Terahertz Time-Domain Spectroscopy of Human Blood

Caroline B. Reid, George Reese, Adam P. Gibson, and Vincent P. Wallace, *Member, IEEE*

***Abstract*—In the continuing development of terahertz technology to enable the determination of tissue pathologies in real-time during surgical procedures, it is important to distinguish the measured terahertz signal from biomaterials and fluids, such as blood, which may mask the signal from tissues of interest. In this paper, we present the frequency-dependent absorption coefficients, refractive indices, and Debye relaxation times of whole blood, red blood cells, plasma, and a thrombus.**

***Index Terms*—Biomedical engineering, medical imaging, terahertz technology.**

I. Introduction

THE spectroscopy of blood and its constituents is well known over many sections of the electromagnetic spectrum. The infrared spectroscopic analysis of blood serum plays a critical role in diagnosing and monitoring a wide variety of disorders [1]. In the visible and near infrared range [2], the spectral differences in oxy- and deoxy-hemoglobin are readily utilized in pulse oximetry and imaging [3]. At longer wavelengths, Wolf *et al*. [4] measured the broadband dielectric spectroscopic properties of human blood over the frequency range from 1 Hz to 40 GHz and modeled its behavior using Debye theory; and Gabriel *et al*. [5] developed a parametric model to describe the variation of dielectric properties of tissues including blood as a function of frequency. The measured spectrum from 10 Hz to 100 GHz was modeled with four dispersion regions. To date, little has been published on the spectroscopy of blood in the terahertz frequency range.

As terahertz frequency radiation (100 GHz–10 THz) is highly absorbed by water, and water is one of the main constituents of tissue, penetration depths in this frequency range are shallow, ranging from typically a few hundred microns in high water content tissues to centimeters in tissues with a high fat content [6], [7]. One would expect the terahertz spectrum of blood to be dominated by water (over 50%) and thus not have any specific spectral feature useful for diagnostic purposes. However, the potential use of THz technology in the clinical environment for *in vivo* tissue diagnosis makes the knowledge of blood absorption spectrum and refractive index in the THz frequency range important. The number of reported biomedical studies using THz includes teeth [8], [9], healthy skin and basal cell carcinoma in both *vitro* [10] and *in vivo* [11], excised breast cancer [12], colon cancer [13], liver [14], and burns [15], [16]. Some of these potential applications of THz technology to medicine are to determine tissue pathologies in real time [17]. This has great implications for, for example, determining disease-free margins during surgery, thus reducing the reliance on subjective surgical procedures. One major potential problem for use in the clinical setting is the presence of biomaterials and fluids, e.g., blood, which could contaminate a THz signal. It is, therefore, important to know the THz properties of blood.

In this paper, we present the first spectroscopic measurements of whole human blood, two of its constituents (red blood cells and plasma) and a blood clot (thrombus) in the terahertz region. We also investigate the possible origins of the spectral differences of the samples by fitting to the Debye relaxation times and by determining the spectra of pure hemoglobin molecules.

Blood is composed of red blood cells, white blood cells, and platelets suspended within plasma. Blood is, by volume, typically 45% red blood cells, 55% plasma, and a very small amount of white blood cells. Plasma is composed predominantly of water (92%) and dissolved proteins and salts (8%). Red blood cells contain hemoglobin, each molecule of which consists of four protein subunits that contain iron and are responsible for blood's characteristic red color. White blood cells defend the body against infection. Platelets are involved in the formation of blood clots (thrombus), which consist of a solid mass of coagulated platelets and proteins (mainly fibrin) [18].

II. Methods

A. Experimental Method

A standalone portable THz system, the TPI Spectra1000 (TeraView Ltd., Cambridge, U.K.), was used in this study. A full description of the system operation is given elsewhere [19]; however, it is briefly described here for clarity. The system consists of a 250 mW Vitesse 800 (Coherent Inc., Santa Clara, CA, USA) mode-locked Ti:Sapphire oscillator, and uses photoconductive devices for both THz generation and detection. The

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C. B. Reid was with the Department of Medical Physics and Bioengineering, University College London, London, WC1E 6BT, U.K. She is now with Laser- und Medizin-Technologie GmbH, 14195 Berlin-Dahlem, Germany (e-mail: c.reid@lmtb.de).

