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Analysis of Intrinsic Stochastic Fluctuations of the Time Response of Adsorption-Based Microfluidic Bio/Chemical Sensors: the Case of Bialyte Mixtures

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Abstract – Real-time in situ operation of bio/chemical sensors assumes detection of chemical substances or biological specimens in samples of complex composition. Since sensor selectivity cannot be ideal, adsorption of particles other than target particles inevitably occur on the sensing surface. That affects the sensor response and its intrinsic fluctuations which are caused by stochastic fluctuations of the numbers of adsorbed particles of all the adsorbing substances. In microfluidic sensors, such response fluctuations are a result of coupled adsorption, desorption and mass transfer (convection and diffusion) processes of analyte particles. Analysis of these fluctuations is important because they constitute the adsorption-desorption noise, which limits the sensing performance. In this work we perform the analysis of fluctuations by using a stochastic model of sensor response after the steady state is reached, in the case of two-analyte adsorption, considering mass transfer processes. The results enable estimation of the ultimate sensing performance of adsorption-based microfluidic bio/chemical sensors of different sensing areas, operating in bialyte mixture environments.

I. INTRODUCTION

Microfluidic bio/chemical sensors are highly sensitive devices for detection of biological specimens or chemical substances [1]-[3]. A significant advantage of these devices compared to conventional laboratory equipment is their capability of real-time in-situ operation. However, such applications assume the use of native samples taken from the environment or living organisms, which are of complex composition.

In adsorption-based devices sensor response is determined by the number of adsorbed particles of a certain species on the sensing surface. In microfluidic sensors this number is determined both by adsorption-desorption (AD) processes and mass transfer (MT) processes (convection and diffusion of particles toward the sensing surface and away from it). In the case of native (complex) samples, not only particles of the target substance, but also those of other substances existing in the sample can be adsorbed,

due to the non-ideal sensor selectivity. Therefore, it is necessary to take into account AD processes and mass transfer of all the adsorbing substances in the analysis of sensor response. This is also true for the analysis of intrinsic response fluctuations that originate from the inevitable fluctuations of the number of adsorbed particles, which determine the AD noise and the sensor minimal detectable concentration.

Analysis of AD fluctuations of sensor response is performed by using stochastic models. The models that take into account the coupling between AD and MT processes are derived for the case of an ideally selective sensor, in which only the target substance is adsorbed on the sensing surface [4], [5]. Recently a stochastic model that takes into account MT was presented for adsorption of two substances, and it was used for the analysis of the expected number of adsorbed particles of both species, which determines the sensor response kinetics [6]. However, until now, the analysis of fluctuations was not performed by using a stochastic model of sensor response in the case of two-analyte adsorption, and considering MT.

In this work we first give a review of the sensor response stochastic model in the case of coupling of adsorption-desorption and mass transfer of substances present in a bialyte mixture. The model enables investigation of the influence of various parameters on sensor response fluctuations. We use the steady-state form of the model for the analysis of variances and the covariance of the stochastic numbers of adsorbed particles depending on the sensing surface area, which determine the intrinsic fluctuations of sensor response. This analysis is useful for estimation of the ultimate noise performance and the minimal detectable signal of adsorption-based sensors (e.g. plasmonic, surface/bulk acoustic wave, micro/nano-cantilever, nanowire FET sensor) of different sensing areas.

II. MODELING OF SENSOR RESPONSE

The mathematical model that describes the stochastic AD processes on the sensing surface, coupled with mass transfer in the sensor microfluidic chamber for the case of a bialyte mixture is obtained starting from the Master equation for the bivariate gain-loss processes and the definitions of the first and the second moments of a random vector variable $\mathbf{N}=[N_1 \ N_2]$, where N_1 and N_2 are the stochastic numbers of adsorbed particles of the two

