Rapid Detection of Infectious Envelope Proteins by Magnetoplasmonic Toroidal Metasensors

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ABSTRACT: Unconventional characteristics of magnetic toroidal multipoles have triggered researchers to study these unique resonant phenomena by using both 3D and planar resonators under intense radiation. Here, going beyond conventional planar unit cells, we report on the observation of magnetic toroidal modes using artificially engineered multimetallic planar plasmonic resonators. The proposed microstructures consist of iron (Fe) and titanium (Ti) components acting as magnetic resonators and torus, respectively. Our numerical studies and following experimental verifications show that the proposed structures allow for excitation of toroidal dipoles in the terahertz (THz) domain with the experimental Q-factor of 18. Taking the advantage of high-Q toroidal line shape and its dependence on the environmental perturbations, we demonstrate that room-temperature toroidal metasurface is a reliable platform for immunosensing applications. As a proof of concept, we utilized our plasmonic metasurface to detect Zika-virus (ZIKV) envelope protein (with diameter of 40 nm) using a specific ZIKV antibody. The sharp toroidal resonant modes of the surface functionalized structures shift as a function of the ZIKV envelope protein for small concentrations (~pM). The results of sensing experiments reveal rapid, accurate, and quantitative detection of envelope proteins with the limit of detection of 24.2 pg/mL and sensitivity of 6.47 GHz/log(pg/mL). We envision that the proposed toroidal metasurface opens new avenues for developing low-cost, and efficient THz plasmonic sensors for infection and targeted bioagent detection.

KEYWORDS: terahertz plasmonics, toroidal metasurface, immunosensing, Zika-virus envelope protein, detection

Manipulation and active control of an incident intense radiation by metallic objects have been demonstrated using localization of plasmons in subwavelength dimensions.1,2 Providing real-time spectral response control, plasmonic has emerged as a promising technology for tailoring fast, efficient, and tightly integrated nanodevices for photonic applications.1–3 Rising demands for miniaturized and multifunctional all-optical devices requires advances in integration of the next generation of photonic circuits. Among several potential applications of plasmonics technology, the biomedical applications still need to be improved for quick infection diagnosis and real-time pharmacology purposes.4–8 Plasmonic metasurfaces with exotic electromagnetic response have been relatively better developed for advanced label-free detection in biosensing applications in the spectral ranges from near-infrared wavelengths7 to the terahertz (THz)5,9 and microwave10,11 frequencies. It is well-accepted that THz frequencies are highly compatible with human tissues due to the absence of ionization hazard because of the low energy of the incident radiation (in the range of a few meV).5,9,12,13 This spectacular advantage of THz plasmonic structures accompanied by cost-effective and easy microfabrication techniques (photolithography) stimulated researchers to exploit THz plasmonics for immunosensing applications.14,15

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As a promising technique, THz spectroscopy allows for noninvasive, noncontact, nondestructive, and label-free biomarker detection and therefore attracted growing interest for biomedical and clinical applications.\(^{15-19}\) It is shown that electromagnetic field enhancement and confinement by metallic THz components facilitate detection of targeted bioagents such as specific proteins, antibodies, and so forth.\(^{9,16,17,19}\) Despite such a unique potential, the selectivity and sensitivity of THz metasurfaces for immunosensing applications have not been analyzed comprehensively due to mismatch between resonance frequency of nanoscale biotargets and metasurfaces. This is because of nonresponsivity of micro- and nano-organisms with the size of approximately \(\lambda/100\), causing near-transparency to the incident radiation, and therefore reflecting poor scattering cross section.\(^{22}\) This challenge in THz metamaterials can be circumvented using two approaches: (1) introducing nanosize particles (e.g., nanospheres)\(^9,23\) on the microscale plasmonic chips to trap and bind biological objects and monitor their effect on the spectral response, and (2) excitation of ultrasharp antisymmetric resonances (with high-\(Q\)-factors) to show supersensitivity to the small environmental variations. Here, by using the high-\(Q\) advantage of magnetic dipolar toroidal moment, the behavior of this mode is analyzed for the presence of ZIKV envelope protein and its specific antibody. Zika is a new medical threat across the world as an infectious disease which causes serious health disorders, possibly leading to death.\(^{24,25}\) Various methods have been introduced and conducted for practical detection of this type of infection such as reverse transcriptase-PCR,\(^{26}\) antibody-based methods (e.g., ELISA),\(^{26}\) point-of-care (POC) molecular detection,\(^{27}\) and electrochemical biosensing.\(^{28}\) Despite the growing research, most of these applications suffer from high costs, lack of sensitivity and repeatability, and complex processing. Therefore, providing an all-optical microscale metasurface with an ability to detect picomolar concentrations of ZIKV envelope protein would help us to tailor practical, easy to fabricate, and accurate detection mechanism with high reliability.

