



Biochemical sensing with terahertz microfluidics: Recent progress and future prospects[☆]

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ABSTRACT

The terahertz spectral region has garnered significant attention for label-free chemical and biological sensing due to its molecular fingerprints, low energy characteristics, and remote sensing capabilities. Microfluidic platforms are particularly attractive because microchannels are made from inexpensive biocompatible materials, preventing environmental contamination, and require only micro to nanolitre sample volumes for manipulation. These platforms offer the advantages of simple design, easy fabrication, lightweight prototypes, and real-time measurements. In this manuscript, we review state-of-the-art terahertz microfluidic technology with a focus on liquid-based high sensitivity terahertz microfluidic devices and systems. This includes material platforms, the physical mechanisms underlying their characterization methods, and fabrication methodologies. Next, we explore further applications of microfluidics, such as the optoacoustic effect, particle capture, active amplitude control, frequency-agile multiplexing, imaging, and signal processing. Finally, the future prospects of terahertz microfluidic in biochemical sensing applications are also discussed.

1. Introduction

Water serves as an essential liquid in various physical and chemical reactions on Earth [1–8]. In recent decades, researchers have progressively developed a wealth of information on the dynamic rearrangements within the hydrogen vibration of water [9–14]. Due to the strong collective and intermolecular motion exhibited by water at terahertz (THz) frequencies, it provides a dynamic perspective for studying the stability and structure in water [15]. The vibration frequencies of molecular movements such as hydrogen bonds in liquid are within THz range, enabling observation of fundamental thermodynamic properties [16]. For instance, THz spectroscopies of aqueous solutions have been used to demonstrate the molecular thermodynamics of water [17], and the molecular motions in liquid exhibit unique spectral features in THz regime [18].

However, owing to the strong THz absorption by polar water, the penetration depth of THz waves in water is short, and the measured signal is weak, making it quite difficult to study the dynamic properties of biological information in aqueous solutions using THz technology [19,20]. Generally, there are several methods to address the challenges of working with water or polar liquids in THz aqueous photonics. Firstly, thin water films have been generated to produce THz waves due to aqueous ionization in water by laser incidence [21,22], as shown in Fig. 1a. Due to the fluidity of the water film, it can quickly replenish itself. In addition, the water film is also used to measure the THz Kerr effect. This is because other materials exhibit strong Kerr effect responses under THz wave excitation, which obscure the Kerr effect signal in liquid water, making it difficult to obtain water signals [18]. Secondly, individual water molecules can be studied through THz spectroscopy. Here, individual water molecules are trapped in the nanometer

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gap between sources and drain electrodes [23]. By utilizing the nanometer gap between the source and drain electrodes, the THz wave is focused on individual fullerene molecules, as shown in Fig. 1b. Thus, by measuring electrode's photocurrent, extremely small absorption can be detected. Thirdly, microfluidic technology is employed to quantitatively detect the content of biological samples in liquid aqueous solutions [24]. Microfluidic chips offer very small sample volumes, low cost, and fast analysis, with advantages such as minimal liquid usage, tightly sealed fluids, and precise micro-scale fluid control, and the THz absorption by water is significantly reduced. Furthermore, sealed microfluidic devices can effectively prevent liquid evaporation [25]. A typical THz chip consists of microfluidic channels made of low-loss materials, enabling liquid circulation through input and output ports, as shown in Fig. 1c [26].

Compared to opto-microfluidics [27], mechanical microfluidics [28] and electrical microfluidics [29], THz microfluidic technologies have their unique advantages. From biochemical point of view, many molecular vibrations in the intramolecular and intermolecular domains are located in THz range, thereby generating unique fingerprint signatures. Furthermore, hydrogen bonds in nucleobase and van der Waals interaction in amino acids strongly interact with THz radiation, thereby generating a unique spectral signature. To measure these THz related features, new and advanced microfluidic THz sensing techniques are preferred. For this reason, THz microfluidics may provide complementary methods to conventional microfluidic approaches. Table 1 provides pros and cons when compared THz microfluidics with other techniques (opto-microfluidics, mechanical microfluidics and electrical microfluidics).

There are some review articles mentioned about THz microfluidic recently. For instance, in 2018, Zhang et al. presented recent progresses on tunable microfluidic metamaterials. The active manipulation on the microwave, THz wave, IR wave, and visible light are demonstrated through different microfluidic metamaterials [6]. At the same time, Salim et al. presented state-of-the-art metamaterial inspired microfluidic bio/chemical sensors (passive devices ranging from gigahertz to THz range) with an emphasis on metamaterial sensing circuit and microfluidic detection [30]. However, above review articles only focused on microfluidic metamaterials on all spectrum, THz waves occupies only a small part. In addition, other types of THz microfluidic devices, such as reflective, waveguide, and transmission line, have not been mentioned. In 2020, Alfihed et al. presented an overview of THz spectroscopy with a focus on its implementation within microfluidic platforms and explored such relationships with insight given on the design and material considerations for the effective integration of THz spectroscopy in

Table 1

Comparison of THz microfluidics with opto-microfluidics, mechanical microfluidics and electrical microfluidics.

Microfluidic types	Advantages	Disadvantages
THz microfluidics	They can obtain unique THz molecular solution features by light/matter interaction at THz frequencies.	Their size and materials should fit in THz system and measurement. Water's strong absorption may be a major hindrance for THz spectroscopy.
Mechanical microfluidics	They can measure mechanical properties of biochemical solutions, such as viscosity, cell weighing/mass, density, etc, and are easy to be miniaturized into a handheld device.	Fragile suspended microstructures make integration with microfluidics difficult. They still require extra electrical or optical units to read or amplify the signal.
Opto-microfluidics	They indicate the light/matter interaction happens at visible or infrared wavelengths for biomolecular detection. Optical imaging can also achieve cell counting/morphology analysis and flow cytometry.	The sophisticated optical arrangements with minimal vibration are required. Microfluidics materials must be highly transparent and well-polished.
Electrical microfluidics	They primarily measure the electrical property change from the interaction of the targeted analyte solution and the electrode surface during bio-reaction events, and can be operated independently without microscopes or centrifuges.	Targeted analytes can't affect the electrical signal due to limited Debye length in the high ionic strength solution.

microfluidic platforms. But the THz microfluidic platforms in this review belongs to only simple chamber type transmission microfluidic [5]. It lacks the introduction of complicated microfluidic integrated with metamaterial, nanomaterial, waveguide, transmission line, etc. Our previous review emphasized the trace detection of metasensors based on the unique THz fingerprint information, which is long ignored in THz trace detection. However, it mainly focused on THz metasensors and sensing principle instead of microfluidic [24].

The limitation of THz metamaterial microfluidic is due to the fact that the molecular vibrational modes of the water based samples is weak, resulting in the limited specific detection. Since the fingerprint spectrum induced phenomenon requires a sufficiently strong interaction

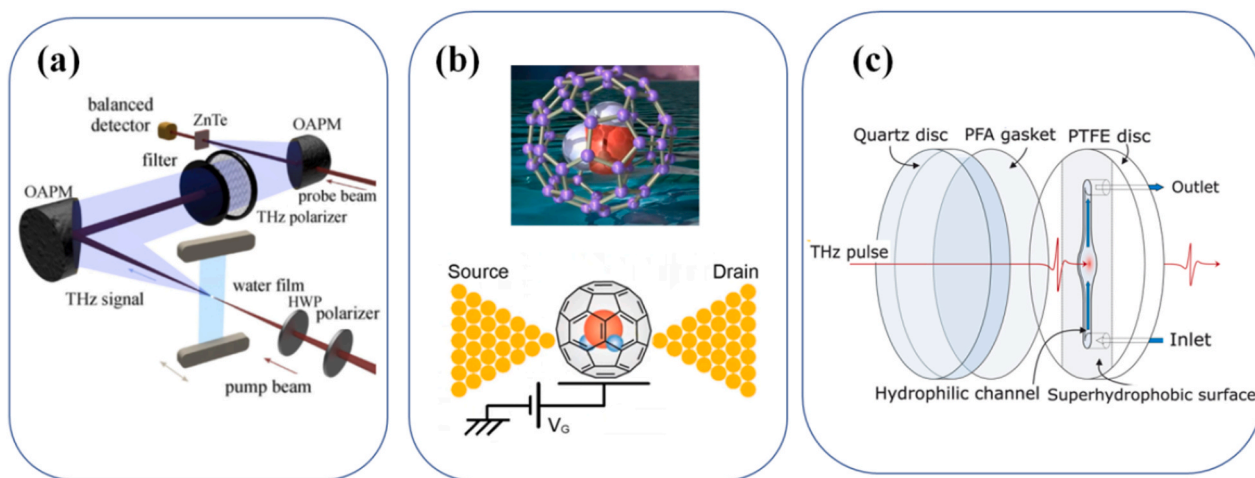


Fig. 1. a Schematic of using water film as THz generation. Reprinted with permission from Ref. [22]; b Schematic of single water molecules inject and isolate a single H₂O molecule in the fullerene cage. Gate electrode to tune electron number on the molecule. Reprinted with permission from Ref. [23]; c The geometry of the microfluidic chamber. Reprinted with permission from Ref. [26].

between the molecule and the metasensor, high-concentration solutions are needed for experiments, in contrast to the trace-level sensing experiments. Reducing liquid volume and updated more flexible microfluidic detection system are urgently required. More recently, the rapid development of THz microfluidic platforms, particularly their integration with emerging metasurfaces, nanomaterials, and transmission line circuits, has attracted broad attention for applications such as biochemical analysis and particle/cell capture. Therefore, it is imperative to systematically summarize the latest global advancements and trends in THz microfluidic technology. In this review, we demonstrate THz microfluidic technology and focus on liquid-based THz microfluidic systems in biochemical sensing, including materials for THz microfluidics, the integration of microfluidic technology with THz functional devices and physical mechanisms, as well as the microfluidic fabrication processes. Additionally, we discuss the latest applications of microfluidic technology in fields such as biomedicine and signal processing, including photoacoustic effects, particle capture, active amplitude control, frequency-flexible multiplexing, imaging, and signal processing.

2. Microfluidic materials

Microfluidic materials need to be low loss in the THz region. For example, low absorption coefficient THz materials such as cyclo-olefin polymer (COP) (Fig. 2a) [31], glass (Fig. 2b) [32], and high-resistance silicon (HR-Si). Polydimethylsiloxane (PDMS) has received particular attention due to its gas permeability, enabling it to provide oxygen and buffering functions, which is suitable for handling live cells (Fig. 2c) [33]. However, PDMS has higher absorption in the THz range compared to other THz polymer materials. Additionally, silicon dioxide, quartz, PDMS, and COP are visible and can serve as effective THz microfluidic materials to see the liquid inside. Si-based microfluidic devices are opaque in visible spectrum, but transparent in the THz range. This property can be combined with the rich Si micromachining technology to manufacture THz microfluidic chambers. Fig. 2 d1-d4 show schematic

diagrams of etched cavities and ports, capillary arrays, 3D patterns, and 3D pyramids on Si wafers [34–37]. Furthermore, ultraviolet (UV) curable properties of SU-8 photoresist make it a suitable packaging material for microfluidic devices.

3. Microfluidic classification

THz microfluidic platforms can be effective and roughly divided into four types such as transmission, reflection/attenuated total reflection (ATR), waveguide and transmission line, as described in Fig. 3.

Generally, these microfluidic devices can be categorized into chamber or channel types. Cavity-type devices are simple to fabricate and can be combined with various functional devices (e.g., metasurfaces), but they require a larger volume of liquid and cannot achieve complex microfluidic channel functions. Channel-type devices are more complex to fabricate, use less liquid and can realize more complex microfluidic functions (e.g., cell detection). Table 2 summarizes the main points of different examples of THz microfluidics in the development of THz liquid photonics.

3.1. Transmission

The integration of transmission THz spectroscopy with microfluidic methods, combined with the specific biological effects of the substances to be measured, enables both qualitative and quantitative detection of biochemical substances in THz range.

3.1.1. Conventional microfluidics

Conventional transmission microfluidic devices have wide applications in THz biochemical detection due to design simplicity and ease of fabrication. The performance is closely related to the thickness of the polar liquid layer, as they have a significant absorption effect [5,31,32,34,38–47]. In early work by researchers at the University of Arizona, the microfluidic design was combined with additional electrochemical effects to achieve cell capture, as shown in Fig. 4a. The microfluidic device

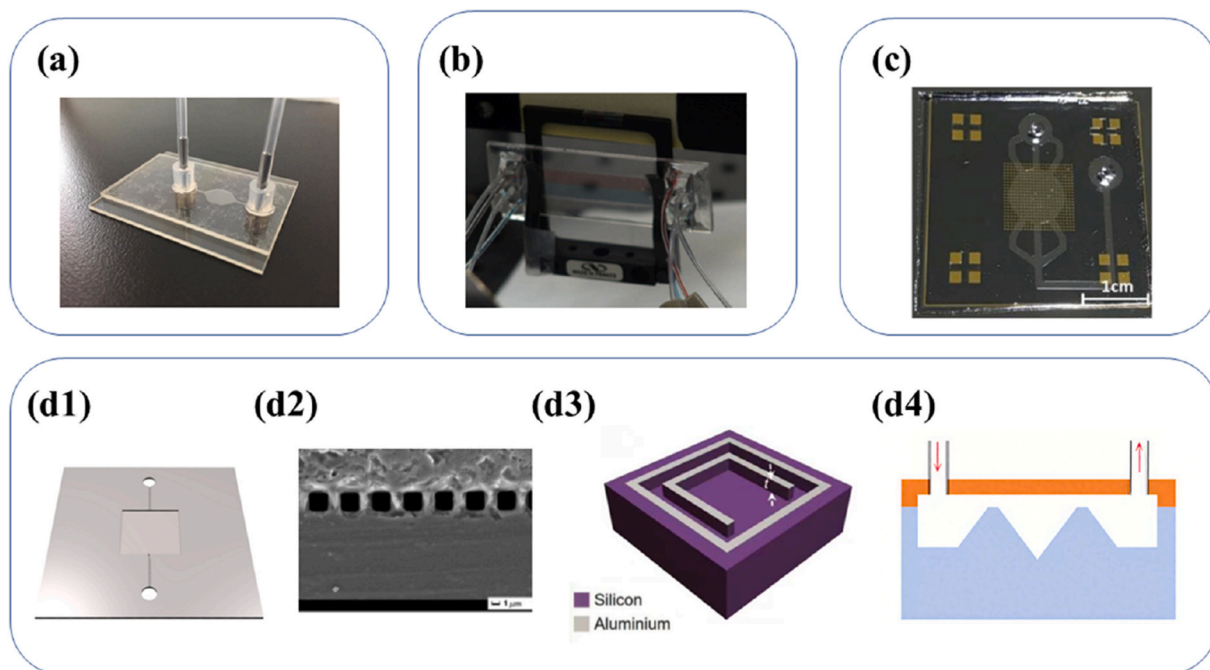


Fig. 2. The microfluidic materials. **a** The microfluidic chip with two COP substrates containing a hexagonal liquid area. Reprinted with permission from Ref. [31]; **b** The microfluidic channel microfabricated by bonding two fused quartz substrates. Reprinted with permission from Ref. [32]; **c** Microfluidic channels fabricated by a PDMS. Reprinted with permission from Ref. [33]; **d** Microfluidic devices made by etched Si wafer with **d1** chamber (Reprinted with permission from Ref. [34]), **d2** capillaries (Reprinted with permission from Ref. [35]), **d3** 3D patterns (Reprinted with permission from Ref. [36]) and **d4** pyramid structure (Reprinted with permission from Ref. [37]).

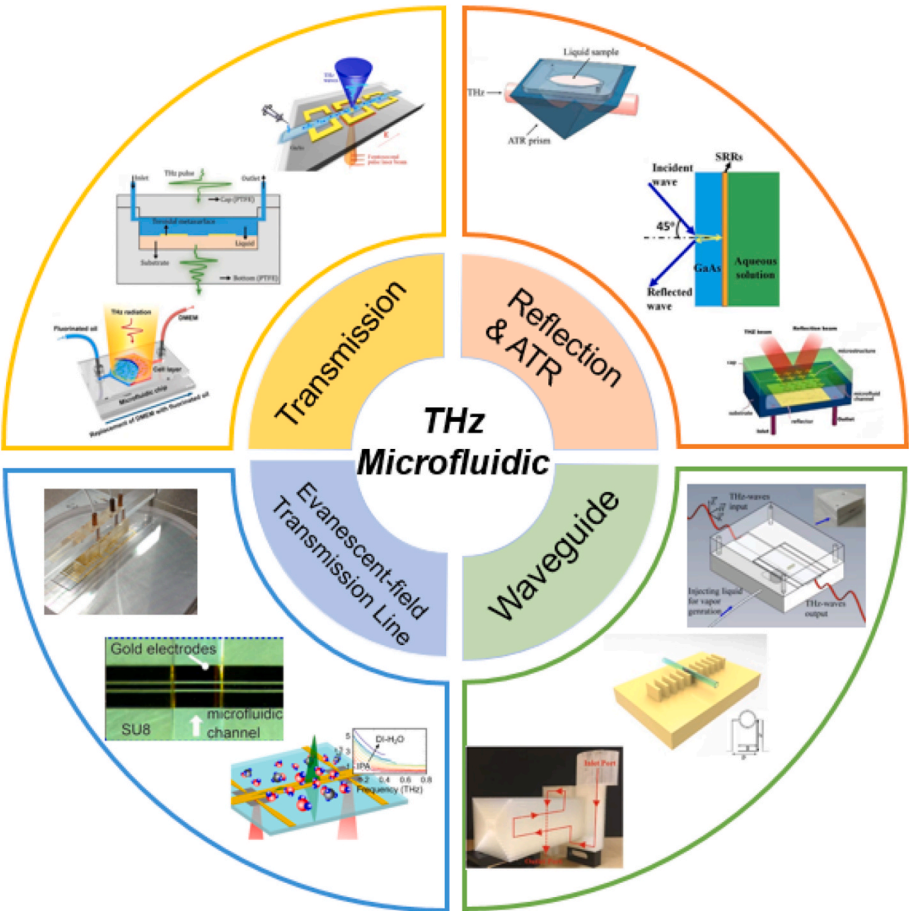


Fig. 3. Overview of THz microfluidic devices.

Table 2
THz microfluidic main features.

THz microfluidic categories	Highlights	Concerns
Transmission	Easy to exhibit lab-on-a-chip function, showing strong ability to achieve imaging and spectroscopy applications	requirement of optimal polar liquid thickness to avoid absorption and complex analysis to remove interference effect
Reflection/ATR	Permittivity of polar liquid extracted by reflection spectroscopy without consideration of polar liquid thickness	Need slab or bulk prism, and not suitable for integration
Evanescent field transmission line	Longer interaction length with THz radiation, excellent signal-to-noise ratio, easy to achieve on chip integration	Design and manufacture with average complexity
Waveguide	Compatibly combine with the microfluidics, can easily be used in conjunction with fluid process	Not suitable for integration (fiber and metal waveguides)

is made of a 1.44 mm thick PDMS layer and 300 μm thick channels, containing two electrodes. These electrodes capture different cells through non-uniform electric fields and dielectrophoretic forces [44, 46], such as transporting *E. coli* cells to high electric field regions, T cells to low electric field regions, and distinguishing cell types based on the THz transmission response. To reduce water absorption-induced THz signal loss and recover the fingerprint resonance peaks, Cheon et al. combined cryogenic spectroscopy with microfluidic cells and detected

the resonance peaks of 5-methylcytosine and methylated DNA in aqueous solutions, as shown in Fig. 4b [45]. Although these substances are dissolved in water, freezing replaces the water molecules with ice molecules, reducing absorption. Even with a spacer layer thickness of 300 μm , methylation characteristic signals located around 1.6 THz can still be obtained. Furthermore, Fu et al. utilized a microfluidic device to investigate live cells. The device used two COP windows with 1000 μm thick bonded to polyethylene terephthalate (PET) spacing, creating a microchannel with 200 μm wide (Fig. 4c). By injecting fluorinated oil (gray region) as an optical clearing agent, water molecules surrounding the cells (red region) were eliminated, reducing THz absorption [31]. When fluorinated oil was used, there was a significant difference in THz signals of cells compared to when no cells were present. Table 3 summarizes the performance of traditional transmission microfluidic chambers. We can see that transmission microfluidics with micro-channel show much lower minimum liquid volume than that with chamber, which benefits for reducing water absorption.

