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Development of a multianalyte optical sol–gel biosensor for medical diagnostic

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ABSTRACT

This work describes the design and fabrication of a novel multianalyte biosensor platform for medical diagnostic applications. The sensor platform consists of a photonic waveguide-based optical circuit used to deliver excitation light to multiple sensor windows on the platform. The platform is fabricated by UV-photopatterning of photocurable hybrid organic–inorganic sol–gel materials. The sensing mechanism is based upon the detection of fluorescently labelled antibodies, in order to determine the concentration of specific analytes in a test solution. Fluorescence is excited by means of the evanescent wave in each sensor window. It is shown that the sensing properties of the platform can be dramatically enhanced by increasing the intensity of the evanescent field of the light propagating in the optical waveguide by a precise design of a high refractive index layer deposited at the waveguide surface. This work proved the concept of employing a waveguide-based photonic platform for the detection of fluorescently labelled antibodies, with μg/ml detection levels, and as such, we believe this system has immense potential for future applications as a medical diagnostic platform.

1. Introduction

Though the development of single analyte biosensors has revolutionized the monitoring of critical diseases, such as glucose metres for diabetes, the development of biosensors with multianalyte capability is still a current major scientific and technological challenge. This topic has been intensively investigated over the past decade with contrasted results being achieved. Probably the most investigated biosensors are those utilizing optical transduction techniques [1], with luminescence based optical biosensors being extremely popular [2]. Some limited work has been carried out on other multianalyte biosensors utilizing electrochemical [3] and thermal transduction techniques [4]. Of the luminescence based biosensors, the approach that has gained most attention is that of evanescent wave excitation [5–7], and its main and most highly cited proponent has been the group at the Naval Research Laboratory in Washington. Here, they have developed since the late 1990s, a multianalyte array biosensor which has been used by the defense forces for detection of biowarfare threats [8]. They have demonstrated good performances with consistent low detection limits on a number of bio-defense threats as well as food borne pathogens. The weakness of this implementation lies in the use of polydimethylsiloxane channels for biosensor spot deposition, giving large sensor spots that negatively impact signal-to-noise performance from a biological and detection point of view. Zeptosens in Switzerland have produced a commercially available technology, also utilizing the highly efficient evanescent wave excitation [9]. Their bioanalytical system is based on proprietary planar waveguide technology, which allows multiplexed, quantitative biomolecular interaction analysis with high sensitivity in a microarray format. They claim that the innovative planar waveguide technology results in a 50-fold higher signal to noise ratio compared to conventional microarray readers. A multianalyte electrochemical biosensor has been demonstrated by Wilson et al. [10]. Up to 8 simultaneous analyses were conducted on one chip, though this approach still suffers from the practical issues related to electrochemical detection.

In this paper, we propose the development of a waveguide based integrated photonic platform for the detection of disease markers. This platform is developed employing a standard photolithography fabrication process and low-cost photocurable organic–inorganic hybrid sol–gel material [11,12]. These materials combine simultaneously the flexibility and photoreactivity of organic polymers, required for the photolithography fabrication process, and inorganic groups that provide optical transparency and mechanical

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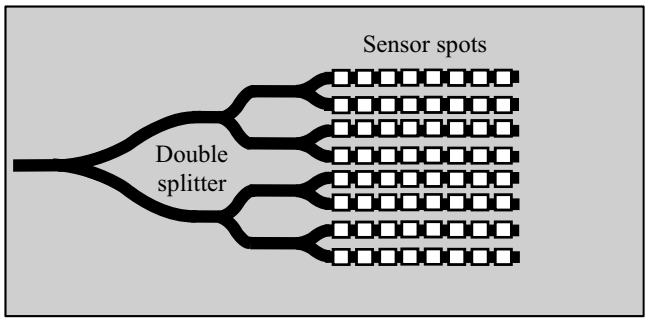

Fig. 1. Design of the multianaltye biosensor platform.

stability to the final platform. The sensing phenomenon exploits the evanescent field of the light propagating within channel optical waveguides to excite fluorescently labelled antibodies immobilized at the surface of the optical waveguide and the subsequent emitted fluorescence is detected with a CCD camera. The sensor platform and materials formulations were designed from simulation studies conducted with the Olympios software. These simulations demonstrated the importance of correctly specifying the material refractive index to achieve single-mode waveguides. They also highlighted the necessity to deposit a high refractive index layer (HRIL) on top of the optical waveguides in order to increase the intensity of the evanescent field responsible for the sensing performance of the platform.

Though similar label-free photonic platforms have been developed from silicon technology based on CMOS fabrication techniques for the detection of biological molecules [13,14], the main difference and novelty of our study consist of the employed materials, fabrication technology and the possibility to control the sensitivity of the biosensor platform by depositing a HRIL on top of the sensing areas.

