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A tunable continuous wave (CW) and short-pulse optical source for THz brain imaging applications

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Abstract
We demonstrate recent advances toward the development of a novel 2D THz imaging system for brain imaging applications both at the macroscopic and at the bimolecular 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 toward 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: THz imaging, brain imaging, difference frequency generation, supercontinuum generation

(Some figures in this article are in colour only in the electronic version)

1. Introduction

To date many methods for detecting disease or identifying the risk of developing a disease in the future rely on the detection of biomolecular interactions between a target molecule in the biological sample and a detectable probe molecule. The probe molecule, since it is related and bound to a detectable label, is typically identifiable. For instance, infection in a subject caused by an infectious agent, such as a virus, can be identified by detecting the binding of a labeled antibody probe to a viral protein.

In medical research and especially in neuroscience research, current and future trends 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 new methods for discovering novel markers that have an influence on specific traits in psychiatric and neurological diseases, expecting to also take advantage of next-generation imaging technologies that will potentially allow for the 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.

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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.

The use of single terahertz radiation to detect molecular binding events provides numerous advantages over currently available detection methods. In the case of terahertz, labels are not necessary for detection. Additionally, terahertz radiation does not cause fluorescence and therefore background levels are reduced. Another advantage of using terahertz radiation is that in order to obtain the biomolecular signature of the sample, the excitation of the sample to high energy levels which may potentially alter the molecules and their interactions, is not necessary. Finally, in terahertz spectroscopy by using low-energy radiation instead of ultraviolet, visible or near-infrared radiation, only one grating is needed to obtain a meaningful result.

In recent years, considerable effort has been invested in the development of applications of the THz frequency regime (0.1–5 THz) for the detection and characterization of biological material focusing on their interaction with THz radiation [1–5], as well as for the detection of skin cancer by means of THz imaging [6]. Nevertheless, this part of the electromagnetic spectrum still remains 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. In the existing medical imaging techniques it is possible to predict the feasibility of imaging in specific applications. This is feasible due to the availability of sufficient information about the relevant attenuation characteristics of tissue for the determination of radiation penetration and image contrast. Although differences between tissues have already been demonstrated [7–9], there is still only limited information available about the human tissue properties in the THz regime.

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

2. Materials and methods

2.1. THz imaging system

The block diagram of the 2D THz imaging system is shown in figure 1. A laser source generating two coherent CWs (continuous waves) or pulsed optical signals drives an antireflection coated GaAs dipole emitter that yields a THz beam at its output. The frequency of the resulting THz beam is determined by the spectral distance of the two beating optical waves, and can be varied by properly adjusting the spacing of the optical signals. The generated THz radiation is collimated through an off-axis paraboloidal mirror and is subsequently focused on the specimen under test. Propagation through the specimen causes the power and phase of the THz probe signal to change according to the specific tissue composition. The THz probe is subsequently refocused via two additional paraboloidal mirrors and is combined with a copy of the original THz wave before entering an antireflection-coated ZnTe 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 the 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.

2.2. Optical DFG source

A key design parameter for the 2D 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 2D THz imaging system as it has the potential for narrow linewidth and wide tuning range [10]. 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 [11, 12] obtaining narrow linewidth; however, the 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 the two modes from a single pulsed laser [13], which however is limited by the available bandwidth of the seed laser. In sections 2 and 3 we demonstrate a novel scheme for a DFG-optical source tunable in the range of 0.4–2 THz, with the potential to provide both CW and pulsed waveforms, and frequency tunability across the entire range of 0.3–10 THz.

