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Terahertz biosensing with a graphene-metamaterial heterostructure platform

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ABSTRACT: Terahertz (THz) radiation attracted great interest in the fields of material characterization, nondestructive security screening, clinical diagnostics, and identification of chemicals and molecules. Label-free THz sensing of trace amount of targets including biomolecules is promising because of their rich spectral fingerprint in this electromagnetic region; however, improving the sensitivity remains to be a challenge, partially due to the limitations of THz sources and detectors. The resonantly enhanced electromagnetic fields in metamaterials and metasurfaces offer a potentially viable solution, although highly complicated decoration process is still needed for biosensing on the surface of metamaterials. Here we demonstrate a simple biosensing platform by integrating a monolayer graphene on a THz metamaterial absorber cavity, where the introduction of sensing targets results in a large change of the metamaterial resonant absorption (or reflection) because of their strong interaction with graphene. We experimentally show its ultrahigh sensitivity through detecting trace amount of chlorpyrifos methyl down to 0.2 ng. Using simple decoration steps and utilizing DNA to capture thrombin, we further show the feasibility of this platform serving as a sensitive biosensor.

1. Introduction

Terahertz (THz) waves fall between microwaves and infrared light in the electromagnetic spectrum and inherit the richness of photonics as well as electronics. Recent progress in sources and detectors has transformed the so-called ‘THz gap’ into one of the most rapidly growing fields of research, including a strong effort to develop a high-performance THz sensing technology. The localized resonances excited in metamaterials show a dramatically enhanced electromagnetic field near the metallic structures,[1,2] which offers an extremely attractive approach to enable new applications in the THz regime.[3–8] In the past years there have been extensive studies in the resonant response in metamaterials and metasurfaces for a variety of unusual properties and functionalities,[9,10] and in tuning their resonant response[11,12] through integrating active functional materials to enable external stimuli such as electrical,[13] thermal,[14] or optical actuations.[15,16] Although not directly related to biosensing, they inspire us to look at the possibility, and our recent study shows that metamaterials can serve as a promising signal-enhancing tool and greatly improve the sensitivity of target detection such as antibiotics.[17] However, much efforts are still needed in developing new metamaterial sensor architecture to further improve the sensitivity, and to address issues such as the complex decoration process for target capture as antibody or aptamer is compulsory to typical metal/dielectric materials used in metamaterials.

A plausible solution is using graphene because, unlike conventional bulk materials, graphene interacts with external molecules in its close vicinity through delocalized π -electrons,[18] and the interaction of external molecules and Dirac electrons does affect the doping level of graphene.[19,20] Graphene has attracted huge attention in many fields owing to its unique electronic, optical, mechanical, and thermal properties.[21–24] In the mid-infrared and THz

region, graphene has been used to demonstrate tunable plasmonics[25–31] and biosensing.[32] Owing to the great biomolecular affinity via π -electrons, graphene has been applied to DNA hybridization and aptamer sensing,[33,34] especially combining the fluorescence technology.[22,35,36] Such intriguing properties make graphene a very promising material in potential applications including optical modulators and sensors.

Here we demonstrate an efficient THz *graphene-metamaterial sensor* (GMS) for label-free sensing applications. We present the first experimental demonstration of a THz graphene-metamaterial heterostructure exhibiting an intensity modulation depth up to 35% with the presence of chlorpyrifos methyl molecules. We show that analytes with π -electrons like chlorpyrifos methyl, which interacts with graphene through π - π stacking,[37,38] have a higher sensitivity than analytes without π -electrons, such as fructose. By adopting this scheme of a GMS, the sensing limit of chlorpyrifos methyl can reach down to 0.2 ng, demonstrating an effective sensitivity for trace amount of analytes. We further use this prototype device as the first THz graphene-metamaterial biosensor, and experimentally realize the thrombin detection with simple decoration steps.

