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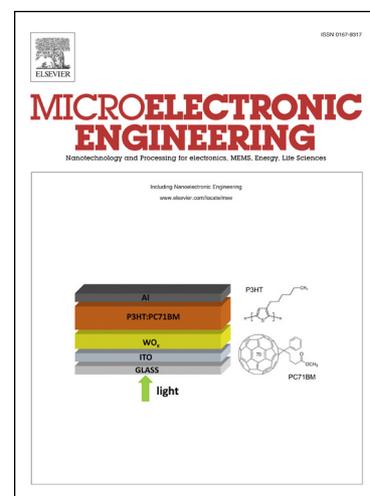
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Fluctuations of the Number of Adsorbed Molecules due to  
Adsorption-Desorption Processes Coupled with Mass Transfer and Surface  
Diffusion in Bio/Chemical MEMS Sensors

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**Abstract**

In this study we have developed, for the first time, the comprehensive theoretical model of the fluctuations of the number of adsorbed molecules in MEMS chemical and biological sensors, taking into account the processes of mass transfer, adsorption and desorption, and surface diffusion of adsorbed molecules. It is observed that the shape of the fluctuations spectrum contains information about various parameters of the adsorbed analyte and that even the analytes with the same affinity for the same binding sites have different spectra. The numerical calculations performed using the derived theory show that the influence of surface diffusion on the fluctuations spectrum can be significant. The practical value of this work stems from the fact that the fluctuations of the number of adsorbed molecules can be a dominant noise component in affinity-based bio/chemical sensors. Therefore, the derived theory is useful for development of the methods for the detection of analytes based on frequency domain analysis of the measured fluctuations. The recognition of an adsorbed analyte using sensors with non-functionalized sensing surface will also be considered using the presented theory.

*Keywords:* chemical sensor, biosensor, adsorption-desorption, mass transfer, surface diffusion, fluctuations

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## 1. Introduction

A large group of chemical and biological MEMS sensors is based on the detection of target molecules adsorbed on the active sensor surface [1]. The response of such sensors is determined by the number of adsorbed molecules, and their selectivity is achieved through functionalization of the sensing surface with specific probe molecules. The target analyte concentration and the rate constants of the interaction processes between the target and probe molecules are usually obtained from the steady state data and from the change in time of the measured parameter during the period of the steady state establishment. However, the unavoidable fluctuations of the number of adsorbed molecules also contain information about the analyte and all processes coupled with the binding reaction [2-4]. Such processes are adsorption-desorption (AD) processes, mass transfer (flow and diffusion) of the target molecules through the sensor reaction chamber to and from the surface adsorption sites [5], and surface movement (e.g. surface diffusion) of adsorbed molecules [6], as it is shown in Fig. 1a (the flow-through reaction chamber is assumed, which is the case in microfluidic devices, e.g. micro/nanofabricated sensors, such as microcantilever, as well as SPR (surface plasmon resonance), FBAR (thin Film Bulk Acoustic wave Resonator), QCM (Quartz Crystal Microbalance), graphene-based sensors etc.). The fluctuations of the number of adsorbed particles cause fluctuations of the sensor's output signal and thereby affect the sensor's ultimate performance: the total sensor noise and the minimal detectable signal. Therefore, the analysis of fluctuations is important for: 1. determination of sensor limiting performance; 2. obtaining additional information about the adsorbate and its transport and AD processes (e.g. parameters useful for adsorbed analyte recognition); 3. optimization of sensor design (the dimensions and geometry of both the sensor reaction chamber and the sensing surface) and experimental conditions (the flow rate of the sample through the reaction chamber, the surface density of the functionalization sites, etc.), with the aim of improving the sensor performance.

----- Fig. 1 -----

Experimental data show that adsorption of different types of analytes has a different influence on the spectrum of the fluctuations of the sensor signal [7, 8], i.e. that the spectrum contains a unique adsorbate signature. This indicates that it could be possible to devise novel methods for detection of analytes based on the measured fluctuations in the frequency domain, in which it would not be necessary to functionalize the sensor surface, so the same single sensor can be used for detection and recognition of different analytes. However, a complete theoretical basis for interpretation of these experimental data does not exist. Therefore, it is impossible to be certain

which of the fluctuation generation mechanisms produces the measured spectrum containing information about the adsorbed analyte. It is not known which parameters of the analyte and the processes occurring at the sensor surface, as well as the geometrical and physical parameters of a sensor determine the observed characteristic spectrum elements. Therefore, if we wish to deduce information about an analyte from the experimentally determined fluctuations spectrum and perform optimization of the sensor design, it is necessary to devise a theory of fluctuations which would take into account as many mechanisms and processes relevant for the response formation as possible.

