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Review

The theory, technology, and application of terahertz metamaterial biosensors: A review

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ABSTRACT

Terahertz metamaterial biosensors combine terahertz time-domain spectroscopy with metamaterial sensing to provide a sensitive detection platform for a variety of targets, including biological molecules, proteins, cells, and viruses. These biosensors are characterized by their rapid response, sensitivity, non-destructive, label-free operation, minimal sample requirement, and user-friendly design, which also allows for integration with various technical approaches. Advancing beyond traditional biosensors, terahertz metamaterial biosensors facilitate rapid and non-destructive trace detection in biomedical applications, contributing to timely diagnosis and early screening of diseases. In this paper, the theoretical basis and advanced progress of these biosensors are discussed in depth, focusing on three key areas: improving the sensitivity and specificity, and reducing the influence of water absorption in biological samples. This paper also analyzes the potential and future development of these biosensors for expanded applications. It highlights their potential for multi-band tuning, intelligent operations, and flexible, wearable biosensor applications. This review provides a valuable reference for the follow-up research and application of terahertz metamaterial biosensors in the field of biomedical detection.

1. Introduction

Terahertz (THz) waves are generally defined as electromagnetic waves ranging from 0.1 to 10.0 THz, located between the microwave and infrared bands [1]. This special band position enables it to have both electronics and photonics properties. They have a wide spectrum range and good directionality, which is suitable for high-speed data transmission [2]. In addition, THz waves have low photon energy and high penetration, thus promoting their wide application in fields such as military communication, security detection, and imaging, especially in biomedical sensing [3–10]. Specifically: 1) Since most biomolecules have unique fingerprint spectra in the terahertz band, the classification and identification of substances can be achieved. It covers the energy range of hydrogen bonding and weak interactions, providing greater sensitivity to molecular vibrations, rotations, and conformations, thereby providing a detailed insights into molecular structure [11,12]. 2) The low photon energy of THz waves (millivolts scale) ensures that they don't cause ionization damage to biomolecules, highlighting their biological safety [13,14]. 3) Because the terahertz wave is more sensitive to polar molecules (e.g., water), it is possible to analyze the characteristics of samples based on the water content. It even has potential applications in therapeutic interventions. For example, the resonant terahertz field can manipulate the conduction of calcium channels to correct Ca^{2+} deficiency in degraded calcium channels and to induce apoptosis of calcium-overloaded tumor cells [15]. Currently, for biological samples with a high content of target molecules (tissue-grade samples, compression-grade samples, etc.), highly sensitive and accurate detection can be achieved using conventional terahertz detection techniques [16]. However, the sensitivity of conventional THz detection techniques is limited in the context of medical and clinical detection, where target molecule concentrations are typically low. The mismatch between the response cross-section of molecules (nanometer scale) and the THz wavelength (sub-millimeter scale) hinders the trace detection capabilities of THz waves, falling short of the requirements for early medical screening [17].

Metamaterials, as a class of artificial composite structures emerging in recent years, provide a promising solution to enhance the sensitivity and precision of THz technology for the detection of micro- to trace-level biological samples [18,19]. According to the practical application requirements, through the artificially carefully designed and optimized structural units, metamaterials can achieve arbitrary dielectric constant and permeability customization so as to have extraordinary electromag-

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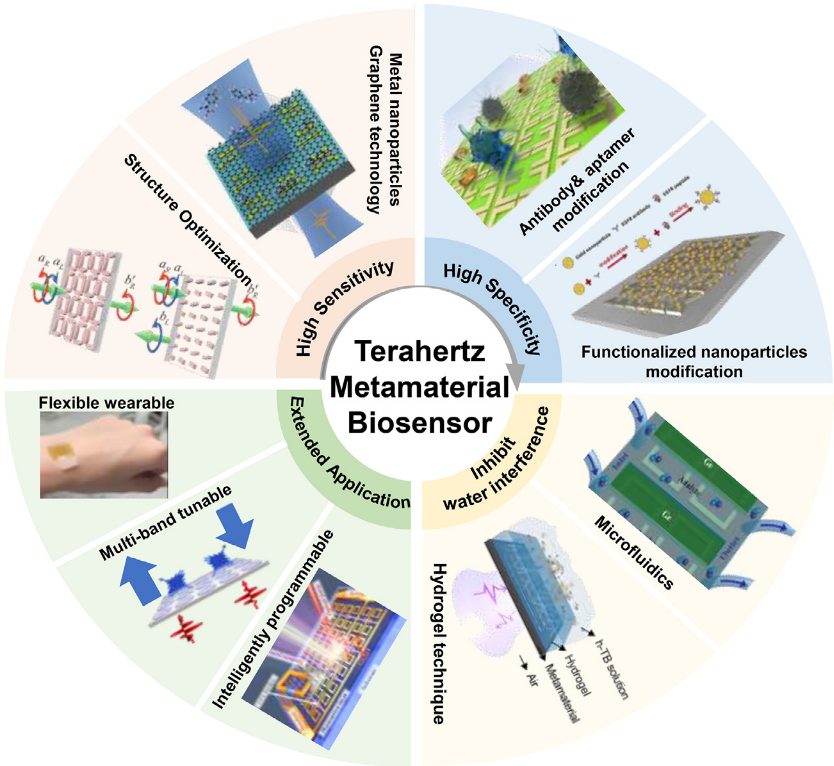

Fig. 1. The performance enhancement and extended applications of THz MM biosensors [29–34,51,71,83].

netic wave regulation ability. In terms of biosensing, metamaterials can achieve a substantial enhancement of the local light field, that is, amplify the interaction between matter and metamaterials [20,21]. Therefore, highly sensitive detection of trace biological samples can be realized, thus contributing to the early diagnosis of diseases [22]. Compared with traditional biosensors, terahertz metamaterials have the characteristics of fast sensitivity, high biosecurity, no label, and a smaller detection amount.

However, current THz metamaterial biosensors (MM biosensors) still have three challenges: 1) Sensitivity doesn't satisfy the needs of early screening for diseases. 2) Lack of qualitative identification ability. 3) The absorption interference of THz waves by water in biological samples. Therefore, based on the practical demands of medical clinics, this paper reviews a variety of emerging technologies to solve the three major problems of sensors. In terms of sensitivity, selecting substrate materials with lower capacitance and optimizing device geometries have been shown to improve sensitivity. Quartz, cyclic olefin, and polyimide are proposed as alternatives to traditional high-resistance silicon substrates [23]. Meanwhile, the cell geometries of devices are designed and optimized to stimulate new coupling modes: electromagnetically induced transparency (EIT), toroidal dipolar (TD), quasi-bound states in the continuum (QBIC), etc. Furthermore, the combination with metal nanoparticles and graphene can further amplify the sensing signal [24,25]. To promote specificity, the surface of biomaterials can be modified using antibodies and aptamers, allowing for the differentiation of specific signals and enabling highly accurate qualitative analysis. This improvement is crucial for the early screening of critical illnesses. To overcome water absorption interference, methods such as self-referential reflection [26], microfluidics [27], and hydrogel technology [28,29] are effective. These methods not only reduce the interference but also preserve the activity of the sample, increasing the potential for immediate clinical application. This paper also provides the future research direction of THZ MM biosensors, highlighting their potential in multi-band tuning, flexible wearable, and intelligent programmable applications in the field of biosensing (Fig. 1).

2. The mechanism and manufacture of THz MM biosensors

2.1. The mechanism of biosensors

The mechanism of THz MM biosensors can be explained by surface plasma waves. Surface plasma wave refers to the electron density wave propagating along the metal surface caused by the interaction between freely vibrating electrons and photons [30]. In the THz frequency range, the skin depth of electromagnetic waves is limited, which inhibits the formation of plasma on the metal surface. By designing the metamaterial's structure, local electromagnetic energy is enhanced to achieve a good match with the sample to be measured, thereby enhancing the interaction between THz waves and the material [35–37]. THz MM biosensors typically employ two sensing methods: 1) Detecting shifts in the resonance frequency that result from changes in the refractive index of the surrounding environment. 2) Measuring changes in the amplitude of spectral absorption peaks, which are induced by the object being measured on the device's surface. The resonance frequency shift in these biosensors can involve both single- and multiple-resonance modes. The sensor's performance is assessed based on these shifts and amplitude variations [38].

2.2. The fabrication of biosensors

The fabrication of THz MM biosensors involves a range of micro- and nanofabrication techniques, such as photolithography, nanoimprinting, fiber-optic drawing, and template deposition methods. Photolithography is a common approach for sensor preparation, encompassing the creation of metallic and non-metallic structures as well as thin-film deposition [39]. Different metamaterial structures require different microprocessing techniques. Planar metamaterials typically use single-layer lithography. This involves metal deposition followed by the development of the firm mold and de-gumming to achieve the desired metal structure [40]. In contrast, three-dimensional metamaterials are typically achieved using multilayer lithography techniques through alternating stacking and nesting of dielectric and metal structures. For tunable metamaterials, a sleeve engraving technique is utilized, combining multilayer metal and non-metallic structures. This technique enables dynamic structural changes in response to external stimuli. [41,42]

3. The sensitivity enhancement methods for THz MM biosensors

For early screening of diseases, the concentration of disease markers in the body is very low. Therefore, the sensitivity of THz MM biosensors needs to be as high as possible. It needs to have the ability to detect the target at very low concentrations. The sensitivity (S) of a THz MM biosensor is defined as the shift in resonant frequency corresponding to a change in the unit refractive index of the analyte, which reflects the refractive index sensing performance of the device. In the terahertz band, the unit is THz/RIU, and the formula is $S = \Delta f/\Delta n$, where Δf is the frequency shift of the resonance peak and Δn is the change in the refractive index of the analyte [21].

