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# RECENT DEVELOPMENTS OF TERAHERTZ TECHNOLOGY IN BIOMEDICINE

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Terahertz technology is continually evolving and much progress has been made in recent years. Many new applications are being discovered and new ways to implement terahertz imaging investigated. In this review, we limit our discussion to biomedical applications of terahertz imaging such as cancer detection, genetic sensing and molecular spectroscopy. Our discussion of the development of new terahertz techniques is also focused on those that may accelerate the progress of terahertz imaging and spectroscopy in biomedicine.

## 1. Introduction

Terahertz technology has recently created much interest in the scientific community. Terahertz ($1\,\text{THz} = 10^{12}\,\text{Hz}$) radiation lies between the microwave and infrared regions of the electromagnetic spectrum (EM). The terahertz region is typically defined as ranging from 0.1 to 10 THz in frequency or $3.33\,\text{cm}^{-1}$ to $33.3\,\text{cm}^{-1}$ in wavenumbers. In wavelength terms this corresponds to 3 mm to $30\,\mu$m. This region has only recently been explored due to a previous lack of terahertz sources. In fact, it was commonly referred to as the 'terahertz gap' before advances in semiconductor physics enabled the so-called gap to be bridged.

From the low frequency end of the EM spectrum, power from sources based on electronic devices, such as those used in mobile phones, rolls off at frequencies beyond a few hundreds of GHz as the circuits become unresponsive. Although it is theoretically possible to use frequency multipliers to obtain frequencies above this, it is challenging due to low efficiencies. In contrast, from the high frequency end of the EM spectrum, high energy radiation such as gamma ray or x-ray is produced by transitions in the atomic nucleus or inner electrons; while ultraviolet, visible and infrared radiation is typically associated with transitions between atomic and molecular states. Sources based on these inter-band transitions, such as semiconductor laser diodes, have historically only extended down to the order of tens of THz, thus leaving a gap where neither electronic nor optical mechanisms dominated.

However, in 1975, David Auston at AT&T bell Laboratories developed a photoconductive emitter gated with an optical pulse that led towards bridging the terahertz gap — the 'Auston switch' emitted broadband terahertz radiation up to 1 mW.[1] In the following decades many improvements in the generation and detection of coherent terahertz radiation enabled terahertz time domain spectroscopy and imaging techniques to be pioneered.

Figure 2 is a schematic diagram of a typical terahertz pulsed imaging system in reflection geometry. In this example the terahertz radiation is both emitted and detected by low-temperature-grown GaAs photoconductive devices. A near infrared femtosecond pulsed laser is used to excite the carriers in the photoconductive emitter, and the subsequent relaxation of these carriers results in the emission of terahertz radiation. As illustrated in Fig. 2, the laser beam is separated into the pump and probe beams by a beam splitter. The pump beam is focused onto the photoconductive emitter and a silicon lens is used to focus the output beam onto the off-axis parabolic (OAP) mirrors. Similarly a silicon lens is used in conjunction with the photoconductive detector. The terahertz pulses reflected from the sample are re-collimated using another pair of OAP mirrors and focused onto a photoconductive receiver. By sweeping the optical delay through the entire terahertz pulse (at for instance a rate of 15 Hz) the time-domain terahertz waveforms can be

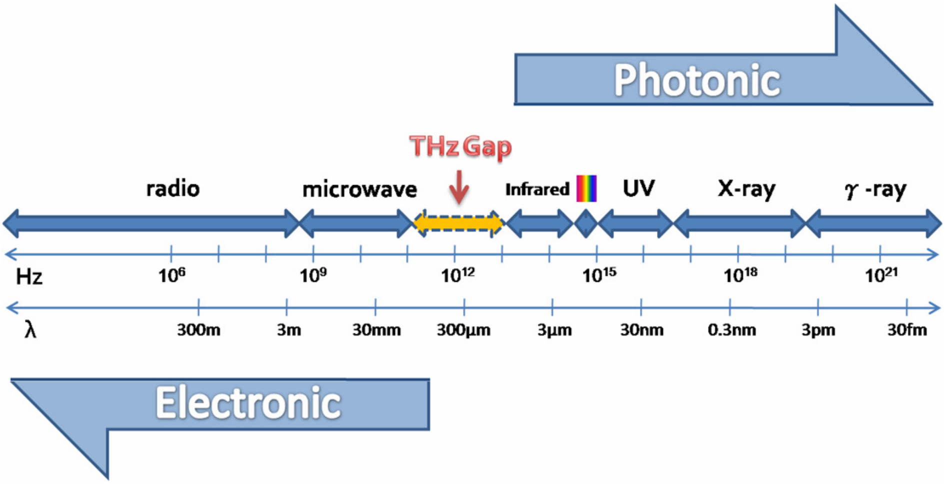


Fig. 1. The terahertz region of the electromagnetic spectrum lies between the infrared and microwave region, where neither photonic nor optical mechanisms dominate.

