Terahertz Technology in Biology and Medicine

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***Abstract*—Terahertz irradiation and sensing is being applied for the first time to a wide range of fields outside the traditional niches of space science, molecular line spectroscopy, and plasma diagnostics. This paper surveys some of the terahertz measurements and applications of interest in the biological and medical sciences.**

***Index Terms*—Applications, biology, medicine, technology, terahertz.**

I. INTRODUCTION

AFTER OVER ten years of niche applications in the space sciences, molecular spectroscopy, and plasma diagnostics, the field of *terahertz technology* is entering a true Renaissance. While major strides continue to be made in submillimeter-wave astronomy and remote sensing, the past few years have seen an unprecedented expansion of terahertz applications, components, and instruments. Popular interest in this unique frequency domain has emerged for the first time, spanning applications as diverse as contraband detection and tumor recognition. Already there are groups around the world who have applied specialized terahertz techniques to disease diagnostics [1], recognition of protein structural states [2], monitoring of receptor binding [3], performing label-free DNA sequencing [4], visualizing and cataloging absorption and contrast mechanisms in otherwise uniform tissue [5], [6], and radiation effects on biological samples and biological processes [7]. A commercial terahertz imaging system has recently begun trials in a hospital environment [8] and new heterodyne imagers with much deeper penetration into tissue have begun to emerge [9]. Former eastern block countries such as Russia have been involved in submillimeter-wave biological investigations using specialized backward-wave tube sources for over four decades [10].[1] Current European involvement in this field is very strong and follows from the large research program "THz-Bridge,"[2] which began in February 2001. U.S. interest has historically been confined mostly to astrophysics and spectroscopy, but biological applications have been building steadily since the introduction of fast pulse time-domain imaging techniques in the mid-1990s [11], [12].[3] Solicitations for instruments and enabling terahertz components have since filtered into U.S. agency proposal calls from the Department of Defense (DoD) and the National Aeronautics and Space Administration (NASA), to the National Science Foundation (NSF) and the National Institutes of Health (NIH). Japan has just formed a new society, i.e., the "THz Technology Forum," which will focus resources in this quickly evolving field.

In this paper, the emerging field of terahertz technology in biology and medicine is surveyed. Limitations and advantages of working at these longer-than-infrared (IR) wavelengths are reviewed. Both confirmed, and a few somewhat controversial applications, are highlighted. Emphasis is placed on frequencies from 300 GHz to 3 THz—the submillimeter-wave band. One of the goals of this paper is to acquaint an engineering audience with the field. Due to his background, the author has an acquired bias in the area of microwave techniques, as opposed to the much more prevalent terahertz optical pulse modalities that are currently being employed. Hopefully this will provide a slightly different point-of-view from earlier papers on the subject. For the interested reader, additional information can be found in three recent textbook compendiums [13], [14],[4] and special issues [15],[5] [16][6] of the *Journal of Biological Physics* (Dordrecht, The Netherlands: Kluwer) and *Physics in Medicine and Biology* (Bristol, U.K.: IOP). The latter includes two especially nice topical review papers by groups at The University of Leeds, Leeds, U.K. [17], [18].

II. SUBMILLIMETER WAVES IN BIOLOGY AND MEDICINE

A. Overview

When one looks grossly at the frequency range from 300 GHz to 3 THz, traditionally termed the submillimeter-wave band[7]

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[1] Reference [10] is available in translation by emailing the author at: phs@caltech.edu.

[2] [Online]. Available: http://www.frascati.enea.it/THz-BRIDGE/index.html

[3] Reference [12] is an excellent review article with almost 500 references.

[4] Reference [14] is two volumes, which were published in June and December 2003.

[5] Reference [15] contains papers from the "THz-Bridge Workshop," Capri, Italy, Sept. 29–Oct. 2, 2002.

[6] Reference [16] contains papers from the "First International Conference on Biomedical Imaging and Sensing Applications of THz Technology (BISAT)," Leeds, U.K., Nov. 29–Dec. 1, 2001.

[7] *A brief note on terminology*: In this paper, the terms "terahertz" and "submillimeter-wave" are considered to be synonymous, i.e., they refer to the same bounded region of the electromagnetic spectrum. The conventional frequency range for the submillimeter-wave regime, in the U.S. at least, is 300 GHz–3 THz (1 mm–100 μm). This is band 12, as defined by the International Telecommunications Union (ITU) in the late 1940s. Furthermore, for RF engineers, it is conventional to use wavelength, not frequency, to label spectral domains, i.e., centimeter wave, microwave, millimeter wave, and submillimeter wave. The term *terahertz* has been very loosely applied to the submillimeter-wave domain, but, in fact, it has no official bounding values as far as the author knows, i.e., the upper limit could 10, 30, or even 300 THz (band 14 of the former ITU). Since many of the techniques and much of the science that has been investigated under the title of "terahertz" actually falls in the low submillimeter, i.e. 300–1000 GHz, it seems appropriate to use submillimeter wave when referring to this energy regime. That being said, the author bows to popular culture and leaves terahertz in the title of this paper.

