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Analysis of the Fundamental Detection Limit in Microfluidic Chemical and Biological Sensors

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***Abstract*—Detection limits in microfluidic chemical and biological sensors, which determine the range of analyte concentrations reliably detectable by the sensor, are important sensor parameters. The lower limit of detection, defined as the lowest concentration that can be distinguished from noise, has its minimum determined by the fundamental adsorption-desorption (AD) noise, inevitable in adsorption-based devices. In this work, we analyze this fundamental detection limit, particularly considering the influence of mass transfer processes in microfluidic devices. For that purpose, we derive the expression for the sensor's signal-to-noise ratio (SNR), which takes into account the AD noise, and then the equation for the minimal analyte concentration at which the SNR has a sufficiently high value for reliable analyte detection. Subsequently, we analyze the mass transfer influence on the sensor's maximal achievable signal-to-noise ratio and on the fundamental detection limit. The results of the analysis show a significant mass transfer influence on these important sensor performance metrics. They also provide guidelines for achieving the sensor's best possible detection performance through the optimization of the sensor design and operating conditions.**

***Index Terms*—Microfluidic sensor; biosensor; chemical sensor; detection limit; mass transfer; signal-to-noise ratio.**

I. Introduction

Detection of chemical substances or biological species (viruses, bacteria, DNA, proteins, cells), and measurement of their concentration in samples are performed in order to monitor the pollution present in the environment, food and water, or the health condition of living organisms. Therefore, their significance in environment protection, agriculture, food industry and healthcare is high. In these fields it is especially important to obtain reliable measurement results in a short period of time, and often at locations which are far from laboratories where conventional sample analysis can be performed. The concentrations to be detected are typically very low, requiring very sensitive measurement equipment and methods. Current research activities are aimed toward the development of highly sensitive and portable chemical and biological sensors based on micro- and nanotechnologies, which are recognized as promising for the mentioned applications. Among them are microfluidic adsorption-based sensors [1, 2].

In microfluidic devices a sensing element is placed in a reaction chamber, which is a part of a microfluidic system for sample delivery and analyte detection. The principle of operation of adsorption-based chemical and biological sensors is based on the adsorption-desorption (AD) process of analyte particles (gas atoms or molecules, biomolecules or micro-organisms) on the sensor's sensing surface, which causes a measurable change of some of the sensor's parameters, and yields the sensor's output signal. Therefore, the output signal is determined by the number of adsorbed analyte particles, which depends on the analyte concentration in the analyzed sample.

The instantaneous number of adsorbed particles depends on AD and mass transfer (convection and diffusion) processes of analyte particles, by which they are transported through the sensor's reaction chamber to and from the adsorption sites on the sensing surface where they bind and unbind. The random nature of these coupled processes results in inevitable stochastic fluctuations of the number of adsorbed particles, and therefore in stochastic fluctuations of the sensor's response, known as AD noise. This fundamental noise sets the ultimate noise performance of adsorption-based sensors, determining the maximal achievable signal-to-noise ratio (SNR), and the minimal detectable analyte concentration. The AD noise analysis is, therefore, significant for optimization of adsorption-based sensors in terms of improved sensing performance. It is based on the stochastic analysis of fluctuations of the number of adsorbed analyte particles.

Stochastic mathematical models for the analysis of fluctuations of the number of adsorbed particles that take into account mass transfer processes, are rare [3-5]. While those presented in [3, 4] consider coupled AD process and diffusion of analyte particles, the stochastic model presented in [5] takes into account the coupling of AD process, diffusion and

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convection, which corresponds to realistic operating conditions in microfluidic sensors. In the mentioned literature the stochastic models were used for the analysis of the expected value and variance of the number of adsorbed particles, which reveal the stochastic response kinetics and sensor AD noise, as well as for the analysis of the maximal possible sensor's SNR. The influence of mass transfer on sensor's SNR and detection limit has not been quantitatively analyzed in particular until now.

In this work, starting from the stochastic response model of adsorption-based sensors, which considers the influence of coupled stochastic AD and mass transfer processes on the change of the number of adsorbed particles [5], we derive the expression for the sensor's SNR that takes into account the AD noise. Subsequently we obtain the equation for determination of the minimal analyte concentration at which the SNR has a sufficiently high value for reliable analyte detection. After that, we analyze the SNR and the minimal concentration level of the analyte in microfluidic chemical and biological sensors, considering the influence of mass transfer of particles on these important sensor performance metrics. In numerical simulations that we perform, we consider the range of mass transfer coefficients typical for macromolecules that are detected by state-of-the-art biosensors. The presented results enable the analysis of the dependence of the minimal detectable signal on the sensor design parameters, and are useful for achieving the improved sensing performance.

