Terahertz Metastructures for Non-invasive Biomedical Sensing and Characterisation in Future Healthcare

Shohreh Nourinovin, *Student Member, IEEE,* Miguel Navarro-Cía, *Senior Member, IEEE,* Muhammad M Rahman, Michael P Philpott, Qammer H. Abbasi, *Senior Member, IEEE,* Akram Alomainy, *Senior Member, IEEE,*

***Abstract*—Terahertz (THz) radiation has promising potential in the biosensing field as a non-ionizing, non-invasive, and label-free method, especially in the early detection of fatal diseases like cancer. It is situated between the microwave and infrared region of the electromagnetic (EM) spectrum and hosts many rotations, vibrations, and librations of biomolecules. However, it suffers from poor sensitivity, small penetration depth, low contrast, and long-wavelength for small biological sensing. These drawbacks give a great opportunity to THz metamaterials. These periodic artificial structures can be designed to provide a localized EM field enhancement leading to the increased interaction of the external stimuli with the analyte and form a highly sensitive biosensor. This paper reviews fundamental and latest cutting-edge research works in biological sensing particularly early cancer detection using THz metasurfaces. With a focus on recent advances, the first part covers examples of THz metasurfaces based on both classical and higher order modes of plasmonic-like resonances. Consequently, we overview different methodologies for biosensing with high Q-factor THz metasurfaces and novel enhancing techniques for low-concentration cancer biomarker solutions. Finally, we provide a summary and comparison of different approaches and outlook for future healthcare developments with THz metasensors.**

***Index Terms*—Terahertz, Metasurface, Metamaterial, Biosensing, Early cancer detection**

I. INTRODUCTION

According to a recent report [1] from Cancer Research Agency of World Health Organization, cancer is a dominant cause of mortality worldwide, leading to 10 million death only in 2020. Diagnosing the patient from the early stages tremendously rises the chance of diagnosing. Current clinical cancer detection approaches including X-ray, MRI, and biomarker analysis not only fail to provide a precise border of the malignant tissue, especially in the early stages of cancer but also can be invasive and lead to tissue damage. Recent progress in EM biosensor technologies has the potential to deliver a point-of-care diagnosis and surpass conventional methods regarding accuracy, time, and cost.

THz radiation refers to the frequency band spanning 0.1 to 10 THz and has beneficial properties, including non-ionization and non-invasive behaviour due to low photon energy (unlike X-rays), phase sensitivity to water, spectral fingerprinting, penetration capabilities (outperforming MRI), and relatively good resolution, which made it an ideal tool in medical spectroscopy and imaging [2]–[4].

Although remarkable progress has been made in the areas of terahertz spectroscopy and imaging in cancer detection, it still suffers from some deficiencies, including penetration depth, contrast, and sensitivity. These drawbacks motivate the work on THz metamaterial-enhanced biosensors

Metamaterials are artificial structures often made of resonators with a size scale smaller than the wavelength of external stimuli. Their electromagnetic properties can be altered by chemical composition and the internal structure, position, and orientation of each of the constitutive resonators, called meta-atoms or meta-molecules. The vast development of this field started with the early work of Veselago [5], and seminal works of Pendry [6], and Smith [7] to demonstrate the first metamaterial with negative refractive index. The surface version of metamaterials is called metasurfaces, which are the 2D equivalent of conventional metamaterials. They have the advantage of occupying less physical space with a high degree of compactness that enhances the radiation efficiency and provide less-lossy structures [8].

Among a wide range of metamaterial and metasurfaces applications, biosensing, especially in the THz range, stands out. In such an application, the incident stimuli propagate through the surface of the resonators and couple with their surface current. This phenomenon provides a localized EM field enhancement that strengthens the interaction of the analyte with the interrogating field. Such strong interaction is manifested in resonance changes, such as frequency, amplitude, and Q-factor and leads to a massive improvement in the sensitivity of a biosensor system [9]–[11].

Several review papers have addressed recent development in the area of THz metasurfaces [12] [13], which a few of them have focused on biological and thin-film sensing with THz metasurfaces [14]–[17]. To the best of our knowledge, while there are numerous review papers in early cancer detection with THz spectroscopy and imaging [18] [19], there is a lack of focused survey on covering the recent progress in the early