Currently, researchers mainly enhance the device's sensitivity by reducing electromagnetic radiation loss and combining other enhancement techniques. Firstly, the radiation loss introduced by the device itself can be reduced by choosing a low-dielectric constant substrate or optimizing the substrate thickness. In addition, optimizing the MM biosensor's unit structure also improves performance. The novel resonance mechanisms, such as EIT, TD, and QBIC mechanisms, demonstrate potential for high sensitivity by enhancing light-matter interactions and reducing radiation losses [40,41]. Secondly, sensitivity can be increased by enhancing analyte metamaterial interactions, including the combination of analyte molecules with gold nanoparticles or with graphene. The former results in the formation of a target with higher reflectivity, yielding a larger frequency shift. The latter increases the interaction with the object to be measured through the stacking between π-bonds, obtaining a larger amplitude shift and thus achieving a significant increase in detection sensitivity. In this review, we focus on discussing the impact of novel techniques on sensitivity enhancement, paying attention to both the introduction of novel resonance mechanisms in metamaterials and their combination with enhancement techniques.

3.1. Introduction of novel resonance mechanisms

By optimizing the unit structure of the MM to introduce novel resonance mechanisms, we can realize the strong coupling mode in the unit, thus improving the quality factor (Q-value) of the device. This promotes stronger light-matter interactions, leading to improved sensitivity. The Q-value represents the resonant cavity's ability to confine the optical field's energy. A higher Q-value indicates a better confinement capability, meaning the resonant field of the metamaterial is less likely to couple with free space, thus reducing radiation loss [21]. In the terahertz band, the Q-value is calculated using the formula [22]:$Q = \omega_0/FWHM$, where ω_0 is the resonance's center frequency and $FWHM$ is the full width at half maximum of the resonance. In this discussion, we will concentrate on three coupling modes [23]: EIT, TD, and QBIC.

3.1.1. THz MM biosensors based on the EIT mechanism

EIT is a quantum interference phenomenon originating from quantum systems. When a medium absorbs light of a particular frequency (probe light) and is illuminated by light of a similar frequency (pump light), the two types of light interfere with each other. This interaction weakens the medium's absorption of the probe light. The released energy transfers to the coupling field, creating a sharp transparent window in the absorption spectrum [42,43]. In THz MMs, EIT is commonly observed in bright-bright and bright-dark coupling modes. Bright-bright coupling involves resonance between all unit structures and the incident THz wave, typically occurring in asymmetric structures. The incident wave excites surface current oscillations, which in turn excite a magnetic dipole that interacts weakly with free space. This resonance between the electric and magnetic dipoles facilitates EIT, enhancing sensitivity due to low radiation loss. Bright-dark coupling, on the other hand, is the interaction between modes that resonate with the incident THz wave (bright modes) and those that do not (dark modes). This coupling is seen in structures combining bright (often metal strips) and dark (often metal surface resonant open rings) elements. The bright mode is excited by the incident wave, generating an electric field that excites the dark mode. The resulting phase cancellation interference between bright and dark modes produces transmission peaks characterized by low radiation loss, high quality factor, and sensitivity [44].

Many THz MM biosensors based on EIT effects have been designed and demonstrated for their high sensitivity and device performance. In 2021, Zhang et al. [45] proposed a metamaterial biosensor composed of a cut line and an open ring resonator. The horizontal cut line, along with two diagonal open rings perpendicular to the incident polarization direction, forms a narrow bright mode, while other structures form a wide dark mode. Theoretical simulations indicated a sensor sensitivity of up to 496.01 GHz/RIU. Experimental results demonstrated that this EIT biosensor could detect maximum sensitivities close to 248.75 kHz/cell ml^{-1} for both mutant and wild-type glioma cells. Distinguishing between mutant and wild-type glioma can be achieved by observing changes in resonance frequency and amplitude. This metamaterial biosensor holds significant potential for identifying glioma cell types at low concentrations, paving the way for advanced biosensing technologies.

In 2023, Wang et al. [46] designed a perfectly symmetric periodic MM biosensor based on square rings with different sizes of openings (Fig. 2b). The device exhibited polarization insensitivity at 2.05 THz and a sensitivity of up to 504 GHz/RIU. The minimum number of cells required for detection by this EIT sensor was 1/30th of that of conventional clinical methods. And the time consumed was reduced to 1/20th of that of pathology detection. Four cell types were successfully differentiated based on the frequency shift and transmittance variations, which allows the characterization of cells in both normal and cancerous states.

In addition, the EIT effect in toroidal dipolar metamaterials has attracted greater attention. In 2023, Ma et al. [47] designed a metamaterial biosensor with double-split circles and cut lines (Fig. 2c). In this case, the double-split circle is used to excite the ring dipole resonance, and the cut line is used to excite the electric dipole moment. Two transparent windows were obtained by interference between the magnetic dipole moments excited between the two electric dipole moments. With Q values of 21 and 28 and a sensitivity of up to 378 GHz/RIU, the device achieves highly sensitive detection of E. coli and S. aureus. The lowest detected concentration reached about 104 cfu mL^{-1}. By combining the EIT effect and the ring dipole resonance, the device sensitivity and Q value were significantly improved.

3.1.2. THz MM biosensors based on the TD mechanism

TD mechanism can be divided into magnetic toroidal dipoles and electric toroidal dipoles, the main difference being the difference in polarization currents. Magnetic toroidal dipoles are generated by currents that flow along the meridian of the ring's surface. Electric toroidal dipoles are the result of currents that flow tangentially to the ring's surface. In traditional materials, achieving TD resonance poses a challenge. Unlike conventional materials where toroidal dipole resonance is difficult to achieve, terahertz metamaterials can increase the toroidal dipole magnetic moment while suppressing the electromagnetic moment by adjusting the arrangement of the unit structure, which is usually achieved by the structure of the SRR combination in the opposite direction [48].When a THz wave is incident perpendicularly on the surface of the metamaterial, the opposing open rings will create a counter-loop current, which excites a magnetic dipole in the reverse direction [49]. This excitation generates a closed magnetic field conducive to ring dipole resonance. The resonance phenomenon shares similarities with

