

REVIEW

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# Terahertz spectroscopy in biomedical field: a review on signal-to-noise ratio improvement

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## Abstract

With the non-ionizing, non-invasive, high penetration, high resolution and spectral fingerprinting features of terahertz (THz) wave, THz spectroscopy has great potential for the qualitative and quantitative identification of key substances in biomedical field, such as the early diagnosis of cancer, the accurate boundary determination of pathological tissue and non-destructive detection of superficial tissue. However, biological samples usually contain various of substances (such as water, proteins, fat and fiber), resulting in the signal-to-noise ratio (SNR) for the absorption peaks of target substances are very small and then the target substances are hard to be identified. Here, we present recent works for the SNR improvement of THz signal. These works include the usage of attenuated total reflection (ATR) spectroscopy, the fabrication of sample-sensitive metamaterials, the utilization of different agents (including contrast agents, optical clearing agents and aptamers), the application of reconstruction algorithms and the optimization of THz spectroscopy system. These methods have been proven to be effective theoretically, but only few of them have been applied into actual usage. We also analyze the reasons and summarize the advantages and disadvantages of each method. At last, we present the prospective application of THz spectroscopy in biomedical field.

**Keywords:** Terahertz spectroscopy, SNR improvement, Metamaterial, ATR spectroscopy, Agent, Mixture algorithm, System optimization

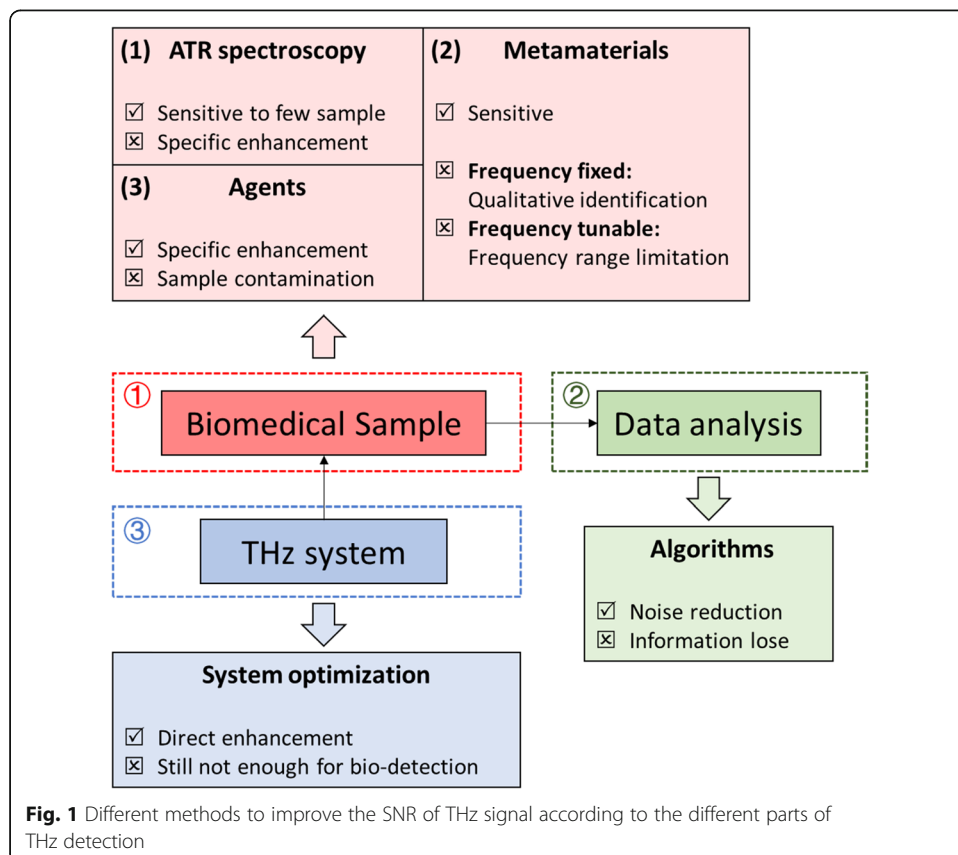
## Introduction

Terahertz (THz) wave lies between the millimeter and infrared regions, whose frequency is from 0.1 to 10 THz (corresponding to the wavelength from 0.3 mm to 30 mm) [1]. Therefore, THz wave exhibits features of both sides. Some of the features, such as non-ionizing, non-invasive, high penetration, high resolution and spectral fingerprinting [2, 3], make THz wave a potential tool in biomedical field. Based on THz spectroscopy, many groups succeeded to obtain the fingerprint spectra of medicines [4–8], biomarkers [9–13], deoxyribonucleic acid (DNA) [14–17] and images of different cancers [18–25]. However, merely little work further studied the identification of biomarkers in actual biological samples, such as tissue, blood and urine. For these

samples, various substances (such as water, proteins, fat, fiber and other organic components) are contained and the target substances often take a small part, resulting in the signal-to-noise ratio (SNR) for the absorption peaks of target substances are very small and then the target substances are hard to be identified.

Here, we present the related THz biomedical researches during the past few years working on the SNR improvement. We classify these works into three parts, as shown in Fig. 1.

The first part of SNR improvement for THz signal is about the biomedical sample treatment. Three methods are mainly discussed: attenuated total reflection (ATR) spectroscopy, metamaterial and agents (including contrast agents, optical clearing agents and aptamers). (1) ATR spectroscopy method is based on the interaction between sample and evanescent wave generated from crystal-sample interface, which is sensitive and needs few sample. However, as there is a wavenumber-dependent variation in penetration depth, the obtained ATR signal must be calibrated [26]. Furthermore, the evanescent wave interacts with each substance in the mixture sample, which makes it a total enhancement instead of specific/biomarker enhancement. (2) Metamaterial is a highly sensitive biosensor which can enhance SNR at specific frequency. There are two types of metamaterials: resonant frequency fixed metamaterials and resonant frequency tunable metamaterials. The frequency fixed metamaterial exhibits slight frequency shift of its resonant peaks when the sample covers on it (due to the change of total dielectric constant), therefore it can only reflect the change of dielectric constant, which cannot be used for the qualitative identification of target substances or biomarkers. The



frequency tunable metamaterial can be used to obtain dielectric constant of sample at a wide range of frequency, which is essential for qualitative identification, but its frequency range is limited to the material's Fermi level. (3) Contrast agents use nanoparticles to enhance the contrast of adjacent areas during the THz imaging. Optical clearing agents are the liquids that transparent to THz wave. By washing the sample with these agents, water in the sample can be replaced by the agents, which can improve the transparent of sample for THz wave. Aptamers can bind with specific molecules such as amino acids, proteins or medicines, which can be used as a filter. However, the use of agent will cause sample contamination, which cannot be used for other tests.

The second part of SNR improvement for THz signal is the application of algorithms to reconstruct the data. This method can eliminate the irrelevant information and remain useful information of sample data, but during the data processing, some useful/relevant information may be lost. Therefore, the use of algorithm needs to be optimized according to different samples or parameters.

