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TOPICAL REVIEW

Terahertz Imaging and Sensing for Healthcare: Current Status and Future Perspectives

MAVIS GEZIMATI AND GHANSHYAM SINGH, (Member, IEEE)
Centre for Smart Information and Communication Systems, Department of Electrical and Electronic Engineering Science, University of Johannesburg, Auckland Park Kingsway Campus, Johannesburg 2006, South Africa

Corresponding author: Ghanshyam Singh (ghanshyams@uj.ac.za)

ABSTRACT There is a keen interest in the exploration of new generation emitters and detectors due to advancements in innovation of new materials and device processing technologies which have opened up new frontiers in the Terahertz (THz) spectrum. Therefore, it is necessary to review the developments in THz technology for healthcare applications, their impact, implications and prospects for ongoing research and development. This paper provides a broad overview of the current status and prospects of application of THz imaging and sensing for the healthcare domain. We present current knowledge, identify existing challenges for wide scale clinical adoption of THz systems and prospective opinions to facilitate research and development towards optimized and miniaturized THz systems and biosensors that provide real operational convenience through emerging trends. Firstly, we provide an overview of the THz imaging and sensing techniques that exploit properties of THz generation and detection with emphasis on terahertz time domain spectroscopy (THz-TDS) and THz Metamaterials. The mechanisms of tissue image contrast and the application of THz imaging and sensing for biomedical applications in particular, the cancer detection application is reported. Secondly, an outlook toward the advancements in THz technology in the interface of healthcare 4.0 and its enabling technologies is explored for next generation smart and connected healthcare systems. Third, we identify the merits and existing challenges in THz cancer imaging and sensing and suggest prospective opinions to pave way to ongoing and future research. Further, we discuss the recent advances in THz imaging development and the contribution of near-field techniques based on plasmonic, and resonance based metasurfaces, waveguides etc. for breaking the diffraction limit towards development of THz systems that are convenient for point of care. We bring researchers a roadmap for future research scope.

INDEX TERMS Cancer, healthcare 4.0, imaging, spectroscopy, sensing, terahertz technology.

I. INTRODUCTION

Currently, the terahertz (THz) regime of the spectrum is rapidly becoming a research hotspot with great potential to bring a new era in the healthcare industry including in biomedical imaging for cancer among many other biomedical applications of THz imaging, spectroscopy, and sensing. The Global Terahertz (THz) market size was valued at USD 420 million in 2022 and is predicted to reach USD2,879 million by 2030, with a Compound Annual Growth Rate (CAGR) of 23.8% between the 2022-2030 period [1]. The evolution of advanced technologies, emergence of new diseases, population health management, better informed customers and inventions are some among many other factors which are improving the demand of THz technology in healthcare. This has led to the ongoing research and developments in the advancement of THz devices that are capable of sensing [2], [3], [4], monitoring and detection [5], imaging, spectroscopy [6] and characterization [7]. THz radiation has been investigated in the healthcare domain for diagnosis and monitoring of other disorders including foot diabetes, skin dehydration, wounds, burns, dentistry, dermatology etc. [8]. The application of THz technologies like THz imaging, sensing and THz Time Domain Spectroscopy

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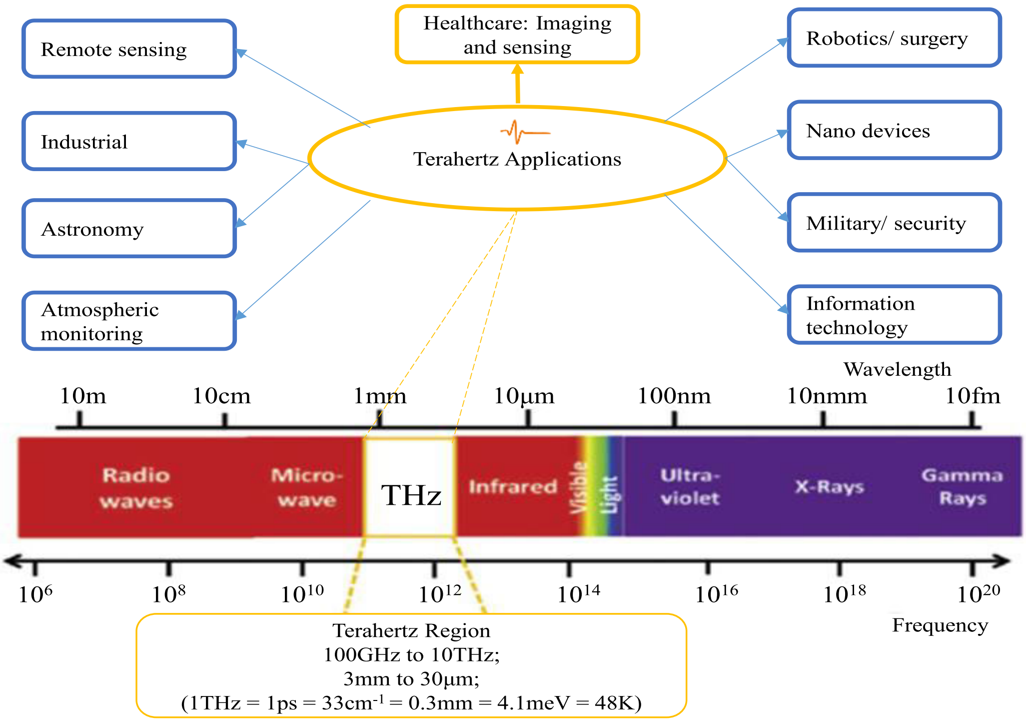


FIGURE 1. The electromagnetic spectrum and its potential application.

(THz-TDS) have also advanced in other applications like non-destructive testing (NDT), surveillance and security checks, material characterizations etc. and is expected to expand. The focus of this paper is on the application of THz technology for biomedical imaging and sensing of cancer as shown in Fig 1.

The "Terahertz radiation" is also termed T-rays, THz waves or THz light [9]. As shown in Fig. 1, the THz region ranges between the frequencies 0.1–10 THz and wavelength 3mm to 30μm, where $1\text{THz} = 1\text{ps} = 33\text{cm-1} = 0.3\text{mm} = 4.1\text{meV} = 48\text{K}$ [10]. Due to a vast difficulties related to detectors and sources, the THz frequency regime of the spectrum has been previously called the "Terahertz gap" [11]. The significance of crossing the gap have been identified through realization of THz frequency as spectrum of molecular vibrations e.g., molecular rotational, crystalline photon, torsional as well as inter-and intra-molecular vibrations [12]. Spectral features of THz radiation, namely, non-invasive, non-ionizing, spectral fingerprinting, polar substances phase sensitivity, a good resolution of less than 1mm, its penetration capabilities and the coherent detection properties makes the technology interesting for spectroscopy, imaging and sensing in healthcare applications. Further, THz waves based technology presents unique characteristics which are attractive to biomedical applications because they are non-ionizing and non-invasive because of the low photon energy of the radiation i.e., 0.4 – 41meV [13]. These unique characteristics of THz technology, coupled with spectral fingerprinting, label free characteristics with accuracy and precision enable real time image guided cancer tissue removal and facilitate for early, more precise diagnosis.

Being non-ionizing implies the biomolecules in the tissue of interest are not ionized by the radiation [14] and there is no significant amount of tissue damage caused. The non-invasive procedure for imaging could capacitate for real-time in-vivo cancer detection and diagnosis, regular screening and patient monitoring [13]. This hypothesis is supported by several previously reported investigations whereby safe exposure levels have been achieved on the basal keratinocytes [15], on blood leukocytes [16] as well as mammalian cells of humans.

The phase sensitivity of THz waves to the polar substances namely, body fluids level and water provides better contrast and strong absorption as compared to that of the X-rays [9]. Significantly high sensitivity of THz radiation to the polar liquid molecules like water is the common endogenous marker for tissue contrast caused by an increased vascularity in the cancer and tumor which results in a local increase in the water molecule content and increased blood supply to the infected tissue [9]. The presence of water molecules in diseased tissues causes high absorption coefficient of the water molecules at THz frequencies i.e., $\alpha = 200\text{cm}^{-1}\text{at}1.0\text{THz}$ [17]. As the THz waves propagate through media with water concentration, the radiation diminishes due to high absorption, the differences in water molecule content in tissues and cells results in contrasting THz radiation responses. Thus, the small fluctuations in water content of tissues and flow of blood could be differentiated making it an important property for the detection and monitoring of different types of cancerous tumors (tissues with tumor have more water molecule content compared to healthy tissue) [18]. The THz radiation energy level coincides with energy of molecular rotational and vibrational modes as well as intermolecular vibrations like hydrogen bonds which is enable to reveal of hydrogen bond orientation [19]. Another image contrast parameters and cancer biomarkers those have been reported to contribute to THz image contrast include structural changes, cell-density, electrical interactions between agents and biological tissue as well as tissue substances like proteins, fiber and fat etc. [20], [21], [22], [23]. Also, the THz radiation is capable of evaluating the state of bacteria i.e., dead or live based on the changes in hydration levels [13]. This paper provides an overview of the fundamental and latest cutting-edge research in the direction of THz imaging and sensing for healthcare applications, particularly, early detection of cancer. The recent advances towards compact and miniaturized THz systems, integration with healthcare 4.0 enabling technologies are reported. The existing challenges, research opportunities and future prospects are presented.

A. RELATED WORK

Several review studies have been previously reported. Banerjee et al. [24] have highlighted the THz waves prospect for the medical applications. An overview of THz technology – materials and devices in various biomedical application fields was given, including the comprehensive review of THz imaging and spectroscopy setups for tissue and cell imaging. The authors also documented the chip integrable THz device technology and their applications, with discussion of THz devices based on 2D materials including transition metal dichalcogenides and carbon based 2D materials. The review of THz sources and detectors and the biomedical application of THz systems have been presented in [25]. The various ways of THz power generation are based on optical or electronic techniques and their advantages, disadvantages, with various physical phenomenon are well presented. The detection techniques are also reported as well as the potential medical application of THz imaging, new research and development of the THz technology are described. In their other work, Banerjee et al. [26] have also reported the methodological, empirical and theoretical concepts with examples of applying novel technologies such as Internet-of-Things (IoT), machine learning, big data analytics and robotics etc. to the THz spectrum based healthcare technology. Emerging trends such as telemedicine, Artificial Intelligence (AI), Internet of Robot Things, Telerobotic surgery etc. have been discussed in detail in the context of THz healthcare. The advances in wearable, smart devices, various advances in IoT for data collection and analysis through machine intelligence for health issues prediction were discussed in the THz healthcare context. Further, they described the evolution and expansion of the emerging technologies in THz healthcare systems for biomedical research.

The impact of THz technology - imaging and spectroscopy in the pharmaceutical industry and research background have been summarized in a study presented in [27], including 3D imaging capability of pulsed THz for basal cell carcinoma and the power of THz in various application industries. In [18], Son et al. have reviewed the biomedical THz state-of-the-art techniques, methodologies and applicable potential techniques that could revolutionize healthcare industry. They surveyed some techniques for wet tissue penetration depth enhancement where they discussed methods for reaching internal organs like endoscopy and otoscopy. Further, explained the principles of operation of some THz based sensors with diabetes, breathing conditions and blood disorders sensing examples. Many of the THz biomedical applications are reported in cancer imaging including in detection of oral, skin, gastric, brain and breast cancers. Moreover, the potential of cancer treatment through demethylation of malignant DNA by the use of a specific high-power frequency of THz radiation are also reported with its potential as a cancer biomarker. In a similar work by Danciu [9], the detection of digestive cancers using THz based technology has been reported. A summary of the THz waves characteristics, their various tissue interactions and the available THz technologies i.e., THz tomography, spectroscopy and endoscopy are also reported. The review has mainly focused on reporting the research progress in THz based detection of digestive cancers – esophageal, oral, gastric, hepatic, colonic and pancreatic cancer tumors. A review of the Terahertz Pulsed Imaging (TPI), its techniques or principles, performance and applications in Biomedicine particularly, in the detection of various cancers are outlined in [28].

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 Basal Cell Carcinoma (BCC) skin cancer, colon and breast cancers described using various intelligent approaches [29]. The application of THz imaging and spectroscopy has been reviewed [30] in which both the continuous and pulsed imaging techniques based on THz waves optical properties are used to diagnose melanoma and non-melanoma of skin tissues, assessment of scars, dysplasia and diabetes. The authors 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. [31], 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 the nervous system at the level of molecules, organisms and cells were investigated in [32]. They highlighted the future perspectives and application of THz in neuroscience and showed the nerve cell membranes, cytokines and gene expressions to be affected by THz radiation.

An overview of the state and applications of continuous wave THz (CW-THz) imaging methods for biomedical samples was given in [33], with a presentation of the principle and conditions of continuous wave THz point by point scanning methods. They reported the characteristics of CW

THz 3-dimensional imaging techniques, features and applications of CW THz full field imaging, they discussed CW THz imaging the biological applications. The research status, progress, advantages & limitations that hinder technological development for clinical adoption and future developments in CW THz are also summarized. This 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 has been reviewed and reported in [28]. They outlined the THz pulsed radiation detection techniques based on TPI and their biomedical applications. 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 presented. Example application studies of TPI for in vivo and ex vivo cancer observations through the THz radiation properties are discussed. They also addressed the limitations associated with THz imaging technology for enhancement of penetration depth and sensing capabilities for biomedical applications. They noted the rapid developments in THz imaging technology and its increasing potential as a medical imaging modality, however more attention has been stated which is required in the applications of PEAs and more technological developments required for clinical adoption of TPI systems.

In a study reported by Wang [34], the recent developments in THz imaging technology and its application for breast tumor identification is reported. They noted the potential application of THz imaging and spectroscopy systems for breast cancer detection, with a discussion of the breast tissue dielectric properties within THz range, THz radiation sources, imaging & spectroscopy systems and THz imaging for breast cancer. The methods for improvement of data collection, processing and resolution based on chemo metrics are summarized. They also presented future research scope to address challenges in the direction of THz breast cancer imaging.