II. THEORETICAL ANALYSIS

The fluctuations of the output signal of adsorption-based chemical and biological sensors result from various kinds of noise, i.e. the noise originating from the stochastic nature of physical processes (AD and mass transfer) which are essential for analyte detection by the sensing element, and the noises from the sensor transduction mechanism and the read-out circuitry. The former, known as AD noise, poses the fundamental detection and quantification limits of analyte concentration, inherent to all adsorption-based devices. In some cases, AD noise can dominate compared to other noise sources [3]. Assuming that the transducer noise and the noise of read-out circuitry are minimized by applying appropriate techniques, reduction of the inevitable AD noise remains a means of achieving the sensor's best possible detection performance, i.e. maximization of sensor's signal-to-noise ratio and approaching its lowest possible detection limit. Therefore, the analysis of the sensor SNR excluding the transducer and read-out circuitry noise yields the guidelines for lowering the fundamental detection limit.

By assuming a linear relation between the sensor response and the number of adsorbed particles, the expected value of stochastic response is $\langle r\rangle = m\langle N\rangle$ (where $\langle N\rangle$ is the expected value of the number of adsorbed analyte particles, and m is the proportionality factor equal to the average contribution of a single particle adsorption to the sensor response), sensor's AD noise is $\sigma_{r,AD}^2 = m^2\sigma_N^2$ (where σ_N^2 is the variance of the number of adsorbed particles), so the sensor's maximal SNR (the ratio of signal power and noise power), which is determined only by the fundamental AD noise, is

$$SNR = \frac{< N >^2}{\sigma_N^2} \tag{1}$$

Here we consider the SNR in the steady state (established after all transient processes have ended), in which the measurements are preferably carried out in practice. We use the stochastic model presented in [5], describing the number of adsorbed particles that randomly fluctuates due to coupled AD and mass transfer processes. Based on the model, the steady-state expected value and variance of the number of adsorbed particles are given by expressions

$$\langle N\rangle = \frac{N_m k_a C}{k_a C + k_d + \frac{k_a k_d}{k_m A}} \tag{2}$$

$$\sigma_N^2 = k_d\langle N\rangle \frac{\left[1 + (N_m - \langle N\rangle)\frac{k_a}{k_m A}\right]^2}{k_a C + k_d + \frac{k_a k_d N_m}{k_m A}} \tag{3}$$

respectively, where C is the concentration of target particles in the analyzed sample, N_m is the number of adsorption sites on the sensing surface, k_a and k_d are the adsorption and desorption rate constants, k_m is the mass transfer coefficient which models the combined effect of diffusion and convection on particle transport to the surface adsorption sites and from them, and A is the sensing surface area. k_m depends on geometrical parameters of the sensing system, the flow rate of the sample, and the diffusivity of the analyte [6]. Based on Eqs. (1)-(3) we obtain

$$SNR = \frac{k_a C N_m}{k_d} \cdot \frac{\left[k_a C + k_d\left(1 + \frac{k_a}{k_m A}\right)\right]\left[k_a C + k_d\left(1 + \frac{k_a N_m}{k_m A}\right)\right]}{\left[k_a C + k_d\left(1 + \frac{k_a}{k_m A}\right)\left(1 + \frac{k_a N_m}{k_m A}\right)\right]^2} \tag{4}$$

This expression clearly shows the dependence of the sensor's maximal achievable SNR on the mass transfer coefficient, and thus enables the analysis of the influence of mass transfer process on the SNR.

The dynamic range, defined as the range of analyte concentrations reliably detectable by the sensor, is also one of important sensor characteristics. The upper limit of the dynamic range is determined by the sensor saturation, i.e. the limited number of adsorption sites on the sensing surface. It will not be considered in this paper. The lower limit of the

dynamic range is the lowest concentration that can be distinguished from noise. This detection limit is determined as the analyte concentration level at which the sensor's SNR is equal to a minimal acceptable value for reliable detection. Let us assume that it is a value F. The condition $SNR=F$, where the SNR is given by Eq. (4), yields the equation for the fundamental detection limit C_{min}

$$\begin{aligned}&(k_aC_{\min})^3\frac{N_m}{k_d}+(k_aC_{\min})^2\left[N_m\left(2+\frac{k_a}{k_mA}+\frac{k_aN_m}{k_mA}\right)-F\right]\\&+(k_aC_{\min})\left[(N_m-2F)k_d\left(1+\frac{k_a}{k_mA}\right)\left(1+\frac{k_aN_m}{k_mA}\right)\right]\\&-Fk_d^2\left(1+\frac{k_a}{k_mA}\right)^2\left(1+\frac{k_aN_m}{k_mA}\right)^2=0\end{aligned} \tag{5}$$

By numerically solving the Eq. (5) for C_{min} for a series of the coefficient k_m values, the analysis can be performed of the mass transfer effect on the minimal concentration that can be reliably detected at the required SNR value F.

III. Results and Discussion

By using the derived expressions (Eqs. (4) and (5)) we analyze the SNR and the minimal concentration level at which the SNR has the required value that ensures reliable analyte detection in microfluidic chemical and biological sensors. We particularly consider the influence of mass transfer of particles on these important performance characteristics, after the steady state of all relevant transient processes has been reached.

A biosensor for detection of macromolecules (proteins), with the sensing surface area $A=10^{-11}$ m^2, and the adsorption sites surface density $n_m=N_m/A=3\cdot10^{17}$ 1/m^2 is used in the analysis. The parameters of the AD process are $k_a=1.33\cdot10^{-19}$ m^3/s and $k_d=0.08$ 1/s. The range of the mass transfer coefficient k_m is from 10^{-6} m/s to 10^{-1} m/s.

