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Abstract. Terahertz (THz) time-domain spectroscopy systems permit the measurement of a tissue's hydration level. This feature makes THz spectrometers excellent tools for the noninvasive assessment of skin; however, current systems are large, heavy and not ideal for clinical settings. We previously demonstrated that a portable, compact THz spectrometer permitted measurement of porcine skin optical properties that were comparable to those collected with conventional systems. In order to move toward human use of this system, the goal for this study was to measure the absorption coefficient (μ_a) and index of refraction (n) of human subjects *in vivo*. Spectra were collected from 0.1 to 2 THz, and measurements were made from skin at three sites: the palm, ventral and dorsal forearm. Additionally, we used a multiprobe adapter system to measure each subject's skin hydration levels, transepidermal water loss, and melanin concentration. Our results suggest that the measured optical properties varied considerably for skin tissues that exhibited dissimilar hydration levels. These data provide a framework for using compact THz spectrometers for clinical applications. © *The Authors. Published by SPIE under a Creative Commons Attribution 3.0 Unported License. Distribution or reproduction of this work in whole or in part requires full attribution of the original publication, including its DOI.* [DOI: 10.1117/1.JBO.18.12.120503]

The terahertz (THz) region of the electromagnetic spectrum is defined as frequencies ranging from 0.1 to 10 THz. In recent years, numerous THz sources, detectors, and transmission technologies have been developed.[1–3] These advancements have facilitated the development of numerous novel applications. A few examples include nondestructive imaging, security screening, quality control of food and pharmaceuticals, ultrafast computing, and wireless communications.[1–3] Several medical and biological applications are also under development to improve detection and diagnosis of skin cancers, burns, and other pathologies.[4–12]

Despite the elevated interest to develop THz-based applications, few basic science research investigations have been conducted to better understand the fundamental mechanisms governing THz-tissue interactions. In fact, only a few studies have been conducted to characterize the optical properties of *in vivo* human tissues at THz frequencies.[8,13,14] In addition, previous studies were performed with conventional THz spectrometers, which are not amenable for field applications. In this study, we demonstrate that a portable THz time-domain spectroscopy (TDS) system can be used to accurately measure the optical properties of human skin tissue at THz frequencies.

A total of 35 human subjects were recruited in adherence to an approved Institutional Review Board protocol. Subjects were composed of both genders and varied ethnic backgrounds. Measurements were made from three skin regions: ventral (inner) forearm, dorsal (outer) forearm, and palm. Prior to experimentation, each exposure area was prepped with an ethanol swab to reduce surface dirt and oil. The selected zones were then marked with a washable highlighter and photographed subsequently. Participants were then directed to undergo THz measurements in addition to Mexameter and Tewameter probes measurements as outlined in Fig. 1(a).

In this study, we used a THz-TDS system composed of a mini-Z THz-TDS system and a skin reflection unit [Fig. 1(b)]. The mini-Z THz TDS system generates broadband THz radiation using a photoconductive (PC) switch technique, originally pioneered by Auston et al.[15] In brief, the PC switches function by using a laser with a short pulse (femtoseconds) to excite a biased PC antenna consisting of metallic striplines deposited on semiconductor materials. When the optical pulse interacts with the semiconductor material, it generates electron holes in the conduction valence band, and thereby creates photocarriers. These photocarriers are then accelerated toward the anode using a DC bias, and this results in the creation of an appreciable photocurrent in the PC antenna. Since these time-varying photocurrents occur in the subpicosecond range, they thereby emit broadband electromagnetic radiation at THz frequencies. In this system, we used a 780-nm pump laser operating with a pulse duration of 100 fs (Zomega Terahertz Corporation, East Greenbush, New York). Signals were collected from 0.1 to 2.0 THz using an electro-optical crystal (1-mm thick) made of zinc telluride (ZnTe).