3.1.2. Metamaterials

Metamaterials are artificial materials with much smaller single elements than the wavelength of light. The mechanism for enhancing sensitivity through metamaterials involves strengthening the spatial interaction between the aqueous solution and resonance modes of metamaterials [48–55]. The high sensitivity originates from the maximum overlap between the analyte and the highly localized THz field. Combining metamaterials with microfluidic devices can enhance sensitivity and further reduce the volume of liquid required in measurements. When THz waves are incident vertically onto the metamaterial microfluidic device [56–65], high-Q resonances are excited, creating strong field confinement in localized regions. As a result,

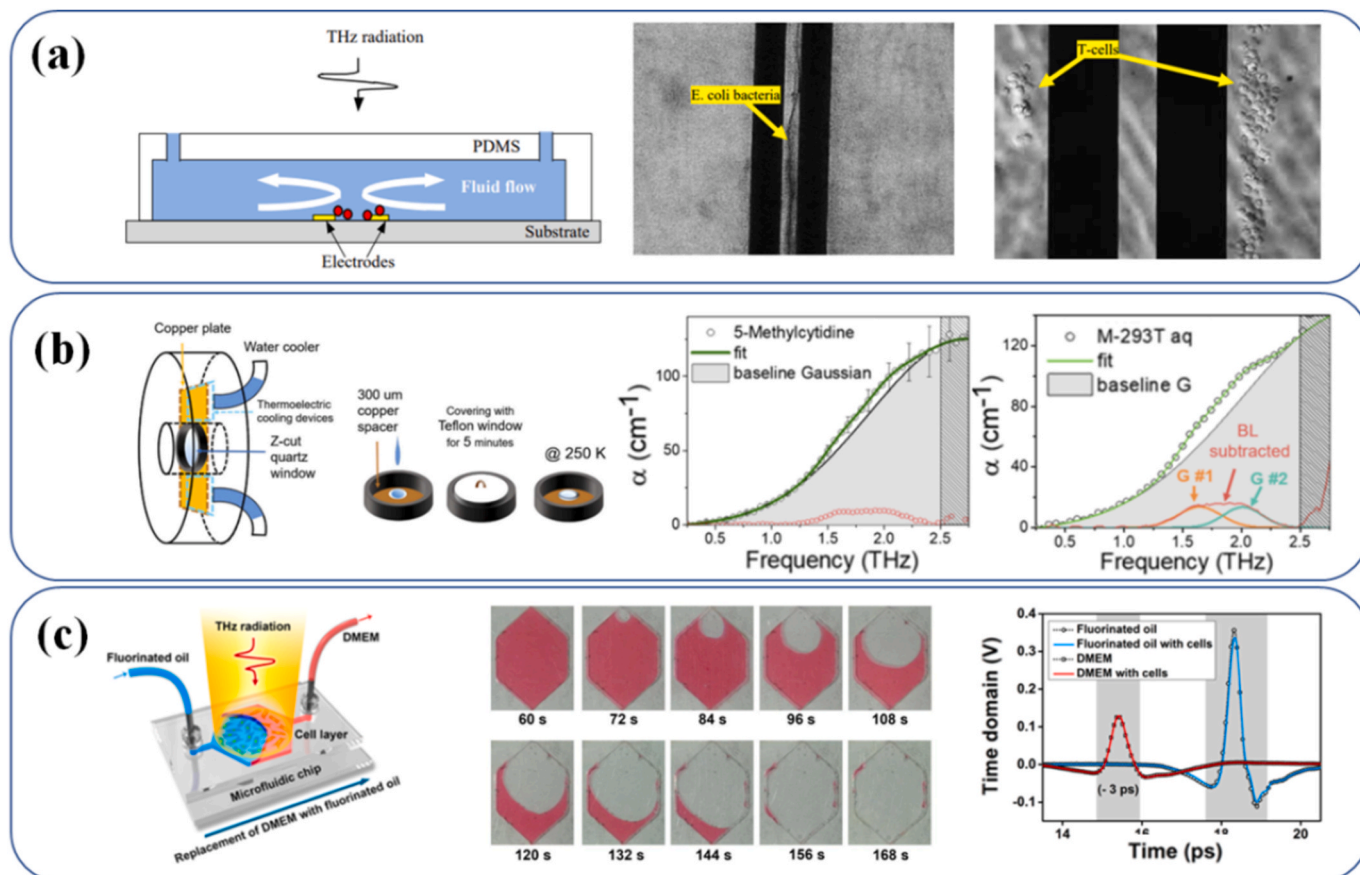


Fig. 4. **a** A lab-on-a-chip microfluidic configuration for identifying *E. coli* bacteria(left) and T-cells (right). Reprinted with permission from Ref. [46]; **b** microfluidic configuration with frozen solution to retrieve fingerprint spectra. Reprinted with permission from Ref. [45]; **c** THz time domain waveform with microfluidic and optical clearing agents. Reprinted with permission from Ref. [31].

Table 3

Transmissive microfluidic.

THz microfluidic categories	Microfluidic Material	Dimension	Liquid/performance	Reference (year)
Transmissive microfluidic with chamber& microchannel	COP-Si	Chamber/50 μm	BSA solution, 100 mg/mL	[42]
	Si-Si	Chamber/300 μm	Alcohol/water concentrations	2008
	Two fused quartz	Chamber/50 μm, 20 μL	Water and IPA-H ₂ O mixtures, real-time THz detection	[34]
	PDMS-glass	Chamber/300 μm	E. coli and T-cell solution, An absorption signature of E. coli bacteria. 0.11 THz	2010
	Quartz(cap), Quartz(substrate) photoresist (spacer)	Chamber/55 μm, 10 μL	MUC1/Anti-MUC1 aptamer in PBS solution, Detection limit 1 pmol/μL	[32]
	Silica glass (cap)	Microchannel/2.4 μm*2.4 μm, ~0.6 μL	microcystin aptamer, DNA solution, 0.92 and 0.23 μg/μL	2013
	Si (substrate)	Chamber/300μm75μL, frozen	5-mC and M-293T solutions	[40]
	Quartz window	Chamber/300μm75μL, frozen	5-mC and M-293T solutions	2016
	COP (cap)-PDMS (substrate)	Chamber/0.1 cm	Changes of F-actin aggregation morphology in Caco-2 cells after daily irradiation with 0.1 THz	[46]
	Polytetrafluoroethylene (PTFE) (substrate)	Chamber/100 μm	BSA solutions 5 mg/mL	[40]
	PFA gasket (cap)			2017
				[35]
				2019
				[45]
				2020
				[31]
				2021
				[26]
				2022

refractive index (RI) changes of the analyte in the local region will cause a shift of the resonance frequency. Here, we introduce several typical metamaterial microfluidic systems from four aspects.

3.1.2.1. Enhanced modes. There are several resonances that can be used for microfluidic sensing applications, such as lattice [61,66], toroidal [63,67], inductive-capacitive (LC) [68,69], dipole [70], quasi-bound

state in the continuum (QBIC) [71,72], etc. For instance, Ng et al. reported a THz microfluidic sensor with lattice mode oscillations. The microfluidic device consists of two 100 μm thick polyethylene naphthalate (PEN) covers and substrates spaced 50 μm apart, with a rectangular metal array photolithographed on the PEN substrate (Fig. 5a). When a slight change in the liquid RI occurs between the substrate and the sample, a distinct lattice resonance can be observed at 389 μm (0.77

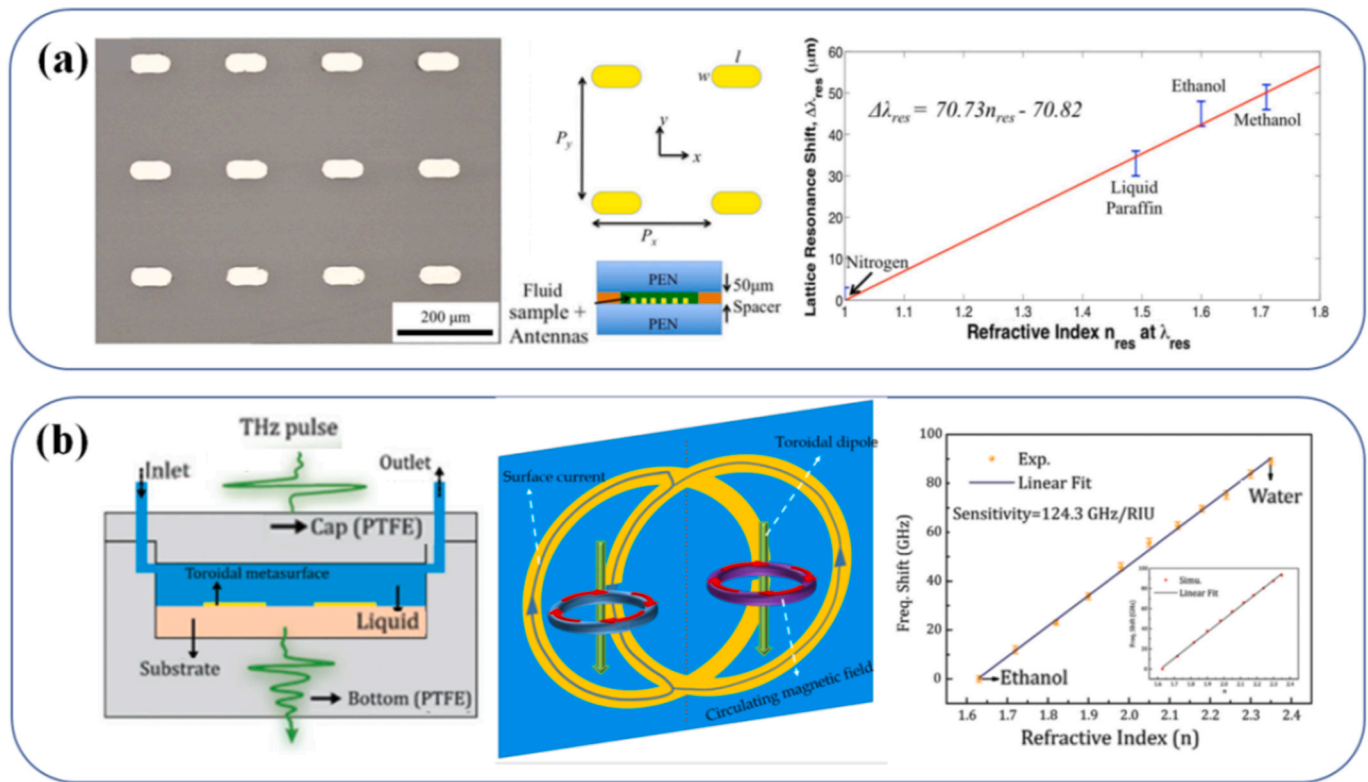


Fig. 5. **a** Microfluidic metasurface device that can excite (a) lattice mode (Reprinted with permission from Ref. [61]) and (b) toroidal mode (Reprinted with permission from Ref. [63]).

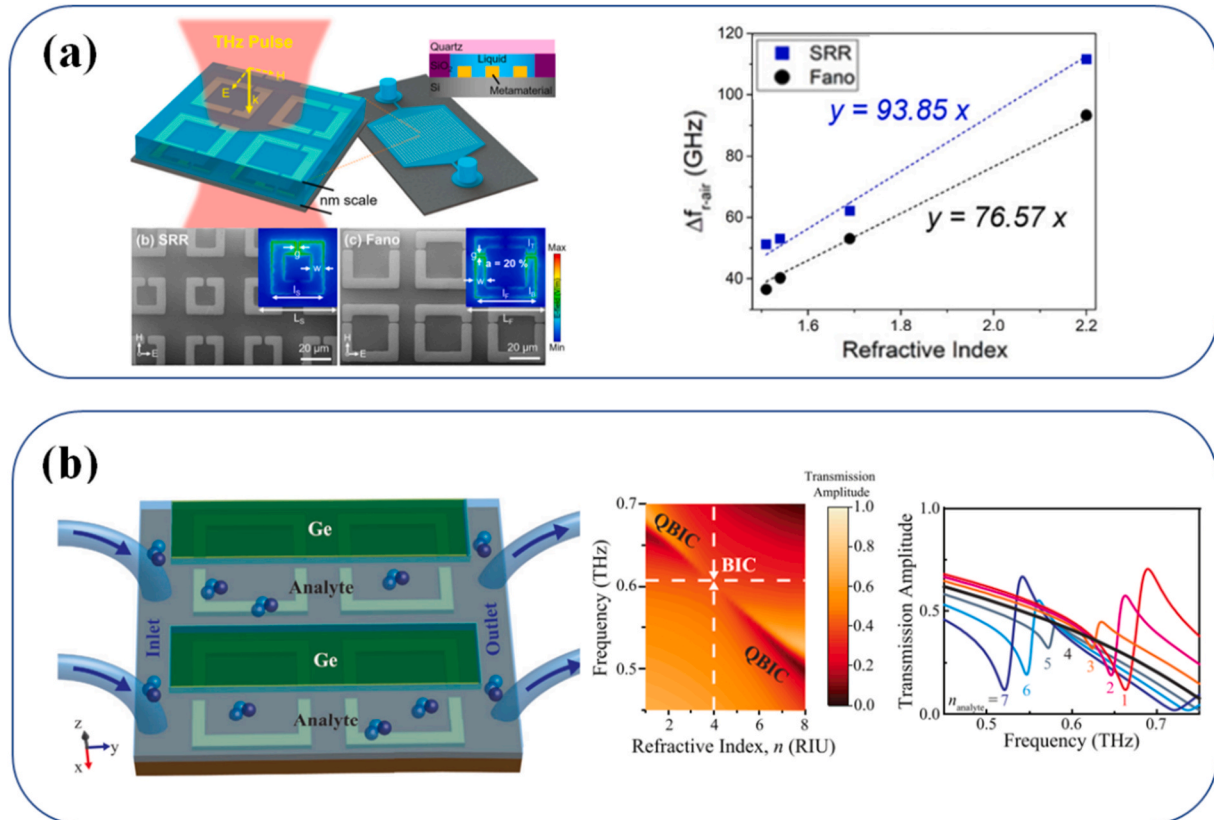


Fig. 6. **a** THz metamaterial nanofluidic device with SRR that can excite dipole and Fano resonances. Reprinted with permission from Ref. [58]; **b** Illustration of the Ge microchannels with input and output flow, showing the collapse and revival of the QBIC resonance with fluid thickness of $h = 500 \text{ nm}$ between the Ge strips and liquid. Reprinted with permission from Ref. [60].

THz), with Q factor of approximately 20, figure of merit (FoM) of 3.80, and a sensitivity of 70.73 $\mu\text{m}/\text{RIU}$ (128 GHz/RIU) [61]. Another ideal resonance mode suitable for microfluidic applications is the ring dipole mode, which effectively reduces far-field radiation modes. For instance, Xu et al. demonstrated a novel metasurface combined with a microfluidic platform, which generated a dual-ring dipole resonance to enhance the sensitivity of polar liquid analytes (Fig. 5b). The experimental detection sensitivity for ethanol-water mixed solutions was 124.3 GHz/RIU [63].

3.1.2.2. Nanometer spacing. Common THz microfluidic research confines aqueous solutions to micron-scale spaces and utilizes THz metamaterials for sensing applications in aqueous environments [34,61,62,73,74]. However, shrinking the liquid volume to nanoscale can significantly reduce water absorption, which will help achieve detection at the minimum liquid volume. Confining the liquid to nanoscale space also efficiently delivers molecules to the sensing volume. Current research in the microfluidic field has minimized the interaction space to the nanoscale [75,76]. For example, a nanoscale microfluidic THz metamaterial sensing platform has been demonstrated and used for chemical and biomolecule sensing. The platform includes a series of metal resonators with an intrinsic Si substrate and silica pillars supporting the nanoscale fluid channel height (160 nm). Fig. 6a shows a microscope image of the split-ring resonators (SRRs), which excite LC and Fano resonance modes. For liquid sensing, the analyte droplet (100 μL) is initially placed into the nanoscale fluid cavity with a pipette, followed by pressing and sealing the quartz substrate onto the metasurface. In Fig. 6a, the calculated sensitivity is 93.85 GHz/RIU (LC mode) and 76.57 GHz/RIU (Fano mode) [58]. In another nanoscale gap microfluidic design based on the BIC mode, half of the unit cell uses a Ge layer to achieve a microchannel, and the liquid flows into the uncovered part, as shown in Fig. 6b. The thickness of fluid spacing is maintained at 500 nm. The RI difference between the liquid and the cladding material leads to the

QBIC and causes a resonance frequency shift in the generated QBIC. The sensitivity is 24.5 GHz/RIU. The RI of Ge, used for constructing the microchannel, introduces a new degree of freedom, enabling flexible adjustment of the BIC and high-Q QBIC resonance positions based on microfluidics, integration, resolution, and application needs [60].

3.1.2.3. 3D metamaterial. The limitation for sensitivity improvement in microfluidic sensors lies in the weak localized surface field of planar metamaterials in the presence of liquid samples [77]. Some researchers have improved the sensitivity of microfluidic devices by further optimizing the structure and periodic arrangement of 3D metamaterials. By using silicon etching, when the liquid is filled into the sensor, the surface field is significantly confined in the quasi-3D etched microfluidic space. The physical mechanism is that the effective RI of the metamaterial surface is reduced, and the localized electric field is enhanced in the space, optimizing the localized surface field of quasi-3D metamaterials in the presence of polar liquid samples. From a microfluidic perspective, 3D metamaterials with a fully enclosed structure provide the liquid space required for microfluidics, as shown in Fig. 7a [36]. The substrate (Si) is sealed by poly-methylpentene (TPX) fixtures, and the cavity in the middle is sealed by a convex front cover made of TPX material. The quasi-3D metamaterials can induce electromagnetic-induced transparency (EIT) effects. Hence, the strong enhanced field space in liquids causes a larger frequency shift when the quasi-3D metamaterials are filled with liquids. The sensitivity of the EIT metamaterials is 0.312 THz/RIU when the substrate is etched to 15 μm , which is 9.8 times higher than when there is no etching [36]. Other studies have reported the integration of THz 3D metamaterials with microfluidic technology based on photonic crystal (PC) sensors [56], which use direct-write technology to assemble glass cement ink into microstructural channels to form a stack structure. Through these microfluidic 3D PCs, different fluid media can be injected for various THz technology applications. Fig. 7b compares the THz transmission characteristics of only phosphate

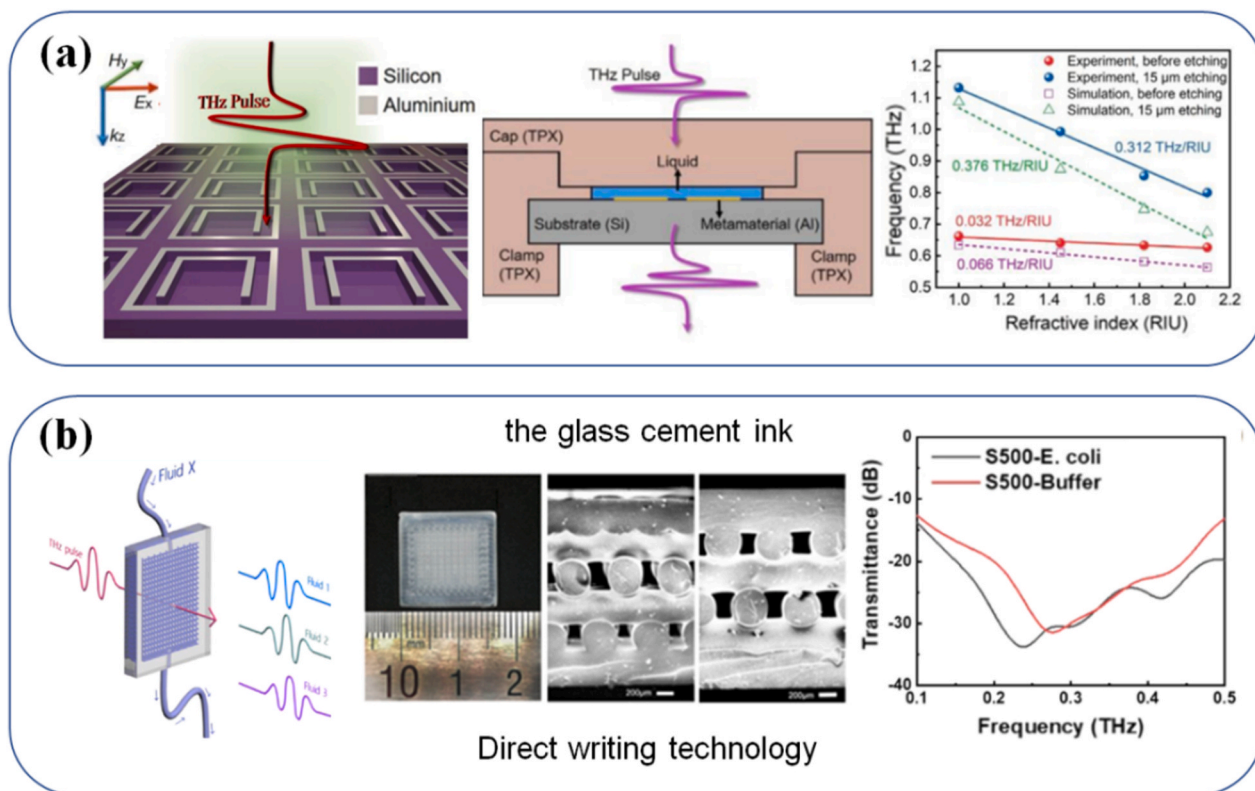


Fig. 7. a 3D EIT metamaterial microfluidic of the sample cell assembly with 15 μm etching. Reprinted with permission from Ref. [36]; b A microfluidic 3D THz PC sample and measured THz transmission properties filled with PBS or E. coli in the PBS. Reprinted with permission from Ref. [56].

buffer solution (PBS) and *E. coli* cells in PBS(*E. coli*). The THz stopband of the PBS is around 0.27 THz, while the stopband of the *E. coli* is around 0.23 THz. Therefore, the microfluidic 3D PCs can clearly detect the presence of *E. coli* cells in the PBS.