In 1947, the ITU designated the highest official radio frequency bands [extremely high frequency (EHF)] as bands 12–14, where band 12 spanned 300 kMc–3 MMc (mega-megacycle), where 1 MMc = 1 THz. Bands 13 and 14 covered 3–30 and 30–300 THz, respectively. 30 THz or 10-μm wavelength is generally considered far-IR and 300 THz or 1 μm would fall in the near IR.

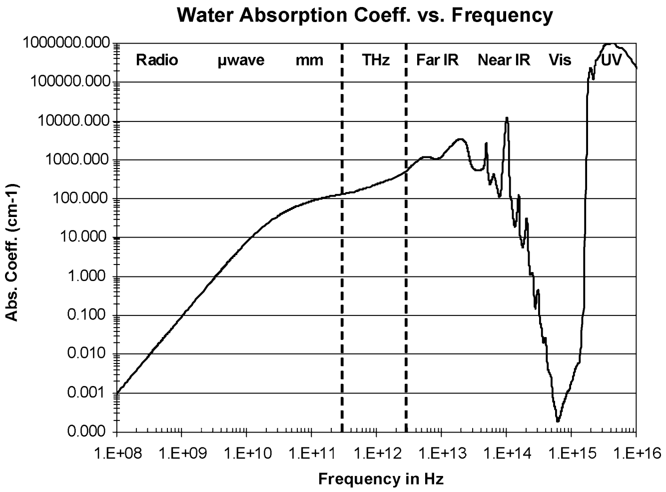

Fig. 1. Absorption coefficient of triply deionized water at 292 K between 100 MHz and the ultraviolet (UV). Generated from data printed in [21, Table I].

(100 μm $< \lambda_0 <$ 1 mm), it is immediately clear that it has some basic electromagnetic properties that might lead one to think there should be some applications to the life sciences. The energy levels are very low (1–12 meV), therefore, damage to cells or tissue should be limited to generalized thermal effects, i.e., strong resonant absorption seems unlikely. There is spectroscopic interest, however, since energies of $\sim 10^{-21}$ J are consistent with discrete molecular vibrational, torsional, and librational modes in liquids and solids [19], [20]. From an imaging standpoint, this wavelength regime is appropriate since the diffraction limited spot size is consistent with the resolution of a 1990's vintage laser printer ($1.22\lambda_0 = 170$ μm at 2160 GHz or 150 dots/in). At 1 THz, the resolution could be as good as a decent computer monitor ($\sim$70 dots/in). Submillimeter-wavelength scale implies that terahertz signals would pass through tissue with only Mie or Tyndall scattering (proportional to f^2) rather than much stronger Rayleigh scattering (proportional to f^4) that dominates in the IR and optical since cell size is $\ll \lambda_0$.

B. Water Absorption and Detection

As submillimeter-wave astronomers and RF semiconductor engineers know very well, two material properties dominate propagation at terahertz frequencies: electric susceptibility and bulk conductivity. The over-arching characteristic, as far as terahertz interaction with biological materials is concerned, is *absorptive loss* due to dielectric polarizability.

As shown in Figs. 1 and 2, the broad absorptive loss of terahertz energy in pure deionized liquid water [21, Table I]–[23][8] is so strong it rivals the best black body load. This strong absorption follows a Debye relaxation model (spherical rotation in a viscous media) in polar liquids at least up to 1 THz [24]. If one assumes a Beer's law power penetration dependency in x, $P_{\text{out}}/P_{\text{in}} = e^{-\alpha x}$, the absorption coefficient α is higher than 500 cm^{-1} at 3 THz or over 2000 dB/cm!

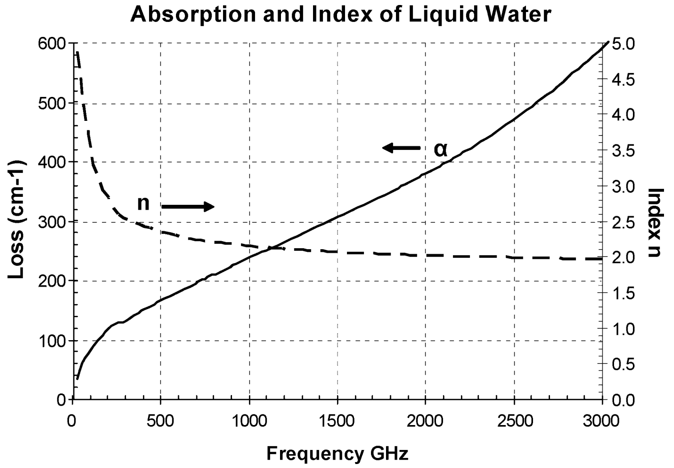

Fig. 2. Absorption coefficient and index of refraction for deionized water between 100–3000 GHz. Generated from data available from J. Bertie, Univ. Alberta, Edmonton, AB, Canada [23].

