Terahertz Spectroscopy Brings a New Dawn of Biological Research

White Paper

by

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2/8/2008

Terahertz Radiation

The 'terahertz gap' encompasses frequencies from ~0.3 THz to ~10 THz (Fig. 1) in the electromagnetic spectrum, lying between microwave and infrared. The radiation (T-Ray) in this band is invisible to the naked eye. Unlike X-ray, terahertz radiation is intrinsically safe, non-destructive and non-invasive. It creates a powerful spectroscopic and imaging technique for characterizing molecular structures. Terahertz spectroscopy enables 3D imaging of structures and materials, and the measurement of the unique spectral fingerprints of different chemical and physical forms.

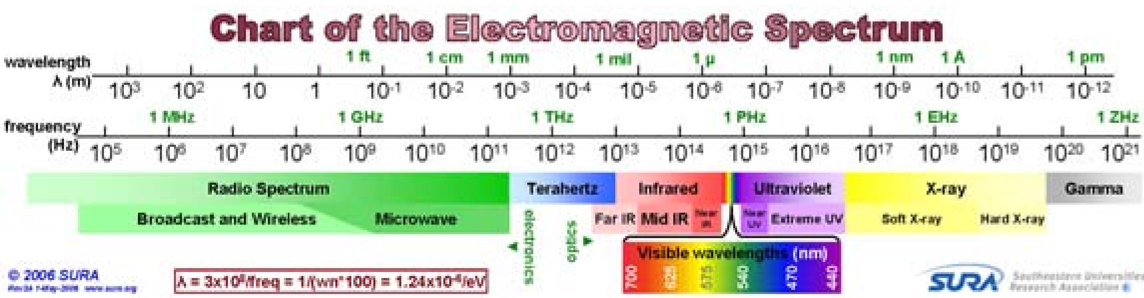

Fig. 1. The terahertz gap on the electromagnetic spectrum (courtesy of SURA).

ARP is the first company to develop a dendrimer based high power terahertz source and spectroscopy technologies which exploit the terahertz radiation, the unexplored region of the electromagnetic spectrum. Our patent pending terahertz technology creates spectroscopic information with unique spectroscopic signatures not found at other wavelengths. It resolves many of the questions left unanswered by complementary techniques, such as optical imaging, Raman and infrared. Terahertz technology also produces faster results than X-ray and in the pharmaceutical industry enables non-destructive, internal, chemical analysis of tablets, capsules and other dosage forms.

Terahertz radiation has a few remarkable properties. Many common materials and living tissues are semi-transparent and have 'Terahertz fingerprints', permitting them to be imaged, identified, and analyzed. Moreover, the non-ionizing properties of Terahertz radiation are inherently safe for screening application. These unique properties were unexploited up until a few years ago because there were no commercial sources of terahertz radiation. ARP has recently filed patent applications for a relatively high power terahertz source made from a polymeric nanomaterial called dendrimer. Combined with this proprietary technology, ARP's experience and patent portfolio offer new opportunities to the biological and pharmaceutical industry for research, development and manufacture.

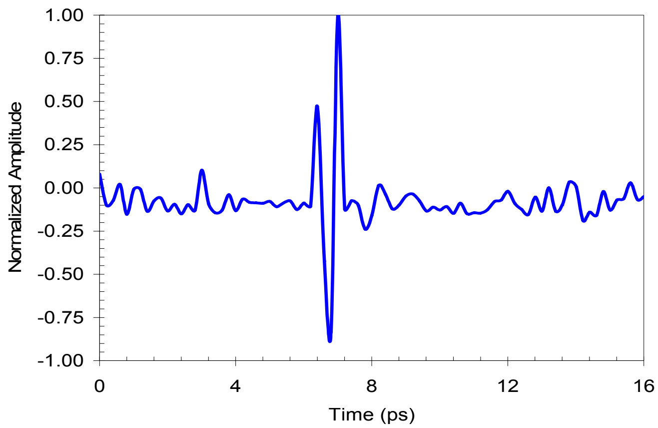

Fig. 1. A typical pulse of terahertz radiation obtained from ARP's dendrimer source. © 2007, ARP Inc.