3.1.2.4. Nanomaterials. Photoelectrical nanomaterials, such as graphene and carbon nanotubes (CNTs), can also be integrated with THz microfluidic metamaterial devices, to enhance the ability of capturing target molecules. Graphene possesses a large sensing area, adjustable optoelectronic properties, and excellent biocompatibility, and has therefore been widely applied in biosensing [57,78,79]. In Fig. 8a, compared to single microfluidic devices and microfluidic devices based on metamaterials, the graphene-based microfluidic device shows more significant transmission changes with increasing concentration of glycerol dichlorohydrate (DCH) solution, proving the excellent sensing performance of the metasurface-graphene microfluidic structure. CNTs have high electrical conductivity, and the ability to efficiently adsorb analytes through van der Waals forces, which can also enhance the sensitivity of microfluidics [59,80,81]. For instance, Xie et al. demonstrated that fluid chips based on metasurfaces and CNTs can enhance optical dynamic of tartaric acids in THz range, while withstand the huge THz water-induced absorption, as shown in Fig. 8b. The limit of detection (LoD) is 11.0 mg/L, and its sensitivity is superior to that of optical rotation scatterometers or circular dichroism spectrometers [59]. Therefore, microfluidic devices based on nanomaterials and metasurface hybrid structures have great potential for achieving effective biosensing. Table 4 lists the performance of transmission metasurface microfluidic devices.

3.1.3. Hot spots

The above reported devices have only used single large microfluidic chamber positioned over the entire metamaterial area to control the

liquid layer thickness [30,58,61,73,82–86]. However, the field-enhanced regions are localized, and by designing optimized microfluidic channels to selectively cover specific field-enhanced areas, the sensitivity of microfluidics per unit volume can be further enhanced while minimizing the required liquid volume. Several research groups have recently reported progress in optimizing microfluidic channels that cover specific “hotspots” of field enhancement. For example, the Tonouchi group developed several microfluidic metasurface chips that use near-field coupling between metal elements and localized THz radiation to detect small-volume liquid samples [87,88]. The THz microfluidic chip consists of a double-gap SRR pattern that can excite LC resonance. The microfluidic channel does not cover the entire SRR metasurface, but only the gap regions where the electric field is enhanced. This microfluidic chip was used to detect a 318 pL commercial mineral water solution in microchannels of different hardness, with LoD of 31.8 fmol (10 mg/L), as shown in Fig. 9a [87]. In Fig. 9b, the double-gap symmetric SRR mode is replaced by a double-gap asymmetric SRR, to excite Fano and quadrupole resonances. The LoD for a 128 pL solution is 1.4 fmol (2 mg/L) [89]. Recent optimizations of microfluidic chip structures have also employed the “I-design” metasurface structure [90,91], as illustrated in Fig. 9c. The THz field is strictly confined to the gap region of the “I-design” metasurface. For a solution with an actual volume of 85 pL, the LoD is as low as 472 amol (1 mg/L). For far-field microfluidic measurements, Emma’s group enhanced the interaction between THz and the liquid by arranging the microchannel in the field enhanced gap region of a bowtie array metasurface (Fig. 9d). The microchannel requires only 0.13 μ L of liquid, with a unit-volume sensitivity of 552 GHz/RIU/ μ L [93]. Moreover, by introducing substrate-integrated patterned microfluidic channels into the complementary asymmetric split-ring resonators, the sensitivity can theoretically be further increased to 893 GHz/RIU/ μ L, with a liquid volume requirement as low as 7.55 nL [92]. Fig. 9e compares the

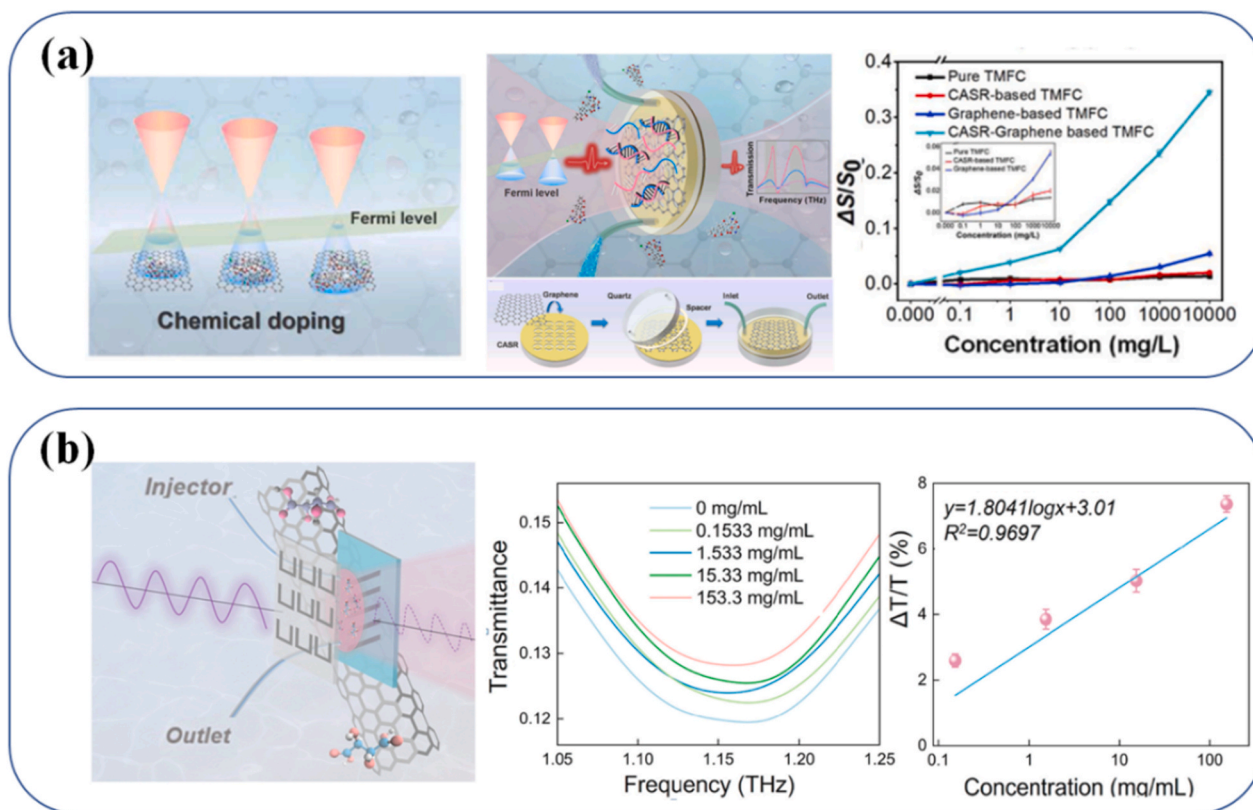


Fig. 8. a The mechanism of THz metasurface-graphene microfluidic biosensing and effective transmission changes of different TMFCs (THz microfluidic chips) with respect to DCH concentrations. Reprinted with permission from Ref. [57]; b Schematic of CNTs-based microfluidic chip, and THz transmission spectra of L-tartaric acids versus concentration. Reprinted with permission from Ref. [59].

Table 4

Transmissive metasurface microfluidic (one big chamber).

Categories and highlights	Microfluidic Material	Dimension	Mechanism	Liquid/performance	Reference (year)
Enhanced mode	PEN(cap)-PEN (substrate)	Chamber/50 μm	Lattice mode	Liquid paraffin, Ethanol and methanol, $Q = 20$, FoM 3.8, 70.73 μm /RIU(128 GHz/RIU)	[61] 2011
Enhanced mode	PDMS(cap)- Si (substrate)	Chamber/50 μm	LC resonance	Ethanol, methanol, water, 81.4GHz/RIU	[62] 2016
Enhanced mode	PTFE	Chamber/28 μm	Toroidal resonance	mixed ethanol-water, 124.43GHz/RIU	[63] 2021
Nanometer spacing	Quartz plate (cap) intrinsic Si (substrate)	Chamber/160 nm	LC and Fano resonance	Water, methanol, ethanol and isopropyl alcohol (IPA), 93.85GHz/RIU (LC) and 76.57GHz/RIU(Fano) Adenosine triphosphate ATP aptamer 0.1 μM	[58] 2018
Nanometer spacing	Ge stripe, SRRs and COC (substrate)	Chamber/500 nm	Quasi-BIC	NA, Sensitivity 24.5 GHz/RIU for 500 nm-thick analytes and 19.5 GHz/RIU for 300 nm-thick analytes	[60] 2022
3D metamaterial	Cured glass cement (bottom, top, 3D woodpile)	Space/ $12 \times 12 \times 1.6 \text{ mm}^3$	3D PC photonic band gap	PBS with E. coli	[56] 2019
3D metamaterial	TPX-Si	Chamber/20 μm	EIT, with field enhanced	Alcohol, glycerin and water, 0.312THz/RIU	[36] 2022
Nanomaterial	Quartz(cap) -quartz (substrate)	Chamber/10 μm and 25 μm	Interaction between chemical molecules and graphene, Fano resonance	DCH solutions, Detection limit: 0.1 mg/L	[57] 2021
Nanomaterial	CNTs(top), Si (substrate)	Chamber/40 μm	LC resonance	DNA sequences of E. coli O157:H7, LOD:100 nM Tartaric acids, LOD: 11.0 mg/L	[59] 2024

performance metrics of THz transmission microfluidic with chamber and hotspot sensors, including minimum liquid volume and LoD. We can see that transmission “hot spot” microfluidics show much lower minimum liquid volume than that with chamber, which benefits for reducing water absorption. By integrating emitter with microfluidic and using near-field THz waves, minimum liquid volume and limit of detection of the “I-design” microfluidic metasurface can achieve amazing values 85 pL (1 mg/L), exhibiting excellent performances. Table 5 summarizes the mechanisms/performances of the THz “hotspot” microfluidic sensors.

3.2. Reflection

3.2.1. Reflection measurement for liquid: application introduction

THz reflection structures and ATR structures can effectively solve the measurement problems of polar liquids, as the THz signal only penetrates a small portion of the polar liquid in contact with the low-loss substrate [63]. Fig. 10a demonstrates a practical application scenario of THz reflection-based bottled liquid detection [94]. There is no need to take out the liquid from the bottle and measure it, and the commercial bottle is directly serves as the interface for the liquid. The reflected THz waveforms from PET bottles containing water, ethanol, and dioxins show clear reflection, weak reflection, and almost no reflection, respectively. In the ATR method for measuring polar liquids, the THz signal faces total internal reflection (TIR) at the prism surface where the prism contacts the liquid [95,96]. Fig. 10b illustrates a schematic of a handheld measurement unit and the THz ATR module for real-world applications. The ATR module was simply immersed in the liquid to measure four different polar liquids without distinct spectral fingerprints, and spectral differences could be distinguished. These two practical application examples demonstrate the powerful capability of the reflection platform to measure THz-strong absorption liquids. However, to achieve quantitative detection of solutions with different concentrations, a microfluidic platform should be introduced.

3.2.2. Reflective and ATR technologies integrated with microfluidic

3.2.2.1. Reflection microfluidic. The reflection THz liquid measurement method at different temperature was first reported by Jepsen et al., as shown in Fig. 11a [98]. This method uses the reflection coefficient at the interface to infer the dielectric constants of different liquids. As it does not require penetrating the liquid layer, this method can determine

alcohol concentration in glass and PET bottles [99]. Furthermore, combining reflection THz time-domain spectroscopy (THz-TDS) with metamaterial sensors enables high-sensitivity THz sensing of aqueous solutions [100]. For example, Wu et al. used a reflection metamaterial sensor (Fig. 11b) to study ethanol-water mixtures and NaCl aqueous solutions [86]. This sensor can be used to identify solvent concentrations and types. Miyamaru et al. [101] demonstrated high-sensitivity THz sensing of glycerol-water mixtures on metamaterial surfaces using reflection THz spectroscopy (Fig. 11c). The detection sensitivity was eight times greater than in the case without the metamaterial structure.

3.2.2.2. ATR microfluidic. Another method to address the limitations of transmission spectroscopy measurements for highly absorbing materials is THz ATR spectroscopy [13,102]. The ATR technique was proposed by Hirori et al. in early stage to obtain the RI of liquids [103]. As illustrated in Fig. 11d, the integration of ATR with microfluidics can act as a carrier setup for biomolecular solutions detection, reducing the strong water absorption. It is also independent of liquid thickness, eliminates standing waves, and simplifies the subsequent spectral calculation process [104]. For example, combining THz-TDS with ATR microfluidics has been applied to detect DNA molecules with single-base mutations in clinical diseases [105], and can distinguish between healthy genes and the Huntington’s Chorea gene [106]. Another ATR microfluidic design involves integrating THz paraffin [107] or HR-Si [108] prisms with the spoof surface plasmon polariton (SPPs) mode excited by the metasurface to enhance liquid detection sensitivity, as shown in Fig. 11e. The spoof SPPs mode is localized in a tiny liquid-filled resonance cavity, enabling sufficient interaction space, leading to a frequency shift of spoof SPPs resonance in the ATR spectrum. Recently, the complementary SRRs metasurface have been directly integrated with ATR prisms to enhance THz-range microfluidic sensors for aqueous solutions. The metasurface pattern consisted of complementary SRRs was lithographed on the top surface of a 20 mm $\times$ 25 mm HR-Si, as shown in Fig. 11f. This structure effectively prevents multiple reflections of THz waves that occur due to Otto configuration. The sensitivity is four times higher than traditional ATR. Table 6 summarizes the performance of reflection and ATR microfluidic devices.

3.2.3. Reflective microfluidic devices by exciting cavity modes

In the above reflection/ATR schemes, the weak interaction with liquids still hinders signal-to-noise ratio (SNR) and sensitivity.

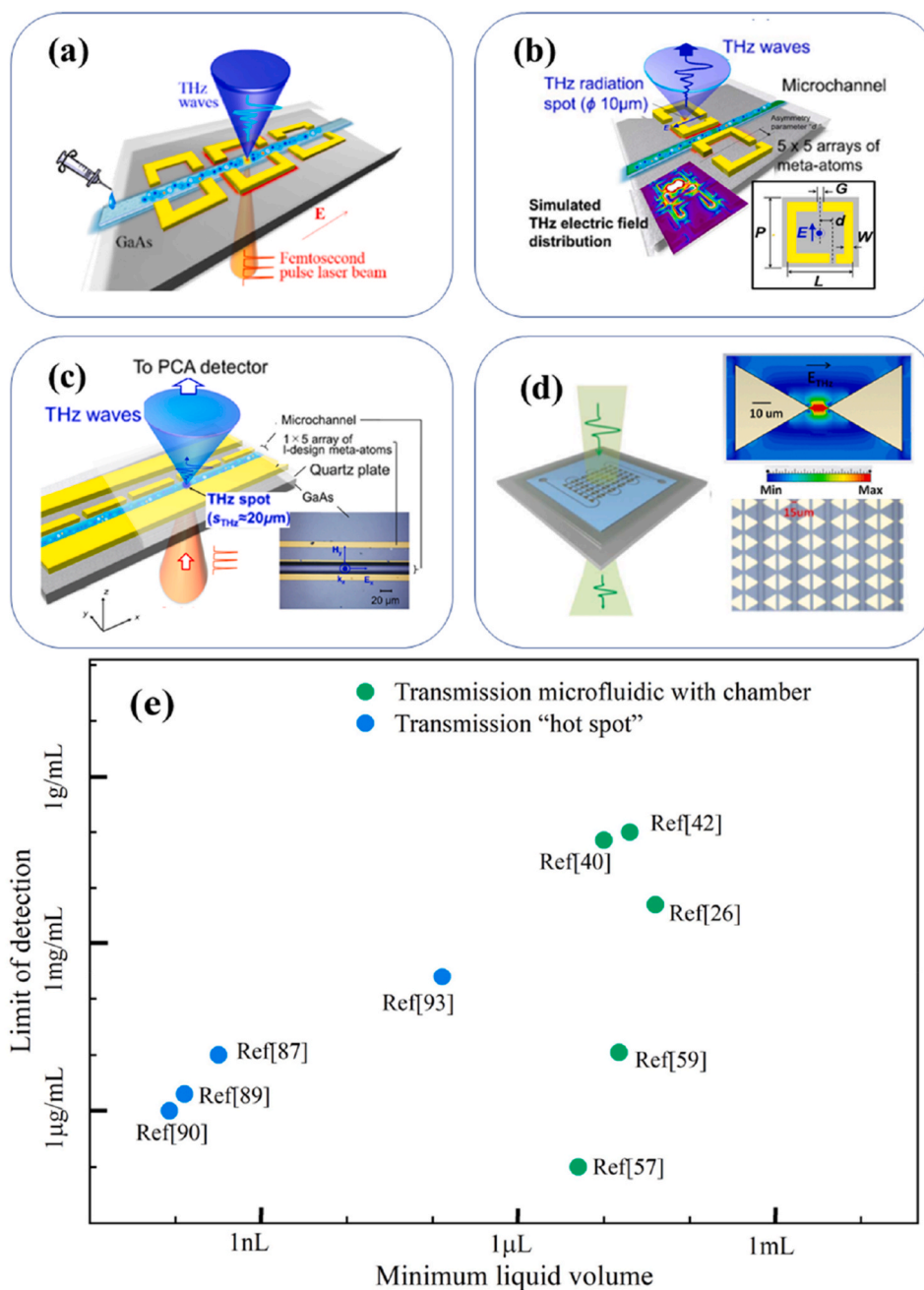


Fig. 9. THz microfluidic chip consisted of **a** double gap symmetric SRRs. Reprinted with permission from Ref. [87]; **b** Asymmetric SRRs. Reprinted with permission from Ref. [89]; **c** "T" design metasurface pattern. Reprinted with permission from Refs. [90,91]; **d** Bow-tie array. The microfluidic channel was only passing through hot spots in unit cell (the confinement of the electric field is high). Reprinted with permission from Ref. [93]; **e** Comparison of the performance metrics of THz transmission microfluidic with chamber and hot spot sensors, including minimum liquid volume and LoD.

