



Terahertz cancer imaging and sensing: open research challenges and opportunities

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Abstract

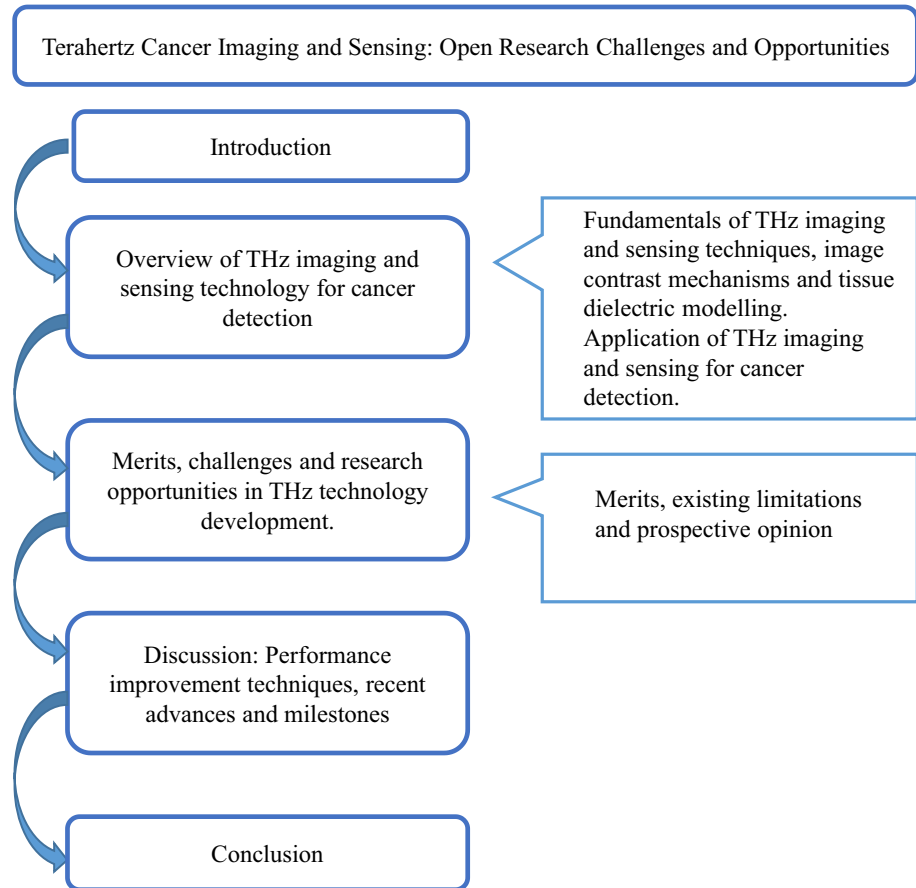
There has been a rapid development of THz technology—sources, detectors and various THz imaging and sensing techniques. The THz technology demonstrates great potential as a modality for early, label free, non-ionizing and non-invasive detection of cancer. Some progressive technological development milestones have been achieved in this regard, however, to become clinically competitive and to provide the sought after real operational convenience, there is need for further research and development to overcome the existing challenges. This paper provides recent trends and perspectives through identification of existing challenges for the development of THz imaging and sensing systems that can evolve into actual medical modalities. We provide an overview of various aspects of THz technology, including techniques for imaging and sensing, mechanisms for THz image contrast and models for tissue dielectric responses to THz waves. The THz imaging application for detection of various cancers is briefed. The advantages of THz cancer imaging and sensing as well as the existing challenges are identified, with recommendations provided in contribution to future research. Further, some recent THz imaging and sensing developments such as the near-field methods to break the diffraction limit including waveguides, resonance and plasmonic metasurfaces are discussed. We emphasize the contribution of analytical algorithms that are based on machine learning, in particular, deep learning for the development of THz technology.

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Graphical abstract



Keywords Cancer detection · Challenges · Merits · Terahertz technology · Terahertz imaging and sensing · Biomedical application · Research opportunities · Recent trends

1 Introduction

Terahertz (THz) regime of the Electromagnetic (EM) spectrum has been formerly known as the “THz gap”, it lies in between the microwave and infrared spectra, in the transition from electronics to photonics (Lewis 2017). With the advancements in technological development leading to the realization of new emitters and detectors, the THz spectrum is recently gaining research interest in diverse applications such as nondestructive testing (NDT), astronomy, wireless communications, and quality and security inspection. There has been a more recent growing potential application in the biomedical imaging and sensing domain, particularly, for cancer detection. THz radiation is desirable for biological tissue imaging and sensing owing to the unique features of the THz waves as compared to

that of the conventional Gamma Rays and X-Rays radiation. The photon energy of THz waves is too low to pose any ionizing hazard, i.e. they are non-ionizing and further the imaging and sensing based THz radiation is characterized by the capability for early, label free, non-invasive cancer detection with capability to provide phase and spatial and spectral information, they are also highly sensitive to polar molecules and capable of spectral finger printing (Malhotra and Singh 2021a). The high sensitivity of THz waves is attributed to the fact that low frequency vibrations of molecules such as hydrogen bonds and Van der Waals are excited by THz radiation.

Over the past two decades, various aspects of THz technology development have been explored to facilitate its wide scale application, however, it is still not fully explored, not yet sufficiently established and still associated with many challenges that constrain the development of efficient, inexpensive, reliable, robust and compact THz detectors and sources. Ultimately, this slows down the development of THz systems that can provide convenience in the real operational environments i.e. that are optimized and miniaturized (Gezimati and Singh 2023a). Some of the limiting factors of THz imaging and sensing tools include low sensitivity, diffraction limited spatial resolution, limited penetration depth and low acquisition speed as reported by Lee et al. (2021). The low acquisition speed in conventional THz systems such as the THz time domain spectroscopy (THz-TDS) and THz pulsed imaging (TPI) is because of the raster scanning and utilization of focal plane arrays to achieve 2D THz imaging. More recently, the use of THz computed tomography (THz-CT) promises to enable faster and 3D imaging, also the use of near-field THz imaging, dispersive spectrometers and tunable or broadband sources etc. demonstrates great potential to improve performance of THz systems in various applications (Zhan et al. 2023).

In this paper, the recent trends and future perspective in the application of THz technology for cancer detection is provided through identifying existing challenges as well as research opportunities in contribution to the facilitation of the ongoing development of THz systems that are highly sensitive and reliable, which will evolve into real operational environment imaging modality. We recommend the application of machine learning and deep learning based analytic algorithms for the improvement of THz data denoising, sampling, extraction, image reconstruction etc.

1.1 Related work

The development of THz imaging and sensing technologies as well as their potential application for the biomedical detection of cancer have gained so much research interest over the past two decades. Several studies have explored the various aspects of THz technology development and their application. Some challenges still remain that provide research opportunities. A recent roadmap study (Valušis et al. 2021), reported some developmental advances in THz imaging systems for systems that are optimized and miniaturized with enhanced functionality, reduced power consumption and eventually provide convenience in real operational environments. This has been suggested to be achieved through solid state electronic components for THz sensors and arrays that could operate under room temperature as well as the on-chip integration of these components with diffractive optical components. They provided the review of techniques such as THz Nano-imaging, computational imaging, THz holography, spatial filtering, beam forming, light field imaging, continuous wave imaging and passive THz imaging etc. as well as the role of artificial intelligence in THz systems. This study also provided their opinion on the contemporary scientific as well as technological challenges in the field of THz technology and provided extrapolations

of further THz imaging developments, however, their focus of application was not cancer detection. In another roadmap article (Yan et al. 2022), the strategies for moving from ex vivo and in vitro measurements in THz imaging towards enabling in vivo measurements has been provided. Most of the experimental studies have so far been exploiting ex vivo observations due to the limitations associated with low penetration depth and lack of flexibility of THz systems. The ex vivo measurements are however prone to inaccuracies related to excised tissue sample property alterations and deteriorations incurred during tissue sample pre-treatment and sampling handling. The development of effective and bio-safe contrast agents to enable in vivo THz imaging has been recommended to develop clinically competitive THz imaging systems.

In Lindley-Hatcher et al. (2021), the existing challenges and opportunities in development of real time THz imaging systems for skin cancer to enable improved strategies for cancer treatment have been studied. To achieve this, the application of robotics and their integration with THz systems has been proposed to enable increased location of geometries of the living body that are complex to locate. Another study Malhotra and Singh (2021b), evaluated the challenges and opportunities that are associated in the development of reflection and transmission configuration based THz imaging modalities. They discussed the novelty of THz systems over conventional modalities like X-Ray as well as highlighting the diffraction limit challenge in relation to THz imaging, spectroscopy and THz-CT. The possibility of exploring new possibilities in THz liquid photonics and eventually interaction of lasers and liquids has been reviewed in Zhang et al. (2022). They reported the challenges, opportunities and recent progress of THz emission from liquids. Many other studies have reviewed the challenges in THz technology development for various applications such as 5G mobile networks (Huang et al. 2022), THz spectroscopy and THz imaging in biomedical studies (Yu et al. 2019; Son 2015). More related studies for aspects of THz technology review are summarized in Table 1.

1.2 Motivation

Despite the unprecedented research efforts that have been put to develop and improve THz imaging and sensing for their wide scale application, the technology is not yet fully exploited. Much focus in the previously reported THz imaging and sensing studies has been on the improvement of the instrumentation for example antenna (Poorgholam-Khanjari and Zarrabi 2021; Apriono and Hidayat 2021; Kazemi 2021; Samanta et al. 2021; Yadav et al. 2021; Malhotra and Singh 2021c), biosensors (Yang et al. 2021; Azab et al. 2021; Liu et al. 2021; Zhan et al. 2021; Li et al. 2021; Lin et al. 2020) detectors (Habib et al. 2021) and probes (Chan and Ramer 2018). However, less work has been done for acquired images quality improvement and clinical decision support improvement. The identification of existing challenges and opportunities in the development of THz systems will pave way to continuous research and facilitate wide scale adoption.

