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Review - 75 Years - Special Edition

Terahertz Spectroscopy Applied to Diagnostics in Public Health: A Review

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HIGHLIGHTS

- Terahertz (THz) spectroscopy may help to detect and identify proteins.
- THz has been used in clinical diagnosis of pathogens including Coronaviruses.
- Platform of THz may be used as tool for disease control and public health.

Abstract: Terahertz (THz) spectroscopy is an emerging technology that is that is bringing a number of technical breakthroughs in several scientific applications. This review aimed to describe potential applications of THz spectroscopy at the biochemistry and molecules detection for food industry, environment monitoring and diagnostics, and present the importance of such technological platform in disease control and Public Health.

Keywords: diagnosis; terahertz; covid-19; pandemics; sars-cov-2; innovation; technology; public health; spectrometry; technological platform.

INTRODUCTION

One of most interesting areas for natural phenomenon exploration may be found at the spectral Terahertz (THz) region [1]. Recently, due to unique properties of THz emission, a series of techniques have been extensively used in a variety of application. Resonance of perceptible frequency (digital impressions or signatures) of several sizes may be located at the THz frequency range, promising significative impact over different areas [2].

THz radiation is a frequency at the magnitude of 1 trillion oscillations per second. The correspondent wavelength is around few tenth of millimeter and is located at the spectrum of electromagnetic radiation between superior portion of micro-wave (wave length at millimeter range) and the inferior portion of infrared (wave length at hundredth of millimeter range) [3,4] This results in a series of optical or semi-optical proprieties (such as light) and ways of propagation/penetration near to other electromagnetic waves [5].

The THz radiation may naturally occur in our environment, as part of solar spectrum and by natural radiation at the terrestrial atmosphere. Despite such abundance, the non-ionizing character of this radiation and lack of THz practical emitters have left the biological meaning of this region of electromagnetic spectrum relatively unexplored for some time. Distinct proprieties, along with the development of new sources of THz and the broad spectrum of current application, have presented ideal conditions for the comprehension of interactions between THz radiation and biomolecules [6].

The electromagnetic spectrum region, with wave frequencies located between approximately 300 GHz and 10THz (Table 1), has an intriguing characteristic that semiconductors, such as transistors and lasers that generate radiation at frequencies above and below this range, respectively [7]. This range named by TeraHertz GAP range had considerable advances in the last decade in equipment development, which allowed to envision a wide field application.

Table 1. Comparison of electromagnetic wavelengths and radiation source

Electromagnetic Spectrum Region	Frequency Range (HZ)	Radiation Source
Radio Waves	< $3{,}0 \times 10^9$	Electronic
Micro-waves	$3{,}0 \times 10^9$ a 300×10^9	
TeraHertz Gap	**300×10^9 a 10×10^{12} or 300 GHz a 10 THz**	**Optoelectronic**
Infrared	10×10^{12} a $4{,}3 \times 10^{14}$	Optical
Visible	$4{,}3 \times 10^{14}$ a $7{,}5 \times 10^{14}$	

The applications of TeraHertz technology large-scale have been restricted and represents a challenge to scientists [8]. THz optoelectronic techniques may be a necessary to THz components and systems due to potential of generation and detection of reasonable THz signals. Different optoelectronic tools may be contributed to optoelectronic compact THz systems development for THZ imaging and spectroscopy with decreased size and price [9].

The usually THz radiation sources used comprise: a) harmonic multipliers of tunable microwave sources, b) vacuum electronics c) supercontinua generated by ultrafast lasers and photoconductive switches, and c) difference-frequency mixing of tunable continuous-wave lasers [8]. Recent studies have shown different sources to THz radiation, for example: a) air plasma [10]; b) spintronic next-generation ultra-wideband [11]; and c) Gas-phase molecular laser [8].

Different spectrometry techniques may acquire data from samples of different levels, leading to complex spectral data. Hidden information in such data may be used in a combination with algorithms of efficient modeling. The algorithm of modeling is a method of rapid development which may extract the information characteristics, classify, and characterize them in an efficient form. With the rapid development of algorithm, more studies focusing on the implementation of object detection, classification of images and other fields of computational vision [12].

Applications on food industry and environment

Due to described characteristics, identification of molecules through identification of THz waves has been shown to be innovative and promising, highly explored at the food industry, for example. Terahertz (THz) spectroscopy has been used to identify proteins in processed food, once heating may affect in extractability of proteins in molecular extraction techniques [13]. Terahertz absorption spectroscopy was successfully used in qualitative analysis to differentiate three isomers trehalose, a nonreducing sugar extensively of food industry [14].

