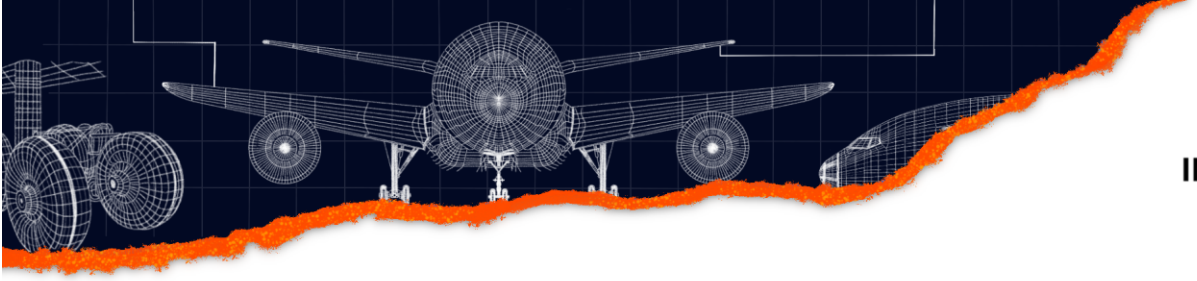

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EDITORA

MATHEMATICAL MODELING IN ENZYMATIC BIOSENSORS

MODELAGEM MATEMÁTICA EM BIOSSENSORES ENZIMÁTICOS

MODELADO MATEMÁTICO EN BIOSENSORES ENZIMÁTICOS

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ABSTRACT

Enzymatic biosensors are highly specific and sensitive analytical devices capable of quantifying analytes quickly and at low cost, making them attractive for clinical, environmental, and industrial applications. However, quantitatively predicting their response requires robust mathematical models that integrate reagent diffusion, enzyme kinetics, and current generation. The objective of this chapter was to present the fundamental equations for developing models based on partial differential equations of Michaelis-Menten kinetics to describe substrate and product diffusion in the enzyme layer and calculate the generated electrical current. In summary, these models can aid in the design of biosensors, are applicable to the study of electrochemical behavior, and provide a useful tool for predicting the analytical response of these devices.

Keywords: Enzymatic Biosensors. Biotechnology. Mathematical Modeling. Partial Differential Equations.

RESUMO

Os biossensores enzimáticos são dispositivos analíticos de alta especificidade e sensibilidade, capazes de quantificar analitos com rapidez e baixo custo, tornando-os atrativos para aplicações clínicas, ambientais e industriais. Entretanto, prever quantitativamente sua resposta exige modelos matemáticos robustos que integrem difusão de reagentes, a cinética enzimática e a geração de corrente. O objetivo deste capítulo foi apresentar as equações fundamentais para o desenvolvimento de modelos, baseados em equações diferenciais parciais da cinética de Michaelis-Menten para descrever a difusão do substrato e produto na camada enzimática e o cálculo da corrente elétrica gerada. Em síntese, os modelos podem auxiliar no desenho de biossensores, sendo aplicáveis no estudo do comportamento eletroquímico e fornecem um instrumento útil para previsão da resposta analítica desses dispositivos.

Palavras-chave: Biossensores Enzimáticos. Biotecnologia. Modelagem Matemática. Equações Diferenciais Parciais.

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RESUMEN

Los biosensores enzimáticos son dispositivos analíticos altamente específicos y sensibles, capaces de cuantificar analitos con rapidez y a bajo coste, lo que los hace atractivos para aplicaciones clínicas, ambientales e industriales. Sin embargo, la predicción cuantitativa de su respuesta requiere modelos matemáticos robustos que integren la difusión de reactivos, la cinética enzimática y la generación de corriente. El objetivo de este capítulo fue presentar las ecuaciones fundamentales para el desarrollo de modelos basados en ecuaciones diferenciales parciales de la cinética de Michaelis-Menten para describir la difusión del sustrato y del producto en la capa enzimática y calcular la corriente eléctrica generada. En resumen, estos modelos pueden facilitar el diseño de biosensores, son aplicables al estudio del comportamiento electroquímico y proporcionan una herramienta útil para predecir la respuesta analítica de estos dispositivos.

Palabras clave: Biosensores Enzimáticos. Biotecnología. Modelado Matemático. Ecuaciones Diferenciales Parciales.

