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Influence of glucose concentration on blood optical properties in THz frequency range

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Abstract: Non-invasive blood glucose sensing is still actual scientific task for more safe and comfort diabetes care. This article shows correlation between blood optical properties and its glucose concentration. The transmission spectra of whole blood have been studied by the time-domain THz spectroscopy in the frequency range from 0.3 to 0.5 THz. Biosamples were produced from the same person with the diabetes mellitus during a short time period after the insulin injection have been used. Frequency dispersions of blood optical properties are obtained. Based on frequency dispersions, the dependences of blood glucose concentrations with the refractive index and permittivity are presented. This work is a part of the complex investigation, which focuses on the development of a non-invasive glucose measuring technique. Registering dependences between blood glucose level and blood optical parameters allows for using the reflective spectroscopy techniques in future for non-invasive blood glucose level sensing.

Key words: spectroscopy; terahertz; glucose; diabetes mellitus

葡萄糖浓度对 THz 频段血液光学特性的影响

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摘要:无创性血糖检测仍是糖尿病患者护理安全舒适的现实科学任务。本文研究了血糖光学特性与血糖浓度之间的相关性。用时域 THz 光谱研究了全血在 0.3 ~ 0.5 THz 频率范围内的透射谱。在注射胰岛素后的短时间内,由同一糖尿病

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患者产生了生物样品。得到了血液光学特性的频散特性。基于频散,给出了血糖浓度与折射率和介电常数的关系式。这项工作是复杂研究的一部分,重点是无创葡萄糖测量技术的发展。记录血糖水平与血液光学参数之间的依赖关系,使得将来可以使用反射光谱技术进行无创血糖水平检测。

关　键　词:光谱学;太赫兹;葡萄糖;糖尿病

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1 Introduction

Optical properties of whole blood are important parameters in biophysical investigations and medical diagnostics[1-2]. Variations in cellular and biochemical composition of whole blood markedly affect the values of different optical parameters like absorption, scattering, refractive index etc[1,3-6]. Such changes of optical properties can be valuable diagnostic signs as they reflect the dynamics of a particular pathological process. To apply this in diagnostics, it is necessary to investigate the influence of separate biochemical parameters on different optical characteristics of whole blood[7-8]. Among these parameters the blood glucose level is significantly important. It is a valuable predictor of diabetes mellitus[9].

At present, there is a trend to develop diagnostic method for blood glucose level estimation by THz time-domain spectroscopy(TDS)[10-11]. It was shown that the reflection from human skin varies according to the blood glucose level during a standard test for glucose tolerance. In addition, it was shown that the absorption coefficient and the refractive index of blood plasma of rats with severe experimental diabetes differ significantly from these parameters in normal rats and rats with mild diabetes[12]. The latter group of rats was characterized by significant deviations of biochemical parameters, such as glucose and corticosterone levels, from normal values[13-14].

As indicated above, the composition of blood can affect optical properties of blood plasma. It was shown that there is a inverse dependence between the THz absorption coefficients and the number of red blood cells[15-17] as well as between the sub-THz absorption coefficients and blood triglyceride concentration[15]. The development of non-invasive methods, requires studying the whole blood. Therefore, there is a need to investigate the effect of different glucose levels on the optical properties of whole blood.

There are some researches of glucose level sensing using optical coherence tomography (with sensor on the ear)[18], Raman spectroscopy (with sensor on the cornea)[19], time of flight[20-21] and others, but currently no one is available on market[22]. Moreover, each of them is bulky and expensive method. Glucose level sensing using THz TDS has promising prospects due to making THz technologies more cheap, effective, compact and stable, for example as in quasi-TDS technology[23].

It is still a lack of the data about the effect of human whole blood glucose levels on the refractive indices and absorption coefficients. This paper presents the results of transmission THz spectra measurements of whole blood of one person with diabetes mellitus during a short time period after insulin injection. These results will be useful for development of non-invasive method based on reflective signal measurement from nail bed.

