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Silicon Wire Waveguide Label-free Biosensor Arrays

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Abstract: We report multiplexed label-free measurements of biomolecular interactions using silicon wire waveguide sensor arrays. The sensors are addressed using both wavelength division multiplexing and power broadcasting approaches. We demonstrate the real-time monitoring of antibody-antigen reactions using complementary and mismatched IgG receptor-analyte pairs and bovine serum albumin. The measured level of detection for each sensor element corresponds to a surface coverage of less than ~ 0.02% of a protein monolayer. The two addressing approaches are compared.

OCIS codes: (130.6010) Integrated Optics: Sensors; (230.5750) Resonators; (130.3120) Integrated optics devices; (120.0120) Instrumentation, measurement, and metrology.

Quantitative monitoring of biomolecular interactions is important in a variety of applications including genetic identification through DNA hybridization, drug screening and pathogen detection through binding of drug compounds or antigen to antibody proteins. Due to the complex nature of most biological reactions, the ability to carry out multiplexed measurements is necessary for viable sensor technologies.

Silicon photonic wire evanescent field sensors have recently attracted much attention for label-free biosensing. These sensors are based on the interaction of the waveguide mode evanescent field with molecules adsorbed to the functionalized waveguide surface. In previous work we have developed sensor elements based on micro-ring resonators (MRR) and Mach-Zehnder interferometers (MZI) for high precision monitoring of phase changes induced by the biomolecular binding events [1, 2]. Due to the high refractive index contrast, the optical field in SOI photonic wire waveguides with submicron dimensions is strongly localized in the immediate proximity of the waveguide surface, particularly when operating in the TM polarization. This property results in a very high response to surface adsorptions [2]. These wire waveguides can also be bent with radii as small as 5 μm to form compact sensor arrays, taking full advantage of what integrated optics has to offer.

Here we report our investigation of sensor arrays using two methods to address the sensing elements. The first method uses wavelength division multiplexing (WDM) to address MRR sensors arranged in series and coupled to a common bus waveguide. The sensing signals are the resonance wavelength shifts of individual resonators measured at a common output. The second method uses power broadcasting to couple light of a fixed wavelength to an array of MZI sensors, and the sensing signal is measured as an intensity variation at the respective sensor outputs. We report on the design, fabrication and sensing measurements of these arrays, and compare the two addressing approaches.

To interrogate phase changes in a MRR or MZI device, either the associated wavelength shift in the transmission spectra or the intensity variations at a fixed wavelength may be used. Wavelength interrogation mitigates the influence of intensity drifts and places no limit on the sensing dynamic range. This method can be implemented using a tunable light source with accurate wavelength control and a photodetector at each output port. MRR sensors have sharp resonance features, and wavelength interrogation can differentiate minute phase changes. By placing several resonators of different radii in series and coupling to a common bus waveguide, several sensors can be measured using a single photodetector. For MZI sensors which have a sinusoidal output spectrum, wavelength interrogation offers little advantage. They are better suited for intensity interrogation, which only requires a light source with a fixed wavelength, and the input light can be directed to individual sensors using light splitting methods such as y-junctions, multimode interference couplers or star-couplers. To record the intensities at an array of outputs, an imaging camera is a suitable choice. Issues related to the intensity drift do need to be contented with.

An optical image of a fabricated MRR sensor array is shown in Fig. 1a. The resonators have a radius of ~ 20 μm , and the increment in the ring size allows the identification of the origin of measured resonances. The smallest resonator is covered with a thick SU8 cladding layer and optically isolated from the sensing medium. It serves as a reference for the cancellation of common mode signals arising from environmental variables such as temperature. The other four rings are exposed to the sensing medium through a window in the protective SU8

layer. For the MZI array shown in Fig. 1b, the reference and sensing interferometer arms are ~ 1.8 mm long spiral waveguides contained in a circular area of $130\text{ }\mu\text{m}$. The reference branch is protected by the same SU8 layer, and the two arms are optically balanced to reduce the temperature dependence. The input light is directed to six sensors using cascaded y-junction power splitters.

