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Improved detection limits of protein optical fiber biosensors coated with gold nanoparticles

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ABSTRACT

The study presented herein investigates a novel arrangement of fiber-optic biosensors based on a tilted fiber Bragg grating (TFBG) coated with noble metal nanoparticles, either gold nanocages (AuNC) or gold nanospheres (AuNS). The biosensors constructed for this study demonstrated increased specificity and lowered detection limits for the target protein than a reference sensor without gold nanoparticles. The sensing film was fabricated by a series of thin-film and monolayer depositions to attach the gold nanoparticles to the surface of the TFBG using only covalent bonds. Though the gold nanoparticle integration had not yet been optimized for the most efficient coverage with minimum number of nanoparticles, binding AuNS and AuNC to the TFBG biosensor decreased the minimum detected target concentrations from 90 nM for the reference sensor, to 11 pM and 8 pM respectively. This improvement of minimum detection is the result of a reduced non-specific absorption onto the gold nanoparticles (by functionalization of the external surface of the gold nanoparticles), and of an optical field enhancement due to coupling between the photonic modes of the optical fiber and the localized surface plasmon resonances (LSPR) of the gold nanoparticles. This coupling also increased the sensitivity of the TFBG biosensor to changes in its local environment. The dissociation constant (K_d) of the target protein was also characterized with our sensing platform and found to be in good agreement with that of previous studies.

1. Introduction

Interest in biosensors extends not only to research but also to industry applications where detection, diagnosis and determination of biomolecules are high priorities. Some such industry fields include food- and water-quality control, security, and health, all of which have a continuously increasing demand for biosensors. The current challenge is to design simple, inexpensive, accurate, sensitive and reliable biosensor platforms. In response to this, many devices and methods have been developed to detect binding events, though optical measurement is the most widely used of the transduction methods. Among optical-based biosensors, optical fibers are new, tiny, flexible platforms that are being used with increasing frequency as biosensor transducers. Optical fibers are able to make quick and sensitive responses, and can be employed as an intrinsic or extrinsic biosensor (Nguyen et al., 2012). The biosensors presented in this work were intrinsic-type, label-free biosensors, utilizing a single-mode tilted fiber Bragg grating (TFBG). This optical fiber biosensor platform was classified as an evanescent wave sensor and combined various technologies to create a simple and robust platform that has been successfully applied to a wide range of interactions (Maguis et al., 2008). Recently, the Albert group has demonstrated that the efficiency of such TFBG sensors can be further improved by coating the fiber with a thin metallic layer, thus allowing the excitation of surface plasmon polaritons (Shevchenko et al., 2011). By the same principle, the Albert group also showed that TFBG are able to excite localized surface plasmon resonances (LSPR) in nanoscale particles (Bialiayeu et al., 2012). The unique optical property of supporting LSPR have made noble metal nanoparticles the subject of much research interest, and they are also of key importance in various studies of biological applications, including bioactive colloidal crystals (Gosecka et al., 2011), immunodiagnostic assays (Bousalem et al., 2005), chemical sensors (Gehan et al., 2010; Kaewsaneha et al., 2013), biosensors (Bedford et al., 2012; Bernand-Mantel et al., 2010), plasmonic nanostructures (Fang and Zhu, 2013), and hybrid nanocomposites (Rozenberg and Tenne, 2008; Spitalsky et al., 2010; Zou et al., 2008). This popularity and diversity stems from the fact that LSPR, compared to surface plasmon resonances (SPR), are much more localized, allowing for probing processes at the platform interface with spatial sensitivities well within the nanometer scale (Anker et al., 2008; Mayer and Hafner, 2011; Piliarik et al., 2012).

The majority of nanoparticle-enhanced SPR studies reported to-date have been focused on the use of DNA-functionalized gold nanoparticles (typically 10–15 nm in diameter), because of the

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well-established procedures for the preparation of DNA conjugates on planar gold surfaces (Gosecka et al., 2011; Hayashida et al., 2005). However, for planar detection of SPR, there are currently very few reports concerning larger nanoparticles sizes or non-spherical particles for the detection of proteins or nucleic acids (Sendroiu et al., 2009; Sim et al., 2010; Yu and Irudayaraj, 2007). The most complete study of this line of investigation to-date compared different nanoparticle shapes and sizes as part of a sandwich assay in combination with a gold SPR chip for the detection of thrombin to demonstrate that attomolar concentrations can be detected by this technique (Kwon et al., 2012). Branching from the utilization of LSPR with a gold planar surface, other studies using silica nanoparticles have been reported (Lin et al., 2009; Lin et al., 2010; Patolsky et al., 2006). For instance, Li et al. (2013) showed that transistor biosensors using silicon nanowires for the detection of protein could reach detection limits on the order of femtomolar concentrations. However, the study and work presented herein is the first known report of coupling TFBG and noble metal nanoparticles for the fabrication of biosensors.

These experiments were carried out using an unmodified and inexpensive standard telecommunication single-mode fiber. From the optics point of view, it is well known that a single-mode fiber's transmission power loss is less than 4%/km (Corning, 2010), making optical fibers well suited for remote operation over large distances (up to several kilometers). Moreover, the flexibility of optical fibers allows for a very robust sensor that is also simple to manufacture and to measure, using widely available instrumentation developed by the telecommunications industry. A TFBG transducer also offers very important advantages for sensor platforms in its temperature insensitivity and the preservation of the fiber's structural integrity under stressful environments (Albert et al., 2013; Chan et al., 2007).

