

Review article

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Biosensing with optical fiber gratings

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Abstract: Optical fiber gratings (OFGs), especially long-period gratings (LPGs) and etched or tilted fiber Bragg gratings (FBGs), are playing an increasing role in the chemical and biochemical sensing based on the measurement of a surface refractive index (RI) change through a label-free configuration. In these devices, the electric field evanescent wave at the fiber/surrounding medium interface changes its optical properties (i.e. intensity and wavelength) as a result of the RI variation due to the interaction between a biological recognition layer deposited over the fiber and the analyte under investigation. The use of OFG-based technology platforms takes the advantages of optical fiber peculiarities, which are hardly offered by the other sensing systems, such as compactness, lightness, high compatibility with optoelectronic devices (both sources and detectors), and multiplexing and remote measurement capability as the signal is spectrally modulated. During the last decade, the growing request in practical applications pushed the technology behind the OFG-based sensors over its limits by means of the deposition of thin film overlays, nanocoatings, and nanostructures, in general. Here, we review efforts toward utilizing these nanomaterials as coatings for high-performance and low-detection limit devices. Moreover, we review the recent development in OFG-based biosensing and identify some of the key challenges for practical applications. While high-performance metrics are starting to be achieved experimentally, there are still open questions pertaining to an effective and reliable detection of small molecules, possibly up to single molecule, sensing *in vivo* and multi-target detection using OFG-based technology platforms.

1 Introduction

Optical fiber gratings (OFGs) are being increasingly proposed as optical platforms for label-free biosensing as promising alternatives to the most traditional ones based on surface plasmon resonance (SPR) or on interferometric configurations. OFGs have been demonstrated to offer comparable performance with respect to more classical optical platforms, but with the intrinsic advantages of the optical fibers, such as high compactness and potential miniaturization, as well as high compatibility with optoelectronic devices (both sources and detectors) and, last but not least, multiplexing and remote measurement capability as the signal is spectrally modulated.

Nanotechnology can offer a further impulse to OFG diffusion by means of the implementation of nanostructures or nanostructured coatings directly grown or deposited onto their surface. As a matter of fact, this action can lead to a great improvement of the field interaction at a molecular scale between the device and the surrounding environment [1] and also to the excitation of SPR, localized SPR (LSPR) [2], and lossy mode resonance (LMR) phenomena [3]. In fact, nanostructured coatings or patterns can induce strong changes in the properties of the light traveling through the fiber and, then, can represent a cost-effective, innovative, and valid option able to develop label-free biosensors and, thus, to quantify and monitor the biomolecular interactions in real time. The most challenging and critical issue concerns both the manufacturing and the deposition/growth of these nanostructures, with many time-consuming and difficult manufacturing steps, sometimes hard to be optimized and not always capable to lead to reproducible results, which involve high-technological level and expensive machines.

Figure 1 shows a schematic illustration of the biosensing capability of an OFG. Thanks to its particular configuration, as explained in the following section, the transmission properties of the light in an OFG are modulated by changes in the refractive index (RI) of the solution in the region surrounding the fiber, due to the presence of

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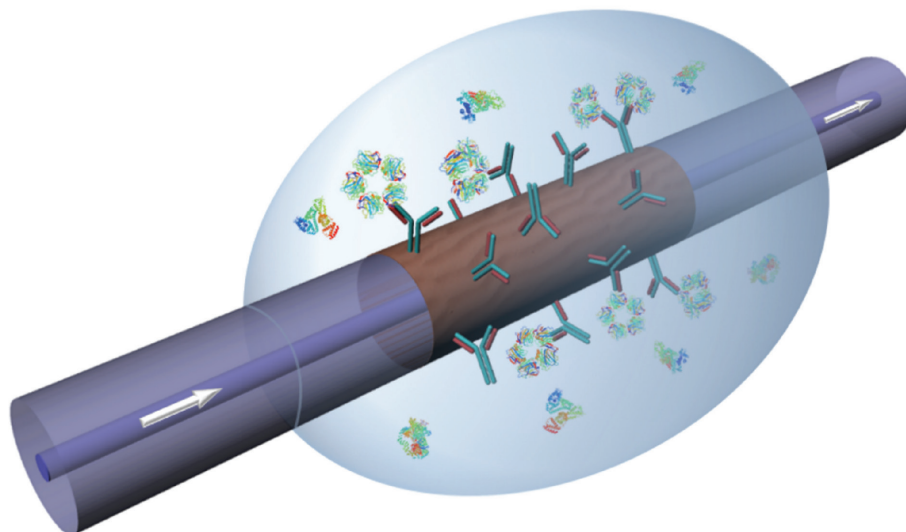


Figure 1: Schematic illustration of the surface sensing of biomolecules by an optical fiber-based device coated with a nanometric scale overlay.

The biological recognition element (here drawn as an antibody) is covalently bound onto the functionalized surface of the overlay (wrinkled brown) leading to the formation of a sensing biolayer, and the specific target (ring-shaped pentameric antigen) will specifically interact with the recognition element, generating a change in the optical signal traveling in the fiber (white arrows). Any other non-specific biomolecules present in the complex matrix (e.g. serum albumin) will not bind to the receptor on the sensing layer, thus, not generating any change in the optical signal traveling in the fiber.

an evanescent wave outside the fiber, penetrating within the external medium for distances of the order of hundreds of nanometers. The implementation of a sensing biolayer on the fiber surface containing a biological recognition element (BRE), selective to a well-defined target, gives the opportunity to detect surface RI changes associated to the biochemical interaction between the target and the biolayer.

The present review article, after a description of the different types of fiber grating for biosensing, of their basic principles and on how nanotechnology meets OFG-based sensing platforms, goes through the great many of the OFG-based biosensors in terms of utilized BRE and investigated target with particular attention to the nanomaterial/nanolayer, if used.

2 Fundamentals

An OFG is a diffraction structure that entails a periodic modulation of the RI in the core of a single-mode fiber. This structure satisfies the phase-matching condition between the co-propagating fundamental core mode and other modes, which can be counterpropagating core mode, cladding modes, or radiation (or leaky) modes [4], with a consequent controlled and efficient power transfer between modes in the optical fiber. Depending on the

grating pitch Λ (i.e. RI modulation period), OFGs can be classified in short-period gratings or simply called fiber Bragg gratings (FBGs) and in long-period gratings (LPGs).

In the case of an FBG, the grating pitch is typically of the order of hundreds of nm. This structure allows satisfying the phase matching between the fundamental core mode and the respective counterpropagating core mode; when an optical signal reaches the grating region, a part of the power is reflected, and the remaining is transmitted. Therefore, the grating acts as a wavelength-selective mirror or rejection filter according to the well-known Bragg condition [4]:

$$\lambda_{\text{res}}^{\text{FBG}} = 2n_{\text{eff}}^{\text{core}} \Lambda \quad (1)$$

where $\lambda_{\text{res}}^{\text{FBG}}$ is the resonance wavelength at which the coupling occurs, and $n_{\text{eff}}^{\text{core}}$ is the effective RI of the core mode. Standard FBGs are intrinsically sensitive to physical parameters, such as temperature, strain, and pressure; thus, they are widely used for measuring those parameters [4]. Conversely, standard FBGs are not sensitive to the changes in the surrounding RI (SRI) because the light is confined within the fiber core, unless suitable solutions or configurations are adopted to allow the evanescent field of the core mode to interact with the external medium.

One solution is attained by partially or totally removing the fiber cladding through etching [5], polishing [6], or by writing FBGs directly in microfibers [7, 8], i.e. fibers

with a diameter of a few micrometers. In all these cases, the evanescent wave extends outside the fiber, and consequently, the resonance wavelength of the reflected signal depends on the SRI that affects the $n_{\text{eff}}^{\text{core}}$ value [see equation (1)]. Figure 2A illustrates the principle of operation of an etched FBG (EFBG). The RI sensitivity of these devices is highly dependent on the diameter of the fiber in the region containing the grating. The lower the fiber diameter, the higher the sensitivity, although this process introduces higher fragility and higher difficulties in fiber handling.

