**In vivo** spectroscopy of healthy skin and pathology in terahertz frequency range

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**Abstract.** Biomedical applications of terahertz (THz) technology and, in particular, THz pulsed spectroscopy have attracted considerable interest in the scientific community. A lot of papers have been dedicated to studying the ability for human disease diagnosis, including the diagnosis of human skin cancers. In this paper we have studied the THz material parameters and THz dielectric properties of human skin and pathology *in vivo*, and THz pulsed spectroscopy has been utilized for this purpose. We have found a contrast between material parameters of basal cell carcinoma and healthy skin, and we have also compared the THz material parameters of dysplastic and non-dysplastic pigmentary nevi in order to study the ability for early melanoma diagnosis. Significant differences between the THz material parameters of healthy skin and pathology have been detected, thus, THz pulsed spectroscopy promises to become an effective tool for non-invasive diagnosis of skin neoplasms.

1. Introduction

The problem of skin cancer diagnosis is of high importance in medical science, and novel methods based on modern physical principles are being developed in order to solve this problem. Recently terahertz (THz) technology, in particular, THz pulsed spectroscopy [1,2], attracts considerable interest of scientific community as a possible instrument of medical diagnosis [3–36].

THz pulsed spectroscopy appeared at 1975 as a result of Auston’s research of semiconductor photoconductivity under the femtosecond optical pumping [2]. It was developing at the end of the XX century with an appearance of highly-stable femtosecond lasers, and many techniques for THz pulse generation and detection appeared [1]. The methods for THz material parameter characterization [3–11] and algorithms for THz time-of-flight tomographic studying the internal structure of sample by means of THz pulsed spectroscopy [12–15] have been developed. THz pulses spectroscopy has been applied for the purposes of medical diagnosis. It has been implemented for studying the skin cancers, and the ability for diagnosing the basal cell carcinoma have been demonstrated [16,17]. Numerous researches have been dedicated to diagnosis of colon tissue cancer [18,19], to intraoperative diagnosis of breast cancer [20,21], to sensing in
corneal tissue [22], enamel tissue [23], liver [24], and blood [25], and to studying the skin burns [26,27]. In paper [28] the intrinsic biomarkers for non-melanoma skin cancer detection with THz spectroscopy have been introduced. Possibilities for bacteria detection via THz spectroscopy [29] and for THz molecular spectroscopy [30–33] have been introduced.

Recently, a lot of attention is paid to early diagnosis of melanoma, which is reported to be the most dangerous skin cancer [34], and THz pulsed spectroscopy should be considered as a possible method for solving this problem [35]. The present paper is dedicated to studying the THz material parameters and THz dielectric properties of healthy skin and pathology in vivo. We are studying and analyzing the THz material parameters of basal cell carcinoma and healthy skin, as well as material parameters of dysplastic and non-dysplastic pigmented skin nevi. Thus, the ability for early non-invasive diagnosis of skin neoplasms is considered.

2. Materials and methods
Let us describe an experimental set-up and the method for reconstructing the THz material parameters of healthy skin and pathology in vivo. We are utilizing compact THz pulsed spectrometer, based on generation of THz pulses in photoconductive antenna and detection of THz field in electrooptical detector [14,36]. Detail description of set-up operation principle is out of the present paper scope; it could be found in papers [14,36]. The set-up allows determination of complex amplitude reflectivity of in vivo tissue in range from 0.1 to 2.5 THz.

![Schematic representation of THz waveform detection during the reflection mode sample characterization](image)

**Figure 1.** Schematic representation of THz waveform detection during the reflection mode sample characterization: (a) corresponds to measuring the empty SiO₂-flat, (b) corresponds to measuring the SiO₂-flat with the gold mirror placed behind it, and (c) corresponds to measuring the SiO₂-flat with the sample placed behind it. Note, THz beam is focused on the interface between the SiO₂-flat and the sample of interest.
The procedure for reconstructing the material parameters of in vivo tissue (sample) could be described as follows. Figure 1 schematically represents the process of measurements, where thick quartz flat is utilized for sample fixation. Three THz waveforms are being detected: (a) corresponds to the reference THz waveform reflected by the empty SiO$_2$-flat, $E_r(t)$; (b) corresponds to the THz waveform reflected by the flat with the gold mirror placed on its back-side, $E_m(t)$; and (c) corresponds to the sample THz waveform, reflected by the flat with the sample of interest placed behind it, $E_s(t)$. Let us define Fourier spectrums of $E_r(t)$, $E_m(t)$, and $E_s(t)$ with $\tilde{E}_r(\nu)$, $\tilde{E}_m(\nu)$, and $\tilde{E}_s(\nu)$.