In a recent study [2], we presented an analysis of the fluctuations of the number of adsorbed molecules taking into account the mass transfer process in biosensors in which the spatial distribution of adsorbate concentrations can be approximated by the two-compartment model. However, the measured noise spectrum suggests that noise due to surface diffusion may dominate the observed noise [9].

In this paper, we consider, for the first time, the fluctuations of the number of adsorbed molecules taking into account the processes of mass transfer, adsorption and desorption and surface diffusion of adsorbed molecules. We present the analytical expression for the spectral density of the fluctuations and the results of the quantitative analysis. Having in mind that the contribution of the fluctuations of the number of adsorbed molecules to the total sensor response fluctuations increases with decreasing dimensions of the sensor, due to which the spectrum of these fluctuations in micro and nanosensors may be dominant in certain frequency ranges, we analyze the possibility to develop new methods for analyte detection. These methods would be based on fluctuation spectrum measurements in non-functionalized sensors and use the presented theory to obtain information about the analyte from a measured spectrum.

## 2. Theoretical considerations

We investigate a bio/chemical sensor with a flow-through reaction chamber, in the middle of which is a sensing element, i.e. the surface of length  $L$  and area  $A$ , where binding of the target (analyte) molecules occurs (Fig. 1b). The binding site can be a functionalizing molecule immobilized on the sensing surface for the selective adsorption of the target molecule, or a non-functionalized surface adsorption site.

The binding reaction (adsorption) may occur when the analyte molecule comes in the vicinity of the surface binding site. Therefore, along with adsorption and desorption processes, analyte particle

transport processes (convection and diffusion), by means of which particles are carried to and from the binding sites, are also important for the sensor response generation. While the direction of convection is determined by the sample flow through the chamber, and it is parallel to the adsorption surface, the direction of bulk diffusion depends on the spatial distribution of target analyte concentration in the chamber. The diffusion of adsorbed particles from one binding site to another (surface diffusion) occurs on the sensing surface. We introduce the following assumptions: 1. the surface density of the binding sites,  $n_m$ , is uniform; 2. only one molecule can be bound to an adsorption site; 3. all binding sites are equivalent (i.e. they have the same value of the adsorption rate constant  $k_f$  and the same value of the desorption rate constant  $k_r$ ); 4. absence of any reaction between the adsorbing molecules; 5. no non-specific adsorption occurs; 6. binding coupled with transport processes leads to the formation of a thin layer depleted of adsorbing molecules adjacent to the sensing surface; 7. the steady state distribution of the adsorbed molecules is uniform on the sensing surface.

The number of the adsorbed molecules,  $N(t)$ , is a random process, due to stochastic nature of adsorption-desorption processes coupled with mass transfer and surface diffusion. We analyze the fluctuations  $\Delta N$  of the number of adsorbed particles around the steady state value  $N_e$ . For the system geometry as shown in Fig. 1b ( $L_c/W_c > 10$ ,  $W_c/H_c > 10$ ), which is common in microfluidic sensing devices, it may be assumed that relevant quantities do not depend on the coordinate  $y$  [10]; accordingly, the processes of adsorption and desorption, mass transfer, and surface diffusion at the sensing surface are linked by the following one-dimensional diffusion equation

$$\frac{\partial \Delta N}{\partial t} = \frac{\partial}{\partial x} \left( D \frac{\partial \Delta N}{\partial x} \right) - \frac{\Delta N}{\tau} \quad (1)$$

Here  $D$  is the surface diffusion coefficient, which in general can be a function of the spatial coordinates and the surface coverage. However, we assume its constant value (both in time and space), which is valid for small equilibrium surface coverages [6], small variations of the coverage around the equilibrium value, and a spatially uniform surface density of adsorbed molecules in the steady state.  $\tau$  is the ‘‘lifetime’’ of the fluctuations of the number of adsorbed molecules

$$\tau = \left( \frac{dd_{eff}}{dN} - \frac{da_{eff}}{dN} \right) \Bigg|_{N=N_e}^{-1} = \frac{1}{k_r + k_f C} + \frac{k_r k_f n_m / k_m}{(k_r + k_f C)^2} \quad (2)$$

obtained from the effective rates of increase and decrease in the number of adsorbed molecules ( $a_{eff}$  and  $d_{eff}$ , respectively), considering AD process coupled with the mass transfer (convection and bulk diffusion) and using the two-compartment model approximation for the analyte concentration distribution in a reaction chamber ( $C$  is the concentration in the sample injected in the chamber, and  $k_m$  is the mass transfer coefficient) [2].

