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Biosensor Time Response and Noise Models That Take into Account Spatial Rearrangement of Adsorbed Biomolecules †

Ivana Jokić *, Miloš Frantlović, Olga Jakšić, Katarina Radulović and Stevan Andrić

Institute of Chemistry, Technology and Metallurgy, National Institute of the Republic of Serbia, University of Belgrade, 11000 Belgrade, Serbia; frant@nanosys.ihtm.bg.ac.rs (M.F.); olga@nanosys.ihtm.bg.ac.rs (O.J.); kacar@nanosys.ihtm.bg.ac.rs (K.R.); stevan@nanosys.ihtm.bg.ac.rs (S.A.)

* Correspondence: ijokic@nanosys.ihtm.bg.ac.rs

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Abstract: In order to improve biosensor performance, it is important to develop mathematical models of sensors' temporal response and noise, which include the effects of processes and phenomena relevant to the real applications of these devices. Here, we present a novel, more comprehensive response and noise models that consider the rearrangement process of biomolecules upon their adsorption on the sensing surface. We evaluate the extent of the influence of this process for various rates of rearrangement and adsorption–desorption processes. The development of such models is indispensable for the correct interpretation of the measurement results and also for the estimation and improvement of sensor performance limits, yielding the more reliable detection of the target agent in the analyzed samples.

Keywords: sensor noise; sensor time response; adsorption; biomolecular rearrangement; protein conformation; protein sensor; mathematical model

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1. Introduction

The growing need for high-performance in situ biosensing is driving the development of micro/nanobiosensors, which have already shown a significant potential for the highly sensitive detection of biological specimens or biologically relevant chemical substances in applications such as the real-time monitoring of biological pollution in the air, water, and food, or the health conditions of living organisms [1–3]. Research efforts are being made to push their performance further beyond the current limits. In this sense, it is important to investigate physical processes and phenomena that inevitably affect the generation of the sensor's response and its fluctuations, thus setting a fundamental performance limit. The basis of these investigations is the development and application of mathematical models of sensor time response and noise, which take into account all relevant processes.

Adsorption-based biosensing relies on the reversible adsorption process of biomolecules on a sensing surface. In addition to producing the response of the sensor, this process, stochastic in nature, is also a source of noise that affects the performance of micro/nanosensors. There are several sensor response and noise models that take into account different additional processes coupled with adsorption, depending on a specific practical case [4–7]. The spatial rearrangement of adsorbed biomolecules is an additional process that changes the binding/unbinding kinetics to a two-step process behavior and, therefore, affects both the sensor's time response and its fluctuations. We present the improved models of the sensor time response and noise, which consider biomolecular rearrangement and evaluate the extent of its influence for various rates of rearrangement and adsorption/desorption processes. The development of improved mathematical models of sensor temporal response and noise, which include the effects pronounced in the real applications of these devices, is indispensable for both a correct interpretation of the measurement

results and estimation of sensor performance limits and, thus, for the achievement of the reliable detection of the target agent in analyzed samples.

2. The Models of Biosensor Response and Noise

The adsorption of biomolecules (especially proteins) on a sensing surface, or their affinity-based binding to other biomolecules that are used for sensor functionalization, is often followed by a change in their structure and/or orientation from one configuration to another [8,9]. There are many different variants of such changes, which can be encompassed by the term "molecular rearrangement". Apart from the spatial configuration of adsorbed molecules, their rearrangement also alters their properties in terms of functionality and even an affinity towards surface adsorption sites: the adsorbed molecules can be bonded to the adsorption sites more or less strongly than when they are in their original configuration. Let us assume that protein molecules can be reversibly adsorbed only in one configuration (configuration A), that the rearrangement of adsorbed molecules from configuration A to another configuration (B) is reversible, that the change in the configuration of adsorbed molecules does not influence the occupancy of the sensing surface, and that the adsorbed particles in configuration B can also be desorbed (Figure 1). In that case, the instantaneous numbers of adsorbed particles in the conformations A and B, N_A and N_B, are determined by the equations of the mathematical model, which is, at the same time, the sensor's temporal response model (assuming that the response is proportional to the number of adsorbed particles):

