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Highly sensitive detection of molecular interactions with plasmonic optical fiber grating sensors

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ABSTRACT

Surface Plasmon resonance (SPR) optical fiber biosensors constitute a miniaturized counterpart to the bulky prism configuration and offer remote operation in very small volumes of analyte. They are a cost-effective and relatively straightforward technique to yield in situ (or even possibly in vivo) molecular detection. The biosensor configuration reported in this work uses nanometric-scale gold-coated tilted fiber Bragg gratings (TFBGs) interrogated by light polarized radially to the optical fiber outer surface, so as to maximize the optical coupling with the SPR. These gratings were recently associated to aptamers to assess their label-free biorecognition capability in buffer and serum solutions. In this work, using the well-acknowledged biotin–streptavidin pair as a benchmark, we go forward in the demonstration of their unique sensitivity. In addition to the monitoring of the self-assembled monolayer (SAM) in real time, we report an unprecedented limit of detection (LOD) as low as 2 pM. Finally, an immunosensing experiment is realized with human transferrin (dissociation constant $K_d \sim 10^{-8}$ M^{-1}). It allows to assess both the reversibility and the robustness of the SPR-TFBG biosensors and to confirm their high sensitivity.

1. Introduction

Surface Plasmon resonance (SPR)—the excitation by light of surface Plasmon waves propagating at the interface between a noble metal (most often gold or silver) and a dielectric finds many applications in (bio)chemical sensing (Homola, 2006; Andersson et al., 2010; Dostálek et al., 2007). Thanks to their micrometric scale dimensions, optical fiber SPR sensors enable practical applications not possible with the bulky Kretschmann prism configuration, such as remote operation in very small volumes of the order of microliters (Slavik et al., 2002; Jeong et al., 2013). To excite SPR in optical fiber-based plasmonic sensors, light initially confined in the fiber core has to be locally outcoupled and brought into contact with the surrounding medium. Practically, this can be achieved either mechanically by polishing (or etching) the cladding so as to expose the evanescent wave to the surrounding medium or by using radiative fiber gratings (refractive index modulations imprinted in the fiber core thanks to its intrinsic photosensitivity) such as long period gratings (LPGs) or tilted fiber Bragg gratings (TFBGs). They both couple the core mode to cladding modes that propagate towards the cladding-surrounding medium interface and are therefore sensitive to surrounding refractive index (SRI) changes (Verma et al., 2008; Schuster et al., 2012; Shevchenko et al., 2010; Baldini et al., 2012). In this work, we make use of TFBGs that inherently possess all the advantages of optical fibers. In comparison to other optical fiber SPR configurations, they gather the additional benefits of keeping the fiber integrity while yielding intrinsically temperature-insensitive measurements (Albert et al., 2013), which is particularly worthwhile to obtain highly sensitive SRI measurements.

A standard fiber Bragg grating (FBG) consists of a refractive index modulation in the core of an optical fiber that is imprinted perpendicular to the propagation axis. An FBG acts as a selective mirror in wavelength, reflecting some wavelengths around a characteristic one, so-called Bragg wavelength. The latter is sensitive to temperature and mechanical strain but, as it results from light coupled in the fiber core, it is not influenced by SRI changes. A TFBG corresponds to a core refractive index modulation angled by a few degrees with respect to the perpendicular to the propagation axis. This induces two kinds of couplings: the self-backward coupling of the core mode at the Bragg wavelength and numerous couplings between the core mode and backward-going cladding modes at resonance wavelengths below the Bragg wavelength. Contrary to the Bragg resonance, the cladding mode resonances are modified by SRI

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changes (Laffont and Ferdinand, 2001; Caucheteur and Mégret, 2005; Chan et al., 2007), depending on the SRI value with respect to their own effective refractive index value.

TFBGs yield SPR generation when a nanometric gold coating is deposited all around the fiber section, which further increases their sensitivity to SRI changes (Caucheteur et al., 2011; Voisin et al., 2011). It reaches more than 500 nm/refractive index unit (RIU) in the SRI range between 1.32 and 1.42, yielding an intrinsic resolution better than 2×10^{-6} RIU when using a measurement device accurate to 1 pm (as provided by interrogation techniques based on a tunable laser source). This high resolution combined to a quality factor of 10^5 and signal-to-noise ratio greater than 50 dB opens the path to biodetection (Shevchenko et al., 2011). Another important feature of these sensors is their self-immunity from temperature fluctuations as the Bragg wavelength provides an absolute reference. Measurements are therefore normalized with respect to the Bragg wavelength shift to get this intrinsic compensation.

In practice, the SPR generation can only occur when the light launched into the TFBG is polarized radially to the fiber surface. A remarkable property of TFBGs is that they excite spectrally distinct cladding mode families with fields radially polarized (so-called P-polarized modes) and azimuthally polarized (S-polarized modes) at the cladding boundary (Caucheteur et al., 2011). P-polarized modes couple to the SPR and are therefore strongly attenuated with respect to neighboring cladding mode resonances, which is not the case for S-polarized modes.

