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# Terahertz technology for biophotonics: a general overview and recent advances in THz spectroscopy toward biology

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## ABSTRACT

In this conference, we will discuss the advancements in Terahertz (THz) spectroscopy and imaging regarding biophotonics applications. In recent years, THz technology helped various fields, from fundamental physics to industrial process control. THz spectrometers offer a wide spectrum range and high dynamic range, enabling the analysis of semi-transparent materials and living tissues. THz imaging has shown potential in applications such as cancer detection, diabetes foot syndrome, burn wound analysis, and plant hydration assessment. Spectroscopy in the THz range is particularly promising for studying biological systems, including proteins and their compounds. However, challenges such as the strong absorption of water, temperature stability, and small sample sizes need to be overcome. Techniques like scanning microscopy, integrated photonics, and metallic broadband approaches have been explored to enhance THz analysis. Despite the challenges, THz technology has found industrial applications and efforts are being made to improve data processing and error evaluation. Additionally, a proposed method aims to enhance the resolution of THz systems, making them suitable for gas spectroscopy and the sensing of volatile organic compounds relevant to biology.

**Keywords:** Terahertz, Time domain spectroscopy, biophotonics

## 1. INTRODUCTION

Today, recent commercial THz spectrometers record a spectrum from 0.2 to 6 THz and reach up to 100 dB of dynamic range, with recording time from video frame to minutes depending on the desired signal to noise ratio. This set up provided an amazing tool to perform spectroscopy in a range where source and detector were extremely inefficient in the past. Therefore, this open myriad of opportunities driving the commercialization of THz TDS spectrometer at the beginning of the millennium. This has opened up a wide range of applications, from fundamental physics to process control in the industry. A natural outcome of this progress is the broader use of Terahertz technology across many different disciplines. However, this also comes with the not insignificant corollary of producing exciting, but sometimes unreliable, results, specifically in the field of biophotonics [1].

To better understand the spread of the technics it is important to understand that In the THz range, many materials and living tissues are semi-transparent, and can be imaged, analyzed and identified. In addition, THz electromagnetic radiations are non-ionizing, allowing wide range of applications from security to detect hidden weapon and explosives to in medicine to replace X-ray in specific cases. This proceeding will quickly review the recent and less recent results in THz imaging for biology and medicine and then elaborate on THz spectroscopy towards these applications. I will focus on what THz time domain spectroscopy reveals in solid, liquid and gas samples. Specifically, I will explain how to retrieve information on the picosecond dynamics of carriers in the samples and their relevance to biology in the three phases of matter.

## 2. SHORT SUMMARY OF THZ TECHNOLOGY FOR IMAGING FOR BIO APPLICATIONS

Thanks to the non-ionizing nature of the THz ranges, imaging applications have attracted a lot of attention. Two important features of THz imaging are that the only limitation of short time exposure is determined by the heating from the beam, and the low penetration depths of the beam limit the inspection to only the uppermost tissue layers. Water absorbs tremendously in the THz range, and therefore THz imaging is very sensitive to any variation in the water or humidity content of a tissue or biological material. This drove the first studies on the detection of dermal cancer, taking

advantage of the humidity variation between normal and cancer cells and being exactly in the depth range of interest [2]. Similar studies continue to this day, but they have not yet reached clinical application level [3]. Among other examples, one can cite the use of THz imaging for diabetes foot syndrome analysis [4] or [5], and for burn wound cicatrization [6, 7]. Another application envisioned from the early beginning is the cavity detection in dentistry [8, 9]. Still in biology, but on plants, several reports have mentioned the capability of Terahertz imaging and hyperspectral imaging to retrieve the hydration of plant leaves [10, 11].

All these examples are based on the sensitivity of THz technology to water content of tissues and are still published engineering journal rather than in medical ones. The author of this proceeding found a few clinical trials (2) is ongoing on the topics and is eager to see their results and significance.