In another study, 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 has been reviewed [35]. They reported the recent THz imaging and spectroscopy progress in the diagnosis of cancer, with its potential to help doctors and researchers to get an insight into the cancer infected tissue area. They regarded THz spectroscopy efficient to identify the 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.

THz technology – THz imaging and spectroscopy has been introduced in another study [36], and a short overview of THz technology advances and its application for cancer diagnosis are highlighted. Being located between microwave & infrared region, 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 non-ionizing hazard on biological tissue cause the technology to be interesting for biological applications. The image contrast between cancer and healthy tissue has been attributed to the local increase of blood supply and water content as well as the tissue structural differences [36]. Further, the progress in THz imaging developmental advances from 1999 to 2021 in plant, burn wound and foot diabetes imaging applications have been reported in [37] and other THz biomedical application studies particularly for cancer have been reported in [31], [33], [34], [35], [38], [39], and [40].

B. MOTIVATION

Although conventional cancer imaging modalities like Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI) and X-Ray etc. have fully developed to provide spatial information of cancer. However, the THz imaging is an emerging complementary modality with great potential to offer not only the cancer spatial information but also information that is tumor specific such as physiological and molecular properties of cancer cells, concurrent functional and quantitative information as well as biomarker tracking [41].

C. CONTRIBUTION

It is apparent from the above reported studies that THz imaging and sensing systems are proving great potential in the healthcare domain and many efforts are ongoing to rapidly improve their performance. Therefore, it is necessary to give a broad overview of the developments in THz technology for healthcare applications, its impact, implications and prospects for ongoing research and development. More specifically, the authors' contribution to the THz technology for healthcare application are as follows:

- We provide an overview of the THz imaging and sensing techniques which exploit properties of THz generation & detection with emphasis on THz-TDS and THz Metamaterials.
- The mechanisms of tissue image contrast and the application of THz imaging and sensing for biomedical applications, in particular cancer detection is reported.
- An overview related to THz technology in the interface of healthcare 4.0 and its enabling technologies is explored for next generation smart and connected healthcare systems.
- We identify the merits and existing challenges in THz cancer imaging and sensing and suggest prospective opinions to pave way to ongoing and future research.
- We discuss the recent advances in THz imaging development and the contribution of near field techniques based on plasmonic, and resonance based

metasurfaces, waveguides etc. for breaking the diffraction limit towards development of THz systems that are convenient for point of care.

- We bring a roadmap for researchers with future research scope.

D. ORGANIZATION

The remainder of the work is organized in the next sections as illustrated in Fig. 2. Figure 2 illustrates the scope of this paper. An overview of the THz generation/detection, imaging and sensing techniques are reported in Section II. In Section III, the development of THz technology in the interface of healthcare 4.0 and its enabling technologies are presented. The salient features, research challenges and prospective opinions in the development of THz technology for cancer are discussed in Section IV. In Section V, an outlook for recent advances, milestones and future of THz technology development is given. Finally, the paper is summarized in Section VI.

II. OVERVIEW OF THz TECHNOLOGY FOR THE HEALTHCARE DOMAIN

In this section, the various aspects of the THz technology in the context of biomedical applications are presented. The overview of main THz radiation generation and detection techniques, THz imaging and sensing techniques, THz image contrast mechanisms and potential applications of THz technology for biomedical detection with more focus on cancer is given.

A. THE THz RADIATION SOURCES AND DETECTORS

There are different types of THz sources, the main ones are as follows [42]:

- Thermal sources are black body radiation based, which emit in the THz range at low intensity form 2K. Examples include the Mercury lamp that has a spectrum spanning the entire THz range. The generated waves are however incoherent, and energy is low.
- Electronic sources include high frequency transistors, Gunn diodes and frequency multipliers, they generate monochromatic THz waves of up to 1THz. Backward Wave Oscillators (BWO) also generate coherent THz radiation of up to 2THz.
- Quantum Cascade Lasers (QCL) generate monochromatic THz waves whose frequency depends on the structure of the semiconductor as they are based on inter-sub-band transitions in the semiconductor quantum wells. The generated THz power by QCL is of order few mW, efficiency of order 10-5 and tunability ranging between 1.2 THz to 4.9THz varying with the used structure of semiconductor. The dimensions of wells must have Nano scale precision, in order to design the QCL. THz generation requires finer precision as the inter-sub band transition is done between two states with very close energy levels, which complicates the experimental population inversion and tunability between the sub bands. The operation of QCL at low temperatures limits their applications.
- Gas lasers use optical pumping of gas molecules to generate THz waves. Gas molecules exhibit strong rotational transition in the THz range, which enables transition of laser between two vibrational levels and photon emission in the THz domain. Optically pumped gas lasers have efficiencies and power of order 10^{-2} – 10^{-3} and 100mW, respectively, with emission range from 0.1THz – 8THz. Each gas has its emission line, and the most commonly used gases are CH3OH, CH3F, COOH, NH3 and CH2F2. The major drawbacks of Gas lasers are that the tunability is not possible due to dependence of generated spectrum on gas intrinsic properties, optical pumping of 9-11μm excite rotational levels and very bulky sources are made from the combination of gaseous amplifying medium and pump laser.
- The most widely used THz sources are the optoelectronic sources called THz antennas or photoconductive antenna (PCA), consisting of separated metallic electrodes deposited on a substrate. The THz generation mechanism is that prior to optical excitation, a capacitive energy exists stored between the gap in form of accumulated positive and negative charges at the anode and cathode respectively. The charge magnitude depends on the geometry of the device, gap resistivity and bias voltage. The gap resistivity depends on concentration of carrier in the photoconductor such that when the gap is excited with an optical pulse it results in a sharp increase of carrier concentration and a drop in resistivity causing THz frequency oscillations in metallization of the antenna by the response of the bias field. THz is also generated through optical injection of current into the antenna electrodes directly. The photocarriers generated in proximity sufficient enough to the antenna electrodes gets collected before recombining, acting as a driving current that can induce THz oscillations in the antenna provided that the induced pulse is sufficiently short [10], [25], [31], [43], [44], [45].
- Another THz source includes the quadratic Frequency Difference Generation (FDG) process in nonlinear crystals. Some of the important THz emitters and detectors are electro-optical sources, photoconductive antennas, electronic sources, bolometers, pyroelectric, heterodyne mix receivers and Golay cells [46].

B. THz IMAGING AND SPECTROSCOPY

There is rapid development of techniques for generating and detecting THz radiation to come up with instrumentation for THz spectroscopy and THz imaging. Considerable efforts have been made to improve THz systems in terms of power, sensitivity and efficiency of THz sources and detectors so as to narrow the ‘THz gap’ and enable wider applications. THz continuous wave (CW THz) imaging and spectroscopy,

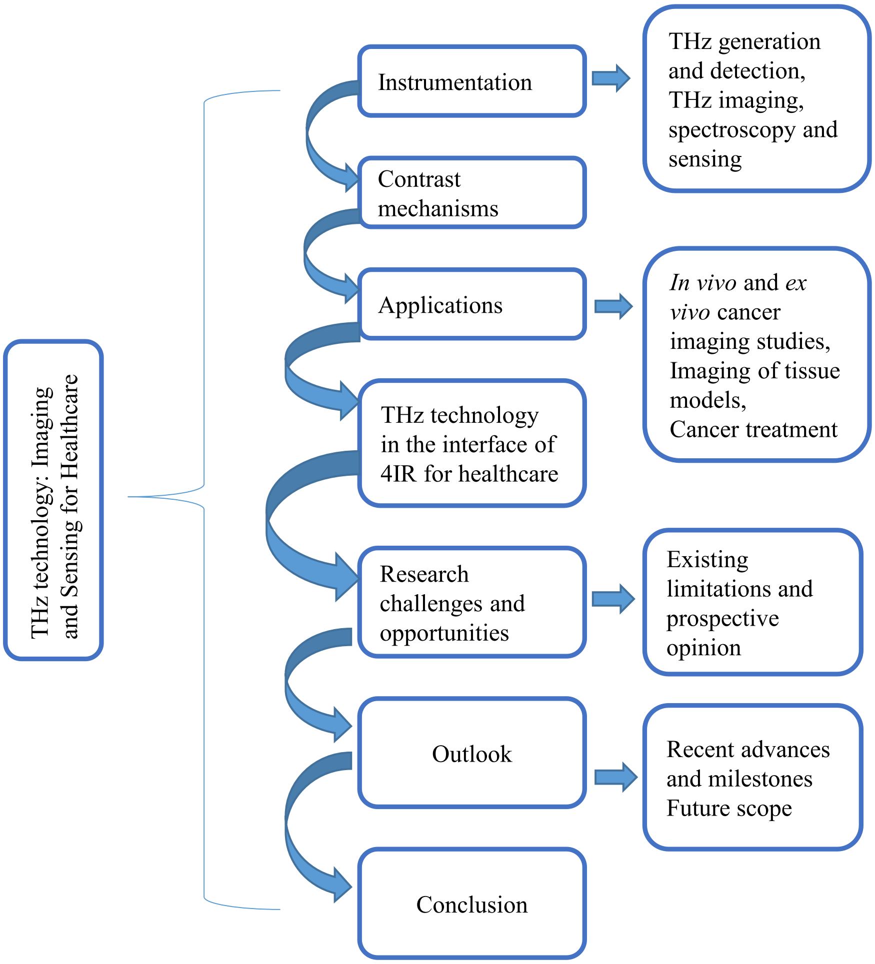


FIGURE 2. Outline of this review.

THz pulse imaging (TPI) and THz time domain spectroscopy (THz TDS) are the main THz imaging and spectroscopy techniques differing in emission mode, detectors, sources, experimental protocols and required information. They are considered the most promising for biomedical imaging applications with enhanced image contrast and selectivity especially when used together with novel contrast agents. Other most conventionally known THz imaging techniques are the electro-optic imaging, close field imaging, single shot imaging, bi-static THz wave imaging, dark field imaging, THz tomographic imaging with Fresnel lenses and THz computed tomography (THz CT). The detailed overview of various THz techniques for radiation generation and detection as well as the various applications are beyond the scope of this chapter. Here we focus on the THz pulsed imaging (and THz time domain spectroscopy) systems used for imaging and spectroscopy interchangeably and their biomedical research applications for cancer.

As shown in Fig. 3, the THz system is essentially made up of emission, detection and beam guiding components. The THz pulsed wave imaging (TPI) and spectroscopy systems are commonly known as THz-TDS systems and involve emission of pulsed THz signal and time domain detection (Fig. 3). The optical setup of a THz-TDS system is mainly made up of the femtosecond (fs) laser, beam splitter and optical delay line, then other optics like attenuators, gratings, laser amplifier, wave plates, optical choppers etc. may be involved. The fs laser generates a beam which gets split to the delay line and the transmitter. A pair of reflectors then collimates the THz beam, and the target object is imaged when placed at the THz beam's focus. In more detail, the optics control the delay of the beam between the pumping and probing beams sent to the emitter and detector respectively to sample the waveform in time domain. The THz-TDS systems can be interchanged with imaging by switching the scanning mechanism i.e., through movement (lateral translation) of the sample with the illumination beam stationery so as to perform point to point collection of the signal. In 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 grid and continuously scanned or pixel by pixel scanned in raster mode. The acquired information is obtained from the data acquisition card (DAQ), quantized to bits for further

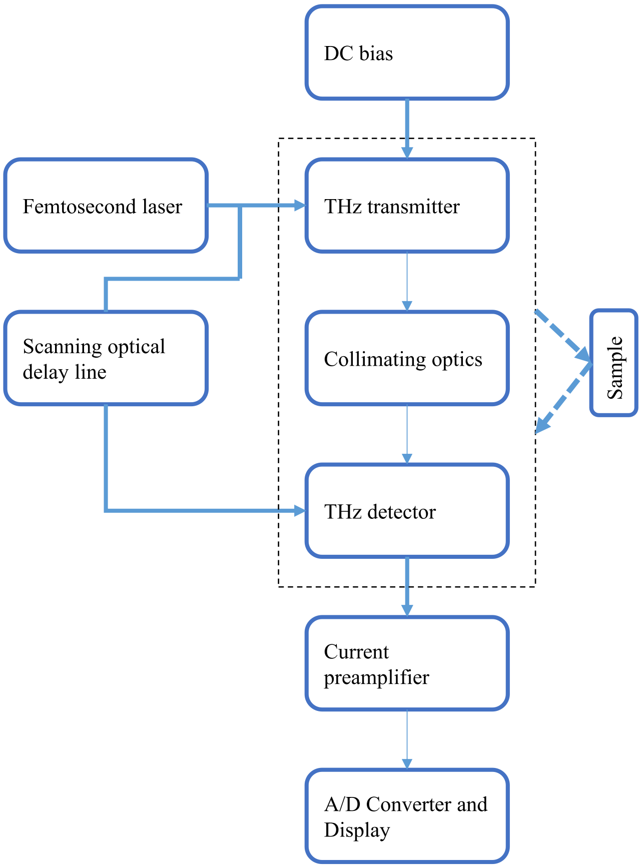


FIGURE 3. The block diagram for basic THz TDS.

image processing [28]. The outstanding features of THz-TDS systems like providing broad bandwidth, picosecond level resolution, field detection ability which comprise of both phase and magnitude information for the spectrum make them useful for various applications [30], [47], [48].

