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Real time THz imaging - opportunities and challenges for skin cancer detection

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It was first suggested that terahertz imaging has the potential to detect skin cancer twenty years ago. Since then THz instrumentation has improved significantly: real-time broadband THz imaging is now possible and robust protocols for measuring living subjects have been developed. Here we discuss the progress that has been made as well as highlight the remaining challenges for applying THz imaging to skin cancer detection.

The greatest benefit from THz imaging of skin cancer would be if it could be used for real-time diagnosis of patients, and for that, we need real time THz imaging in a configuration that would be suitable for imaging various skin locations. Real-time THz imaging has until recently only been possible using THz array cameras and high-power THz beams produced using, for example, high power femtosecond lasers, or THz quantum cascade lasers. The former are expensive, not portable and could affect gene expressions due to the high peak-intensity, while the latter work mainly at cryogenic temperatures adding high running costs. Breakthroughs made in THz spatial light modulation have enabled compressive sampling techniques to be applied to room temperature THz spectroscopy systems and achieve real time imaging[1,2]. In compressive imaging a pattern is imprinted onto the THz beam, which is measured by a single THz detector. By rapidly changing the pattern a THz image can be reconstructed computationally. To create the pattern, THz modulators based on silicon are currently a good choice, where optical illumination (which causes photo modulation of the silicon) is controlled by a digital mirror device. We envisage that this "single pixel imaging" approach will likely be the way forward for *in vivo* cancer diagnosis.

The incidence of basal cell carcinoma (BCC) in the UK has increased by approximately 250% since the 1990s, with 137,000 new cases in the UK each year[3]. There is a pressing need to improve the efficiency of *in vivo* diagnostics and surgical procedures. Delayed diagnosis and incomplete excision of tumours are key factors in squandering resources, greatly increasing patient morbidity. Existing techniques for diagnosis and treatment of several cancers have their limitations: e.g. for skin cancer, the initial diagnosis is performed by visual inspection and biopsy (which typically takes two weeks to process). The gold standard for skin cancer removal is, Mohs micrographic surgery during which tissue is removed and then examined under a microscope until the margins are clear, this is time consuming and expensive. If the extent of tumours could be determined using THz imaging prior to surgery, procedures would be faster, excision would be definitive and reconstruction better planned.

THz light is fundamentally more suited to detecting abnormalities in tissues than other emerging technologies, such as Optical Coherence Tomography (OCT), owing to its wavelength. In particular, water has strong absorption at THz frequencies resulting from hydrogen bonds[4]. Optical frequencies do not resonate with hydrogen bonds, and while the shorter wavelength (λ) of optical light means it is easier to achieve higher resolution, there is also more scattering (proportional to $1/\lambda$), and more attenuation[5]. This makes it harder for optical techniques to image deeper into the tissue. X-ray computed tomography (CT) using contrast enhancers and MRI functional imaging are able to identify cancer in the gastrointestinal tract with millimeter resolution, but it is difficult to map their information precisely to the patient during surgical removal. THz light offers the perfect middle ground for resolution and penetration depth and is also complemented by its intrinsic sensitivity to hydrogen bonds.

In vivo THz images from a case study of patients with BCC in 2004 suggested that it is possible to detect skin cancer hidden beneath the skin using THz imaging[6]. Spectroscopic studies by MacPherson and colleagues in 2006 showed that the fundamental THz properties of freshly removed (excised) skin cancer tumours are statistically significantly different from healthy tissue and it is thought that the differences are primarily due to changes in water content of the tissue[7]. More recently Zaytsev et al. performed *in vivo* measurements of healthy skin, dysplastic nevi (precancerous moles) and non-dysplastic nevi (regular moles) on four patients[8]. It was found that there was significant contrast between the tissue types. This reveals the potential of THz imaging for identifying not only the presence of skin cancer but also features in the skin which if left could develop into cancer.

