Materials for phantoms for terahertz pulsed imaging

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Abstract

Phantoms are commonly used in medical imaging for quality assurance, calibration, research and teaching. They may include test patterns or simulations of organs, but in either case a tissue substitute medium is an important component of the phantom. The aim of this work was to identify materials suitable for use as tissue substitutes for the relatively new medical imaging modality terahertz pulsed imaging. Samples of different concentrations of the candidate materials TX151 and napthol green dye were prepared, and measurements made of the frequency-dependent absorption coefficient (0.5 to 1.5 THz) and refractive index (0.5 to 1.0 THz). These results were compared qualitatively with measurements made in a similar way on samples of excised human tissue (skin, adipose tissue and striated muscle). Both materials would be suitable for phantoms where the dominant mechanism to be simulated is absorption (~ 100 cm^{-1} at 1 THz) and where simulation of the strength of reflections from boundaries is not important; for example, test patterns for spatial resolution measurements. Only TX151 had a frequency-dependent refractive index close to that of tissue, and could therefore be used to simulate the layered structure of skin, the complexity of microvasculature or to investigate frequency-dependent interference effects that have been noted in terahertz images.

1. Introduction

Phantoms are commonly used in medical imaging for quality assurance, calibration, research and teaching. They may include test patterns or simulations of organs, but a tissue substitute medium is required in both applications. Such media include water-equivalent materials for X-ray computed tomography, agarose gel for MRI and gels containing scatterers such as graphite for ultrasound.

Terahertz pulsed imaging is a developing medical imaging modality (Fitzgerald *et al* 2002b). The first clinical applications are underway in dermatology (Woodward *et al* 2003) and dentistry (Crawley *et al* 2003), laboratory applications are under investigation (Berry *et al* 2004) and intraoperative applications will follow. Terahertz radiation is strongly absorbed by water (Kindt and Schmuttenmaer 1996) and the applications currently being investigated have been chosen to take account of this, being those where water absorption does not prevent the acquisition of useful results. Firstly they are situations in which the limited depth of penetration in human tissue, of the order of a few millimetres (Arnone *et al* 1999) is not a limitation and secondly the clinical conditions are those where it is likely that tissue water content will be a useful indicator of disease state. Test objects without tissue substitutes have been used to date (Fitzgerald *et al* 2002a) but, in the same way as for the other modalities, there will be a need for imaging phantoms that include a tissue substitute material. These might be used for depth calibration, organ simulation, research into artefactual effects and system performance measurements. The aim of the work described here is to identify a suitable tissue substitute material to use for terahertz pulsed imaging.

The technique of terahertz pulsed imaging is described elsewhere, for example (Mittleman 2003). It relies on the detection of pulses of terahertz radiation after they have been transmitted through, or reflected from, a subject. The pulses have a full width half maximum duration of the order of a picosecond and the signal is usually recorded over a period of approximately 30 ps. A range of frequencies is present because it is a pulsed imaging technique (the precise range and relative amplitudes depends upon the instrumentation used). It is therefore important when choosing a tissue substitute to examine its behaviour over a range of frequencies; the time domain behaviour of a pulse from a specific instrument would not necessarily give data transferable to other instruments.

The terahertz frequency range is usually defined to extend from 0.1 to 10 THz, which means that the interaction of the radiation with a medium would conventionally be considered using electromagnetic terminology at the low frequency extreme (permittivities), and by optical descriptions at the high frequency extreme (refractive indices). In this work an optical description has been adopted, so the transmission, propagation and reflection of pulses is governed by Fresnel equations, and the material is characterised by its complex refractive index. This may also be expressed in terms of the frequency-dependent linear absorption coefficient and refractive index.

From a survey of the literature regarding phantoms used at adjacent wavelengths in the electromagnetic spectrum, the gelling agent TX151 (Chou *et al* 1984)and napthol green dye (Iizuka *et al* 1999) were identified as the most promising candidates for tissue simulation in the terahertz frequency band. The former material was selected as it has been used in the microwave band to simulate high water content material. Napthol green dye was selected it has been used in the near infrared to simulate tissue when investigating radiation-induced changes. Although many materials chosen for use in the near infrared are selected because of their scattering characteristics, this was not the case for napthol green dye and this encouraged us to investigate it in the terahertz band. In the terahertz regime Rayleigh scattering is considerably reduced compared with the near infrared, and is therefore a less important criterion for tissue simulation. We have previously measured the optical properties of a range of tissue samples using a terahertz imaging system (Berry *et al* 2003) and the aim of the work described here was to determine which candidate material had properties most similar to those of tissue in the 0.5 to 1.5 THz range. In this preliminary investigation we sought materials whose properties were consistent with those measured for tissues i.e. with values within ± 10% across the frequency range.

