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Improving the Sensitivity of Radar-based Breast Imaging Algorithms in Diverse Patient Populations

Presented by:
Declan Denis O’Loughlin

to:
Electrical and Electronic Engineering,
College of Engineering and Informatics,
National University of Ireland Galway,

in fulfillment of the requirements for the degree of
Doctor of Philosophy.

Supervised by:
Martin O’Halloran

Co-supervised by:
Edward Jones
Martin Glavin

September 2018
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Declaration of Originality

I, the Candidate Declan Denis O’Loughlin, certify that this thesis entitled “Improving the Sensitivity of Radar-based Breast Imaging Algorithms in Diverse Patient Populations”:

• is all my own work;

• has not been previously submitted for any degree or qualification at this University or any other institution;

• and where any work in this thesis was conducted in collaboration, appropriate reference to published work by my collaborators has been made and the nature and extent of my contribution has been clearly stated.

Name:
Declan Denis O’Loughlin
Abstract

Radar-based imaging is an emerging modality for breast cancer screening. Two commercial radar-based imaging devices are being tested in patient imaging studies. Promising initial results have highlighted the potential of the technology but have also identified that breast composition varies substantially from individual to individual. The breast composition is known to impact image quality, motivating the primary research objective: to develop novel radar-based breast imaging algorithms to address the normal variance of breast composition observed in the population.

Firstly, fundamental assumptions of radar-based imaging algorithms are examined. The results of this analysis indicate that accounting for the dielectric properties of the patient-specific breast positively impacts the sensitivity of radar-based imaging in patient populations with normal breast variance. Using breast phantoms mimicking normal variation in breast composition, it is shown that using one population mean estimate of the dielectric properties may not be suitable to reconstruct images of all breasts.

Secondly, a novel radar-based imaging algorithm is developed that can account for the dielectric properties of the patient-specific breast. The proposed algorithm is tested using experimental data from breast phantoms and also evaluated using five clinical case studies from the University of Calgary. The algorithm is applied to patients both with and without breast disease. These results suggest that the proposed algorithm can help improve the sensitivity in patients with breasts of differing tissue composition without impairing the specificity. However, both the experimental imaging results and clinical case studies highlight that achieving high specificity in dense breasts may be a potential challenge. More work needs to be done to investigate factors affecting the specificity of radar-based imaging.

In summary, this thesis indicates that accounting for the patient-specific breast is important to achieve high sensitivity using radar-based breast imaging. A novel algorithm is proposed and tested that could be used to improve the sensitivity of radar-based breast imaging without negatively impacting the specificity.
Acknowledgements

First and foremost, I would like to thank my primary supervisor, Dr Martin O’Halloran, and co-supervisors, Dr Edward Jones and Dr Martin Glavin, for all their help, direction and guidance throughout my PhD. Your continued interest in my work and professional development is greatly appreciated and your unwavering enthusiasm was invaluable to me. To all the staff of Electrical and Electronic Engineering, in particular, Mary Costello, Myles Meehan, Martin Burke, Liam Kilmartin, Dr Maeve Duffy, Dr Fearghal Morgan, Prof. Peter Corcoran and Prof. Gearóid Ó Laighin, thank you for always supporting me.

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<td>BAVA-D</td>
<td>balanced antipodal Vivaldi antenna with director. 107</td>
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<tr>
<td>BI-RADS</td>
<td>Breast Imaging—Reporting and Data System. 40, 49, 54, 57, 107, 112, 118</td>
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<tr>
<td>CrDAS</td>
<td>channel-ranked delay-and-sum. 38</td>
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<tr>
<td>CT</td>
<td>computerised tomography. 57</td>
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<tr>
<td>DC</td>
<td>Dartmouth College, NH, USA. 29, 31, 33, 34, 39, 44, 47, 48</td>
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<td>DCIS</td>
<td>ductal carcinoma in situ. 16, 17, 23, 26, 41</td>
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<td>DCT</td>
<td>discrete cosine transform. 95, 152</td>
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<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine. 39</td>
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<td>DMAS</td>
<td>delay-multiply-and-sum. 38</td>
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<td>DWT</td>
<td>discrete wavelet transform. 94, 156</td>
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<td>FDA</td>
<td>Federal Drug Administration. 2</td>
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<td>FQM</td>
<td>focal quality metric. 90, 93–95, 98, 100–102, 104, 125, 152, 154, 155</td>
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<td>FWHM</td>
<td>full width at half maximum. 69, 108, 111</td>
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<td>HTA</td>
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<td>HU</td>
<td>Hiroshima University, Japan. 30, 33–36, 41, 71</td>
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<td>IDAS</td>
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<td>MARIA®</td>
<td>Multistatic Array Processing for Radiowave Image Acquisition. 4, 29–31, 33–35, 37–40, 43, 50, 53, 57, 64, 69, 71, 125, 127</td>
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<td>MDAS</td>
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<td>MU</td>
<td>McGill University, Quebec, Canada. 30, 33–36, 42, 43, 58, 71</td>
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<tr>
<td>PCB</td>
<td>printed circuit board. 34</td>
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<td>PLA</td>
<td>polylactic acid. 65</td>
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<td>PSF</td>
<td>point spread function. 90–92, 95–98, 104</td>
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<td>SCR</td>
<td>signal-to-clutter ratio. 41, 69–71, 93, 97, 98, 121, 122, 127</td>
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<td>SubMinature Version A. 65</td>
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LIST OF ABBREVIATIONS

SMR  signal-to-mean ratio. 93, 114, 116, 118, 121, 122, 127
SU   Shizuoka University, Japan. 30, 31, 33–35, 71
SUST  Southern University of Science and Technology, China. 30, 31, 33–36, 41, 69, 71
VGF  volume glandular fraction. 57–59, 62, 63, 65, 66, 70, 78, 79, 81–84, 86–89, 100–102, 124
VNA  vector network analyser. 65–67
WHO  World Health Organization. 1, 123
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<tr>
<td>$c_0$</td>
<td>The speed of light in free space.</td>
<td>68, 73, 75, 91</td>
</tr>
<tr>
<td>$c_{\text{min}}$</td>
<td>The minimum speed of propagation of electromagnetic energy.</td>
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<tr>
<td>$d_{\text{max}}$</td>
<td>The longest propagation path.</td>
<td>68</td>
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<tr>
<td>$E$</td>
<td>The total electric field.</td>
<td>27, 37</td>
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<tr>
<td>$E'$</td>
<td>The incident electric field.</td>
<td>27, 37</td>
</tr>
<tr>
<td>$E^s$</td>
<td>The scattered electric field.</td>
<td>27</td>
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<tr>
<td>$E_{a,\omega}(a')$</td>
<td>The total electric field sampled at location $a'$ after a single frequency incident electric field at angular frequency $\omega$ is transmitted from location $a$.</td>
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<tr>
<td>$G_b(r', r)$</td>
<td>Green’s Function of the background medium.</td>
<td>27</td>
</tr>
<tr>
<td>$I(r)$</td>
<td>Image intensity at the point $r$.</td>
<td>28, 38, 68, 91</td>
</tr>
<tr>
<td>$j$</td>
<td>The imaginary unit.</td>
<td>28, 38, 68, 91</td>
</tr>
<tr>
<td>$k_0$</td>
<td>Free-space wave number.</td>
<td>27</td>
</tr>
<tr>
<td>$N_C$</td>
<td>The number of independent channels used for imaging: reciprocal pairs contain redundant information.</td>
<td>65</td>
</tr>
<tr>
<td>$P(\omega)$</td>
<td>The incident pulse at angular frequency $\omega$.</td>
<td>28, 91</td>
</tr>
<tr>
<td>$r_{\text{max}}$</td>
<td>The maximum radius of the tumour phantom.</td>
<td>92</td>
</tr>
<tr>
<td>$r^T$</td>
<td>The location of a point scatterer representing a tumour.</td>
<td>91</td>
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<tr>
<td>$S_{a,a'}$</td>
<td>The response received at antenna location $a'$ after transmission from the antenna at the location $a$ in the time domain.</td>
<td>38</td>
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<tr>
<td>$T$</td>
<td>After synthetic focusing, the length of signal over which the energy is calculated.</td>
<td>38</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>The maximum propagation time of electromagnetic energy.</td>
<td>68</td>
</tr>
<tr>
<td>$w(r)$</td>
<td>Per point weighting factor used to prioritise points where tumours are more likely.</td>
<td>28, 37, 38</td>
</tr>
<tr>
<td>$w_{a,a'}(r)$</td>
<td>Per channel weighting factor used to prioritise signals based on antenna beamwidth or relative locations of the antennas and points of interest.</td>
<td>28, 37, 38</td>
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**LIST OF SYMBOLS**

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<thead>
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<tbody>
<tr>
<td>$A$</td>
<td>The set of incident antenna locations where the incident electric field, $E_i$, is generated sequentially for each antenna location. a. 28, 38, 65, 67, 68, 91</td>
</tr>
<tr>
<td>$A'$</td>
<td>The set of receiving antenna locations where the total electric field, $E$, is sampled while the incident electric field is being generated. 28, 38, 67, 68</td>
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<td>$C$</td>
<td>The measured dielectric properties of breast tissues removed during cancer surgeries. 47</td>
</tr>
<tr>
<td>$C_1$</td>
<td>The measured dielectric properties of Group I healthy breast tissues removed during breast cancer surgeries, i.e. healthy breast tissues containing less than 30% adipose tissues. 46</td>
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<tr>
<td>$C_{II}$</td>
<td>The measured dielectric properties of Group II healthy breast tissues removed during breast cancer surgeries, i.e. healthy breast tissues containing between 30% percent and 85% adipose tissues. 46</td>
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<tr>
<td>$C_{III}$</td>
<td>The measured dielectric properties of Group III healthy breast tissues removed during breast cancer surgeries, i.e. healthy breast tissues containing greater than 85% adipose tissues. 46</td>
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<tr>
<td>$C_T$</td>
<td>The measured dielectric properties of tumour tissues removed during breast cancer surgeries, i.e. those containing greater than 85% adipose tissues. 46</td>
</tr>
<tr>
<td>$D_A$</td>
<td>The average dielectric properties of the regions of the breast deemed to correspond to adipose tissues measured using microwave tomography. 46, 48, 49</td>
</tr>
<tr>
<td>$D_G$</td>
<td>The average dielectric properties of the regions of the breast deemed to correspond to glandular tissues measured using microwave tomography. 46, 48, 49</td>
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<td>$R$</td>
<td>The measured dielectric properties of healthy breast tissues removed during breast reduction surgeries. 47</td>
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<td>The measured dielectric properties of Group I healthy breast tissues removed during breast reduction surgeries, i.e. healthy breast tissues containing less than 30% adipose tissues. 46</td>
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<tr>
<td>$R_{II}$</td>
<td>The measured dielectric properties of Group II healthy breast tissues removed during breast reduction surgeries, i.e. healthy breast tissues containing between 30% percent and 85% adipose tissues. 46</td>
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<tr>
<td>$\mathcal{R}_{\text{III}}$</td>
<td>The measured dielectric properties of Group III healthy breast tissues removed during breast reduction surgeries, i.e. healthy breast tissues containing greater than 85% adipose tissues. 46</td>
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Reduction of morbidity and mortality due to breast cancer has long been a goal for health-care [1]. Although incidence and mortality rates vary worldwide, breast cancer is the fifth leading cause of death due to cancer overall, the most frequent cause of cancer death for women, and the second most common cause of cancer death for women in more developed regions [2].

Migration studies have suggested that lifestyle or environmental factors are major determinants of breast cancer risk: for example, women of Asian ethnicity living in the United States had a 60% higher risk compared to those who were living in Asia [3]. For postmenopausal women, the majority of breast cancer risk is attributable to nonmodifiable risk factors such as earlier age at menarche, taller height or breast composition, but as many as a third of breast cancers are associated with modifiable risk factors such as weight gain, alcohol consumption and physical activity [4].

As long as breast cancer cannot be entirely prevented, much focus is given to early detection of the disease. Early detection is achieved through asymptomatic screening and early diagnosis [5]:

- screening programmes that aim to detect both cancers and pre-cancers in asymptomatic populations;
- and early diagnosis through improved public and professional awareness of the signs and symptoms of breast cancer.

Asymptomatic screen programmes are widespread, and are recommended by the World Health Organization (WHO) for many healthcare systems [5]. However, recent studies have suggested that asymptomatic screening using mammography may be having little or no impact on mortality rates, but potentially leading to many cases of overdiagnosis and overtreatment [6]–[8].

However, it can be difficult to evaluate the benefits of asymptomatic screening programmes. Whereas screening can lead to overdiagnosis and treatment of disease that would not have resulted in mortality, screening may also lead to lower patient morbidity and allow patients a greater choice of less
invasive treatments [9]. Additionally, no consensus exists as to the optimal population to screen nor the optimal screening frequency. The effectiveness of mammographic screening can vary with both age and frequency among other factors: sensitivity for younger women (40–44) can be as low as 68.6% compared to 83.3% for older women (80–89 years old). Specificity also varies with age and breast density, and can be as low as 89.1% [10].

Furthermore, x-ray mammography uses ionising radiation and it has been shown that exposure to ionising radiation (0.25 to 20 Gy) is associated with increased breast cancer risk [11]. To avoid unnecessary exposure to ionising radiation, the maximum annual dose a woman may receive from mammography is limited to 3 to 4 mGy by the Federal Drug Administration (FDA) in the US [9], but estimating the risk from this low ionising radiation exposure is complex [11]. Although, there is evidence to suggest that mammography is associated with breast cancer risk particularly for younger women [12], many studies conclude that the carcinogenic effect of mammographic screening is small compared to the benefits [11]–[13]. A report from 2007 suggests that a single mammography examination at the age of forty is associated with a lifetime risk of fatal breast cancer due to radiation exposure of 1.3 to 1.7 in 100,000 [13]. Another study suggests that 86 cancers and 11 deaths due to radiation-induced breast cancer would occur per 100,000 women as a result of mammographic screening between the ages of 40 and 74 [12].

The limitations of mammography in terms of sensitivity, specificity and ionising radiation have motivated researchers to propose and evaluate microwave imaging as an alternative screening modality. Microwave imaging has been evaluated in many early-stage clinical studies over the last twenty years with seven different operational microwave imaging systems [14]–[37]. Studies with 150 participants with and without disease suggested that it may be possible to distinguish benign and malignant tumours based on the dielectric properties in quantitative reconstructions. Later studies which used a qualitative reconstruction technique demonstrated particularly encouraging sensitivity of 86% in the 42 participants with dense breasts [21]. Surprisingly, sensitivity was higher than the 54% reported for the 24 participants with less dense breasts, although the authors caution that the number of participants was too small to permit extensive statistical analysis. The early-stage clinical studies to date have mainly recruited women from symptomatic breast clinics and sensitivity was the primary outcome recorded.

The encouraging results from these operational microwave imaging systems and early-stage clinical studies have motivated further research into microwave breast imaging. The preliminary results suggest that the detection of malignancies in the breast using microwave imaging is possible;
however, more development is needed to bring microwave imaging from the research bench to widespread clinical adoption [38]. This new stage of development motivates the work in this thesis, and the specific challenges addressed are discussed in detail in the following section.

1.1 Motivation

Microwave imaging is a promising breast imaging modality that can address many of the limitations of mammography. Using low-power microwave energy, typically between 0.5 to 9 GHz [38], microwave imaging is non-ionising and safe for the patients being scanned [39]. Microwave imaging hardware has the potential to be low-cost [40], [41] and many patient imaging studies have reported that the scans were comfortable [26], [34].

Patient imaging studies to date have had study populations between 2 and 223 participants and contained healthy volunteers, women with benign breast disease and women with cancer [38]. However, in all patient imaging studies, study participants were recruited from symptomatic breast clinics [21], and many studies do not control for selection biases such as race [16], [33]. The patient imaging studies have also used exclusion criteria based on breast size (e.g. 310 to 850 mL in [21]) or the location of the breast disease (only patients with suspicious areas not in the axilla were included in [26]). Future patient imaging studies will include larger and more diverse study populations, including a variety of breast sizes, shapes and tissue composition. The next generation of systems in these larger trials will need to be suitable for all patients regardless of breast composition and will be used to estimate the sensitivity and specificity of the imaging modality for a given population.

Breast composition can vary substantially between patients in clinical practice [42]. The breast can contain many tissues, including glandular tissues (high dielectric properties) surrounded by a loose connective tissue stroma comprising adipose (low dielectric properties) and fibrous tissues (high dielectric properties) [43]. The proportions of glandular tissues and loose connective stroma can vary between individuals, as can the proportions of adipose and fibrous tissues in the loose connective stroma [42]. Tumours also have high dielectric properties [44], [45], typically higher than any other healthy tissues in the same breast [45], [46]. Microwave imaging exploits the contrast between the dielectric properties of the tumour tissues and other breast tissues. Other benign breast diseases such as cysts can also have high dielectric properties.

Radar-based imaging is a leading technique for image reconstruction from scattered microwave energy. Radar-based imaging algorithms (known as
beamformers) have been used in six of the seven patient imaging studies to date, in patient imaging studies varying from two [36], [37] to over two hundred participants [19]–[25]. Radar-based imaging is a qualitative technique, seeking to identify areas in the breast where the dielectric properties differ from the surrounding tissues. Many algorithms have been developed to reconstruct images of the breast, and a number of review articles and introductory books have been published describing the theory of beamformers [47]–[49]. However, few optimised and open-source implementations of beamformers exist, although the theory of the methods is well understood [49]–[51]. Beamformers have been compared in numerical, experimental and patient imaging studies [52]–[54], however, in many cases, the comparisons include only experimental cases with tumour phantoms or patients with disease [55].

The largest radar-based imaging studies have been conducted with the Multistatic Array Processing for Radiowave Image Acquisition (MARIA®) system, originally developed at the University of Bristol and now developed commercially by Micrima Ltd. (Bristol, the UK). Initial experience with MARIA® and experimental breast phantoms suggested that dense and heterogeneous breast phantoms were the most challenging to image [56]. However, preliminary results from 66 patients found higher sensitivity in more dense breasts compared to less dense breasts (86% for dense breasts compared to 54% for lucent breasts) [21]. Although the authors caution that the study size is too small to permit extensive statistical analysis, this unexpected finding motivates research into the effects of breast composition on beamformer performance. A new patient imaging study is underway using a new generation of the MARIA® system with an estimated enrolment of 994 participants (NCT03302819).

Fundamentally, beamformers use knowledge of the propagation of electromagnetic energy within the imaging domain to “synthetically focus” scattered energy to points within the imaging domain. However, neither exact knowledge of breast tissue composition nor the dielectric properties of the breast are known. Hence, the majority of beamformers rely on assumptions to construct the propagation model, which can be broadly divided into two categories:

1. simplifying the imaging domain for a given patient by assuming it is a single homogeneous medium;

2. using the same propagation model for all patients.

All six radar-based patient imaging studies have assumed a simplified imaging domain for a given patient. These assumptions are integral to implementing the beamformer as exact knowledge of the structure and composition of the
CHAPTER 1. INTRODUCTION

breast interior is not known at the time of imaging. However, the breast is known to be heterogeneous, and the impact of these assumptions is not well studied. Similarly, all six radar-based patient imaging studies have used the same propagation model for all patients. The breast varies from patient-to-patient, and also for a given individual over time due to age and other factors [42]. Moreover, accounting accurately for breast composition has been shown to impact the image quality [57], [58].

Although some studies have proposed methods to estimate patient-specific propagation models [31], [57]–[60], a number of unanswered questions regarding the effect of these assumptions on microwave imaging algorithmic design, testing, validation and efficacy remain. In particular:

1. how to determine the dielectric properties of the simplified propagation model used for imaging?

2. does fixed-value estimation negatively affect the clinical efficacy of radar-based imaging in terms of sensitivity and specificity?

3. are the characteristics of correctly reconstructed images different from the characteristics of incorrectly reconstructed images?

4. and what image features can be used to distinguish images containing tumours from images without tumours, blind to the clinical diagnosis of the patient?