The high sensitivity of THz light to water also means that the THz signal is strongly attenuated and has a very limited penetration depth in tissue – thus THz scanning would experience great difficulty in detecting deep tumours[7]. The penetration depth depends on the signal-to-noise ratio of the THz imaging system, therefore global efforts to improve the signal processing and/or the THz instrumentation have significant

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impact on the feasibility of this application. The early studies which identified the contrast between healthy and cancerous tissues opened the door to further research investigating the origin of the contrast and which other types of cancer can be identified using THz imaging. However, due to the limited penetration depth of THz light in biological tissues the *in vivo* studies are largely focused on observing the skin whilst other cancer types have been identified following the removal of the tissue in *ex vivo* studies.

In 2006 Fitzgerald et al. demonstrated that THz imaging can be used to identify areas of cancerous tissue in excised breast samples from cancer patients. The area of the cancerous region identified from the THz image was found to have moderate correlation with the results obtained when the samples underwent routine histological tests[9]. Bowman et al. also found contrast between breast cancer, the healthy fibrous tissue surrounding the tumour and the healthy fatty tissue in the breast[10,11].

In addition to investigating potential applications of THz imaging for the diagnosis of various cancers, studies have also been performed using THz imaging to investigate other diseases or changes in the skin. One of the largest scale tests of the potential of THz imaging to address a clinical need is the study by Hernandez-Cardoso et al. which demonstrates the success of THz imaging in diagnosing diabetic foot syndrome[12]. This study was able to find significant differences in the THz response of the skin on the underside of the feet of healthy and diabetic subjects, as shown in Figure 1(a).

THz imaging has also been explored as a possible approach for assessing whether reconstructive skin flaps will be successful, Bajwa et al. performed an *in vivo* study measuring the change in the water content of partially and fully islanded skin flaps[13]. It was found that the THz images showed a significant difference between the study groups 24 hours after the procedure, while the visible image did not yield a significant difference until 72 hours after the procedure. This means that THz imaging could yield earlier results about the viability of skin flaps for reconstructive surgery.

Another potential application which is very promising is the assessment of burn wounds. For example Tewari et al. performed *in vivo* measurements comparing the THz response of burnt regions of rat skin to the visual observations of the same regions. The initial results are shown in Figure 1(b), where the change in the burnt region can be seen with increasing time following a contact thermal injury[14]. The follow up study focused on the potential of THz imaging as a technique for the classification of the severity of burn wounds[15]. Additionally, Taylor et al. used fresh porcine tissue to observe with THz imaging the effect of burning the skin and found that they were able to identify the burn even underneath 10 layers of gauze[16]. In a 2020 study, Osman et al. performed *in vivo* THz measurements on porcine skin which had been burnt for different durations[17]. They were able to define a spectral parameter which was capable of classifying burns based on their depth.

THz imaging has also been used to image skin to learn more about the mechanisms by which the skin responds to various treatments such as the application of moisturisers. Ramos-Soto et al. investigated the effects of common moisturiser ingredients on an excised sample of porcine skin[19]. This study took advantage of the *ex vivo* nature of the work by placing the moisturiser sample onto the skin and measuring the underside of the skin to observe how much of the moisturiser penetrated through the skin sample.

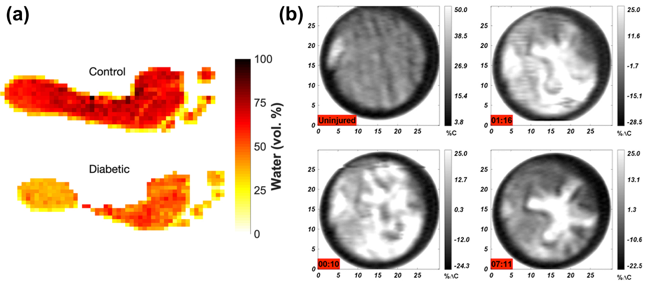

FIG. 1. Examples of the application of THz imaging for diagnosing skin conditions. (a) The average hydration measured in the feet of healthy or diabetic subjects. (b) THz images of healthy rat skin (top left) and increasing time intervals after being burnt with a '+' shape. Part (a) and (b) reprinted from references[12] and[14], respectively, under Creative Commons Attribution 4.0 International License.

