Graphene oxide functionalized long period fiber grating for highly sensitive hemoglobin detection

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ABSTRACT

We present graphene oxide (GO) nanosheets functionalized long period grating (LPG) for ultrasensitive hemoglobin sensing. The sensing mechanism relies on the measurement of LPG resonant intensity change induced by the adsorption of hemoglobin molecules onto GO, where GO as a bio-interface linkage provides the significant light-matter interaction between evanescent field and target molecules. The deposition technique based on chemical-bonding associated with physical-adsorption was developed to immobilize GO nanosheets on cylindrical fiber device. The surface morphology was characterized by scanning electron microscope, atomic force microscopy, and Raman spectroscopy. With relatively thicker GO coating, the refractive index (RI) sensitivity of GO-LPG was extremely enhanced and achieved -76.5 dB/RIU, -234.2 dB/RIU and +1580.5 dB/RIU for RI region of 1.33-1.38, 1.40-1.44 and 1.45-1.46, respectively. The GO-LPG was subsequently implemented as an optical biosensor to detect human hemoglobin giving a sensitivity of 1.9 dB/(mg/mL) and a detectable concentration of 0.05 mg/mL, which was far below the hemoglobin threshold value for anemia defined by World Health Organization. The proposed GO-LPG architecture can be further developed as an optical biosensing platform for anemia diagnostics and biomedical applications.

Keywords: Anemia; Biosensor; Graphene oxide; Hemoglobin; Long period grating; Optical sensor.

1. Introduction

For decades, a variety of efforts have been made to develop accurate and low expense chemosensors and biosensors for the applications in food safety, environmental monitoring, clinical analysis, and healthcare sectors. Anemia is a common concern in geriatric health with estimated prevalence increasing with advancing age [1,2]. Anemia is typically defined using the World Health Organization (WHO) criteria of hemoglobin levels lower than 130 mg/mL for men and 120 mg/mL for women [3]. Anemia has serious consequences for some clinical and functional outcomes in the elder population. Abnormal blood hemoglobin concentrations always relate to other diseases, such as thalassemia, stroke and diabetes [4,5]. It has been reported that an almost 2-fold increase in the occurrence of Alzheimer disease among patients with anemia [6]. The impact of anemia on quality of life, functional abilities and recovery from illness must be received much clinical attention.

The electrochemical biosensors assisted with curcumin nanoparticles and carbon dots have been developed to determine the hemoglobin concentrations [7-9]. However the traditional biosensors are usually time consuming, labeling required, complicated and expensive. Recent years, optical fiber sensors based on fiber Bragg gratings (FBGs), long period gratings (LPGs) and tilted fiber gratings (TFGs) have been widely investigated for chemical and biomedical applications [10-15]. Fiber sensors own the advantages of electromagnetic interference immunity, miniaturized size, multiplex, label-free, and real-time detection. However, the major challenge is the lack of high sensitivity for applications with low concentration of analyte. The sensitization techniques have been developed to improve the refractive index (RI) sensitivity by coating the fiber device with thin-film materials, such as Langmuir-blodgett, carbon nanotube (CNT), zinc oxide (ZnO), titanium dioxide (TiO_2) as well as metallic coatings [16-21].

To date, 2D-nanomaterials including graphene, transition metal dichalcogenide and phosphorene have received significant attentions due to their unique mechanical, electronic, optical and chemical properties [22-24]. Grephene is a novel carbon nanomaterial that contains a flat monolayer of carbon atoms tightly packed into a 2D honeycomb lattice. As an oxidized derivative of graphene, graphene oxide (GO) is strongly hydrophilic and water soluble due to the presence of oxygen-containing groups such as hydroxyl, epoxy, carboxyl on its basal plane and sheet edges. GO exhibits favorable biocompatibility which provides the capability to install biomolecular linkages on the surface as a biosensing platform for the detection of DNA, glucose, and protein [25-28]. The

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enriched oxygen-containing functional groups on GO causes it to be served as sites for immobilization of various biomolecules through covalent bonding. In addition, GO could adsorb biomolecules by noncovalent interactions such as hydrogen bonding, π-π stacking, and electrostatic interaction [29]. The noncovalent interactions make GO as an ideal sensing material for hemoglobin detection. GO/hemoglobin composite hydrogel based on electrostatic interaction was reported for enzymatic catalysis [30]. GO-metal organic framework composites were developed for the selective isolation of hemoglobin based on π-stacking interaction between GO and hemoglobin [31].