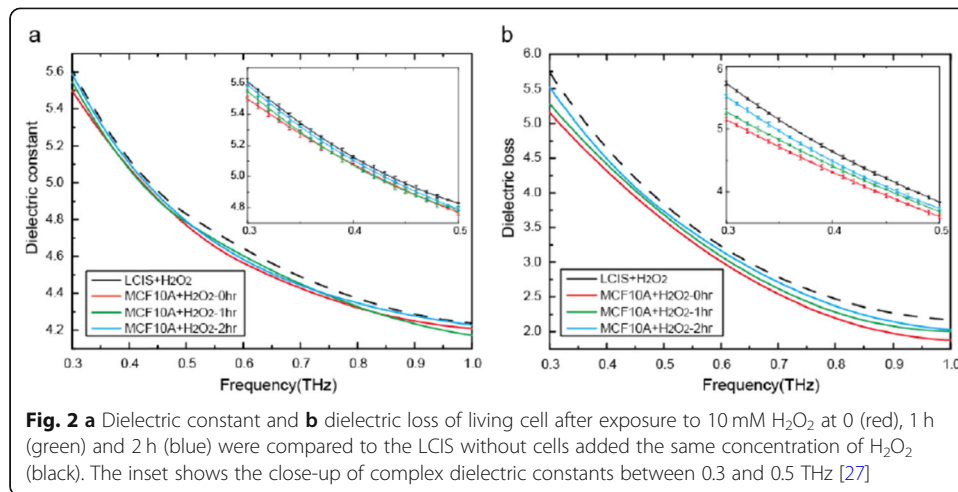
For most biomedical studies based on THz spectroscopy, these two parts above are two main research directions for the SNR improvement without the modification of THz system. However, to detect these biomedical sample with high SNR, the most direct way is to enhance the intensity of THz source or the sensitivity of THz detector. Currently, many groups are specially study the optimization of the THz system. In the third part, we simply introduced the optimization works of the THz system that may be used in biomedical detection.

At the last of the paper, we present the prospective of THz spectroscopy applied in biomedical field. This review may provide some references for the further studies of signal enhancement methods.

### **Treatment of biomedical sample**

The biomedical sample usually contains various substances, resulting in the SNR for the absorption peaks of target substances are very small and then the target substances are hard to be identified. Therefore, some treatments of biomedical samples are needed to enhance the THz resonance of target substances. Currently, using ATR spectroscopy, fabricating metamaterials and utilizing agents are three main research directions.

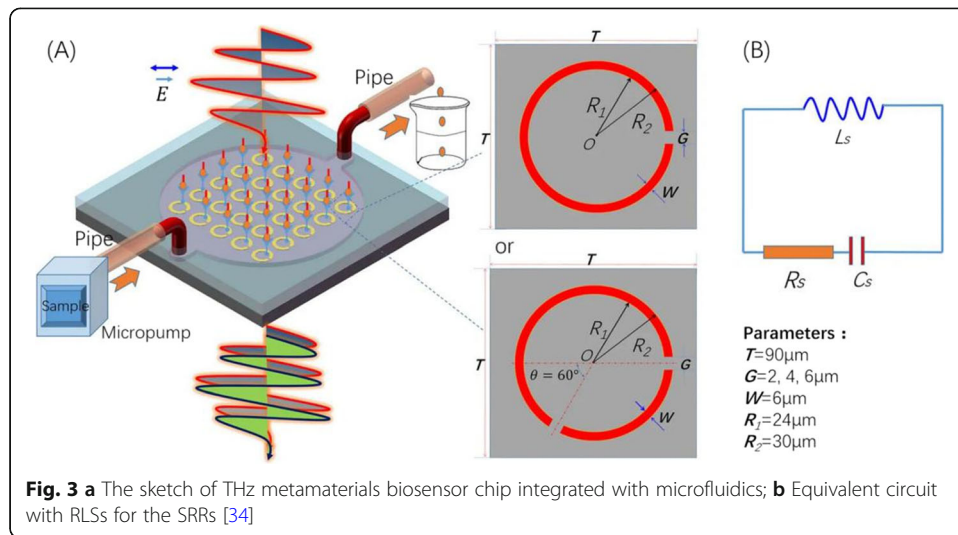
Different from the conventional THz spectroscopy, for THz ATR spectroscopy, a crystal is used to hold the sample and terahertz wave irradiates the crystal-sample interface to generate evanescent wave. The evanescent wave extends into and interacts with the sample [27], leading to the high sensitivity detection for the few sample. Therefore, many groups conducted biomedical researches based on ATR spectroscopy. In 2013, Shiraga et al presented a method to determine the complex dielectric constant of a cell monolayer based on ATR spectroscopy, whose imaginary part of the dielectric constant showed a lower absorption of slow relaxation mode than that of the liquid medium [28]. In 2015, Grognot et al measured permeabilization of epithelial cells based on ATR [29]. The cell layers displayed a 6% to 8% peak-amplitude relative contrast compared to the medium alone. In 2018, Zou et al monitored oxidative stress response of living human cells based on ATR THz time-domain spectroscopy [30]. As shown in Fig. 2, the dielectric constants were unchanged after the cell exposure to  $H_2O_2$ , while a slight increase of dielectric loss during time course of  $H_2O_2$  exposing was observed. In 2019,



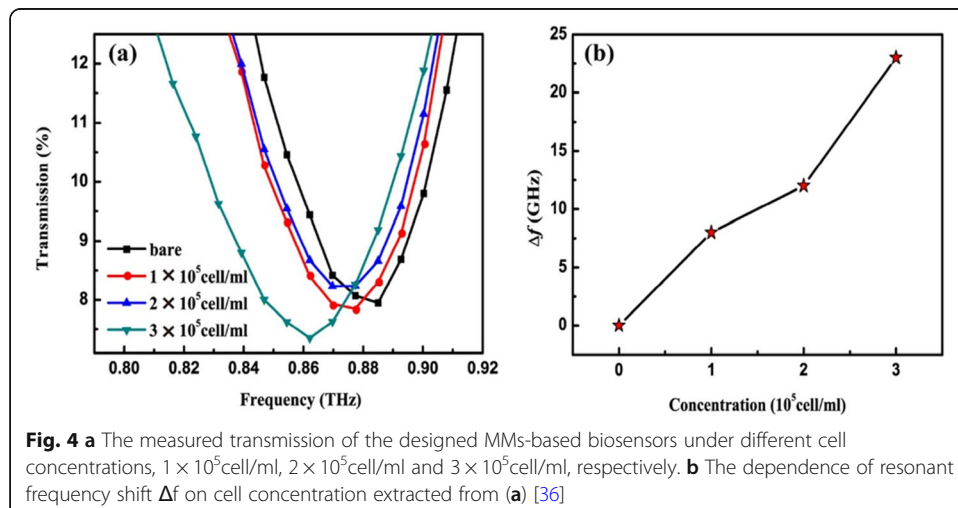
Huang et al investigated the hydration state of amino acids based on THz time-domain ATR [31]. The results showed the decreasing of the dielectric loss with increasing in the L-threonine concentration within the band of 0.2 ~ 1.5 THz, and the lowest concentration they tested was 0.34 mol/L. Wang et al studied the dielectric characteristics of living glial-like cells by the ATR spectroscopy [32]. The experimental results showed that the dielectric responses were related significantly to the cell number, intracellular fluid, and cell structure, and they also found that the absorption of glioma cells was higher than that of normal cells.

