Towards a complete Lab-On-Chip system using integrated Mach-Zehnder interferometers

Hacia un sistema completo Lab-on-Chip basado en interferómetros de Mach-Zehnder integrados

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ABSTRACT:

This article deals with our last steps towards the implementation of a Lab-On-Chip (LOC) platform which could be used as a portable testing device for diagnostics. As sensing elements we employ integrated Mach-Zehnder Interferometers (MZI) realized with Si/SiO₂/Si₃N₄ waveguides of micro/nano dimensions, based on Total Internal Reflection (TIR) propagation. MZI sensors, that have already shown their high sensitivity for biosensing applications, are currently being implemented in a multiplexed configuration. We present here the first results of the design and simulation of a multiplexed MZI platform with 4 channels for the simultaneous detection of different analytes. Moreover, we describe a novel phase modulation technique which solves some of the problems inherent to standard MZI sensor. This modulation technique does not require additional fabrication process and will directly provide a linear phase response. Concerning the light coupling into the waveguides, it is achieved by the use of diffraction grating couplers, favoring the passage from bulky laboratory equipment to delocalized applications. We also describe an optimized process for surface biofunctionalization to bind the bioreceptors for target recognition and its validation with an immunoassay.

Key words: Photonic Biosensor, Mach-Zehnder Interferometer, Lab-On-Chip, Microfluidics, Grating Coupler, Phase Modulation, Biofunctionalization.

RESUMEN:

En este trabajo presentamos los progresos realizados en el desarrollo de una plataforma Lab-on-Chip (LOC) para ser utilizada como dispositivo de diagnóstico portátil. Como elemento transductor utilizamos interferómetros Mach-Zehnder (MZI), fabricados con guías ópticas de dimensiones micro/nanométricas en Si/SiO₂/Si₃N₄ y basados en propagación por reflexión interna total. Estos transductores interferométricos han demostrado una alta sensibilidad para aplicaciones biosensoras y están dispuestos en una configuración multiplexada. En este trabajo presentamos los primeros resultados del diseño y de la simulación de una plataforma multiplexada en la que se han diseñado cuatro canales para la detección simultánea de diferentes analitos. Además, presentamos un nuevo sistema de modulación de fase para solucionar algunos de los problemas característicos de la señal interferométrica del MZI. La implementación de esta técnica óptica de modulación permite obtener directamente una señal lineal sin necesidad de incluir más pasos de fabricación. El acoplamiento de la luz en las guías de onda se lleva a cabo mediante redes de difracción que proporcionan al dispositivo un nivel mayor de integración y lo acercan al objetivo final de pasar de los costosos análisis de laboratorio a un análisis rápido, de bajo coste y portátil. Presentamos también un protocolo optimizado de biofuncionalización, empleado para inmovilizar los elementos bioreceptores específicos al analito de interés y su validación mediante un inmunoensayo.

Palabras clave: Biosensor Fotónico, Interferómetro Mach-Zehnder, Lab-on-Chip, Microfluídica, Redes de Difracción, Modulación de Fase, Biofuncionalización.

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1. Introduction

Nowadays, most clinical tests are time-consuming, expensive and have to be performed by specialized technicians in laboratory environments. These sophisticated techniques typically require labeling of the samples or reagents with fluorescent or radioactive tags. Therefore, there is an unmet need of having reliable diagnostic tools that ensure a sensitive, rapid, affordable and simple analysis, particularly in the clinical practice. These new methods could enable the decentralization of clinical diagnostics to point-of-care settings, allowing tests in primary care facilities and outpatient clinics, in hospital units, workplaces and homes, among others.

The last decade has seen an increasing number of works devoted to the realization of an integrated system trying to fulfill these requirements [1,2]. The advantages offered by micro/nano systems rely in fact on the potential offered by nanoscale approach, leading to smaller, faster and cheaper devices [3]. Reactions can take place in reduced volume chambers, meaning a lower consumption of reagents and shorter analysis time. Furthermore silicon technology, matured mainly in the microelectronics field, can be adopted and adapted to the field of biosensing and life science applications. The basic idea of an integrated system is to gather in the same platform all the different operations necessary to perform an assay: from sample preparation (filtration, homogenization) to sensing and data processing. Even if the technology for each component fabrication is mature, their integration is still a compelling challenge and must be carefully designed since it is not merely the sum of the basic units. Some examples involving the integration of optics, microfluidics, detection and signal processing units can be found in references [4] and [5].