In this work, we report a highly sensitive biosensor based on GO-coated LPG for hemoglobin detection. In our experiment, a new deposition method based on chemical-bonding associated with physical-adsorption has been developed. By this approach, the GO nanosheets were deposited over the cylindrical surface of LPG. The surface morphology and the coated material were characterized by Scanning Electron Microscope (SEM), Atomic Force Microscopy (AFM), and Raman spectroscopy. With GO deposition, the sensitivity of LPG has been extremely enhanced both in lower and higher RI regions. In further, the GP-LPG has been implemented as optical biosensor for the detection of human hemoglobin showing a high sensitivity.

2. Materials and methods

2.1. Materials

The aqueous dispersion of graphene oxide, sodium hydroxide (NaOH), (3-Aminopropyl)triethoxysilane (APTES), and human hemoglobin were purchased from Sigma-Aldrich (United Kingdom). Methanol, ethanol, acetone, and deionized (DI) water were purchased from Thermo Fisher Scientific Inc. (United Kingdom).

2.2. Principle of LPG

A long period grating is typically formed by a periodic refractive index modulation in the order of hundreds of micrometers in fiber core. The perturbation of RI in fiber core results in light coupling from the fundamental core mode to the forward-propagating cladding modes, yielding a series of attenuation bands in transmission spectrum with corresponding wavelength satisfying the phase matching condition [11]:

$$\lambda_{\text{res}} = (n_{co}^{eff} - n_{cl,i}^{eff})\Lambda \quad (1)$$

where n_{co}^{eff} and $n_{cl,i}^{eff}$ are the effective refractive indices of core and ith cladding mode, Λ is the grating period. The RI sensitivity of LPG is dependent on the phase matching condition, in which the effective refractive indices of the cladding modes depend upon the difference between cladding refractive index (CRI) and surrounding-medium refractive index (SRI). For a conventional bare LPG, the highest sensitivity occurs at the SRI value approaching the CRI by the higher order mode [13]. However, when the SRI exceeds the CRI, the core mode couples with radiation modes and the phase matching condition will no longer be satisfied.

The transmission power T of the attenuation bands is given by [12,20]:

$$T = 1 - \sin^2(\kappa L) \quad (2)$$

where L is the length of LPG, and κ is the coupling coefficient between LP_{vj} and $LP_{\mu k}$ mode:

$$\kappa = \frac{\omega}{4P_0}\int_{\phi=0}^{2\pi}\int_{r=0}^{\infty}\Delta\varepsilon(r,\phi,z)\psi_{vj}(r,\phi)\psi_{\mu k}^{*}(r,\phi)rdrd\phi \quad (3)$$

where ω is the FWHM of grating profile, P_0 is the power of the mode, $\Delta\varepsilon(r,\varphi,z)$ is the permittivity variation, $\psi(r,\phi)$ is the transverse field of the cladding mode, and r and ϕ represent radial and angular field, respectively. The coupling coefficient is determined by the overlap integral of core and cladding modes and by the amplitude of the periodic modulation of the mode propagation constants.

In the case of a conventional bare LPG, the intensity T changes slowly with the increase of SRI, providing poor sensitivity as intensity sensor [13]. In the case of a coated-LPG, due to the electric field distribution varies rapidly, the coupling strength would change and consequently enable film coated LPG as intensity sensor with good sensitivities [16-21]. The coating layer could make a transition from cladding guided modes to overlay guided modes as well as radiation modes.

2.3. Deposition of GO nanosheets

A 15 mm-long LPG with a period of 400μm was UV-inscribed in H_2-loaded single mode fiber with point-by-point fabrication technique. After the UV exposure, the grating was annealed at 85 °C for 24h to remove residual hydrogen and stabilize its optical properties.

