Terahertz Reflection Imaging of Paraffin-embedded Human Breast Cancer Samples: Some First Results

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Abstract: Several studies have shown that terahertz (THz) pulsed imaging has the potential of identifying the margins of human breast cancer in paraffin-embedded tissue samples. Before using this technique for the assessment of cancer margins during breast-conserving surgery, it is important to study the validity and reproducibility of previously published results. In the present paper, we describe some first results in the characterization of paraffin-embedded human breast cancer tissue through THz reflection imaging based on measurements provided by a newly acquired THz time-domain spectrometer. First, we measured the THz reflection impulse response of these samples using this spectrometer. Second, we processed, for one selected breast cancer tissue sample, the recorded data to generate preliminary images of (1) several maps of parameters extracted in the time- and frequency-domains, and (2) a map of the absorbance.

1 INTRODUCTION

One of the promising application of terahertz pulsed imaging (TPI) is the characterization of biological tissues, where terahertz (THz) means 10^{12} Hz. In particular, TPI has shown potential for identifying human breast cancer during breast-conserving surgery (Fitzgerald *et al*., 2006; Yu *et al*., 2012).

A key issue with this surgery is the more than 20% rate of re-operation after postoperative histopathological analysis of the cancer resection margins (Jacobs, 2008). This rate results from the current lack of accurate intraoperative cancer margins assessment tools.

As a member of the TERA4ALL project consortium that aims to promote THz technology applications across the Walloon Region of Belgium, our group investigates the use and validation of TPI in breast cancer margins assessment, in the context of reducing the re-operation rate of a breast-conserving surgery.

Previous studies (Fitzgerald *et al*., 2006; Ashworth *et al*., 2009; Hassan *et al*., 2012; Bowman *et al*., 2017) have already presented promising results of significant contrast between normal and cancerous breast tissues when TPI is applied to freshly excised or dehydrated paraffin-embedded (PE) samples.

Although the water content of the tissue has been shown to contribute significantly to the tissue's optical properties in the THz range, it has been suggested that the interaction of THz radiation with this tissue may also be sensitive to other factors, such as the tissues structure, the cell density, and the presence of certain proteins (Fitzgerald *et al*., 2006). These factors could explain why imaging contrast between different tissue regions can also be demonstrated for dehydrated samples (Bowman *et al*., 2017).

In this paper, we describe some first results in the characterization of PE human breast cancer tissue samples through TPI in reflection mode using measurements obtained by a newly acquired THz time-domain (TD) spectrometer (Fig. 1).

Figure 1: Picture of the THz time-domain spectrometer TeraPulse 4000 (TeraView Ltd, Cambridge, UK).

There are two motivations for the choice of considering these samples for this first stage of research. First, they are easy to obtain (from biobanks), to carry, and to store. Second, additional testing on PE human breast cancer samples would be

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required in order (1) to investigate the reproducibility of previously published results, (2) to potentially improve the methodology used to obtain these results, and (3) to provide a better understanding of the origin of contrast in TPI without the presence of water in the tissue samples.

2 EXPERIMENT & METHOD

PE human breast tissue samples of various thicknesses (10, 20, 30, and 50 µm), containing both normal and cancerous regions, were provided by the Biobank of the University Hospital of Liège (Biothèque Hospitalo-Universitaire de Liège). The present study was approved by the local ethics committee of the University of Liège, Liège, Belgium (Ref: 2017/175).

We used the THz TD spectrometer TeraPulse 4000 (TeraView Ltd, Cambridge, UK) to record the impulse response (IR) of theses samples in open air (Fig. 1). The experimental setup is schematically represented in Fig. 2.

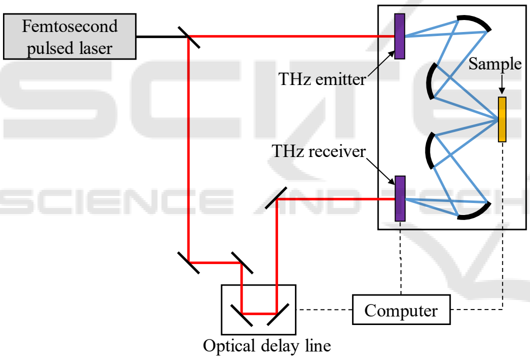

Figure 2: Schematic diagram of the experimental setup used to measure the reflection THz IR of the sample.

The samples were mounted on glass slides. Thus, we used the THz TD spectrometer in reflection mode as THz radiation is strongly attenuated in glass. Prior to scanning each sample, the reference IR (i.e., no sample in the THz beam) was recorded from a gold-coated alignment mirror (not shown in Fig. 1).

