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Infrared and terahertz in application to biomedicine

Abstract

A number of potential advances of infrared and terahertz technologies in application mainly to biomedicine are shortly discussed. In spite of the fact that there are well established imaging and spectroscopic techniques used in biomedicine there exists some problems where IR and THz technologies are the challenging technologies that can provide information not available from other techniques.

Keywords: Biomedicine, infrared, terahertz.

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Introduction

Infrared (IR, wavelengths region λ ≈ 0.7 μm-30 μm) and especially terahertz (THz, radiation frequency range ν ≈ 0.1-30 THz, wavelengths region λ ≈ 3 mm-30 μm)[1,2] technologies have become one of the major fields of applied research that, to a great degree, are driven by potential applications in biomedicine. These technologies can provide information not available from other techniques.[3] The IR technologies in applications to biomedicine are known since 1950s and there exist numerical publications on these problems. Concerning the THz technique the matter is relatively new but the number of publications since 1970s is grown exponentially. A search with keywords involving "terahertz" and the traditional terms "far infrared" and "sub-millimeter waves" accepted here as THz waves within ν ≈ 0.1-30 THz comes up with thousands of hits that confirms ongoing interest in this technique[4] including applications in biomedicine. Today potential and existing IR and THz technology applications are broad in such diverse fields as astronomy, military and surveillance applications, telecommunications, energy control, space research, missile systems, and defense, signature analysis, biomedicine, etc. [5–8] In biomedical applications these technologies are frequently used for breast cancer diagnostics both in preclinical research settings as well as in the clinical assessment of patients,[9–12] though they can be applied for a number of other biomedical tasks.[13,14] Because of the relatively large width of the THz spectra THz radiation is of great importance in terms of fundamental researches as well as in technology and life sciences, as in this region rotational and vibrational lines of a lot of substances are located e.g. of molecules like proteins or DNA.[15,16]

Typical IR technology applications can be separated in two major groups. On the one hand, there are near IR (NIR, λ~0.7 to 1.1 μm) and short wavelength IR (SWIR, λ~1.1 to 2.5 μm) spectral regions, which are commonly employed for the assessment of artworks (e.g., paintings and frescoes) since some painting pigments are semi-transparent to the IR in these spectral bands and some other are not (e.g., carbon based). In this region, also IR spectroscopy is applied in biomedical science. On the other hand, there is an infrared thermography, which involves detection of the surface and subsurface layers of objects on the differences in thermal signatures in the medium IR wavelength IR (MWIR, λ~2.5 to 7.0 μm) and long IR wavelength (LWIR, λ~7.0 to 15.0 μm) spectral bands. In biomedicine applications mostly thermography and spectroscopy are applied in LWIR and MWIR spectral regions.[9] In biomedical applications, IR technologies may serve as one of the additional imaging methods (limited as a primary breast cancer diagnostic,[3,17] when compared with other better developed techniques. However, interpretations of thermo graphic images depend on the specialists qualification and may lead to errors and uneven results. Thermography has a potential in screening the breast cancer diagnostics detecting the growth of malignant tumor (with relatively good resolution of ~1.5 mm2)[3] due to increase of the internal temperature captured by thermograms. Infrared thermography has emerged in recent years as an attractive and reliable technique to address complex non-destructive (NDT) problems.[12] THz waves are relatively short to provide spatial resolution of less than 1mm. Yet they are long enough to penetrate most nonmetallic substances, such as materials used to make clothing, rucksacks, etc.[18] However, contrary to IR region where imaging as a rule is passive, due to the lack of appreciable terahertz power in the thermal background, it is necessary to use for imaging an illumination (THz sources).

