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Advances in terahertz technology for cancer detection applications

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Abstract

Currently, there is an increasing demand for the diagnostic techniques that provide functional and morphological information with early cancer detection capability. Novel modern medical imaging systems driven by the recent advancements in technology such as terahertz (THz) and infrared radiation-based imaging technologies which are complementary to conventional modalities are being developed, investigated, and validated. The THz cancer imaging techniques offer novel opportunities for label free, non-ionizing, non-invasive and early cancer detection. The observed image contrast in THz cancer imaging studies has been mostly attributed to higher refractive index, absorption coefficient and dielectric properties in cancer tissue than that in the normal tissue due the local increase of the water molecule content in tissue and increased blood supply to the cancer affected tissue. Additional image contrast parameters and cancer biomarkers that have been reported to contribute to THz image contrast include cell structural changes, molecular density, interactions between agents (e.g., contrast agents and embedding agents) and biological tissue as well as tissue substances like proteins, fiber and fat etc. In this paper, we have presented a systematic and comprehensive review of the advancements in the technological development of THz technology for cancer imaging applications. Initially, the fundamentals principles and techniques for THz radiation generation and detection, imaging and spectroscopy are introduced. Further, the application of THz imaging for detection of various cancers tissues are presented, with more focus on the in vivo imaging of skin cancer. The data processing techniques for THz data are briefly discussed. Also, we identify the advantages and existing challenges in THz based cancer detection and report the performance improvement techniques. The recent advancements towards THz systems which are optimized and miniaturized are also reported. Finally, the integration of THz systems with artificial intelligent (AI), internet of things (IoT), cloud computing, big data analytics, robotics etc. for more sophisticated systems is proposed. This will facilitate the large-scale clinical applications of THz for smart and connected next generation healthcare systems and provide a roadmap for future research.

Keywords Advances · Biomedical · Cancer · Diagnosis · Early detection · Generation and detection · Instrumentation · Terahertz technology · Terahertz radiation

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1 Introduction

Early diagnosis, timely treatment and regular monitoring contribute significantly to reducing cancer caused mortality rates (Siegel et al. 2020; Viale 2020). The modern diagnosis techniques motivated by advances in technology which are capable of providing functional and morphological information for early, label free and non-invasive cancer detection have been investigated and validated and are complementary to the conventional ones (Peng et al. 2021a, 2020a; Fu et al. 2022). The modern techniques are THz imaging, infrared imaging, ultrasonic imaging, photo-acoustic and scanning near-field microscopy, coherent Raman scattering spectroscopic imaging, Raman scattering microscopy, digital holography microscopy, optical coherence tomography, super resolved imaging techniques, second harmonic generation imaging and two photon fluorescence. Recently, the improvement of THz sources and detectors, device portability and flexibility have stimulated the realization of potential and capability of THz radiation based technology to detect the slight changes in early stage cancer cells among other biomedical applications (Gong et al. 2020). The salient features of THz radiation make it a viable imaging tool such as having low photon energy (4 meV at 1THz) which is not sufficient for tissue atom ionization unlike γ-rays and X-rays. Due to low THz wave electron energy, no obvious damage is caused to the biological tissue and the hydration state can be observed under physiological state. Also, the energy level coincides with energy of molecular rotational and vibrational modes as well as intermolecular vibrations like hydrogen bonds. The THz radiation high sensitivity to polar molecules like water etc. is the most commonly used endogenous marker for tissue contrast caused by increased vascularity in the cancer and tumor (Danciu et al. 2019). Even though the high THz absorption by water limits its penetration depth from tens to hundreds of microns of tissue, it is adequate for visualizing epithelial tissue for example skin and superficial layers in vivo. The low frequency motions enable molecular identification through their spectral signatures in the THz region, therefore it is attractive for early cancer detection.

The THz pulsed imaging (TPI) based on coherent detection enables, the THz electric field profile to be recorded such that its phase and amplitude can be estimated and based on these parameters, the broadband optical parameters i.e., the refractive index and absorption coefficient parameters are obtained. As a result, the TPI enables both the functional and morphological information to be obtained (D’arco et al. 2020). The identification of cancer characteristic spectral lines through the use of THz pulsed spectroscopy has enabled early stage monitoring of slight cancer cell changes (Gong et al. 2020). The differences in tissue’s optical properties have been mostly attributed to the increased availability of less bound and free water molecules in cancer and tumor due to increased vascularity, edema and increased metabolism. Firstly, the relaxation processes and water molecules intracellular vibration modes ranging within sub-picosecond and picosecond resonate with the THz range. Therefore, the dielectric response of tissue cells has been shown by THz spectroscopy to reflect water dynamics (Zhang et al. 2019). Secondly, the evaluation of tumor cells hydration can be achieved by THz spectroscopy without cryogenic treatment or hydrogenation. Additional image contrast parameters and cancer biomarkers that have been reported to contribute to THz image contrast include but are not limited, to increased blood supply to the cancer affected tissue, cell structural changes, molecular density, interactions between agents (e.g., contrast agents and embedding agents) and biological tissue as well as tissue substances like proteins, fiber and fat etc. and more are still being explored (Peng et al. 2021a, 2020a; Fu et al. 2022). Here, we provide a broad review of the advancements in the technological development of THz technology for cancer imaging applications.

As shown in Fig. 1, the paper is structured as follows: firstly, the fundamentals, principles and techniques for THz radiation generation and detection, imaging and spectroscopy are introduced. Second, the application of THz imaging for the detection of various cancers is presented, with more focus on the in vivo imaging of skin cancer. The various methods and recent advances towards THz systems that are optimized and miniaturized are also reported. Lastly, the open research challenges are discussed and the integration of THz systems with novel technologies are proposed. This will facilitate the large-scale clinical applications of THz for smart and connected next generation healthcare systems and provide a roadmap for future research.

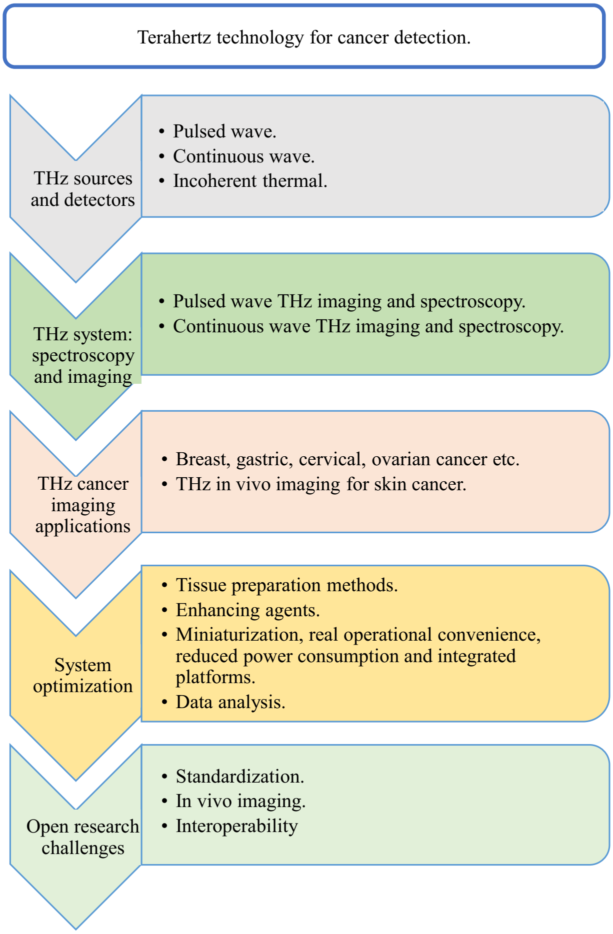


Fig. 1 Structure of this paper

1.1 Related work

An overview of the state and applications of continuous wave THz (CW THz) imaging methods for biomedical samples are discussed in Zhang et al. 2021a, with a presentation of the principle and conditions of CW THz point-by-point scanning methods. Zhang et al. (2021a) have reported the characteristics of CW THz 3-dimensional imaging techniques, features and applications of CW THz full field imaging with its biological applications. The research status, progress, advantages and limitations that hinder the THz technological development for clinical adoption and future developments in CW THz are also summarized. This reported study is limited to CW THz imaging technology and its application for biomedical samples.

The potential application of THz radiation based technology as a useful tool in medicine emerging from advancements in THz technology have been extensively reviewed in D'arco et al. (2020) and the THz pulsed radiation detection techniques based on TPI and their biomedical applications are outlined. The advantages of THz pulsed radiation-based imaging are summarized, with illustration of the commercially available sources of pulsed THz radiation and corresponding coherent and incoherent detectors as well as schematic layouts for transmission and reflection TPI operating modes are also presented. Example application studies of TPI for in vivo and ex vivo cancer observations through the THz radiation properties are discussed. Further, the limitations associated with THz imaging technology for enhancement of penetration depth and sensing capabilities for biomedical applications are addressed. D'arco et.al. (2020) also pointed out the rapid developments in THz imaging technology and its increasing potential as a medical imaging modality, however more attention was stated to be required in the use of penetration enhancing agents (PEAs) and more technological developments required for clinical adoption of TPI systems.

The recent developments in THz imaging technology and its application for breast tumor identification is reported by Wang (2021) and exploited the potential application of THz imaging and spectroscopy systems for breast cancer detection, with a discussion of the breast tissue's dielectric properties within THz range, THz radiation sources, and imaging with spectroscopy. The methods for improvement of data collection, processing and resolution based on chemometrics are summarized. In addition, the future research scope to address challenges in the direction of THz breast cancer imaging are also explored.

The potential biomedical application of THz technology, imaging and spectroscopy specifically for cancer, based on the features exhibited by THz radiation including low ionization energy and ability to identify biomolecules using their spectral fingerprints are reviewed in Peng et al. (2020b). Further, they reported the recent THz imaging and spectroscopy progress in the diagnosis of cancer, with its potential to assist doctors and researchers to achieve an insight of cancer infected tissue area. They regarded THz spectroscopy efficient to identify biomarkers of cancer through component analysis. They also discussed the advantages and disadvantages of THz technology for cancer and auxiliary techniques for signal to noise ratio (SNR) improvement.

The THz technology—THz imaging and THz spectroscopy has been introduced in Yu et al. (2012) with a short overview of THz technology advances and its application for cancer diagnosis. Being located between the microwave and infrared region, the THz waves are strongly sensitive to and attenuated by water through strong absorption. The characteristic properties of THz radiation such as low photon energy implying nonionizing hazard on biological tissue cause the technology to be interesting for biological applications. The image contrast between cancerous- and healthy-tissue has been attributed to the local increase of blood supply and water content as well as the tissue's structural differences (Yu et al. 2012). Further, Son et al. (2019) have reviewed the THz biomedical state-of-the-art techniques, methodologies and applicable potential techniques that could revolutionize the healthcare. They surveyed some techniques for wet tissue penetration depth enhancement where they discussed methods for reaching internal organs like endoscopy and otoscopy. Further, they explained the principles of operation of some THz based sensors with diabetes, breathing conditions and blood disorders sensing examples. Much of the THz biomedical applications are reported to be in cancer imaging including in detection of oral, skin, gastric, brain and breast cancers. They also reported the potential of cancer treatment through demethylation of malignant DNA by the use of a specific high-power frequency of THz radiation as well as its potential as a cancer biomarker.

The detection of digestive cancers using THz based technology are reported by Danciu et al. (2019). A summary of the THz waves characteristics, their various tissue interactions and the available THz technologies i.e., THz tomography, spectroscopy and endoscopy are well presented. The review is mainly focused on reporting the research progress in THz based detection of the digestive cancers—esophageal, oral, gastric, hepatic, colonic and pancreatic cancer tumors.

The novel applications and future potential of THz sensing have been discussed and the optimization methods for THz data's reflectance spectral responses in diagnosis of BCC (basal cell carcinoma) skin cancer, colon and breast cancers described using various intelligent approaches (Vafapour et al. 2020). Further, the application of THz imaging and spectroscopy have been reviewed in Nikitkina et al. (2021), in which both the continuous- and pulsed—wave techniques were used to diagnose melanoma and non-melanoma of skin tissues, assessment of scars, dysplasia and diabetes. They also highlighted the potential of THz based imaging and spectroscopy as an instrument for research and therapeutics. In a related work by Gong et al. (2020), the applications of the biological effects of THz in biomedicine and the characterization techniques of THz in detection of cancer, protein, amino acids & polypeptides, DNA etc. are reported.

The mechanisms and biological effects of THz waves on molecular level nervous system, organisms and cells are investigated in Zhang et al. (2021b). The future perspectives and application of THz in neuroscience highlighted and the nerve cell membranes, cytokines and gene expressions to be affected by THz radiation are presented (Zhang et al. 2021b).