These unanswered questions motivate the primary research objective of this thesis: to develop novel beamformers to address the substantial variance in breast composition observed in the population. The primary research objective is achieved in a number of stages:

1. evaluating if fixed-value estimation of the dielectric properties affects tumour detection in terms of sensitivity in breast phantoms of varying composition;

2. identifying characteristics of correctly and incorrectly reconstructed radar-based breast images;

3. proposing suitable cost functions that reward correctly reconstructed images and penalise incorrectly reconstructed images;

4. testing the proposed cost functions using experimental images as well as patient images from an operational microwave imaging system.
To facilitate the primary research objective, breast and tumour phantoms modelling variation in breast composition were fabricated and open-source imaging code was developed. The specific contributions described in this thesis are summarised in the following section, including the thirteen publications arising from these contributions.

1.2 Thesis Contributions

Significant contributions are presented in this thesis addressing the effects of interpatient variations in breast tissue composition on image quality, tumour detection and clinical efficacy. The specific novel contributions are summarised below, in particular:

- designing, building and testing of an experimental microwave radar-based imaging system hardware in accordance with the current state-of-the-art operational system design;
- development of free, open-source, extensible imaging software with implementations of leading beamformers and patient-specific estimations methods (available with documentation and user guides at https://www.github.com/EMFMed/MERIT);
- fabrication of breast and tumour phantoms modelling interpatient variation in breast tissue composition and differences in tumour shape and size observed in clinical practice;
- detailed evaluation of the limitations in terms of sensitivity of current beamformers due to variance in breast tissue composition observed in the population;
- fundamental analysis of the impact and importance of breast tissue composition as an input parameter to radar-based beamformers;
- identification of characteristics of correctly reconstructed microwave radar-based images compared to characteristics of incorrectly reconstructed images;
- proposal of cost functions that reward correctly reconstructed images and penalise incorrectly reconstructed images;
- testing of the proposed cost functions using the experimental microwave imaging system and the breast and tumour phantoms presented in this thesis;
CHAPTER 1. INTRODUCTION

• analysing the performance of the proposed cost functions in sample clinical case studies.

These contributions are described in detail in the following chapters, including: the breast and tumour phantoms and experimental hardware in Chapter 3; effects on sensitivity and specificity of patient-specific estimation in Chapter 4; proposal of cost functions to reward correctly reconstruction images in Chapter 5; and performance in clinical case studies from a leading operational microwave imaging system in Chapter 6. These novel contributions have been published in six journal articles and seven conference publications which are listed in the following sections. Where appropriate, these journal and conference publications are referenced in the relevant chapters of this thesis, and the first page of each published contribution is included in Appendices B and C.
1.2.1 Journal Publications


CHAPTER 1. INTRODUCTION

1.2.2 Conference Publications


1.3 Thesis Structure

The remainder of this thesis describes the background, experimental system, methods and results used to address the primary research objective.

Chapter 2 describes the background to this thesis, beginning with breast anatomy, interpatient variation and the types of breast abnormalities observed in clinical practice. Leading breast imaging modalities are described, including the advantages and disadvantages of each technology. Next, the theory of microwave imaging is explained, including a comprehensive review of operational microwave imaging systems. Finally, the remaining challenges to clinical adoption are discussed based on a review of operational microwave imaging systems and patient imaging studies, including the current understanding of the dielectric properties of human breast tissues, difficulties regarding patient movement and both inter- and intrapatient variation.

Chapter 3 presents the experimental data and hardware acquisition system used to help answer the primary research objective of this thesis. The motivation, design and fabrication of the breast and tumour phantoms is also presented. The breast phantoms are designed to model the interpatient variation in breast tissue composition observed in the population in terms of the proportions of adipose, glandular and fibrous tissues in the breast. The tumour phantoms were manufactured in a variety of shapes and sizes, modelling both benign breast diseases and invasive breast cancers.

Chapter 4 compares and contrasts fixed-value and patient-specific dielectric properties estimation in terms of sensitivity. Using the experimental test cases from Chapter 3, the feasibility of using fixed-value estimation in a realistic population is considered. The potential impact on the specificity is also considered. This analysis helps evaluate if patient-specific estimation is necessary to achieve high sensitivity in a realistic population, without impairing the specificity.

Chapter 5 proposes cost functions that can be used for patient-specific dielectric properties estimation. A simplified analytical model is used to identify characteristics of correctly reconstructed images which are compared to the characteristics of incorrectly reconstructed images. The cost functions are then tested using the breast and tumour phantoms from Chapter 3.

Chapter 6 evaluates the cost functions developed in Chapter 5 using five clinical case studies from a study at the University of Calgary. The data presented in Chapter 6 is used to investigate if the proposed method is robust in the presence of noise from patient movement and other challenges associated with real patient data.

Finally, Chapter 7 summarises the thesis, discussing the main results and conclusions. Additionally, future work is identified to improve the patient-
specific estimation methods presented in this thesis, and also the next steps
for microwave radar-based imaging necessary for clinical acceptance of the
imaging methodology.
Background

Work from this chapter was published in IEEE Transactions on Biomedical Engineering in 2018 in a review paper entitled “Microwave Breast Imaging: Clinical Advances and Remaining Challenges.”

In this chapter, the fundamental basis of microwave breast imaging is discussed, beginning with the anatomy of the breast, the current state-of-the-art in microwave breast imaging and identifying the key challenges that need to be addressed for microwave imaging to be adopted clinically.

Firstly, an overview of the anatomy of the human breast is presented, including the types of growth abnormalities that can occur. Benign breast diseases, abnormalities associated with increased cancer risk, known and suspected precursors of cancers and invasive cancers are all considered. Leading breast imaging modalities are summarised including the advantages, disadvantages and types of growth abnormalities detected with each modality. Recent developments with respect to asymptomatic breast screening are reviewed, including the benefits and risks in terms of both morbidity and mortality.

Next, the fundamental basis of microwave breast imaging is introduced, beginning with the electromagnetic scattering equation and briefly summarising the assumptions and approximations used in the leading reconstruction approaches. The design and operation of microwave imaging hardware and software is reviewed and particular focus is given to those systems that have been evaluated on patients.

The available clinical evidence from patient imaging studies is comprehensively reviewed in terms of patient populations, key findings and next steps. Finally, the remaining challenges to clinical translation are identified based on the patient imaging studies, including how the primary research objective of this thesis helps to address these challenges.
CHAPTER 2. BACKGROUND

2.1 Breast Anatomy and Physiology

The human female breast is a rounded eminence lying within the superficial fascia anterior to the upper thorax [42]. The breast size and shape can vary substantially between individuals based on genetic, racial or dietary factors, and also based on the age, parity and menopausal status of the woman. The nipple projects from the centre of the breast anteriorly, and the site of the nipple can vary depending on the breast shape and size. A disc of skin, known as the areola, surrounds the nipple, which is generally pink or brown in colour, and the colour can vary depending on parity or general melanisation of the body.

The breast interior is composed primarily of lobes, shown in Fig. 2.1, which contain a network of glandular tissue including branching ducts and terminal secretory lobules interconnected by a connective tissue stroma. The breast contains between fifteen and twenty lobes, from which lactiferous ducts carry milk from the terminal secretory lobules to the exterior of the breast. The lactiferous ducts converge on the areola and open on to the tip as small orifices. Lobes may not form discrete territories but can merge at their edges.

The interlobular connective tissue stroma is dense and fibrous, whereas the interlobar connective tissue stroma has a loose texture. Fibrous tissues are found both surrounding the glandular components and also in the interlobar connective tissue stroma, often connecting the glandular tissues to the skin. Both the proportions of adipose and fibrous tissues in the interlobar stroma as well as the overall proportion of fibrous and glandular tissues in the breast can vary between individuals. Breasts with a higher proportion of fibrous and glandular tissues are referred to as more dense, and breast density tends to decrease with age or for individuals who have had more than two children. Density tends to be higher in small breasts or those who have undergone hormone replacement therapy [61].

Abnormal growths, known as neoplasms, can also occur within the breast. In many cases, neoplasms form a mass which is known as a tumour. As with all neoplasms, tumours can be broadly divided into three main categories [62]:

1. benign: tumours without the ability to invade neighbouring tissues or metastatise, and these are discussed in Section 2.1.1;

2. \textit{in situ}: tumours that have not invaded other tissues but have the potential to develop into cancer and are summarised in Section 2.1.2;

3. and malignant: tumours that have invaded the surrounding tissues or have metastatised, considered in Section 2.1.3;
CHAPTER 2. BACKGROUND

Figure 2.1: Medical illustration of the anatomy and internal structures of the female breast including the lobules, lobes, lactiferous ducts and lymphatic drainage system. Also shown is the nipple, areola and the convergence of the lactiferous ducts from the breast lobes on the areola. The interlobar connective tissue stroma is loose containing varying proportions of adipose and fibrous tissues, whereas the interlobular connective tissue stroma is dense comprising mainly fibrous tissues.

Malignant neoplasms, known simply as cancer, are a leading cause of death (second most common in the United States [63]); breast cancer is the second most common cancer in the general population (10%) and the most common amongst women (23%) [64]. The primary tumour (arising from the initial uncontrolled growth) may become life-threatening by obstructing vessels or organs; however most primary tumours do not compromise survival when confined only to the breast [65]. Death is most commonly caused by the spread of the primary tumour to other sites in the body (known as metastatis), principally through the lymphatic system but also via the blood vessel route [66]. The breasts are the site of malignant change in as many as 1 in 8 women [42].

Other changes, due to infections or hormonal responses among others,
can also occur in the breast. In some cases, such as fibroadenomas, the changes are harmless and rarely treated, in others, such as fat necrosis, the changes may mimic cancer and require further investigation. A brief overview of the types of breast abnormalities that are observed is presented in the following sections [9], [67]: benign changes that are not associated with cancer risk in Section 2.1.1; abnormalities associated with increased risk of breast cancer in Section 2.1.2; and cancers of the breast in Section 2.1.3.

2.1.1 Benign Breast Changes

A number of benign changes can occur in the breast which may or may not be treated depending on the nature of the change. For some changes such as fibroadenomas, the change may not be treated unless causing discomfort to the patient. Other changes such as cysts, may need further investigation for diagnosis and to rule out the possibility of cancer.

Adenosis refers to an increased number of small terminal ductules which is often associated with a proliferation of stromal tissue. Known as sclerosing adenosis if the tissues harden or are damaged in some way, adenosis has no significant malignant potential. However, adenosis is often associated with microcalcifications, which may require further diagnostic tests to rule out cancer. For example, sclerosing adenosis is the most common pathologic diagnosis in patients undergoing needle-directed biopsy for microcalcifications in many series.

Cysts are fluid-filled, epithelial-lined cavities that may grow to palpable masses containing as much as 30 mL of fluid. Although common (developing in at least 1 in 14 women), cancer in a cyst is exceedingly rare (lower than 0.1% of cases contained intracystic carcinoma), and there is no evidence associating cyst formation with increased risk of cancer. Cysts are influenced by ovarian hormones and are most commonly observed in women between 35 years of age and menopause.

Duct ectasia can occur when the lactiferous duct becomes blocked or clogged, potentially causing discharges. Although surgical intervention is not normally needed and it is not associated with increased cancer risk, duct ectasia can mimic cancer by forming palpable masses. Fat necrosis can also mimic cancer (palpable mass with calcifications), and often occur as a result of breast trauma, surgery or radiation treatment. Potentially requiring a biopsy to diagnose or remove, this lesion has no malignant potential.

Fibroadenomas are benign solid tumours comprising stromal and epithelial elements. Fibroadenomas are the second most common tumour found in the breast, and often arise in the late teens or in the early reproductive years. Cancer in a newly discovered fibroadenoma is very rare, and fibroadenomas
are not normally surgically excised unless continuing to grow or causing discomfort. Complex fibroadenomas may slightly increase the risk of breast cancer.

Hamartomas, or fibroadenolipomas, are benign proliferations of glandular, fibrous and fatty tissues encapsulated in a thin layer of connective tissue. Hamartomas are mostly asymptomatic and often grow at the same rate as surrounding tissues. Although mainly detected through breast imaging, hamartomas may form a palpable lump. Although not directly associated with breast cancer risk, cancer may coincidentally develop within the cells of the hamartoma.

Papillomas can occur in the epithelial-lined breast ducts, often near the areola. Many are small (less than 1 cm) but can grow as large as 4 cm. Papillomas are often associated with cystic structures and may cause pain, lumps or discharges. Papillomas are not associated with increased risk of breast cancer except potentially in women with multiple papillomas. Biopsy is often needed to diagnose or remove these growths.

2.1.2 Breast Changes Associated with Increased Cancer Risk

Unlike the breast changes discussed in the previous section, some breast changes are associated with increased risk of cancer. Some changes, such as hyperplasia, are considered risk factors whereas other changes, such as ductal carcinoma in situ (DCIS), can be precursors to cancer, although the progression of in situ carcinomas is not completely understood [68].

Radial scars are a type of abnormality known as a complex sclerosing lesions. Radial scars can appear similar to cancer mammographically as they are also characterised by irregular spiculations in the surrounding stroma. Although the gross abnormality is rarely more than 1 cm in diameter, larger lesions may form palpable tumours with many characteristics similar to cancers. Radial scars, although rare, are associated with a modestly increased risk for breast cancer and often need to be excised to rule out cancer.

Benign epithelial proliferative breast disease can also occur in the form of hyperplasia of the epithelial cells with or without atypia. Neither ductal nor lobular hyperplasia are considered precursors to malignancy, but are associated with increased cancer risk [9]. Ductal hyperplasia ranges from mild (three or four epithelial cells in thickness) to moderate or florid when more pronounced or altering the shape of the duct [65]. Both ductal and lobular hyperplasia are considered a normal physiological change occurring during a woman’s monthly cycle. Similarly, atypical hyperplasia of the
epithelium is not considered pre-malignant, but as a risk factor for breast cancer [9]. Distinguishing between normal hyperplasia, atypical hyperplasia and carcinoma in situ is not always easy, but despite uncertainties, there is agreement that the presence and type of proliferative epithelial hyperplasia determines the risk for subsequent breast cancer and that the risk is between one to five times higher than controls [65].

Between 15% and 30% of all diagnosed breast cancers are carcinomas in situ. Although common, the clinical significance and optimal treatment of breast carcinomas in situ are uncertain for both patients and clinicians [68]. Additionally, breast carcinomas in situ do not always completely express the hallmarks of invasive cancers, meaning progression to invasive cancer does not always occur [69], [70]. The two major types of breast carcinoma in situ are:

- DCIS: which is considered a true precursor to invasive breast cancer and accounts for 80% of breast carcinomas in situ;
- and lobular carcinoma in situ (LCIS) which is associated with increased risk of invasive breast cancer but is not a direct precursor to invasive cancer.

Although initially believed to be a malignant lesion, LCIS is now more commonly regarded as a risk factor for invasive cancer and recognised by its conformity to the outline of the normal lobule. DCIS, however, is a more heterogeneous lesion morphologically [71], rarely presenting as a pure lesion of one morphological type, but more commonly mixed. DCIS can transform into invasive cancer, however the grade of invasive cancer tends to be associated with the grade of the original carcinoma in situ [67].

DCIS is associated with increased mortality, particularly among those of black ethnicity or those younger at time of diagnosis. For these women, mortality is often due to an ipsilateral second primary invasive cancer. However, some patients die of DCIS without experiencing an in-breast invasive cancer prior to death [72]. Although finding that mortality risk increases due to diagnosis of an ipsilateral second primary invasive cancer, the observational study of 108,196 women noted that prevention of reoccurrence through radiotherapy was not associated with a reduction of the 10-year mortality rate [72]. DCIS commonly coexists with other invasive cancers in the breast, but the two phases of the malignancy are in step with each other morphologically [67].
2.1.3 Invasive Breast Cancers

Breast cancers arise primarily in the epithelia of lobules or ducts (known as carcinomas). Other cancer types can occur in the breast but are more rare. Primary breast sarcomas, beginning from the stroma, account for fewer than 1% of all breast cancers and less than 5% of all soft-tissue sarcomas [73]. Primary breast lymphoma is also rare, accounting for less than 0.5% of all breast cancers and 1 to 2% of all extra-nodal lymphomas [74]. Breast cancer also affects mainly women: male breast cancer is rare, accounting for fewer than 1% of cases [75].

Invasive breast cancers are a heterogeneous group of lesions that can vary with regard to clinical presentation, histopathology, molecular features and biological potential. Cancers are typically classified based on the growth pattern and cytologic features of the invasive cells [76]. Two broad classifications exist, ductal and lobular, although these do not indicate the site of origin as most cancers arise in the terminal duct lobular unit regardless of classification [77]. Rather, the distinction was chosen to highlight the histological similarities between lobular carcinoma in situ and invasive lobular carcinoma, as well as the multicentric and bilateral nature of lobular carcinoma in situ [9].

The majority of invasive breast cancers present as invasive ductal carcinomas (76%), often called invasive ductal cancer of no special type to distinguish it from the other subtypes. The prognosis of invasive ductal cancer varies according to tumour size, histologic grade, lymph node status and other prognostic factors [9]; however, even with this group, prognostically favourable subtypes can be identified. Invasive ductal carcinomas are normally pure lesions, but can also have a minor component of one or more histological types.

Invasive lobular carcinomas constitute the second most frequent type of invasive breast cancer (8%). Typically characterised by multifocality in the ipsilateral breast, invasive lobular carcinomas are more often bilateral or multicentric than other types of invasive cancer [9], and are often difficult to detect on mammography [78]. Invasive lobular carcinoma co-exists with lobular carcinoma in situ frequently. There is uncertainty as to whether there is a different prognosis for invasive lobular carcinoma when compared to invasive ductal carcinoma, and the extent of invasive lobular carcinomas are often underestimated from physical examination.

Many imaging modalities are used for breast imaging which can identify some of the benign breast diseases and invasive breast cancers described in this section. For certain benign diseases, the imaging modality can be used for diagnosis: for example, ultrasound can be used to distinguish solid and
cystic masses [9]. However, individual imaging modalities are rarely used alone for diagnosis, but more often in combination with other techniques. For example, physical exam, mammography, and fine needle aspiration form the so-called, triple assessment criteria [79], [80]. The following section describes leading imaging modalities, their clinical indications and advantages and disadvantages. In the case of x-ray mammography, the imaging modality is used as both a diagnostic and asymptomatic screening tool, whereas for ultrasound and magnetic resonance imaging, the primary clinical indication is for diagnostic purposes only.

## 2.2 Breast Imaging Modalities

A number of breast imaging modalities have been proposed and are currently used [9], including x-ray mammography, ultrasound, magnetic resonance imaging, molecular breast imaging and thermography. New advances using these techniques are also being developed, such as digital breast tomosynthesis which is a three-dimensional imaging technique also based on x-rays [9]. Many of these imaging modalities have also been proposed for use with asymptomatic screening programmes, although x-ray mammography remains the only currently accepted screening modality [5].

As early as 1966, clinical studies of mammography screening of asymptomatic populations was reported to improve patient outcomes [81]. However, recent studies have suggested that asymptomatic breast screening using mammography has little to no impact on breast cancer mortality rates [7], [8]. In light of this uncertainty, the principles of asymptomatic screening are discussed in Section 2.2.1 including the challenges to evaluating efficacy. The remainder of this section includes a brief overview of three leading imaging modalities: x-ray mammography, ultrasonography and magnetic resonance imaging in Sections 2.2.2 to 2.2.4 respectively. The benefits and limitations of each modality are discussed, including the breast diseases, both benign and malignant, that are detected with each modality.