Recent work prior to this study had demonstrated that silver nanowires can be used to significantly amplify the sensitivity of the TFBG sensor by introducing large and distinct anisotropy with respect to optical transmission (Bialiayeu et al., 2012). With this amplification of sensitivity in mind, it was decided to transfer this technique to a biosensor application. Two biosensors using gold nanoparticles (nanospheres and nanocages respectively) were studied and compared to a reference biosensor without nanoparticles. The amplification performance of the gold nanoparticles with respect to the enhancement of the LSPR was monitored by the detection of a protein. The goal of this study is to determine the influence of the nanoparticles' shape or surface area in contact with the biosensor platform on the LSPR properties, as evidenced by spectral shifts of the TFBG response due to LSPR changes. The gold nanospheres (AuNS) obtained for this study had a maximal absorbance in colloidal solution at a wavelength of 530 nm, whereas the LSPR of the gold nanocages (AuNC) in colloidal solution is in the visible and near-infrared (vis–NIR) range depending on the size and porosity of the nanocages (Skrabalak et al., 2008). The nanocages also provide a larger contact area as binding can occur on the inside surfaces. The TFBG spectral region of interest ranges from 1520 to 1620 nm, because of the high quality factor resonances that can be generated at those wavelengths. Gold nanoparticles were of interest for this range because of their LSPR sensitivity within the near-infrared (NIR) and infrared (IR) ranges of the electromagnetic spectrum when arranged in supported nanostructures, including when deposited on optical fibers, as described in this work. In previous work it was determined that the propagating modes of optical fibers are strongly perturbed within the region of interest by very sparse coatings of metallic nanoparticles (Bialiayeu et al., 2012; Shao et al., 2011; Zhou et al., 2013). This perturbation is caused by coupling between the resonance of the fiber cladding-mode and the localized plasmonic resonances of the nanoparticle coatings, including collective resonance modes that occur at longer wavelengths. The result of such coupling is the increase of the effective refractive index of the fiber's cladding-modes thereby causing measurable wavelength shifts of the grating resonances. The effective refractive index of an optical fiber is typically altered by varying the type and nature of the fiber's cladding (Albert et al., 2013), though in the work presented here, the cladding is instead modified by the interaction of gold nanoparticles.

Molecular recognition is the main criterion of general biosensing, thus the essential component of an effective biosensor is the ability of a specific molecular recognition probe to selectively target the desired analyte. For this study, biotin was chosen as the target molecule. The biotin molecules were to be bound to avidin molecules that had been covalently attached to the gold nanoparticles, which were in turn immobilized on the TFBG surface. Biotin/avidin combination chemistry has been used extensively as a model in protein sensing, primarily because of the strong attraction between the two ($K_d = 10^{-15}$ mol/L). The complex biotin/avidin has been applied successfully as molecular recognition probes for a variety of sensor techniques, including prism-based SPR and surface-enhanced Raman spectroscopy (Fu et al., 2013), as well as nanoscale field-effect transistors (Li et al., 2013). Utilizing the advantages of this well-known complex with its strongly recognizable affinity and signature in combination with the easily-obtained and durable platform of a TFBG, determining the effectiveness of a biosensor comprised of gold nanoparticles on the surface of a single-mode fiber platform was the key interest in this study. The experimental results indicated that the nanoparticle-incorporated biosensors can be used for the real-time monitoring of both the self-assembly of the sensing film on the TFBG surface, as well as for the detection of protein at various concentrations in aqueous solutions. The dissociation constant (K_d) of the target biotin bound to the avidin biosensor surface was also determined and was found to be comparable to that found in other biotin/avidin complex studies.

2. Materials and methods

2.1. The TFBG basic sensor

The optical fiber sensor used was made up of a standard single-mode optical fiber (Corning SMF-28) with a TFBG inscribed in the fiber's core. The TFBG was manufactured using intense ultraviolet light at 193 nm from a pulsed laser incident source on a phase mask, inscribing the grating in the fiber's core. The grating's planes were inscribed with a tilt of 10° relative to the normal axis of the fiber (as seen in Fig. 1). This angle allowed the sensor to operate in aqueous solutions with refractive indices between 1.31 and 1.34 RIU. After the grating was inscribed, a thin gold mirror was formed by electroless deposition on the downstream end of the Bragg grating. This technique is based on the reduction of metallic ions from a solution to a solid surface without electrical potential (Bialiayeu et al., 2011; Hrapovic et al., 2003). The interest of depositing a mirror at the end of the fiber is in that it allows a convenient and easy use of the sensor since it can be simply dipped directly into the testing and sampling solutions. In a TFBG sensor, coupling between the forward-propagating core-modes and the counter-propagating cladding-modes occurs, yielding a familiar transmission spectrum (inset in Fig. 1(B)). The molecular recognition event is measured through changes in the spectral transmission response of the TFBG (as described in Section 2.4 below).

2.2. Synthesis of gold nanocages

Gold nanocages were synthesized by a two-step process involving the synthesis of silver nanocubes followed by the galvanic