International Journal of Community Medicine and Public Health
Movsisyan M et al. Int J Community Med Public Health. 2024 Jun;11(6):2450-2454
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20241512

Review Article

Applications of terahertz waves in medical diagnostics: a literature review

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Received: 31 March 2024
Accepted: 13 May 2024

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ABSTRACT

Terahertz (THz) waves, occupying a unique position bridging microwave and infrared wavelengths, exhibit promising potential across diverse domains, particularly in medicine. With attributes such as non-ionizing nature and notable resolution capabilities, THz waves offer avenues for non-invasive medical applications. In cancer diagnosis, THz spectroscopy emerges as a pivotal tool for qualitative and quantitative analysis of biomarkers, enabling swift and accurate differentiation of substances based on molecular structure. Despite challenges such as limited penetration depth in tissue, THz imaging proves invaluable in discriminating cancerous tissues from normal ones during surgery. In this paper we have summarized recent research results on practical implementation of THz waves in medicine. Recent advancements in in vivo imaging showcase promising results, although challenges persist in human-based studies due to tissue complexity. Integration of advanced algorithms enhances the accuracy of cancerous tissue identification. Additionally, THz spectroscopy finds versatile applications in pharmaceuticals and life sciences, offering insights into molecular interactions critical for drug efficacy and understanding protein conformations. Further advancements in THz systems, including enhanced light sources and detectors, are crucial to propel biomedical research forward. Establishment of a comprehensive THz spectrum database will augment existing data, emphasizing the potential of THz waves to revolutionize medical diagnostics and treatment modalities.

Keywords: Terahertz waves, THz spectroscopy, Medical diagnostics, Cancer diagnosis, Literature review

INTRODUCTION

Terahertz (THz) waves, falling within the frequency range of 0.1 to 10 THz, occupy a unique position in the electromagnetic spectrum, bridging the realms of microwave and infrared wavelengths.[1] This positioning affords THz waves a hybrid nature, inheriting characteristics from both spectra. Notably nonionizing and non-invasive, THz waves exhibit phase sensitivity to polar substances, facilitating applications such as spectral fingerprinting and coherent detection.[2] With impressive resolution capabilities of up to 50 µm and notable penetration abilities, THz waves present promising avenues across various domains, including medicine, oncology, dentistry, and biology. Particularly in medical contexts, their non-ionizing nature renders them suitable for both in vivo and ex-vivo inspection with minimal harm. THz spectroscopy emerges as a pivotal tool for qualitative and quantitative analysis of cancer biomarkers, offering the capacity to differentiate substances based on molecular structure, polymorph, and chirality. While microwave spectroscopy shares some capabilities, its longer wavelength imparts comparatively lower resolution, underscoring the superiority of THz waves in this regard. In cancer diagnosis and surgery, THz imaging proves invaluable, enabling the discrimination of cancerous and peritumoral tissues from normal tissue with clear delineation. However, the depth of penetration is constrained by water absorption, limiting its utility primarily to surface or excised tissue imaging. Despite this limitation, rapid tissue imaging during surgery is facilitated by THz technologies. Biomarker detection, crucial in cancer diagnosis, benefits greatly from THz spectroscopy's ability to swiftly and accurately identify spectral "fingerprints" associated with different substances. As a potential tool for rapid cancer staging, THz spectroscopy, when combined with advanced algorithms, holds promise. Nonetheless, challenges persist, particularly regarding the signal-to-noise ratio (SNR) in spectral results due to limitations in THz source energy. Efforts to enhance spectral SNR are underway, aiming to improve biomarker detection in mixed samples and bolster the efficacy of THz imaging and spectroscopy in medical applications.

APPLICATIONS OF TERAHERTZ WAVES

Table 1 provides a short summary of studies on THz for ex-vivo applications. In their recent review, Peng et al delved into the application of THz imaging and spectroscopy in cancer diagnosis over the past five years, emphasizing the critical role of early detection in improving patient outcomes. Their examination revealed that THz imaging holds promise in effectively distinguishing cancerous tissue from normal tissue, primarily leveraging disparities in water content. However, the limited penetration depth of THz waves, restricted to approximately 1mm due to their high absorption by water and tissue components, currently confines the application of THz imaging in oncology to excised tissues or surface layer examination through reflection imaging systems.[3]

Over the last five years, only two studies have achieved successful in vivo imaging utilizing a pulsed THz reflectometric imaging system. Ji et al successfully obtained images of gliomas in live tumour model mice, achieving a resolution of 250 µm, where tumour tissue exhibited a higher intensity signal compared to adjacent normal tissue.[15] Similarly, Wu et al obtained images of brain gliomas in model mice with a resolution of 200 µm using a THz reflection imaging system with 2.52 THz continuous waves.[16] Despite these advancements, in vivo THz imaging research remains primarily in its experimental stages.