1.3 Contribution

In this paper, the various aspects of THz imaging and sensing for the ultimate development of highly sensitive, reliable THz systems that will eventually evolve into medical modalities for cancer detection are explored. The paper provides recent trends and perspective in the THz imaging and sensing with identification of remaining challenges and research opportunities. More specifically:

Table 1 Other reported related literature reviews

Ref	Technique	Approach	Results	Limitations
Danciu et al. (2019)	THz tomography, endoscopy and spectroscopy	Review of THz technology for digestive cancer	Potential of digestive cancer detection using THz demonstrated Potential of THz based cancer treatment	Focused on the application of THz technology for digestive cancers
D'arco et al. (2020)	THz pulsed imaging	An overview of the TPI technology, its techniques, principles and cancer detection application has been given Outlined techniques for pulsed THz radiation emission and detection	TPI showed potential to detect various cancers	Limitations of TPI including slow scanning and limited penetration depth More attention required for THz penetration agents' development and ultimately the development of THz technology for its clinical adoption
Vafapour et al. (2020)	THz sensing	The future potential and applications of THz sensing have been discussed	THz sensing demonstrated great potential for the cancer detection application	Intelligent approaches are required to optimize reflectance and spectral response of THz data for cancer diagnosis
Nikitkina et al. (2021)	THz imaging and spectroscopy	Review of the pulsed wave and continuous THz wave-based THz imaging and spectroscopy for skin tissue assessment	Diagnosis of skin melanoma and assessment of dysplasia, diabetes and scars using their optical properties demonstrated Potential of THz technology for therapeutics and research	Further development of THz technology required
Gong et al. (2020)	THz technology	THz application and biological effects of THz in biomedicine have been reviewed They reported the THz techniques for cancer detection and characterization of DNA, protein and amino acids	Capability of THz technology for the biomedicine application demonstrated	The biological effects of THz radiation still under investigation

Table 1 (continued)

Ref	Technique	Approach	Results	Limitations
Zhang et al. (2021a)	THz technology	They investigated the biological effects and mechanisms of THz waves at molecule, cell and organism level on the nervous system	THz technology demonstrated potential for neuroscience and shown the response of gene expressions, cytokines, and cell membranes to THz radiation	Need for methodology standards establishment
Zhang et al. (2021b)	CW THz imaging	The review of CW THz imaging, its principles and scanning methods for biomedical samples scanning has been given	The THz imaging techniques based on CW THz demonstrated potential for biomedical application	Limited to CW THz imaging Technology still not yet fully established, and a lot of limitations still hinder its development
Wang (2021)	THz imaging	They reported the recent advances in the development of THz imaging and spectroscopy for breast cancer detection The dielectric responses of breast tissue in the THz range have been discussed	The potential of THz imaging for breast cancer detection has been noted	Need for THz data processing, collection and resolution improvement through chemometrics
Peng et al. (2020a)	THz imaging and spectroscopy	The progress in the development of THz technology and its application for cancer have been reviewed	The unique features of THz radiation such as non-ionizing and spectral fingerprinting for biomolecule identification have been emphasized THz technology promises to be a potential tool to assist doctors with insight of infected tissue The THz spectroscopy has been regarded as efficient for cancer biomarker identification	Low signal to noise ratio Need for further technology improvements

Table 1 (continued)

Ref	Technique	Approach	Results	Limitations
Yu et al. (2012)	THz imaging and spectroscopy	They reviewed the advances of THz technology in biomedical applications The sources of THz image contrast have been discussed	Suitability of THz radiation for biomedical applications due to non-ionizing hazard	THz waves strong sensitivity to water i.e., high absorption by water molecules
Castro-Camus et al. (2022)	THz imaging	The developmental progress of THz imaging from 1999 to 2021 has been reported for biological and medical applications such as plants, wound, burn and foot diabetes assessment	The development of THz imaging technology has significantly progressed over the years	Further developments are still required for clinical adoption
Cheon et al. (2017), Son (2013)	THz technology	Reports for THz biomedical application	THz technology exhibits great potential in the biomedical application as a clinical modality	There is need for continuous technology development
This paper	THz imaging and sensing	Present perspective and recent trends of THz imaging and sensing is investigated through the identification of existing challenges and research opportunities to facilitate the development of reliable and sensitive THz systems that can evolve into actual medical imaging modalities	THz systems demonstrate potential as actual medical modalities	As reported in this paper

- We give an overview of various aspects of THz technology, techniques for imaging and sensing, mechanisms for THz image contrast and models for tissue dielectric responses to THz waves.
- The THz imaging application for detection of various cancers is briefed.
- The advantages of THz cancer imaging and sensing as well as the existing challenges are identified, with suggestions provided in contribution to future research.
- Some recent THz imaging developments such as the near-field methods to break the diffraction limit including waveguides, resonance and plasmonic metasurfaces are also discussed.
- We emphasize the contribution of analytic algorithms that are based on machine learning, in particular deep learning for the development of THz technology.

1.4 Organization

The remaining sections of the paper are organized as shown in Fig. 1.

In the second section, the overview of THz imaging and sensing technology aspects for detection of cancer is presented; where the imaging and sensing techniques, THz image contrast sources and models for tissue dielectric response are highlighted, with the THz cancer imaging applications summarized. In the third section, the identified merits, challenges and research opportunities in THz imaging and sensing for cancer are presented. The advancements in the THz technology development are discussed in the fourth section and conclusion and future scope summarized in the fifth section.

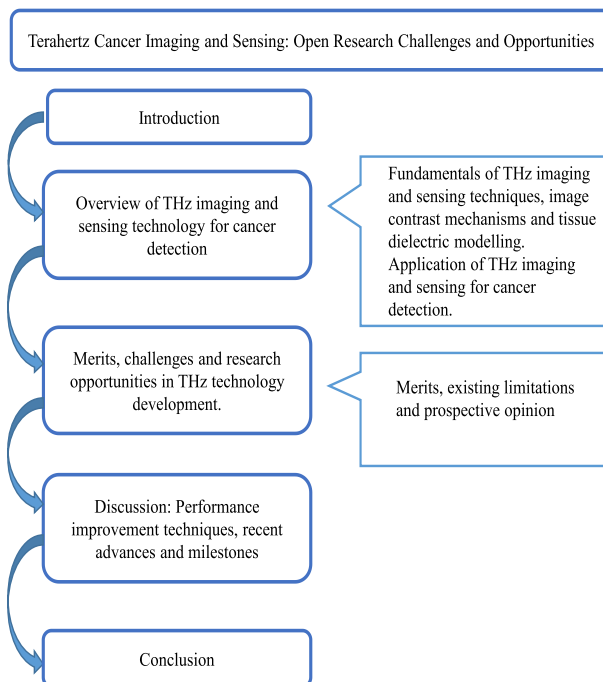


Fig. 1 Structure of this paper

2 Overview of THz imaging and sensing technology for cancer detection

The ability to distinguish and characterize certain structures in the image is the goal of imaging. The aim of medical imaging is going one step further; image contrast should be good enough to both highlight and characterize normal tissue and lesions. The evolution of new image contrast parameters in THz imaging will make it possible to visualize the flow, strain, function and stiffness of the human body tissue. In this section, the imaging and sensing aspects the THz technology are presented. An overview of the THz imaging and sensing techniques, image contrast mechanisms and application of THz imaging and sensing for cancer detection are exploited.

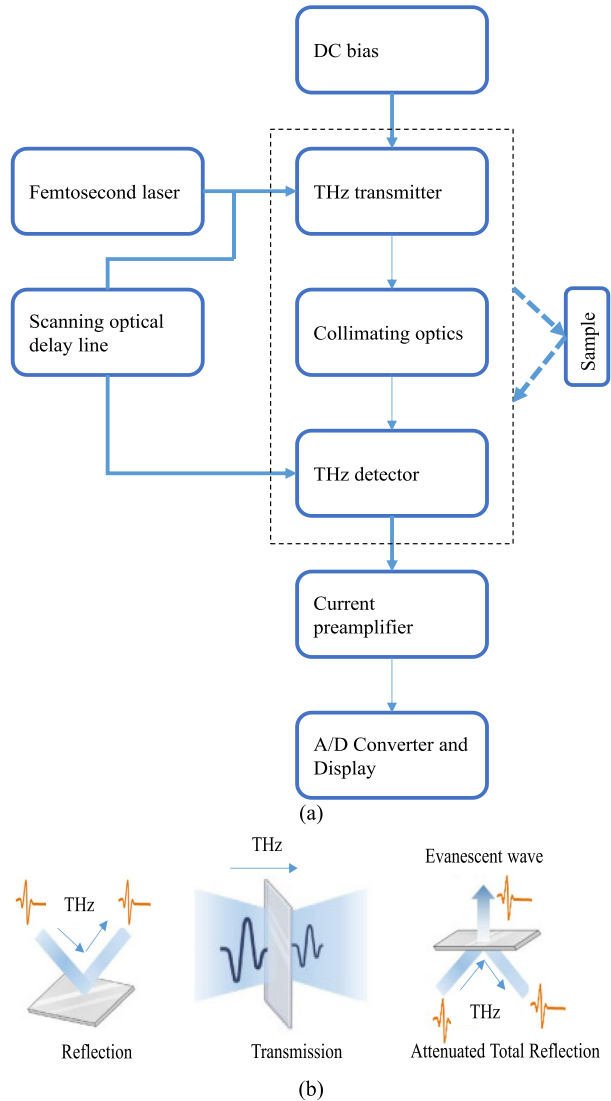
2.1 Overview of THz imaging and sensing techniques

The development of THz technology is rapidly advancing towards new techniques for THz radiation generation and detection, which will ultimately develop more efficient and convenient THz imaging, sensing and spectroscopy systems (Malhotra and Singh 2021a). The main technologies for THz imaging and spectroscopy are the pulsed THz wave based including the THz pulsed imaging (TPI) and THz time domain spectroscopy (THz-TDS) as well as the continuous THz wave-based systems i.e., THz continuous wave (CW) imaging and spectroscopy systems. The other known THz imaging techniques include the THz endoscopy, THz-ATR (Attenuated Total Reflection), THz near-field imaging (for example, frequency modulated continuous wave (FMCW) radar imaging) (Gezimati et al. 2023), close field imaging, full-field imaging, electro-optic imaging, bi-static THz wave imaging, single shot imaging, dark field imaging, THz computed tomography (THz-CT), THz Ptychography and THz tomographic imaging with Fresnel lenses etc. The THz spectroscopy systems include the THz-TDS, Fourier Transform Spectroscopy (FTS) and the photo-mixing spectroscopy systems are well presented in Gezimati and Singh (2023b).

Here, we focus on the TPI and THz-TDS systems which are the most commonly used THz systems in biomedical applications and can be used interchangeably through mode switching. The typical block diagram of the THz-TDS system is shown in Fig. 2a, mainly comprising components for THz wave emission, detection and beam guiding. The femto-second laser is used as the light beam source. The beam splitter splits the optical pulse to provide a detection pulse and the optical delay line adjusts the path length of the pulse. As the path length of the detection pulse is changed, the test signal is measured as a function of time. The sample's amplitude and phase information are obtained via the detector and conversions are performed into the optical parameters i.e., the refractive index and absorption coefficient parameters of the biological sample. The optical path passes through the sample in three main optional ways; reflection, transmission and ATR as illustrated in Fig. 2b.

THz biosensing for label free, noninvasive sensing has been realized through the techniques such as THz surface plasmon sensing (e.g., surface plasmon polaritons (SPPs)), plasmonic antennas, resonant waveguides and more recently metamaterials (MM) which are an artificial electromagnetic subwavelength structure with potential for highly sensitive detection. The metamaterials exhibit unique electromagnetic properties including negative refractive index, anomalous reflection, cloaking and optical magnetism and sub-diffraction

Fig. 2 Schematic of the **a** THz TDS system and **b** THz pulse path



limited focusing etc. as reported in details in Banerjee et al. (2022) and Faruk and Sabah (2019).

They are capable of highly sensitive, low cost and fast detection of thin or minute biological substances with high specificity through strongly localized and enhanced fields. The most common metamaterials' structural configurations are the split ring resonators (SRR) and the complementary SRR (CSRR). Several THz metamaterials designs have been investigated for cancerous cells detection to facilitate point of care diagnosis owing to their compactness and small detection volume. The principle of detection is based on scattering parameters that are induced by the unique dielectric property variations corresponding to the diseased and healthy tissues that are sensed by the metamaterials' resonator. More specifically, the resonance frequency of THz metamaterial is comparable to the

biomolecular vibrational frequency and cancer biomarkers are some of such biomolecules. Several metamaterials design have been explored for highly sensitive detection of cancer cells as reported in Banerjee et al. (2022), the circular ring resonators have been merged on a GaAs substrate and a 99% absorption at 3.71THz, 1447 GHz/RIU sensitivity with 92.75 quality factor (Q-factor) are achieved. More studies have been explored on metamaterial based THz biosensors for early detection of various cancer markers including liver cancer (Salim and Lim 2018), glioma cells (Zhang et al. 2021c), cervical cancer (Li et al. 2021). More recent works have been reported an advanced THz imaging and sensing techniques for cancer detection including in Li et al. (2021), Sadeghi et al. (2023) and Kucheryavenko et al. (2021).

