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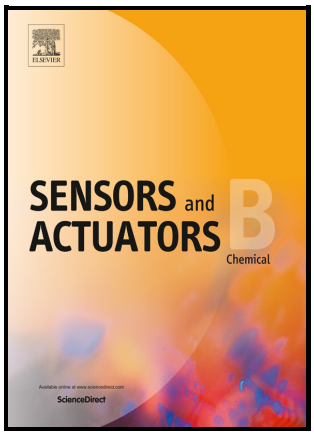

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Sensitivity Tunable Biosensor Based on Graphene Oxide Coated Excessively Tilted Fiber Grating

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ABSTRACT:

Biosensors play a significant role in biomedical, clinical and disease diagnosis areas. Here, we proposed Langmuir adsorption model to explain sensing mechanism of biosensor based on excessively tilted fiber grating (Ex-TFG) functionalized with graphene oxide (GO). Due to GO containing plenty of six-membered rings and oxygen-containing groups, the biomolecules can be easily adsorbed through π-π interaction and hydrogen bond. The whole interaction process obeys the Langmuir adsorption model in which there always an equilibrium during detecting process, inducing the sensor with tunable bio-sensitivity and detection range. Three biosensors based on Ex-TFG coated with three different amount of GO were investigated for hemoglobin (Hb) detection experiment, showing pronounced bio-interaction induced resonance shifts. The experiment results indicate that GO coating has enhanced the surface biological activity of Ex-TFG, making the Ex-TFG sensitive to the Hb biomolecule solutions. The three GO coated Ex-TFG sensors have the bio-sensitivity of 3.83 nm/(mg/ml), 4.33 nm/(mg/ml), and 8.21 nm/(mg/ml), and the detection range of 0.8mg/ml, 0.6mg/ml and 0.4mg/ml, respectively, which are in good agreement with the prediction from the Langmuir adsorption model. By controlling the amount of the bio-functionalized materials, the bio-sensitivity and detection range of the Ex-TFG based biosensors can be easily designed.

Keywords：

Langmuir adsorption, graphene oxide, selectable sensitivity, dynamic detection range

Introduction

The biomarker is a significant biochemical index in human body, such as messenger RNA, insulin, hemoglobin (Hb) and so on[1], which could reflect a certain biomolecules characteristic in the general physiology, pathology in the organism, or process of treatment [2]. With the continuous progress of life science and biotechnology, the detection of biomarker molecules has become an important focus of current research, which would be essential for disease identification, early diagnosis and prevention, and monitoring during treatment. To date, the main methods to test biomolecules are based on electrophoresis, UV absorption and western blotting[3]. Electrophoresis detection is easy operation, fast and less sample consumption, but time consuming and vulnerable to be disturbed. UV absorption is operation easy and response fast, but associated with poor accuracy and low susceptibility to interference. Western blotting technique has the advantages of large analysis capacity, high sensitivity and strong specificity, however, it is inconvenient to use in outpatient, not sustainable to cross reaction and

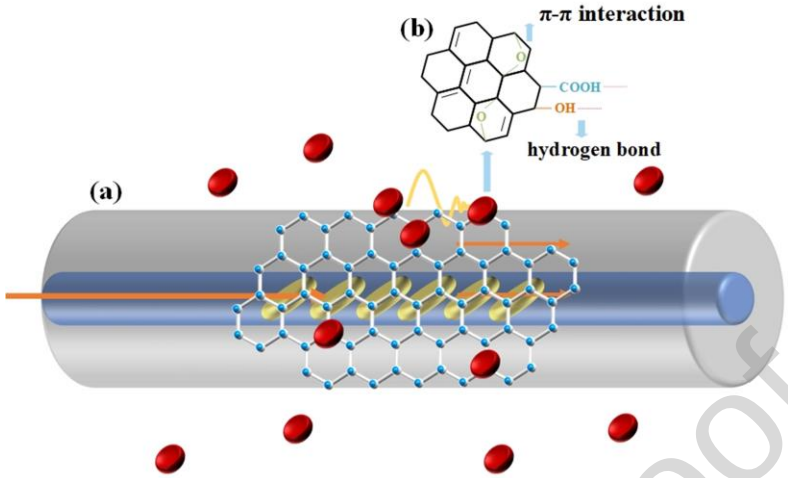

Figure 1. (a) Schematic diagram of fiber optical biosensor based on GO coated Ex-TFG, which provides a platform