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analytes. The model is in the form of five differential equations

$$\frac{d \langle N_i \rangle}{dt} = \langle A_i(N_1, N_2) \rangle - \langle D_i(N_i) \rangle \quad (1)$$

$$\frac{d \sigma_i^2}{dt} = \langle A_i(N_1, N_2) \rangle + \langle D_i(N_i) \rangle + 2 \langle (N_i - \langle N_i \rangle) [A_i(N_1, N_2) - D_i(N_i)] \rangle \quad (2)$$

$$\frac{d \sigma_{12}}{dt} = \langle (N_1 - \langle N_1 \rangle) [A_2(N_1, N_2) - D_2(N_2)] \rangle + \langle (N_2 - \langle N_2 \rangle) [A_1(N_1, N_2) - D_1(N_1)] \rangle \quad (3)$$

Here $\langle N_i \rangle$ is the expected value and σ_i^2 is the variance of the number of adsorbed particles of the type i ($i=1$ or 2), $\sigma_{12} = \sigma_{21}$ is the covariance of the random variables N_1 and N_2 , while A_i and D_i are the probabilities of increase and decrease of the number of adsorbed particles of the i^{th} substance by one in unit time, respectively. Each of Eqs. (1) and (2) replaces two equations of that system, of which one is obtained for $i=1$, and the other one for $i=2$. The system of Eqs. (1)-(3) is obtained by assuming that at any given moment a change of the number of adsorbed particles is possible for one substance only, by $+1$ or -1 . The transition probabilities in unit time, A_i and D_i , are determined by using the two-compartment model [7] to approximate the temporally and spatially dependent concentrations of substances in reaction chambers of microfluidic sensors. Such concentrations are a result of the coupling of AD processes, convection, and diffusion of analyte particles of two substances. By assuming 1:1 competitive binding of analyte particles to adsorption sites on the sensing surface, and the Langmuir adsorption, the two-compartment model yields the following expressions for the probabilities of transition between the adjacent states of the random vector variable \mathbf{N} [6]

$$A_i = k_{ai} \frac{C_i + \frac{k_{di} N_i}{k_{mi} A}}{1 + \frac{k_{ai} (N_m - N_1 - N_2)}{k_{mi} A}} (N_m - N_1 - N_2), \quad D_i = k_{di} N_i$$

where C_i is the concentration of the i^{th} analyte in the sample entering the microfluidic chamber, k_{ai} and k_{di} are its adsorption and desorption rate constants, k_{mi} is the mass transfer coefficient of the analyte i [7], N_m is the number of surface binding sites, and A is the sensing surface area (the binding sites surface density, which is the parameter used in the numerical simulations, equals N_m/A).

Eqs. (1)-(3) become the system of equations for the first two moments after the Taylor expansion of bivariate functions $A_i(N_1, N_2)$, centered at the expected values. In the steady state the system is

$$A_{ie} - D_{ie} + \frac{1}{2} \left[\frac{\partial^2 A_i}{\partial N_1^2} \sigma_{1e}^2 + 2 \frac{\partial^2 A_i}{\partial N_1 \partial N_2} \sigma_{12e} + \frac{\partial^2 A_i}{\partial N_2^2} \sigma_{2e}^2 \right] = 0 \quad (4)$$

$$A_{ie} + D_{ie} + \left[2 \left(\frac{\partial A_i}{\partial N_i} - \frac{\partial D_i}{\partial N_i} \right) + \frac{1}{2} \frac{\partial^2 A_i}{\partial N_i^2} \right] \sigma_{ie}^2 + \left(2 \frac{\partial A_i}{\partial N_j} + \frac{\partial^2 A_i}{\partial N_1 \partial N_2} \right) \sigma_{12e} + \frac{1}{2} \frac{\partial^2 A_j}{\partial N_j^2} \sigma_{je}^2 = 0 \quad (5)$$

$$\frac{\partial A_2}{\partial N_1} \sigma_{1e}^2 + \left(\frac{\partial A_1}{\partial N_1} - \frac{\partial D_1}{\partial N_1} + \frac{\partial A_2}{\partial N_2} - \frac{\partial D_2}{\partial N_2} \right) \sigma_{12e} + \frac{\partial A_1}{\partial N_2} \sigma_{2e}^2 = 0 \quad (6)$$