2. Methods

The terahertz measurements from the two candidate materials were taken in transmission mode, using the Leeds pulsed terahertz imaging system during May and June 2003. Terahertz pulse generation was by electro-optical generation in a zinc telluride crystal (Mittleman 2003). One hundred averages of a time series of 512 points separated by 110 fs were used.

Three measurements were acquired, each from different areas of each sample. The error for all thickness measurements on the samples was ± 2 μm. Each time series was transformed to the frequency domain using the fast Fourier transform, where the points were separated by 0.018 THz.

TX151 (The Oil Research Centre, Lafayette, LA, USA) is a white powder that solidifies when mixed with water to give a material with the consistency of rubber. Three different concentrations were prepared at room temperature using a magnetic mixer. The ratios of TX151 powder to distilled water by volume were: Gel A 1:4; Gel B 1:2 and Gel C 1:1. Three thicknesses (50 μm, 100 μm, 470 μm) of each of the TX151 gels were prepared and mounted between two 2 mm thick TPX plates. Gels thicker than 470 μm attenuated the pulse too much for measurements to be made. The reference measurements were made by making the measurements through the two TPX plates and an air gap of the same thickness as the relevant TX151 sample.

Three concentrations of liquid napthol green dye were prepared at room temperature by dissolving powdered dye in distilled water, where the percentages of dye to distilled water by mass were: Dye A 10%; Dye B 15% and Dye C 20%. The dye samples were placed in a plastic bag of thickness 52.4 μm ± 0.1 μm between two polyform windows. A micrometer screw gauge was used to change the separation of the polyform windows allowing four thicknesses (400 μm, 450 μm, 500 μm, 550 μm) of dye to be measured at each concentration. The reference measurements were made by recording a pulse through the two polyform windows and the plastic bag inflated with air to the appropriate thickness.

The materials used to support the samples, TPX (Mitsui plc, UK) and polyform (Dow Corning, Orion, Bradford, UK), were chosen for this purpose because they have been shown (Birch and Nicol 1984,Zhao *et al* 2002) to have very low absorption in the terahertz region and refractive index independent of frequency.

It was assumed that the samples were of sufficient thickness to ensure that the measured pulse did not include contributions from etalon effects, i.e. that the total measurement time of the pulse was less than the time taken for internal reflections to reach the detector. The absorption coefficient at each frequency $\mu(\upsilon)$ may then be found from the slope of a linear

regression fit of $\ln(I(\upsilon)/I_0(\upsilon))$ to thickness x, assuming equation (1), where $I(\upsilon)$ is the intensity of the spectrum obtained by Fourier transformation, at frequency υ.

$$\frac{I(\nu)}{I_0(\nu)} = \exp(-\mu(\nu)x) \tag{1}$$

In a similar way, the frequency-dependent refractive index $n(\upsilon)$ was found from the slope of a linear regression fit of the frequency-dependent phase difference to thickness x, according to equation (2)(Kindt and Schmuttenmaer 1996).

$$\Phi(x,\nu) - \Phi_0(\nu) = \frac{2\pi\nu(n(\nu)-1)}{c}x \tag{2}$$

The noise level was calculated from the high frequency tail in the amplitude spectrum from the thinnest sample. At each frequency, different inclusion criteria based on the noise level were applied for the two calculated parameters. For the absorption coefficient, measurements at a given frequency were included only where $\sqrt{I(\upsilon)}$ from the thinnest sample was greater than the noise level by a factor of e (2.7) or more. For the refractive index calculations, measurements at a given frequency were included only where $\sqrt{I(\upsilon)}$ in the amplitude spectra of both the thinnest and the thickest samples was greater than the noise level by a factor of e or more. This stricter criterion was used because it excluded measurements made at frequencies affected by the large amplitude fluctuations associated with absorption by water vapour. These fluctuations were identical in the measured and reference spectra, and so cancelled out in Equation (1) for absorption coefficient, but they contributed to the uncertainty in the measurement of phase difference in Equation (2).