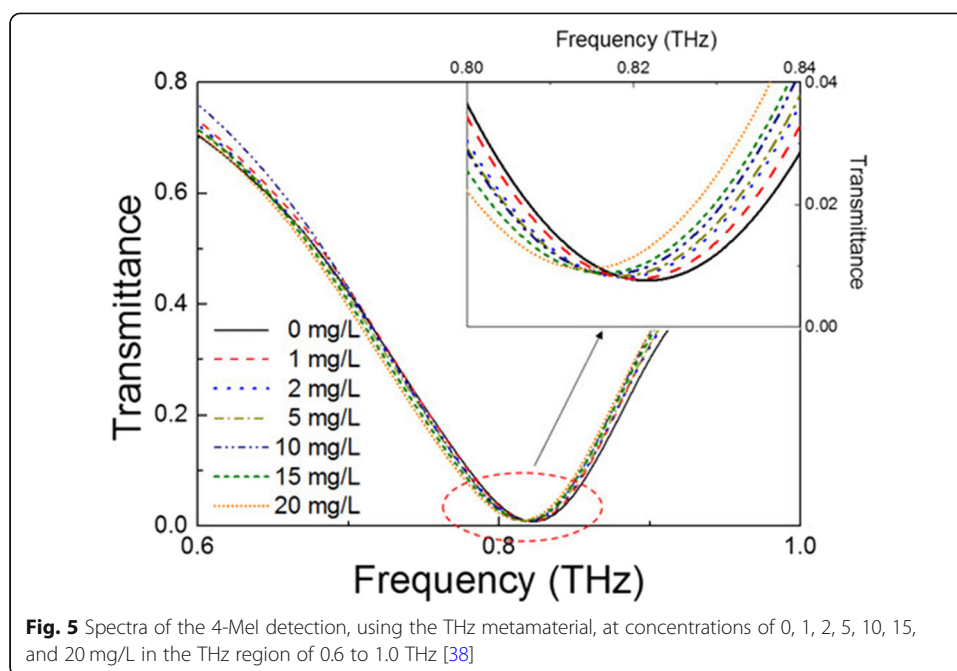
Compared to the normal THz spectroscopy, the THz ATR spectroscopy shows a higher sensitivity. However, its sensitivity enhancement is for all the substances in the sample, which still cannot solve the problem of accurate recognition of the target biomarker.

Metamaterials are structure devices with a special designed layer usually made from metal or graphene, which is sensitive to the change of dielectric constant of sample. Therefore, metamaterial can reflect the subtle change of the sample itself. In past few years, many groups developed various kinds of metamaterials, whose enhanced frequency is fixed. In 2016, Hu et al constructed a metal microstructure array-dielectric-metal structure integrated with microfluidic. The sensitivity of their structure is 3.5 THz shifting per Refractive Units Index (THz/RIU) [33]. In 2017, Geng et al integrated two kinds of THz metamaterials biosensor with microfluidics as shown in Fig. 3. The two-gap-metamaterial was used to detect AFP and GGT-II (two kinds of liver cancer biomarker). The detection limit were about 19 GHz resonance shift (5  $\mu$ g/ml) and 14.2 GHz resonance shift (0.02524  $\mu$ g/ml) for GGT-II and AFP [34]. Al-Naib et al designed conductively coupled split ring resonators with the average sensitivity level of  $3.0 \times 10^4$  nm/RIU/unit-volume and up to  $5.7 \times 10^5$  nm/RIU/unit-volume at selected spots [35]. In 2018, Zhang et al designed a metamaterial biosensor with the sensitivity of 82 GHz/RIU. Figure 4 shows the results of different amount of cancer cells HSC3 on the biosensor, which indicated the limit of the biosensor was approximately estimated to  $1 \times 10^5$  cell/ml [36]. Qin et al demonstrated a metamaterial composed of metal ohm ring arrays, which is applied in detecting different concentrations of carbendazim. Resonant peaks of metamaterial move to a lower frequency as the concentration increases and the detection limit is 5 mg/L, which is about 104 times enhancement compared to



the squash method for THz-TDS detection [37]. Shin et al demonstrated a sensitive metamaterial with a metal array to detect 4-methylimidazole (4-MeI), a carcinogenic substance. The resonance frequency decreased and the transmittance increased as the 4-MeI concentration increased, shown in Fig. 5. The lowest concentration they tested is 1 mg/L [38]. Hong et al developed hybrid slot antenna structures with silver nano-wires (AgNWs) were employed. The sensitivity increased upon the introduction of AgNWs with an enhancement factor of more than four times. They tested the devices using PRD1 viruses, and obtained an enhancement factor of 2.5 for a slot antenna width of  $3\mu\text{m}$  [39]. 2019, Keshavarz et al demonstrated a metamaterial surface composed of an H-shaped graphene resonator located on a semiconductor film. Three subtypes of Avian Influenza (AI) viruses, namely, H1N1, H5N2, and H9N2 viruses, were tested on the surface. The resonant frequency for H1N1, H5N2 and H9N2 were 1.668 THz, 1.665 THz and 1.641 THz, and the magnitude of the reflection were 61.4%, 67% and 60.9%, respectively [40]. Zhao et al proposed THz metamaterial-based reflection spectroscopy for label-free sensing of living cells by a self-referenced method. The