The reflection module was utilized in order to measure the optical properties of human skin in reflection geometry. The reflection module consists of a 2-mm-thick TPX® Polymethylpentene window. The properties of the TPX, which are fairly constant across most of the THz frequency range (0.1 to 3 THz), exhibit index of refraction values close to 1.46 and an absorption coefficient of roughly 0.5 cm^{-1}. A total of five time domain measurements were collected for each skin region tested. A total of 250 waveforms were used to determine the average spectra for each tissue. Due to the large difference in refractive index between the TPX window and air, multiple reflections of the Terahertz pulse occur within the window. Usually, these reflections would interfere with the main pulse and appear as ripples in the resulting sample transmission spectrum, which is called the Fabry–Pérot effect. However, in this experiment, with 2-mm TPX window, refractive index equal to 1.46, the time delay between two reflected pulses is 19.5 ps. This time delay is long enough to separate different

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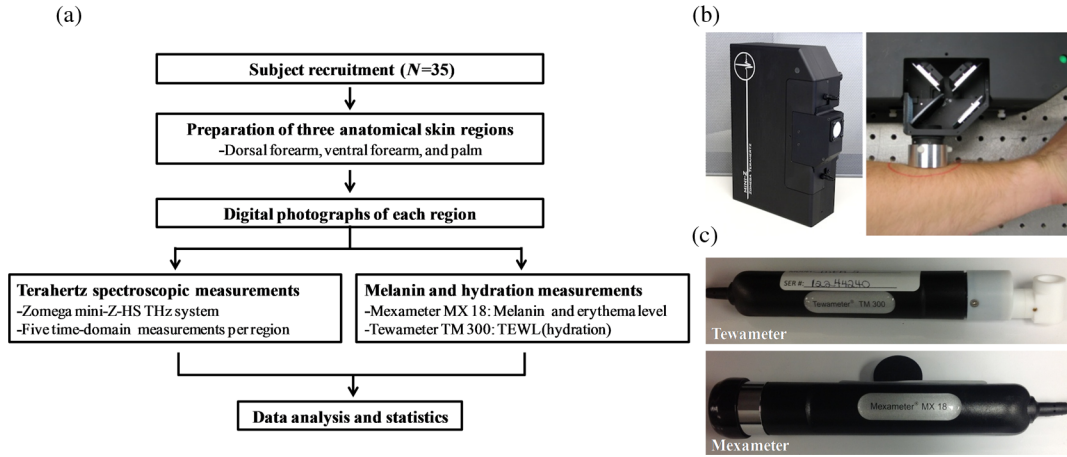
Fig. 1 Terahertz time-domain spectrometer for the measurement of the optical properties of human skin *in vivo*. (a) Experimental methodology. (b) Image of Mini-Z™ THz spectrometer and reflection measurement accessory. (c) Image of tewameter and mexameter probe devices.

multiple-reflection pulses in the time domain. In this case, the extraction for the skin refractive index is quite straightforward. This peak is a direct result of the reflection at the TPX-skin/metal interface. At this interface, the reflection coefficient R can be written as:

$$R = \frac{n_{\text{TPX}} - n_{\text{skin}}}{n_{\text{TPX}} + n_{\text{skin}}}.$$

Therefore, the refractive index of skin can be calculated using:

$$n_{\text{skin}} = n_{\text{TPX}} \frac{1 - R}{1 + R}.$$

Let us assume the reflection coefficient for the referenced metal is -1. Then

$$n_{\text{skin}} = n_{\text{TPX}} \frac{1 + \frac{R_{\text{signal}}}{R_{\text{ref}}}}{1 - \frac{R_{\text{signal}}}{R_{\text{ref}}}}.$$

Spectra were processed using the following method: (1) Collect and align the reference and signal pulses; (2) Fourier transform signal and reference, and convert to amplitude and phase; (3) Calculate the frequency spectrum power; (4) Calculate the frequency dependent fraction of reflected power $R(f)$; (5) Calculate relative phase $\Theta(f)$ by subtracting reference from signal. We then used the following expressions to directly compute the index of refraction (n) and the extinction coefficient $\kappa(\omega)$: $n = n_0 \times (1 - R)/[1 + R - 2 \times (R)^{1/2} \times \cos(\Theta)]$ and $k = n_0 \times [-2 \times (R)^{1/2} \times \sin(\Theta)]/[1 + R - 2 \times (R)^{1/2} \times \cos(\Theta)]$. Lastly, we computed values for the μ_a using the $\kappa(\omega)$ values and the following expression: $\mu_a = 4\pi\kappa/\lambda$.