Reconstruction of sample material parameters, $\tilde{n}_2(\nu)$, could be performed via the minimization of an error functional

$$\tilde{n}_2(\nu) = \arg\min_{\tilde{n}_2(\nu)} \left\{ \Phi(\nu, \tilde{n}_2(\nu)) \right\} = \arg\min_{\tilde{n}_2(\nu)} \left\{ M(\nu, \tilde{n}_2(\nu)) + A(\nu, \tilde{n}_2(\nu)) \right\},$$

where $\nu$ is an electromagnetic wave frequency,

$$M(\nu, \tilde{n}_2(\nu)) = \left| \tilde{H}_{exp}(\nu) - \tilde{H}_{th}(\nu, \tilde{n}_2(\nu)) \right|^2,$$

$$A(\nu, \tilde{n}_2(\nu)) = \left| \phi \left[ \tilde{H}_{exp}(\nu) \right] - \phi \left[ \tilde{H}_{th}(\nu, \tilde{n}_2(\nu)) \right] \right|^2,$$

$\tilde{H}_{exp}(\nu)$ and $\tilde{H}_{th}(\nu, \tilde{n}_2(\nu))$ are experimental and theoretical transfer functions corresponding to the reflection mode measurements, $|.|$ and $\phi[.|.$ are operators, which extract modulus and phase of complex functions. Experimental transfer function has the form

$$\tilde{H}_{exp}(\nu) = \frac{\tilde{E}_s(\nu) - \tilde{E}_r(\nu)}{\tilde{E}_m(\nu) - \tilde{E}_r(\nu)},$$

and theoretical transfer function is based on the model, which assumes multiple THz wave reflections within the SiO$_2$-flat

$$\tilde{H}_{th}(\nu) = \frac{\tilde{R}_{12} - \tilde{R}_{10} + \sum_{j=1}^{N} \left( \tilde{R}_{12}^{j+1} - \tilde{R}_{10}^{j+1} \right) \tilde{R}_{10}^{2j}}{\tilde{R}_{13} - \tilde{R}_{10} + \sum_{j=1}^{N} \left( \tilde{R}_{13}^{j+1} - \tilde{R}_{10}^{j+1} \right) \tilde{R}_{10}^{2j}},$$

In equation (4) operator $\tilde{P}_1 = \tilde{P}_1(l, \nu)$ is based on the Beer-Lambert-Bouguer law

$$\tilde{P}_\beta(z, \nu) = \exp \left( -i \frac{2\pi\nu}{c} \tilde{n}_\beta(\nu) z \right),$$

describing the light propagation through the $\beta$ dissipative medium along certain distance, $z$, and $c$ is a speed of light in vacuum. Operators $\tilde{R}_{10} = \tilde{R}_{10}(\nu)$, $\tilde{R}_{12} = \tilde{R}_{12}(\nu)$, $\tilde{R}_{13} = \tilde{R}_{13}(\nu)$ are based on the Fresnel formulas

$$\tilde{T}_{\xi\zeta}(\nu) = \frac{2\tilde{n}_\xi(\nu)}{\tilde{n}_\xi(\nu) + \tilde{n}_\zeta(\nu)}, \quad \tilde{R}_{\xi\zeta}(\nu) = \frac{\tilde{n}_\zeta(\nu) - \tilde{n}_\xi(\nu)}{\tilde{n}_\xi(\nu) + \tilde{n}_\zeta(\nu)},$$

