Fiber optic sensors based on fiber-optic ball resonators for applications in biosensing

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DOI:10.31868/RFL.2024.242-243

Summary: Fiber optic biosensors are minimally invasive devices that perform a specific detection of biomolecules, through the analysis of reflection or transmission spectra. The operation with single-mode telecom fibers at infrared wavelengths makes it possible to achieve high performances, thanks to the excellent mode stability, while designing sensors having a low cost per unit. In this work, we present our latest results using fiber-optic biosensors based on ball resonators (BRs), fabricated using a CO2 laser splicer and functionalized using a silanization process. The BR fabrication is a rapid and repeatable process, leading to sensors that have quasi-random spectral features that can be interrogated through optical backscatter reflectometry. We present the BR sensors for a various range of targets that include protein-based cancer biomarkers, viruses, cells, and the exploitation or analytes such as saliva or tears.

Optical fiber biosensors (OFB) are an emerging technology that makes use of miniature optical devices, fabricated on or within an optical fibers, to sense biomolecules at low detection limits and high specificity [1]. The structure of a biosensor relies on a refractive index (RI) sensor, that can detect changes in the environment surrounding the fiber in the sensing area; this can be converted into a biosensor by means of a functionalization process, which deposits bioreceptors (such as antibodies or aptamers), on the surface of the sensing area. When the bioreceptors bind to the target molecules, a response proportional to the concentration of the molecules can be observed. OFB have been reported for a broad range of biological targets, spanning from protein-based cancer [2] and cardiac [3] biomarkers, to glucose molecules [4], up to viral particles [5], and even to cells that have size larger than the wavelength [6].

Plasmonic biosensors [7] and other intensity-based sensors currently represent the most popular OFB technology, as they have a simple layout and have large sensitivity. However, these approaches have two main drawbacks: they rely on large-core, multimode fibers which are sensitive to bending and twists, reducing the biological accuracy when the sensors are used *in situ*; and they operate in transmission, while *in situ* operation would better use a more compact reflective probe.

In order to overcome these limitations, we propose the use of sensors designed for single-mode fibers (SMFs), employed in long-haul telecommunications and therefore having low cost and low attenuation. Since the SMF propagates only the fundamental mode, the sensing accuracy in biological applications in excellent even with sensors having lower RI sensitivity.

In this work, we present and review the biosensors developed on SMF fibers based on the ball resonator (BR) concept. The BR device can be inscribed using a CO_2 laser splicer, using methods derived from the fabrication of diffractive lenses [8]. When fabricated on the tip of a SMF, the reflection spectrum appears as a low-reflectivity signal, characterized by a random pattern. An accurate detector, such as an optical backscatter reflectometer, can interrogate the BR devices using intensity or polarization changes as the main output parameter [9].

The functionalization of BR resonators relies on a silanization method, using antibodies as bioreceptors to be immobilized on the surface of the devices [10]; alternative methods based on nanomaterials have also been proposed in order to expand the sensitivity [11].

The applications of BR-based biosensors are broad, thanks to the versatility of the device and its label-free sensing potential. At first, BRs have been demonstrated for the detection of cancer biomarkers at low detection limits (sub-femtomolar), showing a log-linear trend over a wide range of concentrations and an excellent repeatability [12]. This was demonstrated through the detection of CD44, both in static conditions, and more recently by a dynamic detection packaging the CD44 probe for intravenous use [13]. A second case of application was reported for the detection of viral threats using BR sensors, which was implemented both by tracking the proteins expressed by vaccinia poxvirus [14], and by detecting the whole viral particle using sensors functionalized to antibodies binding to the target proteins [15]. Finally, we show the application of BRs to the detection of CD44 cells, showing an output response log-linear over a wide range of concentrations and a low detection limit [16].

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