Challenges persist in human-based studies, notably the complexity of human tissue composition compared to mouse tissue, leading to biased spectral analysis. Additionally, individual variations in tissue content contribute to discrepancies in THz wave absorption and refraction among subjects, hindering accurate identification of cancerous areas. Recent efforts have integrated algorithms to differentiate cancerous tissue from normal tissue based on spectral differences, yielding promising results. For instance, Qi et al combined THz spectroscopy with a fuzzy rule-building expert system (FuRES) and fuzzy optimal associative memory (FOAM) for cervical carcinoma diagnosis, achieving a classification accuracy of 92.9±0.4% for FuRES and 92.5±0.4% for FOAM in a test involving 52 cervical tissue sections.[17] Similarly, Liu et al merged THz spectroscopy with principal component analysis, locality preserving projections (LPP), and Isomap for hepatic tumour identification.[18]

In parallel, Ajito has demonstrated the versatile implementation of THz spectroscopy in pharmaceuticals, life sciences, and medical diagnostics.[19] Operating within the frequency range between radio waves and light, THz waves offer molecular-level insights into various phenomena, including crystalline phonon modes, low-frequency molecular vibration modes, and gas rotation modes. Notably, THz spectroscopy excels in capturing lower modes of molecular vibration associated with intermolecular bonds, providing valuable molecular network information critical in understanding protein conformations, drug efficacy, and molecular interactions in the life sciences and biotechnology fields (Figure 1).

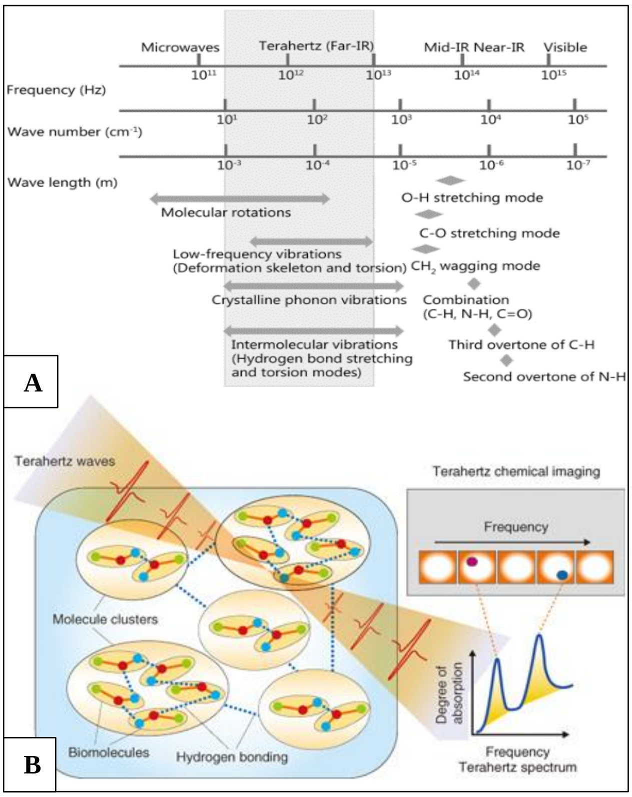

Figure 1: Molecular information that can be obtained from THz waves (A) characteristic absorption frequencies of molecules and crystals in the microwave, THz-wave, and infrared domains (2008 The Japan Society of Analytical Chemistry, with alterations); and (B) schematic illustration of the relationship between molecular networks, THz spectra, and THz images corresponding to each peak.

THz spectroscopy emerges as a distinctive tool for scrutinizing molecules or crystalline structures that engage in weak interactions, such as hydrogen bonds and weak intermolecular interactions. Offering versatility in accommodating various sample forms, THz spectroscopy supports multiple measurement methods, including transmission, reflection, attenuated total reflection (ATR), and polarization measurements. While transmission measurements are straightforward, ATR proves more effective with samples in water and highly polar solvents due to their strong absorption at THz frequencies. Employing ATR involves closely contacting the sample material with a high refractive index crystalline medium, allowing total reflection at the interface and measurement of the reflected THz radiation, thereby enabling spectrum acquisition based on absorption strength.

