Analysis of the Time Response of Chemical and Biological Microfluidic Sensors with a Micro/Nanoscale Active Surface

Ivana Jokić, Zoran Djurić, Katarina Radulović, Miloš Frantlović, Katarina Cvetanović Zobenica

Abstract—**After a review of a deterministic model of time response of microfluidic adsorption-based chemical and biological sensors, we present an approximate model for efficient analysis of stochastic response, which takes into account a random AD process coupled with convection and diffusion of target substance particles. Subsequently, we present the results obtained by the comparison of the two response models (deterministic and stochastic) used for sensors with different micro/nanoscale active surfaces, and intended for detection of substances present in different concentrations. In this way we can distinguish the cases in which the use of the deterministic model is justified from those in which the use of the stochastic model is necessary. The presented findings enable more accurate interpretation of measurement results obtained by using sensors with micro/nanoscale active surface, as well as optimization of their design.**

Index Terms—**Microfluidic sensor; biosensor; chemical sensor; deterministic time response; stochastic time response.**

I. INTRODUCTION

MICROFLUIDIC adsorption-based chemical and biological sensors are promising devices for real-time, in-situ and low-cost analysis of samples taken from the environment, food or living organisms, for detection of the presence and measurement of the amount of a target chemical substance or biological specimen [1]. Their principle of operation is based on the process of reversible binding of the target particles (molecules, atoms, ions, microorganisms) on the sensor's active surface, which causes a change of the sensor's measurable parameter and yields the sensor's response. Several types of such sensors exist: plasmonic sensors (SPR – Surface Plasmon Resonance), sensors with micro/nanocantilevers, piezoelectric sensors with bulk acoustic waves (FBAR – thin Film Bulk Acoustic Wave, QCM – Quartz Crystal Microbalance) or sensors with surface acoustic waves (SAW – Surface Acoustic Wave), nanowire FET sensors etc. The difference between them is e.g. in the physical mechanism of conversion of the binding events into a sensing parameter and in the physical nature of that parameter (optical, mechanical, electrical).

Key physical processes for binding of particles to the sensing surface are the adsorption-desorption (AD) process and the mass transfer process (convection and diffusion). In the former, the target particles bind to surface adsorption sites due to a certain affinity, and unbind from them. In the latter, the particles present in a microfluidic channel are transported to or from the binding sites. The sensor time response is determined by the time evolution of the number of adsorbed particles, $N(t)$, which is the result of coupling of the AD process and the mass transfer process. Due to the random nature of these coupled processes, the number of adsorbed particles randomly fluctuates, causing inevitable stochastic fluctuations of the sensor response, known as AD noise.

Analysis of the response of chemical and biological sensors in practice [2, 3] is usually performed by using theoretical models based on macroscopic formulations. In such models, the change of N in time is determined by the difference of instantaneous adsorption and desorption rates, and it is a function of the time dependent concentration in a close vicinity of adsorption sites, defined by the convection-diffusion equation (a partial differential equation) and its initial and boundary conditions. In many kinds of microfluidic sensors, the mentioned complex mathematical model can be significantly simplified by using the two-compartment model (TCM) for describing the concentration of target particles, which changes in space and time due to the combined effect of mass transfer, adsorption and desorption. The viability of the model for approximation of sensor response kinetics is experimentally confirmed [3-5]. In such macroscopic models the random character of $N(t)$ is averaged out, and it is obtained as a deterministic value.

Stochastic models deal with the random process $N(t)$: its expected value reveals the binding kinetics (i.e. the response kinetics), and the variance is the measure of sensor AD noise. As they take into account the influence of individual events of particle binding and unbinding to the surface adsorption sites

Ivana Jokić is with the Institute of Chemistry, Technology and Metallurgy – Center of Microelectronic Technologies, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia (e-mail: ijokic@nanosys.ihtm.bg.ac.rs).

Zoran Djurić is with the Serbian Academy of Sciences and Arts, and Institute of Technical Sciences of SASA, Knez Mihailova 25, 11000 Belgrade, Serbia (e-mail: zoran.djuric@itn.sanu.ac.rs).

