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In-situ detection of density alteration in non-physiological cells with polarimetric tilted fiber grating sensors

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ABSTRACT

Tilted fiber Bragg grating (TFBG) biosensors can be used as a cost-effective and relatively simple-to-implement alternative to well established biosensor platforms for high sensitivity biological sample measurements in situ or possibly in vivo. The fiber biosensor presented in this study utilizes an in-fiber 12° tilted Bragg grating to excite a strong evanescent field on the surface of the sensor over a large range of external medium refractive indices. The devices have minimal cross-sensitivity to temperature and their fabrication does not impact the structural integrity of the fiber and its surface functionalization. Human acute leukemia cells with different intracellular densities and refractive index (RI) ranging from 1.3342 to 1.3344 were clearly discriminated *in-situ* by using the differential transmission spectrum between two orthogonal polarizations for the last guided mode resonance before "cut-off", with an amplitude variation sensitivity of 1.8×10^4 dB/RIU, a wavelength shift sensitivity of 180 nm/RIU, and a limit of detection of 2×10^{-5} RIU. The detection process was precisely controlled with a micro-fluidic chip which allows the measurement of nL-volumes of bio-samples. The proposed in-fiber polarimetric biosensor is an appealing solution for rapid, sub-microliter dose and highly sensitive detection of analytes at low concentrations in medicine, chemical and environmental monitoring. @ 2013 Elsevier B.V. All rights reserved.

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1. Introduction

The detection of small changes in biological samples, due to cell growth or death for instance, is often carried out in aqueous solutions (saline). Such changes are inevitably associated with refractive index (RI) changes, and some of the most sensitive bio-detection methods (like surface plasmon resonance (SPR) sensors and resonant waveguide grating sensors) are actually based on very sensitive refractometry. It was recently demonstrated that drug response and pathological changes in cells which were separated from a human acute leukemia cell line (K562) by using discontinuous sucrose gradient centrifugation (DSGC) were associated with intracellular density changes (Liu et al., 2011). It is the purpose of this paper to demonstrate that a simple tilted fiber Bragg grating refractometer (TFBG) can be used to monitor those intracellular density changes effectively, thanks to a novel data analysis method for the differential polarimetric spectral transmission of the TFBG. In particular, the discrimination of a group of biological samples, named S40, S50 and S60, has been achieved through a high sensitivity RI measurement by using a 12° TFBG sensing probe. By comparing the slight RI difference between S40, S50 and S60 (ranging from 1.3342 to 1.3344), we studied the relationship between the intracellular density of cells and their RI, which might provide a potential way to verify the hypothesis for "density alteration in non-physiological cells (DANCE)" in response to drugs and pathological changes in cells (Liu et al., 2011). However, the mechanisms of DANCE are not clear. It has been hypothesized that change of metabolism mode, change of cell membrane function, and pathological changes in the cells might be the causes for DANCE. Therefore, study of DANCE might be helpful to the understanding of drug resistance, development of new drugs, separation of new subtypes from a cell population, forensic analysis, and discovery of new physiological or pathological properties of cells.

2. Polarimetric TFBG sensor

Fiber sensors are ideally suited for rapid, μL-volume and sensitive detection of analytes at low concentrations in medicine, environmental monitoring and food safety, because the sensing platform is compact (cm in-length, compatible with optofluidic

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microsystems) and cost-effective (well-established grating fabrication process, existing broad base of commercial instrumentation for sensor interrogation, such as LEDs, laser diodes, photodiodes, and CCDs). Fiber optic also allows for data collection in situ and remotely from large distances (Leunga et al., 2007; Fan et al., 2008; Homola, 2008). Of the many possible fiber optic biochemical sensing schemes, the recently developed TFBG platform is generating interest because of its many unique properties (Albert et al., 2013). High resolution sensing is achieved by measuring the positions of resonances in the transmission (or reflection) spectrum that have: (1) high sensitivity, up to 500–1000 nm of wavelength shift per unit change in refractive index; (2) narrow linewidths (100 pm and less); (3) high signal-to-noise ratio (>40 dB) because of the use of low loss fibers and devices; (4) temperature insensitivity arising from the absolute power and wavelength reference provided by the resonance of the core mode guided light. These features have led to demonstrated limits of detection of 10^{-5} in refractive index (Caucheteur et al., 2011) and 10^{-12} M in protein concentrations in solution (Lepinay et al., 2014). Finally, TFBGs are easy to manufacture and do not require physical deformation or degradation of the fiber itself, thereby ensuring device reliability and low fabrication cost in volume quantities (TFBG use the same manufacturing platform as the un-tilted FBGs that are widely deployed in the telecommunications and structural sensing industries).

