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Review

Trends and challenges of refractometric nanoplasmonic biosensors: A review

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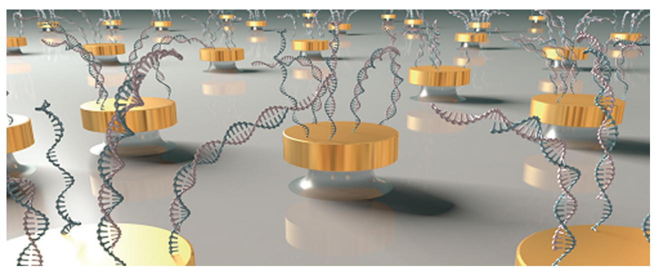
HIGHLIGHTS

- We compare the state-of-the-art of refractometric SPR and novel LSPR biosensors.
- We discuss different performance enhancing strategies for LSPR biosensors.
- We give an overview of relevant analytic studies carried out with LSPR sensors.
- We discuss how metal nanoparticles are used to create more integrated biosensors.
- We point out issues that should be overcome to make LSPR sensors more competitive.

GRAPHICAL ABSTRACT



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ABSTRACT

Motivated by potential benefits such as sensor miniaturization, multiplexing opportunities and higher sensitivities, refractometric nanoplasmonic biosensing has profiled itself in a short time span as an interesting alternative to conventional Surface Plasmon Resonance (SPR) biosensors. This latter conventional sensing concept has been subjected during the last decades to strong commercialization, thereby strongly leaning on well-developed thin-film surface chemistry protocols. Not surprisingly, the examples found in literature based on this sensing concept are generally characterized by extensive analytical studies of relevant clinical and diagnostic problems. In contrast, the more novel Localized Surface Plasmon Resonance (LSPR) alternative finds itself in a much earlier, and especially, more fundamental stage of development. Driven by new fabrication methodologies to create nanostructured substrates, published work typically focuses on the novelty of the presented material, its optical properties and its use – generally limited to a proof-of-concept – as a label-free biosensing scheme. Given the different stages of development both SPR and LSPR sensors find themselves in, it becomes apparent that providing a comparative analysis of both concepts is not a trivial task. Nevertheless, in this review we make an effort to provide an overview that illustrates the progress booked in both fields during the last five years. First, we discuss the most relevant advances in SPR biosensing, including interesting analytical applications, together with different strategies that assure improvements in performance, throughput and/or integration. Subsequently, the remaining part of this work focuses on the use of nanoplasmonic sensors for real label-free biosensing applications. First, we discuss the motivation that serves as a driving force behind this research topic, together with a brief summary that comprises the main fabrication methodologies used in this field. Next, the sensing performance of LSPR sensors is examined by analyzing different parameters that can be invoked in order to quantitatively assess their overall sensing performance. Two aspects are highlighted that turn out to be especially important when trying to maximize their sensing performance, being (1)

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the targeted functionalization of the electromagnetic hotspots of the nanostructures, and (2) overcoming inherent negative influence that stem from the presence of a high refractive index substrate that supports the nanostructures. Next, although few in numbers, an overview is given of the most exhaustive and diagnostically relevant LSPR sensing assays that have been recently reported in literature, followed by examples that exploit inherent LSPR characteristics in order to create highly integrated and high-throughput optical biosensors. Finally, we discuss a series of considerations that, in our opinion, should be addressed in order to bring the realization of a stand-alone LSPR biosensor with competitive levels of sensitivity, robustness and integration (when compared to a conventional SPR sensor) much closer to reality.

Contents

M.-Carmen Estévez graduated with a Bachelor of Chemistry in 1998 and obtained her M. Sc. and Ph.D. in Chemistry from the University of Barcelona in 1999 and 2005, respectively. After her Ph.D., she joined the University of Florida in 2006 as a postdoctoral researcher until 2008 where she focused on the production and applications of fluorescent nanoparticles in bioanalytical applications. In 2009 she joined the Nanobiosensors and Bioanalytical Applications group at the *Institut Catala de Nanociencia i Nanotecnologia* (ICN2) and CSIC, where she is focusing on surface biofunctionalization and clinical diagnostics applications of label-free optical biosensors.

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Marinus A. Otte obtained his B.Sc. (2005) and a M.Sc. Degree (2008) in Applied Physics at the Delft University of Technology (Netherlands). In 2013, he obtained his Ph.D. in Physics at the Autonomous University of Barcelona (UAB), for his work carried out in the Nanobiosensors and Bioanalytical Applications Group at the *Institut Catala de Nanociencia i Nanotecnologia* (ICN2) and CSIC. During this period, he developed different performance enhancing strategies for refractometric nanoplasmonic sensors. Currently, he continuous as a postdoctoral researcher in the same group, focusing his interest on different nanophotonic applications.

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1. Introduction

Driven by the increasing need for sensitive, fast, cost-effective, low-reagent-consumption and ease-of-use biosensors for applications in the clinical and biomedical field, a myriad of biosensing configurations and devices has appeared in the literature during the last decades. In connection to this, a major unmet diagnostic demand is the necessity of reliable compact