1 INTRODUCTION

Mathematical modeling has played a crucial role in advancing biotechnology, enabling the understanding, optimization, and prediction of behaviors of complex biological systems. One of the milestones of this evolution was the application of differential equations to describe biochemical phenomena, such as those that occur in bioreactors and other biotechnological processes. These mathematical models have been fundamental in representing biochemical interactions and transformations more accurately, in addition to enabling the identification of patterns that are essential to understand the behavior of biological systems1

The importance of mathematical modeling in biotechnology goes beyond the mere quantitative representation of phenomena. It organizes disconnected information about biological processes, corrects flaws in conventional understanding, and provides a logical analysis of the interactions between the components of the system. This approach, which is based on techniques for analyzing enzyme kinetics, mass and energy balances that contribute to a detailed understanding of biochemical processes, is essential for the development of new therapies, diagnostic products and solutions for environmental and health detections2. The use of mathematical models also allows the optimization and control of biotechnological processes, such as biomass production and biocatalysis, which involve enzymes or microorganisms in specific chemical reactions3.

In particular, the mathematical modeling of enzymatic biosensors has gained prominence, given the growing demand for sensitive, selective, and fast-response detection devices. Biosensors are used in a wide range of applications, including the detection of glucose, lactate, and other biomarkers, representing an alternative to conventional analysis methods4. Modeling these systems is essential for understanding their behavior and performance under different operating conditions, allowing them to predict and optimize their responses. In this context, the application of differential equations and mathematical simulation techniques has proven to be a powerful resource for the development of models that can improve the performance of biosensors by determining the ideal parameters for each specific application5.

The research presented in this chapter aims to understand the mathematical modeling of an enzymatic biosensor, focusing on the application of differential equations to simulate and predict its behavior. The objective is to comment on developed models, evaluate the relationship between the biosensor parameters and their response, and identify the ideal limits for the operation of these devices. Thus, modeling can contribute to improving the efficiency and applicability of biosensors in various areas of biotechnology and health.

2 ENZYMATIC BIOSENSORS: DEFINITION AND CLASSIFICATIONS

Enzymatic biosensors are analytical devices that use enzymes, such as biological recognition elements, to detect and quantify specific substances in a sample. These devices combine an enzyme with a physical or chemical transducer that converts the biological interaction into a measurable signal6. The basic functioning of an enzyme biosensor involves immobilizing the enzyme on a surface capable of detecting measurable changes after occupying the active site. When the substance of interest (analyte) is present in the sample, it occupies this site of the enzyme, producing a specific signal of the enzymatic reaction. This signal is the result of a change in a physical or chemical property, such as pH, temperature, electrical potential, among others, which is detected by the transducer.

Enzymatic biosensors offer high specificity due to the selectivity of enzymes by their substrates. This means that they can differentiate between very similar substances, making them very useful instruments in a variety of applications, including medical diagnosis, environmental monitoring, food quality control, and biotechnology7.

2.1 CLASSIFICATION OF ENZYMATIC BIOSENSORS ACCORDING TO THE TYPE OF TRANSDUCER

Enzymatic biosensors can be classified based on the type of transducer used in electrochemical, optical, thermal, or piezoelectric. Each type offers specific advantages depending on the desired application8.

Electrochemical biosensors are the most common and can be subdivided into three main categories. **Amperometric**, capable of measuring the current generated by the oxidation or reduction of an analyte on the surface of the electrode. Glucose oxidase is a typical example of an enzyme used in amperometric biosensors for the detection of glucose in the blood. **Potentiometrics**, detect the change in the electrical potential caused by the interaction of the analyte with the enzyme. A common example is the selective ion biosensor, which uses an enzyme membrane to detect specific ions. **Conductometric tests** measure the change in the electrical conductivity of the medium resulting from the enzymatic reaction. These sensors are used to detect changes in the concentration of ions.

Optical biosensors detect changes in optical properties, such as absorption, fluorescence, and luminescence, caused by the interaction between the analyte and the enzyme. They can also be subdivided into three types. **Fluorescent**, they use enzymes that, when interacting with the substrate, produce or modify fluorescence. They are very sensitive and can detect very low concentrations of analytes. **Luminescent**, they are based on the emission of light resulting from an enzymatic reaction. An example is the use of luciferase for

the detection of ATP. **Colorimetrics**, measure the color change resulting from the enzymatic reaction. They are simple and easy to use, and are often used in quick tests.