### 2.2.1 Rationale for Asymptomatic Screening

Fundamentally, the rationale for cancer screening programmes is that early detection leads to early treatment and ultimately improved patient outcomes in terms of both mortality and morbidity. In the absence of methods for preventing breast cancer, regular screening programmes are widely recommended for asymptomatic women [5]. A positive screening result in an
CHAPTER 2. BACKGROUND

Figure 2.2: Visualisation of the challenges associated with assessing asymptomatic screening programme efficacy. Two possible biases are shown: (a) lead time bias and (b) length bias. Lead time bias occurs because asymptomatic screening necessarily increases the time between diagnosis and death when compared to detection through symptoms, even if disease progression is not altered through treatment. Length bias occurs for diseases with both indolent and aggressive cases, asymptomatic screening is more likely to identify indolent cases which may never have become symptomatic if left untreated. (b) shows four cases, two indolent tumours which are detected by screening and two aggressive cases which are symptomatic before detection via screening. In both cases, the arrow represents initial uncontrolled growth to symptomatic.

individual rarely provides direct evidence of disease; screening is normally followed by further diagnostic tests to determine whether disease is present.

Three factors need to be considered for a screening programme [82]:

1. the disease targeted is serious with significant morbidity or mortality;
2. the screening test is easy to perform, inexpensive, accurate and safe;
3. the health care system must be able to properly care for all those who receive a positive screening result.

Additionally, the risk–reward ratio is important to consider: if the screening test is cheap, comfortable, safe and accurate (risk is low), asymptomatic screening may be more beneficial. However, a number of challenges exist when evaluating screening programmes according to these factors.

Establishing a causative relationship between screening and mortality reduction is challenging. A positive association between asymptomatic screening and reduced mortality can be impacted by a number of biases. Two such possible biases, lead time bias and length bias, are illustrated in Fig. 2.2.
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Lead time bias (Fig. 2.2a) occurs when disease is detected earlier in the disease progression in the screened population when compared to the unscreened population. The time between detection due to screening and symptomatic presentation is known as the lead time, and necessarily lengthens the time between diagnosis and death due to screening, even though this additional time may not alter disease progression, and screening may ultimately have no impact on mortality.

Length bias (Fig. 2.2b) occurs when the disease includes both indolent and aggressive cases. The indolent cases are growing more slowly and more likely to be identified by screening than through symptoms. The aggressive cases are likely to be asymptomatic for shorter periods and less likely to be detected by screening. As mortality is likely to be higher for the aggressive cases, this can give the impression that screening is beneficial even though screening may simply be identifying more indolent cases that would not have resulted in mortality if untreated.

Secondly, establishing the accuracy of the test can be difficult. Test accuracy is generally assessed considering two types of errors:

1. false positives: where the test indicates disease for a healthy individual;
2. and false negatives: where the test indicates no disease for an individual with disease.

Two main criteria are used to evaluate these errors [82]:

1. the sensitivity: the proportion of individuals with disease who correctly test positive for disease;
2. and the specificity: the proportion of healthy individuals who correctly test negative for disease.

Screening tests need to limit the number of false positives to reduce the risk of unnecessary interventions, discomfort, anxiety and overdiagnosis of cancers that would not have resulted in mortality if undiagnosed [9]. The risk of a false positive is also cumulative and increases with the number of times a screening test is repeated. Screening tests also need to limit the number of false negatives so individuals with disease are identified when an early intervention could positively impact the patient outcome.

Finally, the health care system needs to be able to fully investigate all positive screening results. Further diagnostic tests are required to distinguish false positives from true positives and this additional testing has a cost implication for the health service. One study estimates that fully evaluating
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all false positive screening results costs the health service an additional 33% of the cost of the original screening programme [83].

Although mammography is the only recommended imaging modality for asymptomatic breast screening, both ultrasound and magnetic resonance imaging have also been proposed, either individually, or in combination with other modalities [9]. The following sections (Sections 2.2.2 to 2.2.4) summarise the advantages and disadvantages of these imaging modalities (x-ray mammography, ultrasonography and magnetic resonance imaging) as screening tools. The current clinical use of these modalities is also discussed including new clinical indications which are being researched.

2.2.2 X-ray Mammography

Mammography of the breast has been performed for nearly one hundred years, and randomised control trials studying the benefits of mammography with as many as 60,000 participants have been reported as early as 1966 [81]. Although recommendations on screening frequency and the optimal patient cohort to screen vary depending on the resources of the given health care system, most organisations suggest mammographic screening of asymptomatic women [5]. Mammography can also be used diagnostically, although suspicious clinical findings are generally followed up with surgical consultation, even if imaging is negative [9].

Mammography operates by transmitting low energy x-rays (typically between 25 kV and 32 kV) through the breast and measure energy which has been transmitted through the breast, i.e., energy not absorbed by the breast tissues [9]. The x-ray attenuation coefficient varies depending on the tissue type:

- adipose tissues have low absorption and are shown on a mammogram as dark areas;
- glandular and fibrous tissues have higher absorption and are shown on a mammogram as white areas;
- and finally calcium has the highest absorption, also shown as small white dots.

An example mammogram of a cancerous tumour is shown in Fig. 2.3a.

To minimise thickness of tissue that the x-rays must penetrate, immobilise the breast and limit the radiation dose received, the breast is compressed between two parallel plates as part of the normal imaging procedure. This
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can be uncomfortable and also relies on operator training to maximise the breast volume that is included in the imaging domain.

Healthy glandular tissues and cancerous tissues have very similar x-ray attenuation coefficients, with a contrast as low as 1:1.1 reported [84]. This means that dense but healthy tissues can mask the appearance of non-calcified cancers. Thus, the sensitivity of mammography in individuals with high breast density can suffer: a study of 329,495 women found sensitivities of 87% in women with less dense breasts, but 62.9% in women with extremely dense breasts [10].

Two other factors need to be considered when evaluating the contrast between healthy and cancerous tissues:

- mammography benefits from the photoelectric effect which can enhance the contrast between healthy and cancerous tissues [85];

- microcalcifications have much higher x-ray attenuation than surrounding tissues, and can be used to help detect breast cancers [9].

The reasons why microcalcifications are associated with carcinomas are not well understood, nevertheless, microcalcifications are used when interpreting screening mammograms [86]. Microcalcifications as small as 50 µm can be detected [9], although high spatial resolution is required [87], [88]. Mammography is successful at detecting small tumours, especially DCIS, due to the microcalcifications visible in images. Other benign breast diseases such as fibrocystic changes are also associated with calcifications, requiring the radiologist to rely on location, morphology, distribution and number of calcifications in determining the risk of malignancy from a mammogram.

Clinical efficacy of mammography can vary based on the individual’s age and breast density, operator skill and radiologist’s experience. Additionally, mammogram interpretation can vary internationally: studies have found that North American mammograms are more likely to be adjudged abnormal compared to screening mammograms in other countries [89]. However, the same study notes that the cancer yield from final diagnosis was similar in North American and other countries, although more DCIS was detected.

Over half a million women have participated in eight prospective randomised trials of screening mammography [67]. Recent reviews have indicated that asymptomatic breast cancer screening with mammography is having little to no effect on breast cancer mortality rates [7], [8]. However, as highlighted in the previous section, the true benefit of screening is difficult to evaluate. Other confounding factors include the practice of assessing mortality reduction among all women invited to be screened rather than the
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women who actually participated in the screening programme [90]. Moreover, mammographic screening may lead to decreased morbidity as cancers detected earlier in the disease progression are more likely to be treated by less invasive treatments: Women whose cancer is detected early have more treatment options than women where more advanced disease is detected [91].

In summary, mammography remains the only asymptomatic screening programme recommended [5] although the benefits are uncertain and in question. Mammography also suffers from a number of well understood limitations, most particularly poor sensitivity in individuals with dense breasts. Suspicious mammograms require further investigation such as biopsy, but also breast ultrasonography used for mammographic mass classification as discussed in the following section.

2.2.3 Ultrasonography

Breast Ultrasonography has been suggested for the characterization of breast masses for over fifty years [92]. Originally indicated to distinguish between solid and cystic breast masses, breast ultrasound is now more common for evaluating clinical complaints such as pain or lumps, further characterization of mammographic or magnetic resonance imaging findings or guiding breast biopsies [9]. For example, a breast ultrasound of a cyst is shown in Fig. 2.3b. Although generally performed as a result of suspicious findings from a
mammogram, ultrasound is recommended as the first imaging modality for pregnant women or those under the age of thirty [9].

Ultrasonic uses soundwaves above the threshold of human hearing (at most 20 kHz in healthy young adults) to image the breast. The most common form of ultrasound imaging is B-mode ultrasonography where short bursts of ultrasound energy are broadcast from transducer elements and echos from tissues at various depths are recorded [93]. Two-dimensional images of the breast can be reconstructed as fast as 30 Hz.

Although few studies have assessed interobserver variability, an experienced technologist is important [9]. Ultrasonography is typically conducted using a handheld transducer, requiring a lot of time and experience for a whole breast scan. The ultrasound equipment itself is also important variable that can impact the image quality [93]. Automated whole-breast ultrasonography has the potential to improve consistency and accuracy when compared to handheld ultrasonography, and early clinical results are promising [94], [95].

However, there is no data available to show that asymptomatic screening using breast ultrasonography is effective in reducing breast cancer mortality [67]. The largest trial to date of ultrasonographic screening included 2662 women and is known as the ACRIN 6666 trial [96]. Although 4.2 more cancers per 1000 women were detected as a result of screening with both ultrasound and mammography compared to screening with mammography alone, the additional screening with ultrasonography resulted in more false positive events and an increase in the biopsy rate from 2% to 5%.

### 2.2.4 Magnetic Resonance Imaging

Magnetic Resonance Imaging has also been used for nearly thirty years for breast cancer detection [97]. Magnetic resonance imaging can be very sensitive for breast cancer in high risk populations, ranging between 71 to 100% compared to 16 to 40% using mammography with the same high risk cohort [98]. However, magnetic resonance imaging is not very specific and studies suggest that 8% to 15% of all women screened with magnetic resonance imaging are recalled unnecessarily [9]. Although clinical indications are evolving and sometimes controversial, magnetic resonance breast imaging is indicated for those at high risk of breast cancer or for measuring response to neoadjuvant chemotherapy. A sample magnetic resonance image of a cancerous tumour is shown in Fig. 2.3c.

Magnetic resonance imaging required the patient and area to be imaged to be placed within a strong magnetic field of at least 1.5 T and the benefits of higher field strengths (such as 3 T) are not yet proven [9]. Magnetic resonance
breast imaging relies on the intravenous injection of a paramagnetic contrast agent, typically gadolinium which was first used over 30 years ago [97]. The premise of breast magnetic resonance imaging is that the contrast agent is rapidly taken up by cancer cells followed by a rapid washout. As breast cancers enhance more rapidly than surrounding tissues, rapid scanning times are important between two to seven minutes after contrast agent injection [9].

Although highly sensitive for both invasive cancers and DCIS that are mammographically, sonographically and clinically occult, the low specificity means magnetic resonance imaging is not indicated for those at low risk of breast cancer. The specificity of magnetic resonance imaging may also be affected by the menstrual cycle [99]. Magnetic resonance imaging is also prohibitively expensive, making it unsuitable for asymptomatic screening regardless of risk.

2.3 Microwaves as an Imaging Modality

Microwave breast imaging has been proposed as an alternative or complementary imaging modality for breast health monitoring [34], asymptomatic breast screening [21] or for monitoring treatment [18]. Microwave breast imaging can be comfortable [26] and low-cost [40], addressing some of the limitations of the imaging modalities reviewed in the previous sections. Microwave breast imaging has the potential to be repeatable [100] and less operator-dependent than breast ultrasonography. Moreover, microwave breast imaging can be very fast (less than one minute [21]), particularly when compared to magnetic resonance breast imaging.

Microwave imaging uses electromagnetic radiation in the microwave frequency band (typically between 0.5 GHz and 9 GHz) to infer the dielectric properties or contrast within a given volume, known as the imaging domain. Microwave imaging algorithms can be classified based on the types of reconstructions generated:

- qualitative approaches: identifying areas within the imaging domain where the dielectric properties differ from the surrounding areas (a contrast in dielectric properties);
- and quantitative approaches: reconstructing the actual dielectric properties for given points within the imaging domain.

Mathematically, microwave imaging algorithms are approximations of
solutions of the electromagnetic scattering equation [47]:

\[
E(r') = E^i(r') + k_0^2 \int \int \int_V \chi(r) \left[ \tilde{\varepsilon}_s^2(r) - \tilde{\varepsilon}_b^2(r) \right] G_b(r', r) \cdot E(r) \, dr
\]  

(2.1)

where the total field, \( E(r') \), is the superposition of the incident field, \( E^i(r') \), and the scattered field, \( E^s(r') \). The scattered field, \( E^s(r') \), at the point \( r' \) can be calculated from the volume integral of the Green’s function of the background region of interest, \( G_b(r', r) \), the contrast, \( \chi(r) \), between the complex permittivity of the scatterer, \( \tilde{\varepsilon}_s(r) \), and the complex permittivity of the background, \( \tilde{\varepsilon}_b(r) \), and the total field, \( E(r) \), over the region of interest, \( V \). In Eq. (2.1), \( k_0 \) represents the complex wave number of free space. The incident field, \( E^i(r') \), is the electric field that would exist in the region of interest, \( V \), if the scattering objects did not exist. The electromagnetic scattering equation, shown in Eq. (2.1), is inherently non-linear as the total field, \( E(r') \), depends on a convolution of the total field, \( E(r') \), with the scattering contribution of all points in the region of interest, denoted as \( r \in V \).

Three broad categories of algorithms have been investigated for image reconstruction:

- **tomography**: a quantitative approach where propagation paths through the imaging domain are used to reconstruct the dielectric properties of the imaging domain;
- **radar-based**: a qualitative approach where the total field is successively synthetically focused to points within the imaging domain to estimate the energy originating from that point;
- **and holography**: a qualitative approach where a linear system of equations is determined from Eq. (2.1) at all points and frequencies and solved in the Fourier space.

The focus of this thesis is microwave radar-based imaging, which has been used in many clinical studies to date [19]–[37]. Radar-based imaging algorithms (beamformers) use knowledge of propagation within the imaging domain to synthetically focus the sampled scattered signals to points within the imaging domain. The synthetically focused signals for a given point are added together and the energy of the summed signals calculated. The synthetic point of interest is then scanned through the imaging domain to reconstruct the entire image. At points with a large contrast (a malignant
tumour), the summed signal will have comparatively larger energy compared to the energy of the summed signal at points with little or no dielectric contrast (the rest of the breast). This basic technique is known as the delay-and-sum (DAS) beamformer, and many other extensions to this technique have been proposed which are reviewed in Section 2.3.4.

Mathematically, the DAS beamformer can be represented as:

\[ I(r) = w(r) \int_{\Omega} P(\omega) \int_{A} \int_{A'} w_{a,a'}(r) E_{a,\omega}(a') \exp[j\omega \tau_{a,a'}(r, \omega)] \, da \, da' \, d\omega \]

(2.2)

where for each point in the imaging domain, \( r \in V \), the scattered signals, \( E_{a,\omega}(a') \), are synthetically focused by the propagation delay, \( \tau_{a,a'}(r, \omega) \) to that point. A number of weights can be applied:

- \( w_{a,a'}(r) \) which can be used to prioritise signals based on the antenna beamwidth or distance to the point of interest;
- \( P(\omega) \) which is the illumination pulse and can be used to prioritise certain frequencies;
- and \( w(r) \) which can be used to prioritise points where tumours are likely.

The DAS beamformer typically sets these three weights to unity.

Compared to the existing imaging modalities reviewed in Section 2.2, radar-based imaging has many potential advantages. Firstly, the use of non-ionising energy compared to x-ray radiation of mammography or digital breast tomosynthesis makes imaging safe for women of all ages. Moreover, the technique does not require compression of the breast making it more comfortable and tolerable than mammography or other techniques requiring compression [26], [34]. Secondly, the technique has the potential to be less operator-dependent than ultrasound imaging, and automated signal verification has been included in recent microwave imaging systems which can be used to guide the operator [21]. Thirdly, the technique can be implemented with low-cost and well-understood hardware, and it has been suggested that leveraging developments in microwave technology from other applications can improve the efficacy and lower the cost of the device [101]. Finally, both the hardware acquisition and imaging can be performed more quickly than mammography or magnetic resonance imaging making the DAS beamformer comfortable, tolerable and easy-to-use.

The rest of this section reviews the design of microwave imaging systems in detail. Each stage of the imaging process is reviewed, beginning with
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the patient interface in Section 2.3.1 which is used to couple the microwave energy into the patient breast. The acquisition hardware used to sample the total field is reviewed in Section 2.3.2 and it is important that both the patient interface and acquisition hardware are designed with clinical use in mind. Artefact removal algorithms that are used to remove the skin reflection are reviewed in Section 2.3.3. Artefact removal is an important stage in the imaging process as the skin reflection may be orders of magnitude larger than the reflections from the breast interior. Next, the imaging algorithms are discussed in Section 2.3.4, many of which are variants of the original DAS beamformer shown in Eq. (2.2). Finally, the results of the patient imaging studies published to date are reviewed in Section 2.3.5, comparing the patient populations, abnormalities detected and key lessons learned. The review presented in this section helped inform the design of the experimental imaging system described in Chapter 3, and also to identify assumptions inherent to the imaging operator that are discussed in Chapter 4.

Particular focus is given in this section to systems which have been used in clinical studies, termed “operational systems” in this thesis. Seven such operational systems have been used with healthy volunteers or with patients with both benign breast abnormalities and invasive cancers. These seven operational systems are listed below in order of the largest trial conducted with each system. Beginning with the first clinical demonstration of microwave imaging in 2000 [14], microwave imaging has been tested on hundreds of women across the seven systems:

1. a system developed at Dartmouth College, NH, USA (DC) that has been used in a number of clinical trials beginning in 2000 [14]–[18]. The largest trial to date considered 150 patients with and without disease [15];

2. the MARIA® system was developed at the University of Bristol, UK and a number of clinical results have been published since 2010 [19]–[25]. The system is now being commercially developed by Micrima Ltd., Bristol, UK and has been tested with 86 and 223 patients with and without disease in [21] and [25] respectively;

3. the Tissue Sensing Adaptive Radar (TSAR) system was developed by the University of Calgary, AB, Canada and was tested with a clinical trial involving 8 patients published in 2013 [26]. The system is currently being used in ongoing clinical trials [27]–[29]. Additionally, a complementary system for bulk permittivity measurement has been developed tested with two women with no history of breast disease [30], [31];
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4. a radar-based system has also been presented in 2017 from the Southern University of Science and Technology, China (SUST) [33]. Results were presented from a Phase I clinical investigation with 11 women to date;

5. a handheld, radar-based system developed at Hiroshima University, Japan (HU) [32] has been trialled with five women with breast disease in 2017;

6. a wearable system has been developed at McGill University, Quebec, Canada (MU) [102], [103]. The repeatability of the imaging process, patient comfort and variations due to the menstrual cycle were analysed in a clinical trial with 13 healthy women in 2016.

7. a conformal system has also been developed at Shizuoka University, Japan (SU) [36], [37]. Three different models were developed using 6, 18 and 30 antennas respectively to accommodate different patient breast cup sizes.

MARIA® is being used in an ongoing study (Clinical Trials Identifier: NCT03302819) with an estimated enrollment of 994 participants. A competing system, Wavelia, developed by Microwave Vision Group (Villebon-sur-Yvette, France) is currently being used to image patients at the National University of Ireland Galway [39], [104].

Many differences can be observed between the designs of the seven operational systems and the clinical studies. For example, the following features can impact significantly on clinical use:

- how the patient is positioned: prone, supine or seated;
- system portability: wearable, handheld or integrated;
- how the breast is positioned relative to the antennas: immersed in a coupling medium, in contact with a coupling shell or in direct contact with antennas;
- design complexity: moving internal parts, calibration required, is the scan automated?;
- and clinical study populations and study outcomes.
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2.3.1 Patient Interface Design

Firstly, the patient interface is considered. A number of positioning methods have been proposed for microwave breast imaging systems. Of the systems examined in this work, five (DC, MARIA®, TSAR, SUST and SU) are designed so that a prone patient lies on an examination table, with the breast pendant through an opening in the table. This means the breast can be illuminated from all angles in the coronal plane, resulting in many transmission paths through all parts of the breast. Tumours located close to the chest wall could be potentially more difficult to image compared to tumours located closer to the antennas with this approach as was found with one of eight participants in [26].