Using the "transport noise" approach for one-dimensional diffusion and generation-recombination processes [11, 12], we have devised an analytical expression for the spectral density of the fluctuations of the number of adsorbed particles  $S(f)$ ,  $\omega=2\pi f$ , shown in the normalized form as

$$\frac{S(X)}{4 \langle \Delta N^2 \rangle \tau} = \frac{1}{X^2} \left\{ 1 - \frac{1}{2\beta X} [(2-X)\sqrt{X+1}(1-e^{-\beta\sqrt{X+1}} \cos(\beta\sqrt{X-1})) + (2+X)\sqrt{X-1}e^{-\beta\sqrt{X+1}} \sin(\beta\sqrt{X-1})] \right\} \quad (3)$$

where  $X=(1+\omega^2\tau^2)^{1/2}$ ,  $\beta=L/(2D\tau)^{1/2}$ ,  $\langle \Delta N^2 \rangle = k_r k_f C n_m A \tau / (k_r + k_f C)$ .

The obtained expression shows the influence of various parameters on the spectral density, thus enabling us to investigate both the separate influences of AD, mass transfer and surface diffusion, and their combined effect on the fluctuations spectrum.

Starting from Eq. (3), known expressions valid for two limiting cases can be obtained:

1. when the diffusion time constant  $\tau_D=L^2/(2D)$  is much greater than  $\tau$ , Eq. (3) is transformed into the expression for the fluctuations spectral density for the case of AD process coupled with mass transfer [2]

$$S_{AD,MT}(f) = \frac{4 \langle \Delta N^2 \rangle \tau}{1 + (2\pi f)^2 \tau^2}$$

2. when  $\tau_D \ll \tau$ , Eq. (3) is transformed into the expression for the spectral density of fluctuations due to surface diffusion [11, 3]

$$S_{SD}(\theta) = \frac{N_e L^2}{D\theta^3} [1 - e^{-\theta} (\cos \theta + \sin \theta)]$$

where  $\theta=L(\omega/(2D))^{1/2}$ .

### 3. Results of numerical calculations and discussion

Using the presented theoretical model, an analysis is performed in order to estimate the influence of the surface diffusion on the spectrum of the fluctuations of the number of adsorbed molecules.

Figs. 2a and 2b show the normalized spectral density of the fluctuations of the number of adsorbed molecules as the function of the parameters  $\beta=L/(2D\tau)^{1/2}=(\tau_D/\tau)^{1/2}$  and  $\omega\tau$ . A change in the shape of the fluctuations spectrum depending on the ratio of the constants  $\tau_D$  and  $\tau$  can be observed. While the first frequency ( $\omega_{c1}=1/\tau$ ) at which the decrease in the magnitude of the spectral curve is observed in the presented diagrams is determined by the time constant  $\tau$  (which means that it does not depend on surface diffusion), different values of surface diffusion parameters influence the low-frequency ( $\omega\ll 1/\tau$ ) value of the fluctuations spectrum and the shape of the curve at frequencies  $\omega>1/\tau$ . It can be concluded that the influence of surface diffusion on the fluctuations spectrum becomes significant for  $\beta<0.1$ . Then another frequency,  $\omega_{c2}$ , is observed at which the spectral curve bends, and its value is determined by the constant  $\tau_D$ . In the presented diagrams it can be seen that  $\omega_{c2}>\omega_{c1}$ . In particular, for a given analyte (i.e. for a constant diffusion length  $(D\tau)^{1/2}$ ) the influence becomes more prominent if the characteristic dimension (length  $L$ ) of the sensing surface is smaller.