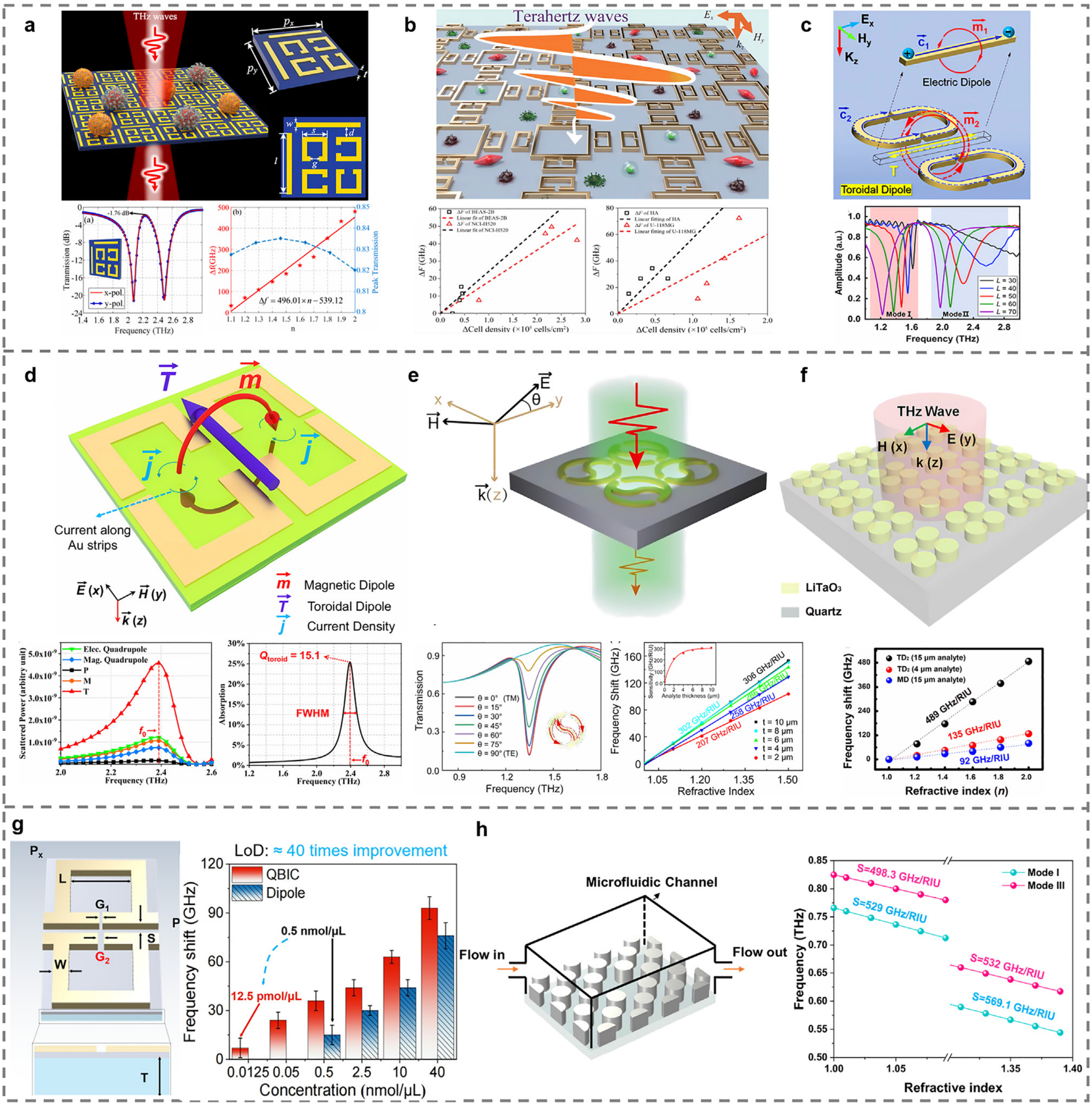

Fig. 2. Summary of the optimized structures of THz MM biosensors. (a) An EIT-based cut-line opening ring MM biosensor [45]. (b) An EIT-based perfect opening square ring MM biosensor [46]. (c) An EIT-based double-split circle cut-line MM biosensor [47]. (d) A TD-based mirror-image gold-opening MM biosensor [51]. (e) A TD-based fractured Chinese THz ring metamaterial biosensor [52]. (f) A TD-based asymmetric cylindrical metamaterial biosensor [53]. (g) A QBIC-based asymmetric MM biosensor [60]. (h) A QBIC-based all-media MM biosensor [61].

the far-field contributions of both the ring polar moment and the electric dipole moment. By disrupting the interference between these contributions, a magnetic excitation is induced that significantly mitigates electromagnetic radiation and scattering losses. This reduction in losses, in turn, enhances the sensitivity and overall performance of the metamaterial biosensor. [50]

In recent years, many high-quality and sensitive THz TD metamaterial biosensors have been fabricated and utilized. In 2021, Zhang et al. [51] presented a metamaterial biosensor consisting of two mirrored gold open-ring resonators (Fig. 2d). The sensitivity of the sensor was as high as 485.3 GHz/RIU. The resonance frequency drift was <0.66% and the transmittance variation was kept below 1.33% over an oblique incidence angle range of 0° to 30°, exhibiting high angular stability. By detecting the differences in transmittance and frequency shift of three lung cancer cells (Calu-1, A427, and 95D), the device was able to directly differentiate between analyte cell types and their concentrations in just one measurement.

In 2023, Liu et al. [52] based their work on high-quality planar annular dipole resonances found in fractured Chinese Taiji rings. A novel polarization-independent THz ring sensor was designed by combining four THz rings into a circular unit (Fig. 2e). The biosensor exhibits highly sensitive sensing characteristics for ultrathin analytes and refractive indices. In the frequency range of 1.345 THz, the analyte at 4 μm coating thickness can reach a value of 258 GHz/RIU, which is a much higher performance than previous sensors of the same type and successfully achieves the detection of Alzheimer's disease-associated Aβ proteins at low concentrations (0.0001 mg/m to 10 mg/mL).

The potential of TD with weak coupling to electromagnetic fields for developing highly sensitive metamaterial biosensors is significant. However, achieving high-quality factor TD resonances in these devices presents a challenge.

In 2021, Wang et al. [53] conducted a study on the aberration of the bound state that preserves the symmetry of the continuum spectrum in a fully dielectric metamaterial. This metamaterial was made up of an array of high-index tetramer clusters. They achieved this by designing a cylindrical structure with asymmetric clusters (Fig. 2f). By adjusting the asymmetry of the clusters, it is possible to convert the TD resonance into an ultra-high Q leakage resonance. This low-loss TD resonance, characterized by an extremely narrow linewidth, is highly sensitive to alterations in the refractive index of the surrounding medium. It exhibits an ultra-high sensitivity level of 489 GHz/RIU and a FOM value as impressive as 253.52. The asymmetric metamaterial structure, which possesses an ultra-high Q-factor, is particularly adept at detecting small frequency shifts. These shifts are induced by the small size of the analyte. This capability makes the structure suitable for the detection of trace analytes, allowing for precise quantitative analysis.

3.1.3. THz MM biosensors based on the QBIC mechanism

In photonic systems, the bound-in-the-continuum state (BICs), also known as radiation-free localized states, appears as energy bound in the continuum and can't be coupled with radiation in free space [54–56]. Theoretically, BICs are endowed with an infinite quality factor and exhibit a non-radiative characteristic with a spectral linewidth that approaches zero. However, these ideal properties are challenging to observe in practical applications. To bridge the gap between theory and application, researchers have introduced external perturbations to the BICs. They transform the BICs into observable quasi-bound states with a high quality factor, known as QBIC [57,58]. This mechanism enables a substantial enhancement in sensor sensitivity, which is a critical advancement. The development of QBIC has far-reaching implications, particularly in the high-precision, quantitative detection of target molecules at extremely low concentrations.

Recently, many scholars have carried out extensive design studies on THz MMs based on the QBIC mechanism and have realized applications in biosensing. In 2021, Wang et al. [59] present an ultra-sensitive THz metasensor based on QBIC Fano resonance, which consists of three gold microrods arranged periodically and can sense solutions with ∼nM concentrations. In 2023, Liu et al. [60] designed an asymmetric structure on a metallic metamaterial (Fig. 2g). By controlling the interference coupling between electric quadrupoles and magnetic dipoles, ultra-high Q resonances up to 503 were excited, and huge increases of 400% and 1300% in the energy of the light field confined by the metamaterial as well as in the effective sensing area were achieved, respectively. The range and intensity of the interaction between light and matter are greatly broadened. Moreover, the QBIC resonance of this metamaterial has a high refractive index sensitivity up to 420 GHz/RIU, and the direct detection limit of homocysteine (Hcy) molecule is 12.5 pmol/μL, which is about 40 times that of the classical dipole mode.

In 2023, Saadatmand et al. [61] engineered a silicon wafer-based MM biosensor for dual refractive index and temperature sensing (Fig. 2h). The device produced three resonances: magnetic toroidal dipole, quadrupole, and electric toroidal dipole. An asymmetric design yielded two ultra-high Q-factor quasi-bound states in BIC resonances. The sensor exhibited high sensitivity for liquid (S_l = 569.1 GHz/RIU) and gas (S_g = 529 GHz/RIU) detection using magnetic toroidal dipoles, and slightly lower sensitivity for electric toroidal dipoles (S_l = 532 GHz/RIU, S_g = 498.3 GHz/RIU). Additionally, it provided precise temperature monitoring with a sensitivity of 20.24 nm/°C. This study offers a significant reference for developing accurate, qualitative trace substance detection in the THz range.

3.2. The enhancement of the sample signals

3.2.1. THz MM biosensors combined with metal nanoparticle systems

The dielectric constant of metal nanoparticles is much higher than that of biological samples, and they are unable to induce surface plasmon resonance in the THz band alone [62]. When they are combined with the substance to be tested, the product has a larger overall refractive index and absorption cross-section, with a more pronounced THz response, and more distinct resonance changes can be observed in the spectra. This means that THz MMS biosensors combined with metal nanoparticle systems can effectively enhance the frequency shift of the detection results and amplify the detection signals, thus achieving a significant increase in device sensitivity. Notably, when nanoparticles with the same concentration and diameter and different materials are deposited on the metamaterial, the reflection index of the object to be measured is the only variable. Therefore, the frequency shift is only affected by the dielectric constant, and gold nanoparticles with a higher dielectric constant can achieve a significant increase in sensitivity [63]. Furthermore, within a 50 nm range, selecting nanoparticles with larger diameters not only suggests a greater thickness of the analyte but also correlates with higher sensitivity [64]. This insight is valuable for optimizing the design of biosensors for superior detection capabilities.

In 2016, Xv et al. [65] combined gold nanoparticles (AuNPs) with a THz MM biosensor for the first time, significantly increasing detection sensitivity by at least 1000x. Afterwards, more and more researchers began to focus on the possibility of developing with the combination of AuNPs with metamaterials technology. In 2022, Yang et al. [66] introduced a cutting-edge THz biosensor. This sensor leveraged the coupling of metamaterials with nanoparticles and a technique known as chain substitution amplification. It was specifically designed for the detection of mRNA samples (Fig. 3a). Under optimal conditions, the sensor demonstrated excellent sensitivity, with a detection limit as low as 14.54 μm. Notably, miRNA-21 showed a linear response across a concentration range from 1 μm to 10 μm. The sensor's accuracy was further validated through sample recovery tests, which yielded results between 90.92% and 107.01% when measuring miRNA-21 in spiked clinical serum samples. This high-sensitivity biosensor is poised to advance nucleic acid analysis and cancer diagnosis.