Therefore, scientists have combined the reflection structure with a Fabry-Pérot (FP) microfluidic resonator. Dubroiu et al. found that when a collimated THz radiation is obliquely incident on a Si prism, the FP cavity can be cleverly designed to detect alcohol content in aqueous solutions, which is different from the aforementioned Si-Dove prism ATR structure [110]. With this method, the concentration measurement of water-ethanol mixtures can be achieved within the range of 3 %–5 %. Researchers at the University of Adelaide further designed a microfluidic liquid FP cavity separated by a metal reflector and a Si cover, as shown in Fig. 12a [111]. The enhanced optical path allows the device to detect ethanol concentration changes in water as low as 0.5 %, with the required liquid volume in the microliter range. Furthermore, Jing et al. reported a microfluidic channel sensor based on a metamaterial cavity

mode by etching inverted pyramid-shaped doped Si, as shown in Fig. 12b [37]. The radiation loss of sensor can be adjusted by optimizing the carrier concentration of doped Si, achieving a liquid sensing sensitivity of 500 GHz/RIU. Besides Si materials, micro-nano metal thin film structures can also serve as covering layers for microfluidic devices to facilitate THz wave coupling and confinement within the microfluidic layer. Hu et al. proposed a metal-dielectric-metal (MDM) microfluidic device (Fig. 12c), where the Si cover in the FP cavity microfluidic design is replaced by a metal microstructure array, thereby increasing the microfluidic interaction region. The microfluidic chamber also acts as the dielectric layer of the MDM. The theoretical (experimental) sensitivity of this device is 3.5 (0.22) THz/RIU [83,112]. If the guided-mode resonance (GMR) mode replaces the FP mode, the maximum sensitivity

Table 5

The sensing mechanisms and performance of “hot spot” microfluidic.

THz microfluidic categories	Microfluidic material	Dimension	Mechanism	Liquid/performance	Reference (year)
“hot spot” microfluidic with extremely tiny volume	GaAs, quartz plate cap	Width of 26.5 μm , A depth of 10 μm , 318 pL	LC circuit	The minerals solution by water, 10 mg/L	[87] 2018
	500- μm -thick quartz substrate, 500- μm -thick quartz cap, photoresist channel	Channel/15 μm *15 μm , 0.13 μL	Bow-tie dipole mode	IPA–water mixtures and BSA solutions, 0.25 mg/mL	[93] 2019
	500- μm -thick GaAs wafer.	Microchannel/width = 16 μm , depth = 10 μm , width = 2.2 mm, 128 pL	Fano resonance, Quadruple resonance	Mineral water, Glucose water, 2 mg/L	[89] 2019
	2-gap SRRs	Channel/3 μm , 7.55 nL	EIT	Water, 893 GHz/RIU/ μL	[92] 2022
	Substrate and cover, fused silica glass	Microchannel/width = 25 μm , depth = 10 μm , width = 2 mm, 85 pL	LC/Fano resonance	Glucose-water solutions, 1 mg/L	[90] 2022
	500- μm -thick GaAs wafer. Strip design with split gap				

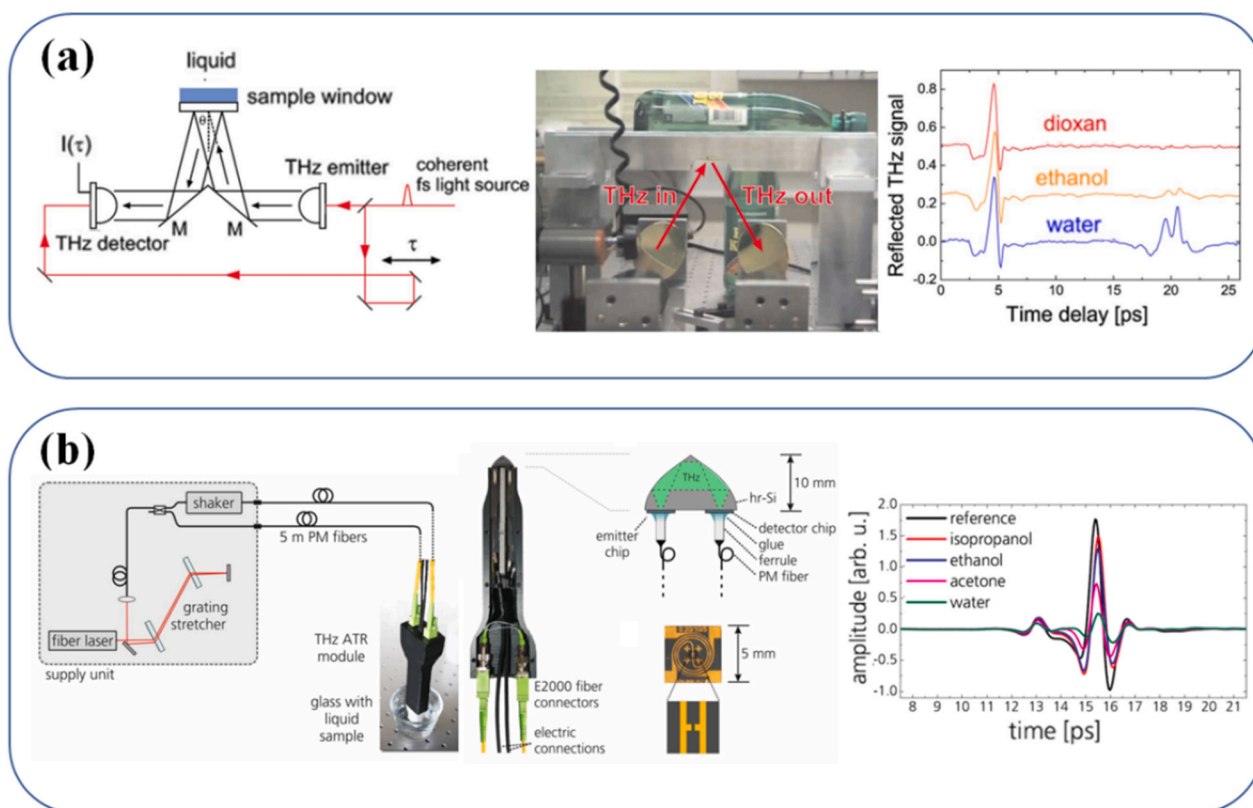


Fig. 10. **a** THz nondestructive liquid measurement by reflection spectroscopy. Reprinted with permission from Ref. [94]; **b** THz real time liquid measurement by handheld ATR spectroscopy. Reprinted with permission from Ref. [97].

of this cavity-mode microfluidic device is 438 GHz/RIU, with a Q (FoM) of 1879 (692), which is two orders higher than the Q and FoM of the MDM microfluidic sensor [113]. Table 7 summarizes the performance of reflection microfluidic devices with different cavity modes.

3.3. Waveguide type

3.3.1. Metallic waveguides

The THz functional devices mentioned above rarely reserve microfluidic channels directly, so the channels need to be customized in the later stages. On the other hand, waveguide microfluidic devices can seamlessly connect microfluidic channels into the waveguide structure, achieving strong interactions between electromagnetic waves and liquids [114,115]. For example, Mittleman's team designed a waveguide microfluidic device that integrates microfluidic channels with a parallel

plate waveguide (PPWG), as plotted in Fig. 13a. The microfluidic channel is fabricated by micron-sized strip grooves on a metal structure, with the required liquid volume in the microliter range. The unloaded Q factor of the microfluidic device can reach 98. The liquids in the experiment were nine different chain-length organic compounds, from C_8H_{18} octane to $\text{C}_{16}\text{H}_{34}$ hexadecane. The refractive indices of nine organic substances increases monotonically with the number of carbon atoms, and the measured sensitivity reached 91.25 GHz/RIU [116–118]. The THz waveguide microfluidic devices described above are bulk waveguides, which cannot achieve miniaturization and integration [119–122]. You et al. proposed a microstructure-based microfluidic waveguide device to enhance the miniaturization and integration of waveguide-based microfluidic technology [83]. In this structure, a THz metal rod array (MRA) based waveguide is integrated into a microfluidic structure made of two metal sheets. The MRA surface can excite THz

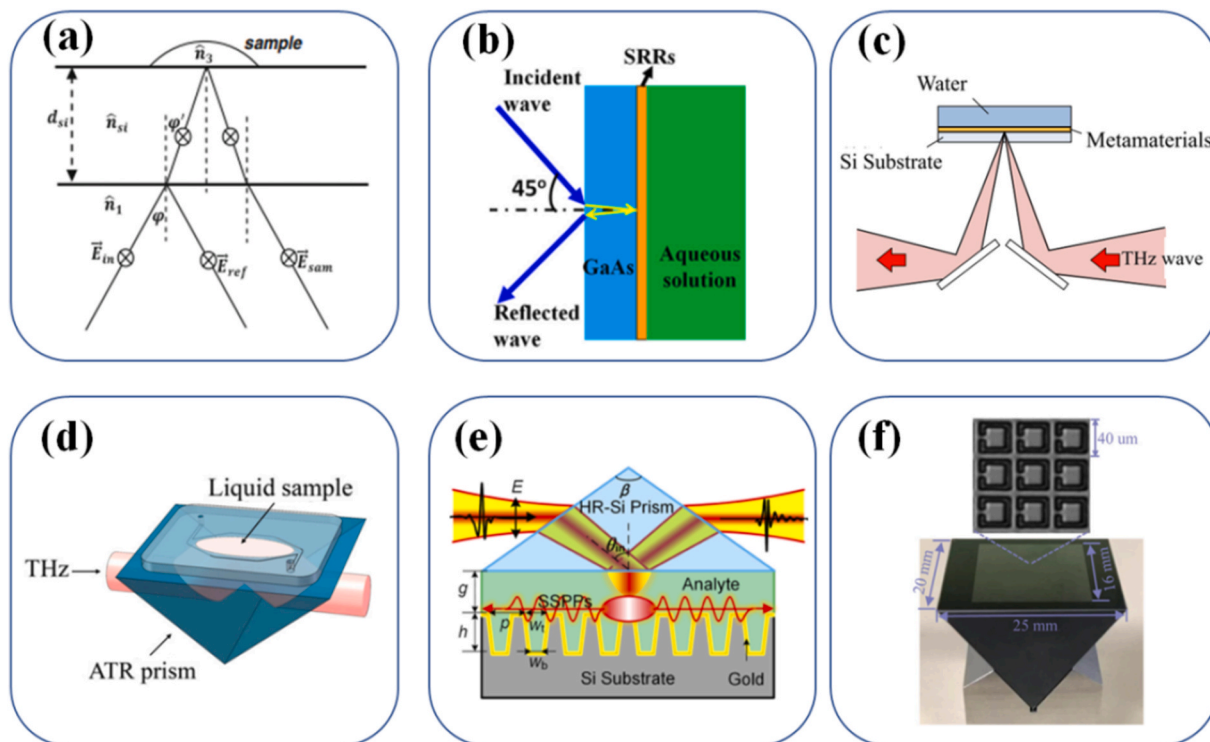


Fig. 11. **a** Detailed view of the reflection geometry. Reprinted with permission from Ref. [98]; **b** Reflective geometry for GaAs based metasurfaces. Reprinted with permission from Ref. [86]; **c** Reflective geometry for Si based SRRs with water. Reprinted with permission from Ref. [101]; **d** THz ATR microfluidic cell. Reprinted with permission from Refs. [105,106]; **e** Exciting Spoof SPPs on grating metasurface with Otto configuration. Reprinted with permission from Refs. [107,108]; **f** Geometry of the ATR SRRs based microfluidic sensor. Reprinted with permission from Ref. [109].

Table 6

Performances of Reflection & ATR microfluidic devices.

THz microfluidic categories	Microfluidic material	Channel/Chamber dimension	Mechanism	Liquid/performance	Reference (year)
Reflection	Si	NA	TIR	Ethanol-water solutions and Sugar solutions Measurement the permittivity of liquid from 0.1 to 1.0 THz	[98] 2007
Reflection	GaAs (substrate) and SRRs (gold)	NA	TIR-LC	Ethanol-water solution and Aqueous solution of NaCl. Sensitivity 0.3 amp/mol/L	[86] 2013
Reflection	500 μm thick Si (substrate), CSRRs	NA	TIR-LC	Water-glycerol mixtures. Sensitivity: 8 times higher than using Si substrate.	[101] 2014
ATR	PDMS cap, Si (prism)	Chamber/200 μm	ATR	Four oligonucleotide samples LOD: 0.5 $\mu\text{g}/\mu\text{L}$	[106] 2020
ATR	HR-Si Prism+ Metagrating	190 μm for PE/45 μm for Si	ATR-SPP	Sensitivity: 0.31 THz/RIU(Water) to 0.85 THz/RIU(Gasoline)	[108] 2019
ATR	Si Prism (substrate), CSRRs	NA	ATR-LC	Sucrose solution, Sensitivity: 4 times higher than the conventional ATR	[109] 2020
ATR	Wax prism+ Metagrating	NA	ATR-SPP	Sensitivity: 0.49 THz/RIU. LOD: 0.02 RIU (resolution of 10 GHz)	[107] 2013

pseudo-surface plasmon modes, with a PC-like bandgap observable in the spectrum [123]. The liquid molecules in the microfluidic channel can directly change the THz phases excited by the MRA. Experimentally, three colorless liquids, acetone, methanol, and ethanol, were successfully differentiated, and their THz phase dynamic real-time changes during the evaporation process are shown in Fig. 13b [124]. The required liquid volume is only 0.05 mL, and the detection limit is 0.1 mmol [124]. Another waveguide microfluidic design presents a liquid sensing platform integrated with a pseudo-SPP domino waveguide and a microfluidic capillary [125–127]. The microfluidic capillary is embedded between the domino pillars (the highest field region), with a required liquid volume in the nanoliter range. The liquid in the capillary interacts with spoof SPP mode, and small RI changes lead to shifts of the

cutoff frequency of the domino waveguide. The sensitivity can be characterized by the inverse of the transmission rate change (T) versus the RI change n , $S = \partial T / \partial n$, with a theoretical maximum sensitivity of 1.89/RIU, as shown in Fig. 13c.

3.3.2. Spoof plasmonic resonator

Besides microfluidic sensing platform with 3D spoof SPP domino waveguide, the spoof SPP mode can also be integrated with microfluidic technology on a planar waveguide. The microfluidic device can be positioned either on the spoof SPP waveguide or within the resonance cavity of the spoof local surface plasmon (LSPs) in the waveguide [129], as depicted in Fig. 14a. The spoof LSP resonance cavity consists of a periodically patterned wavy disk structure, with the microfluidic

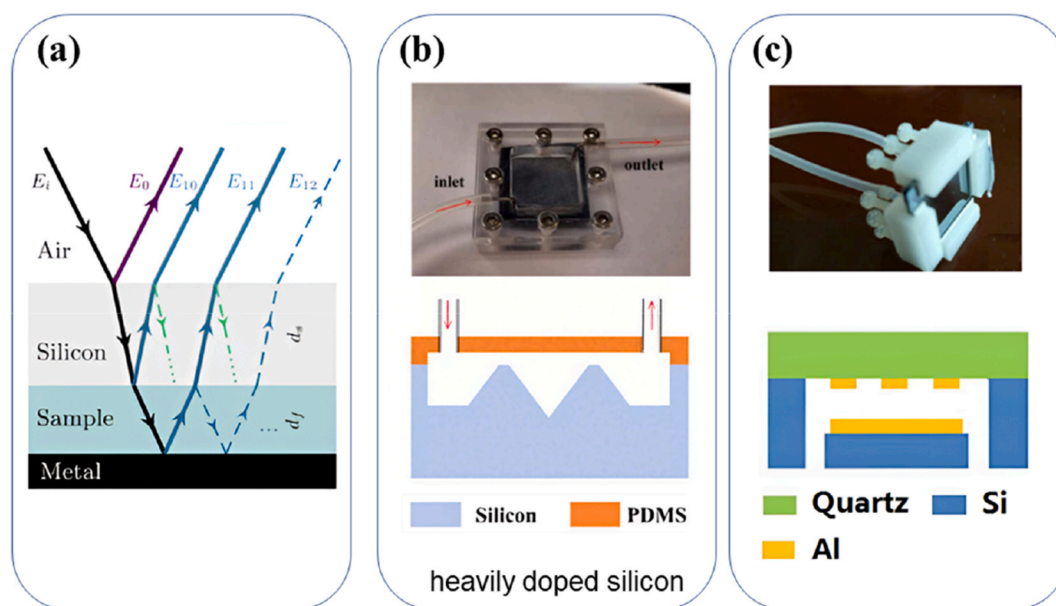


Fig. 12. **a** Reflective microfluidic devices based on FP resonance. Reprinted with permission from Ref. [111]; **b** Microflow channel sensor based on inverted pyramidal and V-shaped cavities. Reprinted with permission from Ref. [37]; **c** Microfluidic device based on MDM absorber. Reprinted with permission from Ref. [83].

Table 7

Performance of different reflective microfluidics with cavity modes.

THz microfluidic categories	Microfluidic material	Channel/chamber dimension	Mechanism	Liquid/performance	Reference (year)
Reflective microfluidics with cavity modes	Si (cap), metal(substrate)	Chamber/72 μm	FP resonance	Ethanol-water mixture, 8 GHz per percent ethanol	[111] 2017
	PDMS(cap) V-shaped heavily doped Si (substrate)	Chamber/50 μm	Metamaterial perfect absorber	BSA solution, 500GHz/RIU, Q = 23, FOM = 9.4	[37] 2022
	Quartz(cap) metallic film (substrate)	Chamber/12 μm	Metamaterial perfect absorber	Ethanol, glucose 0.22THz/RIU, or 0.31Hz/RIU, FOM = 4	[83] 2016
	Si (cap)-metal-coated dielectric gratings (substrate)	Chamber/30 μm	Guided Mode Resonance	Glucose, 438GHz/RIU, Q = 1879, FoM = 692 (Theory)	[113] 2018

channel positioned close to the groove area. Made from PDMS, its size spans the radius of the spoof LSPs, enabling the liquid to cover the electric field enhancement region (hotspot) of the spoof LSPs. The Q factor and sensitivity of this microfluidic device are 192 and 13.5 MHz/mg·ml⁻¹ for glucose concentration detection [130]. In a different planar waveguide microfluidic system, researchers combined a spoof SPP planar waveguide with three SRRs and liquid-wall microfluidics to measure varying concentrations of sucrose solutions [131,132], as illustrated in Fig. 14b. The microfluidic setup features a 2 × 1.5 mm rectangular liquid wall created from photoresist at the center of the planar waveguide. A 0.2 μL solution flowed into the liquid wall, and different sucrose concentrations resulted in the resonance frequency shift [132]. The frequency shift for 0.25 mg/ml solution relative to the water frequency was 1.4 GHz, with sensitivity approximately 18 times higher than the performance in Ref. [131].

3.3.3. Fiber waveguide microfluidic

THz fiber waveguide microfluidic sensors also feature seamless integration [133–137]. For example, by introducing a defect in a Bragg fiber reflector, a defect mode is excited in the band structure, as illustrated in Fig. 15a [138,139]. Therefore, by integrating the microfluidic channel into the photonic band gap (PBG), the RI of the liquid can be obtained by tracking the frequency corresponding to the defect mode. The RI small change typically manifests as a shift in the narrow-band resonance, with the sensitivity around 0.23 THz being 110 GHz/RIU [140]. Besides the aforementioned PBG fiber-based microfluidic platform, dielectric hollow-core fibers also serve as THz microfluidic

channel sensors (Fig. 15b). This dielectric hollow-core fiber can be a readily available plastic tube, with both THz waves and liquid confined in the hollow channel, which enhances the interaction between light and matter, achieving a sensitivity close to 22.2 GHz/RIU [120]. In addition, the promising characteristics of photonic crystal fibers (PCFs) are also potential microfluidic candidates [141–144]. Fig. 15c presents a THz microfluidic sensor based on PCFs for detecting alcoholic beverages. In the Zeonex substrate, an elliptical air hole array forms the microfluidic channel in the PCF. Ethanol is used as the analytical liquid with a RI of 1.354. The sensitivity for ethanol can be obtained using formula $1.354/n_{\text{eff}} \times e$, where n_{eff} represents the effective RI of the fiber transmission mode, and e is the light-matter interaction coefficient. The relative sensitivity is 68.8 % [145]. Another dual-core microfluidic PCF is shown in Fig. 15d. In this structure, the dual cores are arranged in parallel, with the right core carrying microfluidic liquid. The sensing principle is transmission modes coupling in both fiber cores [146]. The transmission mode power in the core filled with liquid will be gradually reduced, since polar liquids strongly absorb THz waves. The sensitivity of the x-polarization modes is 78.095 THz/RIU [147]. The dual cores can also be arranged vertically in the microfluidic PCF, as shown in Fig. 15e [146]. Table 8 summarizes the performance comparison of different fiber microfluidic devices.

3.4. Evanescent field transmission line

The characterization of the complex permittivity of chemical or biological liquids is another important application of THz microfluidics.

