Health Information Science

Xiao-Xia Yin
Sillas Hadjiloucas
Yanchun Zhang

Pattern Classification of Medical Images: Computer Aided Diagnosis

Springer

Health Information Science

Series editor

Yanchun Zhang

More information about this series at http://www.springer.com/series/11944

Xiao-Xia Yin · Sillas Hadjiloucas
Yanchun Zhang

Pattern Classification of Medical Images: Computer Aided Diagnosis

Springer

Xiao-Xia Yin
Victoria University
Melbourne, VIC
Australia

Yanchun Zhang
Victoria University
Melbourne, VIC
Australia

Sillas Hadjiloucas
Biomedical Engineering, School of
Biological Sciences
University of Reading
Reading
UK

ISSN 2366-0988 ISSN 2366-0996 (electronic)
Health Information Science
ISBN 978-3-319-57026-6 ISBN 978-3-319-57027-3 (eBook)
DOI 10.1007/978-3-319-57027-3

Library of Congress Control Number: 2017938557

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

This book discusses recent advances in biomedical sensing as well as image analysis and processing techniques so as to develop a unified framework for computer-aided disease diagnosis. One of the aims is to discuss different approaches that will enable us to efficiently and reliably identify different features that are present in biomedical images. Another aim is to provide a generic framework for image classification.

The following four biomedical imaging modalities are considered: terahertz (THz) imaging, dynamic contrast-enhanced MRIs (DCE-MRIs) including functional MRI (fMRI), retinal fundus imaging and optical coherence tomography (OCT). THz imaging is chosen as it is a very promising emergent diagnostic modality that complements MRI. Under certain circumstances, it can also be independently used to identify and assess disease proliferation. OCT is a non-invasive imaging technique relying on low-coherence interferometry to generate in vivo, cross-sectional imagery of ocular tissue, and it complements fundus photography. Furthermore, OCT data sets have a structure similar to that found in THz imaging and MRI. Commonalities in these data structures can be explored by developing a unified multichannel signal processing framework for biomedical image analysis. Integration of complementary data sets provides additional features which can assist in inferring disease proliferation.

This book also provides an account of recent advances in artificial intelligence (AI) algorithms that may be applied to the multichannel framework discussed. Feature extraction and classification methods taking into consideration recent advances in support vector machine (SVM) and extreme learning machine (ELM) classifiers are also explained, and these formulations are extended to higher dimensional spaces for multiclass signal classification. The discussion also provides some future directions for machine learning approaches using Clifford algebra classifiers and deep learning architectures with geometric neurons. These recent advances can potentially lead to particularly powerful artificial intelligence AI algorithms that may one day automate several diagnostic processes.

Because of the multidisciplinary exposure of the subject, this book should be useful to final-year undergraduate or graduate students and research practitioners in

Biomedical Engineering, Applied Physics and Computer Science departments, who have already some familiarity with the topics discussed and are interested in learning about the latest advances on the subject. The different topics covered should also provide new ideas for discipline hopping, improving employability and career progression.

In addition, Chaps. 3–6 this book provides a generic framework for biomedical signal processing and classification which should be useful to computer science practitioners and AI software developers entering the biomedical field. The proposed multichannel framework points towards the direction of developing an open software architecture for signal denoising and feature extraction upon which specialized routines – tailored to different biomedical applications – can be developed. This is also beneficial from a software standardization perspective.

One of the issues commonly encountered in biomedical image analysis is that scientists from different disciplines focus on the different aspects associated with an image. A molecular spectroscopist will be focusing on locations in an image where efficient energy exchange between the excitatory signal and the tissue under study has taken place. This process would include the identification of specific ro-vibrational lines (for gases) or bands (for liquids and solids) as biomarkers under different physiological conditions. In contrast, an engineer would be focusing on signal processing, whereas a computer scientist on identifying the boundaries between different types of tissues or identifying and suppressing artefacts arising from different illumination conditions. In contrast, clinicians would be mostly concerned with the identification of different types and the pathological state of tissue as well as the visualization of small regions in the body and the mapping of opaque objects using a particular imaging technique. All these scientists tend to operate at different levels of complexity across a range of hierarchy levels from molecules all the way to the cellular, tissue, organ or organism level. The diversity of processing algorithms and the fact that modelling at one level of hierarchy does not scale well to higher levels of complexity due to the multiparametric emergent properties of biological media, are major contributing factors that have impeded progress towards automating the diagnostic process. An effort has been made to account for these different perspectives.

This book is, therefore, structured as follows:

Chapter 1 provides a general introduction to THz spectroscopy and then focuses on THz-transient spectrometry. The different system configurations and types of signals recorded are explained. The MRI imaging modality is also introduced. The tensorial nature of the MRI signal is also explained. THz and MRI time series analysis are placed in a common signal processing framework on the basis of the data structures associated with single pixels or voxels. An introduction to retinal fundus imaging as well as optical coherence tomography is also provided. Similarities and differences between these four different measurement modalities are highlighted.

Chapter 2 provides an overview of clinical applications using the four imaging modalities discussed in Chap. 1. This includes biomedical applications of THz spectroscopy and MRI, contrast imaging on the basis of tissue water content,

identification of biomarkers and the visualization of tissue oxygenation levels on the basis of the BOLD signal observed through fMRI. In addition, possibilities for combining THz spectroscopy and MRI with other sensing techniques using a multichannel framework are highlighted. Finally, recent advances in the application of fundus imaging to disease diagnosis and the application of OCT imaging for the visualization of increased vascularization in mammograms as well as the detection of abnormalities in infant brains are reported.