Of the five table-based systems, three (DC, TSAR and SUST) are completely integrated into the examination table requiring a tank of coupling medium to operate. One (SU) is also integrated into a table but uses suction to maintain contact between the breast and the antennas. The fifth (MARIA®) is integrated into a compact unit that can slide beneath the examination table to facilitate breast sizing and cleaning between each patient [21], with a small volume of coupling medium used. Table-based systems do not image the axilla as well as the other portions of the breast [26], attributed to the minimum distance between the antenna and the chest wall in the sagittal direction due to the thickness of the table (often 2 cm or more for patient comfort).

In the five table-based systems (DC, MARIA®, TSAR, SUST and SU), there are three main possibilities for securing the pendant breast:

- the breast hangs freely in air and the shape is determined by gravity;
- the breast is immersed in a coupling medium and the breast surface is deformed naturally by the medium (DC, TSAR, SUST);
- the breast is fitted to a surface within the system, directly in contact with the antennas or a coupling shell of a biocompatible material (MARIA® and SU).

Air-based systems have been considered experimentally [105] but air-based systems are susceptible to breast movement during the scan caused by patient breathing or movement. Coupling medium-based systems are also susceptible to patient movement during the scan, and disinfection between scans can involve emptying the tank of coupling medium. Metrics to quantify the differences between successive scans due to patient movement have been proposed [100].

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Table 2.1: Comparison of operational breast imaging systems in terms of patient populations, patient positioning and interface, and acquisition hardware.

<table>
<thead>
<tr>
<th></th>
<th>DC</th>
<th>MARIA®</th>
<th>TSAR</th>
<th>HU</th>
<th>SUST</th>
<th>MU</th>
<th>SU</th>
</tr>
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<tr>
<td>Largest trial:</td>
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<td>223</td>
<td>8</td>
<td>5</td>
<td>11</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
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<td>10 s</td>
<td>30 min</td>
<td>14 min</td>
<td>4 min</td>
<td>5 min</td>
<td>3 min</td>
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<td>prone</td>
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<tr>
<td>Coupling:</td>
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<td>shell</td>
<td>medium</td>
<td>shell</td>
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<td>✓</td>
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</tr>
<tr>
<td>Array type:</td>
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<td>synthetic</td>
<td>synthetic</td>
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<td>hardware</td>
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<td>frequency</td>
<td>frequency</td>
<td>time</td>
<td>frequency</td>
<td>time</td>
<td>frequency</td>
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<td>vivaldi</td>
<td>planar slot</td>
<td>horn</td>
<td>microstrip</td>
<td>stacked patch</td>
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<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>Artefact:</td>
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<td>averaging</td>
<td>adaptive filtering</td>
<td>differential</td>
<td>rotation</td>
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<td>DAS</td>
<td>DAS</td>
<td>DAS</td>
<td>DAS</td>
<td>DAS</td>
</tr>
</tbody>
</table>
CHAPTER 2. BACKGROUND

Coupling shell based systems can have poor contact between the breast and the shell, and require manual or automated checking of the quality of the contact. Early clinical experience with the MARIA® system identified this as a challenge to repeatability [19], [20]. Coupling shell based systems often use small volumes of a medium to ensure efficient coupling of microwave energy into the breast, as in MARIA® [21], particularly for breasts smaller than the radome.

In contrast, the wearable system from MU has all hardware integrated into a bra. The bra is slightly undersized to ensure good contact between the breast and the antennas. Additionally, a thin layer of coupling medium is needed to maintain contact between the antennas and the breast. The system at HU is designed to be placed on the breast of a supine patient and the breast is in contact with a plastic dome covering the antennas. Both HU and MU are compact systems, with antennas, excitation and acquisition hardware and signal routing integrated into a single system [40].

Early studies based on numerical simulations indicated superior imaging performance when the breast is surrounded by antennas due to shorter average propagation paths [106]. Recent studies have also examined planar imaging systems with promising initial results [107]. The seated (MU) or supine systems (HU) may have difficulty in adequately covering all parts of the breast surface; particularly, the surface of all four quadrants, where approximately 16% of tumours are located [108]. However, both systems (MU and HU) are compact, facilitating use outside a clinical setting. This could be particularly useful in monitoring applications such as neoadjuvant chemotherapy, where assessing the tumour response to therapy is important.

Antenna arrays can be designed in three primary ways:

- synthetic arrays: where a small number of transmitting antennas, receiving antennas or both move during the patient scan to create a larger synthetic array (e.g. DC, TSAR, SUST, HU);
- hardware arrays: where the individual antennas do not move, but the entire array may be rotated for repeated scanning for artefact removal or other processing reasons (e.g. MARIA® and SU);
- stationary arrays: where there are no moving parts (e.g. MU).

Stationary arrays simplify the system mechanically as there are no moving parts. However, due to the comparatively larger number of antennas typically used compared to synthetic arrays (such as 16 in the wearable system by MU), calibration of the acquisition hardware and switching matrix can be difficult. Hardware arrays typically do not have any moving parts...
that could potentially collide with the pendant breast, which increases the safety of the design. Hardware arrays can also be challenging to calibrate due to the large number of antennas and the rotation of the array. Moving arrays, with typically fewer antennas, are easier to calibrate, however, there can be a decreased noise floor due to the movement of the system. Equally, care needs to be taken so that the antennas or mechanical parts cannot collide with the breast in the case of error. The system from DC consists of a ring of 16 antennas that can be moved vertically to image different coronal slices of the breast, whereas TSAR consists of a rotating single antenna with four degrees of freedom that is moved to 200 positions around the breast.

### 2.3.2 Acquisition Hardware Design

DC, MARIA®, TSAR, SUST and SU all acquire data in the frequency domain using a stepped frequency sine wave, whereas MU and HU collects backscattered data in the time domain. Historically, time domain acquisition hardware has been cheaper than the equivalent frequency domain acquisition hardware. However, in recent years, the cost of frequency domain acquisition hardware has reduced, as demonstrated by an experimental system from the Politecnico di Torino [109], [110].

Many antenna types have been used in operational systems, including:

- monopole antennas in DC;
- cavity-backed slot antennas in MARIA®.
- Vivaldi antennas in TSAR;
- planar slot antennas in HU;
- horn antennas in SUST;
- flexible microstrip antennas in the wearable system from MU;
- and stacked patch antennas in SU.

The flexible microstrip antennas used in the wearable system from MU are designed to easily conform to a wearable system, and one printed circuit board (PCB) with flexible substrate was used to provide all signal routing, simplifying system assembly and calibration.

The time to image a single breast (the patient scan time) varies depending on the acquisition hardware, the antenna array type and mechanical movement required. As the patient is required to remain motionless throughout the scan, faster scan times help mitigate the negative effects of patient
movement and breathing during acquisition [20]. Stationary arrays have the potential to be the fastest, as the patient scan time is limited only by switching and hardware acquisition time. Hardware arrays can also be very fast, although the total acquisition time is increased as multiple scans need to be taken at different rotation angles. The total patient scan time using hardware arrays can still be very fast: for example, the maximum acquisition time using MARIA® can be as short as a minute per breast, including time to position the patient breast. Synthetic arrays can require longer patient scan times, up to approximately thirty minutes in the case of TSAR. In comparison, the total time for mammography and ultrasound is often between ten and fifteen minutes depending on the type of test and image quality, similar to the total patient time for MARIA®. Magnetic resonance imaging may take forty-five minutes or more, which is comparable to the total patient time for patient imaging using TSAR.

These features are summarised in Table 2.1.

2.3.3 Artefact Removal Algorithms

The acquisition hardware and patient interfaces described in the previous two sections are used to sample the total field around the breast after illumination with energy in the microwave frequency band (typically between 0.5 GHz and 9 GHz). The raw scattered signals, \( E_{\text{raw}}(a') \), contain a number of additional signals that may obscure the tumour responses, including a large reflection from the skin, noise and antenna effects. These artefacts need to be removed before beamforming with Eq. (2.2) or any tumour response will potentially be obscured.

Many artefact removal algorithms have been proposed in the literature [111]–[118]. In many cases, the artefact removal algorithms are most suited to one particular patient interface or system. Most algorithms rely on some simplifying assumptions:

- that the raw scattered signals are dominated by early-time artefacts before the tumour response;
- and that artefacts recorded at neighbouring antennas are similar whereas the tumour response at neighbouring locations are dissimilar.

Of the six operational systems that use radar-based imaging reviewed in this chapter—MARIA®, TSAR, HU, SUST, MU and SU—a variety of artefact removal algorithms are employed:

- MARIA® and SU use rotational subtraction [116];
• HU uses averaging subtraction [111];

• TSAR and SUST use variants of adaptive filtering techniques [112], [113];

• and MU uses differential imaging [34].

Rotational subtraction employs the physical rotation of a hardware antenna array to collect two scans of the patient breast [116]. Objects not on the axis of rotation should have a different response after rotation, and the skin response is assumed to not change due to the rotation. No studies in the literature have examined this assumption in detail, nor determined the optimal angle of rotation. Recent work from an experimental system from Ewha Womans University has investigated similar methods which may perform better for tumours located on the axis of rotation [119].

Averaging subtraction artefact removal first averages all scattered signals in the time domain and subtracts the average signal from each scattered signal individually [111]. Early-time reflections, such as the skin, appear similarly in all scattered signals and are removed, whereas reflections from the breast interior appear at different locations in time in each scattered signal and are preserved after application of the artefact removal algorithm.

Adaptive filtering extends averaging subtraction by estimating the early-time artefact as a filtered combination of all scattered signals [112], [113]. Compared to averaging subtraction, adaptive filtering is less affected by variation in the scattered signals due to local variation in skin thickness. The operational system at SUST has used adaptive filtering for the first phase of the clinical trial with 11 healthy women, and the study suggests that adaptive filtering performed similarly to rotational subtraction but without having to acquire two patient scans [33].

Finally, it is envisaged that the wearable system from MU would be used to regularly monitor breast health and that a number of previous scans of a given patient would be available for comparison [34]. MU utilises differential imaging, where after processing to compensate for breast positioning variations, a scan of a patient on a previous occasion is subtracted from the current scan. The differences between successive scans could be used to monitor the breast changes that occurred between the successive scans.

2.3.4 Imaging Algorithms

DAS was the first radar-based algorithm to be proposed and has been used with both monostatic and multistatic acquisition hardware [120], [121]:

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monostatic DAS uses only signals where the total field, $\mathbf{E}(\mathbf{r})$, is sampled at the same location as the generation of the incident field, $\mathbf{E}_i(\mathbf{r})$: i.e. $\mathbf{a} = \mathbf{a}'$ in Eq. (2.2);

and multistatic DAS where the total field, $\mathbf{E}(\mathbf{r})$, is sampled at other locations spaced around the breast, i.e. $\mathbf{a} \neq \mathbf{a}'$ in Eq. (2.2).

A number of modifications and extensions of the basic algorithm have been proposed, though many have been tested with simulated or experimental data only. In general, all of the modifications and extensions of the basic algorithm are suitable for use with both monostatic and multistatic acquisition. Additionally, comparative studies have primarily focused on improvements in image quality in test cases containing tumours only, without analysing the effects in test cases without tumours.

Three main types of additions to Eq. (2.2) have been proposed which include methods to:

- calculate $w(\mathbf{r})$ to reward points where tumours are more likely based on epidemiological studies or based on the scattered signals;
- estimate $w_{a,a'}(\mathbf{r})$ to prioritise certain signals in the imaging summation based on distance to the points of interest or antenna patterns;
- improve the quality of the input signals prior to applying the imaging operator.

However, although many extensions to DAS have been proposed in the literature, the majority of radar-based patient imaging studies have used DAS for image reconstruction as is shown in Table 2.1.

Two common extensions to DAS are called improved delay-and-sum (IDAS) and modified delay-and-sum (MDAS). IDAS has been used for all patient imaging studies involving MENTRA®, the only operational imaging system to use an algorithm other than DAS.

IDAS calculates a “quality factor” to measure the degree of coherence at each synthetic focal point within the imaging domain. The quality factor is calculated by fitting a polynomial to the cumulative energy summation [122]. Using the quality factor rewards points with a high degree of coherence, while suppressing points with a low degree of coherence, hence suppressing clutter in the image.

MDAS estimates a “coherence factor” which is used as $w(\mathbf{r})$ in Eq. (2.2). The coherence factor is calculated as the ratio of the total energy of the summed signal to the sum of the energy of the input signals [56]. Points with a high degree of coherence should show much greater energy in the
summed signal than the sum of the energies in the input signals, rewarding points with a high degree of coherence.

Channel-ranked delay-and-sum (CrDAS) calculates $w_{a,a'}(r)$ based on the estimated propagation distance to the synthetic focal point [123]. This extension to DAS assumes that signals from closer to the points of interest will carry more meaningful information and be less distorted than those that have propagated further.

Finally, delay-multiply-and-sum (DMAS) extends DAS by improving the quality of the input signals to the imaging operator. DMAS operates by pairwise multiplying the input scattered signals prior to summation and after synthetic focusing [124]. Although this does not increase the amount of independent information, this method artificially increases the number of channels in the summation. The DMAS beamformer assumes that signals with a high degree of coherence should be rewarded by multiplication, whereas incoherent signals should not increase in energy after multiplication.

Rewriting the generic beamforming equation shown in Eq. (2.2) in the time domain is the most common practical implementation, although it has been suggested that imaging in the frequency domain can improve the image quality due to discretisation errors in the time domain sampling [125]. In the time domain, Eq. (2.2) can be written as:

$$I(r) = w(r) \int_0^T \int_A \int_{A'} w_{a,a'}(r) S_{a,a'}(t - \tau_{a,a'}(r)) \, da \, da' \, dt$$  \hfill (2.3)$$

where the time domain response of each channel, $S_{a,a'}(t)$, can be calculated using the Inverse Fourier Transform or equivalent:

$$S_{a,a'}(t) = \int_{-\infty}^{\infty} E_{a,\omega}(a') \exp[jt\omega] \, d\omega$$  \hfill (2.4)$$

Windowing the synthetically focused signals is common in the time domain, typically using a rectangular window as in Eq. (2.3). The window length, $T$, can vary from as short as a single time sample (2 ps used in TSAR [26]) to 50% longer than the excitation pulse (55 ns used in MARIO® [21]). Windowing is more computationally intensive in the frequency domain (complex convolution compared to real multiplication) and is not typically performed [125].
2.3.5 Patient Imaging Studies Results

A number of clinical trials with the seven operational systems have been conducted, with patient populations varying from 2 to 223 patients. Despite differences in acquisition hardware and image reconstruction techniques, many of the patient imaging studies highlighted encouraging results.

Dartmouth College, NH, USA (DC)

A study with the DC system was conducted with patients undergoing neoadjuvant chemotherapy \[18\] to monitor the response to the treatment. Eight patients with locally-advanced breast cancer were imaged between five and eight times during their treatment. Two patient cases are presented in detail:

- firstly, a patient with locally advanced cancer on the right side of the breast. By Day 44 of treatment, microwave images showed a diminished tumour size which correlated well with the size determined during surgery;
- secondly, a patient whose tumour did not respond to treatment. Images from Day 52 indicated increased dielectric properties in the tumour region compared to Day 0, which was also consistent with the clinical observation from surgery.

This study found that conductivity was correlated with the pathological response at 30 days for all eight patients. This indicated that the microwave images could predict the clinical outcome, helping oncologists determine the most appropriate future treatment. Although using tomography, these results are also very promising for radar-based imaging, as they indicate that there is an \textit{in vivo} contrast in dielectric properties in the microwave frequency band. One of three primary outcome measures of an ongoing trial with MARIA\textsuperscript{®} is also considering monitoring of patients undergoing neo-adjuvant chemotherapy or endocrine therapy (Clinical Trials Identifier NCT03302819).

MARIA\textsuperscript{®}, Micrima, Bristol, UK

Two generations of the MARIA\textsuperscript{®} system have been evaluated with patients: M4 \[21\] and M5 \[25\]. Both M4 and M5 have similar hardware, but M5 was redesigned to facilitate improved clinical use by reducing the acquisition time and processing data immediately so that an image compatible with Digital Imaging and Communications in Medicine (DICOM) was reconstructed.
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within two minutes [22]. In total, 223 patients cases have been analysed with both generations [25]. All recruited patients had an ultrasound and mammogram, as well as cytological or histological examination if appropriate. The patient scan using MARIA® was conducted before any surgical intervention or biopsy. The breast was inserted into a coupling shell with a small amount of coupling medium with similar dielectric properties to the coupling shell applied to improve contact. The quality of contact between the breast and shell was evaluated, and two scans were taken (approximately one minute in total) where the antenna array was rotated between each scan to facilitate removal of skin reflections and other signal artefacts.

The first trial with 86 patients found overall sensitivity of the MARIA® system to be 74% [21]. All images were generated and analysed blind to the clinical status of the patient. Most interestingly, of the 42 patients with dense or very dense breasts (according to Breast Imaging—Reporting and Data System (BI-RADS) classification), sensitivity was 86% compared to 69% and 79% for the original radiologist report and a blinded review by another radiologist respectively. Although the number of patients is still too small to draw definitive conclusions, the study notes the very encouraging results among patients with dense breasts. Patients with dense breast are at higher risk of developing breast cancer and patients with dense breasts are considered a more challenging case for mammography compared to patients with lucent breasts.

A further trial with more participants is underway with a next generation system, technically identical to the previous system but redesigned with clinical use in mind. Early indications from this trial are consistent with the previous study [22]–[25]. In particular, overall sensitivity across both trials is 75%, with sensitivity of 86% for cancers in dense tissue (28 cases to date).

TSAR, University of Calgary, Alberta, Canada

The largest trial with TSAR was conducted using 8 patients with varied clinical history, including patients with and without breast disease [26]. The latest generation TSAR system uses a single antenna with four degrees of freedom, and further clinical trials are planned with this newest generation [27]–[29]. All patients in the study had suspicious areas in the breast. However, only suspicious areas not located in the axilla of the breast were included as it can be challenging to cover this area with table-based systems [26]. Each patient was scanned using magnetic resonance imaging prior to a patient scan with the TSAR system.

Considering three patients with distinct disease (Group A), two patient images showed responses consistent with the known clinical history of the
patient. The third patient image may have shown a response corresponding to a focal lesion of invasive ductal carcinoma, however it is not certain if the extensive disease in the patient’s breast was within the imaging region. For three patients with multiple suspicious lesions (Group B), results are more difficult to interpret as the clinical cases were complex and some malignancies were removed prior to imaging with TSAR. However, in one notable case, DCIS that was only found during post-mastectomy histology does appear to have been detected by TSAR and not from mammography or magnetic resonance imaging. For two patients without disease (Group C), the images showed responses with comparable signal-to-clutter ratios (SCRs) to images of patients from Groups A and B. This may suggest that it is difficult to distinguish false positive and true negative cases. However, overall image magnitude was lower for images of patients with disease (Group C) when compared to patients with disease (Groups A and B), which indicates that the imaging magnitude may be important when distinguishing false positive and true negative cases.

Southern University of Science and Technology, China (SUST)

A trial with eleven healthy patients with varying levels of hyperplasia has been presented with the system at SUST [33]. The eleven women were recruited as a first phase of a large-scale clinical trial and were aged between 22 to 47. The preliminary results presented show more energy in the reconstructed image of a breast with hyperplasia compared to both the contralateral breast of the same patient, and a different patient without hyperplasia. Future phases of trials using this system are planned in China, which will be the largest with predominately Asian women. On average, Asian women have denser breast composition than European women, suggesting that these results will be important in estimating the clinical efficacy of microwave imaging in dense breasts.