expensive to operate. Hence, it is necessary to develop an excellent performance biosensor technology with advantages of operation easy, online real-time detection and high sensitivity to detect biomolecules. With the development of the optical fiber sensor (OFS), the OFS based biosensors have shown the advantages of small size, high sensitivity, and fast response [4], which fully satisfy the needs for miniaturization, intelligence and online monitoring of biomolecular and biomedical detection. Considerable research works based on OFS have been reported in the past, which mainly focused on the microfiber [5,6], tilted fiber Bragg grating (TFBG) [7,8] based surface plasmon resonance (SPR) sensor, long period grating (LPG) [9,10] and excessively tilted fiber grating (Ex-TFG) [11,12]. These OFSs are sensitive to the surrounding environment refractive index (RI), however, for most of biomolecule solutions with concentration of 0-1mg/ml, the RI of the aqueous can only induce $<10^{-5}$ RI difference, which is difficult to be detected directly. To achieve biological trace detection, there are two ways to realize the bio-detection based on OFS: 1) Enhancing the RI sensitivity of OFS with orders of magnitude ($>10^{-5}$), but for ultra-high RI detection, the inevitable disadvantage is the temperature sensitivity of OFS, which can lead to the cross- talk error during the sensing process[13]; 2) Surface bio-activity enhancement or functional modification of OFS, which can promote the interaction between the sensors and biomolecules, thus greatly increasing the concentration of biomolecules within the detection area of OFS [14]. It is clearly that the

second method is the more commonly adopted approach. So far, the most frequently used method to enhance the surface bio-activity of OFS is to functionalize a layer of nanomaterial with good film formation ability, as well as convenient availability and modification, such as gold nanoparticles, zinc oxide, carbon nanotube, black phosphorus, graphene oxide (GO) and so on [15,16]. As a novel 2-D nanomaterial, GO has been widely applied in biosensing area taking the advantages of excellent biocompatibility and abundant binding sites [17]. Liu et al. [18] developed an ultrasensitive label-free antibody-antigen immunosensor based on GO functionalized LPG for IgG recognition. Jiang et al. [19] reported a label-free biosensor based on GO and glucose oxidase functionalized (GOD) Ex-TFG for low concentration glucose detection. Liu et al. [20] proposed a biosensor based on GO-coated LPG for hemoglobin (Hb) detection, which utilized GO to increase the RI sensitivity of the biosensor and to adsorb Hb biomolecules. Chen et al. [21] exhibited a plasmonic TFBG integrating gold and protein Set7 for in-situ detection of the small biomolecule S-adenosyl-L-homocysteine. These biosensors have achieved the goal of high sensitivity and online monitoring, however, most of the techniques just demonstrated the bio-sensing capability, which neither systematically discussed its detection mechanism nor quantitatively analyzed the performance of the biosensor. In addition, the biosensor performance is one of the important evaluations for the future commercial application of optical fiber sensors.

In this paper, we proposed Langmuir adsorption model to explain sensing mechanism of GO-coated Ex-TFG based biosensor, in which the Ex-TFG as a biosensor showed high RI sensitivity and low temperature cross-talk, and functionalized by using the nanomaterial of GO with excellent optical and biocompatibility properties, and performed the test on protein target of Hb biomolecules. Based on the Langmuir equation, we have quantitatively evaluated the Ex-TFG sensing features with GO functional modification for protein detection, and systematically explored the response of biosensor to Hb biomolecules concentration, which has exposed that the amount of GO coating will affect the detection range and sensitivity of the biosensor. The experimental and theoretical analysis have shown a good consistence, providing a design principle for a tunable sensitivity and detection range biosensor, which may be suitable for biosensing applications with optimum performance.

Theoretical analysis

The sensing system includes the biosensors based on Ex-TFGs coated with a monolayer of GO and subjected to the detection of Hb biomolecules (shown in Fig.1(a)). The GO layer on the Ex-TFG has high surface-to-volume ratio area and abundant functional groups, which is favorable for adsorbing biomolecules. OFS sensing relies on the change of evanescent field to measure the RI variation. During the sensing process, the biosensor surrounding is filled with a great quantity of Hb biomolecules, and the Hb biomolecules increase with the concentration of Hb biomolecules solution, however, the RI changing of the Hb biomolecules solution is too weak to be detected, but the Hb biomolecules adsorbed by GO layer through π-π interaction and hydrogen bond interaction [22] can greatly induce the perturbation to the evanescent field of grating, resulting in the wavelength shift of cladding mode resonance of the Ex-TFG to be detected. For π-π interaction and hydrogen bond interaction, there is always an equilibrium state between the adsorbed biomolecules and the GO layer, in which the amount of adsorption and desorption is the same and the biosensor reaches saturation macroscopically. Such adsorption process usually be called as Langmuir adsorption [23], and obeys the Langmuir, which could be expressed as:

