Biosensors and Bioelectronics ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios

Multiplexed detection of lectins using integrated glycan-coated microring resonators

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ARTICLE INFO

Article history:
Received 10 November 2015
Received in revised form
7 January 2016
Accepted 20 January 2016

Keywords:
Biosensor
Nanophotonics
Sensor Optimization
Noise
Glycoprotein

ABSTRACT

We present the systematic design, fabrication, and characterization of a multiplexed label-free lab-on-a-chip biosensor using silicon nitride (SiN) microring resonators. Sensor design is addressed through a systematic approach that enables optimizing the sensor according to the specific noise characteristics of the setup. We find that an optimal 6 dB undercoupled resonator consumes 40% less power in our platform to achieve the same limit-of-detection as the conventional designs using critically coupled resonators that have the maximum light–matter interaction. We lay out an optimization framework that enables the generalization of our method for any type of optical resonator and noise characteristics. The device is fabricated using a CMOS-compatible process, and an efficient swabbing lift-off technique is introduced for the deposition of the protective oxide layer. This technique increases the lift-off quality and yield compared to common lift-off methods based on agitation. The complete sensor system, including microfluidic flow cell and surface functionalization with glycan receptors, is tested for the multiplexed detection of Aleuria Aurantia Lectin (AAL) and Sambucus Nigra Lectin (SNA). Further analysis shows that the sensor limit of detection is 2×10^{-6} RIU for bulk refractive index, 1 pg/mm^2 for surface-adsorbed mass, and ~10 pM for the glycan/lectins studied here.

1. Introduction

Integrated photonic resonators are sensitive, on-chip transducers suitable for various sensing applications (Hunt and Armani, 2010; Fan et al., 2008). Their miniature size allows the realization of large microarray sensors on a single chip that is of interest in many biosensing applications such as the detection of DNA (Rong et al., 2008), microRNA (Qavi and Bailey, 2010), toxins (Ghasemi et al., 2013), blood biomarkers (Washburn et al., 2009), and aptamers (Park et al., 2013). The resonance wavelength of a typical resonance-based integrated photonic sensor changes when the desired analyte binds to its surface, resulting in a change in the transmitted power through an optical waveguide that is coupled to the resonator.

Integrated photonic dielectric resonators have been demonstrated in different material platforms including silicon (Si) (Claes et al., 2010), silicon nitride (SiN) (Heideman et al., 2012; Lee et al., 2010), indium phosphide (InP) (Ciminelli et al., 2013), and polymers (Chao et al., 2006). Stoichiometric SiN is an appropriate choice as it is compatible with both CMOS fabrication processes and the majority of surface functionalization protocols. In addition, SiN has a relatively small thermo-optic coefficient (TOC) making the device less susceptible to temperature variations. Despite several temperature compensation techniques proposed for integrated photonic resonators (Gylfason et al., 2010; Kirk et al., 2011), the temperature difference between the sensor and the reference resonators is still a source of device-level thermal noise. Small TOC of SiN results in the suppression of this thermal effect by one order of magnitude compared to Si, InP, gallium arsenide, and titania (Della Corte et al., 2000; Gülsen and Naci Inci, 2002). Furthermore, stoichiometric SiN has two important advantages in terms of the system cost. First, it can be deposited using inexpensive processes such as low-pressure chemical vapor deposition (LPCVD). Second, it is transparent to near infrared and visible wavelengths, which enables the use of low-cost light sources and Si photodetectors in the system.

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http://dx.doi.org/10.1016/j.bios.2016.01.051
0956-5663/

In addition to the material platform, the sensor performance depends on its geometry. A proper figure of merit (FOM) for optimization of a sensor is its limit of detection (LOD) (Chamanzar et al., 2010), defined as the smallest quantity of target analyte that the sensor can reliably detect (Ghasemi et al., 2014). For optimization of LOD in resonance-based sensors, typical design procedures seek to minimize $1/(Q \cdot S)$, where Q is the quality factor of the resonance; and S is its sensitivity, which is defined as the ratio of the resonance shift to the quantity of the analyte bound to the surface of the resonator (Fard et al., 2014). On the other hand, it is a well established design procedure to maximize the signal-to-noise ratio (SNR), with the "signal" typically defined as the extinction of the resonance (i.e., the difference between on-resonance and off-resonance transmitted power). However, in case the optimization requires a compromise between the SNR and Q of the resonator, a unified approach encompassing both of these factors simultaneously is required. Despite important research efforts on the noise performance of resonance-based sensors (White and Fan, 2008), such a unified approach is missing from the literature. Not only this optimization leads to lowest LOD, it is also crucial for large scale integration of highly multiplexed sensors, where power consumption and heat generation are main limitations. In applications where a low LOD is not necessary, the optimization approach described here can be used to minimize the power consumption at the same LOD level.