One of first applications using THz spectrometry has happen in the identification of fecundated eggs immediately following chicken laying, due to its conformational alterations, allowing significative savings on industry costs [15]. Other potential use of THz spectrometry is the monitoring and quantification of carbohydrate molecules in plants by identifying a peak at the THz spectrum related to this carbohydrate. Transgenic rice seeds may be identified with an excellent assurance rate due to conformational alterations of their carbohydrate molecules [16]. In addition, THz may be capable to determine water status of plants under drought conditions [17].

Another application of THz methodology is the environmental control. Water and sewer are an important concern for public health. Several harmful microoganism may pollute different water sources and related species need a disinfectant able to remove them from the contaminated water. Some studies have shown the utilization of nanoparticles rich in magnesium or zinc with inhibitory effect in such microbiota. Same studies have indicated the possibility of identifying these nanoparticles in water, by THz radiation, applied to quality control [18]. In a recent study, THz has shown efficiency to measure several lipids synthesize by *Scenedesmus obliquus* microalgae, a renewable source of biodiesel [19].

Applications in Biomedicine and Diagnostics

The number of THz applications in biological and medical fields has significantly raised in recent years due to its unprecedent sensitivity to the content of water in animal tissues [20]. Experimental study has shown that THz irradiation may increase sperm motility associated to intracellular calcium concentration. This result highlights THz as a potential reproductive technology to improve *in vitro* sperm activity [21].

The first studies at the THz region about the contrast between healthy and sick tissues have focused on alterations related to such content (essential to healthy tissues) [22]. Measurements of water concentration in several samples applying THz have been already described, showing promising results with precise analysis of water contents [2].

Besides, this technique is non-invasive and totally harmless for living organisms, once THz has around three magnitude orders (less energy than necessary for ionization) which majority of spectroscopy sources in the time domain of THz [20].

However, not only water may cause the observed differences in refraction indexes. Molecular structural changes potentially present in sick tissue have been described and may affect the THz response. For example, methylated DNA, early found in cancer tissue, may give a distinct resonance in the THz reading [22]. For that reason, in biology and medicine, such sources of THz low frequency are widely applied for conformational investigations, molecular changes, chemical reaction, and many other applications [1].

The THz technology has significantly improved in recent years, in a way that THz image has become more accessible and easier to use, with a growing interest in biomedical applications [22]. In an experimental study, THz has been used to measure homocysteine, and has shown higher accuracy when compared to laser Raman spectrum for concentration detection, the reference method to determine pathological disease stage associated to homocysteine in human plasma and urine [23]. In addition, a recent study has endorsed the quantitative and real-time identification of homocysteine in human liquid by terahertz spectroscopy [24].

Oncological diagnosis

Cancer biomarkers have played a significative role in providing information for specific diagnosis. Particularly, carcinogenesis may cause chemical products and structural changes in cell DNA, and detection of such alterations would be important to identify tumors. Several research groups have characterized the spectral properties of DNA at the range of THz frequency [25]. In such way, regulation of genic expression may be closely related to carcinogenesis, reason of which, at the DNA evaluation, metilation may be a key factor on cancer research. Since there is a characteristic frequency of metilated DNA at THz region, radiation THz may play an important role on metilation activity for cancer therapy [26].

THz waves can directly detect changes on mutilated DNA because characteristic energies are on same frequency region. Besides, levels of THz energy are not high enough to damage DNA by ionization, as previously described [25]. These properties enable THz waves to be adequately use in non-invasive biomedical images for cancer diagnosis [3,4].

The THz imaging has been suggested for identification of skin burning and cancer. Studies have demonstrated influence of concentration and distribution of melanosomes and melanin on skin at the spectroscopic proprieties of THz [27].

THz technology has been rapidly developed and applied to “label-free” diagnosis of malignant diseases with different classifications and locations, in other words, detection without requirement of any compound or enzyme marker. They provide the capacity of detecting a tissue tumor in picoseconds, and the depth of probing in tissues is on microns, with spatial resolution in inferior scale than millimeters. Some studies have demonstrated such diagnostic methodology in glioma surgeries, pointing out the potential advantage of THz diagnosis on this type of cerebral intra-operatory spectroscopy [28]. Based on Guidelines of the American Society for Radiation Oncology, an evaluation technique of efficient margin need not only to detect cancer at the surgical rim of tissue, but also detect wider margin width that may significantly reduce the recurrence risk. Images of THz spectral potence and tomographic images have shown a good qualitative comparison with pathological approach. Results have been successfully evaluated with pathology images, showing strong differentiation between carcinogenic and health tissues for all recently excised tissues [29,30].