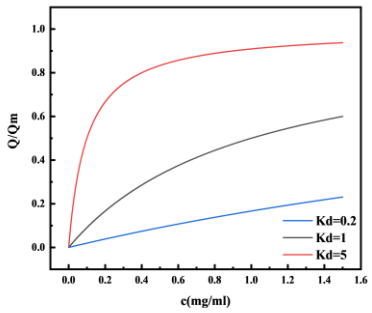

Figure 2. Equilibrium adsorption capacity Q for different adsorption equilibrium constant K_d.

$$\frac{Q}{Q_m} = \frac{1}{\frac{1}{K_d c} + 1} \quad (1)$$

Where, Q is the equilibrium adsorption capacity, Q_m is the maximum adsorption capacity of the biosensor, which is a fixed value for a certain material, K_d is the adsorption equilibrium constant, and c is the equilibrium concentration of solution.

Relatively, the adsorption equilibrium constant K_d represents the sensitivity trend of the biosensor in the corresponding sensitivity curve, which determines the performance of the biosensor. The K_d value depends on the amount of GO coating on the sensor surface, in which the more GO is, the higher the sensitivity. Different trends of the equilibrium adsorption capacity Q with three different value of K_d are plotted in Fig.2. As shown in the figure, the equilibrium adsorption capacity Q exhibits a linear trend for K_d =0.2, which corresponds to a lower sensitivity of the sensor. For K_d =1, the trend of equilibrium adsorption capacity Q is non-linear, which gradually increasing and reaches a saturation level at high concentration. For K_d =5, the equilibrium adsorption capacity Q dramatically increasing even at a low concentration and quickly reaches a saturation level and remains unchanged at high concentrations. Comparing the three curves, the larger value of K_d means a better adsorption performance and high sensitivity, but as it is saturated quickly, the detection range is limited. Therefore, it is important to optimize the K_d value for a biosensor with tunable sensitivity and detection range.

Material and fabrication

Materials.

(3-aminopropyl) triethoxysilane (APTES), single layer GO dispersion, and lyophilized powder of human hemoglobin were all purchased from Sigma-Aldrich (China). Sodium hydroxide (NaOH) was supplied from Sinopharm Chemical Reagent Co., Ltd.

Experimental setup.

The experimental setup of Hb sensing consists of a super-broadband light source, in-fiber linear polarizer, polarization controller, and optical spectrum analyzer. During the experiment, the two ends of Ex-TFG were fixed by fixtures to keep the grating flat and avoid the effects of stress and bending. And the whole process was carried out at room temperature.

GO surface functionalization process.

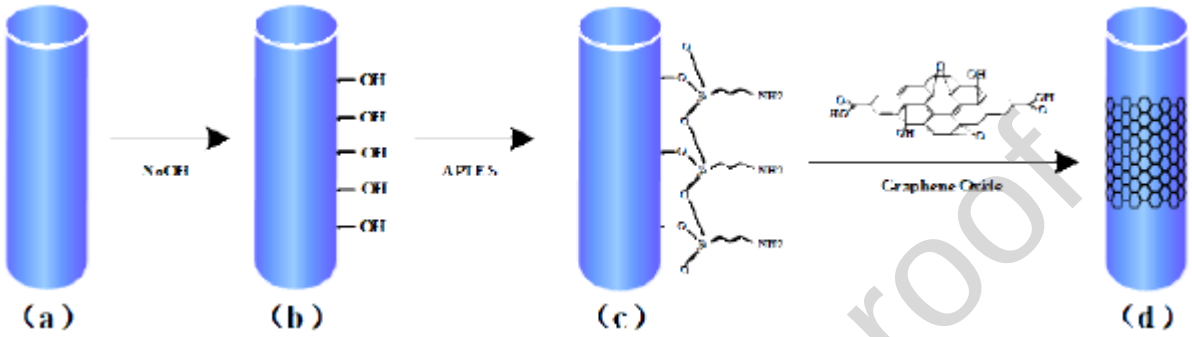

Figure 3. Process of GO coating (a) Bare Ex-TFG; (b) Hydrophilic treatment Ex-TFG; (c) APTES embellishing Ex-TFG; (d) GO functionalized Ex-TFG.

