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Nanofluidic terahertz metasensor for sensing in aqueous environment

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The terahertz spectral region has received tremendous attention for label free chemical and biological sensing, due to the presence of molecular fingerprints, low energy characteristics, and remote sensing capabilities. However, a major hindrance for the realization of a high performance terahertz bio-chemical sensor comes from the large absorption of terahertz waves by aqueous solution. Here, we overcome this limitation by confining the analyte-aqueous solution in a nanovolumetric fluidic chamber, integrated on metamaterial resonant cavities. The metamaterial resonators confine electromagnetic fields in extremely subwavelength space and hence allow for the enhanced interaction between the nanovolumetric analyte-aqueous solution and terahertz waves, while minimizing the absorption loss. We compare the sensing performance of split ring resonator and Fano resonator systems as metamaterial resonators. As a demonstration of chemical sensing, three alcoholic solutions with different concentrations were measured. Selective adenosine triphosphate (ATP) sensing capability was examined through ATP aptamer functionalization on gold metamaterials, where a decrease in the transmittance value was observed as the ATP concentration increased. The proposed sensing approach has the potential to be an effective tool for molecular analysis through exploiting the advantages offered by low energy terahertz, subwavelength metamaterial resonators and nanofluidic technologies. Published by AIP Publishing. https://doi.org/10.1063/1.5041485

Chemical and biomolecular sensing utilizing electromagnetic waves are of great demand owing to its high effectiveness and sensitivity.¹⁻⁷ Among various optical sensing methods, terahertz (THz) spectroscopy (0.1-10 THz) is considered as one of the most promising tools towards biological sensing, since the fingerprint vibrational frequency of most chemical and biological molecules (protein, RNA, and DNA) lies in this spectral region.^{8–12} Moreover, the lower ionization energy of the THz waves allows for non-destructive sensing with less thermal fluctuations.^{13,14} Hence, THz spectroscopy enables noncontact, non-destructive, and label-free optical sensing for chemical and biological studies. Nevertheless, the detection of the trace amount of analyte using THz spectroscopy is limited. Thus, methods such as THz attenuated total reflection spectroscopy and metamaterials have been developed, which increases the interaction strength between the analyte and the incident THz waves significantly and hence allows for a much higher sensitivity and SNR values.^{15–17} Among these approaches, the metamaterial has emerged as the most promising platform for high performance sensing application, owing to its versatility of design, ease of fabrication, and integration with complementing technologies such as micro/nanofluidics.18-20

Metamaterials are artificially engineered materials, consisting of an array of subwavelength structures that can be designed to achieve many interesting electromagnetic

metamaterials can be actively reconfigured by changing the material properties of the surrounding medium or resonator geometry to form active metadevices.²⁹ Alternatively, the high sensitivity of the metamaterial to the surrounding medium can also be exploited as an efficient sensing platform.^{30–33} The enhanced sensitivity of the metamaterial comes from the strong confinement of electromagnetic fields in a subwavelength region and hence provides a pathway for reducing the analyte volume. This is extremely critical for sensing of biological molecules in aqueous solution, since THz absorption by water is significantly large and has been a challenge to THz spectroscopy for biological sensing.³⁴ Earlier reports using the THz metamaterial for sensing of sugars,³⁵ yeast,³⁶ virus,^{37,38} and other biomaterials^{39,40} have been carried out under dehydrated conditions.⁴¹ Few studies have demonstrated sensing with THz metamaterial in aqueous environment by confining aqueous solution at the microscale level.^{34,42–45} However, further reduction of the analyte volume to the nanoscale level would aid in much higher sensitivity of detection as the absorption from water could be greatly reduced. More interestingly, confinement of liquid in extremely small space also allows for efficient delivery of molecules to the sensing area, and the recent effort in the field of microfluidics has scaled down the interaction space to nanometer size.^{46,47} Hence, the confinement of chemical

properties such as cloaking,²¹ negative refractive index,²² perfect absorption,²³ and many more.^{24–28} The properties of

