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Terahertz Microfluidic Metamaterial Biosensor for Sensitive Detection of Small Volume Liquid Samples

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Abstract—**Metamaterial assisted terahertz (THz) label-free bio-sensing has promising applications. However, the sensitive THz detection of highly absorptive liquid samples remains challenging. Here, we present a novel multi-microfluidic-channel metamaterial biosensor (MMCMMB) for highly sensitive THz sensing of small volume liquid samples. The multi-channels are set mostly in the strong electric field enhancement area of the metamaterial, which significantly decreases the liquid amount and enhances interaction between the sensing targets and the THz wave (thus increasing the sensitivity). The sensing results of isopropyl alcohol (IPA)-water mixtures and bovine serum albumin (BSA) solutions based on the bow-tie array metamaterial with multi-channels demonstrate the effectiveness of this proposed design and the great potential in THz bio-sensing. This design has the advantages of being highly sensitive, label-free, cost-effective, easy to operate and only needing a tiny liquid volume. Thus our device provides a robust route for metamaterial assisted THz label-free bio-sensing of liquid-based substances.**

***Index Terms*—Terahertz spectroscopy, biomedical spectroscopy, metamaterial, microfluidic.**

I. Introduction

Metamaterial (MM) devices can be used for label-free sensing of trace samples due to their sensitive response to subtle changes in the dielectric properties of the surrounding medium and strong electric field enhancement at specific locations on the resonator geometry [1], [2]. The vibrational and rotational energy bands of many biological macromolecules are located in the terahertz (THz) frequency range [3], [4]. MM assisted THz label-free bio-sensing combines the advantages of both MM and THz techniques and has attracted much attention recently [5]-[17]. For example, many types of MM structures have been used for highly sensitive THz detection of biological samples, such as proteins, DNA, microorganisms and cells [5]-[10]. However, as the strong absorption of polar liquids can dampen the resonance effect of MMs, most previous studies are limited to dry or partially hydrated samples [5]-[16].

Water is the key solvent of most biological substances, so it is desirable to realize bio-sensing of water-based substances and overcome the strong absorption issues. Microfluidic techniques enable a small volume of sample to be measured and this overcomes issues of high attenuation in hydrated samples. Furthermore, microfluidic chips are low cost, and able to do rapid analysis [18], [19]. Recently, microfluidic techniques have been introduced into MM THz sensing, however, in the far-field, most devices reported hitherto have only used one big microfluidic channel on top of the whole MM area to control the liquid thickness [20]-[27]. Thus, there is great scope to optimize the sensing performance. For example, the near-field microfluidic MM chips (employing the near-field coupling between the metal-atoms and the local THz emission) were proposed to achieve small volume liquid sample detection [28], [29]. However, for this approach, a high-performance nonlinear optical crystal and an additional THz pulse detection module are needed. Furthermore, the signal to noise ratio (SNR) achieved is not very high.

In this paper, we propose a multi-microfluidic-channel metamaterial biosensor (MMCMMB) to further increase the detection sensitivity and decrease the liquid sample amount, which can be used in all the standard THz time-domain spectroscopy (TDS) systems. By setting the multi-channels to be mostly located in the more sensitive regions of MM, significant enhancement of the THz-analyte interaction can be achieved. To test our approach, we designed and fabricated a bow-tie array MM with multi-channels and measured different liquid samples.

This work is a significant extension of our conference abstract [30], in which only the basic design concept was presented. More details of the design, simulation and fabrication for the proposed device are included in this paper. The sensing measurements of isopropyl alcohol (IPA)-water mixtures and bovine serum albumin (BSA) solutions based on

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the proposed MMCMMB were also implemented.

II. METHODOLOGY

The bow-tie array MM design is depicted in Fig. 1. The 50-μm-side /10-μm-gap bow-tie array MM (equilateral triangles, 100-nm-thick Au, 500-μm-thick quartz substrate) was simulated by the frequency domain solver in the CST Microwave Studio [31]. In the simulation, the quartz substrate was modeled as a lossless dielectric with dielectric permittivity $\varepsilon = 4.41$ [32] and the Au conductivity was set as 4.56×10^7 S/m [33]. The incident THz polarization was set as the direction of the arrow in Fig.1(a). The amplitude transmission $t(\omega)$ was obtained by the following equation $t(\omega)=\left|\tilde{E}_s(\omega)/\tilde{E}_r(\omega)\right|$, where $\tilde{E}_s(\omega)$ and $\tilde{E}_r(\omega)$ are the fast Fourier transformation of the sample and reference THz pulses, respectively, ω is the angular frequency. An identical quartz substrate was adopted as the reference.