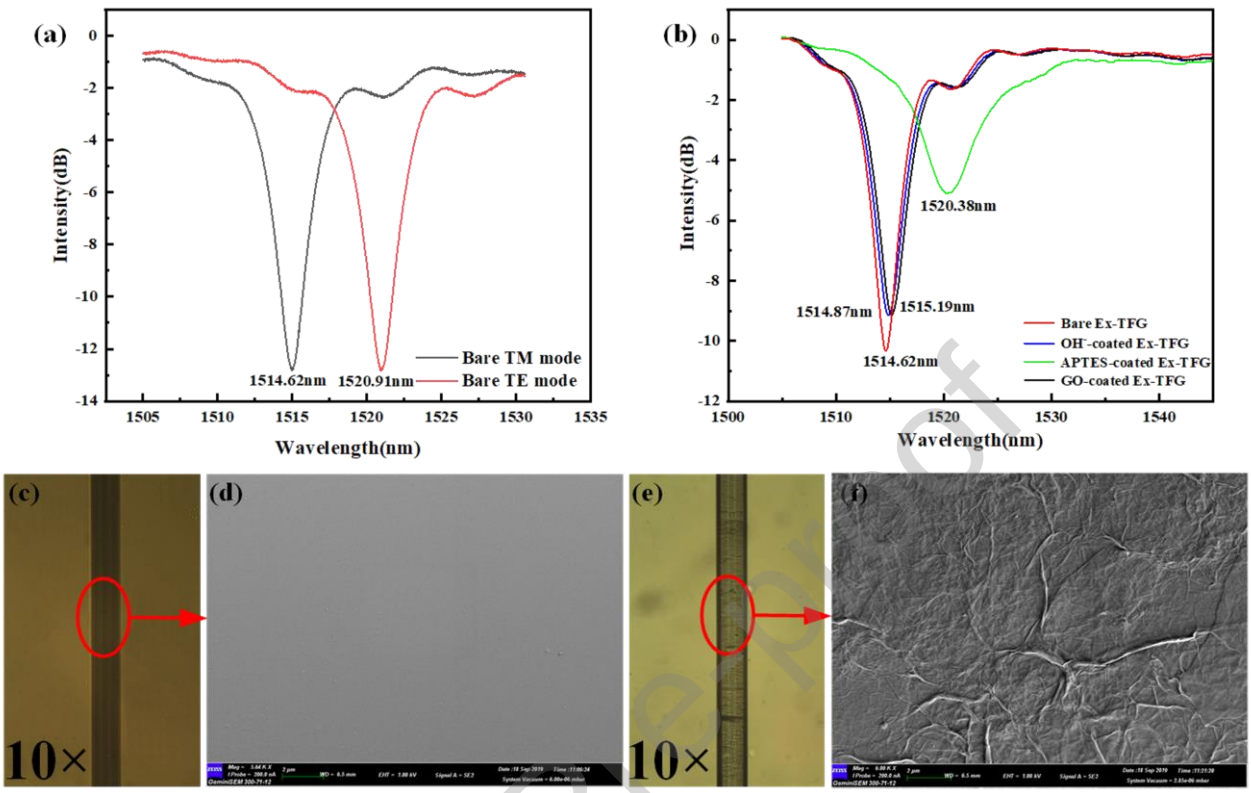

Figure 4. (a) The TM mode and TE mode transmission spectrum of Ex-TFG; (b) The transmission spectra of TM mode during functionalization process; (c) 10× Microscope graph of bare Ex-TFG; (d) SEM graph of bare Ex-TFG, which shows a smooth surface; (e) 10× Microscope graph of GO coated Ex-TFG; (f) SEM graph of GO-coated Ex-TFG

In order to enhance the Hb biomolecules adsorption of Ex-TFG, we adopted the deposition technology based on physical adsorption and chemical bonding to deposit GO on the Ex-TFG. Before deposition, we used alcohol and deionized (DI) water to wash the grating surface several times to keep it clean. The Ex-TFG was firstly immersed in the cleaned Ex-TFG in NaOH solution (5% v/v) for 2 hours to activate the hydroxyl groups (-OH) on the surface of the grating. Then, the treated Ex-TFG was soaked in APTES solution (5% v/v) for 30 minutes to form Si-O-Si bonds. After silanization, the Ex-TFG was placed in the GO dispersion solution (2mg/ml) for 1 hour. Amino groups of APTES were combined with epoxy group of GO, so that the GO was gradually deposited on the grating surface. After each step of immersion, we washed the grating thoroughly several times with ethanol and DI water to clean the grating surface to remove the extra substances and dried it in air for 30 minutes to keep it stable. The functionalization process is shown in Figure.3.