A sample of interest was then scanned point-by-point in two orthogonal directions characterized by x- and y-coordinates using a mapper unit (not shown in Fig. 1). The scanning produced at each scan point a full IR (signal), referred to as the measurement at this point. The spatial scan step was 200 µm in each direction. In addition, we used the TeraPulse software to apply a fast Fourier transform (FFT) to the IR obtained at each scan point, yielding the associated frequency response (FR).

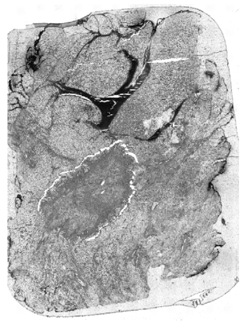

Figure 3: Picture of a 50 µm-thick sample.

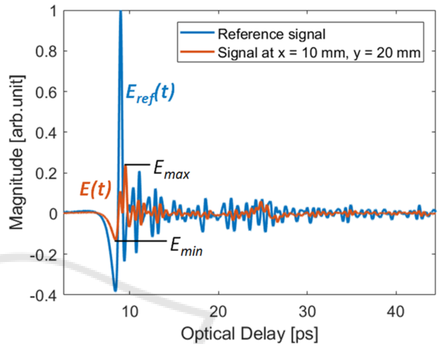

Figure 4: Example of a recorded IR of the sample, in red, and the recorded reference IR (using a gold-coated alignment mirror), in blue.

In this paper, we consider the results from the 50 µm-thick sample shown in Fig. 3. Fig. 4 shows an example of (1) a recorded reflected THz IR from the surface of this sample and (2) the corresponding reference IR.

We extracted several parameters both from the IR recorded directly in the TD and from the FR computed in the frequency-domain (FD). These parameters are described later.

For each TD (respectively FD) parameter, we assigned the parameter value at each measurement point to a pixel in an image in order to create a THz TD (respectively FD) image of this parameter.

We obtained the preliminary THz images by assigning the following TD and FD parameters to each pixel (corresponding to a measurement point):

- The normalized amplitude of the sample IR at a given optical delay t_d, i.e.,

$$\frac{E^{pixel}(t_d)}{\max_{pixel} |E^{pixel}(t_d)|}, \qquad (1)$$

where $E^{pixel}(t)$ is the amplitude of the IR (at the measurement point of interest (Fig. 4)).

- The normalized peak-to-peak amplitude of the sample IR (Fig. 4), i.e.,

$$\frac{E_{max}^{pixel} - E_{min}^{pixel}}{\max_{pixel} |E_{max}^{pixel} - E_{min}^{pixel}|}, \tag{2}$$

- The normalized magnitude of the sample FR at a given frequency f, i.e.,

$$\frac{A^{pixel}(f)}{\max_{pixel} |A^{pixel}(f)|}, \tag{3}$$

where $A^{pixel}(f)$ is the magnitude of the sample FR (at a given measurement point of interest).

- The absorbance of the sample at a given frequency f, is calculated using the Beer-Lambert relation, i.e.,

$$-\log_{10}\left(\frac{A^{pixel}(f)}{A_{ref}^{pixel}(f)}\right), \tag{4}$$

where $A_{ref}^{pixel}(f)$ is the magnitude of the reference FR (obtained from the reference IR).

3 RESULTS & DISCUSSION

Figures 5-8 depict preliminary THz reflection images of the aforementioned TD and FD parameters for the 50 µm-thick PE sample. These parameters are given in arbitrary units ([a.u.]) or without units in the case of the absorbance ([-]).

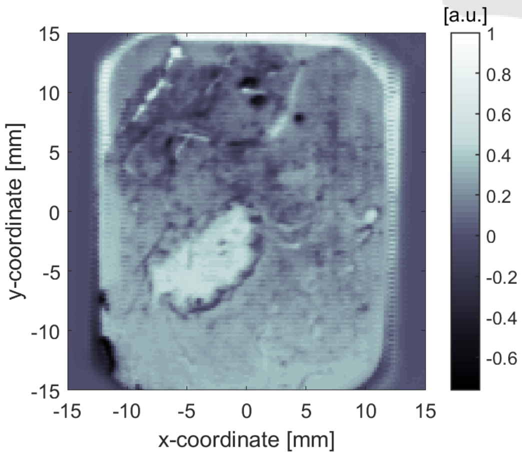

Figure 5: THz TD image obtained using the normalized amplitude of the IR at optical delay t_d of 9 ps, as defined by Eq. (1).