Sh.Nourinovin and A.Alomainy are with the School of Electronic Engineering and Computer Science, Queen Mary University of London, London E1 4FZ, U.K. (e-mail:s.nourinovin@qmul.ac.uk; a.alomainy@qmul.ac.uk), M.Navarro-Cía is with the School of Physics and Astronomy, and the Department of Electronic, Electrical and System Engineering, University of Birmingham, Birmingham, B15 2TT, U.K. (e-mail: m.navarro-cia@bham.ac.uk), M.M.Rahman and M.P.Philpott are with the Centre for Cell Biology and Cutaneous Research of Bilzard Institute, Queen Mary University of London, London E1 2AT, U.K. (e-mail: m.m.rahman@qmul.ac.uk; m.p.philpott@qmul.ac.uk), Q.H.Abbasi is with the James Watt School of Engineering, University of Glasgow, Glasgow, G12 8QQ, U.K. and the School of Electronic Engineering and Computer Science, Queen Mary University of London, London E1 4FZ, U.K. (e-mail: Qammer.Abbasi@glasgow.ac.uk)

cancer detection with THz metasurfaces. Fig.1 illustrates the increasing accelerating trend of publications in the area of metamaterials and metasurfaces along with their applications in sensing and, more specifically, in early cancer detection.

This paper provides comprehensive classification of the THz metasensors and focus on the recent experimental efforts to improve early cancer detection. The review introduces classical plasmonic-like THz metasurfaces and their advanced subtypes, including extraordinary transmission and nanoparticles-enhanced THz metasurfaces. The second section reviews the area of high Q-factor metasurfaces using higher-order EM modes leading to Fano resonance and electromagnetically induced transparency-like (EIT-like) effect.

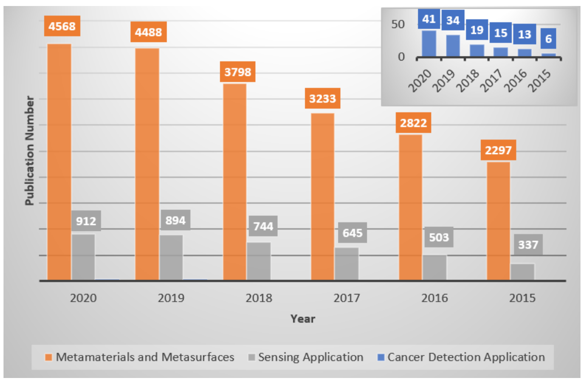

Fig. 1: Exponential growth of publication numbers in metamaterials and metasurfaces along with their application in sensing and cancer detection in recent years (reported from web of science).

II. Classical THz Plasmonic-like Metasurfaces

EM waves can couple to surface plasmones at optical and infrared frequencies to make a propagating wave at the metal-dielectric interfaces, the so-called surface plasmon polariton (SPP). At THz frequencies (below plasma frequency), metals are good conductors and can often be modeled as simply perfect conductors; this prevents them from supporting SPPs. To exploit the capability of SPPs in the THz regime, one practical solution is to use metals with a textured surface that enables SPP-like modes, so-called spoof surface plasmon. Within the metamaterial paradigm, it becomes possible to engineer a wide variety of spoof surface plasmons [20].

Split ring resonators (SRRs) are key elements in the classical plasmonic-like metamaterials. They play a principal role in advanced biological and biochemical sensors. Since their first demonstration around four decades ago, detecting small analytes, including cancerous tissue, has remained challenging. To overcome these challenges, novel designs based on different resonance modes have been developed in recent years [21]–[24].

Among the very recent research works in this area, ref [25] proposed a plasmonic metasurface made of mirror-asymmetric SRRs (Fig. 2), which exhibited a resonance with a change in the polarization of the THz wave. In the experiment, two types of lung (A549) and liver (HepG2) cancer cells were cultured on the metasurface biosensor. Then, by measuring the THz transmission spectra, the dependency of Δf and the fitted phase slop on the cancer cell concentration at different polarization degrees was investigated. When the cell concentration reached the highest number of 5×10^5 cells/ml, Δf in all polarization degrees reached 213 GHz and 198 GHz for lung and liver cancer, respectively. Therefore, this antibody-free recognition method based on considering polarization change as a sensing index can be promising in recognition of label-free cancer cells.

The loss of apoptosis allows cancer cells to survive longer. It is significant to develop sensitive detection methods to detect cell apoptosis under the effect of anti-cancer drugs. In ref [26], authors introduced an SRR-based THz metamaterial with non-bianisotropic resonance to detect the apoptosis of cancer cells. This work consists of an SRRs array on a dielectric layer, with a resonance response at 0.85 THz. The simulation showed a redshift in the transmission spectra in the existence of the sample with a theoretical sensitivity up to 182 GHz/RIU depending on the refractive index. In the experiment, the cell concentration raised from 1×10^5 cell/ml to 3×10^5 cell/ml, and then the effect of the drug concentration was observed on the apoptosis of cancer cells HSC3. The results demonstrated that the frequency shift increased with growing cancer cells, and then with adding the drug in a period from 24 to 72 hours, the frequency shift gradually decreased. Based on the result, the cancer cells were effectively killed, and apoptosis was active.

