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A compact multichannel spectrometer for label-free monitoring of biochips for point-of-care testing

Fabian Dortu^{1*}, Hendrik Von Horsten¹, Damien Bernier¹, Maxime Denti¹, Ana.L Hernandez², Rafael Casquel², Miguel Holgado², Theo Veenstra³, Paula Ciaurriz⁴, Edurne Tellechea⁴, Fátima Fernández⁴, Iñaki Cornago⁴, MaríaV. Maigler⁵, Jean-Pierre Vilcot⁶, Sophie Maricot⁶, Juriy Hastanin⁷, Cédric Lenaerts⁷, Aline Roobroek⁸, Sylvain Deprez⁸, Yves Hernandez¹

¹Multitel, Parc Initialis 2, Rue Pierre et Marie Curie, 7000 Mons, Belgique.

²Centre for Biomedical Technology, Optics, Photonics and Biophotonics Laboratory, Campus Montegancedo, Universidad Politécnica de Madrid, 28223 Madrid, Spain.

³LioniX International BV, Hengelosestraat 500, 7521AN Enschede, The Netherlands.

⁴Naitec, Polígono Mocholí, Plaza Cein, 4, 31110, Noain (Spain).

⁵Bio Optical Detection. Centro de empresas de la Universidad Politécnica de Madrid. Pozuelo de Alarcón, 28223 Madrid Spain.

⁶Institut d'Electronique, de Microélectronique et de Nanotechnologie (IEMN), UMR CNRS 8520, Université des Sciences et Technologies de Lille 1, Avenue Poincaré, BP 60069, 59652 Villeneuve d'Ascq, France.

⁷Centre Spatial de Liège, Avenue du Pré Aily, 4031 Liège, Belgium.

⁸Materia Nova, 1 Avenue Nicolas Copernic, Mons Belgium.

*Correspondence: dortu@multitel.be; Phone number (+32 65 34 28 77).

ABSTRACT

We present three optical multi-channels spectrometers for the interrogation of label-free biosensors based on different kinds of transducers : resonant nanopillars (RNP), microring resonators (MRR), localized and propagative surface plasmon resonance (LSPR and SPR). Light is collected from the multi-channel biosensors (up to 12-channels) with optical fibers and is remapped to a packed straight line forming the input slit of the spectrometers. The combination of high resolution CMOS sensors and embedded signal processing makes it possible to extract the resonant wavelengths of the transducers with a precision in the range of 1-20 pm depending on the type of transducer. The performance of the three transducer / spectrometer systems has been evaluated in the framework of EU and regional projects for the monitoring of chemical pollutants found in oceanic waters (FP7 - EnviGuard), crop health monitoring (Interreg France-Wallonie-Vlaanderen - SmartBioControl/BioSens) and bioreactor monitoring (EutoTransBio - APTACHIP).

1 INTRODUCTION

Point-of-care and in-field testing (POCT) is demanded by many application sectors, from medical diagnostics to environment and production monitoring. Many of these tests are based on immunologic binding of an analyte to a biochemical probe which is pre-immobilized on the transducer surface of a biochip. It makes it possible to detect and even quantify chemical and biochemical compounds like virus, bacteria and biomarkers in fluid samples. In general, multiplexing is a highly demanded feature as it allows making replicas of the sample under test, to reference the sample with an analyte non-specific transducer, and even tests different analytes on the same chip.

Many biochip technologies have been developed in the field of label-free sensing, which require spectral interrogation in order to take full advantage of the transducer response. This kind of transducers includes propagative and localized surface plasmon resonance (SPR and LSPR), photonic crystals, resonant nanopillars (R-NPs), and microring resonators (MRR). In consequence multiplexed spectrometers with suitable resolution and acquisition/processing speed is needed, while, at the same time, remaining compact and low cost (a few 1000 €).

