



# Electrochemically directed biofunctionalization of a lossy-mode resonance optical fiber sensor

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**Abstract:** In this work, we present a direct electrochemical biofunctionalization of an indium-tin-oxide-coated lossy-mode resonance optical fiber sensor. The functionalization using a biotin derivative was performed by cyclic voltammetry in a 10 mM biotin hydrazide solution. All stages of the experiment were simultaneously verified with optical and electrochemical techniques. Performed measurements indicate the presence of a poly-biotin layer on the sensor's surface. Furthermore, dual-domain detection of 0.01 and 0.1 mg/mL of avidin confirms the sensor's viability for label-free detection.

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## 1. Introduction

The recent advances in nanotechnology and photonics have opened the possibility to develop a new generation of flexible, portable, versatile, and high-performance optical fiber sensors, such as those based on lossy-mode resonance (LMR). Thanks to the flexibility and relatively high sensitivity this new approach has emerged in the last two decades and found numerous applications such as refractive index (RI) [1], voltage [2], pH [3], humidity [4], and chemical detection [5,6]. Moreover, due to high RI sensitivity, numerous studies have been also reported on label-free biosensors based on the LMR effect [7,8]. This optical effect takes place in the presence of a thin film on an optical fiber. However, specific conditions for the electric permittivity of the substrate (fiber), thin overlay, and external medium must be fulfilled. Generally, the real part of the film's permittivity must be positive and at the same time higher in magnitude than its imaginary part and the permittivity of the analyte [7]. Thus, to obtain the LMR an adequate material for fiber overlay needs to be chosen. Many thin-film materials when deposited on silica glass allows obtaining LMR. These materials, among others, include semiconductor and metal oxides or nitrides (indium-gallium-zinc oxide [9], silicon nitride [10], indium-tin-oxide (ITO) [11], fluorine-doped tin oxide (FTO) [12], tin oxide [13], zinc oxides [9,14], indium oxide [15], titanium oxide [16], as well as hafnium, zirconium and tantalum oxides [17], diamond-like carbon films (DLC) [18] and various polymers [3]. Some of these materials, e.g., ITO [19–21] and FTO [12], thanks to their unique properties, such as good electrical conductivity and suitable bandgap [22], have already been reported as capable to work in two domains, where optical and electrochemical (EC) interrogations of the sensor were simultaneously possible. As multiple

domain sensors, they provide enhanced information about the analyzed target, improve detection range, cross-verify measurements and thus reduce false-positive results. This, in turn, is very important during biosensing investigations where low limits of detection and high specificity are expected. However, label-free biosensing applications require chemical modification of the sensor's surfaces. A chemical functionalization is required to immobilize a receptor of interest on the sensor's surface enabling high binding selectivity of targeted biomaterial. In the majority of reports on non-metal coated biosensors, poly(methylmethacrylate) polymeric (Eudragit L100) [13], (3-Aminopropyl)triethoxysilane (APTES) [23], or 3 (Triethoxysilyl)propylsuccinicanhydride (TESPSA) [24] depositions have been used to anchor biological molecule. Some of the silane compounds at the surface need to be additionally activated by a chemical coupling reaction with homo- or heterobifunctional cross-linker molecules that contain additional bioactive groups. Other reported approach employs a layer-by-layer coating of the LMR sensor's surface with oppositely charged polymers [25]. For example, to detect a C-reactive protein (CRP) [26], polymer bilayers containing Poly (allylamine) hydrochloride and Poly (sodium 4-styrenesulfonate) that are positively and negatively charged, respectively, have been used. After the formation of 4 bilayers a receptor i.e., DNA aptamer has been immobilized by electrostatic interactions as DNA is negatively charged. Although these chemical processes are essential for reaching selectivity of the sensors, a great majority of them is very time-consuming (from 2 to 4 h), require further modifications and curing of the deposited layer (from 2 to 48 h), and can induce a change in sensor properties, i.e., sensitivity and character of the spectral response of the sensor [24]. Moreover, due to the multiple steps, the processes may result in a lack of repeatability and stability.

Thus, where possible, other, simpler sensor surface biofunctionalization methods are highly expected. As one of them, EC-induced attachment of various compounds to the sensor's surfaces can be considered as a great alternative to chemical functionalization. The electropolymerization outstands other methods due to its easiness, precise positioning of the chosen compound, and short process time. Moreover, the electropolymerization is just a one-step process. However, the application of this method requires the surface of the sensor to be electrically conductive and EC-active. Electropolymerization has already been applied to ITO-LMR for its application in chemical sensing i.e., direct detection of Ketoprofen [27]. The process was conducted also to enhance the EC-activity of the sensor [28].