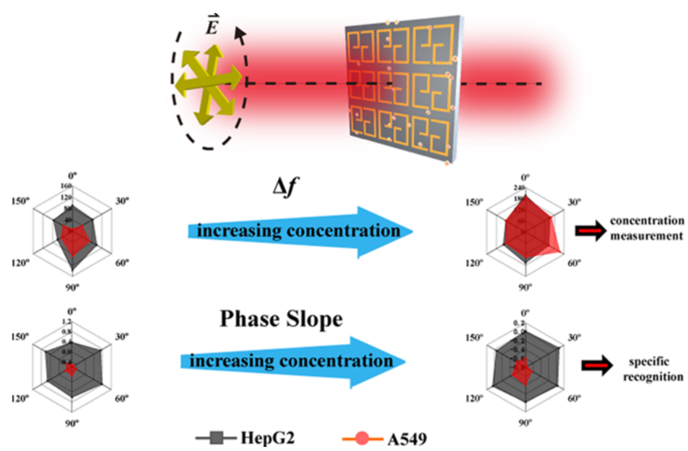

Fig. 2: Detection of A549 and HepG2 cancer cell with a plasmonic THz metasurface based on Δf and phase slopes on the cancer cell concentrations at different polarizations [25].

III. Extra Ordinary Transmission Metasurfaces

The extraordinary transmission effect is generally attributed to the resonant excitation of surface plasmon modes, occurring at a metal-dielectric interface. To manufacture these devices, one approach is applying arrays of tiny apertures on a metallic plate. Each hole is a non-resonant element, and the transmission originates from the interaction of the incident wave and leaky-mode of the excited periodic hole array that runs along the surface as they leak energy away from it [27] [28]. This causes a robust local-field confinement in the metallic aperture and makes them highly sensitive to minor changes around the aperture. Thus, they have been extensively employed in the biosensing tools to provide accurate and fast detection of various biological molecules [29].

The first introduction of this type of terahertz metasurface for sensing purposes was investigated by Miyamaru *et al.*. [30] by drilling holes in thick metal sheet. The recent research works demonstrated that the strength of the resonance and the corresponding line shape of a metallic hole array are highly dependent on the periodicity, hole shape, material properties of the metal and substrate, the aspect ratio of holes rotation with respect to the lattice vectors and type of array [27] [29] [31]. Refs [32] and [33] proved that rectangular apertures exhibit stronger resonances while circular apertures are more sensitive to the polarization. Ref [34] also investigated the effect of the conductivity of the material of the hole array metals on the transmission peak amplitude.

To be specific to the THz early cancer detection domain, Maosheng *et al.* [35] designed a terahertz plasmonic-like metamaterial by piercing periodically arranged hexagonal holes on a gold plate with a polyimide substrate (Fig.3(a)) and compared the sensing functionality from both transmission and reflectance response of the biosensor. To test the functionality of the biosensor, samples of liver cancer in five levels of 1×10^4, 5×10^4, 1×10^5, 3×10^5 and 5×10^5 cells/ml concentrations were cultured on the surface of the hole array plasmonic metamaterial. As claimed by Fig.3(b), when the concentration of liver cancer changes from 1×10^4 to 5×10^5 cell/ml , the frequency shift (Δf) increases from 30.6 to 45.9 GHz for the transmission spectrum and from 15.3 to 30.6 GHz for the reflectance spectrum. They have compared the transmission and reflectance response and concluded that although the device cannot distinguish cell concentration within the orders of magnitude between 1×10^4 and 5×10^4 cells/ml, it can detect the magnitude of cancer sample between 1×10^4 and 1×10^5 cells/ml based on x-polarized reflectance spectrum.

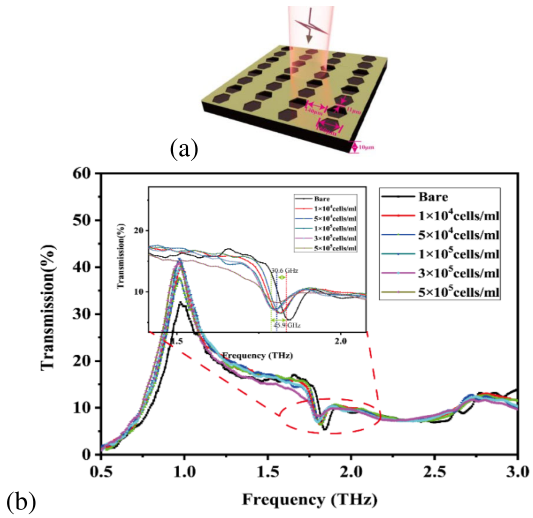

Fig. 3: (a) Schematic of a terahertz plasmonic metamaterial based on hexagonal holes [35]; (b) Related experimental y-polarized reflection for different liver cancer cell concentrations.

