Non-enzymatic D-glucose plasmonic optical fiber grating biosensor

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ABSTRACT

Saccharide sensors represent a broad research area in the scope of sensing devices and their involvement in the medical diagnosis field is particularly relevant for cancer detection at early stage. In that context, we present a non-enzymatic optical fiber-based sensor that makes use of plasmon-assisted tilted fiber Bragg gratings (TFBGs) functionalized for D-glucose biosensing through polydopamine (PDA)-immobilized concanavalin A (Con A). Our probe allows a live and accurate monitoring of the PDA layer deposition leading improved surface biochemistry. The SPR shift observed was assessed to 3.83 ± 0.05 nm within 20 min for a 2 mg/mL dopamine solution. Tests performed in different D-Glucose solutions have revealed a limit of detection close to 10^{-7} M with the highest sensitivity in the 10^{-6} to 10^{-4} M range. This configuration has the capability to overcome the limitations of current enzyme-based solutions.

1. Introduction

Saccharide sensors represent the largest part of the worldwide sensors market and occupy a significant position in scientific bioresearch. This trend can be explained by the relevance of such devices in food industry, biotechnology, medical diagnosis involving the blood sugar level, pathogens or cancer detection among others (Alderman et al., 1999; Kejík et al., 2010; Moore et al., 2005; Staiano et al., 2004; Vinoth et al., 2018; Wang and Lee, 2015). Besides the necessary accurate control in the frame of diabetes mellitus monitoring, saccharides sensing was demonstrated to play an important role in the early cancer diagnosis (Kejík et al., 2010). Indeed, saccharides and their glycoconjugates are involved in many biochemical mechanisms (e.g tumour proliferation, invasion, metastasis, etc.) in cancer development. Furthermore, certain molecular-scaled changes happen in the tissue environment, preceding the tumour apparition (Saffroy et al., 2007). Therefore, the use of cancer biomarkers such as tumour saccharides can offer the possibility to detect cancer at very early stage. Glucose is an aldohexose ($C_6H_{12}O_6$) isomer but merely the D-glucose stereoisomer is essential for human body. This D-isomer, major saccharide in human blood, is metabolized by cells through the use of a glycolyze process leading to the adenosine triphosphate (ATP) production, the energy source of living organisms. Numerous methods exist to achieve glucose

sensing and most of them consist of electrochemical sensors (Hwang et al., 2018), fluorescence-based sensors (Russell et al., 1999), colorimetric detection (Dong et al., 2012) and optical sensors (Sun et al., 2018; Yuan et al., 2018; Hang et al., 2018). The advantages of optical sensors and more especially optical fiber-based sensors are numerous and justify the choice of their use in biotechnology. Indeed, these sensors provide fast, label-free and minimally invasive sensing of miscellaneous analytes (e.g. proteins, bacteria, antigens, macromolecules, etc.) (C. Caucheteur et al., 2015b; Ribaut et al., 2017). Moreover, they are flexible, nanoscaled and inexpensive, and can be fully biocompatible (Sun et al., 2018).

Among the existing optical fiber-based transducer, D-shaped, U-shaped, tapered fibers or fiber gratings are mainly used. In a standard telecommunication grade fiber, light is confined in the core whereas for optical fiber sensing, the aim is to make light interact with the surrounding medium. Hence, the core light is brought into contact with the surrounding environment by partially or totally removing the fiber cladding, and in some cases, a part of the core is also eliminated (e.g. D-shaped fiber). Tilted fiber Bragg gratings (TFBGs) combined to surface plasmon resonance (SPR) excitation are particularly relevant. In the latter, the entire mechanical integrity of the fiber is preserved. Indeed, an FBG is a permanent and periodic modification of the refractive index (RI) inside the fiber core and this structure acts as a pass-band filter