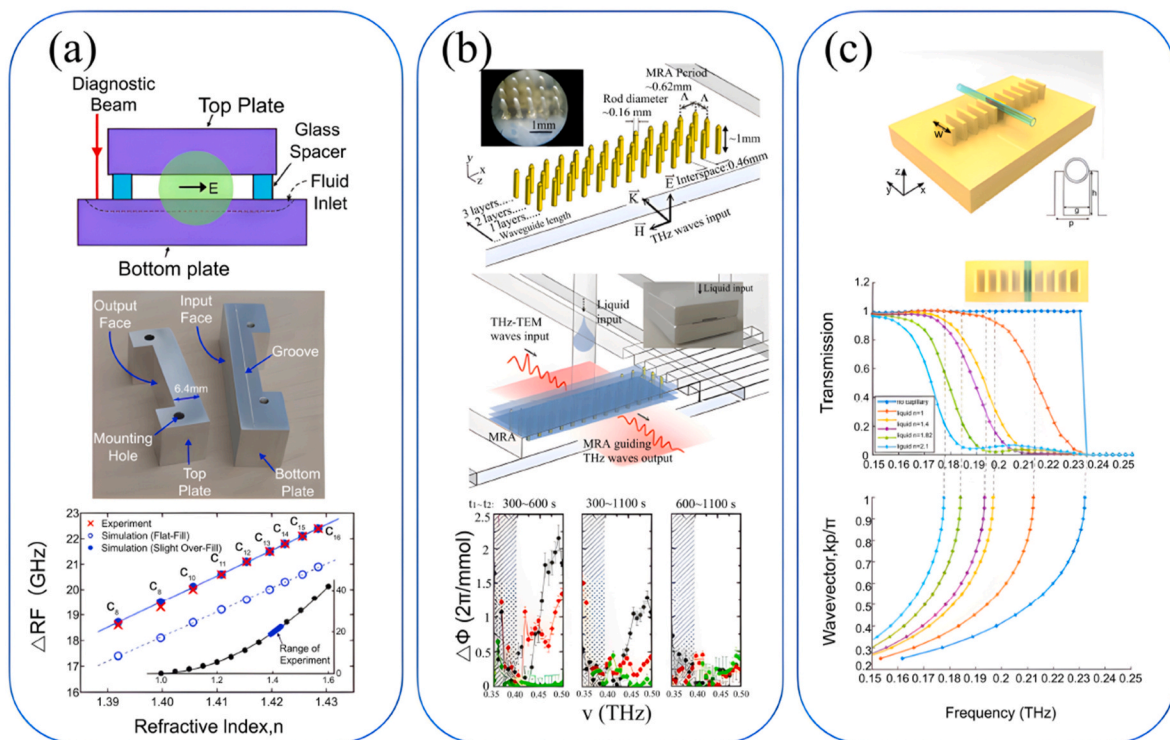


Fig. 13. **a** The assembled PPWG integrated with microfluidic channel. Reprinted with permission from Ref. [116]; **b** Diagram of a MRA waveguide microfluidic, and THz phases with different volumes (evaporation times are also shown). Reprinted with permission from Ref. [124]; **c** Schematics of the tapered domino waveguides integrated with micro-capillary, and transmission spectra/dispersion curves for capillary with and without a liquid. Reprinted with permission from Ref. [128].

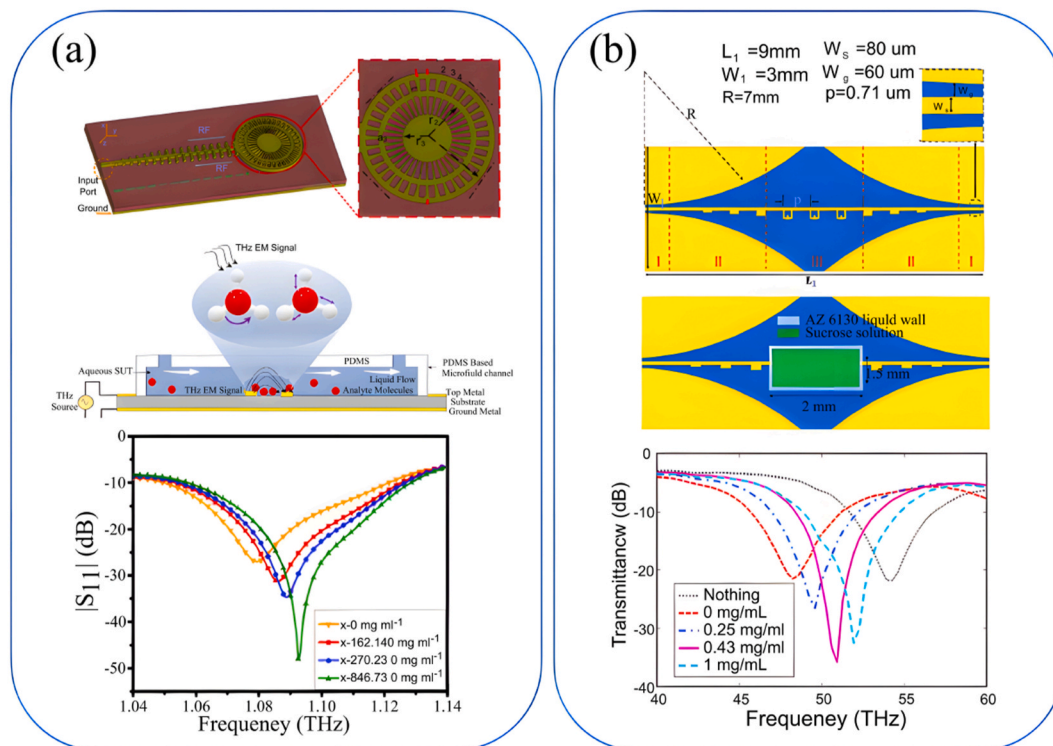


Fig. 14. **a** Layout of the spoof SPPs sensor integrated with microfluidic PDMS channel, and reflectivity (S_{11}) with different glucose concentration. Reprinted with permission from Ref. [130]; **b** Spoof SPP biosensor with in-series SRRs and microfluidic for liquid detection, and measured spectra with various sucrose concentrations. Reprinted with permission from Ref. [132].

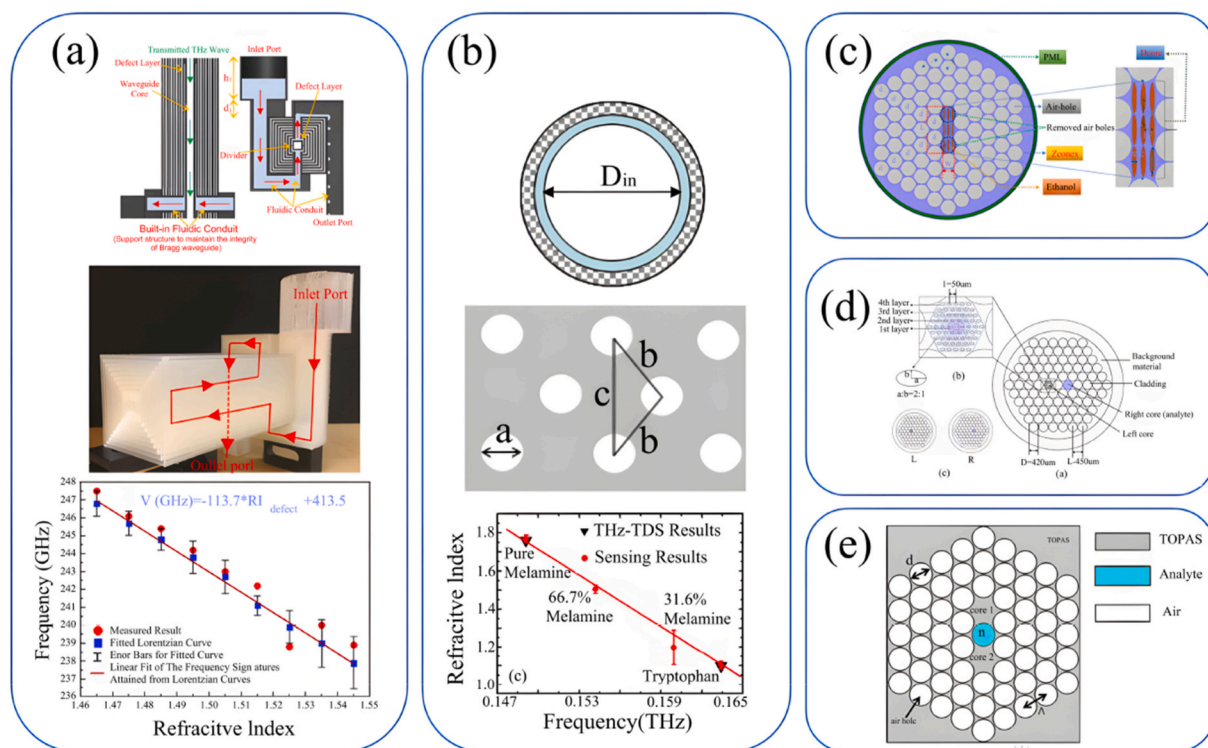


Fig. 15. **a** The schematics of THz fluidic Bragg waveguide. Reprinted with permission from Ref. [140]; **b** a pipe microfluidic waveguide with D_{in} of 12 mm. Outer layer can act as microfluidic layer. Reprinted with permission from Ref. [120]; **c** Cross section of the PCFs-based THz microfluidic sensor. Reprinted with permission from Ref. [145]; **d** Cross section of THz microfluidic PCFs with dual cores. Reprinted with permission from Ref. [147]; **e** microfluidic PCF with vertical two cores. Reprinted with permission from Ref. [146].

Table 8
Waveguide type based microfluidic devices.

THz microfluidic categories	Microfluidic material	Channel/chamber dimension	Mechanism	Liquid/performance	Reference (year)
PPWG	Metal	Channel/472 μm *412 μm , 8 μl	PPWG resonant cavity	91.25 GHz/RIU, Q = 98, 3 dB = 3 GHz	[116] 2009
MRA	Aluminum (cap) glass (substrate)	Channel/1.4 mm*1.0 mm	Metamaterial waveguide mode	Acetone methanol ethanol, detection limit 0.1 mmol	[124] 2017
Domino waveguide	Quartz capillary	Channel/inner diameter 120 μm	Spoof SPPs	1.89/RIU, 1.54/RIU (tapered); 90 μm Particle: 0.15/RIU homogeneous, 0.35/RIU tapered	[128] 2017
Spoof SPPs waveguide	PDMS wall and cap	Channel/outer radius = 110 μm	SSPP + SLSP	Glucose solution, Q = 192, Sensitivity 13.5 MHz/mg/mL LOD: 22.2 mg/ml(Theory)	[130] 2021
Spoof SPPs waveguide	AZ 6130 photoresist	Liquid wall/thickness = 5 μm height = 10 μm .	Spoof SPPs	Ovarian cancers Sensitivity 5.6 GHz/(mg/ml)	[132] 2022
PBG waveguide	Photosensitive resin	Channel/Length = 17.4 cm, width = 1.3 cm and height = 0.8 mm	Core-guided and defect-bound Bra-gg mode	Mineral oil and cinnamon essential oil, sensitivity:110 GHz/RIU	[140] 2019
PCF	Liquid-hole PVC on the PP pipe surface	Air-hollow/air-hole diameter1.1 mm, spacing1.40 mm, diagonal 2.70 mm	Anti-resonance	Melamine-tryptophan mixture Sensitivity: 22.2 GHz/RIU	[120] 2009
PCF	Zeonex elliptical liquid holes	Channel/length = 890 μm , width = 220 μm	PC-Defect mode	Ethanol, Relative sensitivity: 68.87 %	[145] 2018
PCF	ZeonexE48R circular liquid-core	Channel/450 μm	PC-Defect mode	NA, Sensitivity = 78.095 THz/RIU (x-polarization) or 110.931 THz/RIU (y-polarization)	[147] 2021
PCF	TOPAS based liquid-hole	Channel/470 μm	PC-Defect mode	NA, Sensitivity: 1827300 nm/RIU for analyte's RI 1.46.	[131] 2020

In Section 3.1, we discuss the precise measurement technique combining free-space microfluidic devices with THz-TDS [34]. However, the reflections from two microfluidic cavity surfaces can introduce interference fringes (etalon), interfering with the measurement data. The transmission line (TL) is an on-chip non-resonant structure based on the rapidly decaying field, which does not introduce interference fringes [148–150]. When TL is integrated with microfluidic channel [151,152],

the rapidly decaying THz field induced by liquid leads to the velocity and intensity changes of THz signal transmitted on the chip. This allows the derivation of the broadband THz time-of-flight (TOF) RI and attenuation coefficient of the liquid, enabling fast, low-loss, on-chip integrated measurement of the THz band liquid dielectric constant [153–156]. Existing THz microfluidic liquid chip-level systems based on evanescent field include microstrip lines (MSL) [157], planar Goubau

lines (PGL) [158,159], and coplanar waveguides (CPW) [160], with substrates made from materials like quartz [161,162], gallium arsenide (GaAs) [163], and polymers (e.g., Tsurupica [162], polyimide [164]). In the following, we present this THz microfluidic liquid chip-level system from both active and passive viewpoints.

The active TL integrates a THz antenna (transmitter) on the chip and is excited by femtosecond lasers [165–180]. In 2006, scientists first reported an active microfluidic sensing chip based on THz MSL. The THz waves are generated and detected by dual photoconductive antennas integrated on the chip, as illustrated in Fig. 16a. The microfluidics employs a container made of polyethylene (PE) material, bonded to the MSL channel. The system successfully characterizes the permittivity of water over the spectral range from 30 GHz to 1.5 THz. Furthermore, a THz active microfluidic TL chip with a flexible polyimide film has also been reported, used for measuring the dielectric constant of liquids in cylindrical capillaries, as shown in Fig. 16b [178]. In this case, the flexible polyimide film enables more precise measurements of liquids in microfluidics with curved boundaries, while the use of glass-walled capillary microfluidics eliminates the complex fabrication and packaging processes often associated with PDMS microfluidic channels. Another active microfluidic chip based on a PGL TL is shown in Fig. 16c (PC1 and PC2 are a pair of photoconductive antennas integrated on the chip) [179]. In this design, the propagation direction of the microfluidic channel and the PGL aligns, enhancing the overlap space between the evanescent field and the microchannel. A 100 μm microfluidic channel is created by curing PDMS on an SU-8 mold. The channel is then bonded to the benzocyclobutene (BCB) surface of the TL chip. Fig. 16c also shows the measured complex permittivity of the alcohol series liquids. Compared to the THz-TDS, this on-chip THz microfluidic TL has a narrower bandwidth.

In contrast to active TL microfluidic chips, in passive TL microfluidic

chips, the THz source do not integrated with the detector on the chip, requiring the THz waves to be coupled into the TL chip [181–202]. Fig. 17a shows a passive CPW TL overlaid by an SU-8 microfluidic on the chip [192]. A THz source (WR5.1, frequency range 140–220 GHz) from the vector network analyzer (VNA) and a pair of picoprobes were used. This passive chip successfully characterized the dielectric constant of deionized water. Fig. 17b presents another passive on-chip TL microfluidic chip. The microfluidic chip has a silicate wafer substrate, with a photolithographed metal CPW TL and a PDMS microfluidic channel fabricated using an SU-8 mold. The channel is clamped to the wafer with an acrylic glass strip, ensuring a good seal, and the required liquid volume is only 40 nL. This chip measured the dielectric constant of deionized water from 0.1 to 110 GHz at 22 °C, and the dielectric constant was found to be similar to that of protein solutions [203] and cell suspensions [204]. Table 9 summarizes the performance parameters of TL-based microfluidic technologies.

4. Microfluidic exploration

THz microfluidic devices not only enable biochemical sensing and detection, but also serve for multifunctional control of THz waves and broader applications. We introduce a wider range of novel applications based on THz microfluidic devices to highlight the importance and dynamic potential of THz microfluidic technology, as depicted in Fig. 18.

4.1. Optoacoustic

The liquid in the microfluidic chip can achieve the THz optoacoustic effect (THz-OA), as shown in Fig. 19. The microfluidic chip includes a temperature control module, with the materials being 5 mm thick PDMS and 200 μm PDMS/300 μm quartz, as illustrated in Fig. 19a [205]. By

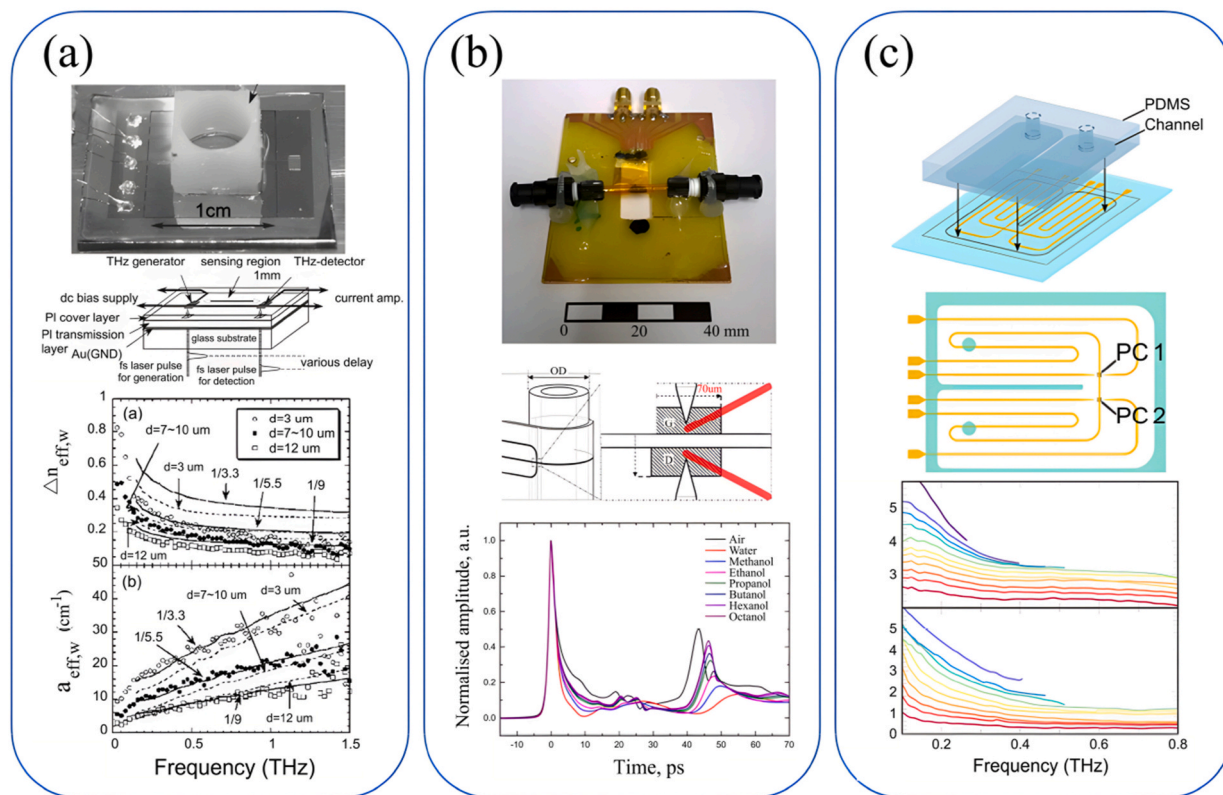


Fig. 16. a Schematic view of the MSL integrated with PE vessel microfluidic. Reprinted with permission from Ref. [157]; b Schematics of the PGL on flexible substrate wound on a capillary and reflection spectra. Reprinted with permission from Ref. [178]; c Schematic of the PGL chip with an microchannel, and measured complex permittivity of octan-1-ol (yellow), hexan-1-ol (orange), butan-1-ol (purple), propan-1-ol (red), ethanol (green), and methanol (blue). Reprinted with permission from Ref. [179]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

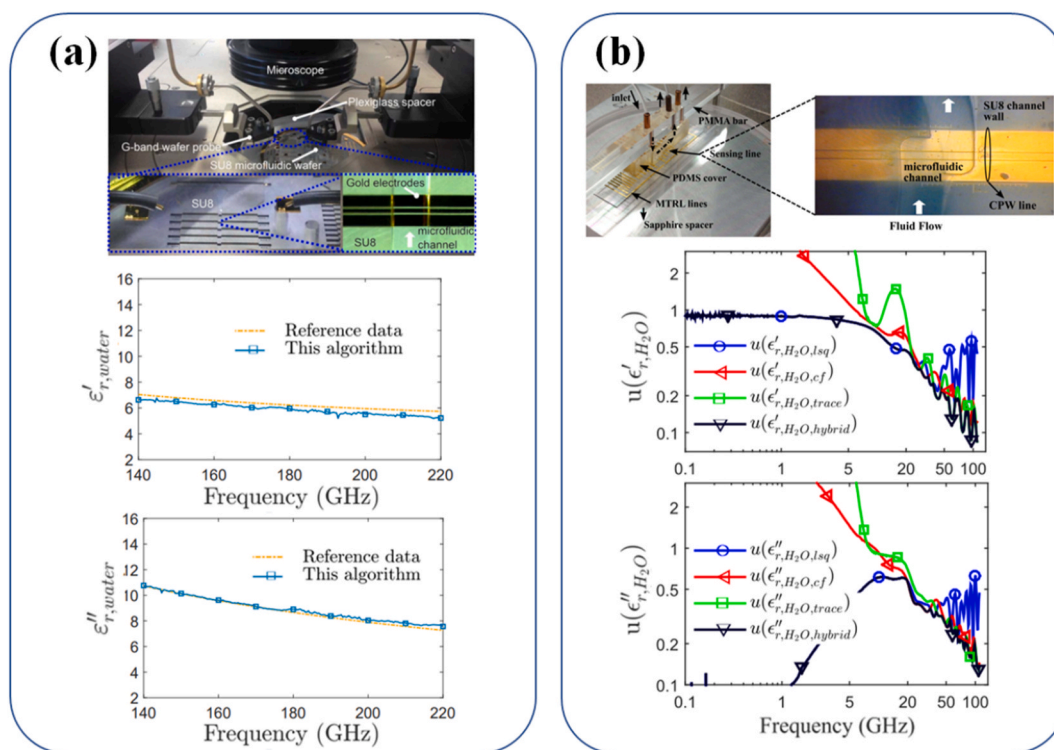


Fig. 17. a Microfluidic CPW-TL for 140 GHz–220 GHz complex permittivity of pure water measurement at 25.4°C. Reprinted with permission from Ref. [200]; b Photograph of the microfluidic channel filled with deionized water and corresponding complex permittivity. The dashed lines indicate the fluid flow. Reprinted with permission from Ref. [201].