It was recently demonstrated that gold-coated TFBGs functionalized with aptamers can be used for label-free biosensing (Shevchenko et al., 2011). Protein detection in buffer and serum solutions was achieved in micromolar concentrations. In this work, we use the well-acknowledged antibody–antigen affinity mechanism to further assess the unique protein detection and quantification capabilities of these SPR-TFBGs. We are aware to go one step backward in terms of biomaterials technology with respect to the use of aptamers but this is useful to evaluate the performances of the proposed biosensors in terms of both sensitivity and limit of detection (LOD) and to compare them with other optical fiber biosensors. We report two kinds of experiments, with the biotin–streptavidin pair and with human transferrin. The biotin–streptavidin couple has been used as a reference in a wide variety of new device studies and in a lot of bioanalytical applications (Scott Phillips and Cheng, 2007; Takahashi et al., 2012). This great interest is largely due to the exceptionally high affinity (dissociation constant $K_d=10^{-15}\,M^{-1}$) and the subsequent stability of this non-covalent interaction. The most straightforward method to immobilize biotin on a gold surface is a self-assembled monolayer (SAM) composed of alkanethiols functionalized with biotin (Seifert et al., 2010). This is what we have exploited in this work.

As a follow up to (Shevchenko et al., 2011; Caucheteur et al., 2013), we exploit here the differential behavior of cladding mode resonances in the vicinity of the SPR mode to monitor the SAM formation and to finely measure streptavidin concentrations. For this, functionalized SPR-TFBG biosensors were immersed in phosphate buffered saline (PBS) with streptavidin molecules at very low concentrations ranging from 10^{-11} to 5×10^{-4} g/ml. We report the highest spectral variations ever obtained with gold-coated TFBGs biosensors, allowing to reach a limit of detection equal to 2 pM.

Finally, an immunosensing experiment is reported with human transferrins. They are iron-binding blood plasma proteins that control the level of free iron. They are also associated with the immune system and reflect the presence of pathologies such as iron deficiency anemia. It is thus clinically relevant to identify and quantify such proteins. In this work, they were chosen for their K_d value equal to $10^{-8}\,M^{-1}$ to demonstrate that our immunosensor can operate well in real biochemical conditions. Transferrins also allow to demonstrate the reversibility of the binding, the regeneration of the biosensor and to further assess its robustness. To do so, an SPR-TFBG with antibody transferrin immobilized on gold was put into contact with different human transferrin solutions (concentrations ranging between 10^{-7} g/ml and 10^{-3} g/ml). The regeneration is obtained with glycine and NaCl.

2. Materials and methods

2.1. Materials

2.1.1. Tests with the biotin–streptavidin couple

Biotinylated alkyl thiol (mercaptoundecyl-hexaethyleneoxy biotin amide) was purchased from Nanoscience Instrument (Belgium). Ethanol in HPLC grade was purchased from Sigma-Aldrich (Belgium) and used without further purification as solvent for thiols incubation. Alexa Fluor-488-streptavidin was purchased from Invitrogen (Belgium). Its molecular weight is equal to 55,090 g/mol. Phosphate buffer saline (PBS) solution from PAA laboratories (Austria) was used as solvent for streptavidin anchoring.

2.1.2. Tests with human transferrin

6-Mercaptohexanoic acid (90%) purchased from Sigma-Aldrich (Belgium), Human Holo-Transferrin from R&D systems (UK), Antibody anti-Transferrin from AbD Serotec (Germany), N-hydroxysuccinimide (NHS) from Sigma-Aldrich (Belgium), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) from Sigma-Aldrich (Belgium), glycine at pH=2 from Sigma-Aldrich (Belgium) were used as received. HBS-EP 1X purchased from GE Healthcare (Belgium) was diluted 10 times with Milli-Q water before use.

2.2. Fabrication of the SPR-TFBGs

1 cm-long TFBGs were manufactured into hydrogen-loaded telecommunication grade single-mode optical fiber using a 1090 nm period uniform phase mask and a frequency-doubled argon-ion laser emitting at 244 nm. The mask was tilted in the plane perpendicular to the optical fiber axis, as illustrated in Albert et al. (2013). TFBGs were obtained by a single scan of the laser beam (width: 0.6 mm; averaged power: 60 mW) along the phase mask at the speed of 20 μm/s. An external tilt angle of 6° was chosen with respect to the perpendicular to the optical fiber axis to ensure strong coupling to cladding modes characterized by an effective refractive index close to water (1.33). Right after the inscription process, the gratings were annealing at 100 °C during 24 h to remove the residual hydrogen and to stabilize their physical properties.

A 50 nm gold coating (99.99% purity target) was then deposited on the TFBGs using a standard sputtering process. The vacuum was obtained in the chamber starting from ambient air. Two consecutives depositions were made in the same conditions, with the optical fibers rotated by 180° between the two processes to ensure that 100% of the surface is covered by gold.

2.3. Development of the SPR-TFBG biosensors

2.3.1. Biotinylation of the SPR-TFBGs outer surface

The gold-coated TFBGs were first thoroughly rinsed with ethanol and cleaned under ozone atmosphere to remove unwanted contaminants. To obtain the SAM at the outer surface of the sensors, they were then immersed in a solution of biotinylated thiols (mercaptoundecyl-hexaethyleneoxy biotin amide) dispersed in ethanol. Thiols incubations were done during 16 h at room temperature in a 1 mm thick