boundary conditions were the viscous initial concentrations of the enzyme, substrate, and inhibitor used in the experiment. The physical content of the complex formation rate constants was studied, basing on this, the most appropriate constants were selected in such a way that the simulated response coincided with the experimental examination of the biosensor. Based on the results of numerical modeling, the constant response of the biosensor for the determination of α-chaconine was selected. The obtained results of numerical modeling are especially relevant in the development of new biosensors and when working with toxic substances. In further research, it is necessary to investigate the states of equilibrium and stability [36, 37, 38] of the developed mathematical model of the potentiometric biosensor based on butyrylcholinesterase for the inhibitory determination of α-chaconine, to develop software complex of the mathematical model of biosensor [39, 40] and design of cyber-physical systems for medical and biological process [41, 42, 43], taking into account intelligent big data system based on scientific machine learning [44]. Applying the results of previous works, the use is particularly promising array-based sensors take advantage of the integration of multiple recognition elements on a single microdetector [45]. Biosensor-based intelligence will play more important role in the construction of microbial cell factory [46].

6. Aknowledgements

The work was performed and supported by Erasmus+ Project No. 2022-1-PL01-KA220-HED-000088359 entitled by "The Future is in Applied Artificial Intelligence" (FAAI) [47], which aims to join together HEIs and businesses. In this context, this project has to bridge the current artificial intelligence (AI) skills gap, build an AAI ecosystem of key partners, promote AI business opportunities, support the creation of internship programs in AI. The FAAI project activities are focusing on HEI trainers, undergraduate and postgraduate students, and business managers. Furthermore, the project is promoting among business and young people the enormous opportunities provided by AI to build the ecosphere of modern society. The given work results are within the framework of the FAAI work package 2 entitled by "Good practices in the use of Artificial Intelligence and Machine Learning" and are presenting real cases that are offered for studying of applied AI.

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