Influence of creatinine and triglycerides concentrations on blood optical properties of diabetics in THz frequency range

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Abstract: This paper is devoted to research influence of creatinine and triglycerides on THz optical properties of blood for diabetes care purposes.

1. Introduction
The amount of diabetics is growing every day. The number of patients suffering from diabetes had amounted to more than 230 million people by the year 2010, which is estimated as 3.5% of the whole world adult population [1]. According to expert forecasts, this number is projected to double by the year 2025, which is going to be 7% of whole Earth population. It was calculated that every 10 seconds someone in the world dies due to diabetes and its complications that consists 3 million people per year. Late diagnosis of diabetes and poor control are the main causes of diabetes complications, which determine the morbidity and mortality of diabetics. The escalation of hypoglycemia, even subclinical, associated with an increase in cardiovascular mortality by 2-2.5 times, and cardiovascular events 4 times [2]. At the same time, episodes of hypoglycemia were present in 39% of study patients with CGMS control. Morbidity and mortality from macrovascular diseases also highly associated with different characteristics of blood glucose levels: hyperglycemia, normoglycemia, glycemic variability. Thus, increasing of the glycated hemoglobin level from 6% to 9% provides the microvascular complications risk increasing in 4 times [3].

At the moment, the blood glucose level measurements are performed by glucometers [4,5]. This method requires making a finger puncture for every measurement. About five punctures per day should be done for proper glucose monitoring, which is about 1800 punctures per year. Besides, each measurement by glucometer requires a distinct test strip. Expenses for 1800 test strips could be estimated as about 450 euros per year. It is also necessary to take into account that each puncture has a risk of blood poisoning. Using non-invasive techniques for glucose level control could reduce the amount of possible risky manipulations by 1800 per year. Moreover, it is worth mentioning that only eight of ten fingers are suitable for puncturing, and the constant skin damage which cannot be avoided is quite annoying for the patients.
Last decade the most popular topics in terahertz science is a development of THz filters [6, 7], which may be used in biomedicine diagnostics due to change of filter resonant frequency caused by the surrounding. At pathology of blood it may be revealed the changing of relaxation time of biomolecules namely the varying of dispersion of refractive index of whole blood in terahertz frequency range. However it needs to take in account the influence of THz radiation on biological objects [8,10]. The previous results of this scientific work were devoted to construction calibration graph for detecting glucose levels in blood using refractive index in order to control diabetes [9]. The main aim of this investigation is to determine the influence of creatinine and triglycerides on THz optical properties of blood for diabetes care purpose.

2. The investigated biological objects overview

The samples with different concentration of creatinine and triglycerides were chosen for investigation because of simple detection these components levels in diagnostic laboratories using common tests. Low female level of creatinine concentration is considered to vary from 53.0 to 70.7 μmol/l (equiv. 954 to 1272.6 μg/dl), normal level from 70.8 to 106 μmol/l (equiv. 1274.4 to 1908 mg/dl) of the blood plasma (this type of glucose concentration measuring system is generally used in medical practice). Also low level of triglycerides concentration is considered to be lower than 1.77 mmol/l (equiv. 31.86 mg/dl), normal female level higher than 1.77 mmol/l (equiv. 31.86 mg/dl) of the blood plasma.

Compared samples had almost same compositions of blood plasma, but they had significant differences in creatinine or triglycerides levels. In addition, the results were observed at different glucose levels in blood plasma. The concentration of components was determined by professional medical laboratory of Federal Almazov North-West Medical Research Centre [11].

![Figure 1](image_url). The schematic sample preparing for measurement process.

The sample consists on “Goryaev camera” type container (see the Figures 1, 2) with drop of blood plasma. This type of container provides us stable thickness of sample and protects drying of biological fluid.
The blood plasma samples were compared because blood contains solid inclusions that distort the signal, while the plasma has uniform consistency.

3. Experimental setup
The optical properties of blood plasma samples were studied in the frequency range of 0.1-1 THz using the time-domain spectrometer in transmission mode. The photo and scheme of the setup were shown in Fig. 3 and Fig. 4 correspondingly.
Figure 4. Schematic diagram of the set up (FL-1 - femtosecond laser based on potassium-yttrium tungstate crystal activated with ytterbium (Yb: KYW), generating femtosecond pulses; $F_{1,2}$ – a set of teflon filters for IR wavelength range cutting off, BS – beamsplitter, DL – optical delay line, $M_{1,2,3}$ – 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, PM$_{1,2}$ – parabolic mirrors, Ch - chopper.

Broadband pulsed THz radiation was generated using a photoconductive antenna (undoped InAs crystal) by irradiating it with femtosecond pulses of an ytterbium laser (wavelength - 1040 nm, pulse duration - 120 fs, pulse repetition frequency - 75MHz, power - 1 W). THz radiation had the following output characteristics: spectral range from 0.05 to 2 THz, average power - 30 uW, pulse duration - 2.7 ps. The main power was concentrated at the frequency range from 0.12 to 1.1 THz. THz radiation was generated by a gallium arsenide crystal in the magnetic system, then passed through a teflon filter (which cuts wavelengths shorter than 50 μm). After that, the radiation passed through the sample fixed in a focal plane perpendicularly to the beam. With the simultaneous incidence of the femtosecond probe beam and THz beam passed through the sample on the electro optical CdTe crystal, THz pulse induced birefringence of the probe beam in the crystal due to the electrooptical effect. The birefringence magnitude is directly proportional to the intensity of terahertz wave electric field in the time point $E(t)$. These data are required to calculating $E(\omega)$ using Fourier transform.