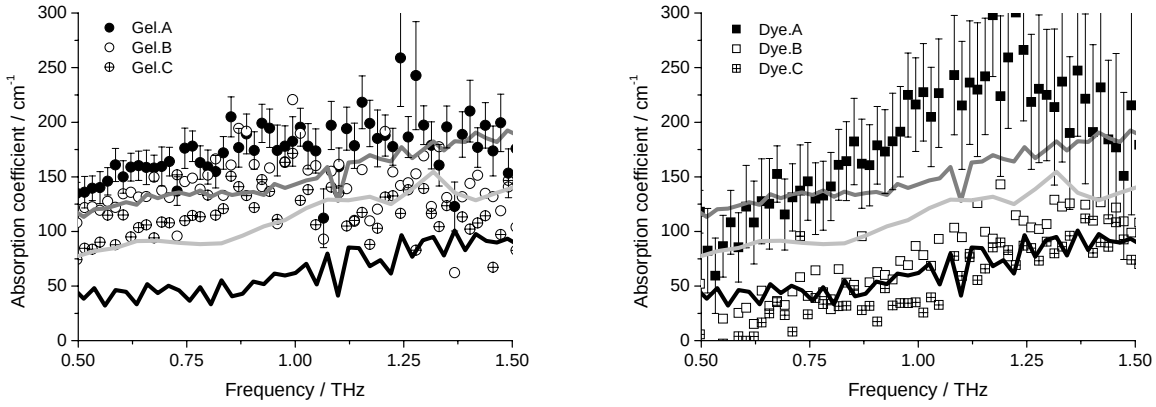
For calculation of phase, the time series representing the pulses were zero padded to 4096 points before Fourier transformation, to reduce the risk of phase changes between successive points exceeding 2π. This can lead to errors in the phase result arising from the phase unwrapping (Ghiglia and Pritt 1998), which is an integral part of the calculation. Additionally, a phase correction was applied to ensure that individual plots of phase to frequency intercepted the origin. This was necessary because uncertainty in the value of the phase at low frequency, arising from the low signal to noise ratio, were otherwise propagated to higher frequencies by the phase unwrapping algorithm, resulting in errors in the calculated

phase differences used in equation (2). Errors were estimated from the residual standard deviation of the calculated regression lines. To aid clarity of presentation, error bars are shown in the figures only for the lowest concentrations of the materials.

The measurements of frequency-dependent absorption coefficient for excised samples of human adipose tissue, skin and striated muscle have previously been published (Berry *et al* 2003). The frequency-dependent refractive indices were calculated from the same experimental data using equation (2).

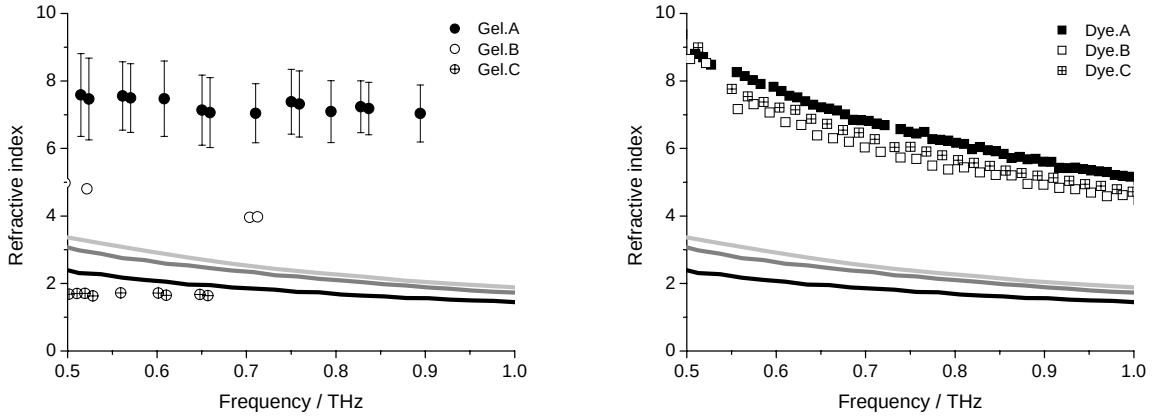
3. Results

The absorption coefficient results are shown in Figure 1, and those for refractive index in Figure 2. It was necessary to truncate the refractive index results at 1 THz because of a discontinuity in phase introduced by water vapour absorption peak at 1.07 THz. (Martin 1967) Gaps in the results arose from the use of the stricter noise criterion for the refractive index.