Another approach relies on the intrinsic SRI sensitivity of the cladding modes excited by a tilted FBG (TFBG) [9]. In a TFBG, the periodic modulation pattern is uniformly blazed (or tilted) by an angle θ with respect to the fiber axis. This structure allows the coupling to circularly and non-circularly symmetric co-propagating or counter propagating cladding modes, with the direction of the coupled light depending on the tilted angle of the TFBG [10]. In this case, the transmitted spectrum shows a series of narrow attenuation bands corresponding to the coupling with different cladding modes always located on the left side (shorter wavelengths) of the main attenuation band corresponding to the coupling with the fundamental core mode, as occurring in a standard FBG. Figure 2B illustrates the principle of operation of a TFBG. For TFBGs, the Bragg condition given in equation (1) is slightly modified in order to take into account the resonance wavelength of each m -th cladding mode $\lambda_{\text{res}(m)}^{\text{TFBG}}$ [10]:

$$\lambda_{\text{res}(m)}^{\text{TFBG}} = (n_{\text{eff}}^{\text{core}} - n_{\text{eff}}^{\text{clad}(m)}) \frac{\Lambda}{\cos \theta} \quad (2),$$

where $n_{\text{eff}}^{\text{clad}(m)}$ is the effective RI of the m -th cladding mode. The cladding modes are guided by the cladding; thus, the light reaches the cladding-surrounding interface, and as a result, their effective RIs depend on the SRI. With the increment of the SRI, the resonance wavelengths of these cladding modes shift to longer wavelengths with the intensity that progressively drops to fit a smooth loss curve. Typical tilt angles range between 4° and 16° [10]. More recently, super tilted FBGs, where the tilt angle is greater than 80° , have also been proposed as RI sensors [11].

In an LPG, the periodic modulation ranges usually between $100 \mu\text{m}$ and $700 \mu\text{m}$, satisfying the phase matching between the fundamental core mode and co-propagating cladding modes. As a result, several attenuation bands centered at discrete wavelengths appear in the transmitted spectrum, with each attenuation band corresponding to the coupling to a specific cladding mode. The resonance wavelength $\lambda_{\text{res}(m)}^{\text{LPG}}$ will satisfy the following phase-matching condition [12]:

$$\lambda_{\text{res}(m)}^{\text{LPG}} = (n_{\text{eff}}^{\text{core}} - n_{\text{eff}}^{\text{clad}(m)}) \Lambda \quad (3)$$

The spectral width of the attenuation bands varies from few nanometers up to tens of nanometers depending on the physical length of the grating, and this value increases with the order of the cladding mode [13]. Compared to FBGs, the spectral width of the LPG attenuation bands is almost two orders of magnitude greater. Because of the dependence of the phase-matching condition with the effective RI of fiber cladding, as clearly stated in equation (3), LPGs are intrinsically sensitive to the SRI exhibiting changes in the position of the $\lambda_{\text{res}(m)}^{\text{LPG}}$. With the increment of the SRI, the resonance wavelengths shift to shorter wavelengths. Figure 2C illustrates the principle of operation of an LPG.

According to Figure 2, the typical grating lengths of LPGs and FBGs (TFBGs and EFBGs) are $10\text{--}40 \text{ mm}$ [4] and $10\text{--}20 \text{ mm}$ [10], respectively, depending on the used manufacturing technique. TFBGs and LPGs are usually inscribed in single-mode optical fibers with a diameter of $125 \mu\text{m}$, whereas in EFBGs, the fiber diameter is reduced below a few μm up to the complete removal of the fiber cladding.

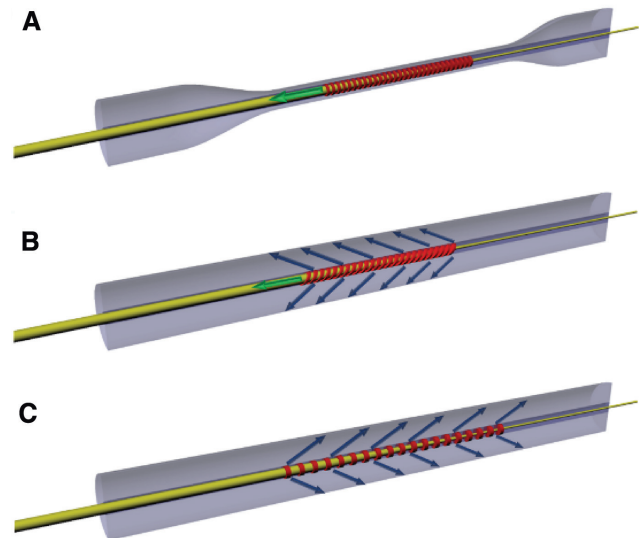


Figure 2: Schematic illustrations of the three different OFGs used for RI sensing along with their respective coupling mechanism sketched with arrows (green: counterpropagating core mode; blue: counter-/co-propagating cladding modes): etched FBG (A), tilted FBG (B), and LPG (C).

Given the coupling between the fundamental core mode and cladding modes, the light intensity (yellow cylinder) decreases after the interaction with the grating. In the case of both EFBG and TFBG, an RI change will induce a shift of the resonant attenuation bands toward longer wavelengths; conversely, in an LPG, an RI change will induce a shift of the resonant attenuation bands toward shorter wavelengths.

The sensing principle of OFGs for the measurement of RI changes relies on the evanescent field interactions at the boundary between the fiber and the surrounding medium. The evanescent field propagates in the direction of the fiber axis with an exponential decay perpendicular to the interface fiber/surrounding medium. In an OFG, this interaction occurs either for the cladding modes coupled by the grating at the interface cladding/surrounding medium (TFBGs in Figure 2B or LPGs in Figure 2C) or for the core mode under etching conditions at the interface fiber/surrounding medium (EFBGs in Figure 2A). Therefore, the RI sensitivity of OFG-based platforms is highly dependent on the penetration depth of the related evanescent field, which is the distance from the interface at which the amplitude of the electric field decreases at a factor of $1/e$ in its exponential decay. Clearly, the larger the penetration depth, the greater the portion of radiation interacting with the surrounding medium, leading to a higher sensitivity. In addition, high-order modes are less bound to the guiding structure, extending further into the external medium (deeper penetration), and hence, they are more sensitive to the SRI making them more suitable for sensing purposes. It should be observed that this sensitivity is related to volume changes of the RI, and much more attention should be paid when surface changes of the RI take place. This happens, for example, in OFG-based biosensors, where the RI modulation comes from the interaction between the analyte under investigation and a BRE immobilized directly on the fiber or on the fiber coating layer, as discussed in detail in a previous review [14].

As the thickness of a biolayer (tens of nm) is generally lower than the penetration depth of the evanescent field (typically 200–400 nm) [15], the interaction involves only the biolayer and a portion of the evanescent field of the selected mode, causing a wavelength shift that is expected to be smaller than that related to a bulk RI change.

It is known from literature [14] that the maximum sensitivity of “untreated” OFGs, i.e. the bare fiber without any external coating (around 2000 nm RIU⁻¹), is achieved when the SRI is close to the fiber cladding RI (~1.45 RIU), whereas for lower values of SRI (~1.33–1.34 RIU), which is the typical range considering aqueous solutions, these sensors are barely sensitive (20–60 nm RIU⁻¹, depending on the coupled mode) [16]. Therefore, suitable strategies must be adopted to improve this sensitivity and make OFGs a valid tool for high-performance biosensing. In the first one, the sensing region of the device is coated with a nm-thick layer with a RI higher than that of the fiber cladding. For some specific conditions, related to the values of RI and thickness of the layer as well as of the SRI, the light coupled by the grating can be guided in the coating,

thus, leading to huge changes in the propagation conditions of the optical signal [17]. In fact, the high refractive index (HRI) coating pulls the light toward the surrounding medium extending its evanescent field, resulting in an improved sensitivity of the device to the SRI. Therefore, by carefully adjusting the overlay thickness, it is possible to tune the maximum sensitivity into the desirable range of RI [18] for both LPGs [18, 19] and TFBGs [20]. The second strategy, which concerns LPGs only, consists of coupling the core mode to a high-order cladding mode (11th–14th) near its turn-around point (TAP) in its phase-matching curve [21]. These gratings can be achieved with Λ in the range of 130–200 μm and exhibit a dual-peak attenuation band in the telecommunication wavelength range (1.2–1.7 μm) that merges into a broader one at the TAP. These TAP LPGs show the highest RI sensitivity among the LPGs manufactured on a bare fiber [22]. Another completely different approach to enhance the intensity of the evanescent field is to excite surface plasmon polaritons and, thus, to use the well-known surface plasmon resonance (SPR), which takes place at the interface between a negative and positive permittivity material stimulated by the incident light. SPR occurs when the real part of the metallic film permittivity is negative and higher in magnitude than both its own imaginary part and the permittivity of the material surrounding the film [23]. This condition can be satisfied using a metallic thin layer (40–60 nm). Recently, OFGs have been used as a valid option to excite SPR due to its core-cladding efficient coupling mechanism and physical robustness, especially in the case of TFBGs [24] and LPG [25].

