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MATHEMATICAL MODELING OF HYBRID BIOSENSOR AND DETERMINATION OF AMPLIFICATION FACTOR

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ABSTRACT
A hybrid biosensor for measuring of cathechol was developed and experiments with him are done. A mathematical model for that amperometric co-substrate sensitive system with bio-chemical amplification is described in this article. The first order kinetics is adopted. A system of six differential equations which described that measurement system is composed, limiting conditions are accepted and the solutions for substrate, co-substrate reducing agent and medial product found. An expression of output current, which is proportional to measured substrate for that biosensor system with bio-chemical amplification, is found. The amplification factor G for that hybrid biosensor is determined

KEY WORDS:
biosensor, mathematical modeling, transfer function.

1. INTRODUCTION

The development and investigation of biosensor systems [1,2] undoubtedly, include and creation of mathematical models, which describe processes flowing in those complex measuring systems. In [3] it has done completely describing of the problems connected with mathematical modeling on biosensor systems. In the present work we propose mathematical modeling of a new model of biosensor systems, and namely hybrid with bio-chemical amplification of the output current. That biosensor system has developed in previous work [4]. The hybrid biosensor systems are [5] biosensors with have more then one biosensitive material –enzyme, tissue microorganism or had a presence of other agents. The running biochemical or chemical processes are more then one in result we receive a biosensor with new properties. In the given paper that is amplification of the output current, because there has a cyclic reaction in the research medium.

2. PRESENTATION OF THE MATHEMATICAL MODEL

The output current of the biosensor $I = f(So)$ give us connection between output current of the biosensor **I** and concentration of the measured substrate So. At the fig.1 is shown the model of the given biosensor. It has three membranes - dialyze, active and gas-permeable membrane, and an electrochemical cell of the basic transducer in which an anode, cathode and electrolyte are situated.

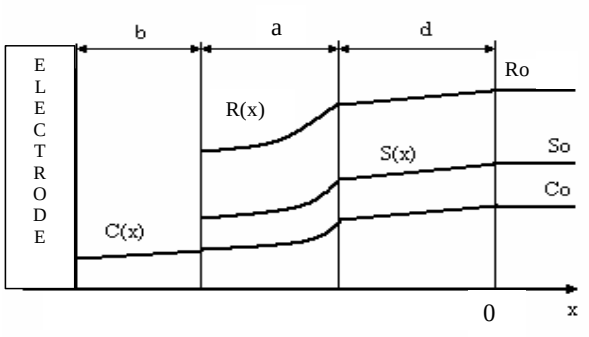

Fig. 1. Three substrate one enzyme biosensor system model.

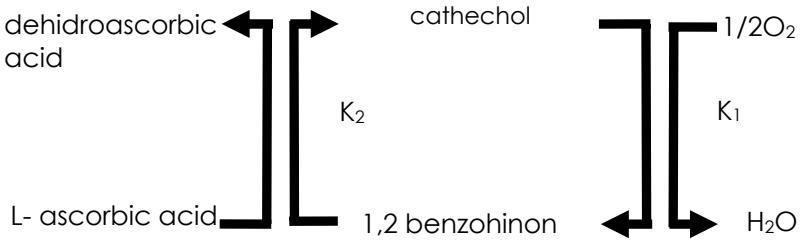

Fig. 2. Cyclic reaction in the researched medium

The electrode (cathode) is electrochemical active. Active membrane with thickness a, is situated between gas-permeable membrane with thickness b and dialyze with thickness d . The active membrane is made from potato tissue in which preliminary are removed phenols. x –is the current coordinate. Biosensor is dip into solution with concentration of substrate So and there is added the reducing agent L – ascorbic acid, which will turn the cyclic reaction. In the active membrane whish is like enzyme reactor, the measuring substrate is converted into product. Oxygen which is necessary for the running of the enzyme catalyzing reaction ensured from the air. The rest of the oxygen is passing through the gas-permeable membrane and by depolarizing the cathode is resulted an output current I. That current is measured with oxygen-meter.

At the fig.2 is given the scheme of cyclic reaction which is flowing in the medium.

Here: K_1,K_2 –are constants connected with velocity of reactions; K_1 is connected with the velocity of enzyme reaction. Enzyme is tyrosinase. K_2 is connected with velocity of chemical reaction; P_1 – first product; P_2 – second product – dehidroascorbic acid; S – measured substrate – cathechol; C – cosubstrate – oxygen; R – reducing agent – L- ascorbic acid; L – medial product –1,2 benzohinon.