Figure 2(*a*) depicts the block diagram of the optical part of the THz source. It consists of a dual-wavelength optical source and exploits the effect of DFG in the following photoconductive dipole emitter producing an electromagnetic

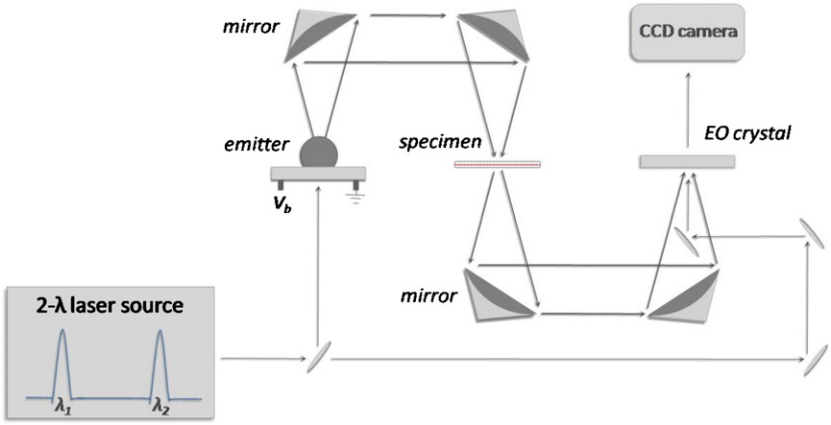

Figure 1. Block diagram of the 2D THz imaging system.

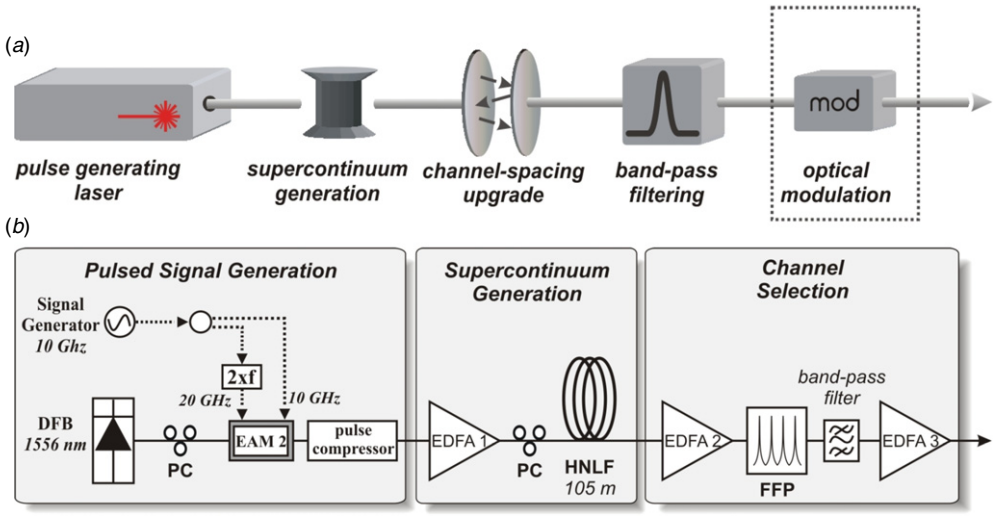

Figure 2. (*a*) Block diagram and (*b*) experimental setup for the tunable-DFG source. PC: polarization controller, 2xf: electronic frequency doubler.

wave at a frequency that equals the channel spacing between the two respective optical lines. A dual-CW optical signal is generated by employing the supercontinuum generation of a short optical pulse in a highly nonlinear fiber (HNLF) with subsequent spectral filtering [14]. The experimental setup of the optical-THz source is shown in figure 2(*b*). A CW light beam emitted at 1556.2 nm 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 8 ps optical pulses at 10 GHz, which are subsequently launched in a nonlinear fiber compressor reducing their pulsewidth to 2.9 ps. The compressed pulses are then amplified to 28.8 dBm in an erbium-doped fiber amplifier (EDFA) and enter 105 m of HNLF ($\gamma = 10.5\ \mathrm{W^{-1}\ km^{-1}}$, $D = 1.21\ \mathrm{ps\ nm^{-1}\ km^{-1}}$), stimulating the effect of supercontinuum generation and resulting in a broadened optical spectrum with 10 GHz-spaced optical lines spanning across a bandwidth of more than 50 nm. This signal 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 harmonics that match the FFP transmission peaks are selected at the output of the filter according to the general condition:

$$k \cdot \mathrm{FSR} = n \cdot \mathrm{RR}, \tag{1}$$

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 to their beating at the dipole emitter. Using this technique, a dual-CW coherent optical signal is generated with tunable frequency spacing, which enters the THz emitter to generate a frequency-tunable CW THz signal. The experimental evaluation of the DFG source in the CW mode is presented in section 3.