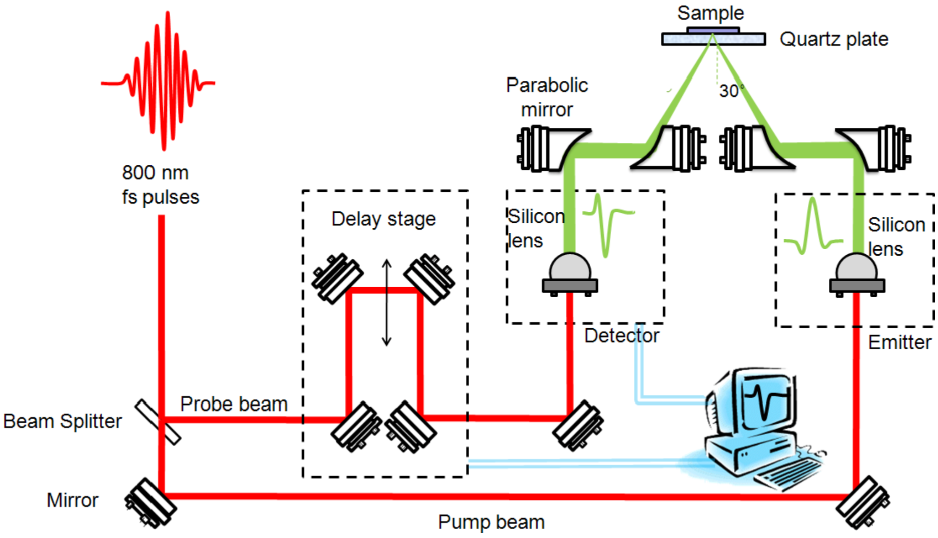
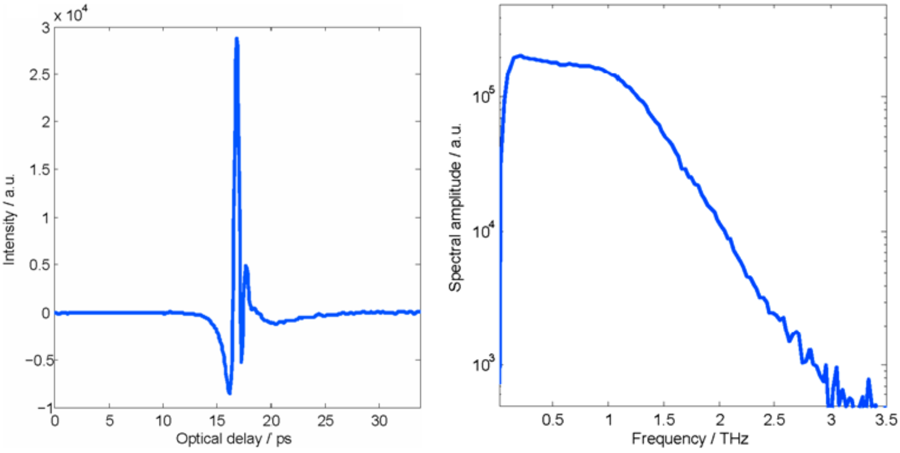


Fig. 2. Schematic diagram of a terahertz pulsed imaging system with photoconductive detection and emission in reflection geometry.



(a) (b)

Fig. 3. Time domain (a) and frequency domain (b) nitrogen-purged reflection geometry measurements of a mirror.

obtained. The entire terahertz optics can be raster scanned in the x–y plane to form an image with attainable resolutions at 1 THz of 350 $\mu$m laterally and typically 40 $\mu$m axially.

A typical reflected waveform from a mirror placed on the quartz imaging plate is depicted in Fig. 3(a). This time domain waveform can be Fourier transformed into the frequency domain (Fig. 3(b)) to obtain spectral information. In this case we see that we have a usable bandwidth of about 3 THz. Since there are tails of strong water absorptions extending into the terahertz regime, it is necessary to remove the moisture in the air surrounding the terahertz optics. Nitrogen gas is a popular choice for this and can be used at a rate of about 5 liters per minute to purge the air (depending on the set up). It is also possible to generate terahertz radiation using optical heterodyne conversion, or photomixing, which can be achieved using two continuous wave lasers.[2] This method produces a single frequency output which is limiting when looking for spectral features. Therefore, our review focuses on pulsed terahertz imaging methods due to their broadband output enabling us to investigate more spectral features.

Compared to other parts of the electromagnetic spectrum, which have already been extensively studied and have led to a variety of applications, the terahertz gap is still a relatively a new region for scientists and engineers to explore. Terahertz technology has been probed for applications in many fields such as biomedicine,[3] telecommunication,[4] public security,[5] astronomy[6] and condensed-matter physics.[7] Several unique features of terahertz radiation are advantageous compared to other frequencies. For instance, terahertz radiation could be suitable for security applications as it can penetrate common packaging materials such as plastic, paper, wood and ceramics. Moreover, terahertz spectroscopy can detect intermolecular vibrations such as hydrogen bonds that are present in biological molecules and can thus be used for unique spectral fingerprinting of absorptions only found in the terahertz regime. Indeed, terahertz radiation is very sensitive to water content. For example, early experiments utilizing terahertz imaging were demonstrated by Hu and Nuss in 1995[8] where they reported a terahertz image showing different water concentration in a leaf. Their research into other biological samples also mapped out the contrast of meat and fat within a piece of bacon. Their work inspired the idea to apply terahertz imaging on biomedicine. Since then, many studies have been carried out to explore the potential applications in this field. The sensitivity to water allows terahertz radiation to distinguish tissues with different water content. Because it is so strongly attenuated by water, it can typically only travel a few millimeters in tissue. This limitation can be overcome by doing reflection imaging, and in this way great detail can be obtained about the surface of the sample. For example terahertz images of skin cancer (basal cell carcinoma) have shown contrast between the diseased and healthy tissue. There are also some researchers exploring its application on differentiating between different cells and organs.[9]

Since the energy level of 1 THz is only about 4.14 meV (which is much less than that of x-rays), it does not pose an ionization hazard unlike x-ray radiation, and thus it lends itself to medical applications. Research into safe levels of exposure has also been carried out through studies on keratinocytes[10] and blood leukocytes[11,12] neither of which have revealed any detectable alterations. In this review we summarise recent terahertz research carried out in biomedical related areas including: terahertz spectroscopy of biomolecules and pharmaceuticals; terahertz imaging of organs and tissues; and the development of terahertz systems.