4. Results

During the experiments the signals passed through an object and air were recorded (reference signal through air, object signal through bottom of camera, object signal through top of camera, object signal through camera filled blood plasma). Each of them is the dependence of the amplitude on time.
Figure 5. Example of typical THz temporal waveform.

Further, the THz waveforms were processed using Spectrina M5 program (see the Figure 6) which performs the Fourier transform and the extraction of optical properties [12, 13-16].

As a result, such properties of the blood plasma were obtained: dispersion of the complex refractive index, the absorption coefficient, the penetration depth, the complex permittivity.

After consideration of results, the comparison was made between the refractive indices as a function of concentration categories of creatinine and triglycerides in the sample.
Figure 7. The dependence of dispersion of the real part of the blood plasma refractive index on the creatinine concentration level at woman. The concentration of glucose in these samples is located between 4.5 – 5.5 mmol/l (81 – 99 mg/dl).

Figure 8. The dependence of dispersion of the real part of the blood plasma refractive index on the creatinine concentration level at woman. The concentration of glucose in these samples is located between 8.5 – 9.5 mmol/l (153 – 171 mg/dl).
As you can see, the increasing of creatinine concentration provides increasing the blood refraction index. This influence is evident at both glucose concentration groups.

Figure 9. The dependence of dispersion of the real part of the blood plasma refractive index on the triglycerides concentration level. The concentration of glucose in these samples is located between 4.5 – 5.5 mmol/l (81 – 99 mg/dl).

Figure 10. The dependence of dispersion of the real part of the blood plasma refractive index on the triglycerides concentration level. The concentration of glucose in these samples is located between 6.5 – 7.5 mmol/l (153 – 135 mg/dl).
These graphs show us that the increasing of triglycerides concentration have not specific dependence on the blood refraction index.

5. Conclusion
The dependence of the refractive index of blood on the creatinine concentration was shown. The dependence of the refractive index on the triglycerides levels was not observed. These results confirm that each patient required individual calibration of perspective glucometric device. These data may be useful for development of non-invasive terahertz diagnostic methods of diabetes.

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References
[1] Braun K. et al. 2012 Diabetes research and clinical practice 98.1 164-168
[2] Stratton I. et al. "Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study," Bmj. 321.7258, 405-412 (2000).
[3] Zoungas, Sophia, et al. "Severe hypoglycemia and risks of vascular events and death," New England Journal of Medicine 363.15, 1410-1418 (2010).
[4] Cohen M. et al. "A comparison of blood glucose meters in Australia," Diabetes research and clinical practice Vol. 71(2), 113-118 (2006).
[5] Engel L., Delaney C., Cohen M. "Blood glucose meters: an independent head-to-head comparison," Practical diabetes international Vol. 15(1), 15-18 (1998).
[6] Terekhov Y. E., Khodzitsky M. K., Grachev Y. V., Sedykh E. A., Belokopytov G. V., Zhang, X. C. 2013 SPIE NanoScience+ Engineering 8806 88062Q
[7] Girich A., Khodzitsky M., Nedukh S., Tarapov S. 2011 Terahertz and Mid Infrared Radiation 159-164
[8] Geyko I. A., Smolyanskaya O. A., Sulatsky M. I., Parakhuda S. E., Sedykh E. A., Odlyanitskiy E. L., Zabolotniy A. G. 2015 European Conferences on Biomedical Optics 9542 95420E
[9] Gusev S. I., Borovkova M. A., Strepitov M. A., Khodzitsky M. K. 2015 European Conferences on Biomedical Optics 9537 95372A
[10] Duka M. V., Dvoretskaya L. N., Babelkin N. S., Khodzitskii M. K., Chivilikhin S. A., Smolyanskaya O. A. 2014 Quantum Electronics 44(8) 707
[11] Federal Almazov North-West Medical Research Centre webpage,” Federal Almazov North-West Medical Research Centre, 25 September 2015, <http://www.almazovcentre.ru/?lang=en> (25 September 2015).
[12] Zhang X. C. and Xu J., [Introduction to THz wave photonics], Springer, New York, 49-52 (2010).
[13] Gurvitz, E. A., et al. "Development of 3D Anisotropic Artificial Dielectric Metamaterial for THz Frequency Range," PIERS Proc. 2022-2025 (2014).
[14] Denisultanov, A. K., et al. "Optical properties of graphene on quartz and polyethylene substrates in terahertz frequency range," PIERS Proc., 2022-2025 (2014).
[15] Onushchenko, P. A., et al. "Observation of terahertz radiation absorption in CdSe quantum dots," Proc. SPIE 9502, 950216-950216-7 (2015).
[16] Strepitov, E. A., et al. "Investigation of the optical properties of normal fibroblasts and fibroblasts cultured with cancer cells in terahertz frequency range," European Conferences on Biomedical Optics, 95420M-95420M-6 (2015).