TECHNICAL DIGEST

9TH INTERNATIONAL THz-Bio WORKSHOP

19th-23rd April 2021

ETTORE MAJORANA FOUNDATION AND CENTRE FOR SCIENTIFIC CULTURE

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Italian National Agency for New Technologies, Energy and Sustainable Economic Development

Istituto per il rilevamento eletromagnetico per l'ambiente
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9th International THz-Bio Workshop
April 19 – 23, 2021

The millimeter wave and terahertz regions are frontier areas for research in physics, chemistry, materials science, biophysics, biology, and medicine. The interest in novel imaging, sensing and spectroscopy in the above communities has grown steadily during the past twenty years, as new instrumentation, as well as new techniques and new applications have become available.

In 2010 a workshop series entitled "International THz-Bio Workshop" started in Korea with the support of the Ministry of Education, Science and Technology. In 2016 its international organizing committee was encouraged to consider a rotation of this workshop series between different geographical areas. It was then decided to host the THz-Bio Workshop 2017 at ENEA-Frascati in Italy. After the success of this event it was decided to hold the 9th International THz-Bio Workshop at the “Ettore Majorana Foundation and Centre for Scientific Culture” in Erice, Sicily from April 30 to May 3, 2020, in the frame of the activities of the Erice International School of Bioelectromagnetism. Following the outbreak of the Covid-19 pandemic, several attempts were made to reschedule the workshop dates, still maintaining the possibility to hold the meeting in person. In spite of this effort, and in order not to miss the opportunity of this event for the scientific community, we finally decided to hold the THz-Bio Workshop exclusively online.

To allow for the widest participation, the Workshop is now organized in five days, from Monday, April 19 to Friday April 23, 2021. As a result, the new program includes 51 presentations (19 Keynote, 20 Oral and 12 Poster) distributed over 12 technical sessions covering a variety of scientific issues in the Terahertz and adjacent parts of the Infrared and Microwave spectral regions, ranging from Spectroscopy and Mechanisms of Interaction to Biological Effects, Biolmedical Imaging and Medical Applications, as well as 5G Technology. Two of the above sessions are devoted to an overview of the Attract project, recently funded by the EU (Grant No 777222) to cover technological aspects of THz radiation.

We hope that the Workshop can provide an opportunity for discussion, stimulate further studies, and contribute to the development of this exciting field of research.

Gian Piero Gallerano and *Olga Zeni*
ENEA-Frascati CNR-IREA, Naples
THz-Bio Workshop Co-chairs

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Maria Rosaria Scarfì (CNR-IREA, Naples, Italy)
Directors of the EISBem School

The International School of Bioelectromagnetism
Ettore Majorana Foundation and International Centre for Scientific Culture, Erice (Sicily)-Italy

The Centre for Scientific Culture in Erice (Sicily, Italy) is named after the great Italian scientist Ettore Majorana and hosts about 140 permanent international Schools on very different research areas, among which physics, biology, medicine, chemistry, astronomy, environmental science, sociology and journalism.

Topics in Bioelectromagnetics have come to Erice many times in the past, with International courses and workshops on non-ionising radiation, and today many participants of those courses contribute greatly to the development of this research field.

Following the request of the European Bioelectromagnetics Association (EBEA) and the Italian Inter-University Centre for the study of the Interaction between Electromagnetic Fields and Biosystems (ICEmB), in 2003 the Ettore Majorana Centre established a Permanent School of Bioelectromagnetism, named after Alessandro Chiabrera, who is considered as a master by the young scientists of the two organizations (http://www.eisbem.eu/).

Since then, nine Courses have been organized, covering different topics in Bioelectromagnetics, spanning from basic research and methods to specific aspects, such as biomedical applications, biophysical mechanisms of interaction, epidemiology.

This kind of School, which is unique in its character (being not overlapping with other initiatives), is a successful response to one of the most important duty of any scientific community and association, namely, to prepare a new generation of informed and well trained young researchers.

The 9th International THz-Bio Workshop is the tenth event organized in the framework of our School. It will be held fully on-line due to the COVID-19 pandemic but we sincerely hope that another event can be organized on-site, to let the THz-Bio community experience the strict synergy between the participants in the unique fascinating atmosphere of the Ettore Majorana Center.

Ferdinando Bersani and Maria Rosaria Scarfi

Directors of the Erice International School of Bioelectromagnetism

Session 1.1:
Medical Applications I

Erice, Sicily

Cell Demethylation using Resonant Terahertz Radiation for Potential Cancer Treatment

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***Abstract*—Carcinogenesis involves DNA methylation which is a primary alteration in DNA in the development of cancer before genetic mutation. Because the abnormal DNA methylation is found in most cancer cells, assessment of DNA methylation using terahertz radiation can be a novel optical method to detect and control cancer. The methylation has been directly observed by terahertz spectroscopy in the terahertz region and this epigenetic chemical change could be manipulated to the state of demethylation using resonant terahertz radiation. Demethylation of cancer cells is a key issue in epigenetic cancer therapy and our results may lead to the treatment of cancer using electromagnetic waves.**

I. INTRODUCTION

TERAHERTZ electromagnetic waves, whose spectrum lies between microwave and infrared regions (0.1-10 THz), have been utilized for the diagnosis and imaging of cancer [1-3]. In the effort of finding a specific signal in such measurements, a terahertz resonance fingerprint of cancer has been directly observed at 1.6 THz for several types of cancer [4]. The resonant signal is believed to originate from the aberrant methylation in DNA which is an epigenetic modification before genetic mutation in the development of cancer. If it is a true resonant feature, this might be controlled or manipulated by using a terahertz radiation at the frequency.

In the presentation, the details of finding the terahertz resonance of cancer DNA coming from methylation and the manipulation to demethylation using resonant terahertz radiation will be explained. Also, how the demethylation is related to cancer treatment will be discussed.

II. RESULTS

DNA methylation plays a role to regulate gene expression. Because abnormal regulation of gene expression can cause carcinogenesis, DNA methylation is a critical factor in cancer research and treatment. In aqueous solutions, we tracked and observed the molecular resonance of genomic DNA at 1.6 THz from two controls (293T, M-293T) and five cancer (PC3; prostate cancer, A431; skin cancer, A549; lung cancer, MCF-7; breast cancer, SNU-1; gastric cancer) cell lines, using freezing technique and baseline correction [4].

The resonance peak of spectrum presents the existence and quantity of methylation in DNA, but also the target for manipulation of DNA methylation to control gene expression in cancer DNA by breaking its bond. To break the methylation resonantly, we irradiated a resonant high-power terahertz radiation, which is generated from a $LiNbO_3$ crystal driven by 1-kHz regenerative amplifier and has a limited bandwidth around the resonance frequency of DNA methylation by a bandpass filter, onto some types of cancer DNA. The DNA from human embryonic kidney cell line (293T) was utilized as a control and a part of it was artificially methylated to give M-293T by DNA methyltransferase enzyme (DNMT). The M-293T was divided into two and one of them was irradiated with high-power terahertz radiation. The methylation level of M-293T was high but it was decreased to half close to the level of 293T after the exposure.

To identify the effect in actual cancer DNA, we applied high-power terahertz radiation on some types of blood cancer DNA to assess the demethylation. The blood cancer DNA experiment was performed in the same method with the M-293T. The degree of DNA methylation was significantly decreased in most of the blood cancer, although the demethylation ratios varied according to cell line (approximately 10 - 70%) [5]. Also, the effective demethylation of melanoma cells, without extracting the cancer DNA, was achieved using a resonant terahertz radiation [6].

III. SUMMARY

The result demonstrates that the molecular resonance of cancer DNA exists in the terahertz region and this can be controlled by the irradiation of high-power terahertz radiation. This is the first result using an optical technique for manipulating DNA methylation. The manipulation of methylation in cancer DNA is an important issue in epigenetic cancer therapy because aberrant DNA methylation can lead to abnormal gene expression. Although there are several chemical inhibitor drugs for DNA demethylation, which reduce aberrant DNA methylation in cancer cell, they still have a high risk of side effects. Because our method is a non-invasive, non-ionizing and non-labelling technique, and uses specific resonance frequency, it can be a great solution to achieve a novel cancer therapy with few side effects. This implies that, like genetic scissors in biology, terahertz technique may be applied as ‘epigenetic scissors’ which could lead to the demethylation of cancer DNA.

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Terahertz in vivo imaging for improved skin diagnosis and treatment

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***Abstract*— For THz *in vivo* imaging to be used in a clinical setting, a robust, accurate and fast imaging protocol is needed and patient invariant parameters must be identified. Here, we outline the advances we have made in various aspects of THz instrumentation, devices and data processing.**

I. INTRODUCTION

TERAHERTZ technology has advanced significantly in recent years and THz systems are becoming more versatile and compact. This has facilitated more studies of biomedical applications. My recent research has highlighted the need for developing a robust protocol for *in vivo* imaging as there are many variables that need to be taken into account [1]. For example, the contact pressure [2] between the skin and the imaging window will affect the THz response, as will the duration for which the skin is in contact with the window. When the skin contacts the window, it is "occluded" therefore water cannot leave the skin surface leading to an increased surface hydration, this occlusion process can be tracked using THz imaging as THz imaging is so sensitive to changes in water content and thus skin hydration [3]. These variables which effect the THz measurement can be controlled using a protocol which gives the skin time to recover after occlusion and instrumentation which makes it possible to control the contact pressure applied by the subject as shown in Fig. 1. Recent work by my group has demonstrated that such protocols can be used to successfully obtain repeatable results evaluating the effect of applying a commercial moisturiser on the THz response of skin.

So far when monitoring the occlusion process, we have used a point measurement in a representative area of the skin, but in the future, we plan to be able to monitor this process using video rate THz imaging. Our group is making progress in this area by exploiting THz modulators in the total internal reflection geometry [4].

II. RESULTS

In this talk I will discuss the recent advances in our THz instrumentation and analysis. I will also present *in vivo* measurements of 20 volunteers, taken before and after applying three different moisturiser ingredients. In addition to the THz measurements, we have also taken measurements using a corneometer (able to measure skin hydration) and a tewameter (able to measure the transepidermal water loss) the present gold standard in skin hydration evaluation used by companies testing the effects of skin products, optical images were also taken of the region using a USB microscope.

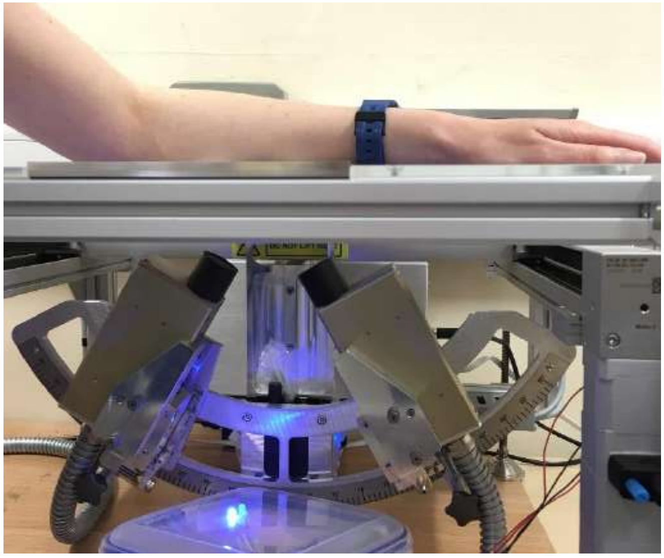

Fig. 1. Photograph of the THz in vivo imaging system. The LEDs are used to give real time feedback of the contact pressure between the skin and the imaging window.

III. ACKNOWLEDGEMENTS

This work was supported by the Research Grants Council of Hong Kong (project number 14206717), the Impact Postdoctoral Fellowship Scheme at the Chinese University of Hong Kong, the Hong Kong PhD Fellowship scheme (QS), EPSRC project EP/S021442/1 and the Royal Society Wolfson Merit Award (EPM).

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Application the THz spectroscopy and holographic approach for diagnostics of dry pellets of human blood plasma

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Abstract—**This work describes the promising approach for the diagnostic of diseases, such as diabetes, by using the THz spectroscopy and THz holography method. In this paper, dry pellets consisting of human blood plasma (normal and diabetic) were designed; these objects were analyzed in various THz laboratories in Russia, PCA-analysis of THz spectra was apply to separate the normal and diabetic groups; we proposed the holographic approach that provides sufficient information to reconstruct the spatial distribution of complex refractive index of the sample.**

INTRODUCTION

Verification of the physical and mathematical models by comparing the results of numerical modeling with the results of real measurements on phantoms and biological objects is an actual problem of THz biophysics. As shown in some THz laboratories [1-2], the blood plasma is one of the most promising object of study, since changes among its composition caused by pathological processes may considerably affect the optical properties of the blood plasma of humans and animals in the THz frequency range. In this paper, firstly, dry pellets consisting of human blood plasma (normal and diabetic) were created for this work; secondly, these objects were analyzed in various THz laboratories in Russia, using THz pulsed spectroscopy and a high-resolution THz spectrometer based on a backward wave oscillator, PCA-analysis of THz spectra was apply to separate the normal and diabetic groups; third, we proposed the holographic approach for diagnostics of biological phase object, that allows to register hyperspectral holograms in the detection plane and to provide numerical wavefront propagation to the object plane.

I. Material and Method

Human blood plasma samples were frozen at a temperature of -80 ◦C and lyophilized by freeze-drying VaCo 2 (ZirBus, Germany) at a temperature of -50 ◦C and a pressure of 3 Pa (Laboratory of Almazov National Medical Research Centre). The dry mixture of 200 mg blood plasma substance has been pressed into a flat pellet in a steel press-mold with a diameter of 5 mm on a Corvette 590 hand press (Enkor, Russia) at a pressure of 500 kg / cm^2.

In this work, the samples were studied on a pulsed terahertz setup in transmission mode in two different laboratories (ITMO University [1] and MSU [2]). A high-resolution terahertz spectrometer based on a backward wave lamp (IPM RAS [3]) was also used.

Biochemical parameters of the human blood plasma were measured to control the results of the study in the clinical diagnostic laboratory of Almazov National Medical Research Centre (Russia). Plasma glucose concentration was increased in diabetic plasma, which is common for diabetes mellitus.

II. Results and Discussion

The groups of the THz spectra have a rather compact distribution in the principal component space. Also, the groups of the THz spectra are fully spatially separated. Using a high-resolution THz spectrometer, the spectral lines of substances were detected in blood plasma samples.

We demonstrated the ability of holographic approach to reconstruct spatial properties of investigated object in terms of two-dimensional distribution of refractive index, as well as frequency-dependent refraction in each point of the pellets (see Fig).

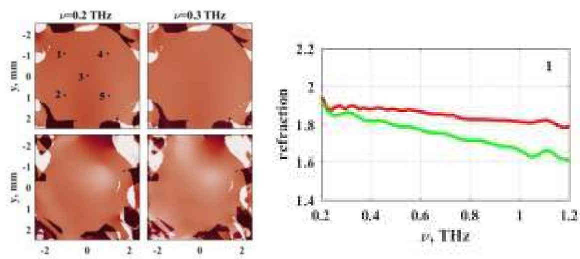

Fig. Spatial distribution of reconstructed refractive index for healthy and diabetic sample. Label 1 shows spatial point where we plotted refractive index versus frequency. Green line corresponds to healthy sample and red corresponds to the diabetic one.

III. Acknowledgments

The reported study was funded by RFBR according to the research project #17-00-00275 (#17-00-00270, #17-00-00272, #17-00-00184, #17-00-00186), 18-51-16002 and by the Government of the Russian Federation (Grant 08-08).

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Remote Diagnostics of Human Psychoemotional States by the Infrared – Terahertz Image from Face Areas

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***Abstract*—One of the promising directions of development of contactless techniques for assessment of human psychoemotional states (PES) is the elucidation of the relationships between the psychophysiological indexes and electromagnetic radiation in IR and THz ranges. The purpose of this work is to develop a complex approach to diagnostics of PES by combining psychophysiological data with simultaneous registration of IR - THz images of a human face in stress situations.**

I. Introduction

Objective diagnosis of human psychoemotional state (PES) is an extremely important and socially significant problem. The development of modern technologies for diagnostics of PES (emotions, stress, anxiety, etc.) is characterized by the transition from contact methods to remote ones that allow PES to be assessed in real time without contacting the object under study [1]. In our previous work we proposed a new approach to diagnostics of human PES, based on the analysis of the THz contribution to the total signal while simultaneously recording the IR and THz emissions (IR-THz image) from a recipient's face in stress situations [2]. The developed IR-THz image processing algorithm allowed extraction of the informative contribution, determined by the THz radiation, from the total signal perceived by the recording system. It was shown that using cluster analysis of IR-THz images it is possible to divide the test subjects into classes according to the type of reaction of the circulatory system under stressful conditions: namely, in some people stress enhances the blood flow, while in others it causes vasospasm and, as a result, a decrease in blood circulation intensity. The purpose of this work is to develop a complex approach to diagnostics of PES by combining psychological and psychophysiological data with physical measurements based on correlations between of IR-THz image of a subject face and galvanic skin response (GSR).

II. Results

This Registration of IR–THz images and psychophysiological parameters of the subjects was carried out using developed instrumental diagnostic complex, including the IR–THz detector NEC IR/V-T0831C, the software package 'Egoskop' (Medicom MTD), the personal computer and the seat with backrest drive. The IR/V-T0831C detector allows the registration of IR – THz images of the object under study in the spectral range from 1 to 30 THz (from 9 to 300 mm). The scheme of the experiments included simultaneous registration of physiological parameters of PES and IR-THz radiation of volunteers in stressful situations with cognitive, physical or physiological loading. Based on physiological measurements and psychological testing a comprehensive psychophysiological assessment of the recipients' PES was performed. The results of analysis of the IR-THz radiation, captured from the participant faces, were used to find the correlation of the parameters of IR-THz images with the data of measurements of galvanic skin response.

III. Conclusion

There is a statistically significant moderate correlation between the intensity of IR-THz in the forehead and GSR (Spearman coefficient = 0.334, $p < 0.05$). It is important to note that this correlation is observed in the range of ± 2 seconds relative to each GSR peak. This is quite an significant result, considering that all currently available measurements of IR radiation (without expansion into the THz range) and GSR indicate the presence of a large time lag between the appearance of the IR signal (> 10 s) and the generation of the GSR (3-5 s) [3]. The correlation of the intensity of IR-THz radiation in the forehead with GSR along with data concerning possibility to use THz waves for assessment of blood vessels [2] open the perspectives for development a new methodology for distant monitoring the PES based on IR-THz imaging of the face.

The work has been supported by the Russian Foundation for Basic Research (Grant No.17-29-02487), by the Ministry of Science and Higher Education within the State assignment FSRC "Crystallography and Photonics" RAS, by the Interdisciplinary Scientific and Educational School of Moscow University "Photonic and Quantum Technologies. Digital Medicine".

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Session 1.2:
5G Technology

Erice, Sicily

This is Your Brain on 5G

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***Abstract*— The rapidly expanding release of 5G wireless communications networks has spurred renewed concerns regarding the interactions of these higher radio frequencies with living species. In this study we examine in detail the relationship between RF exposure levels and absorption in ex vivo bovine brain tissue and a brain simulating gel at 1.9 GHz, 4 GHz and 39 GHz as relevant to the current (4G), and upcoming (5G) spectra.**

I. Introduction

UPCOMING fifth generation (5G) wireless communication systems will greatly expand the available RF bandwidth and correspondingly, the number of RF devices connected, and in use. By necessity, this will greatly increase the already ubiquitous RF exposure that is now present on all living species, wherever wireless technology is employed. The fact that 5G is based around new and significantly higher frequency sources with dramatically different focusing and penetration properties in tissues makes it essential that we better understand and quantify the absorption, reflection and scattering properties of such radiation in and on biological tissue as a function of frequency, power and exposure time in order to provide fundamental guidelines for release of the technology, for public safety and for setting National policies and standards.

II. Results

In this presentation we employ standard RF waveguides with well-defined field and power patterns for coupling calibrated RF power at each of 3 representative 4G and 5G frequencies (1.9, 4 and 39 GHz) into fresh bovine brain and a common tissue simulating gel. We derive accurate power dependent temperature coefficients (dT/dP) as a measure of exposure applicable to all of these wavelengths. We also compare the heating characteristics of brain tissue with the gel and show that there is a very strong deviation in the response of the gel and the brain tissue at the higher 5G frequencies. We observe that brain tissue has a much broader linear range of radiation absorption and subsequent temperature rise. This finding negates some of the advantages of using such tissue simulating gels when evaluating thermal transport effects in the millimeter-wave bands. The high precision dT/dP data tabulated from the brain tissue measurements at frequencies of 1.9, 4, and 39 GHz, over exposure times up to 30 minutes and depths of 1 to 21 millimeters can be used to accurately predict the magnitude of heating over a wide range of power levels and help to elucidate, and extend downwards, the boundaries between designated thermal and nonthermal regimes. Our simple, but highly accurate thermal measurement method is believed to be one of the most sensitive experimental demonstrations for ex vivo tissue and has a demonstrated detection of 1mW at 29 and 39 GHz and a temperature change limit of less than 0.1 degree C. We examine the RF beam penetration, absorption and diffusion at our three representative 4G and 5G frequencies, and show that at 39 GHz the impact of RF heating is higher at every depth studied and confined to a very small surface region in the tissue, and can produce a temperature rise of more than 60 degrees C in the tissue with only 1W of incident power and an exposure time of only a few minutes! We also derive, we believe for the first time, accurate values for the thermal diffusivity of bovine brain tissue at 1.9 and 4 GHz (1.25×10^{-7} and 1.18×10^{-7} m^2/s, respectively) from our new and prior MRI measurements. Our measurements are supported by finite difference time domain simulations showing in detail, the distribution of RF source power with depth and surface area in the tissue. Finally, we show experimentally the effects of rapid pulsing of the power at different RF frequencies (1us, 1ms and 1s at 50% duty cycle) and pulse lengths of short (1s) and long (30s) duration with single on/off RF cycles in both brain tissue and gel.