$$\frac{dN_A}{dt} = k_{aA}C(N_m - N_A - N_B) - k_{dA}N_A + k_{BA}N_B - k_{AB}N_A \quad (1)$$

$$\frac{dN_B}{dt} = k_{AB}N_A - k_{BA}N_B - k_{dB}N_B \quad (2)$$

Here, k_{aA} and k_{dA} are the adsorption and desorption rate constants of the protein with configuration A, k_{dB} is the desorption rate constant of the protein with configuration B, k_{AB} and k_{BA} are the rate constants of the transformation of adsorbed molecules from configuration A to B and back, C is the concentration of the protein in the sample, and N_m is the total number of adsorption sites on the sensing surface. The numbers of adsorbed particles, N_{As} and N_{Bs}, obtained by solving Equations (1) and (2) assuming $dN_A/dt = 0$ and $dN_B/dt = 0$, determine the steady-state sensor response:

$$N_{As} = \frac{(k_{dB} + k_{BA})k_{aA}C}{(k_{AB} + k_{dB} + k_{BA})k_{aA}C + k_{dA}(k_{dB} + k_{BA}) + k_{dB}k_{AB}}N_m \quad (3)$$

$$N_{Bs} = \frac{k_{AB}}{k_{dB} + k_{BA}}N_{As} \quad (4)$$

Both the adsorption and rearrangement processes are stochastic in nature, so the numbers of adsorbed particles fluctuate around the values determined by Equations (3) and (4). These fluctuations, ΔN_A and ΔN_B, constitute the inevitable intrinsic sensor noise. The analysis of this noise is based on the Langevin approach for the two-variable gain-loss stochastic processes [10], and such a process is one consisting of the mutually dependent processes ΔN_A and ΔN_B. The analysis starts from the Langevin form of Equations (1) and (2), which are obtained after substituting $N_A = N_{As} + \Delta N_A$ and $N_B = N_{Bs} + \Delta N_B$ and adding the suitable Langevin stochastic source functions (η_A and η_B) on the right side of Equations (1) and (2). The resulting equations obtained for fluctuations are solved in the frequency domain for $\Delta N_A(\mathrm{j}\omega)$ and $\Delta N_B(\mathrm{j}\omega)$ (knowing that the spectra of the Langevin stochastic source functions for that class of stochastic processes are white [10]; $\omega = 2\pi f$, where f is the Fourier frequency). Since the fluctuations of the total number of adsorbed molecules are $\Delta N = \Delta N_A + \Delta N_B$, their power spectral density (PSD) is $S(\omega) = \Delta N(\mathrm{j}\omega)\Delta N(-\mathrm{j}\omega)$, and, by

using the obtained frequency domain solutions for $\Delta N_A(j\omega)$ and $\Delta N_B(j\omega)$, the final form of the PSD of noise is obtained:

$$S(f) = S_{LFNM}\frac{1+(2\pi f)^2\tau_{III}^2}{[1+(2\pi f)^2\tau_I^2][1+(2\pi f)^2\tau_{II}^2]} \quad (5)$$

where

$$\tau_{I,II} = \frac{2}{K_{11}+K_{22} \pm \sqrt{(K_{11}-K_{22})^2+4K_{12}K_{21}}} \quad (6)$$

$$\tau_{III} = \frac{\sqrt{d_{As}+d_{Bs}}}{\sqrt{(K_{22}-K_{21})^2 d_{As}+(K_{11}-K_{12})^2 d_{Bs}}} \quad (7)$$

$$S_{LFNM} = 4(d_{As}+d_{Bs})\frac{\tau_I^2\tau_{II}^2}{\tau_{III}^2} \quad (8)$$

$$K_{11} = k_{aA}C + k_{dA} + k_{AB},\ K_{12} = k_{aA}C - k_{BA},\ K_{21} = -k_{AB},\ K_{22} = k_{dB} + k_{BA} \quad (9)$$

$$d_{As} = (k_{dA}+k_{AB})N_{As},\ d_{Bs} = (k_{dB}+k_{BA})N_{Bs}. \quad (10)$$

This completes the models of sensor response and noise.