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thanks to small Fresnel reflections at each period of the Bragg grating. For some wavelengths around the so-called Bragg wavelength, these reflections are in-phase and the constructive interference between the forward-going and backward-going light waves lead to a strong peak (attenuation) in the reflected (transmitted) light spectrum. Nevertheless, light remains in the core, since the RI is higher in the cladding, ensuring propagation by total internal reflection. To counteract this, a small tilt (typically 1°–10°) with respect to the perpendicular axis to the fiber core can be made and this feature couples light in the cladding into numerous tens of cladding modes. Since each excited cladding mode is characterized by a definite wavelength and corresponds to a loss in the light core intensity, the transmission spectrum of a TFBG exhibits a set of resonances resulting in a narrow-band comb-like spectrum (Erdogan and Sipe, 1996; Guo et al., 2016). It is worth to notice that the Bragg peak is not sensitive to the surrounding medium but to the stress and temperature variations. This feature provides a self-referenced system for biochemical measurements. The refractive index sensitivity can be significantly enhanced by the use of the SPR effect. A plasmon is a periodic oscillation of electrons that usually occurs at the interface between a metal and a dielectric. This excitation can be implemented in a convenient way with a TFBG by covering the grating part with a thin metal layer (typically 40–50 nm). One of the most commonly used metal is gold, among others, for biocompatibility and stainless reasons, which can be deposited by sputtering, evaporation or electroless plating. In addition to the thin metal layer-dielectric interface requirements, the incident light wave must be perpendicularly polarized to the interface (P-polarized) and exhibit a tangential component identical to that of plasmon wave. Excitation of surface plasmon absorbs a part of light energy in a certain wavelength range depending on the refractive index of the immediate surrounding medium. Therefore, it explains the resonance attenuation visualized in the light spectrum when the conditions are satisfied. The polarization state is a major parameter to tune in order to excite the SPR (Caucheteur et al., 2016; González-Vila et al., 2017; Ribaut et al., 2017). Using optical fibers, this can be easily achieved with inline polarizers or polarization controllers.

With regard to biorecognition element, the surface functionalization of the sensor can be achieved by means of the so-called Concanavalin A (Con A) protein. This lectin protein (i.e. a carbohydrate specifically binding protein) is a homotetramer presenting saccharide binding sites which can be inhibited by D-glucose molecules (Becker et al., 1975) using reversible hydrogen bonds (Ambrosi et al., 2005). The use of such protein is interesting and conducts to the inherent advantage of non-enzymatic sensors fabrication. In fact, enzymatic-based sensors represent the largest part in the glucose sensing field and many of them use glucose oxidase or glucose dehydrogenase enzymes as detection method (Wang and Lee, 2015). In spite of their excellent sensitivity, this type of sensors suffers from several drawbacks as a lack of robustness against temperature and pH variations resulting in incorrect readouts. The fact that they are also subject to biofouling justify the investigation of non-enzymatic alternatives. However, to cover gold-coated fiber with proteins, an intermediate layer is needed to create a strong adhesion on the gold metal layer. An inexpensive and widespread solution to solve this issue is to cover the fiber with a polymer prior to attach the bioreceptor (i.e. Con A). An appropriate candidate is the dopamine (DA), a well-known molecule with a nature-inspired utilization. Indeed, it is importantly involved in the adhesion mechanism of mussels (Lee et al., 2009, 2006) to various types of inorganic or organic substrates such as metal, glass, polymer, etc (Zhou et al., 2014). Dopamine is a monomer able to self-polymerize in the presence of tris(hydroxymethyl) aminomethane (Tris), most of the time in basic condition, and form a continuous layer. In this reaction, a part of catechol groups belonging to dopamine oxidize into benzoquinone (Li et al., 2013) and the formers polymerize to form polydopamine (PDA) while the remaining quinone and catechol functions are expected to react with other chemical compounds. These functions are able to form strong covalent bonds with the amine ($-NH_2$) or thiol ($-SH$) groups of biomolecules through Michael addition or Schiff base reactions (Lynge et al., 2011). Hence, Con A can be immobilized on the PDA film by the establishment of covalent bonds between the amine group of the lysine residues and the quinone (or catechol) groups belonging respectively to the protein and the polymer (C. Y. Li et al., 2011; F. Li et al., 2011; Morris et al., 2009). In case of alkaline conditions, chemical balance moves to quinone groups from catechol ones (Lynge et al., 2011). The initiation of the layer formation begins through the chemically adsorbed monomers on gold which first lead to nanoscaled aggregates, followed by polymers formation with heavier molecular weight. A study has shown that a rapid magnetic stirring of the solution during the reaction has a real impact on the polymerization process by dramatically increasing the polymer thickness and reaction kinetics in comparison with a static deposition method (Zhou et al., 2014).