As a reducing agent is used L- ascorbic acid because it reduce 1,2 benzohinone to cathehol and turn the reaction towards enzyme oxidizing of cathehol in the presence of enzyme tyrosinase [6,7]. The oxygen consumed with enzyme reaction is not compensating from cyclic reduction of L - ascorbic acid. Therefore if L - ascorbic acid is not influence of enzyme there will be cyclic reaction on substrate. Consuming of dissolved oxygen will continue while concentration of substrate is run out, after some cycles. This scheme shows that current is amplificated when L –ascorbic acid presences in the research medium. The reactions can be explained with following equations:

$$\begin{aligned} S + C &\xrightarrow{K_1} L + P_1 \\ L + R &\xrightarrow{K_2} S + P_2 \end{aligned} \qquad (1)$$

In those reactions predominate processes of diffusion and the second Fik's low is in action. System of differential equations for the first order have the following mode

$$\begin{aligned} D_S \frac{d^2S}{dx^2} &= K_1S - K_2L - K_2R \\ D_L \frac{d^2L}{dx^2} &= K_2L - K_1S \\ D_R \frac{d^2R}{dx^2} &= K_2R \\ D_{P_1} \frac{d^2P_1}{dx^2} &= -K_1S \\ D_{P_2} \frac{d^2P_2}{dx^2} &= -K_2R \\ D_C \frac{d^2C}{dx^2} &= K_1S \end{aligned} \qquad (2)$$

here: D_S,D_L,D_R,D_{P1},D_{P2},D_C are diffusion coefficients of substrate, medial product, reducing agent, first and second product, and co-substrate in active membrane with thickness a.

In the result of enzyme and chemical reaction in the research medium concentration decreasing of oxygen producing decreasing of output current, in steady state regime it is given with expression

$$I = nFADc\ dC/dx, \qquad (3)$$

here: n are the number of electrons taking part in the electrochemical reaction, F - Faraday's constant , A –surface of cathode [m^2], I – output current[A].

3. SOLUTION OF THE EQUALS SYSTEM DESCRIBING BEHAVIOR OF HYBRID BIOSENSOR

Because products P_1 and P_2 are not electrochemically active, the system is reducing to:

$$\begin{aligned} D_S \frac{d^2S}{dx^2} &= K_1S - K_2L - K_2R \\ D_L \frac{d^2L}{dx^2} &= K_2L - K_1S \\ D_R \frac{d^2R}{dx^2} &= K_2R \\ D_C \frac{d^2C}{dx^2} &= K_1S \end{aligned} \qquad (4)$$

We examine system for b=0 and d=0. Limiting conditions are

For $x = 0 \quad S(0) = So$
$x = 0 \quad R(0) = Ro$ (5)

$x = 0 \quad C(0) = Co$
For $x = a \quad C(a) = 0$ (6)
co-substrate is run out.

Also limiting conditions are known

$$\left.\frac{dS}{dx}\right|_{x=a} = 0, \left.\frac{dL}{dx}\right|_{x=a} = 0, \left.\frac{dR}{dx}\right|_{x=a} = 0 \tag{7}$$

We are looking for changing of substrate S(x), medial product L(x), gradient of co-substrate $\left.\frac{dC}{dx}\right|_{x=a}$ and of the reducing agent R(x).

Let we introduce these parameters

$$\frac{K_1}{D_S} = Q_1^2, \quad \frac{K_2}{D_L} = Q_2^2 \quad \frac{K_2}{D_R} = Q_3^2. \tag{8}$$

System of those four differential equations (4) is solved analytically and for the R(x) is received

$$R(x) = \frac{R_0}{1+e^{2Q_3 a}} e^{Q_3 x} + R_0 \frac{e^{2Q_3 a}}{1+e^{2Q_3 a}} e^{-Q_3 x} \tag{9}$$

After remake of that expression is received the following mode for reducing agent R(x)

$$R(x) = \frac{R_0 ch(Q_3(a-x))}{ch(Q_3 a)} \tag{10}$$

The final expression for the substrate S(x) is

$$S(x) = \frac{ch\left(\sqrt{Q_1^2 + Q_2^2}.(a-x)\right)\left(S_0 - \frac{K_2(D_R - D_L)R_0}{D_L(Q_3^2 - Q_1^2 - Q_2^2)D_S} - \frac{Q_2^2(D_S S_0 + D_R R_0)}{D_S(Q_1^2 + Q_2^2)}\right)}{ch\left(\sqrt{Q_1^2 + Q_2^2}.a\right)} + \tag{11}$$
$$+ \frac{K_2(D_R - D_L)R_0 ch(Q_3(a-x))}{D_L(Q_3^2 - Q_1^2 - Q_2^2)D_S ch(Q_3 a)} + \frac{Q_2^2(D_S S_0 + D_R R_0)}{D_S(Q_1^2 + Q_2^2)}$$

For the gradient of co-substrate dC/dx at x = a is received the expression

$$\frac{dC}{dx} = \frac{Q_1^2 Q_2^2 (D_S S_0 + D_R R_0)}{2D_C (Q_1^2 + Q_2^2)} a - \frac{C_o}{a} + + \frac{K_1}{aD_C} \left(\frac{S_o - M - N}{Q_1^2 + Q_2^2} \left(1 - \frac{1}{ch\sqrt{a}} \right) + \frac{M}{Q_3^2} \left(1 - \frac{1}{ch(Q_3 a)} \right) \right) \tag{12}$$