----- Fig. 2 -----

Fig. 3 shows the normalized spectral density of the fluctuations multiplied by  $f$ , for three different analytes and one single sensor of the characteristic length  $L=2\ \mu\text{m}$ . The parameters of the adsorbates are  $\tau_1=\tau_2=\tau_3=100\ \text{s}$ ,  $D_1=6.5\cdot 10^{-9}\ \text{m}^2/\text{s}$ ,  $D_2=1.8\cdot 10^{-9}\ \text{m}^2/\text{s}$ ,  $D_3=3.5\cdot 10^{-11}\ \text{m}^2/\text{s}$ . The values are selected with the idea of applying the presented theory on actual analytes and in an actual device. We used the experimental results shown in Ref. [8], obtained by measuring the spectrum of fluctuations of the output signal of the graphene chemical sensor in the presence of different analytes. The experimental value for the time constant  $\tau$  is of the order of 100 s [8]. Since it has been experimentally demonstrated that the maximum of the spectrum multiplied by  $f$  indicates the type of the analyte, we use the expression derived for the fluctuations spectrum in order to obtain the frequency  $f_{max}$  where the maximum of the function  $fS$  occurs. The derived approximate expression is  $f_{max}\approx 0.59D/L^2$ . By using this expression and the values of  $f_{max}$  experimentally obtained

in [8] for acetonitrile, methanol and tetrahydrofuran, we obtained the above values for the analyte diffusion coefficients  $D_1$ ,  $D_2$  and  $D_3$ , respectively. The corresponding diffusion time constants equal  $\tau_{D1}=3\cdot 10^{-4}$  s,  $\tau_{D2}=10^{-3}$  s, and  $\tau_{D3}=0.057$  s; accordingly,  $\tau_D \ll \tau$ , and the fluctuations spectrum is predominantly determined by the surface diffusion. The inset in Fig. 3 shows for the same three analytes the calculated spectral density of the sensor noise,  $S_{TOT}$ , multiplied by  $f$ , which takes into account  $1/f$  noise together with the noise due to fluctuating number of adsorbed particles. The latter is obtained by applying the theory presented in this paper, while the parameters of the  $1/f$  noise spectral density used in the calculations are determined using the experimentally obtained curves for a graphene-based gas sensor [8]. The curves shown in the inset are in good agreement with the experimentally obtained curves shown in [8]. This agreement between theoretical and experimental results could mean that the maximum obtained experimentally originates from the fluctuations in the number of adsorbed particles, caused by surface diffusion, the AD process and bulk mass transfer.

----- Fig. 3 -----

It is observed in Fig. 3 that the frequency which corresponds to the maximum of the function  $f \cdot S$  differs for different analytes. Hence the fluctuations spectrum contains information about the analyte that can be used in its identification. It can be concluded from the example given in Fig. 3 that it is possible to distinguish between different analytes, including those that have a similar affinity for binding to the same adsorption sites (the same  $\tau$  for the three analytes in the example), based on the frequency of the maximum, if they have different surface diffusion constants. This opens possibilities for the development of novel methods for detection of various analytes using a single non-functionalized sensor, based on the fluctuations spectrum measurement.

#### 4. Conclusion

A theoretical model of the fluctuations of the number of adsorbed molecules in MEMS bio/chemical sensors is devised, taking into account the processes of adsorption and desorption, mass transfer, and surface diffusion of target molecules. The performed numerical analysis provides an insight into the qualitative and quantitative influence of surface diffusion on the spectrum of the fluctuations. It is shown that this influence increases for smaller diffusion time constants. For a given analyte the influence of surface diffusion becomes more prominent if the characteristic dimension (length) of the sensing surface is smaller. It is also observed that the shape of the

fluctuations spectrum contains information about various parameters of the adsorbed analyte and that even the analytes with the same affinity for the same binding sites have different spectra.

The practical value of this study stems from the fact that the fluctuations of the number of adsorbed molecules in micro/nanosensors can dominate over other fluctuation generating mechanisms in a certain frequency range. Therefore, the derived theory is useful for development of methods for detection and characterization of analytes based on frequency domain analysis of the measured fluctuations. Especially interesting is the applicability of this theory for analyte recognition based on the fluctuations spectrum, which enables detection of multiple analytes using a single non-functionalized sensor. Furthermore, the presented theory may be used for estimation of the sensor's limiting performance.

