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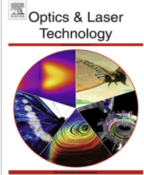

Full length article

Hybrid inorganic/organic photonic crystal biochips for cancer biomarkers detection ☆

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ABSTRACT

We report on hybrid inorganic/organic one-dimensional photonic crystal biochips sustaining Bloch surface waves. The biochips were used, together with an optical platform operating in a label-free and fluorescence configuration simultaneously, to detect the cancer biomarker Angiopoietin 2 in a protein base buffer. The hybrid photonic crystals embed in their geometry a thin functionalization poly-acrylic acid layer deposited by plasma polymerization, which is used to immobilize a monoclonal antibody for highly specific biological recognition. The fluorescence operation mode is described in detail, putting into evidence the role of field enhancement and localization at the photonic crystal surface in the shaping and intensification of the angular fluorescence pattern. In the fluorescence operation mode, the hybrid biochips can attain the limit of detection 6 ng/ml.

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1. Introduction

Bloch surface waves (BSW) propagating at the interface between a one dimensional photonic crystal (1DPC) and an external medium [1,2] have been suggested for label-free biosensors [3,4]. When used in a classical Kretschmann-Raether [5] total internal reflection (TIR) configuration, similar to surface plasmon resonance (SPR) sensing schemes [6], the BSW biochips feature very low angular resonance widths compared to that of SPR, due to the low losses in the dielectric stacks [7]. The optimization of the 1DPC stack, in terms of geometry and materials, offers the possibility to improve the label-free limit of detection (LoD) [8].

Moreover, the strong field localization and enhancement at the 1DPC surface favor utilizing BSW coupled fluorescence emission [9]. Coupling the label-free operation to a second detection scheme relying on the emission of fluorescent labels can lead to a complementary analysis and a decrease of the LoD [10,11].

We report here on the application of a combined label-free and fluorescence biosensing platform [12] to the detection of the Angiopoietin-2 cancer biomarker in buffer solutions. The platform makes use of disposable biochips fabricated by depositing 1DPC onto injection molded plastic substrates. Here the 1DPC is constituted by an inorganic multilayer that is topped by an organic nanometric layer providing the chemical functionalization of the biosensor's surface. For biosensing platforms based on the resonant excitation and detection of surface electromagnetic modes, such as surface plasmon resonance (SPR) [6], the possibility to embed the organic functionalization layer in the biosensor's structure and to tune the 1DPC geometry permits to keep the resonance inside the excitation/detection angular windows, while optimizing the sensitivity. In SPR, as an example, the deposition of a thin organic layer on a gold coated biochip shifts the SPR outside the usually narrow angular operation window, without any possibility to compensate by changing the thickness of the gold layer.

With respect to our previously published results [13–16], this is the first time we report on cancer biomarkers detection assays with a combined label-free and fluorescence platform and making use of 1DPC hybrid biochips with a polymeric surface chemical functionalization.

2. BSW biochips

The geometry of the 1DPC used in this study is shown in Fig. 1a. A dielectric multilayer was directly deposited on a prismatic organic substrate (TOPAS, $n_s = 1.530$) by plasma ion assisted deposition (PIAD) under high vacuum conditions [17]. Then the multilayer was coated with an organic poly-acrylic acid (ppAA) functional thin film by a plasma polymerization technique and making use of a plasma enhanced chemical vapour deposition reactor [18]. The geometry of the underlying inorganic part of

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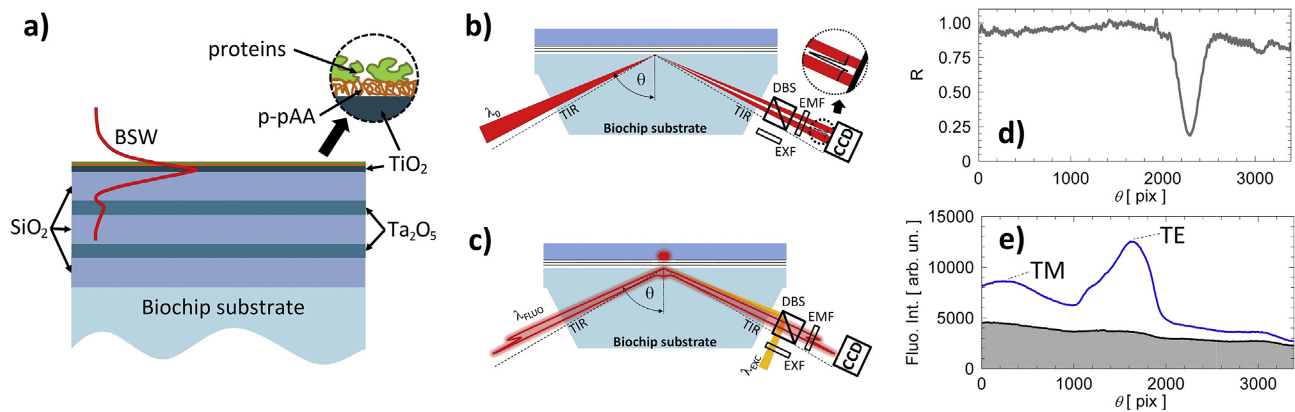

Fig. 1. (a) 1DPC geometry including the polymer functional ppAA film (not to scale). Sketches of the label-free (b) and fluorescence (c) modes of operation. (d) TIR angular reflectance profile, with the biochip in buffer. (e) Fluorescence emission at the end of an assay where Ang2 was detected (blue curve) and before starting the experiment (black curve). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the 1DPC was designed in a way that, after adding the organic functional film/layer, the characteristics of the overall 1DPC are optimized for both label-free and fluorescence sensing.