The simulation results are shown in Fig 1. The 50-μm-side /10-μm-gap bow-tie array MM has a resonance peak at 2.06 THz. The strongly confined area of electric field is mainly located in the gap region of the bow-tie unit, which is the most sensitive area for bio-sensing applications. Thus, the multi-channels are set in the middle of all the bow-tie units. All the multi-channels should be connected together with an inlet and an outlet. The schematic diagram of the proposed THz MMCMMB based on bow-tie array MM is shown in Fig.2(a).

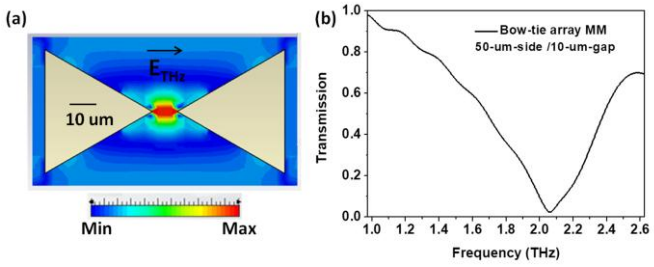

FIG.1. (a) Simulated electric field distribution of the bow-tie unit at the resonance frequency. (b) Simulated transmission spectrum of the bare bow-tie array MM.

To test the feasibility of this design, the sensitivity of the multi-channels with different width (15-μm-thickness) was firstly simulated and calculated. The simulation results are shown in Fig.2(b). The SU-8 photoresist was used to construct the channel and was set to be a lossless dielectric ($\varepsilon = 3.24$) in the simulation [22]. The sensitivity per unit volume is defined as the resonance frequency shift of unit refractive index change for a unit volume sample in the multi-channels [34]. The simulated sensing performance demonstrates that the sensitivity decreases significantly with the increase of the channel width. The 15-um-width microchannels are adopted in the study by also considering the alignment difficulty during the micro-fabrication.

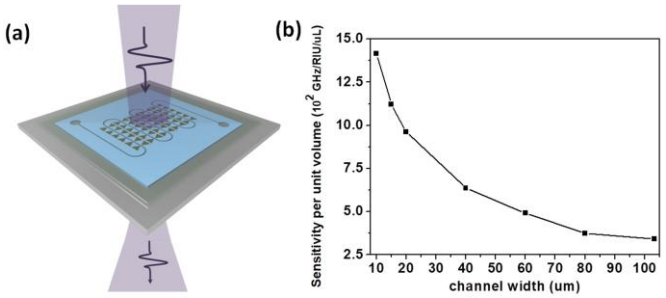

FIG.2. (a) Schematic diagram of the proposed device based on a bow-tie array MM. (b) Simulated sensitivity per unit volume for different channel width based on a bow-tie array MM.

The procedures included in the fabrication process are shown in Fig.3 and briefly described next. The photolithography process was first implemented to construct the bow-tie array pattern on the 500-um-thick quartz substrate. Later, 20-nm-thick Cr and 100-nm-thick Au were deposited via the E-beam evaporation technique followed by the lift-off procedure to acquire the bow-tie array MM (Fig.3(a)). The microfluidic multi-channels with 15/15 μm width/thickness were aligned and patterned on top of each bow-tie gap using SU-8 photoresist (Fig.3(b)). Another 500-μm-thick quartz substrate was used as a sealing material due to its high transparency in the THz range (Fig.3(c)). A 5-um-thick SU-8 photoresist was spin-coated on the quartz substrate as an adhesion layer (Fig.3(d)).