The exquisite properties of plasmonic structures with symmetric and antisymmetric geometries allow for achieving spectral lineshapes as pronounced resonant modes in the optical band reaching to the far-infrared region (FIR).\(^{29,30}\) The response of these resonant modes to the polarization variations of incident radiation and physical changes in their surrounding medium have triggered development of fast switches and high-precision sensors.\(^{31-33}\) Recently, successful examples of plasmonic lineshapes have been introduced for practical photoswitching applications based on Fano-resonant metallic assemblies,\(^34\) asymmetric lineshapes in Mach–Zehnder interferometers,\(^35\) electromagnetically induced transparency (EIT),\(^33\) and Lorentzian spectral lineshapes.\(^36\) The corresponding line width of these resonant modes are defined by full-width at half-maximum (fwhm), known as quality-factor (\(Q\)-factor).\(^37\) The sharpness and depth of these resonance lineshapes play a crucial role in developing advanced high-\(Q\) integrated devices.\(^38,39\) However, sustaining strong resonance coupling between optically excited modes in planar 2D structures is difficult and achieving ultrasharp and substantially high-\(Q\) factor lineshapes is a serious challenge.

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**Figure 1.** (a) Artistic perspective of compositional plasmonic resonators assembly as a unit cell on a silicon host. (b) Top-view schematic of the microstructure unit cell with an introduction to geometrical components. (c) SEM image of fabricated plasmonic structures in arrays for the unit cells with the gap spots between surrounding and central resonators of \(D_g = 3 \mu m\) with \(L = 240 \mu m\), \(R = 50 \mu m\), \(W_1 = 30 \mu m\), and \(W_2 = 40 \mu m\). (d) Magnified SEM images for each unit cell with \(D_g = 3 \mu m\).
Recent analysis have shown that plasmonic metasurfaces composed of 3D\(^{30-42}\) and 2D\(^{43,44}\) unit cells can be tailored to support distinct toroidal multipolar modes which are categorized in different resonant mode families far from the classical electromagnetic modes.\(^45\) These hardly distinguishable modes can be identified as the magnetic multipoles that are condensed into a single spot corresponding to a unique current density.\(^46\) In the toroidal moment limit, oscillating radial components of the current density are included in the radiative fields, giving rise to the formation of a unique family of dynamic toroidal multipolar modes.\(^42,47\) Toroidal dipolar resonant mode has been observed in 3D structures; however, challenging and complex fabrication processes limit their practical applications.\(^45,48-51\) Therefore, excitation of toroidal multipolar modes in planar 2D structures has received growing attention recently due to their easy fabrication and characterization.\(^45,50-51\) The primary problem with 2D structures is the inherently weak coupling of magnetic fields at the dielectric spacers of the resonators, which makes detecting the magnetic toroidal modes very difficult. Confinement of the incident magnetic field inside a unit cell into a rotating torus loop is another problem correlated with planar structures. Such challenges can be resolved by tailoring well-engineered plasmonic structures as well as selecting appropriate metallic compositions in fabrication of unit cell resonators. This strategy would allow for designing THz metasurfaces supporting sharp resonant modes that are proper for precise immunosensing assays.