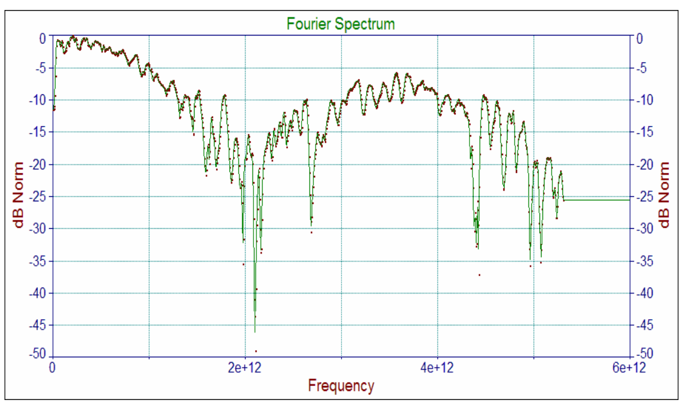

Fig. 2. Typical terahertz spectrum obtained via Fourier transform spans over 5.5 THz from ARP's terahertz source. © 2007, ARP Inc.

Terahertz Applications

A few important applications are briefly discussed below.

1. Molecular Structure

The sensitivity and specificity of Terahertz spectroscopy to both intermolecular and intramolecular vibrations in different chemical species enable investigation of the crystalline state of drugs e.g. polymorphism. The use of pulsed terahertz imaging in proteomics and drug discovery determines protein 3D structure, folding and characterization. Additionally it is very sensitive to DNA hybridization and other interactions.

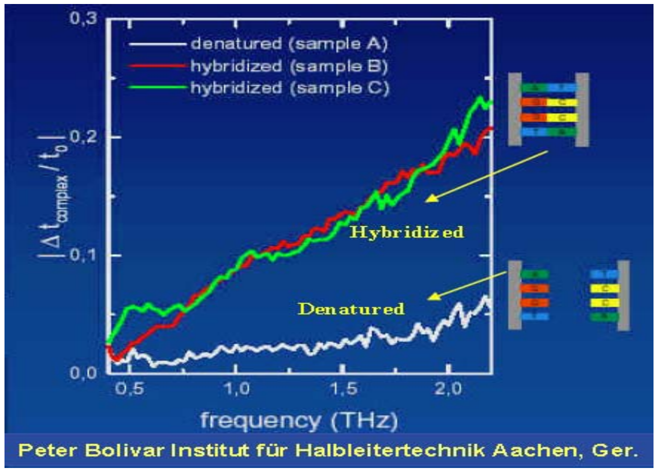

Fig. 3. Comparison of terahertz spectra through hybridized (annealed) and denatured (melted) samples of DNA. Adapted from M. Brucherseifer, M. Nagel, P. H. Boliver, H. Kurtz, A. Bosserhoff, and R. Buttner, 2nd EMBS/BMES Conf., Houston, TX, Oct. 23–26, 2002, pp2331.

Terahertz spectroscopy provides rapid identification of the different crystalline forms of drug molecules – the polymorphs – which can display different solubilities, stabilities and bioavailability and therefore are an important factor in the therapeutic efficacy of a drug. Detecting and identifying the different polymorphs and understanding the mechanism and dynamics of polymorphic inter-conversion, is an important milestone in selecting the optimum form for further development and manufacture. Not only is it possible to detect the differences between pure specimens of the polymorphs but terahertz spectroscopy can distinguish between specific polymorphic forms in the tablet formulation.

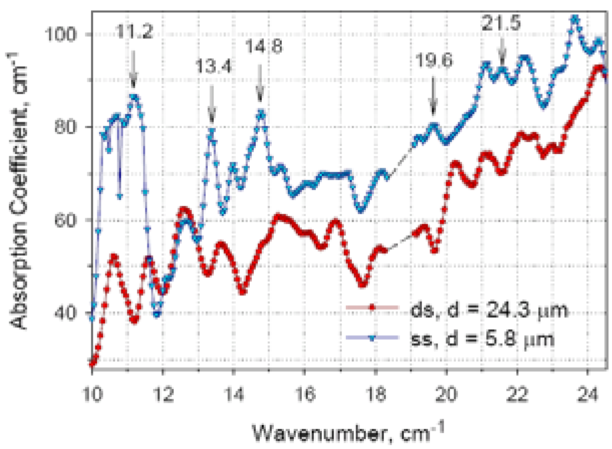

Fig. 4. Biomaterial identification: THz Absorption Spectroscopy of Bio-Molecules. Single- and double-stranded DNA. From T. Globus UVA, Oct 2005, MIT, also see T. Globus et. al., Journal of Biological Physics, 29, 89–100 (2003).