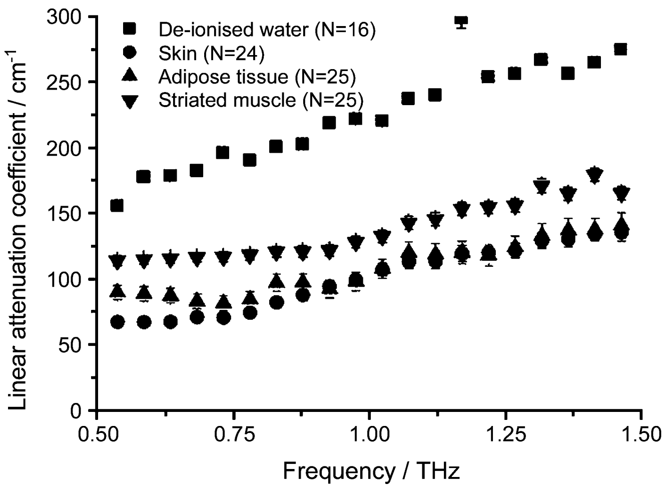

Fig. 3. Absorption coefficient for water, skin, adipose (fatty) tissue, and muscle at terahertz frequencies. $N = \#$ of samples. Reprinted with kind permission of Springer Science and Business Media [6].

Things are only slightly better in tissue [6] (Fig. 3). Human blood has a low-frequency resistivity similar to undoped silicon (60–140 $\Omega \cdot$ cm [25]) and, hence, would be lossy even without the water absorption. Typical tissues (fat, cerebral cortex, liver, muscle) have much higher bulk resistivity ($> 1000\,\Omega \cdot$cm) [26] at least at megahertz frequencies. Since the materials are really composed of both conducting and nonconducting particles in suspension or in layers, high-frequency values will certainly differ. To the author's knowledge, no RF measurements on *in vivo* resistivities have been made. Considering dielectric loss, some very careful measurements at 120 GHz using a high-power free electron laser source [27] yielded $\alpha = 75, 71, 79$, and 83 ± 3 cm^{-1} for blood, serum, saline solution, and culture medium, respectively. These differences are very small considering the high level of absorption and, thus, would make it very hard to distinguish samples in an uncontrolled environment.

Turning from absorption to reflection, the refractive index n of distilled water (1.33 at optical wavelengths) is around 80 at

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[8] Reference [23] plottable data available from J. Bertie, Univ. Alberta, Edmonton, AB, Canada. [Online]. Available: http://www.ualberta.ca/~jbertie/JBDownload.HTM#Spectra

1 GHz [28],[9] but drops to around 2 in the submillimeter (n is similar for blood and many tissue types) [6]. This gives a reflection coefficient for normally applied terahertz energy that returns approximately 11% of the incident signal. Fortuitously, due to their water content, the refractive indices of many biological materials change significantly with frequency between 100–1000 GHz (Fig. 2). Careful measurements of reflection coefficient versus frequency (often easier than transmission in very absorptive samples) can, therefore, be more useful than absorption in distinguishing tissue types [6].

Since most tissues are immersed in polar liquids, dominated by polar liquids or preserved in polar liquids, the exceptionally high absorption losses at terahertz frequencies make penetration through biological materials of any substantial thickness impossible. However, the same high absorption coefficient that limits penetration in tissue also promotes extreme contrast between substances with lesser or higher degrees of water saturation. This property has proven advantageous in the examination of the properties of water uptake and distribution in plants [29], as well as in the severity of burns on necrotic skin samples [30] and in tumor morphology [31]. Hadjiloucas and Bowen [32] go through a very detailed analysis for measurement limits and errors in a transmissometer based on a dispersive Fourier transform spectrometer (FTS), which they used to determine water content of leaf samples [29]. For optical pulse techniques with signal-to-noise of 100, Mittleman *et al.* [33] estimated the minimum detectable concentration of water in samples to follow $Nx = 10^{16}$ cm^{-2}, x being the thickness and N being the number of water molecules/cm^3. For the heterodyne system described in [34] operating at 2.5 THz, changes in transmitted power of 0.01 dB (0.23%) are measurable with millisecond averaging. Assuming an absorption loss α of 475 cm^{-1} at 2.5 THz, and invoking Beer's law, a water film thickness change of $\Delta x = 5 \times 10^{-6}$cm can be detected. Given a beam radius of $\sim \lambda_0 = 125$ μm (typical Gaussian waist radius, ω_0 for $f/D = 1.5$ optics), the measured change is $\pi\omega_0^2\Delta x \cdot 3.34 \times 10^{22}$ mol./cm^3 $= 8.3 \times 10^{13}$ water molecules. In a 1-mm thick sample, this would represent a change of approximately five parts in 10^5. Perhaps surprisingly, the power law behavior for transmission through liquid water seems to hold even when the water is dispersed throughout an absorptive solid (Fig. 4) [35]. This extends the usefulness of the differential absorption method for terahertz measurements. For much more sensitive water concentration measurements (at the expense of path length), it is advisable to work at the broad absorption maximum near 6 THz, where α approaches 1200 cm^{-1} or on other even higher frequency water absorption features [36]. It should also be noted that the absorption of water increases significantly with temperature in the submillimeter [37] so that *in vivo* losses will be higher than in equivalent *ex vivo* room-temperature samples.

