
Journal of Biological Physics **29:** 257–261, 2003.

Terahertz Pulsed Imaging of Skin Cancer in the Time and Frequency Domain

R.M. WOODWARD[1,2], V.P. WALLACE[1], D.D. ARNONE[1], E.H. LINFIELD[2] and M. PEPPER[2]
[1]*TeraView Limited, 302/304 Science Park, Milton Road, Cambridge, CB4 OWG, UK*
[2]*Cavendish Laboratory, University of Cambridge, Madingley Road, Cambridge, CB3 OHE, UK*

Abstract. Terahertz Pulsed Imaging (TPI) is a new medical imaging modality for the detection of epithelial cancers. Over the last two years this technique has been applied to the study of *in vitro* basal cell carcinoma (BCC). Using time-domain analysis the contrast between diseased and normal tissue has been shown to be statistically significant, and regions of increased terahertz (THz) absorption correlated well with the location of the tumour sites in histology. Understanding the source of this contrast through frequency-domain analysis may facilitate the diagnosis of skin cancer and related skin conditions using TPI. We present the first frequency-domain analysis of basal cell carcinoma *in vitro*, with the raw power spectrum giving an insight into the surface features of the skin. Further data manipulation is required to determine whether spectral information can be extrapolated at depth. These results highlight the complexity of working in reflection geometry.

Key words: Cancer, epithelial, frequency domain, skin, terahertz imaging, time domain spectroscopy

1. Introduction

Epithelial cancer, which includes skin, breast, and colon cancer, accounts for more than 85% of all cancers. Basal cell carcinoma (BCC), one type of skin cancer, provides a good model for the study of epithelial cancers using TPI. BCC is the most common form of cancer worldwide in white populations and has a reported annual incidence of over one million in the US (American Cancer Society, 2002). Large or infiltrative BCCs are best removed using a technique called Mohs' Micrographic Surgery (MMS) [1]. This is time consuming and expensive as the tumour is excised in stages and assessed histologically during surgery. The ability to assess the direction of sub-clinical spread and define the histological subtype of the tumour pre-operatively, may simplify MMS to a single layer excision, saving time, money and patient discomfort. The study of BCCs using terahertz pulse imaging (TPI) has helped identify its potential as a pre-operative tool for MMS [2].

The first *in vitro* measurements on skin cancer demonstrated the ability of TPI to differentiate BCC from normal skin [3]. The first *in vivo* measurements on skin highlighted the potential of TPI as an *in vivo* tool for the study of skin hydration levels, with the ability to produce B-scan THz images [4, 5]. Studies on the shape

of the waveform in the time-domain have enabled differentiation between diseased, normal and inflamed tissue [5, 6]. These results have opened up the application of TPI in the medical field for the study of skin cancer and related skin disorders. Understanding the source of the contrast observed in the time-domain through spectral analysis may potentially aid diagnosis. Although THz time-domain spectroscopy (TTDS) has been used for the study of proteins, it has not yet been applied for the study of skin cancer *in vitro* [7].

This paper examines the THz images of BCC in the frequency-domain and compares the results to THz images produced using time-domain techniques [5, 6]. Time-domain analysis allows differentiation between surface and depth features within the tissue. Frequency-domain analysis is more complex; surface features currently dominate the frequency-domain spectra, although some depth information is still present, thus only surface information can be retrieved. The results presented here highlight the complexity of extrapolating spectral information at depth when working in reflection geometry.

2. Experiment

Our TPI system uses THz reflection geometry, the operation of which has already been described [4, 5]. The system has a bandwidth of 0.1 THz to 2.7 THz (3 mm–110 μm) and an average power of about 1 mW. The spatial resolution is diffraction limited with an approximate pan-chromatic lateral resolution of 350 μm. The time resolution of approximately 0.5 ps corresponds to a depth resolution in the skin of 40 μm. The penetration depth of approximately 1 mm into the skin tissue is limited by the dynamic range and stability of the system. The signal to noise ratio for a typical THz waveform is $>$6000:1.