Our work aims to conduct a preliminary study to develop a non-enzymatic TFBG SPR-based D-glucose biosensor functionalized using Concanavalin A proteins as specific bioreceptors. This study intended to reap the benefits from the multiple advantages intrinsically offered by TFBG optical sensors and to combine them with the polyvalent binding behaviour of PDA and the proper affinity of Con A to D-glucose ($K_{D(D-glucose)} = 1.25 \times 10^{-3}$ M) (Wang and Anzai, 2015). The effectiveness and the sensitivity of this sensor were assessed by tracking the sensing response in different D-glucose solutions. These experiments were performed in phosphate buffered saline (PBS), a standard medium for bioassays, within a large concentration range (10^{-8} to 10^{-2} M) relevant for medical prospects (Moore et al., 2005). The objective was to provide a new solution in the TFBG SPR-based D-glucose sensing way by offering a very efficient and sensitive detection tool in the biorecognition field.

2. Material and methods

2.1. Chemicals

D-glucose ($C_6H_{12}O_6$, anhydrous) was purchased from Merck. Phosphate Buffered Saline (PBS) from Thermo Scientific was used to prepare the different D-glucose tested solutions. Tris HCl 99% (2-Amino-2-(hydroxymethyl)-1,3-propanediol hydrochloride or $NH_2C(CH_2OH)_3 \cdot HCl$) and Tris base (2-Amino-2-(hydroxymethyl)-1,3-propanediol or $NH_2C(CH_2OH)_3$), jointly used with milliQ water to prepare Tris buffer (pH 8.5) necessary to the dopamine polymerization, were purchased respectively from Alfa Aesar and Merck. Dopamine hydrochloride 99% ($C_8H_{11}NO_2 \cdot HCl$) from Alfa Aesar assumed the role of intermediate layer to ensure the adequate adhesion between gold coated TFBGs and bioreceptors. The latter refers to Concanavalin A (from Canavalia ensiformis, jack bean) which was provided by EMD Millipore Corp (affiliate of Merck KGaA). In order to prepare the solution required to immobilize Con A on PDA, calcium chloride ($CaCl_2$) and manganese chloride ($MnCl_2 \cdot 4H_2O$)) were purchased from UCB.

2.2. SPR-TFBG elaboration

First, the photosensitivity of a standard silica telecommunication-grade single-mode optical fiber (Corning SMF28) was amplified by hydrogenation. It was stripped over a few centimetres to remove the polymer jacket and allow the photo-inscription of a TFBG. A 1 cm long TFBG was produced inside the core of the uncoated hydrogen-loaded fiber segment (outer diameter 125 μm) after an isopropanol cleaning to remove polymer residues. The inscription process was performed thanks with the phase-mask technique involving an ArF excimer laser emitting at 193 nm. The phase-mask was characterized by a uniform periodicity of 1088 nm and was orthogonally tilted by 8.5° with respect to the UV beam axis. After that, TFBGs were heated to 100 °C in an oven during 24 h to remove remaining hydrogen. This step is required to stabilize the gratings and maintain their long-term integrity. Finally, to
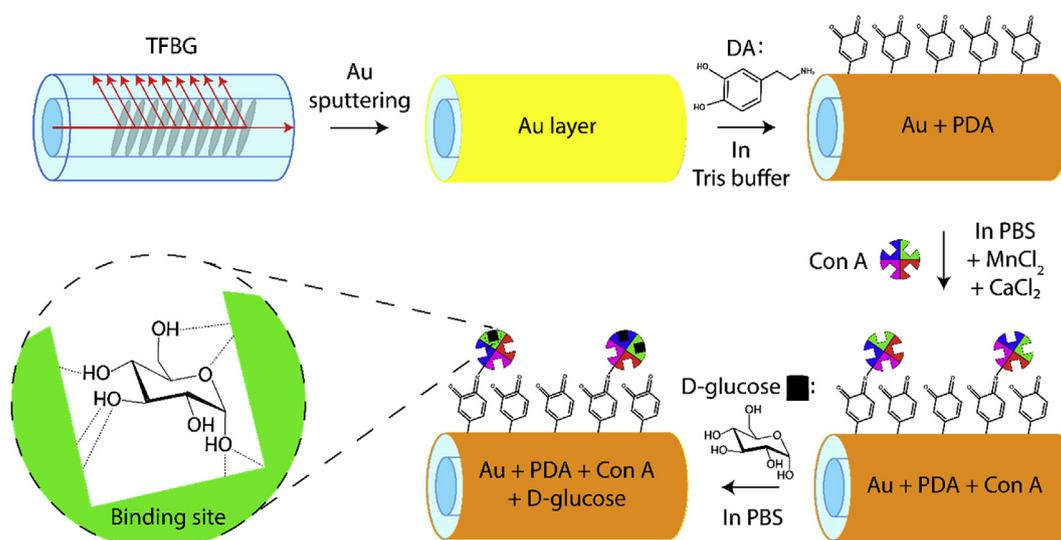
Fig. 1. Elaboration and sensing principles of the D-glucose SPR-TFBG biosensor functionalized using polydopamine-immobilized concanavalin A.