Terahertz spectroscopy can differentiate between different hydrate forms. Lactose, one of the most commonly used excipients in the pharmaceutical industry, forms at least three different hydrates: the most widely used α-monohydrate, the α-anhydrate and a β-anhydrate form. These three hydrate forms exhibit terahertz spectra that can be used for both quantitative and qualitative analysis.

The terahertz region also provides unique sensitivity to lattice structure enabling qualitative and quantitative analysis of crystalline and amorphous materials.

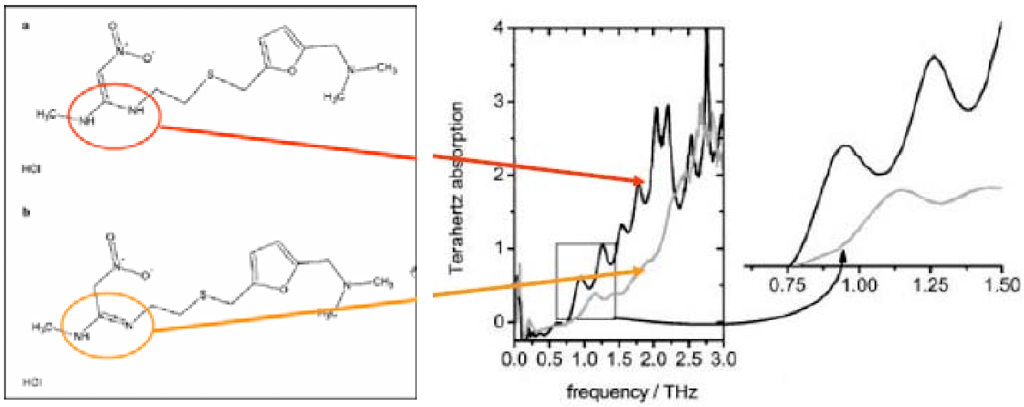

Fig. 5. T-Ray observations of the two conformationally distinct polymorphic forms of ranitidine hydrochloride (a primary constituent of common heartburn medication) have been made on commercial pressed tablets with definite distinguishing spectral characteristics that might be attributed to vibrational phonon modes. (From: P.F. Taday, et. al., "Using Terahertz Pulse Spectroscopy to Study the Crystalline Structure of a Drug: A Case Study of the Polymorphs of Ranitidine Hydrochloride," Journal of Pharmaceutical Sciences, vol. 92, no. 4, pp. 831-838, April 2003).

2. Time resolved THz spectroscopy of protein folding

Proteins fold, catalyze reactions, and transduce signals via binding to other biomolecules. These processes are driven by motions with characteristic time scales ranging from femtoseconds (fs) to milliseconds (ms). The characteristic modes from which such motions collectively emerge often cause large amplitude deformations of all or part of the protein. Temperature tuning reveals when certain modes are frozen out, while the Terahertz spectroscopy can cover fast relaxation kinetics on fs time scale during which a protein rearranges its overall structure.

3. Oncology: Non-invasive molecular signature of epithelial cancer

It is estimated that more than 85% of all cancers originate in the epithelium. Excision biopsy to remove tissue from the body and examining it under a microscope is the gold standard for cancer diagnosis. ARP's terahertz technology has the potential to greatly improve conventional biopsy and associated surgery by more precisely identifying the areas to be excised thereby reducing the number of procedures and facilitating earlier and more accurate diagnosis. As the technology matures, it may be possible to perform biopsies using live terahertz imaging of affected area, making possible point of care optical biopsy.

ARP is seeking collaboration with clinical customers and partners to provide imaging and spectroscopic capabilities for tissue and disease classification ex vivo on excised tissue. We are also seeking partners to develop in vivo intra-operative probes for tissue conservation surgery and endoscopic applications on patients. Extensive work has been reported by other groups on skin and basal cell carcinoma, and clinical work can be extended to breast and other types of tissue.

