TERAHERTZ SPECTROSCOPY OF BIOLOGICAL SYSTEMS

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Abstract  Following recent developments in instrumentation, the terahertz part of the electromagnetic spectrum, lying between the microwave and infrared regions, now offers considerable potential for the study of the structure, dynamics and function of biological systems. The energies involved in many key biological processes lie in the terahertz frequency range, such as protein conformational changes and the collective motion of DNA base pairs along the hydrogen-bonded backbone. Terahertz spectroscopy is also a very sensitive probe of water in biological systems.

This chapter will consider the terahertz spectroscopy of biological systems at three levels of increasing scale and complexity: the macromolecular, cellular and organism levels. Relevant instrumentation and spectroscopic techniques will be introduced, and biomedical applications, such as label-free detection of DNA mutations and non-invasive biopsy to distinguish between normal and cancerous tissue, will be described. The particular challenges involved in carrying out terahertz spectroscopy of biological systems will be considered, together with some possible future directions.

1. Introduction

The terahertz range covers frequencies between 100 GHz and 10 THz, corresponding to wavelengths from 3 mm down to 30 \( \mu \)m. In the past, terahertz spectroscopy has been challenging, particularly due to the lack of convenient sources of terahertz radiation. However, recent technological advances have enabled the development of terahertz systems having unprecedented levels of sensitivity and sub-picosecond time resolution. Later sections of this chapter will show how spectroscopy in this range can provide a unique window on the structure and behaviour of biological systems. Prior to this, it will be helpful to consider the operation of a basic terahertz time-domain spectroscopy (TDS) system.

Terahertz TDS relies on ultrafast pulsed lasers for both the generation and coherent detection of broadband terahertz radiation. Systems are typically based around Ti:sapphire lasers emitting pulses of near-infrared (NIR) radiation with pulse widths of a few tens of femtoseconds. Such pulses contain frequency components spanning a bandwidth of several THz but are centred on an infrared wavelength of around 800 nm (equivalent to

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a frequency of 375 THz). To be useful for terahertz spectroscopy, this output wavelength has to be shifted into the terahertz range whilst retaining as much of the bandwidth as possible. There are two broad approaches to achieving this: photoconductive generation and optoelectronic generation.

Photoconductive generation makes use of a metallised antenna structure photolithographically defined on the surface of an electrically insulating substrate. The antenna may be a simple planar dipole-like structure, with the two arms of the dipole connected to a dc bias supply. Underlying the gap between the dipole arms is a patch of semiconductor material, typically radiation damaged silicon on a sapphire substrate. With no illumination from the laser, the semiconductor region is non-conducting and no current flows through the antenna. However, when a pulse from the laser falls on the semiconductor, photocarriers are generated and current flows through the antenna. The current persists until the photo-excited electrons relax back to the semiconductor valence band after the laser pulse has subsided. As a consequence of the current flow, a terahertz beam is radiated from the antenna with a pulse width rather longer than the laser pulse width; typically a few 100 fs. The resulting terahertz pulse typically has a bandwidth spanning 0.1–3 THz.

In optoelectronic generation, the Ti:sapphire laser pulse is incident on a material with a non-linear second order susceptibility, such as a crystal of ZnTe. The non-linearity results in difference frequency generation between the different frequency components in the input laser pulse. The beam emerging from the crystal is therefore composed of these difference frequencies, and can span a bandwidth from 0.1 to 35 THz. However, the level of phase matching that can be achieved between the incident and emerging beams can limit the output frequency range and impose structure on the output spectrum. Attention has to paid to the crystallographic orientation to achieve maximum efficiency.

Gated detection of the terahertz beam can, again, be accomplished in two ways. Photoconductive detection employs an antenna structure similar to that used for photoconductive generation. A terahertz signal can only be detected when the semiconductor region is illuminated by an NIR pulse from the ultrafast laser. If this is the case, an incident terahertz signal will drive a current in the antenna. For a train of terahertz pulses, the resulting average current can be measured using conventional electronics. Varying the delay between the terahertz pulse and the NIR gating, or probe, pulse enables the shape of the terahertz pulse to be recorded.

In electro-optic detection, the terahertz pulse is incident co-linearly with the NIR probe pulse on a crystal (e.g. ZnTe) that exhibits the linear Pockels effect. If no terahertz pulse were present, an incident linearly polarized NIR beam would emerge from the crystal with a circular polarization. If a terahertz pulse is incident, the NIR birefringence of the crystal changes via the linear Pockels effect and the NIR probe beam emerges with an elliptical polarization. The degree of ellipticity depends on the terahertz field amplitude. A quarter-wave plate and Wollaston prism can be used to resolve the emergent NIR beam into orthogonal linear polarization components, which can be detected with a pair of balanced photodetectors. The terahertz field amplitude is directly proportional to the difference between the NIR intensities detected by the photodetectors. Again, the delay between the terahertz pulse and NIR probe pulse can be changed to record the shape of the terahertz pulse in the time domain.