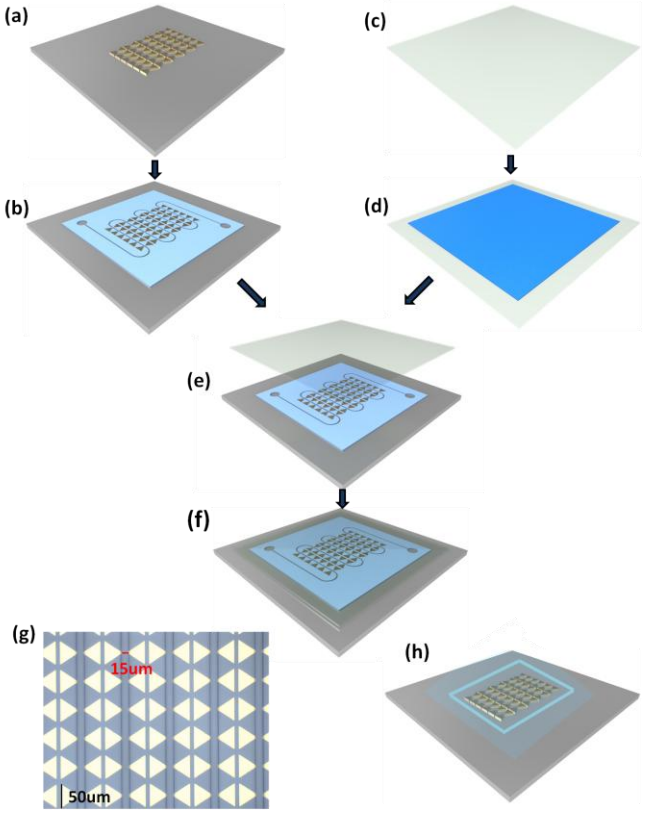

FIG.3. Fabrication procedures of the proposed device. (a) Bow-tie array MM. (b) Constructed microfluidic multi-channels on the bow-tie array MM. (c) Quartz substrate. (d) 5-um-thick SU-8 photoresist on the quartz plate. (e) Adhesion of the quartz plate with photoresist to the MM with microfluidic multi-channels. (f) Exposure to the ultraviolet light to make a strong seal. (g) Microscopic image of the fabricated device (15-um-width multi-channels in the sensitive area of bow-tie array MM). (h) Schematic diagram of the one big channel design based a bow-tie array MM with the same dimension.

Subsequently, this quartz plate with uncrosslinked photoresist was flipped and adhered to the MM with microfluidic multi-channels (Fig.3(e)). Finally, the bonded microfluidic MM device was exposed to the ultraviolet light to crosslink the adhesive photoresist layer (Fig.3(f)), thus creating a strong seal to prevent liquid leakage during the measurements [22]. The active area is about 64 mm^2. The corresponding microscopic image of the fabricated device is shown in Fig.2(g), which demonstrates the good alignment between the microchannel and the bow-tie gap. For comparison, a bow-tie array MM (same dimension) with only one 15 μm-thick big channel on top of the whole MM area was also fabricated with the similar steps. The schematic diagram of the one big channel design is shown in Fig.3(h). The big channel is wide enough to cover all the bow-tie array elements.

III. Experimental Details and Results

The sensing performances of the fabricated sensors were tested in a typical transmission THz spectrometer. The devices were placed in the focused point between the THz transmitter and receiver. The polarization of the incident THz field was vertical to the multi-channels. The amplitude transmission spectra were calculated. The used liquid volume is recorded. The sensitivity per unit volume (S) is defined as the resonant frequency shift of unit refractive index change for unit volume sample [34]. The figure of merit (FOM) is calculated as FOM=S/FWHM, where FWHM is the full width at half maximum in the amplitude transmission spectra.

Firstly, the water sensing performance was measured and compared between the proposed MMCMMB and the previous sensor with one big channel on top of the whole MM area. The water was injected into the multi-channels or the one big channel. The experimental transmission spectra results before and after water injection are shown in Fig. 4. The fabricated MM without the multi-channel has a resonance absorption dip at 2.08 THz, while the resonance frequency of the MM with multi-channel is located at 1.96 THz. The resonance frequency difference between the two devices is caused by the SU-8 photoresist used to construct the multi-channels. The transmission spectra after water injection demonstrate that the proposed MMCMMB largely decreases the damping effect to the MM resonance caused by the water absorption [1, 35].

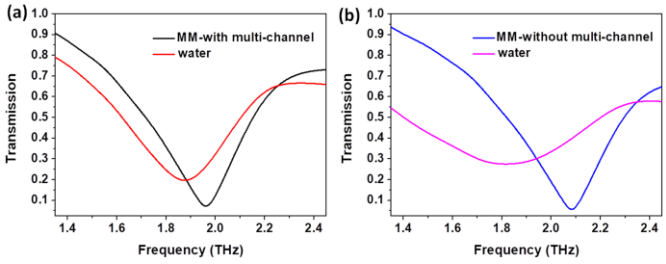

FIG.4. Transmission spectra measurements: (a) the MMCMMB (MM with multi-channel, black line), and with water injected into the multi-channels (red line). (b) Bow-tie array MM with only one big channel on top of the whole MM area (MM without multi-channel, blue line), and with water in the channel (magenta line).

The comparison results are shown in Table 1. The proposed new design requires much lower liquid volume to be injected and the FWHM after water injection is much smaller. Furthermore, the sensitivity per unit volume, especially the figure of merit is much higher for the multi-channel design. This fully demonstrates the effectiveness of the proposed MMCMMB design compared to the previous design with only one big channel.