Further, the review of THz technology for various biomedical applications have been extensively reported in (Gong et al. 2020; Wang 2021; Cheon et al. 2017; Son et al. 2013; Zhang et al. 2021c) and the recently reported review of THz technology for biomedical applications are presented in Table 1.

1.2 Motivation

Currently, there is need for efficiency improvement of cancer diagnostic and surgical procedures. The delayed cancer diagnosis and inaccurate tumor excisions result in increased cancer caused morbidities. The existing medical imaging modalities are not yet capable of detecting cancer cells at an early stage for example, X-ray and computed tomography (CT), moreover, they are based on ionizing radiation which is not tissue friendly for repeated

Table 1 Summary of the Recently Reported technical reviews for biomedical applications

Reference	Technique	Approach	Results	Limitations
Yan et al. (2022)	THz imaging	Progress of THz imaging towards in vivo imaging for medical applications was discussed Development of THz image contrast agents was reported	A roadmap was given for THz medical imaging from in vitro towards in vivo imaging	In vivo THz imaging still suffers diffraction limited spatial resolution More developments are still required for large scale implementation of THz imaging The review mostly focused on developments in THz imaging towards in vivo imaging
Valušis et al. (2021)	THz imaging	Review of advances in THz imaging towards miniaturized and optimized systems Current state of THz sources, detectors, sensors, arrays and THz techniques	A structured and comprehensive review of recent advances in THz imaging was given Opinion on challenges and extrapolations for further THz imaging evolution was given	Requirement for a balance between compact emitter power and sensitivity in THz imaging systems is a challenging task The review focused more on the industrial applications of THz imaging
Castro-Camus et al. (1999)	THz imaging and THz TDS	Review of the THz imaging progress based on THz imaging 3D mapping of water distribution in wounds, plants	Considerable evolution of THz systems over 20 years Great promise of THz imaging as a versatile measurement tool	High cost of THz systems limits the wider market access The medical application focus of the review was on burn wounds
Wang et al. (2022)	THz TDS imaging	Developments of THz TDS based systems including near field and tomography were highlighted Outlook on performance improvement was given	The significant performance achievements of THz TDS were displayed	Focus was more on improving scanning speed through fast imaging components Need for femtosecond resolution in THz, fast acquisition and flexibility
Peng et al. (2021b)	THz technology	Review of THz technology application in biomedical research A three step one way THz model for biomedical detection was proposed	Significant contribution was made to the early, accurate and rapid detection of diseases	The dynamic monitoring is expected to achieve real time imaging

Table 1 (continued)

Reference	Technique	Approach	Results	Limitations
Shur and Liu (2022)	THz imaging and sensing	Applications of THz technology for cancer imaging	Potential of TeraFET based detectors and arrays for biological sample detection with increased sensitivity and resolution	More developments of the technology is required for more accurate detection
Mukherjee and Chatterjee (2020)	THz technology	Review of: THz sources and detectors THz applications in biomedical imaging	A compact review of THz sources and detectors was given	The review mostly focused on overview of developments in THz sources, detectors and application
Banerjee et al. (2020)	THz imaging	Review of concepts and applications of THz imaging in healthcare	Promising possibility of extension of novel technologies like IoT, Machine learning etc. was reported	Lack of standard methodologies and computational models High cost of THz systems Need for improved speed, accuracy and reproducibility of analytical data
Amini et al. (2021)	THz technology	Applications of THz radiation for bio-sensing, diagnostic and clinical treatments were reported	The potential of THz technology as a future diagnostic and treatment clinical tool was emphasized	The review focused on the applications of THz technology for medical treatments and diagnostics
Lindley-Hatcher et al. (2021)	Terahertz imaging	The progress of THz cancer imaging for epithelial cancers like colon cancer and skin cancer was reported They proposed the possibility of integrating THz imaging systems with robotics (Terabotics) for real time THz cancer imaging Development of fast, compact probes	The potential of THz imaging technology to perform real time imaging was reported	Very high initial cost of THz equipment

Table 1 (continued)

Reference	Technique	Approach	Results	Limitations
This review	THz imaging, spectroscopy and sensing	Comprehensive review of the advances in THz technology for cancer applications Example applications of THz technology for early cancer detection are presented Recent advancements towards optimized and miniaturized THz systems are reported The integration of THz technology with novel technologies for smart and connectedness is proposed as scope for future work	As reported in this work	Lack of standardized detection frameworks, Unavailability of sufficient THz imaging training datasets for ML algorithms High cost of commercially available THz equipment for academic research use

assessments. The application of THz based cancer imaging could significantly contribute to the reduced mortality rates as it's capable of early, non-invasive and non-ionizing cancer diagnosis, with clear margins for definitive excisions and therapies.

A technology is needed that assists surgeons with intra-operational and real-time detection of tumorous tissue margins precisely, in order to eliminate the need for repeated surgeries when remaining malignant tissue is identified post-surgery. The American Society for Radiation Oncology stated that "Negative margins (no ink on tumor) optimize ipsilateral breast tumor recurrence. The wider margins widths do not significantly lower this risk" (Schnitt et al. 2015). Thus, an accurate margin assessment is needed to still maintain excision of tissue (El-Shenawee et al. 2019). The THz based scanning's ability to differentiate between different molecules based on their water content renders it of great potential for early tumor detection, repeated assessments, for monitoring patients and patient follow up (Danciu et al. 2019). Much focus in the THz imaging and sensing studies has been on the improvement of the instrumentation for example antenna (Poorgholam-Khanjari and Zarrabi 2021; Apriono 2021; Kazemi 2021; Yadav et al. 2021), biosensors (Yang et al. 2021a; Azab 2021; Liu 2021; Zhan 2021; Li 2021; Lin et al. 2021) detectors (Habib et al. 2021) and probes (Chan and Ramer 2018). However, significantly less work has been done for acquired images quality improvement and clinical decision support improvement.

1.3 Contribution

In this work, we have presented a broad overview of the advancements in the technological development of THz technology for cancer applications. The techniques used in THz radiation generation and detection, and their principle of operation are reviewed. From the analysis of reported THz cancer image investigations, we deduce the suitability of THz imaging for in vivo imaging of skin cancer. The authors contributions are summarized as follows.

- We have presented a brief overview of the fundamentals, principles and techniques for THz radiation-based technology, generation and detection, imaging and spectroscopy.
- The application of THz imaging for the detection of various cancerous biological tissues is presented, with more focus on the in vivo imaging of skin cancer.
- Data processing techniques for THz data are briefly reported.
- Further, we identify the advantages with existing challenges in THz based cancer detection and report the performance improvement techniques.
- The recent advancements towards THz systems that are optimized and miniaturized are also presented.
- Moreover, the integration of THz systems with artificial intelligent (AI), internet of things (IoT), cloud computing, big data analytics, robotics etc. for more sophisticated systems is proposed. This will facilitate the large-scale clinical applications of THz for next generation healthcare systems and provide a roadmap for future research direction.

1.4 Organization

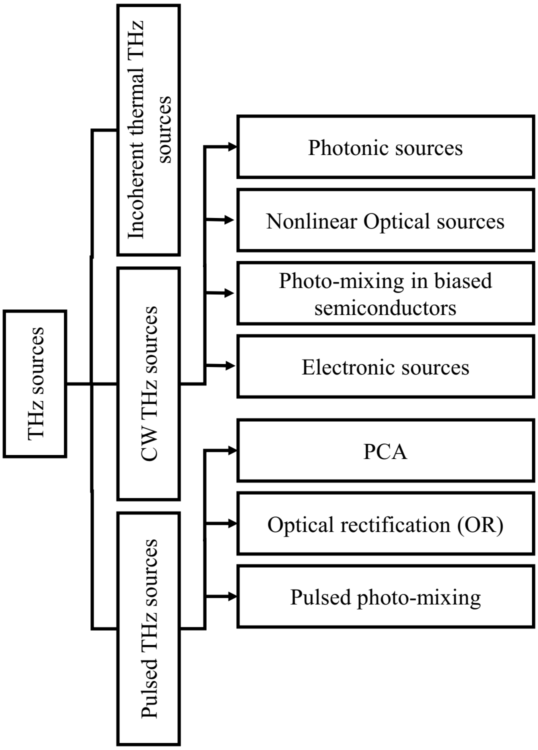
The remainder of the work is organized in the next sections as follows: in Section II, an overview of THz sources and detectors is presented. The THz spectroscopy and imaging techniques are reported in Section III and the applications of THz technology for cancer detection are summarized in Section IV. In Section V, the aspects of THz opportunities, limitations, performance improvement approaches and recent advances in THz technology development are discussed. Finally, the summary of this work is given in Section VI.

2 THz sources and detectors

There is rapid development of techniques for generation and detecting THz radiation to come up with equipment for THz spectroscopy and THz imaging (Nikitkina et al. 2021). The THz instrumentation schemes are broadly categorized based on the type of THz radiation generated, pulsed wave THz and continuous THz wave radiations.

Based on the THz radiation generated, the two broad categories of THz radiation generation schemes as shown in Fig. 2 are the continuous wave (CW) and the pulsed wave. The sources of THz radiation include CW THz sources, incoherent thermal THz sources and pulsed THz sources. As the names suggest, in CW, the THz generated is a continuous waveform (i.e., producing single or separate discrete frequencies) while in the pulsed, there are pulses of THz radiation (with broadband frequency output). The pulsed THz sources include photoconductive antennas (PCA) which uses transient current, pulsed photo-mixing and optical rectification (OR). The CW THz sources include nonlinear optical sources, photonic sources, electronic sources and photo-mixing in biased semiconductors (Wang 2021). The most common sources for generating CW THz radiation are diodes, quantum cascade lasers (QCLs) and high-speed transistors. Through the photo-mixing and frequency multiplication, parametric conversion and backward wave oscillators, tunable CW

Fig. 2 THz radiation generation



THz waves are obtained, while for broadband CW radiation, globars and mercury lamps are used. The most common detectors are Golay cell or Li–He bolometers, pyroelectric detectors as well as emitters and detectors which are solid state based where for instance grapheme is used (Nikitkina et al. 2021).

The terahertz pulsed imaging (TPI) uses a coherent detection method in which the THz signal's amplitude and phase values are measured, enabling refractive index, absorption coefficient parameters to be obtained. In TPI systems there are several techniques used for the detection and generation of THz radiation characterized by output of broadband frequencies (ranging tens—hundreds GHz to several THz). The mostly used sources for generation of pulsed THz radiation are based on optical rectification (OR) using nonlinear optical crystals (NLO), biased photoconductive antennas (PCAs), carrier tunneling and plasma in the air. Most commonly used approaches are based on PCA and OR where the infrared (IR) femtosecond lasers which emit in near infrared (NIR) are used. In PCA, the principle of operation is such that a beam of pulsed laser illuminates a PCA gap composed of thin semiconductor film of high resistance with two contact pads of electrical property. When the bias voltage and laser beam are applied, there is in turn generation of a photocurrent and free carriers are accelerated by the static bias field thereby producing broadband THz frequency to the free space (Malhotra and Singh 2021; Malhotra et al. 2018). In OR, NLO centrosymmetric crystals are used to generate THz broadband from 0.1THz to more than 40THz. The NLO based crystals include organic NLO, 4-N, N-dimethylamino-4'-N'-methyl-stilbazolium tosylate (DAST) and 4-N, N-dimethylamino -4'-N'-methyl-stilbazolium 2,4,6-trimethylbenzenesulfonate (DSTMS). The principle of OR based sources is that intense beams of NIR laser are propagated through crystals, non-linear effects of second order occur thereby low frequency of DC polarization is developed leading to an electromagnetic single cycle pulse radiation with broad frequency spectrum (from 0 Hz to a particular maximum value). Alternatively, the charges acceleration can lead to radiation of electromagnetic waves, and when certain conditions are reached, the produced electromagnetic waves lie in THz range. The acceleration of electrons can be achieved in vacuum, air or semiconductors by using application of bias voltage over the gap, or by laser beam's second harmonic and fundamental frequencies nonlinear four wave mixing in various gases or in air or using an intense pulse of laser. Another technique for THz pulsed radiation generation is surge whereby when bias voltage is applied on the semiconductor quantum wells (QWs), the THz radiation is produced through mechanism of polarized electron hole pairs production (D'arco et al. 2020).