Given the fact that skin color and condition vary depending on a variety of factors (e.g., age and racial background), we used the Mexameter® MX 18 and Tewameter® TM 300 probes manufactured by Courage + Khazaka electronic (Cologne, Germany) to quantify skin color and transepidermal water loss (TEWL), respectively [Fig. 1(c)]. The Mexameter® MX 18 is a dual index meter that measures a tissue's absorption and reflection at several visible and infrared wavelengths. These measurements permit the determination of the relative concentration of melanin and hemoglobin, which are the primary components contributing to skin color. The Tewameter® probe measures the density gradient of the water evaporation from the skin indirectly by the two pairs of sensors (temperature and relative humidity) inside the hollow cylinder.

Figures 2 and 3 contain the average optical properties for each skin sample region plotted as a function of frequency. The data show that for all tissues the index of refraction decreases with increases in frequency [Fig. 2(a)]. The slopes for each data trace are comparable for all tissues; however, skin from the ventral forearm exhibits the highest index of refraction. Our statistical analyses indicate several salient points [Fig. 2(b)]. First, the differences between the index of refraction for dorsal and ventral forearm samples are statistically insignificant at most THz frequencies. Second, the index of refraction for palm skin and dorsal forearm are statistically significant. These differences are most pronounced at lower THz frequencies (i.e., 0.2 to 0.7 THz). Finally, the magnitude of the index of refraction varies the most between tissues in the 0.2 to 0.4 THz frequency range. This data suggest that THz systems which utilize these lower frequencies may be best for differentiating between different tissue types.
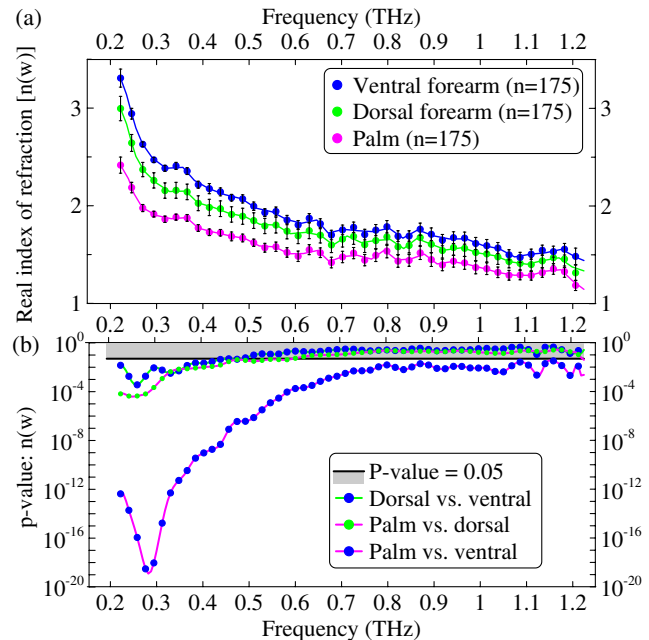

Fig. 2 The index of refraction of human skin. (a) Real index of refraction (*n*) plotted versus frequency (THz). (b). Statistical power as a function of frequency. The *p*-values were computed using a student t-test. Spectra for skin from ventral forearm, blue circles; dorsal forearm, green circles; and palm, pink circles. Data are expressed as means ± SD, with $n = 175$.

Figure 3 contains the mean absorption coefficient values for each skin sample region. The data show that for all tissues tested, the absorption coefficient increases with frequency from roughly 50 cm^{-1} at 0.2 THz up to 300 cm^{-1} at 1.2 THz. These values are comparable to those reported in previous reports.[7,8,11–13] Our statistical analyses indicate that the magnitude of the absorption coefficient is comparable for all tissue regions that we measured [Fig. 3(b)]. At most frequencies the differences were insignificant; however, subtle significant differences do appear between 0.2 and 0.4 THz and between 0.8 and 1.0 THz. These data further suggest that THz systems operating between 0.2 and 0.4 THz may be best suited for differentiating between different tissue types.