THz chemical imaging (TCI) provides a valuable technique for discerning the two-dimensional or three-dimensional distribution of molecules based on a sample's THz absorption spectrum. This method proves particularly useful in analysing the distribution and concentration of chemical substances within samples. Furthermore, the ability of THz waves to traverse non-polar materials like plastics and paper commonly used in packaging facilitates the imaging and analysis of pharmaceuticals concealed behind THz-transparent materials.[20-23] THz radiation's minimal impact on materials renders it suitable for non-invasive detection of biological materials, rendering TCI especially promising for analysing living materials or medical samples, including teeth, skin, and cancer tissue.

In the realm of medical diagnostics, the application of THz technology holds considerable significance. Despite being in the nascent stages, numerous studies have explored its potential applications, including the diagnosis of burns, identification of pathologies, and detection of foreign matter through THz tomography. THz spectroscopy, particularly utilizing techniques like THz time-domain spectroscopy, offers insights into molecular "fingerprints," aiding in the detection of hazardous chemicals, drugs, and diseases through express-analysis of exhaled gases and quality control of food and agricultural products. THz spectroscopy's capability to discern the structure and dynamics of proteins and DNA, as well as differences in tissue humidity, structure, and chemical composition, underscores its potential for early disease diagnosis.

Advancements in THz systems for biomedical research hinge upon the development of enhanced light sources and detectors with improved characteristics. Promising directions include quantum cascade and graphene lasers, along with photoconductive antennas featuring plasmon nanoelectrodes, which obviate the need for cryogenic cooling systems and offer adjustable operating frequencies and bandwidths, crucial for both emission and detection modes.

In a related article, Fu et al provide comprehensive insights into the progress of terahertz spectroscopic techniques for substance detection and recognition across various domains, including biomedicine, agriculture, food production, and security inspection, highlighting the fundamental principles and diverse applications of terahertz spectroscopy.[24]

The advantages of THz spectroscopy in substance detection and identification encompass a range of critical attributes, including biosafety, unique identification properties, impressive penetration capabilities, coherence, high resolution, and the detection of both micro and trace substances. Presently, across disciplines such as biomedicine, security inspection, agriculture, and artwork identification, researchers increasingly favour spectroscopic techniques tailored to specific substances (Figure 2).

Table 1: Summary of ex-vivo THz imaging studies.

Authors, Years	THz system	Imaging target	Results
Martin et al, 2016[4]	A continuous-wave THz imaging system working at 0.584 THz with circular polarization	Fresh tumor and normal human skin tissue specimens	Contrast between cancerous and normal tissues was found with a resolution of 0.15 mm
Bowman et al, 2016[5]	A pulsed THz imaging and spectroscopy system	Excised paraffin-embedded breast tissue with breast invasive ductal carcinoma	The carcinoma areas exhibited lower transmission and higher reflection than normal areas as defined based on pathology
Yamaguchi et al, 2016[6]	A reflection THz time-domain spectroscopy system	Fresh and paraffin-embedded tissues from a rat glioma model	A difference of 0.02 (0.8–1.5 THz) in the refractive index was found between glioma and normal area
Wahaia et al, 2016[7]	A continuous-wave THz imaging system working at 0.59 THz	Dehydrated human colon tissues	The imaging resolution reached 500 µm
Grootendorst et al, 2017[8]	A handheld THz pulsed imaging system	Freshly excised breast cancer samples	The identification accuracy of cancerous areas reached 75%
Bowman et al, 2018[9]	A pulsed THz imaging and spectroscopy system	Freshly excised murine xenograft breast cancer tumors	Comparison with pathology results showed an accuracy above 80%

Continued.