2 Experimental setup

The optical properties of blood samples were studied in the frequency range of 0.1 – 1.0 THz using THz TDS in transmission mode[24-25]. The scheme of the setup is shown in the Fig. 1.

Broadband pulsed THz radiation is generated by means of an InAs semiconductor in the magnetic

field of 2.0 T by irradiating it with femtosecond pulses of an Yb:KYW laser (wavelength of 1 040 nm, the pulse duration of 120 fs, the pulse repetition frequency of 75 MHz, the power of 1 W). THz radiation has the following output characteristics: the spectral range from 0.05 to 2.0 THz, the average power up to 30 W, the pulse duration of 2.7 ps. The main power is concentrated at the frequency range from 0.3 to 0.5 THz. THz radiation passes through a teflon filter (which cuts the wavelengths shorter than 50 μm). After that, the radiation passes through the sample fixed in a focal plane perpendicularly to the beam. THz pulse affects the anisotropy of the electrooptical CdTe crystal. As a result, the THz pulse induces birefringence of the probe beam in the crystal due to the electrooptical effect. The birefringence magnitude is directly proportional to the amplitude of terahertz radiation electric field in the time point $E(t)$. These data are required to calculate $E(\omega)$ using the Fourier transform.

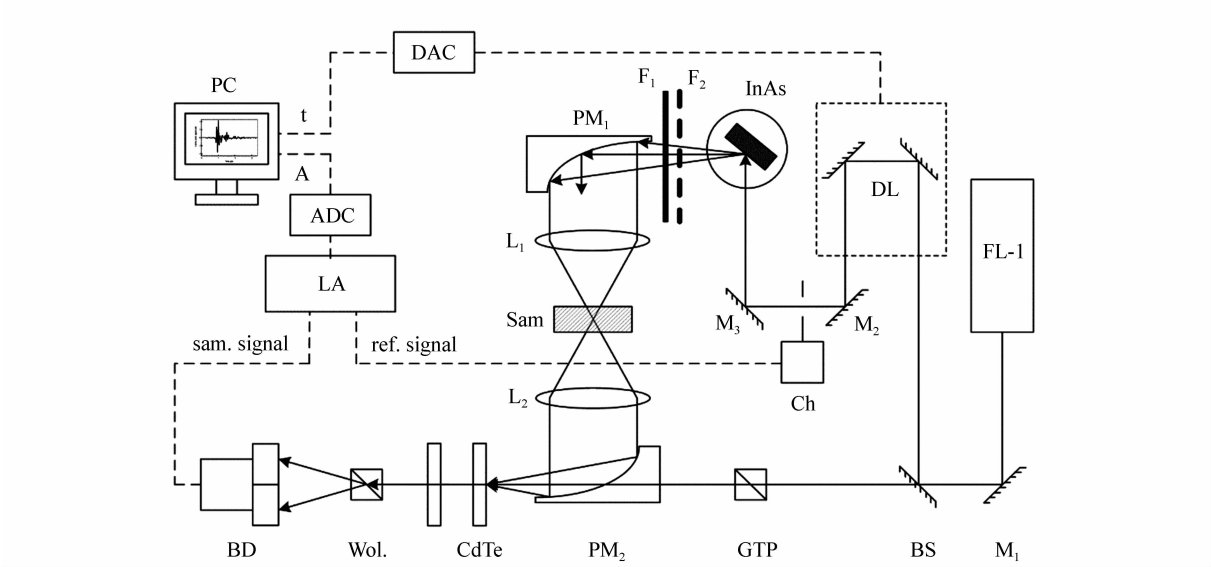

Fig. 1 Schematic diagram of the setup (FL-1: femtosecond laser based on potassium-yttrium tungstate crystal activated with ytterbium (Yb:KYW), generating femtosecond pulses; F1,2: a set of teflon filters for IR wavelength range cutting off, BS: beamsplitter, DL: optical delay line, M1,2,3: mirrors, Sam: investigated sample, Wol.: Wollaston prism, CdTe: electro optical cadmium-telluric crystal, BD: balanced detector, LA: lock-in amplifier, PC: personal computer, GTP: Glan-Taylor prism, PM1,2: parabolic mirrors, Ch: chopper, DAC: digital to analog converter, ADC: analog to digital converter