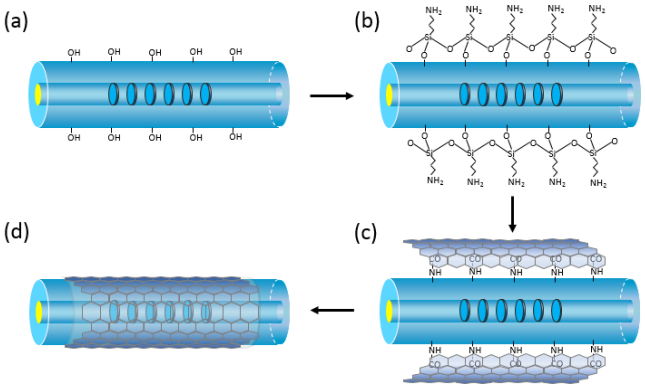

Fig. 1. Schematic of GO deposition on cylindrical fiber device.

In this work, the deposition technique based on chemical-bonding associated with physical-adsorption was developed to deposit GO nanosheets on cylindrical fiber device. As shown in Fig. 1, the LPG was initially cleaned with acetone to remove the residual contaminant on fiber surface. Then the LPG was alkaline treated by immersion in 1.0 M NaOH solution for 1 h at room temperature to enrich the number of hydroxyl group (-OH) on the surface, washed with deionized (DI) water thoroughly and dried (Fig. 1a).

For the silanization (Fig. 1b), the alkaline-treated LPG was firstly immersed in 5% APTES solution (v/v in ethanol) for 1 h at room temperature to form Si-O-Si bonding on the surface, followed by washing with ethanol to remove unbound monomers and baked in an oven at 70 ºC for 30 min to improve the stability of APTES monolayer.

After APTES silanization, the LPG was incubated in 1ml of 1.0 mg/mL GO aqueous solution contained in a custom-made mini-bath, which was placed on a hot plate at 42 °C for 3 h. The epoxy group of GO reacted with amino group of APTES-silanized fiber surface, hence GO nanosheets were gradually deposited on the fiber surface (Fig. 1c) while the aqueous solution was being slowly evaporated by heating. Afterwards, another two cycles of physical-adsorption procedures were conducted. The GO solution (1 ml of 1.0 mg/mL) was added into mini-bath to immerse the LPG. The aqueous solution was being slowly evaporated by heating at 42 °C for 3 h while solid GO nanosheets were gradually and physically adsorbed onto fiber surface. When the entire LPG was emerged out of the solution, a brownish coating was observed on the fiber surface (Fig. 1d).

2.4. Measurement system and data analysis

The interrogation system (Fig. 2) was employed for the measurement of optical properties of GO-LPG and biochemical sensing. A broadband light source (BBS) was used to launch the light into fiber device and the transmission spectra were captured by an optical spectrum analyzer (OSA, Agilent HP86140, Agilent Technologies Inc.). The data was analyzed using a customized program which automatically defined the resonant wavelength and intensity by the centroid calculation method. To avoid the thermal and bend cross-talk effects, the fiber device was mounted on a homemade straight V-groove container with two ends fixed and all chemical experiments were performed in a fume cupboard at a controlled room temperature of 22.0 ± 0.1 °C.

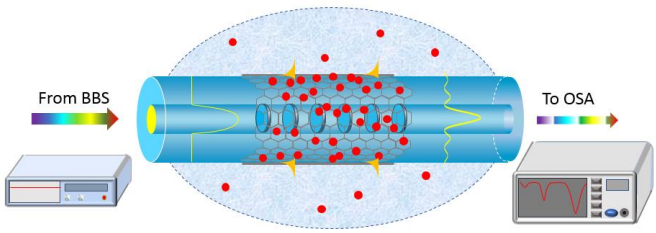

Fig. 2. Schematic illustration of measurement system.

3. Results and discussion

3.1. Surface morphological characterization

The surface morphology of GO-deposited fiber was characterized by optical microscope, SEM, and AFM. The initial microscope image (Fig. 3a) shows a clear boundary between bare and GO-coated sections, demonstrating a successful deposition on fiber surface. The surface coverage was examined by SEM with the magnification of 1000×. The detailed texture in Fig. 3b indicates that the GO nanosheets have been deposited onto fiber to form a homogeneous layer over the entire cylindrical surface. Moreover, the thickness of GO overlay after 3 cycles' deposition was determined by AFM. As shown in AFM tapping mode topographic image (Fig. 3c) and the height profile (Fig. 3d), the thickness of GO overlay is identified as around 501.8 nm.