The sensing principle of the TFBG refractometer proceeds as follows. Incoming core guided light interacts with a permanent refractive index grating that has been inscribed in the fiber by intense ultraviolet light irradiation through a diffractive phase mask. A tilt in the orientation of the grating planes favors the coupling of light to modes guided by the cladding instead of the core (Fig. 1a). Since the cladding diameter is very large (>100 μm, almost 100 times the wavelength) a large number of modes can be excited, each at a specific wavelength, resulting in a fine comb of resonances in the transmission spectrum of the grating (Caucheteur et al., 2013). The resonance with the longest wavelength corresponds to the most well guided mode, the single core guided mode in the fibers that are used for this work. This resonance is inherently insensitive to events outside the cladding and is used as a power and wavelength reference (all the core and cladding mode resonances have the same temperature dependence and hence shift together with temperature, thereby removing the influence of this parameter on measurements) (Chan et al., 2007). Further resonances at decreasing wavelengths correspond to cladding guided modes with increasing amounts of evanescent fields extending outside the cladding boundary (typically over a thickness of the order of 2 μm above the cladding surface). When the immediate environment of the TFBG changes within the region sampled by the mode evanescent fields, the resonance positions of the corresponding cladding modes change accordingly (Fig. 1b). The largest resonance shift occurs when the evanescent field of the modes overlaps maximally with the perturbation, usually for the least guided resonances, i.e., at the shortest wavelengths (Chan et al., 2007). However, at further decreasing wavelengths there comes a point at which the grating couples light to modes that are no longer guided by the cladding. These leaky modes have resonance positions that do not shift in wavelength in response to outside refractive index changes, but only in amplitude (Laffont and Ferdinand, 2001; Chen et al., 2008). The boundary between guided and leaky modes is called the “cut-off point” (as the red stars marked in Fig. 1b) and the last guided mode before this point has the maximum extent of evanescent field penetration in the external medium (and hence the largest sensitivity). The operating point (i.e., the range of wavelengths where modes have maximum sensitivity, near the “cut-off point” for instance) determines the choice of tilt angle: increasing the tilt angle shifts the maximum of the resonance amplitudes towards lower wavelengths (Albert et al., 2013). Finally, a further mode selection mechanism can be used to refine the sensing capabilities of the TFBG. By launching linearly polarized light in the core, two very different families of cladding modes can be selected: modes with radially polarized evanescent fields (hereafter named P-modes, as they are P-polarized relative to the tilt plane), and modes with azimuthally polarized evanescent fields (S-modes) (Caucheteur et al., 2011; Thomas et al., 2012; Alam and Albert, 2013; Guo et al., 2013). Fig. 1c shows the horizontal component of the electric field for representative S- and P-modes. Since S- and P-modes have different reflection characteristics at the boundary, a comparison of the relative changes observed in a pair of S- and P-modes provides a self-referenced tool to measure even smaller changes at the cladding surface than un-polarized TFBGs (Voisin et al., 2011; Caucheteur et al., 2013; Voisin et al., 2014). In this paper, we present new analysis techniques that make optimum use of this difference. These techniques are introduced in Section 4.

For bio-chemical applications, the TFBG can be used for label-free sensing when provided with a functionalized coating whose refractive index can be modified by the selective attachment of certain types of molecules or cells. The same label free techniques

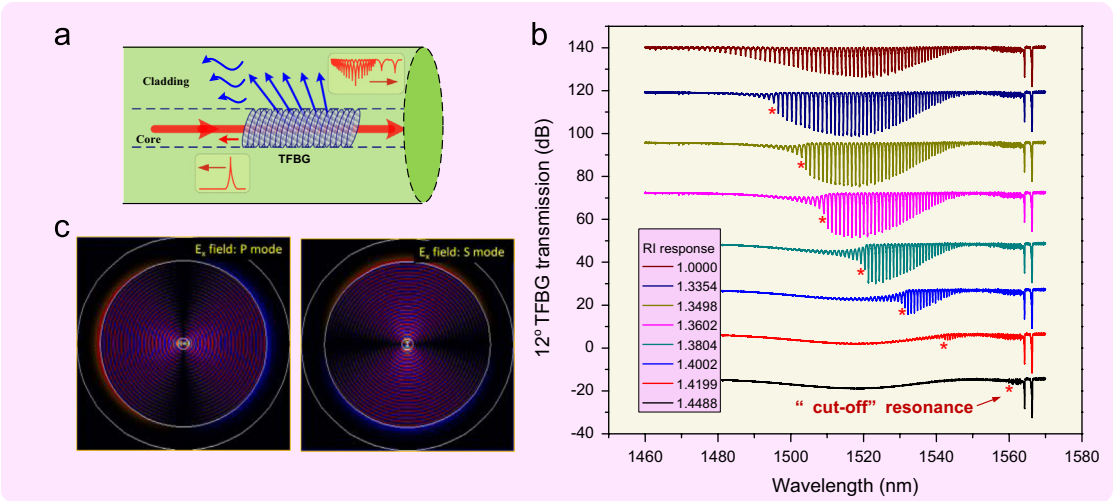

Fig. 1. Polarimetric TFBG sensor: (a) schematic diagram of TFBG, (b) spectral response of 12° TFBG versus surrounding RI, (c) simulated horizontal component of the transverse electric field of representative S- and P-modes near “cut-off”.

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