The following chapters take the view that the problem of developing automated classifier solutions for assessing disease progression should be seen as the tuning of three different modules that may be individually optimized for particular samples and data sets: the data acquisition imaging module, the data denoising pre-processing and feature extraction module and finally the classifier module. Tuning may be tailored separately for each module according to the features resolved by each measurement modality so as to optimize the classifier learning process.

Chapter 3 discusses different signal denoising methodologies applicable to both THz and MRI systems as well as fundus photography and OCT. Data windowing, apodization, parametric model fitting and multiresolution feature extraction methodologies with wavelets as well as adaptive wavelets for both THz and MRI data sets are also reviewed. The above discussions are effectively focusing on robust feature extraction and selection strategies, firstly from a single pixel perspective and then from an imaging perspective. Benefits from adopting a fractional order calculus approach to detect features in an image are explained. Recent advances in fundus image denoising are also highlighted. A multiresolution image fusion scheme that could be used to combine MRI with THz data sets is proposed. This chapter then discusses several feature selection strategies for both THz and MRI data sets. In the case of THz data sets features in time, frequency or wavelet domains associated with single pixels are considered. In the case of MRI data sets, the discussion focuses on features observed across entire images, taking into consideration textural information. Spatiotemporal correlations across different areas in an image, as identified through fMRI, are discussed. Advances in a graph-theoretical framework that can potentially elucidate such correlations are also mentioned. In addition, feature extraction and selection in retinal fundus imaging and OCT are reviewed.

Chapter 4 discusses recent advances in different classifier methodologies, with an emphasis on complex support vector machine and extreme learning machine approaches. An extension to multidimensional extreme learning machine classifiers is provided. Examples of binary as well as multiclass classification tasks using THz data sets are presented. The performance of other classifiers such as multimodal logistic regression, and naïve Bayesian, in performing classification of THz data sets is compared. In addition, some recent advances in clustering and segmentation techniques for THz data sets as well as for fundus images are discussed. Current methods for automatic retinal vessel classification are highlighted, as it is envisaged

that the improved edge detection algorithms discussed in the previous chapters in conjunction with the proposed classification methodologies, can lead to better discrimination between arteries and veins. Finally, this chapter discusses some recent advances in automated image classification using performance criteria directly developed by clinicians.

Chapter 5 provides a more in-depth analysis of MRI data sets. A recently developed spatiotemporal enhancement methodology for DCE-MRIs that makes use of a tensorial multichannel framework is explained. Examples from breast tumour reconstruction are provided to showcase the proposed methodology. It is shown that tumour voxels registered in three-dimensional space can be reconstructed better after increasing contrast from background images using the proposed methodology. The algorithm can be used to perform both feature extraction and image registration. This chapter also discusses the general structure of supervised learning algorithms for functional MRI data sets. Advances in supervised multivariate learning from fMRI data sets that promise to further elucidate brain disorders are discussed. Finally, the general structure of topological graph kernels in functional connectivity networks is explained. The prospects for developing machine learning algorithms that would automatically provide spatiotemporal associations of brain activity across different regions using graph theory methodologies are discussed. A more critical view of what may be achieved taking into consideration limitations in the fMRI measurement modality is provided. Finally, some recent advances from the computer vision community of relevance are highlighted as possible future research directions.

Chapter 6 provides an outlook to future multichannel classifiers, incorporating multiple features in their input space. Such approaches are also suitable for classifying multidimensional tensorial data sets. The discussion focuses on Clifford algebra-based feature classification. A multichannel approach enables the fusion of information acquired from multiple images at different time stamps, so it can potentially elucidate disease progression. In addition, this chapter discusses recent advances in deep learning as related to MRI as well as THz imaging data sets. The use of geometric neurons which can combine information from complementary sensing modalities is highlighted as an important future research direction for feature extraction and classification in MRI. In addition, the proposed Clifford framework could also benefit the THz imaging community, providing improved classification results when these systems undergo clinical trials.

Chapter 7 provides some concluding remarks related to the recent advances in signal processing and classification across the four imaging modalities discussed throughout this book. It aims to highlight how progress in each of the above research areas can be shared to accelerate progress across different biomedical imaging modalities. Furthermore, this chapter summarizes some of the main aspects of the unified multichannel framework that was developed throughout this book. Finally, this chapter concludes by providing some future directions towards a generic framework for the automated quantitative assessment of disease proliferation. It is envisioned that in the near future, a combination of several biomedical sensing modalities will be integrated through sensor fusion and that artificial

intelligence techniques will efficiently use the complementary information, to improve disease diagnosis.

The authors would like to gratefully acknowledge Dr. John W. Bowen from Reading University, Prof. Roberto K.H. Galvão from Instituto Tecnológico de Aeronáutica, São José dos Campos, Brazil, and Prof. Derek Abbott from the University of Adelaide for their valuable discussions over the years that have led to the development of our current understanding of the topics discussed in this book.