1) FUNDAMENTALS OF THz PULSED IMAGING

As previously explained, TPI extends from the THz TDS technique, to obtain objects' images, raster scanning of 2-dimensional point to point is performed together with coherent detection. Thereby recording the temporal information of each one of the point pixels. 1D data of frequency domain or time domain extracted are then converted to some physical parameters. Normalization enhances contrast of the image and can be summarized as follows [28]:

Time domain: Amplitude of Electric field at fixed time: $E_{x,y}(t_0)$

Main peak normalized amplitude: $max\{|E_{x,y}(t)|\}/max\{|E_0(t)|\}$

Main peak time delay with respect to reference: $t(max\{|E_{x,y}(t)|\}) - t(max\{|E_0(t)|\})$

Frequency domain: Spectral amplitude at fixed frequency: $E_{x,y}(v_0)$

Phase: $\phi_{x,y}(v_0)$

For the time domain, when the THz pulse interacts with a sample, there can be a delay, broadening or attenuation of the pulse signal relative to reference. The amplitude of the 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, measurement of reflected echo is done in terms of the amplitude and/or phase. 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 application of the Fourier transform on the temporal electric pulse where the amplitude indicates losses and phase relates to refractive index. When 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 short extraction of THz wave amplitude and phase is enabled in THz TDS. The Fresnel coefficients enable parameters of complex refractive index, absorption coefficient to be obtained and in turn the complex permittivity [28]. The differences in refractive indices of different tissues could depend on tissue pathological status.

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 time domain maximum peak through the use of the reference function [49]. 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 giving information of contrast for the sample 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. SNR determines maximum absorption coefficient which is in turn determined by accuracy of signal's amplitude and phase rather than samples. In 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 [49], [50], [51]. Additional THz imaging and spectroscopy techniques include near-field THz imaging, THz Computed Tomography (CT), THz endoscopy and holography etc.

2) THz ENDOSCOPY

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 by [38].

Another conventional modality such as magnetic resonance imaging (MRI), Computed Tomography and Positron Emission Tomography (PET) etc. that are capable of detecting distant and local cancer tissues are associated with limitations such as not able to perform early cancer detection and high cost. The THz endoscope exhibits great potential to perform early cancer diagnosis in internal organs such as gastro internal and colon cancer etc. with cheaper and faster diagnosis capability. Waveguides are a crucial part of the THz endoscope unit and here we will explore some of the THz waveguides previously reported.

Continuous efforts are being made to develop THz waveguides with minimal losses associated with propagation during transmission and minimal dispersion that can effectively transmit THz waves over long distances in confined places. The ideal parameters of THz waveguides for THz endoscopes are flexibility, low propagation loss, good confinement, low GVD (Group Velocity Dispersion), high coupling efficiency, miniature size and no cut off frequency [52]. The two major categories of THz waveguides are the metallic and dielectric waveguides as shown in Fig. 4. Metallic structures are capable of guiding THz waves since THz radiation is not dissipative in metallic components. Dielectric waveguides, another class of non-planar waveguides also known as fibers since they have circular cross sections and are bendable as well as used at higher frequencies. Different types of metallic and dielectric waveguides and various configurations have been reported in detail in [53], including the handheld THz probes for intraoperative / in vivo studies of cancer and other tissues.

C. THz IMAGE CONTRAST MECHANISMS

THz technology enables the spectrum and image to be concurrently acquired, thus making it possible to extract morphological features and intrinsic properties of biological system from the phase information and amplitude of a THz wave. The primary THz image contrast mechanisms are the water molecule content and structure of a tissue. Due to increased vascularity, edema and increased metabolism in cancer tissue, the interstitial water content in cancer significantly differs from that of normal tissue. The relaxation processes and water molecules intracellular vibration modes ranging within subpicosecond and picosecond resonate with the THz range. Thus, the tissue image contrasts in THz between healthy and cancerous or tumor tissues have been mostly attributed to the higher optical parameters (absorption coefficient and refractive index) in cancer and tumor tissues relative to healthy tissue, the higher content of water molecules in tumours being the contributing factor [48]. Cancer cells cause an increase of vasculature around the affected tissue i.e., increased blood supply and content of water which becomes a natural tissue contrast mechanism for THz imaging. Another image contrast mechanism is the structure and formation of tissue for example higher density of cells in cancer, such that the THz imager's spatial resolution is dictated by diffraction limit. In scar and healthy tissues, the contrast has been attributed to tissue structural differences as a result of reconfiguration and deposition of the collagen matrix during scar formation [31], [54]. Evaluation of tumor cells hydration can be achieved by THz spectroscopy without cryogenic treatment or hydrogenation. Other 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 [20], [21], [22].

1) PERMITTIVITY-BASED TERAHERTZ IMAGING FOR TISSUE CONTRAST

The differences in dielectric responses (conductivity and relative permittivity) of tissue (brain, breast and skin) have also been reported to cause image contrast [34]. Biological tissues are dispersive materials, and their dielectric responses depend on frequency such that the frequency is inversely proportional to relative permittivity and directly proportional to conductivity. Therefore the dielectric response of tissue cells has been shown by THz spectroscopy to reflect water dynamics [55].

Dielectric modelling of tissue properties provide parameters that can be used for accurately discriminating the tissues [56], making it possible to understand the interaction of tissue and THz waves. This paves way for further tissue investigations including for medical screening based on tissue property changes. The quantification of THz waves' interaction with tissue has been widely explored through dielectric and structural models for extraction of tissue parameters in the THz regime. Dielectric models have been used for example single Debye, double Debye and Cole-Cole models etc. to characterize tissue complex permittivity which is a reflection of molecular interaction with THz radiation [34], [57]. Effective Medium Theories (EMT) include the Bruggeman model,

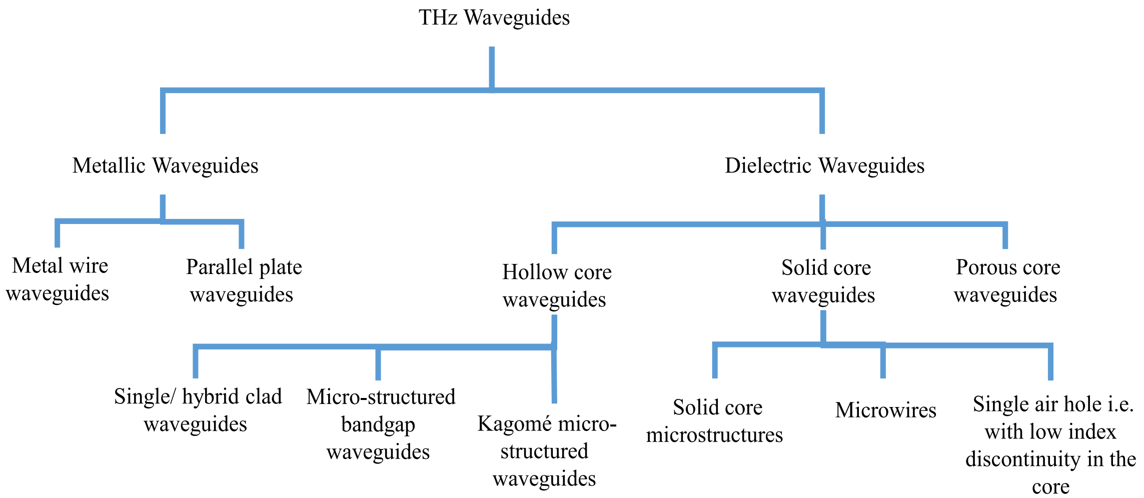


FIGURE 4. **THz waveguides.**

Maxwell Garnett (MG) and Landau Lifshitz Looyenga (LLL) models [47]. Another models include the Cole Cole models [56], and stratified media theory. The dielectric models have been explored to characterize dielectric response i.e., complex permittivity and conductivity of samples, resembling multilayer structures. When the biological background of the sample i.e., the sample's permittivity and dehydrated tissue is given, the water volume fraction in the sample can be estimated. The accuracy of underlying sample permittivity is crucial for all Effective Media Approximations (EMAs). The Debye models and Finite Difference Time Domain (FDTD) techniques have been proposed to model THz dielectric response for example the Double Debye models were used to extract dielectric parameters for analysis of collagen [58], of skin [55], [59], [60], brain [61] and breast tissue [62].

D. BIOMEDICAL APPLICATIONS OF THz IMAGING AND SPECTROSCOPY

In this subsection the applications of THz imaging and spectroscopy for some of the most common biomedical applications are briefly presented.

Several applications of THz imaging technology in the biomedical area have been reported including and not limited to the ones in Table 1.

E. APPLICATIONS OF TERAHERTZ IMAGING FOR CANCER

The THz technology for imaging and spectroscopy exhibits salient potential as a biomedical imaging modality especially in oncology. The application of THz technology for delineation of various cancerous tissues have been recently explored mostly through the use of formalin fixed and paraffin embedded tissues, phantoms and freshly excised tissues including tissues obtained from tissue banks. The source of contrast has been mostly attributed to the differences between absorption coefficients and refractive indices of normal tissues and cancerous tissues. As reported in this work, application of THz imaging for localization of cancer has been recently investigated for the types of cancer including breast, lung, brain, digestive, skin and prostate cancers as well as its great potential in cancer treatment. The low photon energy, non-ionizing, unmatched sensing, non-invasive properties of the THz waves-based imaging exhibits great potential in the diagnosis of cancer, its treatment, patient care and follow ups. The focus here is more on the in vivo and ex vivo imaging of cancer.

1) IN VIVO IMAGING

THz imaging technology has shown the ability to identify cancer tissue and determine cancer margins in vivo. Delimiting the precise cancer tissue boundary is vital for further resection and preventing recurrence of cancer in subsequent treatments, which is a trade-off of THz imaging over conventional MRI. However, in vivo imaging has been mostly applied in tissue of the epidermal layer such as skin, due to the limited penetration depth of THz waves. The THz pulsed spectroscopy has been used to detect various skin melanoma in a series of studies including [30], [40], [60].

The investigation of skin cancer in THz imaging has been performed in many studies. In one of the studies [113], highly sensitive skin cancer detection was done through the use of a water and THz based Metamaterial (MM) semiconductor film. Reflection geometry THz pulsed imaging (TPI) for skin tissue and skin related cancers were applied. The proposed device's refractive index (RI) sensing application was shown by introducing 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 semiconductor film i.e., the indium antimony, InSb and water. They first showed the potential of potential of the MM for ultra-sensitive Refractive Index bio sensing applications like sensing BCC

TABLE 1. Biomedical applications of THz imaging.

References	THz techniques used	Application	Results
[63], [64]	• THz Imaging, THz spectroscopy and sensing	• COVID 19	• High precision long distance temperature, real time measurement for COVID 19 using THz imaging. • Potential of THz spectroscopy for diagnostic breath analysis
[65]–[71]	• Terahertz Spectroscopy	• Diabetes	• Great potential for the measurement of blood glucose concentration non-invasively, based on the measured refractive index. • Diabetic subjects were found to exhibit lower skin hydration levels. • Differences in blood plasma spectra of diabetic vs. non-diabetic.
[30], [72]–[79]	• THz reflection imaging, • THz Time domain Spectroscopy	• Scar healing tracing • internal injuries	• Dissimilarities in reflected THz waves between the scar tissues and healthy tissues • Lower absorption coefficient in scar tissue relative to healthy tissue. • Scar healing and treatment tracing. • Use of THz TDS to detect internal injuries in brain and liver.
[30], [80]–[85]	• Terahertz Spectroscopy Imaging	• Tissue water content Hydration monitoring	• Visualization and monitoring of various tissue hydration levels including skin tissue.
[86]–[89]	• Terahertz Spectroscopy	• Dental Imaging	• Characterization of dental tissue for dental diagnosis
[77], [90]–[93]	• Terahertz radiation and sources	• Therapy	• Possibility of non-ionizing treatment
[94]–[105]	• Terahertz Spectroscopy	• DNA and Protein measurements	• Absorption spectra measurements for DNA dynamics and different protein samples
[29], [106]–[112]	• THz TDS	• Blood plasma analysis	• The dielectric properties of blood plasma and its biochemical analysis were found to be correlated in thyroid cancer patients using THz TDS at 0.05THz – 1.6 THz frequency range.
As reported in the next subsection	• Terahertz Imaging	• Oncology	• Localization of various cancerous tumors.

and normal skin. The sensitivity of the biosensor was approximately 117 μm/RIU. 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, incident light was made to shine perpendicular to the device in 1- 1.5THz range, then simulated the reflective light for both healthy and BCC cases. The resonance frequency of the reflection spectrum was about 1.38THz when the bio-detector was 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 has 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) was used for reflected wave differences calculation of normal tissue compared to BCC [114].

In [107], the authors have used TPI to detect skin cancer, 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 was performed. The ANN algorithm had an accuracy of 94.117%. 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 [115]. Another study reported in [30], has reviewed the THz spectroscopy and THz imaging whereby both the continuous and pulsed techniques were used 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.

2) EX VIVO IMAGING

Ex vivo THz imaging also constitutes a label free, complementary method for pathological studies. Ex vivo THz imaging whereby the biological tissues excised from humans and animals has been extensively studied in the imaging of reproductive systems, digestive systems, nervous system, respiratory system, oral and breast etc. [24], [116], [117].

Several studies have been reported where various techniques of the THz imaging technology were applied for breast cancer localization ex vivo. In one study by El-Shenawee et al. [116] the potential was realized for THz imaging and THz spectroscopy for cancerous tissue (tumours) detection on human and animal excised breast tissue. The tumor tissue of interest included cancer manifested as fibro glandular (healthy connective tissue), lobular or infiltrating ductal carcinomas and fat. For further evaluation of THz imaging and potential usage of contrast agents, phantom breast cancer tissues have also been developed [116]. Validation of the THz results has been done with pathology images which showed a great distinction of healthy and cancerous tissues using freshly excised tissues and other tissue types. Invasive breast cancer surgical treatments are mainly mastectomy which involves the full removal of breast and lumpectomy whereby only the tumor bulk and margin are removed. The latter is mostly preferred.

a: MATERIALS AND METHODS

The TPS Spectra 3000 was used where Ti:Sapphire infrared laser is used for excitation of THz antennas that are fabricated on low temperature GaAs substrates to obtain the experimental results in this research. The test sample was positioned in reflection mode. The antenna generated THz signal of pulse width ~280 fs for first maximum and ~587 fs & ~287 fs for the first and second minimum respectively is directed to the sample through mirrors and interchanging the modules for reflection and transmission. Fourier transform is performed on the pulse results in time domain to frequency domain of 0.1 to 4 THz spectrum.