3 Sample preparation

In the experiment, 8 blood samples were used. Each sample had different glucose concentration. Investigated samples were obtained from the same person during short time period (about 2 hours). This fact helped us to provide the stable concentration of blood components (excluding glucose concentration) to avoid multiple dependences within the time of experiment. The study was performed in accordance with Good Clinical Practice (GCP) and with the 1964 Helsinki declaration and its later amendments.

The first step of sample preparation was increasing glucose level of the diabetic patient up to hyperglycemia level. It is quite a fast process so samples were obtained during the time of decreasing glucose level after insulin injection.

This experiment contained samples with the following glucose concentrations shown below in the Tab. 1.

Tab. 1　The list of the glucose concentrations of samples used in experiment

Sample No.	mmol/L	mg/dL
1	3.0	54.0
2	3.8	68.4
3	6.2	111.6
4	9.2	165.6
5	11.0	198.0
6	14.9	268.2
7	18.0	324.0
8	19.0	342.0

The glucose concentrations in the blood were measured twice per a sample using Abbott Freestyle Optium[26] glucometer. This electro-chemical glucometer model is widely used in clinical research[27].

The blood drops were located inside a special polymethyl methacrylate (PMMA) container (Fig. 2, Fig. 3).

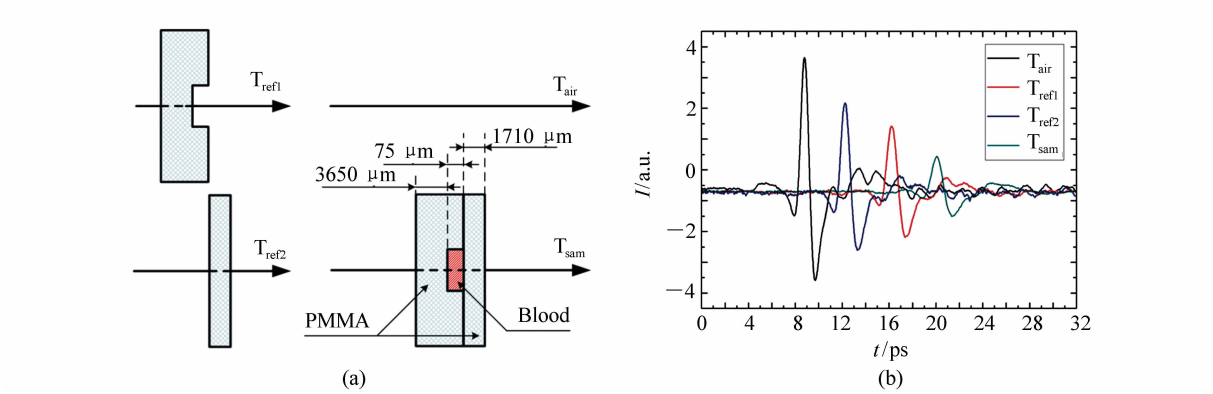

Fig. 2　(a) The scheme of sample preparation and (b) experimental signals

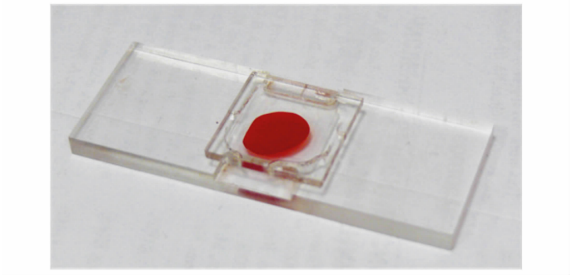

Fig. 3　Polymethyl methacrylate (PMMA) container with blood

In the middle, this container has a recess which is 75 μm in depth. This type of blood holder can keep stable thickness of a sample and protects biological fluid from drying. Moreover, PMMA is transparent for the THz radiation.