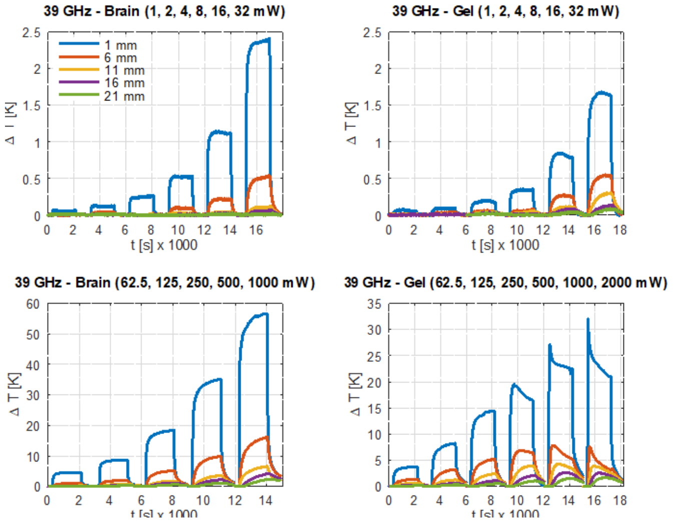

Fig. 1: Sample of experimental temperature rise (dT) vs. time (t) and power (P) for brain (left column) and gel (right column) at 39 GHz. The curves correspond to temperature measurements at the power levels of 1, 2, 4, 8, 16, 32, 62.5, 125, 250, 500, 1000 and 2000 mW and depth of 1, 6, 11, 16 and 21 mm, respectively.

III. Summary

The talk will cover very extensive RF exposure measurements on brain and gel samples at 4G and 5G frequency bands (including CW and pulsed exposures with varying duty cycles, power levels from 1mW-2W, and exposure time), FDTD simulations of the incident power and field distribution in the samples, and derivations of the linear thermal diffusion coefficients for the samples. The conclusions are startling and will help set the groundwork for future 5G exposure studies in tissue.

What do we know about 5G Wireless Communication and Health Effects?

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***Abstract*—The introduction of the fifth generation (5G) of wireless communication will increase the number of high-frequency-powered base stations and other devices. The question is if such higher frequencies (here, 6–100 GHz, millimeter waves) can have a relevant health impact.**

I. INTRODUCTION

HERE, around 100 relevant publications were deeply analysed performing in vivo or in vitro investigations. Each study was characterized for: study type (in vivo, in vitro), biological material (species, cell type, etc.), biological endpoint, exposure (frequency, exposure duration, power density), results, and certain quality criteria.

II. RESULTS

Eighty per cent of the in vivo studies showed responses to exposure, while 58% of the in vitro studies demonstrated effects. It has to be pointed out that about half of the studies are in the range up to 10 mW/cm2 (ICNIRP limit 1 mW/cm2) and the responses affected all biological endpoints studied. Based on these data, there is no indication that higher power densities would cause more reactions, since the percentage of reactions in all groups is already 70%. However, there was no consistent relationship between power density, exposure duration, or frequency, and exposure effects.

III. SUMMARY

In summary we can say, that the available studies do not provide adequate and sufficient information for a meaningful safety assessment, or for the question about non-thermal effects. There is a need for research regarding local heat developments on small surfaces, e.g., skin or the eye, and on any environmental impact. Our quality analysis shows that for future studies to be useful for safety assessment, design and implementation need to be significantly improved.

Poster session 01:

Spectroscopy Tech-Med Technology

Erice, Sicily

THz Sources and Activities at the ENEA Center of Frascati

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***Abstract*—In recent years THz radiation has been widely used in different research and application fields, ranging from security, to cultural heritage conservation, from medicine to biological applications. The THz research group at ENEA has a long term experience with sources and systems operating in this spectral range, which is useful to develop applications in several fields, including biology and medicine. The main THz sources and systems operating at the ENEA center of Frascati are described, together with their actual and potential applications.**

I. INTRODUCTION

IN the '90s the THz spectral region, also known as Far Infrared (FIR) was practically unexplored, due to the lack of sources and applications. Sources were lacking due to the fact that the spectral region was in between the region of microwaves, where the electronic generation of radiation is easy to obtain, and the infrared region, where optical generation is possible. At the beginning of the '90s in the ENEA center of Frascati three useful sources were available in this spectral region: a FIR gas laser, providing narrow fixed frequency laser emission, a compact Free Electron Laser (FEL) providing powerful tunable emission in the region between 0.1 and 0.15 THz [1], and a Cherenkov FEL operating between 0.18 and 0.33 THz [2].

The peculiar characteristics of THz radiation and the flexibility of the FEL sources made it possible to design several experiments. The first comprehensive review about the effects of THz radiation on biological cells was carried out in the framework of the THz-BRIDGE EU project [3], utilizing the FEL as irradiation source, due to it's ideal characteristics for biological applications: high peak power, high local electric field, with a low average power, thus excluding heating effects. Over the next years more efforts were devoted to the development of THz imaging systems in the field of cultural heritage and for biological applications. In more recent years the complex and expensive FEL sources were replaced by cheaper and small solid state sources, aimed at developing portable devices, specifically designed for a single application [4]. Meanwhile, in light of the growing interest in tokamak plasma diagnostics applications of THz-TDS techniques, a new testing setup has been developed in Frascati [5]. The system, based on THz generation from ultrashort laser pulses and detection via optical rectification or photoconductive antennas, has a great potential to study fusion applications in Frascati and worldwide. The spectral windows covered by the THz-TDS spans from 0.1 THz to 4 THz.

II. RESULTS

The increasing interest of the scientific community regarding THz radiation produced a quick growth in the available sources and detectors, in the spectral range from 0.1 THz to 0.4 THz, and such sources, together with more conventional ones in the 20-40 GHz range, were utilized to build up systems in this spectral range, to perform optical measurements and imaging experiments.

One of our most interesting devices was originally developed to perform in depth analysis on frescoes, to monitor degradation, with particular focus on detachments and humidity damages.

The same device is now being utilized to perform analysis on the degradation of mosaics [6], where biological weeds can produce the detachment of the stone tiles. The ability of the THz imaging system to detect the presence of water under the mosaic tiles has been demonstrated and more experiments are scheduled to check the limits of such a technique to identify biological material. A similar activity was started to provide results about the degradation of rich decorated leather wallpapers (Fig. 1), utilized in 16th and the 17th century, in most of the noble residences [6].

Fig. 1. ENEA portable THz imaging system, performing measurements on leather wallpapers. Courtesy of Baroque Museum at Ariccia (RM) [6]

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Terahertz filter-gratings

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Abstract — **We explore the possibility of combining a terahertz grating and a THz mesh filter in a one layer device. The structures could be produced in aluminum by laser cutting.**

I. INTRODUCTION

A mature THz technology requires not only emitters and receivers but also a variety of optical components. This includes simple lenses, reflectors, waveguides, filters and gratings. One class of established, well known filters are mesh filters, which were first reported in 1967. The standard fabrication procedure for these structures is photolithography which is somewhat cumbersome. Recently, it was shown that such filters can be produced by laser cutting of an regular aluminum foil [1]. Also THz gratings produced by this method were recently demonstrated [2]. If one would like to combine the function of both structures one would need two structured aluminum layers and position them one after the other. Here, we explore the possibility to combine the functionality of both structures in a one-layer device.

We simulated a diffraction grating formed by 327.5μm stripes of metal alternating with void stripes forming a total period of 1310μm. In addition, we simulated a combined structure in which we replaced the air stripes with a frequency selective metamaterial made out of void crosses on the metal plate. The crosses are formed by two orthogonal slots of 170μm length and 40μm width (3 cross rows fit in each space period originally void in the conventional diffraction grating). Such a structures could be produced by laser cutting e.g. with a frequency-doubled Nd:YAG laser. Details of such a cutting system can be found in [3].

To determine the performance of such a structure the simulations mentioned earlier were carried out using the finite element time-domain solver CST MICROWAVE STUDIO. The material parameters of aluminum were taken from the CST database.

While Fig.1 shows the typical pattern of a diffraction grating, the combined structure does show a more complex behavior in Fig.2. "Hotspots" are shown at the intersection of the diffraction arms with the ~800GHz band, which is consistent with the resonance frequency of the cross-metarmaterial filter. In addition, the fourth diffraction order is intensity-enhanced with respect to the other orders. This can be explained by the additional periodicity introduced by the metamaterial, which has a period of ¼ of the original diffraction grating.

Additional simulations (not shown) were performed changing a variety of geometrical parameters such as the grating period and the cross dimensions. By doing this we could control the position of the diffraction orders and the hotspots independently, demonstrating the possibility of engineering application-specific devices for telecommunications among other applications.

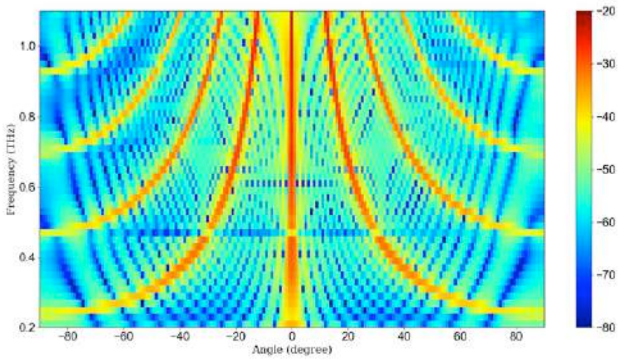

Fig. 1. Relative intensity (in dB) of the diffracted radiation as function of the angle and frequency for the conventional diffraction grating obtained from full electromagnetic simulation. The results are consistent with the analytically expected behavior.

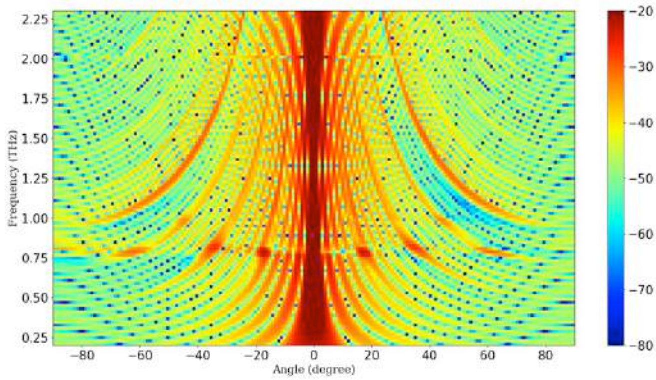

Fig. 2. Relative intensity (in dB) of the filter-grating structure.

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Session 2.1:
Attract Project I

Erice, Sicily

Breakthrough detection and imaging technologies from idea to real world application

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***Abstract*— Breakthrough innovations are more important than ever to solve the 21st Century's major societal challenges as we have specially learned with the still ongoing COVID-19 pandemic. Can new networks of sensors be installed in big farms to make agriculture more productive and less energy-intensive? Can smarter use of monitoring and Big Data analysis make factories work better, cheaper and greener? Can we use sensors to help the visually impaired navigate the world more easily? Can we develop better forms of online learning? Can we pioneer ways to monitor our changing climate more accurately and cost-effectively and develop strategies to mitigate the damage? Answering these questions requires an open innovation mind-set so that breakthrough innovation concepts and technologies can be rapidly identified, assessed and industrially scaled by multiple experts throughout the innovation value chain. Many technologies leading to breakthrough innovations with a big impact on people's lives stem from fundamental research. Nevertheless, their pathway to be transformed into tangible new benefits for citizens and business is often fruit of chance. ATTRACT is a pioneering initiative bringing together Europe's fundamental research and industrial communities to lead the next generation of detection and imaging technologies and therefore streamline the translation of science into societal benefits.**

ONE PAGE SUMMARY NOT AVAILABLE FOR PUBLISHING

Development of an active terahertz spectro-imaging system

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***Abstract*— The presentation will describe the basics and the initial steps towards the development of a novel hyperspectral imaging set-up in the terahertz. Applications of the system in the biomedical and the agri-food industry, in which terahertz spectroscopy has already demonstrated very interesting features, will be discussed.**

I. INTRODUCTION AND DESCRIPTION OF THE SYSTEM

CURRENT hyperspectral terahertz imagers need to perform either a frequency or a spatial scanning, strongly restricting acquisition times and therefore the possibilities for most practical applications. We propose a novel approach based on a sophisticated dual-comb terahertz radiation source that illuminates the target area enabling the direct characterization of the spectral response of a sample simultaneously at every pixel of the image and at a rate that is orders of magnitude faster than any other comparable system.

The system is based on an electro-optic terahertz dual-comb generator providing absolute frequency accuracy, and freely adjustable resolution that results on an absolute flexibility in the configuration of the frequency range of interest and the number of frequencies to analyze. The method presented here takes advantage of the inherently high mutual coherence between individual combs on an electro-optic dual-comb source. This allows intermode beat note linewidths in the mHz providing a virtually unlimited compression on the downshifted comb lines in the RF spectrum. Hence, all the teeth of the combs can be mapped to very low frequencies, making it possible to directly detect the interference between combs by a camera (with a suitable optical/frequency range) capable of operating at a few tens of frames per second.

The set-up of the illumination system, similar to that described in [1], is shown in Fig. 1.

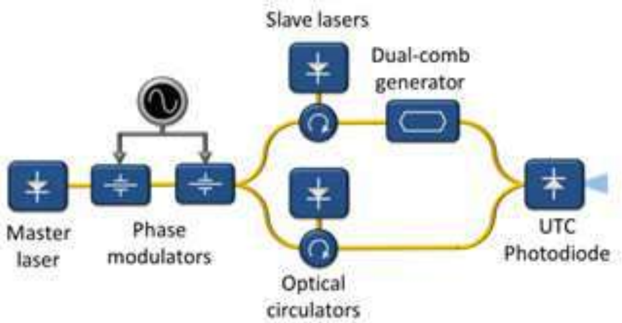

Fig. 1 Block diagram of the illumination system.

This illumination signal enables a fully multiplex approach in which the low-frequency interferograms are detected by all the pixels of the camera synchronously to provide simultaneous spectral and spatial characterization.

II. APPLICATIONS

In the terahertz range there are already cameras of up to 0.1 megapixels available [2] enabling fast imaging of terahertz waves. These devices operating in conjunction with the terahertz source presented above provide the strong possibility of revolutionizing nondestructive testing, quality classification and inspection in food, agricultural and pharmaceutical industries. In the same way, and equally important, the accuracy that the system proposed provides could be vital for ensuring the consistency in the study of complex biological samples, molecules and cells. To this respect, many important steps have already been taken [2, 3].

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Nonlinear THz studies at the TeraFERMI beamline

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***Abstract*—TeraFERMI is the THz beamline of the FERMI Free Electron Laser. The beamline is based on a Coherent Transition Radiation source providing intense and broadband THz pulses in the MV/cm range. These fields are used to achieve THz control of matter and to push materials well into their nonlinear regime.**

I. INTRODUCTION

Fermi is the seeded Free Electron Laser (FEL) in Trieste (Italy) operating in the 100 – 4 nm wavelength range and open to external users since 2012. TeraFERMI is the THz beamline of the FERMI FEL, extracting THz light (0.3-10 THz) from the beam dump section by a Coherent Transition Radiation source. A 33m-long beamline transports the THz pulses in the experimental hall, where the beam is delivered to a standard optical table. The high peak power (from MW to GW) that can be stored in one single pulse makes TeraFERMI a suitable source for nonlinear THz spectroscopy studies, from condensed to soft matter.

II. RESULTS

The beamline performances have been first characterized with the help of calibrated pyroelectric detectors, and a home-made step-scan Michelson interferometer. During standard user operation conditions the beamline produces THz pulses whose energy ranges from 15 to 60 µJ per pulse, with a bunch charge of ~700 pC, and a bunch length of about 1 ps, as measured at the end of the LINAC. This results in energies at sample up to 35 µJ per pulse. The spectrum, normally extends up to 4 THz. However, upon optimization of the electron beam specific for TeraFERMI, energies at source up to 100 µJ, and a spectral extent up to 12 THz were measured.

In order to characterize also the time-structure of the THz pulses, we have performed Electro-Optic-Sampling measurements (EOS) with the help of an IR fs laser source synchronized to the Fermi Optical Master Clock [1].

An example of EOS measurement during standard beamtime operations is shown in Fig.1. Interestingly, the full energy profile has a duration of about 2 ps, with a main sharp peak containing 60% of the energy of the full pulse. The measured THz peak can be fitted with a gaussian profile, corresponding to a Δt=112 fs. The power spectrum related to this electric field shape is reported in Fig. 1c). The spectrum extends up to about 4.5 THz, roughly corresponding to the maximum detectable signal in a ZnTe EOS crystal, due to the presence of an optical phonon centered at 5.3 THz.

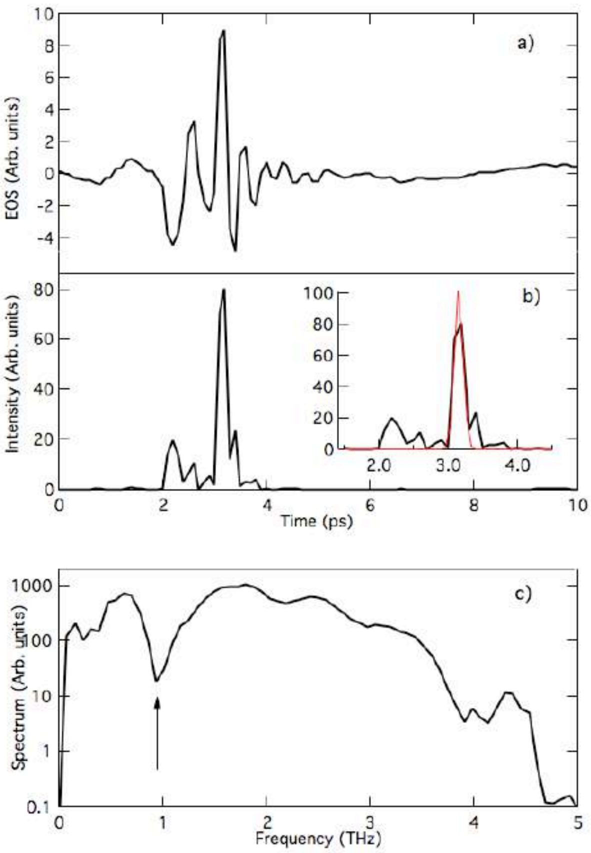

Fig. 1. a) Representative EOS measurement, acquired by averaging 10 shots for each position of the delay line. b) Intensity time profile obtained by evaluating the square of the EOS profile shown in a). The red curve is a Gaussian fit to the main peak. c) Intensity spectrum obtained by calculating the magnitude squared of the Fourier Transform of the spectrum in a).The arrow indicates the dip in the spectrum at about 1 THz which may result from the interference of a long wavelength (~0.9 THz) and shorter wavelength (~2 THz) components.

III. SUMMARY

TeraFERMI produces broadband high peak power THz pulses that can be used to perform non-linear THz spectroscopy. In the case of life sciences, TeraFERMI can be used to investigate the non-linear response of fast solvation dynamics of biological matter caused by THz-induced structural changes. This can be achieved by either performing fluence-dependent THz absorption measurements or through time-resolved pump-probe spectroscopies. In the latter case a synchronized IR source is also available at TeraFERMI, thus allowing to investigate novel material's properties as the so-called THz Kerr effect (TKE) [2], through THz-pump/IR-probe schemes.

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Session 2.2:
Attract Project II

Erice, Sicily

Between photonics and electronics: 2D materials for THz technologies

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***Abstract*— Its peculiar band structure and charge transport characteristics naturally suggest graphene could offer a perfect platform for a new generation of high-performance devices operating in the THz range of the electromagnetic spectrum. This talk will review recent results in the development of high-speed modulators and electronic detectors; it will also discuss perspectives towards the implementation of graphene-based deeply sub-wavelength THz emitters and lasers.**

GRAPHENE is attracting considerable attention for a variety of photonic applications, including fast photodetectors, transparent electrodes in displays and photovoltaic modules, saturable absorbers. Owing to its high carrier mobility, gapless spectrum, tuneable chemical potential, and frequency-independent absorption coefficient, it has been recognized as a very promising element for the development of detectors and modulators operating in the Terahertz (THz) region of the electromagnetic spectrum, which is still crucially lacking in terms of solid-state devices [1].

In the last few years, progress in the realization of graphene-based THz photonic devices has advanced very rapidly. In this talk I will focus first THz detectors based on antenna-coupled graphene field-effect transistors (FETs) [2,3,4], discuss the various mechanisms involved in their operation, and examine extension to other 2D materials and integration into future THz cameras.

I will also address the development and applications of electrically switchable metamaterial devices [5] as well as the prospects for the use of graphene in a new generation of THz sources, either directly as active element [6], or as waveguide optical component. In the latter case, graphene could be implemented within quantum cascade lasers and act as saturable absorber for mode-locked operation [7], or even replace one of the metal layers in micro-disk resonators, yielding a huge reduction in size and possibly approaching a thresholdless lasing regime.

Finally, schemes to implement coherent control of absorption in graphene will be analysed [8], as well as perspectives of observing few-electrons intersubband THz polaritons in extremely subwavelength graphene microcavities, opening a path for implementing novel forms of photon-photon interactions and for realizing complex, purely photonic quantum devices.

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Tunable superconducting GHz-THz radiation sensors

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***Abstract*—Gigahertz and terahertz radiation detection has strong impact in basic science and industrial applications. Here, we propose and realize superconducting radiation sensors with unprecedented and *in situ* tunable sensitivity. In particular, we present detectors based on the temperature-to-phase conversion mechanism and miniaturized extra-sensitive transition edge sensors.**

I. INTRODUCTION

Radiation in the GHz-THz range has attracted growing interest from both basic science and applicative points of view. On the one hand, the gigahertz band covers several phenomena in astronomy [1], such as cosmic microwave background (CMB), axion-like particles search, black holes emission, comets and galaxy formation. On the other hand, THz rays (T-rays) present an alternative to x-rays (which are ionizing) for security scanners, materials inspection, packaged food quality control, and biological imaging for medical purposes thanks to their ability to pass through non-polar materials, such as paper and plastic [2]. Nowadays, the most sensible and widely used detectors are superconducting sensors, such as transition edge sensors (TESs) and kinetic inductance detectors (KIDs). In general, the performance are of these devices set by the fabrication process and limited by used materials. Therefore, conceiving and realizing extra-sensitive radiation and *in situ* tunable detectors might bring GHz and THz technology to the next level.

II. RESULTS

Superconducting sensors take advantage of the change of electronic temperature in the active region driven by radiation absorption. As a consequence, the marriage of heat mastering [3,4] and electronic charge control in superconducting hybrid structures allows to design new concepts for ultra-sensitive radiation sensors.

Here, we propose a new class of cryogenic radiation detectors based on the temperature-to-phase conversion (TPC) process [5], and we show how to optimize the performance of conventional TESs.