The spectroscopy measurements were done to characterize the tissue regions of human breast that were freshly excised. A small piece of fresh excised tissue was mounted between a 0.1 mm thick spacer with two quartz windows in a sample holder and measurements done at single point, in transmission mode and room temperature. Nitrogen gas purging was utilized for water vapor removal from the measurement, also an average of about 1800 signals taken for reduction of random noise. To minimize the phase and amplitude errors when extracting and the refractive index and α absorption coefficient, inversion algorithm was used in 0.1 THz to 4 THz range.

The THz imaging of the freshly excised tissues was done through utilization of modules for the transmission and reflection orientations resulting in three images made up of the THz fresh tissue image, pathology image as well as THz FFPE image. Measurements were then taken through sample scanning and comparison of the reflected or transmitted signal to the reference signal. For phase changes compensation, it is vital to normalize the measured signal with the reference. Then the THz image were generated through single frequency magnitude or time domain peak at each point, reference signal deconvolution, integrating spectral power in frequency domain or implementation of signal processing for cancer classification. The results demonstrated a clear contrast between cancer and fat tissue, but the contrast wasn't clear between cancer and fibro-glandular tissue.

In a similar study, an analytical and experimental comparison was presented between the transmission and reflection modes of THz imaging for assessment of breast carcinoma of paraffin embedded breast tissue of a human. Models of reflection and transmission imaging have been developed and acquired the refractive index tissue samples with their absorption coefficient measurements at a fixed 30° angle of incidence. After validating the model using bovine tissue, they applied the technique on human lobular carcinoma slices (20 and 30 μm) and infiltrating ductal carcinoma to investigate the tissue differences. Clear distinction between carcinoma with healthy tissue is obtained in both the modes, the reflection mode more sensitive to the phase variations and increased resolution (with margins of cancerous regions and fibro glandular regions, fatty and also between fibro glandular and the fatty regions clearly distinguished) with more feature consistency in images with high power pathology in comparison to the transmission mode [118].

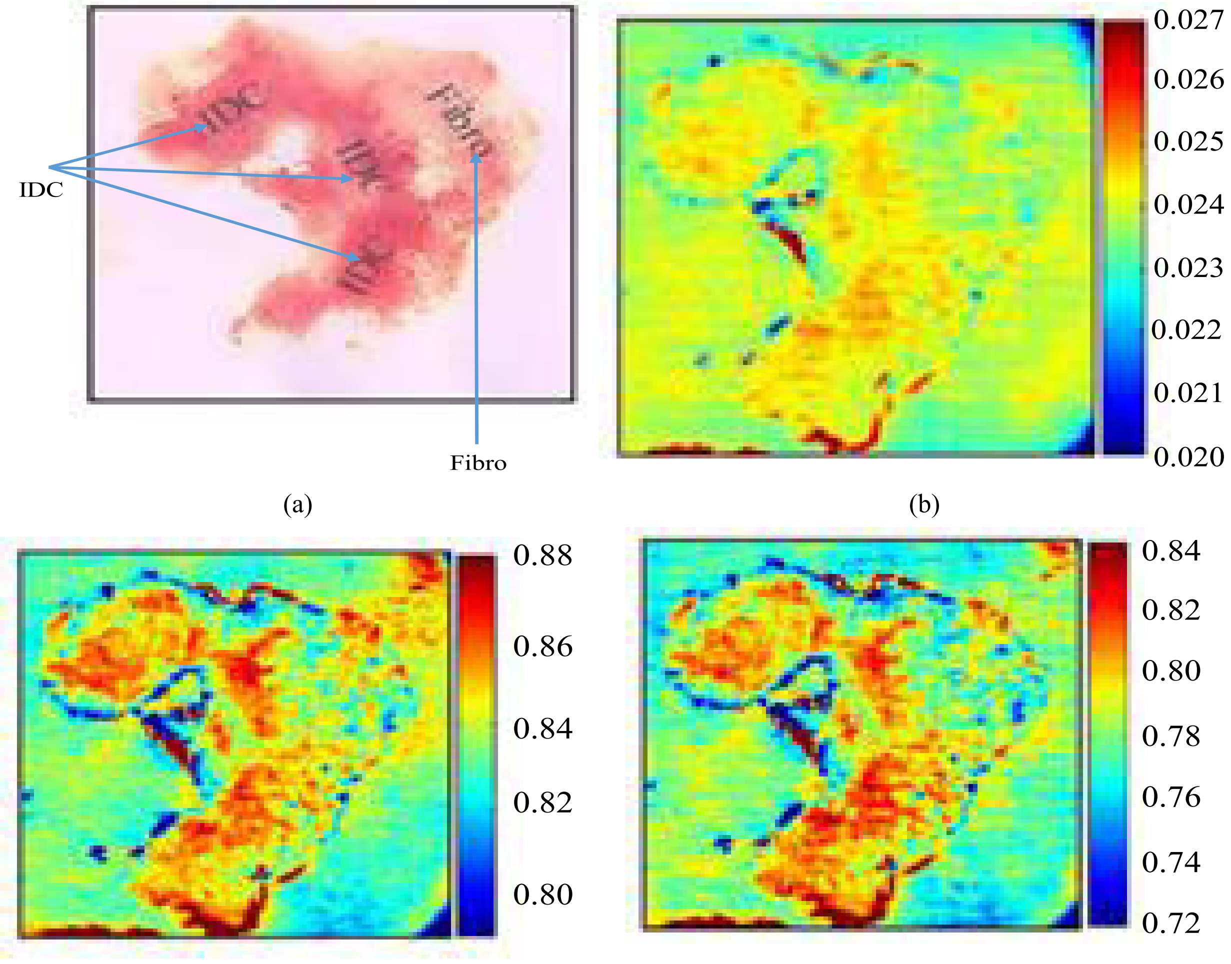
In a recent study as reported in [119], the authors have used a combination of morphological dilation and refractive index thresholding to classify malignant and benign breast tissues so as to enhance the performance of tumor margin delineation for conserving surgeries. The image acquisition has been performed employing TPS3000 THz system in reflection mode. Further, the authors have conducted a histology routine where dilation geometry performances are associated with different thresholds evaluation. The achieved results shows the great potential of the combination of tissue fundamental optical properties (based on refractive index) and morphological dilation for greatly aiding breast conserving surgeries [119]. A test-retest and validation of the contrast between healthy and cancerous tissue are examined using THz-TDS on dehydrated breast tissues mounted on Teflon plates as reported in [108]. It has been revealed for the samples with good adhesion to Teflon plates, the correlation of THz image contrast with respective histo-pathological results is high and reliable in a controlled environment. In another study, the breast cancer images were clearly observed using a developed THz based microfluidic chip using nonlinear optical crystal and an aperture less THz near field microscope for increased sensitivity and spatial resolution [110]. An improved spatial resolution was achieved through the development of a THz near field microscope of 10 μm which was used for performing imaging on human breast cancer tissues that were paraffin embedded and they successfully visualized local inhomogeneities in cell density of the breast ductal carcinoma invasively [120]. Furthermore, the other studies that have shown that THz imaging can be used for accurately differentiating between breast carcinomas and healthy fibro glandular tissue etc. using various techniques have been reported including [34], [121], [122], [123], [124], [125], [126], [127], [128], and [129].

Typical THz cancer images obtained from THz breast cancer imaging studies are reported below.

Breast tissue obtained through mastectomy of one 46 year old European/American female with tissue thickness 2 and 10 μm and the corresponding THz images shown in figure 4 reported by [34] and [130], as shown in Fig. 5(a), the H&E (Hematoxylin and Eosin) stained slide with low pathology is shown indicating IDC and fibrous regions and defined by a pathologist. The time domain-based image of deconvolved electric field color bar ranging from 0.02 to 0.027 is shown in Fig. 5(b) while Fig. 5(c) and Fig. 5(d) present the frequency domain images (at the respective frequencies of 1.5 and 1.75THz). From the obtained images, the THz imaging in reflection mode demonstrated more capability to discriminate the heterogeneous regions of breast tissue. Ex vivo THz cancer imaging studies have also been reported for lung cancer [131], brain [61], [132], [133], Digestive Cancer [9], prostate cancer [90], cervical [111], ovarian [134].

3) THz IMAGING OF PHANTOMS

Due to the challenges associated with obtaining human tissue for THz imaging experimental studies, a couple of studies have explored the development of tissue models, also



(a) (b) (c) (d)

FIGURE 5. THz breast cancer images a) low pathology H&E stained image, b) Time domain THz image c) THz frequency domain image at 1.5THz and d) THz frequency domain image at 1.75THz [34], [130].

known as phantoms. The THz imaging of phantoms have been investigated in cancer detection studies including [109], [135], [136], [137], [138], and [139].

4) THz FOR TREATMENT OF CANCER

The potential for cancer treatment method was presented based on malignant DNA electromagnetic demethylation. Wealth of evidence has been shown that malignant DNA demethylation significantly contributes to recovery of the gene expression, reduction of tumor size and inducing of cell apoptosis [140], [141], [142]. Specific demethylation drugs like decitabine have been reported to achieve the effects [143]. Use of resonant high power THz radiation absorption for demethylation has been reported to possibly induce a similar effect and provide an enhanced efficacy in the treatment of cancer.

F. THz FOR TREATMENT OF CANCER

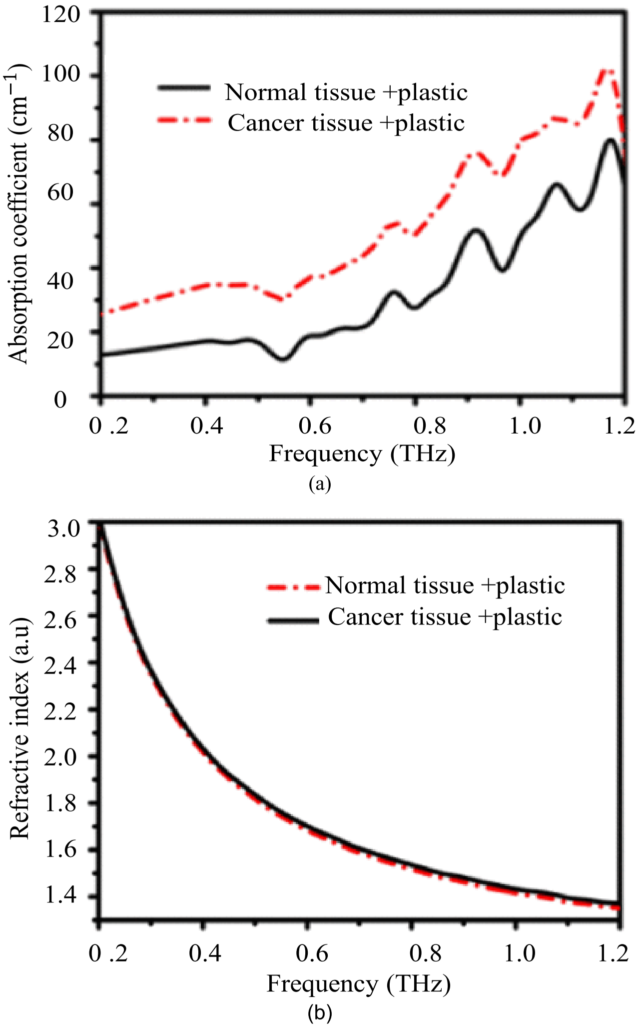
Research on noninvasive and label free THz sensing has been recently leveraged through various techniques. High specificity and high sensitivity THz sensors using metamaterials and THz plasmonic antennas enable elimination of interference signals by screening target spectral fingerprints for cell detection.

Here, the focus for THz sensing is on THz metamaterials (MM) for fast and low-cost THz detection. Metamaterials are artificially fabricated and periodically arranged structures of dielectric and/or sub-wavelength metallic elements also known as THz metamaterial absorbers (TMA) which make use of their rich spectral fingerprinting in the EM region. They are unique structures that exhibit unique properties such as anomalous reflection, negative refractive index, sub-diffraction limited focusing, cloaking and optical magnetism with ability to absorb the incident EM radiation [144], [145]. Additionally, metamaterials that have well designed structures are capable of sensitive detection of minute/ thin biological and chemical substances through enhanced and strongly localized fields [146]. The application of TMA has been explored in different frequency bands and in diverse sensing applications through shifting the parameters of their absorption spectra. TMA THz sensing has been demonstrated in measuring analyte thickness [147], detection of biomolecules, design of temperature sensors [148], detection of environmental refractive index and design of refractive index sensitive biosensors with square ring resonator (SRR) [149] through excitation of localized resonances in metamaterials, this offers an attractive approach to attract new THz regime applications [150].

The most common configurations or topologies of metamaterials structures are the split ring resonators (SRR) and the complementary SRR (CSRR). The SRR configuration is realized on the substrate surface and is made up of a ring-shaped metallic pattern which provides inductance, and a high capacitance is provided by the narrow opening gap. The dual SRR structure makes up the CSRR and is realized by etching out a ring shaped pattern from copper cladded on surface of the substrate [145], [151]. Here, we report various TMA designs that have been proposed for detecting cancerous cells towards facilitating point of care diagnosis owing to compact devices size and small detection volume. The fundamental principle in such applications is based on scattering parameter (reflection/ transmission coefficients) induced by the sensed parameters i.e., unique dielectric changes owing to the permittivity, refractive index or permeability variations of the metamaterial resonator corresponding to diseased and healthy tissues. In other words, the THz metamaterials' resonance frequency is comparable to biomolecular vibrational frequency, the biomolecules include cancer biomarkers. One such study proposed a design that merged circular ring resonators on a gallium arsenide substrate which achieved 99% absorption at 3.71THz, 1447GHz/RIU sensitivity with 92.75 quality factor (Q-factor) and resonance frequency that shifts with altering the encompassing medium's refractive index in the range 1.3-1.40 for cancer cell detection [144].