The proposed THz source configuration can also be utilized for the generation of a THz pulsed signal by employing an additional optical $LiNbO_3$ modulator after the optical

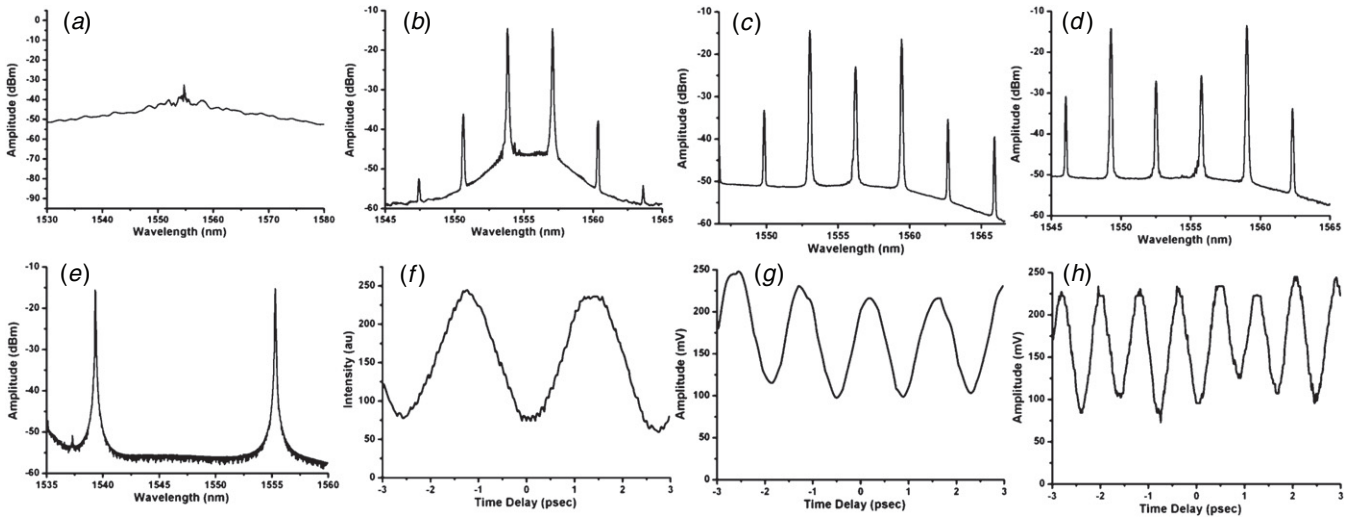

Figure 3. Experimental results. (*a*) Supercontinuum spectrum at the output of the HNLF (span: 50 nm), (*b*)–(*e*) generated optical spectra, spaced at (*b*) 396 GHz (span: 20 nm), (*c*) 792 GHz (span: 20 nm), (*d*) 1.188 THz (span: 20 nm) and (*e*) 2 THz (span: 25 nm). (*f*)–(*h*) optical autocorrelation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

bandpass filter. This is shown schematically in the dotted box in figure 2(*a*). By driving the optical modulator with an electrical pulsed signal at MHz or GHz rates, coherent optical pulses are generated on each selected CW line and their beating at the dipole emitter provides a respective THz pulsed signal at a carrier frequency equaling the optical CW signal wavelength difference. The pulsed operation of the THz source is investigated through numerical simulations in section 3.

3. Results

The optical-DFG source was experimentally evaluated in CW operation for different frequencies of the generated DFG signal. The potential of the developed source for pulsed operation was validated through numerical simulations. The obtained results are presented below.