and biological samples in aqueous solution in nanospace not only reduces the water absorption of THz waves but also improves the detection efficiency of the THz metasensor. In this work, we experimentally demonstrate a nanofluidic THz metamaterial sensing platform and exploited its potential in chemical sensing and biological molecule detection. The platform consists of an array of metallic resonators with silicon dioxide (SiO₂) pillars in between to support the nanoscale interaction space. Different alcohols in water solution were selected to demonstrate the sensing capability of the proposed platform. Furthermore, we explored the biosensing capability of the device using adenosine triphosphate (ATP) through surface functionalization of ATP aptamer on the surface of gold (Au) resonators. Our study shows the potential application of THz metasensors with high sensing performance of chemical and biological molecules in a highly absorptive aqueous environment.

The concept of the THz metasensor integrated with nanofluidics is illustrated in Fig. 1(a). The main components of the sensor consist of metamaterial resonators and SiO₂ channel on the intrinsic silicon (Si) substrate. SiO₂ pillars were placed in between the metallic resonators to support the nanofluidic chamber sealed by a quartz plate. Two popularly used metamaterial resonator configurations for sensing, splitring resonator (SRR) and Fano resonator, were explored. The resonators were made of 120 nm thick Au. The THz waves were incident normally on the metamaterial and excited the desired resonance modes of each resonator. The transmission response of the metamaterials was measured to observe the changes induced by the target chemical and biological samples. In order to achieve THz sensing with high effectiveness and low water absorption, the channel height was designed to be 160 nm, slightly higher than the metal height of 120 nm, which is limited by the skin depth of Au at THz frequencies. This 40 nm space above the metal



FIG. 1. (a) Schematics of the ideal THz metamaterial nanofluidic sensor and its cross-sectional device structure. Scanning electron microscopic image of the fabricated THz metamaterial chip with SRR (b) and Fano resonator (c) and their simulated electric field distribution where a field confinement can be seen in the gap region ($g = 2 \mu m$, $w = 6 \mu m$, $l_S = 26 \mu m$, $L_S = 40 \mu m$, $l_F = 38 \mu m$, and $L_F = 50 \mu m$). Here, l_T and l_B represent the length of each metal pattern on top and bottom, respectively.

resonators allows the analyte to fully cover the resonator surface as well as the capacitive gaps of the SRRs and Fano resonators.

Figures 1(b) and 1(c) show the scanning electron microscopic images of the fabricated SRR and Fano resonators, respectively. The SRR structure consists of a square metal ring with a capacitive gap. When the THz wave is incident normally on the sample with the electric field parallel to the gap of SRR, the inductive-capacitive (LC) resonance is excited with a strong field confinement in the capacitive gap [inset of Fig. 1(b)]. The LC resonance frequency is determined by the inductance (L) of the metal ring and the capacitance of the gap (C), as $f_r = 1/2\pi\sqrt{LC}$.³⁷ Hence, the change in the refractive index of the material in the capacitive gap will lead to a corresponding spectral shift in the LC resonance frequency of the SRR. On the other hand, the Fano resonator consists of two metallic split-rings with an asymmetry in their structural dimension and when the electric field of the incident THz wave is perpendicular to the gap bearing arms, Fano resonance mode is excited.²⁴ Similar to SRR, a strong electric field confinement can be observed in the capacitive gaps of the Fano resonator [inset of Fig. 1(c)] and thus results in excellent sensing capability. In the case of the Fano resonator, the resonance characteristics strongly depend on the asymmetry parameter,⁴⁸ described by a = $(l_B - l_T)/(l_B + l_T) \times 100\%$. Increasing asymmetry gives lower quality factor resonance but with higher resonance strength. As illustrated in Fig. 1(c), the designed Fano resonator has an asymmetry parameter of 20% aiming at stronger resonance in order to overcome possible water absorption in the THz region.