The TPC mechanism occurs in dc superconducting quantum interference device (dc-SQUID) composed of superconductor-normal metal-superconductor (SNS) mesoscopic Josephson junctions (JJs). In particular, temperature-driven rearrangements of the phase gradients in the interferometer under the fixed constraints of fluxoid quantization and supercurrent conservation are predicted. This allows sizeable phase variations across the junctions for suitable structure parameters and temperatures. We show that the TPC can be a basis for sensitive single-photon sensors or bolometers with the possibility to *in situ* tune their sensitivity by means of an external magnetic flux. Integrated with a superconducting quantum interference proximity transistor SQUIPT as a readout set-up. By designing an aluminum superconducting ring interrupted by two copper normal metal nano-wires we can estimated the predicted performances of a TPC detector. Operated as calorimeter, this TPC architecture can provide a large signal to noise S/N ratio > 100 in the 10 GHz-10 THz frequency range, and a resolving power larger than 100 below 50 mK for THz photons. In the bolometric operation, electrical NEP of about 10^{-23} W/Hz$^{1/2}$ is predicted at 50 mK. Additionally, we provide the fabrication protocol and first experimental characterization of an Al-based TPC sensor performed at cryogenic temperatures in a He3-He4 dilution refrigerator.

Transition edge sensors take advantage of the strong variation of resistance at the superconducting-to-normal-state transition. The TES sensitivity is limited by the operation temperature and the electronic thermal conductance. On the one hand, we decreased the operation temperature by growing synthetic superconductors with low critical temperature (T_C). To this end, we fabricated Al/Cu bilayers with T_C~130 mK thanks to the superconducting proximity effect. On the other hand, we decreased heat exchange by miniaturizing the active region and implementing Andreev mirrors for thermal diffusion. From the experimental data, in the bolometric operation we deduced a thermal fluctuation limited noise equivalent power NEP~3x10^{-20} W/Hz$^{1/2}$, while for single-photon detection we obtained a frequency resolution of 75 GHz. Notably, these values are at least one order of magnitude better than existing state of the art TESs.

III. SUMMARY

We showed how heat management can be exploited to design and realize extra-sensitive superconducting radiation sensors in the GHz-THz range. In particular, we proposed an innovative radiation sensor based on the TPC mechanism that promises unprecedented performance. In addition, we designed and realized TESs with optimized geometry and composition.

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Graphene based THz detectors: focus to bio-applications

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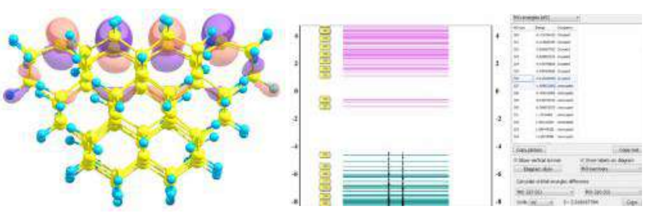
Abstract—**The review of modern trends in THz detection based on graphene and other 2D materials will be presented. The original results for integrated Graphene – Diamond (111) / (100) heterostructures as material base for tunable THz detectors of bolometer type is discussed. The biocompatibility issues of graphene made THz detectors are addressed.**

THE main drawback of existing THz components is their restricted tunability, which is the must for future and emerging THz devices. That is why graphene, which optical and electromagnetic properties are easily and smoothly adjustable in a controllable way by chemical doping, mechanical deformations, and biasing, is one of the best material base for THz detectors, such as photodetectors and bolometers.

Along with conventional ways to tune the graphene electromagnetic response, the influence of substrate used for graphene handling and processing has to be taken into account. In this communication, we will discuss the influence of (111) and (100) diamond substrates on the electronic band structure as well as optical and electromagnetic properties of graphene.

We have studied the equilibrium morphology, electronic structure and Raman spectra, of the interface between a graphene monolayer and the diamond C(111) and C(100) surfaces (Gr/Diamond) using non-empiric quantum chemical density functional theory (DFT) simulation in the cluster approximation.



We found that for (111) surface the optimum epitaxial interface morphology contains a wavy graphene structure that is covalently bonded to the substrate. In turn, the formation of a Van der Waals bonds between graphene and the substrate was shown for the (100) surface. Further, the electronic structure and density of states (DOS) was calculated for the nanoflakes and cluster under study. An estimate was made of the localization of the occupied molecular orbital and the lower unoccupied molecular orbital (HOMO and LUMO, respectively).

The main tendencies in the tuning of electronic structure and Raman spectra of diamond and graphene during the formation of hybrid Gr/Diamond structures are analyzed. The influence of the diamond substrate on the THz electromagnetic constituents for the doped graphene due to its interaction with the diamonds surfaces are discussed and compared with the experimental data collected for graphene transferred to monocrystalline diamond.

The next important issue is the biocompatibility of graphene integrated with diamond support for biomedical needs. Graphene/diamond substrates used for THz sensing were checked for providing cellular viability and stable functional state, preserving sterility and at the same time allowing real-time analysis and control of environmental conditions and cellular activity.

Taking into account extremely high, almost perfect THz absorption ability of Gr/Diamond in THz range along with high sensitivity and noise to power ratio, as well as proved in vitro biocompatibility of graphene/diamond interface the possibility to use Gr/Diamond as the material basis for bioTHz sensing is confirmed.

Acknowledgements: This work was financially supported by Radiation tOlerant THz SensOR (ROTOR) EU project (through the open call to ATTRACT EU project), Academy of Finland Flagship Programme, Photonics Research and Innovation (PREIN), decision 320166. P.K. is supported by Horizon 2020 IF TURANDOT project 836816.

Session 2.3: Technical

Erice, Sicily

Lytid solutions for THz technologies and applications

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***Abstract*—Lytid is a French company engaged in translating scientific innovation in the THz domain into reliable, cutting edge products. Two different, complementary technologies have been adopted for developing THz sources: Quantum Cascade Laser and Schottky diodes.**

I. INTRODUCTION

ACCESSING the THz domain is nowadays an attractive perspective for exploiting the tremendous potential of this frequency range in a wide field of applications: medical imaging, high-tech non-destructive testing, hazardous gas sensing, molecular spectroscopy. However, the THz range has been for long time ignored due to the lack of sources and detectors capable of working in what has been named the « THz gap ». Many efforts have been made in order to fill this gap and last developments resulted in photonics and electronics sources in the sub-THz and THz range of frequency. Since its creation in 2015 Lytid is supporting and valorizing technological innovations in the THz and sub-THz domain. Two core technologies have been adopted by Lytid for developing THz sources: Quantum cascade laser and Schottky diodes. This work is a brief review of QCL technology for THz photonic sources, underlining methods and challenges of integration into a compact, user-friendly, powerful source of continuous radiation covering the range between 2 and 5 THz. Last advancements and perspectives of Schottky diodes technology for sub-THz electronic sources will also be addressed, with focus on the highly flexible modularity of the source that allows to cover bandwidth between 75 GHz and 640 GHz. Finally, an example of application of Lytid's sub-THz source will be shown as witness of the exceptional potential of this technology.

II. LYTID'S TECHNOLOGIES

One of Lytid's core technology is the Quantum cascade Laser (THz QCL). QCLs are semiconductor lasers exploiting the intersubband transitions in cascaded quantum wells of the conduction band. In this kind of device, the emission frequency is defined by the engineered structure of the conduction band [1] [2] rather than the energy gap between conduction and valence band, as for standard bipolar semiconductor lasers. Consequently, the emission frequency is independent of the material and it can be selected by tuning the size and width of the quantum well where the radiative emission takes place. Engineered band structure of QCL devices allows two main advantages with respect to standard semiconductor laser. First of all, emission frequency is not defined by the semiconductor gap: longer wavelengths can be emitted, from 60 μm to 150 μm. Second, the quantum well structure of the same material can be engineered in different ways, allowing the emission of different frequencies, from 2 to 5 THz. Several challenges had to be tackled before turning this quantum technology into a tool suitable for science and industry. Among them was developing compact laser drivers designed for the specific needs of THz QCLs and integrating a high performance, highly reliable cryogen-free cooling system. Nowadays the ultra-compact, reliable, mW level TeraCascade1000 QCL source is available on the market.
A complementary technology for generating THz radiation belongs to the electronic domain. Schottky diodes are passive non-linear electronic components working as frequency multipliers. Schottky diodes are metal-semiconductor junction. The simplicity of this structure translates into the possibility of miniaturization, which in turn causes a low junction capacitance due to the reduced size of the active area [3]. Low junction capacitance and high switching speed make the Schottky diodes ideal for high frequency multiplication. Subsequent Schottky diodes can thus convert a commercial low frequency (8MHz to 20 GHz) generator into a sub-THz source. Lytid adopts and transfers the Schottky diodes technology developed for the space program JUICE, into a robust, ultracompact, powerful (hundreds of mW) and user-friendly sub-THz source emitting from 75 to 640 GHz (TeraSchottky).

III. APPLICATIONS

The two above-mentioned sources offered by Lytid cover most of the sub-THz and THz spectrum, opening a wide range of applications. THz radiation has been demonstrated to be particularly suitable for *in vivo* microscopy of surfaces under the skin, due to its harmlessness, high penetration, low scattering and good spatial resolution. In addition to these intrinsic properties of THz radiation, a mW power level radiation is preferable to increase the SNR. Moreover, a compact, robust and cost-effective source would be more easily integrated in a portable system adapt to a medical environment. Resuming all these benefits, TeraSchottky source has been selected by Università La Sapienza as THz source for developing a reflection microscope for dermatology.

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Exploring Terahertz Applications in Emerging Sciences and Technology

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[2]Electron Mec
[3]Form Factor Corp.
[4]Hitech-Maury corp.

***Abstract*— Until recently, THz technologies were bulky and expensive systems used only for radio astronomy, RADAR, and lab R&D. Over the past decade, we have seen a revolution in THz technology and applications. Advances in THz device and systems designs, materials research and process technologies provide new very compact transmitters and receiver subsystems as well as higher power sources at these tremendously high frequencies. The potential of THz advanced research and commercial applications have already been demonstrated. Research is pushing existing test frequency boundaries to the terahertz (THz) extremes. THz frequencies will be utilized for new applications in biotechnology, imaging, materials analysis and metrology, 5G & 6G communications, and automotive. Continued growth in terahertz applications requires the availability of quality THz components, transmit & receive devices and systems, as well as high performance test & measurement equipment. Virginia Diodes Inc products has been creating and enabling this THz technology since 1996. VDI offers hundreds of mature products for use and operation in the 30-3000 GHz range. The following applications will be briefly reviewed.**

Metrology Electron Mec Partners: Virginia Diodes, Form Factor and Maury will feature some examples of Instrumentation for Metrology from millimeter-wave to THz. 5G and 6G –As the demand for higher data rates increases, so does the need for a higher frequency band for being able to transmit huge amounts of data to address consumers' hunger for ever increasing data usage. The Internet of Things requires new advances in high frequency communication systems.

Chemical Fingerprinting – One of the first imaging applications using THz is chemical finger printing. With this application, one can scan different materials or packages to detect what is inside them without destroying the object or without having to open the packaging. Security Imaging-Commercial THz systems are used today to image people and groups of people that may pose a threat in airports, subways, secure portals, etc.

Dynamic Nuclear Polarization NMR systems- DNP-NMR spectrometers enable extended solid-state NMR experiments with unsurpassed sensitivity for exciting new applications in biomolecular research, material science, and pharmaceuticals.

Automotive-THz technology is playing a critical role in advanced automotive applications including auto collision avoidance RADAR and low latency communication for autonomous vehicles.

ONE PAGE SUMMARY NOT AVAILABLE FOR PUBLISHING

Highly sensitive broadband terahertz cameras for biology laboratories

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***Abstract*— In this communication, we present two terahertz cameras particularly suited for biology laboratories. The cameras come with 2 sensor flavors of up to 32x32 pixels with a sensitivity better than -35 dBm, and a bandwidth ranging from 100 GHz up to 2 THz. It is bundled with a dedicated software application featuring live visualization of the terahertz beam with beam alignment and beam quality metrics. Moreover, it allows raw frames recording of up to 500 fps thanks to its high speed ethernet connectivity. The camera made by TiHive Technologies is commercially available for numerous laboratory and industrial applications.**

I. INTRODUCTION

Terahertz is a key frequency band for biology applications since it can reveal very specific tissue properties such as the presence and quantity of water, the classification of tissues, and the detection of cancerous cells. Utility has been shown not to limit itself to monitoring and detection, but also to include the interaction and interruption of biological processes thanks to this frequency band's specific properties. Consequently, a growing number of biology labs are equipping themselves with terahertz instruments.

Research in these fields is sustained by the fast improvement of terahertz sources' output power, sensors' sensitivity, and as importantly improvements to the form factor and large-scale deployment capacity of such systems.

Today, research progress would greatly benefit from a multipixel imaging and sensing camera that would not be limited to low acquisitions rates with mediocre sensitivity. In addition, plug and play operation of a compact camera would be a substantial gain. Finally, a simple tool for helping scientist and operators with beam alignment and profiling would save a significant amount of time while ensuring precise, reliable measurement.

TiHive technologies proposes a terahertz camera fitting the above-mentioned laboratories' needs and that is both very compact and very sensitive in the 0.1-2 THz range. Its key features are detailed in the next section.

Fig. 1. TiHive's Compact THz Camera

II. TERAHERTZ CAMERA MAIN FEATURES

The terahertz camera presented by TiHive Technologies is available in a very compact 6x6x6 cm^3 format and comes with its viewing and recording software application. It is available in two different flavors: the 0.85 THz camera equipped with a 32x32 pixel sensor, with a nominal sensitivity better than -35 dBm (~300 nW) at 0.85 THz (with a sensitivity ranging from around 100 GHz up to 2 THz). The 0.3 THz flavor embeds a 13x13 pixel sensor with a nominal sensitivity better than -40 dBm (100 nW) at 0.3 THz (with a sensitivity ranging from below 100 GHz up to 1 THz). It only takes a standard 12V supply, an ethernet connection, and switches on in seconds. Thanks to its patented sensor technology, it does not trade sensitivity against acquisition rates and can provide up to 500 fps (frames per second) at the nominal very high sensitivity.

A software application has been developed and tested that allows live viewing of any terahertz beam as well as recording in several file format. The camera and its associated software are designed for acquisition of large amount of data at high data rates. Specific post-processing using the camera raw data will help getting the most out of your terahertz data.

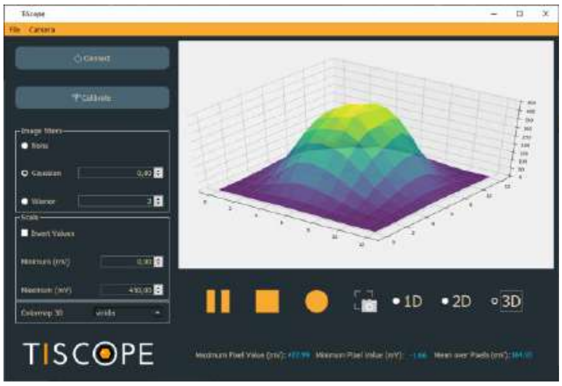

Fig. 2. TiHive's Terahertz viewing and recording application

Live beam viewing comes in 1, 2 or 3 dimensions with customizable scales and beam statistics that makes beam alignment and profiling as simple as "Hello".

III. SUMMARY

TiHive technology has presented its terahertz camera and the associated software. It is designed to embrace the main challenges faced by biology labs using terahertz instruments. It stands out by its performance, compactness, and ease of use. Request a demo and talk to our experts at www.tihive.com.

ACKNOWLEDGMENT

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 947166.

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Poster session 02: Attract Project

Erice, Sicily

Graphene Golay micro-cell arrays for a color-sensitive terahertz imaging sensor

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***Abstract*—Our aim in this research is the improvement of currently existing sensors with the use of advanced materials and technology, for the use in the field of terahertz imaging. The new sensor will be much faster and economic with respect to current industrial devices, with specific frequency-dependent sensitivity (color-like) bringing new possibilities in this field.**

I. INTRODUCTION

IN the electromagnetic spectrum, just between the microwaves that we use in our WiFi and Bluetooth devices and the infrared light, there is a mostly unexplored region, named the TeraHertz (THz) gap, consisting of electromagnetic (EM) waves with frequencies comprised between 0.1 to 10 THz, which is waiting to be exploited[1].

While affordable THz laser sources are available on the market since the demonstration of the first quantum cascade THz laser by a group of Italian scientists in 2002[2], partner of this proposal, the development of affordable and lost cost THz detectors for imaging (the equivalent of the CCD for the visible light) was much slower. The bulky array of gear currently used to measure terahertz waves is clunky and expensive, making it impractical outside of a lab.

Our project aims to apply new advanced materials and technology like graphene and microlithography to improve the responsiveness and efficiency of the Golay cell sensor invented and used in the astronomical field for the detection of infrared radiation, to broaden its field of application to terahertz radiation. Furthermore, we intend to design a final device that includes an array of this sensor leading to a high spatial resolution in comparison with current commercial sensors.

II. RESULTS

The Graphene-based Golay Micro-cell (GGM) were fabricated by micromachining technology on suspended silicon nitride membrane and sealed transferring a graphene monolayer to cover the hole. To measure the cell's sealing properties and graphene's ability to adhere to the substrate, a preliminary test was carried out in which a prototype of a single Golay cell was subjected to heating with the intention of observing the expansion of the air present inside the cell. The graphene deflection was evaluated with an optical profilometer and the heating of the cell took place through a Peltier element placed under it. During the heating phase an expansion of the membrane was observed, followed by a relaxation during the temperature maintenance phase. This indicates a variation in the pressure inside the cell during the experiment, showing that the system allows sealing of a small space, responding quickly to the variation in the internal pressure due to heating.

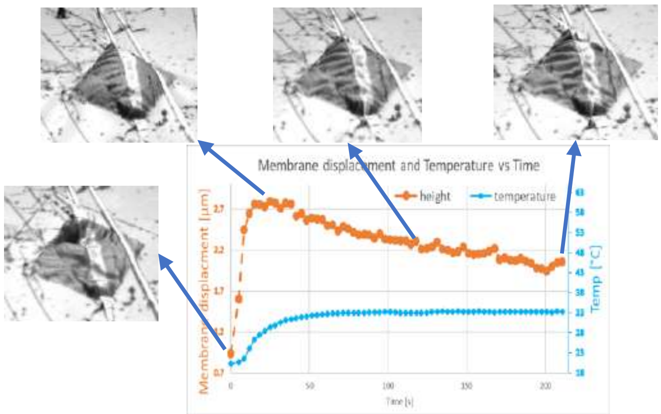

Fig. 1. Expansion of the graphene membrane of a single cell golay sensor by heating the cell through a peltier element. In particular, it is possible to observe how the initially corrugated membrane is relaxed by pressure and then relax at a constant temperature.

The relaxation of the membrane, on the other hand, may be due to an air leak present inside the cell during heating.

These heating tests have also been repeated cyclically over time demonstrating the cell's ability to preserve its properties even subject to fatigue stress conditions.

Parallel to the single-cell sensors, the first arrays of cells covered by graphene were manufactured, however the collapse of the graphene covering some cells prevents validating the data in comparison to the single cell and it's still in progress.

III. SUMMARY

Prototypes of advanced golay cells have been effectively designed and built, in which graphene plays a fundamental role as it seals the golay cell and at the same time has a high deformability in the presence of a modest pressure variation close to ambient temperature. This demonstrates the potential of this new generation of terahertz radiation sensors capable of offering good performance at a lower cost than commercial analogues.

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Phase-contrast THz-CT for non-destructive testing

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***Abstract*— We demonstrate a robust implementation of a THz-Computed Tomography (THz-CT) system for non-destructive testing of plastic profiles [1]. The main components of the system are a fast THz Time-domain spectrometer (THz-TDS) and a self developed image reconstruction algorithm based on an extended version of the Radon model – specifically developed to utilize the transmitted THz pulse phase. The reconstructed sample cross-sections show excellent agreement within ±100 µm.**

I. INTRODUCTION

MOTIVATED by the goal of reducing material losses during production and increasing the energy efficiency in the extrusion process of plastic profiles, we investigate the possibilities for online non-destructive testing using THz-CT. The aim of this project is to build a THz CT setup and develop an accurate data evaluation algorithm for image reconstruction of highly complex plastic profile geometries.

Our THz-CT setup consists of a THz-TDS system in transmission geometry with sample translation and rotation stages. In contrast to classical X-ray CT, where the transmitted signal intensity is used for image reconstruction, our THz-CT system can additionally measure the acquired signal phase induced by the refractive index of the sample.

The interaction of THz radiation with the sample is generally described by Maxwell's equations and is therefore strongly affected by diffraction and refraction on the sample surface. For this work, we have developed a modified version of the commonly known Radon model. We have further developed an algorithm to access the phase information, as it is specifically available in THz imaging. For our use-case of plastic profiles, it is shown that reconstruction based on phase information is superior to conventional intensity-based reconstructions. As shown in this work, the main reason for the increased robustness of our approach is that the measured pulse phase is not affected by diffraction and scattering. The development of a more advanced reconstruction algorithm, which further accounts for refraction is currently in progress.

II. RESULTS

In order to demonstrate the robustness of the developed approach, Fig. 1a shows a 3d printed (natural PolyPropylene) circular profile with the letters *THZ* inscribed and the corresponding phase contrast reconstruction (using Landweber iteration). The sample geometry is clearly identifiable.

For quantitative evaluation, two further samples with more ordinary geometries are presented. The quality attribute for each reconstruction is the sample wall thickness, compared to a mechanical reference measurement. Fig. 1b shows a linear spiral and the corresponding reconstructed image. The quantitative evaluation was done by thresholding and edge detection (blue line). It was found that the wall thickness of the inner structures of the spiral is inaccurately reconstructed as an increasingly thick wall. We state that this artifact appears as a consequence of refraction on the curved sample surface.

Fig. 1c shows a more realistic plastic profile, consisting of planar elements only. The sample boundary (green line) was detected by applying the linear Hough transform to the detected sample edges. Excellent agreement between the mechanical reference measurement within ±100 µm was found.