3.1. CW operation

Figure 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 (50 nm), as shown in figure 3(*a*). By using subsequent spectral filtering, two CW lines with appropriate spacing are isolated. The tuning of the DFG frequency is obtained by either changing the repetition rate of the pulsed source or replacing the FFP filter. Both techniques for DFG frequency tuning will be demonstrated in this paper. By combining the techniques it is possible to achieve a wide range of DFG frequencies thus covering a large part of the THz spectral region with minor modifications to the setup. Figures 3(*b*)–(*d*) show experimental results for a 396 GHz FFP filter (finesse = 1350). In this case the repetition rate of the pulsed-laser source is fine-tuned within a range of 150 MHz in order to satisfy equation (1) for different values of integers k and n. DFG signals at 396 GHz, 792 GHz or 1188 GHz are thus generated using the same FFP filter. Larger tuning steps can be obtained by replacing the FFP with a higher FSR filter, as shown in figure 3(*e*), where a FFP with FSR equal to 2 THz and a finesse of 500 has been employed. 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 can be confirmed by figures 3(*f*)–(*h*) that depict the autocorrelation traces of the 396 GHz, 792 GHz and 1188 GHz DFG signals revealing highly stable waveforms. Output power in all cases is 15 dBm, being equal to the saturation power of EDFA 3.

3.2. Pulsed operation

The pulsed operation of the developed DFG source was investigated through numerical simulations. Figure 4 demonstrates the simulation results obtained with the developed model using the VPI optical simulation platform, when the THz pulsed signal generation is targeted. The source configuration as well as the signal and the component parameters used in the simulation were the same as in the experimental procedure, employing additionally a $LiNbO_3$ Mach–Zehnder modulator driven by 100 ps electrical Gaussian pulses at 1.5625 GHz and used for modulating the selected CW optical lines after exiting the bandpass filtering element, as shown in the dotted box in figure 2(*a*). The optical pulses obtained at every selected optical channel were forced to beat at the dipole emitter yielding a respective pulsed signal at a THz carrier frequency. Figure 4(*a*) shows the supercontinuum-generated optical spectrum spanning across the entire C-band and being in close agreement with the experimentally generated supercontinuum spectrum of figure 3(*a*). Figures 4(*b*)–(*d*) illustrate the filtered optical lines spaced by 396 GHz, the generated 100 ps wide pulsed signal carried at 396 GHz and its corresponding spectrum, respectively. Figures 4(*e*)–(*g*) depict the respective selected optical lines,

