Sensitivity Analysis of Enzyme-Substrate-Inhibitor Interaction Based on Nonlinear Dynamic Model

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Abstract: The development of electrochemical biosensors is cutting-edge in current research in medicine, biology, and ecology. The modeling and study of the enzyme-substrate-inhibitor interaction are required for biosensor design. The aim of the paper is to construct a three-stage model for an electrochemical biosensor and to perform its sensitivity analysis. The research is based on the Morris method. The main results are concerning the comparative impact of the model parameters related to biochemical reaction rates on the dynamics of the changes of the concentrations of enzyme, substrate, inhibitor, three complexes, and the reaction product throughout three stages. The results have both theoretical and practical relevance as the model parameters studied come from a real case study of biosensors for alpha-chaconine.

1 INTRODUCTION

Sensitivity analysis meaning the study of the effects of different parameters on outputs plays an important role in system research. Such impacts are studied based on both experimental and simulated data. Mathematically it can be described as the importance of factors in nonlinear relations. The complexity of the sensitivity analysis is essentially growing for the systems incorporating spatial and temporal relations.

Morris sensitivity was formulated in [1] at first. In [2] the method was extended by selecting a subset of trajectories from a large set, to maximize their spread and may the factors to deviate greatly. The work [3] generalizes Morris method for the dependent inputs.

Till now Morris analysis leaves a popular tool for the purpose of qualitative research of the systems. The comparison of Morris with the Sobol' techniques is presented in [4] for environmental models. In [5] Spearman, Sobol, and Morris approaches are compared for the purpose of radiological impact assessment of a nuclear power plant discharge.

Currently, the most promising approach appears to be global sensitivity one which is based on the concept of the active subspace against variance-based methods like Sobol' and Morris ones. In [6] active subspace technique is compared with variance-based methods using different test functions. Being more computationally effective, however, the development of the global sensitivity technique requires expanding methods for approximating the gradient of the model function.

Last time Morris method with modifications has actively been used in a variety of applications, including energy storage [7], building engineering [8], urban water supply [9], [10], environmental modeling [4], [11], safety systems [12] etc.

The given research is devoted to electrochemical biosensor designing which requires analysis of the interaction of multiple substances determined by a series of rate constants. Biosensor outputs are featured by the parameters, the temporal and spatial impacts of which should be investigated.

The reactions which are used in electrochemical biosensing come from the reactions that are catalyzed by an enzyme. They are commonly known as reversible [13] or irreversible [14] reactions. The irreversible one-complex Michaelis-Menthen (IR1CMM) mechanism is a keystone in modeling enzyme kinetics. Its reaction scheme

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + P$$

represents two-step process [15, 16, 17], where the enzyme E combines with the substrate S to form a complex C which then breaks down into the product P releasing E in the process.

Michaelis-Menthen model was further developed and applied for describing various reactions lying at the base of the electrochemical biosensor design. In

the work [18] we have developed and studied the generalized model of multi-substrate multi-inhibitor interactions using the law of the delayed mass action. The method for the estimation of the model parameters based on the machine learning technique was offered.

The objective of the given work is to implement the sensitivity analysis of the biosensor model with the respect to the impact of the reaction rates on the change of the concentrations of the substances.

The experimental data was gathered from the alpha-chaconin biosensor. For the purpose of the biosensor design, three-stage experiment was used [18]. To identify the parameters of the mathematical model of the biosensor for the determination of alpha-chaconin, a comparison of simulated and experimental responses was carried out. Potentiometric measurements were carried out after placing the transducers in the measuring cell, which was filled with 5 mM phosphate buffer with a pH of 7.0. The solution was stirred. After stabilization of the output signal (the first stage), the necessary amount of substrate was added to the measuring cell (the second stage), and after stabilization of the response to the substrate, certain volumes of concentrated solutions of alpha-chaconin were introduced to measure the level of inhibition (the third stage). Initially, based on the results of the experiment, the response of the butyrylcholinesterase biosensor to the addition of butyrylcholine chloride to the substrate cell and the subsequent introduction of alpha-chaconine was obtained.

2 MODEL DESCRIPTION

Let $n_e(t)$, $n_s(t)$, $n_i(t)$, $n_p(t)$, $n_{es}(t)$, $n_{ei}(t)$, $n_{esi}(t)$ be concentrations of enzyme, substrate, inhibitor, product, as well as enzyme-substrate, enzyme-inhibitory and enzyme-substrate-inhibitory complexes, which change over time t; k_s, k'_s, k_i, k'_i, and k_p be the corresponding rate constants of the forward and backward reactions of complex formation and the product; a be a constant whose numerical value determines the inhibition or activation of the enzyme. The change in product concentration time is directly proportional to the response of the biosensor.