THz biosensors based on gap SRR and two gap SRR integrated with microfluidics for early stage detection of liver cancer markers have been proposed [151]. Such biosensors have been noted to overcome water absorption into the trace biomolecules. In another study [152], a magnitude variation of the metamaterial inspired, label free biosensor that provides analyte information has been proposed for molecular classification of glioma cells using a two degree of variations. The proposed metamaterial biosensor was made up of SRR and cut wires to realize polarization independent EM induced transparency which experiences both magnitude and resonance variations when analyte properties change and explained using the theory of coupled oscillators model. The biosensor achieved a theoretical sensitivity of 496.01GHz/RIU and the results indicated the wild type an mutant type gliomas were able to be distinguished directly from the variation observations, with great potential application in molecular recognition of glioma cells [152].

The use of THz metamaterial biosensors has been leveraged for the early detection of cancer cells, in [153], the detection of cervical cancer using a THz biosensor with two resonance absorption frequencies f_1 and f_2 of 0.286 THz and 0.850 THz respectively was proposed. Initially, the experiment was set up using the THz TDS for testing the experiment. The cervical tissue samples were obtained from four patients who had been diagnosed with cervical squamous cell carcinoma. The tissue samples were prepared using dehydration then paraffin embedding and cut to 10μm thickness. Using the conventional THz TDS, the refractive index and absorption coefficient parameters of the tissue samples were obtained as shown in Fig. 6. The absorption coefficient and refractive index parameters of the cancerous tissues are more than those of healthy of normal tissues owing possibly to increased water molecule content in cancer and more proteins, capillaries and larger nucleus in cancerous tissues.



(a)

(b)

FIGURE 6. **Experimental results using THz TDS (a) Absorption coefficient and (b) Refractive index of samples from patient.**

The process of calculating refractive index and absorption coefficient parameters using the conventional method is time consuming and complex. Moreover, as shown in Fig 8(b), in the early stages of cancer, the refractive index differences

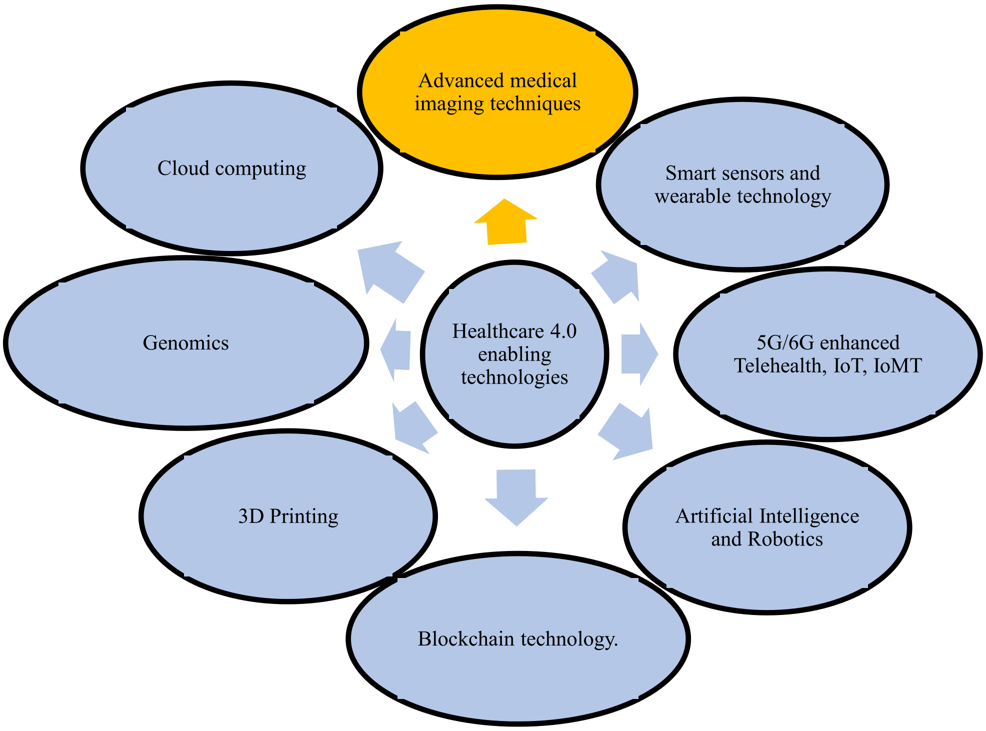


FIGURE 7. Healthcare 4.0 enabling technologies.

for cancerous and normal tissues are very small and thus difficult to distinguish. As a result, the THz metamaterial sensor was used to fast distinguish between the early-stage cervical cancer and normal tissue. The THz transmission spectra of the cancerous and normal tissue samples were obtained. The resonant frequencies were found to be sensitive to the ambient change in cervical cancer tissue's dielectric properties compared to normal tissues using the resonance frequency shift. The sensitivities for the f1 and f2 resonant frequencies were found to be 29 and 74GHz/RIU respectively, with the THz metamaterial biosensor with double resonant absorption frequencies method of cervical cancer detection shown to have more accuracy, being label free, fast and simple with clinical potential [153].

Highly sensitive and specific THz metamaterial biosensors were also fabricated for cancer detection [144], pancreatic cancer biomarker called exosomal microRNA with high accuracy [154], CA125 and CA199 cancer biomarkers [155], type A549 lung cancer cells [156], carcinoma cells [157], [158], [159], [160], skin cancer [114], [161], breast cancer [162], [163], colon cancer [164]. Plasmon based metamaterial biosensors that use Graphene were also proposed that are a breakthrough invention due to being highly sensitive, low cost prototyping, fabrication, design and inherent configurability [151], [165], [166], [167], [168], [169], [170]. Table 2 summarizes the most recent 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.

III. THz TECHNOLOGY IN THE INTERFACE OF HEALTHCARE 4.0

The evolution of industrial revolutions has recently emerged into the 4th Industrial revolution (4IR) also known as Industry 4.0. Industry 4.0 paradigm is based on concepts like the Cyber- Physical System (CPS) – which integrates communication, computing, and control. The major technologies involved in Industry 4.0 for cloud computing-based automation and data exchange are the Internet of Things (IoT), Artificial Intelligence (AI), Could & Fog Computing and Big Data Analytics. Other technologies including 5G technology, wireless internet, Augmented Reality, cryptography, Content based Image Retrieval (CBIR) and use of semantic database (DB) design were also involved in the novel industrial revolution. The fourth revolution embraces innovation of the medical and healthcare field as well through manufacturing and automation of new technologies, robots, software, sensors, and various advanced information technologies to healthcare thereby creating innovative routes and new opportunities for instance patient care, tools & devices, and customized implants. Advances in technology have led to the digitalization of healthcare through the application of Information and Communication Technologies (ICTs) also known as eHealth. The eHealth system is revolutionizing towards healthcare 4.0 (HC4.0) through adoption of the AI, IoT, Big Data as well as Cloud and Fog Computing technologies enabling new healthcare associated processes like personalized & remote patient monitoring, home care, virtual multiple care, telemedicine, Electronic Medical and Health Records etc. It is all about

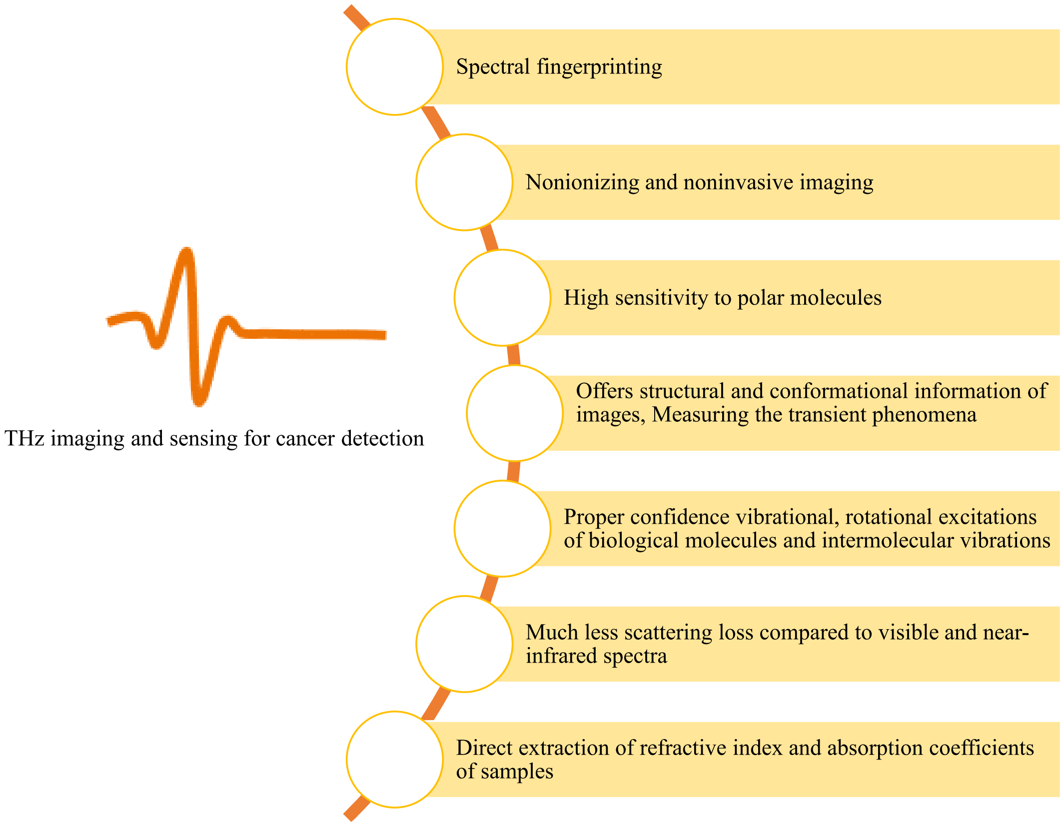


FIGURE 8. Salient features of THz radiation-based cancer imaging.

TABLE 2. Recent cancer studies in THz imaging, spectroscopy and sensing.

Ref.	Technique	Cancer tissue	Results
[171]	• Reflection mode TPI - TPS Spectra 3000	• Rat breast tumor	• Differentiation between fibro-fatty and cancer tissues
[139]	• Reflection mode TPI	• Human and animal breast	• More similarities between human and Sprague dawley rat model tumors relative to transgenic and xenograft mice tumors.
[172]	• Diagnosis based on classification of refractive index and morphological dilation	• Breast	• Sensitivity of 80% and 82%
[173]	• Transmission mode THz pulsed TDS	• Pancreatic ductal adenocarcinoma	• Successful healthy and cancer tissue differentiation
[41]	• THz near field imaging	• Animal tissue	• Potential for μm scale resolution imaging device
[174]	• Graphene based sensor in THz range	• Basal cell carcinoma	• Sensitivity of 6.9THz/RIU and 11.2THz/RIU for healthy and cancer tissue respectively.
[164]	• Water-Based THz Metamaterial absorber	• Colon cancer	• Spectral response change attributed to tissue optical property changes.
[175]	• 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
[153]	• Metamaterial THz biosensor	• Cervical cancer	• Sensitivity of 29 and 74 GHz/RIU for low and high resonant frequencies
[117]	• sub-terahertz waveguide iris probe	• Breast	• Able to detect fat, fibrous and cancer tissues
[176]	• THz holographic and THz near field imaging	• Living body	• Achievable through use of nanoparticle contrast agents

moving towards smart and connected care, which is personalized, patient centric and to the convenience of the patient.

The Healthcare 4.0 Cyber Physical System (HCPS) is made up of computers, storage, communications, interfaces, bio-actuators and biosensors etc. The paradigm of the HPCS enables real world processes observations and patient monitoring during, before and after surgeries by the use of biosensors. The HPCS also contains bio-actuators for accomplishing patient monitoring together with other technologies.

Figure 7 illustrates the typical Healthcare 4.0 driven technologies [177], [178], [179]. These technologies include new medical imaging modalities, AI, IoT & IoMT, cloud computing, Blockchain, smart sensors and wearable technology, genomics and 3D printing as follows; (1) Advanced medical imaging technologies including AI enabled machines from MRI, CT to THz, IR etc. (2) Smart sensors and wearable technology for vital signs monitoring, (3) 5G/6G enhanced Telehealth, IoT, IoMT for connectedness and virtual care (4) AI and Robotics for clinical decision support systems, data analytics, precise surgical tools (5) Blockchain technology – open source distributed database based systems for data integrity and transparency (6) 3D printing for medical device and personalized medicine delivery (7) Genomics for more accurate diagnosis and treatment, personalized and predictive medicine (8) Cloud computing and cloud based storages – PACS, EHR, Data analytics. The emergence of THz technology and the digital evolution of healthcare and biomedical industry bring another dimension in embracing AI, IoT and wireless wearable etc. to revolutionize the healthcare field. In this respect, the wake of the Healthcare 4.0 era and its integration with novel medical imaging technologies like THz imaging for cancer will greatly contribute to reduced cancer caused mortalities through early diagnosis, precise, equitable and personalized care. A briefed review of the digital evolution of medical imaging technology, emerging THz based healthcare data evaluation and diagnosis methods in the interface of healthcare 4.0 technologies including big data analytics, Machine learning, wearable technologies and IoT are reported here.

A. DIGITAL EVOLUTION OF MEDICAL IMAGING

Medical Imaging has greatly improved in the few past decades not only through the advancement of technologies but also through the digital revolution. From the invention of X-ray technology, more imaging technologies have been developed including Computed Tomography (CT), Ultrasound (US) and Magnetic Resonance Imaging (MRI), the novel advancements in MRI include functional MRI through which functionality and connectomics of the brain can be explored by making inferences of the neuronal activities that produce the visualized fMRI raw time series. On the workstations, films are now replaced by digital images which are of high resolution, enabling multiplanar image reconstruction. The digitalization of imaging technology allows teleradiology where remote interpretation of scans is done by clinicians, radiologists etc. in real-time or after the patient goes away from the point of care for increased efficiency, accuracy and convenience. The Big data acquisition, storage, transmission and analysis as well as computer aided diagnostics (CAD) have been enabled through advances in computer software and hardware with cutting edge capability to process images. For the medical imaging storage and management for instance, picture archiving and communication systems (PACS) have been developed. Another result of the digital revolution is the Electronic Health Records (EHR) and Electronic Medical Records (EMR) which substitute hard paper based medical history, health information, clinical notes etc. This enables the integration of hospital and radiology information systems with decision support tools, coding and billing etc.