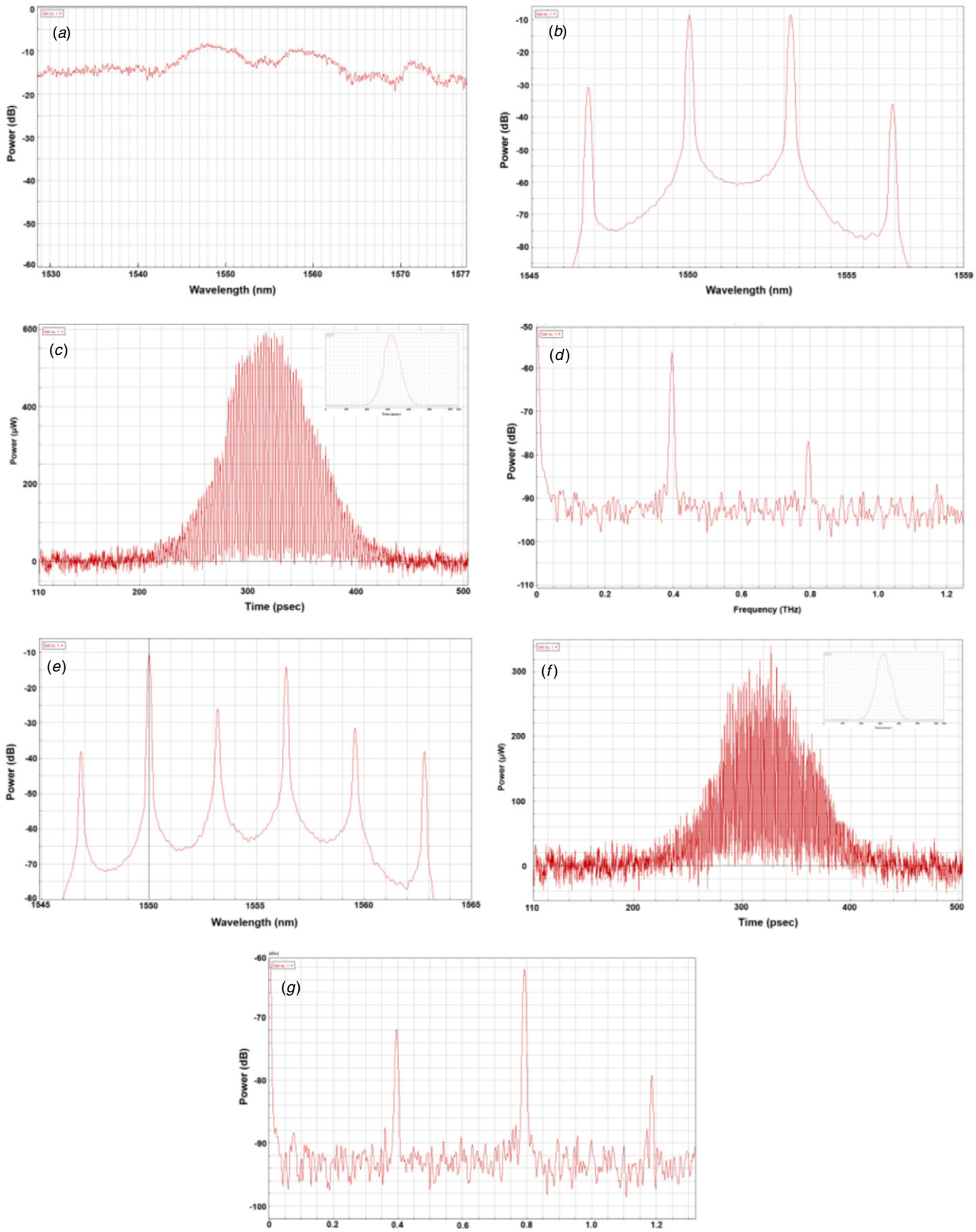

Figure 4. Simulation results. (*a*) Supercontinuum spectrum at the output of the HNLF (span: 50 nm), (*b*) generated optical spectrum spaced at 396 GHz (span: 14 nm), (*c*) generated 396 GHz pulse with the inset showing the respective initial optical pulse, (*d*) 396 GHz signal spectrum (span: 1.2 THz), (*e*) generated optical spectrum spaced at 792 GHz (span: 20 nm), (*f*) generated 792 GHz pulse with the inset showing the respective initial optical pulse and (*g*) 792 GHz signal spectrum (span: 1.3 THz).

the generated THz pulse and its corresponding spectrum when a carrier frequency of 796 GHz is targeted. The insets of figures 4(*c*) and (*f*) show the original optical pulses provided at the output of the modulator prior to their beating. 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 CW and pulsed waves within a very-broad frequency range with minimum adjustments. Moreover, the proposed THz signal generation unit exploits all the advantages provided by the mature optical technology, as it relies on well-established optical techniques and devices in order to produce even short THz pulses in the ∼ps regime. This is mainly due to the inherently strong phase-locking relationship between the optical CW lines that is retained as they propagate along the same optical path due to their supercontinuum-generated origin. To this end, the optical CW lines can be treated as independent signals as they propagate along the same optical link and are still able to provide highly coherent beating terms when entering the dipole emitter.

4. Discussion

The frequency-synthesized THz source comprises an important building block toward 2D THz spectroscopy and imaging. Using the proposed configuration, both THz CW and pulsed waves within a very broad frequency range may be generated with the employment of a simple frequency tuning mechanism. The proposed THz source offers certain advantages compared to conventional techniques for CW [15] and pulsed THz generation [16] and is expected to yield improved performance in terms of frequency resolution and frequency accuracy when applied in a THz imaging system, which will be the subject of our future work. The frequency resolution of the proposed THz imaging system is enhanced due to the narrow linewidth of the generated DFG signal which stems from the coherent nature of the beating modes, whereas frequency accuracy is defined directly by the accuracy of the electronic signal generator. In contrast, for a conventional dual-laser THz system, linewidth and frequency accuracy are limited by the instantaneous linewidth and frequency of each laser [15]. Furthermore, the frequency-synthesized THz source is based on a modular design and thus provides easy reconfigurability between the CW and the pulsed mode. THz imaging will be achieved in either the CW or pulsed modes by integrating the demonstrated optical-DFG source in the 2D THz imaging system shown in figure 1. The generated THz wave through the optical GaAs dipole emitter is collimated and focused to the diffraction limit on the biological specimen. By using digital signal processing (DSP) for real-time acquisition, processing, frequency analysis and display of the spectral data of the THz transients, the proposed THz source is expected to achieve spatial resolution in the order of one wavelength, whereas the acquisition time in CW operation will be less than 200 ms per pixel taking advantage of the long coherence length of the two optical CW frequencies [17]. When operating in the pulsed mode, the expected acquisition time will increase due to the requirement for simultaneous arrival of the THz and laser pulses at the receiver, but it is again expected to be below 300 ms. Also further optimization of the spatial resolution of our THz imaging system is feasible (i.e. submicron resolution by using a sharp metallic tip [18]).