Katarina Radulović is with the Institute of Chemistry, Technology and Metallurgy – Center of Microelectronic Technologies, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia (e-mail: kacar@nanosys.ihtm.bg.ac.rs).

Miloš Frantlović is with the Institute of Chemistry, Technology and Metallurgy – Center of Microelectronic Technologies, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia (e-mail: frant@nanosys.ihtm.bg.ac.rs).

Katarina Cvetanović Zobenica is with the Institute of Chemistry, Technology and Metallurgy – Center of Microelectronic Technologies, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia (e-mail: katarina@nanosys.ihtm.bg.ac.rs).

on the sensor response, as well as the inherent random nature of these events, stochastic models are more accurate in describing the binding kinetics than deterministic models. They describe response fluctuations, which are always present. Based on such models, the stochastic sensor response is usually analyzed by using stochastic simulations. Analytical approximations of stochastic models are also common, because they offer a good insight into the dependences of response statistical parameters on various system parameters, while being more efficient than simulations in which high accuracy requires a long computation time. Approximate stochastic models with analytical closed-form expressions for the expected value and variance exist for simplified practical cases. For example, when it is assumed that the number of particles available for adsorption in the sensor chamber is much greater than the number of adsorbed particles at all times, and the influence of mass transfer is neglected, which implies that the concentration of target particles during the adsorption is constant in space and time in the chamber [6]. In more complex cases (when mass transfer by diffusion exists), statistic parameters of the response are analyzed by using stochastic computer simulations [7].

In this work, we first review a deterministic model of the response of adsorption-based sensors with a microfluidic reaction chamber. Subsequently, we present an approximate model that enables efficient analysis of stochastic response, which takes into account a random AD process coupled with convection and diffusion of target particles. The model is based on the use of TCM and the master equation in order to obtain the equations for the expected value and the variance of sensor response. Finally, we compare the two response models (deterministic and stochastic), considering sensors of different active area and detection of substances with different concentrations, in order to discern in which case the use of the deterministic model is justified, and when the use of the stochastic model becomes necessary.

II. THEORETICAL MODELING OF SENSOR TIME RESPONSE

A sensing element of an adsorption-based chemical or biological microfluidic sensor is placed in a flow-through reaction chamber, where the sample to be analyzed is introduced (Fig. 1a). Target substance particles are transported to and from the adsorption sites on the active sensor surface by both convection and diffusion, characterized by the fluid flow velocity through the chamber, **v**, and the target particles diffusivity, *D*. We assume 1:1 binding of the particles to the adsorption sites, uniformity of all binding sites, and no interaction between the target particles. The temporal change of the number of adsorbed particles, which determines the sensor time response, can be mathematically modeled by using a deterministic or stochastic approach. The deterministic and stochastic models, which will be used for the analysis, are presented in the following part of this Section.

A. Deterministic model

A traditional approach to analysis of adsorption-diffusion-convection systems is to describe a target species by its spatially and time dependent concentration, $C(t,x,y,z)$, inside the chamber, determined by the convection-diffusion equation

$$\partial C / \partial t = -div(\mathbf{v}C - D grad C) \tag{1}$$

with its boundary and initial conditions for the given system. The sensor time response is determined by the amount of adsorbed particles, whose surface density η in an arbitrary point (x,z) of the sensor active surface is given by the equation

$$\partial \eta / \partial t = a_{eff} - d_{eff} = k_a C_s (\eta_m - \eta) - k_d \eta \tag{2}$$

and its boundary and initial conditions. Here the rate of change of η is expressed as a difference between the instantaneous effective rates of increase (a_{eff}) and of decrease (d_{eff}) of η. These rates depend on all physical processes in the system, which influence the change of the number of adsorbed particles. Hence, these rates are the functions of the parameters of convection, diffusion, adsorption and desorption, and they also depend on the exact adsorption-desorption scheme. The expressions for the effective adsorption and desorption rates used here, correspond to the Langmuir adsorption scheme, in accordance with the assumptions from the beginning of Section II. In them, k_a and k_d are the adsorption and desorption rate constants, η_m is the surface density of adsorption sites, and $C_s=C(t,x,0,z)$ is the target substance concentration in the immediate vicinity of the sensing surface. The previous two equations are coupled through the boundary condition of Eq. (2), which corresponds to the active surface of a given sensor.