In this article, by going beyond the conventional plasmonic platforms, we use 2D microstructures composed of iron (Fe) and titanium (Ti) for the magnetic and electric resonators, respectively, to design a set of asymmetric split resonators as meta-atoms to support ultrastrong and narrow magnetic toroidal moments in the THz spectrum. With coupled-resonator effect, the magnetic nature of Fe helps intensify resonating magnetic field at the central block of the plasmonic structure. Therefore, the middle Ti rectangle acts as a meridian for oscillation of circular and closed-loop head-to-tail array of magnetic dipoles. This effect makes the toroidal response line shape extremely sharp, narrow, and deep. Taking advantage of a superb sharp toroidal moment, we analyzed the sensitivity of this dip to the presence of a specific protein attached to the plasmonic system. The target protein was selected as the Zika virus envelope protein (ZIKV) which recently spread causing epidemic disorders such as microcephaly and neurological effects. Here, for the very first time, we developed an all-optical platform for direct detection of ZIKV envelope protein successfully by using a plasmonic THz metasurface via monitoring the behavior of the toroidal moment. In addition to demonstrating accurate detection of ZIKV envelope protein with picomolar (pM) concentration using its respective antibodies, we analyzed the sensitivity, repeatability, reliability, and accuracy of the toroidal THz plasmonic sensor.

**EXCITATION OF MAGNETIC TOROIDAL MOMENT**

Figure 1a shows the schematic view of the proposed planar microassembly unit on a silicon host (not to scale) with the incident THz beam direction and electric field polarization. The geometrical and material descriptions of the resonators and components are demonstrated in a top-view profile in Figure 1b. Figure 1c exhibits an SEM image of the fabricated compositional unit cell arrays on a high-resistivity silicon wafer with the gap distance of \(D_g = 3\) \(\mu\)m between peripheral and central resonators. The magnified SEM image of the planar plasmonic unit cell is presented in Figure 1d. In the calculation of the spectral properties of the unit cells, we used Fe parameters experimentally obtained by Ordal et al.\(^55\) for the satellite split curved resonators. We assumed formation of a few nanometers natural oxide (Fe\(_2\)O\(_3\)) on the Fe structures at room temperature.\(^53\) On the other hand, Palik constants were used for the Ti central rectangular resonator.\(^54\) By launching a THz beam in the \(z\) direction (Figure 1a), the excited local modes lead to formation of circular magnetic fields in the central zone.

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**Figure 2.** (a,b) 3D schematics of the magnetic (\(m\)) and toroidal (\(T\)) resonances around and across the central and surrounding magnetic resonators, respectively. (c,d,e) Electromagnetic response of the compositional THz plasmonic resonator: (i) experimentally obtained normalized transmission amplitude profiles for the unit cells with three different offset gaps, (ii) SEM images for different offset gaps between resonators, (iii) numerically calculated transmission spectra for three different offset gaps.
of the peripheral curved structures. This results in dramatic suppression in the electric dipole moment by the excited magnetic and toroidal resonances.\textsuperscript{43,44} The suppressed dipolar moment is associated with the strong electric resonant mode arising from the central resonator and the weak modes in the curved split resonators. Looking at the magnetic resonance (\textbf{m}) direction in the upper and lower parts of the magnetic split resonators (Figure 2a, not to scale) and central block, strong magnetic fields oscillate in antiphase regime, while the excited weaker magnetic modes at the central resonator acts as an in-phase component.\textsuperscript{32} On the other hand, Figure 2b illustrates the formation of a head-to-tail configuration of the magnetic moments leading to a toroidal dipolar moment (\textbf{T}) at the center of the unit cell created by the currents (\textbf{j}) on the surface of a torus along the circular meridian. The arrows show the current flux direction and magnetic moment (\textbf{m}) oscillation as a close-loop arrangement inside the profile. Obviously, the head-to-tail configuration is performed with 90° angle to the central block due to antisymmetric geometry of the unit cell.