In 2023, Niu et al. [67] developed a ring-shaped MM biosensor, enhanced with functionalized AuNPs, for the highly sensitive detection of carcinoembryonic antigen (Fig. 3b). The AuNPs, with their high refractive index, substantially improved the biosensor's performance. The closed-loop magnetic field created electrical confinement, leading to a high sensitivity of 287.8 GHz/RIU and an ultra-high Q-value of 15.04. The sensor's detection limit was as low as 0.17 ng, as determined through quantitative studies of carcinoembryonic antigen biomarker concentrations. This THz ring MM biosensor, integrated with AuNPs, demonstrates exceptional promise for cancer detection applications.

3.2.2. THz MM biosensors combined with graphene material

Graphene is a two-dimensional material with a unique property: high biomolecular affinity. After binding with biomolecules, the object under test containing π bonds can be easily combined with graphene by π-π stacking to form stable binding products. This greatly increases the absorption cross section of the object under test, which in turn enhances the THz response signal [71]. Additionally, the binding of biomolecules to graphene can induce chemical doping, which significantly alters the material's optoelectronic properties. Graphene MMs used in biosensing are typically p-type doped, with Fermi energy levels positioned in the conduction band, slightly away from the Dirac point [68–70]. This means that an extremely weak external excitation can change the initial Fermi level from the valence band to the Dirac point, making it easier to produce large amplitude changes. Consequently, THz MMS biosensors combined with graphene enable highly sensitive de-

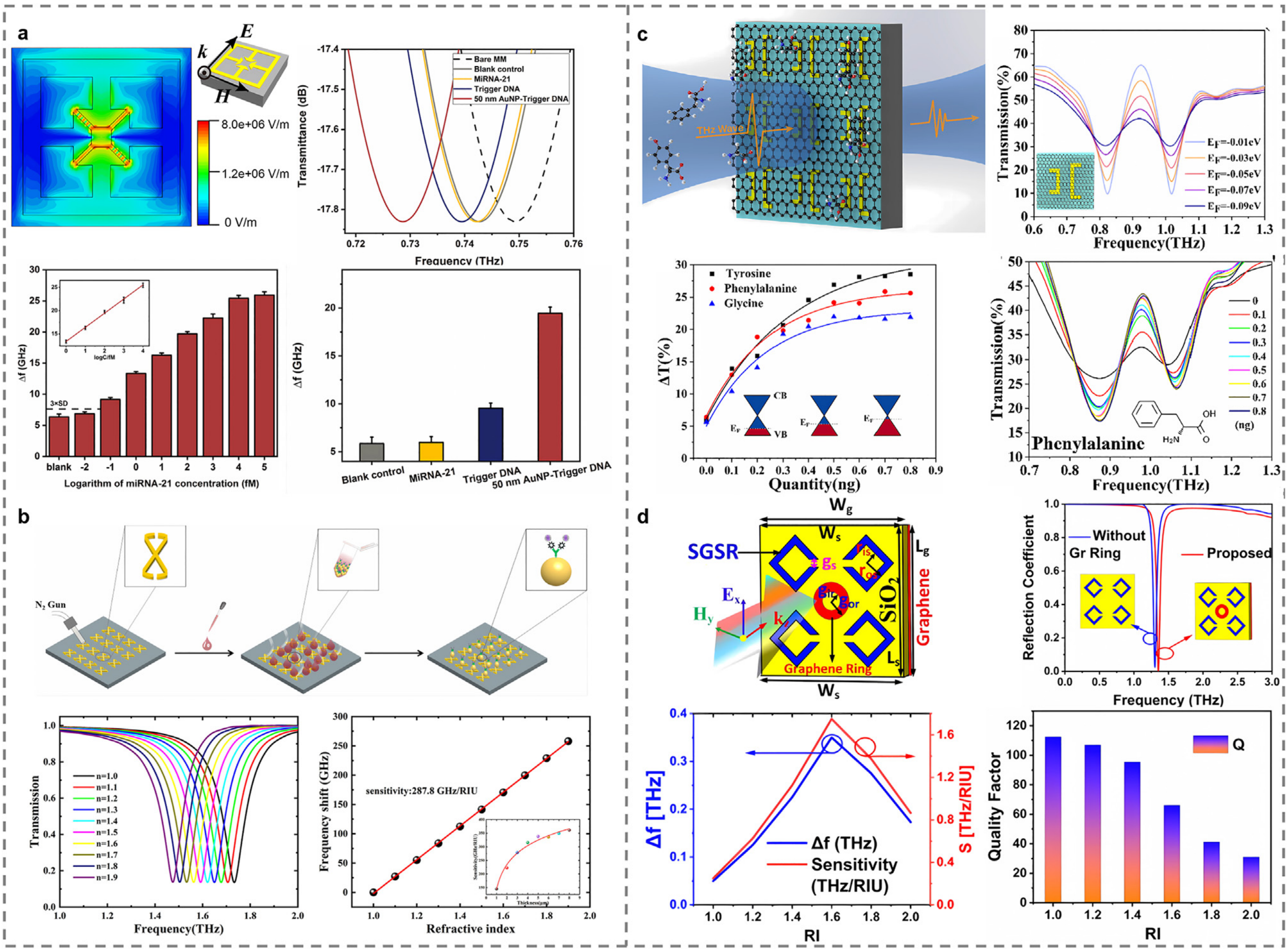

Fig. 3. THz MM biosensors combined with metal nanoparticles and graphene technology. (a) A MM biosensor based on coupling with nanoparticles and chain substitution amplification [66]. (b) A Ring MM biosensor with functionalized AuNPs [67]. (c) A MM biosensor based on ionophore-induced transparent resonance based on graphene technology [72]. (d) A MM biosensor based on ring resonators with graphene technology [73].

tection of biomolecules. A series of graphene THz MM biosensors have been fabricated and studied in recent years. In 2023, Zhou et al. [72] made significant progress with the development of a high-sensitivity metamaterial biosensor that integrates metal and graphene, leveraging plasma-induced transparent resonance. This biosensor achieved a remarkable detection limit of 10 ng/mL. As amino acid content increased, it enabled the efficient identification of three conditions: tyrosinemia, phenylketonuria, and hyperglycemia. The metamaterial sensor, characterized by its high sensitivity and rapid detection capabilities, shows promise for applications in trace molecular sensing and disease diagnosis, marking a notable advancement in the field of graphene-based THz biosensors.

In 2023, Upender et al. [73] designed a THz MM biosensor with four square open-ring resonators coupled by a central graphene ring (Fig. 3d). The strong coupling effect between the resonators and the graphene ring achieves near-perfect absorption at 1.354 THz. The performance of this sensor can be adjusted by the chemical potential of graphene to enhance its versatility. This device demonstrates outstanding sensing capabilities, with a high sensitivity of 17 THz/RIU, a quality factor of 165.09 RIU^{-1}, and 112.5. Despite the reduction of its structural thickness by 3 μm, it is still suitable for integration into nanotechnology devices. Giving it the potential to detect a wide range of viruses, including malaria, dengue, herpes simplex virus, influenza, and HIV, and to differentiate between various types of cancer cells, it holds promise for advancing biosensing applications.

4. Surface modification technology empowers molecule-specific detection of THz MM biosensors

Since THz MM biosensors don't have the ability to recognize different substances on their own, they need to be combined with other techniques to achieve substance-specific recognition. Nowadays, methods to achieve specific recognition of THz MM biosensors include the introduction of antibodies, aptamers, or functionalized nanoparticles to modify metamaterials for sensing [74–76].

4.1. Surface modification based on antibodies and aptamers

Antibodies refer to immunoglobulins that bind specifically to antigens and can be used to detect cells and biomolecules [77,78]. Aptamers refer to single-stranded nucleotides that bind to the molecule to be tested through electrostatic attraction, hydrogen bonding or Van der Waals forces. And they have a wider target range, higher thermal stability, chemical synthesis and less batch variation compared to antibodies [78,79]. The specific binding of aptamers to the devices was carried out by immobilizing the antibodies on the metamaterials using a silanization technique [80,81]. First, the devices were cleaned with acetone and acetone/ethanol and then treated with a piranha solution to increase hydrophilicity. Then, the metamaterials were immersed in 2% 3-aminopropyltriethoxysilane (APTES) toluene to form APTES membranes with carboxyl groups. The carboxyl group was activated with