2. Materials and Methods

A THz time-domain spectrometer system (Z-3, Zomega Corporation, East Greenbush, NY, USA) was used to measure the broadband reflection and/or transmission spectra, covering a spectral range of 0.1-3.5 THz. The system was purged with nitrogen, resulting in less than 1% humidity to prevent THz absorption from water vapor. The signal-to-noise ratio (SNR) was over 60 dB for all the THz spectral measurements and the temperature was 23 ± 1 °C. Tapping-mode AFM was conducted with a Dimension Icon AFM equipped with a ScanAsyst (Bruker AXS, Germany). The scanning area is 3.5 μm by 3.5 μm . The Raman measurements were performed by a LabRAM HR

Evolution Raman microscope system (Horiba Jobin Yvon), where a He-Ne laser (633 nm) was used for excitation.

A 200 nm thick aluminum film was pre-deposited as the background mirror (ground plane) on silicon. Polyimide with a measured permittivity $\epsilon = 2.98 - 0.165i$ (at 1 THz) was deposited on the aluminum film with thickness of 4 μm through spin-coating and thermal-cure in sequence at 80 °C, 120 °C, 150 °C, and 180 °C for 4 hours, 1 hour, 1 hour, and 1 hour, respectively. Gold patch resonator arrays were fabricated on the top using standard photolithography methods, ebeam evaporation of 200 nm gold film, and a lift-off process. The period of THz metamaterials was 140 μm with different patch widths 95 μm , 90 μm and 85 μm . CVD grown single layer graphene (Trivial Transfer Graphene) was purchased from ACS Material (Medford, MA, USA). Graphene was slowly transferred onto the surface of water. Then it was transferred onto the surface of metamaterial absorber by matching the graphene area with the metamaterial structure. The polymethyl methacrylate (PMMA) layer on the top of graphene was removed by acetone after the graphene-metamaterial heterostructure was dried in oven at 100 °C for 20 min.

Fructose, chlorpyrifos methyl and thrombin were purchased from Sigma-Aldrich. Different concentrations of fructose and chlorpyrifos methyl solution were prepared for metamaterials sensing. Before adding fructose or chlorpyrifos methyl sample, monolayer graphene coated metamaterials were clearly washed thrice using the deionized water. Metamaterials with resonant peaks at 0.95 THz were selected for fructose and chlorpyrifos methyl detection. In this work, 10 μL of desired fructose or chlorpyrifos methyl solution was dropped on the surface of monolayer graphene coated THz metamaterials with three duplicates. Then the sample was dried at room temperature before THz measurement. Each spectrum was averaged by four scans.

In aptamers sensing, first, 10 μL of 20 μM TBA solution was added onto the surface of monolayer graphene coated THz metamaterials and incubated for 2 h. Then the sensor was washed thrice by PBS. After that, the sensor was incubated in 100 nM thrombin solution for 1 h. Another monolayer graphene coated metamaterials with TBA was incubated in PBS for reference. PBS and aptamers were purchased from Sangon (Shanghai, China). Finally, monolayer graphene coated THz metamaterials with and without graphene were used for THz measurements.

3. Results and Discussion

The graphene-coated THz metamaterial sensor operating in reflection is schematically illustrated in Figure 1a. The metamaterial structure consists of an aluminum ground plane, a thin dielectric spacer (polyimide), and a planar array of square patch gold resonators, forming a metamaterial absorber.[39] This metal-dielectric-metal structure provides an ultrathin resonant cavity and traps the incident waves, leading to significant field enhancement and near-unity absorption at its resonant frequency.[40–42] A commercially available graphene monolayer synthesized by chemical vapor deposition (CVD) method is then transferred on top of the metamaterial,[43] completing the THz GMS with good uniformity for THz sensing. The graphene monolayer is confirmed by Raman spectroscopy, which reveals a high-intensity 2D peak ($\sim 2680\text{ cm}^{-1}$) and a low-intensity G peak ($\sim 1580\text{ cm}^{-1}$), as shown in Figure 1b.