## Acknowledgments

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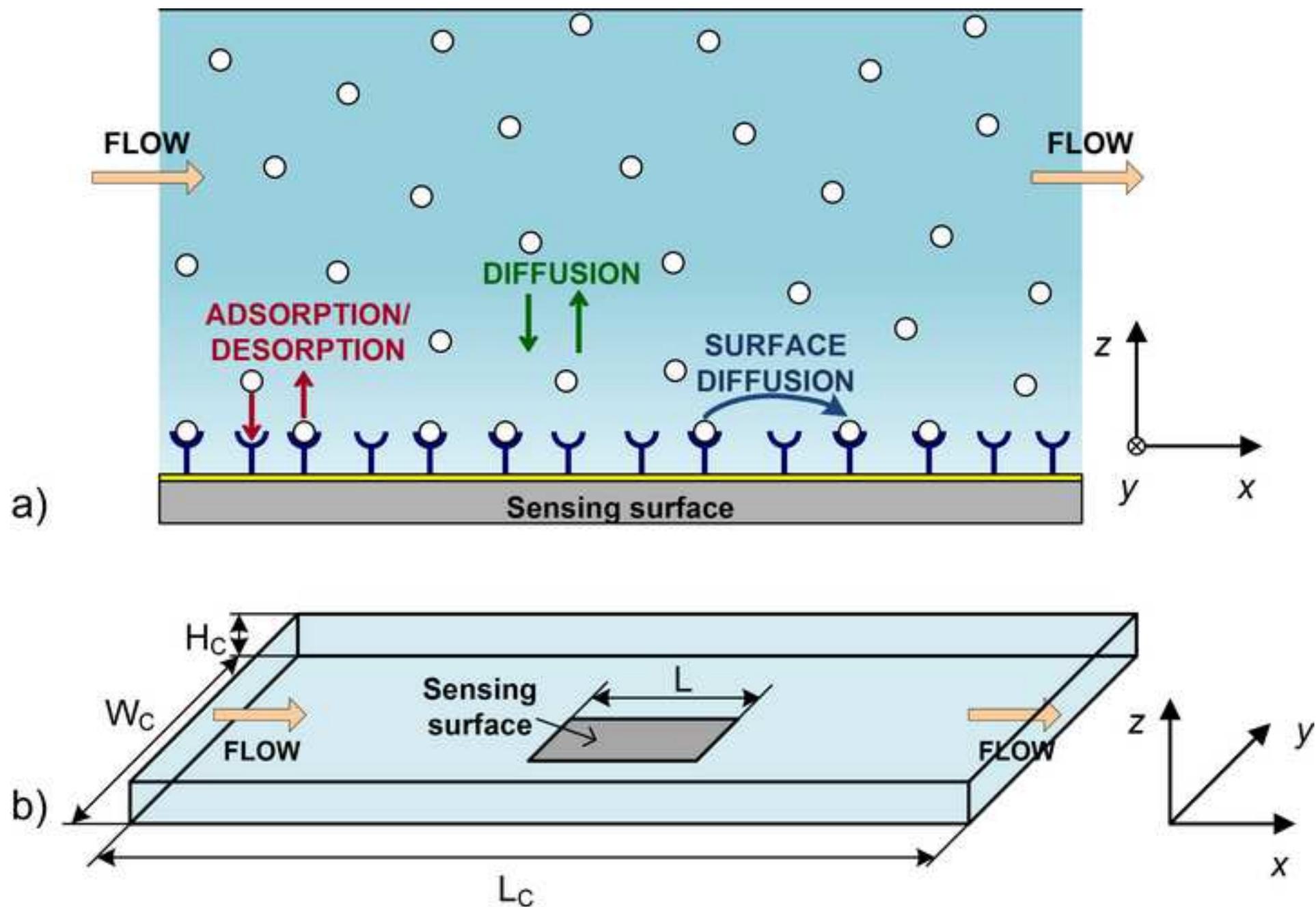
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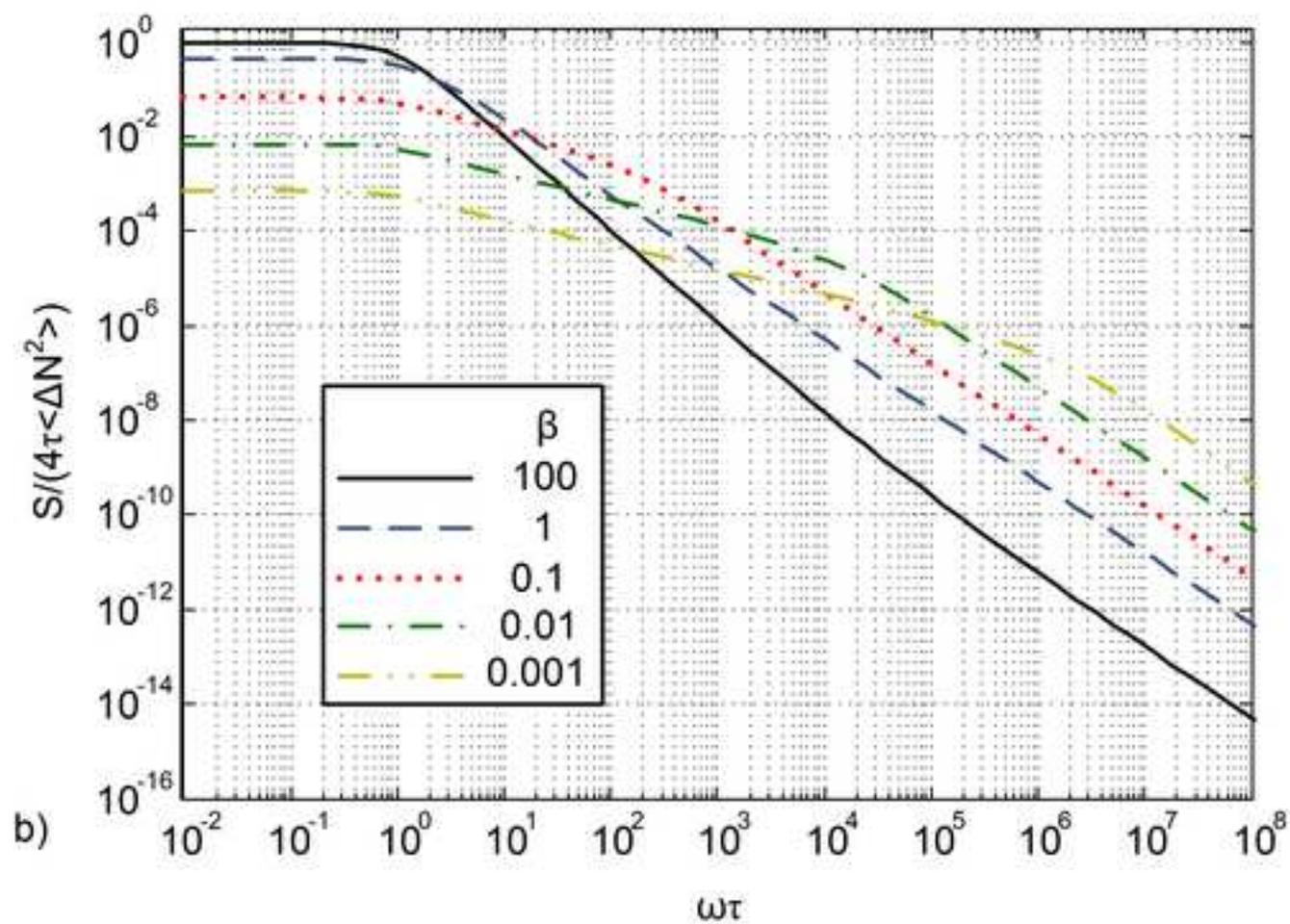
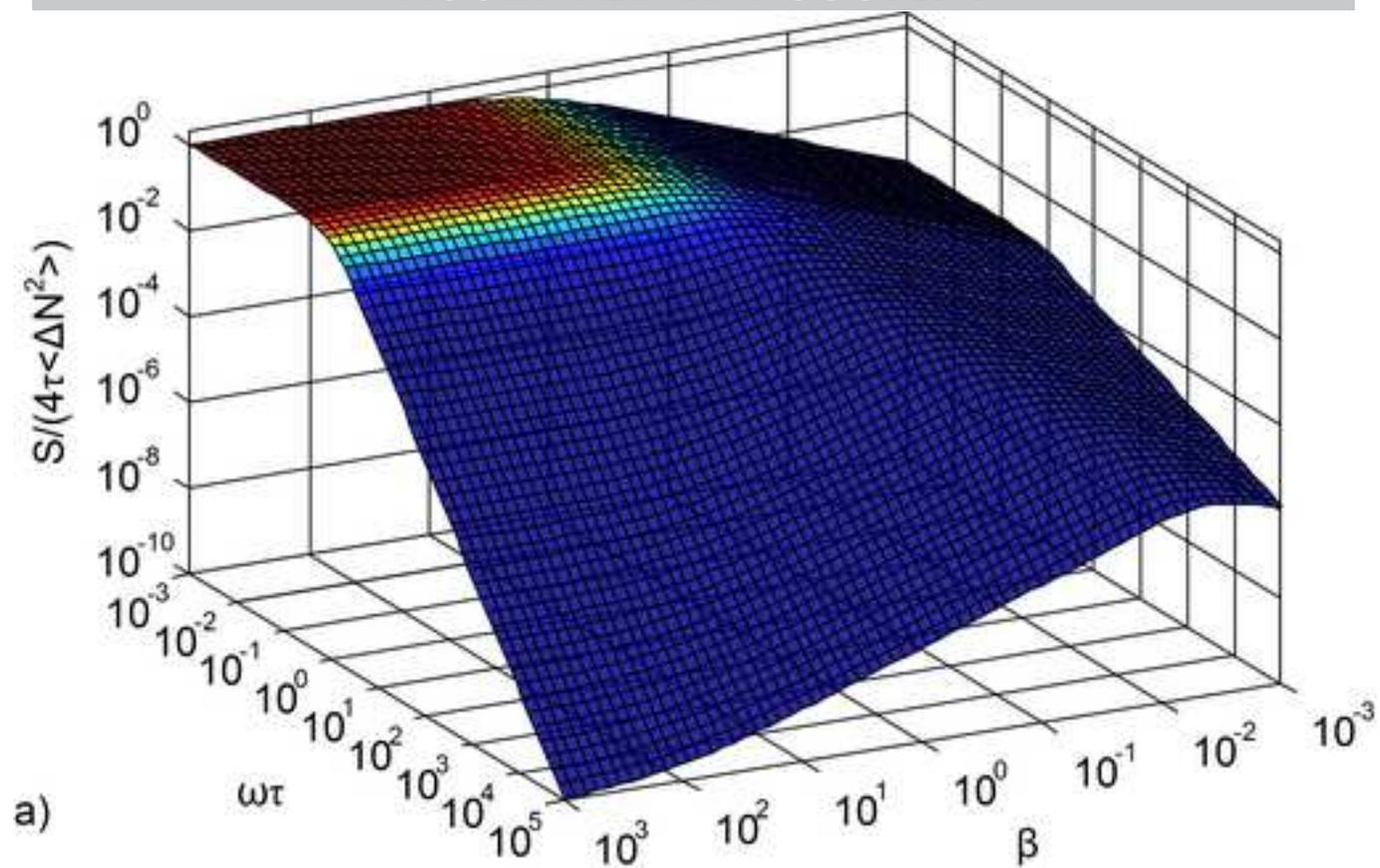
Fig. 1 Schematic representation of a bio/chemical sensor with flow-through reaction chamber: a) the processes relevant for formation of sensor response: adsorption/desorption and transport processes of target molecules, b) sensor system geometry.