Finally, fiber gratings written either in a microstructured optical fiber (MOF) or in a photonic crystal fiber (PCF) have also been used for biosensing applications [26–28]. MOF is a special fiber in which an array of periodic or non-periodic micro holes is present in the fiber cladding surrounding the core. These fibers exhibit unique light-guiding properties and drew the attention in the biochemical sensing due to the capability of using the cladding as a microfluidic channel [29], which can consist of a few big holes (50–60 μm diameter) or of many small holes (3–10 μm diameter) depending on the fiber type. In this case, the evanescent field directly interacts with the liquid passing through the holes, thus, enabling potentially high sensitivity in a small volume of solution while preserving the fiber integrity and geometry. On the other hand, PCF is another class of optical fibers based on the properties of photonic crystals and takes the advantage of its ability to confine light in hollow cores. There are different classes of PCF, including photonic-bandgap fiber (light is confined by band gap effects), holey fiber (air holes in

PCF cross-section), hole-assisted fiber (light is guided by a conventional higher-index core modified by the presence of air holes) and Bragg fiber (photonic-bandgap fiber formed by concentric rings of multilayer film). PCFs may essentially be considered a subclass of the MOFs, where light is guided by structural modifications and not only by RI differences.

3 How can nanotechnology meet OFG-based sensing platforms?

While in the following section the biosensing applications of OFGs are described with particular attention to which type of BRE is used, in this section, some of the most interesting examples applied to OFGs are shown with a special focus on both the used nanotechnology and nanocoatings.

As already mentioned in the Introduction, nanotechnology and nanomaterials can be used to modify the optical properties of optical fibers, leading to changes in the propagation of the optical light. Arghir et al. [1] provided a comprehensive review on different nanoparticles and, in general, nanomaterials suitable to be deposited on optical fiber-based devices. Different nanofabrication techniques have been proposed in literature during the time, ranging from the classical techniques (spin and dip coating, physical and chemical vapor deposition, and electrospinning) up to the more novel techniques (chemical self-assembly monolayer, layer-by-layer electrostatic self-assembly, electrochemical deposition, Langmuir-Blodgett, and nanolithography). All of those, when applied to optical fiber sensors, are described in detail by Zamarreño et al. [2] and Arregui et al. [3]. In the case of OFGs, the use of nanotechnology and nanomaterials can really lead to improved performance of the sensors.

As for biosensing applications, different types of nanocoatings are deposited on the fiber as improved substrates for the implementation of the selective biolayer, such as titania-silica sol-gel-derived nm-thick films [19], thin film of atactic polystyrenes (PS) [30], graphene oxide (GO) films [31], composites of GO film and single-walled carbon nanotubes (SWNTs) [32], or gold nanoparticles [33] with the purpose of improving the performance of the sensor by leading to greater sensitivities and lower detection limits. Figure 3A details the flow chart of the manufacturing steps for coating a μm -thick EFBG with GO and SWNTs, whereas Figure 3B accounts for a SEM image of the proposed sensor. Another interesting biosensing application encompasses the immobilization of a low-weight sequence of DNA, an aptamer, on the fiber surface

to detect a high-specificity target, thrombin, on an EFBG with the aid of a titania layer or of a multilayer of gold and titania [34] or on an TFBG with just a layer of gold [35]. For the biosensing application that involves the detection of cells, TFBGs are used as a sensing device, whereas a 50-nm-thick gold coating deposited on the fiber surface allows exciting SPR phenomenon, thus, leading to an enhancement of the sensitivity for the target analyte [36].

Concerning the applications of nanostructures and nanocoatings deposited on an OFG-sensing device and used to improve the detection of not-strictly biological analytes, it is worth mentioning the layer-by-layer (LbL) deposition of self-assembled polyelectrolyte multilayers deposited on an EFBG [cationic poly-allylamine hydrochloride (PAH)/anionic poly-acrylic acid (PAA)] [37] or on an LPG (PAH/poly-sodium-p-styrenesulfonate [PSS]) [38] for the monitoring of sucrose concentrations.

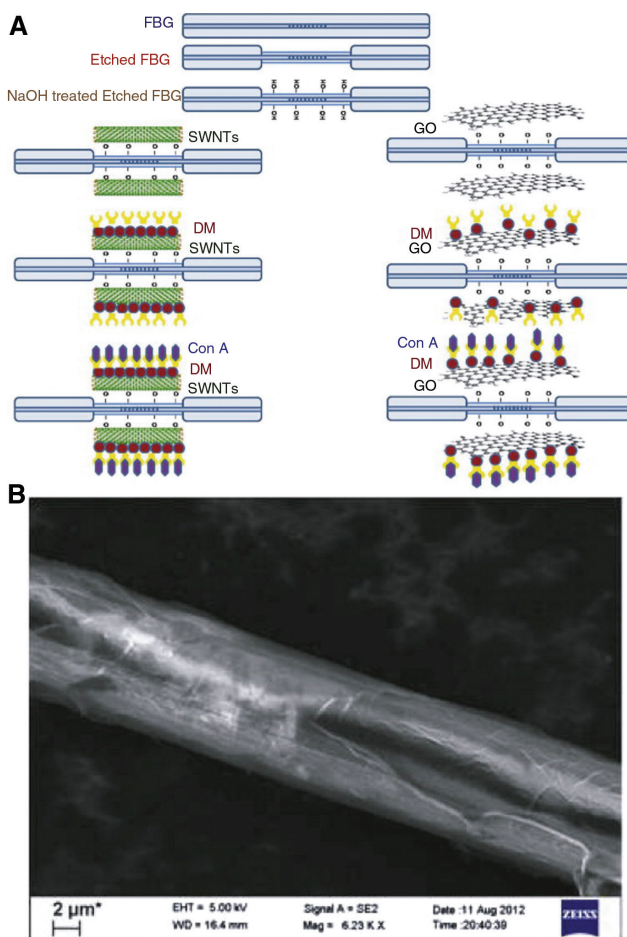


Figure 3: Flow chart of the manufacturing steps for coating an EFBG with GO and SWNTs (A) and a SEM image of the fiber coated with GO (B).

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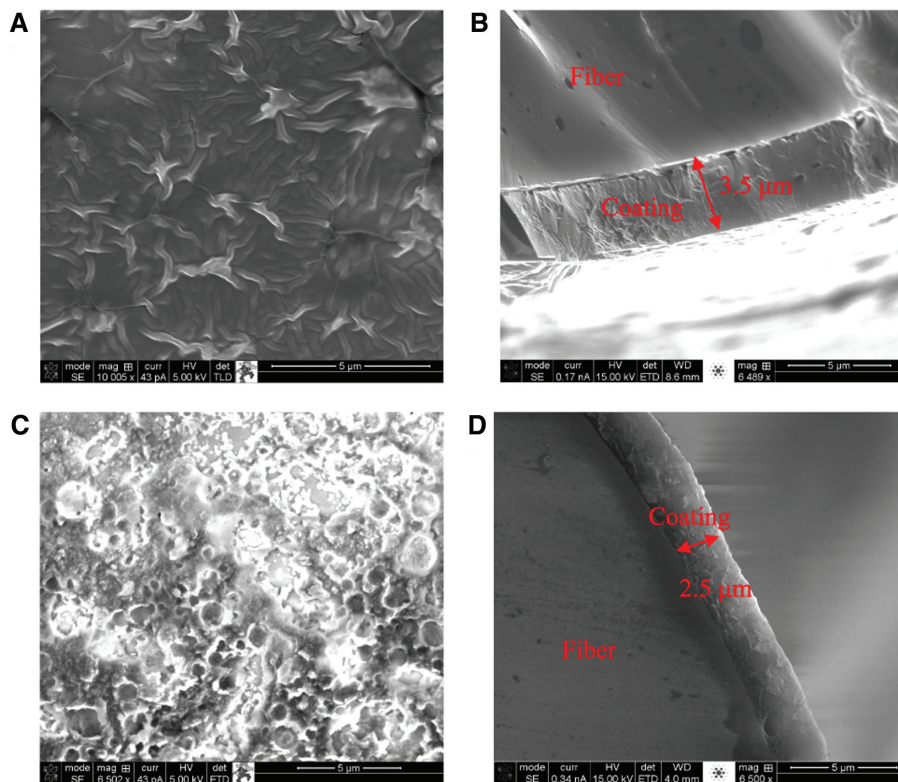


Figure 4: Surface (A) and cross-section (B) SEM images of the deposited coating on the fiber with iron and silica nanoparticles dispersed into polyurethane, and surface (C) and cross-section (D) SEM images of the same sample after the heating process of the coating. Figures adapted with permission from Ref. [39]. Copyright (2013) IOP Publishing.