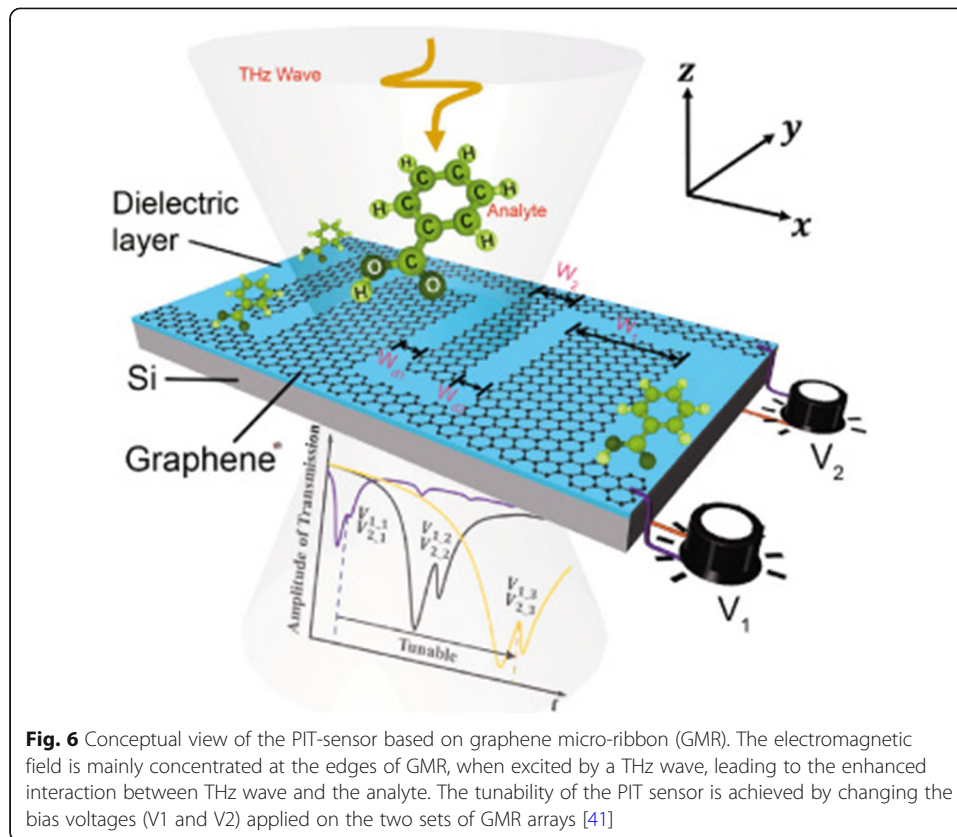




resonant peak intensity increase with increasing cell number, demonstrating a marked linearity with a linear correlation coefficient ( $R^2$ ) of 0.9914 [41]. Roh et al investigated two different THz metamaterials, namely double split ring resonator (DSRR) and the nano slot resonator (NSR), for molecule sensing in low concentration. Glucose and galactose were tested by the metamaterials with the detection limit of  $0.1 \mu\text{g}/\mu\text{L}$  [42].

These metamaterials are proved to be sensitive sensors for biomedical detection. However, these studies only analyzed the resonance peaks of the metamaterials instead of biomedical sample, which means it cannot qualitatively identify the components in the biomedical sample. Therefore, recent researches are only limited to the single sample (only contains target substance, like standard medicine or single type of cell). This indicates that this method can only reflect the total dielectric constant (sample and metamaterial). Any changes of other substances will also cause the dielectric constant change of sample, which will change the total dielectric constant and cause error in identification.

To realize the qualitative identification, the enhanced frequency of the metamaterial must be tunable to neutralize the influence of frequency shift caused by total dielectric constant change after sample covers on the metamaterial. These metamaterials can be made from graphene [43]. For example, in 2018, Tang et al designed a biosensor consisting of two sets of graphene micro-ribbon with different widths shown in Fig. 6, whose resonance peaks can be changed between 1.5 THz to 4.5 THz according to the change of the bias voltages [44]. Through the test of benzoic acid, their result showed the detection limit smaller than  $6.35 \mu\text{g}/\text{cm}^2$ . In 2019, Xu et al proposed a graphene-metamaterial heterostructure platform which can detect trace amount of chlorpyrifos methyl down to  $0.2 \text{ ng}$  [45]. In 2020, Lee et al reported a graphene-combined nano-slot-based terahertz (THz) resonance metamaterial to detect single-stranded deoxyribonucleic acids (ssDNAs) [46]. A maximum relative THz transmittance change of 52% was observed with different types of ssDNA, with the detection limit of  $\text{nmon}/\text{mm}^2$ .

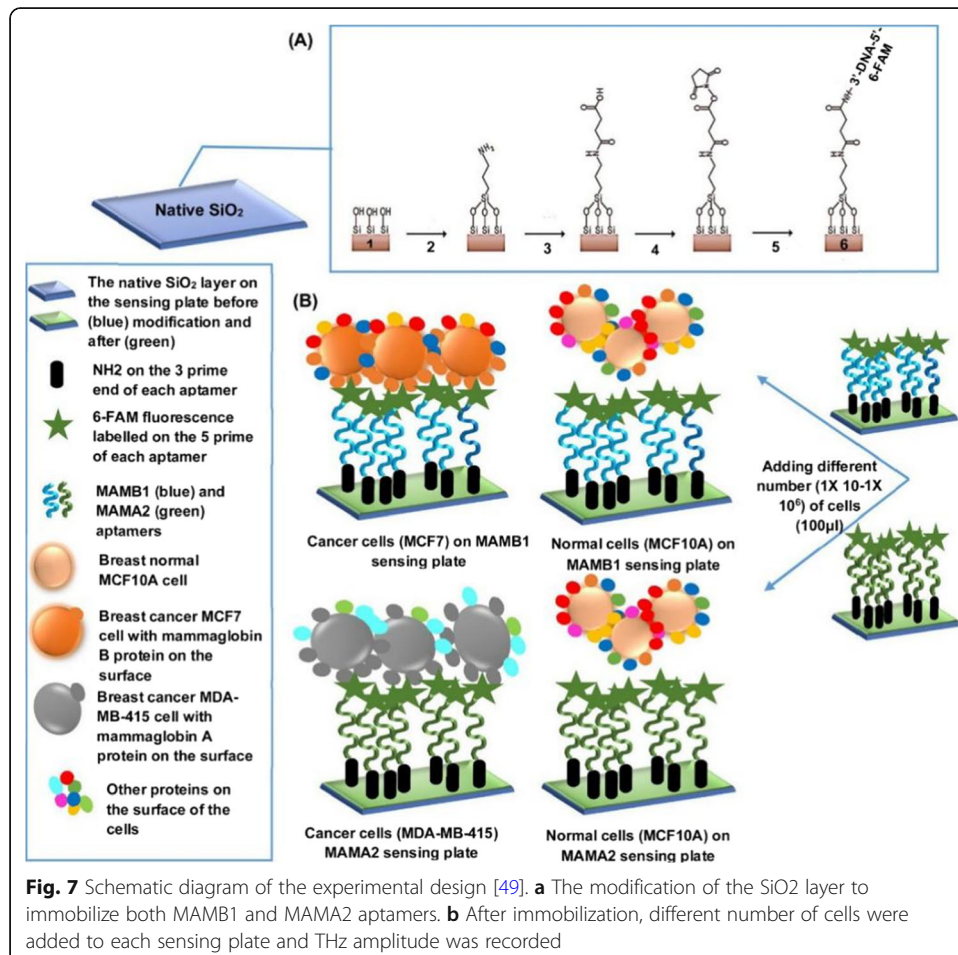


These works of graphene metamaterials can adjust their resonance frequency to neutralize the frequency shift caused by total dielectric constant change after sample covers on the metamaterial, and then obtain samples' dielectric constant in a wide frequency range, which can be used for the qualitative and quantitative recognition of sample components. However, this frequency range is limited to the Fermi level of the metamaterial.

