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# Towards broadband THz spectroscopy and analysis of sub-wavelength-size biological samples

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**Abstract**—We report on our recent progress toward biophotonic applications of terahertz time-domain spectroscopy. First, we developed a technique for the confinement of broadband terahertz pulses to a sub-wavelength-volume, and will present its applications to study biological samples. Second, we will discuss the analysis of terahertz time-trace data from bio samples using our Fit@TDS software based on the time-domain optimization algorithm that enables direct fitting of sample parameters. The combination of those (the experimental and the modelling) techniques is a robust tool for terahertz bio-photonics.

## I. INTRODUCTION

TERAHERTZ (THz) technology has shown increasing development in last years, it has been considered as an efficient non-destructive, non-contact and label-free optical method for biological detection. THz spectroscopy probes delocalized collective vibrational modes in long molecules like sugars, proteins, amino acids, DNA, RNA, etc. Thus, the use of THz spectroscopy has been proposed for a variety of medical and biological applications [1]. However, one of the major issues to solve to enable THz spectroscopy of actual bio-samples is that they are very small compared to the THz wavelength. Therefore, it is mandatory to enable sub-wavelength confinement of the THz electromagnetic field. We have recently proposed [2, 3] a biophotonic device that allows increasing the light-matter interactions to enable THz spectroscopy of very small ( $\sim 1$ -nL volume) samples over a broad range (0.2–4 THz) [4]. Here, we present the results of application of our method to biological samples.

THz spectroscopy made its main achievements using Time-Domain Spectroscopy (TDS). The ability of TDS to measure directly the electric field of a THz pulse gives access to both the phase and the amplitude of the pulse, which makes it a powerful tool to characterize materials. We have recently developed a method (and open-source software called Fit@TDS) to fit time-trace data from THz TDS system enabling the extraction of physical parameters of the sample [5, 6]. The idea is to model a material through parametric physical models (Drude-Lorentz model, Debye relaxation model and time-domain coupled mode theory) and implement it in the propagation model to simulate the time-trace. Then, an optimization algorithm is used to retrieve the parameters of the model corresponding to the studied material. We will implement this method for the analysis of TDS data of bio-samples. Finally, we will discuss the combination of our modelling approach with the technique for broadband TDS of sub-wavelength volume bio-samples.

## II. RESULTS

New features of our software (for the analysis of polar liquids and multilayer systems) will be reported in an independent presentation during the conference. Here, we will focus on its applications to bio-samples. As they are often inhomogeneous, the scattering plays an important role and will be taken into an

account in our software. The preliminary results of the modeling of a THz pulse transmitted through a 1-mm-thick pellet of 70% Polyethylene/30% Fmoc-L-Glu(OtBu)-OH\*H<sub>2</sub>O (Glutamic Acid derivative) is presented in Fig.1., showing the capacity for biological applications.

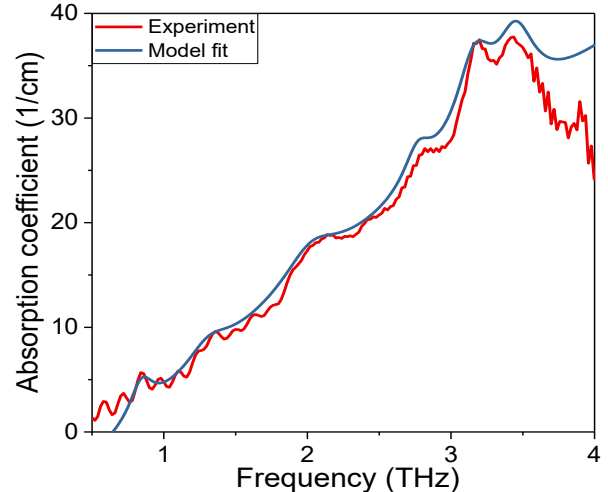


Fig. 1. Spectrum of the absorption coefficient of Glutamic Acid retrieved from experimental and modelled time-trace data.

Another interesting application of the software is the identification of organic inclusions in ice – an example is presented in the Fig.2., where our approach was used to fit the time-trace data recorded in THz-TDS experiment with an ice cube containing lactose crystallites. As we have shown