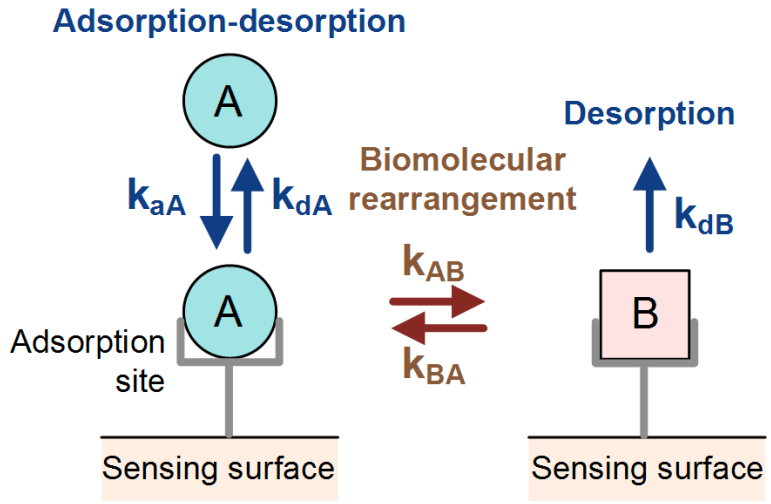

Figure 1. Schematic representation of interaction processes of biomolecules and adsorption sites. The rearrangement process of adsorbed molecules changes their spatial configuration from A to B and back. The adsorption and desorption rate constants, as well as the forward and reverse rearrangement rate constants, are shown near the corresponding arrows.

3. Results of the Analysis and Discussion

We present the results of a case study with the kinetic parameter values of the exemplary protein adsorption: $k_{aA} = 2{\cdot}10^7$ 1/(Ms), $k_{dA} = 10$ 1/s, $k_{dB} = 0.1$ 1/s, $k_{BA} = 0.01$ 1/s, $N_m = 10^{12}$ adsorption sites, $C = 5{\cdot}10^{-7}$ M, and three different values of the forward rearrangement rate constant k_{AB}: 0.25 1/s, 0.5 1/s, and 2 1/s (unit 1 M = mol/dm^3). These parameter values are in the range characteristic for the detection of proteins in biological samples [9,11–13], and they were chosen to illustrate the possible effects of biomolecular rearrangement processes on both sensor response and noise. The results were obtained using the response and noise models presented in Section 2.

Figure 2 shows the time evolution of the number of adsorbed molecules for three cases when a two-way rearrangement process occurs and for the case when the rearrangement does not occur (solid green line). The three cases differ in the ratio of forward and reverse

rearrangement rate constants, k_{AB}/k_{BA}: 25 (dash-dotted blue line), 50 (dashed red line), and 200 (dotted line). A significant change caused by the rearrangement is visible in the response kinetics: the response is slowed down, and the steady-state value increases compared to the case when the rearrangement does not occur. Also, the change in the response kinetics can be seen: from single-exponential (characteristic of AD processes without rearrangement) to two-exponential (two-step kinetics), with a fast starting rise, followed by a slower approach to the steady state. Such two-step response kinetics is experimentally observed [14]. Clearly, such experimental results could not be interpreted by a model that neglects biomolecular rearrangement.

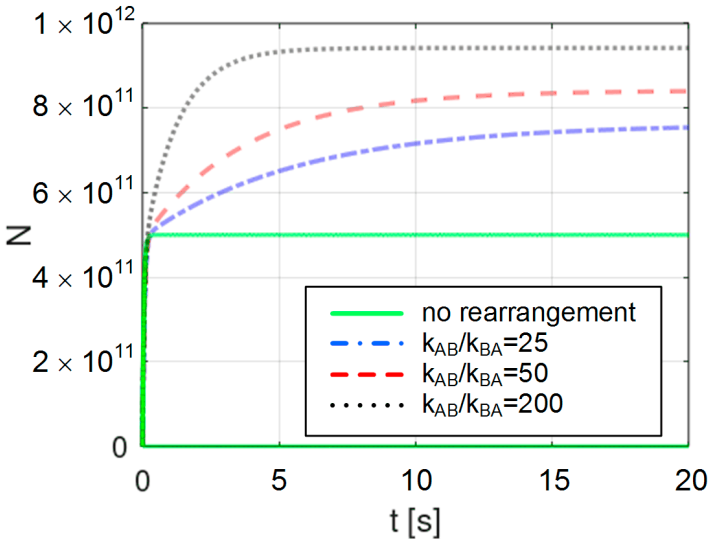

Figure 2. The time evolution of the number of adsorbed molecules, which determines the sensor response kinetics. The three cases when the reversible rearrangement process occurs (with different ratios of forward and reverse rearrangement rate constants, k_{AB}/k_{BA}) are shown, as well as the case when the configuration of biomolecules does not change after adsorption.