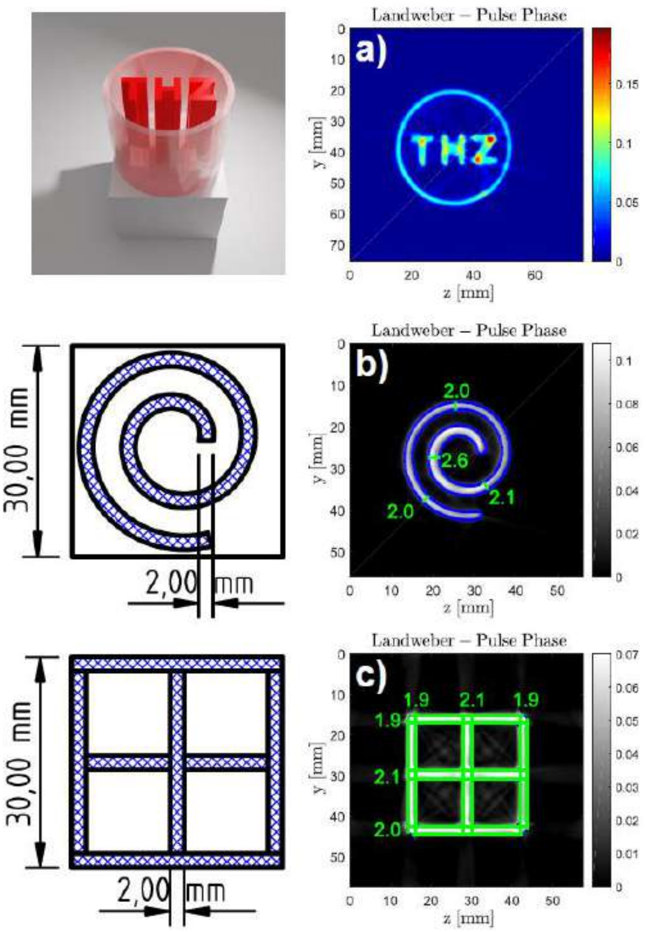

Fig. 1. Cross-sections and reconstructions of 3d printed plastic profiles. For qualitative demonstration, a complex sample with the letters THZ inscribed was reconstructed, yielding excellent agreement with the real sample geometry (a). Quantitative evaluation was done on a curved sample (b) and a planar sample (c). While the curved sample wall thickness deviates due to refraction artifacts, the planar sample could be reconstructed with an accuracy of ±100 µm.

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Taking Hyperspectral Terahertz Imaging to the Industry

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***Abstract*— The aim of this work is to develop a system capable of enabling true terahertz hyperspectral imaging in real time for biomedical applications and the inspection of agri-food products.**

I. INTRODUCTION

TERAHERTZ based spectroscopy provides greater number of benefits in many fields. For example, in the food and agricultural industries, as its application is not just limited to quality control but also to classification.

Specifically, in medical imaging, such system can be proven a tremendous addition for diagnostic purposes in the very near future:

In vivo imaging

Cornea in rabbits was first demonstrated through *in vivo* THz imaging in terahertz range, also scar healing can be detected and analyzed and skin flaps viability for early assessment of 24hrs has been demonstrated. Researchers used Terahertz pulsed spectroscopy to measure dysplastic and non-dysplastic skin nevi and the results reveal differences between diagrams of non-dysplastic skin vs dysplastic skin nevi. THz systems were used to monitor glucose level and observed that possibility is through noninvasive monitoring.

Ex vivo imaging

THz radiation can differentiate between cancerous and non-cancerous cells as demonstrated by *Bowman et al*. and is a more sensitive approach. They examined oral cancers and clearly found better information about diagnosis using the THz imaging approach.

From dental care to organ tissues, THz imaging can help in diagnosis of dental related issues and water faction in tissues. Apart from these biological research areas there are also numerous applications in protein, polypeptide and DNA studies from finding their absorption spectra for identification to diagnosis of cancerous cells in DNA.

Current single pixel spectral analysis is slower one and takes more time and that is what raster scanning does, sample is regularly moved for such spectral analysis process. But in dual comb system the sample is illuminated by dual comb spectra having slight difference in their repetition rates and at the same time enables direct characterization and spectral response of sample at every pixel of the image. The process is faster than other comparable system. This opens a completely new set of opportunities.

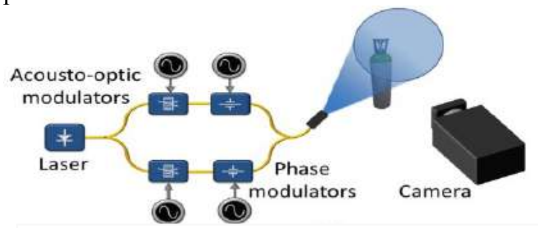
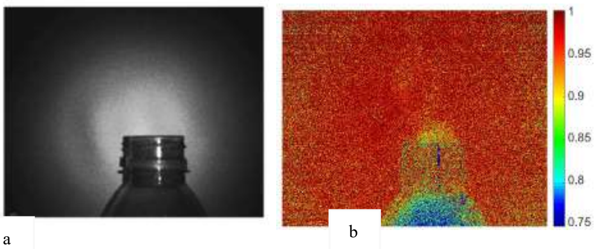


Fig. 1 Block diagram of the dual comb hyperspectral imaging system validated for near IR region.

II. RESULTS

The proposed approach has been demonstrated in the near-IR targeting ammonia in a bottle. The combination band v1 + v3 and the overtone 2v3 of ammonia at 6529 cm^{-1} is targeted by five teeth dual comb (laser central wavelength of 1531.68 nm corresponding to 6528.77 cm-1). The light is then collected by camera and the data is processed to get desired response at 6529 cm^{-1}. Remarkably, in this experiment all the spectral elements are simultaneously retrieved for the 327,680 pixels of the camera sensor from a single unaveraged and unapodized interferogram in a single second.



a b

Fig. 2. a) Shows the bottle containing ammonia and being illuminated. b) Spectral transmittance retrieved by the system.

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Session 3.1:
Spectroscopy I

Erice, Sicily

Confined Water Molecules:
THz spectroscopy of ortho- to para-water conversion

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***Abstract*—Using single cycle THz pulses, we launch coherent wave packets in the low-frequency rotational transitions of an ensemble of $H_2O@C_{60}$ and resolved the coherent emission of electromagnetic waves by the oriented dipoles. At 4 K, the rotation of water attains a long coherent trajectory extended beyond 10 ps; indicating a transition from classical to quantum rotation of H_2O. Also, a change of the pattern of the dipole emission is observed, from a mixture of ortho- and para-water to a more purified para emission after a waiting period of 10s of hours, indicating the inter-conversion of spin isomers of water at cryogenic temperatures.**

I. INTRODUCTION

RESOLVING the real-time coherent rotational dynamics of water are of particular interest because the low symmetry of water molecules and the constraint that is imposed due to the symmetry of the wave functions of the two spin isomers: ortho-water with total nuclear spin of $l = 1$ and para-water with total nuclear spin of $l = 0$. Here we study water encapsulated in the highly symmetrical, homogenous and isolated environment of the inner space of C_{60}. This enables us to study the rotational coherence of water at cryogenic temperatures and capture the conversion of the spin isomers of water through its real-time coherent rotational motions.

II. RESULTS

The $H_2O@C_{60}$ sample are excited by THz pulses with center frequency of ~1 THz, a temporal duration of 0.5 ps and bandwidth of 1.5 THz; the coherent emissions of water molecules are measured using short laser pulses with temporal resolution of ~20 fs using photo-conductive switching method. The lowest rotationnal states are almost unperturbed at low temperatures since the high symmetry of the fullerene cages allows water to rotate freely. The free-induction-decay (FID) emissions of the encapsulated water was measured over the course of ~30 hours. The sample was cooled to $T = 20$ K, and then the temperature rapidly lowered to 4 K. The change of the FID components over the course of 10 hours can be clearly seen in the Fourier spectra of the FID signals of the $H_2O@C_{60}$ in Fig. 1, where the two ortho transitions lose their strength, while the para component becomes brighter. The temporal evolution of the latter amplitude variation, taken from the ortho component $\nu_1 = 0.52$ THz and the para component $\nu_2 = 1.0$ THz given in the right panel.

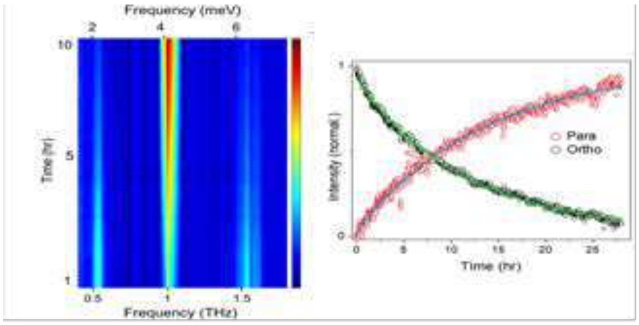

Fig. 1: Ortho-para spin conversion of water at $T = 4$ K. In the time window of 10 hours the ortho lines at ~0.52 THz and ~1.53 THz lose their amplitude (coded dark blue), while the para line at ~1 THz gains larger amplitude (coded red). The right panel shows the kinetics of the amplitude of the para-water (@ 1THz) and ortho-water (@ 0.52 THz). The solid lines are single exponential fits to the experimental data with ortho decay time of 11.22±0.14 hrs and para rise time of 13.5 ± 0.25 hrs..

This manifests the real-time conversion of ortho-to-para spin isomers of water and demonstrate that the coherent rotation of entrapped water molecules lasts for about 15 ps inside its cage at 4 K, to the best of our knowledge the longest coherent rotational motion observed for confined molecules in nano-cages.

III. SUMMARY

We resolve the real-time coherent rotational motion of isolated water molecules encapsulated in fullerene-C_{60} cages by time-domain THz spectroscopy. At temperatures below ~100 K, C_{60} lattice vibrational damping is mitigated and the quantum dynamics of confined water are resolved with a markedly long rotational coherence, extended beyond 10 ps. We also resolve the real-time change of the emission pattern of water after a sudden cooling to $T = 4$ K, signifying the conversion of ortho-water to para-water over the course of 10s hours. The observed long coherent rotational dynamics of isolated water molecules confined in C_{60} makes this system an attractive candidate for future quantum technology.

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Acceleration of collective orientation in nanoconfined water of DMPC

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***Abstract*— The effect of confinement on the hydrogen bonding networks of water molecules encapsulated in phospholipid multilamellar vesicles is investigated by dielectric relaxation spectroscopy. Acceleration of collective orientational dynamics is confirmed experimentally.**

I. INTRODUCTION

The physical and chemical properties of liquid water are profoundly governed by its hydrogen-bonding networks [1]. In the bulk liquid water, the hydrogen-bonded water molecules form an approximately tetrahedral structure that continuously fluctuates on the picosecond timescale. However, the structure and dynamics of water bodies are affected strongly upon introduction of an interface or confinement[2].

A wealth of studies has been mainly conducted on the nature of hydration, and they describe a slow hydration shell consisting of up to several layers of water from the surface [3]. For a nanoconfined water, if the confinement length scale is larger than the hydration layer thickness, the water molecules beyond form a bulk liquid-like phase, giving rise to a simple model of retarded hydration water and an unperturbed bulk-like water beyond the hydration layer [4]

Yet in nanoconfined water environments, some peculiar phenomena have been reported. For instance, the diffusion rate of water in carbon nanotubes (CNT) increases as the CNT diameter decreases, but it is almost identical between graphene sheets regardless of the surface-to-surface distance [5]. As another example, the self-dissociation reaction of water is inhibited in CNT, but it is enhanced between graphene sheets [6]. Analogously, water-hydrogen exchange of biomolecules is rapid in bulk water but drastically slowed down in confinement [7]. These observations indicate that the two-component model of the slow hydration shell and the bulk-like water lacks some descriptive qualities.

A major shortcoming of conventional single-molecular spectroscopic methods, such as vibrational spectroscopy IR, NMR and scattering, nuclear quadrupole resonance, for investigating the nanoconfined water is the lack of information about correlated motion among water molecules, which tends to align their permanent dipoles into the tetrahedral hydrogen bonding network. how they report on the dynamics of a water molecule or a pair of molecules. They may reveal intermolecular phenomena, but necessarily lack important cross-correlations and. Thus they do not report on some properties arising from the collective interactions of the molecules forming a piece of matter, such as the dielectric constant

In contrast, dielectric relaxation spectroscopy (DRS) is a collective spectroscopic method tracking the temporal evolution of the sum dipole of the entire sample instead of the molecular ones. Hence DRS includes not only the temporal behaviour of the molecular dipoles, but also how they move with regards to each other.

II. RESULTS

Our dielectric relaxation measurements show that its collective dynamics are much faster, not slower; at the long range, water dipoles align far more anti-parallel than in bulk-liquid water; the cause behind this drastic change is not the interaction with the confining surface as one would suspect, but arises from geometrical confinement itself.

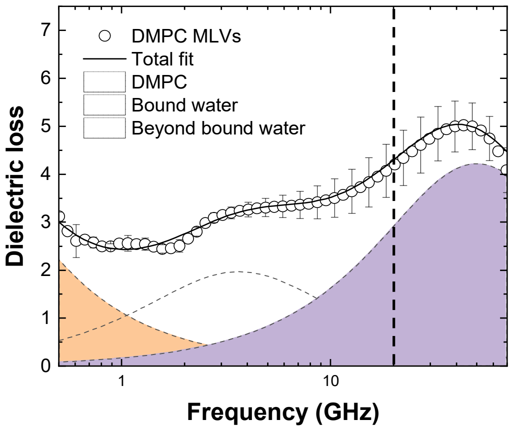

Fig. 1: The dielectric loss spectrum of DMPC MLVs and its decomposition of relaxation modes for the nanoconfined water in the MLVs in DMPC/water

III. SUMMARY

This study reports how the entire water phase behaves differently when nanoconfined, even beyond the surface hydration layer. A counter-intutive collective dynamics acceleration of water due to nanoconfinement was observed, which has been invisible in NMR, scattering, and vibrational spectroscopies.

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Study of THz optical properties of albumin dry pellets with varying glucose concentration

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ONE PAGE SUMMARY NOT AVAILABLE FOR PUBLISHING

Session 3.2:
Medical Applications II

Erice, Sicily

Intraoperative diagnosis of human brain gliomas using THz spectroscopy and imaging

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***Abstract*— In this work, we study the THz optical properties of human brain gliomas ex vivo featuring WHO grades I to IV, as well as of perifocal regions comprised of intact and edematous tissues. The tissue specimens were characterized using the reflection-mode THz-pulsed spectroscopy and histology. The gelatin embedding of tissues allowed for sustaining their THz response unaltered for several hours, as compared to that of freshly excised tissues. We observed statistical difference between intact tissues and tumors.**

I. INTRODUCTION

Gliomas form the most common type of primary brain tumors. Among the prognostic factor of glioma treatment, achievement of its gross-total resection is a crucial one for reducing the probability of tumor recurrence and increasing the patients' survival. Gliomas usually possess unclear margins, complicating their gross-total resection. Existing methods, applied to differentiate between healthy tissues and gliomas, do not provide satisfactory sensitivity and specificity of diagnosis, especially for low-grade gliomas. Terahertz (THz) spectroscopy and imaging represent promissing techniques for the intraoperative neurodiagnosis [1-3]. Early diagnosis of glioma may be achieved by detecting the molecular biomarkers in brain tissues and body fluids [4]. In our work, we studied an ability for the intraoperative diagnosis of human brain gliomas using THz technology.

II. RESULTS

We measured THz dielectric response (optical constants) of gelatin embedded human brain gliomas ex vivo with different WHO grades using THz pulsed spectroscopy. The gelatin embedding of tissues was used in order to preserve them from hydration/dehydration and, thus, to sustain their THz response unaltered for a couple of hours after the surgery, as compared to that of freshly-excised tissues ex vivo. The results of our study demonstrate increased values of THz optical constants of WHO grade I–IV gliomas, as compared to that of intact (healthy) tissues of the human brain. Meanwhile, the THz response of edematous tissues in a perifocal region is close to that of a tumor; thus, edematous tissues might be recognized as a tumor, leading to the false positive results of diagnosis. Our experiments allows for objectively uncover a prospective of THz spectroscopy and imaging for the intraoperative diagnosis of human brain tumors [5, 6]. Considering current developments on THz spectroscopy and imaging, we analyzed an ability to transfer THz technology into a neurosurgical practice. In our opinion, a single-point measurements of tissues using THz spectroscopy or reflectometry could be integrated into modern neurosurgical probes, in order to perform simultaneous intraoperative diagnosis of tissues *in vivo* with further removal of tumorous tissues by their aspiration. For example, sapphire shaped crystals [7] provide a favorable combination of physical and mechanical properties to serve simultaneously as key elements of modern neouroprobes [8] and as highly efficient THz waveguide [9]. Furthermore, THz technology could aid express-histology of excised tissues *ex vivo*, which is nowadays widely-applied intraoperatively to correct the surgery [10].

III. SUMMARY

In conclusion, in our research, we studied a dielectric response of gelatin-embedded human brain gliomas of WHO grade I–IV using THz pulsed spectroscopy. We found statistical differences between the response of intact tissues and tumors; thus, highlighting a prospect of THz technology in the intraoperative neurodiagnosis.

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Early screening of diabetic foot syndrome by terahertz imaging

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***Abstract*—In this work we present the development of a non-invasive technique for the evaluation of the diabetic foot syndrome using terahertz time domain imaging.**

I. Introduction and Background

DIABETES Mellitus is a disease that afflicts 8,5% of the world population [1]. Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin it produces to regulate the blood glucose levels. High blood glucose, over time, severely damages many organs and systems, especially the nerves and blood vessels [2]. One of the consequences of this disease is the condition known as diabetic foot, a set of neurological and vascular complications that cause loss of sensitivity and ischemia in the extremities which favors the development of ulcers that can lead to amputation of the affected limb. This condition affects 20% of diabetics generating extraordinary costs for patients and public health systems and is the leading cause of non-traumatic amputations [3]. Being one of the most common complications of diabetes, it is essential to make an early diagnosis of diabetic foot and thus give it the necessary treatment. Unfortunately, there are no objective methods for making an adequate diagnosis. In this work we used the ability of terahertz radiation to monitor the skin hydration and correlate the result with the deterioration degree of the diabetic foot.

II. Results

In order to quantify the skin hydration, the complex dielectric function of the dehydrated human skin was measured at terahertz frequencies. Subsequently, using effective medium theory, a model of the dielectric properties of human skin was obtained as a function of the hydration degree. Terahertz images of the foot sole of diabetic and non-diabetic subjects were acquired with a THz-TDS system mounted in reflection mode under a polyethylene window on which the feet were placed. Terahertz images of the foot sole of 33 non-diabetic subjects and 38 diabetic patients were acquired but only 21 of the control group and 12 of the diabetic patients were analyzed. Data were processed and, by fitting a theoretical reflectance model to the experimental reflectance, the water content in the skin was determined in every measurement point and new images were formed with the water content information. A non-diabetic subject and a diabetic patient hydration images are shown in Figure 1. From the hydration images, we can observe a remarkable difference regarding the water content in the foot sole skin, with the skin hydration of the non-diabetic subject being significantly larger than that of the diabetic subject.

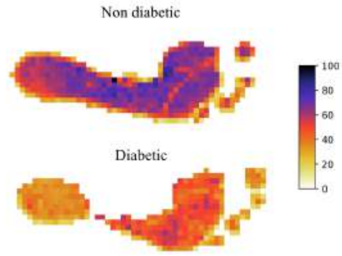

Fig. 1. Hydration images of non-diabetic (top) and diabetic (bottom) subject. The color map represents the skin hydration at the sole of the foot of each volunteer.

III. Conclusion

The feasibility of the proposed technique for the early diagnosis of diabetic foot syndrome is demonstrated [4], [5]. According to the hydration images, we conclude that terahertz imaging is a reliable technique for non-invasively monitoring the hydration degree of the foot sole skin which correlates to the deterioration in the limbs.

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Diagnosing diabetic foot with THz imaging: A progress report.

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Abstract—**During this presentation I will give an overview of recent progress in the use of THz for the diagnostics of the diabetic foot syndrome. There have been improvements from the instrumental aspects of the device and much broader control and diabetic populations have been imaged in comparison to our report from 2017, giving rise to a whole new set of conclusions both for the diabetics and non-diabetics.**

In 2017 the terahertz time-domain imaging technique was reported as a potential tool in the diagnosis of the diabetic foot syndrome.[1,2] In that study, preliminary evidence of the correlation between the presence of diabetes and a decrease in the patient's feet hydration which at its time was easy to detect and quantify by terahertz reflection imaging was presented. Yet, that initial study presented a few deficiencies in terms of the reduced size of the diabetic and control populations, the application of appropriate reference tests to the control group and a potential bias in terms of unequal age distribution between the control and diabetic groups.

Additional measurements were recently made with a much more characterized cohort of diabetics and a random group of controls recruited in a hospital's wait room that include non-diabetic patients with other conditions, and family members of patients with a better overlap of age distribution.

The feet terahertz imaging system underwent significant improvements with respect to the one used in 2017, images of the two feet of each patient are now acquired in a period of 9 minutes with a spatial resolution of 1mm (see Fig. 1).

We will discuss the new findings of this new measurement campaign and how this shine new light in understanding the potential of the THz technique as a diagnostic tool for diabetic foot syndrome, and perhaps other conditions that reflect on the skin hydration, that could include vasculopathies and peripheral neuropathies.

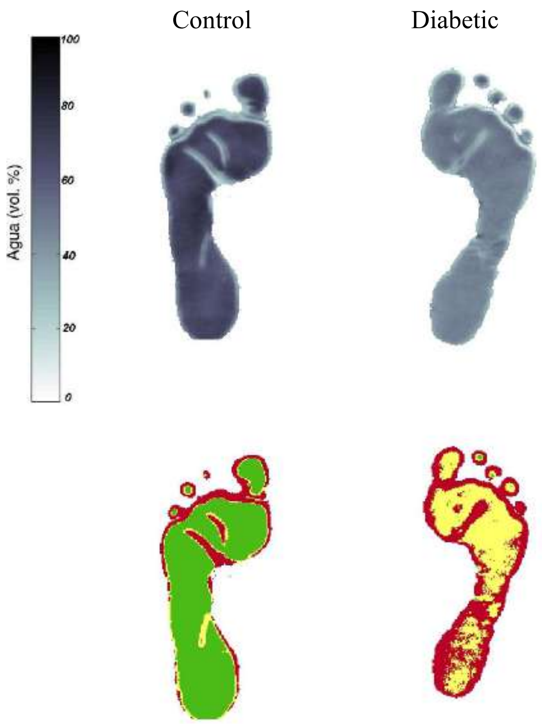

Figure 1. (top left) Hydration image of a non-diabetic patient. (top right) Hydration image of a diabetic patient. (bottom left) Red-Yellow-Green color coded image for the same non-diabetic patient. (bottom right) Red-Yellow-Green color coded image for the same diabetic patient according to the criteria of [2].