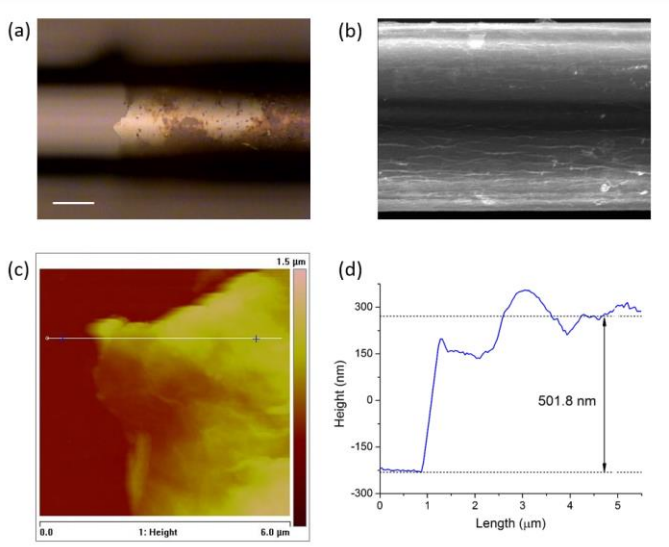

Fig. 3. Surface morphology of GO-coated fiber. (a) Optical microscope image (scale bar: 50 µm), (b) SEM image with the magnification of 1000×, (c) AFM image and (d) height profile of GO overlay.

3.2. Optical characterization of GO-LPG

The measurements of Raman spectra and LPG transmission were carried out to verify the coating material as well as the optical property of LPG. Both bare and coated fiber samples were measured by using Renishaw Raman Microscope 1000 (with 632.8 nm light) with the Raman spectra depicted in Fig. 4a. In comparison with bare sample, the GO-coated fiber shows three typical characteristic peaks (D, G and 2D) in Raman spectrum indicating the presence of GO. The D peak at 1335 cm^{-1} was assigned to local defect and disorder of GO caused by attachment of hydroxyl and epoxide groups on the carbon basal plane and edges. The G peak at 1599 cm^{-1} was due to the first order scattering of the E_{2g} plane of sp^2 carbon atoms [32].

The LPG transmission spectra of the 7th cladding mode [14] with the central wavelength at 1591.6nm (in the air) were monitored before and after the GO deposition. It can be seen from Fig. 4b that the GO coating induces a blue-shift of 3.8 nm in wavelength and an increase of 12 dB in intensity of LPG attenuation band.

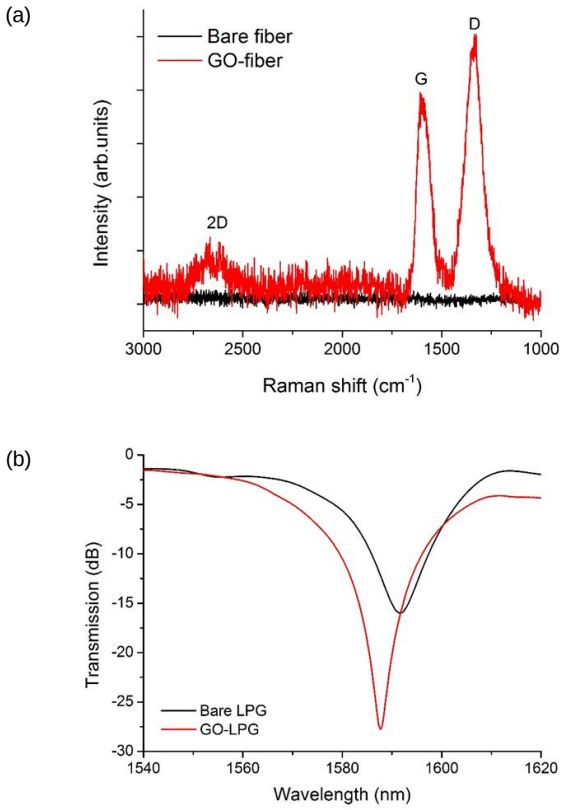

Fig. 4. (a) Raman spectra of bare and GO-coated fibers. (b) LPG transmission spectra before and after GO deposition.