The corresponding transmitted magnetic radiation from the magnetoplasmonic unit cells arrays can be obtained by taking the summation of the scattered magnetic and incident electromagnetic fields. The total contribution of the far-field scattering of the magnetic field (\(H_{\text{scat}}\)) can be written as\textsuperscript{32,45}

\[
H_{\text{scat}} = \frac{k^2}{Z_0A\pi\epsilon_0} [\{[(\textbf{n} \times \textbf{m}_c) \times \textbf{n} + i\textbf{n} \times \textbf{T}_c \times \textbf{n})]\} \times \textbf{n}
\]

where \(k\) is the wave vector, \(Z_0\) is the impedance of the medium, \(\epsilon_0\) is the permittivity of the vacuum, \textbf{n} is a unit vector in the direction of the incident illumination, and finally, \textbf{m}_c and \textbf{T}_c are the magnetic and toroidal dipolar moments, respectively, defined as\textsuperscript{46}

\[
\begin{align*}
\textbf{m}_c &= \frac{1}{2c} \int (\textbf{r} \times \textbf{j}) \, d^3r \\
\textbf{T}_c &= \frac{1}{10c} \int [(\textbf{r} \times \textbf{j}) \textbf{r} - 2r^2 \textbf{j}] \, d^3r
\end{align*}
\]

where \(\textbf{j}\) is the induced current density over the entire volume of the area and \(c\) is the conventional speed of light. To show the strong dependence of the magnetic response to the geometrical parameters, we first analyze the effect of the offset gaps between the peripheral and central resonators on the electromagnetic response as shown in Figure 2c(i)–e(i). This analysis would help us to control the position and sharpness of the induced magnetoplasmonic resonances by varying the offset gap. A sharp magnetic dipolar minimum is observed at \(\sim 230\) GHz (indicated by \textbf{m} in Figure 2c) in the experimentally measured electromagnetic response of the plasmonic unit cell at (a) toroidal and (b) magnetic resonance frequencies. Numerically obtained local \(H\)-field (A/m) snapshots for the toroidal and magnetic resonance confinement and excitation at the gap spot area between resonators in (i) linear and (ii) logarithmic scales. (iii) Cross-sectional vector maps for the magnetic field lines at the position of toroidal and magnetic resonant modes. (c) Simulated surface currents (\textbf{j}) of unit cell at toroidal and magnetic resonances.

Figure 3.
The normalized transmission amplitude profile for \( D_g = 3 \mu m \) which is attributed to an in-phase magnetic mode. On the other hand, an ultrasharp and distinct line shape is induced at \( \sim 203 \) GHz correlating with the magnetic toroidal dipole (T). At this point, the induced magnetic fields in the satellite split resonators and the closed-loop magnetic moment at the offset gap area (the point that both resonators meet each other) cause formation of a head-to-tail configuration of the magnetic dipoles via suppression of the classical modes in a similar fashion that has been reported for 3D structures.\(^{42,46,47,55}\) One should note that inducing such a distinct and pronounced toroidal magnetic moment using conventional planar structures is a serious challenge. Our tailored plasmonic unit cell has an exquisite geometrical asymmetry which is enhanced by using two different materials. The presence of Fe resonators with high magnetic moment and plasmonic properties help formation of a giant magnetic current around the middle Ti rectangle. The good electric and poor magnetic responses of the central Ti block help to prevent destructive interference of the strong magnetic moments arising from peripheral magnetic resonators with the moments from the middle rectangle. As a result, formation of a closed-loop head-to-tail magnetic moment configuration would be possible around the central part of the unit cell. Furthermore, the presence of the substrate below the planar unit cell resonator increases the asymmetry of the entire metasurface. In this regime, formation of multipolar magnetic and electric modes is feasible; however, these modes are not resonant at the toroidal frequency and cannot be observed in the transmission spectrum. By increasing the gap distance between the proximal resonators to 4 and 5 \( \mu m \) homogeneously, we observed a trivial broadening in the line width and suppression of the toroidal dip which dramatically affected the Q-factor of both magnetic and toroidal modes (Figure 2d(i),e(i)). Such a trend can be better understood by analyzing the effect of the offset gap on the circulating head-to-tail toroidal mode. In fact, for larger offset gaps (\( D_g > 4 \mu m \)), the excited magnetic field which contributes to formation of the circulating current becomes weaker, causing a huge mismatch between the induced electromagnetic currents in the peripheral and central resonators. The SEM images for the gap spot variations between Fe and Ti resonators in unit cells are shown in Figure 2c(ii)−e(ii). The experimentally obtained results are in perfect agreement with the simulation predictions (see Figure 2c(iii)−e(iii)). We calculated the corresponding experimental Q-factors as high as \( Q_{exp}^{m} = 14 \) and \( Q_{exp}^{T} = 18 \) for the magnetic and toroidal modes, respectively, using the highest peak and lowest minimum of the induced toroidal dipolar dip.\(^{43,44}\) Achieving such a high Q-factor by a planar metasurface is the direct result of the strong magnetic resonance confinement and weak free-space coupling.

