Editorial **Open Access**

Introduction to the special issue of optical biosensors

DOI 10.1515/nanoph-2017-0053

Prior to the development of analytical devices to assist medical professionals, clinical diagnosis relied mostly on medical history and physical examination. Since many diseases could exhibit similar symptoms, doctors have always sought complementary validation, and rudimentary clinical tests date back thousands of years. For example, the color and odor of urine was utilized in diagnostics. In modern medicine, biosensors – analytical devices used for the detection of an analyte for *in vitro* tests – are a cornerstone of clinical practice, with the sensitivity of standard immunoassays measuring protein biomarkers at picomolar concentrations [1]. Advances in science and engineering in synergy and collaboration with medicine have been crucial for advances in developing biosensor technologies. While the performance of state-of-the-art biosensing technologies is sufficient for the diagnosis of infectious diseases when clear symptoms are present, it falls short – perhaps by a factor of many thousands – when high sensitivity is desired, for example, in cancer [2] or neurological disorders [3].

The biosensors are composed of a biological recognition element specific for the analyte, such as proteins, antibodies, nucleic acids, cell receptors, enzymes, pathogens, organelles, cells, etc., and a transducer element that converts the signal resulting from the interaction of the analyte into an observable and preferably quantifiable signal. Among various transduction mechanisms, those utilizing light interactions are referred to as *optical biosensors*. Optical biosensing arguably dates back thousands of years when subtle change of color of skin or urine was used in diagnostics. Modern optical biosensors have distinct properties and advantages such as high sensitivity, easy adaptation to multiplexed systems, and portable operation capability.

While macroscopic optical observations can provide useful information, much of the biological interactions occur at the microscale or nanoscale. Thus, the synergy of nanotechnology with photonics, or *nanophotonics*, is extremely relevant for the development of next-generation biosensor technologies. Biological phenomena at the microscale and nanoscale have always been extremely intriguing. When Robert Hooke's book of the microscopic world [4] was published about 400 years ago, it provided a first glimpse into previously unseen details. The advent of optical microscopy led to nanoscale observations in the biological world culminating in the 2014 Nobel Prize in Chemistry [5] awarded jointly to Eric Betzig, Stefan W. Hell, and William E. Moerner "for the development of super-resolved fluorescence microscopy".

In this special issue of *Nanophotonics*, we present a collection of articles on optical biosensors. Optics offers various modalities of biological sensing based on how light interacts with the analytes and specific transduction method. While fluorescence can provide exquisite sensitivity down to single molecules, exploitation of optical interferometry and novel optical surfaces and periodic structures can also yield phenomenal sensitivity without requiring any secondary labels. Among exciting recent technological developments in optical biomarker analysis is single-molecule counting or digital detection, an approach that provides resolution and sensitivity beyond the reach of ensemble measurements [6, 7]. Optical biosensors not only provide very high sensitivity but also offer chemical specificity based on optical `signatures. Furthermore, optical detection methods are amenable to integration and applications at the point of care (POC). The articles in this issue present advantages and challenges in optical biosensors.

Zanchetta et al. review recent progress in label-free optical biosensing techniques and their competitive advantages. The article is organized on the basis of the specific analyte type. They argue that direct and real-time detection allows the development of simpler, compact, and rapid analytical methods for different kinds of targets, from proteins to DNA and viruses. In case of small-molecule targets, label-free detection methods become necessary; secondary molecular interactions required for labeling are not feasible. This comprehensive review discusses engineered substrates and optical methods for enhanced sensitivity as well as challenges of detection in complex matrices. They discuss the intrinsic versatility of label-free sensing that enables the integration with biomolecular machinery, as in the case of the molecular tools provided by DNA nanotechnology.

Ozcelik et al. present a current state of optofluidics – a burgeoning field in biosensors that has established itself as a new and dynamic research area for exciting developments at the interface of photonics, microfluidics, and the life sciences. The advances are driven by the strong desire for developing miniaturized bioanalytic devices and instruments that led to integrating optical elements and biological fluids on the same chip-scale system. The article emphasizes the applications of optofluidics in bioanalysis. They discuss photonically reconfigurable devices and show how optofluidic approaches have been pushing the performance limits in bioanalysis, e.g. in terms of sensitivity and portability, satisfying many of the key requirements for POC devices.

Chiavaioli et al. explore optical fiber gratings (OFGs) in their applications in label-free biological sensors. They discuss that OFGs provide a valid and alternative approach for label-free sensing, with the capability of achieving excellent sensitivity. They present that the ability of depositing nanostructures and nanostructured coatings along the surface of OFGs is further enhancing the performance of these sensors. They argue that intrinsic advantages of OFG sensors, such as the miniaturization that can pave the way to their use in places of difficult access, remain unexploited. The article also reviews open questions pertaining to an effective and reliable detection of small molecules, possibly up to single molecule, sensing *in vivo*, and multi-target detection using OFG-based technology platforms.

Schechinger et al. discuss surface-enhanced Raman spectroscopy (SERS) as a solution to facilitating the translation of bioanalytical sensing to the POC. They present the World Health Organization criteria "ASSURED" (Affordable, Sensitive, Specific, User-friendly, Rapid, Equipment-free, and Deliverable) and how SERS can meet these stringent requirements for *in vitro* assay development. They explore SERS as a dynamic technique for POC monitoring because of its high sensitivity (up to fM detection limits) and multiplexing capabilities. They compare various emerging systems in terms of the synthesis, functionalization, and utilization of plasmonic nanoparticles as the SERS substrates within different environments including microwells, microfluidics, and paper-based platforms. They also note limitations of the technology in failing to produce signals as robust and repeatable as current gold standard assays and argue that the promise for SERS at POC will rely on overcoming the barriers in the assays and dedicated, cost-effective instruments.

Martens and Bientsman compare Vernier cascade and Mach-Zehnder interferometer (MZI) – two high responsivity photonics sensors – as transducers for biosensing. They show that the MZI outperforms the Vernier cascade through a better minimum detectable wavelength shift as well as a higher power efficiency, indicating its superiority in this sensing scheme. They discuss that a MZI in combination with an on-chip spectral filter yielded a detection limit comparable with the state-of-the-art sensing mechanisms, paving the way for numerous POC applications.

Ekiz-Kanik et al. argue the importance of the quality of the surface functionalization for optical biosensors especially in the case of label-free, single biological nanoparticle (BNP) biosensors. They review several optical technologies for label-free BNP detectors with a focus on imaging systems and compare the surface-imaging methods including dark-field, surface plasmon resonance imaging, and interference reflectance imaging. They discuss the importance of uniform and smooth surface functionalization and present several methods that have been developed towards addressing this challenge.

Koydemir et al. present a hand-held biosensing platform consisting of a mobile phone-based fluorescence microscope for detection and counting of waterborne parasites (*Giardia* cysts) in large volumes of water. They demonstrate the automation of the detection system using machine learning. This portable and cost-effective platform provides a powerful tool for rapid (under 1 h) and sensitive (limit of detection ~12 cysts per 10 ml) detection of waterborne pathogens in water samples. The platform requires minimal training of the users and can potentially be used in resource-limited settings.

These articles are but a glimpse of the wealth of recent publications in the rapidly growing field of optical biosensors [8]. The synergy of nanotechnology with photonics, or *nanophotonics*, will pave the way for the development of next-generation biosensor technologies that will impact life sciences research and healthcare.

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