The addition of the monolayer graphene results in an obvious change of the metamaterial absorption, as revealed by the reflection curves shown in Figure 1c. These are measured using THz time-domain spectroscopy (THz-TDS) (See Methods), where the reflectance is defined as $R = |E_{\text{sample}}/E_{\text{reference}}|^2$, with E_{sample} ($E_{\text{reference}}$) the THz electric field intensity reflected from the metamaterial sample (silver mirror reference). For the metamaterial structure with gold patch side

length 85 μm and without the monolayer graphene, the reflectance is about 10% at 0.975 THz, indicating intense resonant absorption (Note that the absorption $A = 1 - R$, as the transmission is zero due to the presence of the aluminum ground plane). This sharp resonance peak has shown great feasibility in detecting trace amount targets in recently reported works.[6–8] The reflectance of the graphene-metamaterial heterostructure reaches 55%, accompanied with a red shift of the resonance frequency, as shown in Figure 1c. The monolayer graphene causes a 45% change of the reflectance (or absorption) from the metamaterial absorber, which outweighs most dielectric materials with a similar thickness. The large change of reflectance is due to the slight modification of the dispersion of the top patch resonator array and, thereby, the resonant cavity, by the introduction of the conductive monolayer graphene. The red shift of the resonance frequency and decrease value of quality factor (Q) agree with the literature.[3,6] Similar results are observed (see Figure S2) in graphene-coated metamaterials with different geometry parameters.

The proposed GMS structure allows for strong light matter interactions and enables ultrasensitive detection of analyte layer deposited on the top, as slight modification of graphene properties can result in significant change of absorption. The graphene-coated metamaterial detection of chlorpyrifos methyl molecules deposited from 10 μL 3 mg L^{-1} solution (see Methods) is illustrated in Figure 2a, where a blue shift reflection dip and a higher value of Q -factor can be clearly observed, as compared to those in graphene-coated metamaterial alone. This is in remarkable contrast to the sensing response from a metamaterial without graphene coating, where addition of sensing targets typically causes a red shift and reduced Q -factor as revealed in Figure 2b showing the bare metamaterial detection of 10 μL 3 mg L^{-1} solution of chlorpyrifos methyl. In the latter case, the resonance red shift is due to the increased refractive index and the decrease of Q value

results from the additional damping when sensing targets (here chlorpyrifos methyl) are introduced to the metamaterial.[3,6,44]

The observed sensing response from GMS is caused by the unique interaction of external molecules and the graphene-metamaterial heterostructure. As previously mentioned, external molecules interact with graphene within its close vicinity through delocalized π -electrons. One of the consequences is that the interaction moves the Fermi level toward the Dirac point and decreases carrier density in graphene.[37,38] Correspondingly, the graphene conductivity decreases and the metamaterial resonance enhances, resulting in a reduced and blue shifted reflection dip (increased absorption), as well as a higher Q -factor value. That is, the metamaterial absorber is recovered to the case before the addition of the monolayer graphene shown in Figure 1c. This argument is further validated through performing finite difference time domain (FDTD) numerical simulations (Lumerical) of reflectance from a monolayer graphene-coated metamaterial with Fermi level ranging from 30 meV to 120 meV below the Dirac point. As shown in Figure 2c, the resonant reflectance of graphene-metamaterial is higher (absorption is lower) than that of metamaterials without graphene, in accordance with the results shown in Figure 1c, due to the damped resonance and modified metamaterial absorber cavity by the introduction graphene. When shifting the Fermi level toward the Dirac point, the resonant reflectance of monolayer graphene-coated metamaterial decreases (i.e., absorption increases), together with an increased Q -factor and a blue shift, in good agreement with the experimental observation shown in Figure 2a.

The sensitivity of the GMS device depends on how the external molecules interact with the monolayer graphene. Chlorpyrifos methyl molecule has a benzene ring like structure with π -electrons, which strongly interact with the π -electrons of graphene through π - π stacking, as shown in the inset to Figure 3a. This is in contrast to some other molecules containing no π -electrons in