TABLE I
WATER SENSING COMPARISON RESULTS FOR THE BOW-TIE ARRAY MM WITH AND WITHOUT MULTI-CHANNEL.

	MM without multi-channel	MM with multi-channel
Liquid volume (uL)	0.96	0.13
Frequency shift (GHz)	267	86
Frequency shift per unit refractive index change (GHz/RIU)	223	72
Sensitivity per unit volume (GHz/RIU/uL) S=△f/△n/V	232	552
$FWHM_1$ without water (GHz)	83.7	99.9
$FWHM_2$ with water (GHz)	931.8	350.9
Figure of merit (/RIU/uL) $FOM=S/FWHM_2$	0.25	1.58

△f: resonance frequency shift, △n: refractive index change, V: liquid volume, FOM: figure of merit, FWHM: full width at half maximum. In this calculation, the adopted water refractive index is 2.2 [26].

To further test the effectiveness of the proposed MMCMMB design, the IPA-water solutions were measured. The IPA-water mixtures with the IPA percent of 100%, 75%, 50%, 25% and 0% were tested (100%-pure IPA, 0%-pure water). The refractive index and the absorption coefficient of the IPA-water mixture decrease with the increase of the IPA concentration [22], [26]. For comparison, the IPA-water mixtures were also measured based on the MM with one big channel. The mean value of three repeated measurements for each concentration was adopted for further analysis. The measured transmission spectra and the corresponding FWHM, resonance frequency shift and absorption dip amplitude results of the IPA-water mixtures with different IPA percentage are shown in Fig. 5. In the two scenarios, the resonance frequency has a red-shift with decreasing IPA percentage in the IPA-water mixture. The FWHM increases with the decrease of the IPA percentage in the IPA-water mixture (the THz absorption of the mixture increases). Furthermore, the transmission amplitude at the resonance frequency decreases continuously with the increase of the IPA percent in the IPA-water mixture. Although the resonance frequency shift is smaller for the MMCMMB design, it's important to emphasize that the required liquid volume is much smaller and the sensitivity per unit volume is higher. Moreover, the FWHM of the MMCMMB design after liquid injection is much lower and the corresponding FOM is higher. Thus, high performance quantitative sensing of water-based solutions can be achieved with the MMCMMB assisted THz spectroscopy.