In order to determine whether a strong correlation exists between tissue hydration, melanin content, hemoglobin levels, and THz optical properties, we measured the TEWL and pigment levels for each tissue sample. We plotted the slope for each subject's absorption coefficient versus its respective TEWL, melanin, and hemoglobin values. The mexameter probe data showed that the dorsal skin exhibited the highest concentration of melanin and hemoglobin, followed by the ventral and palm regions. However, these measured values did not show a statistically significant correlation with the optical properties of skin. In contrast, the TEWL data indicate that a fairly strong correlation (R^2) exists between the slope of the absorption coefficient and the measured TEWL values. This finding further underscores the position that THz spectrometers may be useful, accurate tools for noninvasively determining the hydration level of tissues [Fig. 3(c)].

In summary, we measured the optical properties of human skin using a compact THz spectrometer. Spectra were collected from 0.1 to 2 THz, and measurements were made at three regions: palm, ventral (inner), and dorsal (outer) forearm. For all skin samples, the results show that the index of refraction (n) decreases with frequency, and the values for the absorption coefficient (μ_a) increase with frequency. All skin regions exhibited comparable optical properties; however, skin from the ventral forearm and that from the palm exhibits the highest and lowest index of refraction values, respectively. Furthermore, the index of refraction for palm skin and dorsal forearm is statistically significant at most THz frequencies. In addition, the index of refraction values varies the most between tissues in the 0.2 to 0.4-THz frequency range. We also show that for all tissues the absorption coefficient increases with frequency from roughly 50 cm^{-1} at 0.2 THz up to 300 cm^{-1} at 1.2 THz. These values are comparable to those reported in previous reports.[7,8,11–13] Finally, in this work, we demonstrate the slope of the absorption coefficient curves are strongly correlated with the TEWL values for each skin region. This data suggest that THz spectrometers may be a useful tool for measuring the hydration levels of tissues.

Fig. 3 The absorption coefficient (μ_a) of human skin at three different locations. (a) Absorption coefficient (μ_a) plotted versus frequency (THz). (b). Statistical power as a function of frequency. The p-values were computed using a student t-test. Spectra for skin from ventral forearm, blue circles; dorsal forearm, green circles; and palm, pink circles. Data are expressed as means $\pm$ SD, with $n = 175$. (c) The slope of the absorption coefficient (μ_a) of human skin plotted versus the TEWL value measured with Tewameter.

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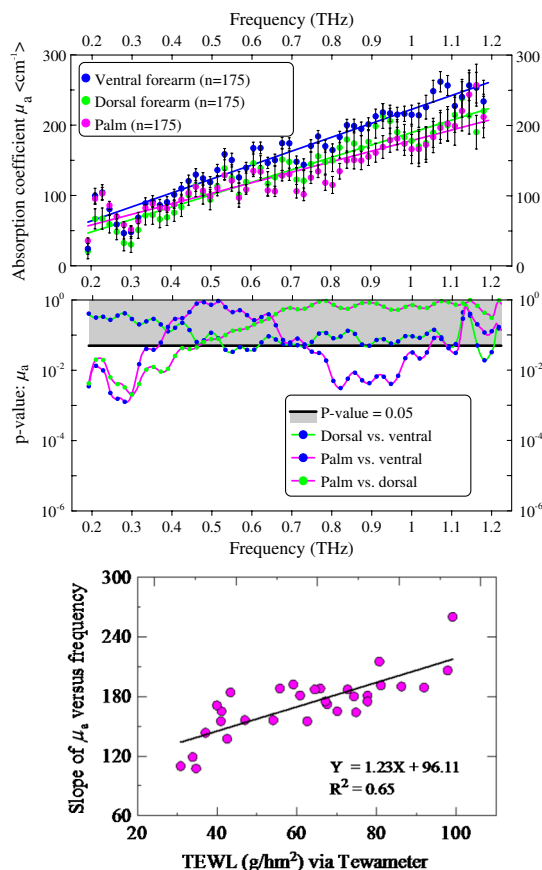15. D. H. Auston, "Picosecond optoelectronic switching and gating in silicon," *Appl. Phys. Lett.* **26**(3), 101–103 (1975).