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Breast Carcinoma Segmentation Based on Terahertz Refractive Index Thresholding

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***Abstract*— A self-reference imaging method, in reflection configuration, was employed to extract from inverse electromagnetic problems the refractive index map of freshly excised breast carcinoma sections. Various thresholding strategies were tested to isolate the malignant pixels from the benign ones. Correlations with pathology images were performed to determine receiver operating characteristics of considered segmentations. To enlarge the field of inquiry, additional investigations towards principal component analysis were performed.**

I. Introduction

A reflection imaging system was employed to record the response of freshly excised breast carcinoma sections to terahertz pulses **[1]**. The refractive index map of tissue samples was extracted by means of inverse electromagnetic problems. The collected maps were then segmented with different classification methods. Chiefly, it consists of defining a refractive index threshold above which, pixels are marked as malignant. However, as pixels are numerical entities rather than biological ones, such a type of rough segmentation are often hardly efficient. Therefore, connected thresholding strategies that consider pixel proximity were additionally investigated. These methods are based on the definition of an influence area that allows to mark as malignant the pixels that were classified as benign, from the refractive index thresholding, but are comprised in the influence zone of a malignant pixel. The efficiency of each segmentation was assessed by filling the associated confusion matrix with regards to the corresponding pathology images, annotated by the pathologist. The resulting receiver operating characteristics corresponding to each segmentation were derived.

Complementary to these studies, principal component analysis (PCA) investigation was investigated **[2]**. Such a procedure does not aim to qualify PCA efficiency for tissue classification, but rather to explore a possible correlation between the contrast exhibited from principal component analysis and pixel malignancy.

II. Results

On Fig. 1 is given the photograph of one of the treated sample as well as the pathology image, the refractive index map at 560 GHz and the pathology mask. Each segmentation was subsequently correlated with the pathology mask. The receiver operating characteristic (ROC) curves were drawn for each segmentation. Fig. 2 depicts ROC curves that were extracted for a specific tissue sample. The two best obtained trade-offs between sensitivity and specificity were, in the study, 79% sensitivity for 82% specificity and 86% sensitivity for 69% specificity. Considering PCA, Fig. 3 shows the distribution of original pixels once projected with respect to their newly calculated coordinates in PCA subspace. Globally, results towards PCA indicate that pixels were clustered in accordance with their malignant or benign nature.

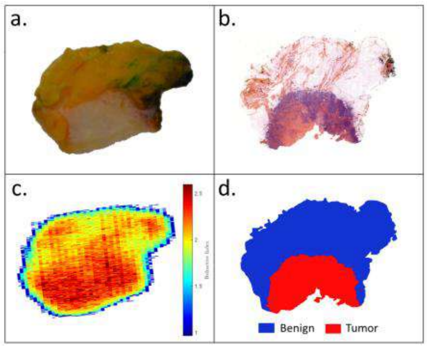

Fig. 1. Example of one of the treated tissue sample. a: photograph; b: pathology image; c: refractive index map at 560 GHz ; d: pathology mask.

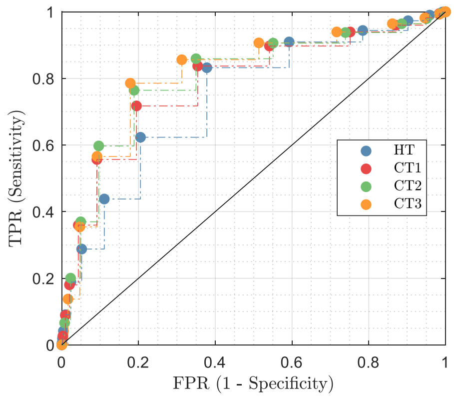

Fig. 2. Typical ROC curves derived from the segmentation of the refractive index map. HT: hard thresholding; CT1, 2, 3: connected thresholding with influence zone that comprises 1st, 2nd and 3rd order neighbor pixels.

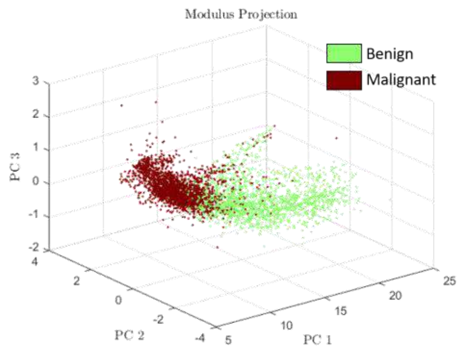

Fig. 3. Example of one of the modulus data set projected on the PC1-PC2-PC3 3D space.

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Field exposure and dosimetry in search of genotoxic effects of THz radiation in vitro

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***Abstract*—Many different studies on bio-electromagnetic interaction research in the THz frequency range exist that come to controversial results. Here, the results of a large exposure campaign searching for genotoxic effects in vitro and the experimental hurdles with regard to sample exposure and dosimetry that needed to be addressed to obtain reliable results are reviewed.**

I. Introduction

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) limits the exposure to electromagnetic fields up to frequencies of 300 GHz [1] and beyond [2] based on well-studied thermal effects. However, independent of the frequency of non-ionizing exposure, many studies claim non-thermal bio-electromagnetic effects without being able to identify the physical mechanism of the effects and a dose-response relationship. In the THz frequency range, many studies of different quality on living organisms, model systems and cells have been performed that do not provide a clear picture whether non-thermal effects exist [3-5].

Based on findings in the *THz Bridge Project*, Korenstein-Ilan et al. [6] reported increased genomic instability in human Lymphocytes after exposure to mm waves below the safety limit. This initiated a larger experimental campaign financed by the German Federal Office for Radiation Protection (Bundesamt für Strahlenschutz – BfS) and conducted by a cooperation of the University of Würzburg, the Helmholtz Centre for Infection Research, the University of Marburg and PTB. In three independent exposure campaigns on two different types of skin cells (primary dermal fibroblasts (HDF) and a keratinocyte cell line (HaCaT)) at frequencies of 106 GHz [7], 380 GHz and 2.52 THz [8], no genotoxic effects were found.

II. Experimental Hurdles and Dosimetry

Many studies on bio-electromagnetic interaction research have severe shortcomings [9]. Very often, the electromagnetic field in the exposure location is not known quantitatively or the cells are not fixed in an inhomogeneous field. The exposure conditions with regard to source stability, temperature, pressure, humidity, CO_2 content of the surrounding atmosphere but also unwanted fields from cell phones and electrical appliances are not monitored. Furthermore, there are often inadequate study designs with regard to insufficient sample and cell statistics, missing positive and sham controls and missing blinded procedures.

In the experimental campaign *Genotoxic Effects of Terahertz Radiation in vitro*, many of these critical points were addressed as adequate as possible. The dosimetry was based on numerical calculation of the field distribution in the sample using *CST Microwave Studio*^{TM} and measurements of the power density traceable to the SI units [10].

III. Results of the Exposure Campaign

Not only the results of the *THz Bridge Project* but also results from an earlier exposure campaign at PTB with mobile communication signals indicated that there might be non-thermal effects [11]. Spindle disturbances in a Human-Hamster hybrid (A_L) cell line were found induced by the electrical field component of a standing wave in a TEM waveguide [12]. Later, these spindle disturbances were found after exposure of cells to THz radiation, as well [13]. Although spindle disturbances were expected to lead to micronuclei formation, no statistically significant genotoxic effects were found using the micronuclei test and the comet assay as end points after exposure with different times and levels at and below the safety limit.

IV. Summary

In this contribution we reviewed a series of field exposure experiments that were conducted to clarify whether exposure of skin cells with THz radiation leads to genotoxic effects. No such effects were found.

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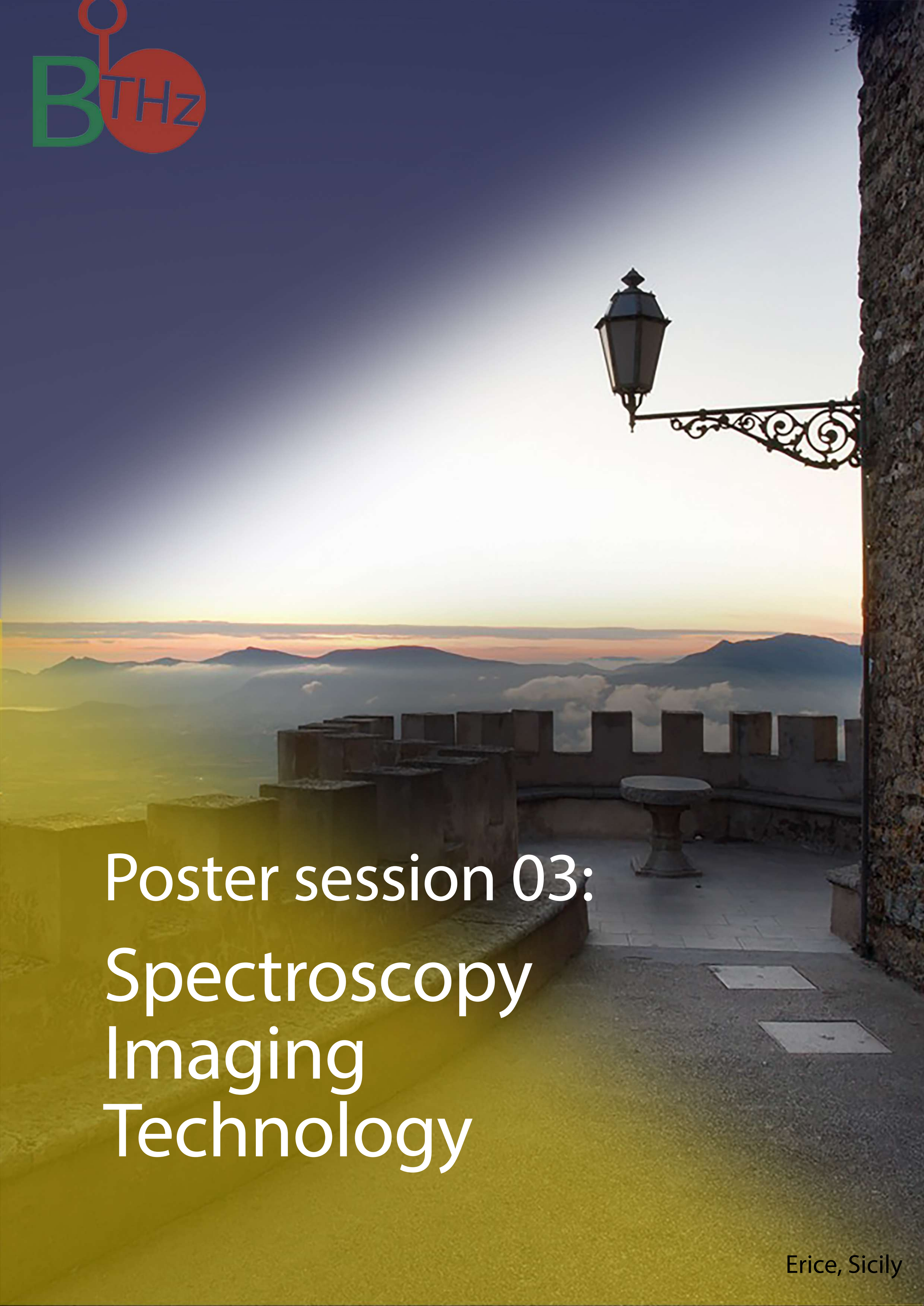
Poster session 03:
Spectroscopy
Imaging
Technology
Erice, Sicily

Investigation of the influence of the stomatal activity on the water content of plant leaves under drought stress using THz spectroscopy

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***Abstract*—We used Terahertz (THz) time-domain spectroscopy in order to compare the water dynamics of wild-type and *ost1-2* mutant of *Arabidopsis thaliana*. We found significant differences in the dehydration dynamics: the mutant dehydrates much earlier due to the lack of stomatal control as a consequence of the mutated OST1 kinase and shows strong oscillations in water content related to the 24 hours illumination cycle.**

I. Introduction

The loss of water of plants through transpiration is mainly regulated by the stomata which also control the uptake of CO_2 for photosynthesis. If water stress occurs, the plant synthesizes ABA (abscisic acid). In response to this hormone, the protein kinase OST1 (open stomata 1) in wild-type Arabidopsis activates the guard-cell anion release channel SLAC1 (slow anion channel-associated 1) which triggers stomatal closure to limit dehydration [1, 2]. For this reason, the guard cells of plants with mutated OST1 do not respond to ABA and therefore cannot close their stomata during the day to reduce water loss; the mutation does not affect the stomata regulation by light [3]. In this contribution we will present THz in vivo measurements of wild-type and OST1 mutated Arabidopsis which show that the mutated variety undergoes severe dehydration earlier than the wild-type one and shows larger day-night water content oscillations.

II. Results

We used Terahertz (THz) time-domain spectroscopy in order to compare the water dynamics of *Arabidopsis thaliana Landsberg erecta* (wild-type) and *ost1-2* mutant. The measurements were performed using a fiber-coupled sensor head mounted on a carousel system. Thus, 7 individual living plants from each genome could be measured every 25 minutes.

Fig. 1 shows the measured transmittance of the plant leaf, the curves shown are representative of 7 independent plants of each genome: since water is highly absorbing in the THz band, the higher the transmittance, the lower the water content.

Within the first few days, each plant can maintain its optimal water status and the day-night cycle is only slightly visible. But after 3 days, the *ost1-2* mutant begins to lose substantial amounts of water under illuminated conditions. Due to the mutated OST1 kinase, the drought induced ABA generation does not result anymore in the closure of the stomata because the signal path is blocked. During night periods, the plant is able to close its stomata and accumulate water which explains the decrease in transmittance and thus the strong oscillations in the water content of the leaf.

The wild-type Arabidopsis can maintain the optimal water status until approximately day 10 by closing its stomata during the illumination period. From this point on, the leaf also dries out during the day, but to a lesser extent compared to the *ost1-2* mutant, whereas the recovery phase is suppressed due to the lack of water in the pot.

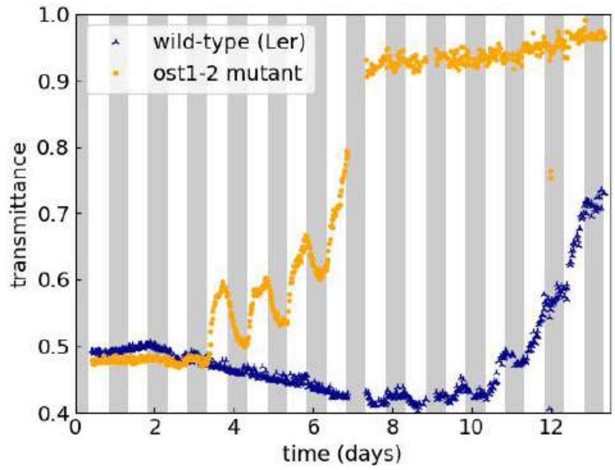

Fig. 1. Transmittance of two plant leaves of wild-type and *ost1-2* Arabidopsis as a function of time. High transmittance corresponds to low water content. Illuminated periods are indicated white, dark periods grey.

III. Summary

In contrast to alternative methods (e.g. the use of pressure sensors), THz spectroscopy allows direct measurement of the water content of a leaf and therefore offers an excellent possibility to investigate genetic influences on the regulation of water content. Our experiments show that the ability to resist dehydration and maintaining the optimal water status of the leaves strongly depends on the ability of stomatal control. Mutants with insensitivity to ABA (due to mutated OST1) are incapable to close their stomata under illuminated conditions. Further investigations considering soil moisture will deepen the knowledge of the stomata role during dehydration.

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THz imaging activities at IREA – CNR

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Abstract— **This communication aims at summarizing the THz diagnostic imaging activities carried out at the Institute for Electromagnetic Sensing of the Environment (IREA) - National Research Council of Italy (CNR). As far as THz device is concerned, the Z-Omega Fiber-Coupled Terahertz Time Domain (FiCO) system equipped with an imaging module is deployed and enhanced thanks to an ad-hoc data processing strategy. Several examples concerning different kind of both known and unknown samples as well as unknown ones will be presented at the conference in order to assess the capabilities offered by the adopted hardware and software technology in different applicative contexts.**

I. Introduction

THE exploitation of electromagnetic waves in the frequency range from 0.1 THz to 10 THz (free-space wavelength ranging from 30 μm to 3 mm) as diagnostic tool is attracting an increasing interest in many applicative fields, among which security, cultural heritage, material characterization, agri-food and biomedical diagnostics [1-3]. The widespread use of THz waves is due to their non-ionizing nature, their capability of penetrating into dry, nonpolar, non-metallic materials, and has been improved thanks to recent technological advances that have allowed the commercialization of compact, flexible and portable systems.

Specifically, Time Domain Terahertz (TD-THz) systems are considered among the new frontier sensing methodologies, because they allow a sub-millimetre cross-sectional representation and give information about position and thickness of possibly inner layers as well as hidden features. Accordingly, they allow to analyse texture and stratigraphy of materials as well as to detect hidden defects or anomalies without implying long term risks to the molecular stability of the exposed object and humans.

However, the effectiveness of THz imaging is crucially dependent not only on peculiar features of the surveyed materials, but also on the adopted hardware devices and data processing approaches.

This communication aims at summarizing the THz imaging activities carried out at the Institute for Electromagnetic Sensing of the Environment (IREA) - National Research Council of Italy (CNR) in different applicative fields.

II. Imaging Activities

IREA owns the Z-Omega Fiber-Coupled Terahertz Time Domain (FiCO) system [4] equipped with an imaging module. The FiCO system collects signals into a 100 ps observation time window, which can be moved along a time scan range of 1 ns according to the path length between transmitter and receiver. The waveform acquisition speed can be up to 500 Hz and the maximum dynamic range (DNR) is 30dB, while the typical DNR is 20dB. The working frequency range is from about 50 GHz to 3 THz. The system is equipped with an automatic positioning system enabling to scan a 150 mm x 150 mm area, with the smallest spatial offset in both directions describing the measurement surface equal to 0.012 mm. It is worth to pointing out that the positioning system allows normal reflection measurements by keeping fixed emitter and receiver and moving the sample under test.

With respect to data processing, an ad-hoc strategy has been designed at IREA to filter data and visualize THz images [5]. This strategy involve three different steps in time-domain aimed at reducing noise, filtering out undesired signal introduced by the adopted THz system and performing (when required) surface topography correction [5]. The first step regards noise filtering and exploits a procedure based on the Singular Value Decomposition (SVD) of the time-domain raw data matrix, which does not require knowledge of noise level and it does not involve the use of a reference signal. The second step aims at removing the undesired signal that we have experienced to be introduced by the FICO system. Indeed, when the system works in a high-speed mode, an undesired low amplitude peak occurs always at the same time instant from the beginning of the observation time window (trace) and needs to be removed from the useful data matrix in order to avoid a wrong interpretation of the imaging results. The third step of the considered data processing chain is a topographic correction, which is necessary in order to image properly the samples surface and its inner structure. Such a procedure performs an automatic alignment of the first peak of the measured waveforms by exploiting the a-priori information on the focus distance at which the specimen under test is located during the measurement phase.

III. Summary

Several representative examples of the IREA THz imaging activities will be presented at the conference in order to assess the capabilities offered by the adopted hardware and software technology in different applicative contexts, such as cultural heritage and quality control of materials, among which food and composite sample.

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Humidity and temperature can affect wire-bound THz communications

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***Abstract*—We show that the water vapour density in the atmosphere strongly impacts on the transmission of 120 GHz waves through a cladding-free polypropylene fibre. We attribute this effect to the growth of a water film around the fibre which attenuates the evanescent field. Further measurements show that also the temperature of the polymer fibre is important as the absorption of polymers is temperature dependent.**

SHORT-range wireless THz communication is likely to become a mass market in the not too far future [1]. Also, THz transmission over polymer wires may find applications, analogous to the glass fibre-based communications at telecom wavelength. As material losses in the THz range in polymers are higher than the losses in glass fibres at telecom wavelengths communication distances will be restricted to a few ten meters. Consequently, in-car communications, or communications between rooms through a ceiling or a wall are conceivable scenarios for wire-bound THz communications. In fact, first THz communications experiments using bare polymer fibres without a cladding have already been performed [2].

Here, we experimentally investigate how the humidity and temperature of the atmosphere affect the transmission of 120 GHz waves through a cladding-free polypropylene fibre. We find that the transmission though this fibre depends on both, the water vapour density (WVD) in the atmosphere and the temperature of the fibre.

We use a commercial round polypropylene fibre with a diameter of 1.75 mm (+-0.05 mm). To determine the transmission through the fibre we employ a CW microwave system from QuinStar Technology operating at 120 GHz. Both, emitter and receiver have a horn antenna attached, into which we stick the dielectric waveguides for end-butt coupling. A part of the modes propagates in air. Hence, not the material absorption is relevant here, but we have to consider an effective absorption coefficient α_{eff} which we determine from experiments with fibres of different lengths at room temperature and very dry air. From these measurements we can determine α_{eff} to be 0.32 m^{-1} corresponding to 1.39 dB/m.

We first perform an outdoor experiment during which 80% of the polymer fibre with a total length of 433 cm was placed in the open. This first experiment which was carried out over the course of 27 hours in May 2019 illustrated the problem: the WVD in the atmosphere largely influences the power transmitted through the fibre. To have more defined conditions we used a climate chamber from "Nüve" (modell ID300) which was recently modified to allow for THz measurements [3]. This chamber allows us to precisely control humidity and temperature around the fibre. The length of the polymer fibre inside this chamber is 217 cm.

We performed an experiment over a course of 60 hours monitoring the received intensity for varying temperature and relative humidity. From these data we can calculate the WVD and can plot the received intensity versus WVD. This plot is shown in Fig. 1. The values obtained for temperatures of 22°C and 13°C are shown as open and full dots, respectively. It is obvious that the received power strongly depends on the WVD. We attribute this effect to the growth of a water film around the fibre which attenuates the evanescent field. The thickness of this film depends on the WVD. See [4] for more details.

We performed further measurements to determine how the temperature of the fibre impacts the transmission through the fibre. It is well known that the absorption of polymers increases with temperature. We set the relative humidity in the chamber to 5% to reduce the WVD to the lowest possible value which could be achieve without special measures. We find that the power transmitted through the fibre drops more or less exponentially with temperature. See [4] for more details.

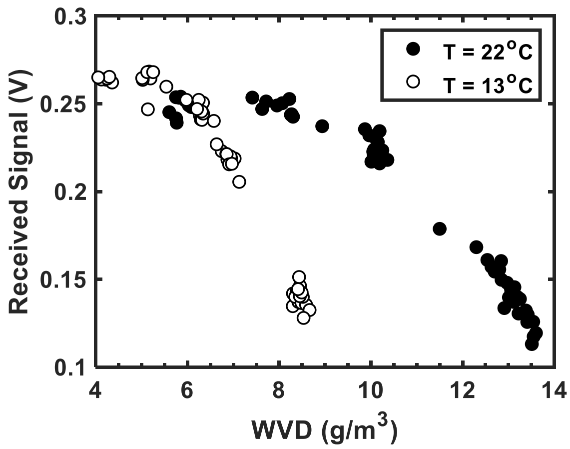

Fig. 1. Transmitted signal as a function of the water vapour density for two different temperatures (full dots correspond to 22 °C, open circles correspond to 13 °C).