Thermal enzymatic biosensors, also known as calorimetrics, operate by measuring the temperature change that occurs due to the specific enzymatic reaction. When an enzyme interacts with its substrate, this reaction can release or absorb heat, and this thermal variation is directly proportional to the concentration of the analyte present in the sample. To detect small changes in temperature, a high-sensitivity thermistor or other temperature sensor is positioned near the area where the reaction occurs. Although they are not as sensitive as other types, the great advantage of these enzymatic biosensors is their robustness and stability, allowing them to be used efficiently in adverse pH or temperature conditions, and with complex samples. Its key features include simplicity of operation and the ability to analyze substrates in multiple dies.

Piezoelectric enzymatic biosensors are analytical devices that utilize the selectivity of an enzyme immobilized on the surface of a piezoelectric material, usually a quartz crystal. The enzymatic reaction with its specific substrate generates a change in mass on the crystal surface. This change in mass, however small, modifies the resonant frequency of the piezoelectric material, a physical phenomenon detected by a transducer. The resulting electrical signal is then correlated with the analyte concentration, allowing for highly sensitive, real-time detection. Key features of these biosensors include label-free detection, speed, and enzyme specificity.

2.2 CLASSIFICATION AS TO THE METHOD OF IMMOBILIZATION OF THE ENZYME

Enzyme immobilization is a key step in the development of enzymatic biosensors, as it directly affects sensor stability, activity, and repurposing. The main methods of immobilization are related to four strategies. In **physical adsorption**, the enzyme is adsorbed on the surface of the transducer through physical interactions, such as Van der Waals, hydrophobic, and ionic forces. This method is simple, but the binding is usually weak and can lead to leaching of the enzyme. In **the covalent bond** the enzyme is covalently bonded to the surface of the transducer. This method provides a strong and stable bond, increasing the lifetime of the biosensor. The third strategy, called **matrix trapping**, consists of encapsulating the enzyme in a polymeric matrix or gel. This method protects the enzyme from harsh conditions, but can limit substrate diffusion. Finally, in **crosslinking,** the enzyme is bound to other enzyme molecules or to a scaffold by means of crosslinking agents. This method creates a stable enzyme network and increases the enzyme density on the surface of the transducer.

2.3 CLASSIFICATION AS TO THE NATURE OF BIOLOGICAL RECOGNITION

Enzymatic biosensors can be classified according to the specificity of the enzymatic interaction. **Substrate-specific biosensors** utilize enzymes that are specific to a particular substrate. For example, glucose oxidase is specific to glucose. **Inhibitory biosensors** detect the presence of specific enzyme inhibitors. These sensors are useful for the detection of contaminants or toxins that inhibit enzyme activity. Activity **biosensors** measure the overall enzyme activity in a sample, rather than focusing on a single substrate or inhibitor. They are useful in metabolic studies and clinical diagnostics.

2.4 THE EFFICIENCY OF AN ENZYMATIC BIOSENSOR

The efficiency of enzymatic biosensors is largely attributed to the specificity of the enzymes used. Enzymes are biological proteins that catalyze specific chemical reactions, which allow the selective detection of a particular substrate in the presence of other components in a sample6. Enzyme specificity is one of the main factors contributing to the high efficiency of enzymatic biosensors, allowing the detection of very low concentrations of analytes in complex samples. In addition, how quickly enzymatic biosensors can provide results is another crucial aspect of their efficiency. According to Grieshaber et al. (2008), electrochemical enzymatic biosensors, in particular, are capable of producing almost instantaneous responses due to the rapid kinetics of enzymatic reactions. This feature is especially valuable in clinical applications, where rapid diagnosis can be vital.

The stability of enzymatic biosensors also contributes to their efficiency. Advanced methods of enzyme immobilization, such as covalent bonding and encapsulation in polymeric matrices, help maintain enzyme activity for prolonged periods, even under adverse conditions10. Techniques such as enzymatic crosslinking not only increase stability, but also allow the reuse of biosensors, reducing costs and improving the sustainability of analytical processes.

The sensitivity of enzymatic biosensors is widely documented11. The combination of highly sensitive transducers with specific enzymes allows the detection of analytes at levels on the order of nanograms per milliliter. This low level of sensitivity is particularly important in areas such as food safety and environmental monitoring, where early detection of contaminants can prevent public health problems and ecological damage.