G. Reese was with the Division of Surgery, Imperial College London, London SW7 2AZ, U.K. He is now with Whipps Cross University Hospital, London, U.K. (e-mail: george.reese@ic.ac.uk).

A. P. Gibson is with the Department of Medical Physics and Bioengineering, University College London, London, WC1E 6BT, U.K. (e-mail: adam.gibson@ucl.ac.uk).

V. P. Wallace is with the School of Physics, University of Western Australia, Crawley, W.A. 6009, Australia (e-mail: vincent.wallace@uwa.edu.au).

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100 fs laser pulses with 800 nm central wavelength at a repetition rate of 80 MHz are split by a beam splitter into a pump and a probe beam. The probe beam is passed through a mechanical translation stage, which is moved at fixed intervals over a finite distance. This acts as a delay line, which changes the relative path length of the probe beam to the pump beam to facilitate the mapping of a whole THz pulse. Using multiple path lengths is equivalent to measuring the THz electric field at multiple instants in time. The delay line operates at a typical scan rate of 15 Hz, but as a pulse can be measured over both the up and the down sweep, a pulse acquisition rate of 30 Hz is achieved. This rate was chosen as an optimum between acquisition time and signal-to-noise ratio (SNR). By slowing the scan rate or by signal averaging, the SNR can be improved at the cost of a corresponding increase in data collection time and vice versa. The time resolution was approximately 200 fs, which is limited by the width of the laser pulse.

The spectroscopy system consists of a sealed sample chamber that can be purged with nitrogen (or dry air) to remove water vapor. Following the delay line, the transmission pulses are focused, using a pair of gold coated off-axis parabolic mirrors onto a pair of z-cut quartz windows, between which a sample is held. The transmitted beam is focused by another pair of mirrors onto a photoconductive detection device.

The liquid sample transmission cell consists of two quartz windows separated by a Teflon spacer which can be between 100 μm to 1 mm thick. It is designed to be used vertically in transmission mode, so to hold liquid samples, rubber rings are placed between the quartz windows and a retaining plate that is tightened to create a water-tight seal. The spacer thickness used in this study was 200 μm. A reference measurement was made in each instance using two pieces of quartz plate held together. All measurements were made at room temperature.

Blood samples were taken from a healthy person by a qualified clinician (G.R.); the samples were centrifuged to split them into separate volumes. Three measurements were made on each of the four constituents: whole blood, plasma, blood cells, and blood clots (or thrombus). Six samples of whole blood were taken and immediately stored in a blood collection tube with an anticoagulant. Whole blood from three of these tubes was transferred to the liquid sample cell for measurement. After centrifuging the three other collection tubes, the plasma was decanted and three separate measurements of plasma were performed. The residual in each of the centrifuged collection tubes containing only cells were measured. Finally, three samples were put into collection tubes with a coagulant to form a thrombus. Being more of a solid tissue-like substance, the cells and the thrombus were measured using a tissue sample holder, described in [20].

For the determination of the absorption coefficients of the hemoglobin molecules, measurements were made of hemoglobin powder, rehydrated to solutions of different concentrations. The hemoglobin powder (Sigma Aldrich) was made into solutions using distilled water at a number of concentrations between 2.5% and 15% hemoglobin by weight. It was assumed that the contributions from the hemoglobin and water in the solutions were linearly additive, that is, the contributions to the measured absorption coefficient μ_a follow (1). Previous studies of aqueous protein solutions have found this trend to be true [21]. The μ_a of the hemoglobin molecules was calculated by subtracting the μ_a of water, normalized for % concentration, from the measured μ_a of the hemoglobin solutions. The absorption coefficients calculated for each individual solution concentration were averaged to achieve a single μ_a value for hemoglobin

$$\mu_{a(\mathrm{molecule})} = \mu_{a(\mathrm{solution})} - \mu_{a(\mathrm{H_2Obulk})}. \tag{1}$$