The MacPherson research group has made significant contributions to the field of THz imaging for biomedical applications. We have previously investigated the underlying THz image contrast mechanisms in biomedical tissues[20,21] as well as developed algorithms and approaches to improve the accuracy of sample characterisation[22,23] and accelerate THz image data acquisition[1]. This more recent work is pushing the state-of-the-art in THz imaging, both in accuracy and speed, opening new prospects for THz imaging *in vivo*.

We are also now able to account for the pores of skin being blocked (occluded) by the imaging window for the duration of the THz measurement. This 'occlusion' process means that the perfusion of water through the surface of the skin is prevented allowing water to accumulate in the outer most layer of skin, the stratum corneum (SC)[24]. We have exploited this phenomenon to pioneer the use of THz imaging to determine rate of water diffusion within the SC during occlusion[25] and this could be a key parameter for detecting hidden skin cancer – something which we will be investigating imminently through our recently funded EPSRC project, Terabotics.

Additional diagnostic information may well be obtained using the setup shown in Figures 2 (a) and (b) to measure the s- and p- polarisation components at two incident angles. In doing this we obtain 4 complementary sets of spectral ratios making it possible to observe for the first time birefringence in the SC at THz frequencies[18]. Figure 2 (c) shows the optical changes in the skin observed with a microscope with 30 minutes of occlusion, the smoothing of the skin as the hydration increases under occlusion can be seen. We also measured the changes in the refractive index of the ordinary and extraordinary components of the SC under this occlusion, as can be seen in Figure 2 (d). We proposed a model in which the SC is composed of corneocyte and lipid layers, this was verified by the measurements and explains the observed birefringence.

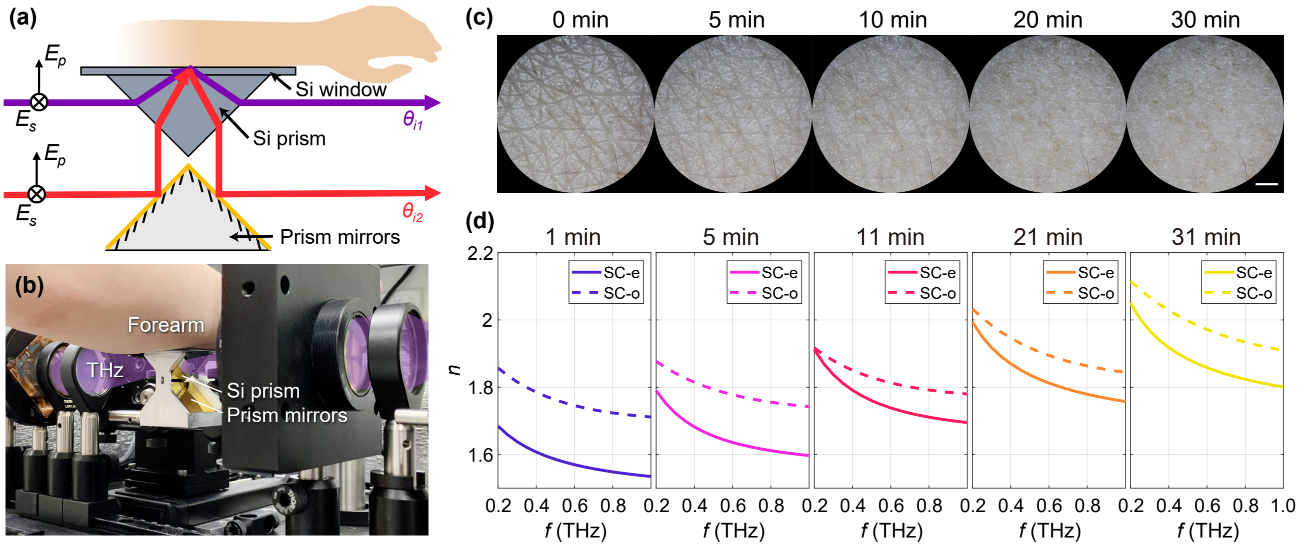

FIG. 2. Terahertz *in vivo* ellipsometric measurement. (a) Schematic of the multiconfiguration ellipsometer. (b) Labeled photo showing the forearm skin measurement in the proposed ellipsometer. (c) Microscope images of skin occluded for 0, 5, 10, 20, and 30 min respectively. The scale bar is 1 mm. (d) Birefringent refractive indices of the stratum corneum extraordinary (SC-e) and ordinary (SC-o) components after 1, 5, 11, 21 and 31 min occlusion, respectively[18]. Fig. 2c is reprinted from reference[18] under the Creative Commons Attribution 4.0 International License. Fig. 2d is plotted using data available from reference[18].