The sensor response is a function of the adsorbed particles surface density, $R=f(\eta)$. The dependence $R=f(\eta)$ and Eqs. (1) and (2) constitute the general form of the mathematical model of sensor response. The model obtains a more specific form by defining the sensor system components and operating conditions. First, a microfluidic reaction chamber of the majority of adsorption-based micro- and nanosensors has the rectangular cross-section, and the sensing surface is usually considered as a rectangular zone. Since the ratio of the chamber width and height is typically large (greater than 10) and the value of the Reynolds number for the native samples is small [3], it is justified to assume a laminar fluid flow with a parabolic velocity profile, and also the uniformity of parameter values in the z-axis direction, which enables the analysis of transport processes to be performed in a 2D (x,y) coordinate system. Then Eq. (1) becomes

$$\frac{\partial C}{\partial t} = -v(y)\frac{\partial C}{\partial x} + D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2}\right) \tag{3}$$

where $C=C(t,x,y)$. The boundary and initial conditions are: $C(0,x,y)=C_{in}$, $C=C_{in}$ for $x=0$ and $\partial C/\partial x=0$ for $x=L_c$ at an arbitrary moment of time, while the one valid for all the points on the sensing surface ($x_1 \le x \le x_1+L_s$, $y=0$) at an arbitrary moment t is

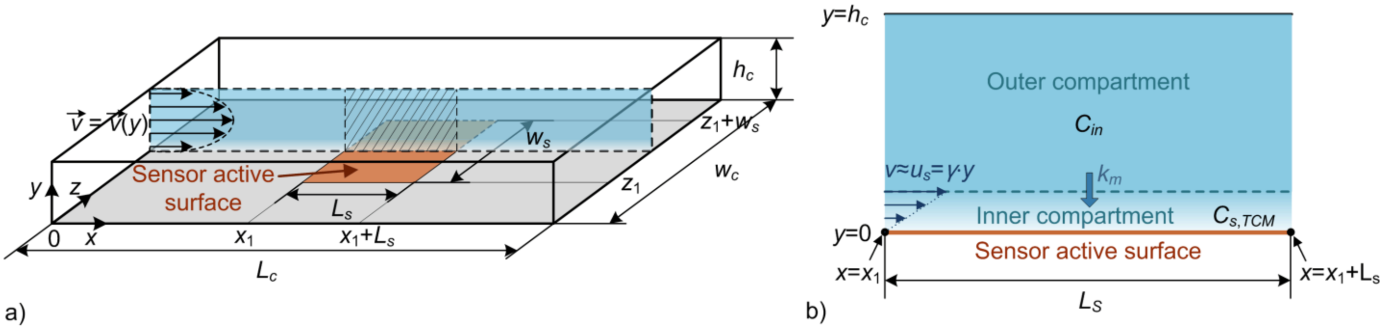

Fig. 1 Adsorption-based microfluidic sensor: a) Schematic representation of the sensing system, b) Cross-section of the microfluidic reaction chamber in the sensing surface zone (shaded part in Fig. 1a) as illustration of the two-compartment model approximation for the target substance concentration in the chamber.

$$D\left.\frac{\partial C}{\partial y}\right|_{(t,x,0)} = \frac{\partial \eta}{\partial t}\,. \tag{4}$$

For the mentioned reasons the quantities in Eq. (2) are also independent on the coordinate z, thus $\eta=\eta(t,x)$ and $C_s=C(t,x,0)$, and the initial and boundary conditions are $\eta(0,x)=0$ and $\partial\eta/\partial x=0$ for $x=x_1$ and $x=x_1+L_s$.

Eqs. (2) and (3) constitute the system which determines the surface density of the number of adsorbed particles. The system is mathematically very complex. However, for different ratios of the sensor system parameters different transport-adsorption regimes of practical relevance can be defined, and then the approximations can be introduced in order to reduce the mathematical complexity. The ratios between the convection, diffusion and adsorption time scales in the given system are of key importance for distinguishing between these regimes and for introducing approximations whose application is justified in such cases.