4. Terahertz in skin cancer

ARP is seeking clinical collaborators to establish the ability of Terahertz technology to distinguish between basal cell carcinoma and other forms of malignant, benign and healthy tissue associated with skin cancer and related diseases. Both extensive ex vivo measurements for tissue classification and histopathological use, and preliminary in vivo measurements directly on patients can be conducted to quantify the information obtained via terahertz spectroscopy.

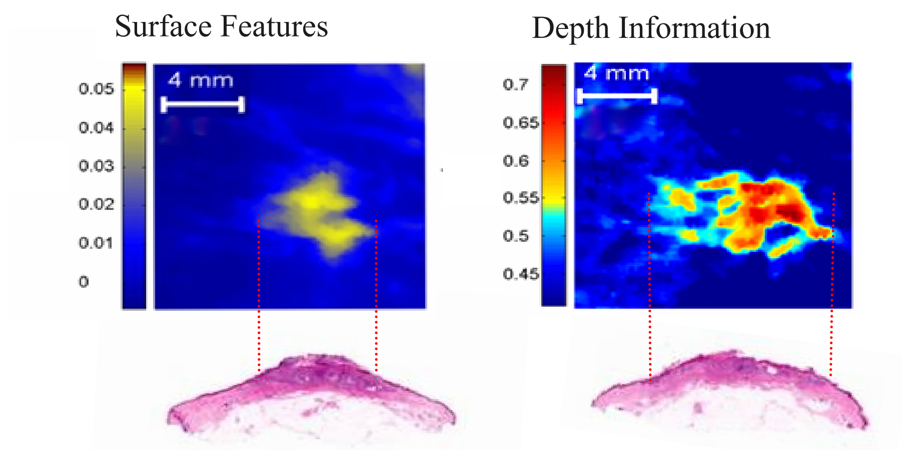

Fig. 6. Terahertz images of skin cancer showing surface and depth information. From Wallace et al, British J. Dermatology, 151:424-432, 2004

5. Pharmaceutical Industry: Tablet integrity and performance

Terahertz imaging gives an unparallel certainty about the integrity of tablet coatings and the matrix performance of tablet cores.

Terahertz image can be optimized for performing 3D analysis on tablets. It can enable customers to determine coating integrity and thickness, detect and identify localized chemical/physical structure such as cracks or chemical agglomeration within a core and to interrogate embedded layers (such as an interface between two layers) for delamination and integrity.

Terahertz measurements may well become the primary method for the nondestructive determination of coating thickness, requiring little or no calibration for most coatings and substrates. It can reveal the thickness, uniformity, distribution and coverage of simple and complex coatings.

Terahertz image can also detect embedded layers and localized chemical/physical structural features in the cores of intact tablets to confirm 3D morphology and blend uniformity.

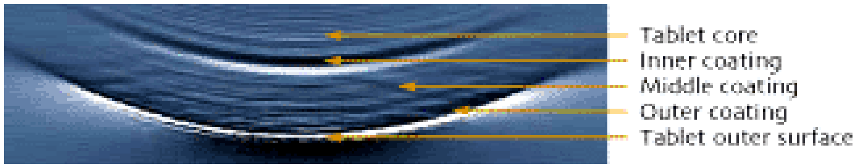

Fig. 7. Terahertz Image can help improve tablet integrity and achieve consistent results (picture courtesy of TeraView).

6. Terahertz in Dermatology

The cosmetic appearance of skin is directly linked to the state of its outermost layer, the stratum corneum. The water-content of the stratum corneum influences its permeability and elasticity. Most skin-care products such as moisturizers act to increase the retained water content of this layer of the skin to enhance its appearance. Quantitative characterization of the hydration-level of the stratum corneum is thus of crucial importance to the cosmetics industry in order to characterize and compare the effectiveness of their products.

7. Oral healthcare

Dental Caries, or tooth decay, is one of the most common human disorders. Caries is initiated as localized destruction of the outside layer of a tooth called the enamel. Acids in the plaque deposits adhering to teeth cause erosion, known as demineralization. Caries proceeds by the creation of a subsurface lesion in the enamel. The lesion may extend to the next tissue layer in teeth, the dentine, without macroscopically visible breakdown or even microcavity formation at the tooth surface. The absence of visual features on the tooth surface makes early detection of tooth decay difficult. X-rays, one of the accepted methods used to detect decay, only reveals the problem at a relatively late stage, when drilling and filling is the only method available to halt the decay. If decay can be detected early enough it is possible to reverse the process without the need for drilling by the use of either fissure sealing or remineralization.