The model of enzyme-substrate-inhibitor interaction is based on the following biochemical assumptions.

- The rate of the change of n_e is additionally proportional to the rates of forward and backward reactions of the enzyme with substrate and enzyme with inhibitor. Let k_s, k_i be the rates of the corresponding forward reactions, k'_s, k'_i be the rates of the backward ones.
- The product of the reaction of the enzyme with the substrate is formed with the rate k_p, which is also the dissociation rate for the complex enzyme-substrate.
- Let the formation rate of enzyme-inhibitor complexes is proportional to the concentration of free (available) enzymes n_e and available inhibitors n_i, and it leads to a decrease of n_e.
- Let the dissociation of enzyme-substrate and enzyme-inhibitor molecules increase the concentration of enzymes.
- Let a be a constant whose numerical value determines the inhibition or activation of the enzyme.

The equations

$$\begin{aligned}
\frac{dn_e}{dt} &= -k_s n_e n_s - k_i n_e n_i + k'_s n_{es} + k'_i n_{ei} + k_p n_{es} \\
\frac{dn_{es}}{dt} &= k_s n_e n_s - k'_s n_{es} - a k_i n_{es} n_i + a k'_i n_{esi} - k_p n_{es} \\
\frac{dn_{ei}}{dt} &= k_i n_e n_i - k'_i n_{ei} - a k_s n_{ei} n_s + a k'_s n_{esi} \\
\frac{dn_{esi}}{dt} &= a k_i n_{es} n_i - a k'_i n_{esi} + a k_s n_{ei} n_s - a k'_s n_{esi} \\
\frac{dn_s}{dt} &= -k_s n_e n_s - a k_s n_{ei} n_s + k'_s n_{es} + a k'_s n_{esi} \\
\frac{dn_i}{dt} &= -k_i n_e n_i - a k_i n_{es} n_i + k'_i n_{ei} + a k'_i n_{esi} \\
\frac{dn_p}{dt} &= k_p n_{es}
\end{aligned}$$

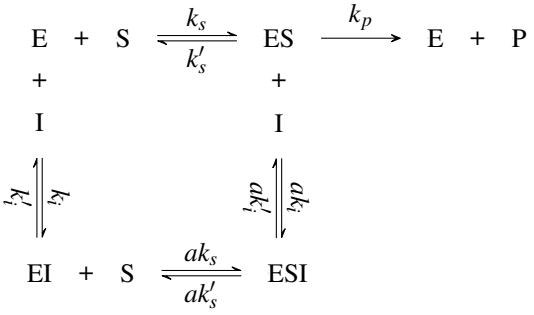
describe the biochemical reactions taking place for concentrations of enzyme, substrate, inhibitor, product, enzyme-substrate, enzyme-inhibitory, and enzyme-substrate-inhibitor.

The first equation is considered for enzyme concentration $n_e(t)$. The first term on the right-hand side, $-k_s n_e n_s$, represents the change in enzyme concentration due to the reaction going with a rate $-k_s n_e n_s$. The rate of this reaction is proportional to the enzyme concentration n_e and to the substrate concentration n_s. The negative sign in this differential equation means that the process of ES formation results in a decrease in the concentration of the enzyme E.

The next term, $-k_i n_e n_i$, similarly to the first term, accounts for the reaction E + I $\rightleftharpoons$ EI. The formation rate of EI complexes is proportional to the concentration of free (available) enzymes $n_e(t)$ and available inhibitors $n_i(t)$, and it leads to a decrease of $n_e(t)$, so it goes in negative.

Dissociation of ES and EI molecules increases the concentration of enzymes. It is taken into account by adding terms $k'_s n_{es}$ and $k'_i n_{ei}$. Formation of the product also releases enzyme molecules as $k_p n_e s$. All the

other equations are composed according to the following reactions



3 METHOD OF MORRIS SENSITIVITY ANALYSIS

Morris proposed his sensitivity analysis method in 1991 [1]. The method is described in details in [19]. This method is also called the elementary effects method [27], which can effectively identify and rank the importance of input parameters of a model by changing the value of only one parameter in an instance and finding its effect on the model output. Therefore, it is possible to calculate the "elementary effect (EE)" of each parameter on the output, one by one, and finally evaluate the influence of all of them on the results. On this basis, sensitivity factors can be compared globally and the nonlinearity of the model can be described qualitatively.