2.2 THz image contrast parameters and tissue dielectric modelling in THz imaging

The source of THz image contrast for diseased and healthy tissues has mostly been from the local changes of water molecule content observed in the differences of tissue's optical parameters (i.e., absorption-and refractive-parameters) as well as dielectric parameters (i.e., dielectric permittivity). This is caused by the increase in vascularity, metabolism and edema in the diseased tissue among other factors. The THz frequency range resonates with the molecular relaxation processes and molecular intracellular vibration modes in the sub-picosecond and picosecond ranges. Therefore, the tissue cell dielectric responses have shown to reflect water dynamics using the THz spectroscopy (Zhang et al. 2019). The origin of image contrast is however, not only from the water molecule content changes in healthy and diseased tissues, a lot of other factors are being realized to contribute to the differences between tissues for example, the differences in the optical parameters have also been attributed to the increase of blood supply to the tissue infected by the cancer. Further, to being highly sensitive to water molecules content, THz waves are also sensitive to the biological composition such as genes, proteins and metabolites that are a key regulator of the development of cancer (Yang et al. 2023).

THz optical properties have been seen to be different in fat and muscle tissues, mainly, as a result of their water content differences, the bacteria cells in infectious diseases are also observed to have significant THz spectrum differences attributed to the small water molecule content differences. Even though the water molecule variations form the contrast basis in most studies, there are other causes of contrast. The changes in the THz optical properties have also been attributed to structural changes in the cells. Additionally, the molecular changes in healthy tissues have also been observed to contribute to the THz response, for example, a distinctive molecular resonance of methylated deoxyribonucleic acid (DNA) found in early cancer stages as illustrated in Cheon et al. (2016) using 1.67THz. Considering, the effects of structural and water content differences on THz optical properties of tissues, the techniques used for preservation of freshly excised tissue and their corresponding effects on the structure, and water content should be considered carefully. Techniques such as slow freezing, gelatin embedding, paraffin and eosin embedding etc. have been widely used. Further, other mechanisms for THz image contrast include THz interaction with various agents such as embedding and contrast agents, the tissue substances such as fiber, proteins, blood and fat as well as molecular density differences are reported in details in Peng et al. (2021), Peng et al. (2020b), Fu et al. (2022), Sun et al. (2017), Gezimati and Singh (2022a). However, more THz contrast parameters are being explored.

The dielectric responses of tissue to THz waves are another factor of THz image contrast. Through the dielectric modelling and using other models like structural

models, the parameters can be quantified (Wang 2021). The mathematical models such as the dielectric models e.g., double Debye model (Truong et al. 2015) has been widely explored. The Debye models have been proposed to model the THz dielectric response for example, the double Debye models (Reid et al. 2010) is used for extraction of dielectric parameters of collagen (Chen et al. 2022a), skin (Zhang et al. 2019; Yang et al. 2017; Peralta et al. 2019), brain (Wang et al. 2021) and breast tissue analysis as elaborated below.

The Debye models could be only precisely model the tissue with at least 70% of water (Yamaguchi et al. 2016). Biological tissues with complicated composition, complicated structures and low water content exhibit wider dispersion may involve molecular structure non-first order kinematics or superposition of the relaxation processes (Wang 2021). Hence, the models are constrained to breast tissue dielectric modeling due to its heterogeneity as it contains protein and fat cells that contain low water. A mixture model comprising of a non-Debye model and single-Debye model could accurately mimic the complex permittivity spectrum of the breast tissue and provide deeper, molecular level contrast mechanism. For very low frequencies (below 0.1THz), the complex permittivity of tissue can be modelled by a single-Debye relaxation model as reported in (Wang 2021):

$$\epsilon = \epsilon_{\infty} + \sum_{n=1}^N \frac{\Delta \epsilon_n}{1 + j\omega\tau_n} \tag{1}$$

where the $\Delta\epsilon_n$ term denotes n-th Debye relaxation process’ of dielectric permittivity dispersion. For higher water content tissues e.g., skin containing about 70% water, the double Debye model comprising of two processes of Debye relation are used to model the dielectric properties of that tissue. For muscle tissue with water content higher than that of skin, a summation comprising five Debye dispersions and a frequency-based conductivity term are used that is:

$$\epsilon = \epsilon_{\infty} + \sum_{n=1}^5 \frac{\Delta \epsilon_n}{1 + j\omega\tau_n} + \frac{\sigma}{j\omega \epsilon_0} \tag{2}$$

The low water content tissues with a complex anatomy and composition often show wider dispersion thus, the molecular structure involve without first order kinematics or several relaxation processes, hence for an accurate modelling of the dielectric properties, the Cole-cole (CC) equation is introduced:

$$\epsilon = \epsilon_{\infty} + \sum_{n=1}^5 \frac{\Delta \epsilon_n}{1 + (j\omega\tau_n)^{1-\alpha_n}} + \frac{\sigma}{j\omega \epsilon_0} \tag{3}$$

where α_n denotes distribution parameter of n-th dispersion. A Havriliak-Negami (HN) relationship introduces α and β empirical exponents to model a non-Debye relaxation that’s constituted by non-exponential relaxation processes from the CC equation:

$$\tilde{\epsilon}(\omega) = \epsilon_{\infty} + \frac{\epsilon_s - \epsilon_{\infty}}{[1 + (j\omega\tau)^{\alpha}]^{\beta}} \tag{4}$$

The mixture model comprising of Debye and non-Debye processes was reported to be best for modeling the breast tissue dielectric properties that is:

$$\tilde{\varepsilon}(\omega) = \varepsilon_{\infty} + \frac{\omega\tau_1\Delta\varepsilon_1 + \Delta\varepsilon_2}{1 + (j\omega\tau_1)^\alpha} + \frac{\Delta\varepsilon_3}{1 + j\omega\tau_2} + \frac{\sigma}{j\omega} \quad (5)$$

where, the complex permittivity's peak real part of breast tissue is produced by the term $\omega\tau_1\Delta\varepsilon_1 + \Delta\varepsilon_2$ at less than 1THz. The existence of two processes of relaxation defined by τ_1 , the time constant is shown through the terms $\Delta\varepsilon_1$ and $\Delta\varepsilon_2$. The fast relaxation mode corresponding high frequency defined by τ_2 has dispersive amplitude denoted by ε_3 while $\frac{\sigma}{j\omega}$ denotes DC-conductivity impact on the tissue's dielectric loss.

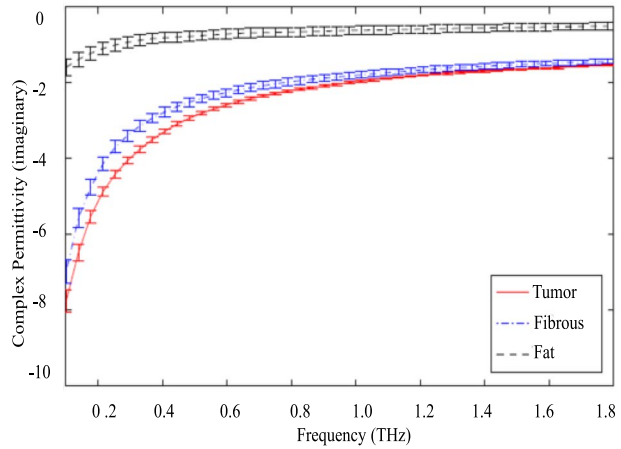
The sum of squared error functions (SSE) has been used for fitting the data and for the proper parameter extraction of the model presented in (5), which compute the complex dielectric permittivity over the THz frequency range. The complex dielectric permittivity of the breast tissues was computed using the spectral data of refractive indices and absorption coefficients measured from 74 breast samples using a THz-TDS system in the transmission mode. The complex dielectric permittivity represents the dielectric response of healthy fibrous tissues, fat and cancer tumor tissue to THz radiation. The breast samples were excised from 20 female patients which preserved in humid and refrigerated conditions. The details of the experimental procedures and measurement geometry have been described fully in Wang (2021). Since the complex dielectric permittivity's imaginary and real parts have been suggested to impact the values of the parameters introduced in (5) differently, the differences in the tumor and healthy tissues have shown the model parameters discriminating potential. The breast tissue has inhomogeneous anatomy and comprises fat cell and proteins where the adipose or fatty tissue has low content of water and thus contributes to the breast tissue dielectric responses. As shown in Fig. 3 reported by Wang (2021) and Hurt (1985), the dielectric response of breast tissues as measured by the spectrum of complex dielectric permittivity is high at lower frequencies and flat at high frequencies. The discriminating complex dielectric permittivity measured against the frequencies—their real and imaginary parts for the healthy breast tissue (fibrous), fat and tumor tissues are illustrated.

The terahertz frequency response over the normalized differences of the average complex dielectric permittivity (real and imaginary parts) of tumour and fat tissue as well as tumour and fibrous tissue are presented in Fig. 4. As can be seen in the figure, for most part of the spectral range, the variation of complex dielectric permittivity (imaginary part) of tumor and healthy is more significant than that of the of the real part (Wang 2021).

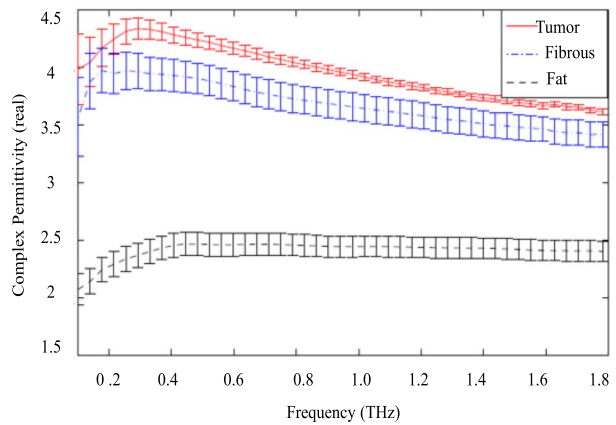
The dielectric models including the double Debye model and effective medium theory have been investigated for various applications in the THz regime for dielectric property estimations. As shown in Table 2 the Double Debye models' express permittivity by its physical properties and the EMT investigates tissue as composite of non-water and water substances. The double Debye model has been regarded better at describing tissue characteristics corresponding to the double Debye parameters and provides better flexibility e.g., for healthy and cancer tissues classifications based on these parameters. Thus, it has been applied to model the dielectric properties of various tissues in the THz domain including breast, skin, prostate and brain etc. However, the double Debye model's accuracy is still questionable for small tissue water concentration and its adaptability to dry tissues like SC still require further investigations.

The single layer, double layer, Fresnel theory and anisotropic SC models are structure models whose accuracy increases when their complexity increases. The merits and demerits of the structural models are presented in the table above and their details have been reported by Sun et al. (2017) and Peralta et al. (2019).

