Towards Brain Imaging using THz Technology

P. Bakopoulos[1], I. Karanasiou[1], P. Zakynthinos[1], N. Pleros[2], H. Avramopoulos[1], N. Uzunoglu[1]

[1] School of Electrical and Computer Engineering, National Technical University of Athens
[2] Computer Science Dept., Aristotle University of Thessaloniki

pbakop@mail.ntua.gr, ikaran@esd.ece.ntua.gr, zakynth@mail.ntua.gr, npleros@csd.auth.gr, hav@mail.ntua.gr, nuzu@esd.ece.ntua.gr

Abstract— **We demonstrate recent advances towards the development of a novel 2-D THz imaging system for brain imaging applications both at macroscopic and at biomolecule level. A frequency synthesized THz source based on Difference Frequency Generation between optical wavelengths is presented, utilizing supercontinuum generation in a highly-nonlinear optical fiber with subsequent spectral carving by means of a fiber Fabry-Perot filter. Experimental results confirm the successful generation of THz radiation in the range of 0.2-2 THz, verifying the enhanced frequency tunability properties of the proposed system. Finally, the roadmap towards capturing functional brain information by exploiting THz imaging technologies is discussed, outlining the unique advantages offered by THz frequencies and their complementarity with existing brain imaging techniques.**

***Keywords**: terahertz imaging, biomolecule "fingerprint", neural function, supercontinuum generation, Fabry-Perot filter, Difference Frequency Generation*

I. INTRODUCTION

Current and future trends in medical research aim at bridging biomolecular information and neural function through studies both in anatomic and functional biomedical imaging, integrating the rapidly advancing research fields of medical imaging/neuroimaging and molecular medicine/genetics. In this context, research has emphasized on new methods for discovering novel markers that have an influence on specific traits in psychiatric and neurological diseases, expecting to take also advantage of next generation imaging technologies that will potentially allow for monitoring of the chemical functions of the cells within these organs and produce real time images of genes and proteins at work within cells.

In this scientific and technological milieu, the widely-acknowledged "THz gap" including the complete frequency range from 100 GHz up to 30 THz makes this region of the electromagnetic spectrum a scientific frontier holding great promise not only for identifying and classifying biomolecules, but also for understanding the underlying molecular dynamics. All molecules (biological, organic, inorganic, etc) have inherent vibrational and rotational spectra that lie in the Terahertz frequency regime with spectral signatures resulting from intra- and inter-molecular interactions. Specific proteins absorb certain characteristic t-ray frequencies, which change their molecular arrangement, or conformation leading to a distinct terahertz "fingerprint" for each biomolecule; sensors can then detect this absorption revealing the identity of the protein.

To this end, THz technology can serve as a viable option for medical imaging envisaging the expansion of current knowledge on biomolecular information and its correlation with neural function. In the recent years, considerable effort has been invested in applications of the THz frequency regime (0.1 - 5 THz) in the detection and characterization of biological material focusing on their interaction with the THz radiation [1]-[5], as well as in the detection of skin cancer by means of THz imaging [6]. Nevertheless, this part of the electromagnetic spectrum remains still almost unexplored and challenging with respect to medical applications, with only scarce information on the optical characteristics of biological materials within the THz gap being available. Although differences between tissues have been already demonstrated [7], there is still only limited information available about the human tissue properties in the THz regime.

In this article, we present recent advances in the development of a novel 2-D THz imaging system and its applications in creating a database of brain tissue optical characteristics at THz frequencies, with the emphasis lying on the investigation of brain tissue samples both at macroscopic as well as at the biomolecule level. The proposed 2-D THz imaging system is capable of acquiring the absorption and phase coefficients of the specimen across a broad frequency range that extends along 0.3 to 10 THz, taking advantage of a novel frequency synthesized THz source that employs a simple frequency tuning mechanism based on spectral carving of a coherent multi-mode optical spectrum.