C. Protein States and Molecular Signatures

Microwave spectroscopists, Earth and planetary scientists, astronomers, and molecular chemists have long been interested in the absorption or emission signatures of low-pressure gases in the terahertz range [38], [39]. However, broad nondescript spectral features from gases at atmospheric pressure, liquids, or solids received much less attention. Renewed interest in the field has been stimulated by a desire to observe the conformational structure, binding states, and vibrational or torsional modes of proteins and oligonucleotides [3], [40]–[42]. Early research in this area employed FTS sytems [43], [44] and Raman spectroscopy [45] (usually limited to frequencies beyond the mid-IR), but time-domain spectroscopy has made these measurements much more accessible [46]. Most of this research is still in the very early exploratory phases, and there is still some controversy as to the capability of both the Fourier-transform and time-domain systems to separate broad spectral absorption signatures from instrument or sample associated effects. With that caveat in mind, applications for broad-band submillimeter-wave spectroscopy in the biological and medical areas are widespread. The most reliable methods involve comparison of reflection or absorption signatures when samples undergo some form of chemical or physical change such as a difference in conformational state, a change of density or polarizability, dehydration, or denaturing or a temperature shift. Broad spectroscopic bandwidth is not required to measure these effects if differential signatures are available [47], although it may help in identifying sample-dependent or systematic errors.

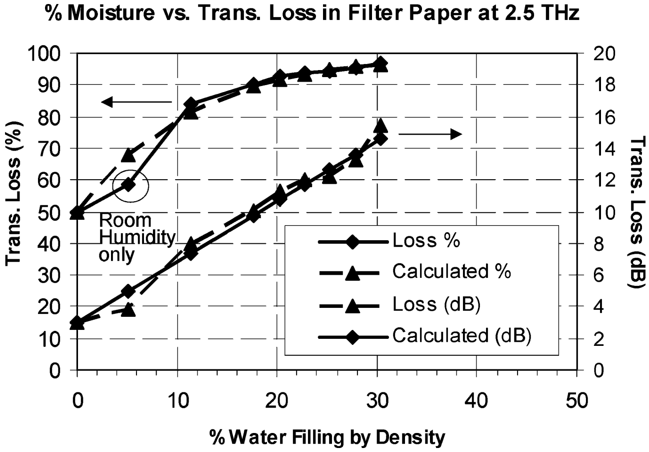

Fig. 4. Transmission loss of liquid water in 0.2-mm-thick filter paper as a function of filling factor at 2.5 THz. The fit to a power law assumes an absorption coefficient of 475 cm^{-1}. The implication is that the water distributes uniformly throughout the volume of the paper and maintains the inter-molecular dielectric loss mechanism in liquids for concentrations above ambient humidity (circled point) [35].

Two applications that hold great promise are measurements of avidin–biotin binding [3] and DNA hybridization [4]. Avidin–biotin binding is used in the biotechnology industry for securing manufactured proteins to surfaces in selective chromatography [48], drug delivery [49], or fluorescent tagging [50]. Determining the timing and presence or degree of binding is difficult without chemical analysis or UV spectrophotometry. It has recently been discovered [3] that the binding process results in a change in the index of refraction of the surface film that can be readily discerned by a change in reflection of a terahertz beam. A similar index change occurs when DNA in solution is hybridized (zipped) [4], [51]. Since the terahertz signal is both remote and nondestructive, this is a fast and powerful method

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[9] Reference [28] is a reprint of the treatise by the Laboratory of Insulation Research, Massachusetts Institute of Technology (MIT), Cambidge, "Tables of Dielectric Materials," which was released in 1953.

for *label-free* determination of the change of state of many biologically important processes. Other transformational reactions are likely to be explored as instrumentation spreads.

More difficult to quantify are conformational changes in state such as the unfolding or bending of molecular chains. Studies of rhodopsin are particularly intriguing [2] and should allow real-time monitoring of changes due to rapidly applied stimuli if systematic effects can be controlled and suitable frequencies selected for the comparisons.

Calculations of terahertz frequency biomolecule vibrational absorption signatures in liquids and solids goes back to the classic work of Fröhlich in the late 1960s [52]. Experimental FTS work on solid films and polar liquids started at the same time [42], [44], [53], [54]. Specific twist and librational modes of DNA were predicted by several groups beginning in the 1990s [19], [55], [56]. However, it is still fair to say that observations of calculated and assigned absorption signatures in protein chains and nucleotides are problematic if not actually controversial [57], [58]. The difficulty is, of course, with the inherently broad spectral signatures, relatively weak differential absorption compared to low pressure gasses, and differences introduced by sample purity, geometry, preparation, temperature, hydration level, and instrument systematics. Nevertheless, there are a growing number of multiply confirmed observations with both FTS and time-domain systems, and a body of evidence is being established for particular resonant signatures, as well as for identification of full compounds [59]. As one might expect from thermal energy considerations at these wavelengths, cooling of the samples greatly narrows any vibrational mode dips and can help with spectral identification [57].