Integrated optical biosensors and, in particular, those based on evanescent field sensing, are very attractive for integration purposes, especially because they allow for compactness, sensitive, real-time and label-free on-site measurements [6-8]. In this field, many research activities focus on Mach-Zehnder Interferometer (MZI) [9-13] which combines the

possibility of developing biosensor microarrays with very high sensitivity.

Our main aim is to develop a highly sensitive platform based on integrated MZI for the real-time detection of substances at the pico/femtomolar level without using fluorescent labels. Such system is fabricated with low-cost technologies of polymer and silicon, through Complementary Metal Oxide Semiconductor (CMOS) compatible processes, meeting the requirements of disposability and portability. Fig. 1 shows a schematic view of our envisioned Lab-On-Chip (LOC). The biosensor microsystem would be assembled by integrating the following parts: i) the MZI sensors in a multiplexed configuration, ii) the flow cells and the flow delivery system (microfluidics), iii) a phase modulation system to convert the periodic interferometric signals into direct phase measurements, iv) the surface functionalization, immobilization and regeneration protocols for the receptor, v) the light sources and photodetectors, and vi) the processing electronics and final packaging.

In the following, we will deal with the sensor working principle, its optical characterization, the implementation of a multiplexed structure, a phase modulation system, the light in-coupling through grating couplers and a optimized protocol for surface biofunctionalization.

Fig. 1. Scheme of our envisioned Lab-On-Chip platform.

2. Mach-Zehnder interferometer sensor

2.a. Sensor working principle

In the standard MZI configuration (Fig. 2), a monochromatic and polarized light ($\lambda=633$ nm)

is split by a Y-junction into two arms, the sensing and the reference arms. After a certain distance, the two signals are recombined in a single arm, producing the interference of both beams. In the sensor area, the evanescent field of the guided light can interact with the environment. For instance a biological reaction occurring in the sensing area will induce a phase change of the propagating field that will result in an intensity variation of the interference pattern at the sensor output.

The high sensitivity of the analysis is guaranteed by the design of photonic structures in which the interaction of the evanescent wave with the external medium is maximized. According to our numerical simulations, this goal can be achieved by using Si_3N_4 core layers with thickness of 150 nm and 75 nm, respectively, for Transverse Magnetic (TM) and Transverse Electric (TE) polarizations over a 2 μm thick SiO_2 cladding on a silicon wafer. To provide single mode behavior, a rib structure of several nanometers height (below 3 nm) and rib width from 2 to 4 μm must be fabricated. More details on the theoretical modelization and sensor optimization can be found in references [11] and [14]. The MZI chip has a total length of 3.5 cm with a sensor area of 1.5 cm and a width of 1 cm. Each chip contains 9 MZI devices and 24 waveguides for test purposes.

Fig. 2. Scheme of a standard MZI. Input signal is split into sensing and reference arms that interfere in a single output waveguide.

2.b. Sensor characterization

The sensitivity of the device is experimentally evaluated by flowing different concentrations of HCl with Milli Q-grade water as a reference

buffer and measuring the phase shift induced by the change HCl- H_2O . Fluids are supplied onto the MZI sensing areas by means of a fluidic cell and a peristaltic pump, ensuring a constant flow. Prior to injection, the refractive index of the HCl solutions is measured with an Abbe refractometer. Figure 3 shows a typical calibration curve $\Delta\phi$ versus Δn , for TM polarization. Insets represent the MZI output signal change corresponding to the change HCl- H_2O .