IV. Enhanced Nano Particle-Based Metasurfaces

There is another family of plasmonic modes, so-called localized surface plasmons (LSPs), which come from the optical excitation of SPs in metallic nanoparticles (NPs). Noble metallic NPs like gold, silver and copper with a controlled geometry can enhance the EM field concentration in metamaterials along with a strong dependency on the environmental media dielectric variation. Any variation in the refractive index of the surrounding media of the NPs, redshift the position of localized surface plasmon resonance (LSPR) to the lower frequencies. The position of LSPR depends on the shape, geometry, and material of NPs [36]. Taking advantage of these features, LSPs have been exploited in a broad range of technological areas, such as chemical and biological sensing [37] [38].

In the context of early cancer detection and diagnosis based on THz NP enhanced metasurfaces, Ke Yang *et al.*, proposed an NP coupled metasurface to detect microRNA (miRNA) samples [39]. MiRNAs are a potential biomarker for the diagnosis and therapeutic monitoring of different cancer types. In this work, the authors used a method of strand displacement amplification (SDA) to provide additional physical copies of amplified products of the miRNA targets to strengthen the sensitivity. The proposed polarization-independent metamaterial consists of planar arrays of SRRs on a silicon substrate (Fig.4(a)-(b)). During the experiment, the SDA reaction amplified the miRNA to make extensive secondary DNA molecules (triggered DNA), which were subsequently combined with metallic nanoparticles to form nanoparticle-trigger DNA complexes. These complexes enhanced the frequency shift of metamaterial resonance and presented good detection sensitivity with a limit of detection (LOD) of 14.54 aM with a linear response for miRNA at a concentration range of 1 fM to pM (Fig.4(c)). The recoveries of miRNA-21 in spiked clinical serum were calculated in the range between 90.92% and 107.01%.

In other recent research works, Kai *et al.* [40], introduced a bow-tie array THz metamaterial enhanced with gold NPs to detect epidermal growth factor receptor (EGFR), which is a significant factor in the proliferation of various cancer cells. In the experiment, EGFR antibodies combined with NPs of different sizes to react with EGFR peptides on the metamaterial structure. The metamaterial response was measured with and without antibodies and NPs to prove their role in sensitivity enhancement.

V. Approaches to High-Q Factor THz Metasurfaces for Early Cancer Detection

Although mentioned plasmonic-like sensors are promising and provide considerable sensitivity and reasonable LOD, it is still demanding to boost the precision of biosensing. Thin film and biological sensing rely on designing high Q-factor metasurfaces with higher sensitivity. In THz resonant-based metasurfaces, an ohmic loss is often negligible because of

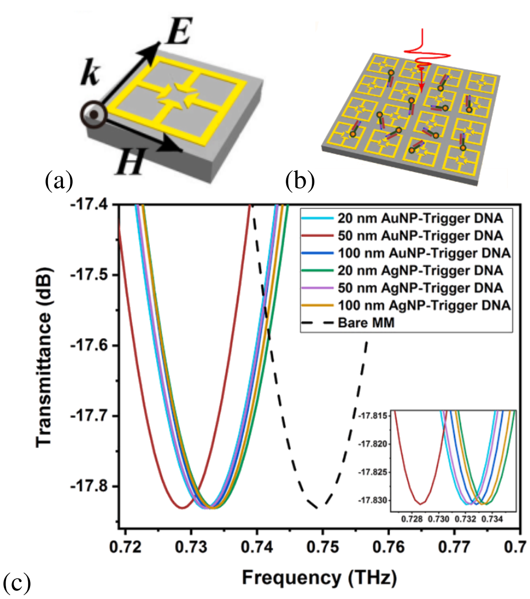

Fig. 4: (a) Unit cell; (b) corresponding THz metamaterial coupled with nanoparticles for microRNA detection [39]; (c) normalized THz transmission spectra of six nanoparticle-trigger DNA complexes in comparision to bare metamaterial. Inset graph shows the magnified signal value from 726.4 to 735.8 GHz.

small interaction length (radiation with metal), and in the case of having a dielectric substrate, related losses can be reduced by choosing a low loss material. Therefore, we are mainly dealing with radiation losses that should be reduced to enhance the Q-factor. To meet this requirement, there are higher-order plasmonic modes, including Fano and EIT-like resonance-based metasurfaces.