In many types of microfluidic sensors, in which the order of magnitude of the reaction chamber height is ≥10 μm, two transport-adsorption regimes are characteristic [8]: the "rapid mixing" regime (the "adsorption limited kinetics" of the target substance binding) and "mass transfer influenced kinetics" regime. The former occurs when the mass transfer processes transport the adsorbate particles to the surface adsorption sites much faster than they bind due to adsorption. Then it is justified to assume that the concentration of the substance in the reaction chamber is spatially uniform, constant in time and equal to the concentration in the sample injected in the chamber, which leads to a significant reduction of mathematical complexity of the problem. Eq. (3) then becomes $C(t,x,y)=C_{in}=\text{const}$. When these conditions are met, η is also spatially uniform, so, based on Eq. (2), the number of particles adsorbed on the sensing surface, $N(t)=A\eta(t)$, is given by

$$dN/dt = k_a C_{in}(N_m - N) - k_d N = a(N) - d(N) \tag{5}$$

($N_m=A\eta_m$ is the total number of adsorption sites, A is the sensing surface area, $A=L_s w_s$). The solution of Eq. (5) has a well-known form

$$N(t) = \frac{k_a C_{in}}{k_d + k_a C_{in}} N_m \left(1 - e^{-(k_d + k_a C_{in})t}\right) = N_e\left(1 - e^{-t/\tau_{rm}}\right). \tag{6}$$

In this case, the equilibrium state, in which the number of adsorbed particles is N_e, establishes with the time constant equal to the AD process time constant τ_{rm}, which depends only on the AD process parameters (the mass transfer influence is negligible). Kinetics of the binding of target particles to the sensing surface is, therefore, "adsorption limited". The "rapid mixing" regime is typical for fast diffusing particles (gas molecules and biomolecules of small mass).

When the adsorption flux towards the sensing surface is much greater than the transport flux, the target substance concentration in the reaction chamber depends on spatial coordinates and time. The change of concentration also influences the kinetics of binding of the particles to the surface, so the binding process depends on mass transfer ("mass transfer influenced kinetics"). This regime is typical for slowly diffusing particles, which includes a majority of biomolecules in liquid samples. At typical convection speeds in microfluidic channels of above-mentioned dimensions, a thin layer depleted of target particles is formed in the reaction chamber, adjacent to the adsorbing surface. This transport-adsorption regime is typical for many biosensors with a flow-through reaction microchamber [3-5, 9].

In this case, a simplified system of equations can be obtained by introducing the two-compartment model (TCM) that approximates the spatial dependence of the analyte concentration in the sensor's reaction chamber [3]. The inner compartment, as defined by the model (Fig. 1b), corresponds to the depleted zone, where the concentration of the substance is variable in space and time. In the outer compartment, which is the remaining volume of the reaction chamber, the analyte concentration is assumed constant, end equal to the concentration in the sample introduced into the chamber, C_{in}. Eqs. (2)-(4) with the TCM assumptions yield the TCM equations, which define the change in the number of adsorbed particles due to the AD process coupled with mass transfer

$$C_{s,TCM}(t) = [C_{in} + k_d N/(k_m A)]/[1 + k_a(N_m - N)/(k_m A)] \tag{7}$$

$$dN/dt = k_a C_{s,TCM}(N_m - N) - k_d N = a_{eff}(N) - d_{eff}(N)\,. \quad (8)$$

Here $C_{s,TCM}$ is the analyte concentration in the immediate vicinity of adsorption sites, determined by TCM, and k_m is the mass transfer coefficient, which is a characteristic of particle transport between the two compartments. According to the model, all parameters are averaged across the sensing surface. The number of adsorbed particles can be obtained by solving Eq. (8) with the condition $N(0)=0$, which is much simpler than solving the system comprised of Eqs. (2) and (3) with their boundary and initial conditions.