Terahertz (THz) spectroscopic investigations of biological samples have been recently performed ranging from the simple crystalline forms of amino acids, carbohydrates and polypeptides to the more complex aqueous forms of small proteins, DNA and RNA [18]. The vibrationally resolved studies of crystalline samples have revealed the exquisite sensitivity of THz modes to crystalline order, temperature, conformational form, peptide sequence and have given unprecedented measures of the binding force constants, properties necessary to improve predictability but not readily obtainable using any other method [19]. THz spectroscopy has enhanced and extended the accessibility to intermolecular forces, length- and timescales important in biological structure and activity.

The functional imaging capabilities of terahertz radiation have also been recently illustrated through the development of T-ray computed tomography, a terahertz imaging technique that allows the reconstruction of the three-dimensional refractive index profile of weakly scattering objects. Terahertz pulse imaging is used to obtain the images of the target at multiple projection angles and the filtered backprojection algorithm enables the reconstruction of the object's frequency-dependent refractive index [20]. The frequency-dependent information may potentially be used to extract functional information from the target, to uniquely identify different materials or to diagnose medical conditions.

Based on the abovementioned, one of the aims of the present research is to create a database of brain tissue optical characteristics at THz frequencies with the emphasis lying on the investigation of brain tissue samples *ex vivo* both at macroscopic as well as at the biomolecular level. Indeed, considerable effort has been directed at further improvements in THz generation and detection technology. However, if further significant advances in the application of THz technology to biology and medicine are to be made, an improved understanding of the various mechanisms which govern interaction between THz radiation and biological tissue is required [21]. Consequently, THz imaging feasibility will be better understood and exploited through the knowledge of the optical properties of various tissues. It is worth noting that there is very scarce information available on the optical characteristics of biological materials in the THz gap [21, 22] and in many cases, absorption coefficients were reported in arbitrary units. Thus, a significant part of the research using the proposed novel 2D THz imaging system will focus on creating a database of brain (and other biological) tissue optical characteristics at THz frequencies.

Additionally, as mentioned also above, the frequency of the intramolecular skeletal vibrational and collective modes of organic crystals, including biomolecules such as saccharides and amino acids, lies in the terahertz (THz) range [23]. 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. Based on spectral specificity, most chemical substances present characteristic absorption features in the THz range. Such features are almost absent under 0.3 THz. So the second aim of the present research is to acquire indirect brain functional information through the measurement of neurotransmitters', e.g. amino acids', fingerprint at terahertz frequencies.

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 [24]. Many methods exist for detecting and quantifying biomolecular interactions, but the 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.

Data regarding brain functionality information are acquired through neuroimaging which is broadly defined as the imaging techniques that provide measures of brain activity [25]. These imaging modalities measure the 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 [26]. 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 comprises information that, after appropriate post-processing, provides a 3D brain mapping of the recorded data.

In view of the recent advances in functional neuroimaging, current and future trends focus on the synchronous combination of imaging modalities by integrating more than one measure 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 [27].

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 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 [28]. Overall, it is evident that profiling of the molecular changes in disease will also expand the scope of body imaging.