Melbourne, Australia — Xiao-Xia Yin
Reading, UK — Sillas Hadjiloucas
Melbourne, Australia — Yanchun Zhang
March 2017

Contents

1 Introduction and Motivation for Conducting Medical Image Analysis 1
1.1 Introduction to Time-Resolved Terahertz Spectroscopy and Imaging 2
1.1.1 Time Domain and Frequency Domain THz Spectroscopy 2
1.1.2 Recent Advances in Simultaneous Time-Frequency Dependent THz Spectroscopy 8
1.2 The Application of Magnetic Resonance to Biomedical Imaging 10
1.3 Placing THz Imaging and MRI Time-Series in a Common Signal Processing Framework 17
1.4 Introduction to Retinal Fundus Imaging 19
1.5 Introduction to Optical Coherence Tomography (OCT) 22

2 Overview of Clinical Applications Using THz Pulse Imaging, MRI, OCT and Fundus Imaging 27
2.1 Recent Advances in the Application of THz Pulse Spectroscopy to Biomedical Imaging 27
2.1.1 THz Radiation Absorption and Detection in Tissue 28
2.1.2 Identification of Compounds with Complex Composition 29
2.1.3 Recent Advances in the Application of DCE-MRI Imaging Techniques to Biomedical Imaging 31
2.1.4 Recent Advances in the Application of fMRI Imaging to Biomedical Imaging 33
2.1.5 Advantages and Shortfalls of T-Rays and DCE-MRI & FMRI 36
2.1.6 Combining MRI with Alternative THz Spectrometric Systems and Other Imaging Modalities 38

2.1.7 Recent Advances in the Application of the Fundus Camera to Disease Diagnosis 45
2.1.8 Recent Advances in the Application of OCT Techniques to Disease Diagnosis 47
2.1.9 Alternative Multichannel and MEMS Based OCT Imaging Modalities 49

3 Recent Advances in Medical Data Preprocessing and Feature Extraction Techniques 51
3.1 Overview of Medical Image Data Preprocessing Strategies 52
3.1.1 Data Windowing and Model Fitting Parametric Approaches 52
3.1.2 Multi-resolution Wavelet Analysis for Noise Removal 53
3.1.3 Current Standards and Recent Developments in Multiresolution Feature Representation in Imaging 57
3.1.4 Recent Advances in MRI Wavelet Denoising 59
3.1.5 Recent Advances in Fundus Image Denoising 60
3.1.6 The Need for a Multiresolution Image Fusion Approach 63
3.2 Overview of Feature Selection Strategies 64
3.2.1 Feature Selection Strategies in THz TPI Datasets 64
3.2.2 Feature Extraction and Selection on the Basis of Cross-correlation Sequences 71
3.2.3 Feature Selection Strategies for MRI Datasets 74
3.2.4 Spatiotemporal Correlations and Cluster Analysis of Brain Activity Using fMRI 79
3.2.5 Feature Selection in Retinal Fundus Photography Following Image Enhancement 85
3.2.6 Feature Extraction and Pattern Identification of Pathology Distortion in SD-OCT Imaging 90
3.2.7 Statistical Analysis Based on Feature Selection Strategies 92

4 Pattern Classification 93
4.1 Introduction to Pattern Classification 93
4.2 Feature Based Mahalanobis Distance Classifiers 94
4.3 Support Vector Machine Classifiers (SVMs) 95
4.3.1 Binary Classification of SVMs 95
4.3.2 Pairwise SVM Classification of Multiple Classes 98
4.3.3 Application of SVM Classifiers to THz-TPI Measurements 99
4.4 Real-Valued Extreme Learning Machine Classifier 101
4.5 Complex Valued ELMs for Classification 103
4.5.1 Review of Complex-Valued RKHS and Wirtinger's Calculus 103

4.5.2 Defining Higher-Dimension Hyprplanes Using Quaternion and Other Division Algebras for Classification . . . 105
4.5.3 Determination of the Maximum-Margin Hyperplanes of CELM . . . 110
4.5.4 Multinomial Logistic Regression Classifier with Ridge Estimators (MLR) . . . 117
4.5.5 Naive Bayesian (NB) Classifier . . . 118
4.5.6 Performance Evaluation of Several Different Classifiers . . . 118
4.5.7 Clustering Techniques to Segment THz Images . . . 121
4.6 Retinal Fundus Image Analysis via Supervised and Non-supervised Learning . . . 123
4.6.1 Fundus Image Vessel Segmentation . . . 123
4.6.2 Algorithmic Detection of the Optic Disk . . . 124
4.6.3 Retinal Vessel Classification: Identifying and Sorting Arteries and Veins . . . 126
4.6.4 Automated Image Classification Using Criteria Directly Developed from Clinicians . . . 127