In this work, we present a 12-channels optical spectrometer customizable throughout the visible and near infrared range to suit the interrogation of label-free biosensors of various types. Our spectrometer system has been customized and evaluated for four transducers types: R-NPs, MRR, SPR and LSPR. Signal processing has been implemented on an

embedded computer to perform all the acquisitions and calculations needed: spectra acquisition, resonant peaks or dips extraction and processing of sensograms for automatic assay analysis.

The spectrometer has been evaluated on resonant nanopillars biochips. A precision (standard deviation) on the resonance monitoring of $\sigma = 2.3 \text{ pm}$ was demonstrated leading to a limit of detection of $\sim 3 \times 10^{-6} \text{ RIU}$. This performance is suitable for monitoring the bioassay as a function of time in order to obtain high signal-to-noise ratio 12-plex sensograms. We also report the measurement precision of propagative SPR ($\sigma < 15 \text{ picometers}$) and microring resonators ($\sigma < 1.5 \text{ picometers}$) to be used respectively for crop health and bioreactor monitoring.

We further investigated the impact of the spectral shape of the resonance on the resolution and precision of the central resonant wavelength extraction. This allows us to estimate σ the best precision of the spectrometer which can be obtained independently from environmental fluctuations impacting the transducers.

2 METHOD

The interrogation system for the monitoring of the resonant transducers consists of a broadband light source coupled to a fibre or fibre bundle (Figure 1.A), an optical probe in close proximity (or contact) to the transducer for illumination and collection of light (Figure 1.C), and the spectrometer itself (Figure 1.B).