Table 2 shows the performances of the commonly used THz detectors (D'arco et al. 2020). For detection of THz pulses, an incoherent and coherent (heterodyne) detector schemes are used. Incoherent detection techniques use power to signal transducers for example bolometers, Golay cells, Schottky diodes, pyroelectric detectors and low

Table 2 Performance of THz Detectors

Detector	Bandwidth (Hz)	THz Coverage (THz)	NEP ($W/Hz^{1/2}$)
Golay cell	$10 - 10^2$	$0.01 - 20^1$ $0.01 - 700^2$	10^{-10}
Cryogenic bolometer	$10^2 - 10^3$	0.1 – 30	$10^{-14} - 10^{-12}$
Pyro-electric	$10 - 10^8$	0.1 – 10	$10^{-10} - 10^{-9}$
Schottky diode	$10^2 - 10^6$	0.1 – 2	$10^{-14} - 10^{-11}$

sensitivity thermopiles (the resistive temperature sensors and bolometers commercially available and used in THz spectrum are cryogenic) coherent detection enables the phase, frequency spectral and power information of the signal to be obtained. Examples of detectors used in coherent detection are Schottky diodes, NLO crystals (or through the electro optical (EO) effect of nonlinear crystals) and PCA. The good performance of the devices is evaluated in terms of high noise equivalence powers (NEP), high sensitivity, good THz coverage and bandwidth of detector (D'arco et al. 2020).

3 THz spectroscopy and imaging techniques

The broad category of THz technology is based on the nature of THz radiation generated. As shown in Fig. 3, the technology is further categorized into THz spectroscopy and THz imaging. THz spectroscopy principle is that the low frequency motion of most biomolecules for example rotation, vibration, van der Waals forces and hydrogen bonds have fingerprint characteristics in the THz spectrum. The analysis of the differences in reflection and absorption parameters enables identification of biomolecular samples using equipment such as the THz time domain spectroscopy (THz-TDS). Depending on THz sources working modes, the THz imaging is categorized into CW THz and TPI. In the next subsections, the detailed overview of THz imaging methods is presented.

3.1 Continuous wave THz imaging and spectroscopy

The THz wave scattering effect whereby intensity distribution is detected, the sources power output is higher in CW THz and the systems are compact and operate in real time. The sources used in CW THz are quantum cascade lasers (QCL), THz gas lasers, backward wave oscillators and Gunn diodes. The most common detectors are the Golay cell and Schottky diodes, pyro-electric cameras and arrays of micro bolometers (Zhang et al. 2021a). The CW THz imaging technologies are described as follows:

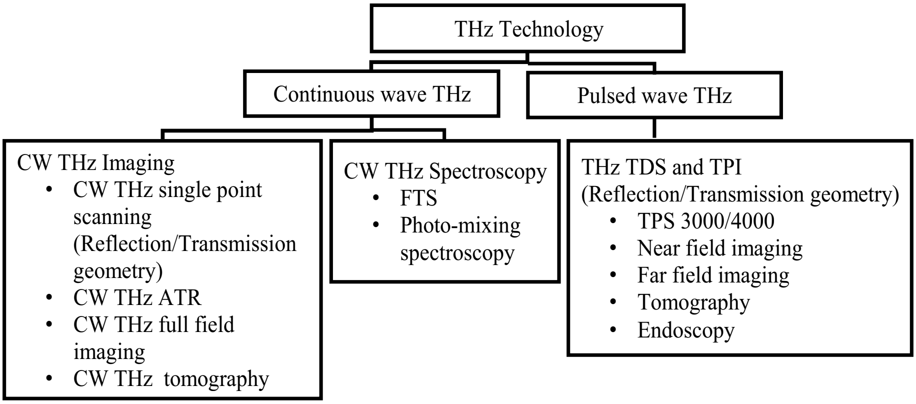


Fig. 3 THz instrumentation summary block diagram

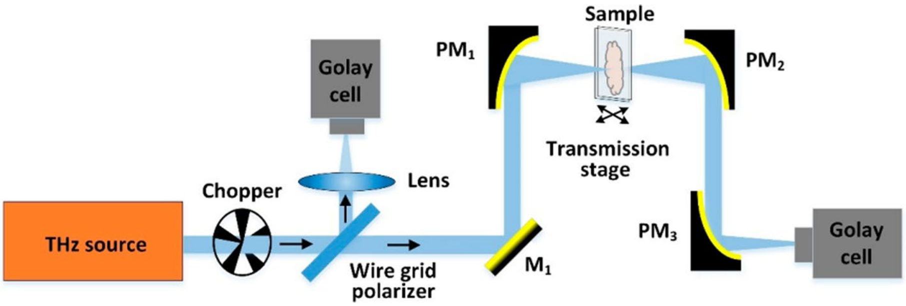


Fig. 4 CW THz single point scanning imaging system in transmission mode (Zhang et al. 2021a)

3.1.1 CW THz single point scanning imaging

The imaging system-based CW THz single point scanning offer advantages of high resolution, high SNR and simple detection principle. The transmission mode geometries of CW THz single point scanning system are shown in Fig. 4.

In the transmission mode, the imaging system of CW THz transmission single point scanning uses two-dimensional (along X–Y direction) translation to do pixel-by-pixel scanning of thin sample (that has a weak THz absorption) placed on incident beam's focal point. A single point detection is used, and the resolution determined by focal beam size incident on sample plane. The example arrangement is shown in Fig. 4 and a leaf can be used for the system performance evaluation. For the reflection mode the geometry for CW THz reflection single point scanning (Zhang et al. 2021a) can either have normal incidence of THz radiation where Golay cell is used as the detector, or the oblique incidence that has elliptic focal spot. The reflection mode is more suitable for the fresh tissues due to high THz wave sensitivity to water. The other THz techniques that use CW THz single point scanning are the CW THz near-filed microscopy imaging and CW THz single point phase contrast imaging.

3.1.2 CW THz polarization single point scanning imaging

This is whereby a polarized laser beam is used incident on a sample and two images may be obtained through co-and cross-polarized detection.

3.1.3 CW THz attenuated total reflection imaging

The CW THz attenuated total reflection (ATR) imaging and spectroscopy systems mainly use properties of the evanescent wave that results from total internal reflection (TIR). To satisfy the condition of TIR i.e., to realize ATR, the THz beam is guided from a denser medium (higher refractive index) to an absorptive less medium (less refractive index) at an angle greater than the critical angle. The detailed principle and geometry of THz ATR has been reported in Zhang et al. (2021c).

3.1.4 CW THz full field imaging

An image acquisition in CW THz full field imaging is faster due to the requirement of lesser optical components as compared to the THz scanning techniques. Based on this, the CW THz ptychography and CW THz digital holography (CW TDH) are being developed. The CW TDH is time two-dimensional approach based on quantitative phase contrast whereby the amplitude and wave distributions can be obtained without scanning and there is high spatial resolution. A numerical digital computation is used for reconstruction. The two variations of CW TDH are off-axis and in-line TDH based on the angle of reference and object beam (Zhang et al. 2021a). The CW THz ptychography is a phase contrast method that does not use lenses, has large field-of-view (FOV) and is based on coherent diffraction. Using the ptygraphical iterative engine (ePIE), the sample's probe and transmittance functions are retrieved.

3.1.5 CW THz tomography imaging

The CW THz computed tomography (THz-CT) imaging method is a three-dimensional (3D) imaging and nondestructive detection approach emanating from X-ray and computed tomography (CT) scan. Due to poor penetration capabilities of THz radiation compared to X-ray, more biological sample contrast and reflection of internal structure can be achieved. The THz CT scan detects the incident beam's one-dimensional Fourier transform over different angles of projection and then the Fourier transform for each projection to construct the cross-sectional image's two-dimensional Fourier transform. The filter back projection (FBP method is the main algorithm used for data processing.

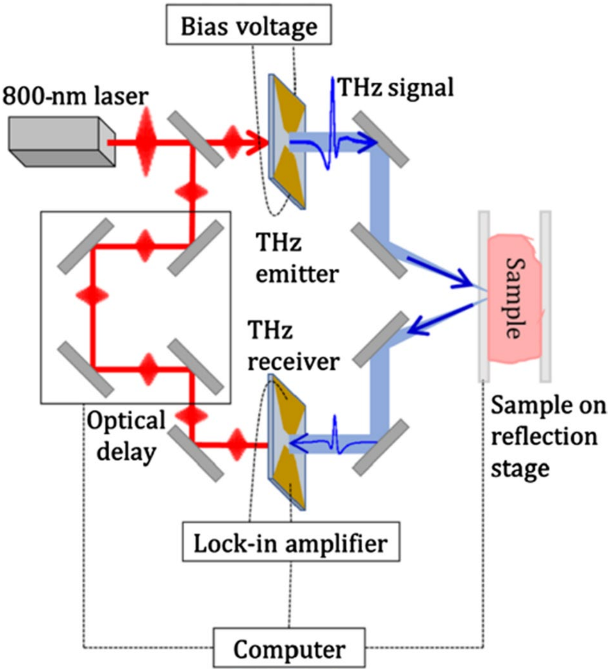
3.1.6 Continuous wave THz spectroscopy

The phase and amplitude information of samples are obtained using the THz spectroscopic instrument, the information of phase and amplitude are then used to obtain optical parameters i.e., the absorption coefficient and refractive index. The three main types of spectroscopies are photo-mixing spectrometer, Fourier transform spectroscopy (FTS) and THz-TDS. The FTS is commonly used to study molecular resonance and possesses wide spectral coverage of 100 GHz to 5THz with higher spatial and spectral resolution even though it's still limited with poor SNR. It utilizes broadband pulsed or CW sources and Michelson interferometer scheme. The photo-mixing spectrometer uses GaAs photoconductor that uses metal electrodes having the frequency offset lasers to generate CW THz. It is made up of two photo-mixers for transmitter & receiver and has resolution of 500 MHz depending on frequency step.

3.2 Pulsed wave THz imaging and spectroscopy

The pulsed wave THz imaging and spectroscopy systems can be interchanged by switching the scanning mechanism i.e., through movement (lateral translation) of the sample with the illumination beam stationary so as to perform point to point collection of the signal. In the spectroscopy, the beam is moved using stages or piezoelectric rotators and/or galvo mirrors. For imaging, the THz beam illuminates surface of the object, sampled by discrete

Fig. 5 THz pulsed spectroscopy system



grid and continuously scanned or pixel-by-pixel scanned in the raster mode. The acquired information is obtained from the data acquisition card (DAQ), quantized to bits for further image processing (D'arco et al. 2020).

For the biological samples, the imaging THz based on pulsed radiation like THz pulsed spectroscopy (TPS) shown in Fig. 5 has been preferred over CW since it results in broader information. The photoconductive antennas (PCA) are mostly used emitters while conventionally they were based on optical plasma rectification and generation. The principle for generation and detection of THz signal in TPI and TPS is such that the PCA emitters generate short THz pulses of sub-picosecond and few THz cycles through the photoconductivity effect followed by femtosecond laser beam. The THz signal of THz radiation mixed with femtosecond laser beam (probe) is then detected by a PCA detector. The imaging in TPS is done through performing sample surface raster scanning using a THz beam focused on the sample surface and can be in either transmission or reflection configurations. The use of holographic and multi-pixel camera-based imaging has also been explored.

3.2.1 Fundamentals of THz imaging

As previously explained, the TPI extends from the THz TDS technique, to obtain objects' images, raster scanning of 2-dimensional point-to-point is performed together with a coherent detection. Thereby recording the temporal information of each one of the point pixels. One dimensional data of frequency domain or time domain are extracted then converted to some physical parameters. The normalization enhances contrast of the image and can be summarized as follows (D'arco et al. 2020):

3.2.1.1 Time Domain

- Amplitude of Electric field at fixed time: $\boldsymbol{E}_{x,y}(t_0)$
- Main peak normalized amplitude: $\boldsymbol{max}\{|\boldsymbol{E}_{x,y}(t)|\}/\boldsymbol{max}\{|\boldsymbol{E}_0(t)|\}$
- Main peak time delay with respect to reference: $t(\boldsymbol{max}\{|\boldsymbol{E}_{x,y}(t)|\}) - t(\boldsymbol{max}\{|\boldsymbol{E}_0(t)|\})$

3.2.1.2 Frequency Domain

- Spectral amplitude at fixed frequency: $\boldsymbol{E}_{x,y}(v_0)$
- Phase: $\boldsymbol{\phi}_{x,y}(v_0)$

For the time domain, when the THz pulse interacts with a sample, there can a delay, broadening or attenuation of the pulse signal relative to reference. The amplitude of electric field corresponds to modality of contrast used for normalizing the image. Also, the main peak's normalized amplitude (ratio of sample's maxima and reference electric field) gives the absorption, reflection / the scattering information of the scanned object. The main peak time delay value relative to reference provides thickness or contrast information through optical changes mapping such that time-of-flight (ToF) method can determine through estimation the target's dielectric information. When the THz pulse is incident on a sample, the measurement of reflected echo is performed in terms of the amplitude and/or phase. The echo pulse ToF gives information of boundaries etc. along the THz path of propagation which enables extraction of 1D depth profile. When 2D scanning is performed, a 3D image is visualized. The spectrum amplitude and phase information are obtained through the application of the Fourier transform on the temporal electric pulse where the amplitude indicates losses and phase relates to refractive index. When the frequency is fixed, the amplitude and phase images can be visualized in frequency domain thereby offering better contrast due to distinct refractive indices than losses. Thus, in the short extraction of THz wave amplitude and phase is enabled in THz TDS. The Fresnel coefficients enable parameters of complex refractive index, the absorption coefficient is obtained in term of the complex permittivity (D'arco et al. 2020). The differences in refractive indices of different tissues could depend on the pathological status of tissue.