describing light transmission and reflection at the interface of $\xi$ and $\zeta$ media ($\tilde{n}_0(\nu) = 1.0$ is a priori known complex refractive index of air, $\tilde{n}_1(\nu)$ is a priori known complex refractive index of SiO$_2$, $\tilde{n}_2(\nu)$ is a complex refractive index of sample, and $\tilde{n}_3(\nu) = 4 \cdot 10^3 - i10^3$ is a priori known complex refractive index of mirror medium). In (4) $N$ corresponds to the number of multiple wave reflections in a SiO$_2$-flat, and $l$ corresponds to priori known thickness of reference quartz window. Note, $N$ is limited by the width of spectrometer time-domain window, thus, only $N = 1, 2$ satellite pulses could be detected utilizing THz pulsed spectrometer.

Described procedure allows estimating the sample material parameters, $\tilde{n}_2(\nu)$, via the reflection mode measurements, and we are implementing it for studying the material parameters of healthy skin and pathology in vivo.
3. Results

We have examined healthy skin and pathology in vivo. Figure 2 shows the material parameters of basal cell carcinoma, dysplastic and non-dysplastic pigmentary nevi, and healthy skin; (a) corresponds to the refractive index, \( n_2(\nu) \), and (b) corresponds to the absorption coefficient \( \alpha_2(\nu) \) (\( \alpha_2(\nu) \) corresponds to light intensity absorption). The following equation defines the relation between \( n_2(\nu) \), \( \alpha_2(\nu) \), and complex refractive index of sample, \( \tilde{n}_2(\nu) \),

\[
\tilde{n}_2(\nu) = n_2(\nu) + i \frac{\alpha_2(\nu) c}{4\pi\nu}.
\]  

(7)

The reliable spectral range for characterizing the material parameters of in vivo tissue is limited both at low-frequency and high-frequency sides. The finite lateral size of skin pathology limits the spectral range at the low-frequency side due to the diffraction limit of THz beam spot. The roughness of skin surface limits the spectral range at the high-frequency side due to the strong scattering of high-frequency spectral components of THz beam on tissue surface inhomogeneities. We have experimentally found that the reliable range is located between 0.25 and 1.05 THz. Observed curves of THz material parameters (figure 2) are statistically distinguishable in low-frequency (< 0.5 THz) and high-frequency (> 0.7 THz) ranges.

Let us consider another approach for experimental data representation. Ordinary it is customary to plot the frequency dependencies of sample material parameters, \( n_2(\nu) \) and \( \alpha_2(\nu) \), or the frequency dependencies of sample dielectric characteristics, \( \varepsilon'(\nu) \) and \( \varepsilon''(\nu) \), (\( \tilde{\varepsilon}(\nu) = \varepsilon'(\nu) - i\varepsilon''(\nu) \) and \( \tilde{\varepsilon}(\nu) = \tilde{n}_2^2(\nu) \)). At the same time, the spectroscopy data is not readily analyzed by such representation. Much more convenient basis for data discussion and analysis could be Argand diagrams (complex plane locus or Cole-Cole diagrams) [37,38], in which the imaginary part of complex dielectric constant is plotted against the real one, \( \varepsilon''(\varepsilon') \), and each point being characteristic of certain electromagnetic wave frequency. Since the material parameters of in vivo biological tissue have a Debye-like character [39,40], it is convenient to represent the THz dielectric characteristics of in vivo tissue using the Cole-Cole diagram representation. The equation, describing the frequency dependencies of \( \varepsilon' \) and \( \varepsilon'' \) for Debye model, has the following form

\[
\varepsilon'(\nu) = \varepsilon_{\infty} + \frac{\varepsilon_0 - \varepsilon_{\infty}}{1 + (2\pi\nu\tau_0)^2}, \quad \varepsilon''(\nu) = \frac{2\pi\nu\tau_0 (\varepsilon_0 - \varepsilon_{\infty})}{1 + (2\pi\nu\tau_0)^2},
\]  

(8)
Figure 3. Cole-Cole diagrams of healthy skin and pathology in vivo: basal cell carcinoma (×), dysplastic pigmentary nevus (◯), non-dysplastic pigmentary nevus (▽), and healthy skin (□).

where \(\varepsilon_0, \varepsilon_\infty\) are model parameters, and \(\tau_0\) is a medium relaxation time. The locus of equation (8) in complex plane representation of experimental results is a semicircle with its center on the real axis, \(\varepsilon'\), and interceptions with this axis at \(\varepsilon' = \varepsilon_0\) and \(\varepsilon' = \varepsilon_\infty\)

In case of multiple-Debye-model describing the sample dielectric characteristics, a set of semicircles exist in the complex plane.