The emerging electromagnetic imaging techniques for medical imaging like the THz technology could provide ease of accurate and real-time views by integrating them with IoT, AI and virtual reality for multidimensional and high-resolution imaging a well as image guided surgeries. Telemedicine which involves areas like telecommunications, informatics, AI, computer engineering, medicine, virtual presence, material science and robotics enhances the depth and convenience of diagnosis, medical assistance, and transmission of medical information. IoT based healthcare technology coupled with AI and Robotics plays a significant role in medical analysis, remote patient monitoring, medical information etc. for accurate diagnosis, analysis, and decision for aiding robotic surgeries. Also, IoT enabled wearable devices combined with mobile applications, data analysis and management tools have been recently developed for heart rate, tracking steps etc. The technology may be as well applied to THz technology through IoT enabled sensors for remote health data acquisition, processing, and analysis for a tremendous technological growth. The integration of THz technology and AI greatly enhances performance of healthcare technology. The thrust here will be on the following for main applications, medical information technology, remote patient monitoring, accurate diagnosis and medical data analytics with reference to novel literature. The major role of THz technology being in preventive, diagnostic, checkup and quality control evaluations. The importance of Internet of Robotic things (IoRT), The Internet of Nano Things (IoNT) and telerobotic surgery is also discussed. IoNT enables the efficient information interchange for Nano things e.g., Nano sensors, Nano processors, Nano antennas, Nano cameras etc., networks and devices.

The THz technology being a fusion and multidisciplinary technology is ubiquitous and includes biomedical imaging and sensing, biosensors, ultrafast wireless communication, Nano devices and military applications. In biomedical imaging and sensing the main methods used are THz spectroscopy, THz Imaging, THz Tomography, THz Endoscopy and Metamaterial Based THz Sensor. THz spectroscopy and Imaging plays a major role in the implementation of IoT, AI and wearable devices since these devices utilize information or data acquired from a host of sensors or imaging or spectroscopic equipment for THz Healthcare technologies applications. The main categories of THz medical imaging are the continuous THz and Pulsed TH imaging. Since the frequency band used THz technology the spatial resolution, sensitivity and signal to noise ratio, the technology can be used for diagnosis of cancerous tissue, distinguishing cells, dentistry, inspection of wounds and burns, colonoscopy, endoscopy, scanning of the full body, brain, breast, breath etc. The early detection of cancer can be done through DNA analysis. All these applications of THz imaging and spectroscopy can therefore be coupled with IoT, AI and wearable technology for advancement of the acquisition, diagnostic and decision system. THz spectroscopy plays a crucial role in the finger printing, recognition and characterization of biomolecules and biomaterials with the help of sensors, devices and computing tools. This is useful in medical applications, and it is thus significant to develop an extensive database for THz spectroscopy.

B. ARTIFICIAL INTELLIGENCE AND ROBOTICS IN THz HEALTHCARE

The capacity of Big Data processing from a huge database by a computer based robotic system is enhanced by AI. The focus of Medical AI is mainly on designing AI frameworks and programs that aid in diagnosis, visualization of contrast and therapy recommendations. The broad focus areas of AI include machine learning, data visualization, data mining, expert systems, neural networks, data streams, tele-robotics and case-based reasoning. The Medical AI system improves patient management, communication and the system's capacity for data transmission and storage through analysis of decision support systems for critical care and observing health professionals' acceptance. AI enables the integration of various technologies for equipment / machines to be able to sense, act, comprehend, and learn so as to perform clinical and administrative functions thereby greatly enhancing delivery of care and interoperability of doctors, patients, systems and vendors of the electronic systems. The application of AI and telemedicine to THz systems provides robust frameworks for patient monitoring, image recognition & interpretation, intelligent assistance, therapy planning, medical information technology, diagnosis, reminder alerts and analysis of data thereby reducing errors associated with human interference as well as reducing costs resulting in convenient virtual assistance and efficient telemedicine. AI enables the analysis of an entire molecule analysis unlike molecule-by-molecule analysis, this leads to the development of knowledge bases which can be compared with other databases for decision support systems and accurate treatments. Through the application of AI, machine learning and robotic technology to THz systems, the development and improvement of IoT is inevitable and will bring improved information interchange, security and configuration revolutionizing the healthcare industry. Telemedicine enables remote consultation, assistance, diagnosis, education, therapy, and management. The types of telemedicine include Tele-education, Telesurgery and Teleconsultation. The development of robotic technology and its application in healthcare have proved to minimize the cost, burden and risk of failure since robotic operations are accurate for instance in surgery. This has also resulted in synergy between patients and healthcare practitioners as well as medicine and engineering & technology. The major features of a robotic system are sensors, programmability, flexibility, and mobility. Through robotic technology, digital imaging technology, EMRs and diagnostics archiving is maintained. Currently the state of healthcare robotics is enhancing access to healthcare systems through real-time access whereby processing of huge data volumes is enabled through transmission paths that are reliable. Recently reported home based robotic tools integrated with wireless wearable technology are enabling remote monitoring of multiple patients and surgeries by clinicians and surgeons. Also, health records are transitioning to electronic records which require reliable security. The application of these technologies to Terahertz imaging and sensing can also be of paramount importance to the innovation of healthcare systems including replacement of prosthetics, physical therapy, education and surgical procedures [26]. A prototype has been reported for a flexible and wearable terahertz scanner by scientists at Tokyo Institute of Technology [180].

The application of machine learning techniques in THz imaging and sensing have been extensively reviewed in [181], [182], [183], [184], [185], [186], [187] and [188]. However, most of the machine learning models that have been explored in THz imaging and sensing for biomedical applications are based on shallow networks due to the unavailability of sufficient training datasets. The application of deep learning algorithms like the Convolutional Neural Networks (CNN) enables system complexity, robustness and multimodal capability [189]. The application of deep learning in this application has been explored in few studies such as [190] and [191]. The development of custom convolutional neural network (CNN) model and fine-tuned, pretrained CNN models capable of multimodal image classification have been proposed in our recent studies [189], [192]. THz imaging systems integrated with Robotics have been recently explored for enhancing flexibility of THz systems for in vivo imaging of body geometry and locations that are not easily accessible. Moreover the Robotic arm geometries in THz systems facilitate the development of compact, flexible and portable THz systems for point of care convenience [37], [40], [47], [193], [194], [195], [196], [197], [198].

C. INTERNET OF THINGS AND WEARABLE TECHNOLOGY IN THz HEALTHCARE

The Internet of Things (IoT) is a novel technology which deals with the network of sensor enabled physical devices or objects – ''things'' also known as nodes embedded with software for connectivity and data exchange with other devices over the internet. A component of the IoT can be for instance an implanted chip for heart rate monitoring or any object capable of data transfer in either small bytes or big bytes over the network. The IoT concept has evolved since the integration of wireless, microelectromechanical and internet technologies by deploying information and computational technology to enable processing of machine generated and unstructured data for further analysis. The mixture of web enabled smart devices with embedded processors make the IoT ecosystem and works on data acquired from sensors through connecting a cloud-based server and IoT gateway.

IoT devices can also connect with other advanced and smart devices and share knowledge without human interference even though they can also accept human given instructions.

The emergence of wearable technology plays a major role in day-to-day operations tracking. These smart integrated IoT devices are sensor enabled whereby the sensors are attached to either the devices or body parts for extraction of data and improve the lives of patients, doctors and everyone. Currently, these devices are permitting real time acquisition of medical data for an improved quality of life and healthcare services. Various domains have been increased through the use of IoT, for instance drug prescription, personalized treatment and diet recommendation. The contribution of IoT to health sector includes applications like tracking daily activities, online diagnosis, remote & real time health monitoring and telemedicine using radio frequency identification and IoT enabled devices. The advancement of technology results in upgrading of conventional hospital systems for automation of appointment booking, bill and medicine payments, medical reports etc. [26]. Similarly, the development of new emerging imaging technologies, for example, THz imaging and IR imaging has not yet been adopted for clinical use. The integration of the new imaging modalities and fourth industrial revolution technologies for example AI, IoT, Big data analytics, virtual reality and cloud computing etc. will revolutionize the healthcare for cancer care by moving from numerical data (vital physiological parameters) to the integration of spatial (image), temporal and physiological data domains towards personalized healthcare which is one of the goals of smart healthcare. In one of our studies [189], we proposed the framework of an IoT enabled CAD system for breast cancer. IoT simulation and cloud processing was performed in the ThingSpeak cloud platform with email alert capability. It will be possible to transmit acquired images/training datasets for cloud training and analysis to reduce the resource requirements at the acquisition center.

IV. DISCUSSION

This section discusses the advantages of THz technology and identifies challenges and research opportunities in cancer imaging and sensing applications.

A. SALIENT FEATURES OF THz TECHNOLOGY FOR CANCER DETECTION

The THz technology – imaging, sensing and spectroscopy has become a research hotspot in the biomedical field with great potential for clinical adoption including for early, noninvasive and label free detection of cancers.. Some of the attractive characteristics and features of THz imaging for cancer imaging applications have been deduced from the reported studies and are presented in Fig. 8.

1) SPECTRAL FINGERPRINTING

The THz waves' photon energy coincides with the energy levels of the low frequency molecular motions such as rotation, vibration, and translation. The molecular specific motions are used to identify biomolecules through measurement of their characteristic spectral signatures in THz frequency range.

2) STRONG ABSORPTION BY WATER

THz waves are sensitive to polar molecules i.e., highly they are absorbed by polar molecules such as water. The absorption coefficient of water at room temperature and at 1THz has been estimated to be 220cm-1 which exceeds the absorption coefficient of biomolecules [31]. The high absorptivity of THz waves by water has been suggested in most experiments to be the main cause of differentiation between cancer and normal tissues due to the tissue's different water molecule content.

3) NONIONIZING AND NONINVASIVE PROPERTIES

The photon energy of THz radiation is low ($\approx$1-10meV) that it is insufficient to cause tissue damage by ionization, thus it is suitable for noninvasive medical imaging for in vivo diagnosis in real time. This is unlike medical imaging modalities that are based on ionizing radiation such as X-Ray. Moreover, compared to visible light and infrared, THz wavelengths are longer and thus exhibit negligible scattering losses in biological tissues [114].

Low photon energy makes them nonionizing in nature, THz quanta energy corresponds with energy of Van der Waals intermolecular interactions and hydrogen bonds, thus interacts with low frequency motions of molecules, free charges and media collective excitations. Reduced Mie scattering effects and increased object penetration depth (compared to Infrared (IR) and visible spectrum) due to small structural inhomogeneities of many objects like biological tissues at THz wavelength scale allows application of the effective medium theory for description and analysis [199], [200], [201].

B. EXISTING CHALLENGES AND PROSPECTIVE OPINION

Several breakthroughs have been achieved in THz imaging, but a lot of limitations are yet to be addressed in ongoing research studies. For example, THz in vivo imaging has been mostly applied in tissue of the epidermal layer such as skin, due to the limited penetration depth of THz waves. The remaining challenges and prospective opinions are discussed in this subsection to facilitate research towards the development of THz systems that can be adopted for wide scale clinical application.

The research challenges and opportunities that will be discussed in this paper are summarized in Fig. 9.

1) DIFFRACTION LIMITED SPATIAL RESOLUTION AND SENSITIVITY

The limitations in performance of THz wave-based technology as an imaging or sensing tool have been significantly contributed by the drawbacks resulting from diffraction limited spatial resolution or low sensitivity, low speed scanning among other factors. Firstly, the sensitivity of THz detection

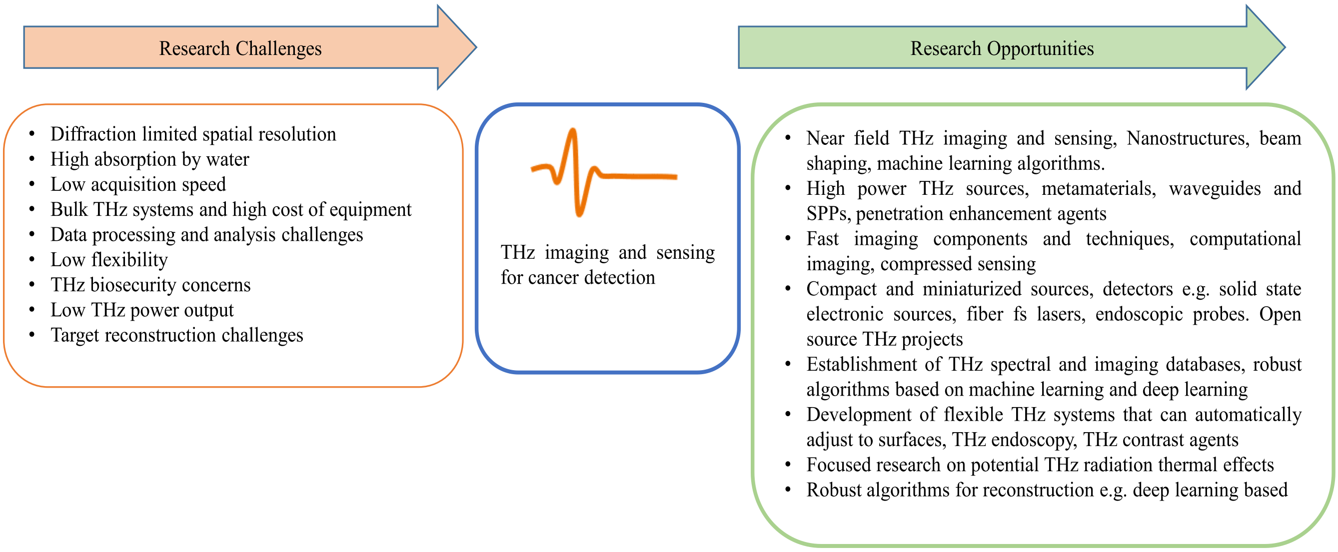


FIGURE 9. **Summary of research challenges and opportunities in THz imaging and sensing for cancer.**

does not yet meet living cell detection special requirements due to the diffraction limit and THz wavelength (0.03-3mm) that is more than live cell detection resolution in the micron or nanoscale. It is still a technical bottleneck faced by THz systems to break the diffraction limit to improve detection sensitivity for biological detection. Diffraction limit also limits the spatial resolution, this can be improved by using higher frequency, since the higher the frequency, the better the imaging effect should be. However, as the frequency increases, the sample's absorption coefficient also increases leading to decreased THz wave penetration depth and Signal to Noise Ratio (SNR). Thus the frequency of 1.5THz has been found to clearly identify tumor area [202]. An optical near field techniques for example using air plasma based emitters or detectors has been proposed to overcome resolution issue in THz imaging [203]. Nanostructures have been utilized for increasing sensitivity and the use of geometrical beam shaping have been realized for improving spatial resolution and enable efficient real time THz imaging. Moreover, progress in analytic algorithms based on machine learning or deep learning can be enabled for image reconstruction, better data sampling, denoising, compressive phase retrieval and efficient computing costs for development of THz systems beyond diffraction limits and absorption cross section.