Figure 3a,b exhibits the numerically calculated local magnetic field (\( \mathbf{H} \)) localization in a standalone unit cell resonator, showing the intense magnetic field confinement at the center of the antenna at the toroidal and magnetic frequencies.
respectively, in both linear and logarithmic scales. In addition, we demonstrated the cross-sectional panels for the magnetic field (H-field) excitation across the plasmonic unit cell at both toroidal and magnetic resonant moments as shown in Figure 3a(iii), b(iii), respectively. These planes provide a better view of the magnetic field disturbance due to formation of heat-to-tail circular magnetic fields at the center of the unit cell. The surface current (j) also simulated for both resonant modes as shown in Figure 3c.

In addition, we analyzed the effect of the geometrical variations in the magnetic peripheral curved resonators on the plasmonic response of the metasurface. To this end, by keeping the width of the central block fixed at $W_2 = 40 \, \mu m$, we reduced the widths of the satellite resonators to $W_1 = 25 \, \mu m$ with the radii fixed to $R = 50 \, \mu m$. Figure 4 shows both simulation and experimental results for three different gaps. With the reducing width of the magnetic components, the strength of the magnetic dipole moment ($m$) decays dramatically and does not radiate as strongly as it has in the previous cases. Therefore, a significant decay is expected in the oscillating magnetic field around the central block (toroidal mode) due to dominant behavior of the excited classical electric dipolar and multipolar moments. It should be noted that despite possessing the prevailing response, both electric and magnetic multipolar moments are not still resonant in this frequency due to poor scattering efficiency. By comparison of Figure 4a and Figure 2a, the significant decay in the corresponding Q-factor of the toroidal mode is clear. In the same way, the magnetic dipole moment also decays dramatically due to both electric and magnetic classical multipolar modes’ dominancy. In this limit, increasing the gap distance between the central and peripheral resonators gives rise to continuing decay in the quality factor of both induced modes (see Figure 4b,c). For $D_g = 5 \, \mu m$, the magnetic dipolar moment almost disappears and is hard to identify in the experiments. The minor blue-shift in the positions of both resonant dips is attributed to the geometrical variations, which can be described by Mie scattering theory.
The insets in simulation profiles (Figure 4a(ii)−c(ii)) are the SEM images of the studied geometrical variations.

**TERAHERTZ TOROIDAL IMMUNOSENSOR**

The unique electromagnetic response of the studied THz structure can be used to tailor highly sensitive and accurate plasmonic sensors. To this end, we prepared a series of chips with the best Q-factor (with the following geometrical parameters: \(D_g = 3 \mu m, L = 240 \mu m, R = 50 \mu m, W_1 = 30 \mu m, \) and \(W_2 = 40 \mu m\)) to achieve precise sensing. The immunosensing samples were prepared in three different configurations: (1) with antibody, (2) with antibody and bovine serum albumin (BSA), and (3) with antibody, bovine serum albumin (BSA), and variant concentration (1 pg/mL to \(10^4\) pg/mL) of immobilized ZIKV envelope protein (see Methods). Figure 5a shows an artistic drawing of the proposed metasurface with the presence of antibody and trapped envelope proteins around and on the plasmonic resonators.