Finally, the miniaturization and portability of enzymatic biosensors are aspects that increase their efficiency12. Xie and Herten (2020) discuss how advances in optical transducer technology have enabled the development of compact and portable biosensors, which can be used directly in the field for fast and accurate analyses. This portability is especially useful

in resource-constrained environments where laboratory analytical methods would be impractical.

2.5 MATHEMATICAL MODELING

Mathematical modeling is a fundamental approach in several areas of knowledge, allowing the representation of real systems through equations and mathematical concepts. Essentially, mathematical modeling consists of translating real-world problems into a set of mathematical expressions that can be analyzed, solved, and used to predict the behavior of dynamic and complex systems13. The construction of a mathematical model involves, initially, the simplification of a real system, identifying the most relevant variables and the relationships between them, in order to create a representation that is as accurate as possible to the real phenomenon.

In practice, mathematical modeling can be applied in various fields, such as engineering, economics, biology, physics, and even the social sciences. For example, in mechanical and civil engineering, mathematical models are often used to predict the behavior of structures under different load conditions, which is essential for the safe and efficient design of buildings and bridges14. In biology, mathematical models can be used to understand population growth or the spread of disease, helping to guide public health policy.

Building a mathematical model usually follows several steps. First, the problem is clearly defined, establishing the objectives of the model and the main variables involved. Then, a mathematical formulation is developed, where assumptions about the behavior of the system are adopted that allow simplifying it. These assumptions are critical as they determine the accuracy and applicability of the model. Subsequently, the model is solved mathematically, which may involve solving differential equations, optimizing functions, or numerical simulations. Finally, the model is validated by comparing the mathematical or computational results with experimental or observational data. If necessary, the model can be adjusted to improve its accuracy and applicability.

An important aspect of mathematical modeling is the interpretation of results. A model may be mathematically correct, but if the initial assumptions are inadequate, the results may not accurately reflect reality. Therefore, mathematical modeling requires a deep understanding of both the actual system and the mathematical tools used15. The ability to mathematically model a system provides a quantitative view that is crucial for decision-making in complex contexts, anticipating behaviors and decisions in applications.

2.6 MATHEMATICAL MODELING APPLIED TO BIOSENSORS

Mathematical modeling can be a very useful step for the development and optimization of biosensors, allowing a detailed understanding of their mechanisms and the prediction of their performance under various conditions. Biosensors are devices that use a combination of a biological component and a transducer to detect and quantify chemicals, biomolecules, or cells. Mathematical modeling helps translate the complex interactions between these parts into mathematical equations that are understandable and applicable in the real context.

The interaction between the analyte and the biological component of the biosensor is fundamental for its functioning. Mathematical models, such as the Langmuir equation, are often used to describe the kinetics of adsorption and bonding of molecules. Langmuir's equation, given by = where θ is the fraction of occupied sites, is the affinity constant, and is the concentration of the analyte, allows us to estimate the maximum binding capacity of the biosensor$\theta \frac{k_\alpha C}{1 + k_\alpha C} k_\alpha C$[16]. In addition, models based on the Michaelis–Menten equation are applied in enzyme systems, where the reaction rate is described by the equation, with the maximum velocity and the Michaelis constant$v = \frac{V_{max}[S]}{k_m + [S]} V_{max} k_m$[17].

The transducer converts the biochemical response into a measurable signal. Mathematical models that describe transducer response are essential to the accuracy and reliability of biosensors. In optical biosensors, the variation in the intensity of reflected or transmitted light is often modeled using the Beer-Lambert equation, where is the absorbance, is the intensity of the incident light, is the intensity of the transmitted light, ε is the molar absorption coefficient, is the concentration of the analyte, and is the thickness of the sample$A = log10\,(I_0/I) = \epsilon clAI_0 Ic\ l$[18].

Dynamic models are used to simulate the temporal behavior of biosensors, which is crucial for systems that operate under varying conditions or need rapid response. Models based on differential equations are employed to describe the reaction kinetics and diffusion dynamics of the analyte on the sensor surface19. For example, the Fick diffusion equation, where is the concentration of the analyte, is the diffusion coefficient and is the Laplacian operator, is used to model the spatial distribution of the analyte in a biosensor.$\frac{\partial C}{\partial t} - D\nabla^2 C = 0C\ D\nabla^2$

Mathematical modeling can also assist in the design of biosensor design. Numerical simulations allow the evaluation of sensor performance under different operating conditions, helping to identify the best conditions to maximize sensitivity and specificity. Techniques such as sensitivity analysis and optimization based on genetic algorithms are often used to adjust parameters and improve the analytical response of these devices20.