### 3. THZ SPECTROSCOPY FOR BIOLOGY AND MEDICINE

Besides their role in imaging, THz technologies are, as well, extremely promising in spectroscopy especially for biologic systems. A controversy between *D'Alembert* [12], *Euler* [13] and *Bernoulli* [14] shined the light on resonant vibrations of objects. The consequences spread from vibrational modes of galaxies to vibrations of violin's strings, to the ones of molecular bonds in infrared spectroscopy. The vibrations eigen frequencies serve as signature for the size, stiffness and structure of a body. The size of a macromolecule like a protein lies roughly in the range from one to 10 nm, making it a biochemical nano-object with a relative symmetry deriving from the repetition of monomers. One can calculate the vibrations eigen frequencies supported by proteins roughly dividing by sound speed in solids, leading to a result lying in the broad THz range. Additionally, since biological macromolecules are polar, these vibrations directly couple to the EM-field similarly to IR absorption lines for molecular bonds and organic functions. This motivated THz spectroscopic studies about the proteins and their compounds, hoping that THz absorption would be able to interrogate vibrational modes across large portions of the bio-molecular framework. Another motivation came from the fact that energy of THz photons is of the same order of magnitude of variety of interesting biological process like proton tunnelling in enzyme catalysis.

Historically, THz spectroscopy used (far)-infrared Fourier transform spectroscopy systems (FTIR), which relied on THz sources and detectors showing poor performances in the so-called THz gap. Coherent systems such as Time domain spectroscopy were game-changers. The setup comes from sub-picosecond electrical sampling demonstrated in *G. Mourou's* group [15] that *D.H. Auston* improved to THz range using non-linear optics [16] for THz emission and detection. Finally, *Grischkowsky et al.* [17] introduced the photoconductive antennas as in most of nowadays systems. It uses a benchtop short pulsed ( $\sim 100$  fs) lasers illuminating a semiconductor at a  $\lambda$  (energy) above the energy band-gap to generate mobile carriers. Effectively, the semiconductor changes abruptly from being an insulator into being a conductor. This leads to a sudden electric current across a biased antenna patterned on the semiconductor and emission of broadband THz pulse. This pulse goes through the sample and is recombined with a controlled delay together with the original laser pulse onto photoconductive or electro-optics material acting as detector. This allows accessing not only to the amplitude but as well to the phases of the THz pulse.

First experiments were performed on pellets made of a mix of caking THz transparent material and dry but hydrated crystal powder of amino acids, nucleobases & nucleosides [18] and polypeptides secondary structure [19]. We recently published, thanks to experiments on lactose [20], that the interpretation for the measured lines links them to inter-molecular phonons or vibrations of the crystal spreading, and thus depicting a structure bigger than a single molecule. In addition, we clearly showed that the hydration level of the molecular crystal changed the whole THz spectrum. Water molecules does not only add lines to the spectrum nor perturbation; but it play a constitutive role in the THz vibrations. In other words, THz spectroscopy allows us to probe nanoscale spreading vibrations and thus sense the 3D nanostructure of the sample through their vibrational dynamics.

Since the 3D nanostructure or conformation of macromolecules mostly defines their functions, such results seeded the hopes to probe the 3D nanostructure of proteins using THz spectroscopy. However, several challenges arose from the theoretical idea up to its realization.

The first challenge, as perfectly explained in [1], there is a major difference between a carbohydrate molecular crystal and an in vivo protein. In the first case, resonant absorption forms clear peaks, but this behavior is unlikely to persist even when the same molecule is randomly dispersed in a liquid or other amorphous medium making interpretation of the results complex.

The second challenge is the strong absorption of water. This strong absorption is an enormous advantage while one wants to sense hydration level or humidity of a tissue, but it is an experimental challenge by making experiments more difficult due to signal loss, and because its absorption varies with temperature [21, 22] with an order of magnitude of the percent per degree. The direct consequence is that it requires keeping a temperature stability below 0.1°C. On the bright side, the strong absorption of water and its variation have been exploited to better understand the relationship between the shape of a protein and the solvent dynamics around it [23, 24, 25], and to better understand the cell membrane [26, 27, 28, 29].