Table 1 The spectra performance of GO-coated Ex-TFG sensor with different GO immersing time

Sample	Immersing time	Wavelength shift	Intensity	Bandwidth
Bare Ex-TFG			19.27dB	1.5nm
Sensor 1	1h	0.57nm		
Sensor 2	1h 10min	1.14nm	13.46dB	2.16nm
Sensor 3	1h 20min	1.61nm	12.07dB	2.43nm
Sensor 4	2h	4.34nm	7.64dB	4.38nm

Results and discussion

To verify the above analysis, we have investigated a series of Ex-TFG with different amounts of GO coating. The Ex- TFGs used in the experiment were designed with 28.8μm axial grating period and 80° tilt angle, and were UV inscribed in SMF 28 fiber by amplitude-mask scanning technique. As previously reported, such Ex-TFGs have high RI sensitivity and low temperature cross-talk [24]. According to our previous work [24], the Ex-TFG is a degenerated structure, thus the light will be coupled into the TM and TE cladding modes (seen in Fig. 4(a) and Fig. S1). Moreover, the RI sensitivity of TM mode is slightly higher than that of TE mode, which was verified in this work (seen in Fig.S2). In the experiment, we select one of the TM cladding modes for the sensitivity analysis.

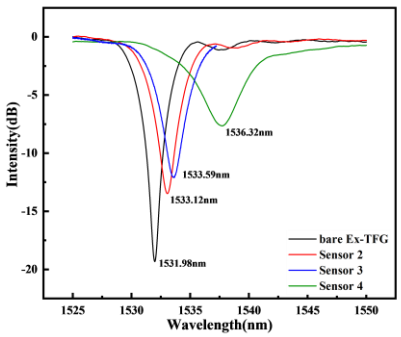

Figure 5. The transmission spectrum with different GO coating quantity.

The dip-coating method was used for GO functional process onto the Ex-TFG, which includes NaOH immersing, APTES embellish and GO functionalization, and the details are given in the previous section. During the functionalization process, we have monitored the wavelength shift of TM resonance peak of the Ex-TFG. As shown in Fig. 4(b), the TM peak is red-shifting as the different layer coated applied to the surface of Ex-TFG, which is because that the coating layers have a higher RI which would add the effective surround RI outer of Ex-TFG within the evanescent field of cladding mode. After the GO coating process, the intensity of TM cladding mode was reduced due to GO layer induced the scattering on the Ex-TFG surface. Furthermore, we have examined the surface of Ex-TFG sensor without and with GO functionalization by using an optical microscope and scanning electron microscope (SEM), and the images are showed in Fig.4 (c)-(e). As shown in Fig.4 (c) and (d), the bare Ex-TFG has a smooth surface, while after the GO functionalization, there is a shadow layer on the surface of the optical fiber (Fig.4 (e)). Employing SEM with 6000 times magnification, we can clearly see the GO-coated Ex-TFG surface has a pleated dense film (shown in Fig.4 (f)), which demonstrated that the GO layer has been successfully deposited onto the surface of Ex-TFG.

In the experiment, the amount of GO coated on the surface of Ex-TFG cannot be measured directly, but it could be controlled by grasping the immersing time approximately, which corresponds to the drift of the cladding resonance peak. Since GO is a high RI material, the wavelength shift of Ex-TFG can represent the amount of GO coating. As shown in Table 1, the four sensors of Ex-TFGs under different GO immersing time with 1h, 1h 10min, 1h 20min and 2h have the wavelength shift of 0.57nm, 1.14nm, 1.61nm and 4.34nm, respectively, in which the longer the immersing time, the more deposited GO amount, and results in the more wavelength shift. Therefore, the amount of GO can be calibrated by evaluating the drift of the TM cladding resonance peak. And the performances of the sensor 2, sensor 3 and sensor 4 were compared with different GO quantity plotted in Fig.5. Moreover, the resonance peak intensity of the four sensors decreases sequentially (shown in Table 1), due to the GO layer enhancing the scattering on the biosensor surface. And the bandwidth of the sensors broadens because of the uneven coating of the grating surface.