The equilibrium number of adsorbed particles can be obtained from Eqs. (7) and (8) when $\mathrm{d}N/\mathrm{d}t=0$

$$N_{e,TCM} = k_a C_{in}/(k_d + k_a C_{in}) N_m\,. \quad (9)$$

It equals the equilibrium value in the "rapid mixing" regime, which means that mass transfer influences the response only during the transient regime.

It is interesting to note that at a high enough value of the parameter k_m (i.e. for fast mass transfer), Eq. (7) becomes $C_{s,TCM}=C_{in}=\mathrm{const}$, and Eq. (8) becomes equal to Eq. (5), so the "mass transfer influenced kinetics" case transforms into the "adsorption limited kinetics" regime.

B. Stochastic model

The random process $N(t)$ belongs to the group of Markov processes, which are constant in time and discrete in values, and are known as gain-loss processes [10]. Possible values of this process, n ($n \in \{0,1,2...N_m\}$), are the states of the process. At an arbitrary moment of time, transitions are possible only between adjacent states. Transition probabilities between states in unit time depend only on the current state. It is also assumed that in a time interval $\delta t \to 0$ the state of the process can be changed only by one, so there can be an adsorption of one particle, a desorption of one particle or the lack of AD events. The probability of transition from n to n+1 state in unit time equals the probability of effective adsorption in unit time, when the number of adsorbed particles is n. It is given by the dependence $a_{eff}(n)$, as defined in Eqs. (7) and (8), and takes into account the combined influence of the AD and mass transfer processes on the increase of the number of adsorbed particles. The transition probability from the state n to the state n-1 in unit time equals the probability of effective desorption in unit time, when the number of adsorbed particles is n. It is given by the expression $d_{eff}(n)$, as defined in Eq. (8). Transition probabilities in the case of "rapid mixing" are given by the mentioned expressions in which $k_m \to \infty$. Taking into account all the possible events whose outcome is n adsorbed particles at the moment t, the probability that the number of adsorbed particles on the sensing surface is n at the moment t, $P_N(n,t)$, is

$$\begin{aligned} P_N(n,t) &= P_N(n-1, t-\delta t)\cdot a_{eff}(n-1)\delta t \\ &+ P_N(n+1, t-\delta t)\cdot d_{eff}(n+1)\delta t \\ &+ P_N(n, t-\delta t)\cdot[1-(a_{eff}(n)+d_{eff}(n))\delta t]\,. \end{aligned}$$

By subtracting $P_N(n, t\text{-}\delta t)$ from the expressions on both sides of the previous equation, dividing by δt and finding the limiting value of expressions on both sides of the obtained equation for $\delta t \to 0$, the master equation is obtained

$$\begin{aligned} dP_N(n,t)/dt &= P_N(n-1,t)\cdot a_{eff}(n-1) + P_N(n+1,t)\cdot d_{eff}(n+1) \\ &- P_N(n,t)\cdot(a_{eff}(n)+d_{eff}(n))\,. \end{aligned} \quad (10)$$

Starting from the master equation, the moments of the random variable can be obtained without determining the expression for the probability distribution of the random variable N, $P_N(n, t)$. Here, we are interested in the expected value $<N>$ of the random number of adsorbed particles, and its AD fluctuations around $<N>$, which are characterized by the variance σ^2. By definition, these two moments equal

$$<N> = \sum_{n=0}^{N_m} n P_N(n,t) \quad (11)$$

$$\sigma^2 = <(\Delta N)^2> = \sum_{n=0}^{N_m} (n - <N>)^2 P_N(n,t) \quad (12)$$

($\Delta N = N - <N>$ is a deviation in the number of adsorbed particles from the expected value at the moment t). By differentiating Eqs. (11) and (12) with respect to t, applying Eq. (10) and performing simple transformations of the obtained expressions, a system of equations is obtained

$$d<N>/dt = <a_{eff}(N)> - <d_{eff}(N)> \quad (13)$$

$$d\sigma^2/dt = <a_{eff}(N) + d_{eff}(N)> + 2\left\langle \Delta N[a_{eff}(N) - d_{eff}(N)]\right\rangle . \quad (14)$$