their molecule structure, which results in a much weaker interaction with graphene, e.g., fructose with the molecule structure shown in the inset to Figure 3b. In order to elucidate this point, here we compare the sensing performance of chlorpyrifos methyl and fructose molecules using GMS. 10 μL of chlorpyrifos methyl or fructose solution with various concentrations are dropped on the graphene-metamaterial device and dried in air. When chlorpyrifos methyl solution was added, in Figure 3a we plot the relative reflectance change from the graphene-metamaterial device, which is defined as $\Delta R/R = (R_{\text{reference}} - R_{\text{sample}})/R_{\text{reference}}$, where R_{sample} ($R_{\text{reference}}$) is the reflectance at resonance with (without) chlorpyrifos methyl. The value $\Delta R/R$ increases rapidly at low concentration (from 0.02 mg L^{-1} to 0.1 mg L^{-1}), and it continues to increase but at a much slower rate when the concentration further increases. We are able to detect a trace amount of target (0.2 ng in this study), and obtain a maximum $\Delta R/R$ of 35% when the concentration is 3.0 mg L^{-1} . In the case of fructose, the relative reflectance change is plotted in Figure 3b as a function of fructose concentration, revealing a similar behavior but with much lower values. It starts to saturate at concentration of 1.0 mg L^{-1} , and the maximum change reaches only $\sim 15\%$. Therefore, the monolayer graphene-coated THz metamaterial sensor exhibits better sensitivity to the external molecules containing π -electrons, here chlorpyrifos methyl. Through the sensitivity of graphene-coated THz metamaterial sensor is still not comparable to graphene biosensor[34] and graphene/gold film hybrid sensor,[45] it is worth noticing that the sensor in our work shows an enhanced sensitivity compared to the utilization of a bare metamaterial.[46] We expect that the operation conditions of our present devices could be further developed to accomplish a better sensitivity by optimizing the device structure design and/or active tuning.

We would like to emphasize that the metamaterial absorber structure plays the most critical role in obtaining such a high sensitivity, while a strong coupling between molecules and graphene

significantly improves the detection sensitivity. This is manifested by the minimal change of THz reflection/transmission when monolayer graphene was transferred onto the surface of a silicon wafer ($1 \times 1 \text{ cm}^2$) and $20 \text{ }\mu\text{L}$ 10 mg L^{-1} of fructose solution was dropped and dried on the surface. We observed no obvious distinctions in the THz transmission spectra (see Figure S3) of monolayer graphene-silicon heterojunction with and without fructose. Compared to the Fermi level change caused by external voltage bias and optical pump excitation,[30] the doping due to the presence of external molecules in a graphene-silicon heterojunction is relatively small, presenting a negligible modulation of THz wave propagation.

The favorable biocompatibility feature of graphene makes it suitable for the development of biosensor technology, such as aptasensors. Aptamers, generated from “systematic evolution of ligands by exponential enrichment” (SELEX) technique, are short single-stranded oligonucleotides (DNA or RNA), which can bind to specific targets resembling antibodies.[47–49] Aptamers behave as a molecular recognition element for recognizing and binding targets with excellent affinity. It is noteworthy that coupling graphene and its derivatives with aptamers has brought a new research direction for developing interesting sensing devices with diverse applications.[50]

Here, we utilize aptamers for thrombin detection, thus demonstrating the concept of monolayer graphene-coated metamaterial as a biosensor. As CVD grown graphene is hydrophobic, while DNA is hydrophilic, DNA cannot be directly adsorbed on the surface of graphene. Therefore, a pyrene is introduced to the thrombin binding aptamer (TBA) sequence: 5'-Pyrene/GGT TGG TGT GGT TGG -3'. [51,52] In this TBA sequence, pyrene is used for adsorption of graphene via π - π stacking. Figure 4a illustrates schematically the biosensing procedure of monolayer graphene-coated metamaterials. First, $10 \text{ }\mu\text{L}$ of $20 \text{ }\mu\text{M}$ TBA solution was added onto the surface of

monolayer graphene-coated THz metamaterial and incubated for 2 hours. Then the sensor was washed three times by phosphate buffer solution (PBS, pH 7.4). Finally, the sensor was incubated in 100 nM thrombin solution for 1 hour. Another monolayer graphene-coated metamaterial with TBA only was incubated in PBS serving as a reference.

Unlike the commonly adopted optical aiming to verify binding of aptamer to graphene surface, which requires aptamers to attach some fluorescent molecules, we use atomic force microscopy (AFM) for the verification of DNA aptamer binding, ensuring that the aptamers are properly immobilized on graphene. The AFM images of 3.5 μm by 3.5 μm area, together with one-dimensional height profiles, are shown in Figure 4b and 4c, respectively, for the sample regions without and with aptamers. The no-aptamer region, as shown in Figure 4b, does not have any distinguishable structure, presenting a <10 nm height profile; whereas the aptamer region reveals structures with a width approximately several hundred nanometers and an average height 40-50 nm. Our AFM results are consistent with those shown in literature,[34] clearly suggesting that aptamers have been successfully bound to the graphene surface and can be effectively used as the sensing platform. The corresponding THz reflection spectra with and without thrombin (100 nM) are presented in Figure 4d. We obtain a distinguishable reflectance decrease ($\sim 4\%$) when thrombin is present on the monolayer graphene-coated THz metamaterial, demonstrating the effective biosensing functionality of the present prototype device.