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Session 4.1:

Mechanisms of Interaction

Erice, Sicily

Terahertz Spectroscopy of Biological Molecules and Tissues

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***Abstract*— The authors report spectroscopic studies for (i) alanine crystal [1-2], (ii) hen egg-white lysozyme irradiated with mid-IR laser [3], and (iii) corneal tissues of rabbit eyes [4]. From these examples, it is elucidated that THz spectroscopy with theoretical analysis is a powerful tool for the studies of biological molecules and biological systems.**

I. Introduction

In recent years, with the progress of the terahertz (THz) wave light source, THz wave applications have attracted much attention. In future wireless communications, the carrier frequency will be extended to the THz frequency region (>0.1 THz), and there is also an increasing concern with the influence of THz waves to biological systems. When we study the influence or interaction of THz electromagnetic waves with biomolecules and biological systems, the absorbed power or energy is the key parameter. The influence or reaction induced in the biological system for the case of high-power and low-power irradiation should be much different. For the case of high power irradiation, the thermal effect may play an important role. To simulate the thermal effects, it is essential to know precise dielectric properties of the biological system under investigation in the THz frequency region.

In this paper, the authors illustrate the usefulness of THz time-domain spectroscopy (THz-TDS) for evaluation of complex dielectric properties of biological macro molecules and tissues in the THz frequency region by THz-TDS studies and theoretical works carried out for (i) L-alanine (enantiomer) and DL-alanine (racemic compound) (ii) hen egg-white lysozyme after a high-power mid-IR irradiation and (iii) corneal tissues of rabbit eyes with high-power THz wave irradiation.

II. THz Spectroscopic study of L-alanine (enantiomer) and DL-alanine (racemic compound)

Biomolecular crystal show relatively sharp absorption bands in the THz frequency region originating from inter-molecular vibrations, whose frequencies and intensities are governed by the crystal structure and its symmetry. For example, poly-crystalline L-alanine (enantiomer) and DL-alanine (racemic compound) show strikingly different absorption bands even though the constituent molecules are same except the handedness. In a recent theoretical study [2], we have revealed that such a difference arises from the IR-activities determined by the crystal space-group symmetry. In addition, it was also found that the intra-molecular motions play crucial roles in determining the IR intensities [1].

III. THz Spectroscopic study of hen egg-white lysozyme with high-power mid-IR irradiation

Irradiation of mid-IR laser resonant to the amide I absorption band (6 μm) can refold the amyloid fibrils of hen egg-white lysozyme (HEWL) (aggregate of lysozyme) to the native-like form and also recover the enzymatic activity of HEWL [5]. THz time-domain spectroscopy was carried out for native lysozyme, aggregate of lysozyme, aggregate with resonant irradiation at amide I, and aggregate with non-resonant irradiation by the authors of [3]. The native lysozyme exhibited a higher THz absorption against the aggregate, and the mid-IR resonant irradiation increased the aggregate absorption close to the native one by the conversion of fibrous aggregate to the non-aggregate state of HEWL [3]. This indicates that THz spectrum is indicative for the conformational changes and thus the activities of the enzyme.

IV. THz time-domain spectroscopy of corneal tissues of rabbit eyes

The dielectric properties of the normal corneal tissue of rabbit eyes were measured *in vitro* in a range from approximately 0.1 to 1 THz by THz-TDS measurement by the authors of [4]. The difference in reflectance from the rabbit eye surface between normal tissues (control) and tissues exposed to high-power terahertz waves (@162 GHz) was also investigated [4]. It was verified that reflectance data calculated from the dielectric constant values and those measured *in vivo* agreed at frequencies under approximately 0.4 THz. When the rabbit eye was exposed to the terahertz waves, the average reflectance decreased significantly owing to the drying process, while the tears caused the reflectance increment. The results suggest that the complicated reflectance changes of the eye surface should be considered for the precise computational dosimetry under the high-level irradiation condition [4].

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Genome-wide mRNA-seq analysis in Human Fibroblasts exposed to 25 GHz

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***Abstract*—This study investigated gene expression modulation in human fibroblasts *in vitro* exposed to 25 GHz. For this purpose a new high-throughput RNA sequencing approach, by Next generation sequencing platform, was used.**

I. INTRODUCTION

THE increasing use of Microwave (MW) and Radiofrequency (RF) technology together with the future perspective of the fifth generation (5G) wireless communication introduction, raised questions about their possible biological and adverse health effects.

Despite several *in vitro* and *in vivo* studies have been carried out to evaluate the biological effects potentially induced by this radiation, the results are rather controversial [1, 2]. In addition to the evaluation of classical biological markers (e.g. genetic damage, cell cycle/proliferation, apoptosis), in the last decades there is a growing interest in the identification of genes that could change their expression profile following exposure to radiofrequency electromagnetic field (RF-EMF). In this research field, the most common approach to identify RF-EMF sensitive genes consist in whole genome screening methods using microarray based technology. However the few large-scale studies performed until now reported unclear results [3,4] making difficult to establish a list of common RF-EMF sensitive genes.

In this context the aim of this study was to evaluate whole gene expression modulation in human fibroblasts *in vitro* exposed to 25 GHz CW radiation [5] using the high-throughput sequencing approach through the RNA sequencing (RNA-seq) technology.

II. RESULTS

Gene expression analysis was performed by mRNA-sequencing on Illumina NextSeq 500 platform on both exposed and sham RNA samples isolated 2 and 24 hours after 20 minutes of exposure to 25 GHz. In order to increase the statistical power 4 experimental replicates were performed. To identify genes differentially expressed Cuffdiff and EdgeR analysis tools were applied on data obtained from sequencing. This analysis showed in exposed cells, some genes with differential expression profiles. After Gene Ontology terms analysis these genes resulted involved in different biological processes. However, the genes identified in this study have to be confirmed by RT-PCR, gold standard for the detection and quantification of gene expression profiling.

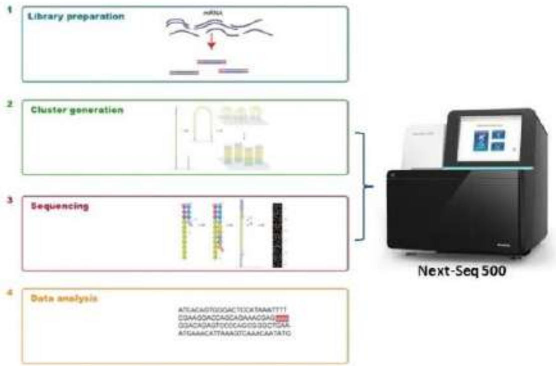

Fig.1. RNA-seq workflow including four basic steps: library preparation (1), cluster generation (2) and sequencing (3) performed on Next-Seq 500 system, and data analysis (4).

III. SUMMARY

The innovative high throughput RNA-seq technology, used in this study, overcomes the limitation of a preselected set of genes allowing the identification of known and unknown transcripts. This promising approach will contribute in the identification of sensitive genes and in understanding the underlying mechanism of possible biological responses and effects induced by RF-EMF.

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Comparison between effective medium theory models for the dielectric response of biological tissues to terahertz radiation

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***Abstract*—In this work, we empirically compare three effective medium theory models for the dielectric response of biological tissue in the terahertz range.**

I. Introduction and Background

EFFECTIVE MEDIUM THEORY (EMT) models are often used to determine the dielectric function of biological tissues in order to study their response to terahertz waves. The most used models to describe such heterogeneous dielectrics are the Maxwell-Garnett (MG), the Bruggeman (BM) and the Landau-Lifshitz-Looyenga (LLL). These three models are constructed on the grounds of some assumptions about the components of the mixture. The MG model assumes spherical inclusions in a material with relatively small dielectric function contrast; BM's model also restricts the inclusions to be spherical but allows a great contrast in the dielectric function of the components; the LLL model allows irregularly shaped inclusions but restrics the dielectric function contrast to be small [1]. In the terahertz regime, particularly in medical and biological applications, EMT is used to quantify hydration in biological tissues. However, owing to the inconsistencies between the biological tissue's components and the assumptions of the models, it is not clear which one is the most appropriate. It must be taken into account that the biological tissue is composed, to a large extent, of water whose dielectric function is much larger than that of any other component of the tissue; in addition, the shape of the components is not spherical. In this work, we obtained the dielectric function of mixtures composed of biological dry tissue and water using THz-TDS. We compare the measurements with the dielectric functions that result from the MG, BM and LLL models.

II. Results

Basil leaves were dehydrated and ground to powder. Pellets were formed to determine the dielectric function of the dry tissue component. Basil-water mixtures were prepared varying the components' volumetric fractions from 0 to 1.0 in steps of 0.1. Each mixture was measured with THz-TDS in reflection geometry and its complex dielectric function was obtained. Moreover, knowing the dielectric function of dry tissue and water [2], the theoretical dielectric function of the mixtures was obtained for the three models. The experimental data was compared with the theoretical curves.

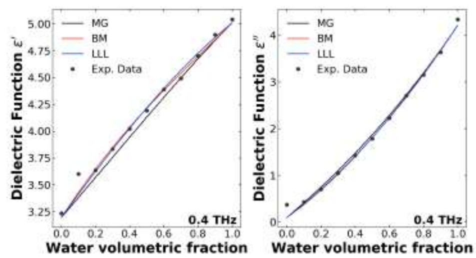

Fig. 1. Real and imaginary part of the complex dielectric function of basil-water mixture as a function of the water volumetric fraction at 0.4 THz. The solid black, red and blue lines represent the theoretical dielectric function given by the MG, BM and LLL models, respectively. The grey dots show the experimental data.

As we can see in Figure 1, the dielectric function of the experimental data coincides with the theoretical curves of the EMT models. Although, we can not see a significant difference between the three models that tell us which of them best fits the experimental data, it is possible to observe that the BM and LLL models behave in a similar way, differentiating more from the MG model. In these two models we see a greater coincidence between theoretical and experimental data. This can be due to the construction conditions. LLL does not limit the shape of the inclusions and BM allows great contrast in the dielectric function.

III. Conclusion

The results obtained in this work show that, although water and basil have a large contrast of dielectric functions, and the shape of the components is not spherical, the LLL and BM models can be properly used to determine the dielectric function of biological tissue [3].

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Terahertz perturbation of the nanoscale biomembrane landscape

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Abstract— **Interfacial water is the primary transducer of stress induced in biological membranes by electromagnetic fields. Experimental observations of neurostimulation with picosecond-duration electric pulses and picosecond-resolution molecular simulations of lipid bilayers in moderate to intense electric fields help to define the physical boundaries of potentially significant terahertz radiation-induced modifications and modulations of water-lipid and water-protein configurations in cell membrane structures and functions.**

I. INTRODUCTION

NONTHERMAL stimulation and perturbation with picosecond electric pulses and terahertz electromagnetic radiation may lead to new, minimally invasive diagnostic and therapeutic procedures and to methods for remote monitoring and analysis of biological systems – plants, animals, and humans. To optimize utilization of these tools we need an understanding of the underlying biophysical mechanisms. Sub-nanosecond (≤ 500 ps) electric pulses induce action potentials in neurons and cause calcium transients in neuroblastoma-glioma hybrid cells, and in complementary molecular dynamics simulations of phospholipid bilayers in intense electric fields membrane permeabilization occurs in less than 1 ns (Fig. 1). Water dipoles in the interior of these model membranes align in the direction of the field, responding at terahertz frequencies to field reversals. Sub-nanosecond lipid electropore formation is similar to that observed on longer time scales – energy-minimizing intrusions of interfacial water into the membrane interior and subsequent reorganization of the bilayer into hydrophilic, conductive structures. This suggests that membrane permeabilization may be the mechanism for the activation of neural cells by picosecond electric pulses.

II. RESULTS

Picosecond membrane reorganization in molecular simulations. How can this be? Since there is no hydrogen-bonded network in the intruding water fingers, the effective relaxation time is much less than it is in bulk water. The isolated water molecules that stack up in the membrane interior during pore initiation have escaped their interfacial associations. A field-stabilized water column penetrating the membrane remains a lower energy configuration for interfacial water than the planar lipid-water junction of an unperturbed bilayer regardless of the 180-degree flips of the individual molecules making up the structures.

One might expect that each picosecond reversal of the electric field direction would "undo" whatever dipole rearrangements had occurred in the preceding cycle, with no net effect, and that since the textbook water dipole relaxation time is on the order of 8 ps [1], water molecule orientation should not be affected by symmetrical electric field reversals occurring at 1 ps intervals. Molecular simulation results are contrary to these expectations. ***Stabilization of intruding water in the applied electric field*** [2] is not reversed when the field direction changes. Transbilayer water bridges grow, rather than shrink, cycle after cycle, and the phospholipid head groups follow.

Terahertz spectral signature of electroporated cells. Electroporation (electropermeabilization) increases the electrical conductivity of biological cell membranes and lowers transport barriers for normally impermeant materials. The interior of the electroporated membrane contains water, unlike the interior of an intact membrane, which should create a signature for detection of the electropermeabilized state. In a previous report, we described the use of terahertz time-domain spectroscopy to detect electroporation in human cells subjected to permeabilizing pulsed electric fields with a commercial terahertz, time-domain spectrometer [3]. We observed a higher absorption of terahertz radiation by pulse-exposed cells than in controls, consistent with the intrusion of water into the membrane into the cell through the permeabilizing structures presumed to be associated with electroporation.

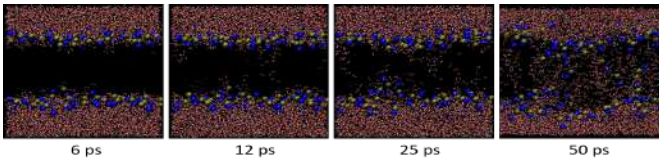

Fig. 1. Permeabilization of POPC bilayer in 500 GHz alternating electric field. Water, then phospholipid head groups bridge the membrane interior in a very high porating electric field with polarity reversals every picosecond. Multiple water bridges appear, followed by head groups, in a few tens of picoseconds.

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Session 4.1: Spectroscopy II

Erice, Sicily

Water status measurements of plants using THz spectroscopy

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***Abstract*—THz spectroscopy is well suited to study the water status of living plants. In this talk we will give an overview on the existing work and approaches.**

I. INTRODUCTION

Terahertz (THz) waves are strongly absorbed by liquid water. Therefore, THz spectroscopy is well suited to study the water status of living plants. This fact has been known for nearly 25 years, since the pioneering work of Hu and Nuss who recorded an image of a freshly cut leaf using THz time domain spectroscopy [1] and Mittleman who visualized the water uptake of a living plant [2]. A quantitative determination of the water status in living plants is desired by plant breeders as well as by plant physiologists. Here, we review the work carried out over the years highlighting a few approaches.

In the years after the first demonstrations mentioned above not much happened, except that it was shown that THz spectroscopy is fast enough to follow fast processes in plants, like e. g. the rapid leaf movements of mimosa pudica after mechanical stimulus (see Fig. 1) [3].

In 2009 Jördens and coworkes presented an electromagnetic model for plant leaves consisting of an effective medium theory which describes their permittivity at terahertz frequencies [4]. This model was later implemented in an algorithm [5].

In 2011 a photomixing based CW system was used for the first time to monitor the water status of plants [6].

The first to observe effects of dark-light cycles and abscisic acid on the water dynamics using a THz TDS system were Castro-Camus and coworkes who studied Arabidopsis thaliana [7].

Water status measurements on living plants are typically carried out over the course of days or weeks. It is not an efficient use of equipment, if a THz is occupied for such a long time, just to measure a single plant. To overcome this limitation Born and coworkers developed a THz TDS system which allows for the continuous monitoring of up to 20 plants simultaneously. By monitoring the relative change in transmission, they were able to narrow down the permanent wilting point of silver fir seedlings [8].

In 2019 Gente et al. presented a first battery operated THz quasi-time-domain spectroscopy system for continuous outdoor in vivo leaf-water monitoring [9].

Over the years also other THz sources have been employed for plant water status measurements. While Pagano et al. used terahertz quantum cascade lasers for transmission measurements [10], other groups used microwave network analysers [11,12].

Finally, an alternative approach by Gente et al. should be mentioned. They measured the scattering of 35 GHz waves from entire plants to determine the plant water status [13].

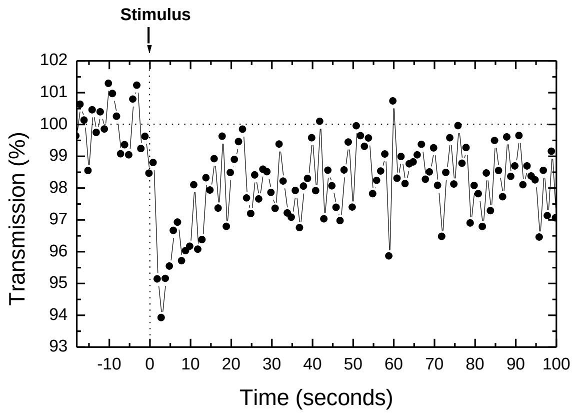

Fig. 1. THz transmission through tertiary pulvini after mechanical stimulus of mimosa pudica. From the drop in THz transmission one can conclude that there must be a net increase of turgor in the tertiary pulvini; from [3].

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Monitoring the Porosity of Pharmaceutical Tablets Using THz Frequency Domain Spectroscopy

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ONE PAGE SUMMARY NOT AVAILABLE FOR PUBLISHING

On-chip Frequency-Domain Terahertz Spectroscopy of Liquids

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***Abstract*— Terahertz spectroscopy of liquid samples is critical for analysing biomolecules in their native environment. However, the high losses due to strong water absorption can severely limit the sensitivity of the measurements. Here, we present S-parameter measurements for on-chip terahertz spectroscopy of highly lossy aqueous solutions between 0.75–1.1 THz. Results show a high signal-to-noise ratio (30 dB) compared to other on-chip methods, enabling detection of changes in complex refractive index as low as Δn = 0.02, and Δκ = 0.003 in highly lossy aqueous environments. These results prove terahertz frequency-domain spectroscopy as a sensitive on-chip method for measuring small dielectric changes in high-loss aqueous solutions up to 1.1 THz, making a step towards integrated, sensitive, and traceable measurements of biomolecules in their natural environment.**

I. Introduction

SPECTROSCOPY at terahertz (THz) frequencies has shown to be a useful method for studying biomolecular dynamics [1], in which water places a key role [2]. However, aqueous solutions present very high losses at THz frequencies (around 1000 dB/cm), which deteriorates the signal-to-noise ratio of the measurements, affecting the sensitivity [3].

A promising method for achieving higher sensitivity than traditionally used THz-TDS is S-parameter measurements using vector network analysers (VNA)—frequency-domain spectroscopy. This method is based on electronic heterodyne technique, that benefit from increased frequency resolution, and signal-to-noise ratio, at the expense of narrower bandwidth analysis. In this paper we present on-chip THz spectroscopy measurements of isopropan-2-ol/water mixtures, measured with vector network analyser, and contact probes.

II. Results

To characterise the samples, we used a planar Goubau line (PGL) integrated with a micro fluidic channel (Fig. 1). The PGL was designed to have ultra-low losses, by fabricating it on a thin—23 µm—polyethylene terephthalate substrate which avoided radiation losses by being suspended in air.

We measured the S-parameters from 0.75 THz to 1.1 THz of the 1 mm long PGL with the microfluidic channel containing isopropan-2-ol/water samples. To compute the real and imaginary part of the samples' refractive index (Fig. 2), we processed the S-parameter measurements with a recently developed general line-line method [4], and compared them to electromagnetic simulations results. The extracted refractive index shows that increases in the isopropan-2-ol concentration causes a consistent decrease in both the real and imaginary part of the samples' refractive index, as expected from the refractive index values of isopropan-2-ol and water.

The results show that on-chip THz frequency-domain spectroscopy measurements—with a typical high signal-to-noise ratio higher than 30 dB—can detect small changes of refractive index in highly lossy aqueous environments. In contrast, similar attempts using on-chip time-domain spectroscopy around 1 THz, could not resolve measurements of samples.

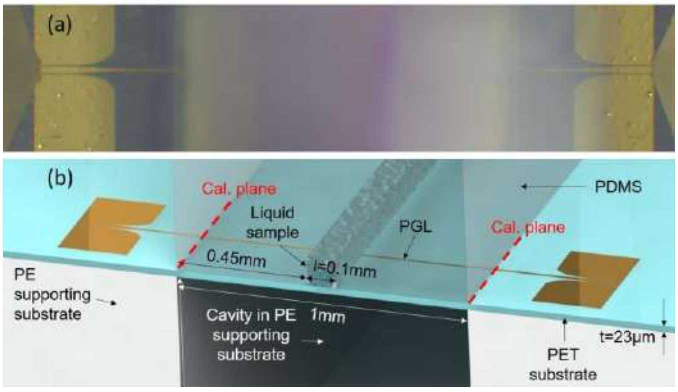

Fig. 1. (a) Micrograph of the planar Goubau lines during the sample measurements. **(b)** Sketch showing a cross-section of the PDMS microfluidic channel—containing the liquid samples—intersecting with the planar Goubau line.

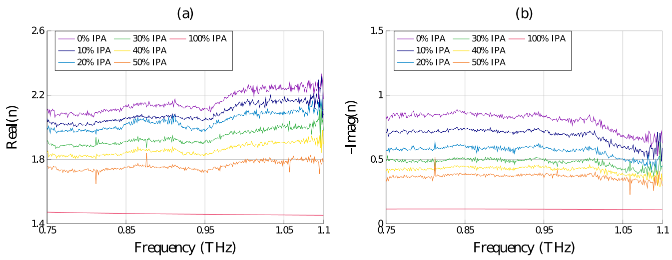

Fig. 2. The high SNR of the measurements allows detection of small refractive index differences. Measured **(a)** real and **(b)** imaginary part of the refractive index of the isopropan-2-ol/water samples. Pure isopropan-2-ol (IPA) is taken as a reference measurement.