where $i=1$ or 2 , $j=1$ or 2 , $i \neq j$ in Eq. (5), $A_{ie} = A_i(\langle N_{1e} \rangle, \langle N_{2e} \rangle)$, $D_{ie} = D_i(\langle N_{ie} \rangle)$, and all the partial derivatives are calculated for $N_1 = \langle N_{1e} \rangle$ and $N_2 = \langle N_{2e} \rangle$. By solving this system we obtain the steady-state expected values, variances and the covariance of stochastic numbers of adsorbed particles ($\langle N_{1e} \rangle$, $\langle N_{2e} \rangle$, σ_{1e}^2 , σ_{2e}^2 , and σ_{12e}), which are a measure of steady-state intrinsic fluctuations of sensor response.

As the sensor response due to adsorption of two substances is $r = m_1 N_1 + m_2 N_2$ (m_1 and m_2 are the weight factors that represent the average contribution of a single adsorbed particle of the first and second analyte to the sensor response), the steady-state variance of sensor response is given by the expression

$$\langle (\Delta r)_e^2 \rangle = m_1^2 \sigma_{1e}^2 + m_2^2 \sigma_{2e}^2 + 2 m_1 m_2 \sigma_{12e} \quad (7)$$

The intrinsic response fluctuations in steady state due to the coupling of AD and MT processes, known as AD noise, are expressed as the square root of $\langle (\Delta r)_e^2 \rangle$, and they are completely determined by the solutions of the system of equations (4)-(6).

III. ANALYSIS OF SENSOR STOCHASTIC RESPONSE

The presented mathematical model is used for the analysis of the steady-state expected values, variances and the covariance of the numbers of adsorbed molecules of two proteins on the surface of a microfluidic biosensor. The parameter values are given in Table I. The results given in Figs. 1 and 2 show the dependencies of these quantities on the sensing surface area in the range from 10^{-13} m^2 to 10^{-11} m^2 .

TABLE I
PARAMETER VALUES

Parameter	Analyte 1	Analyte 2
Concentration	$6 \cdot 10^{17} \text{ 1/m}^3$	$1.2 \cdot 10^{18} \text{ 1/m}^3$
Adsorption rate constant	$1.3 \cdot 10^{-19} \text{ m}^3/\text{s}$	$1.3 \cdot 10^{-20} \text{ m}^3/\text{s}$
Desorption rate constant	0.08 s	0.02 s
Mass transfer coefficient	$2 \cdot 10^{-5} \text{ m/s}$	$2 \cdot 10^{-5} \text{ m/s}$
Binding sites density	$6 \cdot 10^{15} \text{ 1/m}^2$	

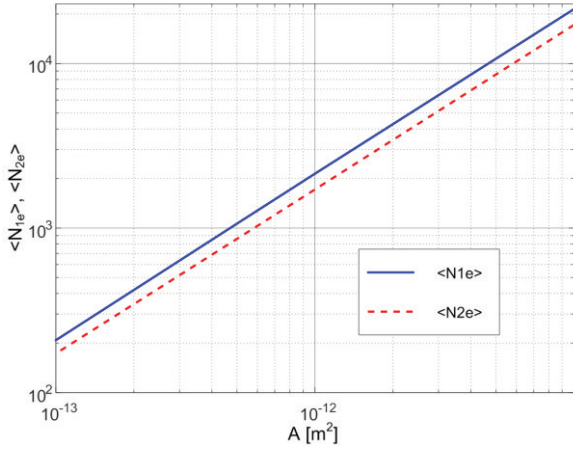


Fig. 1 Expected values of the numbers of adsorbed particles of two proteins depending on the sensing surface area. Two proteins are competitively adsorbed.

