Terahertz Spectroscopy and Modelling of Biotissue

by

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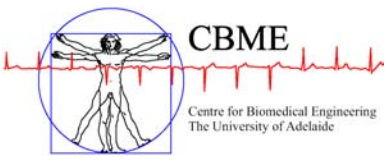

For Sheera

your love and belief in me have made this PhD journey possible

"Throughout the centuries, there were men who took first steps down new roads armed with nothing but their own vision."

The Fountainhead by Ayn Rand (1905–1982)

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Abstract

Pulsed terahertz (THz, or T-ray) research has burgeoned since its inception in the mid 1980s when the first pulses of THz radiation were emitted via electro-optic sampling. At the time, this discovery was a milestone for time domain spectroscopy because existing microwave and Fourier Transform Infrared (FTIR) spectrometers were not sensitive in the 0.1–10 THz frequency range. However, it would take several years before THz generation would become practical for spectroscopic use. In recent years, THz research has progressed to such a great extent that THz generation and detection techniques are now reliable and relatively low-cost, therefore THz has the potential to be used in a vast array of real-world applications ranging from security reinforcement (detection of weapons and explosives) to medical diagnosis (identifying melanomas). Indeed many bodies of research work have successfully demonstrated the efficacy of THz, although many challenges still exist before THz matures beyond the realm of research into everyday life.

This Thesis focuses on the area of THz spectroscopy and modelling of biotissue, with the aim of broadening the application of THz in medicine, particularly in the early diagnosis of Alzheimer's disease (AD). Since the nature of biotissue is complex, THz measurements of biotissue are prone to variability. Therefore, this Thesis includes the study of simpler biological analogues that mimic aspects of biotissue.

The work described in this Thesis makes five major novel contributions to THz research of biotissue: *(i)* the exploration of hydration and storage issues in freshly excised biotissue prior and during THz measurements; *(ii)* the use of snap-frozen biotissue in THz measurements for the purpose of investigating the plausibility of utilising THz sensing to distinguish between healthy and AD-afflicted human brain tissue; *(iii)* the use of THz spectroscopy to non-destructively differentiate between soft protein microstructures containing features of one of the known fibrillar pathogens of AD; *(iv)* the use of THz spectroscopy and full-wave electromagnetics simulation to study scattering from fibrillar structures akin to fibrillar pathogens of AD; and *(v)* transmission line modelling of THz propagation and reflection from stratified tissue layers in the human head.

The first part of this Thesis provides a historical review of the development of THz technology, with emphasis on the contributions of infrared (IR) and microwave research towards the realisation of the various THz generation and detection techniques available today. The various techniques are briefly reviewed prior to a thorough discussion of the types of THz generation and detection techniques used in this Thesis: electro-optic and photoconductive. A review of relevant IR, microwave, and THz medical research completes the first part of this Thesis.

In the second part of this Thesis, novel THz measurements of biotissue are presented and their results discussed. Experiment protocols for the handling and storage of excised biotissue are highlighted to emphasise how storage and hydration can severely alter THz measurements. Novel alternative sample preparation techniques, in the form of lyophilisation and snap-freezing, are presented. Terahertz spectroscopic comparison of healthy and AD-afflicted human tissue reveals promise for a future THz diagnostic tool, but highlights the need to investigate simplified biotissue analogues, such as skin, fat, and proteins. This need leads to the third part of this Thesis.

The third part of this Thesis involves THz spectroscopic study of one analogue of AD-afflicted biotissue: synthetically manufactured microstructures that resemble the proteins associated with AD. Terahertz differentiation of this microstructure from one with a dissimilar shape is revealed, suggesting a new non-destructive application for THz spectroscopy in biomedicine. The mechanism behind the differentiation is believed to be that of scattering, thus the next part of this Thesis explores scattering from more controlled test samples.

The penultimate part of this Thesis utilises a full-wave electromagnetics simulator to explain THz scattering from custom-built fibrillar structures. The novel use of the simulator allows a more accurate means of studying THz scattering, resulting in better agreement between measurement and simulation. The extra dimension of information that mathematical simulation provides leads to the final part of this Thesis, where a feasibility study is performed on the use of THz spectroscopy to study tissue layers in the head, with the aim of determining whether current THz systems can be used for *in vivo* diagnostic studies of tissue layers underneath the skin.

The contributions of this Thesis are important steps in advancing the use of THz in medicine, paving the way for the next generation of experimental and mathematical modelling studies of THz interaction with biotissue, in order to develop reliable THz diagnostic tools of the future.

Statement of Originality

This work contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Gretel Markris Png and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Conventions

The following conventions are adopted in this Thesis:

1. **Definitions.** In this Thesis, the terahertz band is defined as being from 0.1–10 THz (1 THz $= 10^{12}$ Hz).

2. **Acronyms and mathematical symbols.** Acronyms and mathematical symbols used in this Thesis are defined on pp. xxxvii–xli, p. 28, and pp. 52–53.