A thin film of mixed iron and silica nanoparticles was deposited on an LPG and used for the monitoring of corrosion and of environmental changes [39]. Iron nanoparticles were utilized to provide the monitoring of the corrosion process and its rate, whereas silica nanoparticles were combined to enhance the transparency and robustness of the coating. Figure 4A and B shows a SEM image of the surface and the cross-section, respectively, of the LPG sensor coated with iron/silica nanoparticles dispersed in a solution of polyurethane-acetone. Figure 4C and D details a SEM image of the same sensor after the heating process. It can be noted that, after the sensor heating, the film thickness decreased by roughly 1 μm due to the removal of a part of polyurethane, and the surface became porous allowing a direct interaction of the iron nanoparticles with the surrounding environment.

As another example, even if so far demonstrated only for volume RI measurement, a TFBG was coated with chemically synthesized silver nanowires of roughly 100 nm in averaged diameter and several micrometers (3–10 μm) in length [40]. The proposed layer was demonstrated to improve the sensor RI sensitivity of a factor of 3.5 with respect to the uncoated version. The increase

was found to be connected with the excitation of surface plasmons by means of the orthogonally polarized fiber cladding modes of the TFBG. Figure 5A and B accounts for AFM and SEM images of the fiber surface coated with silver nanowires.

An LPG-based fiber probe sensor coated with a zinc oxide (ZnO) nanorod (~100 nm in height) layer was used to detect ethanol vapor [41]. When the sensor is exposed to ethanol vapor, the optical properties of the LPG, i.e. absorption loss and/or RI, change accordingly. The nanostructured overlay was directly grown onto the fiber cladding using an aqueous chemical growth (ACG) process at 80°C for 3 h, seeded in advance by a thin layer of Zn. Afterward, the sample was removed from the solution, and different growth times (from 27 min up to 100 min) were tested. Figure 6 shows different SEM images: a large view (Figure 6A) and the cross-section (Figure 6B) of the ZnO nanorods overlay and close views of the same overlay achieved with two different chemical growth times, 27 min (Figure 6C) and 58 min (Figure 6D).

As another example, an TAP LPG was coated with a nano-assembled mesoporous overlay of alternate layers of poly(diallyldimethylammonium chloride) (PDDA) and SiO₂

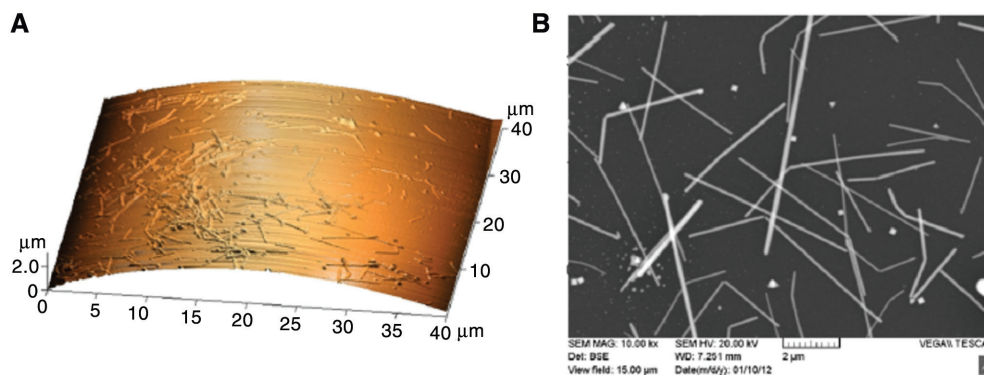


Figure 5: AFM (A) and SEM (B) images of the fiber surface coated with silver nanowires. Figures adapted with permission from Ref. [40]. Copyright (2012) IOP Publishing.

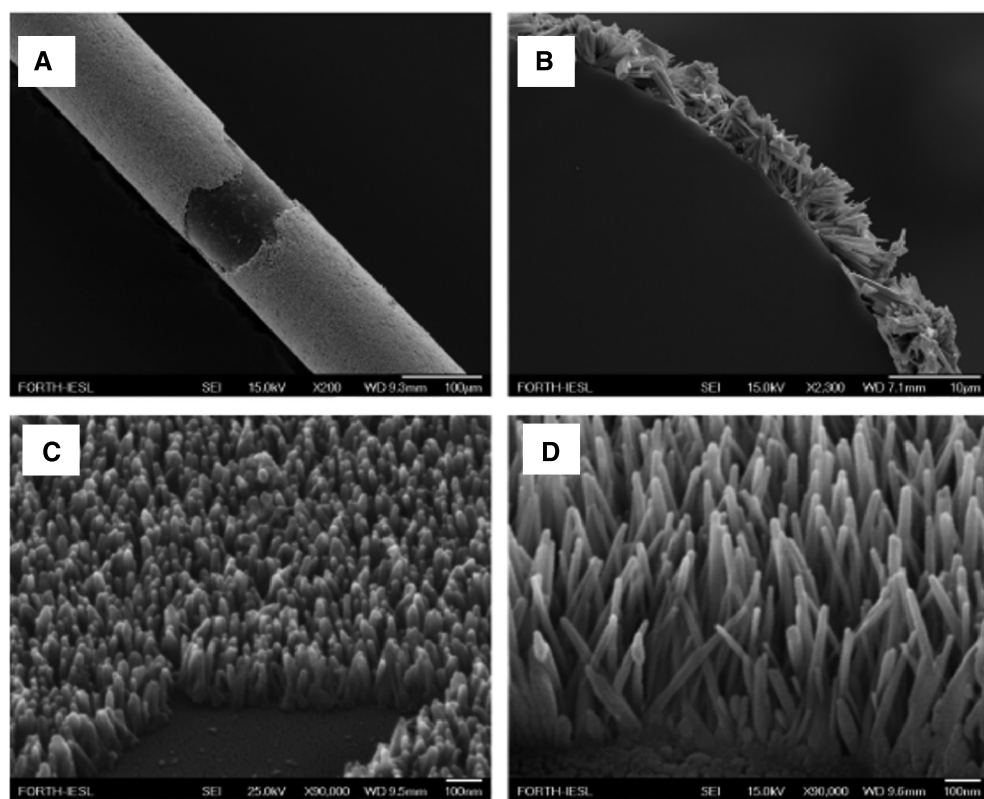


Figure 6: SEM images of ZnO nanorod layer grown onto a silica fiber surface. Large view (A) and cross-section (B) of the coating after 3-h immersion in ACG solution. Close view of the same overlay after 27 min (C) and 58 min (D) of chemical growth. Figures adapted with permission from Ref. [41]. Copyright (2012) OSA.

nanospheres for the detection of ammonia in a water environment [42]. The manufacturing of the sensor is based on a two-stage process: first, the deposition of the mesoporous thin film (PDPA/SiO₂) over the fiber surface using the LbL technique, then, followed by the infusion of tetrakis-(4-sulphophenyl)porphine (TSPP) as functional material into the porous film. The thickness of the overlay depends on the number of the deposition cycles as clearly showed in the

SEM images of Figure 7. One cycle of the deposition process corresponds to an overlay thickness of roughly 50 nm. The chemically induced desorption of TSPP from the mesoporous coating, when the LPG is dipped in aqueous solutions containing ammonia, generates a decrease in the RI of the film, which can optically be detected.

The above-described nanostructures and nanocoatings can effectively be used in biosensing applications.