The final expression for the medial product L(x) is

$$L(x) = \frac{K_1}{D_L ch(Q_2 a)} \left(\frac{S_0 - M - N}{Q_1^2} + \frac{M2}{Q_3^2 + Q1} - \frac{N}{Q_2^2} \right) ch(Q_2 (a - x)) - \frac{K_1 (S_0 - M - N)}{Q_1^2 D_L ch\left(\sqrt{Q_1^2 + Q_2^2}.a \right)} ch\left(\sqrt{Q_1^2 + Q_2^2} (a - x) \right) - \frac{K_1 M}{D_L (Q_3^2 - Q_2^2) ch(Q_3 a)} .ch(Q_3 (a - x)) + \frac{K_1 N}{D_L Q_2^2} \tag{13}$$

.

where: $$M = \frac{K_2 (D_R - D_L) R_0}{D_L D_S (Q_3^2 - Q_1^2 - Q_2^2)} \quad ; \quad N = \frac{Q_2^2 (D_S S_0 + D_R R_0)}{D_S (Q_1^2 + Q_2^2)} \tag{14}$$

Now the output current can be determined, because the gradient of cosubstrate is found.

$$I = nFA \left\{ \begin{array}{l} - \frac{Q_1^2 Q_2^2 (D_S S_o + D_R R_o)}{2(Q_1^2 + Q_2^2)} a + \frac{DcC_o}{a} - \\ - \frac{K_1}{a} \left(\frac{S_o - M - N}{Q_1^2 + Q_2^2} \left(1 - \frac{1}{ch\left(\sqrt{(Q_1^2 + Q_2^2)} a \right)} \right) + \frac{M}{Q_3^2} \left(1 - \frac{1}{ch(Q_3 a)} \right) \right) \end{array} \right\} \tag{15}$$

4. DETERMINATION OF THE AMPLIFICATION FACTOR

We can now determine the gain of sensitivity- G as a the ratio of current from cycling reaction and current from noncycling reaction (K_2 = 0) for the given measured substrate. Because $Q_1^2 >> 1$, $Q_2^2 >> 1$ and $Q_2^2 >> 1$ the expression is

$$G = \frac{\frac{Q_1^2 Q_2^2}{(Q_1^2 + Q_2^2)} aDsSo(1 + \sigma.d)}{2 \frac{k_1 So}{aQ_1^2}} , \tag{16}$$

where σ = Ro/So, d = D_R/Ds. If we consider that $\Phi_1^2 = \frac{V_{m1} a^2}{k_1 D_S}$ and $\Phi_2^2 = \frac{V_{m2} a^2}{k_2 D_R}$ are so called Thiles modules, the term can be written as

$$G = \frac{\Phi_1^2 \Phi_2^2 (1 + \sigma.d)}{2(\Phi_1^2 + \Phi_2^2)} \tag{17}$$

Some calculations are made for the following values of parameters: So = 1μM and reducing agent is changed Ro = 1mM, 5mM and 10mM those are according

experiments [6]. For the enzyme reaction in tissue $\Phi_1^2 = 9$, and for the chemical reaction $\Phi_2^2 = 0.035$ at the fig. 3 are shown the results. Line 1 – for the calculation of G now and line 2 from the paper [6].

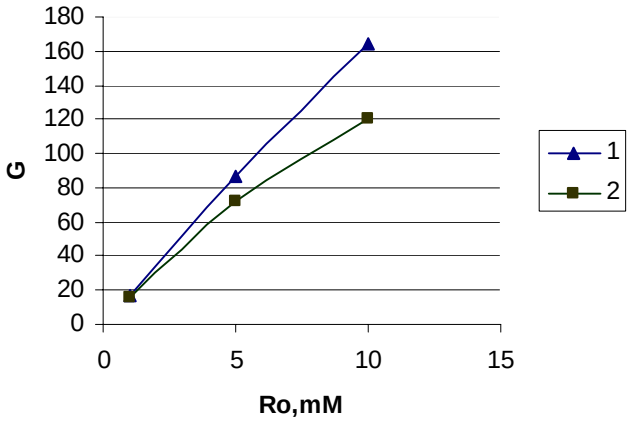

Fig. 3

5. CONCLUSION

- For the hybrid biosensor with bio-chemical amplification for the steady state regime a mathematical model is proposed.
- The system of 6 differential equations for enzyme kinetic of first order is solved.
- The determined expressions for concentration profiles of measuring substrate – S, reducing agent - R, medial product - L and gradient of co-substrate C are received.
- The transfer function I=f(So) is received .
- The amplification factor is determined.

Those expressions can be used for simulating of biosensor system and examine the influence of each parameter over the output current and for optimization of the inner parameters of biosensor system - a, D_S,D_C,D_R,D_L, and investigation of influence of kinetics parameters - K_1,K_2. The purpose can be receiving of maximal measured range, maximal sensitivity and other metrological criterions.

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