Due to use of THz waves in intra-operatory spectrometry, that is, directly on the patient tissue, concerns with biological safety and potential biological applications have been growing, as effects and influences of THz waves were not well established in living organisms [31]. THz waves can be easily absorbed by polar molecules, leading to tissue warmness and production of perceptible thermic effects [31]. However, THz spectroscopy may present high sensitivity to chemical changes in biological molecules, even without causing ionization and considerably minimizing this risk. In such scenario, cancer diagnosis by THz has been attracting high attention, particularly because the THz technique can distinguish the normal from abnormal tissues by spectroscopic images [3,32].

Bacteriological diagnosis

Fast diagnosis of bacterial infections remains a big challenge for medicine. Despite availability of antibiotics, bacterial infections have caused significant worldwide mortality. The main cause of mortality has been considered the late identification of infection source, which leads to inadequate medical treatment [33]. Majority of techniques for microbial detection has required pre-treatment such as fluorescence and culture processes. Thus, new tools for microorganism classification and identification, such as mold, yeast, and bacteria, with basis in their THz frequencies, have been developed and established [34].

THz signals with wavelength of approximately 300 µm (microns) provide a good balance between penetration, deepness and spatial resolution in biological applications, which can identify biological molecules such as water, CO_2, glucose, yeast, proteins, oligonucleotides, viruses and bacteria [33].

Bacteria involved in infections can be identified due to changes in water content of infected tissues [22]. Moreover, charge transportation has been one of the most important phenomena which guarantee the function of biological systems. Extracellular filaments, part of several electrogenic bacteria, may be able to transmit electrons through surprising distances, and which can be identified by THz radiation [35].

Advanced medical tools for bacterial detection would easier the decision making on more individualized therapies, and the THz spectroscopy has recently shown itself as potential method for detection with advances related to characterization of bacterial components [33].

Virological diagnosis

Besides not invasive, the non-ionizing proprieties of THz radiation allow that the technique may be utilized as spectroscopy for even more complex structures. In protein, particularly, the conformational information plays an important role in the molecular interactions that can be analyzed by THz.

As candidate for a fast detection of biomaterials, the system of THz spectroscopy can be considered with an advantage due to its “label-free” diagnostic method. Since the protein spectrum is in the terahertz reading region, the most important conformational information in molecular interactions can be captured [36].

Due to the spatial position of THz range in the electromagnetic spectrum, THz waves are transitory and have high penetration, broadband, coherence and low energy, and can detect the majority of biomolecules such as DNA, RNA and other viral proteins [15].

Virus detection and identification have been of high interest due to their association with severe diseases. In last decades, several detection techniques of viruses including Polymerase Chain Reaction (PCR) and Reverse Transcription PCR (RT-PCR) for identification of DNA and RNA, respectively, have been developed and established. Despite historically very useful, these techniques have been considered fastidious and laborious, and new technologies may allow non-invasive, rapid, and sensitive detection [37].

The effect of THz radiation is specific of gene and exposition, and most likely, occurs at the level of transcription of DNA in RNA. In such context, by computer simulation, the modeling algorithm has shown that prone of DNA promoter, at the transcription moment, is likely one of subjacent factors to the specific gene response to the conditions of applied irradiation [6].

Possibility of virus detection by THz has been demonstrated for causative agents of Influenza H1N1, H5N2 e H9N2, utilizing an experimental configuration of equipment. Another possibility is the detection of Zika virus by THz spectroscopy, also using experimental configuration of equipment. Spectroscopy of THz reflection can be used to detect designed viruses or aptamers designed for reaching the capsid proteins. Aptamers are designed oligonucleotides directed to bind to a specific molecule, tissue, biomarker, or pathogen [38,39].

Flu virus have been characterized by two types of carried surface antigens, hemagglutinin (HA) and neuraminidase (NA), such as H1N1, H5N2 and H9N2. HA is the main surface glycoprotein of influenza A virus, which of subtype H9N2 has been recognized as the most likely pandemic strain, crossing host species barrier and infecting swine and human beings. The THz spectroscopy has been applied to assess the formation of hydration layer around the protein HA of virus [40].

Despite the above reports, few THz studies to date have addressed the diagnosis of virus. Detection of these microorganisms can be a challenge because their frequencies and waves are smaller than the THz wavelength. However, by algorithms of modeling and metamaterials capable of manipulate electromagnetic waves, further studies may be promising [37].

