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Perspective on the applications of terahertz imaging in skin cancer diagnosis

Hamza Abu Owida[1], Jamal I. Al-Nabulsi[1], Muhammad Al-Ayyad[1], Nidal Turab[2], Nawaf Alshdaifat[3]
[1]Medical Engineering Department, Faculty of Engineering, Al-Ahliyya Amman University, Amman, Jordan
[2]Department of Networks and Cyber Security, Faculty of Information Technology, Al-Ahliyya Amman University, Amman, Jordan
[3]Faculty of Information Technology, Applied Science Private University, Amman, Jordan

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ABSTRACT

Applications of terahertz (THz) imaging technologies have advanced significantly in the disciplines of biology, medical diagnostics, and non-destructive testing in the past several decades. Significant progress has been made in THz biomedical imaging, allowing for the label-free diagnosis of malignant tumors. Terahertz frequencies, which lie between those of the microwave and infrared, are highly sensitive to water concentration and are significantly muted by water. Terahertz radiation does not cause ionization of biological tissues because of its low photon energy. Recently, terahertz spectra, including spectroscopic investigations of cancer, have been reported at an increasing rate due to the growing interest in their biological applications sparked by these unique features. To improve cancer diagnosis with terahertz imaging, an appropriate differentiation technique is required to increased blood supply and localized rise in tissue water content that commonly accompany the presence of malignancy. Terahertz imaging has been found to benefit from structural alterations in afflicted tissues. This study provides an overview of terahertz technology and briefly discusses the use of terahertz imaging techniques in the detection of skin cancer. Research into the promise and perils of terahertz imaging will also be discussed.

Corresponding Author:

Nidal Turab
Department of Networks and Cyber Security, Faculty of Information Technology
Al-Ahliyya Amman University, Amman 19328, Jordan
Email: n.turab@ammanu.edu.jo

1. INTRODUCTION

The science and technology underpinning modern imaging has gone a long way since the invention of photography in the 1800s. Light's mysterious properties captivated the attention of many brilliant minds in the same century, leading to the formulation of Maxwell's equations, which describe the famous theory of electromagnetic. It is now commonly accepted that light is an electromagnetic wave and that the fraction of the electromagnetic spectrum occupied by visible light is quite small. During the 20th century, imaging technology expanded much beyond the visible spectrum, giving rise to a wide variety of cutting-edge methods including x-ray radiography, which makes use of subatomic-scale waves, and radar, which makes use of several-meter-scale waves [1]–[3].

The electromagnetic spectrum is being employed in many different ways. The terahertz (THz) spectrum is a subset of the electromagnetic spectrum that is undergoing significant growth and is the focus of this review. Despite the lack of a consensus on its precise definition, the THz band is typically thought to encompass the range of frequencies from 0.1 to 10 THz, or 3 mm to 30 m in wavelength see in Figure 1. There have been several important discoveries and practical applications identified in the study of THz waves in recent years [4], [5], making research into their use a very active and diverse topic in rapid development. The THz spectrum is a transitional region between the microwave and infrared regions, and it exhibits many of the same features and has many of the same potential applications as both of these other wavelength ranges. Among these is millimeter wave, which is viewed by many as the next step forward in wireless communications because of the increased data transfer rates it promises to provide in response to the ever increasing demand for this service [6]–[8].

THz radiation provides novel approaches to probing matter in the fields of sensing and imaging [9]. THz can penetrate most dielectric materials like microwaves do, providing a clear view of what's on the inside with high contrast. When compared to micro-waves, the THz wavelength is narrow enough to also provide significantly greater image resolution. And many molecular entities have distinctive spectral fingerprints in the THz region [10], [11].