B. Analysis Method—Debye Relaxation

The dielectric properties in the low THz frequency range of water have been characterized by several authors [22], [23]. Double Debye theory has been used to model terahertz spectroscopy data of polar molecules [24] and electrolytes [25] and fully hydrated nucleotides [26]. Pickwell *et al*. used finite-difference time-domain (FDTD) techniques and double Debye theory to model the interaction of a THz pulse with a tissue that has been tested against experimental results [19], [20], [27], [28]. Truong *et al*. investigated Debye parameter extraction for characterizing the interaction of terahertz radiation with human skin tissue [29] and Arbab *et al*. has recently shown that a double Debye dielectric relaxation model can be used to explain the terahertz response of both normal and less severely burned rat skin [30]. These results show that tissue can be modeled as a semi-infinite homogenous medium with a dielectric constant similar to that of liquid water [31]. At lower frequencies, single Debye is used to explain the dielectric behavior of blood [4] and elastin [32]. Therefore, as blood is characterized as a tissue like substance with a water content of about 50%, we have applied Debye theory to investigate if relaxation mechanisms can be used to explain differences observed in the absorption and refractive index between whole blood and its components. Debye theory describes the reorientation of molecules that could involve translational and rotational diffusion, hydrogen bond arrangement, and structural rearrangement. The Debye relaxation time τ describes the time necessary for $1/e$ of the dipoles to relax to equilibrium after an impulse. For a pure material, multiple Debye type relaxation processes are possible where the complex dielectric coefficient $\hat{\varepsilon}(\omega)$ is described by (2) [21]. ε_∞ is the real part of the dielectric constant at the high frequency limit, $\Delta\varepsilon = \varepsilon_j - \varepsilon_{j+1}$, ε_j are intermediate values, occurring at different times, of the dielectric constant, τ_j is the relaxation time relating to the jth relaxation process, and ω is the angular frequency. The $\Delta\varepsilon$ term can be considered to be an "amplitude," indicating the "quantity" of that particular relaxation in the material under investigation

$$\hat{\varepsilon}(\omega) = \varepsilon_\infty + \sum_{j=1}^{n} \frac{\Delta\varepsilon}{1 + j\omega\tau_j}. \tag{2}$$

The complex dielectric coefficient of a material is simply related to the complex refractive index $\hat{n}(\omega)$ as described by (2), where $\varepsilon'(\omega)$ and $\varepsilon''(\omega)$ are the real and imaginary parts of the complex dielectric coefficient, respectively. The complex dielectric coefficient of a material can be determined simply from

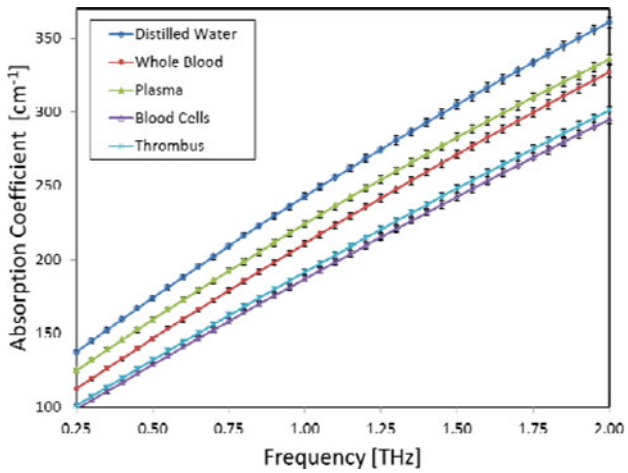

Fig. 1. Absorption coefficient for whole blood, blood cells, plasma, and a thrombus. The error bars represent the average standard error across all absorption measurements, which was 1%.

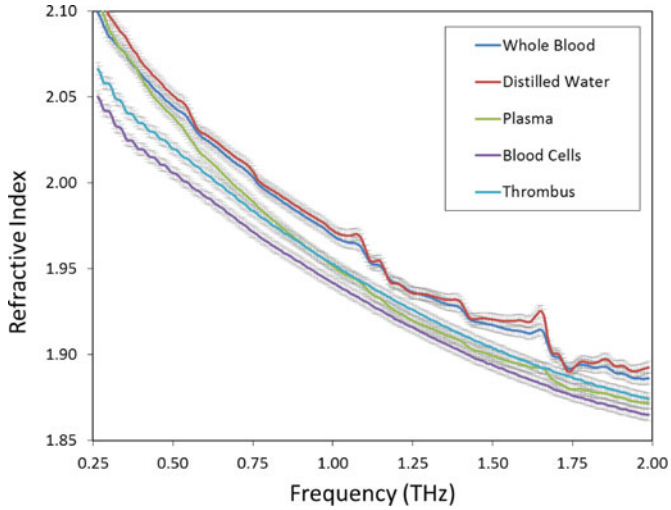

Fig. 2. Refractive index for whole blood, blood cells, plasma, and a thrombus. The error bars represent the standard error for each blood component.

