Photonic lab-on-a-chip nanobiosensors for early diagnostics at the point-of-care

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Portable point-of care (POC) devices for *in-vitro* diagnostics will be a milestone for the achievement of universal healthcare and environmental protection. Motivated by potential benefits such as sensor miniaturisation, multiplexing capabilities and relevant sensitivities in a label-free scheme, Silicon photonics based-biosensors are the most suitable candidates to achieve such ambitious POC devices [1]. These photonic biosensors consist of compact waveguides contained on chips which can be easily miniaturized and fabricated in arrays of identical sensors for multiplexed analysis.

Several years ago we introduced in this area an innovative photonic sensor design based on a bimodal waveguide (BiMW) interferometer [1], a single channel Si_3N_4 waveguide which mechanism is based on the interference of two waveguide modes of the same polarization, operating at visible wavelengths with monochromatic and polarized (TE or TM) light. Light is first coupled into a rib waveguide supporting a single transversal mode. After some distance, this mode is coupled into a thicker waveguide which contains the sensing window and supports two transversal modes. As the fundamental and the first order modes have different evanescent field profiles at the core-cladding interface, the interference pattern is a function of the refractive index in the sensing area. The final layout design included dozens of chip-integrated waveguides into a single wafer substrate using silicon technology ($Si/SiO_2/Si_3N_4/SiO_2$). The single mode waveguide has a thickness of 150 nm of Si_3N_4 (n=2.00) and the bimodal part is 350 nm thick, while the width of the waveguide is of 3 µm. The rib height is below 3 nm. The simplicity of our BiMW design is quite attractive while its sensitivity of around $1x10^{-7}$ RIU in bulk [1] is comparable to more complex interferometric schemes.

We have been working in the full integration of the BiMW technology in a photonic POC platform. For the achievement of the complete platform, several units need to be incorporated, including the BiMW sensors, the microfluidics and the flow delivery system, the multiplexed in and out-coupling of the light and the light read-out. Moreover, a specific and custom-designed biofunctionalization protocol must be developed for each sensor depending of the targeted application. Even if all these individual components are

well known, the subsystem interfaces between them are difficult to optimize and these are still the major barriers to be overcome.

One of the main drawbacks of BiMW sensors is the complex interferometric nature of the output signal which require a modulation system to translate the standard interferometric signal into an unambiguous linear phase response. In order to improve the integration and cost of the final device, we have introduced a new all-optical wavelength modulation system where the emission wavelength of a low-cost commercial laser diode was modulated ±2 nm by controlling its output power. After a Fast Fourier Transform deconvolution, the linear response of the BiMW sensor is obtained [2].

For microfluidics integration, one major constrain is the minimum separation between waveguides (only few hundred of microns). For the fabrication of the microfluidics channels we employ several routes, including polydimethylsiloxane (PDMS) channels fabricated by soft lithography or SU-8 microfluidics delivery channels fabricated at wafer level by standard lithography. We recently have proposed the integration of a fully automated and active PDMS optofluidic system with the BiMW technology [3].

One main challenge for the BiMW POC sensing technology is the demonstration of its utility in the clinical practise being able to handle and directly analyse minimum amounts of body fluids without previous labeling, detecting biomarkers in their natural form. After the development of the appropriate biofunctionalization protocols [4], we have demonstrated the suitability of our BiMW nanophotonic platform for the real clinical diagnostics, as for example: (i) quantitative detection of *Escherichia coli* in undiluted human ascitic fluid from cirrhotic patients at very low concentration (40 cfu·mL^{-1}) [5] (ii) detection of specific tumor-related autoantibodies in serum, which indicates the onset of a colorectal cancer in its preliminary stage (iii) detection and quantification of miR-181a at attomolar concentrations (LOD = 23 aM) directly, and for the first time, in human urine samples of bladder cancer patients with no need for prior sample purification or amplification steps [6]. In all cases, the BiMW nanosensor has shown excellent robustness with high reproducibility and sensitivity, rendering in a valuable tool for fast diagnostics of bodily fluids samples.

References

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