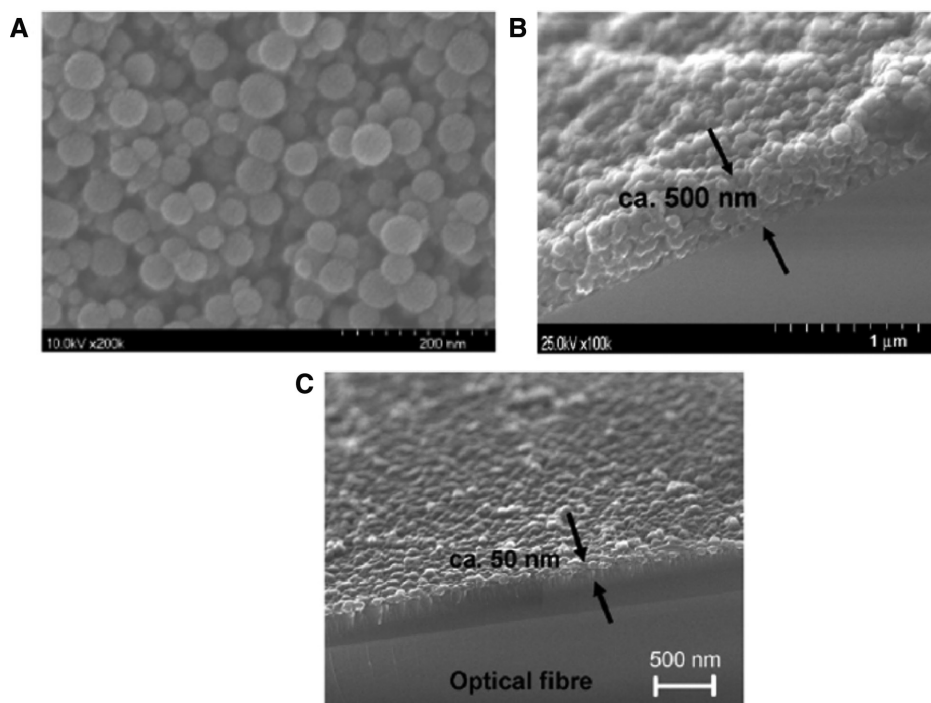


Figure 7: SEM images of surface morphology (A) and cross-section (B) of the 10-cycle (PDDA/SiO₂) film overlay deposited on a quartz substrate as preliminary test. SEM image of cross-section (C) of the same film overlay (one cycle) deposited onto the optical fiber containing an LPG. Figures adapted with permission from Ref. [42]. Copyright (2012) Elsevier.

This last feature will be discussed in detail in the next section. However, in order to achieve the best performance in terms of both RI sensitivity and limit of detection (LOD) of biomolecules, some crucial and essential characteristics of the deposited nano-film should be considered, such as homogeneity, uniformity, surface coverage, electronic interactions between the overlay and the surrounding environment, and the intrinsic material properties (i.e. hydrophilicity rather than hydrophobicity). In particular, the homogeneity and uniformity of the overlay strongly influence the shape and depth of the resonant attenuation bands that, in turn, directly affect the sensor performance. When a not uniform layer is deposited on an optical fiber, the depth of the resonance dramatically decreases, and its shape becomes asymmetric, worsening drastically the sensor performance. In addition, the use of porous coatings surely increases the surface coverage and, hence, the functionalities of the biosensor, but the sensor response time can noticeably increase [19]. Therefore, a trade-off among the film peculiarities and the used substrate should inevitably be envisaged. In general, the typical time required to perform a complete receptor-analyte binding measurement (from the binding interaction up to the washing step) is of the order of 20–60 min [19, 34], which can be reduced down to 5–10 min with an alternative approach involving the initial binding rate [19,

43]. Clearly, these values are not an exclusive characteristic of the OFG-based sensing systems, but are also typical features of all the other optical platforms able to monitor real-time interactions (such as those based on SPR).

4 Applications

One of the earliest applications of optical fiber gratings in biosensing was proposed by DeLisa et al. [43], who developed an immunoassay based on anti-human IgG as BRE and human IgG as antigen. As shown in Table 1, in addition to IgG/anti-IgG immunoassays [19, 30, 43–45], the use of antibodies as BRE was selected for proteic markers (C-reactive protein (CRP) [31], thyroglobulin [50], human transferrin [49]) and for receptors present on cell membranes [47, 48] or bacteria [46].

Not only antibodies but also nucleic acids, such as oligonucleotidic probes (DNA) [8, 52], peptide nucleic acid probes (PNA) [53–55], and aptamers [34, 35, 56, 57], have been also coupled to OFGs for the detection of different targets, consisting of short oligonucleotides, genomic DNA, and even proteins or small molecules (Table 2). Finally, a series of other BREs, based on biointeractions such as enzymatic processes [58, 59], biotin/streptavidin

Table 1: OFG-based biosensors with antibodies as biological recognition elements (BREs).

Grating	BRE	Target	Nanomaterial	LOD	Matrix	Ref.
LPG	Anti-human IgG	Human IgG		700 $\mu\text{g l}^{-1}$	Buffer, heterogeneous protein mixture	[43]
LPG-PCF	Anti-rat bone sialoprotein IgG	Anti-mouse IgG			Buffer	[44]
LPG	Human IgG	Anti-human IgG			Buffer	[30]
TAP-LPG	Mouse IgG	Anti-mouse IgG		70 $\mu\text{g l}^{-1}$	Human serum	[45]
LPG	Mouse IgG	Anti-mouse IgG	Titania-silica sol-gel	8 $\mu\text{g l}^{-1}$	Human serum	[19]
FBG	Anti- <i>E. coli</i>	<i>E. coli</i> bacteria			Buffer	[46]
FBG	Anti-CRP	CRP	GO	10 $\mu\text{g l}^{-1}$	Buffer buffer with urea, glucose, creatinine	[31]
SPR-TFBG	Anti human epidermoid carcinoma cell	EGFR (on A431 cells)		2*10 ⁶ cells ml ⁻¹	Cell suspension	[47]
SPR-TFBG	Anti human epidermoid carcinoma cell	EGFR (on A431 cells)		2*10 ⁶ cells ml ⁻¹	Cell suspension	[48]
SPR-TFBG	Anti-transferrin	Human transferrin		100–1000 $\mu\text{g l}^{-1}$	Buffer	[49]
RT-LPG	Anti-thyroglobulin	Thyroglobulin		Detection range 0.08–88 $\mu\text{g l}^{-1}$	Fine-needle aspiration biopsies	[50]
TFBG	BSA	Anti-BSA		86 $\mu\text{g l}^{-1}$	Buffer	[51]

Table 2: OFG-based biosensors with nucleic acids as BREs.

Grating	BRE	Target	Nanomaterial	LOD	Matrix	Ref.
mFBG	DNA probe	DNA (ON)		0.5 μM	Buffer	[8]
LPG	DNA probe	DNA (ON)			Buffer	[52]
TFBG-SPR	Thrombin aptamer	Thrombin		0.02 μM	Buffer, serum	[35]
LPG + FBG, SPR	Thrombin aptamer	Thrombin	TiO ₂ layer	0.01 μM	Buffer	[34]
LPG	<i>E. coli</i> DNA aptamer	EcOMPs		Detection range 0.1 nM–0.01 μM	Environmental water samples	[56]
LPG	ATP aptamer	ATP	Gold NPs	400 μM	Buffer	[57]
FBG	PNA probe	Genomic DNA	Gold NPs	0.3 $\mu\text{g l}^{-1}$	DNA extracted from GMRR soy	[53]
FBG	PNA probe	DNA (ON; mismatch)	Gold NPs	0.1 μM	Buffer	[54]
TFBG	PNA probe	DNA (ON; mismatch)		0.01 μM	Buffer	[55]

affinity [18, 33, 60–62], virus-specific recognition (bacteriophage T4/*Escherichia coli* bacteria) [63–66] and biomimetic affinity processes with molecularly imprinted polymers (MIPs) [67], have been implemented (Table 3).

4.1 Antibody-based biosensing

In the development of the first grating-based immunoassay, DeLisa et al. [43] used an LPG, functionalized with silane (APTS), on which goat anti-human IgG (antibody), specific for the human IgG (antigen), was immobilized. In buffer solution, a LOD of 700 $\mu\text{g l}^{-1}$ was reached, but they also showed the possibility to use LPGs in a more complex matrix such as a multiprotein mixture and cell lysate from bacteria. The same IgG/anti-IgG immunoassay was also implemented by He et al., Pilla et al., and Chiavaioli et al. [19, 30, 44, 45]. While He et al. [44] used a LPG inscribed

in PCF where the functional groups for BRE immobilization were provided by poly(allylamine hydrochloride), Pilla and co-workers tuned the working point of the LPG into a highly sensitive one, the so-called modal transition region, through the deposition of atactic polystyrene, which creates a high RI overlay [30]. Chiavaioli et al. exploited the properties of LPG, coupling the propagating core mode with a high-order cladding mode near its TAP with the functional groups for BRE-immobilization provided by Eudragit L100. This last configuration allowed reaching a LOD of 70 $\mu\text{g l}^{-1}$ in human serum [45]. Using the same fiber functionalization and immunoassay, the LOD was decreased of roughly an order of magnitude (8 $\mu\text{g l}^{-1}$) by coating a lower-order cladding mode LPG with a titania-silica sol-gel-derived thin film, allowing the grating to work in modal transition [19].