Potential application on SARS-CoV-2 diagnosis

In addition to the other applications described herein, there is a possibility of applying THz diagnostic methodology, including its use in worldwide crise moments as the current pandemics. The COVID-19 may emphasize the importance of careful use of financial and human resources, which may be particularly crucial in Public Health. A good organization and preventive approach must be mandatory [41,42].

The initial cases of the COVID-19 occurred in Wuhan, province of Hubei, China, between December 2019 to January 2020. The World Health Organization (WHO) announced on January 31st the outbreak of COVID-19 in China as a public health emergency of international interest, which was characterized as pandemic on March 11th. The causative virus of COVID-19, SARS-CoV-2, was isolated in January 2020 and identified as a member of β-CoVs [42,43]. The USA has classified the pandemic as national emergency on March 14th, 2020. The virus fast spreading in China and Italy rapidly overcame hospitalization capacity. Due to the uncertainty on the number of SARS-CoV-2 infected persons, mostly asymptomatic, it is hard to evaluate the precision of projections generated by complex epidemiological models [42].

In Brazil, cases increase daily and state most affected is São Paulo, also the most populous. Until April 14, 2020, the mortality rate was 1.361/23.955 (5,68%) [44].

Non diagnosed COVID-19 cases have been a concern on the midst of pandemic and lack of supplies in quantity and quality for RT-PCR. In certain moments, due to shortage of products, pandemic could be monitored only by increase of pneumonia cases at the Intensive Care Units (UCI) at reference hospitals of affected cities [45]. Isolation of cases and tracking of recent contacts, which has been used to control outbreaks of infectious diseases for centuries, was also used at the COVID-19 pandemics. Transmission prior to symptoms onset only could be avoided by monitoring of previous contacts of confirmed cases by diagnostic tests. Infected persons without hospital attendance, likely due to subclinical infection, has been the biggest challenge of COVID-19 practically unstoppable spreading [46].

Studies have suggested that most patients may develop antibodies only at the second week following the initial clinical onset. Thus, COVID-19 diagnosis based on antibody detection by serology may be possible only on clinical recovery phase, sometimes to late for early clinical intervention or transmission interruption. At this point, based on available data to date, the WHO has not recommended the use of rapid serological tests on clinical practice, and encourage the continuing work to identify its usefulness in epidemiological surveillance studies [47].

A high precision diagnostic test for SARS-CoV-2 infection has been necessary to guide a fast action for auto-isolation and early clinical treatment. Testing would also guide decision making on recent contact tracking, therapies for COVID-19 or alternative treatment for negative results, and monitoring of impact of such interventions on public health and directing results of research, such as drug efficacy [48].

The COVID-19 has treated general population, despite asymptomatic cases, due to disease complications and death in some patients. Pneumonia associated to ventilator (PAV) has been a nosocomial infection occurring at the intensive care unit and its diagnostic pattern has been based in clinical criteria and bronchoalveolar lavage. Analysis of exhaled air has been a promising non-invasive method for rapid diagnosis of such pneumonias, as comprise exogen and endogen volatile organic contents (VOCs) which can differentiate sick from health individuals. Captured VOCs in desorption tubes can be measured by gas chromatography and mass spectrometry [49,50].

As the symptoms and signals of COVID-19 have been similar to several other common febrile and respiratory diseases, patient surveillance and management rely on precise diagnostic tests [48]. Analysis of THz waves could be utilized on VOC measurements in SARS-CoV-2 infected patients, as the technique has been already used in other medical applications and diagnosis, as described above. Breathing could be easily and rapidly sampled with the necessary frequency, with a possible measurement, as previously indicated [49]. In the absence of potential successful interventions, a key metric for success of social distancing would be better for a effective epidemiological surveillance [51].

CONCLUSION

This review work, the most recent advances in research on THz technology and its applications were briefly presented, focusing on new studies related to diagnosis. There is a great effort by the international scientific community to better explore the potentialities of THz technology, generating innovations and applications practices. The promising future of THz technology involves great challenges, but the potential for generating knowledge, new products and applications is equally great. In addition, the introduction of THz technology as a diagnostic platform in research institutes can provide viable and rapid results for public health treatments, such as diagnosis of rare diseases, cancer, antibiotic resistant bacteria and many others. Finally, Research Institutes must establish THz spectrometry as technological platforms for the development of emergency solutions, providing solutions that would be crucial in pandemic situations.

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