4　Data acquisition

For each sample, a time-amplitude transmission waveform was taken 100 times and averaged for each timepoint. In addition, transmission waveforms of air, bottom and top parts of container were measured. All the acquired waveforms were converted to their Fourier transforms $E(\omega)$, respectively. Then the THz electric field is:

$$\hat{E}(\omega) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{+\infty} f(t)e^{-i\omega t}\mathrm{d}t = E_0(\omega)e^{-i\varphi(\omega)}, \quad (1)$$

where $f(t)$ is time-amplitude waveform, ω is angular frequency, $E_0(\omega)$ is amplitude data, $\varphi(\omega)$ is phase data.

At the first step, T_{air} and T_{ref1} waveforms were used for data calculation of the bottom part of container, and T_{air} and T_{ref2} for the top part. At the second step, T_{air} and T_{sam} were used for properties calculation of the container with blood. At the third step, T_{ref1}, T_{ref2} and T_{sam} were used to calculate the phase delay and amplitude decrease for the blood layer inside the container. As a result, the refractive index n can be calculated for a sample inside the

container. The real part of the refractive index n_{real} is calculated as:

$$n_{\text{real}}(f) = 1 + \frac{c[\varphi_{\text{sam}}(f) - \varphi_{\text{air}}(f)]}{2\pi f d}, \quad (2)$$

where c is speed of light in vacuum, d is thickness of medium, f is frequency.

The absorption coefficient α is calculated using the amplitude data:

$$\alpha(f) = \frac{1}{d}\ln\left[\frac{E_{\text{air}}(f)}{E_{\text{sam}}(f)}\right]^2. \quad (3)$$

In addition, the penetration depth L is the reverse function to the absorption coefficient α:

$$L(f) = \frac{1}{\alpha(f)}. \quad (4)$$

The imaginary part of the refractive index n_{imag} requires data about the absorption coefficient α:

$$n_{\text{imag}}(f) = \frac{\alpha(f)c}{4\pi f}. \quad (5)$$

Both parts of the permittivity ε use both parts of the refractive index n:

$$\varepsilon_{\text{real}}(f) = n_{\text{real}}^2(f) - n_{\text{imag}}^2(f), \quad (6)$$

$$\varepsilon_{\text{imag}}(f) = 2n_{\text{real}}(f)n_{\text{imag}}(f). \quad (7)$$

All of these optical properties are available as results of Spectrina software[7].

5 Results and Discussion

Based on 8 biosamples, we have investigated the frequency dispersions of n_{real}, α, $\varepsilon_{\text{real}}$, $\varepsilon_{\text{imag}}$ from f in the THz range (as shown in Fig. 4).