2) HIGH SENSITIVITY TO WATER

High absorption of THz waves by polar substances especially water is a big obstacle in THz technology. The absorption coefficient of THz waves by water is as high as 150cm-1 at 1THz which limits the imaging and sensing capabilities of THz through thick tissue. Moreover, THz waves highly sensitive to and high absorption by water molecules limits the penetration depth to tens and hundreds of microns and consequently in in vivo measurements, the probing is limited to target's epidermal or superficial layers and reflection mode THz become the suitable configuration. The strong water absorption of THz waves also makes the analysis of biological tissues, cells and molecules to be suitable for ex vivo examinations under dry conditions and for solid or pre-treated samples, making it a challenge to detect water rich human biological samples and operate in water vapour interfered environments. Thus, THz wave based detection should overcome water sensitivity [28], [204] The penetration depth of THz waves in skin (which constitutes of approximately 70% water) is limited to about 500μm at 1THz. The increased THz absorption of THz waves by polar molecules causes the SNR to be reduced. More sensitive sensors and better free electron lasers can help alleviate this challenge. Some techniques have been shown to increase penetration depth and enhance SNR such as using an intense or high-power THz sources. However, intense sources are prone to cause thermal effects for in vivo applications. Due to the effects of high water absorption limitation, most biosensors such as metamaterials, SPPs and resonant waveguides only operate as refractive sensors, thus another approach is designing configurations that are sensitive to the highly absorptive samples [47].

Further, the complexity of detecting environmental conditions, limit the specificity of detection of THz waves, whereas the biological samples contain macromolecules and different living cells which cause signal interference and target annihilation. Therefore, effective technical methods are required to analyse the images and spectral characteristics from THz detection results. Some tissue preparation methods have been studied to enhance penetration depth and improve SNR such as dehydration, alcohol perfusion, formalin fixing, gelatin embedding, lyophilizing, freezing, paraffin embedding, and paraffin emulsion as well as THz Penetration Enhancing Agents (THz PEAs) and contrast enhancing agents based on nanoparticles etc. [48].

3) LOW ACQUISITION SPEED

Another major challenge in THz imaging systems is long acquisition times. Clinically competitive imaging modalities would require a close to real time interpretation. It is difficult to keep a patient still through the long scanning time, moreover the image suffers timed induced variations. Conventional THz imaging systems use raster scanning (pixel by pixel) in the x- and y- directions which results in fairly slow acquisition of order of 50 pixels/second caused by the linear mechanical motion of the optical delay line. Thus, the slow acquisition has been attributed to the optical delay line and single pixel detector. This hurdle can be overcome using; fast optical delay lines, Electronically Controlled Optical Sampling (ECOPS) and Asynchronous Optical Sampling (ASOPS). 2D electro optic sampling implementation with Charge Coupled Device (CCD) camera, use of 2D THz TDS photoconductive antenna technology, optical rectification, non-mechanical time domain sampling, electro-optical sampling in nonlinear crystals as well as combination of bolometer array THz cameras and digital holography have also been studied. More novel THz imaging techniques have also been reported to provide improved acquisition speed. A pulsed time domain THz system combined with a single pixel camera, near field THz imaging which has achieved six frames per second real time imaging of a 32 × 32 sample using serial acquisition. The same techniques also achieved 10ps time interval in 2.6s of acquisition of a 32 × 32 sample. Thus, with a fast modulator and sufficient signal, these techniques can achieve fast enough acquisition. Continuous wave single wavelength imaging has also been proposed [47], [49]. Recent works have also investigated computational imaging, focal plane arrays, compressed sensing based techniques [37].

4) THz SYSTEM SIZE AND EQUIPMENT COST

Conventional THz systems and instruments are generally bulky in size, which makes them oriented for laboratory-based research. To become next generation modality competitive, THz system have to be compact and miniaturized for point of care operation. Advances in THz technology development are improving towards miniaturized systems such as fiber femtosecond lasers, THz endoscopic probes, ZnTe crystal-based sources and detectors which will in turn reduce the overall THz system size.

THz imaging and sensing systems are currently very expensive due to the high costs of detectors and sources for example ultrafast Ti:Sapphire lasers are costly. A typical THz imaging system cost between USD100000 and USD500000. This hinders THz technology commercialization and impedes the access to THz imaging systems for most academic based research studies. However, the high costs are comparable to the cost of X-Ray, MRI and CT equipment. As THz technological developments are advancing towards solid state electronic THz sources, total cost of THz imaging system may greatly reduce. For facilitating lab based research in THz, an open source project has been developed that enables low cost THz imaging and millimetre wave sensing [205]. Further research and development are required to design THz imaging and sensing systems that have high efficiency and low-cost sources and detectors to facilitate wide scale application of THz techniques and instruments.

5) CHALLENGES IN DATA DRIVEN THz STUDIES

When using TPS systems, data processing is very important. From the power spectrum measurements, the Kramers-Kronig relations have been 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 [206]. 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 [207]. The data processing steps in TPS involve signal pre-processing, denoising, apodization and deconvolution. The final processing steps involve statistical analysis, dimensionality reduction and machine learning approaches.

THz molecular imaging systems should be coupled with data analytic algorithms and other technologies to both enhance image contrast and overcome intense attenuation by water as well as to enable estimation of tumor type and stage than to be confined to differentiating cancer tissue and healthy tissues. Further, data interpretation and analysis are still an obstacle which has been helped by computational modelling and machine learning techniques. Machine learning enable autonomous processing and analysis of data which makes task completion and decision making fast and precise. Machine learning techniques in THz imaging and spectroscopy are useful for data pre-processing, qualitative and quantitative multivariate data analysis and other tasks like compressive sensing, image super resolution and image reconstruction etc. [181].

Therefore, it is currently imperative to rapidly develop and advance THz technology by integrating the technology with machine learning techniques to overcome practical application bottlenecks and meet the escalating market demands. The robustness and generalization ability of machine learning models used for THz data extraction and analysis require urgent attention. The effectiveness of various machine learning models that have been explored on THz cancer datasets are currently limited by the quantity and quality of training THz data. The accuracy of most machine learning models especially deep learning models depends on availability of large training datasets. However, there is still a challenge of unavailability of sufficient training datasets particularly THz cancer image datasets. Lack of availability of human fresh tissue and complexities associated with obtaining the required government mandated and procedural permissions for processing human tissues are also deterring data sources for THz research that would facilitate clinical medical diagnosis applications. [131]. One of the merits of THz imaging is its capability to provide the target's spectral information within a certain frequency range. However, the fingerprint characterization of biological tissue responses is not yet established since there are various inter and intramolecular interactions that can also have contribution of the frequency range. Therefore, there is need to establish biomedical imaging and spectroscopic databases.

The unavailability of sufficient training datasets may cause model training to suffer Overfitting which compromise the prediction model's accuracy and robustness. The machine learning model training accuracy also depend on other factors like parameter optimization and selection. Large training samples are required accomplish learning, training and parameter selection tasks which affect the calculation speed and accuracy of the models [192]. Most machine learning based THz cancer data studies have mostly used machine learning models made up of shallow structures, such models are task specific and less accurate, limiting the large-scale application of such approaches. An in-depth THz spectra and image feature analysis requires more robust models for example deep learning techniques which can automatically learn and extract features. The application of deep learning is attractive for tasks such as noise removal in measurements, discrimination of regions, enhance resolution, image reconstruction and characterization [208].

The application of machine learning algorithms, particularly deep learning techniques for THz data extraction, reconstruction and analysis tasks is a promising step towards improved sensing, speed, accurate localization performance and quality and intelligent THz system development. In the development of Computed Aided Diagnostic (CAD) systems, deep learning systems can help data and result visualization in a way that can be conveyed to medical practitioners to give them clinical decision support for making clear decisions [189]. However, the accuracy and effectiveness of deep learning-based implementations in THz cancer imaging for these data driven explorations require huge datasets for training. Some challenges have already been faced in a deep learning study for THz breast cancer imaging by [190]. These challenges that caused erroneous classifications were found to be caused by pixels scattering near scan edges, lack of precise ground truth because of deformations during paraffin, formalin fixing. Also, the presence of multiple tissues in the THz pixel region were found to be causing false positives. The overlapping electric properties in fat and muscle tissue as well as cancer and muscle make it difficult to differentiate the signals in THz scans and also it is a challenging task to classify artefacts that not related to tissue i.e. not part of the actual tissue [190].

In the future of THz technology development, more advanced and robust machine learning algorithms will be required that are capable of finding accurate and reasonable solutions in circumstances of out of distribution data and far from learned distribution data. Such techniques that will benefit future THz sensing and communication applications include deep learning, multitask learning, meta learning, federated learning, active learning, specialized learning [181], [183].

6) LACK OF METHODOLOGY STANDARDS

The lack of established, commonly accepted standards for THz measurements has resulted in diverse methodologies including configurations of the systems, processing methods and experimental protocols. The relatively standard transmission mode THz TDS measurements of solid samples still exhibit diverged results from different groups based on an international comparison study [209]. This lack of an established standards has also resulted in complications in biomedical measurements which have more variables than solid samples, making it difficult to establish comparability of studies and common standards. Moreover, there are variations of the THz dielectric models and inconsistent protocols for measurement i.e., the models have not yet been standardized, which results in divergent results and constraints model performance comparability and standardization. For example, there is no consensus in skin modelling for skin cancer studies. There is need for standardization of sensing techniques to detect variables of interest, for example to control variables that affect THz response. Moreover, to establish THz safety protocols, there is need for a consensus on the understanding of THz waves effects on bio matter [47].

More robust measurement protocols should be established to alleviate challenges in comparability of results taken from different setups. More accurate, faster THz systems are required before tissue models can be applied for improved interpretation of diversity and complexity of tissue applications which affect tissue responses. Focused research is needed to gradually reduce the divergence of THz studies and ultimately establish standards.

7) LOW FLEXIBILITY OF THz SYSTEMS

In vivo THz imaging and spectroscopy measurements have so far been limited to tissue of superficial and epidermal layers that can be easily accessed like skin, oral, cornea etc. This limitation is due to limited THz wave penetration depth caused by high tissue liquid absorption e.g., water. The in vivo measurements are performed over a flat surface, in reflection configuration to align and receive the THz signal. Therefore, for most of the studies, THz measurements have been performed on excised tissue samples i.e., extracting the region of interest prior to performing measurements which requires tissue treatments to preserve the sample. However, ex vivo measurements are prone to inaccurate measurements associated with altered properties of excised tissue. THz systems show great potential for label free, non-invasive and nonionizing imaging of biological tissue and the ability to perform in vivo imaging of human body and allow for body movements etc. Techniques for high flexibility operation that quickly adjust the alignment according to the surface to be measured are required. THz endoscopy systems are still using single pixel detection which requires precise alignment, and it is difficult to achieve. Other potential solutions include use of robotic arms, passive THz imaging techniques and development of contrast agents [47], [176].

8) THz TECHNOLOGY BIOSECURITY

Due to the low photon energy of THz radiation, the radiation energy is insufficient to pose chemical and ionizing hazard, making it more tissue friendly for repeated assessments than ionizing radiations like X-ray and Gamma Rays. However, with the rapid THz technology developments, investigations are underway for potential biological effects of high-density THz radiation exposure at organism level since they are currently inconclusive. For example, some THz radiation effects of THz radiation that might cause slight hazard to have been reported to depend on the parameters of THz radiation such as power, intensity, frequency, high power density and time of exposure etc. Studies have shown increased depression levels when a mouse model was exposed to high THz power density (0.15THz, 3mWcm^{-2}, 60 minutes), perturbation of wound healing (2.5THz, $0.32\mu\text{Wcm}^{-2}$, 60 minutes), skin inflammatory responses (2.7THz, 260mWcm^{-2}, 30 minutes). Moreover, an in vivo study has suggested that THz radiation can potentially influence tissue damage and cell death at high THz power densities (0.1-1.0THz, $2000\text{-}14000\text{mWcm}^{-2}$) due to thermal effects, however exposure to low THz power density of (1.89THz, 189.92mWcm^{-2}) could not induce damage of porcine skin tissue. More research work is required to understand any effects of high-density THz power exposure on proliferation, morphology, or differentiation of cells and biological molecules. More so, the possible effects of THz irradiation specific intensity and time on cells and tissue genome, proteome and transcriptome variations have raised research interests to reconsider THz irradiation biosafety in biomedical applications [204], [210].