Terahertz imaging is able to distinguish between the different types of tissue in a human tooth; detect caries at an early stage in the enamel layers of human teeth and monitor early erosion of the enamel at the surface of the tooth.

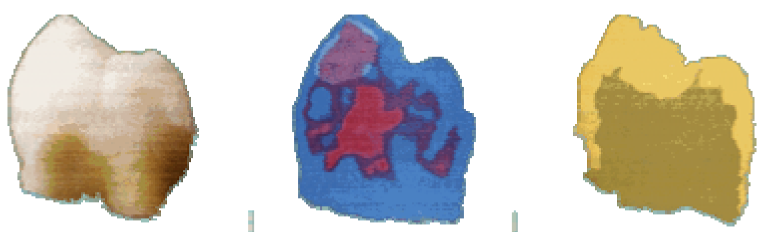

Fig. 8. Left: human tooth. Centre: Image of the tooth demonstrating THz absorption reveals cavities in red. Right: time of flight THz data shows enamel and dentine, which have different refraction indices. Ref. www.frascati.enea.it/THz-BRIDGE/descr_gen2.htm

8. Chemical and bioagent detection through spectroscopy.

Terahertz imaging could be critical as a means of screening for explosives or other prohibited or dangerous chemicals. In addition to its capabilities as a "structural imaging modality", T-ray can provide spectroscopic information on the object in question, from which details of the object's chemical composition may be determined. This has important ramifications in the fight against terrorism and detection of suspicious or prohibited substances.

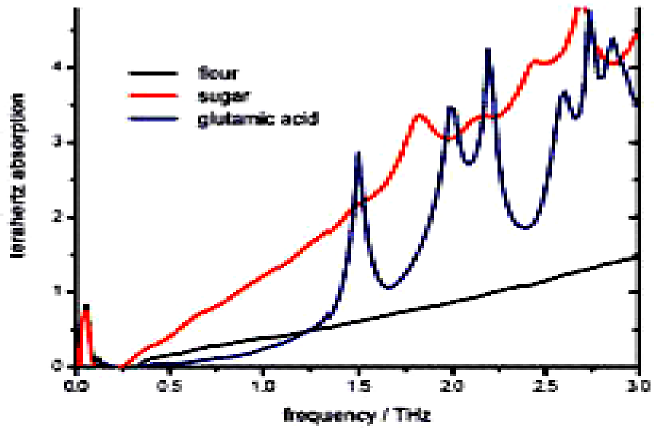

Figure 9. Three terahertz spectra showing glutamic acid, a basic building block of proteins in living matter, compared with two other common powdered substances. (TeraView)

9. Screening

The ability of terahertz technology to "see" through many opaque things such as clothing, box, shoe, etc. has led to successful proof of principle experiments at stand off distances for potential applications in building security, airports and defense. ARP has demonstrated direct imaging of hidden objects and set out to build the world's first practical direct terahertz imaging system, based on a hand held CCD camera that operates much like a regular video camera, but capable of detecting metallic and non metallic weapons and certain explosives. The Company will support defense and government agencies, as well as commercial partners, who wish to further explore this technology.

Fig. 10. A metallic knife hidden behind a thick black cardboard (left) is revealed by shining the terahertz beam (right). The picture is captured by a CCD camera.

Fig. 11. A metallic knife hidden behind a thick dark cloth (left) is revealed by shining the terahertz beam (right). The picture is captured by a CCD camera. © 2007, ARP Inc.

10. Other Applications

There are other applications of terahertz spectrometry and imaging. A few important ones are listed below.

- Food industry process control (e.g., moisture detection).
- Scientific: earth remote sensing, Environmental sensing (pollution detection), Plasma diagnostics.
- Seeing through sand storms, active and passive imaging through dust, smoke, fog etc; all weather active and passive seekers; secure communications; spectrographic sensing of explosives, gases and biologicals.
- High rate and secure data transfer, flame analysis (rocket or jet engine burn optimization).
- Homeland Security - concealed weapon identification, detection of suicide bombers, biological threat detection.
- Detection of voids in the space shuttle foam and in other structural materials.
- Passenger screening, hidden weapons detection, contraband detection.

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