Optics and Laser Technology 107 (2018) 210–215

Contents lists available at ScienceDirect

Optics and Laser Technology

journal homepage: www.elsevier.com/locate/optlastec

Full length article

Sensitivity enhanced SPR immunosensor based on graphene oxide and SPA co-modified photonic crystal fiber

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ARTICLE INFO

Article history:
Received 1 March 2018
Received in revised form 13 April 2018
Accepted 5 May 2018

Keywords:
Immunosensor
SPR
PCF
Staphylococcal protein A
Graphene oxide
Low detection limit

ABSTRACT

A sensitivity enhanced surface plasmon resonance (SPR) immunosensor based on Graphene oxide (GO) composite and staphylococcal protein A (SPA) co-modified photonic crystal fiber (PCF) is developed for human IgG detection. The PCF spliced between two section of multimode fibers (MMFs) is sputtered with gold film, which was then modified with graphene oxide and SPA for further immunosensing. Graphene oxide with abundant functional groups has a large surface area for more biomolecules immobilization and can enhance the interaction between Au film and external medium, leading to the sensitivity increased greatly. SPA can specifically bind the Fc region of the antibodies and has a high degree of orientation for capturing antibodies. Experimental results indicated that the refractive index (RI) sensitivity of graphene oxide modified Au-PCF SPR sensor reaches 4649.8 nm/RIU, which is about 1888 nm/RIU higher than that without graphene oxide film and the human IgG detection limit reaches as low as 10 ng/mL. Such a sensitivity enhanced immunosensor based on graphene oxide and SPA co-modified PCF shows a great promise in biosensing.

1. Introduction

Surface plasmon resonance biosensors [1,2] have important applications in medical diagnostics [3], immunosensing analysis [4,5], food safety detection [6], and DNA hybridization [7], etc., The surface plasmon waves excited by evanescent wave can be used to detect the interaction of external biomolecules. The specific binding between antigen and antibody on the biosensor surface will result in the variation of the external refractive index, leading to the shift of resonance wavelength [8]. Compared with traditional prism-based SPR platforms, the fiber optic SPR biosensor has attractive characteristics of simple fabrication, cost effective, and miniaturization.

A number of structures have been proposed to fabricate optical fiber SPR biosensors, such as reflection-type structure [9], D-shaped fiber [10] and long-period fiber grating [11], tilted fiber Bragg grating [12]. However, the sensing performances of optical fiber SPR biosensor still requires improvements in order to detect small biomolecules or low concentration of analyte and reduce the external interference. Au film has characters of antioxidation and stable chemical properties, but biomolecules adsorbed poorly on Au film surface, which limits the improvement of detection sensitivity. A lot of techniques have been proposed to improve the sensitivity, such as magnetic nano-particles, and colloidal gold nano-particles, etc. [13,14]. However, the size, shape and spacing of metal nanoparticles can affect the sensing performance and the process of nano-particles synthesis and labeling antibodies is complex and time-consuming. Furthermore, the metal nanoparticles on the sensor surface can be easily rinsed away from the sensor surface, resulting in poor repeatability and the decrease of detection sensitivity.

Another alternative method to improve the detection sensitivity is to introduce a biosensitive layer to functionalize the Au film surface to increase the number of immobilized biomolecules. Such as using protein A [15] protein G [16] as a sub-biosensitive layer, have been employed to immobilize biomolecules. Protein A or G can specifically recognizes and binds the Fc region of antibodies.

In order to further enhance the effectiveness of antibodies immobilization to obtain lower detection limit, graphene oxide as a very promising carbon-based nanomaterial displays promising sensing performances for its biocompatibility and large surface area for biochemical sensing [17,18]. Graphene oxide contains of abundant functional groups, such as carboxyl, which is conducive to immobilize biomolecules. These functional groups exhibit excellent immobilization efficiency for biomolecules. This feature makes

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https://doi.org/10.1016/j.optlastec.2018.05.006
0030-3992/

graphene oxide a highly promising candidate as the sensing layer for biosensors.

In this paper, a sensitivity enhanced biosensor based on GO and SPA co-modified photonic crystal fiber is proposed. Compared with traditional optical fibers, photonic crystal fiber has superior properties of a wide range of wavelengths for single mode operation and low temperature effect [19,20], which can reduce the effect of temperature fluctuation on the measurement. The Au film coated PCF surface is co-modified by graphene oxide and staphylococcal protein A to immobilize goat anti-human IgG to detect human IgG. The experimental results showed that the RI sensitivity of graphene oxide coated Au-PCF sensor reaches 4649.8 nm/RIU, which is about 1888 nm/RIU higher than that without graphene oxide. Furthermore, the detection limit of human IgG based on GO and SPA co-modified Au-PCF reaches 10 ng/mL, which is about 30 fold lower than that without graphene oxide modified Au film. The experimental results demonstrated that the sensitivity of the proposed immunosensor based on the graphene oxide and SPA co-modified photonic crystal fiber was enhanced significantly.

2. Materials and measurement

2.1. Materials

N-hydroxysuccinimide (NHS), 11-mercaptoundecanoic acid (MUA), and 1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC) were purchased from Shanghai Aladdin Biochemical Technology Co., Ltd. Mercapto ethylamine (MEA) was purchased from Shandong Xiya Reaent Chemical Industry Co., Ltd. Graphene oxide was purchased from Nanjing Xianfeng Nanomaterials Technology Co., Ltd. Goat anti-human IgG, human IgG, staphylococcal protein A (SPA), phosphate buffer saline (PBS, 0.01 M), and bovine serum albumin (BSA) were purchased from Beijing Ding Guo Chang Sheng Biotechnology Co., Ltd.