3. Results

By Fourier transforming the time-domain waveform before signal processing [5], the frequency-domain spectra of skin tissue can be studied. Figure 1 shows the time and frequency-domain 2D THz images. The time-domain images shows the minimum value in the impulse function, *E*(min) [6], and the 'Time Post Pulse (TPP) value at –1.74 ps [2, 5, 6]. The frequency-domain image shows the reflected power at 0.7 THz.

The minimum impulse function, *E*(min) provides information on the surface features of the skin [5, 6]. Using this technique, the region of inflammation is clearly distinguished from the surrounding normal and diseased tissue, showing an increase in amplitude in the reflected pulse at *E*(min) around the region of inflammation [6]. The time-domain analysis technique TPP provides depth information, and is able to distinguish the diseased tissue from normal skin and inflammation, the results of which agree well with histology [2, 5]. The frequency-domain image looks very similar to the time-domain image *E*(min), and shows an increase in

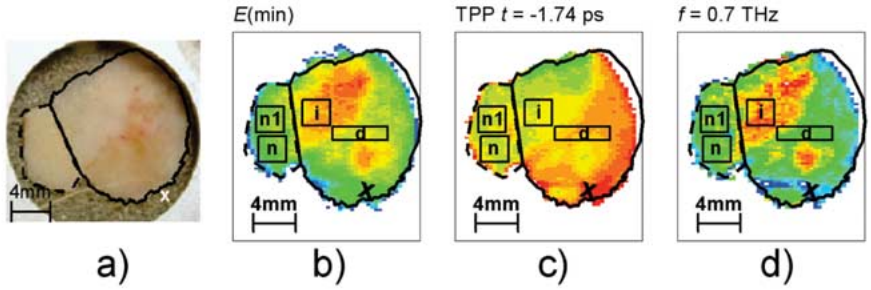

Figure 1. The a) visible, b) E(min) and c) TPP [5] time-domain images and d) the frequency-domain image of BCC and normal tissue *in vitro*. The solid and dashed lines mark the boundaries of the diseased and normal tissue respectively. In the visible image a region of inflammation is present in the top left of the diseased tissue, just visible by the lighter region of tissue, which is clearly visible in the THz images. Area d – diseased; i – inflammation; n, n1 – normal. The area of diseased tissue was chosen as it was within the line of the histology section [2] and away from the suture (X). The 'darker' regions indicate an increase in amplitude of the respective analysis techniques.

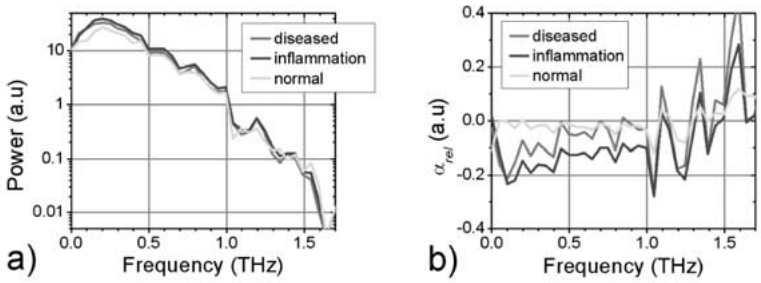

Figure 2. a) The mean raw power spectrum and b) the relative THz absorption α_{rel} of the selected regions of tissue shown in Figure 1.

reflected power within the region of inflammation, indicating a decrease in THz absorption.

In Figure 2, the mean raw power spectra of the selected regions of tissue shown in Figure 1 look very similar. The relative THz absorption, α_{rel} compares the change in THz absorption relative to normal tissue and is determined by

$$\alpha_{rel} = \log\left[\frac{F\{n\}}{F\{d\}}\right]$$

where F$\{n\}$ is the mean raw power spectrum of the region of normal tissue, n, and F$\{d\}$ is the mean raw power spectra of the regions of normal, diseased or inflamed tissue respectively, marked by areas $n1$, d and i in Figure 1. This spectrum highlights the difference in absorption in the diseased and inflamed tissue, compared to the normal tissue. Comparing two regions of normal tissue, n and $n1$, α_{rel} is approximately zero. The region of inflammation shows an approximately uniform

decrease in THz absorption relative to normal tissue up to 1 THz, indicated by the negative value of $\alpha_{rel} \sim -0.1$, whereas the region of diseased tissue looks similar to inflammation at low frequencies and then shows little change in α_{rel} above 0.4 THz. The decrease in relative absorption in the region of inflammation, marked by the increase in power, is clearly visible in Figure 1.