In this paper, we report a direct electrochemical ITO-LMR sensor's surface modification towards its application in label-free biosensing. We have used electropolymerized biotin hydrazide (BH) to form the receptor layer targeted towards selective dual-domain detection of avidin. The binding constant of the avidin-biotin formation complex ( $K_a = 10^{15} \text{ M}^{-1}$ ) is considered as the strongest non-covalent binding occurring in nature [29,30]. Based on these interactions not only immunoenzymatic techniques have been developed [31], but it is also widely utilized to construct many sensors and immunosensors [32–35]. Therefore, applied surface modification greatly expands the application range of the dual-domain ITO-LMR biotin-functionalized sensor.

## 2. Methodology

### 2.1. Reagents

1,1'-Ferrocenedimethanol ( $\text{Fc}-(\text{MeOH})_2$ ), biotin hydrazide (BH), avidin, bovine serum albumin (BSA) were purchased from Sigma-Aldrich and used without further purification.  $\text{K}_3\text{Fe}(\text{CN})_6$ , KCl, were purchased from POCh - Polish Chemical Reagents. 0.01 M Phosphate buffered saline (PBS) solution was obtained from Sigma-Aldrich by dissolving tablets in deionized water to obtain pH 7.4. Then the solution was adjusted to pH 7.0 with 0.1 M HCl using a glass electrode connected to pH meter.



## 2.2. ITO-LMR sensor fabrication

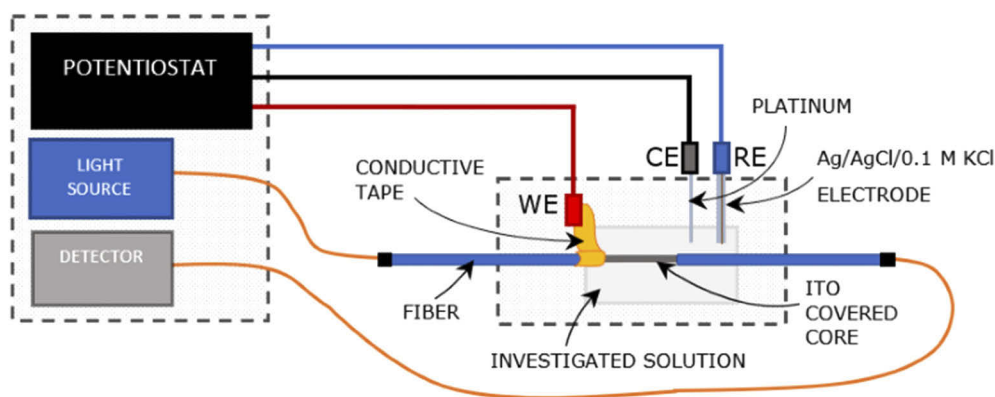
The ITO-LMR sensor is based on 15 cm long polymer-clad silica optical fiber, which had its 2.5 cm long cladding section removed in the middle part. The ITO thin film was deposited by magnetron sputtering in the ultra-high vacuum chamber. The magnetron was equipped with a 3-inch ITO target ( $\text{In}_2\text{O}_3:\text{SnO}_2 - 90:10$  wt%) and supplied by COMET Cito1310 RF source (13.56 MHz, 150 W). The optical fiber sample was rotated during deposition to receive a homogenous coating around the fiber. The deposition at a pressure of 0.1 Pa and Ar flow of 26.4 sccm took 135 min. The sensors' fabrication was followed by optical and EC characterization as described in [23].

## 2.3. Electrochemical and optical setup

Cyclic voltammetry (CV) measurements were performed with a Palmsens EmStat 3+ potentiostat/galvanostat controlled by PSTrace 5.5 software using the ITO-LMR as a working electrode (WE). A platinum wire was used as a counter electrode (CE) and an Ag/AgCl/0.1 M KCl as a reference electrode (RE). The ITO-LMR electrode was EC-investigated both in 1 mM  $\text{K}_3\text{Fe}(\text{CN})_6$  in 0.1 M KCl and 1 mM  $\text{Fc}-(\text{CH}_2\text{OH})_2$  in 0.1 M KCl at scan rate 50 mV/s for 2 cycles in the potential ranging from -0.5 to 0.7 V. Each cycle/scan is understood as applying the potential starting from 0 V  $\rightarrow$  0.7 V  $\rightarrow$  0 V  $\rightarrow$  -0.5 V  $\rightarrow$  0 V and takes  $\sim$  24 seconds.