the measured values for absorption coefficient μ_a and refractive index n using (2) and (3), respectively. The complex dielectric coefficients were calculated from the measured absorption coefficient and refractive indices following (2) for all the samples, and double Debye theory was applied following (2), where the ε_s values were held constant

$$\hat{\varepsilon}(\omega) = \hat{n}^2(\omega) = \varepsilon'(\omega) + i\varepsilon''(\omega) \tag{3}$$

$$\varepsilon'(\omega) = n^2(\omega) - \mu_a^2(\omega) \tag{4}$$

$$\varepsilon''(\omega) = 2n(\omega)\mu_a(\omega). \tag{5}$$

III. Results and Discussion

Transmission spectroscopy measurements were made of whole blood, blood plasma, blood cells, and a thrombus, from which the absorption coefficients and refractive indices of each component was determined. The absorption coefficients of the blood components illustrated in Fig. 1 are shown in comparison to pure water. Even though the spectroscopy system was purged during all measurements, some water vapor lines were still present; therefore, we applied a numerical method for removal of these effects, as described in [33]. Fig. 1 shows that the absorption of pure water is greater than whole blood or any of its components. It is apparent that there is a decrease in overall absorption coefficient as the water content of the blood components is reduced; plasma (≅92% water), whole blood (≅50% water), and packed blood cells. The exception, however, is the blood clot that has the same water content as whole blood. Here, clearly, the effects of coagulation and the formation of a thrombus have affected the absorption coefficient. It is likely that the formation of a thrombus, a protein/fibrin covalently bonded structure, encapsulates much of the water present impeding its ability to absorb THz radiation in the measured range.

The refractive index, shown in Fig. 2, of whole blood and blood components, in comparison to pure water shows, overall, that the refractive index of water is greater than that of the whole blood and components. It would be expected that components with high water content would have refractive indices very similar to pure water and, while this is true of the whole blood sample, this does not appear to be the case with the plasma sample. The refractive index of the plasma at low frequency (0.1 – 0.5 THz) is consistent with water and whole blood, however begins to diverge at higher frequencies. The refractive indices of the blood clot and blood cells appear to be consistently 0.05 below that of pure water.

It is likely that water molecules may interact and weakly bond to polar functional groups on the surface of the blood constituents. The weak bonding of "bound" water to the constituent's surface modifies the vibrations of the water molecules leading to a lower refractive index and absorption coefficient. There are challenges to including both the bound and free water contributions into an effective model: it is difficult to experimentally separate the contributions of bound and free water to the permittivity [34].

The absorption coefficient of the hemoglobin molecules are illustrated in Fig. 3, and are shown in comparison to the absorption spectra for pure water and the red blood cells. The absorption coefficient for pure hemoglobin is lower than that of both water and the red blood cells. One might expect that the spectra for the hemoglobin and blood cells would be similar; however, differences in the spectral shape exist, particularly at the low-frequency range. Previous studies of dry protein and sucrose samples in the THz region have described a monotonic frequency-dependent increase below 2 THz for dry samples of DNA, BSA, cytochrome c, polypeptides, myoglobin, DNA, and collagen [35]–[44]. The monotonic increase with frequency is proposed to be due to a dense collection of overlapping vibrational modes in macromolecules that result in a rapid rise in the density of vibrational modes with frequency followed by a plateau or saturation at higher frequencies. This has been recreated in molecular dynamics simulation studies of several small proteins [36], [41]–[44]. The spectra measured in this study show a strong monotonic frequency-dependent increase up to at least 2.5 THz without any apparent resonances, which

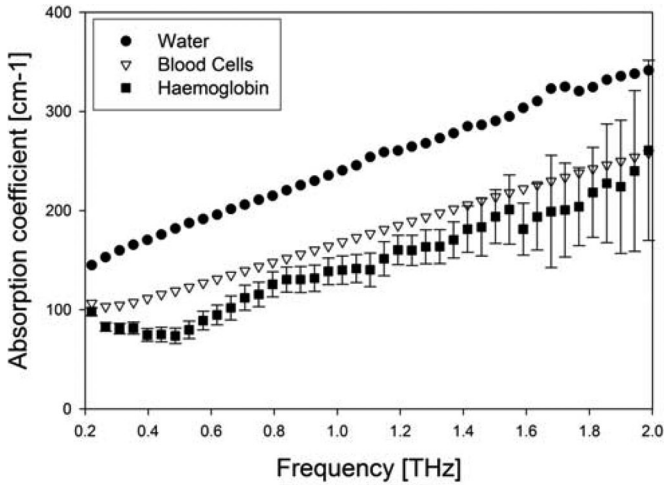

Fig. 3. Absorption coefficient for hemoglobin molecules, blood cells, and pure water.