Table 9
Performance of TL based microfluidic techniques.

THz microfluidic categories	Microfluidic material	Channel/chamber dimension	Mechanism	Liquid/performance	Reference (year)
Evanescent-field TL-active	Capillary quartz tube, Polyimide film substrate	10 μ m thickness wall 3 mm diameter (Hilgenburg GmbH)	flexible curved Goubau line with PCSs	A homologous series of primaryalcohols solution, TOF refractive index detection with improved SNR for TDS	[157] 2016
Evanescent-field TL-active	PDMS Quartz (substrate)	Chamber/100 μ m	Planar Goubau line with PCSs	Complex RI of propan-1-ol, ethanol, and methanol	[178] 2017
Evanescent-field TL-active	Glass substrate, PE vessel	Channel/6 mm diameter	Micro stripline with PCS	Complex permittivity of water	[179] 2006
Evanescent-field TL-passive	SU-8 channel	Channel/400 μ m high and 500 μ m wide	CPW	Deionized water, complex permittivity detection	[200] 2022
Evanescent-field TL-passive	SU-8 channel	Channel/70 μ m	CPW	Deionized water, complex permittivity detection	[201] 2017

using a pump, the liquid is driven into the microfluidic chip to avoid bubble generation because of temperature fluctuations [206]. The backside of the microfluidic chip is covered with a metal strip to block direct THz radiation from hitting the sensor, while permitting the acoustic signal emitted by the liquid to reach the sensor. A coupling agent is achieved by an ultrasonic gel. Here, the microfluidic thickness can be precisely controlled, allowing for accurate regulation of liquid [207,208]. THz time-domain signals for liquid water and different NaCl concentrations at 24 °C show that the amplitude changes in the THz radiation cannot effectively distinguish NaCl concentrations below 0.5 mol/L (see Fig. 19b), which is consistent with the observation that amplitude changes in the THz microfluidic OA system are not significant at 24 °C [205,209]. However, the OA signal measured by the THz microfluidic OA system at 5 °C changes significantly with increasing NaCl concentration, and the sensitivity was improved to 0.05 mol/L. Comparing the changes in THz amplitude with ion concentration between THz-OA and THz-TDS methods, it can be observed that the

sensitivity of the THz-OA microfluidic system is greater at 5 °C [208].

4.2. Particle capture

Individual particles with typical sizes of tens of micrometers are similar to the size of typical biological cells, making high-sensitivity detection of these particles crucial for the biomedical field. Compared to opto-microfluidics techniques, particles with diameters from 50 to 250 μ m and their concentration are suitable to be measured through THz microfluidics [210]. For example, the velocity measurement of silica ballottini particle with diameter of ~212 μ m in paraffin oil [211], or sucrose particles of size ~50 μ m [212] can be characterized at THz microfluidics owing to their distinct absorption peaks. These techniques of THz spectroscopy combined with microfluidic have been adapted in the pharmaceutical industry. To further enhance the sensitivity of terahertz spectroscopy for particles, innovative metamaterial microfluidics featuring energy hotspots have been proposed. For example, polystyrene

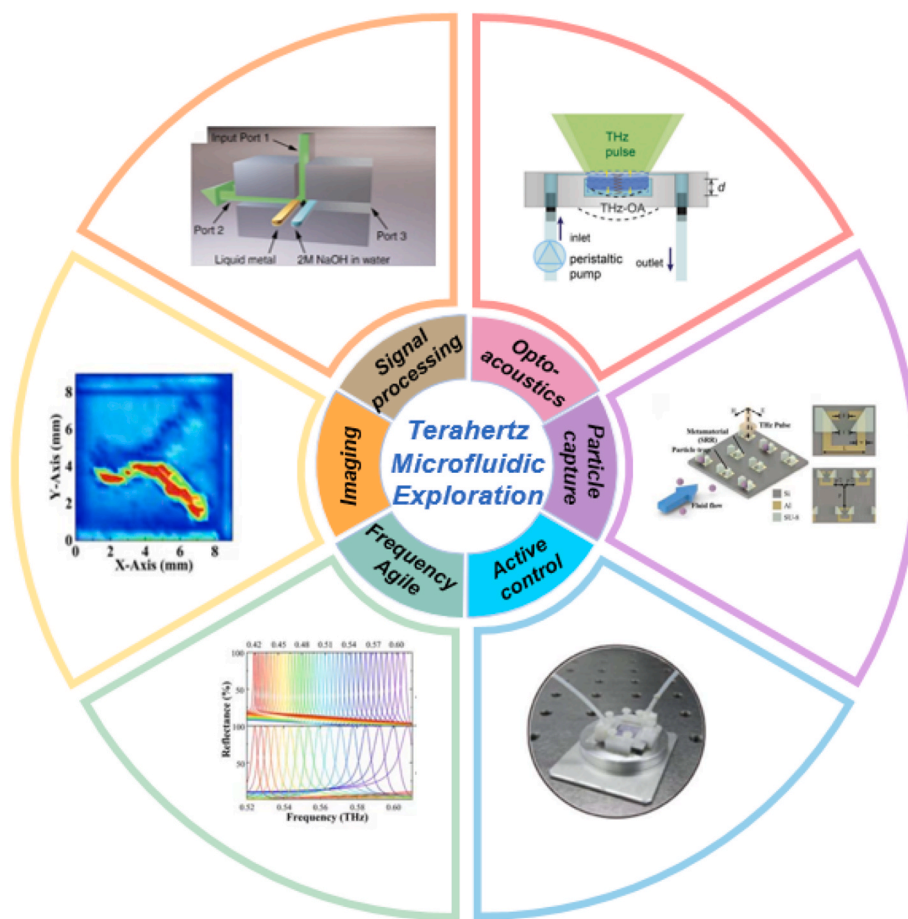


Fig. 18. THz microfluidic explorations.

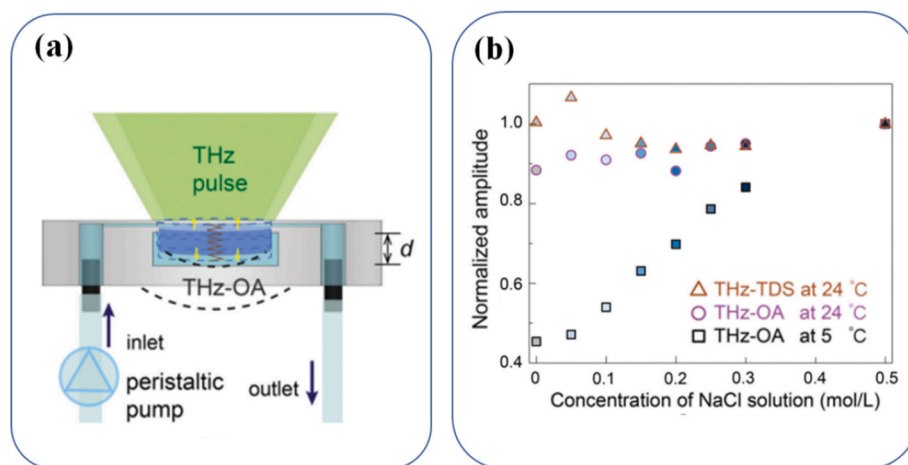


Fig. 19. **a** Diagram of THz-OA signal generation through a microfluidic channel by water circulating. Reprinted with permission from Ref. [205]; **b** Signals of various NaCl solution, obtained by THz-OA effect at 5 °C and 24 °C, and commercially THz-TDS system. Reprinted with permission from Ref. [205].

microparticles are water-suspended particles that have low absorption in the THz band and are commonly used to simulate cells. By designing microfluidic channels capable of capturing particles and integrating them into THz functional devices, precise positioning and high-sensitivity detection of target particles/biological cells can be achieved [213–224]. Ranjan et al. proposed a THz microparticle-capturing microfluidic device, as described in Fig. 20a [85]. The SRR array is arranged in a honeycomb grid, and trapezoidal pairs are made at the air gaps of the SRRs using MEMS technology to

capture suspended particles in the liquid during fluid flow. In the experiment, the distance between the two trapezoidal pairs was finely designed to capture 20 μm -diameter particles in a liquid IPA. The particle capture rate for this structure experimentally reached 15 %, corresponding to a resonance frequency shift of 10 GHz. In addition, the precisely designed plasmonic antenna-integrated microfluidic channel can directly manipulate particles with micrometer diameters, with the required liquid volume on the picoliter scale, as shown in Fig. 20b [225–227]. The THz waves pass through a plasmonic X-shaped antenna,

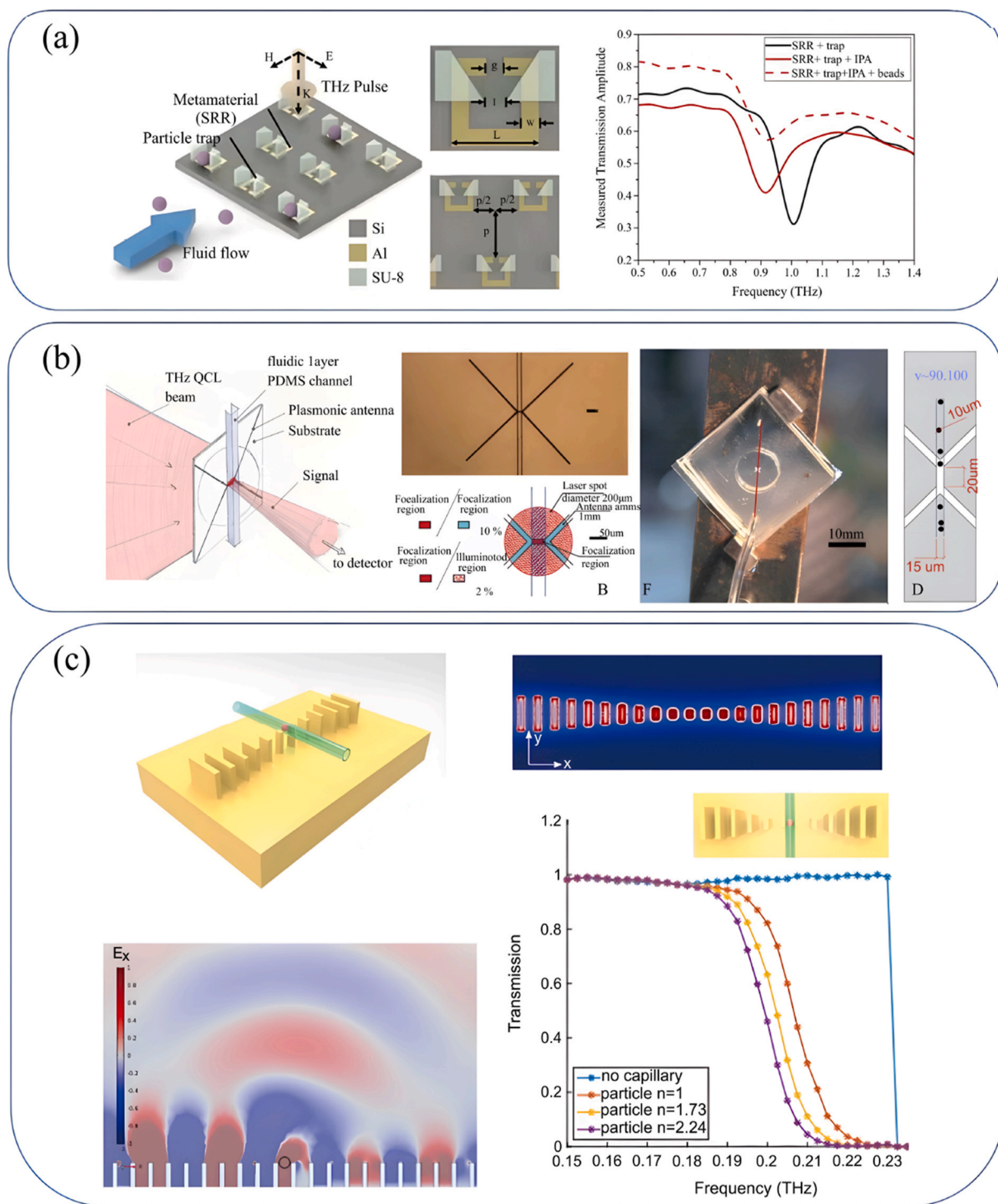


Fig. 20. a The proposed microfluidic metasensor with dual trapezoidal microstructures located at the SRR gap. Reprinted with permission from Ref. [85]; b On chip X shaped chip integrated with microchannel aligned over a plasmonic antenna to realize real time particle capture. Reprinted with permission from Ref. [228]; c Tapered spoof SPP domino waveguide with particles in capillary. Reprinted with permission from Ref. [128].

where the field energy achieves its strongest at the intersection of the X-shape [228,229]. The hollow X-shaped structure is aligned and closely contacted with the PDMS microfluidic channel to ensure a strong overlap between enhanced THz energy and particles passing through the microfluidic channel. The space of the interaction region is 15 pL. Fig. 20b presents the measurement results of a single polystyrene particle (10 μm diameter) passing through the integrated microfluidic channel (15 μm wide) in the X-shaped antenna. When the particle passes

through, the THz transmission intensity is higher due to the low-loss characteristics of the particle than that of water flows, and the real-time dynamic transmission of the particle over time is clearly observed. Therefore, this system successfully combines plasmonic-enhanced structures with standard microfluidic channel technology to achieve real-time monitoring of particle movement. Furthermore, by making slight modifications to the domino waveguide structure from Section 3.3 (Fig. 13c) and using a gradient design, the

width of the domino waveguide can be gradually reduced to the diameter of a single particle, enabling detection of microparticles passing through capillary microfluidic channels, as illustrated in Fig. 20c. Theoretically, placing a 90 μm diameter particle (refractive index of 1.73) at the intersection of the capillary microfluidic channel and the domino waveguide waist provides a detection sensitivity of 0.35/RIU, which is twice the sensitivity of the domino waveguide with uniform width (0.15/RIU) [128]. From these examples, it is evident that THz microfluidic particle detection technology has been validated in the laboratory. These microfluidic chips enable THz microfluidic spectral detection at the scale of several micrometers, laying the groundwork for actual applications.

4.3. Active amplitude control

Microfluidic liquids can serve both as samples to be tested and as active variables for controlling THz waves. Yao et al. designed a microfluidic metamaterials to modulate THz intensity by adjusting the water content in the liquid and changing the damping effect (loss). Fig. 21a demonstrates the experimental results of THz transmission intensity modulation with varying water content in an IPA mixture (flow rate 0.25 mL/h) [230]. The change in THz wave intensity is due to the damping effect caused by higher absorption of water (compared to IPA). The proposed structure can also be used to detect residual water content in various chemical or medical solutions. Researchers from Zhejiang University introduced gold nanorods (GNRs) into the liquid microfluidic platform to achieve efficient THz wave intensity modulation for detecting solution concentrations at the ppm level. As the power of the infrared laser (wavelength 808 nm, matching the resonance peak of GNRs) increases from 0 to 1200 mW, the THz transmission amplitude gradually decreases [231]. This modulation effect originates from the thermal effects and surface plasmon resonance phenomena caused by

GNRs absorbing infrared radiation [232,233]. Then, 20 μL of avidin solution containing 58 $\mu\text{g/mL}$ GNR concentration was driven into the microfluidic chamber. Fig. 21b shows the THz transmission versus avidin concentration under a 600 mW laser power [234], with a detection limit of 0.1 ppm and the ability to overcome the disturbance caused by strong absorption of water [233]. Researchers also used transparent cyclic olefin copolymer (COC) [235–237] microfluidic chips to achieve THz modulation properties of Fe_3O_4 , TiO_2 , and Ag nanocolloids by using magnetic, electric, and optical control, as shown in Fig. 21c [238]. Three nanocolloids show modulation effect from 0.3 to 2.4 THz, with average modulation depths of 36 %. These results enrich THz microfluidic devices application and provide new ideas for the development of functional devices that modulate THz waves using liquid materials.

4.4. Frequency-agile

The reconfigurable frequency-agile devices can actively control the resonant frequency of THz waves and have potential applications in filters, fingerprint spectrum amplifiers, and multiplexing technologies. A new modulation method for frequency-tunable devices involves changing the thickness of the microfluidic layer, which offers advantages of low cost and simplicity. For instance, researchers at Nanyang Technological University showcased a frequency-tunable function based on a PDMS microfluidic liquid metal metamaterial absorber. The microfluidic layer consists of periodic columnar structure cavities embedded in Si material. Liquid metal is driven through the microchannel at the bottom and fills the columnar Si material cavities, as depleted in Fig. 22a. The height of fluidic columns can be adjusted by regulating the space pressure at upper inlet, thus changing parameters of resonators, leading to a resonance frequency shift. As the height increases from 30 μm to 100 μm , the frequency of peak is tuned from 0.246

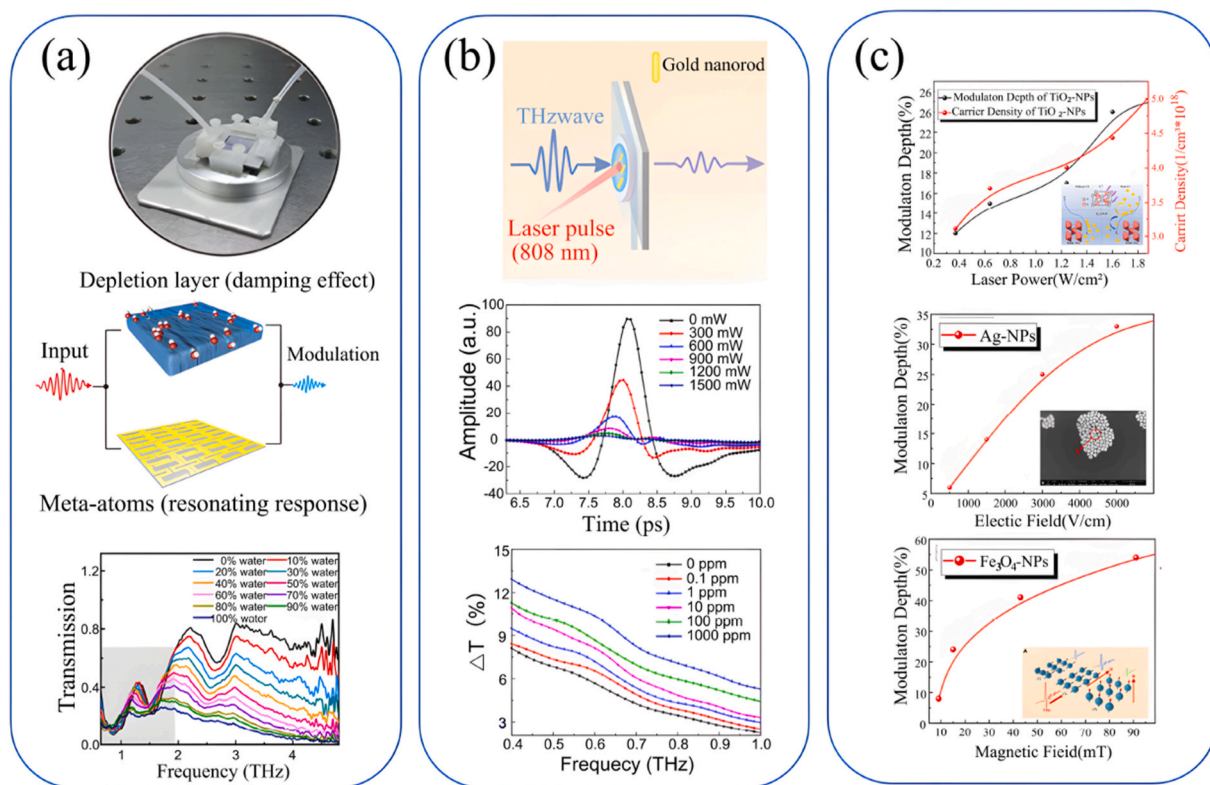


Fig. 21. a Photograph of microfluidic MDM device and its parallel modulation mechanism. Reprinted with permission from Ref. [230]; b THz microfluidic optical modulator based on Si microchannel filled with GNR solutions and detection of avidin aqueous solutions with different concentrations. Reprinted with permission from Ref. [234]; c THz microfluidic modulator based on three nanosols (Fe_3O_4 , Ag, and TiO_2) by using magnetic, electric, and optical fields control. Reprinted with permission from Ref. [238].