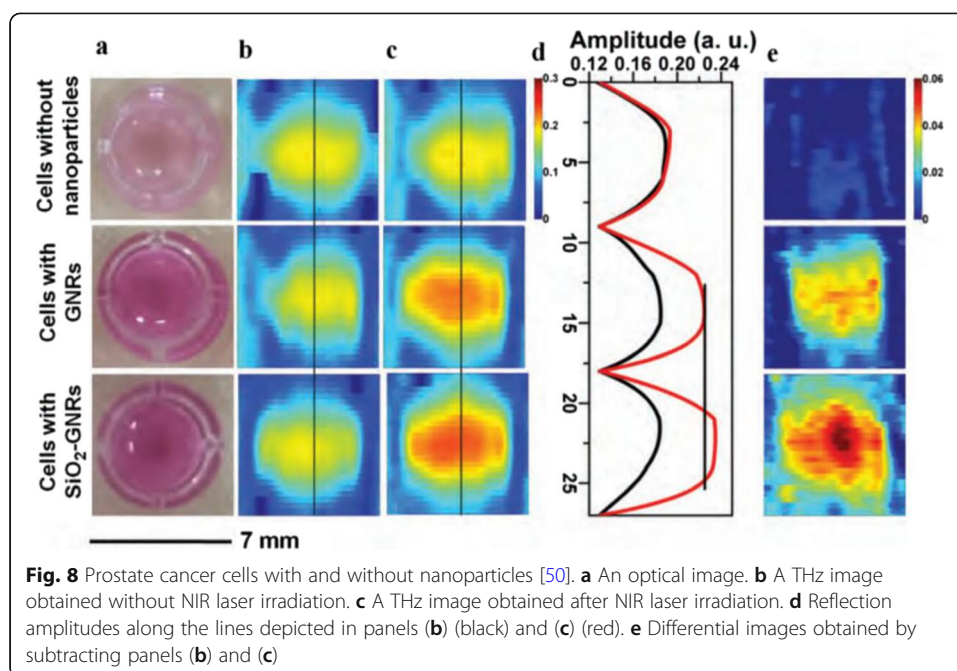
On the other side, some works utilized different kinds of agents to improve the SNR of THz detection. There are mainly three kinds of agents used in these studies: contrast agents, optical clearing agents and aptamers. These agents can enhance the imaging contrast, reduce water effects, or filter the target molecules. For example, in 2016, Zhang et al proposed the superparamagnetic iron oxide nanoparticles (SPIOs), which yields a highly sensitive increment in the reflection terahertz (THz) upon exposure to an alternating magnetic field. They conducted focal-plane imaging experiments using water with and without 4 g/L SPIOs, and the average amplitude in the relative reflection change images of water with SPIOs was  $29.41\% \pm 0.42\%$ , while that of water without SPIOs was only  $0.30\% \pm 0.03\%$  [47]. In 2018, Musina et al used THz wave penetration-enhancing agents (PEA), including polyethylene glycol with different molecular weight, propylene glycol, ethylene glycol, and dimethyl sulfoxide, for optical clearing of tissues. The absorption of PEAs was about three times reduced compared to that of water [48]. In 2019, Hassan et al developed synthetic single stranded (ss) DNA aptamers as agents to be bind to mammaglobin B and mammaglobin A (two proteins overexpressed by breast cancer cells). As shown in Fig. 7, the agent can capture the

cancer cell and neglect normal cells, resulting THz wave only having linear resonance with the concentration of cancer cells [49]. Huang et al designed silica-coated gold nanorods (GNRs) as a contrast agent for imaging of prostate cancer cells. As shown in Fig. 8, The enhancement efficiency of silica-coated GNRs was 5% higher than that of uncoated GNRs and 25.35% higher than that of the sample without nanoparticles [50]. Yang et al used fluorinated oil as an optical clearing agent to replace liquid medium around the living cell. By conducting an independent t test, statistically significant THz spectral differences were observed between the fluorinated oil with and without cells ( $P < 0.05$  at 0.5, 1.0, and 1.5 THz) [51]. Sadrara et al demonstrated hollow InSb microspheres forming dimers and trimers. Electric and magnetic hotspots in the gap between microspheres can be obtained, where electric field intensity enhancements of 10–2880 and magnetic field intensity enhancements of 3–61 in the frequency window 0.35–1.50 THz [52].

These works of agent utilization successfully enhanced the characteristic absorption of specific substances, while the sample containment caused by the addition of extra substance is unavoidable. For some studies in vivo, the chosen agents must be no harmful to human body.



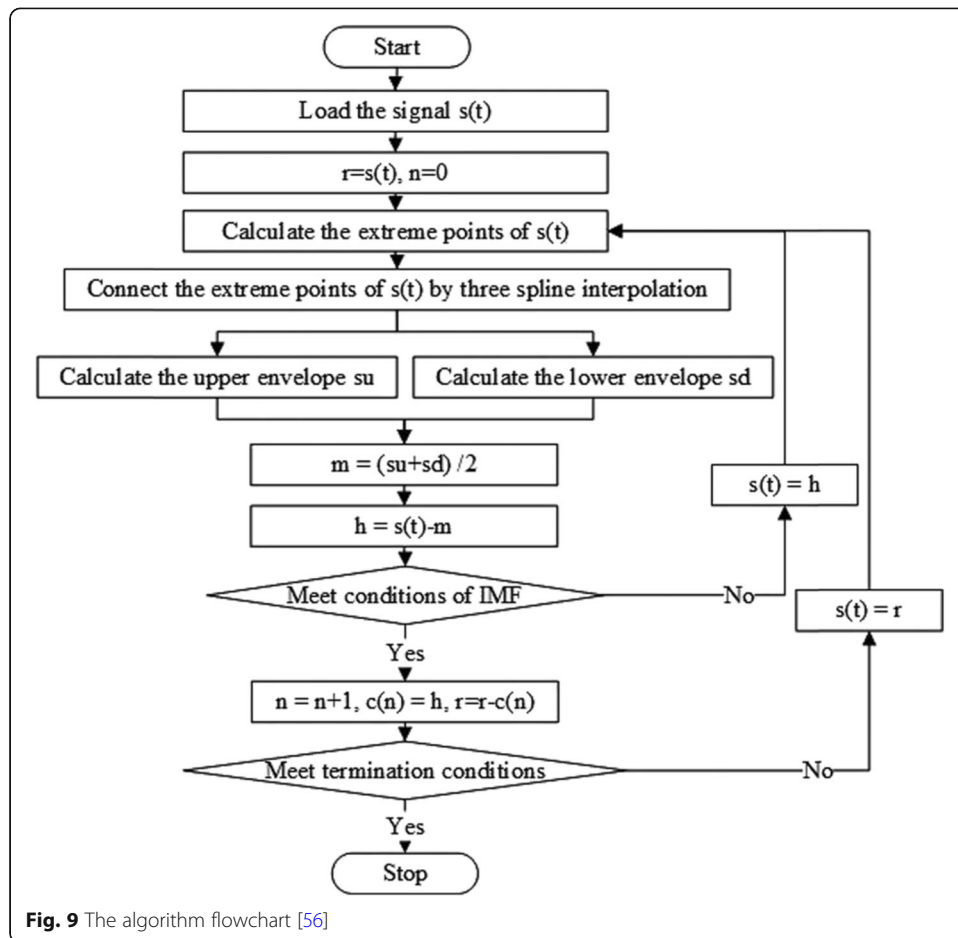




### Algorithms for data analysis

After the detection of samples, various algorithms can be used to further improve the SNR of spectra. Currently, many studies use algorithms to denoise or reconstruct the data. This is an effective way to extract useful information from the spectra. These algorithms are used in the qualitative and quantitative identification of mixture samples, which can increase the identification accuracy.