Fig. 3 The terahertz frequency response over the complex dielectric permittivity of the breast tissues **a** an imaginary part and **b** real part (Wang et al. 2021; Hurt 1985)



(a)



(b)

Fig. 4 Terahertz frequency response over fibrous and fat tissue with tumor- normalized percentage difference in the average complex permittivity (Wang et al. 2021; Hurt 1985)

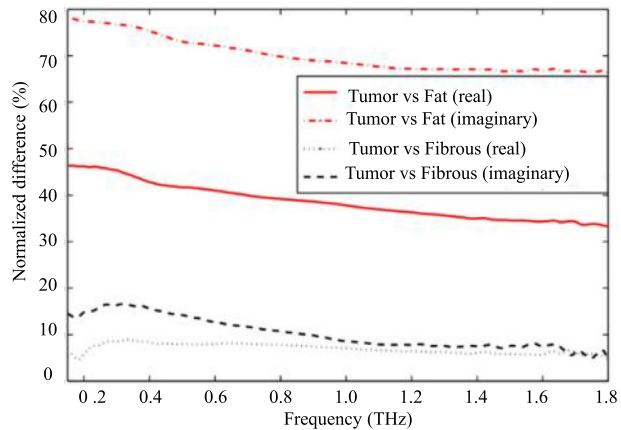


Table 2 Comparison for dielectric and structural models for THz based skin modelling

Model name	Merits	Limitations
Double Debye	Requires very little prior knowledge Physical properties obtained	Questionable accuracy for dry tissues
Single layer	Simple characterization	No comparability between setups Oversimplified Cannot distinguish different tissues
Effective medium theory	Few fittings' parameters Direct water content extraction	May not satisfy EMT assumptions Prior biological background knowledge is required
Fresnel theory/ Stratified media model	Good accuracy Can differentiate epidermis and the stratum conium (SC)	Requires pre-defined water profile Convergence difficult to achieve
Double layer	Clear distribution of water concentration Good consistency with Raman spectroscopy	Needs dielectric models
Anisotropic SC model	Considers birefringence induced by cellular structure of SC No dielectric model used Structural and hydration information obtained	A convergent fit requires multiple uncorrelated measurements

2.3 Application of THz imaging and sensing for cancer detection

The THz-TDS and TPI have been widely investigated for detection of various cancer like skin cancer, breast cancer, oral cancer, corneal cancer, colon cancer, digestive cancer, liver cancer and brain cancer etc. (Nikitkina et al. 2021; Kawashima et al. 2022; Bowman et al. 2018) and have shown ability to precisely delineate tumour tissue. More recently, laryngeal carcinoma samples imaging was performed using the THz-TDS at a frequency of 1.5THz and in transmission mode. The study was performed on three regions of laryngeal carcinoma tissue samples of thickness 80, 100, 150 and 200 μm . Using the THz-TDS in transmission mode, the absorption coefficient and refractive index of the three tissue groups were computed with smallest experimental error achieved by 100 μm thickness sample. As shown in Fig. 5, the HE staining results are shown in Fig. 5a, b shows THz image at 1.5THz, with the darker blue region corresponding to higher absorption value, representing tumour cells and the marking line showing the tumour area. The light blue region represents para-cancerous tissue and green normal tissue. The comparison between the contour shape of the THz image of the laryngeal tumour tissue and HE stained histopathological tissue showed to be roughly similar (Ke et al. 2022).

In Table 3, recent studies on application of THz imaging and sensing for detection of various cancers are presented. The THz technology is therefore noted to exhibit great potential for delineating cancer margins and early, non-ionizing cancer detection with high sensitivity, specificity and improved resolution.

3 Merits, challenges and research opportunities in THz technology development

In this section, the merits, challenges and opportunities in THz cancer imaging and sensing are discussed.

3.1 Merits of THz imaging and sensing for cancer detection

The following unique features of THz waves as presented in Fig. 6 make the technology attractive for novel applications including medical imaging, non-destructive testing, material identification and security inspection:

Fig. 5 Comparison between the laryngeal carcinoma detection **a** HE staining and **b** THz image (Ke et al. 2022)

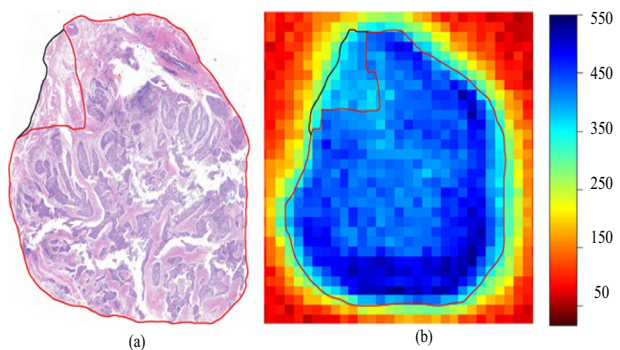


Table 3 Recent applications of THz imaging and sensing for cancer detection

Ref	Technique	Cell/ tissue	Results
Yang et al. (2023)	Near-field THz spectroscopy imaging	oral	High resolution, label free for clear detection of cancer Real time imaging rate, faster than conventional raster scanning using THz TDS and optical microscopy
Anwar and Khan (2023)	THz refractive index sensor based on Metamaterials	Various cancers	A high FOM and sensitivity of 125 RIU-1 and 1.87THz/RIU was achieved within a refractive index range of 1.35–1.39
Shi et al. (2022)	High resolution THz imaging	Gastric cancer	Up to 60 μm resolution achieved Lower THz transmittance in submucosa than mucosa and muscular layers for non-tumorous adjacent tissue Similar THz transmittance in submucosa and mucosa layers of Gastric cancer tissue
Al-Ibadi (2022)	THz spectroscopy and imaging	Breast cancer	Good contrast between different tissues demonstrated through optical and electrical property differences Accurate breast cancer tissue information provided
Jenifer Isabella et al. (2022)	Pulsed THz reflection spectroscopy	Oral tissues	Higher refractive index, absorption and extinction coefficient in malignant tissue than cyst and benign tissue
Zhao et al. (2022)	THz ptychography	Breast cancer	Improved reconstruction Successful imaging of breast tissue phase variation distribution
Vohra et al. (2022)	THz reflection spectroscopy	Breast tumor	Effectiveness of image enhancement agents (glycerol) demonstrated
Zhang et al. (2021d)	THz TDS	Gastric cancer	Clear cancer tissue localization through THz absorption spectra and without H&E staining Identification of carcinoma in situ and cancer tissues

Table 3 (continued)

Ref	Technique	Cell/ tissue	Results
Zhang et al. (2020)	THz spectroscopy and imaging	Prostate cancer	The feasibility of prostate cancer diagnosis using THz waves has been demonstrated based on optical parameter differences
Mohammed et al. (2023)	Photonic crystal fiber sensor	Brain cells for injury, tumor and malignancy	Capable of detecting various brain cells within 1–3THz 97.5% relative sensitivity, Low effective material loss of 0.005942 cm^{-1} Low confinement loss of $1.76 \times 10^{-11} \text{ cm}^{-1}$
Banerjee et al. (2022), Amini and Atlasbaf (2023); Veeravelam et al. (2022), Hu et al. (2021), Peng et al. (2023), Xie et al. (2023)	Metamaterial refractive index-based sensor	Cancer	High sensitivity, quality factor and figure of merit Suitability for early cancer detection demonstrated
Kaurav et al. (2022)	Iris waveguide probe	Breast cancer	Able to detect various breast tissue, tumor, fibrous and fat Positive and negative tumor margin identification within 110–170 GHz Detection depth of 1 mm and lateral sensitivity of 0.2 mm

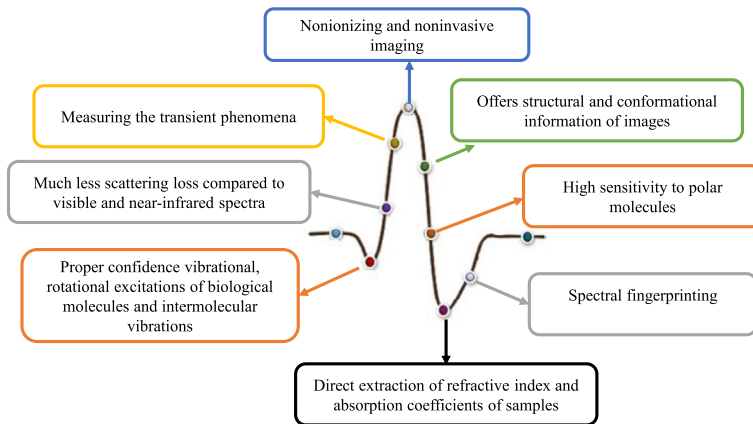


Fig. 6 Attractive features of THz radiation for cancer imaging

- (1) THz waves are non-ionizing in nature owing to their quite low photon energy,
- (2) The quanta energy of THz radiation coincides with intermolecular interactions for example Van der Waals hydrogen bonds, as such they interact with the low frequency motions of free charges, molecules and media collective excitations,
- (3) Resonant spectral absorption peaks—unique spectral fingerprints of molecular crystals and solid-state materials in the THz range
- (4) Sensitivity to polar molecules like water for biological tissue imaging. The hydrogen bonds network in water have broadband relaxation modes in the GHz to THz frequency spectrum, which is the origin of high absorption and permittivity of water in the THz band that makes THz waves to be strongly sensitive to water (Reid et al. 2010),
- (5) Penetration capability at sub-THz frequencies in various non-hydrated dielectric materials for example cloths, paper, plastic and wood,
- (6) Reduced Mie scattering effects and increased object penetration depth (compared to Infrared (IR) and visible spectrum) due to small structural inhomogeneities of many objects like biological tissues at THz wavelength scale thereby allowing application of the effective medium theory for description and analysis, and
- (7) All living organisms have a high water content which is crucial for their interaction with THz waves (Cherkasova et al. 2021; Chen et al. 2022b; Srivastava and Agarwal 2022; Gezimati and Singh 2023c).

The Table 4 summarizes attractive characteristics of THz waves for biological tissues.

3.2 Existing challenges and prospective opinion

Despite the breakthroughs and unprecedented progress made in THz technology development, significant challenges are still hindering the wide scale clinical adoption of THz technology as medical modalities that supplement clinical routines. The existing challenges and strategies to facilitate future wide scale clinical adoption of THz systems as well as the remaining biological effects of THz radiation are discussed to pave way to ongoing and future research. The focus of future prospects of THz development and improvement strategies is on facilitating THz development of THz systems that

Table 4 Summary of THz wave attractive characteristics for biological tissue

Feature	Explanation	Benefits
Sensitivity to polar molecules e.g., water	Natural vibrational and rotational energy levels of many molecules resonate with THz wave band Water molecules are more absorptive than the common macromolecules	Provide contrast between diseased and healthy tissues
Low photon energy	The THz radiation photon energy is insufficient to cause ionization or chemical damage to molecules	Nonionizing, noninvasive method
Spectral fingerprint	Unique spectroscopies of different cells which can be used as fingerprint	Distinguish different cells
Precise data analysis	Can simultaneously obtain THz radiation phase and amplitude	Precise spectral parameter analysis
Less scattering in biological tissues	Longer THz wavelength than visible light	Potential for deeper penetration depth relative to visible light

are compact and optimized to provide convenience in point of care operations. More research work is to be done in THz cancer imaging studies to address continuing limitations including:

- Time consuming sample preparation approaches.
- Lack of methodology and operating procedure standards, strict storage conditions, slice thickness, instrumentation, high water content effects etc.
- Lack of standardization of THz based measurements, processes or models for comparability, reproducibility, and possibly clinical adoption.
- Lack of established databases or repositories to facilitate data centred academic research.
- High signal loss.
- Lack of computational modelling for data management, interpretation, and analysis for decision support.