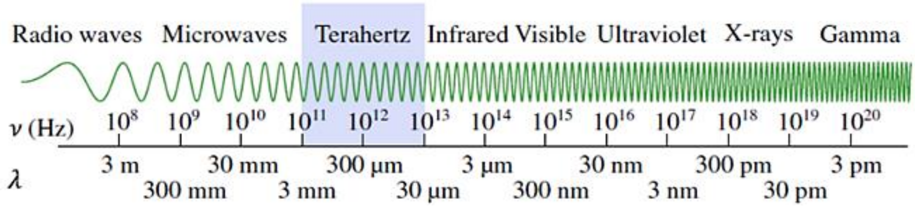

Figure 1. The portion of the electromagnetic spectrum that corresponds to terahertz

2. THE FUNDAMENTALS OF THZ IMAGING

THz radiation generation and detection technology has come a long way in the previous two decades. Currently, there are a number of commercially available systems, and many different groups throughout the world have built up their own THz systems. THz technologies fall into two classifications, continuous wave (CW) and pulsed, depending on the type of laser source being employed. Oscillatory methods can also be used to generate THz radiation, and they are typically cheaper than laser-based approaches [11], [12]. Figure 2 illustration of the THz imaging setup and the specimen arrangement.

Most CW systems have the capability of outputting either a single fixed frequency or several discrete frequencies. The settings on some of them can be adjusted. Photo mixing [11], free-electron lasers [13], and quantum cascade lasers [14] are all viable methods for generating CW THz radiation [11]. As an example of a CW THz system, depicts photo mixing two CW lasers in a photoconductor [15]. When two wavelengths above the bandgap are mixed together (in the visible or near-infrared), beating results. The "emitter" label describes the photo mixing equipment. Data structures and post-processing can be kept straightforward because the CW system's source spectrum is limited and occasionally only intensity information is of importance. Today, a whole CW system can be powered by laser diodes, allowing for its size and cost to be drastically reduced. Because of the information gaps that CW systems can cause, they are often only useful for applications that focus on a narrow range of frequencies [16]–[18].

The most well-known methods, based on photoconductive antennas, which calls for the use of a costly femtosecond laser. Pulsed THz imaging approaches use coherent detection to capture THz waves in the time domain, including both the intensity and phase information, which may then be used to extract spectrum and depth information about the target, because of this significant benefit, coherent THz imaging can be used in additional contexts [18]–[20]. The THz oscillator module consists of a Schottky diode detector, power amplifier for increasing beam power, wideband isolator for eliminating noise, passive tripler for increasing frequency, and horn antenna for signal transmission. Next, a pair of parabolic reflectors will focus the signal into the fiber while maintaining a relatively high extinction ratio. A polyethylene lens at the fiber's business end concentrates the terahertz radiation on the test specimen. To measure the intensity of the signal passing through the sample, a Schottky diode is used as a receiver. A Schottky diode is a semiconductor with a metal-semiconductor barrier; it is capable of rapid switching (within a millisecond), and it is especially sensitive to power fluctuations at low frequencies [21]–[23].

Changes in the biomolecular conformation of protein building blocks like helices and sheets are essential for many of the complex interactions at the molecular level. The dynamic fingerprints of THz frequency vibrations in ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) have been identified in recent years. Additionally, there has been a lot of interest in studying how water molecules interact with proteins. Biological water, also termed hydration water, is the water present in a protein-water network that influences the protein's structure and behavior. Weak attractive forces known as hydrogen bonds emerge between water molecules that have become hydrated and the side chains of proteins. These permit discrimination between the hydration water layer and bulk water, and they impact the dynamic relaxation characteristics of proteins. THz spectroscopy is able to identify the intermolecular effects of hydrogen bonding [24]–[27].