Fig. 1 shows the biosensor's SNR as a function of the mass transfer coefficient at the analyte concentration $C=6\cdot10^{16}$ 1/m^3 (the solid curve). The dashed curve represents the SNR obtained by using the stochastic model that neglects the mass transfer influence [5], according to which

$$SNR_i=\frac{k_aCN_m}{k_d} \tag{6}$$

The diagram in Fig. 1 shows that the SNR value is lower for lower mass transfer rates (i.e, for lower k_m). Hence, slow mass transfer reduces the maximal possible sensor's SNR. In the considered range of k_m values SNR exhibits a change of almost three orders of magnitude. As k_m value increases, SNR monotonically increases and reaches its maximal value equal to that obtained by using the model that does not take into account mass transfer (Eq. (6)). Therefore, when mass transfer is sufficiently fast, its influence becomes negligible. In the analyzed case, mass transfer with the coefficient greater than 10^{-2} m/s does not lead to the decrease of the sensor's SNR.

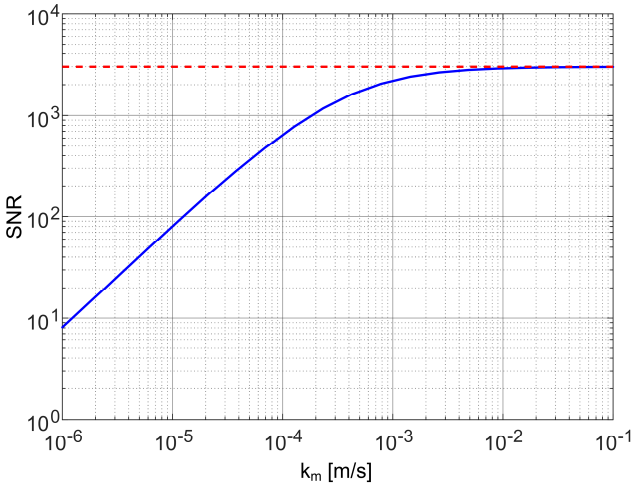

Fig. 1 The sensor's maximal achievable SNR depending on the mass transfer coefficient (solid line), and SNR obtained by neglecting the mass transfer influence (dashed line).

The minimal concentration level for $SNR=9$ (a value considered as required for reliable analyte detection [7]) is shown as a function of k_m in Fig. 2 (solid line). C_{min} obtained from Eq. (6) for $SNR_i=F$

$$C_{\min,i}=\frac{Fk_d}{k_aN_m} \tag{7}$$

i.e. by the analysis that neglects the mass transfer influence, is represented by a dashed line in the same diagram, also for $F=9$.

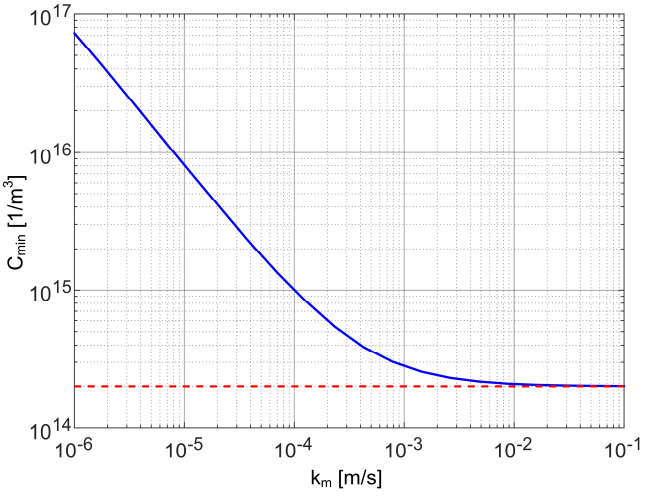

Fig. 2 The dependence of the sensor's fundamental detection limit on the mass transfer coefficient (solid line), and the same parameter obtained by neglecting the mass transfer influence (dashed line).

Fig. 2 shows that mass transfer significantly influences C_{min} in such a way that slow mass transfer increases the

concentration value and thus degrades the sensor performance. When the mass transfer is sufficiently fast, its effect becomes negligible, and C_{min} reaches the lowest value equal to $C_{min,i}$.

The presented analysis shows that it is necessary to consider the mass transfer influence when the optimization of microfluidic sensors and their operating conditions is performed aiming to achieve the required SNR value for reliable analyte detection, i.e. to ensure analyte detection in a certain concentration range.

IV. Conclusions

In this paper the theory is presented that enables the analysis of mass transfer influence on the maximal achievable SNR, and of the lowest detectable analyte concentration in microfluidic sensors. The analysis has shown that a slow mass transfer degrades these important sensor performance parameters.

The mass transfer coefficient is a known function of the sensing system geometrical parameters, the flow rate of the sample through the microfluidic reaction chamber, and the diffusivity of the analyte. Therefore, the presented theory enables the analysis of the dependences of the considered sensor performance metrics on sensor design parameters and operating conditions, and thus provides the means for sensor optimization.

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