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Terahertz radiation emission of liquid metal droplets

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***Abstract*—Terahertz radiation emission from the photoexcited metallic microdroplets was observed for the first time. We found two separated in time femtosecond pulses excitation scheme to be efficient for such targets, while signal at one-pulse excitation was negligible. Spectral and polarization properties of the emitted terahertz radiation and its dependence on delay between pulses were measured.**

***Index Terms*—terahertz radiation, femtosecond laser pulse, nonlinear optics**

Interaction of the intense femtosecond laser radiation with various media is a commonly used process to generate broadband THz pulses. The processes of THz generation in gases, especially under atmospheric pressure have been studied extensively as well as mechanisms which describe them. Earlier it was shown that transient photocurrent describes the observed phenomena well, in some cases intra-atomic non-linearities and macroscopic nonlinearity of the medium starts to play an important role. All these contributions interfere with each other constructively or destructively determining the intensity and the spectral width of the THz spectrum. In this work we demonstrate that gas pressure, phase of the medium (liquid, nano- or micro- structured) can be an additional stage of freedom under the optimisation of intensity of THz radiation.

In the third part of the work we used liquid metallic droplets as a source of THz radiation. Such droplets due to the strong extreme ultraviolet emission at 13.5 nm under ultrashort optical illumination. The process of plasma formation from these droplets has been studied in detail for different lasers. The possibility to provide fresh solid-density targets for each laser pulse leads to development of a new type of THz sources. We report the THz emission from an individual liquid droplet. THz emission has been observed from single droplets of metal, and with radii of the 56 μm. Interaction of the intense femtosecond laser radiation with various media is a commonly used process to generate broadband terahertz (THz) pulses. Usually THz generators based on solid state targets are limited by intensity due to the irreversible material damage. But it was shown that one can improve conversion efficiency with the renewable solid-density targets for the case of the gas cluster jets. In this work we studied terahertz emission from single metallic microdroplets under femtosecond beam illumination. Such targets are being actively studied as a perspective source of the extreme-UV radiation for lithography. Using a special nozzle in the vacuum chamber one can get series of the single droplets of fixed diameter, synchronized with laser pulses. Thus there was a new similar target for each laser pulse, and droplet destruction microseconds after laser-droplet interaction did not affect to the next cycle. We used Ti:Sa regenerative amplifier as the laser source for droplet photoexcitation. Two separated in time femtosecond pulses (up to 720 uJ) were focused on the Sn-In alloy microdroplet 48 um in diameter. We used bolometric detector to measure terahertz power, and utilized Michelson interferometer to get signal spectrum. For the single pulse excitation or for zero delay between pulses no signal was observed. For two-pulse excitation signal strongly depended on energy ratio and delay between pulses. Depending on second optical pulse polarization, THz polarization changed its direction and ellipticity. THz radiation spectrum was wide, its maximum lied near 1.15 THz with FWHM of 1.5 THz.

Self-Assembling of Lysozyme: Structural and Elastic Investigations

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Abstract: **The relation between structural and elastic properties of a crowded lysozyme aqueous solution is presented. Local structures of the system it has been investigated by Infrared absorption, while the viscoelastic response was explored through Transient Grating spectroscopy. A broad band THz investigation by means of time-domain spectroscopy is planned.**

One of the challenges in soft matter science is to relate the molecular interactions and the local structures with the macroscopic properties of the soft material, in particular with viscoelastic dynamic. Our results highlight the direct connection between the conformational variations of the lysozyme protein and the propagation of acoustic waves in the crowded water solution; the protein self-assembling phenomena determines several macroscopic features including the damping/velocities of elastic waves. Moreover, the environmental conditions (temperature and acidity) control the extension of molecular aggregation; from local clusters (crowed solutions) to percolating networks (hydrogel).

I. INTRODUCTION

A wide range of molecular condensed matter can be classified as Soft Matter (SM); these are characterized by a structural self-organization, which defines several macroscopic features. The relationship that exists between the molecular interactions and the environmental changes, leads to the complex behavior of SM [1]. SM based on proteins represents an even more challenging system; in particular, the globular proteins are very relevant in this topic, due to their importance in life science [2]. One of the major goal is to relate the intra- and inter-molecular interactions, that govern the structure of a single protein and its aggregates with the viscoelastic properties of the whole system. Studies of crowded protein solutions are necessary for the understanding of the physics that governs the behavior of the living systems but also in industrial and pharmaceutical fields [3]. Our work is aimed to relate the structural and viscoelastic properties of an aqueous solution of Hen Egg White Lysozyme (HEWL), at low pH and high concentration, by means of spectroscopic techniques. Indeed, the system it has been investigated by Fourier Transform Infrared (FTIR) and Heterodyne Transient Grating (HD-TG) spectroscopies [4, 5], in order to relate protein's structural features with the viscoelastic properties of the entire system. We will focus on the identification of any phonon-like resonance within HEWL hydrogels using THz Time-Domain spectroscopy.

II. RESULTS

HEWL thermal behavior it has been explored taking into account the damping rate of the acoustic wave, estimate using HD-TG measures, and the absorbance value of the Amide II signal, through FTIR spectra. Both variables trend are reported in Fig. 1 for comparison.

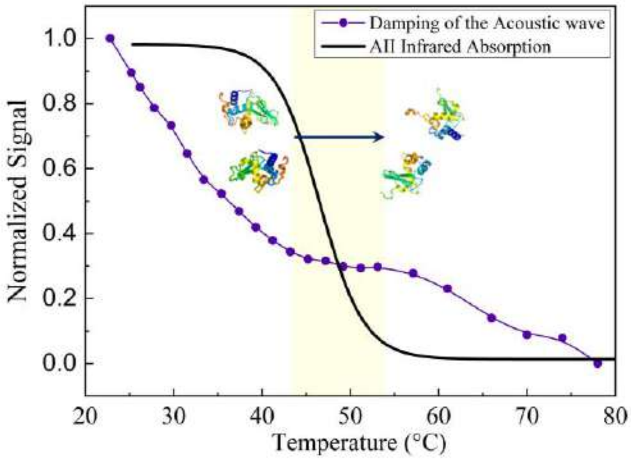

Fig. 1. Acoustic wave damping trend and Amide II absorbance trend, of a concentrated acid HEWL solution, as a function of temperature.

The trend of the acoustic damping rate with temperature shows a clear variation in the range 45-55°C. A comparison with experimental results from FTIR techniques suggests the origin of this elastic phenomenon: the transition of proteins from folded to unfolded state. In fact, the absorbance signal of the Amide II confirms that breaking of the intra-molecular bonds, i.e the proteins denaturation, takes place in an overlapping temperature range. This causes the exposition of the hydrophobic residues of protein, which modulate the aggregation phenomena.

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Poster session 04:

Imaging Technology Tech-Med

Erice, Sicily

THz Near-field Nano-imaging of Streptococcus mutans UA159

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***Abstract*—We demonstrate the THz near-field nano-imaging of alive Streptococcus mutans UA159 utilizing THz scattering near-field optical microscopy (SNOM). Here, it shows that bacteria can be distinguished from other substances by THz near-field imaging. And we can use the THz time-domain spectrometer (TDS) scattering near field microscope(s-SNOM) to obtain the spectrum of different substances (bacteria and extracellular matrix), then analyzing the differences between them from their specific responses in THz. This is of great significance to development of the terahertz near-field biology.**

I. INTRODUCTION

Scattering-type scanning near-field optical microscopy (s-SNOM) seems to be the most viable apparatus that can promises deterministic characterization of optical properties over a broad spectral range and achieve a spatial resolution at the nanoscale[1]. Most of these broadband THz s-SNOM are based on THz time-domain spectroscopy (THz-TDS)[2]. So in principle, it should be able to provide both amplitude and phase spectra in the near-field. In this experiment, a THz wave illuminates the AFM tip and samples which will leads to spatial localization of the light–matter interaction in the near-field region. After suitable discrimination from far-field background, few nanometer spatial resolution can be obtained and there are strong potential applications in biology[3].

Here, we study the characteristics of alive Streptococcus mutans UA159 in THz band by THz s-SNOM with near field nano-imaging.

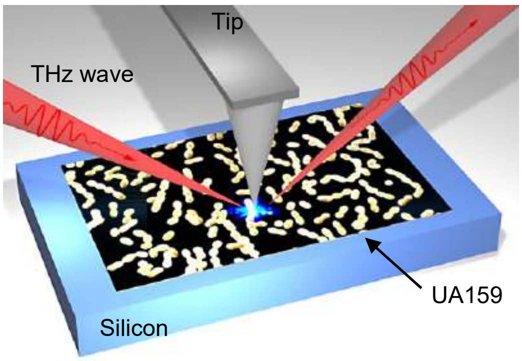

Fig.1 Schematic of THz s-SNOM. Streptococcus mutans UA159 was grown on silicon substrate. THz wave illuminates the AFM tip and samples.

II. RESULTS

Streptococcus mutans UA159 was grown on silicon substrate. Dried the sample half an hour before measurement which can ensure the bacteria alive. So we can measure the most intrinsic nature of the UA159 in the THz band. In this work, UA159 is in nitrogen atmosphere to avoid the effects of water. In our experiment, a THz wave illuminates the AFM tip and UA159 which will leads to spatial localization of the light–matter interaction in the near-field region. Then we obtained the nano-imaging of the alive UA159 as the figure.1 shows. The fig.1(a) is the surface morphology of the UA159 with atomic force microscopy (AFM) and fig.1(b) is the THz near-field imaging with a 1.6μm *10μm. From the figure.1(a), we can find that the bacteria is located at the red triangle and the extracellular matrix at the red dot. At the same time, we obtained the THz near-field imaging as the fig.1(b) shows. The darker area is the bacteria and the brighter area is the extracellular matrix. So we can distinguish the bacteria and the extracellular matrix from THz near-field imaging at the nanoscale which means a different THz near-field character or different light-matter interaction in the THz near-field.

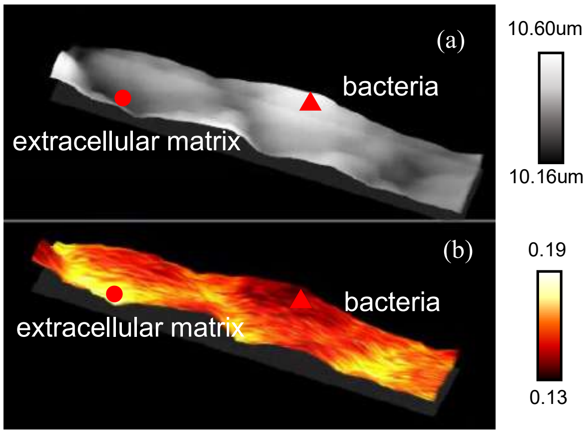

Fig.2 (a) Atomic force microscope imaging (b) THz s-SNOM near-field imaging. The imaging scanning area is 1.6μm * 10μm with 50*50 piont.

In this paper, we demonstrate the THz near-field nano-imaging of alive Streptococcus mutans UA159 utilizing THz scattering near-field optical microscopy (SNOM), which breaks the diffraction limit of THz imaging. Measuring the alive bacteria by THz s-SNOM has important prospects for the study of THz biology.

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Wide Band Compact FELs for Applications in the THz Region

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***Abstract*—The rapid advance of terahertz technologies in terms of radiation generators, systems, and scientific or industrial applications has put a particular focus on compact sources with challenging performances in terms of generated power (peak and/or average), radiation time structure, and frequency band tenability. The aim of the present communication is to demonstrate the feasibility of a Free Electron Laser (FEL) achieving performance comparable to a conventional photoconductive THz source, which is commonly used for time-domain spectroscopy (TDS), in terms of bandwidth and pulse duration. We will also demonstrate that a THz FEL could be very powerful and flexible in terms of tailoring its spectral features.**

I. Introduction

TIME domain-based terahertz (THz) sources have gained more and more attention during the past 15 or 20 years [1], and these systems are now commercially available, reliable, and easy to use. A complementary and alternative approach, based on free electron devices, is discussed in the present communication, with the final aim to project a device for high power broadband THz applications.

The proposed source exploits all the coherence mechanisms that are known in FEL devices. The first is the bunched electron beam generated by RF accelerators. Coherence is, in this case, obtained when the electron bunch length is comparable to the wavelength of the radiation to be generated by the FEL [2]. A second degree of coherence is given considering the relationship among all the electron bunches. In fact, an RF accelerator generates a train of pulses, and if the correlation among all the consecutive pulses is good, the radiation will be emitted at discrete frequencies that are harmonics of the RF [2]. A third degree of coherence can be added if we treat the bunch as a collection of particles distributed in the longitudinal phase space; when the electrons in a bunch are distributed in the longitudinal phase space following an ideal curve [3], the radiation emission, due to each particle is added in phase, maximizing the power extraction during the interaction process.

II. The Study Project

A study project has been realised for a FEL operating from 0.5-1.5 THz. The device is an evolution of the ENEA CATS experiment [4] where the role of the Phase Matching device is now taken by a double frequency RF cavity (DFC). The use of a DFC requires the second frequency to be a harmonic of the fundamental one, in order to be resonant. There are some design parameters that can be set, such as the harmonic number and the relative amplitude ratio, that contributes to the bunch length, but the most relevant is the relative phase between the fundamental and the harmonic frequencies. These parameters establish the slope of the total field in the cavity right where the electron bunch passes.

In order to design an FEL operating at THz frequencies, simulation software that is capable of evaluating several of the characteristics of FEL sources has been developed [5]. This code makes use of the electric field generated inside the DFC, which is used as a phase-matching device. The electrons accelerated by a Linac are injected into the DFC that is fed with the fundamental (3 GHz) and fifth harmonic. The simulation result is reported in Fig.1 and indicates that after the proper optimization, a power spectrum, that ranges from 0.5 to 1.5 THz, is obtained. The integrated power over the macropulse duration and over the total spectral bandwidth, of about 90 kW. It is very important to stress that with this device, due to the RF properties of the accelerator, it is possible to isolate the single harmonic still having an average power for the single frequency of the order of hundreds of watts. This is not possible with conventional THz sources. Moreover, another interesting result is that the single frequency, being a harmonic of the RF, has a temporal structure equal to that of the RF macropulse. In addition, we have to refer to the RF macropulse for its temporal coherence, which for conventional magnetrons and klystrons is usually quite good. On the other hand, if we look at the whole bandwidth, the temporal structure is the well-known train of microbunches separated by the RF period.

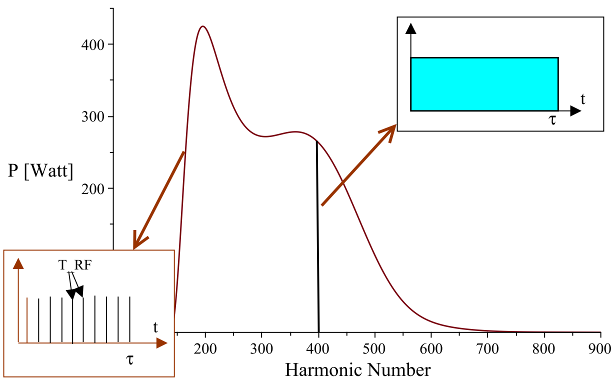

Fig. 1. Simulation of the optimized radiation power spectrum emitted as a comb of frequencies related to the harmonics of the fundamental RF (ν_{RF} = 3 GHz).

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Comparing Techniques for *in vivo* Skin Hydration Measurement

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***Abstract*—If THz imaging is to be developed as a technique for *in vivo* skin hydration assessment it is important to compare it to the gold standards presently used in the skin care industry. This study presents a comparison between THz reflected amplitude, transepidermal water loss and capacitance measurements of the volar forearm before and after treatments with common ingredients in commercial moisturizers.**

I. INTRODUCTION

THE application of THz imaging to *in vivo* measurements of human skin has been developing significantly as we grow in understanding of what variables will have an impact on the result. The strength of THz light as an *in vivo* imaging modality lies in its high sensitivity to water content however this also leads to variables which cause problems if not properly controlled or accounted for.

It has been observed that parameters such as skin occlusion time, pressure and environmental conditions must all be carefully controlled, in doing so a robust protocol for *in vivo* skin measurements using THz light has been developed [1]. This protocol was demonstrated to be successful at quantifying the changes induced in the skin following the application of a commercial moisturizer product [2].

Now THz imaging can be used to take data which is comparable between subjects the next step is to compare it to other techniques which are used within the moisturizer industry to assess skin hydration. The primary two techniques presently in use are corneometetry which measures the capacitance of the skin surface giving a result representing the hydration and the measurement of the transepidermal water loss (TEWL) which indicates the condition of the skin barrier as it measures the loss of water from the skin surface.

A study was conducted to compare the results of using these three imaging techniques to measure regions on the volar forearms of 20 subjects, these regions were measured before and after treatment with 3 different common components of moisturizers. Additionally, images were taken with a USB optical microscope device to make it possible to observe how well the skin absorbed the products being applied. Fig. 1 shows each imaging technique and also an example of the optical images obtained before and after the treatment. This study allowed the repeatability of the techniques to be compared and also the ability of the techniques to measure the contrast in the responses to different types of products.

II. RESULTS

Through previous investigations using THz devices for *in vivo* imaging it was found that when the skin is in contact with a quartz imaging window a decrease in the reflected THz amplitude can be associated with an increase in the water content as the contrast in the refractive indices at the skin quartz interface is reduced in better hydrated skin. Based on this same theory by measuring the refractive index of each of the products to be tested we can predict the expected change which will be observed in the THz response of the skin. On average the observed responses were seen to follow these predicted changes, however some variation in the responses was observed which is thought to be associated with the different initial skin states, for example drier skin does not respond in the same way to the treatment as well hydrated skin.

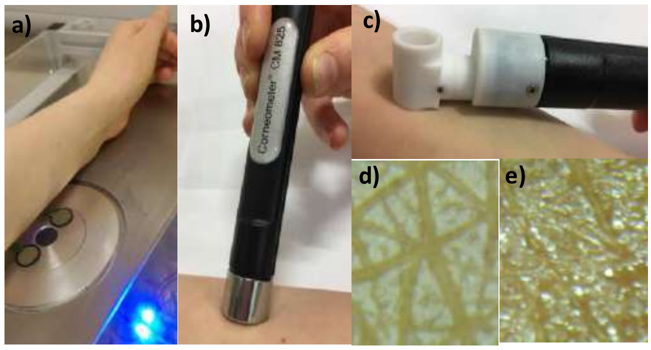

Fig. 1. A summary of the techniques used for the study. a) THz imaging with pressure sensor in place, b) corneometer, c) TEWL measurement, d) optical image of skin before treatment and e) optical image of skin after treatment.

Overall there was seen to be correlation between the reflected THz amplitude and the TEWL and these techniques were able to differentiate between products of different compositions. The corneometer measured the most significant change in the properties of the skin following the treatment however these trends could not be systematically linked to the type of product being applied. THz imaging was demonstrated to be capable of giving repeatable results for the untreated region and was successful at giving consistent trends to presently used techniques.

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Session 5.1:

Biological Effects and Biomedical Imaging I

Erice, Sicily

Biological effects of millimeter waves on neurons and related cells

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ONE PAGE SUMMARY NOT AVAILABLE FOR PUBLISHING

Terahertz diffractive structures for compact skin cancer detection setup

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***Abstract*—A set of terahertz diffractive optical structures for skin cancer diagnosis setup has been designed, optimized, manufactured and tested. Proposed iterative algorithm optimizes off-axis structures, while application of higher order kinoforms allows to maintain smallest details of the structures during manufacturing.**

I. INTRODUCTION

Terahertz radiation spectrum has been drawing researchers' attention since the last few decades, due to its specific features, comprising noninvasiveness, non-ionization, as well as high absorption and dispersion in water – the major component of biological tissues. THz radiation has been shown to be able to detect e.g. skin cancer [1]. Our ambition is to design, manufacture and verify thin diffractive optical elements (DOEs), which would allow development of compact and more applicable THz skin scanner. Utilization of off-axis DOEs is advantageous due to the possibility of sustaining small size of the focal point while significantly reducing minimal focusing distance (in opposition to on-axis diffractive lenses and refractive lenses, respectively).

We have already presented in-reflection inspection setup with plane wave to point emitter lens and point to point detector lens [2]. Further work aims at optimization of inspection setup, by applying point to point lenses on both sides and further reducing focusing lengths. In this publication we present theoretical and experimental comparison of off-axis diffractive structures for THz spectrum.

II. MANUFACTURING AND DESIGN

Elements have been manufactured using additive manufacturing (3D printing) by selective laser sintering (SLS) or using filament methods from Polyamide 12 (PA 12). So far, the main problem with these methods is the smallest thickness of the wall equal to around 0.8 mm and printing resolution of around 0.05 mm (depending on the printing method and device), which happens to be insufficient for the details of the sophisticated DOEs. Therefore, usage of higher order kinoforms (HOKs) is proposed here. Several HOKs of low order have been designed, they work for multiples of the introduced 2π phase shift (here 2π, 4π and 8π) resulting in respectively bigger details of the structures.

Design algorithm is based on propagation in the Fresnel region and iterative algorithm (similar to Gerchberg-Saxton) for optimization of off-axis structures. The algorithm converges fast and in just a few iterations the output light distribution matches well with desired one.

III. RESULTS

Performance of all manufactured structures has been experimentally verified in the setup with frequency multipliers with Schottky diodes emitting and detecting THz radiation.

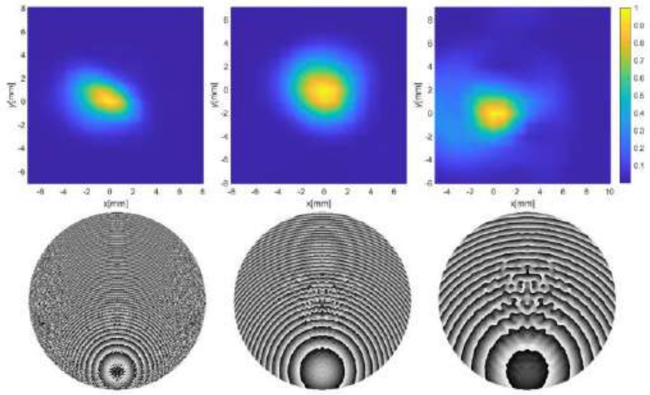

Fig. 1. Comparison of phase delay maps of 1st, 2nd and 4th order kinoforms with normalized intensity distributions in focal planes (from left to right).

Comparison of 1st (diffractive lens), 2nd and 4th order kinoforms as well as corresponding focal spots is presented in Fig. 1. Quality of focusing is improved (reduced ellipticity while maintaining dimensions of the spot), however maximal intensity reduces with the order of the HOK.

IV. SUMMARY

Off-axis diffractive lenses for THz spectral range have been designed, manufactured and tested. Applicability of higher order kinoforms has been shown, offering better manufacturing quality at the cost of increased losses induced by structure thickness. Further work aims at solving this issue by changing of the used material to the one with lower absorption coefficient. Paraffin lenses manufactured by filling 3D-printed moulds are currently considered as the most promising candidate.