excite SPR and benefit from their enhanced sensitivity, the TFBG area was covered by a thin gold layer of 35 nm. This thickness was retained to achieve the best SPR response and drastically improve the refractive sensitivity of the sensor (Caucheteur et al., 2015a,b; Voisin et al., 2014). The deposition process was achieved using a sputtering machine Leica EM SCD 500. Subsequently, gold-coated TFBGs were annealed during 2 h at ~200 °C to strengthen the gold adhesion on the silica surface (Ghorbanpour and Falamaki, 2013).

2.3. Sensors biofunctionalization

First, the optical sensing area was immersed in a DA precursor solution with the aim to cover the TFBG by a PDA intermediate layer through a polymerization process. This thin layer presents reactive quinone functional groups making possible the forthcoming covalent binding of Con A proteins (Fig. 1).

The solution was prepared from pH 8.5 Tris buffer and the monomers were introduced to reach a DA concentration of 2 mg/mL. Once prepared, the precursor solution was shaken at 300 rpm and room temperature (25 °C) during 15 min using a magnetic stirrer to promote oxidative reaction as well as prevent polymer precipitation. This action sharply increases thereby the polymerization kinetics (Zhou et al., 2014). Afterwards, the coated TFBG was carefully cleaned in milliQ water several times to remove the excess of polymer that is weakly and not covalently linked to the sensor. Finally, the TFBG was immersed in a 1 mg/mL Con A solution during an incubation time of 30 min to link the lectin protein to PDA. The PDA coating is important to achieve D-glucose sensing because adsorption of Con A on bare substrates provokes a protein denaturation. Keeping the integrity of this lectin protein is essential for glucose specific recognition. The Con A solution is composed of PBS with addition of 5 mM $CaCl_2$ and 5 mM $MnCl_2 \cdot 4H_2O$, necessary to the protein binding activity towards D-glucose (Becker et al., 1975). Indeed, the Ca^{2+} and Mn^{2+} cations stabilize the conformation of the Con A structure by compelling the adequate orientation of the amino acid residues involved in the ConA D-glucose hydrogen bonds formation (Hardman and Ainsworth, 1972). Both cations are bound to amino acids and can inherently participate to glucose bindings.

2.4. Experimental setup and measurements

A schematic view of the experimental setup is presented in Fig. 2. The SPR TFBG biosensor was connected to an optical fiber interrogator (NI PXIe-1071 from National Instrument) to record the spectral responses. The measurements were carried out in transmission to minimize the signal-to-noise ratio. The optical path is also composed of an isolator and a polarizer. The former prevented the interference in the transmission measurements, because the interrogator operates in reflection mode by default.