5 Introduction to MRI Time Series Image Analysis Techniques . . . 129
5.1 Analysis of DCE-MRI Data . . . 129
5.1.1 Outlook for Future Tensorial Algebra Based Feature and Image Registration . . . 131
5.1.2 Performance Measures . . . 133
5.2 Tensorial Representations in MRI . . . 134
5.3 Extensions to Multi-channel Classifiers . . . 136
5.3.1 Suppression of Background Voxels Through Multi-channel Reconstruction . . . 140
5.3.2 Increased Image Contrast Between Tumours and Background Through Multi-channel Reconstruction . . . 141
5.4 Image Registration of MRIs . . . 143
5.5 Pattern Identification of Spatiotemporal Association of Features in Tumours from DCE-MRI Data . . . 146
5.6 Pattern Classification of Spatiotemporal Association Features in fMRI Data . . . 149
5.6.1 Supervised Tensor Learning of Brain Disorders in fMRI Datasets . . . 149
5.6.2 Supervised Multivariate Learning of Brain Disorders from fMRI Data . . . 151
5.6.3 Topological Graph Kernel on Multiply Thresholded Functional Connectivity Networks . . . 154
5.6.4 Machine Learning Using Information from Brain Graphs . . . 160
5.6.5 Additional Considerations Regarding MRI Feature Extraction Methodologies . . . 161

5.6.6 Recent Relevant Advances from the Computer Vision Community. 163

6 Outlook for Clifford Algebra Based Feature and Deep Learning AI Architectures 165
6.1 Prospects for Medical Image Analysis Under a Clifford Algebra Framework 165
6.2 Outlook for Developing a Geometric Neuron Deep Learning of Time Series Datasets in Medical Images 169
6.3 Prospects for Alternative Classifiers in Deep Learning of Unlabelled Medical Image Data. 177

7 Concluding Remarks 179

References 183

Index 215

Chapter 1
Introduction and Motivation for Conducting Medical Image Analysis

The demand for advanced image analysis techniques stems from the recent proliferation of new biomedical imaging modalities across the electromagnetic spectrum. The number of scans currently performed in most hospital environments has exploded placing unprecedented workloads on personnel associated with their interpretation. At the same time, we are also witnessing remarkable advances in artificial intelligence (AI). New algorithms are paving the way for the provision of automatic image interpretation which can lead to improved diagnosis and better understanding of disease progression. Furthermore, advances in biomedical equipment suitable for home use are also providing new opportunities for the further proliferation of AI systems and lead to advances in networked home care technologies which promise to make possible the remote diagnosis of the onset of disease much earlier than before, thus minimizing the need for consultation by experts. Such practice is also likely to provide almost expert opinion at reduced cost. Through these advances, one can foresee some inevitable developments that will affect how the provision of health care will be managed in the near future across the developed world.

From a signal processing and AI perspective, most of the imaging modalities display some underlining commonalities. In order to establish the generic underlying common problems encountered across the various imaging methods, this book focuses on just four representative modalities that operate at different parts of the electromagnetic spectrum: THz pulse imaging or TPI, MRI, fundus imaging and OCT. The aim of the first chapter is to introduce each measurement modality and explain how they complement each other. This will enable us to introduce in subsequent chapters a possible common framework that can lead to unified signal processing and image classification using machine learning. The common underlying theme in all four diagnostic methods considered is the imaging of tissue at various states of hydration and the possibility of providing diagnosis of the onset of disease or an assessment of disease proliferation on the basis of changes in the physicochemical environment of the cells, e.g. through changes in blood flow or through the use of biomarkers which can also lead to textural changes in the tissue. We first discuss

X. Yin et al., *Pattern Classification of Medical Images: Computer Aided Diagnosis*, Health Information Science, DOI 10.1007/978-3-319-57027-3_1

the technological aspects of THz spectroscopy, the different system configurations commonly used as well as the type of signals generated. An introduction to MRI and recent developments in contrast enhanced imaging is then provided. The need to develop a tensorial representation of the signal to account for anisotropy is also highlighted. This chapter also places THz imaging and MRI imaging in a common multi-dimensional signal processing framework. In addition, an introduction to retinal fundus imaging and OCT imaging is provided. Finally, similarities with the other two imaging modalities are highlighted. The similarity in these data structures naturally leads to a unified approach for data pre-processing and image classification extending pattern recognition to new application areas [1].

1.1 Introduction to Time-Resolved Terahertz Spectroscopy and Imaging

1.1.1 Time Domain and Frequency Domain THz Spectroscopy

Investigations at the terahertz (THz) part of the electromagnetic (EM) spectrum loosely defined between 100 GHz–10 THz are of much relevance to the biological sciences because THz radiation interacts strongly with polar molecules [2–4]. Biological tissue is generally composed of polar liquids so discrimination between tissue types can be made on the basis of water content. The technique is very sensitive in providing contrast between samples at various degrees of water saturation [5–7], and has applications in the evaluation of the severity of burns or partially necrotic skin samples [8] and the imaging of basal cell carcinomas [9–12] which can show an increase in interstitial water within the diseased tissue [5, 13].