Figure 3 shows the noise power spectral density for the same four cases of protein adsorption as in Figure 2. As can be seen, the rearrangement of adsorbed molecules changes the noise spectrum. Instead of one characteristic frequency in the spectrum, there are three characteristic frequencies that determine the positions of two knees and one valley. LFNM also changes (for the given set of parameter values, LFNM increases). The change in the k_{AB}/k_{BA} ratio significantly alters the value of the lower characteristic frequency (it increases with the increase in k_{AB}/k_{BA}), while the influence on the highest frequency is negligible. It is clear that the three characteristic frequencies and the LFNM magnitude contain information about the values of the rearrangement process rate constants. Data about the values of these constants are scarce in the literature in spite of the fact that they can describe the interactions of biomolecules with solid surfaces or other biomolecules, whose characterization is important for the development of medications, implants, and biosensors, as well as for the research of various biochemical processes. The presented noise model can, therefore, be used for the development of methods for the characterization of biomolecular rearrangement processes based on the analysis of experimentally obtained noise spectra.

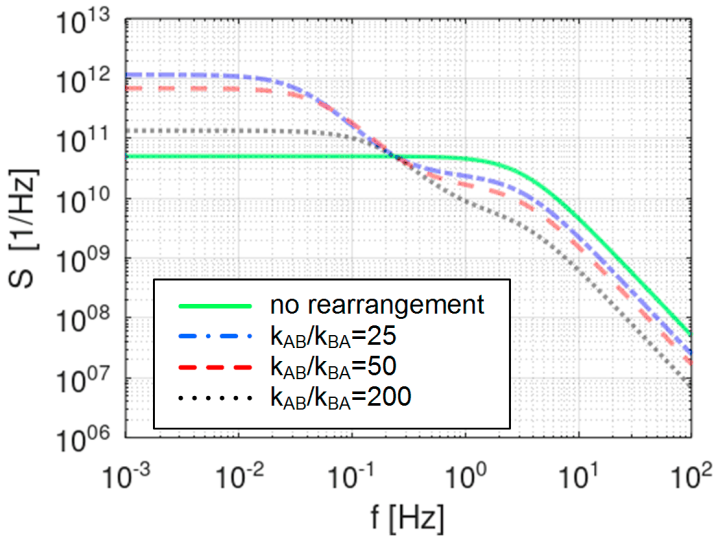

Figure 3. The power spectral density of fluctuations of the number of adsorbed biomolecules, representing the noise spectrum. The same cases are shown in Figure 2.

4. Conclusions

In this work, we developed the response and noise models of adsorption-based biosensors, taking into account the rearrangement processes of adsorbed biomolecules. We obtained the analytical expressions for their characteristic parameters. These models are used for the analysis of the influence of rearrangement processes on the sensor response kinetics and on the sensor's noise described by the spectral density of fluctuations of the number of adsorbed molecules.

Under the influence of the rearrangement process, the response kinetics becomes two-exponential (in contrast to the single-exponential kinetics of biomolecular adsorption, which is not followed by a rearrangement), with a fast starting rise and slow approach to the steady state. The sensor response slows down, and its steady-state value increases.

Due to the random change in the spatial configuration of adsorbed molecules, the noise spectrum changes from the single-knee to the two-knee shape. Three characteristic frequencies of the noise power spectral density and the low-frequency noise magnitude contain information about the rates of the reversible rearrangement process.

The presented sensor response model enables a more accurate interpretation of measurement results, which leads to more reliable biosensing. The noise model provides a better estimation of the ultimate sensor performance. Both the response and noise models are useful for the development of methods for characterization of biomolecular rearrangement processes. This would make it possible to compensate for the lack of data on the values of rearrangement rate constants, which is important for many applications in medicine, pharmacy, biosensing, and fundamental biochemical research.

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