A. *Fano and EIT-like THz Metasurfaces*

Fano resonance-based metasurfaces provide a robust enhancement of EM fields in their vicinity along with higher Q-factor and boost the interaction of the light with the analyte over the metasurface. Fano resonances were originally discovered in quantum physics to explain the asymmetrically shaped ionization of the atom and molecules [41]. Most recently, the theory of Fano resonance was introduced to the field of photonic and then metamaterials [42]. With the similarities of the atomic system, the photonic structure must consist of two resonance elements classified as ”bright” strongly coupling to the incident light with a short radiative lifetime and ”dark” that shows weak radiative coupling to the incident wave and with a long lifetime. In this case, when the resonance frequency of the bright mode is equal to the resonance frequency of the dark mode and their Q-factor contrasts strongly, the Fano resonance is called EIT-like resonance. Exciting EIT-like resonance can be explained through the theory of coupled-resonator model [43]. In the absence of coupling, the energy of the incident wave is scattered into the free space by the bright resonator. When the bright resonator is coupled with the dark resonator, the EM response of the system improves remarkably, and the energy received through the bright mode is passed to the dark mode at the resonance frequency. Consequently, the absorption or scattering losses are significantly suppressed, and a transparency window appears. Approaches to trigger Fano and EIT-like resonance in metasurfaces can be classified into two categories of asymmetric and symmetric resonators.

One common approach to induce Fano and EIT resonance in metasurfaces is breaking the symmetry of coupled resonators. It was initially introduced on the microwave regime [42] and later in THz [44] in a metasurface with a periodic array of asymmetrically SRRs. Consequently, a model with a similar concept of mirror symmetry breaking of a bilayer [45] proposed. Later, the same analysis was done in ref [46] for a THz metasurface made of asymmetric SRR resonators to prove a reverse relationship between Q-factor and intensity of the Fano resonance response.

The high Q-factor Fano and EIT-like resonances can also be excited in symmetric resonators by applying an oblique incidence [47] [48]. The great advantage of this approach is that it is dependent on structure geometry rather than coupling and ease fabrication limitations.

The trend of study of the Fano-resonant-based sensors is also extended using the concept of toroidal resonances. Toroidal resonances are associated with the currents that flow through the torus area. Toroidal metasurfaces offer a remarkable enhancement in the Q-factor of the resonance and also strongly increase the sensitivity of the device [16] [49] [50].

B. *Early cancer cells detection with Fano resonance and EIT-like THz Metasurfaces*

The very first Fano resonance-based THz metasurface that designed especially for thin-film sensing based on asymmetric structures developed by Debus *et al.* [51] and then further followed by Singh *et al.* [52]. Consequently, several research works followed the trend of thin-film sensing based on asymmetric [53] and symetric [54] structures of Fano and EIT-like resonance-based THz metasurfaces.

To narrow the results in the area of early cancer detection, authors of ref [55] designed an EIT-like metasurface based on symmetry-breaking double SRRs over a 25 μm polyimide substrate to detect the oral cancer tissue (see Fig.5(a)). They defined an asymmetry degree of 28 μm between the gap of the coupled SRRs. To measure the sensitivity of the device, different concentrations of the oral cancer cells (HSC3) were deposited over the metasurface. The metasurface alone exhibited a resonance at 1.65 THz. With increasing the cell concentration from 1×10^5 to 7×10^5 cell/ml, the frequency shift increased from 50 to 90 GHz (Fig.5(c)). Following the study, the effect of the anti-cancer drug cisplatin was investigated to observe its effect. After depositing the cisplatin with different amounts and in the action time of 24 to 72 hours, the result of the measurement with THz-TDS showed a 70 GHz blue shift in the transmission spectra, which proved the functionality of the anti-cancer drug. The calculated theoretical sensitivity of the proposed device is 455 GHz/RIU, and the experimental sensitivity is obtained as 900 kHz per cell.

Mentioned results were improved in terms of sensitivity in comparison with the previous work by the same author [56] in the detection of lung cancer with a theoretical sensitivity of 248 GHz/RIU and experimental frequency shift of 50 GHz under 5×10^5 cell/ml. Another analysis is also done in ref [57] for the lung cancer detection with a multiple modes integrated biosensor, based on higher-order Fano metamaterials. These results have been improved in terms of sensitivity and Q-factor in our ongoing work, which its initial results have been published in [58].