2.2. Sensor fabrication

The sketch map of proposed PCF sensor is shown in Fig. 1(a). The end face microscope diagram of PCF is shown in Fig. 1(b). The sensor is designed with a section of PCF fiber (five layers of air holes, the diameter of outer and air hole are 125 μm, 4.8 μm and the air hole pitch is 7.7 μm) spliced between two multimode optical fibers (Corning, diameter-62.5/125 μm) using an optical fiber fusion splicer (Fitel, S178). As is shown in Fig. 1(c), the air holes of the PCF were partially collapsed with a length of 221 μm during the fusion splice process. Then the cleaned portion of PCF with sensing length of 5 mm was sputtered with 5 nm chrome film and a thin gold film with thickness of 50 nm, respectively, using magnetron sputtering instrument (JS-1600, Sun Yi).

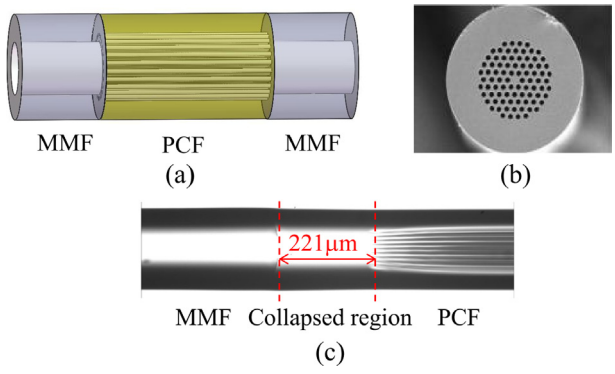

Fig. 1. (a) The schematic diagram of MMF-PCF-MMF sensor. (b) The end face microscope diagram of PCF. (c) The fusing splice diagram of MMF-PCF.

2.3. Graphene oxide modification

The detailed process of PCF surface amination and graphene oxide modification is shown in Fig. 2(a–d). (a) The gold-coated sensor was first cleaned with piranha solution and dried by nitrogen. (b) The cleaned sensor was dipped in 10 mM MEA solution for 4 h for surface amination and rinsed with distilled water. The MEA molecules linked with gold film through Au-S covalent bond and left amine groups (–NH_2) outside for further reaction with epoxy group of graphene oxide. (c) The fiber was immersed in 1 mg/mL graphene oxide aqueous solution contained in a V-groove that placed in a incubator with temperature of 40 °C. Using the evaporation method, graphene oxide film can be immobilized on the sensor surface.

2.4. Refractive index sensing performance

The RI sensing characters of the proposed sensor is an important basic conditions for biological sensing. Therefore, before the Au-PCF and Au/GO-PCF sensor was further functionalized with antibody, the refractive index sensing performances were first evaluated by immersing the sensor into sodium chloride solutions with their refractive indices ranging from 1.33 to 1.37. The sensor was placed in a V-groove refractive index liquid carrier and fixed by a fiber holder to keep straight. A tungsten-halogen lamp (LS-3000, Biaoqi Scientific Corporation, China) with wide spectrum range of 400–1000 nm is used as the light source. An optical fiber spectrometer (Maya2000 Pro, Ocean Optics Inc.) was used to detect the resonance spectrum.

The resonance spectrum of Au-PCF and Au/GO-PCF sensor with sensing length of 5 mm are shown in Fig. 3(a) and (c), respectively. With the increase of refractive index values, the resonance dip shifts to longer wavelength. We can noticed that the Au-PCF exhibits resonance dip shift of 114.74 nm from 589.21 to 703.95 nm. The linear fitting curve between refractive index and resonance wavelength is shown in Fig. 3(b). The experimental results of repeated three times measurements show that the RI sensitivity is 2761.7 nm/RIU. The standard deviation of three times measurements is about 3%, indicating its good reproducibility.

The Au/GO-PCF sensor exhibits resonance dip shift of 181.79 nm from 610.41 nm to 792.2 nm. The refractive index sensitivity reaches 4649.8 nm/RIU, as shown in Fig. 3(d). The standard deviation of three measurements is about 5.5%, which shows the Au/GO-PCF sensor also has good repeatability.

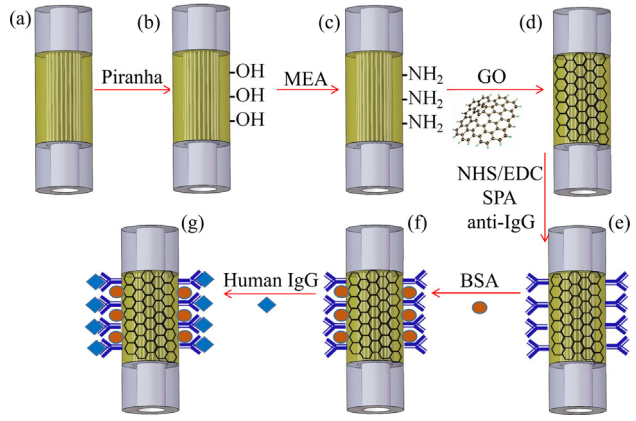

Fig. 2. Procedure of graphene oxide and SPA modification for IgG immunoassay.