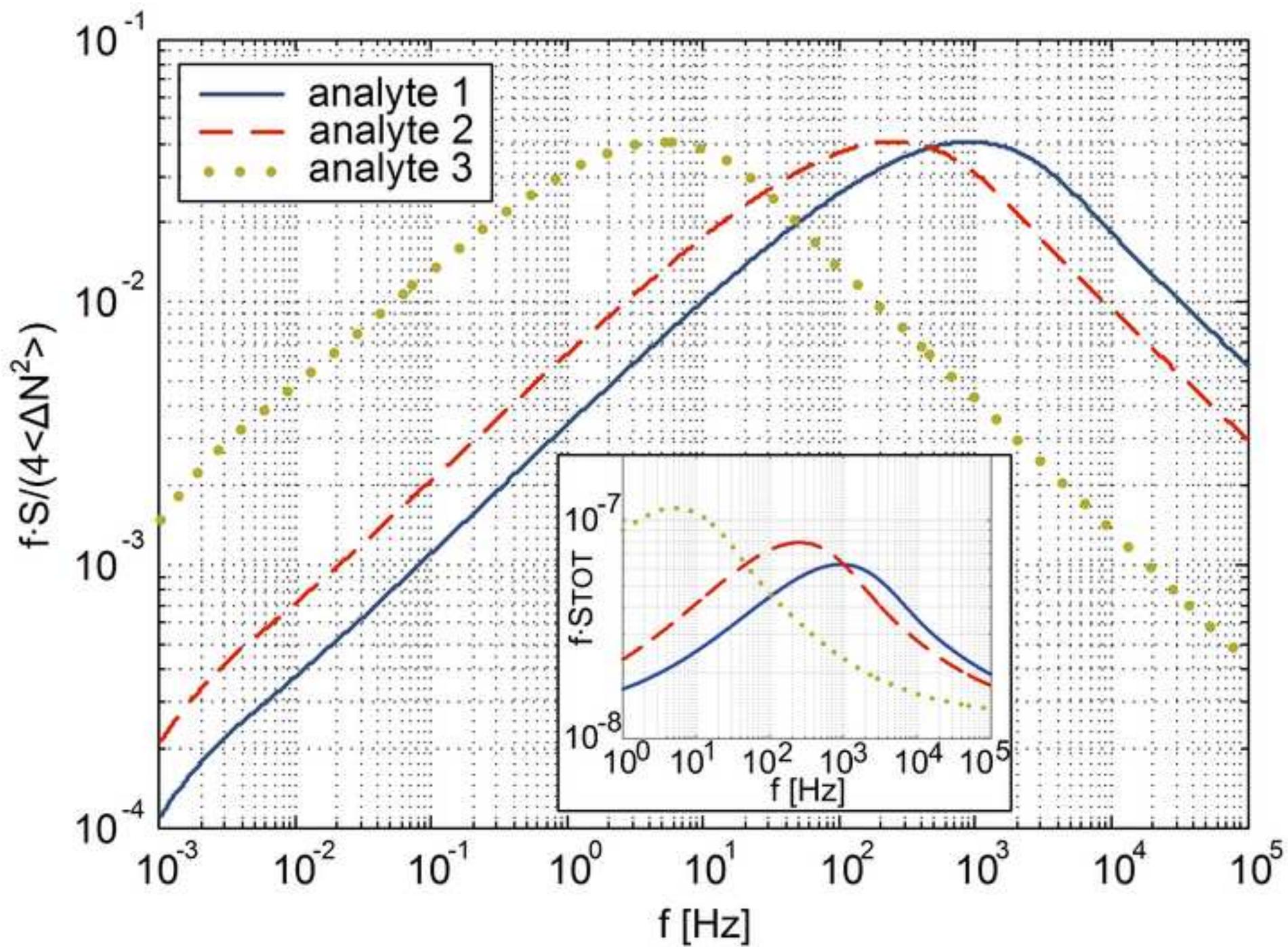
Fig. 2 Normalized spectral density of the fluctuations of the number of adsorbed molecules as the function of the parameters  $\beta=L/(2D\tau)^{1/2}$  and  $\omega\tau$ . a) 3D diagram, b) the cross-sections of the 3D diagram for five different values of  $\beta$ .