II. MATERIALS AND METHODS

The block diagram of the 2-D THz imaging system is shown in Fig. 1(a). A laser source generating two coherent CW (continuous wave) optical signals drives an antireflection coated GaAs dipole emitter that yields a THz beam at its output. The resulting CW THz radiation is collimated and refocused into a ZnTe crystal using two off-axis paraboloidal mirrors, whereas a pellicle beamsplitter interposed in the THz

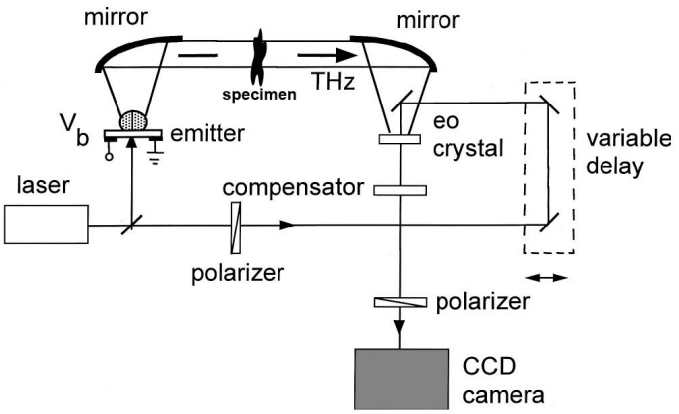

Figure 1: Block diagram of the 2-D THz imaging system.

beam line allows for co-propagation of the optical probe and THz beams through an antireflection coated electro-optic crystal. In this way, the optical probe signal is modulated in the electro-optic crystal by the THz wave leading to the upconversion of the THz beam into the optical domain. The two-dimensional intensity profile of the optical probe beam is then measured using a charge-coupled device (CCD) camera, allowing the collection of information for each image pixel simultaneously. This approach provides information about both the magnitude and phase of the THz radiation by measuring the change in optical probe beam intensity that is directly proportional to the product of the optical probe intensity, the amplitude of the THz field, and a trigonometric function that incorporates the phase of the THz field.

A key design parameter for the 2-D THz imaging system is the linewidth of the generated THz beam, as this defines the attainable resolution bandwidth of the system. Among the proposed techniques for THz generation, Difference Frequency Generation (DFG) is especially suitable for deployment in a 2-D THz imaging system as it has the potential for narrow linewidth and wide tuning range [8]. In this technique, the generated linewidth relies on the relative stability between the optical modes that create the DFG. Stable dual-wavelength operation has been demonstrated by specially-designed dual-frequency lasers [9], [10] obtaining narrow linewidth, however frequency tuning of the DFG frequency is performed mechanically while these devices often involve bulky free-space components. A simple approach to generate phase-locked optical signals is by filtering two modes from a single pulsed laser [11], which however is limited by the available bandwidth of the seed laser. In sections 2 and 3 of this paper we demonstrate a novel scheme for a DFG optical source tuneable in the range of 0.4-2 THz, with the potential to provide frequency tunability across the entire range of 0.3-10 THz.

Fig. 2(a) and (b) depict the block diagram and the experimental setup of the THz source. It comprises a dual-CW optical source and exploits the effect of DFG in the following photoconductive dipole emitter producing an electromagnetic wave at a frequency that equals the channel spacing between the two respective optical CW lines. The dual-CW optical signal is generated by employing supercontinuum generation