While the focus of mentioned research works was refractive index sensing based on the resonance frequency shift, Zhang *et al.* [59] introduced another THz EIT-like metasurface with the observation of both the resonance frequency shift and the magnitude for sensing the glioma tumors. The metamaterial biosensor is composed of SRRs and cut wires (see Fig.6(a)), which exhibits an EIT-like resonance at 2.24 THz. Compared with the mentioned studies, the theoretical sensitivity is improved to 496.01 GHZ/RIU, and the dependency of the peak magnitude to the dielectric loss of the analyte is measured. In the experiment, two types of glioma cells (mutant and wild type) were cultured on the metasurface, and the THz transmission spectra were measured as shown in Fig.6(b). The maximum sensitivity reached 248.75 KH/(cell.ml) for the wild-type glioma tumor cells with a concentration of 8×10^5 cells/ml. Moreover, the resonance frequency shift and peak magnitude variation measurement was used to distinguish mutant and wild-type glioma tumor cells.

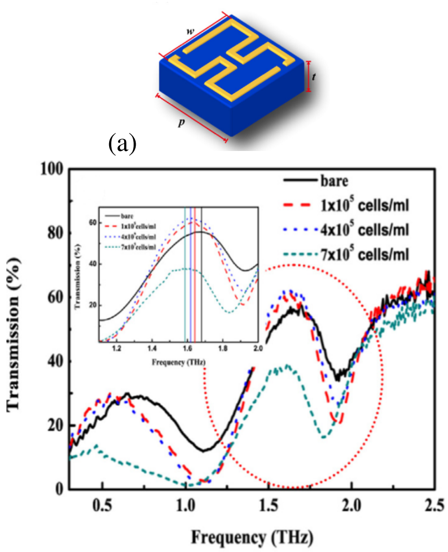

Fig. 5: (a) Unit cell of an EIT-like THz metamaterial for detection of oral cancer [55]; (b) related transmission spectra of the metamaterial under different oral cancer cells concentrations

C. Early cancer biomarker solutions detection with Fano resonance and EIT-like THz Metasurfaces

In addition to the characterization of cancer cells themselves, there are also biomarkers like different proteins as essential biomarkers of malignant tissue and play a critical role in early cancer detection. Traditional biological approaches to detect these solutions, like Enzyme-Linked ImmunoSorbent Assay (ELISA), suffer from time-consuming and less precise results. Detecting solutions of these biomarkers with low concentration can be challenging.

Ning *et al.* [60] introduced a Fano-resonant-based THz metasurface to detect carcinoembryonic antigen (CEA) protein of the cancer biomarker. The metasurface is made of double SRRs, and to make Fano resonance, they made an asymmetry in the structure by rotating and grating forms. In the experiment, CEA solution bonded to antibodies, which have already been deposited on the metasurface. Then, the resonance frequency shift was observed for different CEA concentrations, and a maximum shift of 29 GHz was observed for 500 ng/ml solution.

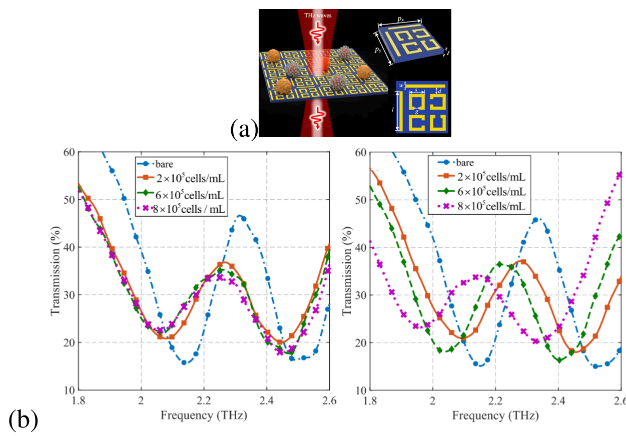

Fig. 6: (a) Schematic of the proposed THz EIT-like metamaterial for detection of glioma tumor [59]; (b) The measured transmission spectra for (left) mutant IDH glioma cells and (right) wild-type IDH glioma cell.

To fix this low sensitivity, a solution was proposed by [61] to detect the solutions of Midkine (MSK) protein. MSK is abnormally expressed in high levels of various malignant tissue and acts as a potential indicator of cancer cells. The authors proposed a THz EIT-like metasurface consists of periodic arrays of split circular gold rings and a concentric closed square gold ring over 10 μm-thick polyimide substrate with an EIT-like resonance at 0.67 THz, as illustrated in Fig.7(a). Different MDK solutions dropped onto the metasurface in the experiment, and a frequency shift and peak amplitude difference were observed, which were comparably small for lower concentrations. For fixing this problem, a full-spectral amplitude difference (FSAD) was done for different concentrations and corresponding pseudo-spectra obtained by applying twice Fourier transforms as shown in Fig.7(b). The results confirm that the LOD of the metasensors can at least reach 0.5 μg/mL and the measurement time reduced to 5 minutes. Moreover, Two-dimensional time-frequency extinction cards of different solutions and MDK concentrations are provided by implementing continuous wavelet transform. The 2D mapping obtained from continuous wavelet transform could detect different solutions clearly.