Two redox couples –  $\text{Fe}(\text{CN})_6^{3-/4-}$  and  $\text{Fc}-(\text{CH}_2\text{OH})_2^{+/0}$  – were chosen due to their different sensitivity towards the surface and different EC behavior in the examined solution.  $\text{Fe}(\text{CN})_6^{3-/4-}$  is a negatively charged, inner-sphere redox probe. The observed electron transfer reactivity in this redox probe significantly depends on preparation, modification, and coverage of the electrode surface [36,37]. On the other hand, the  $\text{Fc}-(\text{CH}_2\text{OH})_2^{+/0}$  is neutral, water-soluble redox couple, belonging to the outer-redox probe. This redox system was chosen due to the lack of any electrocatalytic activity and no adsorption processes observed during the electrochemical measurements [38]. The EC mechanism of both chosen redox couples was described in our previous work [19].

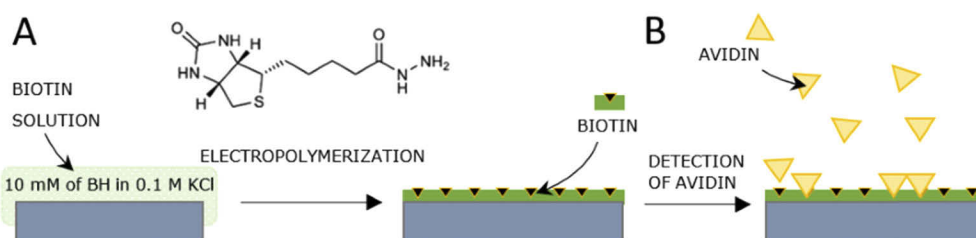
The optical response of the ITO-LMR sensor during the experiment has been interrogated in the spectral range from 350 to 1050 nm using USB4000 spectrometer and HL-2000 tungsten light source (Ocean Optics). The interrogation time was set to 4 ms. The optical data acquisition and processing have been controlled using in-house developed software. The schematic representation of the measurement setup used for the optical-EC investigation is shown in Fig. 1.



**Fig. 1.** Schematic representation of combined optical and EC measurements setup with ITO-LMR sensor subjected to the electropolymerization process. The electrodes were denoted as working (WE), reference (RE), and counter (CE) electrode.

#### 2.4. Electropolymerization of biotin hydrazide

The electrodeposition was studied on bare ITO-LMR sensor used as a working electrode. To perform the electropolymerization process the fiber probe was immersed in 10 mM of BH in the 0.1 M KCl solution and underwent 10 cycles performed in the potential range from 0 to 1.1 V at a scan rate of 50 mV/s (each scan followed the scheme 0 V → 1.1 V → 0 V). Each cycle took ~ 22 seconds, thus, the whole procedure was just ~3 min 40 sec long. The electropolymerization process was monitored by optical measurements as described in Section 2.3. After the functionalization the ITO-LMR was measured optically and EC in presence of 1 mM  $K_3Fe(CN)_6$  in 0.1 M KCl at a scan rate of 50 mV/s for 2 cycles in the potential ranging from -0.5 to 0.7 V. Figure 2 presents a schema of BH electropolymerization on the ITO surface and detection scheme of avidin.



**Fig. 2.** Schematic representation of A) BH electropolymerization process, B) binding of avidin to the biotinylated ITO-LMR surface.

#### 2.5. Avidin detection

The electropolymerization of biotin was followed by the detection of biotin specific glycoprotein – avidin, with two different concentrations, i.e., 0.01 mg/mL, 0.1 mg/mL dissolved in 0.01 M solution of PBS, pH 7.0. After the electropolymerization process, the electrode was immersed in 1% BSA in 0.01 M PBS, pH 7.0 for 30 minutes to block the nonspecific interactions. Next, the ITO-LMR poly-biotin-functionalized samples were incubated in consecutive solutions of avidin for 30 minutes. Then, the ITO-LMR electrode was extensively washed with water and PBS. Each step of the experiment was followed by optical and CV measurements in the presence of 1 mM  $Fc-(CH_2OH)_2$  in 0.1 M KCl at a scan rate of 50 mV/s for 2 cycles in the potential ranging from -0.5 to 0.7 V.