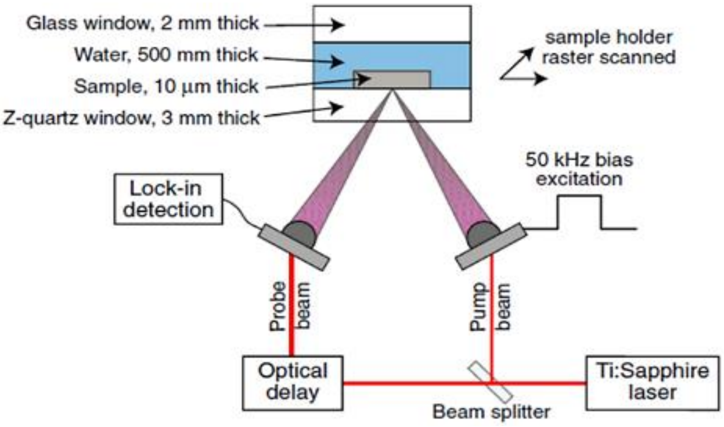

Figure 2. An illustration of the THz imaging setup and the specimen arrangement

3. THE THz IMAGING OF SKIN CANCER DETECTION

In theory, THz imaging might be used to assess for melanoma and the possibility for a reflection geometry THz imaging system to detect skin cancer without causing harm has been established by Woodward *et al.* [28] with capacity to detect basal cell carcinoma was originally demonstrated in ex vivo studies. Scar tissue and areas of inflammation are measured and the THz image shows a stark contrast to normal skin because they retain less water. This article will discuss the various techniques for tissue classification using time domain analysis. The terahertz contrast of basal cell carcinoma is positive compared to normal tissue, while that of inflammation and scar tissue is negative.

The epidermis, dermis, and subcutaneous layers that make up human skin and most basal cells can be found in the area where the basal layer and dermis meet. Research has demonstrated that prolonged exposure to ultraviolet (UV) rays can cause DNA damage in the basal layer, leading to uncontrolled cell division. A tumor formed from these unchecked cells is called basal cell carcinoma (BCC). Getting a BCC diagnosis quickly is crucial for effective treatment. Similarly to the way a tree's roots grow out just below the surface of the soil, BCC's geometry. Although the roots of a tree are not visible from the ground, the tree's trunk and branches are nonetheless essential components. Similar to how just a portion of a BCC's tumor will be visible on the skin; the tumor's lateral extent under the skin's surface will be invisible to the naked eye but is an integral aspect of the tumor that must be excised in order to eradicate the BCC [29]–[31]. Some tumors, according to previous studies, contain more water than normal tissues and the diseased skin exhibits different THz properties than healthy skin [32].

Non-melanoma skin cancers (basal cell and squamous cell skin cancers) have been studied by Zhang *et al.* [33], who used CW THz imaging to determine the intrinsic biomarkers for these tumors and their absorption frequencies. They used a CW system operating at 1.56 THz to determine the concentrations of several substances. The absorption frequencies of these substances were also examined in water suspension to make sure they could be detected in a liquid water setting. One of the results was that tryptophan, like water, is a useful indicator for identifying skin tumors. They determined that tryptophan absorbs at resonance at 1.42 and 1.84 THz [33], [34]. Although the latter are more efficient overall, they require cryogenic temperatures and are therefore less portable than the former and may have an impact on gene expressions due to their high peak-intensity. Improvements in THz spatial light modulation have allowed real-time imaging using room-temperature THz spectroscopy devices using compressive sampling methods. Compressive imaging employs the use of a single THz detector to read off a pattern imprinted onto the THz beam. To rebuild a THz image computationally, a rapidly shifting pattern is required. At present, silicon-based THz modulators are optimal for pattern generation because of their ability to be optically illuminated (resulting in photo modulation of the silicon) under digital mirror control [9], [28], [32]. Since skin cancer is becoming extremely prevalent, there is an urgent need to refine in vivo diagnostics and surgical techniques to better treat the disease. Patient morbidity is greatly exacerbated by resource waste caused by variables. There are limitations to the currently available methods for diagnosing and treating various diseases. Mohs micrographic surgery is the gold standard for removing skin cancer, but it is time consuming and expensive since tissue is taken and then checked under a microscope until the margins are clear. Excision would be more complete, surgeries would go more quickly, and reconstruction could be better planned if the extent of tumors could be assessed by THz imaging before surgery [32], [33], [35].