Another configuration of LPG used in immunosensing [50] is the so-called reflection-type LPG (RT-LPG), which

Table 3: OFG-based biosensors with other biomolecules as BREs.

Grating	BRE	Target	Nanomaterial	LOD	Matrix	Ref.
TFBG	Avidin	Biotin	AuNC, AuNS	8 pM 11 pM	Buffer	[33]
LPG	Biotin	Streptavidin	SiO ₂ :Au NPs	195 µg l ⁻¹	Buffer	[60]
TAP-LPG	Biotin	Streptavidin		<12.5 mg l ⁻¹	Buffer	[61]
LPG	Biotin	Streptavidin	PS nano-layer		Buffer	[18]
SPR-TFBG	Biotin	Streptavidin		2 pM	Buffer	[62]
Ex-TFG in TCOF	Glucose oxidase	Glucose		13–20 mg l ⁻¹	Buffer, plasma	[58]
LPG	Glucose oxidase	Glucose		Detection range 10–300 mg dl ⁻¹	Buffer, plasma	[59]
Etched FBG	Boronic acid	Glucose HbA _{1c}	GO	1 nM glucose 86 nM HbA _{1c}	Buffer, blood	[68]
LPG	Bacteriophage T4	<i>E. coli</i>			Buffer	[63]
TAP LPG	Bacteriophage T4	<i>E. coli</i>		10 ³ cfu ml ⁻¹	Buffer	[64]
TAP LPG	Bacteriophage T4 adhesin	<i>E. coli</i>			Buffer	[65]
Concatenated LPFGs	Bacteriophage T4	<i>E. coli</i>		10 ² cfu ml ⁻¹	Water	[66]
TFBG-SPR	Fibronectin	NIH-3T3 cells			Buffer, cell media	[36]
Etched FBG	Dendrimers	Concanavalin A	SWCNT and GO	1 nM (SWCNT) 0.5 nM (GO)	Aqueous solution	[32]
FBG	MIPs	Maltol		1 µg l ⁻¹	Food samples	[67]

takes the advantage of having single-ended optrode configurations. This approach was recently used for the development of an immunosensor for the thyroid cancer biomarkers present in the needle washouts of fine-needle aspiration biopsies showing a very good sensitivity, with a capability to detect sub µg l⁻¹ concentrations of human thyroglobulin.

Other immunoassay developers used an EFBG as a highly sensitive sensor platform. In particular, Sridevi and co-authors [31] realized an immunoassay for CRP coating the grating with a complex formed by the antibody (anti-CRP) and GO. This complex allowed reaching a quite low LOD (10 µg l⁻¹) with a good specificity even in the presence of other interfering factors such as urea, creatinine, and glucose.

The biosensor configuration described by Voisin et al. [49] uses nanometric-scale gold-coated TFBGs for an immunoassay specific for the human transferrin. The gold coating gives the possibility of SPR generation, which can only occur when the light launched into the SPR-TFBG is polarized radially to the fiber surface. The introduction of SPR effect increases the sensitivity of those platforms to surrounding RI changes, reaching a detection range of 100–1000 µg l⁻¹.

The use of SPR-TFBG was adopted also by other groups [47, 48], which took the advantage of this technology for the development of fiber-optic immunosensors for selective cellular detection through cell membrane protein targeting (Figure 8). In particular, they selectively detect intact epithelial cells as analytes in cell suspensions in the range of 2–5 × 10⁶ cells ml⁻¹ through specific interaction with epidermal growth factor receptors (EGFRs) over-expressed by numerous cancer cells.

Maguis et al. [51] proposed a TFBG for an immunoassay for bovine serum albumin (BSA) using the antigen (BSA, immobilized via electrostatic self-assembled film and linkage with biotinylated BSA protein through avidin-biotin interactions) as BRE and the antibody as the analyte to be detected. An LOD of 86 µg l⁻¹ was achieved. As a special and remarkable case, the use of standard FBGs was proposed by Srinivasan et al. [46], still for cell (*E. coli*) detection via immunosensing, where the sensing mechanism involves the measurement of strain variations induced by the binding interactions.

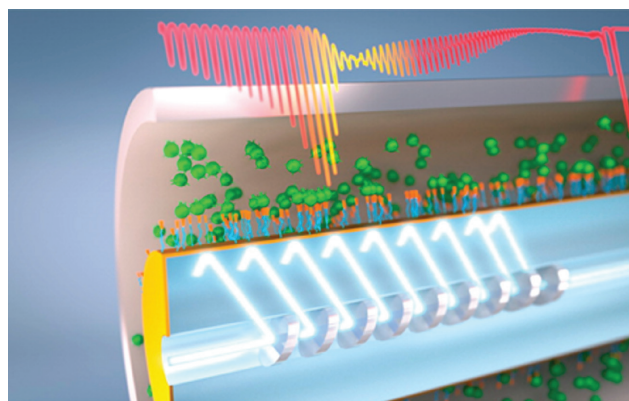


Figure 8: Sensor architecture of a gold-coated TFBG operating in the near-infrared wavelength range at ~1550 nm and yielding optical and SPR sensing characteristics that are advantageous for the analyses of cellular bindings and technical compatibility with relatively low-cost telecommunication-grade measurement devices. Figures adapted with permission from Ref. [48]. Copyright (2015) American Chemical Society.

4.2 Nucleic acid-based biosensing

4.2.1 DNA probe-based biosensing

OFGs have been used in biosensor development coupled to DNA probes for the detection of oligonucleotides (ONs) via hybridization with the major challenge of reaching a high sensitivity. In particular, increase in sensitivity was reached in DNA-based biosensors using LPG with a cladding layer reduced by side polishing, which enhances the interaction between the fundamental fiber core mode and the surrounding medium [52]. The DNA probe was immobilized via electrostatic interaction on a layer of poly-L-lysine (PLL), and the complementary ON target was then injected at a concentration of 1 μM . The authors claim with this method a 2.5-fold increase in sensitivity with respect to previously published similar works based on LPGs [69].

The same assay based on the DNA probe on PLL and hybridization with the ON target has been conducted on a microfiber FBG (mFBG), with the integration into a microfluidic chip that allows the use of low-volume samples [8]. Particular advantages of the system derive from the sensor temperature-self-compensation ability and from the possibility of controlling the RI sensitivity depending on the diameter of the fiber; conversely, as for strong EFBGs, the fragility dramatically increases, and its handling becomes harder. A LOD of 0.5 μM of ON was reached with this sensor.

4.2.2 PNA-based biosensing

Peptide nucleic acids (PNAs) are DNA analogs in which a sugar-phosphate backbone is replaced by a backbone of N-(2-aminoethyl) glycine units linked via a peptide bond [70]. PNA probes, due to their uncharged backbone, do not exhibit any repulsion with negatively charged DNA or RNA, and consequently, they have high affinity and specificity for these complementary nucleic acids even for the discrimination of a single base mismatch. Moreover, they have been shown to be excellent BREs in biosensors due to their chemical and thermal stability [71].

These probes have been widely used coupled to FBGs manufactured on MOFs for the detection of DNA fragments and genomic DNA [53–55], following the same immobilization protocol, based on the silanization of the fiber surface and the subsequent binding of the terminal amine group of the probe to the activated carboxylic groups of the succinic anhydride deposited onto the silane layer. In particular, with the use of an optical fiber

ring cavity sensor with a double-tilted FBG (DTFBG) [55], it was demonstrated that the MOF-based FBG coupled to PNA probes can detect a 0.01- μM concentration of the complementary ON and that it can discriminate between the perfect match ON and an ON with a single base mismatch. The stability and selectivity of PNA probes are here combined with the stability, simplicity, and sensitivity of DTFBGs, which can compensate the effects due to changes in temperature or strain. In Ref. [54], the use of gold nanoparticles in FBGs manufactured on PCFs allows to reach noticeable performance. In particular, the inner surface of the MOF microchannels was coated with the PNA probe and DNA first, and then DNA-coated AuNPs were infiltrated inside the fiber microchannel: the second DNA fixed onto AuNPs served as an amplification system forming a sandwich-like complex onto the sensor. A valuable increase in sensitivity was observed using the second DNA fixed onto the NPs with respect to the undecorated one, and a good selectivity of the sensor, due to the above-mentioned PNA characteristics, was demonstrated by testing a mismatched ON. Finally, in a more recent work [53], the same sensing scheme was applied to the detection of genomic DNA, not amplified by polymerase chain reaction (PCR), extracted from genetically modified roundup ready (GMRR) soy (Figure 9). Exceptional sensitivity and selectivity of the system was demonstrated by the detection of small percentages, 1%–10%, of the target genomic DNA in a large excess of non-specific DNA. The possibility of detecting not amplified DNA directly extracted from the real sample, GMRR soy in this case, represents an important improvement with respect to other biosensors and