4. Discussion

Time-domain analysis is able to retrieve both surface and depth information. Studies on the changes in amplitude and time of the maximum and minimum peaks in the impulse function provide information on the surface properties of the tissue [4–6]. Depth information can be retrieved using the analysis technique 'Time Post Pulse (TPP)] [2, 5, 6].

The raw power spectrum originates predominantly from the main pulse. Thus the 2D THz images plotting the THz power look very similar to the surface features obtained using time-domain analysis techniques. At higher frequencies the power spectrum is close to the noise floor, as the majority of the THz power is contained within the frequency range 0.1–2 THz [5]. Additionally, from 2–2.7 THz, (150–110 μm) there maybe scattering centers within the tissue, such as the rete ridges at the dermal-epidermal junction, which are similar in size to the wavelength of the incident radiation. Thus scattering within the tissue could prevent the retrieval of frequency information at depth, which may be contained within these higher frequencies.

These results demonstrate the complexity of retrieving spectral information of skin tissue in reflection geometry. Further investigation in the frequency-domain and data manipulation is required to determine whether spectral information can be retrieved at depth using reflection geometry.

5. Conclusions

The results presented here have shown the ability of TPI to identify surface features in skin using frequency-domain analysis techniques. The use of time-domain analysis techniques allows the retrieval of information from the skin both on the surface and at depth. Further investigation in the frequency-domain is required, to determine whether spectral features at depth can be retrieved. This paper highlights the complexity of extracting spectral information using reflection geometry.

Acknowledgements

We acknowledge Dr Richard J. Pye from the Department of Dermatology, Addenbrooke's Hospital, Cambridge, UK, who provided the skin samples and EPSRC, TeraView Ltd and Toshiba for their financial support. Terahertz Pulsed Imaging (TPI^{TM}) is a Trademark of TeraView Limited.

References

1. Shriner, D.L., McCoy, D.K., Goldberg, D.J. et al.: Mohs' Micrographic Surgery, *J. Am. Acad. Dermatol.* **39** (1998), 79–97.
2. Woodward, R.M. et al.: Terahertz Pulse Imaging of *ex vivo* Basal Cell Carcinoma, *J. Invest. Dermatol.* **120**(1) (2003), 72–8.
3. Woodward, R.M., Cole, B.E., Wallace, V.P. et al.: Terahertz Pulse Imaging of *in vitro* Basal Cell Carcinoma Samples, In: Technical Digest-Postconference (ed.), *Conference on Lasers and Electro-Optics (CLEO)*, *TOPS* **56** (2001), 329–30.
4. Cole, B.E., Woodward, R.M., Crawley, D. et al.: Terahertz Imaging and Spectroscopy of Human Skin, *In vivo*, *Proc. SPIE* **4276** (2001), 1–10.
5. Woodward, R.M. et al.: Terahertz Pulse Imaging in Reflection Geometry of Human Skin Cancer and Skin Tissue, *Phys. Med. Biol.* **47** (2002), 3853–3863.
6. Woodward, R.M., Wallace, V.P., Pye, R.J. et al.: Terahertz Pulse Imaging in Reflection Geometry of Skin Tissue Using Time Domain Analysis Techniques, In: *Clinical Diagnostic Systems: Technology and Instrumentation*, *Proc SPIE* **4625**(28) (2002), 160–169.
7. Walther, M., Disher, B., Schall, M., Helm, H. and Uhd Jepsen, P: Far-infrared Vibrational Spectra of All-*trans*, 9-*cis* and 13-*cis* Retinal measured by THz Time-Domain Spectroscopy, *Chem. Phys. Lett.* **332** (2000), 389–395.