## 2. Terahertz Spectroscopy

There has been an increasing interest in terahertz spectroscopy of biologically related molecules within the last few years and more and more terahertz spectra are being published. The potential of using terahertz spectroscopy to do label free genetic sensing has been investigated by several groups and the results look promising. Additionally, research on pharmaceuticals has shown that terahertz spectroscopy can distinguish polymorphic forms[13] and monitor molecular dynamics in sugars[14] and proteins.[15]

### 2.1. *Biomolecules*

Genetic engineering is undoubtedly beneficial to the advance of medical science, such as gene diagnosis; gene therapy; and identification of gene mutations and of viral and bacterial genetic signatures. Fluorescent labeling[16] is one of the key and traditional methods for genetic analysis by identifying the genetic bases of DNA (adenine (A), cytosine (C), guanine (G) and thymine (T)). The principle of fluorescent labeling is to first mark the unknown target DNA sequence with fluorescent dyes, then the target sequence binds with a known probe sequence and hybridization occurs when there are matching pair bases. Such hybridization can be determined by optical detection. However, this fluorescent labeling method is a slow process and the fluorescent marker may modify the conformation of DNA sequence thus affecting the precision of detection. Therefore, introducing label-free gene sensing with terahertz could be an alternative approach to achieve a more rapid and precise genetic analysis methodology.

Bolivar *et al.* demonstrated that the label-free sensing technology can be achieved using either free-space or waveguide on-chip THz setups to detect the difference in complex refractive index among hybridized and denatured DNA samples.[17] Comparing the complex transmission difference, they found that hybridized samples resulted in a larger value than the denatured ones. In order to increase the sensitivity, they had repeated the test with resonator structure wave-guided in place of free-space medium. Both experiments proved that the binding states of DNA can be determined by label-free sensing with terahertz radiation.

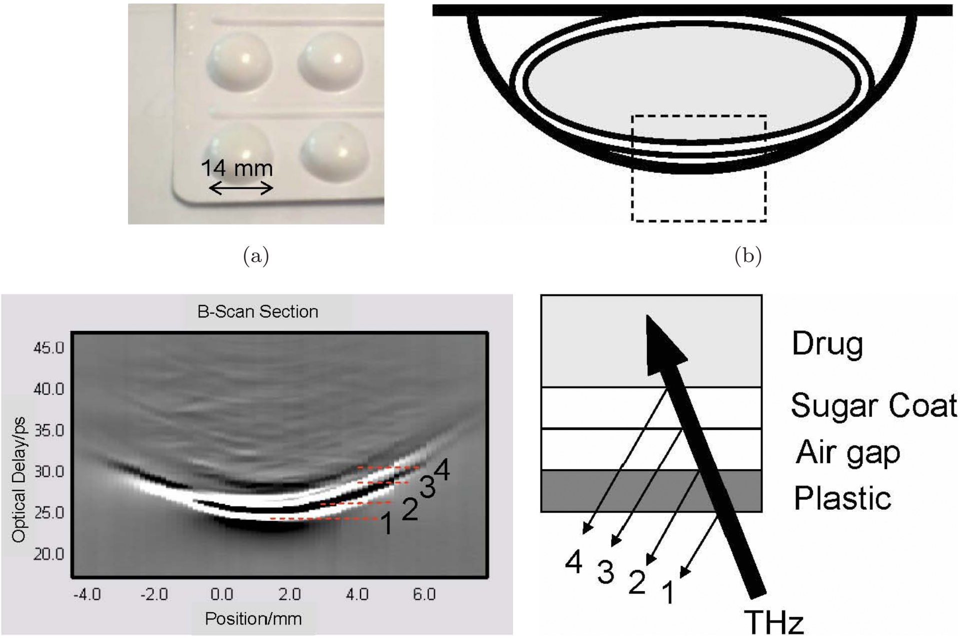
Shen *et al.* demonstrated that terahertz time domain spectroscopy could be used to distinguish between purine and the DNA base adenine.[18] Furthermore, they have observed absorption peaks in the terahertz region for the poly-crystalline nucleosides, and mapped the evolution of these absorption features continuously between 4 and 295 K.[19] Additionally, a recent study conducted by Fischer *et al.* showed that ribonucleic acid (RNA) containing different DNA bases can be distinguished by terahertz techniques.[20] They used terahertz time-domain spectroscopy to measure the dielectric function of two artificial RNA single strands, composed of polyadenylic acid (poly-A) and polycytidylic acid (poly-C). They found a significant difference in the absorption between the two types of RNA strands.

In the above examples there may only be subtle differences between the molecular structures, but because they affect the intermolecular interactions and weak interactions such as van der Waals forces that have terahertz fingerprints, they can be detected using terahertz spectroscopy. To this end Support Vector Machine (SVM) learning algorithms have been applied to obtain effective discriminations between RNA samples and various powdered substances;[21] and the use of THz frequency filters has been investigated to measure the hybridization state of overlaid DNA films.[22]

### 2.2. *Pharmaceuticals*

Terahertz spectroscopy is able to distinguish between polymorphic forms. For instance, carbamazepine, a drug primarily used to treat patients with psychological disorders, converts from form III to form I in a temperature dependent process. The dynamics of this conversion process were monitored using terahertz spectroscopy by Zeitler *et al.*[23] Similarly, Zeitler *et al.* also studied sulfathiazole, a drug which is effective against many pathogenic microorganisms. They found that terahertz spectroscopy was able to reveal distinct spectra for each of the five know polymorphic forms and they related the phase transitions observed to the thermal data. From their investigations we see that terahertz spectroscopy is able to provide complimentary information to other techniques such as Raman spectroscopy, and also be used to detect impurities. Being able to determine the polymorphic form of a drug is very important as it can significantly affect the bioavailability and physiochemical response.[24]