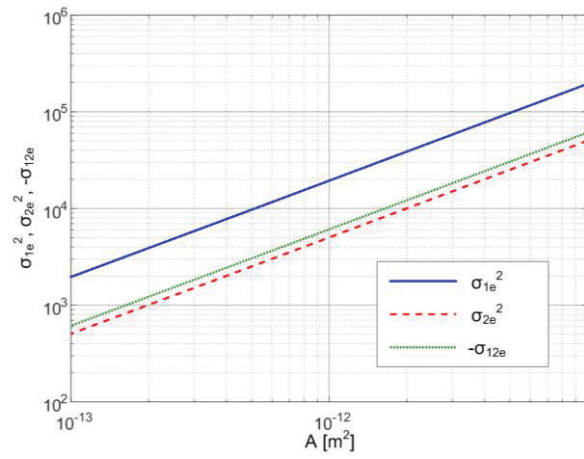


Fig. 2 Variances and covariance of the numbers of adsorbed particles of two competitive proteins depending on the sensing surface area.

As it can be seen in Fig. 1, there is a continuous increase of the expected values of the numbers of adsorbed particles of two proteins as the surface area increases. Also, it can be seen that these two values are close to each other although the analyte 2 has a lower affinity (defined by the affinity constant $K_a = k_{ad}/k_{di}$) for adsorption sites. Therefore, the competitive (in most cases unwanted) adsorption of another substance can significantly affect the expected value of the steady-state sensor response, which equals $\langle r_e \rangle = m_1 \langle N_{1e} \rangle + m_2 \langle N_{2e} \rangle$, although this influence also depends on the values of the weight factors m_1 and m_2 .

Variances and covariance of N_1 and N_2 also increase in sensors of larger sensing areas, as shown in Fig. 2. The covariance is negative, so the diagram shows its absolute value. It is of the same order of magnitude as the variances of the numbers of adsorbed particles. Based on Eq. (7) it can be concluded that, due to the negative covariance value, depending on the values of parameters m_1 and m_2 ,

the steady-state variance of sensor response (and thus the sensor's AD noise) in the case of competitive adsorption can be higher or lower than in the case of single substance adsorption (adsorption of only one substance corresponds to the sensor of ideal selectivity).

The diagrams in Figs. 1 and 2 are general, as they show the statistical parameters that describe stochastic fluctuating numbers of adsorbed particles, so they are valid for any type of adsorption-based sensor (surface plasmon resonance sensors, bulk and surface acoustic wave sensors, microcantilever sensors etc.), regardless of its measurement parameter (refraction index, acoustic wave frequency, deflection or oscillation frequency of a cantilever). When the values of the parameters m_1 and m_2 are taken into account for a given type of sensor, the presented diagrams enable the estimation of the influence of competitive adsorption on the steady-state expected value of sensor response, as well as its fluctuation, i.e. on the sensor's AD noise that determines the sensor's ultimate performance.

IV. CONCLUSION

In this paper the analysis is presented of the steady-state expected values, variances and the covariance of the numbers of adsorbed molecules of two proteins on the surface of a microfluidic biosensor, depending on the sensing surface area. Intrinsic fluctuations of the numbers of adsorbed particles are caused by the stochastic nature of adsorption-desorption and mass transfer processes of two analytes, so we used a stochastic model of sensor response that takes into account the coupling of these processes. Since the results and conclusions stemming from the analysis refer to the numbers of adsorbed particles, they are general in the sense that they are valid for any type of adsorption-based sensor (surface plasmon resonance sensors, bulk and surface acoustic wave sensors, microcantilever sensors etc.) whose response is governed by the number of adsorbed particles on the sensing surface.

The results enable estimation of the quantitative influence of competitive adsorption on the expected value of the steady-state sensor response and its intrinsic fluctuation, i.e. the adsorption-desorption noise and the ultimate performance of sensors with different sensing surface areas that operate in various bianalyte mixture environments. Depending on the type of substances and the values of parameters that relate the number of adsorbed particles and the time response of a given sensor, the response fluctuations can be higher or even lower than in the case of single substance adsorption on the sensing surface.

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