When the environment is a very controlled one, and an absorption signature, even a broad one, can be identified, spectral features can be used to distinguish the presence or absence of particular compounds. A very promising application for terahertz molecular spectroscopy in the pharmaceutical industry is being pursued by Teraview Ltd., Cambridge, U.K., for detecting the presence of unwanted polymorphs in prepared drugs [60]. Observations of the two polymorphic states 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 [61]. Since today's time-domain systems can collect broad spectral data very quickly (tenths of seconds), the applications for these systems in screening production-line pharmacological products, individual elements of which are normally very close in physical structure and appearance, are significant.

Catalogues of terahertz spectral signatures, like those that exist in the IR, from the vast quantity of substances of interest both to the medical and law enforcement communities are just beginning to be established [62].[10] Very carefully collected data on a wide variety of compressed powder samples of both common drugs and illegal substances (using both FTS and direct transmission measurements from strong terahertz sources based on $\mathrm{LiNiO_3}$ generators [63]) have been accumulated by the groups at Riken University, Tokyo, Japan, and Tohoku University, Sendai, Japan, respectively [64], who report specific terahertz absorption signatures from at least 30% of the samples measured. The same group has also pioneered fast multispectral identification techniques (comparison of signatures through or off the same sample at several wavelengths) for distinguishing broad overlapping features [65].

D. Tissue Identification

Although spectroscopic applications for terahertz waves seem to hold the most promise in the biomedical area, there is certainly interest in tissue contrast for *in vivo* and *in vitro* identification of abnormalities, hydration, and subdermal probing. Only a small number of measurements have been made to date, and systematic investigations to catalog absorption coefficient, contrast mechanisms, and refractive index are just beginning to accumulate. Measurements on the absorption and refractive index of biological materials in the terahertz region go back at least to 1976 [43]. Several research groups have investigated excised and fixed tissue samples, either alcohol perfused [66], formalin fixed [5], [6], [67], [68], or freeze dried and wax mounted [69] looking for inherent contrast to define unique modalities. One of the first applications on human *in vitro* wet tissue involved imaging of excised basal cell carcinoma [1], [70]. *In vivo* work has focused on the skin and accessible external surfaces of the body for measuring hydration [71] and tumor infiltration [72]. However, only recently has there been a systematic attempt to quantify the terahertz properties of living tissue. A catalogue of unfixed tissue properties (including blood constituents) is being compiled by groups at The University of Leeds, Leeds, U.K. [6] for frequencies between 500–1500 GHz using a pulsed time-domain system. Difficulties in extrapolating measurements on excised tissue to *in vivo* results are numerous and include uptake of saline (or other infusion medium) from the sample storage environment, changes in hydration level during measurement, temperature-dependent loss, measurement chamber interactions, and scattering effects. Numerous groups have investigated direct transmission or reflection imaging as a means of distinguishing tissue type [67], [69], [73], recognizing disease or tumors [68], [72] penetrating below the surface layers of skin or into organs [74], or simply for contrasting fluid content [71]. It is not clear whether the observed contrast, penetration, or differences in absorption produce images that are unique enough to stand on their own, although much research is still to be done. Since the resolution of terahertz images is generally poor compared to IR, optical, and even magnetic resonance imaging (MRI), the factors that might make direct terahertz images worthwhile are specifically enhanced contrast—as in distinguishing water content or depth of penetration—where shallow subsurface images can actually be the most revealing, as the first few hundred micrometers are hard to image with other modalities. Although it has not as yet been shown, the high sensitivity to fluid composition and the variable conductivity in tissue [25] is likely to lead to statistically significant differences between nominally identical samples taken at different locations in the body at different times or from different subjects. Of course, this may ultimately prove advantageous; however, it seems that, in the short term,

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[10] Dr. G. P. Gallerano, European Nuclear Energy Agency (ENEA), Frascati, Italy. [Online]. Available: http://www.frascati.enea.it/THz-bridge/database/spectra/searchdb.htm.

it will tend to mask sought for differences or contrast that are indicative of disease.