Contrasted regions in the images allow one to distinguish (1) areas of the glass slide with and without a sample, (2) paraffin alone versus excised PE tissue areas, and (3) some defects associated with the sample (such as cracks and regions where the paraffin had detached from the glass slide).

In addition, one can observe, in the images, interesting contrasted regions that may correlate with different types of tissue inside the excised tissue area.

A rigorous comparison with a histopathological analysis is required before drawing any conclusion on the potential meaning of these contrasted regions.

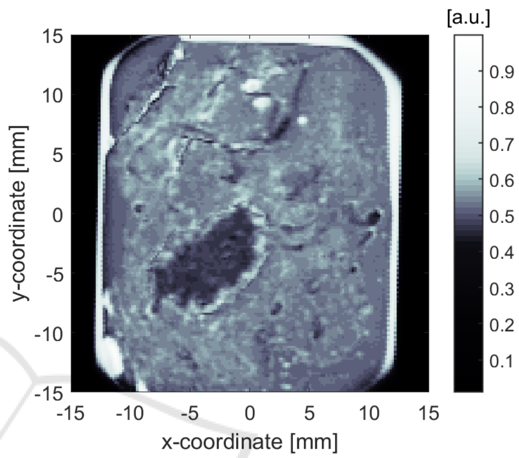

Figure 6: THz TD image obtained using the normalized peak-to-peak amplitude of the IR, as defined by Eq. (2).

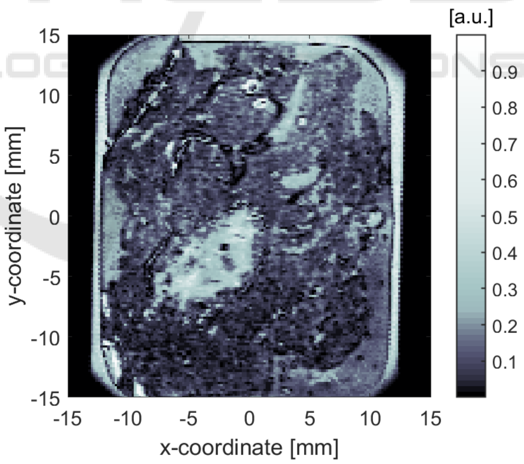

Figure 7: THz FD image obtained using the normalized magnitude of the FR at 2.5 THz, as defined by Eq. (3).

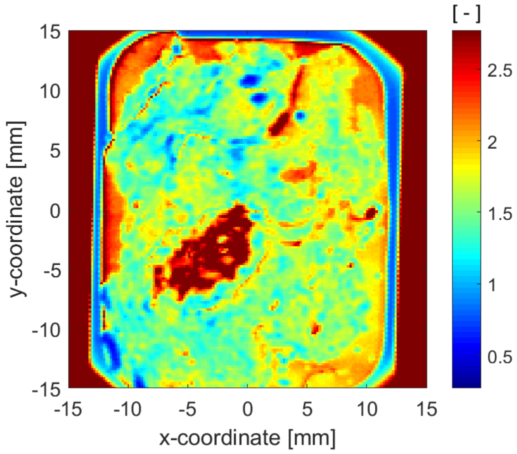

Figure 8: THz FD image of absorbance at 1 THz, as defined by Eq. (4).

4 CONCLUSION & FUTURE WORK

This paper shows preliminary THz images generated from the THz reflection IR of excised PE human breast cancer tissue samples on glass slides, experimentally measured in open air using a newly acquired THz TD spectrometer. Although contrasted regions were identified, one would need to further interpret these images by comparing them to the results of a histopathological analysis.

Future work includes (1) the use of the THz TD spectrometer with water-free (nitrogen-purged) sample compartment for future measurements, (2) the validation of contrasted regions by correlation with a histopathological analysis, (3) the use of a different sample slide material with low THz absorption coefficient allowing TPI in transmission mode, (4) TPI of fresh animal tissue and of fresh tissue phantoms to characterize the optical properties of these materials in the THz range before testing valuable freshly-excised human breast cancer samples, and (5) the development of signal-processing algorithms dedicated to the assessment of breast tumor margins.

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ABBREVIATIONS

The following abbreviations are used in this paper:

TPI	Terahertz pulsed imaging.
THz	Terahertz, 1 THz=10^{12} Hz.
PE	Paraffin-embedded.
TD	Time-domain.
FD	Frequency-domain.
IR	Impulse response.
FR	Frequency response.

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