After representing the nonlinear transition probabilities as Taylor series centered at the expected value in Eqs. (13) and (14), an approximate system of equations can be obtained, which includes the first and the second moment in the form

$$d<N>/dt = a_{eff}(<N>) - d_{eff}(<N>) + (a_{eff}'' - d_{eff}'')\cdot\sigma^2/2 \quad (15)$$

$$\begin{aligned} d\sigma^2/dt &= a_{eff}(<N>) + d_{eff}(<N>) \\ &+ [2(a_{eff}' - d_{eff}') + (a_{eff}'' + d_{eff}'')/2]\cdot\sigma^2\,. \end{aligned} \quad (16)$$

Here the derivatives $a_{eff}' = \mathrm{d}a_{eff}/\mathrm{d}N$, $a_{eff}'' = \mathrm{d}^2 a_{eff}/\mathrm{d}N^2$, $d_{eff}' = \mathrm{d}d_{eff}/\mathrm{d}N$ and $d_{eff}'' = \mathrm{d}^2 d_{eff}/\mathrm{d}N^2$ are calculated for $N = <N>$.

The equilibrium expected value of the adsorbed particles number according to this model is

$$<N>_e = N_m k_a C_{in}/[k_a C_{in} + k_d + k_a k_d/(k_m A)] \quad (17)$$

(obtained from Eqs. (15) and (16) for $\mathrm{d}<N>/\mathrm{d}t=0$ and $\mathrm{d}\sigma^2/\mathrm{d}t=0$). It depends on the mass transfer parameters, contrary to that predicted by the deterministic model (Eq. (9)).

Eqs. (15) and (16), together with the expressions for $a_{eff}(N)$ and $d_{eff}(N)$, determined by using TCM, constitute a simplified stochastic model for efficient analysis of random sensor response, which takes into account the coupling of the random AD process and mass transfer in a microfluidic sensor chamber.

III. RESULTS AND DISCUSSION

As the time response of adsorption chemical and biological sensors is a function (preferably linear) of the number of adsorbed particles, we analyze the time evolution of the adsorbed particles number by using the deterministic model for $N(t)$, and the stochastic model for calculation of the time dependent expectation $\langle N \rangle$, as shown in Section II. We consider a microfluidic biosensor for detection of proteins in a liquid sample, whose active area contains $\eta_m=3\cdot 10^{17}$ 1/m^2 adsorption sites, while the parameters of the AD process and mass transfer are: $k_a=1.33\cdot 10^{-19}$ m^3/s, $k_d=0.08$ 1/s, and $k_m=2\cdot 10^{-5}$ m/s. The curves obtained by using the deterministic model are shown in Figs. 2-5 by dashed lines, while the stochastic model yields the curves shown by solid lines.

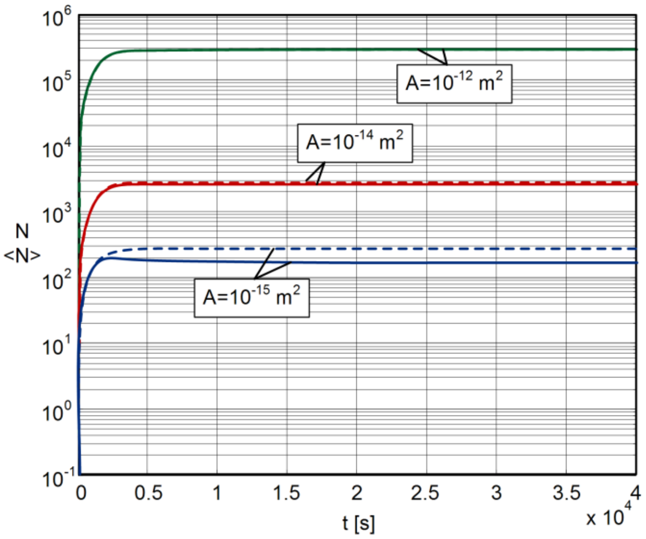

Fig. 2 Time evolution of the number of adsorbed particles obtained by using the deterministic model of sensor response (dashed lines), and the time dependence of the expected value of the adsorbed particles number according to the stochastic response model (solid lines). The target substance concentration is $C_{in}=6\cdot 10^{18}$ 1/m^3.