Because of its shorter wavelength, THz light is more ideally suited to identifying tissue abnormalities than other upcoming technologies like optical coherence tomography (OCT). In particular, because of the nature of the hydrogen bonds in water, THz waves are strongly absorbed by water [36]. While it is easier to attain higher resolution with optical light due to its shorter wavelength [k], this benefit comes at the expense of increased scattering (proportional to 1/k) and attenuation [37]. This limits the depth at which optical methods can image tissue. Although cancer in the gastrointestinal system can be detected with millimeter resolution. THz light is ideal because it provides both high resolution and deep penetration, and it is also sensitive to hydrogen bonds [32], [38].

Evidence from a 2004 case study by Owida *et al* [39] of individuals with basal cell carcinoma utilizing in vivo THz imaging revealed that this method could be used to detect cancer deep into the skin. Statistically significant differences in fundamental THz properties between freshly removed (excised) skin cancer tumors and healthy tissue were found in spectroscopic studies. These differences are thought to be primarily due to changes in the water content of the tissue [40]. Recently, in vivo measurements were taken of normal skin, precancerous moles called dysplastic nevi, and normal moles not affected by dysplasia. This research was conducted on four individuals by Zaytsev *et al.* [41] significant differences in appearance were discovered between the various forms of tissue.

THz light has a great sensitivity to water but a low penetration depth in tissue, making it challenging to use THz scanning to detect malignancies that are deep within the body. For these reason advancements in signal processing and THz instruments around the world are highly significant. Since THz light has a limited depth of penetration in living organisms, in vivo studies often only examine the skin, but ex vivo studies can detect and classify many cancers afterwards when the skin has been extracted [33], [34]. THz imaging was first used to detect malignant tissue in breast tissue samples removed from individuals with cancer in 2006. Findings from standard histological testing showed a moderate concordance with the THz image's pinpointing of the malignant location [42], [43].

Bajwa *et al.* [44] conducted an in vivo investigation evaluating the shift in water content of partially and fully islanded skin flaps to investigate the feasibility of using THz imaging to predict the outcome of reconstructive skin flaps. In the THz images, a statistically significant difference between the study groups was observed 24 hours after the treatment, however in the visible image, a difference did not emerge until 72 hours after the procedure. This means that THz imaging has the potential to provide faster in vivo information on the viability of skin flaps for reconstructive surgery. To study what happens to skin after it's been burned, Taylor *et al.* [45] used THz imaging on freshly harvested pig tissue. Under 10 sheets of gauze, they still found the burn. Osman *et al.* [46] measured THz point-spectroscopy from burns of varied severity in 2020 using a standardized in vivo porcine burn model. To describe each burn, we recovered two reflection hyperspectral parameters: spectral area under the curve between 0.1 and 0.9 THz and spectral slope. A linear combination of these two measures correctly identified deep partial- and superficial partial-thickness burns ($p=0.0159$) compared to vimentin immunohistochemistry, the gold standard for burn depth diagnosis. Researchers have employed THz imaging to examine the results of moisturizers on the skin. Ramos-Soto *et al.* [47] measured the amount of moisturizer that entered an excised sample of pig skin to determine the impact of common moisturizer ingredients.

The arrangement shown in for measuring the s- and p-polarization components at two incident angles may provide further diagnostic information. As a result, ability to observe birefringence in the skin scan (SC) at THz frequencies for the first time using four sets of spectral ratios that are mutually complimentary. After 30 minutes of occlusion, as shown in, the skin's optical properties alter, revealing a smoothing effect due to increased moisture during occlusion. In order to account for the measured birefringence, suggestion a model in which the SC is made up of coenocyte and lipid layers; this model was confirmed by the data. This paves the way for the possibility of employing THz imaging to study changes in cellular structure in addition to hydration changes in the skin [48]–[50]. The robust technique may increase the consistency of in vivo measurements of skin with THz light and the difference in THz response between the skins before and after applying three different types of moisturizers [51]. Stantchev *et al.* [52] demonstrated that a total-internal-reflection (TIR) geometry outperforms conventional transmission and reflection geometries in terms of operational efficiency. A THz modulator working in the efficient TIR geometry can be put in the near-field of skin or other biological samples, allowing for the creation of a single-pixel THz camera with sub-wavelength resolution.