The potential research challenges and opportunities which have been discussed in this paper are summarized in Fig. 7.

3.2.1 Diffraction limited spatial resolution and sensitivity

The major limitations of conventional THz systems are the diffraction limit and low sensitivity so much that the detection sensitivity does not yet meet requirements for detecting living cells which needs to be improved. The diffraction limit causes poor spatial resolution. Some methods for alleviating this limitation have been suggested for example use of higher frequencies to increase the imaging effect. This however causes a decrease in the penetration depth of THz waves and ultimately the SNR (Signal to Noise Ratio) due to increased sample absorption coefficient as the frequency increases. In (Ke et al. 2022), the 1.5 THz frequency has shown to clearly define the cancer tumour margin. More techniques have been suggested to alleviate the diffraction limit drawback and increase THz systems sensitivity such as use of emitters and detectors based on air plasma (Wang et al. 2022), nanostructures and deep learning based analytic algorithms for data sampling and denoising, image reconstruction, efficient computing costs and compressive phase retrieval.

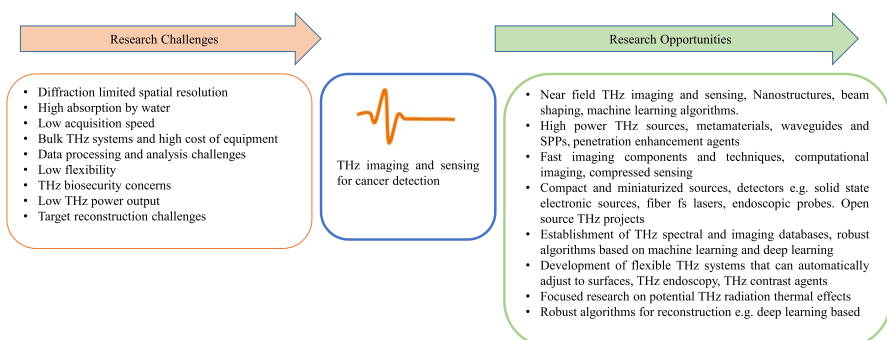


Fig. 7 Summary of research challenges and opportunities in THz imaging and sensing for cancer

3.2.2 High sensitivity to water

THz waves being highly sensitive to water, i.e., a high absorption coefficient of 150 cm^{-1} at 1THz, is a big limitation for THz imaging and sensing in biological tissue applications as the penetration depth becomes very limited (scale of tens to hundreds of microns). The consequence of this is limiting the capability of THz based in vivo measurements to epidermal or superficial tissue layers of the target as well as making the reflection mode THz imaging most suitable. As a result, most experimental studies for THz imaging have explored ex vivo THz imaging on excised tissues and the samples having to pre-treated, solid and kept under dry conditions which limits the ability of THz based exploration of samples that are water rich (for water constitutes 70% of human skin tissue content) as well as constrains their operation in environments that are interfered by water vapour (Yu et al. 2019; D'arco et al. 2020). Some of the techniques suggested to increase THz penetration depth for SNR enhancement include sensors with higher sensitivity, improved free electron lasers and use of intense THz sources. High THz power however raises concerns of thermal effects on biological tissue. Another approach is the design of highly sensitive biosensors such as resonant waveguides, SPPs and metamaterials (Reid et al. 2010). Further, techniques for tissue sample preparation for penetration depth and SNR enhancement include lyophilizing, dehydration, formalin fixing, alcohol perfusion, gelatin embedding, freezing and paraffin embedding. THz PEAs (Penetration Enhancing Agents) as well as the use of contrast enhancing agents for example nanoparticles etc. are also useful in this regard. Researchers are also investigating methods for signal enhancement so as to optimize biosensors including using microfluidic chips, hydrogels and metallic nanoparticles (Zhan et al. 2023).

3.2.3 Low acquisition speed

To be a clinically competitive imaging and sensing modality, there is need to improve the acquisition speed of THz imaging systems to be close to real time. Conventional THz imaging systems like the TPI (THz pulsed imaging) uses raster scanning whereby the acquisition is done pixel by pixel, which causes long scanning times (i.e., imaging speed of the order 50 pixels/second). This is a challenge at the point of care as it is difficult for the patient to remain still over a long scanning duration and moreover it causes some time induced variations to be introduced to the image. The low acquisition speed is caused by the use of a single pixel detector and the optical delay line. To overcome this drawback, some fast components have been suggested including use of fast optical delay lines, ASOPS (Asynchronous Optical Sampling), ECOPS (Electronically Controlled Optical Sampling), Charge Coupled Device (CCD) cameras for implementation of 2D electro optic sampling. The use of techniques such as optical rectification, 2D photoconductive antennas, electro-optical sampling in nonlinear crystals, non-mechanical time domain sampling and combining digital holography, bolometer array and THz cameras have also been suggested. More recently, the combination of a THz pulsed system and the single pixel camera has been shown to improve acquisition speed, achieving a real time imaging speed of six frames per second on a 32×32 target sample through serial acquisition. Other techniques include the use of continuous wave single wavelength imaging (Reid et al. 2010; Wang et al. 2022), computational imaging, compressed sensing and focal plane array based techniques (Castro-Camus et al. 2022; Gezimati and Singh 2022b).

3.2.4 Challenges in data driven THz studies

For overcoming some of the bottlenecks in practical THz technology implementation and to meet the ever rising market demands, there is need to continuously advance the development of the technology and integrating with other technologies such as artificial intelligence, in particular machine learning (Chopard et al. 2021; Xie et al. 2013). There is an urgent need for the ability of machine learning techniques to generalize and be robust in their application for extraction & analysis tasks of THz data (Shang et al. 2019). The effective performance of machine learning models and particularly deep learning models however largely depend on the size of the training dataset, which is currently limited in the THz cancer community. There is a current major challenge of the unavailability of sufficient or shared datasets for THz cancer image data. The expensive costs of human excised fresh tissue from tissue banks as well as the complex ethical procedures and government mandated permissions for acquiring and processing human tissue as well as the high cost of THz imaging equipment are some of the major drawback factors to the establishment of THz cancer datasets which negatively impacts the progress of data centric academic research (Yeo et al. 2019).

Due to insufficient training datasets, the designed deep learning models suffer overfitting, compromising the robustness and accuracy of the models. Apart from training dataset size, the model performance also relies on factors such as parameter selection and optimization. There is need to establish large THz training databases to support data driven studies (Gezimati and Singh 2022c). Deep learning techniques could significantly contribute to the development of intelligent THz systems including CAD (Computer Aided Diagnostic) systems that are crucial for clinical decision support (Gezimati and Singh 2023d). Further they can facilitate the development of fast, highly sensitive THz systems through performance of tasks such as THz data extraction, discrimination of regions, noise removal in measurements, image reconstruction, resolution enhancement, image characterization and analysis.

In a recent study (Liu et al. 2022), potential challenges have been reported in the implementation of deep learning for breast cancer application such as erroneous classifications attributed to ground truth unavailability due to deformations induced by the process of paraffin, formalin fixing as well as scattering of pixels near the edges of the scan. Some false positives have been observed to be caused by multiple tissues that appear in the THz pixel region. It is also a challenging task to differentiate THz scan signals and tissues with electric properties that are overlapping for example muscle and fat tissue or muscle and cancer tissue using statistical inference-based algorithms.

There is need for development of more robust and advanced machine learning algorithms with the capability to accurately find reasonable solutions in the cases where there is far from learned distribution data and out of distribution data. Some of the advanced machine learning techniques with great potential to transform the future of THz cancer imaging and sensing are for example deep learning, federated learning, active learning, meta-learning, multitask and specialized learning (Helal et al. 2022; Jiang et al. 2022).

3.2.5 Lack of methodology standards

Currently, THz experimental measurements lack comparability due to diverse methodologies for example experimental protocols, system configurations, processing techniques and models etc. As an example the THz TDS system, transmission configuration for solid

samples has yielded diverging results by different groups according to a comparative study performed by Naftaly (2016). There is need for establishment of commonly accepted standards in the THz measurements overcome complications in solid sample measurements in biomedical applications which are made up of many variables.

Further, the proposed dielectric models are not standardized and there are inconsistencies in the measurement protocols resulting in diverging results and constraining of model performance, performance comparison and standardization. As an example, there are different models for modelling the response of skin cancer and a consensus has not yet been reached. There is therefore need to standardize the detection variables of sensing techniques, i.e., for control of the variables that affect THz response. There is also need to establish the safety protocols of THz radiation, i.e. to understand the THz radiation effects on bio matter (Reid et al. 2010). The establishment of standard measurement protocols will address the challenges associated results comparability that are obtained from different experimental setups. The ultimate establishment of standards can be achieved through focused research for gradually reducing THz studies divergence.

3.2.6 Low flexibility of THz systems

Due to the effects of low penetration depth, studies on the in vivo THz measurements have focused on observations of superficial layer tissues such as skin, cornea and oral tissues. To successfully perform in vivo THz imaging, the sample has to be on a flat surface and measurement to be done in the reflection mode of the THz imaging system so as to achieve alignment. As a result, most experimental studies have been limited to ex vivo imaging of excised tissue samples. The excised tissue samples require special pre-treatment and are prone to altered tissue properties which compromise the measurements. There is a need to achieve high flexibility of THz systems so as to enable in vivo imaging of the human body and for alignment adjustment according to the target body surface. The use of THz endoscopy for flexible THz system has been suggested even though they are still lacking precise alignment capability due to single pixel detection. The other techniques include robotic arms, development of contrast agents and use of passive THz imaging techniques (Yan et al. 2022; Reid et al. 2010).

3.2.7 THz technology biosafety

Compared to the conventional imaging modalities like the Gamma Ray and X-ray based imagers that uses ionizing radiation, THz radiation-based imagers does not pose the ionizing or chemical hazard on biological since their low photon energy is insufficient to cause radiation. However, the advancements in THz research have raised concerns on the potential thermal and other effects of THz radiation on biological tissue especially when exposed to high-density radiation of the THz range. Though, it is currently inconclusive, some studies have suggested the potential thermal hazards of some high THz radiation parameters such as intensity, power, exposure time, power density and frequency etc. For example, the exposure of high-power density of THz radiation (i.e., 0.15THz, 3mWcm^{-2} , 60 min) have shown to cause an increase of mouse model depression levels, parameters of 2.7THz, 260mWcm^{-2} , 30 min to cause an inflammatory response of the skin and 2.5THz, $0.32\mu\text{Wcm}^{-2}$, 60 min to have caused wound healing perturbation. Further, the low power densities have been demonstrated to not any potential thermal effects or damage on the skin (Yu et al. 2019; Tarabichi et al. 2022). Therefore, there is need for further research to

reconsider the biosafety and potential hazards of THz radiation exposure for facilitating THz systems clinical and wide scale adoption.

3.2.8 Other challenges

Some of the other challenges deterring the THz technology wide scale adoption include the bulkiness of the THz imaging systems that are presently commercially available, making them more suitable for laboratory based use than point of care. There is need for optimization of THz systems to be miniaturized and compact for suitability for real operational environments. Due to the current high costs of THz sources and detectors, the commercially available THz imaging systems typically costs around USD100000 to USD500000 which is a very high cost for academic based research. The development of THz sources based on solid state electronics shows great potential to greatly reduce the overall cost of THz imaging equipment.