Since THz photons have significantly lower energies (e.g. only 1.24 meV at 300 GHz) than X-rays, they have been considered by many as non-invasive. Although non-linear interactions between biological tissue and coherent THz radiation have been predicted by Fröhlich [14] and experimentally verified by the careful work of Grundler and the analysis of Kaiser [15] in the '90s, the current and widely held view is that any measurement technique that operates at THz frequencies should be evaluated using current guidelines on specific absorption rates. These are only associated with the thermal effects of the radiation with the tissue; so from a clinical perspective, such irradiation can be considered as non-invasive. Such a view is also further supported by noting that the Gibbs free energy conveyed in the THz light beam is insufficient to directly drive chemical reactions. For example, the molar energy at a frequency f of 100 GHz would be given from $E = Nhf$ where $N = 6.023 \times 10^{23}\,\mathrm{mol}^{-1}$, Avogadro's number), and $h = 6.626 \times 10^{-34}$ Js (Planck's constant), resulting in a calculated value of only $E = 0.04\,\mathrm{kJ\,mol}^{-1}$ which is so low (approximately 100 times lower than the amount of molar energy required for ATP

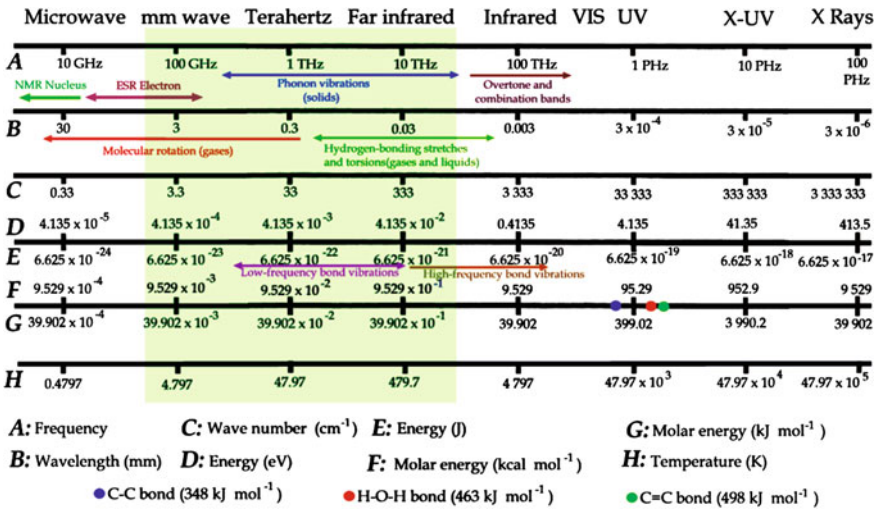

Fig. 1.1 Multidisciplinary interpretation of the electromagnetic spectrum

hydrolysis) that for most practical purposes; we may assume that the interference with biochemical processes would be minimal (Fig. 1.1).

Furthermore, in the THz part of the spectrum, many molecules have characteristic 'fingerprint' absorption spectra [16–18]. Substances in the condensed phase are held together by either ionic, covalent or electrostatic forces, and therefore the lowest frequency modes will be associated with intermolecular motion [19]. The interaction between THz radiation and biological molecules, cells, and tissues can be understood using assumptions of propagation of an angular spectrum of plane waves through the material [21]. Following standard postulates of dielectric theory, a medium may be characterized in terms of its permittivity ε (the ability of the medium to be polarized) and conductivity σ (the ability of ions to move through the medium). At higher frequencies, transitions between different molecular vibrational and rotational energy levels become increasingly dominant and are more readily understood using a quantum-mechanical framework [22]. THz pulse spectroscopy provides information on low-frequency intermolecular vibrational modes [23].

THz imaging can thus be remarkably informative regarding a sample's composition. The Fourier transform of the associated time domain waveform over a broad spectral range allows the calculation of the frequency dependent refractive index and absorption coefficients of the sample. Since wavelengths are longer in the THz part of the spectrum, there is sufficient phase stability in the experimental apparatus enabling the extraction of phase information by varying the time delay between the THz wave and the probe beam [16]. When some materials are sufficiently transparent to THz radiation, it is feasible to measure transmission responses and acquire spectral information. Reflectance imaging is also straightforward, and through the combination of transmittance and reflectance, a spectral absorbance may be inferred. This is not

always possible at the infrared, optical and ultraviolet parts of the spectrum where errors, due to scattering of shorter waves due to the surface roughness of the samples, preclude direct calculations of absorbance. Reduced scattering of THz waves thus minimises errors in inferred absorbance from measurements of transmittance and reflectance. Alternative measurement topologies which provide differential absorption have also been developed; such systems can produce very informative contrast images for the evaluation of disease progression.

Further advantages of imaging using THz radiation include the improved penetration depth within the tissue and the ability to differentiate between organs on the basis of tissue water content. Since 70% of the human body is composed of water, a large proportion of the excitation energy is significantly attenuated and, as a consequence, the resultant spectra in many biomedical experiments may only be unambiguously resolved after the application of elaborate post-processing techniques. Excluding super-resolution techniques, imaging resolution is limited by the diffraction wavelength and is thus inferior to infrared or optical imaging but superior to microwave based imaging modalities.

Although much of the pioneering work in building interferometric spectroradiometers and other continuous wave measurement systems at the THz part of the spectrum took place at Queen Mary College over a period of almost 30 years under the guidance of D. H. Martin [20], it was only during the past two decades that THz science and technology has flourished as a universally accepted new sensing modality. Using continuous wave systems [24], there is a variety of instruments that may be assembled using quasi-optical active and passive components. The AB Millimetre vector network analyser, if available, is the preferred choice for continuous wave measurements with significant signal-to-noise per spectral bin all the way up to 1.2 THz. It is not, however, as user friendly for extracting scattering parameters as other commercially available solutions that operate at lower frequencies. An account of different topologies using null-balance methods can be found in [25] whereas polarimetric measurements for dichroic samples should ideally be performed using the topologies discussed in [26, 27] or Fabry-Perot structures, e.g. [28]. Alternative broadband experimental configurations may include Mach–Zehnder or Martin-Puplett configurations as discussed in [7, 20, 21]. When high power per spectral bin is needed, THz imaging may also be performed (at significant cost) with high-power THz sources under pulsed scanning mode and pulse-gated detection using large scale facilities (e.g. Jefferson lab, FELIX etc.). Currently, however, bio-medical investigations using these facilities are fewer than those performed in the physical sciences e.g. the semiconductor community.