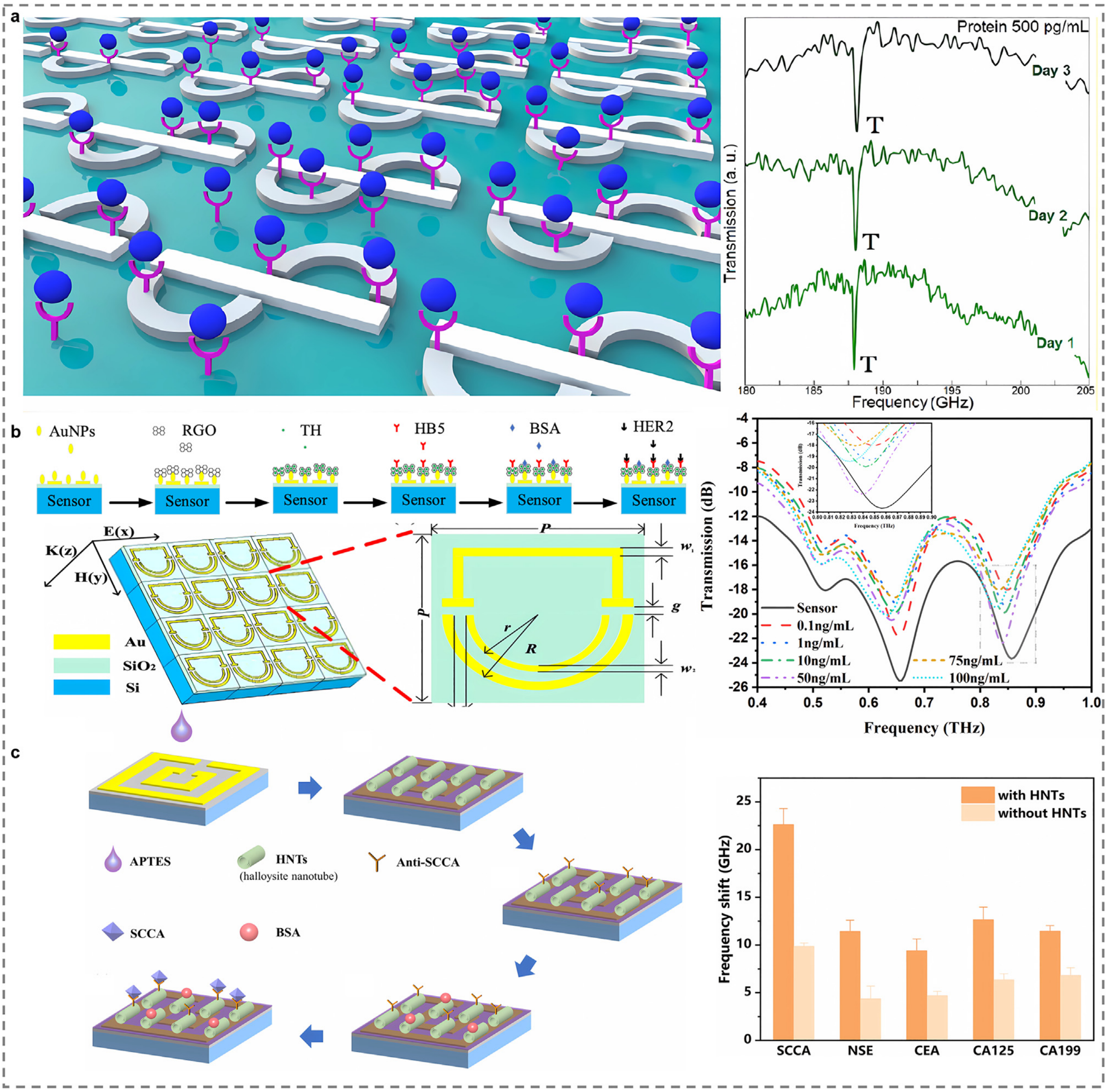

Fig. 4. Antibody, aptamer-modified THz MM biosensors. (a) An antibody-conjugated MM biosensor based on detection of ZIKV envelope proteins [82]. (b) An aptamer-modified THz MM biosensor based on aptamer-modified specific detection of breast cancer markers [83]. (c) An aptamer-modified THz MM biosensor based on aptamer-modified specific detection of lung cancer markers [84].

1-(3-dimethylaminopropyl)–3-ethylcarbodiimide hydrochloride into hydroxysuccinimide in a 2-(N-morpholino) ethanesulfonic acid solution. Finally, the devices are placed in an antibody or aptamer solution for incubation, allowing binding between the metamaterial and the antibody or aptamer. It is important to note that such modifications enable the binding of the metamaterial to specific biomolecules or cells. However, rinsing may affect the activity of the antibody or aptamer, and the method has limited reusability.

In 2017, Ahmadivand et al. [82] pioneered a method for the specific detection of a target virus (ZIKV envelope protein). This method harnessed the immune-binding effect between antibodies and the virus, transcending traditional metamaterial designs by proposing a structure composed of planar plasmonic resonators (Fig. 4a). The subsurface was modified with a ZIKV antibody so that ZIKV envelope proteins could be captured by the subsurface. By obtaining transmission spectra of the plasma MM with different concentrations of ZIKV envelope proteins, the corresponding frequency shifts were recorded. The MM was demonstrated to be highly sensitive to ZIKV envelope proteins, with a detection limit of 24 pg/mL and a structural sensitivity of 6.47 GHz/log (pg/mL).

In 2022, Zeng et al. [83] introduced an aptamer-modified THz MM biosensor for the specific detection of human epidermal growth factor receptor 2 (HER2), a breast cancer marker. This biosensor features an array of two metal SRRs with a 500 nm silica spacer layer to enhance the quality factor (Fig. 4b). The sensor demonstrated a high sensitivity of 108 GHz/RIU at its high-frequency resonance. By modifying the surface with aptamer-hb5 (APT-HB5) at 5 μmol/mL, the sensor could specifically detect HER2 with a detection limit of 0.1 ng/mL, showcasing its potential in cancer diagnostics.

In 2023, Liu et al. [84] developed a THz MM biosensor with a dual split ring resonator. It's designed for detecting squamous cell carcinoma antigen (SCCA), a biomarker for lung cancer (Fig. 4c). Simulations indicated the sensor could achieve a sensitivity of 103 GHz/RIU. The sensor's specificity for SCCA was enhanced by modifying it with kaolin nanotubes and halloysite nanotubes (HNTs), distinguishing it from other biomarkers like carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), CA125, and CA199. The HNTs-modified sensor exhibited a pronounced frequency shift in response to SCCA, confirming its selectivity for this biomarker.

4.2. Surface modification based on functionalized nanoparticles

Antibody and aptamer-modified metamaterial biosensors have advantages of straightforward operation, high sensitivity, and specificity for target analyte recognition.

However, the sensors make it difficult to effectively remove the surface modification molecules after use, resulting in lower reusability and a higher cost of use, which is not conducive to large-scale clinical testing applications [85,86]. Recently, researchers found that the introduction of functionalized gold nanoparticles into the metamaterial is expected to solve this problem. In addition, the introduction of functionalized nanoparticles not only enhances terahertz wave-matter interaction, but also enables highly sensitive and specific detection of different biological samples.

In 2021, Liu et al. [87] developed a butterfly-array THz MM biosensor (Fig. 5a).It was modified with functionalized AuNPs for the specific detection of epidermal growth factor receptor (EGFR), a key transmembrane protein implicated in various cancers [88,89]. The sensor could detect EGFR at a limit of 100 fM, which was further lowered to 10 fM with the use of antibody-modified AuNPs (1 fM = 10^{-15} mol/L). Significantly, the metamaterial functionalized with gold nanoparticle-antibody (GNP-Ab) complexes demonstrated a greater frequency shift and higher sensitivity for EGFR detection compared to metamaterials modified with antibodies alone. Moreover, the use of larger-diameter GNPs in the GNP-Ab functionalization resulted in an even larger resonance frequency shift, indicating that the size of the AuNPs can be optimized to enhance sensor performance.

In 2022, Shi et al. [90] developed a dual-band, fully dielectric MM made up of semi-cylindrical arrays (Fig.5b). The biosensor was functionalized with antibodies (anti-ha)-modified AuNPs. They were dispersed on the metal surface to create a sensor capable of forming immunoconjugates with the HA antigen of the human influenza virus. Detection was successful across a range of concentrations (20 to 50 μg/mL). The introduction of AuNPs resulted in a resonance frequency shift of 87.5 GHz, doubling the shift observed without AuNPs. The biosensor's sensitivity to y-polarized incident THz waves reached 2.96 GHz mL/nmol, indicating the effectiveness of AuNPs in enhancing detection capabilities. This approach is not only limited to viruses but also extends to the specific detection of other disease markers.

In 2023, Chen et al. [91] enhanced a THz MM biosensor by integrating capture hairpin probes attached to AuNPs via thiols. This modification ensured uniform distribution of amplification products on the sensor surface and prevented capillary action from dispersing DNA molecules to the droplet's edge (Fig. 5c). It also boosted the biosensor's surface sensitivity, enabling specific detection of miRNA21. The sensor could detect miRNA21 concentrations ranging from 100aM to 10 nM with a linear response and a sensitivity of 5.56 GHz/lg$C_{miRNA21}$, showing promise for nucleic acid detection applications. In 2023, Wang et al. [92] designed an ultra-sensitive THz MM biosensor based on a split-ring resonator combining functionalized AuNPs conjugated with the specific antibody. The biosensor has a detection sensitivity of up to 674 GHz/RIU for inflammatory markers, showing its application value in the early diagnosis and treatment of sepsis.

5. Overcoming interference with water absorption

The absorption of THz waves by water is a significant challenge for THz MM biosensors. As it can interfere with and reduce signal amplitude, when detecting aqueous samples. To avoid this problem, samples are often dried to create a uniform molecular film on the sensor surface. However, drying can denature biomolecules and cells, which typically require specific aqueous conditions to maintain their activity. Additionally, the detection accuracy is affected by the coffee ring effect [93–95]. Therefore, it's essential to study highly sensitive THz biosensors in aqueous environments. Currently, the combination of microfluidics and responsive hydrogel technology with THz MMs technology is an effective method to overcome this problem under the premise of ensuring the detection sensitivity [96,97].