4. Conclusions

Both graphene and metamaterials represent the most rapidly developing fields of research that have received tremendous attention because of their underlying interesting physics and promising potential applications, particularly in the THz frequency range where sensing technology has encountered great challenges due to the lack of useful materials for high-performance devices.

Taking advantage of the tunable Fermi level of graphene and localized resonance field enhancement in metamaterials, we experimentally demonstrated that monolayer graphene-metamaterial heterostructures can serve as an efficient platform for THz sensing. By adding a monolayer graphene on top of a metamaterial absorber structure, we found that external analytes can tune the resonance absorption magnitude, accompanied with a shift of the peak frequency and a change of Q value, due to the modification of the resonant metamaterial absorber cavity. In our present design, we experimentally showed an absorption change up to 35% when adding chlorpyrifos methyl molecules on top of the graphene-metamaterial heterostructure. We also found that molecules with π -electrons interact with graphene much stronger than those without π -electrons, resulting in a higher sensitivity through π - π stacking. We have experimentally shown that this scheme of graphene-metamaterial sensing is capable of detecting trace amount of analytes, down to 0.2 ng chlorpyrifos methyl in our experiments. We further showed its feasibility serving as a biosensor, and experimentally realized thrombin detection with simple decoration steps. We note that the operation conditions of our present devices are not necessary to accomplish maximal sensitivity. We expect that optimizing the device structure design and/or active tuning (e.g., apply a voltage bias to tune the graphene Fermi level) to realize near zero reflection (unity absorption) at its initial state will greatly improve the sensitivity, therefore featuring a host of THz sensing applications.

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Supplementary Information

The Supporting Information is available free of charge at .

Notes

The authors declare no competing financial interest.

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FIGURES

Figure 1. Monolayer graphene-coated terahertz metamaterial device. **a**, Schematic of monolayer graphene-coated THz metamaterials for reflective sensing of external molecules. **b**, Raman spectroscopy of the monolayer graphene. **c**, Experimentally measured reflection spectra of metamaterials with/without monolayer graphene.

Figure 2. Sensing principle of graphene-coated terahertz metamaterials. a, Experimentally measured THz reflection spectra of monolayer graphene-coated metamaterials with/without chlorpyrifos methyl molecules, showing a large reflection change. b, Experimentally measured THz reflection spectra of metamaterials with/without chlorpyrifos methyl molecules. c, Numerically simulated reflection spectra of monolayer graphene-coated metamaterials with Fermi level ranging from 30 meV to 120 meV below the Dirac point.

Figure 3. Sensing external molecules using monolayer graphene-coated terahertz metamaterials. **a**, Relative reflectance changes when chlorpyrifos methyl molecules are coated using solution with different concentrations ranging from 0.02 mg L⁻¹ to 3.0 mg L⁻¹. **b**, Relative reflectance changes when fructose molecules are coated from solution with different concentrations ranging from 0.1 mg L⁻¹ to 5.0 mg L⁻¹. Insets: Structure of chlorpyrifos methyl and fructose molecules, schematic of their interaction with graphene, and the corresponding Fermi level change in graphene.

Figure 4. Biosensing using monolayer graphene-coated terahertz metamaterials. **a**, Schematic of sample preparation of thrombin on monolayer graphene-coated THz metamaterials used as an aptamer sensor. Also shown in the inset is the schematic drawing of the graphene Fermi level indicating its change at different steps. **b**, AFM image and one-dimensional height profile (solid curve) of a graphene-coated THz metamaterial without aptamer. **c**, AFM image and one-dimensional height profile of a graphene-coated THz metamaterial with aptamer. **d**, Experimentally measured reflection spectra of the monolayer graphene-coated THz metamaterials with/without thrombin. Here 100 nM thrombin solution concentration was used in experiment.