Although there are several THz imaging systems that can be built using continuous wave sources by appropriately adapting the above configurations to perform raster-imaging of the sample [24], the focus of this book is on time domain spectroscopy (TDS) with ultrashort-pulse laser sources because of their recent proliferation. Such systems are more versatile for biomarker identification than their continuous wave counterparts because they are inherently very broadband without requiring liquid-helium cooled detectors (heterodyne based continuous wave systems are more narrow-band and lack such versatility because of the lack of such wide tunability of

the sources). Furthermore THz pulse imaging (THz-TPI) has important applications in in vivo, in vitro and ex vivo biosensing [8, 16, 29, 33]; identifying 'fingerprint' resonances due to overtone and combination bands [5, 30].

At this point it is worth noting that there are several similarities between THz-TDS and the pulsed radar sensing modality. In THz-TDS, the time gated reflections are analysed directly in the time domain by observing their attenuation, phase delay and temporal spread after interacting with matter. Good temporal definition can provide localization of tissue interfaces on the basis of refractive index differences (the real part associated with impedance mismatch and the complex part with the attenuation due to the number of absorbers and their extinction coefficient). Studies in reflection geometry can occasionally also enable the indirect assessment of sample or layer thickness, as well as determining the position of embedded unknown objects, etc. [16].

An important advantage of time-domain systems over their continuous wave counterparts that are plagued by etalon effects is that of being able to perform pulse time gating. This is possible as long as the multiple reflections in the measurement system are sufficiently far apart so as not to be mixed with the molecular de-excitation signals of the sample. The typical time-resolved THz spectrometer used in most of the studies discussed so far, utilize a short coherence length infrared source (centered at around 800 nm) to generate a sub-100 femtosecond duration pulse train with repetition frequency of around 80 MHz. Each infrared pulse, is split into separate pump and probe beams. The pump beam is used to excite an optical rectification crystal, which acts as a T-ray emitter, and the T-rays produced (duration around 200 fs) are collimated and focused onto a sample by a pair of parabolic mirrors. The T-rays emerging from the sample are re-collimated by another pair of mirrors, before being combined with the probe beam in a T-ray detector crystal. As a result, the modification by the sample T-ray and the probe beams propagates through the THz detector crystal co-linearly. The pump beam, which is also transmitted through a chopper, travels through an optical delay stage that is modulated accordingly, so that the pump and probe beams arrive at the detector in a time-coincident manner. The electro-optic detector crystal produces an output that is proportional to the birefringence observed from the interaction of the THz pulse with the time-coincident infrared pulse replica within the crystal. This output is proportional to the T-ray response of the sample and this signal is measured with the use of a balanced optical photo-detection scheme. A lock-in amplifier (LIA) is also used to demodulate the signal, and this avoids $1/f$ (flicker) noise problems that are present in this detector-limited measurement scheme. Typically, THz-TPI is performed through a 2D raster scan after translating the sample in both the x and y direction, while keeping it at the focal plane of the parabolic mirrors. A typical setup [31, 34], is shown in Fig. 1.2.

Details of typical THz transient systems can be found elsewhere [33]. An interesting quasi-optical circuit topology for simultaneous measurements of both transmittance and reflectance that was reported by Ung et al. [35] is shown in Fig. 1.3. In that system, the frequency dependent reflectance $R(\omega)$ and transmittance $T(\omega)$ signatures are given from:

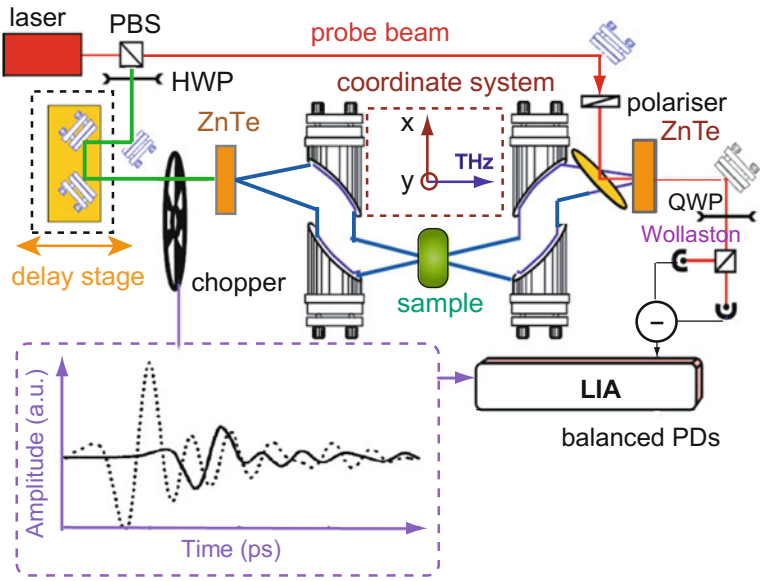

Fig. 1.2 A schematic experimental setup for electrooptic transmission THz imaging with ZnTe as EO generation and detection, illuminated by a femtosecond laser