5.1. Combination with microfluidics

Microfluidic platforms are platforms that allow precise control of tiny fluid volumes in micron-sized channels, enabling labelling-free, reagent-free detection [98–102]. The advantage of using microfluidic systems over macroscopic systems is the reduction of water-induced absorption, resulting in devices with increased sensitivity, wider spectra, and higher spatial resolution [102,103].

Nowadays, THz MM biosensors combining with microfluidics have been widely studied and applied. In 2017, Geng et al. [104] developed MM biosensors with open-ring resonators combined with polydimethylsiloxane (PDMS) microfluidics on a silicon substrate for detecting trace hepatocellular carcinoma biomarkers. Later, in 2019, Zhang et al. [105] introduced a multi-microfluidic channel MM biosensor. This innovation utilized butterfly array MM sensors on a quartz substrate with SU-8 photo responsive microfluidic channels, enhancing sensitivity and reducing liquid consumption.

However, a common limitation in these designs is the "sandwich" structure, where microfluidic channels are placed on the metamaterial and covered. It potentially weakens the metamaterial's resonance and affects signal strength due to multiple layers' THz absorption. In 2023, Li et al. [106] addressed this issue by modeling a THz microwave sensor with an embedded microfluidic channel (Fig. 6a). This design combined the microfluidic cover layer with the substrate, simplifying the structure and enhancing signal strength and sensitivity. Positioning the microchannel beneath the SRRS gap, where the electric field is strongest, boosts the THz-analyte interaction, thereby improving detection sensitivity. This method provides an ideal prototype for the easy fabrication of highly sensitive, label-free, highly sensitive, and non-destructive detection of liquid samples, but experimental validation is lacking.

In 2023, Xu et al. [107] introduced an innovative microfluidic biosensor that combines label-free particle capture with THz sensing capabilities (Fig. 6b). The sensor uses periodic electron-open loop metamaterial (eSRM) arrays, which have multiple resonance characteristics and high sensitivity to the environmental refractive index. As the environmental refractive index changes, the eSRM resonances exhibit a redshift with remarkably high linearity (greater than 0.999) and sensitivities of 159 GHz/RIU, 307 GHz/RIU, and 523 GHz/RIU in transverse electric (TE) mode. Moreover, this device enables both qualitative and quantitative assessment of resonance frequencies for particles with varying radius and refractive indices suspended in ethanol. This advancement in THz MM sensors paves the way for more precise and label-free detection of particles in various media.

Currently, THz MM biosensors with microfluidics are mainly used for single-component liquid samples. The detection of mixed aqueous samples needs to be further explored in the future.

5.2. Combination with the responsive hydrogel

Responsive hydrogels refer to highly hydrophilic 3D polymer networks formed by physical or chemical crosslinking. They can main-

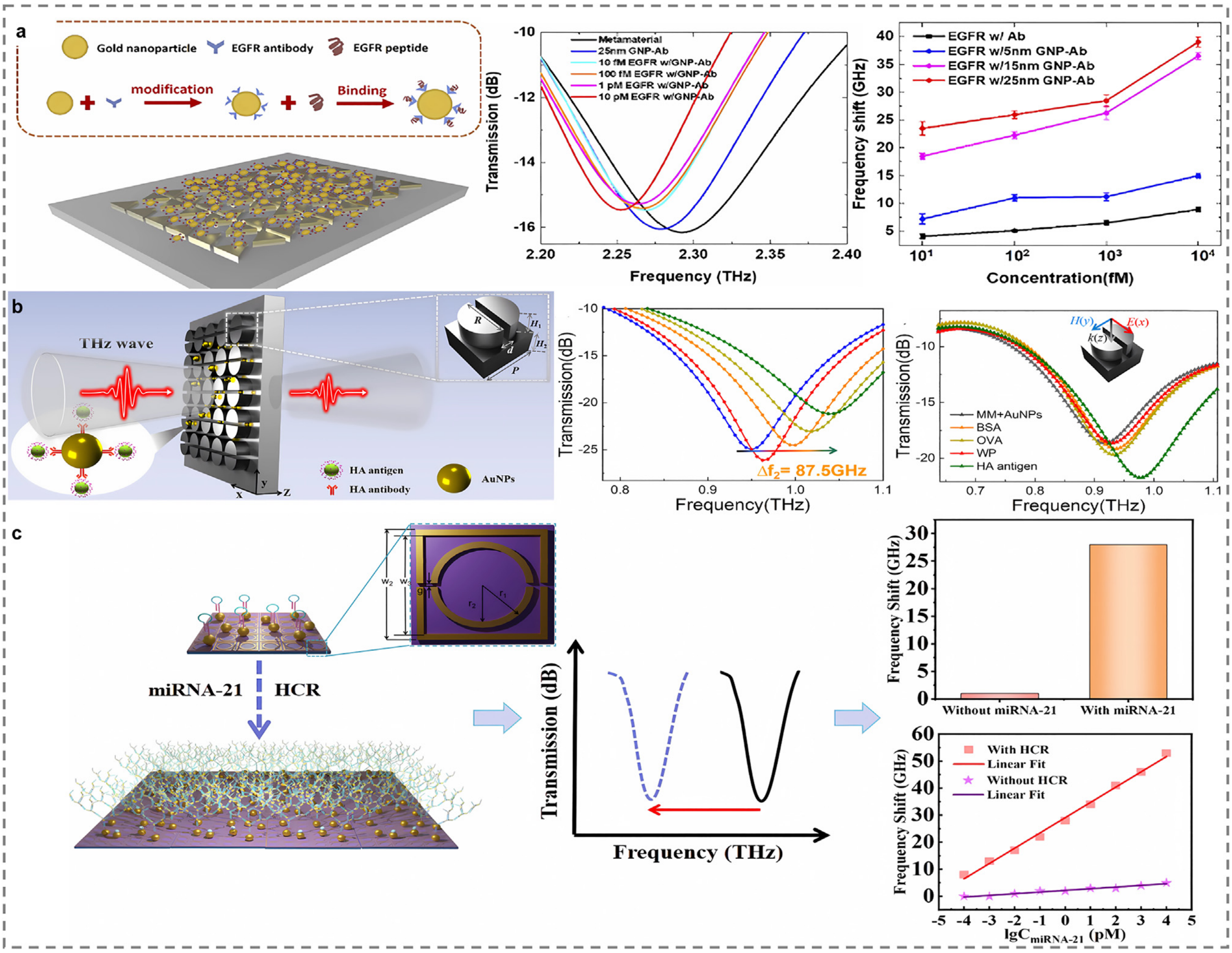

Fig. 5. Functionalized nanoparticle THz MM biosensors. (a) A functionalized nanoparticle-based MM biosensor for detection of specific epidermal growth factor receptor [87]. (b) A functionalized nano-based MM biosensor for detection of human influenza virus HA [90]. (c) A functionalized nano-based MM biosensor for detection of miRNA21 [91].

tain the activity of biomolecules by replacing water and have significantly less interference with THz wave absorption, making them ideal for biosensing applications. Furthermore, the combination of aptamers, antibodies, or specific chemical groups into the hydrogel can enhance the device's specificity and sensitivity, broadening their use in highly specific biosensing [107–111].

In 2021, Zhou et al. [112] developed a THz MM biosensor featuring a human α-thrombin (h-TB) aptamer-responsive hydrogel. They created through in situ polymerization of an aptamer-grafted hydrogel membrane on a silica-based MM (Fig. 6c). This sensor enabled label-free, specific, and quantitative detection of h-TB in an aqueous environment, with a detection limit of 0.40pM in serum—superior to other aptamer-functionalized THz MMs. The use of the aptamer hydrogel notably enhanced the specificity of the sensor for aqueous and serum samples. However, the study focused on reflected signals, and the sensitivity still lagged behind that of dried samples and those analyzed using microfluidic techniques.

In 2023, Zhang et al. [113] proposed an ultrathin, flexible AAPBA hydrogel that marked a breakthrough in THz detection of biomolecules in aqueous solutions (Fig. 6d). By applying a 200 μm-thick hydrogel film to a THz MM with an array of polarization-insensitive double-split-ring resonators, they achieved sensitive glucose detection in water, with a sensitivity of 0.0446 dL mg^{-1} and a detection limit of 1.64 mg dL^{-1}. The biosensor's design allowed for glucose precipitation from the surface using CHES/NaOH buffer, enabling multiple recoveries. Furthermore, the sensor maintained excellent performance even after multiple bending cycles. This innovation points to a promising new avenue for integrating novel hydrogel technology with THz MM sensors.

Nowadays, the research on combining hydrogel technology with THz MM biosensors is still in the preliminary stage. And there is still a gap between the detection sensitivity and that of traditional THz MM biosensors. However, hydrogels hold significant promise for mitigating the strong absorption effects of water on THz waves, potentially paving the way for their use in practical clinical diagnostics.

6. Expanded applications of THz MM biosensors

6.1. Frequency band tunable sensors

Traditional fixed-structure THz MM biosensors limit the functionality of terahertz modulation. Typically, these devices are designed to operate within a single frequency band. And their performance declines sharply when deviating from this center frequency. This inflexibility limits the broader practical use of MMs. Consequently, enhancing the tunability of THz MM biosensors and boosting their sensing capabilities have emerged as key areas of interest in recent research [114,115].