2. Operating principle and simulations

2.1. Operating principle

In this study, the sensing principle aims at exploiting the evanescent field of the light that propagates within the core of channel optical waveguides to excite fluorescently labelled antibodies immobilized at the surface of the optical waveguides. The presence of the antibodies is then detected by collecting and quantifying the emitted fluorescence using a CCD camera. To exploit these intrinsic waveguide properties, the biosensor is based on a double splitter waveguide platform: two 3 dB coupler stages are cascaded to divide the incoming optical light into four optical signals using *Y* branching, as sketched in Fig. 1. Sensing windows are patterned at the waveguide surfaces to allow the realization of the direct immunoassay. This configuration allows equal share of the light to be distributed between the four waveguides issued from the single-mode input and equal interaction levels between the evanescent field and its surrounding environment. Furthermore, the multiple sensor windows are optimum to minimize the uncertainty in the fluorescence emissions, therefore evaluating the performance of the sensor platform with high accuracy.

2.2. Simulations

Singlemode operation for a channel waveguide with a core of $6 \times 6\,\mu m^2$ has been shown by us elsewhere [15,16]. Typically to achieve singlemode conditions at 639 nm, a refractive index contrast of 0.0035 is needed between the core and the cladding of the waveguide. In these conditions, the intensity of the evanescent field

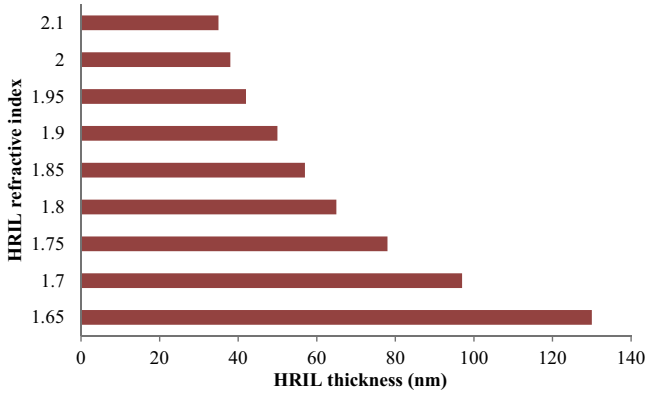

Fig. 2. Correlation between the thickness and the refractive index value of the HRIL in order to maximize the intensity of the EF.

(EF) was found to be close to 1% of the entire light intensity that propagates within the core of the waveguide.

It is however possible, as previously reported in the literature [17] to increase the intensity of the EF by depositing at the surface of the optical waveguide a top layer with a high refractive index (HRIL). In order to enhance the EF, the refractive index value and the thickness of the HRIL have to be carefully modelled. Fig. 2 shows the simulation results that correlate the value of the refractive index to the HRIL in order to maximize the EF at the desired wavelength of 639 nm within the first 50 nm at the waveguide surface. It is found that the optimum thickness to maximize the EF is strongly dependent on the refractive index value and that the greater is the refractive index, the thinner is the required thickness. For instance, for a refractive index of 2.1, which is the value of pure Ta_2O_5 that we aim to employ here, the required thickness is found to be 35 nm. In these conditions, the intensity of the EF was found to be increased by 440 times in comparison with the system without HRIL, as represented in the EF enhancement factor versus Ta_2O_5 thickness in Fig. 3. Here, the error bars for each date point express the spatial periodic variation evanescent wave intensity shown in the simulations images in Fig. 4.

The optical modes propagations for 25, 35 and 45 nm Ta_2O_5 thickness deposited at the waveguide surface in the sensor windows are shown in Fig. 4. This figure shows that a repeating beat pattern is established between the sol–gel waveguide and the Ta_2O_5 layer, which is most noticeable in the case of the 35 nm Ta_2O_5 layer, the thickness providing the optimum evanescent wave enhancement.

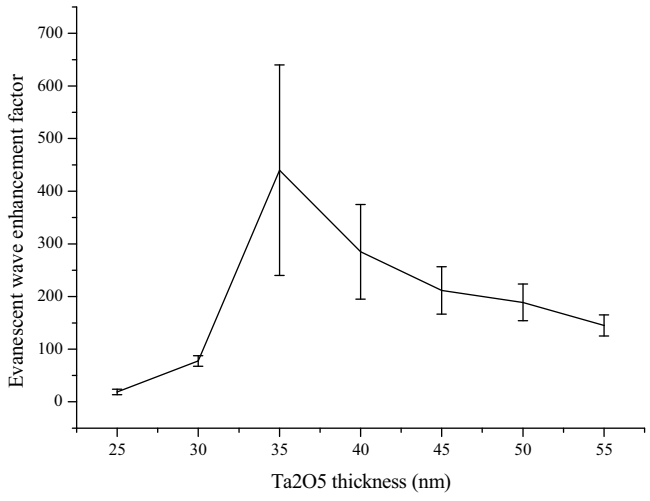

Fig. 3. EF enhancement factor as function of the Ta_2O_5 thickness.