Figure 5b,c shows the SEM images of the presence of immobilized ZIKV antibody on a sample metallic microstructure and a chip covered with antibody-attached ZIKV envelope protein, respectively. These images help explain the binding quality of antibody and capture of biomarker proteins to the bimetallic metamolecules directly right after the deposition in the metasurface.

Figure 6(i),(ii) illustrates the transmission spectra of the plasmonic metasurface for different concentrations of ZIKV envelope protein captured by the antibody. By focusing on the behavior of magnetic toroidal mode, we observed a prominent resonance in the presence of ZIKV envelope protein concentration between 1 pg/mL to \(10^4\) pg/mL. In the earlier section, we observed excitation of the toroidal resonance mode at 203 GHz for the bare resonators. In the presence of the ZIKV antibody, the toroidal mode remained unchanged at 203 GHz due to its optical nonresponsiveness to the incident radiation. For the solution composed of ZIKV antibody plus BSA the magnetic toroidal mode red-shifted to 198 GHz. This is because of formation of a layer on top of the plasmonic sensing device, which affects the entire refractive index of the surrounding ambience and shifting the toroid moment. It should be emphasized that the presence of BSA layer helps improve the ZIKV envelope protein capture by respective antibody effectively and prevents nonspecific binding of ZIKV envelope protein. Adding 1 pg/mL and 10 pg/mL of the target protein did not cause any shift in the position of the toroidal moment and it remained at 198 GHz. However, increasing the concentration to 50 pg/mL and 100 pg/mL shifted the toroidal resonance to 194 and 188 GHz, respectively. Such a large shift in the resonance frequency shows the sensitivity of the toroid dip to the concentration of the infection protein. Interestingly, the narrowness and sharpness of the dipolar toroidal moment is almost unchanged, which helps keep the sensing precision high by keeping the Q-factor high. This is unusual compared to classical plasmonic biosensing systems operating based on antisymmetric resonant lineshapes such as Fano and EIT resonances where perturbation in the environmental refractive index or physical changes cause destructive effects to the line shape quality.

**Figure 6.** Transmission spectra for the toroidal resonant mode behavior for presence of different concentration of ZIKV envelope protein from (i) antibody to 50 pg/mL and (ii) 100 pg/mL to \(10^4\) pg/mL.
modes is caused by their strong dependency on the morphological and geometrical perturbations affecting the spectral response dramatically. Conversely, Gupta et al. and Savinov et al. have theoretically and experimentally verified that the quality of toroidal moment does not decrease by minor morphological variations. Further increases in the concentration of ZIKV envelope protein to 500 pg/mL leads to a shift of the position of the pronounced toroidal resonant dip to 187 GHz. In addition, by increasing the concentration of target protein to 10^3 pg/mL and 10^4 pg/mL, we observed a drastic decay in the quality of the toroidal mode in both cases. Figure 7b presents the frequency shifts (GHz) as a function of protein concentration (pg/mL). ZIKV envelope protein with the concentration ranging from 1 pg/mL to 10 pg/mL did not cause a noticeable frequency shift, reflecting weak sensitivity, while for the concentration ranging from 50 pg/mL to 500 pg/mL a significant red-shift in the frequency of the toroidal mode is recorded. In this study, the limit of detection (LOD) can be defined by LOD = 3(ΣD)/S, where “SD” is the standard deviation of the frequency shift and “S” is the slope of the fitting line (shown by the dashed line in Figure 7a), and the LOD is quantified as ~24 pg/mL. By defining the slope of the toroidal position shift as a function of ZIKV envelope protein concentration, we estimated the sensitivity of the structure as 6.47 GHz/log(pg/mL).