Using the THz TDS system, for example, the commonly used system is the TPS 3000, the spectra and images of samples can be acquired simultaneously using information of amplitude and phase. The three main ways to obtain images from a THz TDS system are raster scanning the sample in transmission mode to produce a 2D image whereby each pulse is placed focused on a focal plane (2 lenses) so as to obtain time domain information and then transformed using Fourier transform to obtain the image's spectral information. This can be visualized as an electric field as a time domain function in which dynamics of picosecond level irradiance are explained. The second method whereby an image is formed due to high absorption, scattering and reflection at the sample boundary is through normalization of the time domain maximum peak through the use of the reference function (Wang et al. 2022). Lastly, the commonly used method is whereby the main peak time delay is mapped with respect to reference to permit changes in optical path on mapped sample and thus providing information of contrast for the material or thickness. Using the Fourier transform, the phase and amplitude information are determined. The beam splitter splits the laser beam, followed by THz pulse generation through the emitter by photoconductivity when a bias voltage is applied, then the pulse advances to interact and carry information of the sample at focal plane. While this process takes place, the movement of optical delay line causes a constant time difference of detection pulse & optical pump to enable coherent detection of THz pulse. The SNR determines maximum absorption coefficient which is in turn determined by accuracy of signal's amplitude and phase rather than samples. In the biomedical applications, reflection mode of THz TDS is commonly preferred over transmission due to water's high absorption of THz radiation which constraints the transmission spectrum of the system (Wang et al. 2022).

3.2.2 Far-field TPI systems

The far-field TPI systems typically involves a pump and probe set up and they are deemed as extended THz TDS system. The femtosecond laser powers the TPI system, first, the laser beam is split using a beam splitter into pump and probe beams. The pump beam is modulated through modulating the bias voltage of THz emitter or using optical or mechanical chopper, then focused on THz emitter. The THz pulse generated is collimated and it's then focused to illuminate the sample, causing transmission or reflection of a THz pulse train or electric field which are then collimated again and refocused to the THz detector that uses pair of lenses or parabolic mirrors. The signal conditioning (filtering and detection) of electrical signal is performed by the lock in amplifier whose analog output is in turn collected and digitized using the DAQ. The temporal sampling of the electric signal is achieved by a delay line such that for every pulse in the signal detected, there are different phase and amplitude information measured. For equal probe and pump optical paths, measurement of the electrical field is performed one instant at a time such that for the whole THz signal to be samples, a delay line is introduced for delaying the beams of probes and pumps (D'arco et al. 2020).

3.2.3 Near-field TPI systems

The diffraction of propagating waves results in wavelength limited resolution and this challenge can be countered by near field (NF) collection of THz pulses i.e., collecting them with sample at a distance comparable to wavelength such that evanescent waves can be detected. The techniques that enable sub wavelength imaging in THz have been explored and various shaped detectors and sources can be used (Malhotra and Singh 2021a).

3.2.4 THz-TDS based computed tomography

The THz Computed Tomography (THz CT) is capable of capturing and reconstructing projected images from various angles thereby obtaining three dimensional (3D) visualizations through point-by-point scanning. The non-mechanical delays like the electronically controlled optical sampling (ECOPS) and asynchronous optical sampling (ASOPS) can be used to reduce scan time, while SNR can be improved by integrating multiple scans and tomosynthesis (Wang et al. 2022).

3.2.5 Near-field THz-TDS

The near-field measurements can address far field diffraction limit, with light mass coupling enhancement and sub wavelength resolution at THz frequency. The near field in diffraction optics is defined as, for a plane incident light wave, the field of light falling outside focal spot of Rayleigh length is the near field. The Rayleigh criterion is used to obtain the spatial resolution. The detection schemes for near field include scattering probes, electro-optic probes metallic aperture probes of sub-wavelength and mixture of THz photonic device and miniaturized photoconductive detectors. The types of near field imaging are aperture based and apertureless (Wang et al. 2022).

3.2.6 THz endoscopy

The endoscopy is an effective detection method for in vivo carcinoma diagnosis since THz penetration depth is limited and adequate for epithelial tissues lining either inside the body or outside. For cancers in internal tissues like digestive organs; colon, gastric, stomach cancers which are located near the mucous membrane surface, THz endoscopy would be the effective method. The technique is associated with challenges like signal attenuation which can be overcome by adopting THz TDS coupled with fiber for THz generation and detection as designed and discussed in Cheon et al. (2017).

4 THz imaging and spectroscopy for cancer applications

THz imaging and spectroscopy are based on non-ionizing radiation which is considered safe for human tissue and repeated assessments. The application of THz imaging and THz spectroscopy technology for various cancer detection have been reported including and not limited to the ones in Table 3.

Table 3 summarizes the reported THz technology experimental studies in cancer applications. All the studies support the potential of THz technology as a clinical tool for cancer imaging with salient features and tissue friendliness. The application of THz technology has also been reported to have great potential in applications like diabetes diagnosis, COVID-19, dental, tracing of internal scar healing and monitoring the hydration levels in vivo (Nikitkina et al. 2021; Taylor et al. 2020; Rao 2020).

5 In vivo *THz imaging for skin cancer*

Even though there is strong THz waves absorption by the water, implying high THz signal attenuation and limited tissue penetration depth (tens to hundreds of microns) which impose difficulties to detect deep tumours, it is adequate for visualizing epithelial tissue, for example, the skin and superficial layers in vivo. Therefore, due to its superficial and accessible location, the skin tissue is most ideal THz imaging target. The THz pulsed radiation based imaging (THz pulsed spectroscopy (TPS) and TPI) has been used for the majority of the THz cancer studies relative to CW imaging because of yielding broader information (Nikitkina et al. 2021; Lindley-Hatcher et al. 2021).

The THz radiation interaction with biological dynamics of skin tissue for example tissue water, separated cells, less polar biomolecules, tissue structure etc. are the basis of image contrast in THz imaging and spectroscopy. The sample features are observed through time domain or frequency domain data of the TPS waveform, for example, the refractive and absorption coefficient over a broad frequency. Some image contrast enhancement approaches based on mathematical analysis, for example, the principal component analysis (PCA), integration technique, signal complexity analysis or linear discriminant analysis

Table 3 Cancer studies in THz imaging, spectroscopy and sensing techniques

Reference	Technique	Cancer tissue	Results
Vohra et al. (2021a)	Reflection mode TPI—TPS Spectra 3000	Rat breast tumor	Differentiation between fibro-fatty and cancer tissues
Vohra et al. (2021b)	Reflection mode TPI	Human and animal breast	Human and Sprague Dawley tumors were more similar relative to transgenic and xenograft mice tumors
Cassar et al. (2021)	Diagnosis based on classification of refractive index and morphological dilation	Breast	Sensitivity of 80% and 82%
Chakraborty et al. (2021)	Transmission mode THz pulsed TDS	Pancreatic ductal adenocarcinoma	Successful healthy and cancer tissue differentiation
Yang et al. (2021b)	THz near field imaging	Animal tissue	Potential for μm scale resolution imaging device
Hlali and Zairi (2021)	Graphene based sensor in THz range	Basal cell carcinoma	Sensitivity of 6.9THz/RIU and 11.2THz/RIU for healthy and cancer tissue respectively
Vafapour et al. (2021)	Water-Based THz Metamaterial absorber	Colon cancer	Spectral response change attributed to tissue optical property changes
Hlali et al. (2021)	Tunable graphene-based sensor in THz range	Breast cancer	Sensitivity of 7.11THz/RIU for healthy tissue and 8.21, 17.51and 20.23THz/RIU for breast tumor
Li et al. (2021)	Metamaterial THz biosensor	Cervical cancer	Sensitivity of 29 and 74 GHz/RIU for low and high resonant frequencies
Kaurav et al. (2021)	sub-terahertz waveguide iris probe	Breast	Able to detect fat, fibrous and cancer tissues
Yan et al. (2022)	THz holographic and THz near field imaging	Living body	Achievable through use of nanoparticle contrast agents
Boutaayamou et al. (2020)	THz TDS (Tera Pulse 4000) (reflection mode)	Breast	THz image contrast were found to be well correlated with histopathological results
Vohra et al. (2019s)	Single point pulsed THz transmission spectroscopy (reflection imaging)	Breast	Tomographic images showed clear distinction between cancerous tissues and healthy tissues

Table 3 (continued)

Reference	Technique	Cancer tissue	Results
Bowman et al. (2015), Bowman et al. (2016)	THz transmission and reflection imaging	FFPE tissues	THz reflection imaging provided more contrast, better resolution and clearer margin than transmission imaging
Bowman et al. (2018a, Vohra et al. (2018)	THz reflection imaging	Mice breast tissue	Contrast between cancerous and fat tissue was reasonable The mice model could not mimic human breast tissue due to absence of fibro-glandular tissue
Ashworth et al. (2009)	Single point THz pulsed THz spectroscopy	Human breast tissue	Highest absorption coefficient refractive index values in cancer (IDC), followed by fat and fibro-glandular tissue Based on the values, a reasonable differentiation between the tissues were observed
Bowman et al. (2015), Cerica et al. (2019), Hassan et al. (2012)	THz pulsed imaging (reflection mode) using THz TDS system	PE human breast tissue	Tissue contrast between cancer and normal tissue was obtained Image contrast was attributed to water, cell density, tissue structure and certain protein type's presence
Bowman et al. (2018b), Gavdush et al. (2019)	Terahertz pulsed imaging	FFPE human breast tissue	Good correlation between THz and especially FFPE tissue
Yeo et al. (2019)	THz TDS (reflection mode)	FFPE lung cancer and small intestines	Contrast of cancer and normal tissues clearly observed attributed to the high absorption characteristics of water in cancerous tissue
Bin Ji et al. (2014)	THz spectroscopy and imaging (reflection mode)	Esophageal carcinoma	The absorption coefficient and refractive index of squamous epithelium tissue of the esophagus was found to be higher than in normal tissues

Table 3 (continued)

Reference	Technique	Cancer tissue	Results
Kashanian et al. (2015)	THz TDS	Gastric carcinoma	THz radiation spectra clearly showed differentiation between gastric cancer and normal tissue
Cao et al. (2021)	CW THz TDS, THz TD ATR	Colorectal cancer	Tumors were found to have greater absorption coefficients as well as refractive indices
Rong et al. (2015)	THz TDS, THz holography	Hepatocarcinoma	Hepatocellular carcinoma diagnosis was based the variations of water content and the presence of liver fibrosis
Brun et al. (2010)	THz	Pancreatic cancer	The system could differentiate between cancerous and noncancerous tissue
Zhang et al. (2020a)	TPI	PE prostate tissue were studies	The results showed a clear distinction between the tumor regions from the other tissue regions
Shi et al. (2021)	Transient THz Spectroscopy	Cervical cancer	The absorption coefficient and refractive indices were found to be higher in cancerous cells
Zhang et al. (2020b, Saha et al. (2021)	CW THz spectroscopy	Ovarian cancer	Continuous wave THz spectroscopy was found to potentially detect label free ovarian cancer
Nourinovin et al. (2022b)	THz TDS	Oral squamous cell carcinoma	High capability of THz technology for early cancer detection was highlighted

can be applied for performance improvement of THz imaging and spectroscopy (Nikitkina et al. 2021; Lindley-Hatcher et al. 2021).