The slope of the curve $\partial\phi/\partial n$ gives the sensitivity of the device that depends on the geometry and combination of materials. In the case showed in Fig. 3 the sensitivity corresponds to 2433 (2π) rad/RIU. The smallest measurable phase shift is considered to be three times the noise-to-signal ratio of the system, in this case $1.44 \times 10^{-4} (2\pi)$ rad. By considering this value and the slope of the experimental calibration curve, the theoretical detection limit can be estimated as 1.8×10^{-7} RIU.

2.c. Multiplexing implementation

The key element of our new microsystem is the realization of a multiplexed MZI, allowing the simultaneous detection of several analytes. In an array configuration, the sensing area of any interferometer can be specifically tailored to be responsive to a particular target. As a result, the complete platform would be receptive to a spread range of analytes allowing a fast multi-screening analysis.

Figure 4(a) shows a possible approach for the implementation of a multiplexed platform. A single laser beam excites the propagation in an arbitrary number of parallel interferometers (in the example, five).

First step of our research has been the realization of double interferometers: a single input waveguide excites two parallel sensors. Calculations and modeling studies with Photon Design software have been done for optimizing the new structures. For instance, Fig. 4(b) shows the simulated field evolution along an optimized multiplexed MZI with four channels: a first Y-junction separates the waveguide into two arms, each of which leading to a second Y-junction that constitute the input waveguide for the two separate interferometers. The aperture angles of

Fig. 3. Calibration curve of the MZI sensor, in case of TM polarization and a Si_3N_4 core of 250 nm. Insets show specific detection of: (A) HCl 0.0125M, giving a $\Delta\phi = 0.24 \times 2\pi$ rad, (B) HCl 0.025M, giving a $\Delta\phi = 0.6 \times 2\pi$ rad, (C) HCl 0.05M, giving a $\Delta\phi = 1.16 \times 2\pi$ rad and (D) HCl 0.1M, giving a $\Delta\phi = 2.15 \times 2\pi$ rad.

Fig. 4. Multiplexing approach. (A) Final objective: an application-driven number of interferometers can be excited from a single input beam, by means of a grating coupler. (B) Simulated field propagation along a multiplexed MZI (4 channels) at $\lambda=633$ nm, for TM polarization. The Si_3N_4 core layer has a thickness of 200 nm, the rib width is 3 μm and the rib height 2 nm.

the three Y-junctions are equal in order to split uniformly the power into the four arms. Previous studies showed minimum losses of 0.2 dB for an angle of $1^\circ 40'$, but this value can be increased till approximately 6° in order to allow multiplexing without increasing the device total length.

These new structures with a single input exciting two interferometers have been recently fabricated at our clean room facilities and are currently under optical characterization. Further studies will increase the level of multiplexing to satisfy market requirements.

3. Wavelength modulation system

MZI biosensors could give false positive reading due to some problems related to the periodic nature of the output signal. There are mainly three issues: (i) signal ambiguities, (ii) intensity variations and (iii) sensitivity fading. These disadvantages can be solved by tuning the phase difference between the arms of the interferometer by using a phase modulation system [10]. A simple way to modulate the phase difference φ between the two beams (reference and sensor arms) of a MZI is to modulate the wavelength of the guided light [15]. Indeed, φ depends of the wavelength λ :

$$\varphi = \frac{2\pi}{\lambda} L(n_{sens} - n_{ref}), \quad (1)$$

where L is the length of the sensor area, n_{sens} and n_{ref} are the effective refractive indices of the sensor and reference arm, respectively. If the variation in wavelength can induce a shift of 2π radians in the output signal, we could be at any time in the optimum measurement conditions. With our system (15 mm for the length of the sensor area and 3% difference in effective refractive indexes), a wavelength variation lower than 2 nm will be sufficient. To obtain such variation, we can take advantage of a well-known semiconductor laser drawback: the wavelength modification due to optical power variation [16]. With the commercial laser diode we use, the ML101J27 (Thorlabs), a wavelength modulation of 2 nm can be achieved by varying the driving current of about 40 mA. The power variation of the laser can be constantly monitored thanks to the extraction of a reference signal.

For the signal analysis, in the case of a periodic wavelength variation, the phase difference induced by the bio-reaction can be directly and unambiguously determined by Fourier analysis of the output signal. Figure 5(A) shows the output of a phase modulated MZI together with the reference signal employed for power normalization while Fig 5(B) shows the Fast Fourier Transform (FFT) evaluated on their normalized ratio.