The unique capabilities of terahertz pulsed imaging and spectroscopy could also be used to inspect drugs,[25] both for the quality of the drug substance, and also for the quality of tablet coatings. Many drugs are administered in tablet form and have a sugar coating to protect the active ingredients. The uniformity of this coating can be measured using terahertz pulsed imaging.[26] This is because terahertz radiation is able to penetrate the tablet coating without damaging the sample. The separations of the reflections from the layers in the tablet can be used to check the quality of the coatings. Additionally, since terahertz radiation can penetrate plastic, we can measure the tablet through the packaging. Figure 4(a) is a photograph of a tray containing 200 mg of sugar coated ibuprofen tablets. The schematic diagram in Fig. 4(b) depicts how the tablet sits in the packaging, and shows that in places there is an air gap between the tablet and the plastic. Thus in the dashed box in Fig. 4(b) there are four main layers that will reflect the terahertz light: plastic, air, sugar coating and the core of the ibuprofen drug. We lowered the packaged tablet into the focus of terahertz beam and took an image from the plastic side as indicated in Fig. 4(d). Figure 4(c) is an intensity map of the time-domain reflected waveforms along a horizontal slice from the image. This is referred to as a B-scan. Due to the differences in optical properties of the four layers, there are reflections



(a) (b)

(c) (d)

Fig. 4. Photograph of a tray containing sugar coated 200 mg ibuprofen tablets; (b) Schematic diagram of packaged tablet geometry; (c) terahertz b-scan image of tablet through the packaging; and (d) schematic diagram of the layers in the dashed box of (b) which cause the corresponding numbered reflections seen in (c).

at each interface. For instance the interface between the air gap and sugar coating results in the reflection seen at label 3 in Fig. 4(c), in this way we can see the position and structure of the tablet inside the packaging. To exploit this ability of terahertz imaging, a terahertz imaging system has been specially designed by TeraView Ltd to image tablets and it has recently become commercially available.

## 3. Terahertz Medical Imaging

### 3.1. *In vivo imaging*

Due to the limited penetration depth of terahertz radiation in tissue, in vivo terahertz studies to date have focused on imaging skin on areas which are easily accessible. For instance measurements of the skin on the forearm and the hand have been used to determine hydration levels.[27] Additionally, the thickness of the stratum corneum can be determined from the optical delay between the reflection off the top surface of the stratum corneum and the reflection off the stratum corneum-epidermis interface.[28] In vivo images of basal cell carcinoma have also shown contrast between diseased and healthy tissue.[28,29] Since water has strong absorptions at THz radiation frequencies[30] and tumours tend to have different water content from normal tissue, a likely contrast mechanism is variation in water content.

### 3.2. *Skin cancer*

One of the potential applications for terahertz imaging in the medical field is to detect or characterize disease. Terahertz imaging has shown tissue contrast for *in vivo* and *in vitro* identification of abnormalities, hydration levels, and subdermal probing.[31] Fixed excised samples, for instance alcohol perfused,[32] formalin fixed,[33,34,35,36] or freeze dried and wax mounted[37] have been studied with a view to determine the underlying contrast mechanisms. The fact that terahertz images of dehydrated samples also showed contrast suggests that there are also some structural differences which terahertz imaging is able to detect. Due to terahertz imaging being more suitable for surface imaging, one of the first medical applications to be investigated was basal cell carcinoma (BCC).[38,39]

Basal cell carcinoma is the most common form of cancer, with about a million new cases estimated in the U.S. each year.[40] Mohs' micrographic surgery (MMS) is a surgical procedure during which histology sections are also taken so as to identify and characterize the tumour margins. Reading the histology of biopsy samples is regarded as the "gold standard" for the diagnosis of tumors and is routine before the operation, but it is time consuming and expensive. Therefore it is worthwhile to investigate if terahertz imaging could be used to diagnose and detect the margins of BCCs. Work by Wallac *et al.* has highlighted the potential advantages of being able to use terahertz imaging to study skin cancer *ex vivo* in time-domain by a Terahertz Pulsed Imaging system used in reflection geometry.[38] The diseased tissue showed an increase in absorption compared to normal tissue, which was attributed to either an increase in the interstitial water within the diseased tissue or a change in the vibrational modes of water molecules with other functional groups. Woodward *et al.* also produced terahertz images of BCC using parameters extracted in the frequency-domain and this provided complementary information to the images produced using time-domain techniques.[41]

P. Knobloch *et al.* imaged histo-pathological samples including the larynx of a pig and a human liver with metastasis.[37] Their terahertz measurements showed that different types of tissue can be clearly distinguished in terahertz transmission images, either within a single image or by a comparison of images obtained for different frequency windows.

### 3.3. *Breast cancer*

Breast-conserving surgery is another area of medicine which may benefit from terahertz imaging. In a similar way to how terahertz imaging could assist the planning of skin cancer surgery, Fitzgerald *et al.* have investigated the use of terahertz imaging to aid the removal of breast cancer intra-operatively.[42] In particular, they study the feasibility of terahertz pulsed imaging to map the tumour margins on freshly excised human breast tissue. Good correlation was found for the area and shape of tumour in the terahertz images compared with that of histology. They have also performed a spectroscopy study comparing the terahertz optical properties (absorption coefficient and refractive index) of the excised normal breast skin and breast tumour. Both the absorption coefficient and refractive index were higher for tissue that contained tumour and this is a very positive indication that terahertz imaging could be used to detect margins of tumour and provide complementary information to techniques such as infrared and optical imaging, thermography, electrical impedance, and MR imaging.[43,44]

### 3.4. *Dental caries*

One of the first potential applications of terahertz to medicine to be investigated was dental imaging. Terahertz radiation is able to penetrate through enamel and dentine and early studies have shown that it is also able to detect caries in *ex vivo* samples.[45] The structure of a healthy tooth is divided into three layers the outermost layer is highly mineralized enamel and this surrounds the dentine layer (which is less mineralized). The center-most layer is a soft tissue pulp. Early caries is a result of mineral loss from the enamel and this causes a change in the refractive index within the enamel. This change in refractive index means that small or subsurface lesions not visible to the naked eye can be identified. Crawley *et al.* presented results for the detection of early stage caries in the occlusal enamel layer of a range of human tooth cross sections using TPI system. Pickwell *et al.* then investigated the correlation of the refractive index changes with mineral loss and found that terahertz imaging was also able to measure the depth of more substantial demineralisation. The benefit of early detection is that the initial stages of demineralization are reversible, and so the need for and discomfort of drilling could be removed.