For example, in 2016, Sterczewski used the Bayesian spectral source separation algorithm to estimate the dehydration kinetics of monohydrated D-glucose with high correlation coefficients of the linear fits to the dehydration model ( $> 0.90$ ) were obtained [53]. From 2016 to 2017, Li et al proposed a self-adaptive genetic algorithm to decrease quantitative errors [54, 55]. The quantitative analysis errors of 12 mixture samples were predominantly below 6% with a standard deviation of 0.0344. In 2017, Qiao et al proposed the Mean Estimation Empirical Mode Decomposition (ME-EMD) de-noising algorithm. The algorithm flowchart is shown in Fig. 9. The de-noising results are shown in Table 1, which is better than that from “Db7” and “Sym8” [56]. Zou et al reported using principle component analysis (PCA) to reconstruct the time-domain THz signal, which can be used for the diagnosis of myelin deficit brain [57]. According to the results of mice samples, the first two PCs explain the 85% of time-domain information and basing on the two PCs, myelin deficit brain and normal brain can be classified with the accuracy of 96.7%. In 2018, Petrov et al presented the iterative and self-healing algorithm for imaging resolution enhancement, 1.21 times enhancement of reconstruction quality in low noise and 1.34 times enhancement in higher noise conditions can be obtained by the algorithm [58]. Peng et al proposed qualitative analysis algorithm based on the wavelet transform, baseline elimination, support vector regression, and loop iteration of samples. The spectra before and after denoising process are shown in Fig. 10. The average correlation coefficient of identification reached 99.135% and the root-mean-square error reached 0.40% [59]. Liu et al demonstrated a self-adaptive algorithm

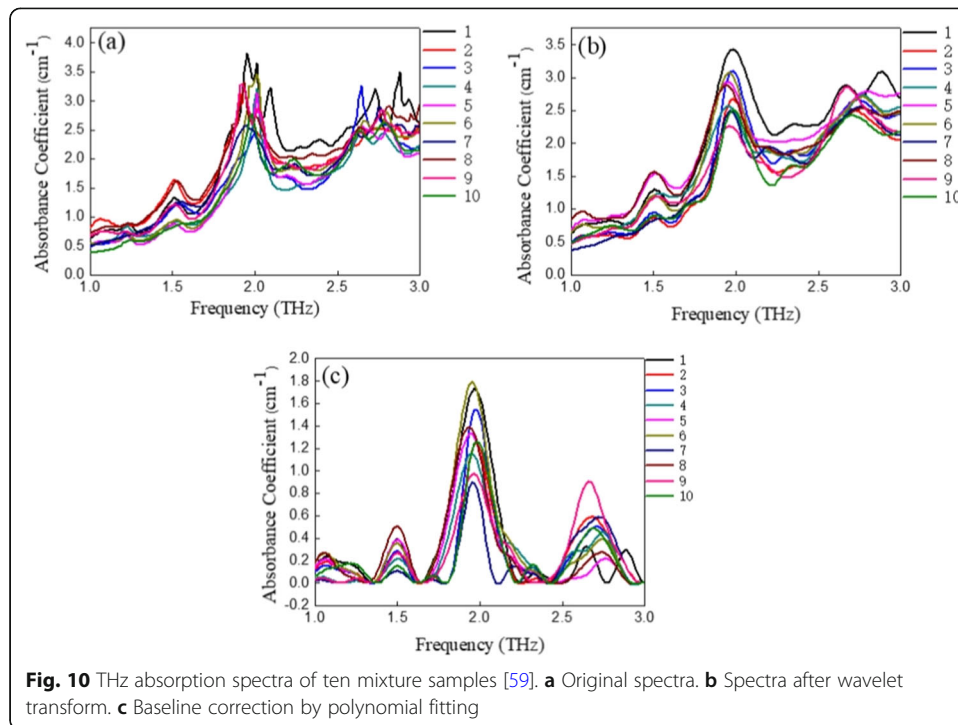


based on the Hilbert-Huang transform or identifying and eliminating atmospheric vapor noise from THz spectra. Monolayer graphene (MG) was tested, showing that strong interference of high-humidity atmospheric water vapor was eliminated and the characteristic peak of MG near 0.7 THz was retained [60]. In 2019, Cui et al applied lifting wavelet transform based on different wavelet basis function to the denoising of terahertz time domain spectrum, achieving a SNR of 60.69 dB and a least RMSE of  $2.85 \times 10^{-5}$  [61]. Huang et al composited multiscale entropy (CMSE) method and clustered by the K-means algorithm to extract THz features of glycoproteins. The average accuracy of their methods was 84.46%, while results from the method of PCA only reached 72.22% [62].

Algorithms can process the signal data to extract effective information and eliminate irrelative information. Therefore, these algorithms can also improve the SNR of spectra indirectly and then realize the effective identification of target substances. In particular, algorithms normally have various parameters that should be properly set according to

**Table 1** Results of the Simulation Experiment [56]

Materials	Original	Db7	Sym8	ME-EMD
SNR	21.7557	24.5401	24.5587	25.3761
MSE	0.0033	0.0024	0.0024	0.0022



**Fig. 10** THz absorption spectra of ten mixture samples [59]. **a** Original spectra. **b** Spectra after wavelet transform. **c** Baseline correction by polynomial fitting

the data. Therefore, wrong setting of the parameters may lead to the information loss of the sample and cause errors in the final spectral recognition.

### Optimization of THz system

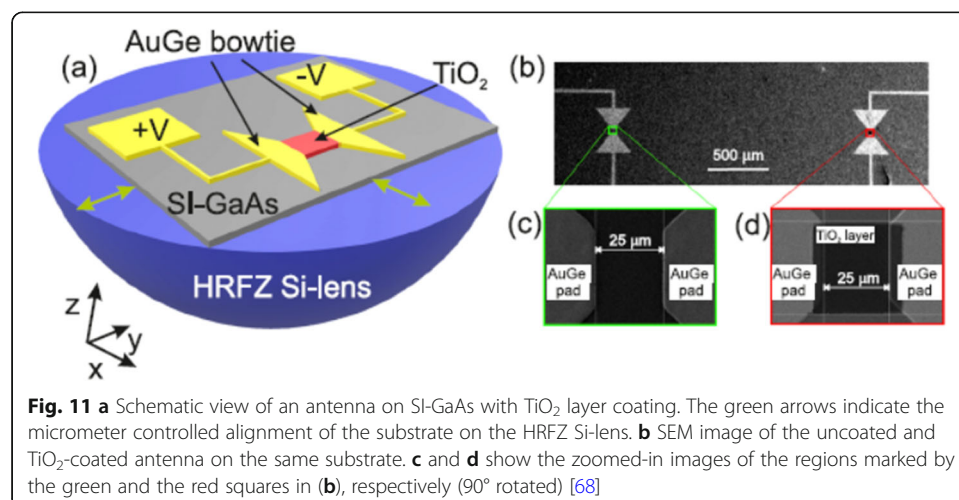
To detect the THz signal passing through the biomedical sample with higher SNR, the most direct way is to enhance the intensity of THz source or the sensitivity of THz detectors. Here, we also simply introduced current works of THz systems' optimization.