After FFT evaluation, the phase information can be directly extracted from the inverse

tangent of the ratio between the third and second harmonics [15]:

$$\Delta\varphi = \arctan\left(\frac{I_{3\omega}}{I_{2\omega}}\right), \quad (2)$$

In this configuration the phase change induced by a biological detection is directly obtained and no more deduced from the intensity interference pattern, solving the problems related to the periodic nature of the MZI output signal.

Compared to modulation techniques employing active optical materials, this new modulation scheme presents clear advantages, as no need for additional data processing and no electrical contacts are required, making it fully compatible with the microfluidics and more suitable for real-time biosensing applications.

4. Diffraction grating couplers

In order to realize a compact, stable and user-friendly LOC platform, the light in-coupling within the sensor chip must be efficiently solved. Coupling efficiency influences the device sensitivity through the signal-to-noise ratio [17]. Even if the well-known end-fire method has shown its utility in laboratory optical bench, it has important limitations for making portable devices as the requirement of bulky equipments and the risk of alignment deviations. Diffraction gratings couplers could be an excellent alternative in terms of suitability for integration and time stability.

Due to the dimensions of the interferometers and to the operating wavelength ($\lambda=633$ nm), the diffractive grating length cannot exceed 100 μm with a sub-micronic period. Figure 6(A) shows the coupling into a 30 μm wide waveguide through a grating coupler. The transition from 30 μm width to 4 μm width waveguide is achieved by linear tapers. Figure 6(B) is a higher magnification optical image of the MZI chip surface with the grating (highlighted figure) and the underlying taper. In Fig. 6(C) a Scanning Electron Microscope (SEM) image of a fabricated grating with a period of 400 nm, a duty cycle of 0.5 and a depth of 40 nm is observed. The grating has been directly written onto the Si_3N_4 waveguide by electron-beam lithography.

Fig. 5. Labview plots of: (A) acquired signals: MZI output, reference and the normalized signal, obtained from their ratio and (B) FFT spectrum showing the first three harmonics of normalized signal.

Fig. 6. (A) Light in-coupling using a grating coupler into a rib waveguide ($\lambda = 633$ nm). (B) Optical image of a grating coupler, with length $L=100$ μm and width $w=30$ μm . (C) SEM image of the grating: period 400 nm, duty cycle 0.5 and etch depth 40 nm.

The optical characterization of the grating couplers was carried out by measuring the efficiency of the coupling as a function of the incident angle. Efficiency has been evaluated as *output power/input power*·100. Figure 7 shows the results of the coupling efficiency in the case of a grating ($L=100$ μm , $w=30$ μm) written onto a rib waveguide, for both TE and TM polarizations. An efficiency of 7.1 % has been achieved in the case of TE polarization, at an angle of $9^{\circ}30'$ that is suitable for the implementation of a compact LOC platform. We are currently working on the realization of gratings onto integrated MZI. With these measurements it will be possible to determine the minimum intensity required to measure a single MZI excited via grating coupler and, as a consequence, the number of multiplexed MZI that could be excited with a single grating.

However, even though the direct writing of the grating by electron-beam is an efficient technique, the compatibility and complexity of

Fig. 7. Scheme of a standard MZI. Input signal is split into sensing and reference arms that interfere in a single output waveguide.

technologies for batch fabrication of the grating and the waveguide on the same wafer is challenging. In order to solve this problem, we are also working on a novel approach where grating couplers are fabricated separately and then attached to the interferometers [17]. Such structures are called "mountable gratings".

Simulations are being performed to determine the optimum grating parameters but also to estimate the tolerance in fabrication to keep a good grating efficiency. The grating structure is made by electron-beam lithography on a Si_3N_4 layer and then covered by a polydimethylsiloxane (PDMS) film. The gratings are optically characterized as a single element and then stuck with the PDMS film to the photonic structures.