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Analysis of diffusion and effects of substances applied over *stratum corneum* samples using THz imaging

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***Abstract*—We propose a three-dimensional analysis of THz normalized-intensity to study the lateral diffusion of a substance applied over tissue samples. Simultaneously, we use the model to analyze the changes in THz absorption which are related to the water content of the tissue. With this, the biological effects of the substance can also be implied.**

I. INTRODUCTION

THE development of real-time imaging methods for testing permeation, diffusion and interaction of topical drugs or substances within tissue is of interest for cosmetology and pharmaceutical research. Terahertz time domain spectroscopy (THz-TDS) is a non-invasive and real-time imaging technique with many advantages that may be used to this end.

Previously, we used THz-TDS imaging for the evaluation of moisturizing-substances effects over *stratum corneum* (SC) [1]. We presented temporal changes of normalized-intensity images obtained from the interaction of humectant substances with SC samples. From these results, we now propose to use a three dimensional analysis to measure lateral diffusion of an applied substance as well as the water-content changes in the tissue samples. The model uses a three dimensional representation of the THz normalized-intensity, as seen in Fig. 1. On one hand, the area within the width at half value of the well (white line) is related to lateral diffusion when measured at sequential times. The diffusion coefficient D of the substance within the samples can be calculated using the diffusion equation given by

$$\nabla^2 P(x,y,t) - \frac{1}{D}\frac{\partial P(x,y,t)}{\partial t} = 0. \quad [1]$$

Here, $P(x,y,t)$ is the solute concentration function. In the model, we assume that the solute is homogenous.

On the other hand, the deepness of the well is related with THz absorption and transmission, The *z* axis in fig. 1 represents changes in normalized intensity of each pixel given by

$$\Delta I_{THz} = \frac{I_{i,j} - I_{i,j,REF}}{I_{i,j,REF}} \quad [2]$$

Where I is the intensity at the pixel *(i,j)* and *REF* stands for reference measurements taken before the application of the substance over the sample [1]. Here, we note that the value of ΔI_{THz} is directly related to the absorption or transmission of the sample. This value also is proportional to water content within the samples.

II. RESULTS

We used an imaging THz-TDS in reflection mode to measure the interaction of glycerin with *ex-vivo stratum corneum* samples [1] and obtain 3D maps as shown in Fig. 1. With the previously described model we calculated the diffusion coefficient of glycerol within the samples. The obtained value was in the order of 10^{-6} cm^2/seg, corresponding to previously reported values [2]. We also confirmed that glycerol acts as an hyperosmotic agent, as reported by Smolyanskaya et al. [3]. For images taken during 30 min, we observed that the deepness of the well decreases, implying less reflection of THz radiation and thus, less water content [4]. With our results we propose a

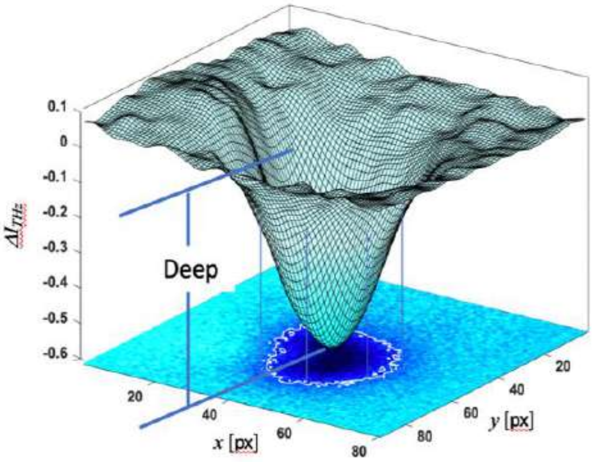

Fig. 1. Three dimensional model of the diffusion of substances and their effects in terms of water content of samples.

methodology for analysis and characterization of topical substances using imaging THz-TDS.

III. SUMMARY

We study the lateral diffusion of topical substances applied over dermal tissue as well as their effects on THz absorption using a three dimensional representation of changes of normalized THz intensity. We calculated the diffusion coefficient of glycerol in tissue and confirmed its hyperosmotic nature using the proposed model.

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Development of a 0.6 THz Reflection Microscope for Dermatology.

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***Abstract*—A terahertz microscope working at specular oblique reflection angle between 30° and 70° has been developed. The operation frequency of 0.6 THz has been selected for anomaly detection under the skin surface of dermatology patients *in vivo*.**

I. Introduction

THERE is a long-standing interest in the development of terahertz microscopy techniques for the in-vivo observation of anomalies below the skin surface. Existing optical techniques, such as epiluminescence and optical coherence tomography are based on visible and near-infrared light and, as such, can penetrate one hundred microns at most. Non-optical techniques based e.g. on ultrasounds can certainly penetrate in-depth, but a clear density-contrast mechanism for the identification of anomalies in the derma and/or in the deep layers of epidermis by ultrasound echoes is still lacking.

Terahertz radiation, in particular in the band 0.4-0.7 THz [1], can penetrate several hundreds of μm under the skin surface (depending on local hydration and structure of the skin) mainly because it is not prone to scattering by skin surface roughness [2], due to its long wavelength around 0.5 mm. The future implementation of super-resolution schemes [3] may provide terahertz microscopes with a lateral resolution of the order of 10 μm, but, in confocal arrangements [4], the image would be taken in the deep layers of the skin.

In this work we present the design, development and test of a variable-angle oblique-incidence reflection microscope operating at 0.6 THz. First results are obtained on skin simulants made of 3D-printed plastic structures embedded in a collagen gel matrix.

II. Microscope

The microscope has been assembled by buying commercial Terahertz components (source, camera and optics) and by designing and then constructing the external mechanical structure. A frequency-multiplied microwave generator (Teraschottky600 by Lytid SaS, France) has been used as the Terahertz source, tunable in the 570-630 GHz range, and capable of emitting a continuous-wave output power around 2 mW. A microbolometer camera with a bandbass filter centered at 600 GHz is employed (TZcam by i2s, France) is used in conjunction with an objective formed by two TPX lenses (by Tydex, Russia) mounted in a tube. Gold-coated parabolic mirrors (Gestione SILO, Italy) are used to focus the radiation produced by the source and emitted by a diagonal horn antenna, onto the sample. The system works at specular reflection angle, variable between 30° and 70°, by displacing both the camera and the source along arc-shaped rails (Fig. 1a). The sample is fixed and the focus is scanned via motors controlling the parabolic mirror position and orientation, as the final aim is to use the system *in-vivo*.

III. Experiment

Pure collagen from pork skin is first prepared in liquid form by dissolving solids in water. Skin simulant structures made of different hard plastic disks, with their surface patterned with a laser writer machine, are embedded into the collagen matrix up to a precisely measure height (see Fig. 1b). the collagen matrix is then let to dry for approximately 1 hour, and a gel is formed, embedding the 3D structured plastic disc.

In the experiment, the image of the reflected spot is recorded by the THz camera (Fig. 1c). The eccentricity of the spot is calculated by standard image analysis algorithms (MatLab Region Props) in order to retrieve preferential orientation of the 3D-printed structures. The thickness of the collagen film on top of the plastic disk has been kept between 100 and 600 μm, beyond the reach of epiluminescence.

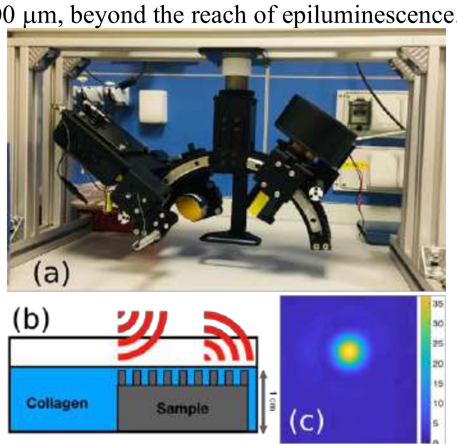

Fig. 1. (a) photograph of the assembled microscope (source with parabolic mirrors on the left arc rail, camera with lens tube on the right arc rail). (b) schematic of the skin simulant sample. (c) image of the reflected spot.

IV. Summary

A reflection microscope operating around 600 GHz at specular oblique angle has been developed. Skin simulant samples made of collagen gel matrix and plastic are under test for future dermatology applications.

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Session 5.2:

Biological Effects and Biomedical Imaging II

Erice, Sicily

Millimeter Waves in Bioelectromagnetics and Body-centric Applications

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Abstract— **Millimeter-wave technologies are considered as very promising for 5G short range communications as well as for body-centric applications including wireless sensors networks and wireless body area networks. The corresponding new usages and services will involve near-field interaction of radiating devices with the human body, both in terms of body impact on wireless device performance as well as in terms of user exposure. This presentation will provide an overview of main features and recent advances in the field of millimeter-wave technologies for biomedical electromagnetics from on-body antennas and propagation for body-centric communications to tissue-equivalent models, characterization, and advanced exposure systems for in vitro and in vivo studies.**

BODY-CENTRIC wireless networks constitute an extremely attractive next-generation wireless technology representing a cognitive interface to higher-level networks (WPAN, WLAN, WMAN, etc.). These emerging systems open new possibilities in the fields of wireless communications, remote monitoring and sensing of the human body activity, detection and localization for a great number of applications (medical, entertainment, defence, smart homes and cities, sport, etc.). They could also play a key role in wireless sensor networks (WSN) and internet of things (IoT) whose economic impact is growing exponentially. Body-centric wireless networks have emerged as an alternative or add-on to traditional wired network systems (e.g. in medical environments), and new exciting applications are now under development (e.g. high-data-rate body-to-body streaming, remote monitoring of patients at home).

The upper limit of the spectrum used for wireless networking has been recently progressively shifting towards the millimeter-wave (MMW) band due to the increasing need in network capacity and high data rates [1]. Wireless data traffic is rising exponentially (nearly a threefold increase in traffic is expected from 2018 to 2021 according to the Cisco global mobile data traffic forecast [2]). Recently, the 60 GHz band has been identified as highly promising for body-centric wireless communications including body-area network (BAN) technologies. One of the main features differentiating the 60 GHz BAN from a lower frequency BAN is confidentiality and low interference with neighboring networks, which has been demonstrated to be crucial for body-centric and inter-BAN communications [3], for instance in military scenarios where communication security is vital [4]. Limited operating range in this band (e.g. shifting the frequency from 70 / 80 GHz to 60 GHz decreases the operating range from 3 km to 400 m [5]) is mainly related to the strong oxygen-induced atmospheric attenuation (typically 16 dB/km). Besides, high data rates can be achieved [beyond several Gb/s], which is extremely attractive to support the increasing demand in data traffic and high data rate transmissions. In addition, the 60 GHz band provides other advantages, such as miniature size of antennas and sensors compared to their counterparts in the lower part of the microwave spectrum. Today, MMW circuits and antennas can be implemented with a high level integration and reasonable cost.

The implementation of 60 GHz technologies, including body-centric applications, is an unavoidable evolution of wireless networks, and first commercial solutions have already emerged for WPAN (e.g. Dell Latitude 6430u, first ultrabook using Qualcomm / Wilocity 60 GHz chipset). The 60 GHz band is unlicensed. Different spectra are allocated depending on countries (e.g. 57–66 GHz in Europe, 57–64 GHz in North America and South Korea, 59.4–62.9 GHz in Australia, 59–66 GHz in Japan [6]). Note that the available bandwidth is hundreds times higher compared to existing wireless technologies at lower microwave frequencies.

A massive deployment of wireless devices equipped with 60 GHz Tx / Rx modules is foreseen in coming years. The corresponding new usages and services will unavoidably involve coupling of radiating devices with the human body, both in terms of the body impact on wireless device performances as well as in terms of user exposure [7]. This includes the near-field interactions of wearable and mobile devices operating in the vicinity of the human body.

This presentation will provide an overview of main features and recent advances in the field of millimeter-wave technologies for biomedical electromagnetics from on-body antennas and propagation for body-centric communications to tissue-equivalent models, characterization, and advanced exposure systems for in vitro and in vivo studies.

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The sub-THz frequency behavior of human sweat ducts

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***Abstract*— Detailed studies of the human skin using optical coherence tomography (OCT) have revealed that the morphological structure of our eccrine sweat ducts is remarkably helical. These findings have raised the hypothesis that sweat ducts can be the biological equivalent of helical electromagnetic entities and hence resemble their behavior by receiving and emitting signals in the sub-THz frequency range. Here we show how this hypothesis evolved and was experimentally tested over the recent years, driven by the prospect of developing remote sensors for obtaining information about our physiological and mental state.**

I. INTRODUCTION

FOR more than 50 years there have been a number reports of non-thermal effects of extremely high frequency microwaves (MMW) on biological systems [1]. The interpretation of these phenomena has proven to be elusive. In 2008, we pioneered the hypothesis that the human skin functions as an array of low-*Q* helical antennas at the sub-THz frequencies [2]. Studies of the morphology of the skin by optical coherence tomography (OCT) revealed that the tips of the sweat ducts that expel the sweat from the gland to the pore at the surface of the skin, have a helical structure (see Figure 1) [3].

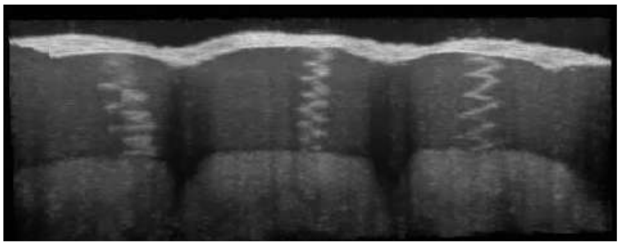

Figure 1 OCT imaging of the sweat ducts in upper epidermis of the human fingertip *in vivo* [3].

This, together with the fact that the dielectric permittivity of the dermis is higher than that of the epidermis, brings forward the assumption that, as electromagnetic entities, the sweat ducts could be regarded as imperfect passive helical antennas with both axial and normal modes. By applying basic antenna theory to the typical duct dimensions, the characteristic frequencies were found to be in the sub-THz frequency range. In this talk, we are going to summarise our findings for the last 15 years.

II. RESULTS

Experimentally we showed that the reflectance of the human skin in the sub-THz region depends on the intensity of perspiration, and correlates with levels of human stress (physical, mental and emotional) [4, 5]. Furthermore, in 2014 we detected circular dichroism in the reflectance from the skin, a signature of the axial mode of a helical antenna [6]. The full ramifications of what these findings represent in the human condition are still very unclear. Recently we have conducted a radiometric study of human emissivity around 500 GHz and 507 GHz on 32 volunteers, the preliminary results of which were reported in Ref [7]. Based on these experiments we were able to conclude that the human skin can be considered as an electromagnetic bio-metamaterial, capable of transmitting the human core black body radiation in the sub –THz range. Furthermore, the efficiency of this mechanism, reminiscent of a low-Q notch filter, is dependent on the effective ac conductivity and the morphology of the sweat duct.

III. SUMMARY

Summarizing our main accomplishments thus far, the novel effect of absorption of sub-THz radiation by human sweat ducts, which operate as low-quality-factor helical antennas was predicted, discovered, and initially studied in my lab. Our findings also indicate that electromagnetic reflectance of skin correlates with the emotional and physical human state. Recent experiments conducted by three groups of American, Japanese and British scientists confirm our conclusions in many respects [1].

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Signatures of $H_5O_2^+$ Cation Formation in Vibrational Spectra of Pigment Melanin Call for Reinterpretation of Previously Published DC Conductivity, EPR and μSR data

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***Abstract*— Water fundamentally affects properties of all biomaterials. However, in the case of pigment melanin, we encounter one of the most complex and impressive hydration-dependent behavior. Being natural polyradical material promising for bioelectronics, melanin was long believed to be an amorphous semiconductor. Later, it was clearly demonstrated that proton component is the main contributor to melanin electric conductivity. The increase of proton contribution was conjugated with the synthesis of semiquinone anion in course of hydration by means of comproportionation reaction model. It explained the general increase of conductivity caused by water adsorption. However, the model was unable to interpret the slight decrease of conductivity at intermediate values of hydration. We performed the study of hydration-dependent permittivity in terahertz (THz) and mid-infrared ranges and revealed signatures of an amusing interplay between water-based proton species in the material. Introduction of $H_5O_2^+$ cation allowed us to explain the local decrease of proton mobility and several other related observations that were previously unapprehended.**

I. INTRODUCTION

Melanin is widely used as a model biomaterial for development of organic electrochemical transistors [1], edible batteries [2], supercapacitors [3], sensors etc. Most of these applications rely on melanin's ability to be an effective proton conductor in the solid hydrated state. Therefore, the increase of mobile proton species concentration is the key necessity for melanin-based technologies [4]. Water content came into the regular focus of melanin studies only in 1996 [5-9]. The experiments with thorough hydration control demonstrated paradoxical behavior of DC conductivity [8] and μSR components [7], namely, consequent fast increase, plateau (or decrease) and increase again. Chemistry of water was limited in those studies by formal reaction of hydronium H_3O^+ formation, i.e., it was more or less absent.

Terahertz spectroscopy is a perfect tool for the study of collective dynamics in various phases including biomaterials. In combination with mid-infrared (MIR) spectroscopy, it gives us an opportunity to track behavior of water-based species and the water-induced transformations of monomers in melanin.

II. RESULTS

We have performed combined THz-MIR spectroscopic investigation of melanin films at several levels of hydration (Fig. 1). Besides the features related to transformation of melanin monomer units, in accordance with the comproportionation reaction model, we observed the distinctive signatures related to transition of dominating proton species from H_3O^+ to $H_5O_2^+$, in both THz and MIR ranges. Those were the decrease of dielectric strength (Δε) of resonance absorption upon continuous hydration corresponding to the well-known Debye feature associated with collective water dynamics [10] and the sharp growth of 3474 cm^{-1} absorption line together with the flattening of intensity for 3608 cm^{-1} peak which we associate with formation of $H_5O_2^+$ ion [11] (fig. 1). Introduction of $H_5O_2^+$ synthesis from H_3O^+ and H_2O in melanin at the definite hydration levels allows to explain the discussed peculiarities of DC conductivity [8] and μSR components behavior [7].

Proton mobility is known to be strongly slowed down by $H_5O_2^+$ formation in solid acids [12], which is rather stable ion [13]. At the same time, $H_5O_2^+$ cation can dominate among other proton species only within the definite range of ratios between water and acidic groups for particular system. Further hydration increases proton mobility [12], also in accordance with the previously published results [7, 8].

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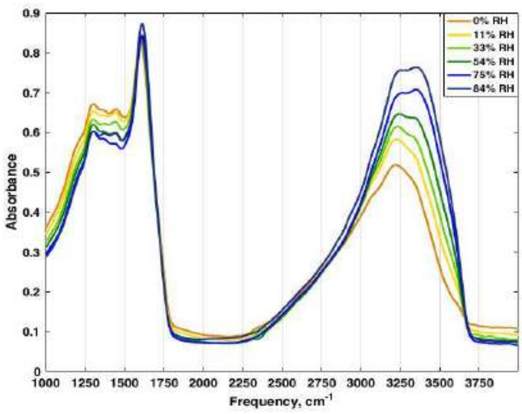

Fig. 1. Absorbance of melanin film under various conditions of relative humidity at 299 K.

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Ferroelectric and Quantum Phenomena in the Electric Dipole Lattice of Water Molecules

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***Abstract*— Water alters its properties fundamentally when confined to surfaces and pores on a nanometer scale. In the extreme case of single H_2O confined to cavities in crystals, we can study the quantum behavior and ordered phases of electric lattice formed by coupled polar molecular dipoles. In a series of broad-band spectroscopic studies of H_2O in beryl, we discovered quantum paraelectric behavior of confined water molecules. Reducing the symmetry of the nano-cavities by going from hexagonal beryl to orthorhombic cordierite results in ferroelectric order-disorder phase transition at *T*≈3 K. Calculations within density functional theory, molecular dynamics and Monte Carlo approaches provide insight into the low-temperature phase of the electric dipole lattice.**

I. INTRODUCTION

Recently, considerable attention has been devoted to the physical properties of lattice of interacting *electric* dipoles. Electrostatic coupling among the dipoles makes such systems qualitatively different from *magnetic* counterparts, yielding novel ordering phenomena. The interplay of quantum tunneling within the localizing potential, fluctuations, and possible frustration among the coupled electric dipoles could provide the possibility to realize quantum electric dipole liquids and glasses, lead to quantum critical phenomena and quantum phase transitions in the electric dipolar systems. Understanding the nature of corresponding phases is of great fundamental and technological interest but is presently still at its infancy.

An ideal playground for corresponding studies is found in dielectrics, which possess crystal lattices containing voids filled with polar water molecules that only weakly interact with surrounding ions but are strongly coupled *via* the long-range dipole-dipole interaction. Spectroscopic studies of the gemstone beryl with 0.5 nm sized pores hosting single H_2O molecules at a distance 5-10 Å allowed to discover incipient ferroelectricity within water subsystem together with a rich set of strongly anisotropic single-particle excitations at terahertz-infrared frequencies [1-4].

II. RESULTS

We have performed broadband (1 Hz up to several THz) spectroscopic investigations of vibrational states of water molecules confined to nanocages of natural crystals of cordierite. We discover [5] a strongly temperature dependent relaxational response at radiofrequencies (Fig.1) that signifies a ferroelectric order-disorder type phase transition at *T*≈3 K within the network of nanoconfined polar H_2O molecules. Computer simulations allow us to identify the low-temperature phase as composed of ferroelectric domains of H_2O dipoles within the crystallographic (*a*,*b*) planes that are altered antiferroelectrically along the *c*-axis.

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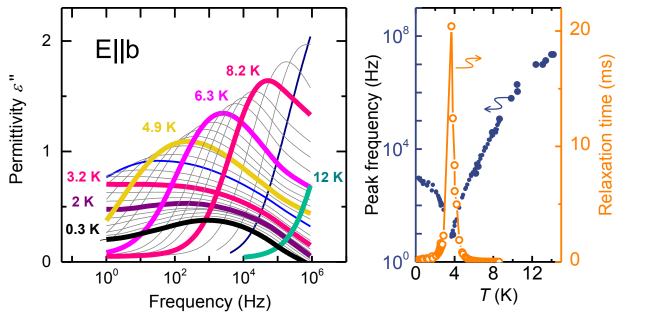

Fig. 1. Left: Radiofrequency relaxation band as a fingerprint of ferroelectric order-disorder phase transition in a network of polar water molecules confined to sub-nanometer-sized pores within crystal lattice of cordierite. Spectra are measured at different temperatures as indicated, for the polarization when electric field E is parallel to the crystallographic *b*-axis. Right: Temperature dependences of the peak frequency ν_p of the relaxation band and of the dipole relaxation time $\tau = (2\pi\nu_p)^{-1}$ indicating phase transition at *T*≈3 K.

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