Fig. 3 The normalized spectral density of the fluctuations multiplied by  $f$ , for three different analytes, with the parameters  $D_1\tau_1>D_2\tau_2>D_3\tau_3$ . The inset shows the calculated spectral density of the sensor noise for the same three analytes,  $S_{TOT}$ , multiplied by  $f$ , which takes into account  $1/f$  noise together with the noise due to fluctuating number of adsorbed particles.

Figure 1

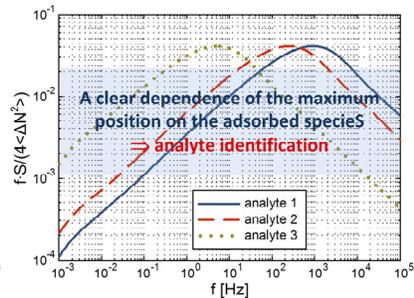
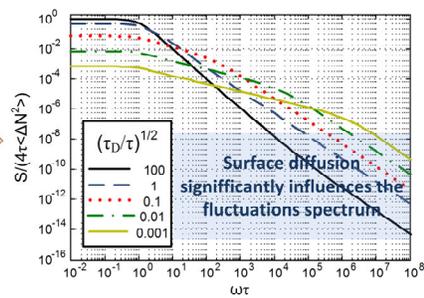
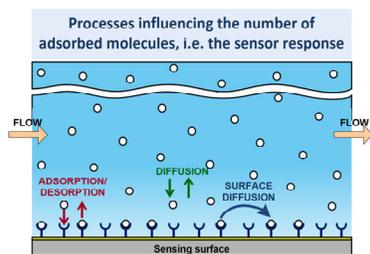






- Theory of fluctuations of the number of adsorbed particles in sensors is devised.
- Adsorption-desorption, mass transfer and surface diffusion are considered.
- The fluctuations spectrum contains information about the adsorbed analyte.
- Novel detection methods based on the fluctuations spectrum analysis are proposed.
- Detection of various analytes using a single nonfunctionalized sensor is suggested.

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