Apart from the mentioned methods to increase the sensitivity of THz metasurfaces for sensing the low concentra-

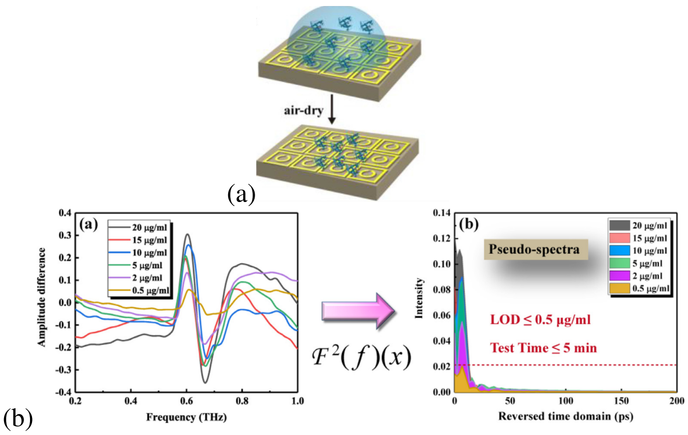

Fig. 7: (a) Schematic of the proposed THz EIT-like metamaterial to detect MDK protein as a cancer biomarker [61]; (b) The full-spectral amplitude difference of different MDK concentrations and corresponding pseudo-spectra obtained by applying twice Fourier transform.

tion cancer biomarker solutions, another effective approach is using microfluidic technology. When a microfluidic chip integrates with the THz metasurface sensor, it can overcome the strong water absorption at the THz regime and strengthen the sensitivity [62]. Zhaoxin *et al.* [63] developed a Fano resonance base THz metamaterial integrated with microfluid to detect the biomarker of liver cancer (Alpha-fetoprotein (AFP) and Glutamine transferase isozymes II (GGT-II)) in the early stage. The metasurface is made of metal SRRs array and poly (dimethylsiloxane) (PDMS) microchannel over a silicon substrate (Fig.8(a)). In this structure, two forms of SRRs have been designed: one with a singular gap and another one with two gaps leading to asymmetric structure displaying a Fano resonance. For the experiment, the biomarker solution coupled to the surfaces of the SRRs through some chemical reactions and THz transmission spectra monitored. Based on the result, with the Fano-resonant structure, a maximum resonance frequency shift of 19 GHz (5 mu/ml) and 14.2 GHz (0.02524 μg/ml) was observed for GGT-II and AFP liver cancer biomarkers, respectively (Fig.8(b)).

VI. Comparison

Table I compares some of the studied papers in early cancer detection with THz metasurfaces. In this table, f_0 is the resonance frequency of the bare metamaterial, S_t stands for theoretical sensitivity, concentration is the maximum sample amount that accounted for the Δf_e (experimental frequency shift) and S_e(experimental sensitivity).

In addition to sensitivity and Q-factor, another significant requirement for metamaterial design is the selectivity of the device. Fano-like resonance depends on the matching the absorption peak of the sample and the resonance of the metamaterials. Furthermore, the plasmons of nanoparticles do not always lie in the THz frequencies, which limits them to be utilized in some sensing applications. In other side, sensing extra small concentrations of proteins and biomarkers

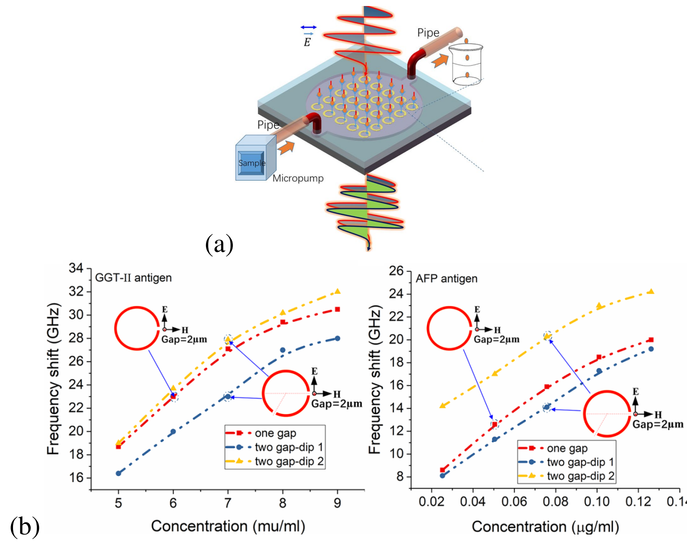

Fig. 8: (a) THz Fano-resonance-based metamaterial integrated with microfluidics for detection of cancer biomarker [63]; (b) Frequency shift spectra for different concentration of (left) GGT-II antigen and fixed concentration GGT-II antibody 1 μg/ml and (right) AFP antigen and fixed concentration AFP antibody 1 μg/ml