THz wave can be generated by many methods including photoconductive antennas, optical rectification, electron accelerator, and laser filament, where photoconductive antennas can generate THz pulses signals without the need of high-power optical sources [63] and became a classical THz resource for THz spectroscopy. However, the biomedical sample usually contains water and other substances which can strongly absorb THz wave. The antenna can't provide enough THz energy for high SNR detection. Therefore, many works focus on the improvement of antenna to obtain the stronger THz signal.

For example, in 2016, Zarrabi et al presented an antenna with cross-shaped nano-aperture structure. By Finite-difference time-domain method analyzing, the field intensity for the antenna with the structure was enhanced by 28.2 times. After added graphene coat and a cross shape chain of silicon dioxide to the structure, the intensity was enhanced by 43.9 times [64]. Zangeneh-Nejad et al proposed a hybrid graphene molybdenum disulphide-based photoconductive antenna, which provides not only high input impedance and reconfigurability but also high values of matching efficiency and radiation efficiency. The simulated results showed the total efficiency of the antenna increases by several orders of magnitude [65]. Collier et al introduced THz antennas

utilizing textured InP semiconductors which shortened carrier lifetimes – ultimately reducing Joule heating and ohmic losses. The carrier lifetimes of the smooth-, fine-, and coarse-textured InP semiconductors are found as respective values of  $200 \pm 6$ ,  $100 \pm 10$ , and  $20 \pm 3$  ps when measured with a pump-probe experimental system [66]. In 2017, Amanatiadis et al showed a graphene plasmonic antenna via synthesized substrates with metamaterial resonators, whose radiation efficiency is calculated at 16.6%, more than four times higher compared to the 3.9% of the usual antenna [67]. In 2018, Gupta et al reported several factors of enhancement in THz emission efficiency from conventional antennas. By coating an 80 nm nano-layer of dielectric ( $\text{TiO}_2$ ) on the active area between the electrodes of a semi-insulating GaAs-based device, shown in Fig. 11, the reflection from the Si-GaAs interface was suppressed by  $\sim 6.9\%$  [68]. In 2019, Kazemi et al used mixed graphene-gold electrodes as electrode material of the antenna, which enhanced the detected THz signal peak amplitude up to 14.31% [69]. Korolev et al reported using nanoimprint lithography to enhance THz emission from  $\text{MAPbI}_3$  perovskite upon femtosecond laser irradiation. The efficiency of THz emission from the nanostructured perovskite was enhanced by 3.5 times as compared with a smooth perovskite film [70]. In 2020, Cheng et al coated THz antenna by an epsilon-near-zero (ENZ) metamaterial superstrate showed in Fig. 12, enhanced the peak gain of the antenna by 45% from 5.37 dB to 7.79 dB [71].

Additionally, there are also some studies about other kinds of THz sources, including two-color laser excitation, spintronic THz emitters, photomixers, and filamentation. For example, in 2018, Jin et al used intense two-color laser pulses exciting liquid water to generate THz wave. Compared with one-color excitation, Their method enhanced the THz energy by two-orders of magnitude [72]. In 2019, Chen et al demonstrated spintronic THz emitters combined with semiconductor materials. A 2–3 order enhancement of the THz signals in a lower THz frequency range (0.1–0.5 THz) is observed [73]. Ironside et al projected a metamaterial-enhanced photomixer shown in Fig. 13(b) compared to the conventional photomixer shown in Fig. 13(a) which generate THz powers in the milliwatt range and exceed the Manley-Rowe limit for frequencies less than 2 THz [74]. In 2020, Koulouklidis et al demonstrated two-color filamentation of femtosecond mid-infrared laser pulses at  $3.9 \mu\text{m}$  generating ultrashort



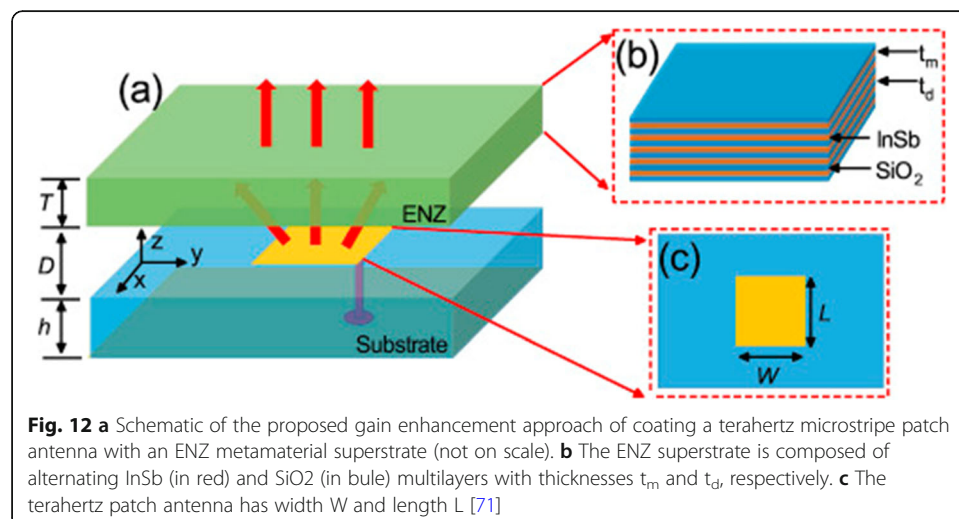
sub-cycle THz pulses with sub-milijoule energy. The results showed THz conversion efficiency of 2.36%, resulting in THz field amplitudes above  $100 \text{ MV cm}^{-1}$  [75].