### 3.5. *Simulation of terahertz radiation in tissue*

Simulating the interaction of terahertz radiation with normal and cancerous tissue is a key step towards understanding the origin of contrast in terahertz images of skin cancer. Since tissue is largely composed of water, Pickwell *et al.*[46] developed a finite difference time domain simulation (FDTD) model, incorporating Maxwell's equations and Debye theory, to describe the propagation of terahertz radiation through water. (Debye theory couples the relaxation of the polarization to the electric field.) Water has two dominant relaxation modes in the terahertz region and so a "double" Debye model was used. They entered the double Debye parameters (which were extracted from experimental data) into the FDTD model to predict the shape of the waveforms reflected off water and found excellent agreement. The model was the applied to normal tissue and basal cell carcinoma.[47] They found good agreement of the model with real data, but with some discrepancies, which can be explained by assumptions in the model, such as requiring homogenous layers, and physical sample differences in ex vivo and *in vivo* measurements. An alternative approach to model tissue phantoms was taken by Walker *et al.* They modeled the terahertz radiation as an ensemble of photons using Monte Carlo methods and also found good agreement with experimental data.[48]

## 4. Terahertz Technologies — Present and Future

In this final section we outline the cutting edge terahertz technologies that could potentially lead to more applications in biomedical and biological fields. Although many *ex vivo* biological terahertz studies have given promising results, there is still a long way to go before terahertz imaging becomes an established medical imaging tool. One limitation for human *in vivo* imaging is the shallow penetration depth of terahertz radiation in tissue, this restricts reflection imaging to the sample surfaces. To overcome this, terahertz probes and endoscopes are being designed and innovative development of terahertz components is progressing rapidly.

### 4.1. *Terahertz endoscopy*

In most of the existing terahertz systems the terahertz waves propagate in free space. These systems usually use a set of lenses and mirrors to guide, focus and collimate the terahertz radiation. Dry air is a very good transmission medium for terahertz propagation. However there are many biological samples of interest that are not readily accessible by a line-of-sight beam. Terahertz wave-guiding may enable investigation of such samples.

When guiding terahertz radiation in different kinds of media, the key issue is how to achieve low loss and low dispersion during the propagation and coupling of terahertz radiation. Middleman's research team at Rice University used their Y-splitter waveguide simply made of bare wire to construct a terahertz endoscope.[49] Its success was demonstrated by imaging the inside of a glass flask and interior of a metal tube. The attenuation coefficient weighted by the pulse power spectrum of the waveguide was reported to be less than $0.03\,\text{cm}^{-1}$ which is very low. This confirms there is great potential to use the bare metal for a terahertz waveguide. Grischkowsky *et al.* have also investigated terahertz waveguiding and tested many other materials and geometries including hollow metallic waveguides (circular and retangular),[50,51] sapphire fiber waveguides[52] and plastic ribbon waveguides[53] to name but a few. Once fully developed, terahertz endoscopy may be able to detect cancers of organs such as the colon and esophagus.

### 4.2. *Terahertz microscopy*

Ryotaro *et al.* at Osaka University developed a reflection geometry scanning probe laser terahertz emission microscopy system.[54] In their system the excitation beam had a diameter of $5\,\mu$m and was irradiated from the vicinity of the surface by an optical-fiber probe. An image of an operational amplifier that was active in an electronic circuit was used to demonstrate the performance of the system — the exact location of the photoexcited area was pinpointed. The spatial resolution of the system was reported to be less than 4 $\mu$m.

### 4.3. *Near field imaging*

Near field imaging is based on the concept of forcing a wave through an aperture smaller than the wavelength of the radiation used. The distribution of the radiation directly behind the aperture is a function of the aperture diameter rather than the wavelength of the radiation and thus sub-wavelength structures can be resolved in close proximity to the aperture. It is called "near field" because these structures must be in the near field, i.e. within one or two wavelengths of the aperture. These principles are well established in scanning tunneling microscopy[55] where a very sharp point is used as the aperture.

Recently, near field imaging techniques have been applied to terahertz imaging. The diffraction limited spatial resolution of conventional terahertz imaging is around 1 $\mu$m to 3 mm. Schade *et al.* used the stable coherent synchrotron radiation terahertz source at BESSY (Berlin) for scanning near-field microscopy in the terahertz region and achieved spatial resolution below the diffraction limit on biological samples.[56] The extremely brilliant source was used to compensate for the intensity losses due to confining the terahertz radiation. Impressively, nanometer resolution has also been achieved using near field methods in terahertz imaging.[57]

Non-contact subwavelength terahertz measurements have recently been made by Cunningham *et al.*[58] They used on-chip waveguides to perform terahertz evanescent field microscopy. The pulsed terahertz radiation was generated and detected by photoconductive LT-GaAs devices, however these devices were then integrated into a terahertz microstrip circuit so as to guide the evanescent electric field generated by the LT-GaAs emitter to the sample of interest. The sample was mounted on a moveable stage directly above the microstrip. Two band stop filters were also incorporated into the microstrip circuit (centered at 260 and 600 GHz) with dimensions $5 \times 82$ and $5 \times 194\,\mu\text{m}^2$. They yielded an active area three orders of magnitude smaller than the diffraction limited spot size of typical free space systems (1 mm$^2$) and lateral resolutions down to 20 $\mu$m were achieved. Due to the small active area, this method could potentially be used to do terahertz spectroscopy on nanolitre volumes of samples such as DNA.[59]