The experimental plan is composed of individually random One-At-a-Time (OAT) experiments. Each model input $X = (k_s, k_i, k'_s, k'_i, k_p, a) \in \mathbb{R}^6$ is assumed to vary across p selected levels in the space of the input factors. Hence, the region of experimentation, Ω, is a 6-dimensional p-level grid. According to the principle of Morris sensitivity analysis, the factors are assumed to be uniformly distributed in the range of $[0,1]$ and are then transformed from the unit hypercube to their actual distribution space.

For a given value of X, the elementary effect of the input factor k_s on the model solution n_e is defined as follows:

$$EE_{k_s}(X,t,\Delta) := \frac{n_e(X + e_1\Delta(k_s^{\max} - k_s^{\min}),t) - n_e(X,t)}{\Delta},$$

where Δ is a perturbation value that is selected from the collection $1/(p-1), ..., 1-1/(p-1)$, p is the number of levels, $X \in \Omega$ is any selected value in Ω, such that the transformed point $X + e_1\Delta(k_s^{\max} - k_s^{\min})$ is still in Ω, and $e_1 \in \mathbb{R}^6$ is a vector of zeros, but with a unit as its first component. The finite distribution of each elementary effect of the input factor k_s on output $n_e(t)$ is obtained by randomly sampling different X vectors from Ω and is denoted by $F_{k_s}^{n_e}$. The distribution for overall outputs is denoted be F_{k_s}.

parameter	k_s	k_i	k'_s	k'_i	k_p	a
minimal value	50	2000	0.5	0.2	0.001	0.1
maximal value	5000	200000	50	20	0.1	0.9

Table 1: Ranges of values of the parameters analyzed.

In a similar way, we may introduce the elementary effects of arbitrary input factors $k_s, k_i, k'_s, k'_i, k_p, a$ on any output from $n_e, n_{es}, n_{ei}, n_{esi}, n_s, n_i, n_p$ and the corresponding distributions.

In addition, Morris proposed two sensitivity measures for each elementary factor, $\mu^\star$ and σ, which are, respectively, the mean and standard deviation of F_{k_s}. In order to estimate these quantities, Morris suggested performing sampling on r elementary effects from F_{k_s} via an efficient design that constructs r trajectories of $(k+1)$ points in the input space, each providing k elementary effects, one per input factor. The formula for computing $\mu^\star$ and σ is given by the following

$$\mu^\star_{k_s} = \frac{1}{N}\sum_{r=1}^{N} EE_{k_s,r}$$

$$\sigma_{k_s} = \sqrt{\frac{1}{N-1}\sum_{r=1}^{N}(EE_{k_s,r} - \mu^\star_{k_s})^2}$$

where $EE_{k_s,r}$ corresponds to the rth EE of k_s and N is the sample size. The higher the value of $\mu^\star$, the greater the influence of the corresponding parameters on the output value of the model. The higher the value of σ, the greater the interaction of a certain parameter with other parameters. Thus, the effect of that certain parameter has on the model output is nonlinear.

4 RESULTS

The effects of rates $k_s, k_i, k^\natural, k'_i, k_p, a$ on concentrations $n_e, n_{es}, n_{ei}, n_{esi}, n_s, n_i, n_p$ were investigated with the help of the method presented above. The sensitivity was analyzed for the parameters at the ranges presented in Table 1.

The charts on the Figure 1 show us the Morris indicators of sensitivity $\mu^\star$, σ for six parameters, namely, k_s, $k^\natural$, k_i, k'_i k_p, a, and their effect on n_e

The plot on the left side displays the change of mean value $\mu^\star$ of the effect of the parameters. We see that the biggest impact on n_e during the time interval (180-300s) is related to the dissociation rate $k^\natural$ (in green).

With time, the influence of the dissociation rate, $k^\natural$, on n_e decreases. Another analyzed factor is k_p.

As you can see after the 300s, this factor has a decisive influence on n_e. Moreover, it can be seen that the value of $\mu^\star$ for k_p is close to a constant value, which means that the influence of k_p on n_e is linear and additive. The least influence on n_e at this stage makes k_s, which decreases over time.

From the σ diagram it can be seen that the seriality of k'_s, k_p, k_s is preserved for non-linearity and the level of interaction of the influence of parameters on n_e. All other parameters have no effect on n_e, which can also be seen from the equations of the model at this stage.