Mathematical modeling in enzymatic biosensors can play a key role in improving and understanding the performance of these devices, offering a detailed quantitative view of the complex interactions between enzymes and analytes. Through mathematical models, it is possible to predict enzyme kinetics, optimize enzyme immobilization, and adjust the operating conditions of the biosensor to maximize its sensitivity and specificity. This is especially relevant in applications where accuracy and speed of detection are critical, such as in medical diagnostics and environmental monitoring. Through modeling, it is possible to identify potential limitations in the configuration of the biosensor and propose improvements even before its manufacture. Thus, the combination of mathematical modeling with technological advances in enzymatic biosensors can improve the development process and also expand the possibilities of application of these devices in new fields, contributing significantly to the evolution of biological detection technologies.

3 APPLIED EQUATIONS REPRESENTATIVE OF MATHEMATICAL MODELS

The development of the mathematical model of an enzymatic biosensor can be divided into two stages: the modeling of the diffusion of substances in the enzymatic layer and the modeling of the electrical response generated by the enzymatic reaction. The objective of this approach is to predict the behavior of the biosensor under different operating conditions, using concepts of diffusion, enzyme kinetics and Faraday's Law.

The modeling of the diffusion of substances in the enzyme layer can be described by Fick's first Law, which quantifies the flow of a substance as a function of the concentration gradient, as expressed in equation (1).

$$J(t) = -D\frac{\partial P}{\partial z} \qquad (1)$$

Where:

is the Jdiffusion flow, is the diffusion coefficient of the species, is the concentration gradient of the species in the axial direction of the enzyme layer. This approach allows modeling the distribution of substrate and product concentration along the enzyme layer, which is fundamental to understand the temporal and spatial variations in the concentrations of the compounds$D\frac{\partial P}{\partial z}Pz^{21}$.

Fick's second Law, equation (2), is also applied to describe the evolution of concentrations in time and space, considering both the temporal and spatial variation of substrate and product concentrations21. The partial differential equations (PDEs) that arise

from this modeling can be solved numerically using the Finite Difference Method (FDM), a technique that stands out for its stability in nonlinear problems.

$$\frac{\partial P}{\partial z} = D \frac{\partial^2 C}{\partial x^2} \qquad (2)$$

Enzymatic kinetics can be described by equation (3) of Michaelis-Menten, which relates the speed of the enzymatic reaction to the concentration of the substrate.

$$v(s) = \frac{V_{max}[S]}{K_m + [S]}, \qquad (3)$$

Where:

v is the reaction rate, is the maximum reaction rate, is the substrate concentration, and is the Michaelis–Menten constant that represents the affinity of the enzyme for the substrate. This equation is used to model the rate of conversion of the substrate to product by the enzyme, providing the basis for integrating enzyme kinetics into the diffusion model$V_{max}[S]K_m$[9]. The integration of Michaelis-Menten kinetics with substrate diffusion allows for a more accurate simulation of the behavior of the biosensor, considering both the transport of substances and the reactions catalyzed by enzymes21.

The generation of electric current in the enzymatic biosensor can be modeled by Faraday's Law, equation (4), which relates the flow of substances to the production of current. The equation used is:

$$I(t) = n \cdot A \cdot F \cdot J(t) \qquad (4)$$

where *I* is the current generated by the reaction, n the number of electrons transferred, Faraday's constant and the surface area of the electrode and FAJ the diffusion flux. The application of this law, together with enzyme kinetics and diffusion, allows the electrical response of an enzyme biosensor to be modeled5.

One of the methods for solving diffusion EDPs is the Finite Difference Method (FDM) that can be applied numerically in computational environments, allowing discretization of temporal and spatial derivatives in a mesh. The approximations used can follow the concentrations at specific points on the surface of the biosensor that can be divided into a grid of points, as represented in equation (5):

$$\frac{\partial C}{\partial t} \approx \frac{C_i^{n+1} - C_i^n}{\Delta t}, \frac{\partial^2 C}{\partial x^2} \approx \frac{C_{i+1}^n - 2C_i^n + C_{i-1}^n}{\Delta x^2} \quad (5)$$

Where:

is the concentration on the knot in the instant. The resulting system has a tri-diagonal matrix structure, typical of one-dimensional diffusion problems, which ensures computational efficiency. The typical boundary conditions applied are: initial condition, $C_i^n in$ $C(t = 0, x) = C_0$; boundary at , fixed concentration ; boundary at , null gradient . Ensuring physical coherence and numerical stability. The usual implementation uses the parameters and , as reported in the literature$x = 0 C = C_0 x = L(\frac{\partial C}{\partial t} = 0) \Delta t = 1s \Delta x = 10 \mu m$[15].