Hiroshima University, Japan (HU)

A trial with five patients was conducted with the compact system from HU [32], [126]. Patients had invasive ductal carcinoma or DCIS. Images were reconstructed by engineers without knowledge of the exact clinical history of the patient. One example is shown where the tumour location in the microwave image matches a magnetic resonance image of the same patient. Images of the other patients are reported as being consistent with the clinical history of the patient.
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McGill University, Quebec, Canada (MU)

Trials with thirteen healthy volunteers were conducted with the wearable system from MU [34]. The study goals were to evaluate the scan comfort and to account for both measurement and biological variabilities in measurement. In general, scans were found to be repeatable, however many sources of variability were identified, such as patient positioning. These factors are especially important in a monitoring context, where the same patient is repeatedly scanned to identify changes in breast structure. As only healthy volunteers were imaged, no sensitivity or specificity information could be reported for this study, so the clinical efficacy of the wearable system is yet to be determined. However, the repeatable scans with a number of volunteers is encouraging.

2.3.6 Remaining Challenges for Clinical Translation

In summary, clinical results have been demonstrated in studies ranging from 2 patients [37] to 223 in the largest trial to date [25], with a variety of breast diseases and none. The studies have hinted at the potential of microwave imaging in specific patient populations, and motivate future clinical studies with larger patient populations and more diverse breast abnormalities. However, the studies also identified potential challenges such as imaging the axilla with TSAR [26] and reliably positioning the breast using the system at MU [34]. It is important that these findings are used to inform and improve both the system and algorithm designs for future imaging prototypes [38], [101].

Many of the challenges faced when imaging patients identified from the clinical studies to date can be categorised in four broad areas:

1. inefficient coupling of microwave energy into the breast [19];
2. changes in the imaging domain during acquisition [19], [34], [127];
3. intrapatient variation due to the menstrual cycle, hormonal changes or weight differences [34];
4. and interpatient variation in breast size, shape and composition [17].

These four challenges can have a large impact on image quality: if microwave energy is inefficiently coupled into the breast (Challenge 1), the tumour response in the scattered signals may be very small or even below the noise floor. Practical solutions employed by the operational systems to overcome
these challenges are discussed in this section, including the aspects of these challenges yet to be resolved.

The patient interface design (as reviewed in Section 2.3.1) can help address Challenge 1. The design of biocompatible coupling media which are stable over time, have appropriate dielectric properties and cheap and easy to replace between patients [128]–[130] improves the quality of the total field recording acquired. Coupling media are often designed with lossy dielectric properties to reduce reflections from the tank boundaries and any other unwanted reflections which may hamper reconstruction [130]. Later generations of MARIA® also include automated quality checking to ensure efficient coupling at all antennas [20].

The acquisition hardware summarised in Section 2.3.2 can also help address Challenge 1. For example, the latest generation of TSAR was designed to increase the penetration of energy into the breast by automatically repositioning the antennas perpendicular to the breast surface [131]. Other types of radome design and acquisition hardware have also been proposed and are being tested experimentally, which could help ensure efficient coupling of microwave energy into the breast. For example, a multi-facted metal chamber in the general shape of a hemiellipsoid with magnetic half-loop probes has been presented [132]. The irregular shape has been shown to improve the reconstruction quality in initial tests and the chamber is designed to maximise penetration of microwave energy into the breast [132].

The imaging domain is also subject to change during the scan as identified in Challenge 2: the breast can move due to patient breathing or discomfort, or blood flow or temperature changes may occur in the living breast tissue [19], [127]. Shorter acquisition times can help minimise the effects of these changes during acquisition, and later generations of MARIA® were designed to acquire the complete scan in under one minute [20], [21]. As with Challenge 1, improved coupling medium design can help immobilise the breast during the scan [128], [129].

Studies using TSAR have looked at the repeatability of the scans considering Challenges 2 and 3, highlighting the types of differences that can occur between patient scans and proposing metrics which can be used to quantify these differences independently [100]. Studies with healthy volunteers from MU have also evaluated the effects of patient position and movement during the scan and analysed the effect of the menstrual cycle and other natural changes on the images [34].

As microwave imaging is used with more diverse study populations, Challenge 4 is becoming increasingly important. Patient interfaces, acquisition hardware and coupling media are now being designed to accommodate more breast sizes and shapes, as highlighted earlier in this chapter. In terms
of interpatient variation in breast tissue composition, many studies have identified that breast composition can affect microwave image quality [27], [57]–[59], [133]–[136]. However, most published patient imaging studies do not adjust the breast composition assumptions on a patient-by-patient basis [21], [26], [32]–[34], [37]. Patient imaging studies from the University of Calgary did identify interpatient variance of breast tissue composition as an important parameter [26] for imaging. Subsequent studies have considered patient-specific beamforming to account for interpatient variance [27], [31], but no comprehensive study on the potential improvements in terms of sensitivity of radar-based imaging have been published.

The exact dielectric properties of human breast tissues is uncertain, although many studies have considered the problem [43]–[45], [137]–[148]. These studies are discussed in detail in the following section with particular emphasis on two aspects which make Challenge 4 difficult to address:

- the large variance in dielectric properties of breast tissues observed between healthy individuals in the population;
- the small contrast between the dielectric properties of healthy and cancerous tissues in a given individual.

### 2.4 Dielectric Composition of the Breast

Fundamentally, microwave imaging relies on a contrast between the dielectric properties of healthy and cancerous breast tissues. If a contrast exists, reflections from cancerous tissues can be isolated and used to reconstruct an image. A large number of studies have investigated the dielectric properties of human breast tissues, and the current understanding of the dielectric properties of human breast tissues is discussed in this section. Evidence from two types of studies is reviewed:

- firstly, dielectric properties studies which used open-ended coaxial probe measurements in Section 2.4.1;
- and secondly, *in vivo* imaging with operational microwave imaging systems (*viz.* systems from DC and TSAR) which have focused on the dielectric properties of healthy or cancerous breast tissues in Section 2.4.2.

Finally, in Section 2.4.3, the current understanding of the dielectric properties of human breast tissues is compared to the reported contrast in x-ray attenuation coefficient (the fundamental basis of x-ray mammography).
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2.4.1 Open-ended Coaxial Probe Measurement

Early studies on the dielectric properties of the human tissues at microwave frequencies primarily focused on the therapeutic use of microwaves [137]–[139]. Several subsequent studies have measured a wide variety of normal and cancerous human tissues (including breast tissue) [140]–[143] and extensive reviews of these studies have been published [144]–[148]. All historic studies report a significant contrast between the dielectric properties of healthy and cancerous breast tissues in the microwave frequency band. However, reported contrast between dielectric properties of healthy and cancerous tissues varies from between 1:2.3 to 1:10 across these different studies [147]. Inconsistencies in measured dielectric properties of both healthy and cancerous tissues were highlighted and analysed in [146]–[148].

In order to address the historical discrepancies, two large-scale studies measured the dielectric properties of healthy and cancerous breast tissue between 0.5 to 20 GHz [43], [44]. The dielectric properties reported are shown in Fig. 2.4. Distinctive features of [43], [44] when compared to the historical studies [137]–[143] include:

- comparatively large sample size (289 patients in total);
- broad frequency range (0.5 to 20 GHz);
- histopathological analysis of the tissue samples;
- correlation of the histopathological analysis with the measured dielectric properties;
- breast tissue samples sourced from the breast reduction surgeries to ensure healthy breast tissues only were measured in the first study [43];
- use of a broadband small-diameter precision open-ended coaxial probe with a small sensing volume to precisely measure the dielectric properties of the tissue just beneath the probe;
- and statistical analysis of the resulting data.

Tissues were categorised into three groups depending on the percentage adipose content of the tissue:

1. high-water-content, containing less than 30% adipose tissues;
2. containing between 30% and 85% adipose tissue;
3. low-water-content, containing more than 85% adipose tissues.
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Figure 2.4: Comparison of the dielectric properties of healthy (left) and cancerous (right) breast tissues from five studies [14], [43]–[45]. The relative permittivity (top row) and conductivity (bottom row) from the following five studies are shown: healthy Group I, II, and III tissues (R_I, R_II and R_III) from breast reduction surgeries [43]; healthy Group I, II and III tissues and tumour tissues (C_I, C_II, C_III and C_T) from cancer surgeries [44]; adipose, glandular and tumour tissues (S_A, S_G and S_T) from cancer surgeries [45]; average properties (D_H) estimated from tomographic images [14]; and properties of regions of adipose and glandular tissues (D_A and D_G) estimated from tomographic images [17]. Figures (a) and (c) highlight how the dielectric properties of healthy breast tissues reported by [14], [43]–[45] vary substantially more than those initially reported in older studies [137]–[143], [145]. Figures (b) and (d) indicate that the tumour properties measured in two leading ex vivo dielectric properties studies—[44] and [45]—are broadly in line (C_T compared to S_T).
Considering only tissues from breast reduction surgeries (from [43], shown as $\mathcal{R}$ in Fig. 2.4), a consistent trend of decreasing dielectric properties with increasing adipose content was found. Additionally, measurement variability was lowest when the sample consisted mainly of adipose tissues, attributed to the homogeneity of the tissue. The highest measurement variability was observed in Group II, which is attributed to the heterogeneity in the tissue composition of this group.

Comparing measured dielectric properties of healthy breast tissues from breast reduction surgeries and from breast cancer surgeries (comparing [43] to [44]; $\mathcal{R}$ to $\mathcal{C}$ in Fig. 2.4), differences were found between Groups I and III from both types of surgeries, but within the variability of each group. Larger differences in dielectric properties were found in Group II between tissues excised in reduction compared to cancer surgeries. These differences were attributed to the characterisation of normal tissue samples; as tissue samples from reduction surgeries tended to have higher adipose content than those from cancer surgeries. When comparing normal tissues and cancerous tissues, healthy samples with no more than 10% adipose tissues were chosen so that the comparison was not biased by high adipose content. A contrast of between 8% and 10% was observed in the permittivity and conductivity respectively, although no statistically significant differences between normal and cancerous breast tissues were observed.

In summary, the dielectric properties of cancerous tissues observed in [43], [44] were consistent with the historical studies [140]–[142]. However, reported contrast between dielectric properties of healthy and cancerous tissues was no more than 1:1.1 compared to a minimum contrast in permittivity of 1:2.3 found historically in [146]. The higher contrast reported in the historical studies was attributed to higher adipose content in the measured healthy tissue samples. The small contrast reported by Lazebnik et al. in [43], [44] would potentially impact the viability of microwave breast imaging in two ways:

- difficulty isolating reflections corresponding to tumour tissues from reflections corresponding to glandular tissues, particularly in dense breasts (affects the sensitivity);
- difficulty distinguishing images of healthy breasts with glandular tissues from images of breasts with tumour tissues (affects the specificity).

However, patient imaging studies have presented more encouraging results. An imaging study with 150 participants (using the DC system) indicated there may be a sufficient contrast between the dielectric properties of healthy glandular and cancerous tissues sufficient for imaging [16].

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Moreover, a small study with 66 participants found that the sensitivity was higher for the patient cohort with dense breasts (86% of 42 participants) compared to the sensitivity for the cohort with less dense breasts (54% of 24 participants). The encouraging results from the small and preliminary patient imaging studies to date have motivated further research in clinical evaluation of microwave breast imaging but also into other factors that may explain the apparently contradictory results from dielectric properties studies (very small contrast: imaging dense breasts difficult) and patient imaging studies (imaging dense breasts potentially possible) [101]. These \textit{in vivo} imaging studies that have analysed the dielectric properties of the breast are analysed in the following section.

\subsection*{2.4.2 Microwave \textit{in vivo} Imaging Studies}

In tandem with the dielectric properties studies reviewed in the previous section, operational microwave imaging systems have also been used to estimate the dielectric properties of human breast tissues. In contrast to the dielectric properties studies in the previous section, the \textit{in vivo} imaging studies do not measure tissue dielectric properties on a millimetre-scale, but rather, they measure the bulk dielectric properties on a centimetre-scale.

Dartmouth College, NH, USA (DC)

In 2000, Meaney \textit{et al.} published the first clinical evaluation of a microwave breast imaging system (DC from Section 2.3) with five women aged between 48–76 who had no abnormalities detected in recent mammograms and were all post-menopausal [14]. This study suggested that the dielectric properties of healthy breast tissues may be higher than previously reported. For example, the average relative permittivity estimated at 900 MHz ranged from 17.22 for an older patient to 36.18 for a patient with dense breast tissue, compared to approximately 18 recorded in [142]. The estimated conductivity (0.6 to 0.7 S m\(^{-1}\)) was also higher than the 0.2 S m\(^{-1}\) measured in [142]. There was also a suggestion of a weak correlation between breast radiographic density and dielectric properties.

Further studies using the same imaging system with 43 healthy women were conducted [15], [17]. The women were aged between 40 and 79, and recent mammograms showed no abnormalities. Images were reconstructed between 0.5 GHz and 1.7 GHz, and good agreement was found in estimated properties of the contralateral breast for all women. Regions of interest were defined corresponding to areas with predominantly adipose tissues, \(D_A\), and to regions with primarily glandular tissues, \(D_G\). Average dielectric
properties increased with radiographic density, and the ratio between the
dielectric properties of areas of glandular tissues and and areas of adipose
tissues also increased with radiographic density. Reported average properties
for the four BI-RADS breast density classes for each tissue type—$D_A$ and
$D_G$—are shown in Fig. 2.4.

Studies were also conducted including patients with abnormalities [16].
150 women aged between 35–81 years of age were included. The BI-RADS
criteria were used to categorise the patients:

- 53 control patients were categorised as healthy (BI-RADS I);
- the remaining 97 patients had suspected abnormalities (BI-RADS IV
  or V).

The 97 patients with suspected abnormalities were later diagnosed with can-
cer, fibrocystic disease, fibroadenoma and some other benign abnormalities.
Regions of interest were defined corresponding to the abnormality, and the
ratio of the dielectric properties of the region of interest to the background
calculated. An increased ratio was observed for cancerous lesions greater
than 1 cm when compared to benign and other abnormalities; potentially
indicating that the dielectric properties of cancerous tissues may be different
to those of healthy or other abnormal tissues.

**TSAR, University of Calgary, Alberta, Canada**

A dielectric properties estimation system has been demonstrated and the
system trialled with two patients [31]. The transmission-based system
is designed to complement TSAR. Measurements of each individual are
repeatable, although the system is expected to overestimate the dielectric
properties of human tissues due to dispersion across the frequency band.
The estimates are intended to improve a time-domain imaging algorithm
which uses a similar averaging effect across the frequency band, so the
overestimation of dielectric properties is not considered problematic. Two
patient cases are discussed and mean relative permittivity values of 51
and 20 were measured. Direct comparisons to other relative permittivity
estimates are difficult due to the expected over-estimation and the effect
of averaging over the frequency band. Recent work has suggested that
alternative estimation methods such as those described in this thesis are
more useful in the context of imaging [27], [59], [100], [149].
Finally, a classification approach has been considered using 48 patient cases acquired using MARIA® [24]. For 17 malignant diagnoses and 31 benign diagnoses consisting of 12 fibroadenomas and 19 cysts, the mean ratio of the high frequency response to the low frequency response (6.4 to 8.9 GHz compared to 3 to 4.6 GHz) could distinguish between cancerous and benign diagnoses with a positive predictive value of 76%. Although only 44 cases were considered, the study suggests that the dielectric properties of benign and cancerous tissues at different frequencies may be helpful in distinguishing between benign and cancerous tissues.

2.4.3 Current Understanding of Breast Tissue Dielectric Properties

Both the microwave in vivo imaging studies and the dielectric properties studies agree that a large variance in dielectric properties of healthy and cancerous breast tissues exists between patients. This large variance motivates the primary research question of this thesis: investigating if accounting for the patient-specific breast can improve radar-based imaging quality and efficacy. However, in other aspects, apparently contradictory conclusions can be drawn from the two types of studies. A number of possibilities have been identified that may explain some of the differences between these two types of study, which can be broadly summarised as follows:

- differences between ex vivo and in vivo dielectric properties measurement [150]–[153];
- breast tissue heterogeneity and subsequent histological analysis [45];
- sensing depth and volume and metrological technique used [154], [155];
- challenges in reporting results due to averaging in light of interpatient variance [18], [45], [46];
- and differences between the dielectric properties measured on a small scale compared to the bulk dielectric properties [154].

For example, it is reported in [44], that in vivo dielectric property measurement of cancerous tissues would not report higher properties compared to the equivalent ex vivo measurement. However, previous studies had reported differences between ex vivo and in vivo dielectric properties measurement [150], [151]. A subsequent study also contends that dielectric
properties measured *ex vivo* differ from those measured *in vivo* [152]. A decrease in measured dielectric properties was observed over the microwave frequency range, which is attributed to tissue dehydration and ischaemic effects. Although there were differences in the *in vivo* and *ex vivo* measurement technique and a small sample size of just six women, this study suggests the need for further investigation of the effect of excision on tissue dielectric properties.

A more recent study characterizes the change in dielectric properties with respect to time from excision [153]. Measured dielectric properties of murine liver were consistent with the literature, but a change of as much as 25% was observed between measurements taken *in vivo* and taken 3.5 h after excision. The change is attributed to tissue dehydration and indicates that the effect of *ex vivo* measurement must be considered when measuring dielectric properties.

Additionally, a key finding of [44] is that breast tissues are highly heterogeneous. The 60 cancerous tissue samples measured in the study were primarily composed of not only cancerous tissues, but also healthy glandular and adipose tissues. The tissue composition was visually evaluated by a pathologist, and some samples used to measure the contrast in dielectric properties between healthy and cancerous tissues contained as little as 30% cancerous tissues.

A recent study by Sugitani *et al.* with 35 patients measured the dielectric properties of 102 normal and cancerous breast tissue samples [45]. Consistent with [44], no significant contrast was reported between healthy glandular and cancerous tissues [45]. However, based on a computerised method of estimating the volume fraction of cells in each sample, tumour samples were found to contain between 10% and 80% glandular tissues and negligible adipose tissues. This finding contrasts with [44] where up to 20% adipose tissues were found in the tumour samples from visual examination by a pathologist. Unlike [44], significant variation was also observed in the dielectric properties of cancerous tissues. These contradictory findings were attributed to differences in classification of samples in each study: where Lazebnik *et al.* used visual assessment from the pathologist, Sugitani *et al.* quantified the volume fraction of cancerous cells in the tissue sample and used Bruggeman’s Approximation Theory to calculate the dielectric properties [156]. An increase in dielectric properties was observed as the proportion of cancer cells in the sample increased. The main conclusion from [45] is that variability in measured dielectric properties of tumour tissues can be attributed to the volume fraction of cancer cells in the tumour sample.

Furthermore, recent studies investigating the sensing volume of open-ended coaxial probes have found that the material within the first few
hundred microns of the probe may have a dominant effect on the measured
dielectric properties \[154\]. This dominant effect suggests that open-ended
coaixial probe measurement may not be suitable for estimating the aver-
age dielectric properties of biological tissue samples on a millimetre-
or centimetre-scale. Therefore, the study concludes that the measurements
in \[43\], \[44\] might need to be reinterpreted because of these limitations in
the dielectric properties measurement technique.

Further studies consider factors that impact the sensing depth and vol-
ume \[155\], \[157\]. It found that the sensing volume is dependent on the
frequency of measurement as well as the dielectric properties of the sample
being measured. The study demonstrates how the sensing volume may vary
appreciably across the microwave frequency band for samples with dielectric
properties similar to biological tissues. Considered together, these stud-
dies, \[154\], \[155\], indicate that care may need to be taken when interpreting
dielectric properties measurements of heterogeneous tissue samples in the
microwave frequency band using open-ended coaxial probes \[158\].

Finally, data presented by Sugitani et al. in \[45\] demonstrates how the
contrast between the dielectric properties of healthy and canceorous tissues can
vary substantially between individuals. For example, Patients 20–24 among
others from \[45\] exhibit a large contrast between the dielectric properties
of healthy and malignant tissues whereas Patients 29–30 show almost no
contrast between these tissues. Moreover, recent work has highlighted that
careful analysis is needed and that comparing averaged dielectric properties
of certain tissue types may obscure contrasts in individual participants \[46\]:
These effects make it difficult to estimate the exact dielectric properties to
expect within the breast, but all studies agree that the dielectric properties
and breast tissue composition vary substantially between patients.