5. Surface functionalization

When developing a LOC system for biosensing applications, sensitivity, selectivity and stability of the bioreceptor are fundamental aspects to be dealt with. Different immobilization strategies can be adopted, according to the particular application, i.e. the nature of the receptor to be immobilized. Covalent binding has demonstrated to be a valid strategy [8], ensuring stable union and applicability to a spread family of biomolecules. For instance, in the case of proteomics applications, the immobilization of the specific receptor onto the sensing area of the

MZI can be performed via amino group of the protein.

Prior to the biofunctionalization step a chemical activation of the surface is mandatory [18]. In our case, the transducer surface is made out of silicon nitride and can be functionalized with the well-known silane chemistry. The silicon nitride surface is initially treated with ozone plasma and then oxidised with a solution of HNO_3 at 10%. Carboxyethylsilanetriol, sodium salt (CTES) is employed as silane agent and the ended carboxylic groups of the silane are afterwards activated through the N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC)/ N-Hydroxysuccinimide (NHS) chemistry [19,20]. The receptor protein is afterwards immobilized by covalent bonding on the sensing area. A schematic view of the surface treatment can be found in Fig. 8.

Contact angle and Atomic Force Microscopy (AFM) techniques have been used for verification of each step of the chemical activation process. Figure 9 shows AFM topography images of the surface after oxidation and CTES exposure.

Fig. 8. Schematic overview of the silicon nitride biofunctionalization. From left to right: nitride surface before treatment, oxidation, silanization, carboxylic group activation and protein immobilization via ammine bond.

Fig. 9. AFM 3D topography images of silicon nitride surface at different levels of functionalization: (A) after oxidation and (B) after 2% CTES incubation.

Fig. 10. Real time monitoring of the sensor response induced by the detection of 0.25 $\mu\text{g/ml}$ mAb-hGH (upper line), giving a phase change $\Delta\varphi=0.5\times 2\pi$ and the detection of 0.25 $\mu\text{g/ml}$ mAb-BSA (lower line), giving $\Delta\varphi=0$.

Biosensing evaluation has been demonstrated by the immunoreaction of the pair hGH/anti-hGH (human Growth Hormone), performed on a single MZI measured in standard conditions (no phase modulation and end-fire coupling). hGH has been immobilized on the sensor surface and its specific antibody has been recognized. Fig. 10 shows the phase change induced by the detection of a specific monoclonal antibody (mAb-hGH), in a concentration of 0.25 $\mu\text{g/ml}$. A monoclonal antibody against a different protein (Bovine Serum Albumin, BSA) has been used as control to check the specificity of the sensor (mAb-BSA).

6. Additional components

To bring the sample in contact with the sensing area, fluidic microchannels have to be integrated with the MZI biosensors. The channels have been designed to be 50 μm in height and 100 μm in width and made by PDMS or/and SU-8 [21]. For connection to the macro world, an acrylic housing is employed.

The final prototype will incorporate all of the individual components, plus the commercial lasers, photodetectors, control electronics and software, sensor readout algorithms, user

interface etc. Instrument control and user interface will be accomplished through discrete electronics rather than a dedicated application-specific integrated circuit (ASIC) chip in order to preserve total flexibility while minimizing time and costs.

7. Conclusions

We are working on the realization of a sensitive, affordable, hand-held and portable device for clinical diagnosis of relevant analytes. The lab-on-chip device includes ultrasensitive MZI biosensors based on integrated optical waveguides ($\text{Si}/\text{SiO}_2/\text{Si}_3\text{N}_4$) which have already shown their ability to detect small variations of the refractive index in the sensor area ($\Delta n_{0,\text{min}}=1.8\times 10^{-7}$) and suitability for biosensing applications. Moreover, the realization of multiplexed MZI will allow the simultaneous detection of several analytes, reducing time and cost of analysis. A wavelength modulation system is also being implemented in order to solve some of the problems due to the periodic nature of MZI signal and simplifying data readout. Regarding the implementation of a portable device, light in and out-coupling into the waveguides will be achieved by the use of diffraction gratings couplers. A versatile silanization method for optimal surface bio-functionalization has been optimized for the detection of specific biomolecular interactions.

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