A polarizer is required to observe the plasmonic signature, characterized by a "pinch" in the insertion loss versus wavelength transmitted light spectrum, as shown in Fig. 2. Actually, several conditions must be respected to excite the SPR (Christophe Caucheteur et al., 2015a; Guo et al., 2016). Amongst the sensitive modes of the spectrum, the measurements were achieved by tracking the wavelength shift of the most sensitive propagation mode during the experiments, reflecting the change of the immediate environment close to the sensor. This mode is situated between the most attenuated mode and the mode of higher intensity to the left of the plasmon resonance (so-called mode 0 or cut-off in previous works) (C. Caucheteur et al., 2015b).

The biosensor detection was assessed in D-glucose solutions of 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 5.10^{-3} and 10^{-2} M with the use of PBS as reference measurement. Moreover, this sensing technique has also allowed a follow of PDA polymerization on the gold layer around the fiber as well as the binding of Con A. Therefore, since these different deposition processes change the refractive index close to the fiber surface, it is possible to monitor the thickness growth of the PDA layer before the binding of Con A.

3. Results and discussion

3.1. Polymerization of the PDA coating and immobilization of Con A protein

After the gold deposition process, the optical fiber was immersed into Tris buffer containing DA monomers solution for the PDA film deposition on the surface of the TFBG area. The polymerization progress was followed in real time by tracking the SPR shift in the transmitted light spectra (Fig. 3A).

The Fig. 3A shows the plasmonic signature displacement as a function of time with a shift which can be directly linked to the increasing polymer thickness on the gold coated TFBGs. This shift was recorded for four singular experiments. The wavelength shift, plotted as a function of time (Fig. 3B), exhibits a very narrow dispersion with a red shift of 3.83 ± 0.05 nm after 20 min. The first five minutes correspond to the beginning of the polymer coating formation and are characterized by an unreliable slight shift in the light spectrum. At this time, the amount of generated PDA is not high enough to be clearly
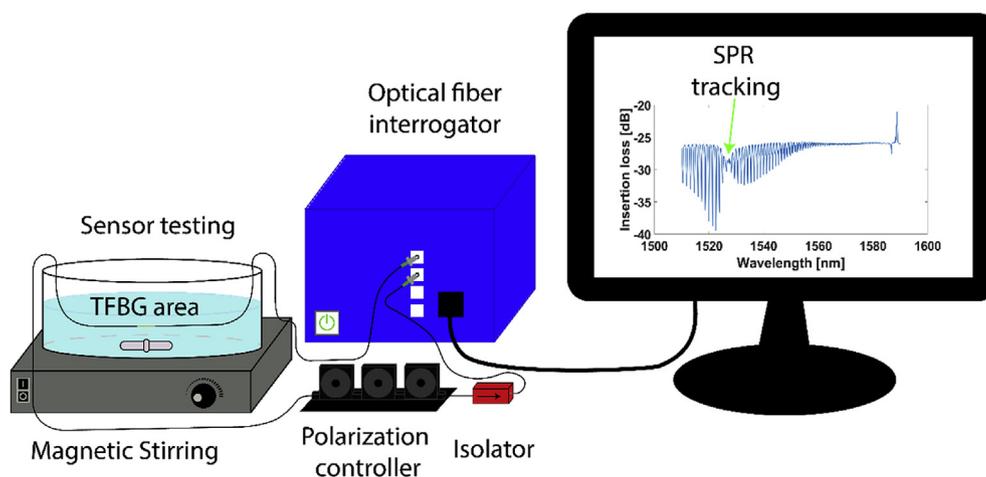
Fig. 2. Sketch of the experimental setup used for the dopamine polymerization.