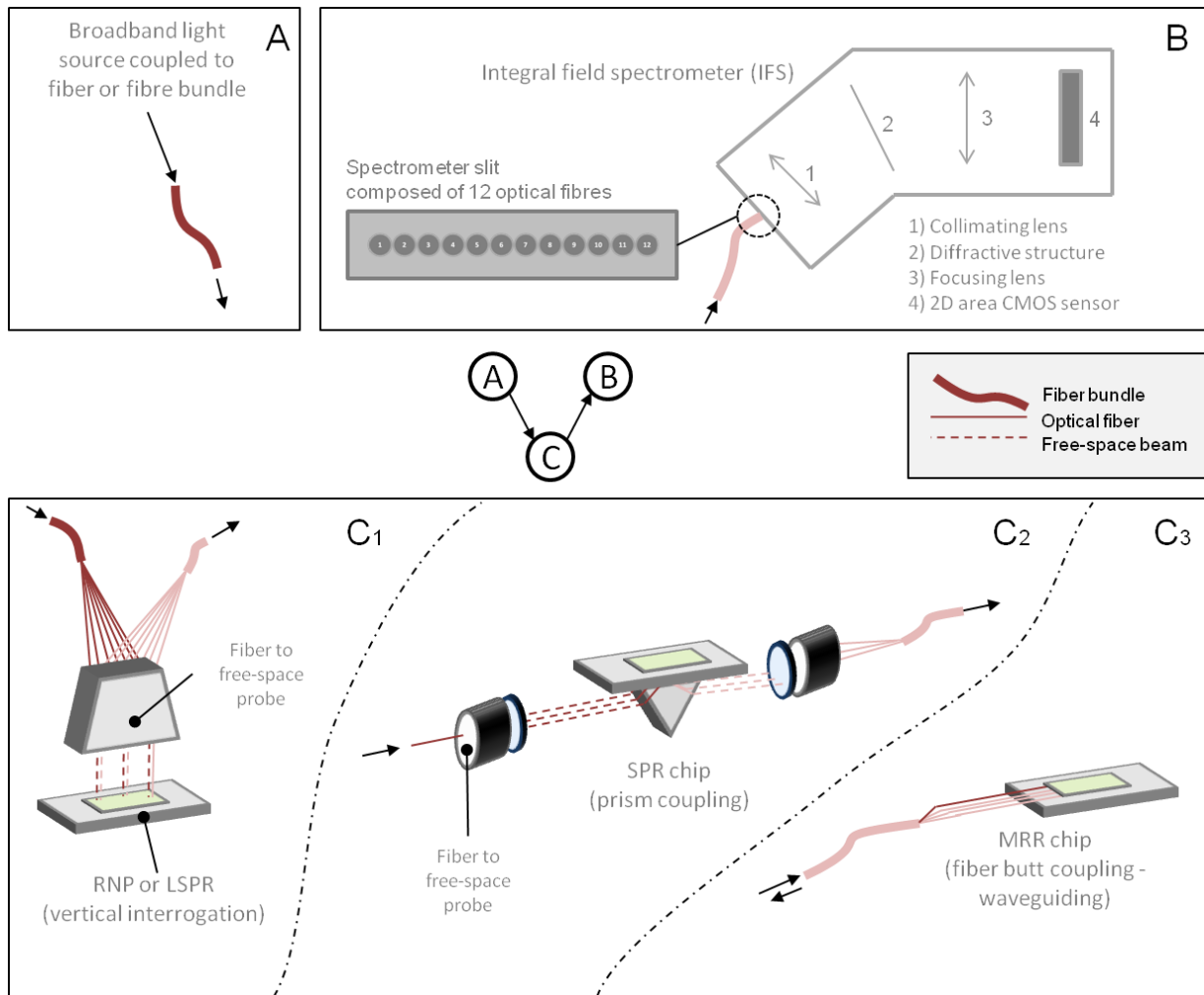


Figure 1 : schematics of the biosensing systems. A. Broadband light source. B. Integral field spectrometer. C₁₋₃. Transducers evaluated in this work including resonant nanopillars (RNP), localized and propagative surface plasmon resonance (L-SPR) and microring resonators (MRR).

The broad band light source (Figure 1.A) is chosen to have a spectral width adapted to each sensor (20 nm for MRR and > 150 nm for others). The optical probe needs to be adapted to the transducer type, i.e. reflection (vertical) interrogation for the R-NP and LSPR, prism coupling for SPR and direct pigtailed in butt coupling for MRR.

The spectrometer has a common design independently from the type of transducer, but the grating period/angle and the CMOS camera sensor pixel resolution and size has to be customized for the required bandwidth and resolution. We have build three spectrometers which each fits the sensor's need (Table 1). The input of the spectrometer is a 12-fibers optical fiber bundle arranged in a packed straight line, with a core diameter adapted to the resolution need. Light originating from the fibers passes through a diffraction grating and is imaged on a CMOS sensor array. The two-dimensional image is processed by an embedded computer-on-chip module to extract high quality spectra with a resolution suitable for the interrogation of each considered transducer (5 to 150 picometers). The central resonant wavelength (spectral dip) of the transducer can further be extracted with non-linear optimization with a 1 to 10 picometers precision (standard deviation of a stable measurement), depending on the transducer type.

Table 1 : Transducer and spectrometer characteristics

Sensor type	Number of transducers	Full width half maximum (FWHM) of the resonance	Spectrometer range (nm)	Spectrometer pixel limited resolution (nm)	Standard deviation σ of the resonant dip position (nm)
(L)SPR	4	100 nm	650 - 965	0.150	< 0.020
R-NPs	12	20 nm	525 - 635	0.068	< 0.003
MRR	8	0.03 nm	840.3 - 858.7	0.005	< 0.001

3 RESULTS

The spectrometer for interrogating the R-NPs was integrated into a complete system with sample filtration and microfluidic fluid delivery within the European Project Enviguard (FP7-OCEAN-2013-614057 with the aim of demonstrating an optical nano-biosensing system for the in-situ detection of three chemical pollutants, PCB, okadaic acid and saxitoxin) in oceanic waters. A standard deviation in the resonance dip position of $\sigma=2.3$ pm was measured while running a buffer in the microfluidic flowcell (Figure 2) [1]. Similar tests were conducted on the LSPR, SPR and MRR sensor chips (Table 1). A substantially larger standard deviation is obtained with the SPR and LSPR sensors owing to their larger FWHM but also their higher sensitivity to environmental fluctuations.