E. Detecting Disease

One of the hopes for terahertz applications in the medical area is in the detection or early characterization of disease. The first uses of the technology in this area has been in the identification of dental caries [75] and in the examination of skin to assess the magnitude and depth of burns [76],[11] to look at wound healing and scarring [72], to determine hydration levels [71], and most recently, to detect the extent of subdermal carcinomas [72]. *In vivo* disease diagnosis is a major driving force for the development of handheld and fast scan portable terahertz imaging systems. Although progress is being made, the competition from other more developed imaging modalities is fierce. Optical coherence tomography, ultrasound, near-IR, and Raman spectroscopy, MRI, positron emission tomography, *in situ* confocal microscopy, and X-ray techniques have all received much more attention and currently offer enhanced resolution, greater penetration, higher acquisition speeds, and specifically targeted contrast mechanisms. That does not preclude terahertz imaging from finding a niche in this barrage of already favorable modalities. There is still no technique that can readily distinguish benign from malignant lesions macroscopically at the surface or subdermally. Skin hydration levels are important for designing percutaneous drug delivery systems, in impacting wound healing, and in assessing the influence of transpiration on disease or cosmetic appliqués [71]. The sensitivity of terahertz signals to skin moisture is very high, and competing techniques such as high-resolution MRI are less convenient.

Wound inspection through dressings or solid casts is another promising area that is being investigated with terahertz imagers [6]. Current techniques use invasive procedures or three-dimensional (3-D) reconstruction through optical illumination that does not penetrate opaque bandaging [77]. Terahertz techniques may be able to image, as well as differentiate, between different tissue states in the distinct stages of wound closure and scar formation. No studies have been reported as yet.

Passive thermal imaging of the body has been an active field for over 40 years. A vast accumulation of information on disease diagnosis and physiological function already exists, including dedicated journals on the subject. IR and microwave thermography are routinely used in neurology, dermatology, oncology, cardiology, rheumatology, ophthalmology, and surgery [78]. Temperature resolution of <0.1 K is required to detect small changes in emissivity and there is a great advantage in working at IR wavelengths near 10 μm (the peak in the black body curve for a 300-K object). Typical temperature gradients in the skin (inner to outer surfaces) vary between 0.2–0.5 K/mm [79]. In the submillimeter-wave region, the Stefan Boltzmann law holds such that the emitted energy ξ from a thermal body varies with the fourth power of the temperature ($\xi = \sigma T^4$, $\sigma = 5.67 \times 10^{-8}$ W/m^2/K^4). Small differences in emissivity in the IR are used to detect everything from nerve damage to breast tumors. Current generation uncooled IR cameras based on microbolometers, quantum-well IR photodetectors, and photovoltaics can attain noise equivalent temperature differences ($\mathrm{NE}\Delta T$) of <0.04 K at a 30-Hz video frame rate [78]. At submillimeter wavelengths, uncooled direct detector technology has not reached this level of performance, but room-temperature heterodyne sensors should be able to compete, at least as single pixels [80], and there is now a strong push toward large format imaging arrays from several sources.[12] The disadvantage from the standpoint of emissivity is the tremendous drop from peak energy output at equivalent body temperature (Wein's law: $\lambda_{\max}(\mathrm{cm}) = 0.2898/T$ has $T \approx 10$ K at 1 THz). However, an advantage lies in the penetration depth from which the thermal energy is originating (subsurface for terahertz), and the contrast that will accrue from this. The emissivity will also vary strongly with hydration in the submillimeter due to the difference in absorption between wet and dry tissue. It seems likely that by tailoring the wavelength as a tradeoff between penetration and resolution, it would be possible to develop a modality that is complementary to IR thermography, but that targets subsurface temperature. The possibility of detecting subdermal hot spots is certainly intriguing. Although submillimeter radiometric instruments that have useful $\mathrm{NE}\Delta T$ exist at several frequencies [39], to the author's knowledge, these instruments have yet to be employed in this way.

A modality that may be of great interest for terahertz systems involves the identification of disease in the vascular, bronchial, and digestive systems through endoscopy and/or catheter insertion. Differences in the reflection signatures of tissues have already been demonstrated *in vitro* [6] and there is a fairly good chance that terahertz systems that can be made compact enough to slide into endoscopic or catheter tubes will be able to distinguish regions of arteriole sclerosis, plaque buildup, fat, scar tissue, or other endothelial anomalies. The technological hold back at this time is in the source and sensor technology, which has yet to be suitably miniaturized (although progress is being made[13]) and in a lack of a low-loss guide media (equivalent to optical fiber) that might be brought to bear. This too is receiving attention [81].[14] Meanwhile, *in vitro* measurements on these particular disease manifestations would go a long way toward determining what limitations and expected levels of contrast would be obtainable once an *in vivo* instrument were available.

There is no doubt that submillimeter-wave penetration, scattering, and contrast mechanisms differ significantly from those of other wavelengths. As instrumentation becomes more affordable, a predictable niche is likely to emerge. However, demonstrating the value of the technique against more established procedures is difficult. The vast amount of algorithm development that has already gone into near- and far-IR imaging systems is directly applicable to the terahertz systems and is just beginning to be exploited. Tomographic reconstruction is still in a primitive state, but has been demonstrated on bone and teeth [74],

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[11] In Reference [76], see especially Section 3.5.

[12] Defense Advanced Research Projects Agency (DARPA)/Microelectronics Technology Office (MTO) research announcement BAA 04-07, "Terahertz imaging focal plane array technology (TIFT)." [Online]. Available: http://www.eps.gov/spg/ODA/DARPA/CMO/BAA04-07/, released Dec. 2003. Proposal text available from the author.

