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Signal-to-Noise Ratio in Adsorption-Based Microfluidic Bio/Chemical Sensors

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Abstract

The noise due to stochastic fluctuations of the number of adsorbed analyte particles, caused by random adsorption-desorption (AD) process coupled with analyte convection and diffusion, is inherent to adsorption-based bio/chemical sensors. It posses the fundamental limit for the detection of analyte. In this study we perform an analysis of the signal-to-noise ratio (SNR) of microfluidic sensors, taking into account their AD noise. We have shown that mass transfer significantly influences the possibility to achieve the acceptable SNR value. It also influences the minimal detectable concentration and also the time necessary to reach the SNR value that ensures reliable real-time detection and quantification of the analyte.

1. Introduction

The operation of adsorption-based chemical and biological sensors is based on the adsorption-desorption (AD) process of the particles of the substance to be detected, which takes place on the sensor's active surface and is accompanied with the processes of particle transport to the surface and from the surface. At low concentrations of the analyte and with the reduction of the size of the sensing surface, the stochastic nature of these processes becomes prominent, resulting in the fluctuations of sensor signal, known as AD noise or bio/chemical noise.

The time response of the sensor is determined by the number of adsorbed particles, $N(t)$, characterized at any time by its expected value, $<N(t)>$, and variance, $\sigma_N^2(t)=<\Delta N^2(t)>$, which is a measure of AD noise. The overall fluctuations of the response are also determined by other noise mechanisms originating from the sensor transduction

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mechanism and read-out circuitry, while the inevitable AD noise determines the fundamental limits of detection and quantification of the analyte, inherent in all adsorption-based sensors.

In this paper, we analyze the above-mentioned statistical parameters of the response of microfluidic sensors and particularly the signal-to-noise ratio (SNR), which is an important parameter for the optimization of sensor performance. In [1] stochastic simulation is used for the analysis of a sensor's SNR, taking into consideration only the transport of analyte particles by diffusion. The time-dependent SNR of a biosensor is analyzed in [2] using a theoretical model that does not take into account mass transfer effects. Here, we present the analysis of the SNR of a microfluidic sensor, where analyte particles are transported by convection and diffusion. Our analysis is based on the equations for the expectation and variance of a random number of adsorbed particles, derived from the master equation. We used a two compartment model (TCM) for the approximation of the spatial distribution of the analyte concentration in the sensor chamber, in order to model the binding kinetics of the analyte particles, taking into account the AD process, the convection and diffusion of particles (the applicability of the model has been experimentally confirmed for various types of adsorption based sensors [3-5]). The goal of the analysis is to investigate the possible influence of the mass transfer effect on the achievable SNR value, on the minimal detectable concentration and also on the time necessary to reach the SNR value necessary for reliable real-time analyte detection and determination of analyte concentration.

2. Theoretical considerations

The stochastic number of analyte particles adsorbed onto the sensor surface, $N(t)$, is a random process which belongs to the class of gain-loss processes [6]. The probability distribution of the random variable N of this type in an arbitrary moment of time t, $t \geq 0$, for the given initial state N_0 ($t=0$ is the moment when the AD process starts on the sensing surface, thus $N_0=0$), is given by the master equation

$$\frac{d}{dt}P_n(N,t) = P_n(N-1,t) \cdot a(N-1) + P_n(N+1,t) \cdot d(N+1) - P_n(N,t) \cdot (a(N) + d(N)) \tag{1}$$

where $a(N)$ and $d(N)$ denote the propensity functions, i.e. the probability of transition from the state N to the state $N+1$ and from the state N to the state N-1 in unit time, respectively. In the considered case, $a(N)$ and $d(N)$ equal the effective rate of increase and the effective rate of decrease of the number of adsorbed particles, respectively, and they take into account the combined influence of the AD process, convection and diffusion on the change of N. When the two-compartment model is used for the approximation of the spatial distribution of analyte concentration in a reaction chamber, these rates are given by the expressions $a(N)=k_a(C+k_dN/(k_mA))(N_m-N)/(1+k_a(N_m-N)/(k_mA))$ and $d(N)=k_dN$ [7] (all parameters are defined in Table 1).

Starting from the master equation and the definitions for the first and the second moment of a random variable the equations for the expectation and variance of a random number of adsorbed particles are obtained [6]

$$\frac{d}{dt}<N>(t) = <a(N) - d(N)> \tag{2a}$$

$$\frac{d(\sigma_N^2(t))}{dt} = <a(\eta) + d(\eta)> + 2\langle(\eta - <\eta>)[a(\eta) - d(\eta)]\rangle \tag{2b}$$

In the case of nonlinear gain-loss processes (where the propensity functions $a(N)$ and/or $d(N)$ are nonlinear functions of N) these equations have the approximate form

$$d<N>/dt = a(<N>) - d(<N>) + (a'' - d'') \cdot \sigma_N^2/2 \tag{3a}$$

$$d\sigma_N^2/dt = a(<N>) + d(<N>) + [2(a' - d') + (a'' + d'')/2] \cdot \sigma_N^2 \tag{3b}$$

Here a' and a'' denote the first and the second derivative of a with respect to N in $N=\langle N \rangle$, and correspondingly for d' and d''.