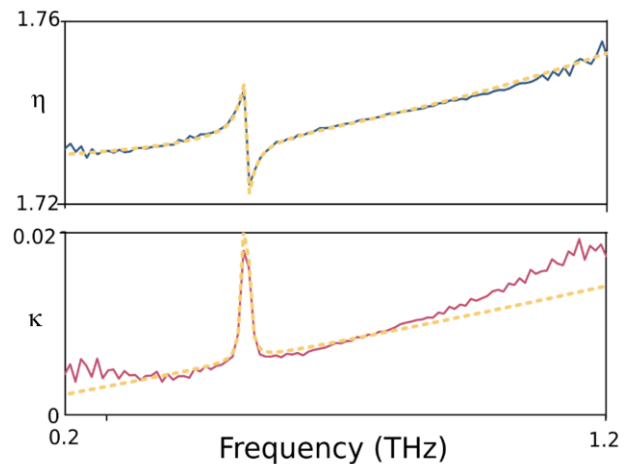
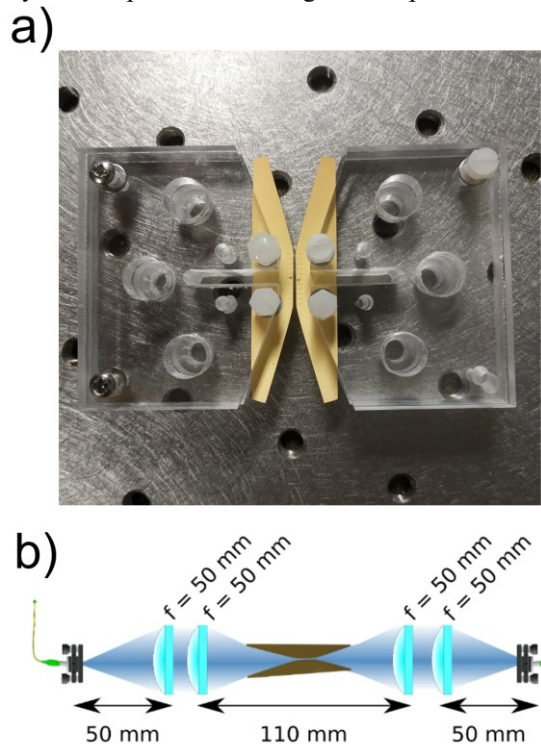


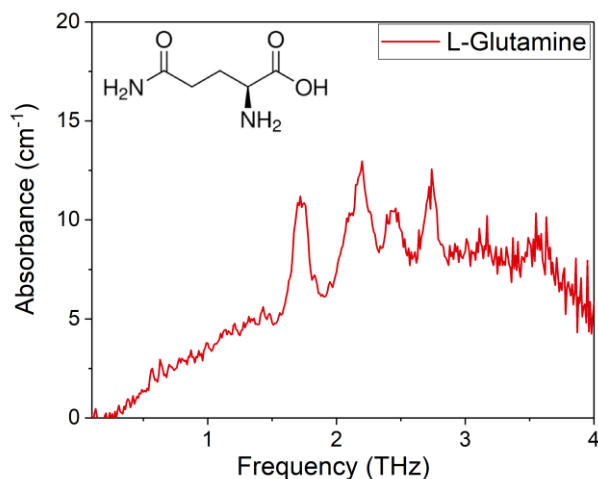
Fig. 2. Spectra of the real ( $\eta$ ) and the imaginary ( $\kappa$ ) parts of the refractive index of ice with lactose crystallite inclusions (the sample was prepared by freezing the aqueous solution of lactose with  $\sim 1$ mol/L concentration – oversaturated solution: presence of micro crystallites  $\sim 9\%$  of volume ratio), retrieved from the experimental data (solid lines) and by fitting the time-trace with Fit@TDS software.

previously, the use of ice is advantageous for characterization of organic samples [7]. It allows to overcome the absorption by water molecules, may serve as a natural matrix for crystallites and is fully compatible with bio protocols. Combined with Fit@TDS software the method gives a way to detect and identify the composition of an organic sample.



**Fig. 3.** a) Photo of the butterfly device. b) Schematics of the THz-TDS experimental setup.

The technological aspect (the design, fabrication, characterization) of our device for the confinement of THz pulses to a minor volume (“butterfly-device”, see Fig.3.) will be reported during the IRMMW-THz 2019 conference as an independent presentation. Here, we will show the results of our



**Fig. 4.** Spectrum of the absorbance of L-Glutamine powder sample of  $\sim 1.5 \mu\text{g}$ , the corresponding volume of  $\sim 1 \text{ nL}$ . The results are obtained using the butterfly device for THz light confinement in THz-TDS Terasmart system by Menlo.

study of various bio-samples using our technique. First, we will show its capacity for broadband spectroscopy of few-nL-volume test samples (lactose monohydrate), then will turn to spectroscopy of proteins and amino acids (the spectrum on 1-nL-volume sample of L-Glutamine powder is presented in the Fig.4. as an example, revealing the strong absorption peaks of L-Glutamine [8]). Finally, we apply the method to study biological molecules used in medical and pharmaceutical research.

### III. CONCLUSION

We present the applications of two methods for the study of sub-wavelength-size bio-samples: the experimental technique for the confinement of THz pulses to a nL volume, and the software to fit the experimental data of bio-samples. Finally, we will discuss the combination of these techniques being an efficient tool for biological and pharmaceutical research.

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