TABLE I
DOUBLE DEBYE COEFFICIENTS FOR WHOLE BLOOD AND BLOOD COMPONENTS

	ε_∞	ε_S	ε_2	τ_1(ps)	τ_2(ps)
Whole Blood	2.1	130[a]	3.8	14.4	0.1
Blood Plasma	1.7	78.8	3.6	8.0	0.1
Blood Cells	3.4	2.5[b]	23.8	410.8	1.8
Thrombus	2.2	130[a]	3.7	16.1	0.1
Water	3.3	78.8	4.5	8.4	0.1

a (Schwan 1983 [48]).

b (ICT 1933).

is consistent with the proposed theory of a dense collection of overlapping vibrational modes.

The determined double Debye relaxation coefficients are given in Table I. τ_1 relaxation for the whole blood, at 14.4 ps, is higher than that of the pure water, suggesting that the red blood cells retard the free water relaxations. The τ_1 relaxation time for thrombus is longer than for water or whole blood, suggesting that the coagulation of the blood results in a greater impedance of the free water present. Interestingly, the τ_1 relaxation for the blood cells is very large. While this is unlikely to correspond to a relaxation of the cell itself or of hemoglobin molecules within the cells as these would be much slower processes, this relaxation may well be due to the slowed relaxation of the associated water surrounding the molecule, which is, approximately, 10^2–10^4 slower than the free water [45]–[47].

IV. CONCLUSION

In this paper, we have measured the absorption and refractive index of whole human blood, plasma, and blood cells over the THz frequency range of 0.2–2 THz. We observed measurable differences in the spectroscopic absorption coefficients and refractive indices of blood and its components, although these differences were small. There appears to be some distinction in the Debye relaxation coefficients for the whole blood and its components. It has been suggested that FDTD modeling of tissues, which incorporates the Debye coefficients, may be of use as an analysis tool in the biomedical field [19], [27] meaning it may be possible to distinguish blood from surrounding biological tissue.

A significant difference could be seen in both the absorption and refractive index spectra of the whole blood and its thrombus, as well as the Debye coefficients. This suggests that measurements taken at THz frequencies are sensitive to the bonding mechanisms within the whole blood. In conclusion, given the high absorption of whole blood and plasma, when THz technology is being used *in vivo* during surgical procedure, the presence of blood needs to be minimized as not to interfere with the diagnostic ability and accuracy of tissue differentiation.

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Caroline B. Reid studied both electrical engineering and medical physics at the University College London (UCL), London, U.K., where she received the Ph.D. degree in terahertz imaging in 2009.

She subsequently was in the UCL's Radiation Physics Department, developing X-ray-based systems for homeland security. In 2013, she joined Laser- und Medizin-Technologie GmbH, Berlin-Dahlem, Germany, to work on Raman spectroscopy and imaging systems for cancer diagnosis.

George Reese is a Surgical Registrar in London, U.K.

Adam P. Gibson studied medical physics in Cardiff and Exeter, U.K. He received the Ph.D. degree in electrical impedance tomography from the University College London (UCT), London, U.K., in 1997.

Since then, he has been with UCL's Biomedical Optics Research Laboratory, developing optical methods for imaging the brain and breast. His research interests include radiotherapy, analyzing routine patient data, and imaging parchment manuscripts.

Vincent P. Wallace (M'02) studied physics at the University College London, London, U.K. He received the Ph.D. degree in medical physics from the Royal Marsden Hospital, London, U.K., in 1997.

He did his postdoctoral research at the Beckman Laser Institute and Medical Clinic, University of California, Irvine. He then joined TeraView, Ltd., to develop biomedical applications of terahertz technology. In 2007, he took up an academic position at the University of Western Australia, Crawley, W.A., Australia. His research interests are in cancer diagnosis, burn assessment, biomedical optics and terahertz technology.