The charts in the Figure 2 show us the Morris indicators of sensitivity $\mu^\star$, σ for six parameters, namely, k_s, k'_s, k_i, k'_i, k_p, a, and their effect on n_s.

The plot on the left side displays the change of mean value $\mu^\star$ of the effect of the parameters. We see that the biggest impact on n_s during the time interval (180-460s) is related to the rate of formation of the enzyme-substrate complex (k_s) which increases with time similar to the speed of product development (k_p). With time, the influence of the dissociation rate, k'_s on n_s decreases.

In the time frame (460-750s), the influence of factors k'_s, k_i, k_s, k_p, k_i is noticeable and it increases with time. It is worth noticing that influence on n_s comes from the dissociation rate k'_s (in green) is greater than influence comes from k_i, k_s, k_p, k'_i parameters. The effect of the factors on parameter σ (on the right) looks very similar except for the effect of the parameters k_p and k'_i. In the time interval (460-750s) the effect coming from the dissociation of the enzyme-inhibitor complex (k_i) outweighs the effect coming from the formation of the reaction product (k_p).

The charts in the Figure 3 show us the Morris indicators of sensitivity $\mu^\star$, σ for six parameters, namely, k_s, k'_s, k_i, k'_i, k_p, a, and their effect on n_i. The plot on the left side displays the change of mean value $\mu^\star$ of the effect of the parameters. In a time frame (180-460s) significant effect on the inhibitor concentration (n_i) of the dissociation constant of the enzyme-inhibitor complex (k'_i) was noted. This influence increases with time. Other parameters k_i, k_p, k_i, k_s are constant over time. In time intervals (460-750s) value that comes from the formation of the reaction product is close to constant, which means that the effect of k_p on n_i is linear and additive. The nature of the changes seen in the graphs σ is similar to $\mu^\star$.

Figure 4 illustrates sensitivity analysis indicators from n_{es} at different stages of modeling. As time passes (180-460s) on left, the effect on n_{es} of the parameter k'_s (in green) and k_s (red) is noticeable, which decreases with time. In contrast, the parameter k_p, denotes the formation of the reaction product which is almost constant over time with a slight upward trend.

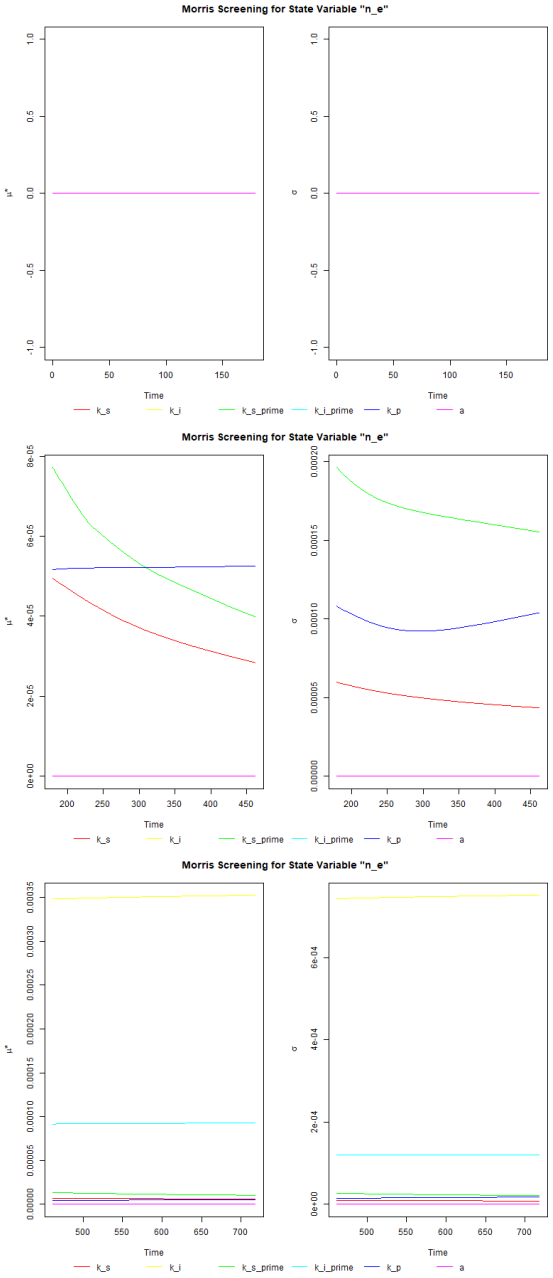


Figure 1: Sensitivity analysis indicators for n_e at the different stages of modeling.