$$R(\omega) = \frac{1-\widetilde{n}(\omega)}{1+\widetilde{n}(\omega)} + \frac{\frac{4\widetilde{n}(\omega)[\widetilde{n}(\omega)-1]}{(\widetilde{n}(\omega)+1)^3} \cdot \exp[-i2\widetilde{n}(\omega)\frac{\omega}{c}d]}{1-(\frac{\widetilde{n}(\omega)-1}{\widetilde{n}(\omega)+1})^2 \cdot \exp[-i2\widetilde{n}(\omega)\frac{\omega}{c}d]} \tag{1.1}$$

$$T(\omega) = \frac{4\widetilde{n}(\omega)}{[1+\widetilde{n}(\omega)]^2} \cdot \frac{\exp\{-i[\widetilde{n}(\omega)-1]\frac{\omega}{c}d\}}{1-(\frac{\widetilde{n}(\omega)-1}{\widetilde{n}(\omega)+1})^2 \cdot \exp[-i2\widetilde{n}(\omega)\frac{\omega}{c}d]} \tag{1.2}$$

where the normal incidence complex refractive index is $(\omega) = n(\omega) - ik(\omega)$ and the absorption coefficient is: $\alpha(\omega) = 4\pi k(\omega)/c$ where c is the speed of light, k is the wave number, d is the sample thickness and the tilde denotes a complex quantity. An alternative phase-sensitive topology is reported in the work by Pashkin et al. [36]. An interesting prospect for dispensing with the conventional x, y, z scanning stages for image formation at the focus of the paraboloids by adopting a metamaterials based scanning technique for image formation is discussed in [37, 38].

The resultant measurement at each pixel position of an image is an entire time-dependent waveform. Therefore, the result from TDS-TPI is a three-dimensional (3D) data set, which then can potentially be mapped to two-dimensional (2D) images [39], where structural and compositional discrimination based on a sample's optical properties may be conveniently performed using pattern recognition algorithms. In the following chapters, sample responses from multiple THz spectrometry experiments are used as examples to provide a generic pattern recognition framework.

The proposed approach extends the range of applications of pattern recognition to emergent sensing modalities [1, 40].

A further advantage of the associated phase stability in THz spectrometers (due to the associated longer wavelength) is that it enables direct measurement of both the real and imaginary (complex) components of the permittivity. A Debye relaxation model can be used to analyze the strong absorption of terahertz radiation in polar liquids at least up to 1 THz [5, 32]. This model can be directly related to the associated intermolecular dynamics. Spectroscopic studies can, therefore, potentially elucidate the way proteins influence the state of water and can lead to further understanding of the role of hydration shells in protein interactions [41, 42].

It is also worth noting that in all of the above experimental set-ups one needs to always consider that there may also be additional pseudocoherence errors because different parts of the beam across its aperture travel different paths through different regions of the sample (if it is of non-uniform thickness), interfering constructively or destructively with each other when they recombine. A recent account of advances in THz metrology discussing errors in both continuous wave as well as THz-transient systems can be found in [43]. Such errors are endemic to much of the THz literature although this is not extensively discussed. Management of these artefacts and their relevance to imaging applications is therefore an open issue requiring further consideration. For the case of reflectometric measurements using continuous wave sources, it is occasionally possible to de-embed the reflection signature from different layers as discussed in the work by Hadjiloucas et al. [44]. The technique has been applied to waveguide measurements but has yet to be applied to reflection measurements of biological tissue when the different strata contain different water content (Fig. 1.3).

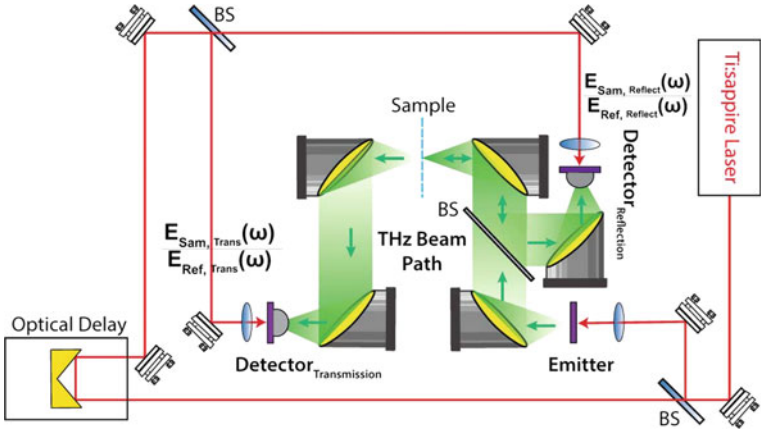

Fig. 1.3 Quasi-optical setup for simultaneous reflection and transmission THz-TDS measurements. The path of the 800 nm laser beam is depicted in *red*, while the THz beam path is shown in *green*, with all beams horizontally polarized. The sample is placed in the focus of the parabolic mirrors and, for a reference measurement in reflection geometry, a mirror is used adopted from [35]

