Towards In-Vitro Point of Care devices for in-situ diagnosis

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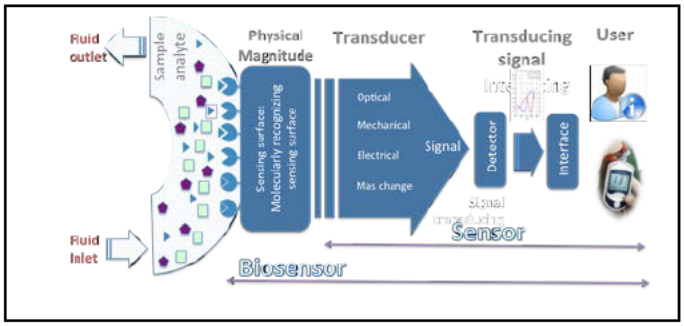
I. INTRODUCTION (*HEADING 1*)

In-Vitro Diagnostic (IVD) based on Immunoassay technology is essential for many sectors, especially for healthcare, clinical and pharmaceutical ones. Most of the IVD systems are still based on labeled technologies, where a chemical amplification takes place. These technologies are used because of their high performance, such as Enzyme Like Immunosorbent Assay (ELISA) or lower cost (qualitative lateral flow systems such as pregnancy tests) [1]. Very basically, a labeled technology for IVD might be compared with analog photographs, where a film after the light exposition must be chemically developed to reveal the result (pictures). The avoidance of this development (or label) step is called label-free technology; where the diagnostic information is immediately and directly obtained from the device, as happen with the digital cameras to obtain the pictures. In other words, the objective is to obtain Point-of-Care devices for in-situ biosensing, where disposable transducers and read-out platforms play a key role. However, despite the significant current advantages developed for label-free biosensing technology, quantitative in-situ IVD tests still need further enhancements.

Because in-situ label-free biosensing has to operate with a limited amount of sample and demanding Limit of Detection (LoD) of the target molecules to be detected, only a limited number of label-free-based biosensing systems have been adopted from the IVD marked. Thus, the break through challenge is to achieve a competitive LoD to avoid the labeling process for quantitative tests and with small volumes of biological samples to offer simple read-out systems in an easy-to-use manner.

II.BIOSENSING SYSTEM DEFINITION

Biosensors are devices able to detect any substance with a high sensitivity by using specific and selective biomolecular recognition in real time. Substances that can be detected are: proteins, DNA, pathogens, virus, bacteria, toxic pollutants, chemical and biological warfare agents (applications almost endless). For in-situ diagnostic characteristics such as fast, direct, label-free, high sensitivity, low sample volume are a must.



There are many types of transducers; among them, the most important ones can be classified in Electrochemical transducers (amperometric, potentiometric and conductimetric), Optical or photonic transducers (Absorbance, Refractive index or interferometry-based photonic structures and Fluorescence), Nanomechanical (Microcantilever and Micro Electro mechanical systems) or Piezoelectric (QCM, SAW).

Independently of the type of transducer, all of them need to incorporate the bioreceptors, the molecules capable of capturing specifically the target biomolecules. Biological receptors are antibodies, enzymes, antigens, DNA, RNA, aptamers, among others. Moreover, the abovementioned target molecules or substances to be detected are in biological samples (urine, blood, serum, tears, water, etc). This gives an idea about the complexity of a biosensing transducer, where interdisciplinary skills are needed.

Among the different types of biosensors, the optical ones are the most sensitive ones. Optical biosensor based on label technologies is related with absorption (imaginary part of the refractive index) or fluorescence. For the case of label-free technologies, the transducers detect small changes in the real part of the refractive index thanks to interferometry profiles or optical resonances. Changes in the resonant modes indicate

changes in the refractive index due to the recognition of biomolecules, that in the visible range are transparent and any absorption is produced. Thus, due to the changes the avoidance of labeling process is feasible.

A. BIOSENSING TRANSDUCERS

Most of the photonic transduces employed for labe-free optical biosensing are connected with standard architectures used in optical communications, such as Mat Zehnder, diffraction grating, ring resonators, disk resonators, etc. This structures are sometimes used for produces dense wavelength division multiplexing devices. The optical response of this architectures, for the case of label-free biosensing, changes due to the increasing real part of the refractive index cased by the selective recognition of target biomolecules. For this reason, without the need of any chemical process this sensing event can be detected. Other photonic structures that can be obtained are surface Plasmon resonant (SPR). Photonic crystals, Bio- photonic sensing cells, etc.