Another way to improve the resolution is to use a superlens. In conventional imaging techniques, evanescent components are lost at the image plane. Their intensity exponentially decreases with distance along an optical path of length of the order of the wavelength of light. The evanescent waves carry sub-wavelength information that can be used to overcome the diffraction limit. A material with negative permittivity and negative permeability not only is able to focus propagating waves just as normal lenses do, but it can also amplify evanescent waves such that all orders of diffracted propagating waves and evanescent waves can be collected at the image plane.[60] Such materials are thus referred to as superlenses. To apply superlensing to terahertz imaging, it has been found that it is only necessary for the lens material to have negative permittivity.[61] Gold and other metals have this property and recent research has been carried out to use thin metal films to enhance the evanescent waves in terahertz imaging.[62] Superlensing can also be achieved using thin slabs of polar crystals, or even by artificial media such as metamaterials and photonic crystals.[63]

### 4.4. *Terahertz computed tomography*

The usual geometries used for terahertz imaging to date are reflection (as illustrated in Fig. 2 with an angle of incidence of 30°) and transmission in which the terahertz is incident perpendicular to the sample and detected after passing through the sample. Pearce *et al.* at Rice University[64] have developed a technique which they call terahertz wide aperture reflection tomography (WART) in which reflection geometry is employed over a variety of incident angles by rotating the sample. From the set of back reflected waveforms, computational tomography algorithms were used to reconstruct the edge map of the sample's cross-section. In a similar way to x-ray CT image capturing methods, by scanning at different heights multiple cross-section images can be put together to reconstruct a three-dimensional (3D) image. Furthermore, this image will also contain terahertz frequency spectral information, so effectively a four dimensional data set is achieved.[65]

## 5. Conclusion

In this review we have introduced terahertz pulsed imaging as a technique with potential applications in medicine and pharmaceuticals. We have briefly looked at some examples of terahertz imaging and spectroscopy and have highlighted the benefits of the unique spectral information which can be obtained. Terahertz technologies have continually advanced since the development of the Auston switch and in this article we have endeavored to give the reader a comprehensive picture of the terahertz status quo.

## References

1. D. H. Auston, "Picosecond Optoelectronic Switching and Gating in Silicon," *Applied Physics Letters* **26**, 101–103 (1975).
2. Ian S. Gregory, Colin Baker, William R. Tribe, Ian V. Bradley, Michael J. Evans, Edmund H. Linfield, A. Giles Davies and M. Missous, "Optimization of Photomixers and Antennas for Continuous-Wave Terahertz Emission," *IEEE Journal or Quantum Electronics* **41**, 717–728 (2005).
3. E. Pickwell and V. P. Wallace, "Biomedical applications of terahertz technology," *Journal of Physics D-Applied Physics* **39**, R301–R310 (2006).
4. T. Kleine-Ostmann, K. Pierz, G. Hein, P. Dawson and M. Koch, "Audio signal transmission over THz communication channel using semiconductor modulator," *Electronics Letters* **40**, 124–126 (2004).

5. Y. C. Shen, T. Lo, P. F. Taday, B. E. Cole, W. R. Tribe and M. C. Kemp, "Detection and identification of explosives using terahertz pulsed spectroscopic imaging," *Applied Physics Letters* **86**, - (2005).
6. C. K. Walker, C. K. Walker and C. A. Kulesa, "Terahertz astronomy from the coldest place on earth," *Infrared and Millimeter Waves and 13th International Conference on Terahertz Electronics, 2005. IRMMW-THz 2005. The Joint 30th International Conference on* **1**, 3–4 Vol. 1, 2005.
7. S. N. Taraskin, S. I. Simdyankin and S. R. Elliott, "The atomic charge distribution in glasses obtained by terahertz spectroscopy," *Journal of Physics-Condensed Matter* **19**, - (2007).
8. B. B. Hu and M. C. Nuss, "Imaging with Terahertz Waves," *Optics Letters* **20**, 1716–& (1995).
9. D. M. Mittleman, R. H. Jacobsen and M. C. Nuss, "T-ray imaging," *Ieee Journal of Selected Topics in Quantum Electronics* **2**, 679–692 (1996).
10. R. H. Clothier and N. Bourne, "Effects of THz exposure on human primary keratinocyte differentiation and viability," *Journal of Biological Physics* **29**, 179–185 (2003).
11. E. Berry, G. C. Walker, A. J. Fitzgerald, N. N. Zinov'ev, M. Chamberlain, S. W. Smye, R. E. Miles and M. A. Smith, "Do in vivo terahertz imaging systems comply with safety guidelines?," *Journal of Laser Applications* **15**, 192–198 (2003).
12. O. Zeni, G. P. Gallerano, A. Perrotta, M. Romano, A. Sannino, M. Sarti, M. D'Arienzo, A. Doria, E. Giovenale, A. Lai, G. Messina and M. R. Scarfi, "Cytogenetic observations in human peripheral blood leukocytes following in vitro exposure to THz radiation: A pilot study," *Health Physics* **92**, 349–357 (2007).
13. J. A. Zeitler and D. A. Newnham, Taday, Philip F., Threlfall, Terry L., Lancaster, Robert W., Berg, Rolf W., Strachan, Clare J., Pepper, Michael, Gordon, Keith C. and Rades, Thomas "Characterization of temperature-induced phase transitions in five polymorphic forms of sulfathiazole by terahertz pulsed spectroscopy and differential scanning calorimetry," *Journal of Pharmaceutical Sciences* **95**, 2486–2498 (2006).
14. H. B. Liu and X. C. Zhang, "Dehydration kinetics of D-glucose monohydrate studied using THz time-domain spectroscopy," *Chemical Physics Letters* **429**, 229–233 (2006).
15. J. R. Knab, J. Y. Chen, Y. F. He and A. G. Markelz, "Terahertz measurements of protein relaxational dynamics," *Proceedings of the Ieee* **95**, 1605–1610 (2007).
16. M. Chee, R. Yang, E. Hubbell, A. Berno, X. C. Huang, D. Stern, J. Winkler, D. J. Lockhart, M. S. Morris and S. P. A. Fodor, "Accessing genetic information with high-density DNA arrays," *Science* **274**, 610–614 (1996).
17. P. H. Bolivar, M. Brucherseifer, M. Nagel, H. Kurz, A. Bosserhoff and R. Buttner, "Label-free probing of genes by time-domain terahertz sensing," *Physics in Medicine and Biology* **47**, 3815–3821 (2002).
18. Y. C. Shen, P. C. Upadhya, E. H. Linfield and A. G. Davies, "Temperature-dependent low-frequency vibrational spectra of purine and adenine," *Applied Physics Letters* **82**, 2350–2352 (2003).
19. Y. C. Shen, P. C. Upadhya, E. H. Linfield and A. G. Davies, "Vibrational spectra of nucleosides studied using terahertz time-domain spectroscopy," *Vibrational Spectroscopy* **35**, 111–114 (2004).
20. B. M. Fischer, M. Hoffmann, H. Helm, R. Wilk, F. Rutz, T. Kleine-Ostmann, M. Koch and P. U. Jepsen, "Terahertz time-domain spectroscopy and imaging of artificial RNA," *Optics Express* **13**, 5205–5215 (2005).
21. X. Yin, B. W. H. Ng, B. M. Fischer, B. Ferguson and D. Abbott, "Support vector machine applications in terahertz pulsed signals feature sets," *Ieee Sensors Journal* **7**, 1597–1608 (2007).