The proposed terahertz imaging system therefore could be used to detect and possibly discover new brain markers related to brain functionality and neurological disease *ex vivo*. Recent findings suggest that an upset in the balance of different excitatory and inhibitory neurotransmitters, may be central to the mechanisms of bipolar disorder [29]. The NMR spectroscopy analysis of post-mortem patient samples from the dorsolateral prefrontal cortex, which controls higher cognitive processes, has shown that people with manic depression have different concentrations of chemicals in this area of the brain than healthy subjects, providing valuable insights into the origins and causes of the disease bipolar disorder, which is a debilitating psychiatric condition characterized by alternating mania and depression, affecting about one in every hundred people worldwide. Although it is known that the condition can be treated relatively effectively using the mood-stabilizing drugs lithium and valproic acid, the reasons why these treatments work are poorly understood [29]. In parallel, the observed changes in people's metabolic signatures may give a target for drug therapy by also indicating how the mood stabilizers used to treat the disorder counteract the changes in the brain allowing us to understand how effective a drug is at correcting these changes.

Moreover, glutamate being one of the building blocks in protein synthesis, is the most widespread neurotransmitter in brain function, considered to be nature's 'brain food' by improving mental capacities. The levels of this amino acid which acts as a neurotransmitter in the central nervous system were increased in post-mortem bipolar brain tissue, but glutamate/glutamine ratios were decreased following treatment [29]. Through the identification of a distinct biochemical profile in patients with bipolar disorder, a better understanding of the origins and causes of the disease may be achieved. Moreover, at excitatory synapses, glutamate released from neurons is taken up by glial cells and converted to glutamine, which is cycled back to neurons. Alterations in this system are believed to play a role in the pathophysiology of bipolar disorder. Recent studies have identified abnormalities in glutamatergic neurotransmission and glial cell function in bipolar disorder through variations of the glutamine/glutamate

ratio [30]. THz technology may add significant knowledge to the understanding of brain function in health and disease by providing biochemical profiling of various neurotransmitters in various conditions.

Recent findings support the abovementioned (claims) aims; a novel study on the use of terahertz (THz) spectroscopy to distinguish between healthy and diseased snap-frozen tissue samples obtained from three regions of the human brain has been recently reported [31]. As protein structures have been successfully probed using THz radiation, the collective vibrational modes of protein plaques can be consequently detected in the THz frequency range. The diseased tissue samples used in the aforementioned study were neuropathologically diagnosed as containing abnormally high numbers of protein plaques consistent with Alzheimer's disease. Results showed some distinction in the THz absorption spectra between the two tissue types, which could be attributed to pathological changes in the diseased tissue [31].

Regarding the appropriate sample preparation for the intended terahertz measurements it should be mentioned that in typical measurements of THz transmittance spectra, the samples are in crystalline powder form pressed into pellets with distilled polyethylene [23]. Biomolecules, however, are generally obtained as a liquid (e.g. aqueous or serum solutions) from tissue or body fluid. In this case, alternative analytical methods applicable to biomolecules in solution may be used, such as the membrane method, in which the sample solution is dropped and dried on a polymer membrane filter before being used in terahertz spectroscopy measurements [23].

Even in the case of tissue measurements with the use of fresh thin (as opposed to preserved) tissue samples which most closely mimic *in vivo* conditions, appropriate tissue handling because of high water content will be pursued. The THz measurements of fresh tissue over time highlight the effect of tissue hydration on tissue texture and dimension, the latter directly influencing the accuracy of calculated optical properties [32]. Techniques (e.g. lyophilization (freeze drying)) as viable solutions for overcoming hydration and freshness problems will be implemented.

In conclusion, the proposed THz imaging system could add significantly to the knowledge acquired through the established neuroimaging techniques by defining the biomolecular markers related to brain functionality and disease *ex vivo*. To this end, THz imaging may be considered 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. The 2D THz imaging modality can be exploited toward creating a database on the brain tissue characteristics in the THz regime, completing the missing piece in the puzzle of brain tissue spectral signatures. Moreover, it could in principle identify the different concentrations of chemicals in brain areas with an emphasis on neurotransmitter levels that relate to brain function and disease. For both application scenarios, a THz source capable of providing both CW and pulsed waveforms across a broad spectral range facilitates the development of an integrated, fully functional imaging modality that can acquire both absorption and refractive index values.

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