In vivo terahertz pulsed spectroscopy of dysplastic and non-dysplastic skin nevi

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Abstract. The results of the in vivo terahertz (THz) pulsed spectroscopy (TPS) of pigmentary skin nevi are reported. Observed THz dielectric permittivity of healthy skin and dysplastic and non-dysplastic skin nevi exhibits significant contrast in THz frequency range. Dysplastic skin nevus is a precursor of melanoma, which is reportedly the most dangerous cancer of the skin. Therefore, the THz dielectric spectroscopy is potentially an effective tool for non-invasive early diagnosis of melanomas of the skin.

1. Introduction
Terahertz (THz) pulsed spectroscopy (TPS) is an effective instrument for characterizing the THz dielectric permittivity, or the THz material parameters of media [1–6], as well as for reconstructing the internal structure of dielectric objects [7–13]. In particular, TPS techniques have been recently applied for medical diagnosis of oral [14], skin [15–17], and colon [18] cancers, and for intraoperative diagnosis of breast cancer [19]. However, numerous medical applications of TPS have not been considered yet, for instance, diagnosis of dysplastic skin nevi. This problem is dramatically important because the dysplastic skin nevus is considered to be a melanoma precursor [20], and the latter is reportedly the most dangerous cancer of the skin [21].

In this paper we show the results of studying in vivo the THz dielectric characteristics of healthy skin, dysplastic and non-dysplastic skin nevi from four patients. We demonstrate that THz dielectric characteristics of dysplastic and non-dysplastic nevi significantly differ. Thus, the ability to use the TPS for early non-invasive diagnosis of dysplastic skin nevi and, as a consequence, of melanomas of the skin, is demonstrated.

2. Materials and Methods
In the present work we use the TPS setup operating in reflection-mode [9]. Generation and detection of THz pulses are performed in LT-GaAs photoconductive antenna and electrooptical detector based on ZnTe–crystal, respectively. The setup allows us to measure the THz reflectivity...
of the sample, and to reconstruct its THz dielectric permittivity (or THz material parameters) in a wide frequency range of 0.1 to 2.5 THz.

During the experimental study we use a reference 1–mm–thick SiO₂–window to fix the tissue. Three THz waveforms are detected for each tissue sample: the waveform \( E_r(t) \) reflected from an empty SiO₂–window; the waveform \( E_m(t) \) reflected from a SiO₂–window with a gold mirror placed behind it; and the waveform \( E_s(t) \) reflected from a SiO₂–window with the sample of interest placed behind it. Let us define the Fourier spectrums of these waveforms as \( \tilde{E}_r(\nu) \), \( \tilde{E}_m(\nu) \), and \( \tilde{E}_s(\nu) \), where \( \nu \) stands for an electromagnetic wave frequency.

We reconstruct the THz dielectric permittivity of the sample \( \tilde{\varepsilon}(\nu) \), such as

\[
\tilde{\varepsilon}(\nu) = \varepsilon'(\nu) - i\varepsilon''(\nu),
\]

where \( \varepsilon'(\nu) \) and \( \varepsilon''(\nu) \) are the real and imaginary parts, respectively. The solution of this ill-posed inverse problem should minimize an error functional [1, 6]:

\[
\tilde{\varepsilon} = \arg\min_{\tilde{\varepsilon}} [\Phi], \quad \Phi = \left| \tilde{H}_{\text{exp}} - \tilde{H}_{\text{th}} \right|^2 + \left| \phi \left[ \tilde{H}_{\text{exp}} \right] - \phi \left[ \tilde{H}_{\text{th}} \right] \right|^2,
\]

where \( \tilde{H}_{\text{exp}}(\nu) \) and \( \tilde{H}_{\text{th}}(\nu, \tilde{\varepsilon}) \) are experimental and theoretical transfer functions, and \( |.| \) and \( \phi[...] \) are operators to extract the modulus and the phase.

We define the experimental transfer function as

\[
\tilde{H}_{\text{exp}} = \frac{\tilde{E}_m - \tilde{E}_r}{E_m - E_r}.
\]