22. C. K. Tiang, J. Cunningham, C. Wood, I. C. Hunter and A. G. Davies, "Electromagnetic simulation of terahertz frequency range filters for genetic sensing," *Journal of Applied Physics* **100**, - (2006).
23. J. A. Zeitler, D. A. Newnham, P. F. Taday, C. J. Strachan, M. Pepper, K. C. Gordon and T. Rades, "Temperature dependent terahertz pulsed spectroscopy of carbamazepine," *Thermochimica Acta* **436**, 71–77 (2005).
24. V. P. Wallace, P. F. Taday, A. J. Fitzgerald, R. M. Woodward, J. Cluff, R. J. Pye and D. D. Arnone, "Terahertz pulsed imaging and spectroscopy for biomedical and pharmaceutical applications," *Faraday Discussions* **126**, 255–263 (2004).
25. M. H. Lu, J. L. Shen, N. Li, Y. Zhang, C. L. Zhang, L. S. Liang and X. Y. Xu, "Detection and identification of illicit drugs using terahertz imaging," *Journal of Applied Physics* **100**, - (2006).
26. L. Ho, R. Muller, M. Romer, K. C. Gordon, J. Heinamaki, P. Kleinebudde, M. Pepper, T. Rades, Y. C. Shen, C. J. Strachan, P. F. Taday and J. A. Zeitler, "Analysis of sustained-release tablet film coats using terahertz pulsed imaging," *Journal of Controlled Release* **119**, 253–261 (2007).
27. B. E. Cole, R. Woodward, D. Crawley, V. P. Wallace, D. D. Arnone and M. Pepper, "Terahertz imaging and spectroscopy of human skin, in-vivo," *Proc. SPIE–Int. Soc. Opt. Eng.* **4276**, 1–10 (2001).
28. E. Pickwell, B. E. Cole, A. J. Fitzgerald, M. Pepper and V. P. Wallace, "In vivo study of human skin using pulsed terahertz radiation," *Physics in Medicine and Biology* **49**, 1595–1607 (2004).
29. V. P. Wallace, A. J. Fitzgerald, E. Pickwell, R. J. Pye, P. F. Taday, N. Flanagan and T. Ha, "Terahertz pulsed spectroscopy of human basal cell carcinoma," *Applied Spectroscopy* **60**, 1127–1133 (2006).
30. S. W. Smye, J. M. Chamberlain, A. J. Fitzgerald and E. Berry, "The interaction between Terahertz radiation and biological tissue," *Physics in Medicine and Biology* **46**, R101–R112 (2001).
31. P. H. Siegel, "Terahertz technology in biology and medicine," *Ieee Transactions on Microwave Theory and Techniques* **52**, 2438–2447 (2004).
32. P. H. Siegel, R. J. Dengler, E. Mueller, C. Readhead and S. E. Fraser, "Scanned pixel heterodyne terahertz imaging," *presented at the British Royal Soc. Terahertz Gap Meeting,* (2003).
33. K. J. Siebert, T. Loffler, H. Quast, M. Thomson, T. Bauer, R. Leonhardt, S. Czasch and H. G. Roskos, "All-optoelectronic continuous wave THz imaging for biomedical applications," *Physics in Medicine and Biology* **47**, 3743–3748 (2002).
34. A. J. Fitzgerald, E. Berry, N. N. Zinov'ev, S. Homer-Vanniasinkam, R. E. Miles, J. M. Chamberlain and M. A. Smith, "Catalogue of human tissue optical properties at terahertz frequencies," *Journal of Biological Physics* **29**, 123–128 (2003).
35. T. Loffler, K. Siebert, S. Czasch, T. Bauer and H. G. Roskos, "Visualization and classification in biomedical terahertz pulsed imaging," *Physics in Medicine and Biology* **47**, 3847–3852 (2002).
36. T. Loffler, T. Bauer, K. J. Siebert, H. G. Roskos, A. Fitzgerald and S. Czasch, "Terahertz dark-field imaging of biomedical tissue," *Optics Express* **9**, 616–621 (2001).
37. P. Knobloch, C. Schildknecht, T. Kleine-Ostmann, M. Koch, S. Hoffmann, M. Hofmann, E. Rehberg, M. Sperling, K. Donhuijsen, G. Hein and K. Pierz, "Medical THz imaging: an investigation of histo-pathological samples," *Physics in Medicine and Biology* **47**, 3875–3884 (2002).
38. V. P. Wallace, D. Arnone, R. M. Woodward and R. J. Pye, "Biomedical applications of terahertz pulsed imaging," *in Proc. 2nd Joint EMBS/BMES Conf., Houston, TX,* (2002).