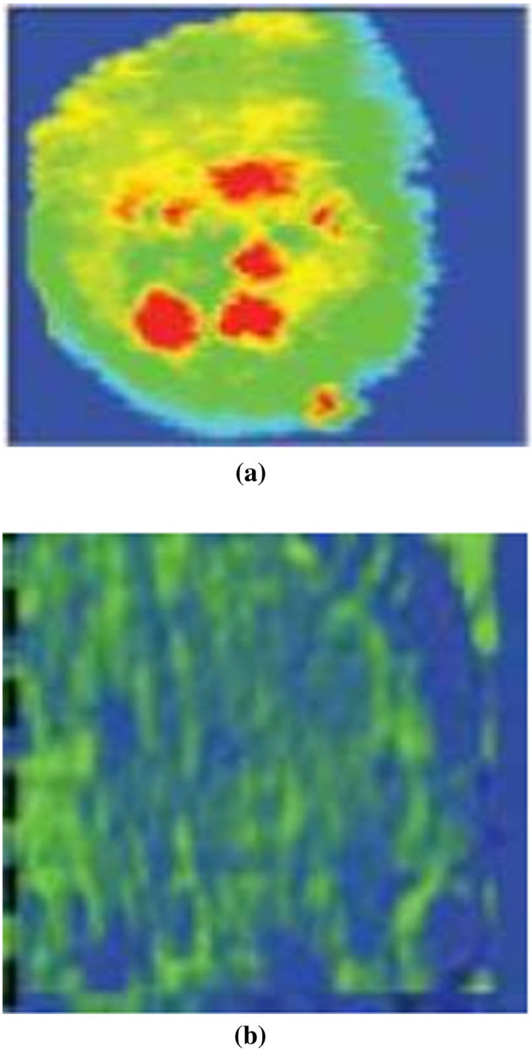
The investigation of various skin cancer types using THz imaging and spectroscopy has been performed in many studies. In one of the studies (Wu et al. 2019), highly sensitive skin cancer detection was done through the use of a water and THz based Metamaterial (MM) semiconductor film. The reflection geometry TPI for skin tissue & skin related cancers were applied. The proposed device's refractive index (RI) sensing application was shown by introducing the sensing materials in the design of the biosensor. To measure the sensitivity of the designed biosensor on detection of Basal Cell Carcinoma (BCC) of the skin and healthy skin was achieved through the change of the effective RI. A MM was developed made up from the semiconductor film i.e., the indium antimony, InSb and water. They firstly showed the potential of potential of the MM for ultra-sensitive refractive index bio sensing applications like sensing BCC and normal skin. The sensitivity of the biosensor was approximately 117 µm/RIU. The skin cancer was detected using TPI by comparison of the THz electromagnetic wave's reflecting spectra from the surface of cancer and normal skin. They also suggested use of the water-based MM device for control of gene expression by placing the device on skin. For this, the incident light was made to shine perpendicular to the device in 1–1.5THz range, then simulate the reflective light for both healthy and BCC cases. The resonance frequency of the reflection spectrum was about 1.38THz when the bio-detector designed on normal skin and 1.382 THz when BCC is placed below the bio-detector and thus the MM design can be used for cancer detection. The use of TPI for BCC have also revealed a significant contrast between healthy and tumorous tissue due to the reflected pulse from anticipated changes in the reflection and RI. The finite difference time domain (FDTD) technique are used for reflected wave differences calculation of normal tissue compared to BCC (Keshavarz and Vafapour 2019).

In (Hakeem and Hassoun 2020), the authors have used TPI to detect skin cancer, they applied image processing and Artificial Neural Networks (ANN) to classify (into normal and abnormal) and detect skin cancer in acquired images where preprocessing and Gabor features based feature extraction are performed. The ANN algorithm had an accuracy of 94.117%.

Figure 6 presents the images extracted from Hakeem and Hassoun (2020), of skin tissue captured by using TPI. The diseased tissue shows increased intensity as a result of THz property changes due to increased blood concentration in cancer tissue relative to that of the normal tissue. The dielectric response of skin tissue at THz radiation are described using the double Debye (DD) model owing the higher water content of skin tumors than that of normal skin (Li et al. 2020). The presented model describes THz radiation with water molecules within human tissue and simulate the Debye relaxation process (reflecting external electric field impact on the water molecules) through the DD equations which are for fitting the dielectric permittivity of the water within the 0.1-THz range. The DD is based on the frequency dependent dielectric function and presented as:

$$\varepsilon_r(\omega) = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_2}{1 + j\omega\tau_1} + \frac{\varepsilon_2 - \varepsilon_\infty}{1 + j\omega\tau_2} \tag{1}$$

where ε_s and ε_∞ the low and frequency static permittivity respectively. ε_2 is intermediate dielectric constant between two relaxation processes. $\varepsilon_2 - \varepsilon_\infty$ and $\varepsilon_s - \varepsilon_2$ are dispersion in amplitude for fast and slow relaxation processes respectively. The molecules are suggested to be in tetrahedral structure in liquid water. As the water gets excited by THz radiation, the structure become perturbed, and it re-orients as a result of the breaking of the tetrahedral



(a)

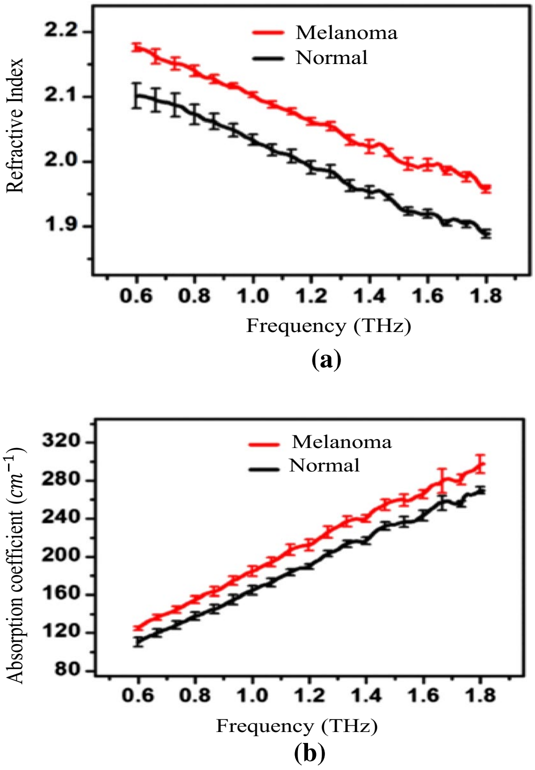
(b)

Fig. 6 The skin images with **a** abnormal tissue **b** normal tissue (Hakeem and Hassoun 2020)

structure. The breaking of the four hydrogen bonds is a slow process (τ_1) and after τ_1, single water molecules are reoriented and move to a new tetrahedral site (fast process (τ_2)) (Truong et al. 2015).

The schematic in Fig. 7, shows that the optical parameters (absorption coefficient, refractive index) are increased in melanoma as compared to that of the normal skin under a THz spectroscopy as reported in Li et al. (2020). Further, Nikitkina et al. (2021) have presented an overview of the THz spectroscopy and THz imaging whereby both the continuous wave-and pulsed wave-techniques were used for skin melanoma and non-melanoma diagnosis, scars, diabetic conditions and dysplasia based on optical properties analysis of THz waves. The potential use of spectroscopy and imaging based on THz for therapy was also highlighted. The cancerous skin tissues and normal tissues were recognized in THz frequency range using a newly designed antenna with higher gain and bandwidth—the Vivaldi antenna in Poorgholam-Khanjari and Zarrabi (2021).

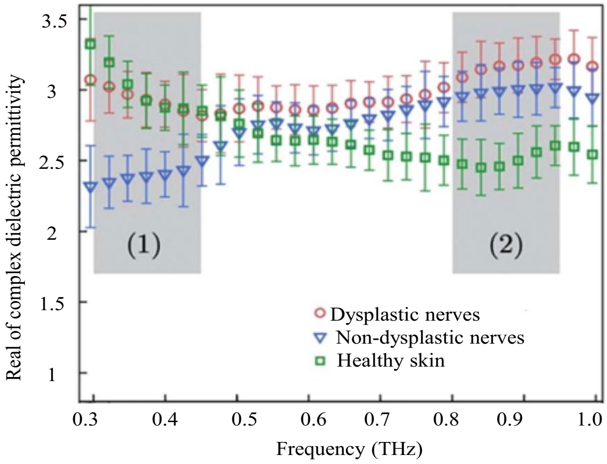
Fig. 7 Melanoma and normal skin parameters **a** refractive index and **b** absorption coefficient (Li et al. 2020)



(a)

(b)

Fig. 8 The real component of complex dielectric permittivity in different skin tissues (Yu et al. 2019a)



Significant optical property differences are also shown in Fig. 8, with clear differences between the dielectric permittivity parameters in healthy, dysplastic and non-dysplastic skin tissues demonstrating the high potential for THz skin diagnostic potential. The reflection geometry is preferred for THz based imaging on thin tissue slices relative

Table 4 Skin cancer studies in THz imaging, spectroscopy and sensing

Reference	THz technology	Cancer/Tissue	Results
Li et al. (2020)	TPS (transmission mode)	Skin melanoma and non-melanoma	Higher absorption coefficient and refractive index was melanoma than healthy tissue which was attributed to increased cell density and water content in cancerous tissue
Vilagosh et al. (2019)	Finite difference TD computational modelling	Frozen melanoma and normal tissue	THz was more permeable to ice than water, resulting in increased penetration depth of THz radiation and clear margin of melanoma due to reflective boundaries
Li et al. (2019)	TPI (reflection mode)	PE cutaneous malignant melanoma	Differentiation of melanoma and non-melanoma was achieved through implementation of morphological and edge detection mathematical computations
Zaitsev et al. (2015)	TPS (reflection mode)	Skin nevi and melanoma in vivo	The ability to differentiate between dysplastic nerve and the non-dysplastic nevi was demonstrated
Zhang et al. (2019)	TPS (ATR)	Skin melanoma and non-melanoma	Increased absorption coefficient and refractive index were observed in melanoma samples which was attributed to slow relaxation and low frequency static permittivity
Moldosanov et al. (2017)	CW THz spectroscopy and THz to IR converter	Human skin	The study showed potential for skin cancer imaging
Goryachuk et al. (2016)	TPS (transmission mode)	Malignant skin of mice	Based on the optical and spectral properties, malignant melanocytes were discriminated from normal skin tissue
Sim et al. (2013)	THz reflection imaging	Frozen oral tissue	Increased penetration depth of THz radiation in ice than liquid water hence more contrast between malignant melanoma in frozen tissue
Zhang et al. (2018)	TPS	Artificial human skin tissue	Higher refractive index & absorption coefficient in melanoma skin than that of normal artificial skin
Joseph et al. (2014)	CW THz imaging (reflection mode) and polarized light imaging	Thick excess cancer samples	Correct tumor identification was achieved due to lower reflectivity in cancer of cross polarized THz images
Joseph et al. (2011)	CW THz imaging (transmission mode)	Skin melanoma tissue	2D images were acquired with a resolution of 0.39 mm in comparison with histology data

Table 4 (continued)

Reference	THz technology	Cancer/Tissue	Results
Titova et al. (2363)	THz pulse exposure	Human artificial skin	The expression levels of genes corresponding to skin melanoma was found to be affected by the THz radiation exposure
Shi et al. (2018)	THz pulse exposure	Methylation in melanoma cells	The technique demonstrated potential of THz radiation for therapy due to reduced methylation by about 10% to 15%
Son and Cheon (2018)	Resonant high power THz radiation	Methylation in melanoma	It was found to be an effective noninvasive technique for melanoma therapy
Zhang et al. (2019)	TPS (ATR)	Skin melanoma and non-melanoma	Higher refractive index and absorption coefficient were observed in melanoma samples which was attributed to slow relaxation and low frequency static permittivity
Arab et al. (2020)	Low power 77 GHz CW radar using miniature hybrid microwave sensor of integrated circuit design	Skin melanoma tissue	The radar was found to be suitable for accurate melanoma detection
Nourinovin et al. (2022a)	THz frequency band measurements	Basal cell carcinoma	Potential for THz based precise diagnosis and early detection
Mohammad et al. (2022)	Millimeter wave to THz near field photonic imaging	Non melanoma skin cancer	Tumor was clearly differentiated from healthy tissues
Veeraselvam et al. (2021)	THz refractive index-based sensor	Carcinoma	The performanceof the THz sensor showed potential for early detection and diagnosis of cancer Peak sensitivity of 476.35 GHz/RIU at 4.065 THz, Q factor of 18.06 at 4.065THz and FoM 0f 2.38 for skin cancer

to transmission configuration because of transmission geometry is greatly affected by tissue morphology and hydration level thus compromising measurements. Most of the studies that have been investigated for THz imaging and spectroscopy application for skin cancer detection are shown in Table 4. The THz spectroscopy was investigated in other skin tissue studies including differentiating muscle and skin tissue, scar healing tracing, skin structure identification (Nikitkina et al. 2021; Li et al. 2020) and diabetic foot syndrome (Hernandez-Cardoso et al. 2022).