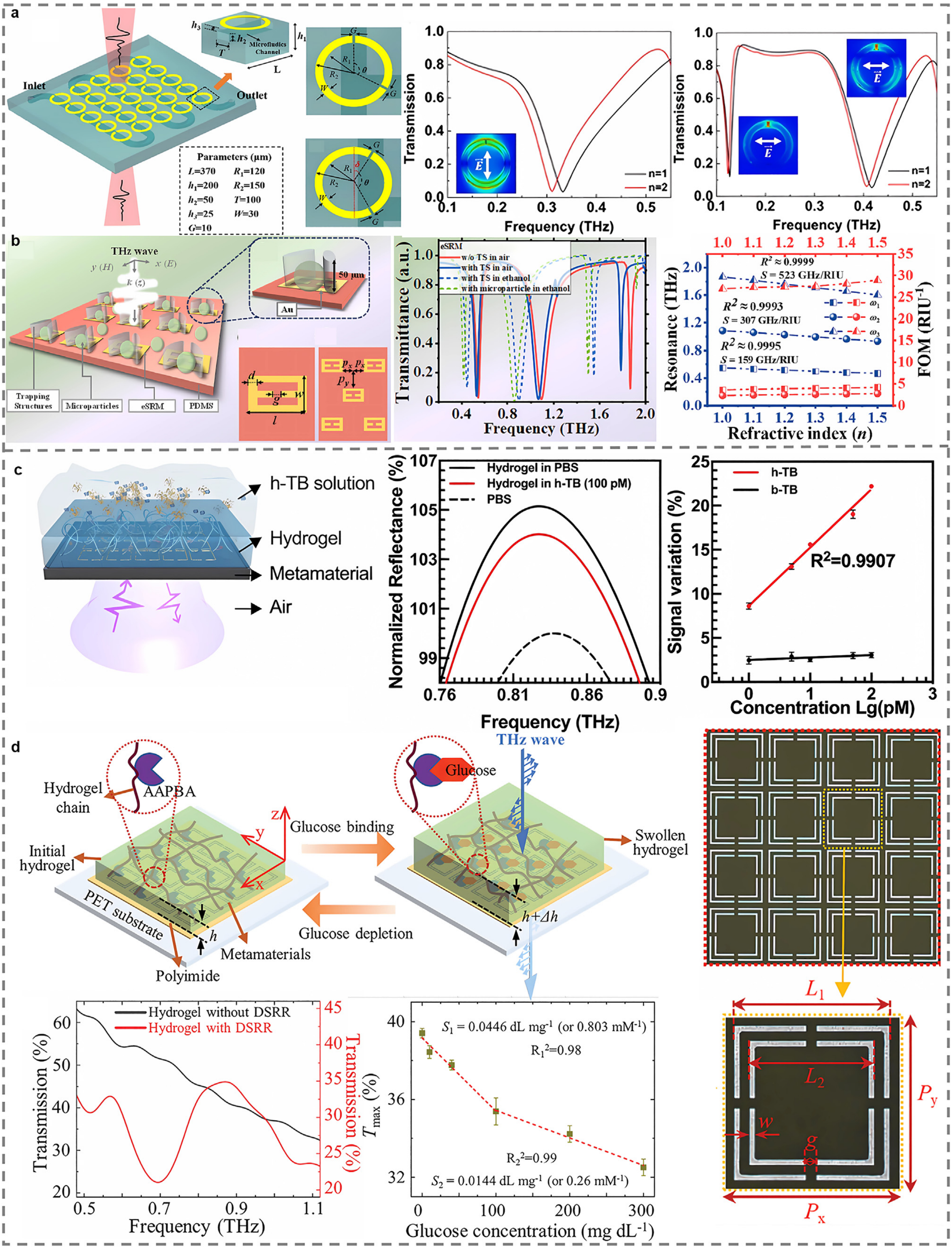

Fig. 6. Suppression method of water absorption interference by THz MMS biosensors. (a) A microfluidics-based MM biosensor for the detection of trace liver cancer biomarkers [106]. (b) A microfluidics-based MM biosensor for label-free particle capture [107]. (c) A hydrogel-based h-TB label-free MM biosensor [112]. (d) A hydrogel-based glucose MM biosensor [113].

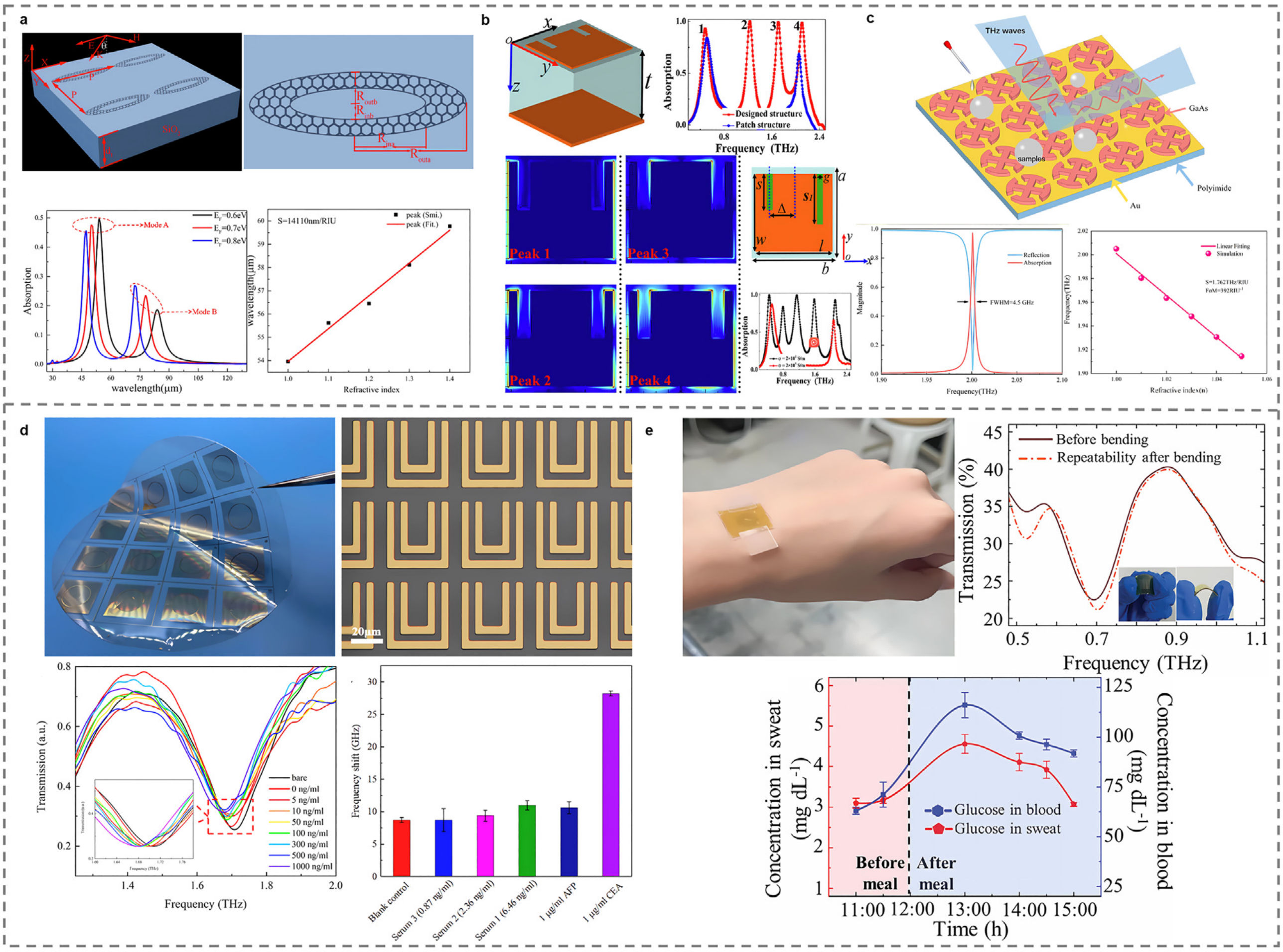

Fig. 7. THz MM biosensors for biomolecular extension applications. (a) A tunable MM biosensor based on graphene technology [116]. (b) An electrically controlled tunable MM biosensor [117]. (c) A flexible MM biosensor [121]. (d) A ultrathin hydrogel flexible MM biosensor [124]. (e) A ultrathin hydrogel flexible MM biosensor [125].

Graphene's electrically tunable properties have attracted the interest of many researchers in the field. In 2021, Qin et al. [116] developed a tunable absorber made up of periodically patterned elliptical annular arrays of graphene MM (Fig. 7a). They used the time-domain finite-difference method to simulate how the spectra would change with variations in the refractive index of the surroundings. Their investigation led to the creation of a structure with a remarkable sensitivity of up to 14,110 nm/RIU. Additionally, they analyzed the tunable dual-band selective absorption properties of a bilayer graphene structure, which achieved a maximum absorption of 49.6%. This work advances the design of graphene-based devices, including optoelectronics, biosensors, and environmental monitors.