is challenging. The lowest possible biomarker concentrations that can be sensed by different plasmonic and Fano-like metasurfaces are limited to a few nano and micrograms/mL, while toroidal metamaterials have the potential of detecting extremely small biomarker concentration. It is also worthwhile to mention that beside nanoparticles, graphene is becoming an enabling platform for metasurface-based sensing wherein specific analytes interact with graphene's delocalized π-electrons. The key point to consider is that the sensitivity of the metasensor depends on how much the external molecule interact with the graphene.

VII. Conclusion and Outlook

This review presents an overview of recent advances and research activities in the area of metastructures at THz for biomedical sensing and characterisation applications, using early cancer detection as an example. Several plasmonic-like models from classical plasmonic-like THz metasurfaces to advanced modes of extraordinary transmission peaks and nanoparticles have been explored. The second part dedicated to the area of high Q-factor metastructures including metasurfaces based on Fano, EIT-like and toroidal resonances. Apart from that, novel technologies to overcome challenges in detection of low concentration of cancer biomarker solutions studied.

Although studies presented here demonstrate a strong potential of THz metasurfaces in biosensing, there are still challenges in enhancing LOD, Q-factor, and sensitivity of tiny biological samples including early cancer cells and biomarkers. Combining different enhancing methods and looking forward to novel designs for triggering higher Q-factor resonances

TABLE I: Comparison of different approaches in early cancer detection with THz metasurfaces.

Ref	Method	Cancer Type	$f_o(THz)$	$S_t(GHZ/RIU)$	LOD	Concentration	$\Delta f_e(GHz)$	$S_e(KHz/cellml^{-}1)$
[25]	CP[a]	lung-liver	1-3	525	$1 \times 10^4 cell$	$5 \times 10^5 cell$	198,213	430
[26]	CP	oral	0.85	182	$1 \times 10^5 cell$	$3 \times 10^5 cell$	23	-
[35]	ET[b]	liver	0.746, 1.8	-	$1 \times 10^4 cell$	$5 \times 10^5 cell$	45.9	
[39]	NP	microRNA biomarker	0.735	-	14.54 aM	1 fM to 10 pM	9.4	-
[40]	NP	EGFR biomarker	2.292	-	100 fM	10 pM	39	-
[55]	EIT	oral	1.67	455.7	$1 \times 10^5 cell$	$7 \times 10^5 cell$	-	900
[59]	EIT	glioma tumor cells	2.24	496.01	-	$8 \times 10^5 cell$	-	248.75
[61]	EIT	MDK biomarker	0.67	-	0.5 µg/mL	20 µg/mL	50	-
[63]	MC[c]	liver	0.5-1	-	-	5 mu/ml	19	-

[a]classical plasmonic-like resonance, [b]extraordinary transmission resonance [c]microfluidics.

and exploring the realm of photonic crystal fibers-based and aptasensors can be promising.

Most of the proposed metastructures for biosensing are mainly limited to theoretical studies, while complex human biological environments and in vivo applications involve many parameters that have rarely been explored. While some research works utilized the 3D artificial human tissue models to study the effect of different constituents, we are still far from genuinely exploring all the effective components of human tissue that account for wave distortion and interpretation.

Current THz characterization investigations are neither uniform nor comparable due to differences in preparations and measurements. Therefore, there is a demand for developing regulated operating processes and reliable databases. Some of the uncertainties in the characterization process are thickness calculation, water content, storage conditions, theoretical sensitivity criterion and THz device instrumentation.

Another bottleneck is data analysis and interpretation. Although computational modelling and numerical models have improved raw THz data analysis, more numerical models are needed for applicable interpretation. Today, one of the trending technologies in data interpretation is machine learning tools that could revolutionize THz characterization of human tissue

Acknowledgment

This research was supported by the School of EECS, Queen Mary University of London, EPSRC (Grant No. EP/S018395/1), the Royal Society (Grant No. IEC/NSFC/191104), and the European Union Horizon 2020 research and innovation program (Grant No. 777714).

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