Then, we have evaluated the RI sensitivity of sensor 1 in the RI range of 1.33-1.41. The RI solutions were prepared by mixing deionized (DI) water and glycerin and calibrated by digital refractometer (IR120) with 10^{-4} RI accuracy. The RI sensing results of bare Ex-TFG and GO-coated Ex-TFG are shown in Fig.6 (a), in which the RI sensitivity of GO-coated Ex-TFG is slightly improved at the RI>1.35 region, because GO has high RI, but almost the same at the RI around 1.33-1.34, compared with the bare Ex-TFG. Furthermore, we designed a series of Hb biomolecules detection experiments to test the GO-coated Ex-TFG biosensors. The concentrations range of Hb biomolecules solution we prepared is from 0.1mg/ml to 1.0mg/ml with interval of 0.1mg/ml, which are disposed with DI water (RI=1.33). The RI of the different concentrations of Hb biomolecules solutions are all the same around 1.3333 measured by with a digital refractometer (IR120), which This illustrates the biosensor based on GO modified Ex-TFG could achieve Hb biomolecules concertation detection through GO adsorbing Hb biomolecules instead of enhancement of the RI sensitivity of the sensor.

Table 2 The sensing performance of GO-coated Ex-TFG sensor with different GO coating amount

Sample	Wavelength shift (GO amount)	Sensitivity	Detection range
Sensor 1	0.57nm	2.46nm/(mg/ml)	0—1.0ml
Sensor 2	1.14nm	3.83 nm/(mg/ml)	0—0.8ml
Sensor 3	1.61nm	4.33 nm/(mg/ml)	0—0.6ml
Sensor 4	4.34nm	8.21 nm/(mg/ml)	0—0.4ml

During the Hb biomolecules concentration detection experiment, the same volume of Hb biomolecules solution was subjected into the entire grating to make sure the Hb biomolecule fully interacted with the sensor, and after each measurement, the grating was cleaned with DI water and alcohol thoroughly. To investigate the sensing principle of the biosensor, we have tested the response of the OH--coated Ex-TFG and GO-coated Ex-TFG during the functionalization procedure, respectively. As shown in Fig.6(b), the Ex-TFG displays a linear response to the Hb concentration after activating hydroxide on the grating surface, which showed the 1.93nm/(mg/ml) sensitivity. Relatively, the sensor 1 of GO functionalized Ex-TFG with 0.57nm wavelength shift exhibits a linear response of resonant wavelength versus Hb biomolecules concentration with 2.46nm/(mg/ml) sensitivity in the concentration of 0-1.0mg/ml (shown in Fig.6 (b)). Essentially, the Hb biomolecules are adsorbed by the GO on the surface of Ex-TFG, the RI of evanescent field of sensors could be exponentially increased, which caused that the TM cladding resonance peak would be redshift. According to the comparing experimental results, the Ex-TFG sensor all had the ability to adsorb Hb biomolecules after each step of functionalization, and the GO-coated sensor could greatly improve the sensitivity of Hb concentration, because GO layer owns not only hydroxide and electrostatic interaction, but also π-π bond, which strengthens the Hb biomolecules combination. As we analyzed above, the bare Ex-TFG was insensitive to Hb biomolecules solution (shown in Fig.6(b)), due to the RI of different amount of Hb biomolecules solution is almost at the same RI around 1.33. And, the GO-coated Ex-TFG sensor could be realized to achieve the detection of Hb biomolecules by activating or joining the bioactive groups on the sensor surface.

So far, most researches mainly focused on how to improve the sensitivity of the biosensor, but ignored to investigate the performance and behavior of sensor itself. In this section, we evaluate the performance of the sensors from its adsorption ability and sensing detection range. Generally speaking, the biosensor could reach higher sensitivity by raising the binding sites through modifying the more amount of GO. In the previous part, the value of wavelength shift could represent the amount of GO deposition, and as increasing the targets binding sites on the outer surface of sensor, the detecting sensitivity to Hb biomolecules would be improved, and the detection range would be decreased correspondingly. And then, we con-