B. OPTICAL READ OUT UNITS

An essential part of a label-free biosensing system is the electronic or opto-electronic device capable of reading out the information given by the transducer. There are a lot of examples of classical equipment based on spectrometers and detectors (photodiodes, APDs, photo multipliers, etc) employed at laboratory scale for monitoring the response of these transducers. However, these tools are far form portable devices for in-situ diagnostic.

Currently, read-out optical techniques are being develop for developing compact devices, where the management of the optoelectronic signals with integrated electronics can be used for developing compact devices. This is the case of a new methodology base on Increase relative optical power (IROP) recently published [2]. With this methodology compact electronic devices can be developed for read-out the optical signals avoiding the source of uncertainty normally used for the optical components, typically the wavelength or wavenumber resolution in spectrometers, being the signal to noise ratio (SNR) the most significant source of uncertainty. This SNR can be reduced thanks to modern electronic components, and therefore, compact optoelectronic devices can be develop even with higher performance of large and costly laboratory equipment. In other words, the development of a cost-effective PoC devices for Replacing a complex and expensive standard laboratory equipment into a portable, cost- effective and simple device is now and important trend for optical label-free biosensing for in-vitro diagnosis.

III. CONCLUSIONS

In this paper we comment about high performance read-out devices can be achieve competitive LoD for a given photonic transducers depending on advanced optical read-out interrogation methods that can be achieved thanks opto-electronic and electronic components. Performance comparison among standard spectrometry based devices and novel compact devices to interrogate optical biosensors for biosensing purposes demonstrate the feasibility to achieve In-Vitro Point of Care devices for in-situ diagnosis.

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REFERENCES

[1] M. Holgado, F.J. Sanza, A.L. Hernandez, A. Lavín, R. Casquel, M.F. Laguna, Description of an advantageous optical label-free biosensing interferometric read-out method to measure biological species, Sensors 14 (2014) 3675-3689.

[2] M. Holgadoa, M.V. Maigler, B. Santamaría, A.L. Hernandez, A. Lavín, M.F. Lagunaa, F.J. Sanza, D. Granados, R. Casquel, J. Portilla, T. Riesgo. Towards reliable optical label-free Point-of-Care (PoC) biosensing devices. Sensors and Actuators B 236 (2016) 765–772

[3] C.D. Chin, V. Linder, S.K. Sia, Commercialization of microfluidic point-of-care diagnostic devices, Lab on a Chip12, (2012) 2118-2134.

[4] F.S. Ligler, C.R. Taitt, Optical Biosensors: Today and Tomorrow. Elsevier; 2008.

[5] A. Lavín, R. Casquel, F.J. Sanza, M.F. Laguna, M. Holgado, Efficient design and optimization of bio-photonic sensing cells (BICELLs) for label free biosensing. Sensors and Actuators B 176 (2013) 753-760

[6] F.J. Sanza, M. Holgado, F.J. Ortega, R. Casquel, D. López-Romero, M.J. Bañuls, M.F. Laguna, C.A. Barrios, R. Puchades, A. Maquieira, Bio-Photonic Sensing Cells over transparent substrates for anti- gestrinone antibodies biosensing, Biosens. Bioelectron. 26 (2011) 4842– 4847.

[7] M. Holgado, C.A.Barrios, F.J. Ortega, F.J. Sanza, R. Casquel, M.F. Laguna, M.J. Bañuls, D. López-Romero, R. Puchades, A. Maquieira, Label-free biosensing by means of periodic lattices of high aspect ratio SU-8 nano-pillars, Biosens. Bioelectron. 25 (2010) 2553-2558.

[8] J. Portilla, A. de Castro, E. de la Torre and T. Riesgo, A Modular Architecture for Nodes in Wireless Sensor Net-works, Journal of Universal Computer Science, 12, (2006), 328-339.

[9] M.F. Laguna, M. Holgado, F.J. Sanza, A. Lavín, A.L. Hernandez, R. Casquel, Optimization of dengue immunoassay by label-free interferometric optical detection method, Sensors (2014) 6695-6700.