The waveguides are $450\text{ nm} \times 260\text{ nm}$ in dimension, patterned using e-beam lithography and etched in an inductively coupled plasma reactive ion etch instrument. The protective SU8 cladding layer is $2\text{ }\mu\text{m}$ thick. Microfluidics channels made in a $50\text{ }\mu\text{m}$ thick SU8 layer are monolithically integrated onto the chips, as indicated in Fig. 2, to facilitate sensing sample delivery. The MZI sensors are placed on a $400\text{ }\mu\text{m} \times 400\text{ }\mu\text{m}$ grid to accommodate the requirements for spotter functionalization and microfluidic sample delivery. Each sensor may be functionalized to attach a different type of receptor molecule. The samples are then silanized in 3-aminopropyltriethoxysilane (APTES) vapour. The sensor arrays were tested using binding reactions between complementary antibody-antigen pairs: goat and anti-goat IgG, and rabbit and anti-rabbit IgG. Using a non-contact robotic spotting tool, the same goat-IgG receptor molecules were deposited on all the sensors in the MRR array, while the sensor elements in the MZI array were individually functionalized. Goat IgG was deposited on sensors 1 and 2 (S1 and S2 in Fig. 1b), rabbit IgG was deposited on sensors 3 and 4, and bovine serum albumin (BSA) blocking was deposited on sensors 5 and 6 to act as a control.

Fig. 1. Optical images of fabricated sensor arrays. (a) MRR array consisting of 1 reference ring and 4 sensing rings in series coupled to a common bus waveguide; (b) MZI array consisting of 6 sensors in parallel, each having a separate output port.

Solutions of anti-rabbit and anti-goat IgG (200 nM) were delivered sequentially, with a phosphate buffered saline (PBS) rinsing step between different analyte solutions. Transmission spectrum of the MRR sensor array prior to fluid exposure is shown in Fig. 2a. The labels in the figure indicate the individual resonators that the resonances originate from. When the analyte solution was delivered to the sensing surface, the sensing ring resonance shifted as the molecules adsorbed to the surface (Fig. 2b). The reference ring only showed minimal shifts which follow the temperature drift experienced by the sensors during the course of the measurement.

Fig. 2. (a) Measured transmission spectrum for the MRR array. The sensing rings are exposed to air in this measurement; (b) Measured spectra for the reference ring and a sensing ring during the sensing experiment shown in Fig. 3a.

The wavelength shift of the MRR array during the sensing experiment is shown in Fig. 3a. With goat IgG receptor on the surface, exposure to anti-rabbit IgG induced a small shift of 0.28 nm . We attribute this response to nonspecific binding of anti-rabbit IgG to the silanized sensor surface, which should be reduced by implementing a blocking step prior to testing. When immersed in the complimentary anti-goat IgG solution, a larger shift of 0.99 nm was observed. The sensing response is uniform for all four elements, with a standard

deviation of 0.01 nm. The reference ring resonance shifted ~ 25 pm during the course of this 2 hour long experiment, as a result of the temperature drift of 0.36°C as recorded on the sample stage [3]. Fig. 3b shows the measured cumulative phase shift induced in the MZI array [4]. The response of sensors 1 and 2, also deposited with goat-IgG, showed similar trend in the response as the ring sensors. For sensors 3 and 4 which have rabbit-IgG on the surface, a strong binding (4.4π) to the anti-rabbit IgG was observed, while exposure to the anti-goat-IgG induced a much smaller shift of 0.06π . The control sensors 5 and 6 were printed with the BSA, which is a commonly used blocking agent that should not bind to either molecule. The BSA effectively blocked these control sensors, giving a cumulative phase response of less than 0.2π during each anti-IgG step.

Fig. 3. (a) Wavelength shift of the MRR sensors when exposed to the mismatched anti-rabbit and complimentary anti-goat IgG solutions. (b) Phase change in the MZI sensors during the sensing experiment, obtained from the intensity variations. Sensors 1 and 2 were printed with goat IgG, sensors 3 and 4 were printed with rabbit IgG, and sensors 5 and 6 were printed with BSA using a microarray spotter. For clarity the sensor response curves have been offset in the plots.

Considering the RMS noise level in Fig. 3 as the minimum detectable response, and assuming the saturated signal of complimentary IgG binding corresponds to a coverage of one monolayer, we estimate that the sensors can resolve adsorptions $\sim 0.02\%$ of a monolayer. This is equivalent to a surface mass density of 0.25 pg/mm^2 . The demonstrated high sensitivity and small footprint are important advantages over the conventional and commercially established surface plasmon resonance techniques.

We have described two types of evanescent field biosensor arrays based on Si photonic wire MRR and MZIs, with the sensing elements addressed using WDM and power broadcasting approaches, respectively. When deposited with the same receptor molecules, the MRR array displayed uniform response between the sensors. When the sensors are deposited with different receptors, multiplexed preferential binding to the respective complimentary targets are demonstrated in the MZI array. WDM addressing of MRR sensors is suitable for low channel count arrays, with the advantage of requiring only a single photodetector. Power broadcasting is simple to implement optically and can easily address several tens or potentially hundreds of sensors, but it requires a more complex data acquisition system utilizing photodetector arrays. When either the output power level or the availability of the photodetector array size becomes a limitation for the simple broadcasting approach, these two addressing methods may be combined to further increase the sensor array channel count.

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