In 2023, Wang et al. [117] introduced a multi-band THz MM absorber featuring a toothed resonator surface structure (Fig. 7b). This design allows for the control of the number of absorption peaks, either increasing or decreasing them, without complicating the design. Furthermore, incorporating temperature-responsive vanadium dioxide into the absorber's surface structure enables dynamic adjustment of its resonance characteristics. Experimental results showed that the absorption peaks can be actively tuned from two-band to even five-band absorption as vanadium dioxide transitions from a metallic to an insulating state. This innovation offers a versatile approach to tuning THz MM absorbers. Also, in 2024, Sun et al. [118] reported a broadband THz micro-photonics sensor based on a pixelated frequency-agile metasurface. The sensor's resonance positions are nearly linearly modulated with the varying Fermi level of graphene. By the synchronous regulation of graphene and C-shape rings, they have obtained highly surface-sensitive resonances over a wide spectral range (~1.5 THz) with a spectral resolution <20 GHz.

Light control is also a common way to modulate MM sensors. In 2019, Li et al. [119] created a metamaterial sensor entirely from the photosensitive semiconductor gallium arsenide. They regulated a photogenerated transparent window by adjusting light intensity, but the material's limitation to a single window narrowed its applications. In 2020, Chen et al. [120] utilized a combination of metallic materials and graphene to form a MM structure. This design featured a closed graphene ring encircling two double-open metal resonance rings of varying sizes. The graphene ring served both as a tunable material and as an explicit mode in the coupling process, enabling the tuning of the transmission peak amplitude without altering the transparent window's position. However, the complex design of the MM was challenging for production. For practical applications, the development of EIT-like MMs that support active modulation across multiple bands holds greater potential for broader application prospects.

In 2023, Wu et al. [121] introduced a high-sensitivity, tunable THz MM sensor based on semiconductor and metal (Fig. 7c). The sensor was composed of a top layer of photosensitive semiconductor gallium arsenide (GaAs), a middle layer of aluminum, and a polyimide bottom substrate. It exhibited an absorption peak at 2.0 THz with a quality-value of 444 and a sensitivity of 1.762 THz/RIU, along with a FOM value of 392 RIU^{-1}. The resonance peak's position and intensity could be actively modulated by altering the conductivity of the GaAs layer through light exposure. This tunable and highly sensitive sensor shows promise for applications in biomedical sensing, disease diagnosis, and the detection of trace substances.

6.2. Flexible wearable sensors

In healthcare, MM biosensors are paving the way for more compact and efficient wearable devices. The development of flexible, wearable metamaterials is guided by theories involving electromagnetic bandgap structures, high impedance surfaces, and artificial magnetic conductors. These devices can conform to body surfaces or be integrated into clothing, allowing for the comprehensive measurement of various physiological parameters such as respiration, heart rate, body temperature, pulse oximetry, blood pressure, and blood glucose during everyday activities [122]. THz MM biosensors offer an advantage over traditional wearable devices by being able to map whole-body physiological parameters rather than just measuring from a single anatomical location. This capability can yield more nuanced health information, which can be communicated to both patients and healthcare providers. As a result, these biosensors hold greater potential for use in clinical settings and daily health monitoring.

In 2022, Fang et al. [123] introduced a flexible THz MM biosensor that uses a polyphenylene diene substrate with a low refractive index. The sensor was modified in a non-metallic region using a three-step method, simplifying the biomarker attachment process (Fig. 7d). The non-metallic modified bulk refractive index sensitivity of this sensor reaches 325 GHz/RIU, which is higher than that of the conventional metallic modification (147 GHz/RIU). Meanwhile, the sensor was consistent with the traditional clinical detection of carcinoembryonic antigen (CEA) markers in breast cancer patients, with a detection limit of 2.97 ng/mL. This flexible THz MM biosensor is expected to be used for the rapid detection of cancer biomarkers in the future. In 2023, Zhang et al. [124] developed a polarization-independent ultrathin THz MM biosensor based on ultrathin hydrogel film covering an ultrathin surface (Fig. 7e). Experiments on the back of human hands enabled the detection of glucose in human sweat with a detection limit of 0.0446 dL mg^{-1}, which is expected to be part of future wearable devices.

Additionally, a reconfigurable wearable antenna with reconfigurable element metamaterials has been developed [125]. The antenna can communicate between sensor nodes, switching between an omnidirectional radiation mode and a broadside radiation mode that facilitates communication with external devices. This design enables wireless signals to travel along the body surface without excessive radiation into the environment, enhancing the energy efficiency of wireless communication [126–128]. However, current experiments involving biological tissue detection with these antennas remain in the laboratory phase. Further evaluation is essential to assess their long-term reliability and suitability for future practical applications in wearable technology and health monitoring [129].

6.3. Intelligent programmable sensors

In practical applications, MMs are enhanced with active components to create active MMs for dynamic control over electromagnetic waves. However, the active MMs still have the problems of small tunability range and little reconfigurability. To address these issues, experts have accordingly developed digital coding and programmable functions based on active metamaterials. Such devices can implement a large number of different functions and switch them in real time with the help of field-programmable gate arrays (FPGAs). More importantly, digitally encoded representations of metamaterials make it possible to bridge the gap between the digital and physical worlds using metamaterial platforms and to enable metamaterials to directly process digital information, resulting in informational metamaterials. The emergence of programmable metamaterials can not only effectively realize the modulation of light but also generate and store multi-state data. This kind of programmable metamaterial with memory function can be extended to other frequency bands, opening up the way for electromagnetic information processing. It is very suitable for single/dual frequency switches, polarization switches, and other devices, and has great research value. In the field of biological detection, it is expected to realize intelligent detection of a variety of substances with high accuracy and sensitivity. But due to a variety of factors, the stage of programmable metamaterials applied in biosensing has not been reported [130–134].

7. Conclusion and outlook

Based on the practical demands of biomedical clinical detection, we have briefly reviewed the principles, novel technical methods, and the expanded applications of THz MM biosensors. To solve the three major problems of sensitivity deficiency, specificity limitations, and water absorption interference in practical applications, researchers are constantly developing new technologies. These innovations aim to enhance sensor sensitivity, improve the specificity of detection capabilities, and amplify the detection signal's strength so that it can realize the detection of molecular markers at very low concentrations, early diagnosis, and screening for major diseases.

In terms of sensitivity enhancement of MMs, two primary methods are effective: optimizing the unit structure of the metamaterial to introduce new resonance mechanisms and combining with other enhancement techniques. Metamaterial biosensors based on TD, EIT, and QBIC mechanisms have been proven to be of great help in improving the sensitivity of devices. Furthermore, the combination of graphene and gold nanoparticles is proposed to enhance the interaction with the object under measurement. This cooperative interaction is expected to amplify the frequency shift and amplitude variation, thereby improving the sensitivity of detection.

In terms of the specificity enhancement of MMs, surface modification is the best method to enhance the sensor performance. Combining with antibodies or aptamers can effectively achieve specific detection of biomarkers. However, the method is affected by washout and has limited reusability. To address these limitations, researchers have turned to functionalized nanoparticles to realize highly specific, sensitive, and reusable THz MM biosensors. For instance, functionalized AuNPs can achieve specific detection, high sensitivity, and stability of the devices, which is important for practical clinical applications. However, it should be noted how to design functionalized nanoparticles to improve the specificity, sensitivity, and robustness of the structures.

To overcome the water absorption interference in the biological samples, the combination of microfluidics or hydrogel technology is an effective method. This approach significantly reduces the strong absorption of THz waves by water, thereby enhancing the detection signal. This enhancement is crucial for improving the device's clinical detection capabilities. Despite its promise, research in this area remains in the early stages, and it still has room to improve the sensitivity of hydrogel technology. Since microfluidics and hydrogel technology are the most promising strategies to address the strong water absorption of terahertz waves, with the advantages of simple and fast operation, greater attention and research should be given to this technology.

Considering the actual clinical testing needs, developing a multi-component test platform is necessary. This platform should be capable of performing simultaneous measurements of various components and cells within complex solutions. The goal is to enable broad-spectrum detection. The urgency of this requirement underscores its importance in advancing diagnostic capabilities. Accurate disease diagnosis necessitates the detection of multiple disease markers, which are often present in multi-component fluids such as blood and urine. Consequently, the device must exhibit high sensitivity and specificity, and its detection signal must be robust against absorption interference. A multi-component test platform is poised to address these requirements. Standardization of sample pre-treatment for this platform is essential, ensuring that specific biomarkers are identifiable and quantifiable with ease—a key aspect of its clinical utility. To harness the full potential of THz MM biosensors, an integrated approach that combines various technologies is optimal. For instance, the fusion of THz technology with temperature variation aids in differentiating microorganisms. Additionally, the synergy of THz technology with liquid crystals or modulated electromagnetic fields enables the detection of chiral molecules [133]. Moreover, combining machine learning and bioinformatics algorithms with large-scale experimental datasets can lead to the development of more efficient tools. These tools can improve the performance of THz biosensors and enhance the sensitivity and specificity of cell and biomolecule detection [135], thereby improving the precision of detection outcomes.

Declaration of competing interest

The authors declare that they have no conflicts of interest in this work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.fmre.2024.11.008.

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