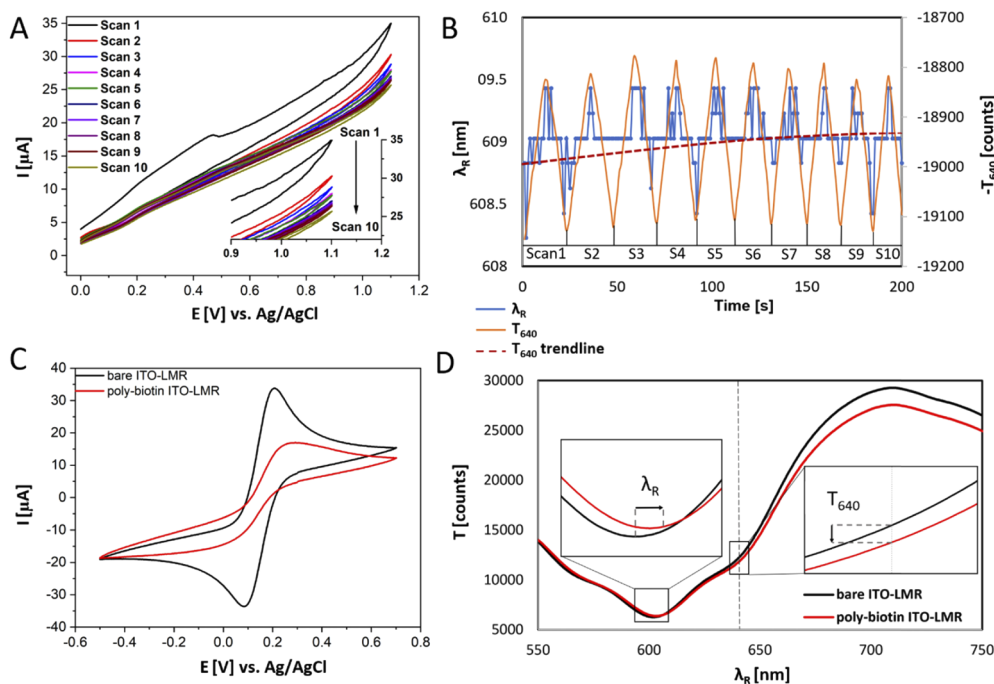
### 3. Results and discussion

#### 3.1. Electropolymerization of biotin hydrazide on the ITO-LMR electrode

The functionalization of the ITO-LMR sensor's surface was performed by the electropolymerization process following a modified procedure described in [39] to cover the ITO electrode by amino derivatives of biotin. The main advantage of the electropolymerization method is its easiness as well as time (~3 min 40 sec) and reagent saving in comparison to other chemical methods. The exact mechanism of the deposition of BH is unknown, however, two probable descriptions were proposed by Davis and co-workers [40]. The first mechanism is associated with the oxidation of carbazoyl group, whereas the second one suggests the formation of a radical cation upon oxidation of the hydrazide group [41].

Figure 3(a) presents the CVs obtained during the electropolymerization process. After the first scan, the anodic peak current significantly decreased. During the next 9 scans, the behavior followed the decreasing trend. It indicates the modification of the electrode surface. Similar

electrochemical behavior was also observed during the modification of gold [40] and flat ITO electrode surfaces [39].



**Fig. 3.** A) CV scans recorded for the ITO-LMR sensor in 0.1 M KCl containing 10 mM of BH. The scan rate was 50 mV/s; B) Change in  $\lambda_R$  and  $T_{640}$  with the progress of the biotin electropolymerization process; (C) CV scans recorded before and after electropolymerization of biotin in the presence of  $K_3Fe(CN)_6$  in 0.1 M KCl. The scan rate was 50 mV/s; (D) Comparison of the ITO-LMR spectral response of the sensor in  $K_3Fe(CN)_6$  in 0.1 M KCl before and after the electropolymerization.

Like many other biological molecules, biotin does not undergo redox reaction and thus observation of current peaks in CV is not possible. That is why the additional redox couples present in the electrolyte are required to follow the changes occurring at the surface of the ITO electrode. To examine the EC immobilization of the biotin, the CV response was verified with the presence of  $Fe-(CN)_6^{3-}$  and  $Fe-(CH_2OH)_2^{+0}$ . The electrochemical properties of the ITO-LMR electrode before and after electropolymerization were investigated by cyclic CV performed in 1 mM  $Fe-(CN)_6^{3-/4-}$  solution containing 0.1 M KCl. Figure 3(c) shows the CVs for the bare ITO-LMR probe before electropolymerization and the signal after the process. Two well-defined peaks are observed for the bare ITO-LMR electrode. The peak to peak separation ( $\Delta E_p$ ) is equal to 117 mV, the anodic peak current to cathodic peak current ratio ( $i_{pa}/i_{pc}$ ) is equal 1, what indicates one electron *quasi*-reversible redox reaction. After the electropolymerization process, the anodic and cathodic peak currents decreased.  $\Delta E_p$  for the poly-biotin-modified electrode increased to 249 mV. It reveals that the electron transfer is blocked in comparison to the bare ITO-LMR electrode. Similar behavior was observed before using  $Fe(CN)_6^{3-/4-}$  as a redox couple [42]. This phenomenon clearly confirms that the ITO-LMR electrode was modified by biotin.

