The Investigation of Blood and Skin THz Response at High Glucose Concentration

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***Abstract*—Studies of a rat blood and skin were carried out using THz-TDs. The transmission and the attenuated total internal reflection geometries have been used for measuring the dielectric properties of the water solutions and biological samples with high glucose concentration. We discuss the reasons for the observed THz sensitivity to diabetes mellitus in the context of changes in the bounded water caused by glucose.**

I. INTRODUCTION

DIABETES and its complications have a high mortality rate in the human population. In this context, the development of new rapid diagnostic methods for this disease and its complications is an urgent problem. THz spectroscopy has not yet found wide application in this field. A distinctive feature of this method is the possibility of measuring directly the refractive index and absorption coefficient. This circumstance makes it possible to obtain a dielectric function of a sample during one measurement, thus more sensitive diagnostic can be developed. In this paper we report the results of studying blood plasma and skin transmission and reflection spectra of the healthy and diabetic rats.

In solvents studies in THz range, there are no sharp spectral features, thus information about small changes in the shape of the broadband spectrum is important. The determination of dielectric function parameters is, however, often dependent on the measurement procedure and requires that the measurement reproducibility is carefully verified. So, simple and reliable methods should be developed. We suppose that changes in the shape of the THz spectrum are mainly due to changes in the relaxation time of water molecules chemically or physically bound to the molecules of interest.

Measurements of the transmission (*T*) spectrum of rat blood plasma make it possible to more accurately determine the properties of the solution at frequencies below 0.3 THz. The reflection (*R*) form prism in the attenuated total internal reflection (ATR) geometry offers the possibility to measure a broader spectrum (at frequencies above 1.5 THz). Therefore we have used both of these methods for analyzing the dielectric properties of the water in samples with high blood glucose concentration. To increase sensitivity in our approach we normalize sample measurements to the spectrum of distilled water. Only in this way small differences caused by glucose concentration become reliably noticeable. Both *R* and *T* complex spectra are further converted to dielectric function spectra and the results from two different measurements geometries can be compared.

The dielectric permittivity of water is widely discussed now and can be described by the two-component Debye model with the Lorentz term [1, 2]:

$$\varepsilon_{water}(\omega) = \varepsilon_{\infty} + \frac{\Delta\varepsilon_1}{1+i\omega\tau_1} + \frac{\Delta\varepsilon_2}{1+i\omega\tau_2} + \frac{A}{\omega_0^{\,2} - \omega^2 + i\gamma_1\omega} + \ldots$$

where $\Delta\varepsilon_1$ and $\Delta\varepsilon_2$ are the relaxation strengths of the two Debye relaxation modes with slow (τ_1) and fast (τ_2) relaxation times, respectively. ε_∞ is the dielectric constant in the high frequency limit. A, ω_0 and γ are the amplitude, frequency and line-width of the Lorentz term, respectively.

Because the first term of the Debye contains $\omega\tau_1 >> 1$, in the THz range we can accurately determine only the ratio $\Delta\varepsilon_1/\tau_1$ but not each of these values separately, that explains large variations of $\Delta\varepsilon_1$ and τ_1 values published in the literature. Wrong decrease of $\Delta\varepsilon_1$ value may be compensated by wrong decrease of τ_1.

II. RESULTS

The experiments were made both in the T geometry with 500 microns thick quvette and in ATR scheme with silicon right angle Dowe prism [1, 3]. The practical advantage of ATR scheme is in the large signal amplitude (|R| is close to 1) for absorbing media such as blood plasma or water. Both ATR and T methods can be used to determine τ_1, and only ATR is suitable for assessing τ_2. ATR scheme is also applicable for *in vivo* skin study.

The most significant difference in the complex reflection spectra R are observed in the frequency range of 0.05-0.5 THz. Moreover, changes in the phase are more pronounced, which may be associated with a change in the relaxation time of water molecules τ_1, the so-called "slow" relaxation. We found that amplitude and phase of the reflection coefficient of rat skin are changed when the blood glucose concentrations rise above the normal level.

We found that the amplitude of the blood plasma absorption and reflection spectra of rats with high glucose concentration differs from those of the healthy rats and water. Glucose concentrations were 24.4±1.9 mM and 6.6±0.4 mM in blood plasma diabetic and healthy rats, respectively. The absorption coefficient of blood plasma was significantly reduced, depending on the diabetes severity [4]. Analysis of the observed differences was performed by comparing the experimental spectra of diabetic rats with a model of the dielectric function of the water.

Assuming that the observed spectral changes are due to changes in the state of the water, we select one of the parameters of the Debye model aqueous solution - $\Delta\varepsilon_1/\tau_1$, leading to the spectral features observed in the experiment (fig. 1). This ratio for water is $\Delta\varepsilon_1/\tau_1$=7.87±0.01 and for blood plasma with high blood glucose concentration is 7.03±0.01. Figure 1 shows that change in transmission of blood plasma diabetic rats are determined only by variations of slow Debye process.