The third challenge for terahertz spectroscopy is the analyze sub-wavelength samples. In fact, many biologic samples are smaller than the wavelength in the terahertz range (from 30 μm to 3 mm). Consequently, the interactions between the electromagnetic waves and the sample are weak. To enhance these interactions, one has to increase the overlap of the light mode with the sample. This field enhancement can be achieved by two ways either using a scanning microscopy or implementing integrated photonics concepts. Both is discussed in the following.

The section discusses two types of THz near field microscopy setups: scattering Scanning Near-field Microscopy (s-SNOM) and laser scanning THz emission or detection microscope (LSTEM or LSTDM). (i) The s-SNOM [30, 31] uses the tip of an Atomic Force Microscope (AFM) to concentrate light and has a resolution similar to the apex radius of the tip (~15 nm [32]). The specificity of such setup in the THz range is again linked to the wavelength; here the tip size is much smaller than the wavelength. However, we recently demonstrated the capability of such systems to probe photonics modes [33, 34] and the nanoscale. However, the extension of the technics to spectroscopic systems able to probe individual protein for instance remains challenging mostly due to the signal to noise ratio. (ii) The LSTEM/LSTDM [35] is a TDS where the sample is in contact with a THz non-linear optics detector/emitter, and the laser gating the emitter/detector scans the surface of the sample. Here, the spatial resolution comes from the laser spot size in the non-linear crystal and is around 1 μm so bigger than an individual macromolecule but smaller than several bio-objects of interest. Since this setup is built around a TDS setup, the spectroscopy is included allowing many results e.g., imaging of breast cancer cells [36, 37]. Using this configuration enhanced by an additional metallic hole, the group of A. Markelz recently demonstrated THz near field spectroscopy of μcrystal of MMs [38, 39] and even polarimetric measurements [40].

Integrated photonics approaches mostly use the quite good quality of metal in the THz range and can be separated in two parts, the broad band and the resonant approaches. Most of the broadband approaches uses a metallic waveguide [41], such as a parallel plate metallic waveguide, for low losses and dispersion. In these waveguides, the lowest energy mode (transverse electromagnetic; TEM) shows no frequency cutoff. However, one needs to use a coupling scheme to enable the THz pulse to enter the waveguide. The first idea was to use cylindrical lenses but this induced a quite detrimental dispersion and was limited by the diffraction in the lens medium. The next approach overcame these limitations using metallic antennas. However, these devices remained a 1D geometry meaning that there were no vertical confinement leading to both weak overlap with the sample and diffraction in the vertical direction. Still, it enabled spectroscopic measurements of thin polycrystalline film of deoxycytidine. Further, this allowed smaller sample size with a nanofluidic integration. Furthermore, we recently demonstrated that the combination of tapered antenna [42] and planar geometry [43, 44] overcomes loss and dispersion, enabling 2D confinement and spectroscopy of 1 nl of dried solution of Glutamic acid [45, 46].

#### 4. CONCLUSION

There is no doubt that THz technology faces several challenges in order to be fully exploited in biology and medicine where reliability and time to market are relatively high. However, it is important to remind those industrial applications are already in place, such as measuring the thickness of automotive paint during painting, or in aeronautics [47]. Similar approaches could be exploited for bio application as it has been used to see the layered structure of sunflower seeds [48]. In any case, in order to reach the next level, the community needs to make advances in data processing and error evaluation, as currently only a very phenomenological approach is used [49]. In fact, there is no standard today to retrieve the uncertainties or the error bars from THz TDS experiments. This drives the efforts of several groups, including our own, to bring TDS data processing to the next level [50, 51, 52, 53, 54, 55] to enable more reliable and repeatable results and even extend the capabilities of the technics to other classes of samples. For instance, we recently proposed a method to improve the resolution of TDS systems by a factor of 30, making them compact and tremendously broadband gas multispecies spectrometers. This could potentially be used to sense a variety of volatile organic compounds of biological interest [56].



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