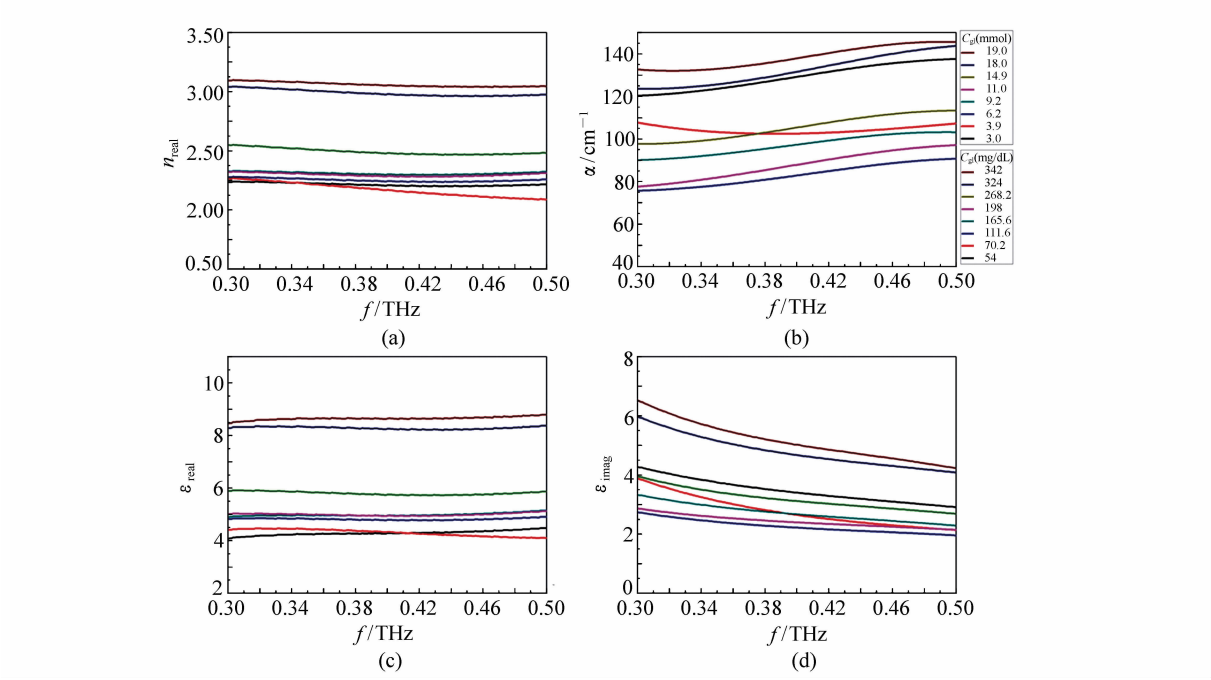

Fig. 4 Dispersions of optical parameters of samples with different glucose concentration c_{glucose}: (a) the real part of refractive index $n_{\text{real}}(f)$; (b) the absorption coefficient $\alpha(f)$; (c) the real part of permittivity $\varepsilon_{\text{real}}(f)$; (d) the imaginary part of permittivity $\varepsilon_{\text{imag}}(f)$

After the data acquisition, the next step is to find dependencies between glucose concentrations and optical properties.

To determine the dependence of blood optical properties with glucose concentration we selected the stable experimental data at 0.3, 0.35 and 0.4 THz. Fig. 5 shows the dependences of glucose concentration with real part of refractive index and with real part of permittivity.

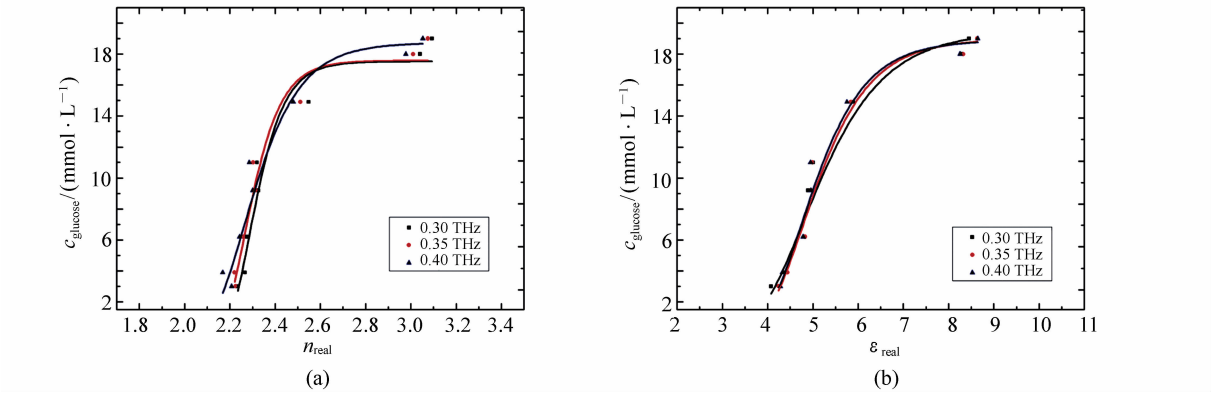

Fig. 5　Dependencies of glucose concentration with (a) the real part of refractive index $c_{glusose}$ and (b) with the real part of permittivity $c_{glucose}(\varepsilon_{real})$ at different frequencies