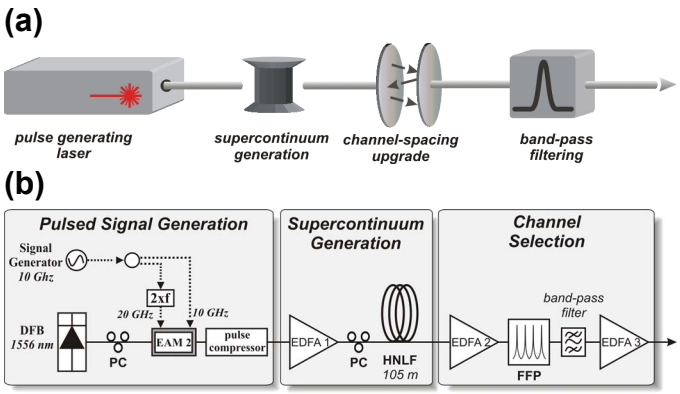

Figure 2: (a) block diagram and (b) experimental setup for the tunable DFG source. PC: polarization controller, 2xf: electronic frequency doubler.

of a short optical pulse in a highly nonlinear fiber (HNLF) with subsequent spectral carving. A CW light beam emitted at 1556.2nm by a distributed feedback laser (DFB) is injected in an Electro-Absorption modulator (EAM) that is driven by two superimposed sinusoidal electrical signals at 10 GHz and 20 GHz respectively, in order to obtain a short switching window. In this way, the EAM acts as a pulse carver producing 8ps optical pulses at 10 GHz that are launched in a nonlinear fiber compressor reducing their pulsewidth to 2.9ps. The compressed pulses are then amplified to 28.8 dBm in an Erbium-Doped Fiber Amplifier (EDFA) and enter 105m of HNLF (γ=10.5 $W^{-1}km^{-1}$, D=1.21 ps/nm/km), stimulating the effect of supercontinuum generation and resulting to a broadened optical spectrum with 10 GHz-spaced optical lines spanning across a bandwidth of more than 50nm. This spectrum is then coupled into a Fiber Fabry Perot filter (FFP) that is used for the spectral selection of the desired CW lines. By multiplying the supercontinuum generated frequency comb with the transfer function of the FFP, only the number of harmonics matching the FFP transmission peaks is selected at the output of the filter according to the general condition:

$$k \cdot FSR = n \cdot RR \quad (1)$$

with FSR denoting the Free Spectral Range of the FFP, RR the repetition rate and k, n being integers. Hence, the FFP output is a series of harmonics spaced at the required DFG frequency that equals $k \cdot FSR$, and different DFG frequencies are obtained not only by changing the FFP filter, but also by fine tuning the repetition rate of the pulsed source. Appropriate additional filtering is performed after the FFP for isolating two of the selected CW lines prior their beating at the dipole emitter.

III. RESULTS

Fig. 3 shows typical experimental results from our DFG source. The generated short pulses enter the HNLF to form a supercontinuum spectrum spanning across the entire C-band (50nm), as shown in Fig. 3(a). By using subsequent spectral filtering, two CW lines with appropriate spacing are isolated. Tuning of the DFG frequency is demonstrated by either changing the repetition rate of the pulsed source or replacing