Development of IR and THz technologies are important in early cancer diagnostics, as a cancer is one of the leading causes of death worldwide. In 2012 there was 8.2 million death data vs. different form of cancer.[19] Cancer is the second leading cause of death and in 2015 was responsible for 8.8 million deaths – nearly 1 in 6 global death.[20] The total number of deaths due to cardiovascular disease read 17.3 million a year, according to the WHO (World Health Organization), causes of death 2008 summary tables.[21] Thus, death data vs. different form of cancer are comparable to cardiovascular diseases and will continue to rise to over 13.1 million in 2030[22] and the economic impact of cancer is significant and increasing. The total annual economic cost of cancer in 2010 was estimated at approximately US$ 1.16 trillion.[20] Among women, the breast cancer disease is one of the prime causes of their death worldwide.[17,21] Breast cancer patients diagnosis can be divided into three cases: in the first case 90% patients diagnosed will undergo surgery to treat the disease, in the second case, 60% will undergo breast conserving surgery, according to breast conserving surgery the primary tumor is removed with a margin of normal tissue around it and remaining mastectomy. Around 10–15% of patients will require the second operation, as the margins are not free of cancer on histopathology.[23] That is why the more accurate techniques are needed to assess resection margins during surgery to avoid the next operation. In the case of THz technology for cancer diagnostics it is conditioned with the strong water absorption as water concentration reveal a lot about the health of human tissue, with water content in cancerous cells higher than in healthy cells.

A variety of applications would not be possible without the use of the THz radiation. The THz waves have low photon energy to ionize atoms and molecules, and this energy is much less to cause cancer and genetic mutations. It does not mean that it is safety for human being as, e.g., the US Federal Communications Commission established maximum permissible exposure limits of 1mW/cm2 for 6 min in the 30–300 GHz frequency range.[24] Moreover, many of the reported mm-wave effects even under low-intensity radiation can produce a variety of bio-effects.[25] Other health effects can be caused by the thermal effects (temperature changes during irradiation) under powerful THz radiation) and THz waves are able to penetrate a large number of opaque in visible or IR ranges organic or inorganic materials without causing their damage. Contrary THz radiation is strongly absorbed by conductive materials and polar liquids such as water. Thereby, such characteristics are suitable for spectroscopy and imaging methods applications to substances with water content. THz imaging for human breast cancer diagnostics is now less advanced comparing to thermography, and further development of the technology and clinical examination are needed to evaluate its feasibility in the clinical environment.[26] Also when carrying out THz breast cancer diagnostics with THz sources, it should be taken into account the power level of radiation that can be harmful for living objects. Because of strong absorption by water in many cases of applications to biomedical (and food), THz imaging and spectroscopic systems can be applied, e.g., for mapping tumor margins (or surface of food products) with not a great depth but about 2mm because of a fatty tissue.[27,28] Moreover, it was found the frequency dependence of absorption coefficient on salt, protein and DNA content. In addition THz water absorption depends on protein structural changes, such as ligand binding or denaturing.[1] The important components of any IR or THz instrumentation are detectors. When comparing the detector properties in the IR and THz spectral regions it can be concluded that the IR and THz detectors are typically different in operational principles. For example, one of these differences lies in the sizes of a detector. In the infrared detectors the sizes of the sensitive elements in arrays are about the wavelengths (connected with diffraction limit - Airy disk diameter $A_{dif} \approx 2.44 \cdot (F/\#)$, where F/# is the optics f-number), whereas the THz ones, though having similar dimensions of pixels, are compared to the wavelength, but only with regard to the antenna dimensions which are about the wavelength □. That is a reason to form large IR matrix arrays with great number of sensitive elements in them (up to ~2 107 pixels) as the pitch d in them is about the wavelength, d ~ 10 - 20 μm. In the THz single detectors and arrays the pitch is again d~λ but λ~1 mm. The difference of the sensitive elements dimensions in the IR and THz arrays is a reason of the much less (several orders) number of pixels in THz arrays.