[13] Handheld sensors are now being advertised at Teraview. [Online]. Available: http://www.teraview.co.uk/pr_probe.asp

[14] Reference [81] is available from the author on request.

[75]. It is the author's opinion that terahertz imaging in the disease area will not replace existing modalities, but may serve as a complement or additional diagnostic tool, just as detailed MRI often follows less specific X-ray observations. As with generic tissue and serum, systematic examination of diseased tissue is in an early phase. The regulatory restrictions of working with human tissue and with setting up patient studies means we may have to wait some time before a definitive set of disease applications comes to light.

F. Affecting Biological Processes

From the advent of the first submillimeter-wave generator tubes in the mid 1960s,[15] investigators were concerned about the adverse health effects of terahertz beams [10]. The focus was not only on direct heating, but on **"информационные"** so-called *informational* effects. These included effects on cell membrane permeability and adhesion characteristics, ATP synthesis, immunoresponse, metabolic rate, excitation of central-nervous-system receptors, electrical impact on the cerebral cortex, and many other biological functions including positive therapeutic benefits of submillimeter-wave irradiation [10]. There were even investigations on "memory" effects, wherein changes in the state of water or water-based tissues after millimeter-wave irradiation were preserved for over 10 min [10]. Some of the early work was stimulated by the predictions of terahertz cell resonances in the papers by Fröhlich [52]. It is impossible for the author to judge whether the results stemming from investigations in the former Eastern block are comparable to measurements being undertaken today in Europe and the U.S. Certainly there is duplication, but the experiments are not always straightforward and the interpretation of results is sometimes controversial. An excellent review of millimeter-wave studies in the former Soviet Republic can be found in [82], but little research is available in the west on submillimeter-wave phenomena. Long-term low-level exposure effects at lower frequencies (millimeter waves) have mostly focused on corneal damage in animals [83].[16] The availability of synchrotron sources with substantial continuous-wave (CW) power at terahertz frequencies will certainly change this situation, and exposure studies are already ongoing [7], [84]–[86]. "THz Bridge" has also undertaken investigations in this area at several laboratories [7], [87], [88].[17] Nothing concrete has yet emerged that would make the case for reducing (or increasing) the current safe exposure level of 10 mW/cm^2 [89] that was set for millimeter-wave radiation back in the early 1980s. Current safe exposure limits, even for the millimeter-wave bands, vary greatly.[18] For terahertz *in vivo* radiation, there is no data, as no *in vivo* studies have been done, but some calculations on the safety of time-domain instruments, as they relate to the existing standards, have been made [90]. Experiments that address many of the issues reported by Russian researchers on the more subtle biological impact of terahertz radiation are just being undertaken in the west [83], [86]–[88]. Since resonant modes in proteins and oligonucleotides have been observed [3], [40]–[42], [58] it may be possible to excite these modes through terahertz exposure and, hence, impact cellular or subcellular processes. If such effects were demonstrated, it might open up a fruitful area of research for treatment, as envisioned so many years earlier [52], [91]—but this possibility seems remote considering the dominance of broad-band water absorption *in vivo*.

G. Terahertz Microscopy

The quest to obtain higher resolution at terahertz wavelengths is driven by the diffraction spot diameter of 1.22λ, which limits pixel resolution to hundreds of micrometers. Since the wavelengths are so large, optical prescriptions follow Gaussian beam formalism [92] and the *f-number* for producing a diffraction limited spot (beam waist $w_0 = \lambda/\theta\pi$, $\theta =$ asymptotic angle) must be very low. This means depth of field is greatly reduced and diffraction (scattering) effects have a big impact on image quality. However, long wavelength means that near-field imaging is much more accessible, and several groups are rigorously pursuing the potential of terahertz imaging using a variety of close-in $(< \lambda/10)$ detectors or probes [93]–[95]. Although it is not yet clear what applications microscopy at terahertz wavelengths will have, the ease of performing near-field probing at these wavelengths has made it an attractive goal for several investigators. Resolution levels below $\lambda/200$ have recently been reported with leaky-wave near-field probes [95] and sub-λ resolution in depth $(< 10\ \mu\mathrm{m})$ has been obtained with interferometry methods [96]. Resolution can be simply enhanced by moving to higher frequencies, and this is also an area of active research for pulsed time-domain systems, as well as CW imagers.

One goal for increased resolution is smaller sample size. This is important for the receptor binding and DNA hybridization applications if femtoliter samples are to be analyzed. Another area that has yet to be explored, but is common in fluorescence microscopy, is pump-probe excitation, wherein an optical or IR laser is used to stimulate terahertz emission. This technique has been employed for atmospheric remote sensing, but at much shorter wavelengths [97].