In short, the exact dielectric properties of breast tissues \textit{in vivo} on a
millimetre-scale are not known, and the optimal measurement technique is
uncertain in light of difficulties in sample handling, tissue heterogeneity and
histology and unknown probe sensing volumes. However, all the studies agree
that the dielectric properties of healthy breast tissues vary substantially
\(5 \leq \varepsilon_r \leq 50\) at 3 GHz) in the microwave range, and that contrast between
the dielectric properties of healthy and cancerous tissues may not be as
large as the 1:10 originally reported \[147\]. Dielectric properties studies also
suggest that interpatient variability may be very high, making it difficult to
determine average dielectric properties representative of the population\[46\].
Finally, promising patient imaging results, even in patients with dense breast
tissue, suggest that it is important to consider evidence from both dielectric
properties studies and microwave \textit{in vivo} imaging studies when evaluating
the contrast between the dielectric properties of healthy and cancerous
CHAPTER 2. BACKGROUND

breast tissues.

In summary, the current understanding is that a contrast between the dielectric properties of healthy and cancerous breast tissues does exist at a centimetre-scale. However, the magnitude of the contrast can be very small in certain patients, and some studies have observed that cancerous tissues from one patient may have lower dielectric properties than healthy tissues from another patient [45], [46]. To help understand if this expected contrast between the dielectric properties of healthy and cancerous tissues is sufficient for imaging, the following section compares the current understanding of the dielectric properties of breast tissues to the current understanding of x-ray attenuation coefficients of breast tissues, the fundamental basis of x-ray mammography.

2.4.4 Comparison to X-ray Attenuation Coefficient

As discussed in Section 2.2.2, the leading asymptomatic screening imaging modality, x-ray mammography, fundamentally exploits the contrast between the x-ray attenuation coefficient of healthy and malignant tissues. However, the contrast between the x-ray attenuation coefficient of healthy glandular and cancerous tissues is no larger 1:1.1 [84], meaning the reported contrast between x-ray attenuation coefficients is no larger than the worst case contrast between dielectric properties of healthy and cancerous tissues reported by Lazebnik et al. in [44]. Despite this small contrast between the x-ray attenuation coefficient of healthy and cancerous tissues, x-ray mammography is currently recommended as an asymptomatic screening imaging modality [5]. However, the sensitivity of x-ray mammography is known to be poorer in dense breast tissue, due to the masking effect of the glandular tissue with similar attenuation to cancerous tissues [9].

It is difficult to compare the contrast between the dielectric properties of healthy and cancerous human breast tissues and the reported contrast between the x-ray attenuation coefficient of healthy and cancerous human breast tissues due to differences in the imaging modalities. Additionally, a large body of clinical evidence is available for x-ray mammography which informs any study of the inherent contrast or method of action. Randomised control trials studying the benefits of mammography with as many as 60,000 participants have been reported as early as 1966 [81], and over half a million women have participated in prospective randomised controlled trials of mammography [67]. In comparison, 223 patients have participated in the largest microwave patient imaging studies to date [16], [25], and a current trial with the MARIA® system is expected to include 994 women.
Additionally, little evaluation of the prevalence or distribution of glandular tissues in the human breast has been included in the dielectric properties studies to date [18]. The breast is known to be heterogeneous, and the contrast between the dielectric properties of healthy and cancerous tissues on a millimetre scale may not be representative of the breast as a whole. Even in breasts categorised as extremely dense according to BI-RADS, there may be as little as 20% glandular tissue by volume [159].

2.5 Conclusions

In this chapter, the background to microwave breast imaging was presented. The current state-of-the-art was reviewed, including recent developments in the field. Firstly, a brief overview of the anatomy and physiology of the human breast was presented in Section 2.1. The substantial variance between individuals in terms of breast composition was highlighted, and benign breast abnormalities which can mimic cancer were discussed. Next, the current understanding of asymptomatic breast screening was discussed in Section 2.2. The current clinical indications, and advantages and disadvantages of each existing imaging modality were highlighted, including the breast abnormalities, benign and invasive cancers, that were detected. Next, the fundamental basis of microwave imaging is introduced, beginning with the electromagnetic scattering equation, which is the starting point for many microwave image reconstruction techniques in use. Microwave imaging hardware and software design is comprehensively reviewed, including a detailed of comparison of the leading microwave imaging systems. The available evidence from patient imaging studies is reviewed, and the remaining challenges for clinical translation of the technology discussed. Finally, the current understanding of the dielectric properties of the human breast is reviewed, using evidence from dielectric properties studies and microwave in vivo imaging studies alike.

From a high-level perspective, breast cancer is a prevalent disease which can result in mortality. Many benign, pre-cancerous and malignant changes can occur in the breast, and early detection of malignant changes can lead to better patient outcomes. For screening, mammography is the only approved imaging modality, however, the use of ionising radiation makes mammography less suitable for younger women, and the sensitivity for patients with dense breasts can be poor. Ultrasound and magnetic resonance imaging are used for certain clinical indications, but neither have been approved for screening.

Microwave imaging has the potential to address these limitations, and encouraging results from early patient imaging studies have motivated more
Chapter 2. Background

research in the area. Microwave imaging is non-ionising and comfortable for the patient and has the potential to be low-cost. Seven operational systems have been used with patients, and the results of these patient imaging studies are being used to guide the next phase of patient imaging studies with larger and more diverse patient cohorts. The primary outcome of the next phase of studies will be sensitivity and specificity.

Breast anatomy is known to change between individuals in terms of volume of fibrous and glandular tissues. Additionally, the dielectric properties of individual breast tissues are known to vary between individuals. This variance in breast composition and dielectric properties can affect the radar-based imaging algorithms which require knowledge of propagation within the imaging domain to reconstruct an image. However, although a number of methods have been proposed which can estimate the patient-specific dielectric properties for image reconstruction, few studies have examined the impact of these methods on expected sensitivity of radar-based imaging. Moreover, proposed methods have typically been tested in true positive cases (experimental cases with tumours or patients with known disease) and the effects on the specificity of radar-based imaging is unknown. The literature lacks a thorough analysis of the impact of breast composition on image quality and the expected sensitivity and specificity of microwave breast imaging.

The review presented in this chapter helps motivate the remainder of this thesis, evaluating the effect of interpatient variation of breast dielectric properties on radar-based imaging. To help address the primary research objective of this thesis, a breast and tumour phantom set and microwave imaging hardware and software were developed which are described in the following chapter. The breast and tumour phantom set models the variance in breast composition seen in the population. The accompanying hardware and software, designed in light of the review of operational imaging systems, is also described, including the image analysis techniques used to determine sensitivity and specificity.
Experimental Test Cases

The experimental system and BRIGID phantom set described in this chapter were developed in collaboration with Bárbara L. Oliveira, who led the design and fabrication of the BRIGID phantom set that has been published by the IOP Biomedical Physics and Engineering Express in a journal publication entitled “Microwave Breast Imaging: Experimental Tumour Phantoms for the Evaluation of New Breast Cancer Diagnosis Systems” in 2018. Declan O’Loughlin led the design of the experimental hardware system and imaging algorithms and acquired the scattered signals used in the remainder of this thesis.

This chapter describes the experimental system and the BRIGID phantom set used to investigate the primary research objective of this thesis: the impact of the variance in breast tissue composition observed in the population on image quality, and sensitivity and specificity. The BRIGID phantom set was developed in collaboration with Bárbara L. Oliveira and has been used in a number of recent journal and conference publications [51], [55], [59], [160]–[162]. The BRIGID phantom set is also freely available for use.

The design, materials, dielectric properties and the final BRIGID phantom set used in this thesis are described in Section 3.1. The scattered signal acquisition is described in Section 3.2, including the hardware design in light of the review of operational systems presented in the previous chapter. The imaging algorithm is described Section 3.3 and the image analysis used to determine tumour detection is explained in Section 3.4. Finally, Section 3.5 concludes this chapter.

3.1 BRIGID Breast and Tumour Phantoms

As discussed in Section 2.1, the tissue composition of the breast varies within a given individual with age, hormonal change and menopause, but
can also vary substantially between individuals based on genetic and other factors. Studies analysing the tissue composition of the breast consider the volume glandular fraction (VGF), which is the volume of tissues labelled as glandular as a proportion of the entire breast volume. Estimates of the VGF of individuals in the population can be used to inform dosimetry measurements for mammography and phantom development for many imaging modalities [159], [163]. Using recent advances in three-dimensional breast imaging, the studies suggest that breast density is visually overestimated from two-dimensional mammograms, due both to the compression and the two-dimensional projective nature of the imaging methodology.

One such study consisting of 2,831 women of varying age and ethnicity [163]. VGF was measured using both three-dimensional breast computerised tomography (CT) and well-calibrated techniques for mammographic estimation. The mean VGF was measured at 19.3% for all women. Over 90% has less than 27% VGF. VGF was found to decrease with age, and one group of women, described as sedentary, over-weight and with a larger breast size had lower VGF on average.

An expanded study looked at 240 women aged between 35 and 82 who were imaged with dedicated breast CT [159]. The study found the mean VGF varied from around 7%–8% for non-dense breasts up to between 15%–25% for dense breasts. VGF decreased with age, breast diameter and cup size, but increased with BI-RADS density.

The breast phantoms used in this study were designed to cover a range of VGF from 0% to 30%, representing more than 90% of women [159], [163]. Although this excludes 10% of women with very high VGF, this is similar to the proportion of the population covered by existing operational systems. For example, MARIA® is currently designed to image breasts from 310 to 850 mL which excludes approximately 50% of women in [159]. If next generation patient imaging studies continue to show the effectiveness of radar-based imaging, it is important that future operational systems will be designed to accommodate more breast sizes and densities.

The dielectric properties were chosen in accordance with the dielectric properties studies reviewed in Section 2.4, in particular those by Lazebnik et al. in [43], [44] and by Sugitani et al. [45]. Although the exact in vivo dielectric properties are not understood precisely, these ex vivo dielectric properties studies represent a worst-case for microwave breast imaging of minimal contrast between the dielectric properties of healthy and cancerous tissues.

Benign breast diseases and breast cancers can also vary substantially in size and shape as summarised in Section 2.1. Benign breast tumours are typically more spherical or ellipsoidal and are characterised by smooth
CHAPTER 3. EXPERIMENTAL TEST CASES

borders; whereas invasive breast cancers have spiculated margins as they
tend to grow in irregular directions as the cancer invades the surrounding
tissues [86], [164], [165]. The tumour phantoms in the BRIGID phantom
set were designed to model both benign and malignant tumours of different
sizes.

3.1.1 Tissue-mimicking Materials

The materials used to fabricate the BRIGID phantom set were chosen:

- to mimic the variance in breast tissue composition in terms of VGF;
- to enable a variety of tumour shapes and sizes to be fabricated;
- and to ensure a large number of diverse test scenarios could be modelled
  for thorough algorithm evaluation.

Many materials have been proposed to approximate the dielectric prop-
erties of human breast tissues in the microwave frequency range [160], [166]–
[176]. The advantages and disadvantages of these materials are discussed
briefly in this section.

Triton X-100 has been shown to model the dielectric properties of human
breast tissues well [169], [170]. Triton X-100 is dielectrically stable with
respect to both temperature and time. However, at the target dielectric
properties of human breast tissues, Triton X-100 mixture is liquid, making
it difficult to model internal tissue and skin. Plastic shells with shapes
derived from magnetic resonance breast images have been used to fabricate
anatomically realistic breast phantoms [171], [172]. However, the effect of
the plastic layers in the breast on the scattered signals has not been fully
characterised [177].

Oil-in-gelatin mixtures can be used to produce breast phantoms with
varied shapes and interiors [166]–[168]. Oil-in-gelatin phantoms solidify
after mixing, and can be used to model internal fibroglandular tissues [167].
However, oil-in-gelatin phantoms are sensitive to environmental conditions
and the dielectric properties can vary substantially over time [167].

Polyurethane has also been proposed for phantom fabrication, using car-
bon black and graphite to alter the dielectric properties [173]. Polyurethane
can be easily moulded during fabrication into glandular and tumour shapes,
mimicking both breast density variance and tumours of difference shapes
and sizes. Polyurethane phantoms have been used to test both TSAR and
MU [173], [174]. After curing, polyurethane phantoms are solid and maintain

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their shape, and have been assessed using a variety of imaging methodologies to assess structural consistency [178].

These material features mean that polyurethane phantoms are suitable for evaluating the research questions in this thesis. The detailed fabrication protocol and verification are described in detail in [160] and are summarised in the following section.

3.1.2 Phantom Fabrication

Considering the breast anatomy discussed in Section 2.1, three main tissue types are modelled in the breast phantoms [21], [167]:

- a skin covering the breast exterior;
- the glandular and dense, fibrous interlobular connective stroma, known collectively as fibroglandular tissues;
- and adipose tissues which form much of the interlobar loose connective stroma.

By varying the volumes of fibroglandular tissue in the breast phantom, the normal variance in VGF observed in the population can be modelled.

The skin of the human breast varies between 1 mm to 3 mm in thickness depending on breast size, hormonal changes and age [179], [180]. The skin of the breast may also change due to invasive breast cancer [42], such as the swelling known as “peau d’orange” (skin of an orange). These breast phantoms do not model breast cancer symptoms involving changes to the skin, as the primary research question of this thesis considers screening of asymptomatic individuals.

Fibroglandular tissues were modelled as conical structures which originate from the areola, mimicking the breast lobes. Five separate breast phantoms with VGF from 0% to 30% were manufactured, allowing the impact of VGF on image quality to be assessed.

After the skin and fibroglandular structures were allowed to cure (between 16 to 24 hours), the breast phantom interiors were filled with an adipose-mimicking mixture. For all breast phantoms, a cavity was left in which a “plug” could later be inserted. For each phantom, one plug of the same adipose material as the phantom was fabricated, which could be inserted into the cavity to model a “healthy” breast phantom without abnormalities.

The same polyurethane base material with different proportions of graphite and carbon black (higher dielectric properties) was used to fabricate tumour phantoms: the material was moulded into the desired shape and
Figure 3.1: Comparison of the dielectric properties of the tissue-mimicking materials in the BRIGID phantom set (used in this thesis) and the dielectric properties of human breast tissues measured \textit{ex vivo} using open-ended coaxial probes [43]–[45]. Both (a) the relative permittivity and (b) the conductivity are shown. Considering the variance in reported dielectric properties shown in Fig. 2.4, the dielectric properties of the modelled tissue types of the BRIGID phantom set correspond well in terms of absolute values and the contrast between the types. The conductivity of the modelled tumour tissue is higher than reported in dielectric properties studies, which will result in higher loss in the tumour phantom. However, due to the small size of the tumour phantom compared to the breast phantom, this higher loss is not expected to unduly impact the scattered signals.

allowed to cure. Each tumour phantom was encased in a plug of the same adipose-mimicking material used to fill the breast phantom, allowing each tumour phantom to be used with each breast phantom.

### 3.1.3 Dielectric Properties of Phantom Materials

Although Section 2.4 has highlighted that uncertainty exists as to the exact \textit{in vivo} dielectric properties of human breast tissues, all studies agreed that the average dielectric properties vary substantially between individuals [14]–[17], [43]–[45], [137]–[148]. The studies by Lazebnik \textit{et al.} and Sugitani \textit{et al.} [43]–[45], are the largest measurement studies of human breast tissues \textit{ex vivo} to date and are used as a guideline for the dielectric properties of the phantoms used in this thesis. In addition, the smallest contrast between the dielectric properties of healthy and cancerous tissues reported in these studies is 1:1.1 [44], which can be considered a worst-case for microwave breast imaging and therefore suitable for test platform development.
Table 3.1: Measured mean dielectric properties of the BRIGID phantom set (used in this thesis) compared to the mean dielectric properties of the breast and tumour phantoms used to test the operational microwave imaging systems described in Section 2.3. Also shown are the mean values from leading dielectric properties measurement studies. Both the relative permittivity, $\varepsilon_r$, and the conductivity, $\sigma$, at 3 GHz are compared, where this data is available for other systems.

<table>
<thead>
<tr>
<th></th>
<th>Skin</th>
<th>Gland</th>
<th>Adipose</th>
<th>Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\varepsilon_r$</td>
<td>$\sigma$</td>
<td>$\varepsilon_r$</td>
<td>$\sigma$</td>
</tr>
<tr>
<td>MARIA®</td>
<td>36</td>
<td>2.0</td>
<td>36</td>
<td>2.0</td>
</tr>
<tr>
<td>TSAR</td>
<td>24</td>
<td>1.6</td>
<td>36</td>
<td>3.0</td>
</tr>
<tr>
<td>MU</td>
<td>35</td>
<td>3.0</td>
<td>37</td>
<td>3.5</td>
</tr>
<tr>
<td>Lazebnik et al. [44]</td>
<td>—</td>
<td>—</td>
<td>51</td>
<td>2.3</td>
</tr>
<tr>
<td>Sugitani et al. [45]</td>
<td>—</td>
<td>—</td>
<td>31</td>
<td>1.9</td>
</tr>
<tr>
<td>BRIGID</td>
<td>32</td>
<td>2.0</td>
<td>43</td>
<td>1.7</td>
</tr>
</tbody>
</table>

The dielectric properties of the internal tissue-mimicking materials in the frequency range of interest compared to the dielectric properties reviewed in Section 2.4 are shown in Fig. 3.1. In terms of both permittivity and conductivity, the dielectric properties of adipose tissues are very similar to those reported by Lazebnik et al. [43], [44] and Sugitani et al. [45].

In terms of permittivity, the range of the permittivity of phantom glandular material lies between the median permittivity reported in both [43], [44] and [45]. The median tumour permittivity is approximately 35% higher than measured in [44] and [45]. However, the contrast between the median permittivity of the phantom glandular tissue and the tumour phantom is 1:1.5. This contrast in permittivity between healthy and cancerous tissues is in the range 1:1.1 and 1:1.7 reported by Lazebnik et al. in [44] and Sugitani et al. in [45] respectively.

In terms of conductivity, the range of conductivities for both adipose and glandular tissues is similar to the measured values in [43], [44] and [45]. Although, the conductivity of the tumour is much higher than the conductivity observed in [44], [45] (more than twice at 3 GHz), this mainly affects losses within the tumour phantom. Due to the small physical extent of the tumour phantoms, the higher conductivity for the tumour phantoms is not expected to have a substantial impact on the scattered signals [160].

The mean dielectric properties of the breast and tumour phantoms at 3 GHz are shown in Table 3.1. The dielectric properties of the BRIGID phantom set are compared to recent experimental phantoms used with operational systems reviewed in Section 2.3 (where available at this frequency) in addition to the mean values from leading dielectric properties studies.
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Figure 3.2: Images of the interior of two breast phantoms in the BRIGID phantom set with (a) 10% and (b) 30% VGF. Both phantoms were then filled with the adipose material, and an opening was left to accommodate the plugs containing either a tumour phantom or the adipose material.

in [43]–[45]. Considering the uncertainty in dielectric properties evident from Fig. 2.4, the dielectric properties of the breast and tumour phantoms used in this thesis are broadly in line with other leading breast and tumour phantoms used with the operational systems. The conductivity of the glandular material at higher frequencies (particularly greater than 3 GHz) is lower than the breast phantoms used with some operational systems, but the conductivity is within the interquartile range reported by Lazebnik et al. in [44]. The conductivity of glandular-mimicking tissue in the BRIGID phantom is 10% or 0.12 standard deviations lower than the mean value reported by Sugitani et al. in [45].

3.1.4 Summary of Test Cases

Finally, the 5 breast phantoms and 22 tumour phantoms are summarised in this section. Each breast phantom can be combined with each tumour phantom for 110 test cases overall. Additionally, each breast phantom can be scanned without a tumour phantom, for five “healthy” comparison cases.