detected by the sensor. The refractive index of the PDA is higher than the used Tris buffer ($RI_{Tris\ Buffer} = 1.33$) and hence the RI of the surrounding medium at sensor surface increases as the polymerization reaction is still ongoing. A wavelength shift of the plasmonic pinch towards higher values is then noticed in the light spectrum as an immediate consequence of the phenomena occurring at the sensor surface. Indeed, the plasmonic wave excited at the metal-dielectric interface by the light coming from the cladding has a penetration depth situated between $\lambda/3$ and $\lambda/2$ (González-Vila et al., 2017) and the gold layer thickness is around 35 nm. Consequently, the TFBGs remain sensitive to the surrounding medium changes on a sufficient distance beyond the gold layer making the following of the polymerization process possible. The polymer formation along the sensor causes light scatterings that modify the RI of the surrounding medium as its thickness growths. This phenomenon results in a red shift of the SPR mode since the plasmonic pinch happens when the effective RI of this mode corresponds to increasing RI of the surrounding medium. Thus, the monitoring of the light spectrum can allow the real-time thickness control of the PDA layer deposited on the sensing area. Hence, experiments demonstrated an accurate and rapid covering of the curved shape optical fibers by the intermediate polymer layer, an important step to allow Con A bioreceptor attachment. The pictures obtained by using an optical microscope in reflection clearly show the presence of PDA after 20 min of polymerization (Fig. 4A and B). For a fiber covered by gold, the metal strongly reflects microscope light and appears highly bright. In contrast, the PDA coated sample appears darker because of the partial light absorption due to the polymer overlap on gold. Otherwise, the polymer layer is thin enough to be transparent to light and allow reflection on gold, making the PDA coating presence easy to appreciate.

The next step was the immobilization of Con A protein on the reactive polymer surface previously established. However, the

biofunctionalization medium nature made the monitoring of Con A attachment really inconvenient. Actually, adsorption of calcium and manganese ions, which are required to obtain the adequate protein conformation, leaded to unreliable measurements impaired by a low signal-to-noise ratio.

3.2. Detection of D-Glucose

D-glucose sensing experiments were performed by immersing the SPR-TFBG sensor in different solutions accounting for a wide range of concentrations. A set of D-Glucose solutions was thus prepared and each of them was successively tested. Spectral response measurements were conducted and analysed by tracking the most sensitive mode shift for each concentration (Fig. 5A). Fig. 5A also focuses on the area of interest, i.e. RI sensitive region of the spectrum, and makes discernible the red-shift of the most sensitive mode which is especially substantial when concentration increases from 10^{-6} to 10^{-4} M. The wavelength shift is 108 pm from the reference in PBS to the 10^{-2} M concentration in D-glucose (Fig. 5B).

For a given concentration, measurements were carried out in a small container with 750 µL of solution. The sensor was immersed in each solution for 20 min to reach the bio-chemical equilibrium between the D-glucose solution and Con A immobilized at sensor surface. The record and the computation of the biosensor response lead to a sigmoid behaviour of the wavelength shift of the most sensitive propagation mode drawn as a function of the D-glucose concentration logarithm (Fig. 5B). This is a typical curve that characterises the bioreceptor-analyte bond when analyte concentration growth (Aliakbarinodehi et al., 2017). The sensitivity of the sensor is much higher for the concentrations ranging from 10^{-6} to 10^{-4} M than the rest of the tested concentrations. This analytical range is well suitable for numerous medical detection
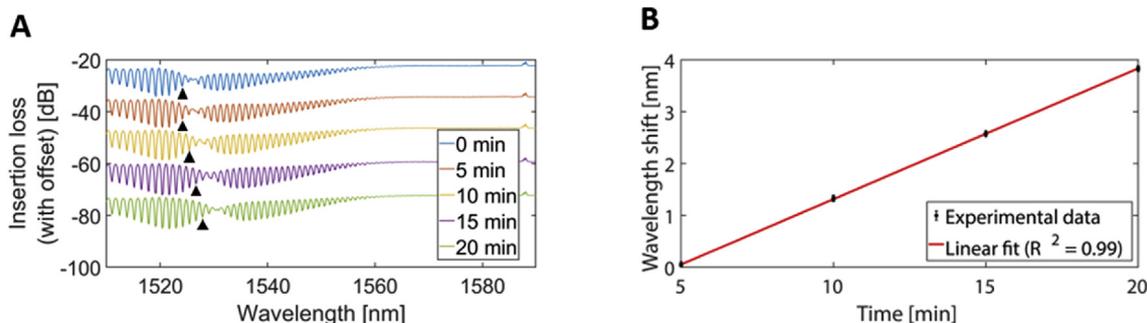