Besides being used to tune the BSW biochip performance [19], the thin organic functional layer permits to covalently graft and immobilize the proteins that are needed to provide the specificity of the biosensor. ppAA thin coatings are a convenient choice for surface chemical functionalization since they do not affect the chemical properties of the biosensors, are conformal, do not need any specific surface pre-treatment for adhesion and can provide different density of functional groups, wettability and chemical stability by simply varying the deposition process parameters [20].

The inorganic part of the 1DPC is constituted of SiO_2, Ta_2O_5 and TiO_2, with complex refractive indices: $n(SiO_2) = 1.474 + j5 \times 10^{-6}$, $n(Ta_2O_5) = 2.160 + j5 \times 10^{-5}$, $n(TiO_2) = 2.28 + j1.8 \times 10^{-3}$ at $\lambda_0 = 670$ nm [17]. Starting from the plastic substrate, the multilayer is constituted by a first SiO_2 layer, which improves the reliability of the overlaying 1DPC, two Ta_2O_5/SiO_2 bilayers and a top TiO_2 layer. The thicknesses of the layers are: $d(SiO_2) = 275$ nm, $d(Ta_2O_5) = 120$ nm, and $d(TiO_2) = 20$ nm.

The thickness of the ppAA thin topping layer was estimated by atomic force microscopy and is $d(ppAA) \sim 40$ nm and the refractive index is $n(ppAA) = 1.52$, obtained by spectroscopic ellipsometry [18].

After chemical functionalization and bio-conjugation, a plastic cover with a soft polymer layer defining a fluidic channel (800 μm wide, 100 μm high, and 27 mm long) is clicked on top of the biochip and permits the injection of fluids for the analysis [12].

3. Read-out configuration

The BSW biochips are mounted in an optical platform and are used in either a label-free or in a fluorescence mode of operation, as shown schematically in Fig. 1b and c, respectively. For the sake of simplicity, in the figures, we do not show the optical components that are used to focus and image the light beams; for a complete description of the optical layout of the platform one can refer to our precedent work [12]. In particular, the optical system is based on the use of cylindrical optics and can simultaneously perform measurements in several different spots aligned along a line over the biochip surface. The rows and columns of the CCD camera (Apogee Ascent with Sony ICX814 sensor) are then used, respectively, for either angular imaging (3388 pixel) or spot imaging (2712 pixel).

In the label-free operation, the BSW biochip is illuminated through a prism coupler in TIR conditions [6,21] by a TE polarized and focused (FWHM above 4°) laser beam at the wavelength λ_0 = 670 nm. The reflected beam is imaged on the CCD. As an example, in Fig. 1d we show the TIR spectrum as a function of the incidence angle inside the prism coupler θ, in a 2.9° angular range (sampled by 3388 pixel). Excitation of a BSW gives rise to a dip in the angular reflectance spectrum at $\theta_{0,BSW}$. The 1DPC was designed to operate at $\theta_{0,BSW} = 69°$ and the thin TiO_2 layer features were tuned to get a narrow width and large depth of the resonant dip.

Fig. 1a illustrates (red curve) the distribution of the TE polarized BSW energy density calculated at λ_0 and in resonance conditions. The BSW is confined at the interface between the 1DPC and the external medium, where the field decays exponentially with a penetration length $L_{pen} = 117$ nm. Given its strong localization, the BSW is very sensitive to refractive index perturbations in the vicinity of the TiO_2 layer and can be used to monitor protein binding events at the biochip surface, as revealed by the shift of the resonant dip.

In the fluorescence operation, the BSW biochip is excited in TIR conditions at an angle θ_{EXC} by a TE polarized and slightly focused (FWHM = 0.64°) laser beam at the wavelength $\lambda_{EXC} = 635$ nm, matching the absorption peak of the specific dye label that we selected for the biological assays (Dylight 650). The effect of the BSW excitation on fluorescence emission is twofold. On one-hand, if θ_{EXC} is such that a resonant excitation condition of a BSW at λ_{EXC} is achieved, the excitation intensity is enhanced at the 1DPC surface, giving rise to an increased fluorescence emission. On the other hand, the emission at $\lambda_{EM} > \lambda_{EXC}$ of the dye-labelled biomolecules possibly captured and excited at the biochip surface, given the large BSW local density of the states [22], is channelled to the BSW modes, which then are radiated through the substrate, as shown in Fig. 1c.

As an example, Fig. 1e shows the angular emission spectrum recorded by the CCD in a 8° angular range; such a wider range is obtained by inserting a cylindrical zoom lens in the detection system. Given that the 1DPC sustains both TE and TM polarized BSW, with different dispersions, the emission is characterized by two angularly separated TE and TM bands. For each band, each angle corresponds to a different wavelength inside the emission spectrum of Dylight 650. In Fig. 1e, the black curve is the measurement for an unlabelled biochip, and accounts for the background signal captured by the CCD due to either stray light from the excitation beam or intrinsic BSW coupled fluorescence of the 1DPC materials. In all experiments reported below such a background was always subtracted from the fluorescence signal in the presence of labels, which is given by the blue curve shown in Fig. 1e as an example.

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