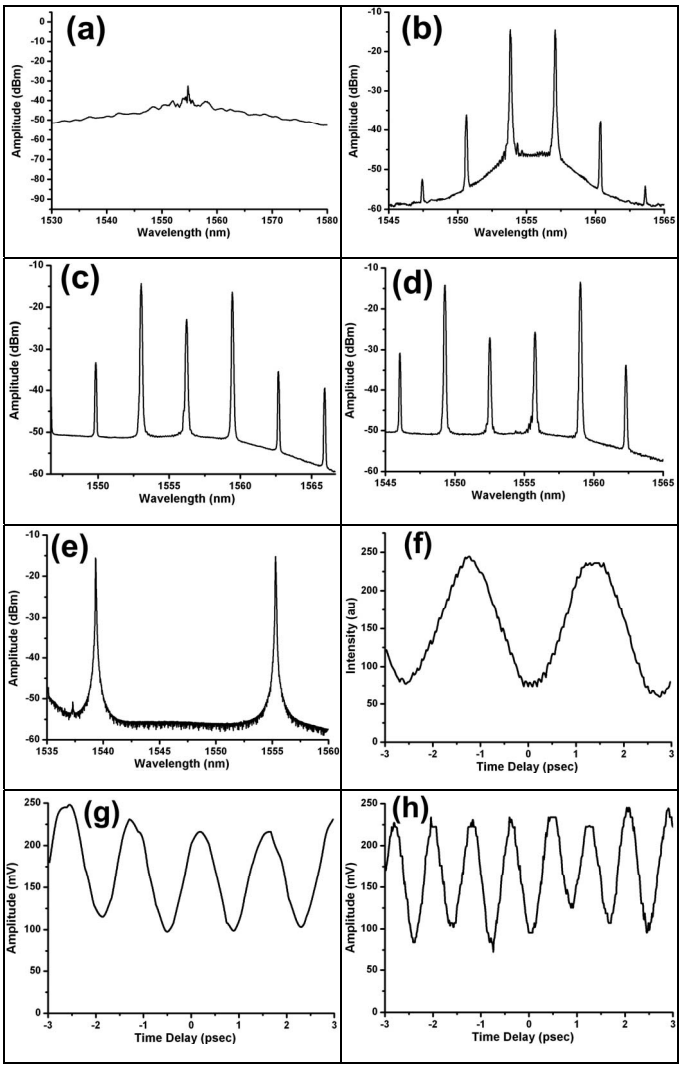

Figure 3: Experimental results. (a) supercontinuum spectrum at the output of the HNLF (span: 50nm), (b)-(e) generated optical spectra, spaced at (b) 396 GHz (span: 20 nm), (c) 792 GHz (span: 20 nm), (d) 1.188 THz (span: 20 nm), and (e) 2 THz (span: 25 nm). (f)-(h) optical autocorrelation traces of the DFG source at (f) 396 GHz, (g) 792 GHz and (h) 1.188 THz.

the FFP filter. Fig. 3 (b)-(d) show experimental results for a 396 GHz FFP filter (finesse = 1350) operating with different repetition rates. DFG signals at 396 GHz, 792 GHz or 1188 GHz are generated using the same FFP, through fine tuning the laser repetition rate according to equation (1). Larger tuning steps can be obtained by replacing the FFP with a higher FSR filter, as shown in Fig. 3 (e) where a FFP with FSR equal to 2 THz and a finesse of 500 has been employed. Output power is 15 dBm being equal to the saturation power of EDFA 3.

The demonstrated THz source relies on a modular design that employs a simple frequency tuning mechanism being entirely determined by the optical filter's resonances and can yield THz waves within a very broad frequency range with minimum adjustments. Moreover, single-mode and highly coherent THz radiation is generated taking advantage of the almost perfectly phase-locking conditions of the selected optical CW lines since they originate from the same optical source. This is confirmed by Fig. 3(f)-(h) that depict the autocorrelation traces of the 396GHz, 792 GHz and 1188 GHz DFG signals revealing highly stable waveforms.

IV. DISCUSSION

The frequency synthesized THz source comprises an important building block towards 2-D THz brain imaging. THz imaging is heralded as the next natural link in the chain of advanced biomedical imaging techniques that have led to the ability to obtain detailed structural and functional information about the human brain. Functional neuroimaging is broadly defined as the imaging techniques that provide measures of brain activity [8]. These imaging modalities measure correlates of brain activity, and aim at linking the relationship between neural activity in certain brain areas to specific mental functions; they are being used, in other words, to map localized cognitive processing. The activation of specific brain regions is related to increased local neural activity and/or increased regional cerebral blood flow, blood volume, blood oxygen content, and changes in tissue metabolite concentration [9].

Common functional imaging methodologies include Positron emission tomography (PET), single photon emission computed tomography (SPECT), functional MRI (fMRI) and functional near-infrared spectroscopic imaging (fNIRS). Also, two other techniques more directly linked to the electrical activity of neurons, electroencephalography (EEG) and magnetoencephalography (MEG), are widely used in research. Neither EEG nor MEG is a true 3D imaging modality, but comprise information that, after appropriate post-processing, provide a 3D brain mapping of the recorded data.