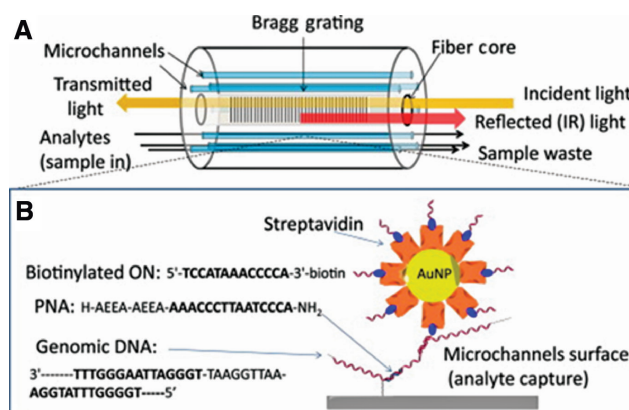


Figure 9: Scheme of the biosensor based on a microstructured fiber with an FBG (A). Scheme of the assay based on the capture of the target genomic DNA by the immobilized PNA probe and the subsequent detection, thanks to the formation of a sandwich with another DNA probe fixed onto AuNPs (B).

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opens up the possibility of using this label-free, compact, and low-volume requiring a sensing system in a real environment, such as food industries.

4.2.3 Aptamer-based biosensing

When dealing with the detection of targets different from nucleic acids and, consequently, not relying on the hybridization reaction, nucleic acid-based biosensors are based on the use of aptamers. Aptamers are short, single-stranded DNA or RNA oligonucleotides, which can bind to different targets by adopting stable three-dimensional sequence-dependent structures [72–74]. They can vary in size from 25 to 90 bases [75], and depending on the primary sequence and on the environmental conditions, they are composed of different structural motifs such as G-quadruplex structures or pseudoknots [76]. These affinity molecules are produced by an evolutionary molecular biology approach called SELEX (systematic evolution of ligands by exponential enrichment) [77], which is performed *in vitro*, thereby, allowing easy control of the selection, itself, and, consequently, of the characteristics of the selected molecules.

Among all the selected aptamers, the thrombin one is the most studied and used as a model system for aptamer-based biosensors [78, 79]. This aptamer has been coupled to TFBGs, used as platform for the implementation of a sensor based on SPR [35]. Several advantages of this type of SPR configuration have been indicated such as its being compact and cost-effective together with the possibility of an intrinsic correction of temperature effects, thanks to the presence of a core mode spectral resonance whose wavelength shift only depends on temperature. The thiolated thrombin aptamer was immobilized onto the gold layer deposited on the surface of the fiber cladding exploiting the direct interaction of the $-SH$ functional with gold. The biosensor was shown to reach a LOD of $0.02\ \mu M$ for thrombin, and a dissociation constant (K_d) for the binding of thrombin with the immobilized aptamer of $0.04\ \mu M$ was calculated. This value of K_d , similar to the other dissociation constant already reported ranging from 0.02 to $0.2\ \mu M$, demonstrated that the attachment of the aptamer onto the sensor layer did not affect its functionality and affinity for thrombin.

In a recent paper, the same aptamer was used coupled to optical fibers in two configurations: LPGs and SPR in optical fibers [34]. LPGs were coated with a 30-nm layer of TiO_2 to increase the RI sensitivity to the surrounding medium, whereas the SPR sensor on fiber was realized by depositing first a 2-nm layer of chromium, to enhance the

adhesion of gold, then a 16-nm layer of gold, and finally a 100-nm layer of TiO_2 . The amine-terminated thrombin aptamer was immobilized on both the sensors via a layer of PLL via electrostatic interaction, and the detection of thrombin was performed at different concentrations in buffer; at the end of the series of measurements, the surface of the sensors was regenerated by the use of a 5% hypochlorite solution. The scheme of the two sensors with the optical setup is illustrated in Figure 10. Both the biosensors reached an LOD of $0.01\ \mu M$ for thrombin with a detection range between $0.01\ \mu M$ and $0.1\ \mu M$ and the possibility of complete regeneration for a new functionalization and assay cycle.

Another popular aptamer used in biosensor and bioassay development is the one specific for adenosine triphosphate (ATP) [80], which has also been coupled to LPGs for the detection of this small molecule [57]. In particular, the aptamer was immobilized on gold nanoparticle (AuNP)-doped macroporous sol-gel-derived films and hybridized with a complementary sequence containing a quencher moiety (QDNA). The presence of the aptamer target molecule ATP induces the conformational change of the aptamer with the consequent binding to ATP and detachment of the QDNA with a large change in RI. This complete assay configuration was compared with the same sensor having the aptamer directly immobilized onto the optical fiber or onto macroporous silica materials without AuNPs and with the sensor not relying on the detachment of the QDNA but on the direct binding of ATP to the immobilized aptamer. This comparison demonstrated the increase in sensitivity when using high surface area and high RI overlays, especially for the detection of small molecules such as ATP. Moreover, the use of the QDNA displacement-based configuration generated a further twofold increase in sensitivity, with a calculated LOD of $400\ \mu M$, and a control on the selectivity of the sensor.

In addition to these two more commonly used aptamers, a further one specific for *E. coli* outer membrane proteins (EcOMPs) has been coupled to LPG for the detection of *E. coli* in buffer and spiked environmental water samples. The aptamer was immobilized by following two different methods either based on electrostatic interaction with PLL or via covalent binding on (3-aminopropyl) triethoxysilane (APTES). The two sensor coatings led to identical sensitivities with a detection range for EcOMPs of $0.1\ nM$ to $0.01\ \mu M$ with the one coated with PLL showing better reproducibility and surface homogeneity. On the contrary, better performance in the analysis of spiked water samples was obtained with the sensor coated via covalent binding of the aptamer.

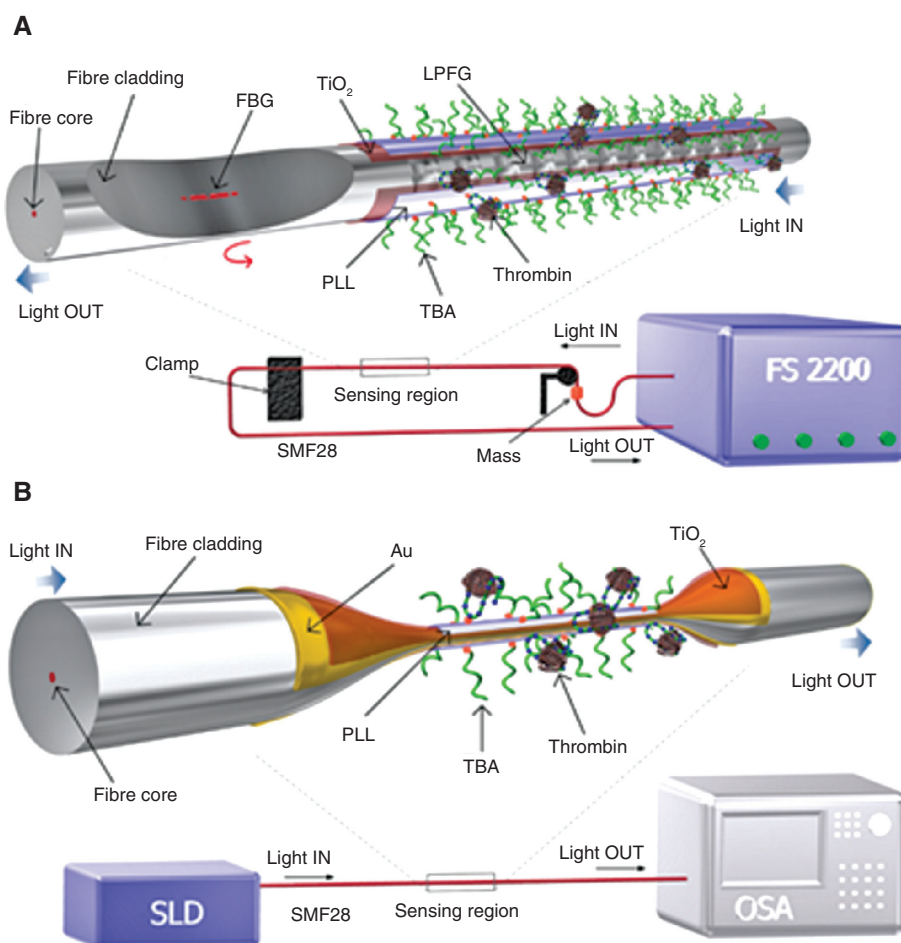


Figure 10: Scheme of two configurations of aptamer-based sensors: LPG coated with TiO_2 (A) and SPR device in etched single-mode fiber coated with Au and TiO_2 (B).