Numerical simulations were carried out using commercially available software CST Microwave Studio to elucidate the spectral sensitivity of the resonators with changing properties of the surrounding analyte medium. The designed SRR and Fano resonator have resonance frequencies at 0.838 THz and 0.864 THz, respectively, in air. These resonance frequencies were optimized through geometrical parameters of the metamaterial resonators to ensure that the resonance frequencies lie within our measurement limit (0.2-1.5 THz) when incorporated with the high index aqueous medium.⁴⁹ As shown in Fig. 2(a), the change of surrounding medium with different refractive indices causes a resonance frequency shift without a change in the resonance strength for both the SRR and Fano resonator. On the other hand, an increase in absorption (loss tangent value) of the analyte reduces the resonance strength, while no significant frequency shift is observed [Fig. 2(b)]. This weakening of resonance, however, can be overcome through the reduction of the channel height as presented in Fig. 2(c). According to the simulation results shown in Fig. 2(a), the amount of resonance frequency shift with respect to air $[\Delta f_{r-air}, (n_{air} = 1.0)]$ is plotted against the refractive index, and a linear relation is observed. This characteristic allows the metamaterial to serve as a refractive index sensor of surrounding analyte medium. However, it should be noted that the transmitted response is a combination of both the refractive index and absorption change in real experiment, and the loss tangent value can be different from that of simulation. We further simulated the electric field distribution in the gap region



FIG. 2. Simulated transmission response of the SRR and Fano resonator (a) with varied refractive indices of the analyte (channel height: $10 \,\mu\text{m}$ and loss tangent: 0.0), (b) with varied loss tangent values (channel height: $10 \,\mu\text{m}$ and n: 1.0), and (c) with varied channel heights (loss tangent: 0.9 and n: 1.0). (d) The resonance frequency shift with respect to air ($n_{air} = 1.0$) when the refractive index of the analyte is varied. (e) The electric field intensity distribution along the z axis at the center of the gap area and the amount of resonance frequency shift with respect to air with varied channel heights (n: 3.0 and loss tangent: 0.0).

along the out-of-plane z (k) axis. A clear exponential decay of electric field can be observed, when receding from the substrate surface. Although the increase in the channel height results in larger resonance shift because a larger volume of the analyte interacting with the extended fields from the resonator cavity, this frequency shift rather saturates at a large channel height [insets of Fig. 2(e)]. For the purpose of reducing THz absorption due to water as well as improving the reaction efficiency, in this work, we experimentally demonstrate a THz metasensor with the thinnest channel height of 160 nm in an actual aqueous environment to examine the device functionality. It is also interesting to note that the Fano resonators give slightly better sensitivity than the SRRs.⁵⁰ However, this difference is not quite significant, since the asymmetry used in Fano resonator design is very large due to the need for higher resonance strength in sensing aqueous solution, which in turn adversely affects the field confinement.

The nanofluidic THz metamaterial sensor was fabricated on a 625 μ m thick intrinsic Si substrate (2 cm × 2.5 cm) with 300 nm thick SiO₂ on top. The photolithography process was used to pattern the nanofluidic channels, and SiO₂ was partially etched by 160 nm using reactive ion etching. The unetched SiO₂ regions formed the supporting pillar, which will hold the quartz capping plate. The second photolithography process was performed to define the metamaterial patterns in the partially etched SiO₂ region. Chromium/Au of 5 nm/120 nm thickness were deposited using thermal evaporation and were lifted off in acetone to form the metamaterial resonators. The fabricated SRRs and Fano resonators were characterized using THz time domain spectroscopy (THz-TDS) system with the quartz capping plate. The THz beam of 5 mm diameter was illuminated at normal incidence on the fabricated metamaterial sample area of $7.2 \text{ mm} \times 7.2 \text{ mm}$. This ensured uniform excitation of resonators in the array, and their collective response was measured. The THz transmission response of the SRRs and Fano resonators in air is shown as the black line in Figs. 3(a) and 3(b), respectively. The LC resonance of the SRR with the air filled nanofluidic chamber was measured to be at 0.872 THz and the Fano resonance was at 0.823 THz, respectively. For liquid sensing, the liquid droplet of the analyte (100 μ l) was first placed in the nanofluidic chamber using pipette and a quartz substrate is then pressed and sealed against the metamaterial chip allowing excess liquid to flow out.