Fig. 2 shows the temporal evolution of the adsorbed particles number for three biosensors of different active surface areas ($1\cdot 10^{-12}$ m^2, $1\cdot 10^{-14}$ m^2, $1\cdot 10^{-15}$ m^2), when the target substance (protein) concentration in the sample is $C_{in}=6\cdot 10^{18}$ 1/m^3. It is obvious that the expected value can be considered as approximately equal to the solution of the deterministic equation for $N(t)$ for sensors with the active area of $1\cdot 10^{-12}$ m^2 and $1\cdot 10^{-14}$ m^2. The difference between the results obtained by using the two models becomes noticeable only in the case of sensors with the smallest adsorption area, which are, for example, nanowire or carbon nanotube mechanical or electrical (FET) sensors. In sensors with a greater active area the difference is negligible.

The conclusion about the influence of the sensing surface area on the difference of responses obtained by using the two models (deterministic and stochastic) is even more obvious from the diagram in Fig. 3. It is obtained for the same biosensors as the one shown in Fig. 2, but for the case of detection of a protein which is in a 10 times lower concentration ($C_{in}=6\cdot 10^{17}$ 1/m^3) in the sample. The difference in the response obtained by using the two models obviously increases as the sensor active surface area becomes smaller. In the considered case, it becomes noticeable in sensors whose active surface area is $1\cdot 10^{-14}$ m^2, and significant when the area equals $1\cdot 10^{-15}$ m^2. This is best seen in Fig. 4 which shows the ratio of the responses calculated according to the deterministic and stochastic models for sensors with different surface areas.

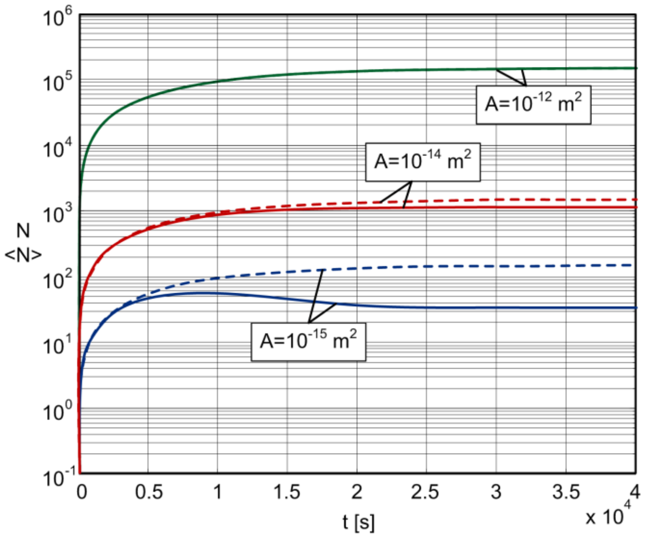

Fig. 3 The number of adsorbed particles obtained by using the deterministic model (dashed lines) and the expected value of stochastic adsorbed particles number (solid lines) as the functions of time, for $C_{in}=6\cdot 10^{17}$ 1/m^3.

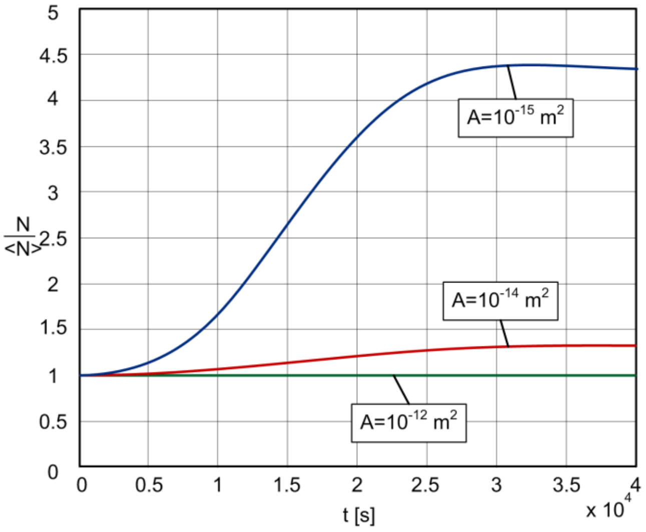

Fig. 4 The time dependence of the ratio of the adsorbed particles number according to the deterministic model and the expected value of the stochastic adsorbed particles number ($C_{in}=6\cdot 10^{17}$ 1/m^3).

