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Research review paper

Point-of-Need bioanalytics based on planar optical interferometry

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ABSTRACT

This review brings about a comprehensive presentation of the research on interferometric transducers, which have emerged as extremely promising candidates for viable, truly-marketable solutions for PoN applications due to the attested performance that has reached down to 10^{-8} in term of effective refractive index changes. The review explores the operation of the various interferometric architectures along with their design, fabrication, and analytical performance aspects. The issues of biosensor functionalization and immobilization of receptors are also addressed. As a conclusion, the comparison among them is attempted in order to delve into and acknowledge their current limitations, and define the future trends.

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1. Introduction — historical background

The 20th century was characterized as the era of information, where the means for acquiring, storing and distributing almost instantaneously information worldwide were developed and have since infiltrated our lives in ways that were unfathomable 50 years ago. A wide range of diverse methodologies and techniques have been developed at a staggering pace in order to enrich the "armory" of scientists in their pursuit to understand and more effectively fight and treat disease, discover new and more effective therapies for hard-to-treat or deadly conditions, achieve prognosis or early diagnosis of ailments even at the asymptomatic stage, effectively screen our food for harmful substances or even help keep the world safe against epidemics or bioterrorist threats. It is not by chance that the 21st century was named the era of biology since a large part of scientific endeavors aim at comprehending the biological pathways that ensure, determine and affect our well-being. In this intense effort, numerous scientists are trying to devise the next generation of biosensors capable not only of analyzing pertinent biological entities related to disease but also of helping in the discovery of new drugs, personalized treatment schemes, pre-cautionary food monitoring, environmental monitoring and safety and security systems. In the greater picture, these advances are to be combined with the "gifts" of the information era and to be communicated through a worldwide net that can set the basis for a better quality of life for every passenger on our blue dot in the cosmos.

The core element of these systems is the "biosensor", which as a word has had a quite large range of meanings. According to IUPAC definition, "A biosensor is a self-contained integrated device which is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element (biochemical receptor) which is in direct spatial contact with a transducer element. A biosensor should be clearly distinguished from a bioanalytical system, which requires additional processing steps, such as reagent addition" (Koyun et al., 2012).

Thus a biosensor consists of two main parts, the specific biomolecule that interacts (binds or recognizes) with the analyte under study and the transducer (exploiting one among a wide range of transduction principles such as optical, piezoelectric, and electrochemical) that translates the output signal resulting from the biomolecular interaction to a signal that is easily measured (typically an electrical or optical signal).

The output signal from the transducer is recorded by an appropriate measuring apparatus that is equipped with all necessary interfaces to the transducer e.g., electrical, fluidic, optical ones. These measuring apparatuses are designed to match the particular needs of the particular transducer. In the most advanced applications the reader is an autonomous unit accommodating processing and optical presentation modules.

Even though the word "biosensor" is a relatively recent term, the principle of biosensing has been applied – unbeknownst as such at the time – hundreds of years ago: the canary in the coal mines is probably the oldest reported biosensor. However by considering the definition above, the first biosensor was introduced by Clark and Lyons who immobilized glucose oxidase (GOD) on an amperometric oxygen electrode surface semipermeable dialysis membrane in order to directly quantify glucose concentration in a sample. In their ground breaking article (Clark and Lyons, 1962) they presented "intelligent" electrochemical sensors (pH, polarographic, potentiometric or conductometric) by adding enzyme transducers as membrane-enclosed sandwiches. Soon enough, the importance of developing devices capable of detecting biological entities and the transformational impact they could bring about became apparent to the scientific community. Indicative is the trend of publications containing the word "biosensor" in their abstract: from 1 in the year 1980 to 57 in the year 1990 and 463 in the year 2000, and to 1735 in the year 2010 (source: www.scopus.com). During the same period, new journals were launched focusing on miniaturized microsystems capable of measuring markers related to human health and the quantitative determination of harmful species in food, water or environmental samples.

During the past decade, another demand has been induced to biosensors: apart from the race for lower limits of detection, higher resolution and dynamic range, multi-parameter analysis capabilities, cost- and time-effectiveness or even the degree of user-friendliness, biosensors are envisioned to break free from the laboratory settings and to become applicable for on-the-spot determinations that are to be transmitted in real-time through the "cloud". A new term was coined to describe the envisioned systems, that of "Point-of-Need", with applications extending to a wide range of diverse areas including human health, food safety, environmental monitoring, and forensics.

Due to the importance of biosensors per se, but also the ever increasing importance of portable biosensing systems and their envisioned applications, significant public and private funding opportunities have become available all over the world via either international or national schemes. Next to these, companies active in the area of analytical devices have started their own research activities trying to develop solutions with particular emphasis on portable and at-the-spot measuring systems addressing the demanding requirements of PoN determinations. Lately, several companies have attracted funding through crowd funding schemes with TellSpec and Consumer Physics raising ~400 K USD and ~2.8 M USD, respectively, for the development of miniaturized tools for the identification of harmful species in food at the Point-of-Need.

Among all the applications, Point-of-Care (PoC) diagnostics are expected to be the largest contributor to the overall biosensors market, holding ~57% share (Source: Markets and Markets survey: http://www.marketsandmarkets.com/Market-Reports/biosensors-market-798.html), since there is a strong need to reform the current healthcare infrastructure in the developed world so as to accommodate for an ever increasing aging population, and to contribute to the amelioration of the healthcare system in the developing parts of the globe. The key players in this industry include F. Hoffmann-La Roche Ltd. (Switzerland), LifeScan Inc. (U.S.), Bayer Healthcare AG (Germany), Abbott Point of Care Inc. (U.S.), Medtronic (U.S.), Siemens Healthcare (Germany), and others.

In addition, important prizes have been announced for the development of holistic solutions that have been able to measure the concentration of multiple analytes at the PoN, with the most recent ones to be:

a) The *Xprize Tricorder*, a 10 MUSD competition to develop a portable, wireless device in the palm of a hand that could monitor and diagnose over a dozen medical conditions (http://tricorder.xprize.org/), and
b) The *H2020 Food Scanner*, a 1 MEuro prize to develop an affordable and non-invasive mobile solution that will enable users to measure and analyze their food intake (http://ec.europa.eu/research/horizonprize/index.cfm?prize=food-scanner).

The intense and long research effort along with public and private funding led to significant technological developments that allowed tremendous progress regarding the development of reliable and miniaturized biosensors for various clinical and non-clinical applications. In