3.3. Enhanced sensitivity of GO coated-LPG

The GO-LPG was implemented for RI sensing of the test solutions. A series of aqueous sucrose solutions were prepared with the measured RI values from 1.3315 to 1.4615. The GO-LPG was placed in a straight V-groove with two ends fixed and the solution was added into V-groove by careful pipetting to cover the entire grating region. After each measurement, both grating device and V-groove were rinsed with methanol and DI water thoroughly.

Fig. 5a plots the transmission spectra of GO-LPG with test solutions of different RIs. There are two different trends for the RI region below and above the CRI (≈ 1.445). For the RI lower than the CRI, the intensity of the attenuation band decreases as the RI increases. This is consistent with the theoretical analysis in Section 2.2. Due to the coating layer, the coupling coefficient Eq.(3) between core and cladding modes decreases as the RI increases. Once the RI is equal to the CRI, the cladding modes are no longer confined by the cladding layer which is acting as an infinite medium and supports no discrete cladding modes, hence a broadband radiation mode coupling occurs with no distinct attenuation bands. When the RI is higher than the CRI, the fiber does not support any bound cladding mode and the re-appeared attenuation band corresponds to leaky mode coupling [18,19]. By increasing the RI, the resonant intensity increases because the leaky mode is better confined by the Fresnel reflection while its wavelength is influenced with a blue-shift.

The intensity change of the attenuation band against the RI is plotted in Fig. 5b. For the RI region below the CRI, the intensity shows a nonlinear behavior for a gradual decrease with RI which is consistent with those LPGs coated with CNT, ZnO, TiO_2 [17-19]. The sensitivity achieves -76.5 dB/RIU and -234.2 dB/RIU for RI range of 1.33-1.38 and 1.40-1.44, respectively, exhibiting 2.5 times and 5 times higher than that of CNT-deposited LPG for the corresponding RI ranges [17]. For the RI higher than the CRI, the resonant intensity increases dramatically against RI. The sensitivity approaches +1580.5 dB/RIU which is 7.3 times higher than that of ZnO-coated LPG [18]. For the case of RI=1.4615, the resonant intensity reaches -28.35 dB, indicating that around 99.8 % of core mode has been coupled into leaky mode, which is extremely high than that of metal oxide-coated LPGs [18,19]. The enhanced sensitivity of GO-LPG may be caused by the unique features of GO material, such as extraordinary large surface-to-volume ratio, high carrier mobility, and excellent optical properties. GO provides strong light-matter interaction between evanescent field and external medium.

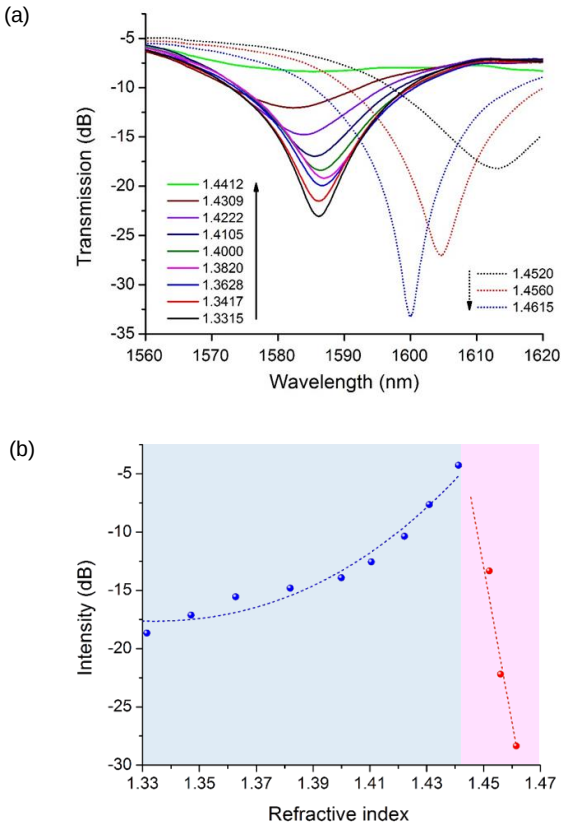

Fig. 5. (a) Transmission spectra of GO-LPG with test solutions of different RIs. (b) The variation of attenuation band intensity against the RI.