In view of the recent advances in functional neuroimaging, current and future trends focus on synchronous combination of imaging modalities by integrating more than one measures of brain function, e.g., hemodynamic and electrophysiological (EEG and fMRI). These multi-modal approaches aim at achieving sufficient temporal and spatial resolution in order to localize neural activity and identify the functional connectivity between different brain regions, hypothesizing that the multi-modal information represents the same neural networks [10].

Besides the impressive advancements in neuroimaging research, even more striking advances have been reported in molecular medicine research. Despite this progress, there has been relatively little integration of the two fields. In this context, current and future trends in medical research aim at bridging biomolecular information and neural function through studies in anatomic and functional biomedical imaging, focusing on methods to discover novel markers influencing specific traits in psychiatric and neurological diseases. The new field of imaging genetics uses neuroimaging methods to assess the impact of genetic variation on the human brain. Ideally, several imaging methods are used in conjunction to achieve an optimal

characterization of structural and functional parameters. The latter are statistically related to the genotype, resulting in a form of a genetic association study. This approach is still relatively novel but the emerging literature and initial results hold great promise that such procedures may lead to the identification of neural processes involved in mediating the effect of genetic polymorphisms on psychiatric disease risk, contributing to the understanding of the pathophysiology of these complex disorders [11].. Overall, it is evident that profiling of the molecular changes in disease will also expand the scope of body imaging.

Many methods exist for detecting and quantifying biomolecular interactions, but established techniques are time-consuming, and often require the use of fluorescent or radioactive labels in order to identify and quantify the analyte. However, the region between the microwave (100 GHz) and optical (30 THz) frequencies, holds great promise not only for identifying and classifying biomolecules, but also for understanding the underlying molecular dynamics.

The interaction mechanism leading to absorption in the THz frequency range in biological material is still under debate, but it seems clear that intramolecular as well as intermolecular interactions play an important role [12]. Based on spectral specificity, most chemical substances present characteristic absorption features in the THz range. Such features are almost absent under 0.3 THz. Biomolecules naturally vibrate at terahertz frequencies, and each has a distinct terahertz "fingerprint." In other words, specific proteins absorb certain characteristic t-ray frequencies, which change their molecular arrangement, or conformation; sensors can then detect this absorption to indicate the identity of the protein. However, there is very scarce information available on the optical characteristics of biological materials in the THz gap [13], [14] and in many cases, absorption coefficients were reported in arbitrary units.

Potential applications of terahertz spectroscopy include pharmaceutical development, medical imaging, and basic scientific studies of protein and DNA structure. The proposed Terahertz imaging system could be used to detect and possibly discover new brain markers related to brain functionality and neurological disease ex vivo. For example, recent findings suggest that an upset in the balance of different excitatory and inhibitory neurotransmitters, may be central to the mechanisms of bipolar disorder [15]. Analysis of post-mortem-patient samples from the dorsolateral prefrontal cortex, which controls higher cognitive processes, has shown that people with manic depression had different concentrations of chemicals in this area of the brain than healthy subjects providing valuable insights into the origins and causes of the disease.

In conclusion, the proposed THz imaging system could significantly add to the knowledge acquired through established neuroimaging techniques by defining biomolecular markers related to brain functionality and disease ex-vivo. More specifically the system will be used to 1) create a database on the optical characteristics of brain tissue in the THz gap 2) identify different concentrations of chemicals in brain areas with an emphasis on neurotransmitter levels that relate to brain function and disease.

V. ACKNOWLEDGEMENT

This research project is co-financed by E.U.-European Social Fund (80%) and the Greek Ministry of Development-GSRT (20%).