3.1 FIT OF THE SIMULATED CURVE TO THE EXPERIMENTAL DATA

To improve the correspondence between the simulated results and the experimental data22, adjustments to the model curve can be performed by means of nonlinear regression. The most common adopted function is an increasing exponential, of the type expressed in equation (6):

$$f(t) = a \cdot (1 - e^{-b \cdot t}) + c \quad (6)$$

This functional form reflects the behavior of systems with first-order kinetics, common in amperometric biosensors. The adjustment can be performed via the least squares algorithm *(curve_fit*, SciPy), in *Python* language, allowing the precise calibration of the simulation parameters, for example with and), against the real data. This process ensures a simulated curve with a coefficient of determination, quantitatively validating model$a = 100 b = 0{,}155 R^2 \cong 0{,}99$[22]. To ensure consistency with the experimental data, the input values used in the simulation should include parameters reported in experimental trials, for example, such as those reported by Baronas et al. (2021), as presented in Table 1:

Table 1

Typical input parameters used in the biosensor simulation

Parameter	**Symbol**	**Value**	**Unit**
Initial substrate concentration	C_0	1	μM
Initial product concentration	P_0	0	μM
Substrate diffusion coefficient	D_s	300	μm²/s
Coefficient of diffusion of the product	D_P	300	μm²/s

Maximum enzyme rate	V_{MAX}	100	µM/s
Michaelis–Menten constant	K_m	100	µM
Enzyme layer thickness	d	100	µm
Number of electrons transferred per reaction	n	2	-
Electrode area	The	0,07*	cm²
Faraday's constant	F	96,485	C/mol

* The electrode area assumed to be 0.07 cm² based on typical amperometric biosensor configurations reported in the literature9,21. Source: prepared by the author based on Baronas et al. (2021).

These parameters are inserted into the previously described mathematical model and used as a basis for the simulation of the values of the electric current over time. From this data, it is possible to generate comparative curves between simulation and experiment.

3.2 ANALYSIS AND EVALUATION OF BIOSENSOR PERFORMANCE

After the application and validation of the model, simulation tests are performed to evaluate the impact of key parameters on the performance of the biosensor, such as the initial substrate concentration (), the maximum enzyme rate () and the thickness of the enzyme layer (d). The high degree of statistical correlation obtained in the adjustments demonstrates that the developed model will be reliable to represent the real dynamics of enzymatic biosensors$[C_0]V_{max}$[21,22.]

After validation, simulation tests are carried out to study the sensitivity of the model to changes in the main parameters. In this step, it is possible to identify, for example, that very high enzyme layer thicknesses () limit diffusion and reduce the final electric current, while substrate concentrations greater than 6,000 µM lead to response saturation$d > 100\ \mu m$[21]. These characteristics are consistent with the literature and reinforce the usefulness of the model for optimizing the design of enzymatic biosensors9.

4 CONCLUSIONS

Mathematical models for predicting the behaviors of amperometric enzymatic biosensors demonstrate the ability to simulate and predict the diffusion of the sample and the generation of the generated current. The simulated response usually presents excellent fit to the experimental data, which validates the structure and parameters adopted in the model. The use of partial differential equations, combined with Michaelis-Menten kinetics and Faraday's law, is effective in describing the enzymatic analytical system.

Compared to modeling approaches, discretization via Finite Difference Method (FDM) and parity analysis provided greater robustness in model calibration and validation. The

sensitivity analysis demonstrates that factors such as enzyme layer thickness and initial substrate concentration play a crucial role in optimizing the biosensor response, corroborating recent results in the literature.

Thus, it is concluded that the modeling applied to enzymatic biosensors not only adequately reproduces the experimental behavior, but also offers reliable subsidies for the design and improvement of these devices. The study contributes significantly to the theoretical understanding of analytical response behavior, supporting its development in clinical, environmental, and industrial contexts.

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