3. **Mathematical units.** The International System of Units (SI) is used throughout this Thesis for units and prefixes.

4. **Spelling.** British English spelling is adopted as default, as defined by the online Oxford English Dictionary (Oxford English Dictionary 2010). American English spelling, where used (e.g. units of length, such as 'meter' and 'submillimeter'; and the technical term 'program'), is as defined by the online Merriam-Webster Dictionary (Merriam-Webster Dictionary 2010).

5. **Typesetting.** This Thesis is typeset using the LaTeX2e software. Gnu Emacs was used as the word processing interface to LaTeX2e.

6. **In-text citation and bibliography referencing.** Harvard style is used for referencing and citation in this Thesis.

7. **Data processing and generation of plots.** Data processing of THz measurements was performed using the MATLAB software, versions 7.5.0 (release R2007b) and 7.6.0 (release R2008a). Manufacturer: the MathWorks Inc. (MathWorks, Inc. 2010). In Chapter 8, the High Frequency Structure Simulator (HFSS, versions 10.1 and 11) software is used in addition to MATLAB. Manufacturer of HFSS: Ansoft (Ansoft 2010).

8. **Colours in schematic diagrams.** In schematic diagrams, THz radiation is depicted in green for convenience, although THz radiation is invisible to the human eye. Laser light is depicted in red.

9. **Generation of schematic diagrams.** Inkscape (version 0.46) and the Gimp (version 2.6.4) were primarily used to create schematics in this Thesis. Adobe Illustrator (version 13.0.0) was used when necessary.

10. **URLs.** The Universal Resource Locators (URLs) of websites used for finding information in this Thesis are provided in the Bibliography Chapter. Access dates are given with each URL to indicate currency.

Nomenclature

Common acronyms used in this Thesis

2D	two dimensional
3D	three dimensional
β-lg	β-lactoglobulin
AC	alternating current
AD	Alzheimer's disease
Aβ	amyloid-β
CT	computed tomography
CW	continuous wave
DC	direct current
DNA	deoxyribonucleic acid
EO	electro-optic
FDTD	Finite Difference Time Domain
FEL	free electron laser
FEM	Finite Element Method
FFT	fast Fourier transform
FIR	far-infrared
FTIR	Fourier Transform Infrared
FTS	Fourier Transform Spectroscopy
FWHM	full width at half maximum
GaAs	gallium arsenide
GHz	gigahertz
HFSS	High Frequency Structure Simulator
IR	infrared
LIA	lock-in amplifier
MRI	magnetic resonance imaging
NMR	Nuclear Magnetic Resonance
OR	optical rectification
PC	photoconductive
PCA	photoconductive antenna

QCL	quantum cascade laser
RF	radio frequency
RNA	ribonucleic acid
RPI	Rensselaer Polytechnic Institute
SEM	scanning electron micrograph/microscope
SNR	signal-to-noise ratio
TDS	time domain spectroscopy
TE	transverse electric
TEM	transverse electric and magnetic
TM	transverse magnetic
THz	terahertz (1 THz = 10^{12} Hz)
T-ray, T-rays	terahertz (0.1–10 THz)
ZnTe	zinc telluride

Common mathematical symbols and constants

c	speed of light *in vacuo*
t	continuous time
ν	frequency
ω	angular frequency = $2\pi\nu$
λ	wavelength
k	wavenumber = $2\pi/\lambda$
$\hat{k}$	complex wavenumber
i	symbol for complex number
ϵ	electrical permittivity
ϵ_0	electrical permittivity *in vacuo*
$\hat{\epsilon}$	complex electrical permittivity = $\epsilon' - i\epsilon''$
ϵ'	$\Re\{\text{complex electrical permittivity}\} = \Re\{\hat{\epsilon}\}$
ϵ''	$\Im\{\text{complex electrical permittivity}\} = \Im\{\hat{\epsilon}\}$
μ	magnetic permeability
μ_0	magnetic permeability *in vacuo*
$\hat{n}$	complex refractive index = $n - i\kappa$
n	$\Re\{\text{complex refractive index}\} = \Re\{\hat{n}\}$
κ	$\Im\{\text{complex refractive index}\} = \Im\{\hat{n}\}$

σ	conductivity
α	absorption coefficient or extinction coefficient
d	material thickness
ϕ	phase in the frequency domain
T	Fresnel transmission coefficient
R	Fresnel reflection coefficient
e	even
o	odd
W	net rate at which electromagnetic energy crosses a surface
ψ	wave equation symbol
E	scalar electric field
$\mathbf{E}$	electric field vector
P	scalar polarisation
$\mathbf{P}$	electric polarisation vector
x	Cartesian or cylindrical x-axis
y	Cartesian or cylindrical y-axis
z	Cartesian or cylindrical z-axis
r	radius of cylinder
ϕ	azimuth
θ	zenith
l	length of cylinder
C	cross section
C_{sca}	scattering cross section
Q	efficiency
Q_{sca}	scattering efficiency
S_{11}	S-parameter (reflection)
S_{21}	S-parameter (transmission)