H. Instrumentation

There is already a large body of literature on the historical development of terahertz components and terahertz instrumentation, i.e., sources, sensors, and spectrometers. These are well covered in the texts by Woolard *et al.* [14]. Most of the work on terahertz imaging to date has been accomplished with fast-pulse time-domain systems [13], however, examples of passive and active direct detection imaging and spectroscopy using traditional spatial FTS systems [38] and heterodyne imaging using fixed-frequency CW systems [9] dot the literature. The two communities, i.e., the time and frequency domains, have begun to interact, and it should not be very long before components

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[15] The first submillimeter-wave vacuum tube oscillators were manufactured in Russia at Istok in the 1960s. These tubes produced low levels of power (milliwatt) from 100 to 1200 GHz and stimulated a large body of work in Russia on the biological effects of low levels of exposure. Tubes in the submillimeter (up to 500 GHz) were also produced by Division Tubes Electroniques, Thomson CSF, Boulogne, France, up until the mid-1980s.

[16] [Online]. Available: http://www.frascati.enea.it/THz-BRIDGE/workshop

[17] [Online]. Available: http://www.frascati.enea.it/THz-BRIDGE/workshop

[18] American Conf. of Gov. Ind. Hygienists (1982)= $10\mathrm{mW/cm}^2$, Amer. Nat. Standards Ind. (1982)= $4\mathrm{mW/cm}^2$, Standards Assoc. of Australia (1985)= $1\mathrm{mW/cm}^2$, ANSI (2000)= $100\mathrm{mW/cm}^2$, U.S. Federal Communications Comm. (2003)= $5\mathrm{mW/cm}^2$ for 6 min.

under development in the molecular spectroscopy and astrophysics fields link with techniques that are dominant in the laser and optical areas and vice-versa. Examples of this blending are already apparent in the applications of new quantum cascade intra-subband lasers [98] and in high signal-to-noise time-domain spectroscopy systems [99]. More and more accelerator and synchrotron facilities are also spinning off far-IR ports for higher power terahertz experiments, and although these facilities will not be appearing in hospitals, they are ideal for performing some of the necessary experiments on the more subtle impacts of terahertz irradiation of biomaterials. The large body of image reconstruction software now being employed for every imaging modality from ultrasound to neutron scattering will also help the terahertz community to establish itself in the medical diagnostic arena. As more researchers enter the field, progress, especially in the instrumentation area, is bound to accelerate. At the moment, it is a bit of a chicken-and-egg problem, as medical and biological applications unique to the terahertz bands have not yet been established.

III. CONCLUSIONS

In this paper, the author has tried to cover many of the topics of current interest to submillimeter-wave technologists in the medical and biomedical areas. Clearly, we are in a very early and mostly exploratory stage of development. This is both a help and hindrance. On the positive side, many years of fruitful investigations lie ahead, certainly with unforeseen benefits. On the negative side, it is extremely difficult to convince sponsors in the medical communities to take such high risks with their limited funding. The cultural gap between the medical and engineering communities is as large as the "terahertz gap." Bridging these two cultures remains a serious challenge. Based on the author's own experiences, the medical community in the U.S. generally do not accept that terahertz imaging produces any useful information about tissues or biomolecules. Those in the terahertz community who are experiencing similar attitudes should take heart from a recent statement by Prof. C. Blakemore, Chief Executive of the Medical Research Council, London, U.K., who, in speaking about the recently awarded Nobel Prize for Medicine to P. Lauterber and P. Mansfield, stated that this work was "an example of how high-risk research can pay off .... When the MRC (Medical Research Council) first funded Sir Peter in the 1970s, we really didn't know if the huge investment in this area would bear fruit. In fact, it surpassed all hopes."[19] Perhaps someday this statement can be applied to terahertz imaging as well. Meanwhile, progress continues at a very rapid pace for what once was an extremely slow-moving niche field. One can no longer say that everything in the submillimeter-wave field derives from the textbooks of the Massachusetts Institute of Technology (MIT) Radiation Laboratory series. This in itself points to tremendous progress.

The danger of oversimplifying or overselling the technology is great, and investigators should remain very diligent about policing their results and claims. However, we must also be careful not to abandon too quickly what at first may appear to be fruitless avenues of investigation, especially when the technology is improving and changing so rapidly. There seem to be real applications for the technology that have already been developed, as well as several still totally untapped avenues of investigation, e.g., radiometry. The terahertz radio astronomy community has been focused over the past 20 years on a single application—the recording of narrow-band spectral line signatures. This application has been sustained at tremendous cost—the Herschel space telescope (only one of a half-dozen space missions with submillimeter-wave sensors [39]) will easily top one-billion dollars and there are ground-based submillimeter-wave observatories supported by almost every developed nation, including more than one station planned for the South Pole. Investment of this magnitude in submillimeter-wave applications for medical diagnostics has certainly not occurred, and is unlikely to occur in what little time remains in the author's own career. However, over the next several years, much will be learned and much will be added to the sparse knowledge base that exists today. As has happened in many other fields, terahertz technology is now experiencing *primo Vere. Aestas est iuxta, et Hiems est remota*—we can only hope, a very long way off!

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