The sensitivity of the nanospace THz metamaterial sensor was studied through the transmission spectra of water (refractive index n = 2.20 and absorption coefficient $\alpha = 220 \text{ cm}^{-1}$) and alcoholic solutions [methanol (n = 1.69 and $\alpha = 100 \text{ cm}^{-1}$), ethanol (n = 1.54 and $\alpha = 60 \text{ cm}^{-1}$), and isopropyl alcohol; IPA (n = 1.51 and α = 50 cm⁻¹)].⁵¹ As each liquid sample has its distinctive refractive index and absorption coefficient in the THz region, they can be identified through the frequency shift as well as change in resonance strength. We plotted the resonance frequency shift against the refractive index of each liquid in Fig. 3(c), and the sensitivity of the metasensor was calculated to be 93.85 GHz/RIU and 76.57 GHz/RIU for the SRR and Fano resonator, respectively. The SRR designed for this work provides similar sensitivity compared to the Fano resonator because we designed the Fano resonator with a high asymmetry parameter, aiming at better robustness to strong water absorption. We calculated the resonance strength (ΔT_s) as the difference between T_{peak} and T_{dip} and plotted against the absorption coefficient of each sample [Fig. 3(d)]. This resonance strength value provides information about the absorption coefficient of the analyte. The designed SRR and Fano resonator showed clear sensing capabilities even for the chemical sample with higher absorptivity.

In order to demonstrate chemical detection in the aqueous environment, we further measured the transmission response of the THz metasensor with varying concentrations



FIG. 3. Measured transmission spectra of SRR (a) and Fano resonator (b) design under different liquid sample environments. (c) The measured resonance frequency shift with respect to air plotted against the refractive index of each liquid sample. (d) The measured resonance strength (ΔT_s) calculated as the difference of T_{peak} (transmittance value at 1.2 THz for SRR, and the highest transmittance value between 0.8 THz and 1.0 THz for the Fano resonator) and T_{dip} (transmittance value at the resonance dip).

of alcohol in water solution. Figures 4(a) and 4(b) present the measured transmission spectra of the SRR and Fano resonator with varied ethanol concentrations. The resonance frequencies of the SRR and Fano resonator were at 0.761 THz and 0.73 THz, respectively, when water was injected. They gradually blueshifted to 0.82 THz and 0.783 THz as the ethanol concentration increased because ethanol has a lower refractive index compared to water. This indicates that the resonance frequency shift from pure ethanol solution to water $(\Delta f_{r-water})$ was 60.37 GHz for SRR and 53.05 GHz for the Fano resonator. Similar transmission spectra were obtained for methanol and IPA solution and the $\Delta f_{r-water}$ and ΔT_s values of each alcoholic solution were plotted against their concentration as shown in Figs. 4(c) and 4(d), respectively. The proposed THz metasensor was capable of detecting both the refractive index and absorption coefficient change caused by the presence of a small amount of alcohol in highly absorbing aqueous solution.