The similar nature of the changes for k'_s and k_s is shown in the graph for σ, on right. The parameter k_p slightly decreases up to 270s, in the interval (271-320s) it remains constant, while from 350-460s) a slight upward trend is noticeable.

Taking into consideration the change of mean value $\mu^\star$ of the effect of the parameters in the time frame (460-750s) the biggest influence on n_{es} comes from k_i (binding constant of complex enzyme-

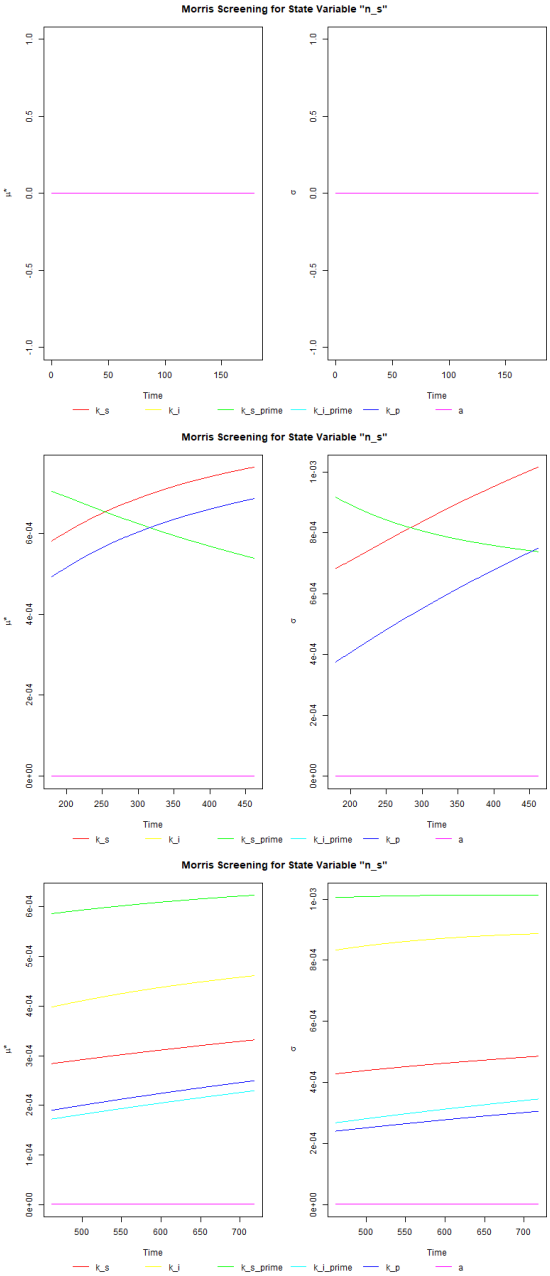


Figure 2: Sensitivity analysis indicators for n_s at the different stages of modeling.