We are applying described Cole-Cole representation to all results of the figure 3. Due to the boundedness of reliable spectral range the Cole-Cole diagrams represent only parts of semicircles; but the experimental data significantly differs for all studied tissues, providing us the ability for principle components selection based on the complex plane locus. We are able to find the differences between basal cell carcinoma and healthy skin, as well as the differences between the dysplastic and non-dysplastic pigmentary nevi.

Dysplastic pigmentary nevus is a melanoma precursor, thus, observed result shows the ability for early melanoma diagnosis, and it is an important problem of dermatology and oncology, since melanoma is the most dangerous cancer of skin [34,35,41,42]. Described results of in vivo spectroscopy allow to conclude that THz spectroscopy could become a powerful instrument for diagnosis of skin diseases, including, skin cancer diagnosis.

4. Conclusions
In the present paper we have measured the THz material parameters and THz dielectric properties of healthy skin and pathology in vivo by by using THz pulsed spectroscopy. The material parameters and dielectric characteristics of basal cell carcinoma, dysplastic and non-dysplastic pigmentary nevus, and healthy skin have been examined. We have found significant differences between THz characteristics of healthy skin and pathology, and this allows to conclude, that THz pulsed spectroscopy could become an effective tool for skin neoplasm diagnosis.

Acknowledgements
This work was supported by the Russian Scientific Foundation, Project # 14-15-00758.

References
[1] Lee Y-S 2009 Principles of Terahertz Science and Technology (New York: Springer)
[2] Auston D H 1975 Appl. Phys. Lett. 26 101-03
[3] Duvillaret L, Garet F, Coutaz J-L 1999 Appl. Opt. 38 409-15
[4] Dorney T D, Baraniuk R G, Mittleman D M 2001 J. Opt. Soc. Am. A 18 1562–71
[5] Pupeza I, Wilk R, Koch M 2007 Opt. Exp. 15 4335–50
[6] Huang S, Ashworth P C, Kan K W C, Chen Y, Wallace V P, Zhang Y-T, and Pickwell-MacPherson E 2009  *Opt. Exp.* 17 3848–54
[7] Balakrishnan J, Fischer B M, Abbott D 2010  *Opt. Commun.* 283 2301–7
[8] Scheller M 2011  *Opt. Exp.* 19 10647–55
[9] Zaytsev K I, Gavdush A A, Lebedev S P, Yurchenko S O 2014  *J. Phys. Conf. Ser.* 486 012018
[10] Kruger M, Funkner S, Bründermann E, Havenith M 2011  *J. Infrared, Millimeter, and Terahertz Waves* 32 699–715
[11] Zaytsev K I, Gavdush A A, Karasik V E, Alekhnovich V I, Nosov P A, Lazarev V A, Reshetov I V, Yurchenko S O 2014  *J. Phys. Conf. Ser.* 486 012018
[12] Kruger M, Funkner S, Brundermann E, Havenith M 2011  *J. Infrared, Millimeter, and Terahertz Waves* 32 699–715
[13] Zaytsev K I, Gavdush A A, Karasik V E, Alekhnovich V I, Nosov P A, Lazarev V A, Reshetov I V, Yurchenko S O 2014  *J. Appl. Phys.* 115 193105
[14] Mittleman D M, Hunsche S, Boivin L, Nuss M C 1997  *Opt. Lett.* 22 904–6
[15] Chen Y, and Pickwell-MacPherson E 2010  *Opt. Exp.* 18 1177–90