This opens the door to the potential of using THz imaging to not only observe hydration changes in the skin but also to monitor changes in the cellular structure.

In addition to occlusion, we have developed our understanding of other variables which can influence the THz response of skin including the pressure of the skin on the imaging window for the duration of an *in vivo* measurement[26]. Identifying this as a parameter which must be controlled has made it possible to develop a robust protocol for measuring the skin with a contact THz system by integrating a pressure sensor into the system to give live and recorded feedback on the pressure applied[27]. We also introduced the definition of a normalised variable which subtracts the change measured in an untreated region of skin from the change measured in the treated region; making it possible to account for natural variation in the skin throughout the duration of the measurement.

After demonstrating the success of the robust protocol in improving the repeatability of *in vivo* measurements of the skin using THz light, we were able to apply this protocol to a larger scale study involving 20 subjects. We observed the change in the THz response of skin following the application of 3 different types of moisturisers and compared the results to the current gold standard for skin hydration assessment: the corneometer[28].

In addition to controlling occlusion we were also able to take advantage of the sensitivity of THz measurements to the effect of occlusion on the skin to measure the efficacy of different burn treatments including occlusion using a silicone gel sheet to increase hydration[29]. We were able to observe the recovery of the hydration of the skin to the initial state and found that this recovery rate depended on the length of time for which the sheeting was applied. We have also been able to use THz imaging to monitor the recovery of scars, we were able to observe contrast between the refractive index of healthy and scarred skin at THz frequencies, even beyond what can be seen by eye[21].

Ex vivo THz imaging also plays an important part in developing our understanding of the changes which can be induced in the skin by different mechanisms, particularly in cases where it may be harder to perform such investigations on living volunteers. We were able to use *ex vivo* THz measurements of porcine skin to observe the efficacy of micro and nano needle patches in enhancing the penetration of drugs through the skin barrier[30].

Before hospitals adopt THz imaging technology on a widespread scale, of critical importance is to be able to obtain the images at fast rates without sacrificing the spectroscopic measurement capabilities of THz spectrometers. This is because amplitude and phase data at multiple frequencies gives vastly more information and insight into diseases, and having this data available in real-time during a skin operation would be much more useful compared to after the procedure when the wound is no longer accessible. There is also the cost consideration; the initial costs of THz systems are still fairly high (around USD 100k). However, this is similar in cost to other devices which have been tested for skin assessment such as the clinical confocal microscope, so should not negatively impact the potential uptake of THz technology for clinical use.

The most promising approach to meet the requirements is single-pixel THz cameras[1,2]. Such cameras can achieve rapid imaging rates, have reasonable costs, and can obtain subwavelength resolution (as the modulator can be placed in the near-field of the object)[2,31,32]. Today the most common spatial THz-light modulators work by modulating the conductivity

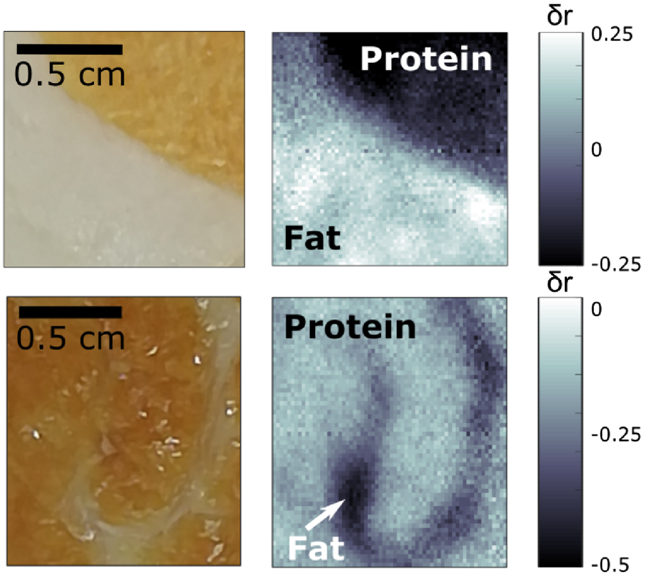

FIG. 3. Optical images (left) and THz images at 140 GHz (right), of porcine tissue samples containing regions of fat and protein as indicated. The THz images were acquired using a single-pixel imaging system. Reprinted from reference[31] under Creative Commons Attribution 4.0 International License.