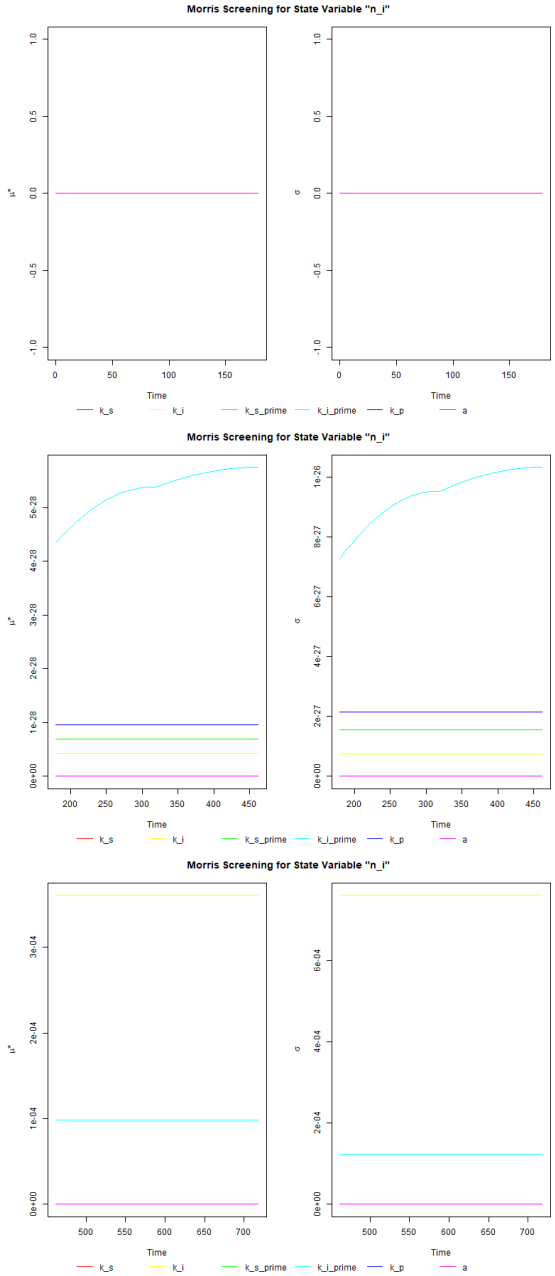


Figure 3: Sensitivity analysis indicators for n_i at the different stages of modeling.

inhibitor) like k_s' (in green), k_i' (in blue) and k_s (in red) the influence of these factors decreases with time. The influence of the parameter (k_p) derived from the formation of the product reaction increases with time. A similar character of changes is shown in the graph for σ.

Figure 5 illustrates sensitivity analysis indicators from n_p at different stages of modeling. As time passes (180-460s) on left, the effect on product concentration of the parameters k_s, k_p, and k_s' is noted. With the passage of time there is a noticeable increase in the influence of the parameters k_p and k_s (for k_s minimally larger) in contrast to the parameter k_s', which decreases over time.

In the time frame (460-750s) There is a noticeable effect on the concentration of the product (n_p) of all parameters, i.e. parameters k_i, k_s', k_p, $k_i\prime$ and k_p. This influence increases with time.

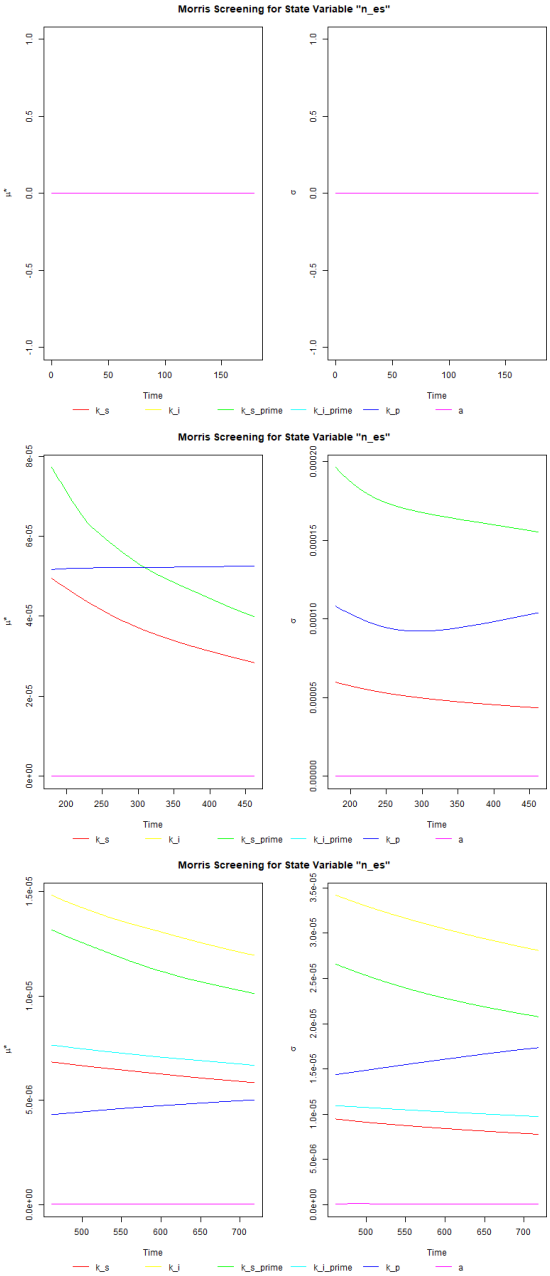


Figure 4: Sensitivity analysis indicators for n_{es} at the different stages of modeling.