The dependence is not linear with the blood glucose concentration above 16 mM/L. This may be due to the change in physical-chemical properties of blood components with high glucose concentration[28-29]. As known hyperglycemia caused by insulin deficiency is accompanied by a large loss of electrolytes, dehydration of tissues and osmolality increase of blood plasma.

By fitting the data with the Gompertz function, we found relationships on few frequencies.

From n at 0.30 THz:

$$c_{glucose}(n_{real}) = 17.517\exp\{-\exp[-11.654(n_{real}-2.2883)]\}, \quad (8)$$

From n at 0.35 THz:

$$c_{glucose}(n_{real}) = 17.5698\exp\{-\exp[-11.11506(n_{real}-2.26704)]\}, \quad (9)$$

From n at 0.40 THz:

$$c_{glucose}(n_{real}) = 18.716\exp\{-\exp[-7.2434(n_{real}-2.2624)]\}, \quad (10)$$

From ε at 0.30 THz:

$$c_{glucose}(\varepsilon_{real}) = 19.426\exp\{-\exp[-1.0065(\varepsilon_{real}-4.7860)]\}, \quad (11)$$

From ε at 0.35 THz:

$$c_{glucose}(\varepsilon_{real}) = 18.9587\exp\{-\exp[-1.2201(\varepsilon_{real}-4.78379)]\}, \quad (12)$$

From ε at 0.40 THz:

$$c_{glucose}(\varepsilon_{real}) = 18.8836\exp\{-\exp[-1.27206(\varepsilon_{real}-4.74102)]\}. \quad (13)$$

These dependencies indicates that quantitative blood glucose levels analysis is feasible by using TDS in THz frequency range. According to this, we can simulate glucose level analysis to make numerical modelling in reflective mode.

It should be noted that results cannot be suited into model of effective medium theory due to that model was developed for non-interacting components[30].

As a result, this work confirms the direction of dependence shown at our previous work[7], but this experiment used more accurate technique, that prevents blood drying and provides stable thickness of blood layer. In addition, we found mathematical functions to use these results in a numerical modelling process. Finally, this work contains wider range of dispersions: not only real part of refractive index, but also absorption coefficient, real and imaginary parts of permittivity.

These results will be used in numerical modelling purposes with software instruments like CST Studio, COMSOL Multiphysics and other. In addition,

results of further experiments in reflective mode in the THz frequency range can be validated by these repeatable data.

At the other hand, the main task for now is increasing of specificity of signal for glucose molecules. We are going to do this by using effect of resonance at specific fingerprint frequencies.

6 Conclusion

The experiment contained 8 blood samples with different glucose concentrations. The frequency dispersions of optical properties of each biosample have been obtained. Based on the data, this paper indicates the dependences of glucose concentrations c_{glucose} with the real part of refractive index n_{real} and real part of permittivity $\varepsilon_{\text{real}}$. The dependences of this kind have been received for the first time in the THz frequency range. The results are helpful in the process of developing a spectroscopic method of blood glucose sensing.

During analysis of dependences it can be seen that model of inert substances mix is not applicable for this experiment. It can be explained due to permanent interaction of blood components.

Collected and calculated data will be useful for estimating quality of results of a non-invasive reflective spectroscopic glucose sensing technique. It will be possible by comparison of calibration curves of this experiment with following ones.

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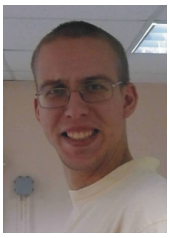

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