Another challenge is associated with THz measurements being prone to scattering effects when a target sample is exposed to THz waves due to particle non-uniformities such as size differences and shape irregularities that alter and affect the accuracy of the optical response of the sample. This can be reduced by grinding or compressing the target specimen to have smooth, fine particles. Also, presently it is difficult to precisely extract the target spectral fingerprints in spectral studies using Fourier transforms due to complex backgrounds and interfering signals, the future realization of sensors with high sensitivity and specificity such as plasmon antenna and meta-materials could be effective in alleviating this challenge.

Other challenges are related to low THz power output of conventional THz emitters such as the photoconductive antennas, whereas higher THz power output in the mW range is desirable for 2D real-time imaging. There is need for algorithms capable of target reconstruction that accommodate reconstruction of 3D targets with shape irregularities for example the human body including in THz computed tomography (Jiang et al. 2022; Rahman 2019). Finally, the other remaining challenge in THz technology application for cancer detection relates to the yet to be achieved image quality as a result of different factors including low resolution, complex noise and presence of artefacts. The exploration of near field THz imaging and development of algorithms for super resolution (Hou et al. 2022) could potentially alleviate this challenge.

4 Discussion

Here, we discuss the potential approaches for performance improvement of THz imaging systems that have been studied to counter some of the formerly stated limitations. Conventional THz imaging and spectroscopy systems have been mainly driven by the optoelectronic THz-TDS systems which are bulky, and laboratory use oriented. Recent advances are making efforts to improve various aspects of THz imaging technology including reduced power and enhanced functionality to provide increased convenience, technology implementation and adoption in real operational environments i.e., through miniaturization and optimization. This has realized the development of compact, room temperature operating and high THz power output THz emitter solutions including sources based on fiber femto-second lasers, mid-infrared and room temperature operating & plasmonic quantum cascade lasers (QCLs), Silicon Nano-transistors, Hetero-junction Field-effect Transistors (HFETs)

or high electron mobility transistors (HMETs), Resonant Tunneling Diodes (RTDs) and vacuum electronic sources. Rapid evolution has also been noted towards compact room temperature detectors and arrays including detectors based on FETs, Diode based sensing and Microbolometers for example Micro-Electromechanical Systems (MEMS). Highly integrated platforms are being developed through Computational Imaging (CI) allowing the connectedness of advanced optics, modern sensing devices and post-acquisition signal processing for improved system performance that enable faster acquisition and such systems include THz compressed sensing, THz holography, THz Fourier Imaging, 3D-THz imaging and THz super resolution imaging like THz near field imaging and Super resolution Orthogonal Deterministic Imaging (SODI). The recent advances in THz nanoscopy and Nano-imaging include scattering type scanning Near-field Optical Microscopy (s-SNOM), Nano slits and THz Scanning Tunneling Microscopy (THz-STM). There have been developments in specialized THz imaging techniques for example light field method, phase sensitive interferometry and homodyne spectroscopy, room temperature THz comb spectroscopy, passive THz imaging and Frequency Modulated Continuous Wave (FMCW) THz imaging which entails radar-based techniques like the Synthetic Aperture Radar (SAR) imaging (Gezimati et al. 2023).

Further, other advances have been realized in THz technology for example, beam forming & diffractive optical components which have realized the miniaturization of passive optical components including gratings, lenses, beam splitters, mirrors etc. and the use of antireflective optical elements or printed passive beam guiding, optical graphite features and meta-materials. System-on-chip solutions for THz imaging can be achieved through integration of on-chip sensing and emitting elements for hybrid THz systems using the CMOS (Complementary Metal Oxide Semiconductor) technology. Spatial filtering in THz range has been realized using dark field imaging and phase contrast and Artificial Intelligence (AI) enabled THz systems have also been realized (Valušis et al. 2021; Yan et al. 2022; Castro-Camus et al. 2022; Gezimati and Singh 2022a).

It's a challenging task to detect trace molecule amounts because of THz wavelength and molecule size mismatch which causes very low absorption cross section. As a result, most research has been limited to samples of solid type. When using THz TDS to measure the absorption spectrum of mixture or compound samples, a significant absorption spectral feature from the host material whose volume fraction is higher can be easily obtained. Thus, samples are mostly prepared in pellet form as a pure substance so as to increase concentration of molecules under high pressure. Water molecules highly absorb THz waves, which makes it difficult to identify molecules that are dissolved in liquids such as water. Approaches for signal enhancement are therefore mandatory such as using modulators or resonators. When the resonator is used to increase THz near field, the absorption cross section of a particular molecule is also enhanced even in aqueous environments. Using a modulator like randomly patterned mask for iterative signal acquisition can achieve increased acquisition speed and simultaneously overcome diffraction limit. Plasmonic metasurfaces that consist of nanoscale resonators enable strong near field enhancement THz enhancement and have been considered excellent for detection of specific molecules. With further developments in the technology of nanofabrication, surface mediated THz sensing have evolved to diverse forms. Some methods of integrating sensing platforms based on metasurfaces with additional sample collectors have been proposed including microfluidic platform that integrate metasurfaces with graphene that improves selective sensing of DNA sequences of foodborne pathogens in liquid environments. Resonance based metasurfaces or beam modulations also enhance THz image contrast for better performance of analysis algorithms (Sun et al. 2017).

The use of THz waves for sensing is also limited by the long wavelengths relative to the sample thickness, which normally is at sub wavelength or molecular level. Some techniques have been previously reported to overcome this issue such as the use of metamaterials, THz Surface Plasmon Polaritons (SPPs) and waveguides. Metamaterials are artificial media with sub wavelength periodic structures consisting of effective electromagnetic properties tailored by their structures. Metamaterials are not limited to sensing but have also been used widely in THz functional devices for modulation, beam control and manipulation of polarization due to their structural design high flexibility, which makes it possible the realization of almost arbitrary THz wave responses. Planar metamaterials known as metasurfaces are used for sensing applications in convenient sample preparation measurements based on amplitude change or resonance shift of the metamaterial sensor.

Waveguides are structures that direct THz beam propagation by providing a tight confinement of the field near guiding structure and a propagation length. These have also been noted to be favorable for sensing thin films and a small amount of analyte, even though the sensitive detection of aqueous samples that are absorptive have not been demonstrated yet. The many forms of THz waveguides include parallel plate waveguides, Micro strip line waveguides, coplanar waveguide lines and dielectric waveguide lines. THz SPPs were originally used for sensitive probing in visible wavelengths. Three approaches have been used to achieve THz SPPs including prism coupled SPPs that are based on doped semiconductors, spoof SPPs based on artificial periodic structures and aperture coupled SPPs with conductor dielectric interface (Reid et al. 2010). THz broadband Fourier transform imaging with resonators have been explored for improved sensitivity and selectivity through the resonance-based sensing chip and is expected to provide same conceptual configuration when integrated with a spatial scanning technique. The THz based Fast Fourier Transform (FFT) has been developed using THz TDS and enhanced sample response as a result of resonance behavior of metasurface for performing spatiotemporal imaging of biochemical. Molecular biomarkers have fingerprint spectral features in the broad THz regime, however the spectral information of the spectral fingerprints can be easily lost when they are dissolved in water or superposed in a mixed form. It is therefore a challenging task to expect sharp fingerprinting for larger biological species such as cells, proteins, or body organs (Lee et al. 2021).

5 Conclusion and future scope

This paper has presented an overview of the existing potential challenges and research opportunities of THz technology-based cancer imaging and sensing applications. THz imaging systems exhibit great potential as a label free, noninvasive, non-ionizing cancer imaging tool. The practical expediency of THz systems is however still limited, relatively immature and facing obstacles such as low efficiency, low power and large THz source dimensions, lack of technical standards for measurement procedures, high THz waves absorption by water leading to limited penetration depth, and low acquisition speed, which paves way to more research opportunities in the areas of THz technology. Thus, significant engineering and research efforts are still required to develop THz imaging and real-time sensing systems which should be compact, portable, optimized and low-cost THz systems that will provide real operational convenience for clinical environment. Future studies could contribute to facilitate clinical adoption of THz imaging tools through the development of compact, cost effective, optimized systems, which investigate the impact

of THz radiation on biological tissues, evolving methodology standards, developing more techniques to overcome limited penetration depth, and establish THz cancer image datasets to facilitate data driven research. Moreover, the establishment of THz cancer imaging and spectral databases might bring breakthroughs to comparability of developed models and facilitate qualitative and quantitative data driven research. Future THz spectroscopy prospects should also focus on the development of convenient, label free and rapid biosensors to enable THz in vivo imaging and point of care tests. Further, an integration of THz systems with new technologies such as internet of things (IoT), artificial intelligence particularly deep learning, should also need to explore for development of smart, connected clinical decision support systems and high-resolution image reconstruction.

The future advances in THz technology development should ultimately facilitate the clinical adoption of THz systems and therefore the advances should be evident through the following improvement aspects. The cost effectiveness and high performance of THz systems in the biomedical imaging of cancer will need to be improved in the aspects of spectral and spatial resolution, imaging speed, amount of information provided by the system, THz power output and sensitive detection. More advanced and robust machine learning algorithms will be required which will be capable of yielding accurate and reasonable solutions in circumstances of out of distribution data and far from learned distribution data. These techniques will be very useful for future THz sensing and communication applications include deep learning, multitask learning, meta-learning, federated learning, active learning, and specialized learning. The fusion of THz technology and deep learning techniques will enable robust and accurate prediction models. The deep learning models will improve in-depth feature extraction, data analysis, clinical decision support system development, super resolution reconstruction, intelligent design of THz structures, and optimize THz software development. Further, to become a clinical and next generation competent imaging modality, THz imaging systems should be developed to be interoperable, capable of in vivo imaging of the whole body and provide real operational convenience.