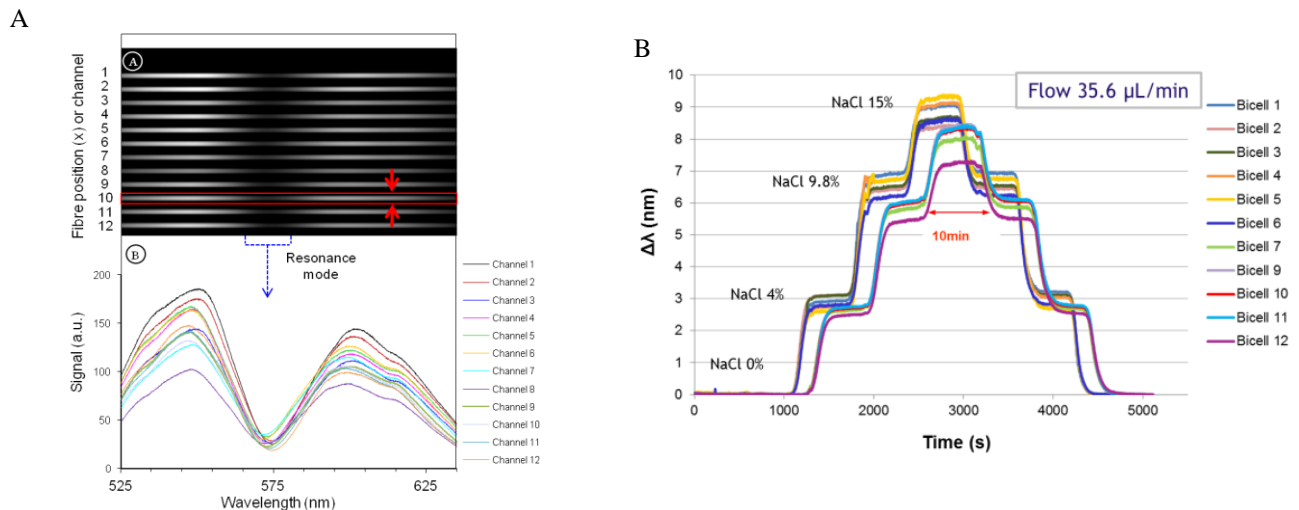


Figure 2 : (A) Full field image captured by the camera. Each horizontal gray track corresponds to a spectrum of a BICELL. The shadow area in the middle of the image corresponds to the position of the resonance mode (it is a dip because light is transmitted through the R-NP at resonance). The height of the red rectangle around channel 10 illustrates the pixel length (~50 pixels) over which the signal is integrated to obtain the one dimensional spectra. (B) Extracted one dimensional spectra from the image. Each dip is fitted with a Lorentzian (not shown) in order to extract the minimum of the dip with a high precision. (Right) Computed sensogram of the 12 channels – representing the wavelength shift ($\Delta\lambda$) over time for different NaCl concentrations in water. The standard deviation over a plateau was used to determine the precision of the measurement.

The measurement rate varies between 0.5 Hz (MRR) and 2 Hz (other transducers) depending on the sensor resolution. When the number of sensors is limited to 4, it is possible to limit the area of interest of the CMOS sensor and subsequently increase the frame rate up to 150 Hz.

4 CONCLUSIONS

We have developed three 12-channels spectrometers and the associated light coupling and collection systems adapted to LSPR/R-NPs, SPR and MRR transducers. In each case, the limit-of-detection (3σ) of the resonant wavelength shift is suitable for biosensing applications. The availability of the full measurement spectra makes the spectrometer usable for the development of the transducers, while the automatic signal processing and precision makes it usable for bioassay developments.

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[1] Hernandez, A. L., Dortu, F., Veenstra, T., Ciaurriz P., Casquel, R., Cornago, I., Von Horsten, H., Tellechea, E., Maigler, M. V., Fernández, F., Holgado, M., "Automated Chemical Sensing Unit Integration for Parallel Optical Interrogation", *Sensors*, 19, 878 (2019).