Barr *et al.* [53] proved this concept by placing biological tissues on a TIR modulator and obtaining images with 700 lm resolution, despite the fact that the diffraction limited resolution for their k 2:15 mm wave source would have been 1:8 cm is an example of the images obtained using this method; the THz images show a distinct separation of fat and protein in the tissues. As they photoexcite silicon with an LED to change its conductivity, the resolution of their method is fundamentally constrained by the photocarrier diffusion dynamics. However, unlike optically based modulators, the resolution of electrically based THz modulators, in which an applied electric field changes the conductivity, will be set by the device manufacturing techniques rather than carrier diffusion dynamics [54]. In vivo investigations have hitherto been restricted to imaging the volar forearm, but this will change with the advent of high-speed THz imaging devices that can be integrated with robotics. Since skin cancer can develop everywhere on the bod including the back, leg, neck, and forehead a system capable of imaging these areas simultaneously with THz radiation is necessary for real-time imaging and detection of skin cancer [55], [56]. The difficulty lies in not only rapidly relocating the imaging system to each place of the body, but also successfully imaging the various complicated geometries present there. The Taylor lab has successfully imaged the eye without touching it using a THz device, but this only worked because of how similar everyone's eyes are [57]. In the case of skin cancer, the affected area may be elevated above the skin's surface, creating a curvature that is difficult to image with either a touch or noncontact method [32], [58].

4. THE THz IMAGING FOR SKIN CANCER DETECTION: PROSPECTIVE AND CHALLENGES

Spectroscopy reveals that proteins exhibit collective vibrational modes at terahertz (THz) frequencies, which are associated with biologically significant functions such as molecular folding and structural stability. Polar liquids, like water, also absorb within the THz range due to hindered molecular rotations and collective dynamic modes, crucially impacting biological interactions. This frequency region is particularly useful because many organic and biomolecular compounds, including pharmaceuticals, show distinct absorption spectra in the THz range, which can aid in identification and structural analysis. The specificity of these absorption features makes THz spectroscopy a promising tool for research in medicinal chemistry, molecular biology, and drug development.

The diffraction-limited spot size at THz wavelengths is comparable to the resolution of a laser printer from the 1990s (1.22 0=170 m at 2.160 THz, or 150 dots/in). One THz is roughly equivalent to the resolution of a high-quality computer monitor (70 dots per inch). In contrast to the much stronger Rayleigh scattering (proportional to f4) that prevails in the IR and optical because cell size is less than the wavelength, THz signals pass through tissue with only Mie or Tyndall scattering (proportional to f2). THz frequencies have very high absorption losses, which make it impossible to penetrate biological materials of any significant thickness. This is because most tissues are immersed in, dominated by, or kept in polar liquids. While a high absorption coefficient inhibits penetration into tissue, it also increases severe contrast between substances with lower or greater water content, which is useful for displaying distinct contrast in medical imaging. However, THz radiation is sensitive to water content, thus the use of fresh biological samples has its advantages and disadvantages while doing experimental research. To begin with, THz pictures may tell malignant tissues from healthy ones because to the water content. However, the distribution of the THz absorption by the water, which may be high enough to limit the THz penetration of the tissues, can impact the detection results. Pre-treatment of samples by freezing, formalin fixing, and paraffin embedding, may be useful in this situation. In addition, the soft tissue structure can be damaged because of the significant absorption of THz radiation by water if the thermal radiation impact of a sample is measured for too long in transmissivity imaging. It is essential to apply the aforementioned techniques to guarantee tissue attachment.

Biopsies are frequently used to diagnose tumors, but they can be a painful and lengthy process that also damages healthy tissue around the tumor's perimeter. Although X-ray computed tomography (CT) and magnetic resonance imaging (MRI) are also diagnostic tools for tumor disorders, they require larger radiation doses to be administered to the patient. Therefore, THz imaging has been an important area of study in recent years due to its quick imaging duration, lack of need for labelling, and reduced radiation exposures to patients. THz imaging allows for precise differentiation between tumors and healthy tissue, but just a few research have shed light on the mechanism responsible for this contrast. The significant absorption of THz radiation by water within the organism is a key cause for their shallow penetration. Since THz radiation is non-invasive, it can only be used for in vivo imaging, with the exception of skin cancer. Currently, tumor resection margins are determined using histology, which is a time-consuming but reliable method. Because of this, ex vivo THz measurements sometimes include tissue freezing, which might result in structural damage.