Figures adapted with permission from Ref. [34]. Copyright (2015) SPIE.

4.3 OFG-based biosensing based on other BREs

A plethora of biomolecules different from nucleic acids or antibodies has also been coupled to OFGs for biosensing applications, ranging from the high affinity couple avidin-biotin, to enzymes and bacteriophages.

The main criterion of biosensing is the specific molecule recognition through a BRE, which selectively targets the desired analyte. In a series of studies, the pair biotin/streptavidin or avidin was used as a demonstrative bioconjugate pair, which shows an extraordinarily high affinity ($K_d \approx 10^{-14}$ M, $K_d \approx 10^{-15}$ M, biotin/streptavidin and biotin/avidin, respectively). These kinds of biosensors are for the great majority characterized by the use of biotin as the BRE and the streptavidin as the analyte to be detected in buffer solutions. Marques et al. [60] developed a sensor based on an LPG modified with a coating of silica core gold shell (SiO_2 :Au) nanoparticles (NPs), which were deposited

using the layer-by-layer method (poly(allylamine hydrochloride) (PAH) polycation layer), reaching a LOD of $195 \mu\text{g l}^{-1}$ of streptavidin. Wang et al. [61], which functionalized a TAP-LPG with adsorption deposition of ionic self-assembled multilayers (ISAMs), used a multi-layer deposition, too. In particular, PAH was used as the polycation, and poly{1-[4-(3-carboxy-4-hydroxyphenylazo)-benzenesulfonamido]-1,2-ethanediyl, sodium salt} (PCBS) was used as the polyanion, forming the bilayer combination. Biotin was then immobilized through the biotinylation of PAH, which is the outer layer of the ISAM film deposited on the TAP-LPG. A LOD lower than 12.5 mg l^{-1} of streptavidin was reached. Pilla et al. [18], which functionalized the fiber surface depositing a nano-scale layer of PS, conducted another similar study using an LPG onto which biotinylated bovine serum albumin (bBSA) was adsorbed. In this case, BSA was used for its strong hydrophobic interaction with PS, while the biotin is the BRE for the streptavidin.

TFBGs were used by Caucheteur et al. [62] adding a 30-nm gold coating for implementing an SPR-based device. The biotin/streptavidin recognition experiments showed a LOD of 2 pM. TFBGs were also used by Lepinay et al. [33], which functionalized the fiber surface with noble metal NPs either with gold nano-cages (AuNC) or gold nanospheres (AuNS). In this study, the immobilized BRE onto the NP was the avidin, while the analyte was biotin. A LOD of 11 pM with AuNS and of 8 pM with AuNC was achieved, respectively.

In addition to biotin/streptavidin, enzymes, such as glucose oxidase (GOD), were also used for the detection of glucose with standard LPGs [59] and excessively tilted FBG (Ex-TFBG) inscribed in a thin-cladding optical fiber (TCOF) to enhance the sensor sensitivity [58]. Both the sensors could specifically detect glucose in physiologically relevant concentrations (10–300 mg dl⁻¹) by exploiting the transformation of glucose in D-glucono-1,5-lactone catalyzed by GOD. The sensor based on Ex-TFBGs demonstrated a high sensitivity with a LOD of 13 mg l⁻¹, and more interestingly, both the biosensors were applied to the detection of glucose in human plasma samples with a good agreement with the reference method used by the hospital providing the samples.

An enhanced detection of glucose and glycated hemoglobin (HbA_{1c}) [68] has been accomplished using EFBGs coated with aminophenylboronic acid (APBA)-functionalized reduced GO (RGO). The biosensor could detect glucose with high specificity in a concentration range covering the clinical relevant range (1 nM to 10 mM), and it could also accurately estimate HbA_{1c} in two blood samples from diabetic patients.

In the challenging field of bacteria detection, *E. coli* in particular, OFGs have been extensively used combined to bacteriophage T4 [63–66]: phages are organisms recognizing their host by specific receptor molecules on their surface, with high sensitivity and specificity to the bacteria and good thermal stability [81]. For all these reasons and being nontoxic to humans, as well as cheap and fast to produce, they emerged as a possible alternative to antibodies in biosensor development. In particular, they have been used, adsorbed, or covalently linked on silanes, as receptors for *E. coli* detection with LPGs and TAP-LPGs, achieving a LOD of 10³ cfu ml⁻¹ [63–65]. In addition, with a particular configuration of LPGs, constituted by two concatenated LPGs one of which serving for temperature compensation, different concentrations, down to 10² cfu ml⁻¹ of *E. coli*, could be detected in water over the wide temperature range of 24°–40°C [66].

An important role in understanding biomolecule interaction and in the study of extracellular membranes

is played by glycoprotein association with lectins and integrins [82]. In this area, two groups have developed FBG-based biosensors exploiting the interaction between concanavalin A (ConA) and mannose-functionalized dendrimers [32] and between fibronectin and fibroblast cells to study the cell response to stimuli [36]. In particular, single-walled carbon nanotubes (SWNTs) and GO-coated EFBGs have been used for the detection of ConA via its interactions with mannose-functionalized poly(propyl ether imine) (PETIM) dendrimers: dendrimers are globular macromolecules that are employed to study biologically relevant interactions, and the mannose-derivatized ones can be used for the investigation of their binding with ConA, a lectin important in the characterization of glycoproteins and other sugar-containing molecules on the surface of cells. Enhanced sensitivity was obtained for the functionalized SWNT and GO-coated EFBGs, in comparison with uncoated EFBGs, due to the attachment of an increased quantity of dendrimers for the availability of a larger surface area and due to the increased RI of the cladding material: the reached ConA LODs with SWCNTs (1 nM) and GO (500 pM) are among the best ones if compared to other sensors developed for the detection of the same target.

A very interesting approach has been presented for the study of cellular behavior, in particular, of cellular response to stimuli [36]. NIH-3T3 fibroblast cells were attached to a TFBG-SPR sensor exploiting their interaction with fibronectin, a glycoprotein known to bind extracellular matrix components such as collagen and fibrin. The sensor output was recorded in time before and after the addition of different cell treatments such as cell detachment from the fiber with trypsin, serum protein uptake, and inhibition of cellular metabolism. Importantly, it was demonstrated that the high sensitivity of the sensor allowed the detection of negligible intracellular changes due to the different tested stimuli, which could be barely visualized by imaging procedures taken as reference methods.

Finally, biomimetic, rather than BREs, can be included in the molecules used for biosensor development based on OFGs. In particular, MIPs have been used as receptors coupled to TFBGs for the detection of maltol, an aroma-enhancer additive [67]. The detection of small molecules such as maltol is a challenging task with these kinds of label-free sensors, and the MIP-coated TFBGs demonstrated good performance in this area: a LOD of 8.1 nM (1 µg l⁻¹) was obtained, and the analysis of real food samples was performed with a detection level near the 87% of the real content of maltol.

5 Conclusions and future perspectives

It is apparent that OGF-based biosensors are a valid and alternative approach for label-free sensing, with the capability of achieving excellent performance in terms of sensitivity and of reaching very low LOD. As described above, the advent of nanotechnology, with the possibility of depositing nanostructures and nanostructured coatings along the surface of OFGs, is extending these possibilities, leading to the development of biosensors characterized by features unexpected up to a few years ago.

What was not still completely exploited with these types of sensors is related to the intrinsic advantages lying in the use of optical fibers, such as the miniaturization that can pave the way to their use in places of difficult access – first of all in clinical settings for *in vivo* applications – and the ease of multiplexing, for example, with a series of gratings inscribed along the same fiber with different optical characteristics in terms of resonance wavelengths, and, obviously, with different BREs deposited in correspondence of each grating toward a multi-target detection. Considering these aspects, OFGs can really become a unique and irreplaceable optical platform in biosensing.

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