6 Discussion

The THz imaging shows great biomedical research as well as clinical potential through its unique spectral features, for example, the non-ionizing, non-invasiveness and label free medical imaging and cell detection. The ability of a medical imaging tool accurately and rapidly detect cancer is critical for early diagnosis, early care and monitoring progress of treatment. The existing technologies like X-ray and computed tomography use ionizing radiation and biological or chemical labelling like use of nuclides. These can adversely affect biological tissue, cell functions and activities thus limiting them to molecular resolution. The significant research on THz imaging and spectroscopy for cancer detection has been investigated for breast, digestive systems, brain, colorectal, cervical, skin and ovarian cancer etc. The experimental studies mostly involved ex-vivo and in-vitro THz imaging of freshly excised human tissue, animal e.g., rat tissue and the use of phantoms. From our analysis, we note the suitability of THz based cancer imaging for the noninvasive and in-vivo detection of cancer at the epithelial tissue layers e.g., skin cancer.

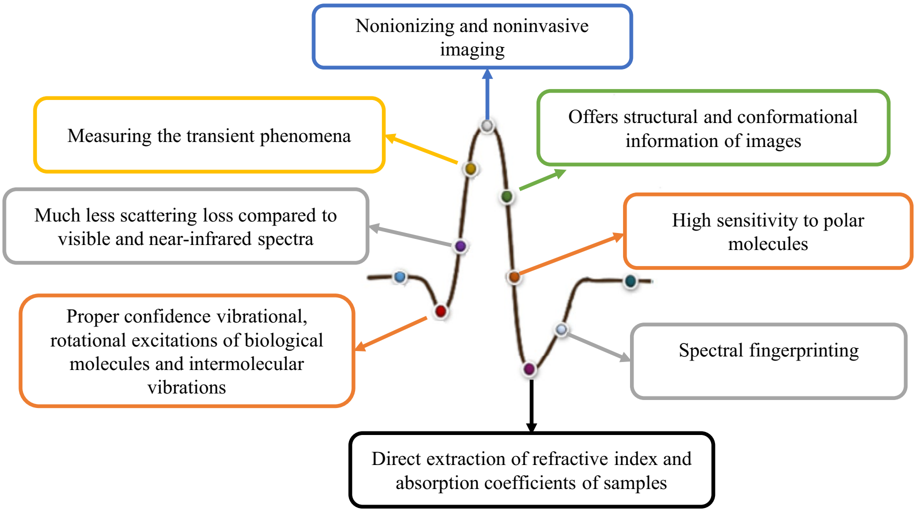


Fig. 9 Attractive features of THz radiation-based cancer imaging

6.1 Advantages of THz imaging for cancer

The attractive characteristics and features of THz imaging for cancer imaging applications have been deduced from the reported studies and are presented in Fig. 9.

Figure 9 shows some of the attractive characteristics and features of THz radiation-based imaging for cancer cells. The detection of cancer cells based on THz radiation is non-ionizing (since its photon energy of 0.4–41 meV is below ionizing radiation) and the non-invasive imaging capability could enable real time, in vivo diagnosis (Danciu et al. 2019). Thus, the THz imaging is tissue friendly for biological tissues proves to be very attractive for repeated scans, treatment follow ups as well as patient monitoring. Being strongly sensitive to the polar molecules like water, the THz waves precisely provide contrast with clear margins between the healthy tissue and cancerous tissue which is a potential tool for early cancer tumor detection (Yan et al. 2022)

The absence of Rayleigh scattering because of cell size being smaller than THz wavelength provides potential for increased image resolution. Also, the frequencies in the THz spectrum show an improved fatty tissue transmittance (Wilmink and Grundt 2011), thus better resolution over Infrared based techniques. The THz imaging is capable of recognizing the specific spectral signatures of molecules in THz range, hence suitable for biomedical applications since tissues from most organs have characteristic absorption in the frequency ranges within THz spectrum (Peng et al. 2020b). These features and characteristics prove the potential of THz technology to become a unique modality that complements the existing medical imaging modalities.

6.2 Open research challenges

Despite the shown massive clinical potential of THz based imaging, the technology development is still at the early stage and still associated with a lot of limitations. The existing challenges and performance improvement approaches will pave the way for future research. The common limitations of THz imaging technology including slow acquisition speed due to raster scanning, poor SNR, low diffraction limited spatial resolution, limited tissue penetration depth have been identified. For the spectral studies, the researchers are still face challenges of extracting target spectral fingerprints out of interfering signals and complex backgrounds through Fourier transforms, which may be realized by future development of high sensitivity and specificity sensors like meta-materials and plasmonic antennas (Yu et al. 2019b).

Due to THz ability to resonate with water and biomolecule vibrational motion on picosecond and sub-picosecond, the THz imaging is able to contrast between pathological, healthy, burned and dehydrated tissues. This enables measurements of the refractive index and absorption coefficient resulting in phase and amplitude information measurements. However, the water highly absorbs THz wave i.e., absorption of 300 cm^{-1} at frequency 1.5 THz for the real operational convenience. 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.

Further, to address continuing limitations including, the more work also needs to be done in THz cancer imaging such as:

- 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 centered academic research.
- High signal loss. Lack of computational modelling for data management, interpretation and analysis for decision support.

6.3 System optimization techniques in THz imaging

Approaches for performance improvement of THz imaging systems have been previously studied to counter some of the previously stated limitations such as.

6.3.1 Tissue preparation methods

The THz radiation is highly sensitive to water content, thus exhibits strong absorption (D'arco et al. 2020) and results in limited depth of THz penetration such that in fresh tissues, the penetration depth is only tens to hundreds microns (in tissue of human skin). These limitations are overcome in research by using thin and/or fixed tissue samples as well as the proper geometry. The challenges associated with keeping the tissues which compromises the measurements include saline uptake, hydration level changes, humidity, scattering effects and temperature changes. For the fresh tissues, when left exposed they dehydrate leading to reduced contrast features on acquisition. Thus, the methods of conserving samples are important. The techniques for tissue sample preparations have been investigated on the excised and fixed tissue such as (Pickwell-Macpherson 2016) (Cheon et al. 2017): (1) Dehydration, (2) Alcohol perfusion, (3) Formalin fixing, (4) Gelatin embedding, (5) Lyophilizing, (6) Freezing, (7) Paraffin embedding, and (8) Paraffin emulsion.

The paraffin embedding is achieved by substituting water with paraffin and enable tissue preservation for a long time without translations of tissue morphology and thereby eliminating water effects (Cheon et al. 2017). The paraffin embedding of tissues increases the THz radiation penetration depth so as to observe the structure and functions of tissue in THz images and can be used for accurate cancer imaging ex vivo. The Formalin fixing is a histopathological diagnosis routine and tissue dehydrating process used to fix and preserve excised tissues by replacing the tissue water with formalin. Lyophilizing is similarly effective for tissue structural preservation and water removal that overcomes limitations associated with variability in THz bandwidth dynamics and thickness of sample. Freezing samples have been applied for penetration depth improvement of THz radiation in tissues, even though it might cause necrosis.

The paraffin embedding requires long preprocessing time and is not usable in vivo, an alternative method for penetration depth improvement is the freezing method whereby the ice reduces THz absorption by water molecules due to vibrational modes that are translated with changes in water state. Thus, like paraffin embedding, the effects of freezing are to reduce water molecule's influence in samples and since freezing does not require sectioning and staining, it can result in faster diagnosis based on THz imaging compared to methods based on frozen biopsy sectioning. Cheon et al. (2017) used this technique to distinguish oral cancer, its ability was also demonstrated for metastatic lymph nodes effective imaging and its potential for in vivo tumor detection of skin or superficial layer. another approaches for example using Oleic acid and gelatin embedding have also been used to maintain tissue moisture content (Pickwell-Macpherson 2016).

6.3.2 Penetration enhancing agents

The major drawback for freezing technique is the requirement for additional freezing equipment and processing and is restricted to excised samples. The THz penetration enhancing agents (THz PEAs) are good alternatives for increased penetration depth and enhanced contrast (Cheon et al. 2017). Good THz PEAs such as Glycerol have less THz absorption as compared to water and have good tissue permeability and should be biocompatible.

6.3.3 SNR enhancing agents

As previously mentioned, the high THz absorption by water in cancer tissues leads to poor SNR of the resulting spectra. Also, since the biological samples contain a variety of substances like water, fat, proteins and fiber, the SNR of the absorption peaks of target substances will be small, making it hard to identify the target substances (Peng et al. 2020a). Several methods have been proposed and applied so as to enhance SNR of THz spectra. The use of nanoparticles as contrast agents have been reported, the use of gold nanorods (GNRs) and super paramagnetic iron oxide (SPIOs) are proposed as a method to increase THz waves reflection in water and onion like carbon (OLC) in nanoscale was proposed for ductal carcinoma (Shi et al. 2020).

The use of optical clearing agents has also been reported for spectral SNR improvement and contrast enhancement like polyethylene glycol, propylene glycol, dimethyl sulfoxide and ethylene glycol, fluorinated oil (Shi et al. 2020). The use of biosensors based on antibodies has been used in cancer detection including a biosensor that included some aptamers coated silicon dioxide layer whereby the antibody only binds to surface of cell protein related to cancer thereby varying the THz radiation absorption of cancer cells compared to normal cells. Biosensors based on meta materials and the use of THz ATR have also been proposed for enhancing SNR spectrum (Peng et al. 2020a; Shi et al. 2020).

6.3.4 Methods for scanning time improvement

The efforts are being made in the THz TDS technologies development for rapidly improving the rate of scanning. The THz TDS imaging is characterized by long raster scan times caused by single pixel detector and mechanical linear motion of the optical delay line. Some techniques being used for scanning time improvement and avoid optical delay line mechanical motions include the use of fast optical delay lines, electronically controlled optical sampling (ECOPS), cavity tuning, asynchronous optical sampling (ASOPS), efficient data collection methods for example 2D THz TDS, implementation of 2D electro optic sampling (EOS), nonmechanical time domain sampling, photoconductive antenna (PCA) integration and optical rectification are also useful for acceleration of THz pulses acquisition. The advent of near field imaging and tomography in THz TDS is also significantly contributing to saving time and offering commercial potential (Wang et al. 2022). Recent works have also investigated computational imaging, focal plane arrays, compressed sensing based techniques (Castro-Camus et al. 1999).

6.3.5 Data processing techniques

When using TPS systems, data processing is very important. From the power spectrum measurements, the Kramers–Kronig relations can be used to obtain complex refractive index or complex dielectric permittivity, however this is not required in TPS since the phase and amplitude in frequency domain will be known (Xie et al. 2013). In THz CT, the filtered back projection algorithm has been used for reconstruction and the combination of compressed sensing and inverse Fresnel diffraction has been investigated for image reconstruction (Shang et al. 2019). The data processing steps in TPS involve signal preprocessing, denoising, apodization and deconvolution. The final processing steps involve statistical analysis, dimensionality reduction and machine learning approaches. The machine learning approaches for THz data preprocessing, processing and analysis have been investigated for example in Park and Son (1186); Wang et al. 2021) but not yet fully explored. Recently, the deep learning algorithms have been found to be attractive for noise removal in measurements, discrimination of regions, enhance resolution, image reconstruction and characterization (Valušis et al. 2021; Gezimati and Singh 2022b).

6.3.6 Recent advances in THz technology

The conventional THz imaging and spectroscopy systems have been mainly driven by 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 femtosecond lasers, mid-IR and room temperature operating & plasmonic QCLs, Silicon nanotransistors, 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).

Further, 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 modulated continuous wave (MCW) THz imaging which entails radar-based techniques like the synthetic aperture radar (SAR) imaging.

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 (Yan et al. 2022; Valušis et al. 2021; Castro-Camus et al. 1999; Gezimati and Singh 2022a, 2022b, 2022c).