of a semiconductor via optical excitation[1,2], although electrical control of the conductivity is expected to be the long-term solution once such technology is further optimized[33]. The angle of incidence of the THz beam onto the surface where the conductivity is being controlled greatly affects the THz modulator efficiency. Stantchev et al, showed that a total-internal-reflection (TIR) geometry has the greatest working efficiency over ordinary transmission and reflection geometries[1].

For near-field imaging a THz modulator operating in the efficient TIR geometry can be placed in the near-field of skin or other biological samples making a single-pixel THz camera with sub-wavelength resolution possible. This idea was demonstrated by Barr et al[31] where they placed biological tissues on a TIR modulator and obtained images with 700 μm resolution where otherwise their diffraction limited resolution would be ~ 1.8 *cm* considering the optics of their $\lambda = 2.15$ *mm* wave source. An example of the images obtained using this approach are shown in Figure 3, where the clear distinction between fat and protein in the tissues can be observed in the THz images. The resolution in their approach is fundamentally limited by the photocarrier diffusion dynamics, as they photoexcite silicon with an LED to alter the conductivity. However, electrical based THz modulators, whereby an applied electric field changes the conductivity, will have their resolution set by the device manufacturing techniques as opposed to carrier diffusion dynamics as is the case with optical based modulators[33].

With all these advances in THz instrumentation and data analysis, the time is right to pursue the integration of THz instrumentation into robotics so that *in vivo* THz data of patients can be obtained. The EPSRC has recently funded a programme grant in this field (PI Emma MacPherson) entitled, Terabotics:Terahertz robotics for surgery and medicine. In this project we will unite THz, surgical robotics and clinical experts in the UK to advance the application of THz technology to cancer. In the five year project, we have plans to apply our findings from THz imaging of skin cancer to colon cancer, which is another epitheleal cancer. As well as developing fast and compact THz probes, we will also develop patient invariant classification parameters. Indeed, improving classification algorithms is a hot topic, especially with the assistance of machine learning in recent years. Traditional segmentation methods based on the optical properties and other features have the merits that data training is not required and results can be clearly interpreted. Examples can be seen in margin delineation of breast cancer and tumor identification[34,35]. Machine learning is gaining more popularity, but a larger sample size is needed. It can utilize multiple spectral features thus a higher classifying accuracy can usually be achieved[36–38]. In our opinion, Terabotics has the potential to establish itself as a new field, not only for medical applications but for industrial applications too eg. quality control of pharmaceuticals[39] and car paint[40].

The integration of high speed THz imaging systems with robotics will facilitate the imaging of a diverse range of body locations, as up until this point many *in vivo* studies have been limited to imaging the volar forearm. A system which can image any area of the body is required if real time imaging and diagnosis of skin cancer using THz radiation is to be achieved as skin cancers can occur in many locations including the back, leg, neck and forehead[41]. The challenge which must be addressed is not only to move the imaging system to each area of the body quickly, but also to be able to image the complex geometries of each location. The Taylor group has had success with non contact imaging of the eye with a THz system, however this was possible due to the uniform shape of the eye and the limited variation between subjects[42]. Additionally, if there is a skin cancer present it is possible the region can be raised above the surface of the skin leading to extra curvature of the region which is challenging to image using contact or non contact systems.

In summary, with THz imaging capabilities improving to be real time, it will soon be possible to do real time imaging of patients. This will give rise to the data needed to develop classification algorithms such that real time diagnosis will be feasible for patients, revolutionising cancer treatment strategies and improving patient outcomes.

Data Availability Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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