9) OTHER CHALLENGES

The other challenges include the scatterings effect that happens when a sample is exposed to THz waves as a result of particle non-uniformities i.e., different sizes and irregular shapes that affect matter refractive index and consequently test results. The scattering effect can be reduced by compressing and grinding specimen into smooth, fine particles. For spectral studies, researchers 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 [115].

a: POWER

A typical THz wave source outputs power of the order of μW i.e., when a pulse oscillator is used at 1W peak output. Depending on the oscillator duty cycle, the peak power ranges of THz waves are from 100μW to 0.1W with SNR in excess of 104. An average of mW output power range or higher is preferred for 2D real time imaging.

b: TARGET RECONSTRUCTION

In most of the reported research of THz imaging for cancer, imaging has been performed on thin, parallel faced samples i.e., excised tissues or on reflection of relatively flat surfaces such as superficial or epidermal layers. In the real operational environment however the irregularly shaped 3D targets like human body needs to be imaged. A lot of algorithms and collection of optics are being developed to overcome this and enable 3D target reconstruction. The THz Computed Tomography (CT) systems have also been developed to reconstruct a 3D targets [181], [211].

Another drawback in the application of THz technology is that so far it has not yet achieved satisfactory image quality due to challenges such as artefacts, complex noise and resolution. The development of super resolution algorithms [212], Compressed sensing and near field THz imaging techniques such as Synthetic Aperture Radar (SAR) imaging etc. can potentially overcome this challenge.

In summary, THz imaging and sensing systems for cancer applications suffer drawbacks that deter wide scale deployment spanning from high system cost, lack of portability and compactness, low reliability or achievable integration cost, lack of scalability and standardization etc. Low cost and compact THz systems can be achieved using single chip solutions such as integrated circuits based on nanoscale CMOS (Complementary Metal-Oxide Semiconductor) technologies and Bipolar CMOS (BiCMOS) [213].

V. OUTLOOK

The recent advances in THz technology development and future prospects are discussed in this section.

A. RECENT ADVANCES IN THz IMAGING AND SENSING

Several milestones have been achieved in THz imaging and sensing technology as shall be discussed in this subsection. As shown in Fig. 10, the THz imagers have rapidly evolved and developed over the years, this is closely associated with the improvements in THz sources and detectors, which has been driven by the limitations in conventional systems including lack of high power and room temperature operating sources, lack of compact and portable THz systems, slow acquisition speed, poor resolution, and signal-to-noise ratio (SNR) etc. Some important milestones have been reached and efforts are ongoing in the development of THz emitters (Em), detectors (Det), flat optics (Flat opt) and THz imaging systems (THz Img) over the past 2 decades as presented in the milestone chart above. Over this period, there has been a general linear increase in the improvement of THz systems in terms of the following metrics: power consumption, reduction in size (miniaturization) and enhanced functionality.

Optoelectronic based THz-TDS systems are conventionally bulky, and laboratory use oriented. Recent advances are focusing on miniaturized, compact, and optimized

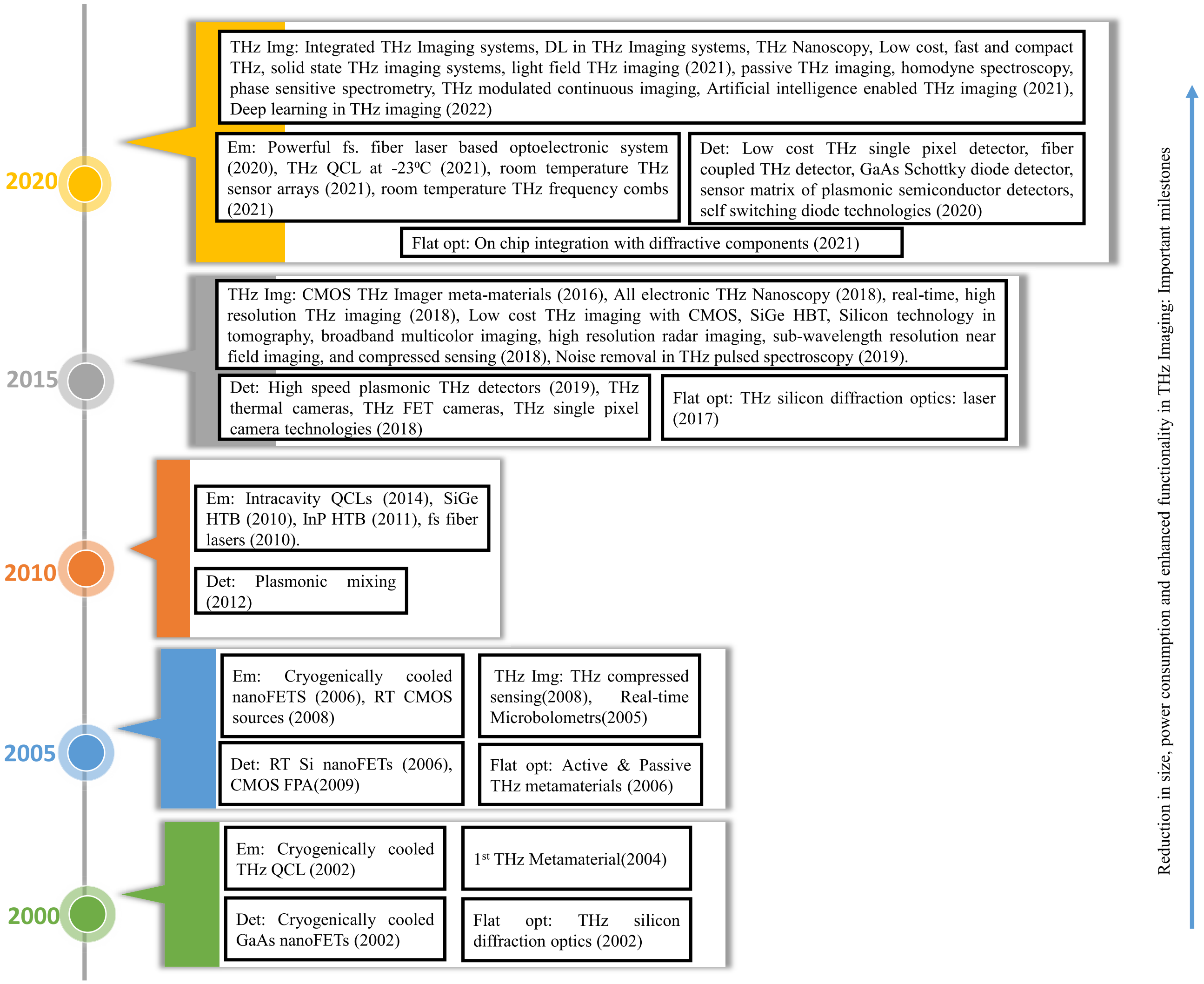


FIGURE 10. Important milestones in THz technology from 2000 to 2022.

THz imaging technology for real operational convenience, enhanced functionality, and reduced power consumption. 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 Nano-transistors, hetero-junction field-effect transistors (HFETs) or high electron mobility transistors (HMETs), resonant tunneling diodes (RTDs) and vacuum electronic sources. Rapid evolution has also been noted towards compact room temperature detectors and arrays including detectors based on FETs, Diode based sensing and Microbolometers for example micro-electromechanical systems (MEMS).

Highly integrated platforms are being developed through computational imaging (CI) allowing the connectedness of advanced optics, modern sensing devices and post-acquisition signal processing for improved system performance that enable faster acquisition. Such systems include THz compressed sensing, THz holography, THz Fourier Imaging, 3D-THz imaging and THz super resolution imaging like the 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 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 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 recently investigated [37], [48], [176], [201], [208].

In terms of reliable and sensitive detection based on resonator-based sensing, it's a challenging task to detect trace molecule amounts because of THz wavelength and molecule size mismatch which causes very low absorption cross section. As a result, most research has been limited to samples of solid type. When using THz TDS to measure the absorption spectrum of mixture or compound samples, a significant absorption spectral feature from the host material whose volume fraction is higher can be easily obtained. Thus, samples are mostly prepared in pellet form as a pure substance so as to increase concentration of molecules under high pressure. Water molecules highly absorb THz waves, which makes it difficult to identify molecules that are dissolved in liquids such as water. Approaches for signal enhancement are therefore mandatory such as using modulators or resonators. When the resonator is used to increase THz near field, the absorption cross section of a particular molecule is also enhanced even in aqueous environments. Using a modulator like randomly patterned mask for iterative signal acquisition can achieve increased acquisition speed and simultaneously overcome diffraction limit. Plasmonic metasurfaces that consist of nanoscale resonators enable strong near field enhancement THz enhancement and have been considered excellent for detection of specific molecules. With further developments in the technology of nanofabrication, surface mediated THz sensing have evolved to diverse forms. Some methods of integrating sensing platforms based on metasurface with additional sample collectors have been proposed including microfluidic platform that integrate metasurface with graphene that improves selective sensing of DNA sequences of foodborne pathogens in liquid environments. Resonance based metasurface or beam modulations also enhance THz image contrast for better performance of analysis algorithms [123].

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

The waveguides are structures that direct THz beam propagation by providing a tight confinement of the field near guiding structure and a propagation length. These have also been noted to be favorable for sensing thin films and a small amount of analyte, even though the sensitive detection of aqueous samples that are absorptive have not been demonstrated yet. The many forms of THz waveguides include parallel plate waveguides, Micro strip line waveguides, coplanar waveguide lines and dielectric waveguide lines. THz SPPs were originally used for sensitive probing in visible wavelengths. Three approaches have been used to achieve THz SPPs including prism coupled SPPs that are based on doped semiconductors, spoof SPPs based on artificial periodic structures and aperture coupled SPPs with conductor dielectric interface [47].

The Fourier transform imaging with resonators in the THz regime of the spectrum have been explored to improve the sensitivity and selectivity through the resonance-based sensing chip and is expected to provide same conceptual configuration when integrated with a spatial scanning technique. The THz based Fast Fourier transform (FFT) has been developed using THz TDS and enhanced sample response as a result of resonance behavior of metasurface for performing spatiotemporal imaging of biochemical. Molecular biomarkers have fingerprint spectral features in the broad THz regime, however the spectral information of the spectral fingerprints can be easily lost when they are dissolved in water or superposed in a mixed form. It is therefore a challenging task to expect sharp fingerprinting for larger biological species such as cells, proteins, or body organs [214].

VI. CONCLUSION

The non-ionizing, noninvasive, label-free and spectral finger printing nature of THz makes it appealing for health applications and is expected to complement the conventional imaging modalities. The THz imaging and sensing has already been shown to work for skin and other types of cancer. Terahertz wound and burn inspections, and terahertz dental imaging, are other immediate candidates with some promising early research. The application of this technology to the novel healthcare technology revolution – Healthcare 4.0 promises major improvements to the success and improvement of this healthcare paradigm. In this paper, we have reported a comprehensive overview of the THz imaging sensing for healthcare applications particularly, cancer detection. The existing challenges have been identified, with recent advances and future prospects for development of robust THz systems. Approaches for performance improvement of THz imaging systems have been studied to counter some of the previously stated limitations. 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 the miniaturization and optimization. In the wake of the Healthcare 4.0 era, the integration of such technologies with emerging advances in medical imaging technologies like THz imaging for cancer will greatly contribute to reduced cancer caused mortalities through early diagnosis, precise, equitable and personalized care. The emerging advances in THz technology in the interface of the internet-of-things (IoT), artificial intelligence (AI), virtual reality and wearable technology are expected to revolutionize the healthcare and biomedical industry, providing ease of real-time, accurate observations and support for image guided surgeries, computer aided diagnosis, remote patient monitoring, multidimensional and high-resolution imaging and medical information technology etc.

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MAVIS GEZIMATI received the B.Tech. degree (Hons.) in electronic engineering from the Harare Institute of Technology (HIT), Zimbabwe, and the Master of Technology degree in biomedical engineering from the Department of Sensors and Biomedical Technology, Vellore Institute of Technology (VIT) University, India. She is currently pursuing the Ph.D. degree in electrical and electronic engineering with the Department of Electrical and Electronic Engineering Science, University of Johannesburg, South Africa. Her research interests include medical imaging technologies and image processing, medical electronics, healthcare technology, machine learning and deep learning, clinical decision support systems, biomedical optics and photonics, electronic medical and health records, and telemedicine.

GHANSHYAM SINGH (Member, IEEE) received the Ph.D. degree in electronics engineering from the Indian Institute of Technology (Banaras Hindu University) Varanasi, Varanasi, India, in 2000. Currently, he is working as a Full Professor and the Director of the Centre for Smart Information and Communication Systems, Department of Electrical and Electronic Engineering Sciences, Auckland Park Kingsway Campus, University of Johannesburg, South Africa. He was associated with the Central Electronics Engineering Research Institute, Pilani, and Institute for Plasma Research, Gandhinagar, India, respectively, where he was a Research Scientist. He was also worked as an Assistant Professor with the Electronics and Communication Engineering Department, Nirma University of Science and Technology, Ahmedabad, India. He was a Visiting Researcher with Seoul National University, Seoul, South Korea. He also worked as a Professor with the Department of Electronics and Communication Engineering, Jaypee University of Information Technology, Wakanaghat, Solan, India. He has more than 23 years teaching and research experience. His research and teaching interests include millimeter/THz wave technologies it's applications in communication and imaging, next-generation communication systems (5G/6G)/cognitive radio/NOMA, resource allocation and management, interference management, applications of 5G/6G in sustainable smart city, industry 4.0/5.0, healthcare 4.0, intelligent transport systems, energy management (IoE), and digital farming. He is the author/coauthor of more than 290 scientific papers of the refereed journals and international conferences and several books and book chapters published by Springer, Wiley, IET, CRC, and Academic press. He has supervised various M.Tech. and Ph.D. theses. He has worked as an editor/an associate editor and a reviewer for several reputed journals and conferences.

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