In this paper, we demonstrate a new concept for the optimization of power consumption in resonance-based integrated photonic sensors. We argue that to achieve optimal LOD, the resonance lineshape curvature at the resonance wavelength is the single important parameter of the lineshape that should be optimized. This parameter includes the contributions of both the linewidth and the extinction (or equivalently, Q and SNR), and thus shrinks the design space into only one dimension. The waveguide-resonator spacing is then used to tune the coupling strength, which in turn tunes the resonance curvature (i.e., the curvature of transmitted power curve of the bus waveguide in the wavelength domain at the resonance wavelength). On the experimental side, a full biosensor based on the optimized elements is fabricated and functionalized with glycan bioreceptor molecules. Glycans are carbohydrate molecules that specifically recognize toxins and other bio-functional molecules (Smith et al., 2010; Song et al., 2011). The solution of target molecules is delivered through a microfluidic flow cell to reduce the response time and minimize the required sample volume (De Vos et al., 2007). Our results show that our optimized sensor can detect multiple analytes with LOD of 1 pg/mm^2 for surface-adsorbed mass, which corresponds to a bulk refractive index LOD of 2×10^{-6} RIU (Refractive Index Unit).

In Section 2, we explain device concept, fabrication, and sensor packaging. The optimization of the resonator-waveguide coupling of the sensor is elaborated in Section 3. The sensor is used for label-free, specific, and multiplexed detection of Aleuria Aurantia Lectin and Sambucus Nigra Lectin as described in Section 4. The discussion and conclusions are presented in Sections 5 and 6, respectively.

2. Materials and methods

2.1. Sensor device nanofabrication

The sensor array consists of five SiN microring resonators coupled to a common bus waveguide, as shown in Fig. 1a. The width of the bus waveguide and the microrings is 500 nm to ensure single-mode operation. The outer radius of each microring is about 8 μm. Slight offsets in the radii of the microrings result in the spectral offsets of their resonance wavelengths. This offset prevents resonance overlap in the spectral domain to avoid crosstalk problem for multiplexed sensing. It should be noted that the addition of organic bio-receptor layers also shifts the resonances of these microring resonators, depending on the size of the bio-receptor molecule and its surface density. This fact should be taken into account if the resonances are to be designed equidistant in the spectrum.

The device thin film stack is fabricated by thermal oxidation of a standard eight-inch Si wafer to grow 4 μm thermal silicon dioxide (SiO_2) followed by the deposition of 240 nm stoichiometric SiN using LPCVD. Thermal oxidation and SiN deposition are performed by Rogue Valley Microsystems (Medford, OR, USA). The device pattern is written into ZEP520A electron-beam resist (Zeon Corp.) by a JEOL JBX-9300FS electron-beam lithography (EBL) system, and transferred into the SiN layer by inductively coupled plasma etching using CF_4 chemistry, leaving no SiN pedestal. Standard ZEP520A spin-coat protocol and a dosage of 220 μC/cm^2 is used for the EBL. We spin ESPACER 300Z (Showa Denko K.K.; Singapore) on baked ZEP520A to prevent excessive EBL charge-up. The resist is rinsed by de-ionized (DI) water for 1 min, developed for 2 min in amyl acetate, and then soaked for 30 s in isopropyl alcohol (IPA). The residual resist after etching is stripped using Microposit remover 1165 (Shipley).

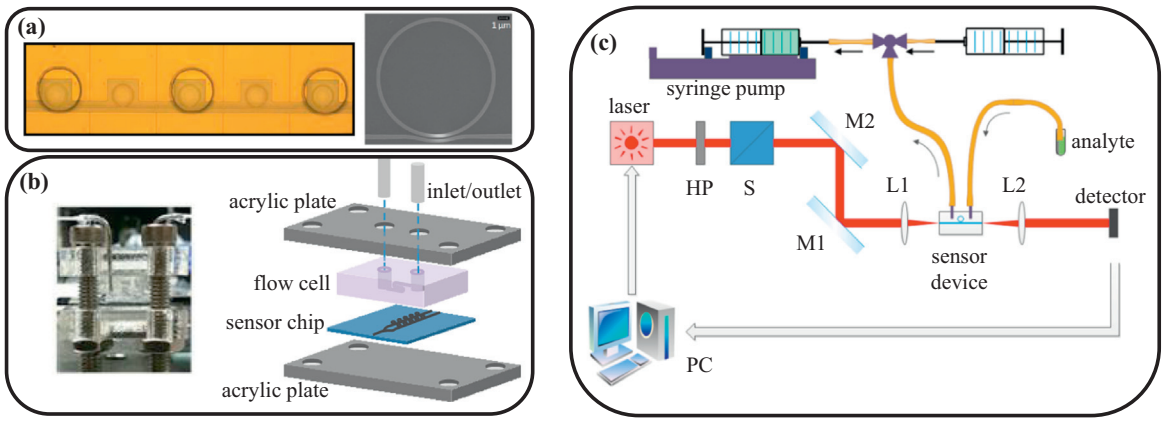

Fig. 1. The components of the sensing system. (a) An optical micrograph of the array of five SiN microrings (left), and a scanning electron micrograph of a SiN microring (right). The width of each microring is 500 nm to ensure single-mode operation, and its outer radius is about 8 μm. (b) The sensor chip, PDMS flow cell, and holder structure assembled together. (c) Laser light goes through a half-wave plate (HP), a polarizing beam splitter (S), two alignment mirrors (M1 and M2), and a long-working-distance lens (L1). Using a second long-working-distance lens (L2), the light leaving the chip is projected onto a photodetector, the data of which is sampled by a data acquisition card and processed by a personal computer (PC). A syringe pump in negative pressure mode draws the analyte solution into the PDMS flow cell and then into a waste syringe.

Please cite this article as: Ghasemi, F., et al., Biosensors and Bioelectronics (2016), http://dx.doi.org/10.1016/j.bios.2016.01.051