(a) (b)

Figure 1. Measured absorption coefficient for (a) TX151 gel and (b) napthol green dye. The solid lines show the values for adipose tissue (black); skin (light grey) and striated muscle (grey) (Berry *et al* 2003)



(a) (b)

Figure 2. Measured refractive index for (a) TX151 gel and (b) napthol green dye. The solid lines show the values for adipose tissue (black); skin (light grey) and striated muscle (grey). Error bars have been omitted from (b) as their length exceeded the length of the ordinal axis.

4. Discussion

TX151 Gel B had absorption characteristics consistent with those for striated muscle and those for TX151 Gel C were consistent with the skin results. Napthol green Dyes B and C had absorption characteristics consistent with those for adipose tissue. TX151 Gel C had a refractive index similar to that for adipose tissue; none of the napthol dyes had a refractive index similar to those of the measured tissues, and these measurements had particularly large errors.

Where the dominant mechanism to be simulated by the phantom is absorption, and simulation of the strength of reflections from boundaries is not important (for example, test patterns for spatial resolution measurements), the B and C mixes of both materials would be suitable. The liquid nature of the napthol green dye would be an advantage for multimodality use, where the same phantom might be filled with a different tissue substitute liquid for each modality. In some cases thicker phantoms, which would be easier to handle than those with sub-millimetre dimensions, might be useful. These would use mixtures with a greater proportion of the dye, leading to lower absorption but would only be valuable if the slope of the absorption coefficient against frequency plot was the same as for the mixtures measured here.

Where the requirement is for refractive index also to be simulated correctly, then only TX151 would be suitable. Such applications include depth calibration phantoms and organ

simulation. TX151 Gel C was 50% TX151 powder and Gel B 33% powder, the reduction in powder doubled the refractive index but had much less effect on the absorption coefficient. There is therefore scope to prepare a series of gels with a range of refractive indices that could be used to simulate the layered structure of skin (Pickwell *et al* 2004,Woodward *et al* 2003), or to prepare structured materials perhaps to simulate the ordered nature of scar tissue or the complexity of microvasculature. Such gels will also be useful for further study of frequency-dependent interference effects that have been noted in terahertz images.

For routine quality assurance measurements a simple two-compartment test object could be built using TX151, with a different concentration of the material in each half. Such an arrangement could be used in reflection or transmission systems. In time domain images, the boundary between the two materials, in the direction of the beam, would be used for measurement of the edge spread function, which would allow derivation of the modulation transfer function. This would allow spatial frequency performance to be predicted and, if combined with the noise power spectrum, would allow fundamental indicators of system performance to be determined including the signal to noise ratio, the detective quantum efficiency, the noise equivalent quanta (Workman and Brettle 1997). The noise power spectrum will also allow poorly aligned raster-scanning to be detected and potentially indicate if there are any dropped pixels (Padgett and Kotre 2004). By using two compartments rather than one, information about the stability of the frequency distribution in the pulse would be available.

The long-term stability of the material has yet to be determined. This is of greater relevance to quality assurance phantoms than those used experimentally over a period of days. Should the material deteriorate with storage it would be necessary to investigate methods for manufacturing single-use phantoms that gave reproducible results.

Measurement of the frequency-dependent refractive index was difficult, especially for the TX151 gels. There are several reasons for the difficulties. An imaging system is deliberately optimised for spatial resolution at the expense of spectral resolution: it has a focused beam and the signal is noisy, particularly in the lower frequencies of the band. This increased the possibilities of errors when unwrapping the phase, arising from the introduction of artefactual phase increments where the signal was noisy. Furthermore, there is the likelihood that errors have been introduced at the lower frequencies because the assumption of plane phase fronts,

implicit in the calculation of refractive index, is not valid for a focused beam (Bowen *et al* 2004). Many points had to be discarded from refractive index calculations because of noise. Unfortunately the materials most affected were those with refractive indices close to those of tissue, leading to rather sparse plots (Figure 2). The system was not purged of atmospheric gases, and water vapour absorption (Martin 1967) introduced discontinuities in the refractive index results. This limited the range of measurements to under 1 THz.

However, as both tissues and candidate materials were measured under the same conditions, such systematic errors would apply to both and we believe that the materials we have identified are good matches to tissue. Our results were obtained by using the frequency domain properties of the materials and may be generalised to all terahertz imaging systems using frequencies in the 0.5 to 1.5 THz range, including continuous wave systems and those with differently composed pulses.

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