3.4. Detection of human hemoglobin

The GO-LPG was performed as a biosensor to detect human hemoglobin. A set of hemoglobin concentrations ranging from 0.0 mg/mL, 0.2 mg/mL, 0.4 mg/mL, 0.6 mg/mL, 0.8 mg/mL and 1.0 mg/mL were prepared with sucrose solution (RI=1.4610) acting as RI buffer. Fig.6a shows the spectra of GO-LPG under different hemoglobin concentrations and Fig. 6b plots the evolution of resonant intensity. It can be seen that the resonant intensity increases by 1.91 dB when the hemoglobin concentration changes from 0.0 mg/mL to 1.0 mg/mL. Defining the concentration sensitivity as the change induced by 1 mg/mL hemoglobin, we have the device sensitivity of 1.9 dB/(mg/mL). If use a low-noise interrogation system with a resolution of 0.1 dB, the GO-LPG could detect a hemoglobin concentration change as small as 0.05 mg/mL, which is far below the hemoglobin threshold value for anemia.

The increase of resonant intensity could attribute to the local refractive index change caused by the adsorption of hemoglobin molecules onto GO, where the measured pH values of hemoglobin concentrations are around 7.0, hence the strongest π−π interactions lead to the most effective adsorption of proteins onto GO [30,31]. Taking into account the advantages of both enhanced RI sensitivity and favorable biocompatibility, GO provides a significant sensing linkage between evanescent field and target biomolecules with enhanced light-matter interaction, consequently exhibiting ultrahigh sensitivity for hemoglobin detection.

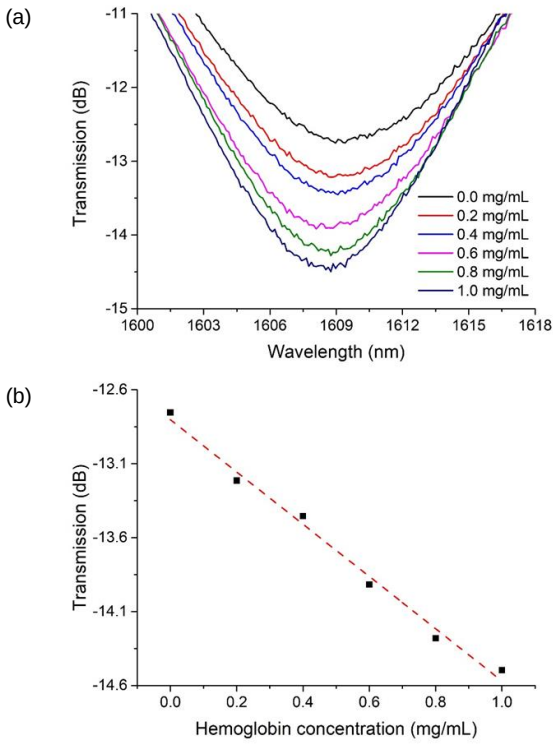

Fig. 6. (a) Transmission spectra of GO-LPG resonance and (b) the intensity change of attenuation band against hemoglobin concentrations.

4. Conclusions

In conclusion, we have presented GO-LPG based optical biosensor for ultrasensitive human hemoglobin detection. The deposition technique based on chemical-bonding associated with physical-adsorption has been developed to immobilize GO nanosheets on cylindrical fiber device with the desirable thickness of 501.8 nm and good uniformity. Surface morphology of GO overlay was characterized by SEM, AFM, and Raman microscope. The GO-LPG has been demonstrated as intensity sensor with the sensitivities of -76.5 dB/RIU, -234.2 dB/RIU, and +1580.5 dB/RIU for RI range of 1.33-1.38, 1.40-1.44, and 1.45-1.46, respectively, showing a superior performance than bare LPGs and other reported thin-film coated-LPGs. The GO-LPG exhibits ultrahigh sensitivity of 1.9 dB/(mg/mL) for hemoglobin detection with the detectable concentration of 0.05 mg/mL, which is quite far below the hemoglobin threshold value (130 mg/mL for men and 120 mg/mL for women) for anemia defined by WHO.

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