An interesting finding of the presented analysis is that the stochastic response kinetics differs from the deterministic response kinetics also in its functional dependence on time. While the stochastic response during the transient regime exhibits an overshoot before it settles at the equilibrium value, that cannot be noticed in the deterministic response (see Fig. 3, the curves corresponding to $A=1\cdot10^{-15}$ m^2).

Fig. 5 shows the results of the analysis of the influence of the target substance concentration on the difference between the sensor response as predicted by the deterministic and by the stochastic model. The analysis is performed for the biosensor with a sensing surface of $A=1\cdot10^{-14}$ m^2, at three different concentrations C_{in} ($3\cdot10^{16}$ 1/m^3, $6\cdot10^{17}$ 1/m^3, $6\cdot10^{18}$ 1/m^3). It can be seen that the difference between the responses predicted by the deterministic and by the stochastic model increases as the target substance concentration decreases.

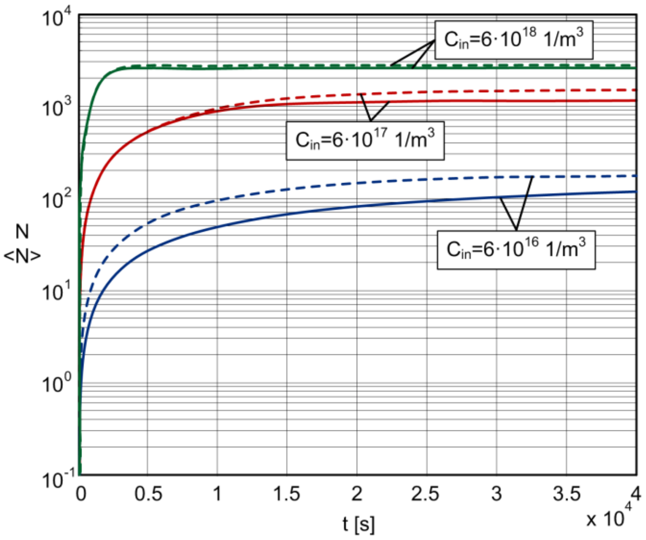

Fig. 5 The time dependence of the number of adsorbed particles obtained by using the deterministic model of sensor response (dashed lines), and of the expected value of stochastic adsorbed particles number (solid lines), for the sensor of sensing surface $A=10^{-14}$ m^2.

The presented results indicate that the stochastic model, being more accurate, is more adequate than the deterministic model for describing the time response of sensors with nanoscale active surfaces, and also when sensors are intended for detection of low concentrations of target substances.

IV. CONCLUSIONS

The results of the presented time response analysis of adsorption-based microfluidic chemical and biological sensors show that application of deterministic approach for modeling of sensor response is justified in the case of sensors with active area dimensions in the micrometer range, at target substance concentrations measurable by current state-of-the-art microfluidic sensors. However, in sensors with smaller active areas, as well as in cases when detection of substances in extremely low concentrations is performed, application of the stochastic model becomes necessary. This conclusion is important due to both the trend of sensor miniaturization (transition of active area dimensions from micro- to nanoscale), and the decreasing values of the minimal detectable signal in the latest sensor generation, with single-molecule detection as the ultimate goal.

The presented approximate model of stochastic sensor response, which takes into account the coupling of the random AD process and mass transfer in a microfluidic reaction chamber, enables efficient analysis of the response as a function of the sensor system parameters and operating conditions. Therefore, it is a very useful tool for sensor design optimization, and for better interpretation of measurement results obtained by using sensors with micro/nanoscale active surface, intended for detection of miniscule amounts of substances. The same model also enables the analysis of variance and sensors signal-to-noise ratio, which is important for the estimation of ultimate sensor performance and their improvement. Such analysis will be a subject of our future work.

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