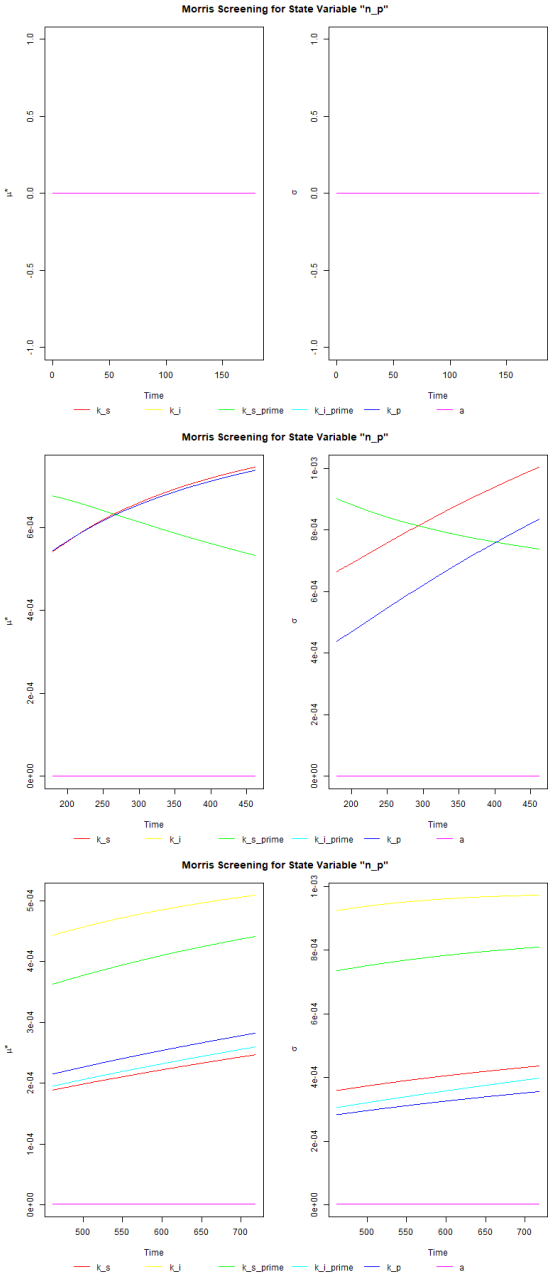


Figure 5: Sensitivity analysis indicators for n_p at the different stages of modeling.

A similar nature of the changes was observed for the σ except for the influence of the parameter k_p, which in the time interval (460-750s) for $\mu^\star$ exceeds the influence from $k^\star$ and k_p in contrast to σ, where its influence is the smallest.

On Figure 6 on the left side, displays the change of mean value $\mu^\star$ of the effect of the parameters on n_{ei}. We see a definite increasing effect over time of the dissociation rate of enzyme-inhibitor complex (k_i') in the time interval (180-460s). Other parameters are constant over time.

A similar character of changes was observed for σ, on the right side. In the time frame (460-750s) character of changes for $\mu^\star$ and σ is also similar. We see the dominant influence of the factor derived from the formation of the enzyme-inhibitor complex (in yellow), which over time is almost constant with a slight upward trend, as is the k_p factor. The k_s' factor de-

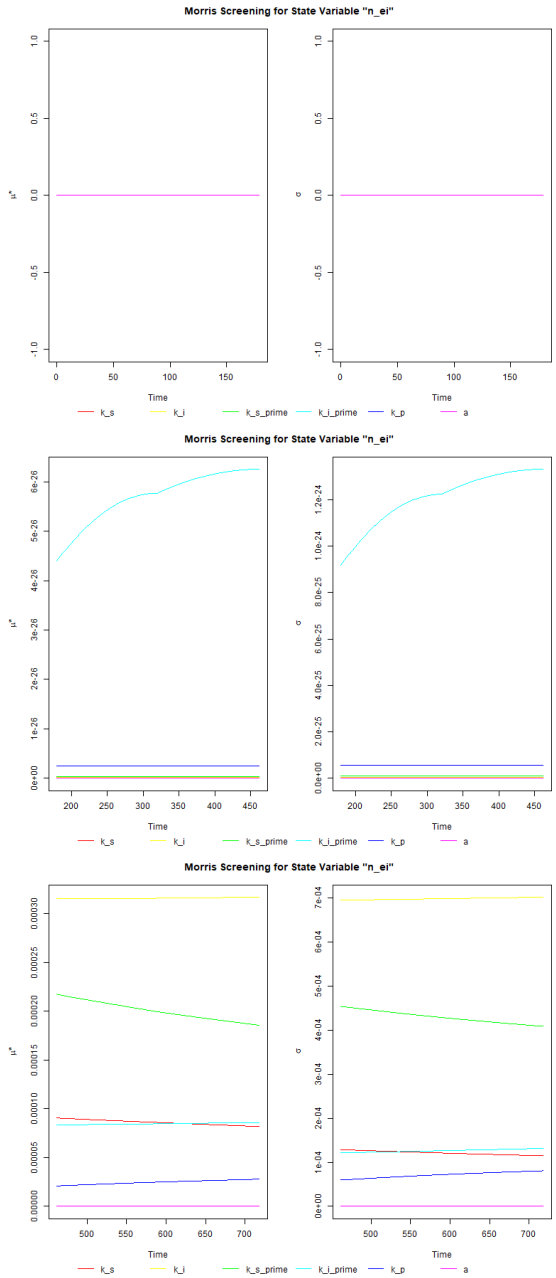


Figure 6: Sensitivity analysis indicators for n_{ei} at the different stages of modeling.