Another difference is connected with mechanism of operation. IR detectors, as a rule are direct detection detectors: intrinsic (inter band optical transitions in semiconductors), extrinsic (optical transitions between the localized states in the forbidden gap of semiconductors and the states in conduction or valence bands), photo ionization detectors (e.g., IR Schottky diodes) and thermal detectors (radiation heats a lattice, free carriers or gas in the close cell (Golay cells)). In the THz spectral region, as a rule, some other mechanisms are typical for detection of THz radiation: non-linear effects in different types of non-linear structures (Schottky barrier diodes, field effect transistors, superconductor-insulator-superconductor structures, hot-electron bolometers, super lattices). With these non-linear structures direct detection (non-coherent) and coherent (heterodyne) detection, which is most effective in long part of THz spectra (<0.3 THz) and microwave region, are implemented. The thermal detectors, cooled and uncooled, which are applied as direct detection detectors, are widely used too. Among the THz imaging and spectroscopy systems for biomedical purposes, there are mainly used systems based on the THz pulse imaging - THz time domain spectroscopy (TDS) and imaging systems, and continuous wave (CW) photo mixer systems.[22]

In TDS instrumentations the photoconductive detection in the broadband THz region is based on antenna detector structures that are similar to structures used for generation of pulsed broadband THz radiation emission spectra by incoming fs laser beam (e.g., sapphire lasers, for Refs. se, e.g.,).[2] These photoconductive detectors as a rule are built on highly resistive low-temperature grown GaAs to provide spectral resolution using fs laser pulse coinciding spatially and temporally with the THz electric field of the incoming THz radiation. By delaying the fs laser pulse relative to the broad THz pulse the time-dependence of the photocurrent can be measured. Since the laser pulse is narrow in comparison to the time duration of the THz pulse from fs laser induced semiconductor emitter, the laser acts as a gated sampling signal. THz TDS and imaging for biomedical applications has advanced considerably. Several commercialized systems are now available and THz TDS systems for biomedical applications have been set up by many groups all over the world. Pulsed systems can provide a broader range of information including frequency domain or time domain information and can be supplied for obtaining depth information and the nature of scattering objects.[29,30] CW imaging that was considered for a long time before[31] allows more simple, compact and lower-cost systems, however yielding only intensity data information. In the field of CW THz biomedical imaging the conventional intensity imaging techniques provide poor contrast in formation of the image. In pulsed imaging THz techniques phase shift introduced on a transmitted signal by the different tissue types can provide enhanced contrast. Required for practicable civil applications existing THz detectors have a number of drawbacks. The cooled ones can be very sensitive (noise equivalent power NEP~10^{-14}-10^{-19} W/$Hz^{1/2}$) but bulky because of non-practical low temperature equipment needed for operation. If uncooled detectors are applied, they are not very sensitive (NEP > 10^{-12} W/$Hz^{1/2}$) to operate in all day-to-day civil applications, or they are slow. Combined with the complexity of handheld THz emitters realization,[32] It explains the difficulties of THz radiation technologies to ensure market penetration with THz systems for cost-effective civil applications. Compared to IR and microwave systems, THz imaging, spectroscopy and communication systems and their important components (e.g., uncooled detectors, sources) are remaining less developed. Because of low-power THz radiation optical schematics based on the THz pulsed technique (as a rule with single detector) raster long time (~ minutes even for small area images~1 cm^2) operation is used.[33] These are among the reasons why at the moment THz wave instrument capabilities are still away in comparison, e.g., with IR or microwave system feasibilities.

Conclusion

IR and THz technology applications today are broad in such domains as astronomy, military and surveillance, telecommunications, security, etc. One of the most topical are biomedical applications, e.g., for breast cancer diagnostics, colon cancer, burn imaging, DNA content, protein structural changes, etc. They make sense to

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be applied in the cases where there is a need of accurate location of tumor margins when conservation of normal tissue is required. It can be expected that potentiality of these technologies will be only in progress in diverse directions in biomedical field. Further work is needed for scientific challenges to provide information not available from other techniques. One of the main barrier in providing healthcare conclusions by using THz technologies is the cost of THz imaging and spectroscopy instrumentation that is mostly related with a high cost of short pulse lasers needed for their applications and that one based on raster technique.

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Conflict of interest

Author declares that there is no conflict of interest.

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