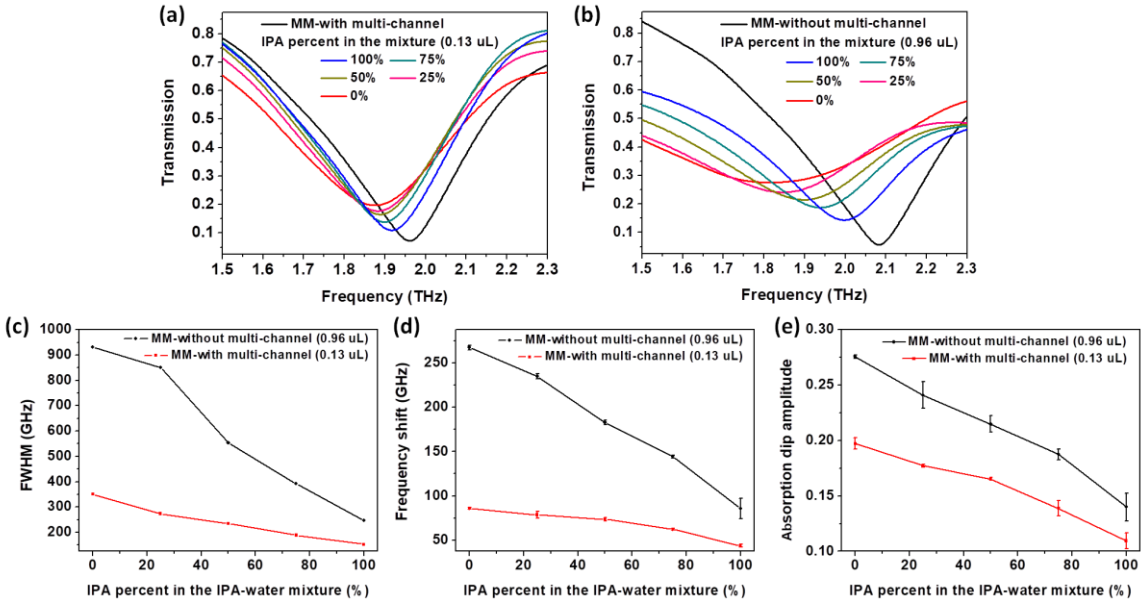

FIG.5. Experimental results for the IPA-water mixtures with different IPA concentrations based on the proposed MMCMMB (MM with multi-channel) and the bow-tie array MM with only one big channel on top of the whole MM area (MM without multi-channel). Transmission spectra for the different IPA-water mixtures based on the MM with multi-channel (a) and the MM without multi-channel (b). (c) FWHM results of the IPA-water mixtures with different IPA concentrations. (d) Average resonance frequency shift results of the IPA-water mixtures with different IPA concentrations. (e) Average absorption dip amplitude results of the IPA-water mixtures with different IPA concentrations.

To test the feasibility of the proposed MMCMMB design for biomedical applications, the BSA water solutions were measured and tested with concentrations of 0.25, 0.5, 1 and 2 mg/mL. Six repeated measurements for each concentration were conducted for further analysis. The measured transmission spectra and the corresponding resonance frequency shift results are shown in Fig. 6. The average resonance frequency shift is 98, 101, 111, 118 GHz for 0.25, 0.5, 1, 2 mg/mL BSA solutions. These results fully demonstrate the feasibility of the proposed MMCMMB design for real liquid-based THz biosensing applications.

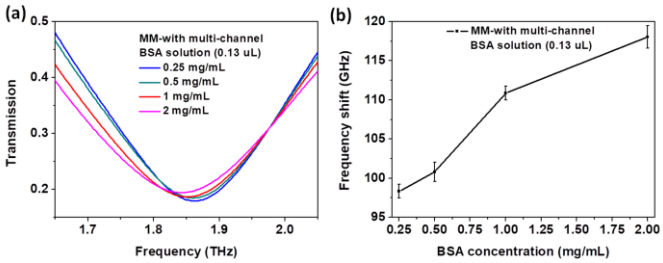

FIG.6. Experimental results for the BSA solutions with different BSA concentrations based on the proposed MMCMMB. (a) Transmission spectra for the different BSA solutions based on the MM with multichannel. (b) Average resonance frequency shift results of the BSA solutions with different BSA concentrations.

The experimental results demonstrate the robust feasibility for sensitive detection of small volume liquid samples based on the proposed MMCMMB. In contrast to the previous design of only one big microfluidic channel on top of the whole MM area [20]-[27], the proposed MMCMMB can further decrease the liquid amount and increase the detection sensitivity. Moreover, the proposed design has a wide scope of applications, as it can be retrospectively adopted in all the standard THz-TDS systems. The measurement steps are easy and the detection SNR is high compared to the near-field microfluidic MM chips [28],[29]. The proposed device can be fabricated on conventional quartz or silicon substrates by the standard microfabrication procedures. The cost is also much lower than the near-field microfluidic MM chips which need a high-performance nonlinear optical crystal.

In the previous studies, the analyte is usually located in the whole area of the MM and the volume of the analyte is large [5-16, 20-27]. If we don't consider the required sample volume, the resonance frequency shift per unit refractive index change in our study (72 GHz/RIU for the multichannel design, 223 GHz/RIU for the one big channel design) is comparable to previous studies (such as, 40 GHz/RIU [13], 220 GHz/RIU [20], 305 GHz/RIU [21]). Nevertheless, our proposed MMCMMB design requires much less sample volume, which is highly desirable for the very expensive and highly absorptive liquid samples. The proposed design can be extended to other MM structures and other frequency ranges. The sensitivity and the FOM can be further improved by optimization of the MM structure, such as using a thinner substrate [11], [12] and higher quality factor resonator [13], [34], [36] (for example, the conductively coupled split ring resonator or the toroidal resonator). Moreover, the overlap of the electromagnetic fields and the sensing analytes can be further improved to achieve higher sensitivity [34]. As for the biosensing applications, the sensitivity and selectivity of the proposed design can be further improved by optimizing the structure parameters to match the resonant frequencies of the detected biological macromolecules and specific reaction between the biological target and binding agent immobilized onto the device [21].

IV. Conclusion

In conclusion, the MMCMMB provides a strong THz-analyte interaction platform for small volume liquid

sensing, which has the advantages of being highly sensitive, label-free, cost-effective, easy to operate and highly compatible. The proposed design has promising applications in real liquid-based biosensing and could accelerate the development of THz lab-on-chip devices.

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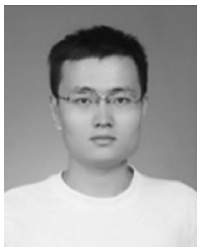

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