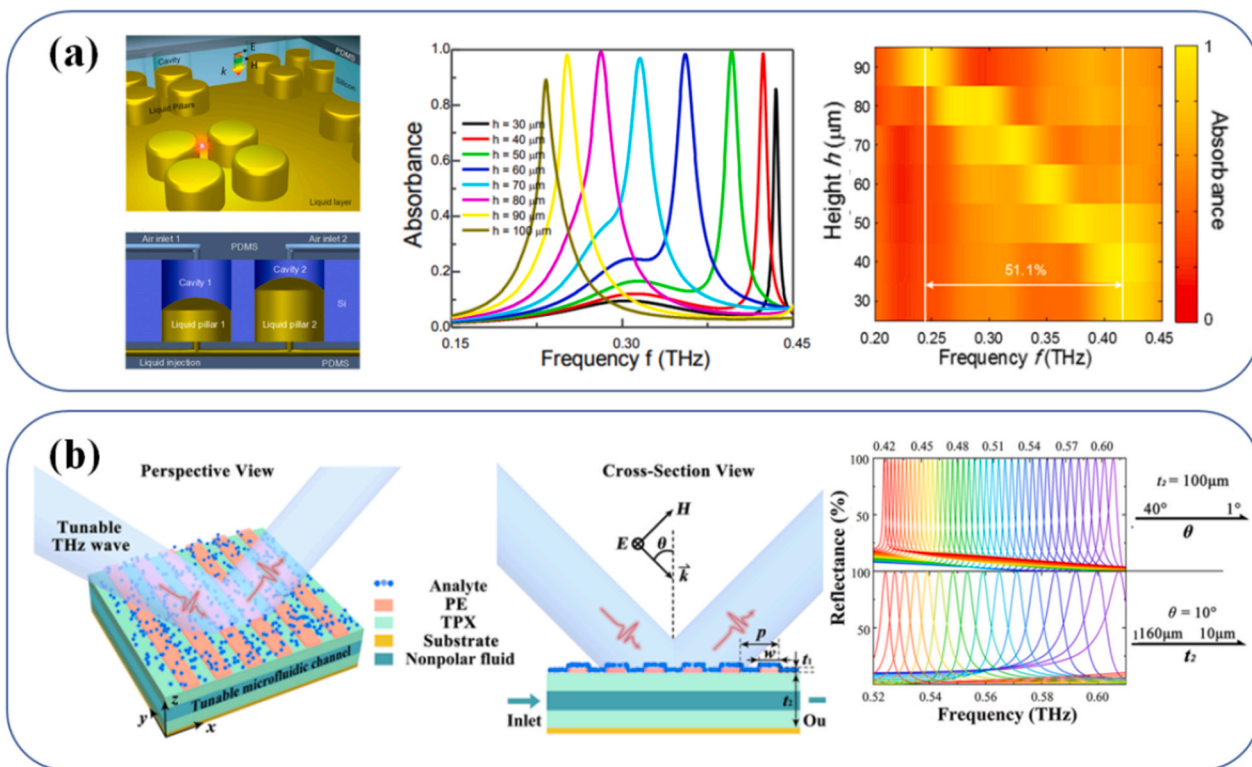


Fig. 22. **a** Frequency agile microfluidic device based on the tuning height of liquid-metal-pillar array. Reprinted with permission from Ref. [239]; **b** the reconfigurable multiplexed frequency agile metasensor by tuning thickness of microfluidic layer, and THz spectra by changing θ and microfluidic thickness t_2 , respectively. Reprinted with permission from Ref. [245].

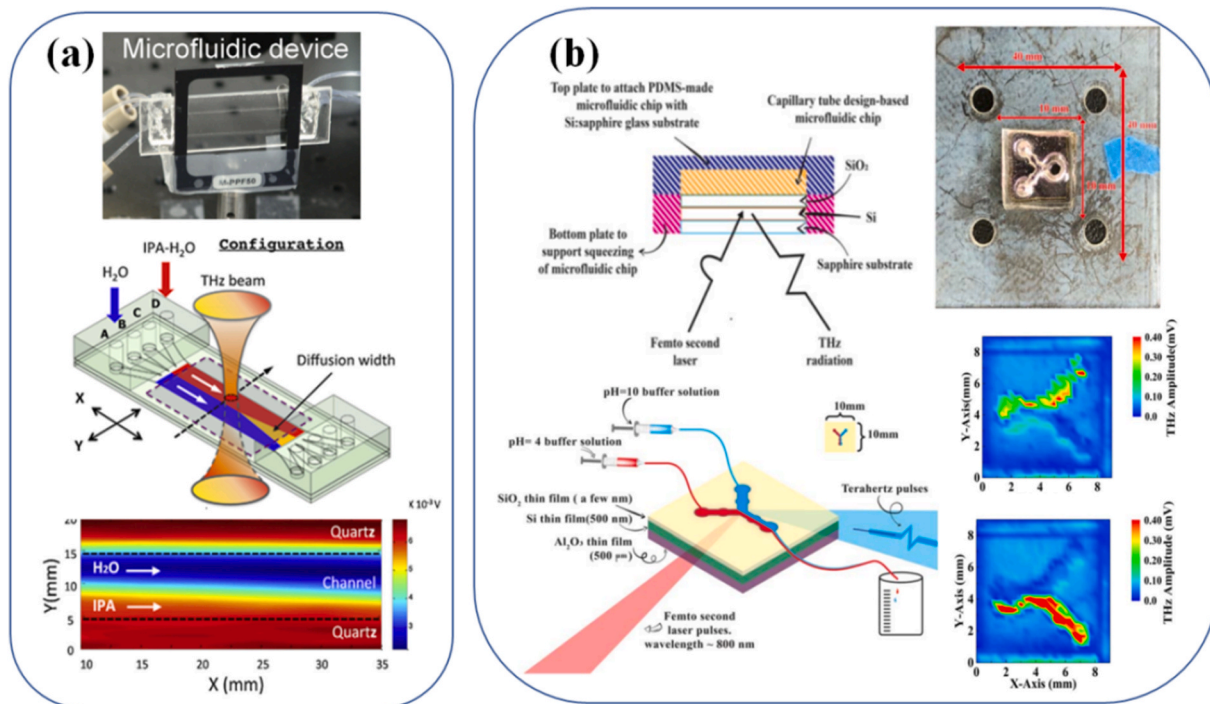


Fig. 23. **a** THz image of water and IPA liquids based on microfluidic chip with quartz micromachined multi-inputs and outputs. Reprinted with permission from Ref. [32]; **b** Schematic arrangement of the preparation of sensing chip including a si-sapphire plate and top attached microfluidic chip. Bottom left: buffer solutions liquids (pH = 4 and 10) driven from inlets and extracted from the outlet. Bottom right: Imaging maps at two fluid rates (0.07 ml/min, 0.15 ml/min) for different pH liquids mixture in the microfluidic channel. Reprinted with permission from Ref. [248].

to 0.415 THz, and the absorption rate remains above 90 % [239]. Therefore, microfluidic technology can continuously control the height of fluidic columns, achieving broadband tunable resonant frequencies. Researchers from Xiamen University achieved fingerprint spectrum amplification using a microfluidic structure. The device includes a PE grating structure and a microfluidic channel encapsulated by a TPX window [240–243]. The liquid in the microfluidic system is a non-polar liquid with a RI similar to that of TPX. MEMS technology is used to control the thickness of the microfluidic layer, achieving broadband resonant frequency multiplexing by combining thickness scanning with angle scanning, as shown in Fig. 22b. Another contribution also achieved a similar broadband resonant frequency multiplexing function by combining microfluidic thickness scanning with grating period parameter scanning [244]. These functions have been successfully applied to signal amplification of molecular THz fingerprint spectra [245–247].

4.5. Imaging

THz can also achieve real-time imaging of liquids in microfluidic channels, thus enabling monitoring of the liquid state. For example, Fig. 23a shows a four-channel THz microfluidic chip that can achieve real-time imaging of liquids. The microfluidic chip encapsulates two 1 mm thick three-input combined main channels made of fused silica microfluidic channels with a depth of 50 μm , a width of 1 cm, and an internal volume of approximately 20 μL . When water and IPA are injected at the same flow rate into two independent liquid inlets, a clear boundary forms between the two liquids in the main channel. When the microfluidic chip coincides with the focal plane of the Schottky diode THz detector, a 2D THz imaging result of the IPA-H₂O interface can be observed, which allows for real-time monitoring and imaging of liquid diffusion, and rapid dynamic response at the liquid intersection (response time of 10 ns) [32]. Japanese scientists had used a THz microfluidic chip to achieve imaging and identification of liquids with different pH values. Fig. 23b demonstrates a THz microfluidic chip used for pH imaging [248]. The chip includes two input channels and one output channel, with the microfluidic channel material being PDMS [249–251], and the substrate is a semiconductor THz antenna that absorbs incident femtosecond pulses and emits THz waves reflected from the surface, as shown in the upper right corner of Fig. 23b. When different buffer aqueous pH solutions flow along the microchannel and interact with the substrate antenna, acidic H⁺ and basic OH[−] ions cause a shift in the antenna surface potential, resulting in different carrier acceleration changes. Consequently, the intensity of the generated THz wave will change as well. In Fig. 23b, buffer solutions (pHs are 4 and 10) are injected into the microfluidic chip. The mixed pH solution is collected at the microfluidic channel outlet at the other end. THz microfluidic images at two liquid fluidic rates (0.07 mL/min, 0.15 mL/min) are also shown in Fig. 23b. The data acquisition time was 32 min, with a scanning area of 56,700 $\times$ 56,700 points (resolution is 333 μm). The experimentally dynamic response of solutions with different

pH values. The results indicate that the THz microfluidic imaging chip can real-time monitor interactions within various fluid solutions, further enabling quantitative study of reactions of molecular in the biochemical field.

4.6. Signal processing

Microfluidic channels were combined with THz waveguides to achieve a reconfigurable, scalable, and multifunctional THz carrier signal processing device [252]. The microfluidic channels are made of glass tubes with a rectangular cross-section, filled with two types of liquids: liquid metal and NaOH electrolyte. The microfluidic channels of both liquids are integrated at the bifurcated exits of the two outputs of T-type waveguide, as illustrated in Fig. 24. Large absorption coefficient is observed in the microfluidic channel with NaOH electrolyte. The insertion and extraction of the microchannel (filled with liquid metal) can be driven electrically [253–255]. When this microfluidic channel is put in, the lower loss part of the waveguide propagation region is a metal wall. As the liquid metal microfluidic channel is withdrawn, the lower part of the waveguide is the NaOH electrolyte microfluidic channel wall, resulting in very high propagation loss, thus achieving a reconfigurable waveguide power switch function [252,256]. Furthermore, the device was used in a THz communication test platform, which generated multiple-carrier-frequencies modulated data streams of 1 Gb/s. Experimental results confirmed the feasibility of data transmission and switching through the device, and the signal extracted from the output port exhibited a very low bit error rate. Table 10 summarizes the applications and explorations of THz microfluidic devices.

5. THz microfluidic fabrication

5.1. Chamber shaped microfluidic

PDMS is widely used in microfluidic devices due to its biological permeability, helping to remove liquid bubbles while maintaining biological activity during microfluidic measurements. SU8 is a photoresist that cures when exposed to UV light and has good plasticity [257]. The typical fabrication process of PDMS microfluidic devices is as follows: first, standard cleaning is performed, then negative photoresist SU8 is applied directly to the Si substrate and heated, followed by exposure and development to form the SU-8 mold. Next, the PDMS liquid is poured into the SU8 mold, and then heated to obtain the PDMS layer. Finally, once the PDMS layer is fully cured, it can be easily peeled off. For the metasurface-integrated PDMS microfluidic devices, after surface modification with oxygen plasma on the metasurface, transforms the hydrophobicity at the interface into hydrophilicity. Then, by aligning and baking the metasurface and PDMS, a metasurface integrated with PDMS microfluidics is obtained. Fig. 25a–c shows the entire process and bonding technique.

For the microfluidic metasurface involving Si material pattern

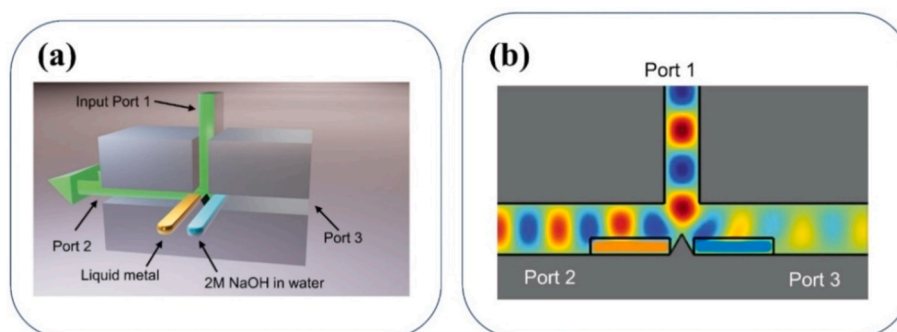


Fig. 24. a A T-junction variable-ratio power splitter with liquid metal and highly absorbing liquid microchannel. Reprinted with permission from Ref. [252]; b Numerical simulations show right side absorbing electrolyte induced signal change (Port 3). Reprinted with permission from Ref. [252].

Table 10

Applications and explorations of THz microfluidic devices.

THz microfluidic categories	Application	Microfluidic Material and formation	Dimension	Liquid/performance	Reference (year)
Transmission	THz-OA	Rear surface: PDMS Front surfaces: PDMS or quartz	Circle with a diameter 3 mm.	CaCl ₂ , NaCl solution Sensitivity = 1.5 amp/(mol/l)	[205] 2021
Transmission	Particle Capture	Quartz SU-8 microfluidic channel and trapezoidal particle trapping, PET cap	two trapezoids distance t = 5 μ m, 25 μ m	Polystyrene particles in IPA solution. 10 GHz frequency shift for 15 % particle trapping rate	[85] 2017
Transmission	Particle Capture	PDMS fluidic layer with 500 μ m thickness	Channel/15 μ m*40 μ m*25 μ m, 15 μ l volume	Polystyrene microparticles 10 μ m and 20 μ m in IPA and water,	[228] 2014
Waveguide	Particle Capture	Quartz capillary	Channel/inner diameter 120 μ m	1.89/RIU, 1.54/RIU (tapered); 90 μ m Particle: 0.15/RIU homogeneous, 0.35/RIU	[128] 2017
Transmission	Active Control	Quartz-Si (cap)	Chamber/35 μ m	IPA-water, detection limit, 60 μ l water in 1 mL of IPA	[230] 2019
Transmission	Active Control	Si channel	Chamber/Si wafer 2 mm-thick quartz A drop of 20 μ l GNR aqueous solution of 58 μ g/ml was inserted into channel	Avidin aqueous Solution, LOD 0.1 ppm. 808 nm pulsed laser/808 nm absorption peak GNR-based THz Modulator	[234] 2020
Transmission	Active Control	COC	Chamber/10 mm*4 mm*0.3 mm	Maximum modulation depths for TiO ₂ , Ag and Fe ₃ O ₄ under the UV EF MF control is 24 % 33 % and 54 %	[235] 2022
Reflection	Frequency Agile	PDMS(cap)-PDMS(substrate) etched Si (spacer)	Pillar/90 μ m	Liquid metal, 0.246 to 0.415 THz tunable (the liquid metal height from 30 to 90 μ m)	[239] 2017
Reflection	Frequency Agile	TPX + metagrating	Channel/10 μ m–160 μ m	Channel thickness from 10 μ m to 160 μ m, with frequency tunability from 0.525 to 0.625 THz	[245] 2023
Transmission	Imaging	PDMS-made capillary	Channels/dimension of sensing chip: 10 mm $\times$ 10 mm	THz imaging of buffer solutions with pH = 4 and 10 (2D contour)	[248] 2021
Transmission	Imaging	Quartz microfluidic device	4 port Channels (depth:50 μ m; width: 1 cm), liquid volume: 20 μ l	Flow rate: 100 μ l/min; 2-D THz chemical Image with an IPA-H ₂ O interface IPA concentration Sensitivity ~3.28 %/mV	[32] 2013
Waveguide	Signal Processing-Active T-junction power splitter	Liquid metal and 2MNaOH in water plug	Glass tubes/200 μ m by 2 mm	20 dB of contrast for electrically switch; >100 GHz Bandwidth; 1 Gb/s data @200 GHz (BER <10 ⁻⁹)	[252] 2018

etching, the typical fabrication process is as follows: first, spin-coat photoresist onto a Si substrate, then expose it under UV light using a patterned plastic mask. After development, reactive ion etching and removal of photoresist is carried out. Then the pattern is transferred to wafer. Next, the upper and lower PDMS layers are produced using the aforementioned photolithography technique. SU-8 is coated on a Si and exposed by using UV light and a mask. After development, the patterned SU-8 mold is obtained. PDMS is injected into the mold, transferring the pattern to PDMS. After curing, PDMS is peeled off the substrate. Finally, the upper PDMS layer undergoes plasma bonding with the Si substrate, and the metasurface structure is created by plasma bonding with the bottom PDMS layer.

PET is commonly used as a sealing material in microfluidic devices. The uncrosslinked SU-8 typically flips the PET and bonds it to the top of the metasurface chip (Fig. 25d). The chip is then exposed to ultraviolet, crosslinking the adhesive SU-8 to form a strong seal that prevents liquid leakage.

For integrated microfluidic TLs [151], the typical manufacturing process is as follows: After preparing the metal film pattern for the TL, a SU8 photoresist layer is spin-coated onto a substrate. Then, the whole substrate is soft-baked, followed by exposure under a photomask. After exposure, a post-bake is performed to finally form the SU8 channel. The alignment accuracy of the microfluidic channels and TL structures manufactured using the SU8 process reaches within 1 μ m [154].

5.2. Channel/capillary shaped microfluidic

The microfluidic channels are more complex to fabricate than

microfluidic chambers due to their smaller cross-sectional area. The micrometer-scale channels are created by using a UV-cured SU8 pattern and an adhesive layer between the PDMS fluid layer (as illustrated in Fig. 26a). UV-curable epoxy resins are commonly used for bonding [258, 259]. The bonding technique typically involves activation (oxygen plasma), then 3-aminopropyltriethoxysilane reaction of the metallized metasurface, which then contacts the plasma-treated PDMS fluid layer [260], forming the PDMS bottom fluid layer containing the microfluidic channels. They are aligned and attached to the COC substrate.