From a technological point of view, THz imaging is thus an emergent complementary imaging modality of much interest within the biomedical community, potentially competing with positron emission tomography (PET) imaging which has picomolar sensitivity but poor spatial resolution and magnetic resonance imaging (MRI), which provides millimolar sensitivity with high spatial resolution. A diffraction limited imaging system operating at 2 THz would have a spatial resolution of 150 μm, which may be considered limiting for many biomedical applications for which this imaging modality offers niche applications (e.g. differential imaging of cancer cells in breast tissue of pregnant or lactating women). From a clinical perspective, tumours need to be identified at the earliest possible developmental stage and, unless suitable THz super-resolution techniques can be adopted (a difficult task since beams are diffractively spreading and the optics community has yet to extend existing algorithms from the infrared to the THz part of the spectrum), it is unlikely that current systems will be adopted by clinicians. Imaging systems integrating either PET or MRI modalities with THz pulse imaging to enable the generation of composite images is the most likely way forward for the integration of this technology in a clinical setting.

1.1.2 Recent Advances in Simultaneous Time-Frequency Dependent THz Spectroscopy

Time-frequency analysis methods have been developed to provide very parsimonious parametrizations of time series datasets and, in this sense, nicely complement other parametrization schemes performed in either time or frequency domains [45, 46]. The wavelet transform (WT) is a popular technique suited to the analysis of short-duration signals [47]. It decomposes the time series signal using two filter banks separating the high (detail) and low (approximation) frequency components of the signal assuming a pre-defined mother wavelet function. The approach provides very efficient de-noising capabilities in the presence of Gaussian white noise and has very parsimonious representation. An important feature of this transform is that it has orthogonal basis functions so that it enjoys perfect reconstruction symmetry, enabling its inverse transform to reproduce the original dataset without loss of information. This is a particularly important property from a biomedical signal processing perspective as software certification for biomedical purposes should require complete traceability of all the data processing steps. A further development in the biomedical signal processing literature has been the use of adaptive wavelets [48], where the mother wavelet is specifically tailored at each decomposition level (wavelet scale), to minimize the least squares error associated with the difference between the transformed signal from its original one. The approach holds great promise for optimizing the extraction of the spectroscopic information contained in each THz pulse transient as well as in THz TPI generally [49–52]. Figure 1.4 showcases the advantages of time-frequency analysis in terms of the reduction in classification errors. To generate this graph, the standard deviation of the noise was varied from 0.001 to 0.5. For

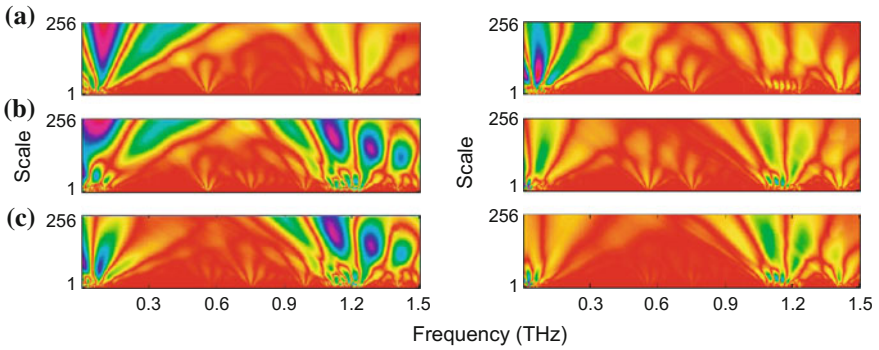

Fig. 1.4 Classification errors (%) as a function of noise level in the interferograms. Nonoptimized db4 wavelet (green), optimized wavelet (*red*) and Euclidean distance (*blue*) classifiers. The inset shows an inferogram of leather with (**a**) no artificially added noise and noise with standard deviation of (**b**) 0.1 and (**c**) 0.5. After [52]

each noise level, 250 noisy patterns were generated for each class (lycra and leather). As can be seen, the classification is much more robust to noise when carried out in the wavelet domain than in the original domain. Moreover, the robustness to noise is further increased by the optimization of the WT.

In addition to the above more elaborate routines, there have also been other examples of studies that incorporate WT pre-processing routines for signal-to-noise-ratio enhancement and classification of THz spectra [8, 53]. Such a pre-processing step enabled the successful discrimination of cancerous from normal tissue in wax-embedded histopathological melanoma sections as well as the classification of dentine and enamel regions in teeth [49]. It is now generally accepted that the performance of a classifier based on the output of a wavelet filter bank is improved over that of an Euclidean distance classifier in the original spectral domain [52]. Finally, an alternative very promising approach for the modelling of de-excitation dynamics, which has its origins to the theory of complex dielectrics, is through the use of fractional order calculus and the fitting of fractional order models. In this approach, the time series experimental datasets are modelled using very parsimonious pole-zero expressions associated with the dynamics of resistive, capacitive or inductive networks [54–56]. Although the fractional-order system identification literature is still in its infancy, it promises to provide much lower residual errors in the identified models, thus significantly advancing the science of chemometrics that is of significance to the further advancement of the discussed biomedical investigations. The approach can account for spectral shifts in amorphous materials as well as de-embed solvation dynamics.

Since dual modality THz/MRI tandem hybrid imaging systems have already been discussed in the literature [57], it is appropriate to look more closely at recent advances in MRI sensing before a combined signal/image processing framework is proposed.