The SNR is defined as $SN(t)=\langle N \rangle(t)/\sigma_N(t)$, where $\langle N \rangle(t)$ and $\sigma_N(t)$ are the solutions of the previous system of equations.

3. Results

Fig. 1 shows the time dependent SNR for the biosensor in the case when the mass transfer influence is pronounced (k_{m1}), and the case of negligible mass transfer influence (k_{m2}), respectively, for different analyte concentrations (the values of all parameters are given in Table 1). The diagrams show that the SNR decreases with the decrease of C, both for rapid and slow mass transfer. Also, slow mass transfer decreases the maximal achieveable SNR value for the given analyte concentration, i.e. the value of k_m determines whether it is possible to reach the required SNR value when the concentration is low. Fig. 2 shows the time necessary for the SNR to reach the value of 3 or 10 as a function of C (SNR=3 corresponds to the limit of detection, and SNR=10 to the limit of quantification [8]). Accordingly, slow mass transfer increases the time necessary to reach the SNR value needed for analyte detection and quantification.
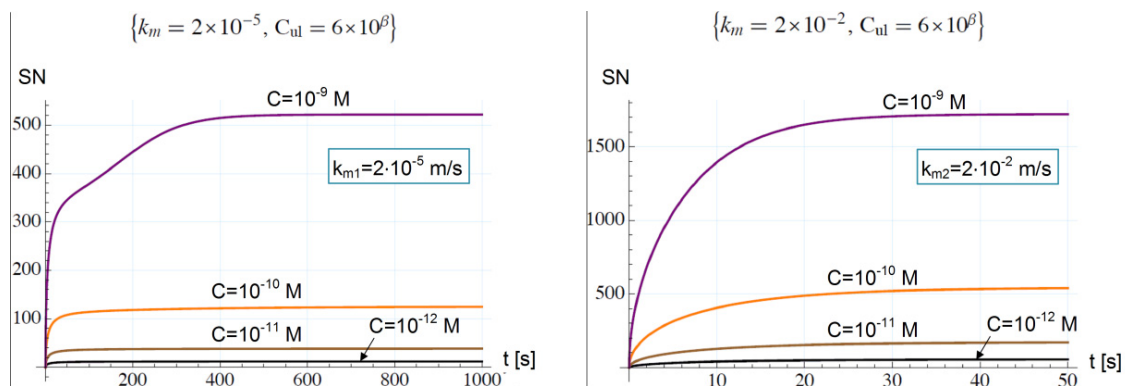

Fig. 1: Time-dependent SNR of a biosensor: (left) when the mass transfer influence is pronounced (k_{m1}), and (right) when the mass transfer influence is negligible (k_{m2}), for different target analyte concentrations.
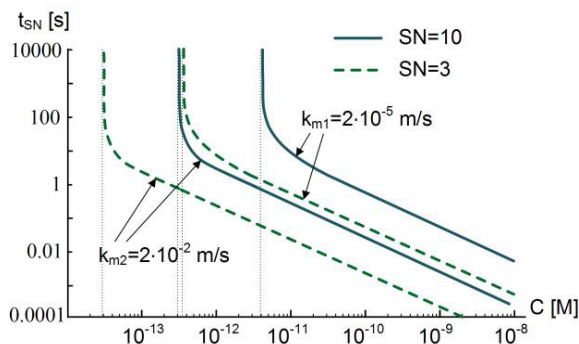

Fig. 2: The time necessary for the SNR to reach the value of 3 (solid lines) or 10 (dashed lines) as a function of C, for two different values of k_m.

Table 1: Parameters and their symbols and numerical values (1 M=1 mol/dm³).

Parameter	Symbol	Numerical values
Association rate constant	k_a	$8 \cdot 10^7$ 1/(Ms)
Dissociation rate constant	k_d	0.08 1/s
Mass transfer coefficient	k_m	$2 \cdot 10^{-5}$ m/s, $2 \cdot 10^{-2}$ m/s
Target analyte concentration	C	10^{-14} - 10^{-8} M
Surface density of adsorption sites	n_m	$5 \cdot 10^{-12}$ m·M
Number of adsorption sites	N_m	$3 \cdot 10^6$
Sensing area	A	10^{-9} m^2

4. Conclusions

The analysis of the signal-to-noise ratio (SNR) of microfluidic sensors, taking into account their AD noise, was performed. It has shown that the SNR decreases with the decrease of the analyte concentration, both for rapid and slow mass transfer. Also, slow mass transfer decreases the maximal achieveable value of the signal-to-noise ratio (SNR) for the given analyte concentration, i.e. the mass transfer rate determines whether it is possible to reach the required SNR ratio when the concentration is low. Slow mass transfer increases the time necessary to reach the SNR value needed for analyte detection and quantification. The analysis is useful for the optimal design of microfluidic sensors for real-time sensing.

Acknowledgements

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