39. R. M. Woodward, V. P. Wallace, R. J. Pye, B. E. Cole, D. D. Arnone, E. H. Linfield and M. Pepper, "Terahertz pulse imaging of ex vivo basal cell carcinoma," *Journal of Investigative Dermatology* **120**, 72–78 (2003).
40. "http://www.skincancer.org/basal/index.php."
41. R. M. Woodward, V. P. Wallace, D. D. Arnone, E. H. Linfield and M. Pepper, "Terahertz Pulsed maging of Skin Cancer in the Time and Frequency Domain," *J. Biol. Phys* **29**, 257–261 (2003).
42. A. J. Fitzgerald, V. P. Wallace, M. Jimenez-Linan, L. Bobrow, R. J. Pye, A. D. Purushotham and D. D. Arnone, "Terahertz pulsed imaging of human breast tumors," *Radiology* **239**, 533–540 (2006).
43. Bolan PJ, Meisamy S, Baker EH and e. al, "In vivo quantification of choline compounds in the breast with 1H MR spectroscopy," *Magn Reson Med* 1134–1143 (2003).
44. S. A. Boppart, W. Luo, D. L. Marks and K. W. Singletary, "Optical coherence tomography: feasibility for basic research and image-guided surgery of breast cancer," *Breast Cancer Research and Treatment* **84**, 85–97 (2004).
45. D. Crawley, C. Longbottom, V. P. Wallace, B. Cole, D. Arnone and M. Pepper, "Three-dimensional terahertz pulse imaging of dental tissue," *Journal of Biomedical Optics* **8**, 303–307 (2003).
46. E. Pickwell, B. E. Cole, A. J. Fitzgerald, V. P. Wallace and M. Pepper, "Simulation of terahertz pulse propagation in biological systems," *Applied Physics Letters* **84**, 2190–2192 (2004).
47. E. Pickwell, A. J. Fitzgerald, B. E. Cole, P. F. Taday, R. J. Pye, T. Ha, M. Pepper and V. P. Wallace, "Simulating the response of terahertz radiation to basal cell carcinoma using ex vivo spectroscopy measurements," *Journal of Biomedical Optics* **10**, - (2005).
48. G. C. Walker, E. Berry, S. W. Smye, N. N. Zinov'ev, A. J. Fitzgerald, R. E. Miles, M. Chamberlain and M. A. Smith, "Modelling the propagation of terahertz radiation through a tissue simulating phantom," *Physics in Medicine and Biology* **49**, 1853–1864 (2004).
49. K. L. Wang and D. M. Mittleman, "Metal wires for terahertz wave guiding," *Nature* **432**, 376–379 (2004).
50. R. W. McGowan, G. Gallot and D. Grischkowsky, "Propagation of ultrawideband short pulses of terahertz radiation through submillimeter-diameter circular waveguides," *Opt Lett* **24**, 1431–1433 (1999).
51. G. Gallot, S. P. Jamison, R. W. McGowan and D. Grischkowsky, "Terahertz waveguides," *J Opt Soc Am B* **17**, 851–863 (2000).
52. S. P. Jamison, R. W. McGowan and D. Grischkowsky, "Single-mode waveguide propagation and reshaping of sub-ps terahertz pulses in sapphire fibers," *Appl Phys Lett,* 76, 1987–1989 (2000).
53. R. Mendis and D. Grischkowsky, "Plastic ribbon THz waveguides," *J Appl Phys,* 88, 4449–4451 (2000).
54. R. Inoue, N. Uchida and M. Tonouchi, "Scanning probe laser terahertz emission microscopy system," *Jpn J Appl Phys 2* **45**, L824-L826 (2006).
55. G. Binning, H. Rohrer, C. Gerber and E. Weibel, "Surface Studies by Scanning Tunneling Microscopy," *Phys Rev Lett* **49**, 57–61 (1982).
56. U. Schade, K. Holldack, P. Kuske, G. Wustefeld and H. W. Hubers, "THz near-field imaging employing synchrotron radiation," *Applied Physics Letters* **84**, 1422–1424 (2004).
57. H.-T. Chen, R. Kersting and G. C. Cho, "Terahertz imaging with nanometer resolution," *Applied Physics Letters* **83,** 3009–3011 (2003).

58. J. Cunningham, M. Byrne, P. Upadhya, M. Lachab, E. H. Linfield and A. G. Davies, "Terahertz evanescent field microscopy of dielectric materials using on-chip waveguides," *Applied Physics Letters* **92**, 032903–032903 (2008).
59. C. Wood, J. Cunningham, I. C. Hunter, P. Tosch, E. H. Linfield and A. G. Davies, "On-chip pulsed terahertz systems and their applications," *Int J Infrared Milli* **27**, 557–569 (2006).
60. J. B. Pendry, "Negative Refraction Makes a Perfect Lens," *Phys. Rev. Lett.* **85**, 3966–3969 (2000).
61. H. Lee, Y. Xiong, N. Fang, W. Srituravanich, S. Durant, M. Ambati, C. Sun and X. Zhang, "Realization of optical superlens imaging below the diffraction limit," *New J Phys* **7**, - (2005).
62. T. J. Yen, W. J. Padilla, N. Fang, D. C. Vier, D. R. Smith, J. B. Pendry, D. N. Basov and X. Zhang, "Terahertz magnetic response from artificial materials," *Science* **303**, 1494–1496 (2004).
63. T. Taubner, D. Korobkin, Y. Urzhumov, G. Shvets and R. Hillenbrand, "Near-field microscopy through a SiC superlens," *Science* **313**, 1595–1595 (2006).
64. J. Pearce, H. H. Choi, D. M. Mittleman, J. White and D. Zimdars, "Terahertz wide aperture reflection tomography," *Opt Lett* **30**, 1653–1655 (2005).
65. B. Ferguson, S. H. Wang, D. Gray, D. Abbott and X. C. Zhang, "Towards functional 3D T-ray imaging," *Phys Med Biol* **47**, 3735–3742 (2002).