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Declarations

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References

- Al-Ibadi, A.: EX vivo terahertz imaging reflection of malignant and benign human breast tumors. *Malays. J. Sci.* **41**(sp1), 17–22 (2022)
- Amini, B., Atlasbaf, Z.: Design and analysis of high-sensitivity tunable graphene sensors for cancer detection. *Opt. Quant. Electron.* **55**(5), 446 (2023)
- Anwar, S., Khan, M.: High-performance terahertz refractive index sensor for cancer cells detection. *Eur. Phys. J. E* **46**(3), 1–12 (2023)
- Apriono, C., Hidayat, M.V.: Distance investigation between two linear array microstrip antenna for terahertz breast cancer imaging. *AIP Conf. Proc.* **2344**(1), 50011 (2021)
- Azab, M.Y., Hameed, M.F.O., Nasr, A.M., Obayya, S.S.A.: Highly sensitive metamaterial biosensor for cancer early detection. *IEEE Sens. J.* **21**(6), 7748–7755 (2021)
- Banerjee, S., Dutta, P., Jha, A.V., Appasani, B., Khan, M.S.: A biomedical sensor for detection of cancer cells based on terahertz metamaterial absorber. *IEEE Sens. Lett.* **6**(6), 1–4 (2022)
- Bowman, T., El-Shenawee, M., Bailey, K.: Challenges in terahertz imaging of freshly excised human breast tumors. In: *Proceedings of the IEEE Antennas and Propagation Society International Symposium and USNC/URSI National Radio Science Meeting (APSURSI 2018)*, pp. 13–14 (2018)
- Castro-Camus, E., Koch, M., Mittleman, D.M.: Recent advances in terahertz imaging: 1999 to 2021. *Appl. Phys. B Lasers Opt.* **128**(1), 1–10 (2022)
- Chan, K.Y., Ramer, R.: Novel concept of detecting basal cell carcinoma in skin tissue using a continuous-wave millimeter-wave rectangular glass filled probe. *Med. Devices Evid. Res.* **11**, 275–285 (2018)
- Chen, X., Lindley-Hatcher, H., Stantchev, R.I., Wang, J., Li, K., et al.: Terahertz (thz) biophotonics technology: instrumentation, techniques, and biomedical applications. *Chem. Phys. Rev.* **3**(1), 11311 (2022a)
- Chen, H., Han, J., Ma, S., Li, X., Qiu, T., et al.: Clinical diagnosis of gastric cancer by high-sensitivity thz fiber-based fast-scanning near-field imaging. *Cancers* **14**(16), 3932 (2022b)
- Cheon, H., Yang, H.J., Lee, S.H., Kim, Y.A., Son, J.H.: Terahertz molecular resonance of cancer DNA. *Sci. Rep.* **6**, 1–10 (2016)
- Cheon, H., Yang, H.J., Son, J.H.: Toward clinical cancer imaging using terahertz spectroscopy. *IEEE J. Sel. Top. Quantum Electron.* **23**(4), 1–9 (2017)
- Cherkasova, O.P., Serdyukov, D.S., Nemova, E.F., Ratushnyak, A.S., Kucheryavenko, A.S., et al.: Cellular effects of terahertz waves. *J. Biomed. Opt.* **26**(09), 90902 (2021)
- Chopard, A., Fauquet, F., Goh, J. S., Pan, M., Mounaix, P., et al.: Teragogic: open source platform for low cost millimeter wave sensing and terahertz imaging. In: *Proceedings of the IEEE National Radar Conference*, pp. 1–6 (2021)
- D'arco, A., Di Fabrizio, M., Dolci, V., Petrarca, M., Lupi, S.: Thz pulsed imaging in biomedical applications. *Condens. Matter* **5**(2), 25 (2020)
- Danciu, M., Alexa-Stratulat, T., Stefanescu, C., Dodi, G., Tamba, B.I., et al.: Terahertz spectroscopy and imaging: a cutting-edge method for diagnosing digestive cancers. *Materials* **12**(9), 1519 (2019)
- Faruk, A., Sabah, C.: Terahertz metamaterial absorber comprised of h-shaped resonator within split-square ring and its sensory application. *Optik* **192**, 162976 (2019)
- Fu, X., Liu, Y., Chen, Q., Fu, Y., Cui, T.J.: Applications of terahertz spectroscopy in the detection and recognition of substances. *Front. Phys.* **10**, 427 (2022)
- Gezimati, M., Singh, G.: Advances in terahertz instrumentation and technology for cancer applications. In: *Proceedings of the International Conference on Infrared, Millimeter, and Terahertz Waves (IRMMW-THz)*, pp. 1–2 (2022a)
- Gezimati, M., Singh, G.: Circular synthetic aperture radar for near-field terahertz imaging. In: *Proceedings of the 5th International Conference on Multimedia, Signal Processing and Communication Technologies (IMPACT)*, pp. 1–5 (2022b)
- Gezimati, M., Singh, G.: Transfer learning for breast cancer classification in terahertz and infrared imaging. In: *Proceedings of the 5th International Conference on Artificial Intelligence, Big Data, Computing and Data Communication Systems (icABCD 2022c)*, pp. 1–6 (2022c)
- Gezimati, M., Singh, G.: Open research challenges and opportunities in terahertz imaging and sensing for cancer detection. In: *Proceedings of the International Conference on Microwave, Antenna and Communication - (MAC2023c)*, pp. 1–6 (2023c)
- Gezimati, M., Singh, G.: Curved synthetic aperture radar for near-field terahertz imaging. *IEEE Photonics J.* **15**(3), 5900113 (2023)
- Gezimati, M., Singh, G.: Terahertz imaging and sensing for healthcare: current status and future perspectives. *IEEE Access* **11**, 18590–18619 (2023a)
- Gezimati, M., Singh, G.: Advances in terahertz technology for cancer detection applications. *Opt. Quant. Electron.* **55**(2), 151 (2023b)

- Gezimati, M., Singh, G.: Internet of things enabled framework for terahertz and infrared cancer imaging. *Opt. Quant. Electron.* **26**, 1–17 (2023d)
- Gong, A., Qiu, Y., Chen, X., Zhao, Z., Xia, L., et al.: Biomedical applications of terahertz technology. *Appl. Spectrosc. Rev.* **55**(5), 418–438 (2020)
- Habib, A., Rashed, A.N.Z., El-Hageen, H.M., Alatwi, A.M.: Extremely sensitive photonic crystal fiber-based cancer cell detector in the terahertz regime. *Plasmonics* **16**(4), 1297–1306 (2021)
- Helal, S., Sarieedeen, H., Dahrouj, H., Al-Naffouri, T.Y., Alouini, M.S.: Signal processing and machine learning techniques for terahertz sensing: an overview. *IEEE Signal Process. Mag.* **39**(5), 42–62 (2022)
- Hou, Z., An, H., He, L., Li, E., Lai, D.: Super-resolution reconstruction algorithm for terahertz images. In: *Proceedings of the 3rd International Conference on Pattern Recognition and Machine Learning (PRML 2022)*, pp. 180–185 (2022)
- Hu, J., Li, M., Wang, Z., Hu, Z., Wang, J., et al.: High-performance terahertz refractive index sensor based on a hybrid graphene tamm structure. *J. Opt. Soc. Am. B* **38**(9), 2543–2550 (2021)
- Huang, Y., Shen, Y., Wang, J.: From terahertz imaging to terahertz wireless communications. *Engineering* **22**, 106–124 (2022)
- Hurt, W.D.: Multiterm Debye dispersion relations for permittivity of muscle. *IEEE Trans. Biomed. Eng.* **32**(1), 60–64 (1985)
- Jenifer Isabella, S. S., Sunitha, K. A., Magesh, K. T., Arjunan, S. P., Pesala, B.: Investigation of formalin-fixed tissue optical characteristics in the range of 200–500 GHz using pulsed terahertz reflection spectroscopy to differentiate oral malignant, benign, and cyst. *J. Spectrosc.* 2022(3627705) (2022)
- Jiang, Y., Li, G., Ge, H., Wang, F., Li, L., et al.: Machine learning and application in terahertz technology: a review on achievements and future challenges. *IEEE Access* **10**, 53761–53776 (2022)
- Kaurav, P., Koul, S., Basu, A.: Sub-terahertz waveguide iris probe for ex-vivo breast cancer tumor margin assessment. *IEEE J. Electromagn. RF Microw. Med. Biol.* **6**(3), 406–412 (2022)
- Kawashima, Y., Masaaki, S., Kuyama, K., Sakai, T., Hayakawa, Y., et al.: Terahertz imaging for formalin fixed malignant liver tumors using two-band beamline at the accelerator facility of nihon university. *Appl. Sci.* **12**(4), 2229 (2022)
- Kazemi, F.: High q-factor compact and reconfigurable THz aperture antenna based on graphene loads for detecting breast cancer cells. *Superlattices Microstruct.* **153**, 106865 (2021)
- Ke, J., Jia, L., Hu, Y., Jiang, X., Mo, H., et al.: Clinical and experimental study of a terahertz time-domain system for the determination of the pathological margins of laryngeal carcinoma. *World J. Surg. Oncol.* **20**(1), 1–11 (2022)
- Kucheryavenko, A.S., Chernomyrdin, N.V., Gavadush, A.A., Alekseeva, A.I., Nikitin, P.V., et al.: Terahertz dielectric spectroscopy and solid immersion microscopy of ex vivo glioma model 101.8: brain tissue heterogeneity. *Biomed. Opt. Express* **12**(8), 5272–5289 (2021)
- Lee, G., Lee, J., Park, Q.H., Seo, M.: Frontiers in terahertz imaging applications beyond absorption cross-section and diffraction limits. *ACS Photonics* **9**(5), 1500–1512 (2021)
- Lewis, R. A.: Terahertz imaging and spectroscopy methods and instrumentation. In: Lindon J., Tranter, G., Koppenaal, D. (eds.) *Encyclopedia of Spectroscopy and Spectrometry*, 3rd ed., pp. 422–426. Elsevier Oxford (2017)
- Li, D., Hu, F., Zhang, H., Chen, Z., Huang, G., et al.: Identification of early-stage cervical cancer tissue using metamaterial terahertz biosensor with two resonant absorption frequencies. *IEEE J. Sel. Top. Quantum Electron.* **27**(4), 1–7 (2021)
- Lin, S., Xu, X., Hu, F., Chen, Z., Wang, Y., et al.: Using antibody modified terahertz metamaterial biosensor to detect concentration of carcinoembryonic antigen. *IEEE J. Sel. Top. Quantum Electron.* **27**(4), 1–7 (2020)
- Lindley-Hatcher, H., Stantchev, R.I., Chen, X., Hernandez-Serrano, A.I., Hardwicke, J., et al.: Real time THz imaging—opportunities and challenges for skin cancer detection. *Appl. Phys. Lett.* **118**(23), 230501 (2021)
- Liu, K., Zhang, R., Liu, Y., Chen, X., Li, K., et al.: Gold nanoparticle enhanced detection of EGFR with a terahertz metamaterial biosensor. *Biomed. Opt. Express* **12**(3), 1559–1567 (2021)
- Liu, H., Vohra, N., Bailey, K., El-Shenawee, M., Nelson, A.H.: Deep learning classification of breast cancer tissue from terahertz imaging through wavelet synchro-squeezed transformation and transfer learning. *J. Infrared Millim. Terahertz Waves* **43**(1–2), 48–70 (2022)
- Malhotra, I., Singh, G. (eds.): Terahertz imaging modalities: state-of-the-art and open challenges. In: *Terahertz Antenna Technology for Imaging and Sensing Applications*, pp. 39–73, Springer, Cham (2021b)
- Malhotra, I., Singh, G. (eds.): Terahertz technology for biomedical application. In: *Terahertz Antenna Technology for Imaging and Sensing Applications*, pp. 235–264, Springer, Cham (2021a)