Breast phantoms with VGF of 0%, 10%, 15%, 20% and 30% were manufactured, and two pictures of the glandular structures before the adipose-mimicking material was added are shown in Fig. 3.2. The glandular structures taper to points at the apex of the hemisphere and grow greater in cross-sectional area as they move towards the base of the hemisphere; mod-
CHAPTER 3. EXPERIMENTAL TEST CASES

Figure 3.3: Images of all 22 tumour phantoms included in the BRIGID phantom set which model the variance in tumour shape and size observed in clinical practice. The tumour phantoms model both benign and malignant cases, where benign cases are characterised by smooth margins and malignant cases are characterised by spicules. Row one \((P_1-P_8)\) shows the low-spiculation tumours \((P_L)\); row two \((P_9-P_{14})\) contains the medium-spiculation tumours \((P_M)\); and row three \((P_{15}-P_{22})\) shows the high-spiculation tumours \((P_H)\).

elling how lobes converge on the areola. The mean thickness of the phantom skin varies from 1.98 mm (20% VGF) to 2.99 mm (0% VGF). The mean relative permittivity of the adipose material varies from \(\varepsilon_r = 7.63\) (20% VGF) to \(\varepsilon_r = 9\) (0% VGF). Cooper’s ligaments (fibrous connective tissue which supports the breast and maintains the breast shape) may cause the dielectric properties of the loose connective stroma to vary more than in the BRIGID phantom set [42], but are not modelled in these breast phantoms nor in other leading breast phantoms.

The tumour phantoms vary substantially in shape (as shown in Fig. 3.3) and in physical extent and volume (as shown in Table 3.2). Three types of tumour phantom were fabricated:

- low spiculation \((P_L)\) which are spheres or ellipsoids of varying dimensions with smooth margins and modelling benign tumours;
- medium spiculation \((P_M)\) which are spheres or ellipsoids with irregular margins modelling malignant tumours;
- high spiculation \((P_H)\) which are fabricated from long thin spicules and model highly spiculated malignant tumours.

The high spiculation cases \((P_H)\) are similar in physical size to the medium spiculation cases \((P_M)\), but have lower mass, as can be seen in Table 3.2.
Table 3.2: The physical dimensions and mass of all 22 tumour phantoms in the BRIGID phantom set. Dimensions for each of the Head–Toe (H–T), Left–Right (L–R) and Front–Back (F–B) axes are shown, along with the tumour phantom name and spiculation degree: low (P_L), medium (P_M) or high (P_H).

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Dimensions (mm)</th>
<th>Mass (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>H–T</td>
<td>L–R</td>
</tr>
<tr>
<td>P_1</td>
<td>P_L</td>
<td>5.2</td>
<td>7.0</td>
</tr>
<tr>
<td>P_2</td>
<td>P_L</td>
<td>8.4</td>
<td>8.8</td>
</tr>
<tr>
<td>P_3</td>
<td>P_L</td>
<td>10.9</td>
<td>11.0</td>
</tr>
<tr>
<td>P_4</td>
<td>P_L</td>
<td>13.7</td>
<td>13.8</td>
</tr>
<tr>
<td>P_5</td>
<td>P_L</td>
<td>20.4</td>
<td>20.7</td>
</tr>
<tr>
<td>P_6</td>
<td>P_L</td>
<td>11.3</td>
<td>20.5</td>
</tr>
<tr>
<td>P_7</td>
<td>P_L</td>
<td>21.7</td>
<td>13.1</td>
</tr>
<tr>
<td>P_8</td>
<td>P_L</td>
<td>11.9</td>
<td>12.4</td>
</tr>
<tr>
<td>P_9</td>
<td>P_M</td>
<td>11.7</td>
<td>15.0</td>
</tr>
<tr>
<td>P_{10}</td>
<td>P_M</td>
<td>15.2</td>
<td>16.6</td>
</tr>
<tr>
<td>P_{11}</td>
<td>P_M</td>
<td>13.2</td>
<td>22.1</td>
</tr>
<tr>
<td>P_{12}</td>
<td>P_M</td>
<td>18.8</td>
<td>14.1</td>
</tr>
<tr>
<td>P_{13}</td>
<td>P_M</td>
<td>14.4</td>
<td>27.0</td>
</tr>
<tr>
<td>P_{14}</td>
<td>P_M</td>
<td>16.6</td>
<td>10.5</td>
</tr>
<tr>
<td>P_{15}</td>
<td>P_H</td>
<td>14.1</td>
<td>17.2</td>
</tr>
<tr>
<td>P_{16}</td>
<td>P_H</td>
<td>20.5</td>
<td>19.5</td>
</tr>
<tr>
<td>P_{17}</td>
<td>P_H</td>
<td>15.8</td>
<td>19.0</td>
</tr>
<tr>
<td>P_{18}</td>
<td>P_H</td>
<td>23.2</td>
<td>17.2</td>
</tr>
<tr>
<td>P_{19}</td>
<td>P_H</td>
<td>23.3</td>
<td>8.7</td>
</tr>
<tr>
<td>P_{20}</td>
<td>P_H</td>
<td>21.3</td>
<td>24.5</td>
</tr>
<tr>
<td>P_{21}</td>
<td>P_H</td>
<td>25.8</td>
<td>12.5</td>
</tr>
<tr>
<td>P_{22}</td>
<td>P_H</td>
<td>21.0</td>
<td>22.8</td>
</tr>
</tbody>
</table>

The lower mass of the high spiculation tumour phantoms (P_H) helps show how the high spiculation tumour phantoms are composed of many thin spicules. The medium and high spiculation tumour phantoms help increase the diversity in the BRIGID phantom set by including tumour phantoms with irregular borders as well as very spiculated tumour phantoms.

3.2 Hardware Signal Acquisition

The review of operational systems presented in Section 2.3 informed the design of the experimental system used in this thesis. The patient interface is designed to be similar to MARIA® [21]: the patient would lie prone on an examination table with the breast pendant through an opening. A small volume of coupling medium would be required to ensure good contact...
CHAPTER 3. EXPERIMENTAL TEST CASES

between the antennas and the breast, particularly in the case of smaller breast sizes. The imaging domain includes the nipple area and anterior portion of the breast. A 2 cm to 3 cm mat would be required for patient comfort that would hinder placing antennas close to the chest wall. This limits coverage of the posterior portion of the breast. At present, operational systems typically cannot accommodate breasts of all sizes (for example, TSAR is limited to cup sizes B and C [26]) and future work will be needed to refine the designs to include more breast sizes and all regions of the breast. For example, table-based systems do not cover the axilla well [26] where up to 2% of primary tumours are located [108].

Flexible microstrip antennas from MU were used [182]; these antennas have been previously used with healthy volunteers over many scans using the wearable system at MU [34]. The antennas were optimised to operate from 2 GHz to 4 GHz and a representative sample of the frequency response of the antenna in contact with the skin of two BRIGID breast phantoms (20% and 30% VGF) is shown in Fig. 3.4a. The antennas are 2 cm by 2 cm square, and 24 antennas are evenly spaced around the radome (as shown in Fig. 3.5a). From an electromagnetic perspective, reciprocal channels contain redundant information, that is:

\[ E_{\alpha, \omega}(\alpha') = E_{\alpha', \omega}(\alpha) \forall \alpha, \alpha' \in \mathcal{A} \]  (3.1)

Therefore, the number of independent channels, \( N_C \), is given by the number of pairs in the antenna array:

\[ N_C = \binom{|\mathcal{A}|}{2} = \frac{24 \times 23}{2} = 276 \]  (3.2)

More independent channels are available in this system compared to the 120 used with healthy volunteers in MU [34], and the number of channels is compared to the other operational systems in Fig. 3.4b.

Fused deposition modelling was used to manufacture the 70 mm radius hemispherical radome which housed the antennas. The radome was printed using polylactic acid (PLA) with an Ultimaker 2+ Extended (Ultimaker, Geldermasen, the Netherlands). The radome has twenty-four openings which securely housed the SubMiniature Version A (SMA) connectors attached to each antenna.

Data were acquired in the frequency domain using a stepped frequency sine-wave at 50 frequency points linearly spaced between 2 GHz and 4 GHz. A ZNB40 2-port VNA and ZN-Z84 24-port switching matrix (Rohde and Schwartz GmbH, Munich, Germany) acquired all 276 independent multistatic channels in 30 s (shown in Fig. 3.5b). Twenty-four coaxial cables 457 mm in
CHAPTER 3. EXPERIMENTAL TEST CASES

Figure 3.4: A representative sample of the frequency response of an antenna used to acquire experimental data is shown in (a) when the antennas are in direct contact with the skin of two phantoms in the BRIGID phantom set (20% and 30% VGF). A comparison of the frequency range, number of channels, domain of acquisition and acquisition time of the experimental system used in this thesis with other operational microwave imaging systems is shown in (b). Coupling media systems are shown with a dotted line (---) whereas coupling shell systems are shown with a solid line (---). Hardware arrays are represented with a cross (+) with synthetic arrays represented with a dot (•).

Figure 3.5: Images of (a) the radome, antennas, antenna array, and (b) the ZNB40 2-port VNA and ZN-Z84 24-port switching matrix (Rohde and Schwartz GmbH, Munich, Germany) used to acquire experimental data in this thesis.
length connected each port of the switching matrix to surface-mounted 50Ω SMA connectors on each antenna which were housed in the radome (both manufactured by Cinch Connectivity Solutions, Waseca, MN, USA).

Prior to use, a full 24-port calibration was conducted which corrected all S-parameters \(S_{x,x}, S_{x,y}\forall (x, y) \in \{1, 2, ..., 24\}\) with the reference plane at the end of the cable connecting the switching matrix and antenna. Due to experimental error, the response of each antenna was different, which would lead to errors in the rotational subtraction artefact removal algorithm. A reference scan taken with a homogeneous breast phantom with skin was taken. This reference scan was used to compensate for differences between the antennas, and a single compensation was applied to all scans before artefact removal and imaging.

### 3.3 Beamforming Methods

Considering the generic beamformer described in Eq. (2.2), the acquisition surfaces, \(A = A'\) can be defined as the 24 antenna locations shown in Fig. 3.5a, and are mathematically described as:

\[
a_i \in A \quad \forall i \in \{1, 2, ..., 24\} \in \mathbb{N}
\]  

A number of other discretisations are required for the practical implementation of the beamforming equation in Eq. (2.2):

- the calibrated S-parameters from VNA need to be processed to remove artefacts such as reflections from the skin as discussed in Section 2.3.3;

- the frequency range, \(\Omega\), is limited to between 2 GHz and 4 GHz to match the antenna characteristics shown in Fig. 3.4a, and is discretised;

- and the imaging domain, \(V\), needs to be discretised and defined.

The hardware antenna array is designed so that for each antenna pair, \((a_i, a_j)\), there is another antenna pair, \((a_x, a_y)\), that is offset by a constant angle around the sagittal axis. The constant offset angle means that the hardware antenna array is rotationally similar and that a rotated scan can be acquired without any mechanical movement of the antenna array.

Thus, rotational subtraction is used to isolate the tumour response from the calibrated S-parameters (described in detail in Section 2.3.3). For example, antennas \(a_1, a_2, a_3\) are in a concentric ring offset from each other by 36°, so the response for channel \(E_{a_1,\omega}(a_2)\) is given by:

\[
E_{a_1,\omega}(a_2) = S_{1,2}[\omega] - S_{2,3}[\omega]
\]
The minimum frequency resolution required can be estimated from the maximum propagation time. The maximum propagation time is proportional to the distance travelled and inversely proportional to the propagation speed: that is, the maximum propagation time is the longest distance at the slowest speed. As the hardware antenna array has a maximum diameter of 140 mm, the upper limit for propagation paths within the radome is twice the radome diameter, or $d_{\text{max}} = 280$ mm. The propagation speed is inversely proportional to the dielectric properties of the imaging domain, which can be estimated as $\varepsilon_{\text{max}} = 50$ for a breast phantom with mainly glandular tissues.

Thus, an upper limit for the propagation time can be estimated as follows given the speed of light as $0.299 \text{ Gm s}^{-1}$:

$$t_{\text{max}} = \frac{d_{\text{max}}}{c_{\text{min}}} = \frac{d_{\text{max}} \sqrt{\varepsilon_{\text{max}}}}{c_0} = \frac{280 \text{ mm} \sqrt{50}}{0.299 \text{ Gm s}^{-1}} \approx 7 \text{ ns} \quad (3.5)$$

This implies that the minimum frequency resolution is:

$$\Delta f|_{\text{min}} = \frac{1}{t_{\text{max}}} = \frac{1}{7 \text{ ns}} = 140 \text{ MHz} \quad (3.6)$$

In this thesis, the frequency resolution is 40 MHz, well below this limit.

Finally, the imaging domain, $\mathcal{V}$, needs to be defined. In this work, it is taken as a grid of points spaced at 2 mm within the hemispherical radome. This is convenient for visualisation and common among the operational systems such as TSAR [26], however, the point distribution could affect the image and methods for defining evenly spread point distributions for spheres have been proposed [183].

Based on these discretisations, the generic beamformer in Eq. (2.2) is implemented as follows:

$$I(\mathbf{r}) = \sum_{\Omega} \sum_{\mathcal{A}} \sum_{\mathcal{A}'} E_{a_i,\omega}(\mathbf{a}_j) \exp j \omega \tau_{a_i,a_j}(\mathbf{r}, \omega_i) \quad (3.7)$$

The challenges in estimating the propagation delay, $\tau_{a_i,a_j}(\mathbf{r}, \omega_i)$, are discussed in detail in the following chapter in Section 4.1.

### 3.4 Image Analysis and Tumour Identification

This section discusses how the images reconstructed using the DAS beamformer are analysed to determine if a tumour is detected or not. The criteria identified are used to help investigate the sensitivity and specificity
in later chapters. A variety of methods for image analysis have been used in patient imaging studies to date, although full details of the criteria for detection are not always published. In some cases (MARIA® and SUST), images are thresholded to 1.5 dB of the maximum image amplitude and the image is normalised when displayed so the maximum image amplitude is the consistent for display [21], [33]. In studies with TSAR, the image is not thresholded, although the study notes that reconciling the image to the clinical history of the patient is difficult [26].

As highlighted in Section 2.3, radar-based imaging is a qualitative imaging approach: the reconstructed image does not directly represent the dielectric properties of the entire imaging domain. Qualitative approaches instead identify areas with contrasting dielectric properties. However, the amplitude of the image is still affected by the dielectric properties of the breast. The amplitude of the images will be highest for areas of large contrast in regions of low attenuation (less dense breasts) and lowest for areas of minimal contrast in regions of high attenuation (more dense breasts). Furthermore, size and shape of scatterers is not directly preserved in microwave radar-based images, but can also affect the amplitude of responses in the images [162].

In this thesis, detection was carried out in two stages:

1. an image was annotated as a positive if a response with SCR of greater than 1.5 dB was observed in the breast;
2. images annotated as positive were considered true positives if the response was within the physical extent of the actual tumour: i.e. the localisation error was less than the tumour radius.

The SCR is defined as the maximum amplitude within the tumour area divided by the maximum amplitude of the clutter, where the clutter is the area of the image outside twice the full width at half maximum (FWHM) of the main response in the image. The benefits of using the maximum image amplitude for detection in terms of specificity are analysed in Chapter 4. Overall, 70% of images were annotated as containing a tumour response, and 30% were annotated as negatives. Selection of a threshold of 1.5 dB was determined empirically, and also the threshold was chosen in line with operational systems such as MARIA® [21] and SUST [33].

In the 70% annotated as containing a tumour, exceptions to the detection criteria above were made, if:

- the secondary response was within 10 mm of the main response (12% of cases): this can occur with large and spiculated tumours in particular. Visually, this appears similar to a single response;
• the secondary response was within 5 mm of the boundary of the imaging domain (29% of cases): this can occur as a result of artefact removal algorithms [60].

These exceptions were also chosen empirically based on visual examination of the images. In addition to further examination of the detection criteria, determining the optimal image domain in terms of point distribution and the boundaries of the imaging domain are outside the scope of this thesis, but these could impact the image detection algorithms.

In the 30% annotated as not containing a tumour, 94% were deemed negative as the response was within 10 mm of the boundary of the imaging domain or touching the boundary. In these cases, the response appeared similar to an artefact due to poor performance of the artefact removal algorithm. The remaining 6% did not meet the SCR criterion nor the exceptions listed above.

To determine the changes in sensitivity due to reconstruction permittivity estimation in the following chapter, the 70% of images annotated as containing a tumour were divided into true positives and false positives. Of the images annotated as containing a tumour, 92% were considered true positives as the primary response was within the tumour area. The remaining 8% were considered false positives, as the tumour was not correctly detected. Of this 8% false positives, five cases (83% of all false positives) were in the most dense breasts and in three of those cases, a tumour would have been reported but in the wrong quadrant of the breast.

3.5 Conclusions

In this chapter, the experimental platform used to evaluate the primary research objective of this thesis were described. The BRIGID breast and tumour phantom set, as well as the experimental hardware and imaging algorithms, have been presented.

The BRIGID breast and tumour phantom set design was described, including how the BRIGID breast phantoms model a realistic variation in VGF from 0 to 30%. VGF is a useful way to quantify the volume proportions of the breast occupied by fibroglandular tissues and by adipose tissues. In addition to the dielectric properties of healthy and cancerous tissues, the VGF is an important factor when designing representative breast phantoms.

The imaging system in terms of signal acquisition, hardware design, artefact removal and imaging algorithms have also been presented. To date, patient imaging studies with microwave imaging have been small in terms
of patient numbers, making extensive statistical analysis difficult. Image analysis and evaluation has also varied: images from many operational systems (TSAR, SUST, HU, MU and SU) are qualitatively compared to the known truth from other imaging modalities or images are compared using quantitative metrics such as SCRs. Images from MARIA® were reconstructed and analysed by an engineer blind to the clinical history of the patient. An image was considered a true positive if responses in the image were consistent with ultrasound and mammography, with subjective allowance for differences between the imaging modalities and uncertainties as to the exact ground-truth. Empirical quantitative detection criteria were proposed in this chapter which are used in the later chapters to determine the expected changes in sensitivity and specificity due to reconstruction permittivity estimation. Although subjective, the quantitative detection criteria described in this chapter are an important first step and necessary to investigate the effects of reconstruction permittivity estimation on sensitivity and specificity in the following chapter.
Patient-specific Beamforming

Work from this chapter was published in the IEEE Transactions on Medical Imaging in 2018 in a journal paper entitled “Sensitivity and Specificity Estimation Using Patient-Specific Microwave Imaging in Diverse Experimental Breast Phantoms”.

A key assumption of radar-breast imaging is that the scattered signals can be synthetically focused to points within the imaging domain. As described in Section 2.3, an estimate of the propagation delay for a signal transmitted from antenna $a$, scattering from a contrast located at $r$ and received at antenna $a'$ is used to implement synthetic focusing. Given knowledge of the dielectric properties of the imaging domain, the propagation delays could be calculated exactly. However, in a practical imaging scenario, this exact knowledge is not available, and the assumptions necessary to estimate the propagation delay in patient imaging studies are discussed in Section 4.1.

As breast tissue composition can vary between individuals, so can the dielectric properties estimates used to calculate the propagation delays. Existing methods to calculate these estimates are categorised and reviewed in Section 4.2. However, the benefits of these methods are uncertain, and no comprehensive study on the benefits of dielectric properties estimation on image quality exists. Three idealised estimation methods are compared, based on existing algorithms from the literature. The three idealised methods are used to identify the benefits and disadvantages of different approaches in accounting for breast tissue composition variation between individuals.

The results in Section 4.3 are presented in three sections, analysing in turn:

- the impact of patient-specific beamforming on the expected specificity using images of breast phantoms without tumour phantoms in Section 4.3.1;

- the improvements in sensitivity achieved using patient-specific beamforming in Section 4.3.2;
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- finally, the effect of errors in the estimation process on the expected specificity in Section 4.3.3.

These results can help determine if robust methods for patient-specific dielectric properties estimation can positively impact the sensitivity without negatively impacting the specificity. These data also highlight the potential challenges to be overcome when designing robust patient-specific estimation algorithms.