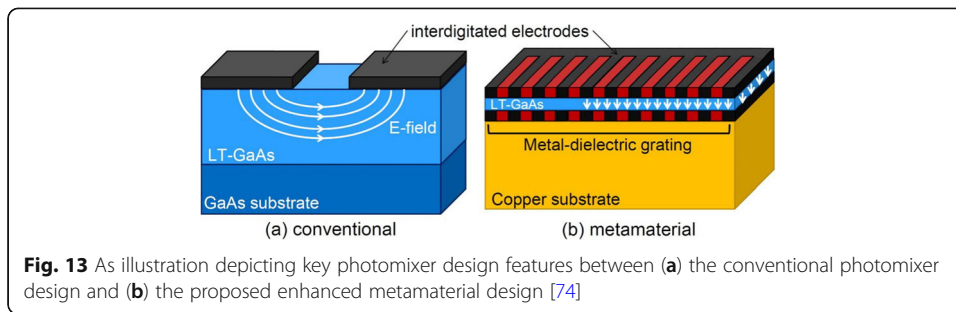
Also, some studies focus on the sensitivity improvement of the detector basing on antenna optimization by additional structure or layers. If the detector can be more sensitive, then the weak signal after passing through biological sample can be effectively detected. In 2016, Mou et al demonstrated a THz detector chip consisting of a differentially fed antenna and a Schottky diode at its terminal, as shown in Fig. 14. The chip showed the gain enhancement of 5.4–7.7 dB within the operating bandwidth [76]. In 2017, Xiao et al designed a grating-coupled structure on the high-resistivity silicon substrate to enhance the ability of coupling terahertz signals. The electric field in the central area of the silicon surface can be enhanced more than 4 times compared with the non-structure silicon substrate [77]. In 2018, Siday et al demonstrated an efficient terahertz (THz) detector based on an optical hybrid cavity. By putting an optically thin photoconductive layer between a distributed Bragg reflector and an array of electrically isolated nanoantennas, the sensitivity is enhanced by 17% [78]. In 2019, Cheng et al proposed sandwiching hyperbolic metamaterials composed of InSb and SiO<sub>2</sub> multilayer with hole arrays. The layer was put between a terahertz dipole antenna and the substrate, which enhanced the near-field electric field intensities by more than three times [79].

Besides the devices optimization, the external factors control is another useful option to increase the SNR of THz signal, such as reduce the humidity of environment, avoid shocks during the measurement and maintain the stability of temperature. Specifically, the improvement of this way may enhance the signal of all substances in the sample, which makes the signal of target substances still be drowned out by that of other substances. Therefore, this method can be an assistant to the previous two methods (sample treatments and algorithms) for the further SNR improvement.

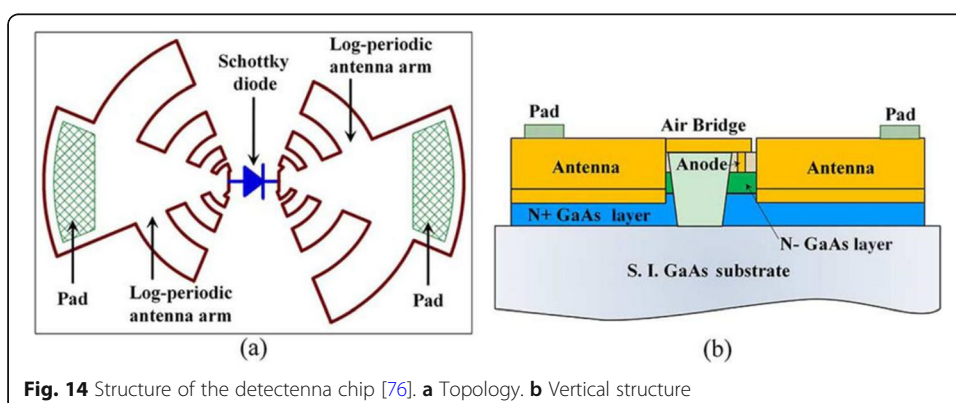
## Discussion

These works improve the SNR of biomedical signal from different aspects such as sample treatment, reconstruction algorithms for data analysis and system optimization. For the treatment of sample, there are three directions. Some works measured the sample





using THz ATR system. This is an effective way to improve SNR but it enhances the resonance of all components in the sample. When the concentration of target biomarker is small, it will still be difficult to identify the biomarker in the mixture sample. Some works tested metamaterials with sample covered. For the metamaterials that their resonant frequency is fixed, they can only analyze the shifting of the resonance peaks to achieve quantitative analysis, which can't be used for qualitative identification of the sample. For the metamaterials that their resonant frequency is tunable, they can adjust the resonant frequency to get the dielectric constant of sample in a wide range of frequency for qualitative and quantitative analysis, but this frequency range is limited to the Fermi level of the metamaterial. Also, change of other substances in the sample will cause error in the final result. On the other hand, some works utilized different agents to enhance the imaging contrast, reduce water effects or filter target molecules. These works realized the resonance enhancement of specific substances, but it will cause sample containment. For the improvement of data analysis methods, many algorithms were established. These algorithms can extract the feature information of target substances in the sample and reduce the effect of noise, which also improve the final SNR. Many works realized the qualitative and quantitative analysis of mixture biomedical sample with higher accuracy based on these algorithms. Most biomedical studies based on THz spectroscopy improved the signal SNR by these three directions, which did not need to modify the THz system. However, the optimization of system is the most direct way to improve the SNR. Currently, some groups specially studied the optimization of THz system. We introduced the optimization works that may be used in biomedical detection. However, as signals of all substances in the sample are enhanced in this



method, which makes the signal of target substance still be drown out by the signal of other substances.

We hope that through this review, readers can get broad understanding of current methods for signal enhancement of THz biomedical detection. For the researchers having difficulty in the THz detection of biomedical sample, this review can provide some experiences which may be helpful. Also, for the future researches on the signal enhancement, here we give our prospective. Sample treatment, data analysis and system optimization methods can be combined, which may further improve the SNR of biomedical sample. Furthermore, sample derivatization can be another direction to improve SNR. If the target substance shows low resonance to THz wave, we can find some chemical reaction that is specific to this substance and transfer the target substance to a new substance with a higher resonance. Also, other substances in the sample that show high resonance to THz wave can be eliminated by this way.

## Conclusions

In this review, we introduced current works for SNR improvements of biomedical signal, including sample treatment (including applying ATR spectroscopy, fabricating metamaterials and adding agents), reconstruction algorithms and system optimization. Each has its advantages and disadvantages:

- ATR spectroscopy is sensitive to few sample but it cannot specifically enhance the resonance of target substances.
- Metamaterials are sensitive biosensors, in which resonant frequency fixed metamaterials can reflect the total change of dielectric constant, but can only be used for quantitative analysis. On the other hand, resonant frequency tunable metamaterials can be used to get the spectra of sample in a frequency range for qualitative and quantitative analysis. However, this frequency range is limited to the Fermi level of the metamaterial.
- Agents can be used for specific enhancement of substances but will cause sample containment.
- Algorithms can extract effective information from redundancy information but some useful information will be lost during the process.
- System optimization is the most direct way to enhance the THz signal, but enhancement of all signal makes the signal of target substance still be drown out by the signals of other substances.

Through these methods introduced, reader can get broad understanding of the approaches of signal improvement during biomedical detection based on THz spectroscopy. And at last in the discussion, we give our prospective of the future researches on the signal enhancement.

## Abbreviations

THz: Terahertz; SNR: Signal-to-Noise Ratio; RI: Refractive Index; ATR: Attenuated total reflection

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## Authors' contributions

Y. P. and Y.M. Z. developed the idea and supervised the project. C.J. S. contributed to the research of current studies. Y. P. and C.J. S. were major contributors in writing the manuscript. All authors revised the paper and approved the final manuscript.

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### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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