Fig. 3. Evolution of the transmitted light spectrum recorded against time during the polymerization process of the gold-coated SPR-TFBG sensor. (A) Mean redshift of the plasmon signature as a function of time during the polymer layer formation. (B)
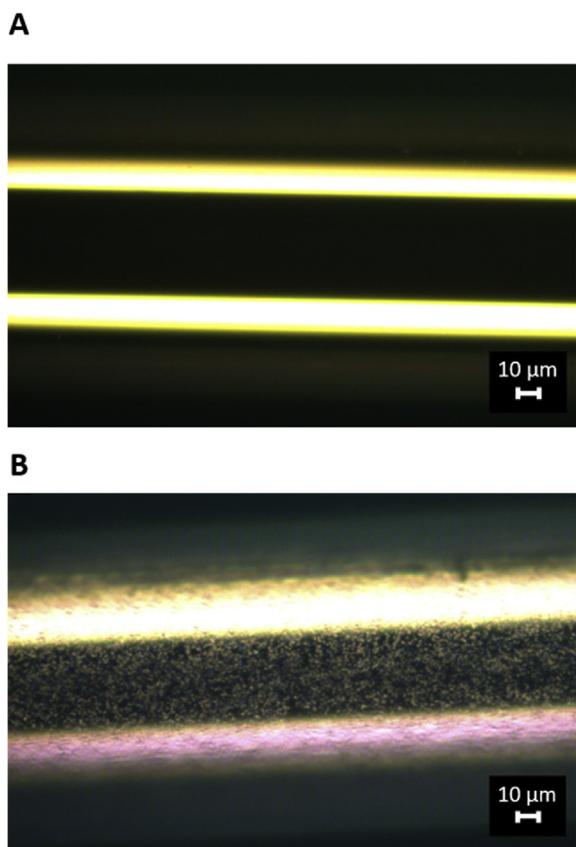
Fig. 4. Optical microscopy in refection of an optical fiber coated only with gold (A) and covered by gold and polydopamine. (B)

purposes (Ganesana et al., 2019; Moore et al., 2005). Refractive index measurements indicated a sensitivity of 688 nm/RIU, which is expected from a SPR-TFBG biosensor (Voisin et al., 2014). Unreliable variations in the signal of the biosensor response for measurements conducted in PBS helped to define a detection threshold of 0.02 nm in wavelength shift to prevent false positive detection which lead to a limit of detection close to 10^{-7} M. Chemical reaction between D-glucose and Con A protein is a dynamic process characterized by a sensorgram including two different parts (Fig. 5C). The first part of the curve immediately shows a wavelength shift when the biosensor is brought into contact with a D-glucose solution. During this period, Con A binding sites are progressively inhibited by D-glucose molecules and, as a result, the biosensor transmitted signal shifts. The second part of the curve depicts the close proximity to the bio-chemical equilibrium reaching for which the biosensor response remains relatively steady. This latter part of the sensorgram is then used in concentration detection. As shown in the bar chart of Fig. 5D, the functionalization of the fiber surface by means of PDA and Con A increases significantly the affinity of the sensor to D-glucose, resulting in an enhanced sensitivity to the carbohydrate molecule. Indeed, experiments in D-glucose solutions with a SPR-TFBG sensor only covered with gold or gold with PDA lead to non-significant variations for the different tested concentrations. Non-specific adsorption of D-glucose on PDA is then very limited. In contrast, the same experiments with a biosensor using PDA-immobilized Con A clearly depict an appreciable shift between each concentration, reflecting the improved affinity and sensitivity of the sensor to D-glucose. Displayed standard wavelength deviations concerned measurements performed over the detection time.