Authors, Years	THz system	Imaging target	Results
Cassar et al, 2018[10]	A pulsed THz imaging system with a reflection mode	Freshly excised breast tissue	The spatial resolution reached 1 mm
Vohra et al, 2018[11]	A pulsed THz imaging system with a reflection mode	Freshly excised and formalin/paraffin-fixed breast tumor tissues from a mouse model	Cancerous areas exhibited the highest reflection and agreed with the pathology results
Yeo et al, 2019[12]	A pulsed THz imaging system with a reflection mode	Paraffin-embedded malignant tissues in human lung and small intestine tissues	The adipose tissue area showed a lower refractive index and with a diffraction-limited spot size of ~360 µm at 1 THz
Okada et al, 2019[13]	A scanning laser THz near-field reflection imaging system	Paraffin-embedded human breast tissue	The spatial resolution reached 20 µm
Bowman et al, 2019[14]	A pulsed THz imaging and spectroscopy system	Freshly excised breast cancer tumors	The cancerous areas exhibited higher absorption coefficients and refractive indexes than normal tissues, and the resolution reached 200 µm

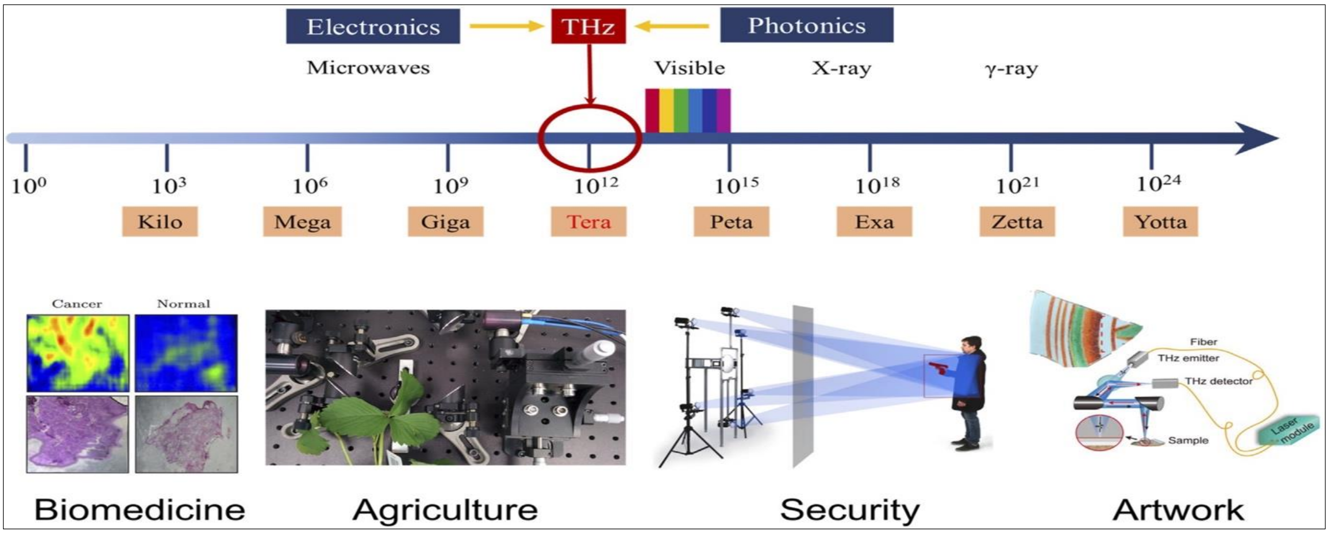

Figure 2: Terahertz spectroscopy and some typical applications. Reproduced with permissions. © 2013 Chinese Physical Society and IOP Publishing Ltd. © 2017 IEEE. © 2020 Springer Science Business Media, LLC.

WAY FORWARD

To propel the application of terahertz spectroscopy forward, the establishment of a more comprehensive THz spectrum database is imperative. Achieving this goal demands thorough investigations across diverse materials using terahertz spectroscopy, which will serve to augment and refine existing data. Nonetheless, it is essential to acknowledge the inherent limitations of THz waves, including constraints in penetration depth, cost, and resolution.

CONCLUSION

In summary, our review of recent research papers delves into the application of THz radiation for diagnosing and treating various diseases and conditions, with a primary focus on its medical implementation. This examination elucidates the comprehensive understanding and advantages of THz waves over conventional radiation sources, highlighting their potential to revolutionize medical diagnostics and treatment modalities.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Movsisyan M, Al-Rossais AA, Sayeed S, Movsisyan G. Applications of terahertz waves in medical diagnostics: a literature review. Int J Community Med Public Health 2024;11:2450-4.