We also analyzed the longevity and repeatability of the demonstrated THz plasmonic biosensors. To this end, samples with the antibody were prepared with the described technique in the Methods section and stored at 4 °C before the measurements. Figure 6c shows the measured transmission spectra for three consecutive days with the ZIKV concentration of 500 pg/mL. The resonance quality remained excellent for 3 days. However, after this period of time, the toroidal dip became broader and dramatically damped. This deterioration also included a significant blue-shift in the position of magnetic resonant mode to the higher energies. Ultimately, we believe that the ability to identify low concentrations of a specific biomarker with low molecular weight will be feasible by using the proposed metasensor. In a comparison between newly reported THz plasmonic biosensing works, we facilitated detection of proteins with the molecular-weight of ∼13 kDa, while the recent achievements show detection of bio-objects with the weight of over 70 kDa using THz biosensors.

CONCLUSIONS

In summary, we have demonstrated excitation of ultrasharp toroidal and magnetic dipoles in THz frequencies using bimetallic asymmetrical planar resonators. Using the magnetic nature of Fe and also the exotic geometrical design of the proposed structure, we achieved an experimentally measured Q factor of 18 for the toroidal resonance. Taking advantage of the high Q toroidal moment resonance, we also demonstrated biosensing capability of the proposed structures. Spectral response of the samples loaded with the relevant antibody to the assays of ZIKV envelope protein with different concentrations shows that limit of detection of ~24 pg/mL and 6.47 GHz/log(pg/mL) is achievable. Further studies proved that the demonstrated biosensing platform could be reliable up to 3 days. The unique geometry of the proposed resonators also results in high polarization sensitivity which allows for their use in THz switching applications. Rapid detection capability combined with the very sharp resonance and easy fabrication of THz resonators compared to its counterparts in optical frequencies make the demonstrated devices a promising platform for biosensing applications.

METHODS

Fabrication of Plasmonic Metasurface. For the fabrication of the proposed devices a two-level lithography based microfabrication process is developed. An undoped and high-resistivity silicon wafer (>10,000 Ω cm) with the crystal orientation of (100) was used as substrate to provide the required transparency in the THz spectra. It was sonicated in acetone for 10 min, and rinsed with isopropyl alcohol (IPA), deionized (DI) water, and dried by nitrogen gas. The lift-off process was performed for 15 min by immersing the samples in acetone. Ultimately, the samples were plunged in remover PG for 120 min at 70 °C heat followed by IPA and DI water rinse. The SEM images shown in the manuscript were obtained using JEOL 6330 tool.

Characterization of plasmonic unit cells. To characterize samples and extract the plasmon response of arrays with and without biological targets, a millimeter wave backward wave oscillator (BWO) setup combined with frequency multiplier (Microtech Instruments, Inc.) and broadband pyroelectric detector (Gentec Electro Optics Inc.) was operated at room temperature. The spectral range of the incident
radiation is between 100 GHz and 1.5 THz. The spectral resolution of the system is 10 MHz.

Preparation of samples for fingerprint biological assay. First, we used both lyophilized 99% bovine serum albumin (BSA) purchased from Sigma-Aldrich, and pH 7.4 phosphate buffer solution (PBS) to dissolve the immunoreagents. The antibody and envelope proteins were purified by diethylaminoethyl (DEAE) column chromatography and presented in 0.015 M potassium phosphate (KH2PO4) and 0.85% NaCl with the pH around ~7.2. For preparing the samples for real-time characterization, 10 μL of Zika antibodies (1 mg/mL) in PBS were locally deposited on the sensing area of THz structures and incubated for 15 min. After washing the chips with PBS, antibody-modified structures were incubated in PBS containing 0.1 wt % BSA for 15 min, and then, in a solution of a recombinant ZIKA diluted in PBS for at least 20 min (The ZIKV envelope protein concentration ranged from 1 to 10^5 pg/mL). Here, the recombinant of ZIKV envelope protein is an artificial ZIKA protein created through genetic engineering process (recombinant DNA technology). The recombinant ZIKA envelope protein in our research was purchased from Sino Biological USA. Once prepared, an antibody-functionalized microfluidic system is 10 MHz.

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