4. Conclusion

In this paper, we investigated a new approach for saccharide biosensing in the field of SPR and TFBG technologies-based sensor. The study was focused on the development of a D-glucose biosensor with the aim to provide a prove of an original concept as an alternative solution to the majority of saccharide biosensors which are enzymatic-
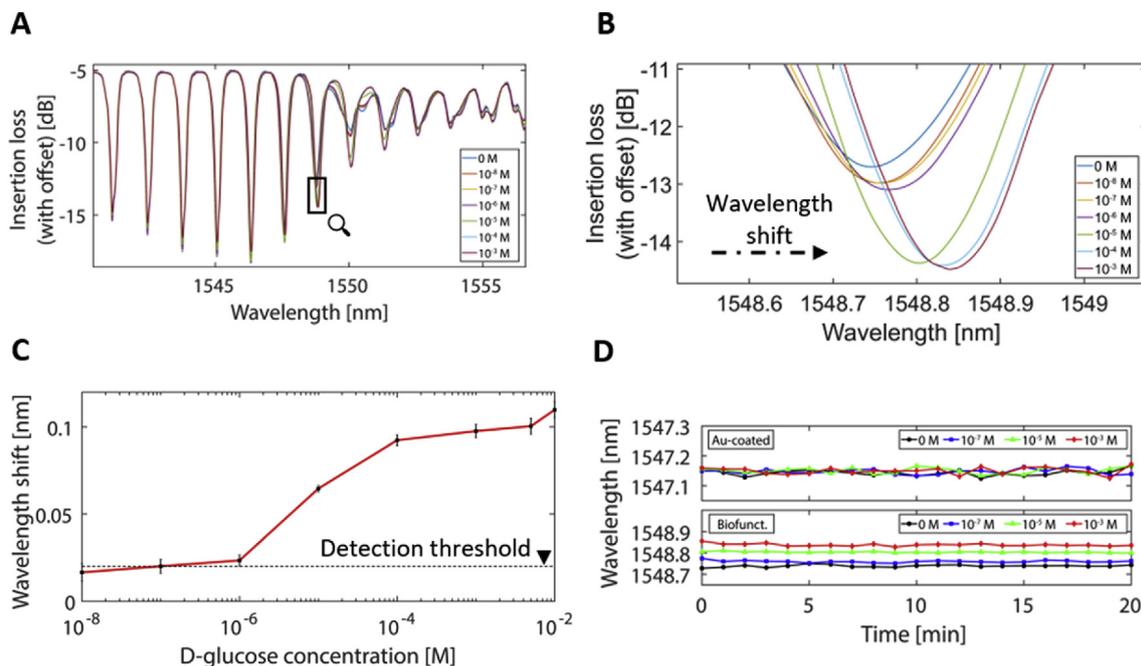

Fig. 5. Transmitted light spectrum of the biosensor recorded during experiments in different D-glucose solutions with a magnification on the redshift of the most sensitive propagation mode. (A) Wavelength shift of the most sensitive mode as function of the logarithm of the D-glucose concentration. (B) Sensorgram showing wavelength shift as a function of detection time for different D-glucose concentration around the detection threshold. (C) Contrast between D-glucose detection experiments achieved with a gold-coated TFBG sensor (yellow bar chart), gold and PDA-coated TFBG sensor (green bar chart) and the SPR-TFBG functionalized biosensor (red bar chart). (D). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

based. A biofunctionalization involving a polydopamine-immobilized concanavalin A layer made possible the production of non-enzymatic SPR-TFBG biosensors. The use of an optical fiber-assisted sensor allowed an accurate monitoring of the polydopamine coating deposition and showed a linear evolution with an SPR shift of 3.83 ± 0.05 nm within 20 min. The D-glucose biosensor was tested in a set of PBS solutions with a D-glucose concentration ranging from 10^{-8} to 10^{-2} M in order to analyse the transmission spectral response of the sensing device. Results showed a high sensitivity in the concentration range of 10^{-6} to 10^{-4} M concentration with a limit of detection around 10^{-8} M. It was experimentally confirmed that the addition of a PDA interlayer prior to Con A bioreceptors attachment significantly increases the surface affinity to D-glucose. The obtained experimental sensitivity highlights the potential of using saccharide SPR-TFBG biosensors for medical diagnosis at early stage. This new approach tested in PBS solutions shows therefore relevant aspects for biomedical prospects.

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Competing interests

The authors declare no conflicts of interests.

Acknowledgements

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