7 Conclusion

As shown from this work, the THz technology's great potential and impressive progress as a novel and innovative modality for the evolution of healthcare, particularly the medical diagnosis of cancer has been investigated. THz technology exhibits great potential to revolutionize healthcare technology towards cancer early diagnosis, treatment and patient care through the THz radiation salient properties such as low photon energy—noninvasive, non-destructive and nonionizing and unmatched sensing. THz technology has been investigated through experimental studies for cancer applications (for the types of cancer including but not limited to breast, lung, brain, digestive, skin and prostate cancers as well as great potential in cancer treatment.) and shows potential as a medical imaging modality that complements the conventional techniques like X-Ray and MRI. Although the advancement of THz based detection has been remarkable through the continuous improvement of the THz instrumentation including equipment, miniaturization, reconstruction algorithms, sources and detectors etc., the development of the imaging technology is still not yet mature and further developments are required for widespread commercial and technological viable application of THz and for clinical adoption. Some of the common limitations of THz imaging include very high cost of commercially available THz equipment, unavailability of standardized tools and methods for enabling results comparison and reproducibility, long scanning speed etc. THz radiation is highly absorbed by water and water containing fluids under tissue of interest causing limited penetration depth. Also, the technology is still associated with lack of discriminative precision, data interpretation, data availability and analysis, low resolution, low SNR, long scanning time, effects of environmental conditions on tissue samples (shape, fluid content etc.). This implies that there is still vast need to explore and expand the THz technology through research and development to address the aforementioned limitations. In future communication, we would like to report on the improvement of the diagnosis accuracy and analysis of the acquired THz cancer images through development of computer aided diagnosis (CAD) system based on machine learning. Further, the future research will investigate the integration of THz technology with AI, IoT, cloud computing, big data analytics, robotics etc. for more sophisticated systems. This will facilitate the large-scale clinical applications of THz and suitability for next generation healthcare that should be smart and connected. The investigations of THz radiation impact on biological tissues can be explored, development of cost effective, compact and sensitive THz imaging systems that can be standardized for clinical trials should be scope for future studies. Also, the establishment of labelled and shared THz cancer image datasets will facilitate data centric studies and support academic research.

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Declarations

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References

Amini, T., Jahangiri, F., Ameri, Z., Hemmatian, M.A.: A review of feasible applications of THz waves in medical diagnostics and treatments. J. Lasers Med. Sci. **12**, 1–8 (2021)

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)

Arab, H., Chioukh, L., Dashti Ardakani, M., Dufour, S., Tatu, S.O.: Early-stage detection of melanoma skin cancer using contactless millimeter-wave sensors. IEEE Sens. J. **20**(13), 7310–7317 (2020)

Ashworth, P.C., Pickwell-MacPherson, E., Provenzano, E., Pinder, S.E., et al.: Terahertz pulsed spectroscopy of freshly excised human breast cancer. Opt. Express **17**(15), 12444–12454 (2009)

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, A., Chakraborty, C., Rathi, M.: Medical imaging, artificial intelligence, internet of things, wearable devices in terahertz healthcare technologies. *Terahertz Biomedical and Healthcare Technologies* pp. 145–165, (2020).

Bin Ji, Y., Kim, S.-H., Jeong, K., Choi, Y., et al.: Terahertz spectroscopic imaging and properties of gastrointestinal tract in a rat model. Biomed. Opt. Express **5**(12), 4162–4170 (2014)

Boutaayamou, M., Cerica, D., Verly, J.G. Terahertz pulsed imaging of dehydrated human breast cancer samples. Proceedings of the International Conference on Infrared, Millimeter, and Terahertz Waves, IRMMW-THz, vol. 2020-Novem, pp. 65–66, (2020).

Bowman, T.C., El-Shenawee, M., Campbell, L.K.: Terahertz imaging of excised breast tumor tissue on paraffin sections. IEEE Trans. Antennas Propag. **63**(5), 2088–2097 (2015)

Bowman, T., El-Shenawee, M., Campbell, L.K.: Terahertz transmission vs reflection imaging and model-based characterization for excised breast carcinomas. Biomed. Opt. Express **7**(9), 3756 (2016)

Bowman, T., Chavez, T., Khan, K., Wu, J., Chakraborty, A., et al.: Pulsed terahertz imaging of breast cancer in freshly excised murine tumors. J. Biomed. Opt. **23**(2), 1–14 (2018a)

Bowman, T., El-Shenawee, M., Bailey, K., Challenges in terahertz imaging of freshly excised human breast tumors. *Proceedings of the IEEE Antennas and Propagation Society International Symposium and USNC/URSI National Radio Science Meeting, APSURSI 2018b*, pp. 13–14, (2018b)

Brun, M.A., Formanek, F., Yasuda, A., Sekine, M., et al.: Terahertz imaging applied to cancer diagnosis. Phys. Med. Biol. **55**(16), 4615–4623 (2010)

Cao, Y., Chen, J., Zhang, G., Fan, S., et al.: Characterization and discrimination of human colorectal cancer cells using terahertz spectroscopy. Spectrochimica Acta Part A Mol. Biomol. Spectrosc. **256**, 1–7 (2021)

Cassar, Q., Al-Ibadi, A., Mavarani, L., Hillger, P., et al.: Pilot study of freshly excised breast tissue response in the 300–600 ghz range. Biomed. Opt. Express **9**(7), 2930–2942 (2018)

Cassar, Q., Caravera, S., MacGrogan, G., Bücher, T. *et al.*, Association of the terahertz refractive index and morphological dilation operations for breast carcinoma detection. Proceedings of the International Conference on Infrared, Millimeter, and Terahertz Waves, IRMMW-THz 2021, 1–1 (2021)

Castro-Camus, E., Koch, M., Mittleman, D.M.: Recent advances in terahertz imaging: 1999 to 2021. Appl. Phys. B Lasers Opt. **128**, 1–10 (2022)

Cerica, D., Nguyen, D., Hernandez, Y., Verly, J.G., Boutaayamou, M., Terahertz pulsed imaging of paraffin-embedded human breast cancer tissue. Proceedings of the International Conference on Infrared, Millimeter, and Terahertz Waves, IRMMW-THz, vol. 2019, pp. 1–2, (2019)

Chakraborty, D., Mills, B.N., Chen, G., Attanasio, A. *et al.*, Pulsed terahertz time-domain spectroscopy of paraffin-embedded pancreatic ductal adenocarcinoma. Proceedings of the International Conference on Infrared, Millimeter, and Terahertz Waves, IRMMW-THz 2021, 1–2 (2021)

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)

Cheon, H., Yang, H.J., Son, J.H.: Toward clinical cancer imaging using terahertz spectroscopy. IEEE J. Sel. Top. Quant. Electron **23**(4), 1–9 (2017)

D'arco, A., Di Fabrizio, M., Dolci, V., Petrarca, M., Lupi, S.: THz pulsed imaging in biomedical applications. Condensed Matter **5**(2), 1–28 (2020)

Danciu, M., Alexa-Stratulat, T., Stefanescu, C., Dodi, G., et al.: Terahertz spectroscopy and imaging: a cutting-edge method for diagnosing digestive cancers. Materials **12**(9), 1–16 (2019)

El-Shenawee, M., Vohra, N., Bowman, T., Bailey, K.: Cancer detection in excised breast tumors using terahertz imaging and spectroscopy. Biomed. Spectrosc. Imaging **8**(1–2), 1–9 (2019)

Fitzgerald, A.J., Wallace, V.P., Jimenez-Linan, M., Bobrow, L., et al.: Terahertz pulsed imaging of human breast tumors. Radiology **239**(2), 533–540 (2006)

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**, 1–16 (2022)

Gavdush, A.A., Chernomyrdin, N.V., Malakhov, K.M., Beshplav, S.-I.T., et al.: Terahertz spectroscopy of gelatin-embedded human brain gliomas of different grades: a road toward intraoperative THz diagnosis. J. Biomed. Opt. **24**(02), 1–6 (2019)

Gezimati, M., Singh, G., Advances in Terahertz Instrumentation and Technology for Cancer Applications. Presented at the International Conference on Infrared, Millimeter, and Terahertz Waves, IRMMW-THz vol. 2022a, pp. 1–2, (2022a)

Gezimati, M., Singh, G., Transfer learning for breast cancer classification in terahertz and infrared imaging. Proceedings of the 2022b International Conference on Artificial Intelligence, Big Data, Computing and Data Communication Systems (icABCD) vol. 2022b, pp. 1–6, (2022b)

Gezimati, M., Singh, G., Internet of Things Enabled Framework for Terahertz and Infrared Cancer Imaging. *Optical and Quantum Electronics (OQEL),* Accepted August (2022c).

Gong, A., Qiu, Y., Chen, X., Zhao, Z., Xia, L., Shao, Y.: Biomedical applications of terahertz technology. Appl. Spectrosc. Rev. **55**(5), 418–438 (2020)

Goryachuk, A.A., Begaeva, V.A., Khodzitsky, M.K., Truloff, A.S.: The optical properties and spectral features of malignant skin melanocytes in the terahertz frequency range. J. Phys: Conf. Ser. **735**, 1–7 (2016)

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)

Hakeem, S.I., Hassoun, Z.A.: Skin cancer detection based on terahertz images by using gabor filter and artificial neural network. IOP Conference Series Mater. Sci. Eng. **928**(3), 32025 (2020)

Hassan, L.A.M., Hufnagle, D.C., El-Shenawee, M., Pacey, G.E. Terahertz imaging for margin assessment of breast cancer tumors. Proceedings of the IEEE MTT-S International Microwave Symposium Digest, pp. 1–3, (2012)

Hernandez-Cardoso, G.G., Amador-Medina, L.F., Gutierrez-Torres, G., Reyes-Reyes, E.S., et al.: Terahertz imaging demonstrates its diagnostic potential and reveals a relationship between cutaneous dehydration and neuropathy for diabetic foot syndrome patients. Sci. Rep. **12**(1), 1–10 (2022)

Hlali, A., Zairi, H.: Graphene based-sensor for basal cell carcinoma detection. IEEE Sens. J. **21**(18), 19930–19937 (2021)

Hlali, A., Oueslati, A., Zairi, H.: Numerical simulation of tunable terahertz graphene-based sensor for breast tumor detection. IEEE Sens. J. **21**(8), 9844–9851 (2021)

Joseph, C.S., Yaroslavsky, A.N., Neel, V.A., Goyette, T.M., Giles, R.H.: Continuous wave terahertz transmission imaging of nonmelanoma skin cancers. Lasers Surg. Med. **43**(6), 457–462 (2011)

Joseph, C.S., Patel, R., Neel, V.A., Giles, R.H., Yaroslavsky, A.N.: Imaging of ex vivo nonmelanoma skin cancers in the optical and terahertz spectral regions. J. Biophotonics **7**(5), 295–303 (2014)

Kashanian, H.A., Ghaffary, H.B., Bagherzadeh, N.C.: Gastric cancer diagnosis using terahertz imaging. Majlesi J. Multimedia Process. **4**(4), 1–7 (2015)

Kaurav, P., Koul, S., Basu, A. Design of sub-terahertz waveguide iris probe for breast cancer tumor margin assessment. Proceedings of the IEEE MTT-S International Microwave and RF Conference, IMARC 2021, pp. 1–3 (2021)

Kazemi, F.: High q-factor compact and reconfigurable THz aperture antenna based on graphene loads for detecting breast cancer cells. Superlattices Microstruct. **153**, 1–9 (2021)

Keshavarz, A., Vafapour, Z.: Water-based terahertz metamaterial for skin cancer detection application. IEEE Sens. J. **19**(4), 1519–1524 (2019)

Li, J., Xie, Y., Sun, P.: Edge detection on terahertz pulse imaging of dehydrated cutaneous malignant melanoma embedded in paraffin. Front. Optoelectr. **12**(3), 317–323 (2019)

Li, D., Yang, Z., Fu, A., Chen, T., Chen, L., et al.: Detecting melanoma with a terahertz spectroscopy imaging technique. Spectrochimica Acta Part A Mol. Biomol. Spectrosc. **234**, 1–8 (2020)

Li, D., Hu, F., Zhang, H., Chen, Z., 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., et al.: Using antibody modified terahertz metamaterial biosensor to detect concentration of carcinoembryonic antigen. IEEE J. Sel. Top. Quantum Electron. **27**(4), 1–7 (2021)

Lindley-Hatcher, H., Stantchev, R.I., Chen, X., Hernandez-Serrano, A.I., et al.: Real time THz imaging—opportunities and challenges for skin cancer detection. Appl. Phys. Lett. **118**, 1–7 (2021)

Liu, K., Zhang, R., Liu, Y., Chen, X., Li, K., Pickwell-Macpherson, E.: Gold nanoparticle enhanced detection of egfr with a terahertz metamaterial biosensor. Biomed. Opt. Express **12**(3), 1559–1567 (2021)

Malhotra, I., Jha, K.R., Singh, G.: Terahertz antenna technology for imaging applications: a technical review. Int. J. Microw. Wirel. Technol. **10**(3), 271–290 (2018)

Malhotra, I., Singh, G. Terahertz antenna technology for imaging and sensing applications. *Terahertz Antenna Technology for Imaging and Sensing Applications*, pp. 75–102, (2021)

Malhotra, I., Singh, G. Terahertz Near-Field Imaging and Sensing. *Terahertz Antenna Technology for Imaging and Sensing Applications*, pp. 217–234, (2021a).