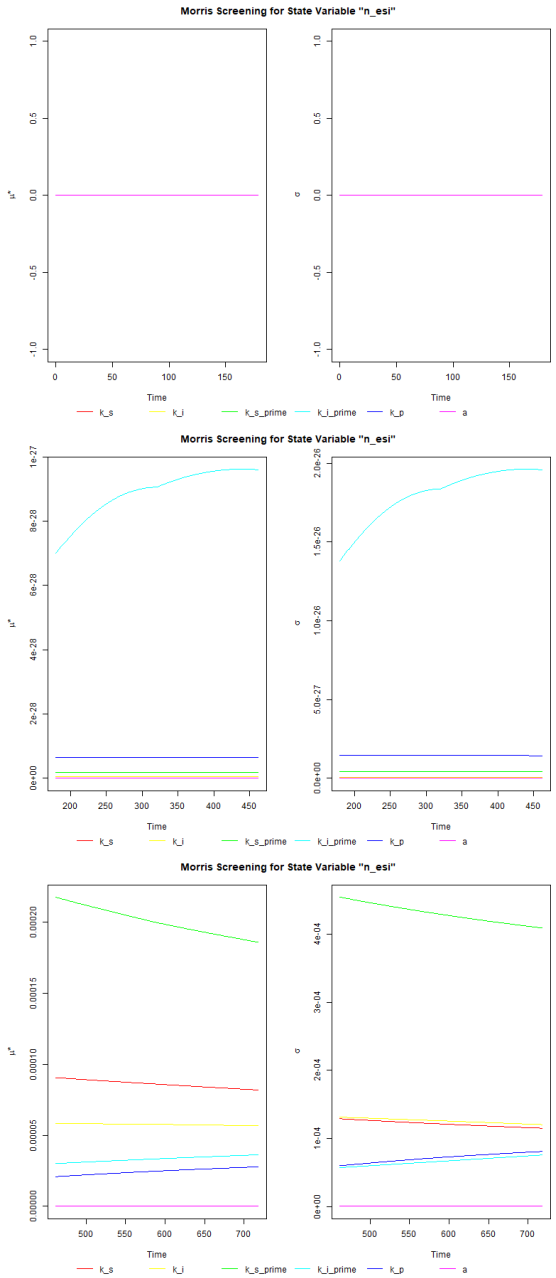


Figure 7: Sensitivity analysis indicators for n_{esi} at the different stages of modeling.

rived from the dissociation rate of complex enzyme-substrate decreases with time, as the k_{si} and k_i' factors for which the nature of the changes is smoother.

As is shown on Figure 7 on left, in time frame (180-460s) significant effect on the inhibitor concentration (n_i) of the dissociation constant of the enzyme-inhibitor complex (k_i') was noted. This influence increases with time. Other parameters k_i, k_p, k_i, k_s are constant over time.

In the time interval (460-750s) the greatest effect on n_{esi} on k_s' (dissociation rate of the enzyme-inhibitor complex), which decreases with time similarly to k_s (binding constant of enzyme-substrate complex). The influence of the parameter k_i on n_{esi} is invariant over time, while the influence of the parameters k_i' and k_p presents a slight upward trend with time. The trend of changes for σ is similar, although it is possible to weigh in the range (460-750s) reduced

influence of binding constant of complex enzyme-substrate(k_s) (in red) and equalization the influence coming from k_i' and k_p.

5 CONCLUSIONS

For the reasons given in the work we have shown the Morris method is powerful tool for sensitivity analysis of the models for biochemical reactions. Here we have applied the method for studying the enzyme-substrate-inhibitor interactions which is used during the design of electrochemical biosensor.

The method can be applied for the comparative investigation of the influence of the parameters (factors) on the model outputs (trajectories). Moreover such study can be conducted for the various stages of the experiment.

In turn it is of importance when constructing the calibration curves basing on the responses of the biosensor.

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