- Malhotra, I., Singh, G. (eds.): Terahertz antenna technology for imaging and sensing applications. In: Terahertz Antenna Technology for Imaging and Sensing Applications, pp. 75–102, Springer, Cham (2021c)
- Mohammed, N.A., Khedr, O.E., El-Rabaie, E.-S.M., Khalaf, A.A.M.: Early detection of brain cancers biomedical sensor with low losses and high sensitivity in the terahertz regime based on photonic crystal fiber technology. *Opt. Quant. Electron.* **55**(3), 1–21 (2023)
- Naftaly, M.: An international intercomparison of thz time-domain spectrometers. In: Proceedings of the International Conference on Infrared, Millimeter, and Terahertz Waves (IRMMW-THz), pp. 1–2 (2016).
- Nikitkina, A.I., Bikmulina, P.Y., Gafarova, E.R., Kosheleva, N.V., Efremov, Y.M., et al.: Terahertz radiation and the skin: a review. *J. Biomed. Opt.* **26**(04), 43005 (2021)
- Peng, Y., Shi, C., Wu, X., Zhu, Y., Zhuang, S.: Terahertz imaging and spectroscopy in cancer diagnostics: a technical review. *BME Front.* **2020**, 1–11 (2020a)
- Peng, Y., Shi, C., Zhu, Y., Gu, M., Zhuang, S.: Terahertz spectroscopy in biomedical field: a review on signal-to-noise ratio improvement. *PhotoniX* **1**(1), 1–18 (2020b)
- Peng, Y., Huang, J., Luo, J., Yang, Z., Wang, L., et al.: Three-step one-way model in terahertz biomedical detection. *PhotoniX* **2**(1), 1–18 (2021)
- Peng, Z., Chen, Z., Hu, F.: Detection of biomarkers using terahertz 2 metasurface sensors and machine learning. *Appl. Opt.* **62**(4), 1027–1034 (2023)
- Peralta, X.G., Lipscomb, D., Wilmink, G.J., Echchgadda, I.: Terahertz spectroscopy of human skin tissue models with different melanin content. *Biomed. Opt. Express* **10**(6), 2942–2955 (2019)
- Poorgholam-Khanjari, S., Zarrabi, F.B.: Reconfigurable vivaldi thz antenna based on graphene load as hyperbolic metamaterial for skin cancer spectroscopy. *Opt. Commun.* **480**, 126482 (2021)
- Rahman, A.: Terahertz reconstructive imaging: a novel technique to differentiate healthy and diseased human skin. *Br. J. Cancer Res.* **2**(1), 228–232 (2019)
- Reid, C.B., Pickwell-Macpherson, E., Laufer, J.G., Gibson, A.P., Hebden, J.C., et al.: Accuracy and resolution of thz reflection spectroscopy for medical imaging. *Phys. Med. Biol.* **55**(16), 4825–4838 (2010)
- Sadeghi, A., Naghavi, S.M.H., Mozafari, M., Afshari, E.: Nanoscale biomaterials for terahertz imaging: a non-invasive approach for early cancer detection. *Transl. Oncol.* **27**, 101565 (2023)
- Salim, A., Lim, S.: Recent advances in the metamaterial-inspired biosensors. *Biosens. Bioelectron.* **117**, 398–402 (2018)
- Samanta, D., Karthikeyan, M.P., Banerjee, A., Inokawa, H.: Tunable graphene nanopatch antenna design for on-chip integrated terahertz detector arrays with potential application in cancer imaging. *Nanomedicine* **16**(12), 1035–1047 (2021)
- Shang, Y., Wang, X., Sun, W., Han, P., Ye, J., et al.: Terahertz image reconstruction based on compressed sensing and inverse fresnel diffraction. *Opt. Express* **27**(10), 14725–14735 (2019)
- Shi, H., Li, T., Liu, Z., Zhao, J., Qi, F.: Early detection of gastric cancer via high-resolution terahertz imaging system. *Front. Bioeng. Biotechnol.* **10**, 1–10 (2022)
- Son, J.-H.: Terahertz molecular imaging and its biomedical applications. In: Terahertz Biomedical and Healthcare Technologies, pp. SF1A.1, (2013)
- Son, J. H.: Challenges and opportunities in terahertz biomedical imaging. In: Proceedings of the 40th International Conference on Infrared, Millimeter, and Terahertz Waves (IRMMW-THz) 2015, pp. 1–2.
- Srivastava, G., Agarwal, S.: Terahertz imaging: timeline and future prospects. In: Das S., Nella A., Patel S.K. (eds) Terahertz Devices, Circuits and Systems, Springer, Singapore pp. 267–287 (2022)
- Sun, Q., He, Y., Liu, K., Fan, S., Parrott, E.P.J., et al.: Recent advances in terahertz technology for biomedical applications. *Quant. Imaging Med. Surg.* **7**(3), 345–355 (2017)
- Tarabichi, S., Al-Raeei, M., Solieva, O.: Improving the accuracy of tumor surgery by thz imaging and making the results of pathological anatomy faster by thz spectroscopy. *Beni-Suef Univ. J. Basic Appl. Sci.* **11**(1), 1–21 (2022)
- Truong, B.C.Q., Tuan, H.D., Fitzgerald, A.J., Wallace, V.P., Nguyen, H.T.: A dielectric model of human breast tissue in terahertz regime. *IEEE Trans. Biomed. Eng.* **62**(2), 699–707 (2015)
- Vafapour, Z., Keshavarz, A., Ghahraloud, H.: The potential of terahertz sensing for cancer diagnosis. *Heliyon* **6**(12), e05623 (2020)
- Valušis, G., Lisauskas, A., Yuan, H., Knap, W., Roskos, H.G.: Roadmap of terahertz imaging 2021. *Sensors* **21**, 4092 (2021)
- Veeraselvam, A., Mohammed, G.N.A., Savarimuthu, K., Vijayaraman, P.D.: An ultra-thin multiband refractive index-based carcinoma sensor using thz radiation. *IEEE Sens. J.* **22**(3), 2045–2052 (2022)

- Vohra, N., Liu, H., Nelson, A.H., Bailey, K., El-Shenawee, M.: Hyperspectral terahertz imaging and optical clearance for cancer classification in breast tumor surgical specimen. *J. Med. Imaging* **9**(1), 14002 (2022)
- Wang, L.: Terahertz imaging for breast cancer detection. *Sensors* **21**(19), 6465 (2021)
- Wang, J., Lindley-Hatcher, H., Chen, X., Pickwell-Macpherson, E.: Thz sensing of human skin: a review of skin modeling approaches. *Sensors* **21**(11), 3624 (2021)
- Wang, X.K., Ye, J.S., Sun, W.F., Han, P., Hou, L., et al.: Terahertz near-field microscopy based on an air-plasma dynamic aperture. *Light Sci. Appl.* **11**(1), 1–9 (2022)
- Wang, Q., Xie, L., Ying, Y.: Overview of imaging methods based on terahertz time-domain spectroscopy. *Appl. Spectrosc. Rev.* **57**(3), 249–264 (2022)
- Xie, Y.Y., Hu, C.H., Shi, B., Man, Q.: An adaptive super-resolution reconstruction for terahertz image based on mrf model. *Appl. Mech. Mater.* **373–375**, 541–546 (2013)
- Xie, D., Li, D., Hu, F., Wang, Z., Zhang, L., et al.: Terahertz metamaterial biosensor with double resonant frequencies for specific detection of early-stage hepatocellular carcinoma. *IEEE Sens. J.* **23**(2), 1124–1131 (2023)
- Yadav, R., Verma, A., Raghava, N.S.: A dual-band graphene-based yagi-uda antenna with evaluation of transverse magnetic mode for thz applications. *Superlattices Microstruct.* **154**, 106881 (2021)
- Yamaguchi, S., Fukushi, Y., Kubota, O., Itsuji, T., Ouchi, T., et al.: Brain tumor imaging of rat fresh tissue using terahertz spectroscopy. *Sci. Rep.* **6**(1), 1–6 (2016)
- Yan, Z., Zhu, L.G., Meng, K., Huang, W., Shi, Q.: THz medical imaging: from in vitro to in vivo. *Trends Biotechnol.* **40**(7), 816–830 (2022)
- Yang, K., Chopra, N., Abbasi, Q.H., Qaraqe, K.A., Alomainy, A.: Collagen analysis at terahertz band using double-debye parameter extraction and particle swarm optimisation. *IEEE Access* **5**, 27850–27856 (2017)
- Yang, K., Li, J., Lamy de la Chapelle, M., Huang, G., Wang, Y., et al.: A terahertz metamaterial biosensor for sensitive detection of micrnas based on gold-nanoparticles and strand displacement amplification. *Biosens. Bioelectron.* **175**, 112874 (2021)
- Yang, S., Ding, L., Wang, S., Du, C., Feng, L., et al.: Studying oral tissue via real-time high-resolution terahertz spectroscopic imaging. *Phys. Rev. Appl.* **19**(3), 34033 (2023)
- Yeo, W.G., Gurel, O., Hitchcock, C.L., Park, S., Sertel, K., et al.: Evaluation of cancer tissue morphology via thz spectroscopic imaging: human lung and small intestine malignancies. *Infrared Phys. Technol.* **97**, 411–416 (2019)
- Yu, C., Fan, S., Sun, Y., Pickwell-Macpherson, E.: The potential of terahertz imaging for cancer diagnosis: a review of investigations to date. *Quant. Imaging Med. Surg.* **2**(1), 33–45 (2012)
- Yu, L., Hao, L., Meiqiong, T., Jiaoqi, H., Wei, L., et al.: The medical application of terahertz technology in non-invasive detection of cells and tissues: opportunities and challenges. *RSC Adv.* **9**(17), 9354–9363 (2019)
- Zhan, X., Yang, S., Huang, G., Yang, L., Zhang, Y., et al.: Streptavidin-functionalized terahertz metamaterials for attomolar exosomal microrna assay in pancreatic cancer based on duplex-specific nuclease-triggered rolling circle amplification. *Biosens. Bioelectron.* **188**, 113314 (2021)
- Zhan, X., Liu, Y., Chen, Z., Luo, J., Yang, S., et al.: Revolutionary approaches for cancer diagnosis by terahertz-based spectroscopy and imaging. *Talanta* **259**, 124483 (2023)
- Zhang, R., Yang, K., Yang, B., AbuAli, N.A., Hayajneh, M., et al.: Dielectric and double debye parameters of artificial normal skin and melanoma. *J. Infrared Millim. Terahertz Waves* **40**(6), 657–672 (2019)
- Zhang, P., Zhong, S., Zhang, J., Ding, J., Liu, Z., et al.: Application of terahertz spectroscopy and imaging in the diagnosis of prostate cancer. *Curr. Opt. Photonics* **4**(1), 31–43 (2020)
- Zhang, J., Li, S., Le, W.: Advances of terahertz technology in neuroscience: current status and a future perspective. *iScience* **24**(12), 103548 (2021)
- Zhang, Y., Wang, C., Huai, B., Wang, S., Zhang, Y., et al.: Continuous-wave thz imaging for biomedical samples. *Appl. Sci. (switzerland)* **11**(1), 1–26 (2021b)
- Zhang, J., Mu, N., Liu, L., Xie, J., Feng, H., et al.: Highly sensitive detection of malignant glioma cells using metamaterial-inspired thz biosensor based on electromagnetically induced transparency. *Biosens. Bioelectron.* **185**, 113241 (2021c)
- Zhang, Y., Han, J., Wang, D., Li, X., Qiu, T., et al.: Application of thz time-domain spectroscopy to diagnose gastric cancer tissues in surgical resected specimens. *J. Infrared Millim. Terahertz Waves* **42**(7), 802–812 (2021d)
- Zhang, E.L., Tsyppkin, A., Kozlov, S., Zhang, C., et al.: Progress, challenges, and opportunities of terahertz emission from liquids. *J. Opt. Soc. Am. B* **39**(3), A43–A51 (2022)
- Zhao, Y., Cerica, D., Boutaayamou, M., Verly, J.G., Georges, M.P.: Terahertz ptychography with efficient fov for breast cancer tissue imaging. *Unconv. Opt. Imaging III* **12136**, 48–56 (2022)

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