REFERENCES

[1] A. Doria, *et al.*, "THz radiation studies on biological systems at the ENEA FEL facility," Infrared Phys. Technol. 45, 339 (2004)

[2] E. Pickwell *et al*., "Simulation of terahertz pulse propagation in biological systems," Appl. Phys. Lett. 84, 2190 (2004)

[3] T. Globus, *et al*., "Sub-millimetre wave absorption spectra of artificial RNA molecules," J. Phys. D 36, 1314 (2003)

[4] D. L. Woolard, *et al.*, "Submillimeter-wave phonon modes in DNA macromolecules," Phys. Rev. E 65, 051903 (2002)

[5] S. E. Whitmire *et al*., "Protein flexibility and conformational state: A comparison of collective vibrational modes of wild-type and D96N bacteriorhodopsin," Biophys. J. 85, 1269 (2003)

[6] R. M. Woodward *et al*., "Terahertz pulsed imaging of skin cancer in the time and frequency domain," J. Biol. Phys. 29, 257 (2003)

[7] A.J. Fitzgerald *et al*., "Catalogue of Human Tissue Optical Properties at Terahertz Frequencies", *Journal of Biological Physics* 129: 123–128, 2003

[8] Brown, E.R., "THz Photomixing," Lasers and Electro-Optics Society, 2007. LEOS 2007. The 20th Annual Meeting of the IEEE , vol., no., pp.790-791, 21-25 Oct. 2007.

[9] C.S. Friedrich et. al., "New Two-Color Laser Concepts for THz Generation", Selected Topics in Quantum Electronics, IEEE Journal of , vol.14, no.2, pp.270-276, March-April. 2008.

[10] Yang, T.; Chan, K.T.; Chen, K.J.; Dong, X.Y.; Tam, H.Y., "Generation of continuous THz wave by a compact dual-frequency semiconductor laser at room temperature," Lasers and Electro-Optics Society, 2007. LEOS 2007. The 20th Annual Meeting of the IEEE , vol., no., pp.866-867, 21-25 Oct. 2007.

[11] M. D. Pelusi, H. F. Liu, D. Novak, and Y. Ogawa, "THz optical beat frequency generation from a single mode locked semiconductor laser", Appl. Phys. Lett. 71, 449 (1997).

[12] M. D'Esposito, Functional neuroimaging of cognition. Seminars in Neurology 20 (2000), 487–498

[13] A. Villringer, U. Dirnagl, Coupling of brain activity and cerebral blood flow: basis of functional neuroimaging. Cerebrovasc Brain Metab Rev 7 (1995), 240-276

[14] H. Laufs, J. Daunizeau, D.W. Carmichael, A. Kleinschmidt, Recent advances in recording electrophysiological data simultaneously with magnetic resonance imaging, Neuroimage 40 (2008), 515-528

[15] A.R. Hariri, E.M. Drabant and D.R. Weinberger, Imaging Genetics: Perspectives from Studies of Genetically Driven Variation in Serotonin Function and Corticolimbic Affective Processing, Biol. Psych. 59 (2006), 888-897

[16] Opportunities in THz Science, Report of a DOE-NSF-NIH Workshop, Ed. by M. S. Sherwin, C. A. Schmuttenmaer, and P. H. Bucksbaum, February 2004, Arlington, VA

[17] W. Smye, J. M. Chamberlain, A. J. Fitzgerald, E. Berry, The interaction between Terahertz radiation and biological tissue, Phys. Med. Biol. 46 (2001), R101-R112

[18] T.R. Globus, D.L. Woolard, T. Khromova, T.W. Crowe, M. Bykhovskaia, B.L. Gelmont, J. Hesler, A.C. Samuels, THz-Spectroscopy of Biological Molecules, J. Biol. Phys. 29 (2003), 89-100

[19] M.J., Lan, G.A. McLoughlin, J.L. Griffin, T.M. Tsang, J.T. Huang, P. Yuan, H. Manji, E. Holme, S. Bahn, Metabonomic analysis identifies molecular changes associated with the pathophysiology and drug treatment of bipolar disorder. Mol Psychiatry, [in press]