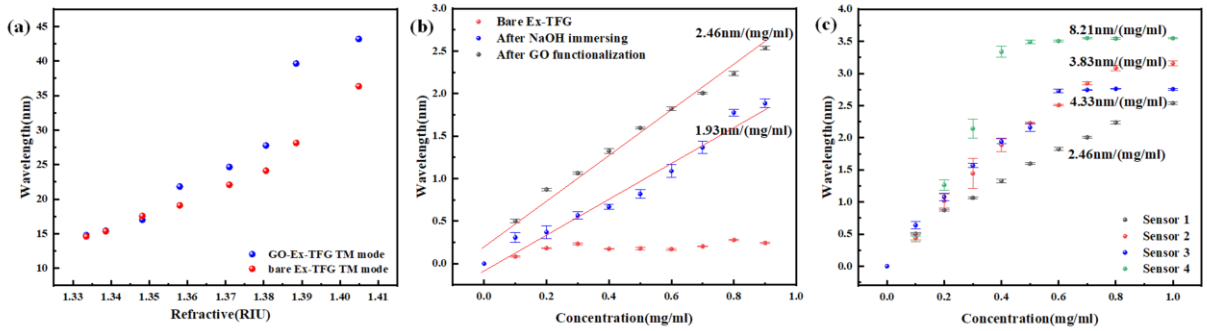

Figure 6. (a) The RI sensitivity of bare and GO-coated Ex-TFG; (b) The sensitivities of functionalization process, whose response are linear relationship; (c) The sensitivities of different GO quantity biosensor, the more GO quantity, the higher sensitivity.

ducted a series of experiments with sensor 2, sensor 3 and sensor 4 with different GO amount, which corresponds to the wavelength shift of 1.14nm, 1.61nm, and 4.34nm, respectively, for exploring the Hb biomolecules concentration sensitivity. Fig.6(c) illustrated the response of biosensors to Hb biomolecules concentration, which have been listed in the Table 2 combined with sensor 1. As a comparison, the four sensors display a growth trend for detection sensitivity of 2.46nm/(mg/ml), 3.83nm/(mg/ml), 4.33nm/(mg/ml), 8.21nm/(mg/ml), respectively, as the GO amount increases. Relatively, the maximum detection concentration gradually decreases for the sensors with 1.0mL, 0.8mL, 0.6mL and 0.4mL. The experiment results show that the sensitivity of GO-coated Ex-TFG is becoming higher as the increasing GO quantity, but the detection range decreases as a result of the biosensor easier to reach saturation at a lower concentration, which is compatible with theoretical analysis above.

Conclusion

In summary, we have investigated the performance of biosensors based on nanomaterial functionalized OFS, which provides the directions for future commercial application. The OFS generally functionalized by nanomaterial, whose sensing principle obeys the Langmuir adsorption mode, exhibiting selectable sensitivity and detection range. The Ex-TFG and Hb biomolecules are selected to verify the proposed theory. In the experiment, we considerately explore the principle and the process of Hb biomolecules detection based on GO coated Ex-TFG, which indicates that the Ex-TFG after OH^- embellish and GO functionalized both could detect Hb biomolecules due to the active groups binding with Hb biomolecules. In addition, we have investigated the sensing performance of GO-coated Ex-TFG sensor with different coating amount, which the results show that the more quantity GO is, the higher sensitivity of the biosensor, but the smaller the corresponding detection range, while the wide detection range and low sensitivity could be obtained on the contrary. Consequently, the selectable sensitivity and detection range biosensor could be realized, which provide more possibilities for further medical and biochemical applications development.

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Biographies

Yuezhen Sun is currently a Ph.D. candidate at Huazhong University of Science and Technology, under the Prof. Zhijun Yan. She received her B.E. degree from School of Optical and Electronical Information at Huazhong University of Science and Technology. Her research interest is the theoretical analysis and application of excessively tilted fiber grating.

CRediT authorship contribution statement

Yuezhen Sun: Conceptualization, Methodology, Validation, Formal analysis, Writing - Original Draft, Visualization, Xiaoxia Guo: Writing - Review & Editing, Project administration, Yarien Moreno: Validation, Investigation, Visualization, Qizhen Sun: Funding acquisition, Zhijun Yan: Writing - Review & Editing, Supervision, Project administration, Funding acquisition, Lin Zhang: Writing - Review & Editing, All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Proposed GO functionalized Ex-TFG based low temperature crosstalk biosensor for biomolecules probing
- For the first time, established Langmuir adsorption law based sensing model of optical fiber biosensor
- Achieved the sensitivity and detection range adjustable biosensor