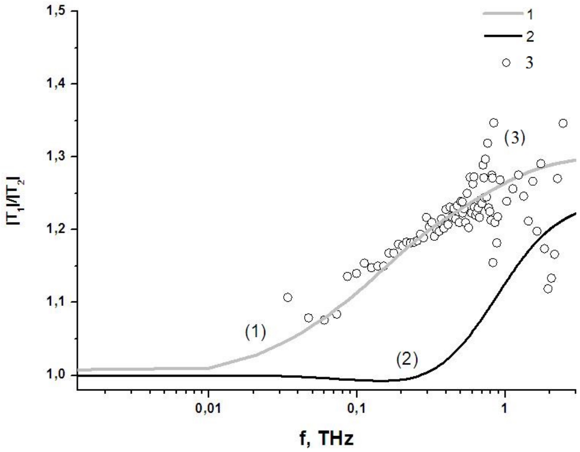
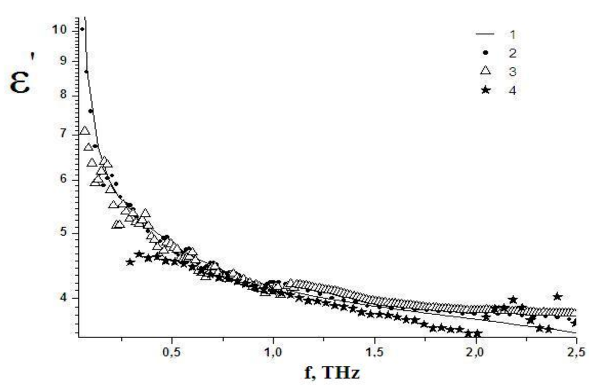


Fig. 1. The relative change in THz response of solution at small variations in the model dielectric permittivity parameters, a comparison with experiment: T_1 - transmission of modified sample (blood plasma), T_2 - - reference transmission (water); 1 – variations of slow Debye process ($\Delta\varepsilon_1/\tau_1$ is decreased 1.2 times); 2 - variations of fast Debye process ($\Delta\varepsilon_2$ is decreased 1.5 times); 3 - the experimental data

We obtained the following set of parameters for describing the blood plasma permittivity of diabetic rats: ε_∞ = 2.6±0.2, τ_1=9.96±0.5 ps, τ_2=0.24±0.01 ps, $\Delta\varepsilon_1$ = 70±2, $\Delta\varepsilon_2$= 1,66±0.03, A=31(THz*2π)^2, $\omega_0/2\pi$= 5.3THz, $\gamma/2\pi$ =7 THz. At the same time the obtained values for the distilled water are consistent with the reference [2].

Thus, τ_1 is increased 1.2-times or $\Delta\varepsilon_1$ is diminished 1.2 times compared with water. It means a decrease in the proportion of water molecules bound by hydrogen bonds or increasing the proportion of free water in blood plasma of diabetic rats. Note, that the method of microwave dielectrometry has previously shown the changes in the ratio free/bound water in diabetic rat erythrocytes [5].

We have used both T and ATR geometry for extracting the dielectric properties of the water in samples with high blood glucose concentration.



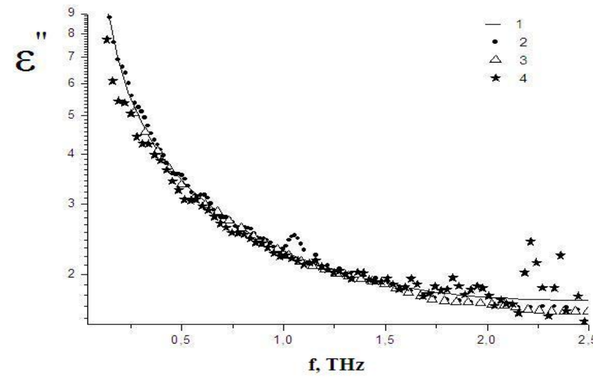


Fig. 2. Real and imaginary parts of the complex dielectric permittivity, reconstructed from measurements in ATR or transmission geometries: 1 - water model, • - from transmission of water (2); Δ - from transmission of diabetic samples (3); from reflection of diabetic samples (4).

Figure 2 shows real (ε') and imaginary (ε'') parts of the complex dielectric permittivity, evaluated from these experimental data. We can see a satisfactory agreement of data obtained by different methods. Thus, from the experimental data on *R* and *T* of the sample one can independently obtain practically the same characteristics of biological samples and improve the accuracy of the extracted values.

III. Summary

We investigated the features of blood and skin THz response of the rats with high blood glucose concentrations. We observed a correlation between the concentration of glucose in blood and a change in the spectrum of its dielectric function in the THz range. The observed change of the spectrum is described with good accuracy by the reduction in the ratio $\Delta\varepsilon_1/\tau_1$ in the Debye model of glucose aqueous solution. Two independent measurement methods - ATR and transmission support our hypothesis. This change in the response of bounded water is the reason of the sensitivity of in vivo THz skin reflection measurements to the presence of diabetes.

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