Because of this, there are still challenges that biomedical THz imaging systems need to conquer before they can be used in clinical settings. Real-time observation and recording detectors for biological samples are challenging to build because THz array detectors lack high sensitivity, dynamic range, and pixels. Diffraction-limited spatial resolution and high-quality THz images are currently unavailable due to a lack of versatile and flexible THz beam shaping devices and THz waveguides, which carry lossless signals to tissues. Tissue sample activity cannot be reliably preserved during THz imaging.

THz frequencies are incapable of penetrating biological materials of any substantial thickness due to the extremely high absorption losses at these frequencies. This is due to the fact that polar liquids are used for preservation purposes by the vast majority of tissues, or that these liquids play a significant role in the environments in which these tissues are found. Medical imaging can benefit from the great contrast between compounds with low and high-water content because of the high absorption coefficient that inhibits chemicals from penetrating tissue. The advantages and disadvantages of the THz imaging approach are broken down and summarized in Table 1.

Table 1. The advantages and disadvantages of the THz imaging approach

Advantages	Disadvantages
Safe and nonionizing radiation	Poor signal-to-noise ratio
penetrate many materials due to the long wavelength	Low-brightness THz radiation
Simpler and more stable	Low contrast between healthy and pathological tissues
Real-time detection at room temperature	Poor source performance

5. CONCLUSION

THz imaging is currently in its early phases of development, but it has a lot of potential to become an important imaging technology in the future, especially for the diagnosis of cancer. It is possible to use the protein's innate sensitivity to water as a natural contrast agent, in addition to applying nanoparticles and IR light, in order to strengthen the contrast between water and cancer cells. This last technique is particularly interesting since it will be feasible to obtain micron resolution by combining THz imaging with IR illumination. This, in turn, will make it possible to examine additional applications. Patients will be able to move at their own pace during imaging thanks to technological improvements in THz imaging that will eventually make it possible to image in real time. The data obtained from this endeavor will be put to use in the development of classification algorithms, which will enable real-time diagnosis and fundamentally alter the approach taken to treating cancer.

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BIOGRAPHIES OF AUTHORS

Hamza Abu Owida Ph.D. in biomedical engineering, assistant professor at the Medical Engineering Department, Al-Ahliyya Amman University, Jordan. Research interests focused on biomedical sensors, nanotechnology, and tissue engineering. He can be contacted at email: h.abuowida@ammanu.edu.jo.

Jamal I. Al-Nabulsi Ph.D. in biomedical engineering, professor at the Medical Engineering Department, Al-Ahliyya Amman University, Jordan. His research interests are biomedical sensors, digital signal processing, and image processing. He can be contacted at email: j.nabulsi@ammanu.edu.jo.

Muhammad Al-Ayyad Ph.D. in electrical engineering, biomedical instrumentation, associate professor at the Medical Engineering Department, Al-Ahliyya Amman University, Jordan. His research interests are big home healthcare settings, medical rehabilitation instrumentation, biomedical measurements. He can be contacted at email: mayyad@ammanu.edu.jo.

Nidal Turab Ph.D. in computer science professor at the Networks and Cyber Security Department, Al-Ahliyya Amman University, Jordan. His research interests include WLAN security, computer networks security and cloud computing security, eLearning and internet of things. He can be contacted at email: n.turab@ammanu.edu.jo.

Nawaf Alshdaifat received the B.Sc. degrees in computer science from AL al-Bayt University and M.Sc. degrees in computer science from the University of Jordan, Jordan, in 2002 and 2011, respectively, and the Ph.D. degree in Computer Science from Universiti Sains Malaysia, Malaysia, in 2023. His research interests include deep learning and machine learning. He can be contacted at email: n_alshdaifat@asu.edu.jo.