The electropolymerization process simultaneously to EC interrogation has been also monitored optically. Figure 3(b) shows the alterations in the optical spectrum during the BH deposition for selected spectral parameters, i.e. LMR wavelength ( $\lambda_R$ ) and transmission at  $\lambda=640$  nm ( $T_{640}$ ). The wavelength for transmission change analysis was selected in the middle of the resonance



slope, where a noticeable variation could be observed. The main motivation of the choice was to match the wavelength of cheaper and widely available laser diodes possible to be applied as a light source when simple, solely power-based interrogation is considered. Furthermore, even though the change in terms of the amplitude is significant in other points, in these locations there is no change in terms of the wavelength. In Fig. 3(d), a comparison of the full spectral response of the ITO-LMR sensor before and after the electropolymerization process is depicted. It is apparent that after the polymerization of BH a shift of  $\lambda_R$  towards longer wavelengths and a decrease in  $T_{640}$  took place. Due to low wavelength resolution of the spectrometer, we simultaneously traced changes in optical power  $T_{640}$ . Since the power resolution is higher it can be treated as a confirmation of a wavelength shift. Although the changes recorded for biotin deposition are close to the resolution of the spectrometer, we cannot expect any significant shifts. The biotin molecule with  $\sim 1.6$  nm size and the RI close to the PBS buffer could not strongly affect the spectrum. On the other hand, such size is enough to change the conductivity of the ITO-LMR electrode. Thus, the spectral shift after biotin deposition is justified considering electrochemical measurements, where blocking of the surface by the biotin, traced as a decrease of anodic and cathodic peak currents, is indisputable (Fig. 3(c)).

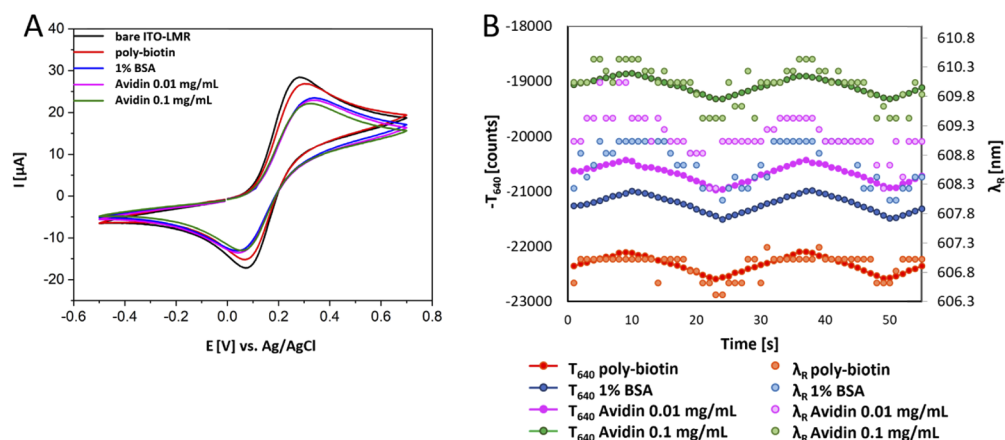
### 3.2. Avidin detection using biotin-functionalized ITO-LMR electrode

To confirm the sensor's viability for label-free detection, the presence of the poly-biotin on the ITO-LMR surface, and stability of the surface's functionalization we performed a series of experiments for the selective immobilization of avidin. During the subsequent stages of electrode modification, both EC and optical measurements were performed. The CVs were obtained in 1mM  $\text{Fc}-(\text{CH}_2\text{OH})_2^{+/0}$  solution containing 0.1 M KCl.