The theoretical transfer function assumes multiple THz wave reflections in the SiO₂–window:

\[
\tilde{H}_{\text{th}} = \frac{\tilde{R}_{12} - \tilde{R}_{10} + \sum_{j=1}^{N} \left( \tilde{R}_{12}^{j+1} - \tilde{R}_{10}^{j+1} \right) \tilde{R}_{10}^{j} \tilde{R}_{12}^{j}}{\tilde{R}_{13} - \tilde{R}_{10} + \sum_{j=1}^{N} \left( \tilde{R}_{13}^{j+1} - \tilde{R}_{10}^{j+1} \right) \tilde{R}_{10}^{j} \tilde{R}_{13}^{j}},
\]

where \( \tilde{R}_{mk}(\nu, \tilde{\varepsilon}_m, \tilde{\varepsilon}_k) \) describes Fresnel reflection at the interface of the \( m \)th and \( k \)th media:

\[
\tilde{R}_{mk} = \frac{\sqrt{\tilde{\varepsilon}_k} - \sqrt{\tilde{\varepsilon}_m}}{\sqrt{\tilde{\varepsilon}_m} + \sqrt{\tilde{\varepsilon}_k}}.
\]

The indexes \( m = 0, 1, 2, \) and \( 3 \) correspond to the air, SiO₂, tissue, and gold mirror media, respectively. \( \tilde{P}_1(\nu, \tilde{\varepsilon}_1, l) \) is based on the Bouguer–Lambert–Beer law describing the THz–wave propagation along a distance \( l \) in the SiO₂–window:

\[
\tilde{P}_1 = \exp \left( -\frac{2\pi\nu}{c} \sqrt{\tilde{\varepsilon}_1} l \right),
\]

where \( c \approx 3 \times 10^8 \) m/s is the speed of light in vacuum.

In Eqs. (4)–(6), the dielectric permittivity of air and SiO₂ (\( \tilde{\varepsilon}_0 \) and \( \tilde{\varepsilon}_1 \)); the effective dielectric permittivity of mirror (\( \tilde{\varepsilon}_3 \)); the number of satellite pulses (\( N \)); and the SiO₂–window thickness (\( l \)) are known \textit{a priori}, and the THz permittivity of the sample (\( \tilde{\varepsilon} = \tilde{\varepsilon}_2 \)), is estimated via Eq. (2). In contrast to the well-known methods used to determine the THz dielectric permittivity via the reflection-mode measurements, for example, see [4], in the described approach we assume multiple THz-wave reflections in the reference window, thereby allowing us to increase the reconstruction accuracy [6].
Figure 1. THz dielectric characteristics of healthy skin and dysplastic and non-dysplastic skin nevi in vivo from four patients: (a)–(d) and (e)–(h) show the real $\varepsilon'(\nu)$ and the imaginary $\varepsilon''(\nu)$ parts of the complex dielectric permittivity, respectively; and the insets from (i) to (l) show the Cole-Cole diagrams $\varepsilon''/\varepsilon'(\nu)$ [22, 23].

3. Results

Figure 1 shows the THz dielectric permittivity of healthy skin, dysplastic and non-dysplastic skin nevi from four patients: panels from (a) to (d) and from (e) to (h) show the real $\varepsilon'(\nu)$ and the imaginary $\varepsilon''(\nu)$ parts of the complex dielectric permittivity, respectively; and the insets from (i) to (l) show the Cole-Cole diagrams $\varepsilon''/\varepsilon'(\nu)$ [22, 23]. The contrast in the experimental data is observed at low (from 0.3 to 0.45 THz) and at high (from 0.8 to 0.95 THz) frequencies. This significant contrast demonstrates the ability to differentiate the dysplastic and non-dysplastic nevi of the skin using the THz dielectric spectroscopy. Because the THz permittivity of biological tissue is described by the Debye [22, 23], double-Debye [24–26] models of dielectric dispersion, or the dispersion models characterized with continuous density function $g(\tau)$ of relaxation times $\tau$ [13]

$$\tilde{\varepsilon} = \varepsilon_\infty + \int_0^\infty \frac{g(\tau) d\tau}{1 + 2\pi i \nu \tau},$$

where $\varepsilon_\infty$ is the dielectric permittivity for $\nu \to \infty$, the differences in the experimental curves (Fig. 1) are associated with differences in the picosecond dynamics in media [27].

In Refs. [1, 28] the principal component analysis was implemented to highlight the ability for differential diagnosis of dysplastic and non-dysplastic skin nevi based on THz dielectric dispersion. The principal components were introduced on the basis of the gradients (average slopes) of $\varepsilon'(\nu)$ or $\varepsilon''/\varepsilon'(\nu)$–curves, and the simple thresholding procedure was applied to differentiate the nevi from all four patient.

The results of the present study demonstrate the potential of TPS use for non-invasive early diagnosis of the dysplastic skin nevi and the melanomas of the skin.

Acknowledgments

This work was supported by the Russian Foundation for Basic Research, Projects #14-02-00781, 14-08-31102, 14-15-00758, 14-08-31124, 14-02-00256.
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