Selective biomolecule sensing may also be achieved through functionalization of molecules such as antibodies and aptamers in a specific region of the device aiming at the targeted sample. Aptamers have emerged as promising alternative sensing probes over antibodies due to their comparable sensitivity, selectivity, and high stability.^{52,53} Among many synthesized aptamers, the ATP aptamer has been used widely as a model system for proof-of-concept testing of various detection techniques.⁵⁴⁻⁵⁶ In this work, ATP sensing capability was examined through functionalizing the Au metamaterial surface with ATP aptamer probes. The ATP aptamer employed in this system was custom synthesized and purified using dual-HPLC with the following sequences and modifications: 5'-methylene blue (MB)-ACC TGG GGG AGT ATT GCG GAG GAA GGT TT-(CH₂)₆-SH-3'.⁵⁷ The aptamer probes were freshly immobilized onto the Au surface before testing.⁵⁸ Briefly, a stock solution of $100 \,\mu\text{M}$ ATP aptamer was first reacted with 10 mM TCEP in a volume ratio of 1:1 for 1 h at room temperature (25°) to cleave the disulfide bond. The solution would become colorless due to the simultaneous reduction of the MB, indicating successful reduction of the disulfide bond. The solution was then diluted with $1 \times PBS$ (pH = 7.4) to 1 μ M. A clean Au metamaterial was then immersed in the $1 \mu M$ aptamer solution for 4h at room temperature, allowing the formation of selfassembled monolayer (SAM) through the thiol-gold interaction. Subsequently, excess aptamers were removed by thoroughly rinsing with ultrapure water. The chip was then treated with 3 mM 6-MCH to passivate the remaining electrode area at room temperature for 4 h. Prior to the measurement, the ATP solution was placed on the Au surface using pipette and incubated for 10 min. As shown in Fig. 5(a), the binding of the ATP aptamer with its target ATP alters its conformation, leading to the change of the local environment. An overall decrease in the transmittance value was observed for both SRR and Fano resonators while the transmittance value did not change significantly between PBS and ATP aptamer functionalized samples [Figs. 5(b) and 5(c)]. The resonance frequency shift was not clearly observed as water is the dominant environment for ATP sensing and no significant refractive index change is expected. In order to examine the decrease in the transmittance value, we further



FIG. 4. Measured transmission spectra of SRR (a) and Fano resonator (b) design with ethanol/water solution of different ethanol concentrations. The measured (c) resonance frequency shift and (b) resonance strength (ΔT_s) with respect to the pure water sample of IPA/water, ethanol/water, and methanol/water mixture in varied alcoholic concentrations.

calculated the transmittance difference at the resonance dip before and after incubation (ΔT_t) for different ATP concentrations [Fig. 5(d)]. When the ATP concentration is 0.1 μ M, the ΔT value was close to 0, and it gradually reached 0.0465 as the ATP concentration increased to 10⁵ μ M. In the case of ATP sensing in the water environment, the Fano resonator provides higher sensitivity in the transmittance difference. This can be due to the larger Au to Si surface area ratio of the Fano resonator compared to SRR. Under our current THz-TDS experimental setup and the device design, the sensitivity needs to be improved for actual ATP sensing application in human body. However, this can be readily overcome through further exploration of selective functionalization methods in the gap region as well as optimization of the resonator design. The improved metamaterial sensor is expected to realize



FIG. 5. (a) Schematic of ATP-aptamer immobilized on Au metamaterials before and after ATP (indicated by the star) binding. Measured transmission spectra of SRR (b) and Fano resonator (c) with simple PBS solution, after ATP-aptamer immobilization, and after ATP binding. (d) The transmittance difference at the resonance dip before and after ATP binding for samples with different ATP concentrations.

more complete and comprehensive study of molecular behavior in the THz region.

In summary, a platform for chemical and biological sensing in the THz region under a highly absorptive aqueous environment is proposed through liquid confinement in nanospace region integrated with metamaterial resonators. We designed and fabricated both SRR and Fano resonators and examined their sensing capabilities using the alcohol-water mixture and ATP aptamer. Through confinement of aqueous solution in a nanospace, clear resonance was observed for the design of both SRR and Fano resonators. Moreover, the change of their surrounding environment led to the resonance frequency shift, resonance strength change, and transmittance change in the measured spectra. The nanospace THz metamaterial sensor can be further explored through advanced selective functionalization methods, optimization of metamaterial design, and integration with the micro/nanofluidic system. The application of lower energy THz waves in chemical and biological sensing in the aqueous environment opens up a research area for label-free, non-destructive molecular study in the near future.

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