Malhotra, I., Singh, G. Terahertz Technology for Biomedical Application. *Terahertz Antenna Technology for Imaging and Sensing Applications*, pp. 235–264, (2021b)

Mohammad, I., Rymanov, V., Makhlouf, S., Stoffels, I. *et al.*, Photonic non-invasive mmw and THz imaging for non-melanoma skin cancer detection. *2022 Fifth International Workshop on Mobile Terahertz Systems (IWMTS)*, pp. 1–5, (2022)

Moldosanov, K.A., Postnikov, A.V., Lelevkin, V.M., Kairyev, N.J.: Terahertz imaging technique for cancer diagnostics using frequency conversion by gold nano-objects. Ferroelectrics **509**(1), 158–166 (2017)

Mukherjee M., Chatterjee S. Chapter 6—THz medical imaging: current status and future outlook pp. 113–125 (2020)

Nikitkina, A.I., Bikmulina, P.Y., Gafarova, E.R., Kosheleva, N.V., et al.: Terahertz radiation and the skin: a review. J. Biomed. Opt. **26**, 1–26 (2021)

Nourinovin, S., Rahman, M.M., Jones, R.C., Philpott, M.P., Alomainy, A. Impact of drug treatment on the electromagnetic properties of basal cell carcinoma cancer in the terahertz band. Proceedings of the IEEE 16th European Conference on Antennas and Propagation (EuCAP), pp. 1–4, (2022a)

Nourinovin, S., Rahman, M.M., Jones, R.C., Philpott, M.P., Alomainy, A. Terahertz characterisation of artificially cultured oral cancer with stem cell lines for healthcare applications. Proceedings of the IEEE International Symposium on Medical Measurements and Applications (MeMeA), pp. 1–5, (2022b)

Park, H., Son, J.H.: Machine learning techniques for THz imaging and time-domain spectroscopy. Sensors (switzerland) **21**(4), 1–25 (2021)

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 (2020a)

Peng, Y., Shi, C., Wu, X., Zhu, Y., Zhuang, S.: Terahertz imaging and spectroscopy in cancer diagnostics: a technical review. BME Frontiers **2020**, 1–11 (2020b)

Peng, Y., Huang, J., Luo, J., Yang, Z., et al.: Three-step one-way model in terahertz biomedical detection. PhotoniX **2**(1), 1–18 (2021a)

Peng, Y., Shi, C., Wu, X., Zhu, Y., Zhuang, S. Terahertz biomedical application research. *Proeeding of the IEEE International Conference on Infrared, Millimeter, and Terahertz Waves,* (IRMMW-THz), vol. 2021b-August, (2021b).

Pickwell-Macpherson, E. Biomedical THz imaging and spectroscopy: high sensitivity is both a blessing and a curse. *Proceedings of the IEEE International Conference on Infrared, Millimeter, and Terahertz Waves, IRMMW-THz* 2016 1–2 (2016)

Poorgholam-Khanjari, S., Zarrabi, F.B.: Reconfigurable vivaldi THz antenna based on graphene load as hyperbolic metamaterial for skin cancer spectroscopy. Optics Communications **480**, 1–8 (2021)

Rao, L. Realization of temperature measurement by passive terahertz imaging. Proceedings of the 13th UK-Europe-China Workshop on Millimetre-Waves and Terahertz Technologies, UCMMT 2020, pp. 1–3, (2020)

Rong, L., Latychevskaia, T., Chen, C., Wang, D., et al.: Terahertz in-line digital holography of human hepatocellular carcinoma tissue. Sci. Rep. **5**(1), 1–6 (2015)

Saha, A., Sil, S., Pal, S., Gupta, B., Basak, P.: Meta sensing ovarian cancer cells at THz from c band radiation biophysics. Lecture Notes Netw. Syst. **165**, 111–122 (2021)

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)

Schnitt, S.J., Moran, M.S., Houssami, N., Morrow, M.: The society of surgical oncology - american society for radiation oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages i and ii invasive breast cancer: perspectives for pathologists. Arch. Pathol. Lab. Med. **139**(5), 575–577 (2015)

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, J., Wang, Y., Chen, T., Xu, D., et al.: Automatic evaluation of traumatic brain injury based on terahertz imaging with machine learning. Opt. Express **26**(5), 6371–6381 (2018)

Shi, C., Wu, X., Peng, Y.: Applications of terahertz imaging technology in tumor detection. Opto Electr. Eng. **47**(5), 190631–190638 (2020)

Shi, W., Wang, Y., Hou, L., Ma, C., Yang, L., et al.: Detection of living cervical cancer cells by transient terahertz spectroscopy. J. Biophoton. **14**(1), 1–7 (2021)

Shur, M., Liu, X. Biomedical applications of terahertz technology. *Advances in Terahertz Biomedical Imaging and Spectroscopy*, vol. 11975, p. 1197502 (2022)

Siegel, R.L., Miller, K.D., Jemal, A.: Cancer statistics. CA Cancer J. Clin. **70**(1), 7–30 (2020)

Sim, Y.C., Ahn, K.M., Park, J.Y., Park, C.S., Son, J.H.: Temperature-dependent terahertz imaging of excised oral malignant melanoma. IEEE Transact. Terahertz Sci. Technol. **3**(4), 368–373 (2013)

Son, J.H. Terahertz molecular imaging and its biomedical applications. *Terahertz Biomedical and Healthcare Technologies*, p. SF1A.1 (2013)

Son, J.H., Oh, S.J., Cheon, H.: Potential clinical applications of terahertz radiation. J. Appl. Phys. **125**, 1–12 (2019)

Son, J.H., Cheon, H. Toward cancer treatment using terahertz radiation: demethylation of cancer dna. Proceedings of the IEEE International Conference on Infrared, Millimeter, and Terahertz Waves, IRMMW-THz, vol. 2018, p. 1139002, (2018)

Taylor, W., Abbasi, Q.H., Dashtipour, K., Ansari, S., et al.: A review of the state of the art in non-contact sensing for covid-19. Sensors (switzerland) **20**(19), 1–19 (2020)

Titova, L.V., Ayesheshim, A.K., Golubov, A., Rodriguez-Juarez, R., et al.: Intense THz pulses down-regulate genes associated with skin cancer and psoriasis: a new therapeutic avenue? Sci. Rep. **3**, 1–6 (2013)

Truong, B.C.Q., Tuan, H.D., Wallace, V.P., Fitzgerald, A.J., Nguyen, H.T.: The potential of the double debye parameters to discriminate between basal cell carcinoma and normal skin. IEEE Transact. Terahertz Sci. Technol. **5**(6), 990–998 (2015)

Vafapour, Z., Keshavarz, A., Ghahraloud, H.: The potential of terahertz sensing for cancer diagnosis. Heliyon **6**(12), 1–8 (2020)

Vafapour, Z., Troy, W., Rashidi, A.: Colon cancer detection by designing and analytical evaluation of a water-based THz metamaterial perfect absorber. IEEE Sens. J. **21**(17), 19307–19313 (2021)

Valušis, G., Lisauskas, A., Yuan, H., Knap, W., Roskos, H.G.: Roadmap of terahertz imaging 2021. Sensors **21**(12), 1–51 (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 (2021)

Viale, P.H.: The American cancer society's facts and figures: 2020 edition. J. Adv. Pract. Oncol. **11**(2), 135–136 (2020)

Vilagosh, Z., Lajevardipour, A., Wood, A.W.: Computational phantom study of frozen melanoma imaging at 0.45 terahertz. Bioelectromagnetics **40**(2), 118–127 (2019)

Vohra, N., Bowman, T., Diaz, P.M., Rajaram, N., et al.: Pulsed terahertz reflection imaging of tumors in a spontaneous model of breast cancer. Biomed. Phys. Eng. Express **4**(6), 1–16 (2018)

Vohra, N., Bowman, T., El-Shenawee, M., Bailey, K. Image reconstruction of freshly excised human breast tumors using terahertz electrical properties. Proceedings of the IEEE International Symposium on Antennas and Propagation and USNC-URSI Radio Science Meeting, APSURSI 2019s, pp. 571–572, (2019s).

Vohra, N., El-Shenawee, M., Bailey, K. Terahertz imaging of enu injected sprague dawley rat breast cancer tumors. Proceedings of the IEEE International Symposium on Antennas and Propagation and North American Radio Science Meeting, APS/URSI 2021a pp. 585–586, (2021a)

Vohra, N., Chavez, T., Troncoso, J.R., Rajaram, N. *et al.*, Terahertz imaging of breast cancer using human and animal models. Proceedings of the IEEE Conference on Antenna Measurements and Applications, CAMA 2021b, pp. 368–371, (2021b)

Wang, L.: Terahertz imaging for breast cancer detection. Sensors **21**(19), 1–17 (2021)

Wang, C., Shi, F., Zhao, M., Ao, J., Jia, C., Chen, S.: Convolutional neural network-based terahertz spectral classification of liquid contraband for security inspection. IEEE Sens. J. **21**(17), 18955–18963 (2021)

Wang, Q., Xie, L., Ying, Y.: Overview of imaging methods based on terahertz time-domain spectroscopy. Appl. Spectrosc. Rev. **57**(3), 249–264 (2022)

Wilmink, G.J., Grundt, J.E.: Invited review article: current state of research on biological effects of terahertz radiation. J. Infrared Millimeter Terahertz Waves **32**(10), 1074–1122 (2011)

Wu, L., Xu, D., Wang, Y., Liao, B., Jiang, Z., et al.: Study of in vivo brain glioma in a mouse model using continuous-wave terahertz reflection imaging. Biomed. Opt. Express **10**(8), 3953–3962 (2019)

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)

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**, 1–12 (2021)

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., Li, J., Lamy de la Chapelle, M., Huang, G., et al.: A terahertz metamaterial biosensor for sensitive detection of micrornas based on gold-nanoparticles and strand displacement amplification. Biosens. Bioelectron. **175**, 1–7 (2021a)

Yang, S., Du, C., Feng, L., Zhang, C., Wu, B. *et al.*, Real-time near-field terahertz spectroscopy imaging. Proceedings of the International Conference on Infrared, Millimeter, and Terahertz Waves, IRMMW-THz 2021b, 1–1 (2021b).

Yeo, W.G., Gurel, O., Hitchcock, C.L., 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., et al.: The medical application of terahertz technology in noninvasive detection of cells and tissues: opportunities and challenges. RSC Adv. **9**(17), 9354–9363 (2019a)

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 (2019b)

Zaitsev, K.I., Chernomyrdin, N.V., Kudrin, K.G., Reshetov, I.V., Yurchenko, S.O.: Terahertz spectroscopy of pigmentary skin nevi in vivo. Opt. Spectrosc. **119**(3), 404–410 (2015)

Zhan, X., Yang, S., Huang, G., Yang, L., 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**, 1–7 (2021)

Zhang, R., Yang, K., Yang, B., AbuAli, N.A., et al.: Dielectric and double debye parameters of artificial normal skin and melanoma. J. Infrared Millimeter Terahertz Waves **40**(6), 657–672 (2019)

Zhang, P., Zhong, S., Zhang, J., Ding, J., et al.: Application of terahertz spectroscopy and imaging in the diagnosis of prostate cancer. Curr. Opt. Photonics **4**(1), 31–43 (2020a)

Zhang, Y., Wang, C., Huai, B., Wang, S., et al.: Continuous-wave THz imaging for biomedical samples. Appl. Sci. (switzerland) **11**(1), 1–26 (2021)

Zhang, J., Li, S., Le, W.: Advances of terahertz technology in neuroscience: current status and a future perspective. Iscience **24**(12), 1–11 (2021b)

Zhang, R., Yang, K., Abbasi, Q., Abuali, N.A., Alomainy, A. Experimental characterization of artificial human skin with melanomas for accurate modelling and detection in healthcare application.

Proceedings of the International Conference on Infrared, Millimeter, and Terahertz Waves, IRMMW-THz, vol. 2018, pp. 1–2, (2018)

Zhang, J., Han, Z., Yuan, C., Liu, S., Yao, S. *et al.*, Label-free characterization of cancerous ovarian tissues with continuous wave terahertz spectroscopy. *AOPC 2020b: Advanced Laser Technology and Application*, vol. 11562, p. 36, (2020b)

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