Figure 4(a) depicts CV curves recorded after incubation in BSA, 0.01 and 0.1 mg/mL of avidin, where each incubation was followed by an extensive washing in PBS and water. Therefore, the registered responses are induced only by interactions at the sensor's surface and were not disturbed by, e.g., RI changes in the volume. Right after the electropolymerization, the ITO-LMR electrode was immersed in a 1% BSA solution to block any nonspecific interactions on the surface. This caused a decrease in the current peak and increased  $\Delta E_p$  from 220 to 270 mV. Next, the ITO-LMR electrode was incubated for 30 minutes in the 0.1 mg/mL of avidin. Although we could observe a decrease of the current peak after the incubation the shape of the obtained voltammograms was very similar to those after BSA. Additionally, the calculated value of  $\Delta E_p$  was at the same level  $\sim 270$  mV as for the previous stage of the experiment. In contrast, the immersion of the ITO-LMR in the second concentration of avidin caused noticeable changes in CV decreasing the peak current and increasing  $\Delta E_p$  to the value of  $\sim 250$  mV.

Figure 4(b) shows the evolution of corresponding optical parameters, namely  $\lambda_R$  and  $T_{640}$  after each step of the experiment. The apparent shift towards longer wavelengths and decreases in transmission corresponds to an increase of the thickness and/or RI of the biological layer on the biotinylated ITO-LMR's surface. Starting from the formation of the BSA layer – the  $\sim 1$  nm shift of  $\lambda_R$  can be noticed. Next, for the avidin molecule, we can observe further changes. It can be seen that the higher concentration of avidin, the bigger the LMR shift towards longer wavelengths is obtained. The most significant change of  $\sim 2$  nm was observed for the 0.1 mg/mL concentration of avidin. All obtained results confirm avidin detection on the ITO-LMR sensor using both electrochemical and optical methods at the level from 0.01 to 0.1 mg/mL.

In this work we focused mainly on the optimization of the electropolymerization process, namely the number of scans, the range of the applied potential, and the concentration of the biotin hydrazide to obtain the effective biofunctionalization. Our aim was more to show a novel modification concept and its verification than to focus on a specific application, a broad range of concentrations or reaching a low limit of detection. Thus, the two avidin concentrations were used mainly to verify the presence of the poly-biotin on the sensor's surface. It must be noted



**Fig. 4.** A) CVs after each step of avidin detection in the presence of 1 mM  $\text{Fc}-(\text{CH}_2\text{OH})_2$  in 0.1 M KCl, scan rate: 50 mV/s; (B) Corresponding change in ITO-LMR  $\lambda_R$  and  $T_{640}$  after each step of the avidin detection experiment.

that this fast and efficient method is also very universal thanks to the presence of the biotin-avidin complex. Such a well-verified modification could be used in the future to detect any biotinylated molecule, such as antibodies, DNA aptamers, peptides, proteins, etc. Up to our best knowledge, there is no other report available on biotin hydrazide functionalization of the optical fiber sensor's surface, where the functionalization is verified optically and electrochemically.

The reported dual-domain system allows for gathering significantly more information on the investigated samples, unlike single domain investigation. Cross-verification of the obtained results is possible within one experiment. Since the sensitivity and its ranges for the two domains may be different, they can serve as a supplement to each other leading to significantly improved performance of the sensor. What is more, it also gives the capability to conduct a functionalization process, (namely the electropolymerization, as reported here) in one domain and monitor its progress using the other one. During label-free sensing with the support of theoretical simulations and knowledge about detected molecules, such as RI, estimation of the thickness and properties such as isoelectric point or permeability of the deposited layer are also possible.

#### 4. Conclusions

In our work, we have demonstrated a simple, one-step method for direct electrochemical biofunctionalization of ITO-LMR sensor's surfaces. The modification was achieved by electropolymerization of 10 mM biotin hydrazide. The process was possible due to the electrical conductivity of the indium tin oxide film deposited on the multimode optical fiber core, which allowed to use the ITO probe as a working electrode. On the other hand, the lossy mode resonance effect enabled the parallel optical measurements. Both cyclic voltammetry experiments and optical measurements performed in the presence of two different redox couples confirmed the presence of poly-biotin film at the ITO-LMR sensor's surface. What is more, we demonstrated its viability for label-free sensing by detection of 0.01 and 0.1 mg/mL of avidin. The biotin-functionalized surface and its interaction with avidin – known from immunoenzymatic tests – can greatly expand the application range of the dual-domain ITO-LMR sensor. Except for the universal character of the reported functionalization, the method outstands other techniques by its easiness (one-step process), repeatability, precise positioning of the compound, and short process time, which is lower than 4 minutes.

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## Disclosures

The authors declare no conflicts of interest.

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