Microfluidic channel on the hotspot of the metasurface is shown in Fig. 26b. Initially, a corner array pattern is created on the substrate using photolithography. The microfluidic multi-channel (with width/thickness of 15 μ m/15 μ m) is patterned at each corner gap. A SU-8 photoresist spun onto the substrate is used as an adhesion and sealing layer, covering the metasurface with the microfluidic channels. Finally, the microfluidic channels are exposed to UV light for strong sealing. Fig. 26c shows another chip with microfluidic channels, containing an 11 $\times$ 11 metasurface array and a separate microchannel.

In multi-microchannel systems, several input holes are usually drilled in the injection area of the chip, and PDMS layers with holes are bonded to the substrate. Then, PTFE tubes are inserted into the outlet and inlet holes, for fluid input and output respectively. 3D printing can also be used to develop microchannel structures made of PDMS, where CAD software and 3D printer are used to design and print a 3D microfluidic chip with inlets and outlets, respectively.

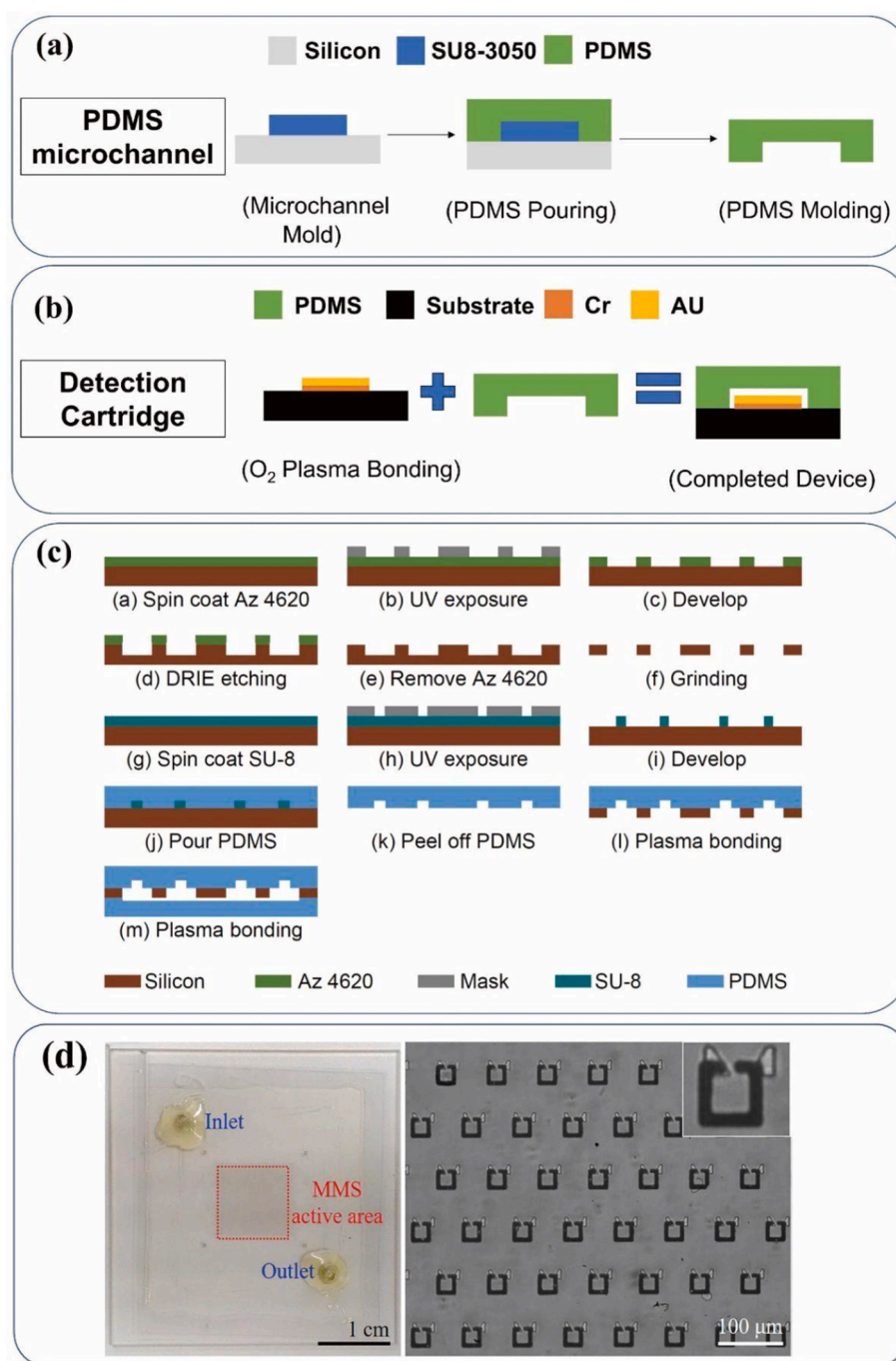


Fig. 25. **a** PDMS microchannel fabrication. **b** Metasurface PDMS microfluidic chip. Reprinted with permission from Ref. [33]; **c** Multilayer microfluidic with Si pattern and PDMS. Reprinted with permission from Ref. [239]; **d** The trapezoidal PDMS traps in the SRRs active area fabricated by MEMS. Reprinted with permission from Ref. [85].

6. Perspective and conclusion

Microfluidics, or lab-on-a-chip, integrates multiple functions of laboratory to a chip, characterized by miniaturization and integration, allowing for detection of minute amounts of fluid. Microfluidic technology has the advantages of fast analysis speed, full automation of sample analysis, and increasing integration scale, offering great potential of low-cost, compact, and disposable detection devices, as shown in Fig. 27a [261–273]. Many techniques have been applied in microfluidic chips, such as mechanical, optical, and electrochemical methods. THz microfluidic is the important complementary method from view of spectrum. In addition, THz technology offers non-contact,

non-destructive, high-sensitivity, and rapid sensing capabilities, with the vibrational frequencies of many bio-molecules also located at THz range. Advanced THz biosensors integrated with microfluidic chips exhibit clear advantages such as miniaturization, non-invasiveness, and ease of operation (see Fig. 27b and c).

The structure based on metamaterials can offer high-quality factors and achieve miniaturization. Over the past decade, researchers had developed metamaterial-based THz sensors, which prevents experimental samples from being exposed to atmospheric conditions, thus avoiding biological contamination. This technology allows for testing of micro-liter or nano-liter volume samples, which provides an effective solution for expensive liquids. Recently, there are some practical case

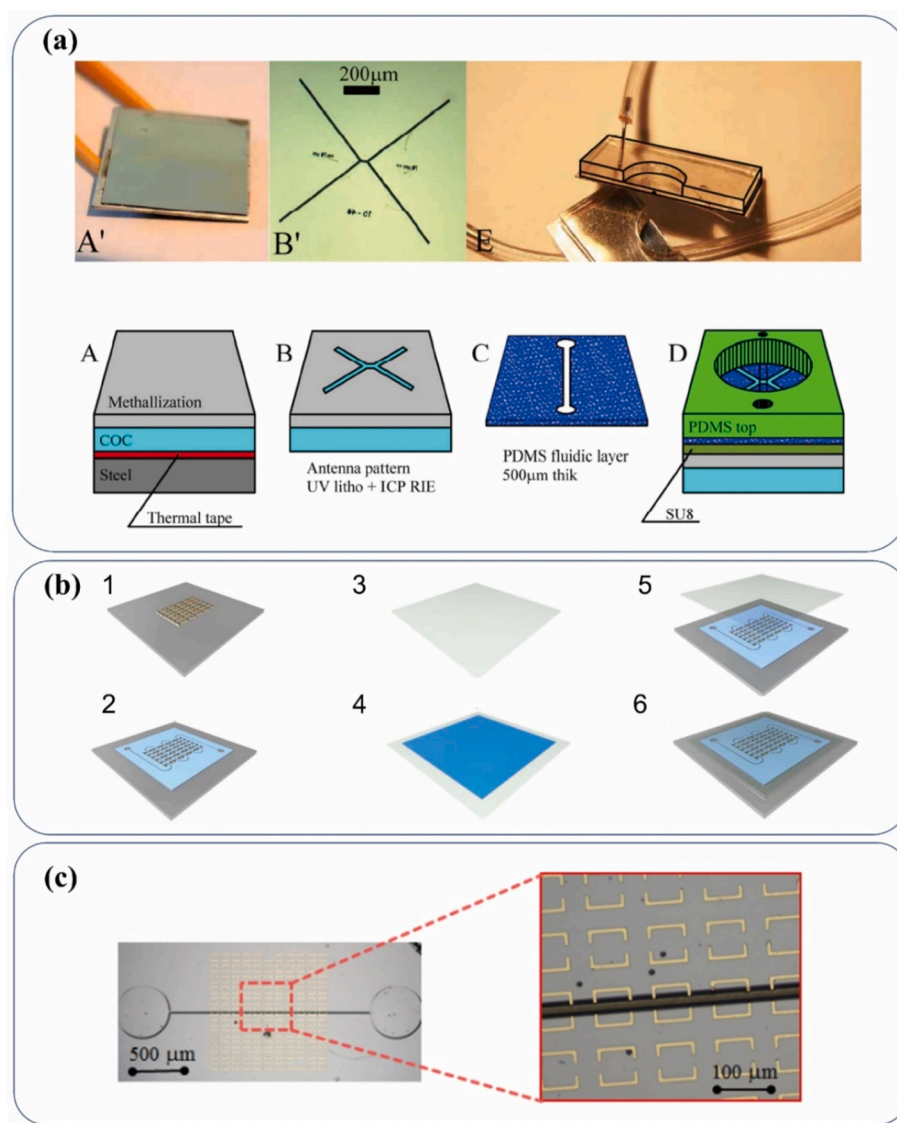


Fig. 26. **a** Schematics representation of the microparticle channel chip fabrication processing. Reprinted with permission from Ref. [228]; **b** Fabrication procedures of the microchannel through bowtie hot spot. Reprinted with permission from Ref. [93]. **c** A fabricated microfluidic chip with 11×11 arrays of meta-atoms and a single microchannel. Liquid solution is penetrated into this channel by dripping to a hole with the diameter of 500 μm . Reprinted with permission from Ref. [87].

studies that validate the real-time capability of these systems. For instance, in Chongqing, China, southwest hospital has successfully used THz microfluidic chip to investigate the MUC1 (MUC1 is a cell-membrane-associated glycoprotein in the mucin family with high molecular weight) and aptamer binding reaction, which has led to discerning diagnostic aptasensors for detecting and monitoring tumor progression. It is mutually complementary with those existing approaches in a label-free manner [40]. Moreover, Shanghai Academy of Environmental Sciences has applied THz microfluidic metasensors combined with the multivariate fusion model (principal component analysis and the neural network classification algorithm) to the recognition of volatile organic compounds (VOCs) in soil. With the limit of detection 2900 mg/kg, which reaches the standard of actual sample concentration, our results provide a new THz meta-sensor platform to trace the detection of VOCs in soil, and have been used to identify hazardous wastes in illegal dumping [25].

To further reduce the losses due to water which is a major hindrance for THz spectroscopy in microfluidic, the nonlinear optical crystal based THz-microfluidic channel chip was proposed. At this design, the microfluidic channel is integrated with THz emitter (nonlinear optical

crystal substrate). Femtosecond pulse laser beams are focused onto substrate (nonlinear optical crystal), and THz-TDS and THz imaging have been realized on solution (picoliters volume) of sub-THz wavelength scale with limit of detection of $\sim\text{fmol}$ or $\sim\text{mg/L}$ by setting microfluidic channel in the vicinity of the THz source (nonlinear optical crystal substrate) generated at the irradiation spots [87,89,90]. Moreover, the losses due to aqueous solution in microfluidic can be partly decreased using the frozen spectroscopic technique. Absorption of ice is much less than that of water [45].

The microfluidic channels are made of biocompatible materials, ensuring the safety of the samples being tested. New materials are used for microfluidic structure to protect both the substrate and the integration of the microfluidic channels with the substrate. Generally, microfluidic chips are fabricated using simple manufacturing processes and cheap materials. For example, more recently, a THz compatible, surface tension confined PTFE based microfluidic flow cell is presented by the researchers from University of Southampton [26]. Compared to PDMS which is much faster to produce but has wide variability in absorption in the THz band, PTFE is a material that has excellent chemical resistance and bio-compatibility, along with low absorption at THz

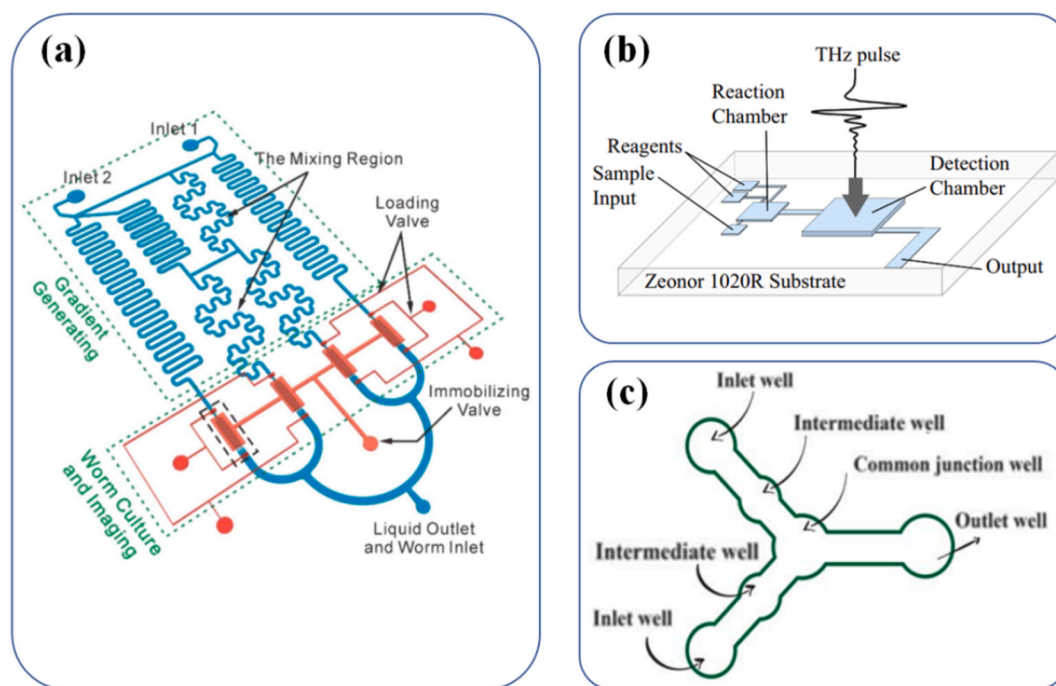


Fig. 27. **a** Diagram of the optical microfluidic chip. The device consists of the generating and the imaging sections. Reprinted with permission from Ref. [273]; **b** A THz microfluidic device which includes fundamental lab-on-chip function. Reprinted with permission from Ref. [42]; **c** Layout of microfluidic chip with reaction chamber. Reprinted with permission from Ref. [248].

frequencies and the low surface free energy characteristic. It is easily machinable making prototyping quick, and its hydrophobicity can aid water confinement in compression sealed devices. A novel combination of plasma treatments of PTFE to provide a strongly localized contrast in wetting characteristics on a single substrate leads to realization of a flow-cell with optimized path-length of aqueous media that exploits surface tension forces to achieve easy confinement of the liquid medium, enabling terahertz spectroscopic measurements of aqueous solutions of biological macromolecules. THz-TDS measurements of a range of concentrations of aqueous BSA are shown to demonstrate the device's efficacy of probing protein hydration dynamics in a transmission configuration. A non-linear trend in the concentration dependent absorption coefficient indicates not the simple exchange of water with protein volume but the presence of a third component (in addition to protein and bulk water volume): hydration shell water, which significantly enhance the performance of THz microfluidic platforms.

Another emerging application of THz microfluidics is in particle-based manipulation with potential applications aimed at the food and pharmaceutical industry, such as silica ballottini particle ($\sim 212\ \mu\text{m}$) suspended in paraffin oil [211], or sucrose particles of size $\sim 50\ \mu\text{m}$ [212]. By utilizing particle-based control tools such as capillary pipettes, researchers can process particles on a chip, providing an isolated environment that minimizes external stimuli. THz microfluidics has successfully detected micrometer-sized microparticles, attracting many research activity [85,128,228].

In immunology, microfluidic technology has become a valuable tool for protein detection in clinical diagnostics and biomedical research. THz metamaterial-based immunosensors have made significant progress in the recognition of specific proteins. Future immunology microfluidic chip designs aim to integrate immunoreactors and electrophoretic separation into microchannels, using THz spectroscopy to measure protein concentration. This design, which combines specific biochemical reactions with microfluidic separation technology, offers significant advantages for precise biochemical analysis [274,275]. Recently, Xie et al. combined nanoscale Au film metamaterials with immunocompetitive assay to design a novel THz immunocompetitive analysis system. The

overlap between THz radiation and the complex substance of gold particles and gold film metamaterials leads to changes in spectral transmission, which is used for the qualitative analysis of chloramphenicol residues. This provides a new perspective for THz biosensing and offers a potential for THz microfluidic immunological metamaterial technologies [276].

The THz microfluidics are expected to drive the progress of compact THz sensors. Most THz biosensors based on microfluidic chips cannot perform real-time monitoring because they cannot function as independent systems. As THz technology advances, portable THz spectrometers are set to fulfill real-time measurement scenarios, such as those in practical diagnostics and Point-of-Care Testing (POCT). Microsystems integration is an important approach to miniaturization and portability. To achieve a fully integrated microsystem, not only the sensors need to be integrated, but also the analysis and testing components. In the future, the next generation of THz biosensors based on microfluidic chips should be fully integrated devices capable of offering real time diagnostics in POCT, eliminating the need for laboratory analysis. The future direction involves addressing current challenges and progress toward ultra-miniaturized, highly integrated THz sensors, wearable devices, non-invasive solutions, and real-time monitoring capabilities. Furthermore, if such biosensors can be integrated with smartphones, they will have enormous potential for applications in daily life. For supplier of THz microfluidic products, Shenzhen Institute of Terahertz Technology and Innovation, City University of Hong Kong as well as Creator Electronic Limited (Hong Kong), can also provide several commercial THz microfluidic disposable modules (Fig. 28) [277]. THz microfluidic devices have already provided unique functions that are not feasible within the optical range, enabling new THz applications, such as photoacoustic sensing, active control, 3D PCs, and wireless 6G sensing [278]. These advances are expected to have a widespread impact on fields such as THz biomedicine, communications, physics, and material science [279].

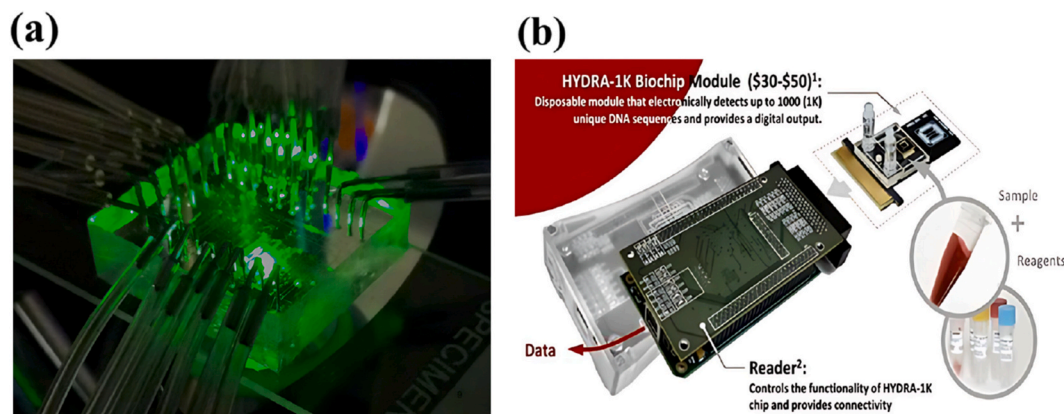


Fig. 28. (a) Microfluidic chip biosensor (b) Commercial THz microfluidic disposable.

CRediT authorship contribution statement

Lin Chen: Writing – original draft, Funding acquisition. **Yifei Song:** Writing – review & editing. **Darren Chin Yao Lim:** Writing – review & editing. **Yiming Zhu:** Writing – review & editing, Visualization, Supervision, Funding acquisition. **Songlin Zhuang:** Conceptualization. **Ranjan Singh:** Writing – review & editing, Visualization, Supervision.

Notes

The authors declare no competing financial interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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