4.1 Challenges in Propagation Delay Estimation

Given exact knowledge of the dielectric properties of the imaging domain, the propagation delay between two points for a wave travelling between those two points can be calculated as follows:

$$\tau_{a,a'}(r, \omega) = \int_{C(\omega)} \frac{1}{c(r', \omega)} dr'$$

(4.1)

where $C(\omega)$ is the propagation path for the wave transmitted at $a$, scattering due to a contrast in dielectric properties at $r$ and received at $a'$, and $c(r', \omega)$ is the propagation speed along the propagation path, $C(\omega)$. As the dielectric properties of human breast tissues are frequency-dependent, both the propagation speed, $c(r', \omega)$, and the propagation path, $C(\omega)$, can vary depending on the frequency of interest.

The propagation speed can be calculated from the dielectric properties of the imaging domain as a fraction of the speed of light in free space, $c_0$:

$$c(r', \omega) = \frac{c_0}{\sqrt{\varepsilon_r(r', \omega)}}$$

(4.2)

There are many challenges in estimating the exact propagation delay:

1. the exact frequency-dependent dielectric properties of the imaging domain are not known;

2. the exact propagation paths through the imaging domain are not known;

3. the breast is heterogeneous and comprises many different tissues;

4. and the breast tissue composition varies from individual to individual, as discussed in Section 2.1.
A corresponding set of assumptions has been used to address these challenges and design a practical beamformer which can be used for imaging in realistic scenarios. These simplifying assumptions can be summarised as follows, that:

1. the dielectric properties are frequency-invariant within the frequency-band of interest;

2. the propagation path is a straight line between the antennas and the point of interest and multipath propagation does not occur;

3. the breast interior is a homogeneous layer of spatially-invariant dielectric properties;

4. and that a population mean of the breast dielectric properties exists that can be used when imaging all individuals, regardless of breast composition.

Together, these assumptions are known as fixed-value estimation in this thesis and are used in all patient radar-based imaging studies to date.

Assumptions 1–3 have been considered in other work. For example, frequency-dependent dielectric properties have been used in numerical studies [57], [185] but all operational systems use Assumption 1 and assume frequency-invariant dielectric properties for reconstruction. Recent studies have suggested that this assumption has a minimal effect on image quality [27]. As can be seen from Fig. 3.1a, the permittivity reported by Sugitani et al. and Lazebnik et al. for all tissue types [43]–[45] varies by less than 10% in the frequency range of interest in this thesis, which would result in an error of less than 5% in the propagation path length at most.

A straight-line propagation path (Assumption 2) has also been assumed by all operational systems and no practical methods to estimate the actual path have been proposed. Studies looking at the effect of Assumption 2 have suggested that it results in, at most, a 3 mm underestimation of the actual propagation path length [28], [186]. Additionally, signals travelling along the shortest path will arrive earliest with the least attenuation, so are expected to be more dominant in the imaging summation process than signals travelling via other propagation paths.

All operational systems use Assumption 3, that the breast interior is a single homogeneous layer with spatially-invariant properties. In most cases, operational systems also assume that the skin and coupling medium have the same dielectric properties, with the exception of TSAR. The imaging domain is divided into three regions when imaging using TSAR: coupling medium,
CHAPTER 4. PATIENT-SPECIFIC BEAMFORMING

skin and breast interior [26]. The skin surface is located using a laser ranging system mounted on the same arm as the microwave antenna, and the skin is assumed to be 2 mm thick. However, TSAR still uses Assumption 2, that a straight-line propagation path exists. Other numerical studies have also divided the imaging domain into three separate layers [57]. Preliminary numerical studies have investigated if more complex representations of the dielectric properties of the breast interior could be used to improve image reconstruction [187]–[189]. However, no practical methods to determine either the internal breast structure or the exact propagation paths exist.

Using Assumptions 1 and 3, the frequency-invariant estimate of the breast interior dielectric properties is known as the “reconstruction permittivity”, \( \varepsilon_r' \), in this thesis. The propagation speed can be estimated from the reconstruction permittivity as follows by simplifying Eq. (4.2):

\[
c(r) \bigg|_{\varepsilon_r'} = \frac{c_0}{\sqrt{\varepsilon_r'}}
\]

(4.3)

and used with Assumption 2 of a straight-line propagation path to simplify the contour integral from Eq. (4.1):

\[
\tau_{a,a'}(r) \bigg|_{\varepsilon_r'} = \frac{\varepsilon_r'}{c_0} \left[ \| r - a \| + \| r - a' \| \right]
\]

(4.4)

The propagation time from Eq. (4.4) is used with the practical beamformer shown in Eq. (3.7) for imaging in the remainder of this thesis.

The primary research objective of this thesis addresses Assumption 4:

- whether a population mean of the reconstruction permittivity exists that is suitable to use when imaging breasts of varied composition;

- and practical methods to find an optimum reconstruction permittivity estimate for the patient-specific breast.

Correct estimates of the reconstruction permittivity maximise energy at the tumour location while minimising energy outside the tumour area. Correspondingly, incorrect estimates of the reconstruction permittivity can lead to incorrect tumour localisation, or greater clutter in the image which can obscure any tumour response.

Due to the assumptions and uncertainties identified in this section, there are many factors that can impact the reconstruction permittivity. The correct reconstruction permittivity is dominated by the dielectric properties of the imaging domain, in particular, the correct estimate is a weighted mean of the dielectric properties of the dominant propagation paths in the imaging operator summation. However, other factors can also impact the correct estimate, in particular:
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• the reconstruction permittivity will be closest to the permittivity at frequencies dominant in the imaging summation;

• propagation paths are underestimated due to the straight-line assumption which may result in overestimation of the reconstruction permittivity to compensate;

• the skin thickness and dielectric properties can vary from patient to patient which can impact the reconstruction permittivity depending on the tumour location;

• artefact removal algorithms can change the tumour response compared to the idealised tumour response from that location, which may impact the optimal reconstruction permittivity;

• reflections come from the margins of the tumour rather than from a single point at the centre, the reconstruction permittivity could be affected by the size and shape of the tumour;

• and the location of the tumour could mean that different paths are dominant in the summation which could affect the optimal reconstruction permittivity.

The following section reviews existing methods for reconstruction permittivity estimation, in particular, how existing methods address the four challenges identified in this section and how the factors listed above can impact the resulting estimate.

4.2 Existing Methods for Patient-specific Beamforming

Several methods have been proposed to estimate the optimal reconstruction permittivity [31], [57]–[60], [149], which can be broadly classified in three categories:

1. time-of-flight methods [31], [58];

2. complementary microwave imaging techniques [57];

3. and parameter search algorithms [59], [60], [135], [149].
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Fundamentally, time-of-flight methods assume that the reconstruction permittivity can be estimated from a number of propagation paths through the imaging volume. Time-of-flight methods are subject to uncertainties in the propagation path, multipath propagation and dispersion in the time-domain. However, they can be used to estimate the spatial distribution of dielectric properties [31]. Time-of-flight methods, themselves, can be divided into two categories:

1. those using a common hardware system for properties estimation and imaging such as [58];
2. or those that use additional hardware such as the complementary system used in [31].

Dedicated hardware in addition to the imaging hardware has also been proposed in the case of TSAR [26], although recent studies have suggested that this method is potentially less effective than parameter search algorithms [100].

Complementary imaging methods use additional microwave imaging reconstruction techniques such as microwave tomography to estimate the effective dielectric properties [57]. Microwave tomography has been successfully used in clinical investigations with up to 150 patients [16]–[18] but can be computationally intensive, particularly for three-dimensional reconstructions at high resolutions [190]. Assuming that the breast consists of one homogeneous layer, as in [57], can reduce the computational complexity while estimating the frequency-dependent dielectric properties of the breast interior.

Thirdly, parameter search algorithms use characteristics of the reconstructed images to optimise the reconstruction permittivity [59], [60]. Parameter search algorithms assume that the characteristics of images reconstructed with incorrectly estimated reconstruction permittivity are different from those reconstructed with correctly estimated values. These algorithms rely on a cost function that rewards images reconstructed with good estimates and penalises those reconstructed with poor estimates.

Three types of reconstruction permittivity estimation are examined in this chapter to identify the most important factors influencing the reconstruction permittivity. The three methods—fixed-value (FV), glandular-dependent (GD) and patient-specific (PS)—are described below, and allow for increasing levels of flexibility in the selection of the reconstruction permittivity estimate:

1. fixed-value estimation: where a single estimate of the reconstruction permittivity is used for all tumour phantoms in all breast phantoms representing the population mean;
2. glandular-dependent estimation: where the reconstruction permittivity is varied based on the VGF of the breast phantom, but not varied based on the tumour size or shape: one estimate is used to reconstruct images of all tumour phantoms in a given breast phantom;

3. and patient-specific estimation: where the reconstruction permittivity is varied based on both the VGF of the breast phantom, but also for different tumour phantoms in a given breast phantom.

Glandular-dependent estimation builds on fixed-value estimation by allowing the reconstruction permittivity to vary depending on the breast phantom density; and patient-specific estimation extends this again by selecting a unique reconstruction permittivity estimate for each individual imaging scenario. These three methods can be used to identify factors impacting the reconstruction permittivity estimate, but also, whether the increased flexibility of patient-specific estimation compared to glandular-dependent estimation can negatively impact the expected specificity.

Fixed-value estimation has been used in all patient imaging studies to date. Glandular-dependent estimation is similar to time-of-flight or complementary imaging methods where the estimate is primarily based on a global average of dielectric properties of the breast, and patient-specific estimation is similar to parameter search algorithms where the estimate can vary based on other factors such as tumour shape and size.

4.3 Results

The three estimation methods outlined in the previous section are used with images of the BRIGID phantom set in Chapter 3 to evaluate the benefits of patient-specific beamforming. Firstly, images of the five breast phantoms without tumours are analysed in Section 4.3.1. This analysis is used to estimate if patient-specific beamforming negatively impacts the specificity. Secondly, the sensitivities using the three reconstruction permittivity estimation methods are compared in Section 4.3.2. This sensitivity comparison is used to identify if the increased flexibility of patient-specific estimation compared to glandular-dependent or fixed-value estimation has a tangible impact on the expected sensitivity. Finally, the change in sensitivity due to errors in the estimates are discussed in Section 4.3.3. By analysing true and false positives using different fixed-value estimates, the possibility of identifying a population mean estimate suitable for imaging all patients is considered. In the following sections, the optimal glandular-dependent
reconstruction permittivity estimates are represented as:

\[ \varepsilon_r^X \quad \forall X \in \{0\%, 10\%, 15\%, 20\%, 30\%\} \]  

(4.5)

where \( \varepsilon_r^X \) represents the optimal glandular-dependent estimate for the breast phantom with \( X \) VGF.

### 4.3.1 Factors Affecting Specificity

The BRIGID phantom set presented in Chapter 3 contains five breast phantoms which can be imaged without any tumour phantoms present. The images of these five phantoms are discussed in this section in order of increasing VGF. This analysis is used to evaluate the effect of patient-specific estimation on the expected specificity, and identify challenges in distinguishing between images containing tumours and images without tumours.

For the least dense phantom (0\%), no image at any reconstruction permittivity estimate was annotated as a tumour. There is little internal variation in dielectric properties in this breast phantom, hence few reflections from the breast phantom interior, meaning the overall image amplitude is very low. Also, signal attenuation within the breast phantom is much lower than more dense breast phantoms (due to the lower dielectric properties), meaning that reflections from any tumours in this phantom would have a high amplitude. This implies that it is possible to distinguish between images of tumours and images without tumours based on the maximum image amplitude for non-dense breast phantoms.

The next most dense breast phantom (10\%) includes a case where glandular-dependent estimation can have a positive impact on the specificity. These two images are shown in Fig. 4.2a and Fig. 4.2b respectively: the image reconstructed using fixed-value estimation (Fig. 4.2b) is incorrectly annotated as containing a tumour; whereas the image reconstructed using glandular-dependent estimation (Fig. 4.2a) is correctly annotated as not containing a tumour.

Examining images from the more dense breast phantom (15\%) highlights a potential difficulty for parameter-search estimation. Two images are shown in Figs. 4.2c and 4.2d reconstructed using two different reconstruction permittivity values within the acceptable range. Figure 4.2c is reconstructed using underestimated reconstruction permittivity, \( \varepsilon_r^t = 9 \); whereas Fig. 4.2d is reconstructed using the glandular-dependent estimate for the 15\% breast phantom, \( \varepsilon_r^{15\%} = 10.25 \). Both the images selected by fixed-value estimation and patient-specific estimation contain a response that could be annotated...
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Figure 4.1: The difficulty in discriminating between true and false positive cases is shown in this figure by comparing the maximum image amplitudes and SCRs of images of all 22 tumour phantoms in four breast phantoms of increasing VGF. The image amplitude and the SCRs of images are highest in breast phantoms with the least VGF. It is more difficult to separate true positives and true negatives based on SCR or image amplitude as the VGF of the phantom increases. True positives are shown in green, false negatives in red and images without tumours are shown in black for all 22 tumour phantoms in each of the four breast phantoms.

as a tumour, suggesting that patient-specific estimation neither impairs nor improves the specificity in this breast phantom (15%).

In the most dense breast phantoms (> 20%), there are many reflections from within the breast phantom due to the glandular structures, and many of the reconstructed images are annotated as containing tumours. In these dense breast phantoms, all three estimation methods (fixed-value, glandular-dependent and patient-specific) select an image annotated as a tumour, even though no tumour is present. Additionally, as the signal attenuation is much higher in these dense breast phantoms, the maximum amplitude of the tumour images is much lower than for less dense phantoms. For example, it can be seen in Fig. 4.1 that the amplitude and SCR of an image without a tumour is higher than one of the correctly identified tumours in the densest phantom (30%). Additionally, comparing the difference in amplitude between tumour and no tumour images in less dense and more dense phantoms, it can be seen that separating images of dense breast phantoms from images of tumours can be difficult. These five test cases hint that clinicians will not be able to rely on the image amplitude alone for diagnosis and that new features are needed to distinguish healthy and
CHAPTER 4. PATIENT-SPECIFIC BEAMFORMING

Figure 4.2: This figure highlights the advantages and disadvantages of reconstruction permittivity estimation in breast phantoms with VGF of (a) and (b) 10%; and (c) and (d) 15%. In the first breast phantom (10%), glandular-dependent estimation in (a) identifies an image where the tumour is correctly not detected, whereas fixed-value estimation in (b) incorrectly identifies an image where a tumour is detected. In the second breast phantom (15%), two images (c) and (d) within the reconstruction permittivity range are incorrectly annotated as containing a tumour, highlighting a difficult for parameter search algorithms to reward the correct image.
Table 4.1: This table shows how the sensitivity in a given patient cohort can suffer without reconstruction permittivity estimation by comparing the three different estimation methods—fixed-value, glandular-dependent and patient-specific. Both sensitivities for 22 tumour phantoms in a given breast phantom (with VGF of between 0% and 30%) are shown, as well as the mean sensitivity for all 110 test cases.

<table>
<thead>
<tr>
<th>Estimation Method</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Fixed-value</td>
<td>91%</td>
</tr>
<tr>
<td>Glandular-dependent</td>
<td>95%</td>
</tr>
<tr>
<td>Patient-specific</td>
<td>95%</td>
</tr>
</tbody>
</table>

Furthermore, Fig. 4.1 shows how although it can be difficult to separate tumour and not tumour images on SCR alone, the maximum amplitude of the images can be helpful, particularly in less dense breast phantoms. In the less dense phantoms (20% and below), the maximum amplitude can reliably separate the images of tumours from the image without a tumour.

In summary, these results indicate that achieving high specificity using microwave radar-based imaging in dense breasts may be challenging irrespective of the reconstruction permittivity estimation used. In these challenging cases, reconstruction permittivity estimation does not significantly impact the expected specificity, positively or negatively. In the less dense breast phantoms, reconstruction permittivity may improve the expected specificity as is shown in Fig. 4.2, although the maximum image amplitude is also useful to discriminate between images with and without tumours in these cases.

4.3.2 Estimated Sensitivity

The sensitivities achieved using the three estimation methods—fixed-value, glandular-dependent and patient-specific—are shown in Table 4.1. Both the sensitivity for 110 test cases and the sensitivities for the 22 tumour phantoms in a given breast phantom (VGF from 0% to 30%) are compared. A number of trends are visible from these data, which are highlighted in this section.

Firstly, the sensitivity decreases as the density increases for all three estimation methods, and is particularly poor in the most dense phantom (30%). This is consistent with previous work from other experimental systems such as [116]. Conversely, patient imaging studies using the same system showed
sensitivities of 54% in less dense breasts and 86% in dense breasts [21]; this may be explained by the use of a higher constant reconstruction permittivity estimate of $\varepsilon'_r = 10$ in the later study. However, future work is needed in larger patient populations to determine the causes for this unexpected disparity in sensitivities achieved in the two cohorts of differing breast densities. Advances in three-dimensional breast imaging have shown that even for dense breasts by BI-RADS classification, the mean volume glandular fraction for 47 women was below 30%; suggesting that this worst-case for microwave imaging is more rare than might be expected from the BI-RADS classification [159].

Secondly, the mean sensitivity using both glandular-dependent and patient-specific estimation is higher than the mean sensitivity of the current standard method, fixed-value estimation; 72% and 80% compared to 65% respectively. This trend is visible in all five breast phantoms. In particular, the sensitivity in the most dense phantom is as low as 18% for fixed-value estimation compared to a possible 45% for patient-specific estimation. Even in a less challenging imaging scenario (10% VGF) fixed-value estimation detects just 59% of tumour phantoms compared to 86% detected using patient-specific estimation.

Thirdly, the optimal reconstruction permittivity when estimated using glandular-dependent estimation increases with breast phantom density, from $\varepsilon'_r = 8.5$ for the least dense phantom up to $\varepsilon'_r = 12.5$ for the most dense phantom as would be expected. Additionally, the range of acceptable estimates narrows with increasing density, meaning that an accurate estimate is more important for denser breast compared to less dense breasts. For example, the tumour phantom $P_{11}$ is detected in the range $8 < \varepsilon'_r < 10.25$ for a less dense phantom (10%); whereas the same tumour phantom is only detected in the correct location at $\varepsilon'_r = 10.25$ for the most dense phantom (30%).

Finally, considering patient-specific estimation, the reconstruction permittivity varies more due to the phantom shape and size in the denser phantoms compared to less dense phantoms. This suggests that the dominant paths in the imaging summation are changing. One reconstruction permittivity estimate, $\varepsilon'_r = 8.5$, is suitable in less dense phantoms regardless of the tumour phantom shape or size, whereas the optimal estimates range from $\varepsilon'_r = 8$ to $\varepsilon'_r = 14$ in denser phantoms (30%). However, as discussed in the previous paragraph, small changes in the estimate in dense breast phantoms can mean the tumour response is obscured, meaning that no single value can be used to reconstruct images identifying all possible tumour phantoms.

To illustrate this point further, Fig. 4.3 shows images of tumour phantoms
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Figure 4.3: The images of a dense breast phantom (VGF of 30%) shown in this figure, show how tumour size can impact the reconstruction permittivity estimate substantially. Images (a) and (b) are reconstructed with lower reconstruction permittivity of $\varepsilon_r' = 10.25$ and images (c) and (d) are reconstructed with higher reconstruction permittivity of $\varepsilon_r' = 12.25$. Images (a) and (c) are of a smaller tumour phantom, $P_{11}$, whereas images (b) and (d) are of $P_{17}$ which is larger. Underestimating the reconstruction permittivity allows the smaller tumour phantom $P_{11}$ to be detected in (a), whereas overestimating the reconstruction permittivity enables the larger tumour phantom to be detected in (d), although neither are visible if images of both tumour phantoms are reconstructed at the same reconstruction permittivity estimate.
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$P_{11}$ and $P_{17}$ in a dense breast phantom (30%). Using one reconstruction permittivity estimate, it is not possible to reconstruct images where both tumour phantoms are identifiable, although $P_{11}$ is clearly visible in Fig. 4.3a reconstructed using $\varepsilon'_r = 10.25$ and $P_{17}$ is clearly visible in Fig. 4.3d reconstructed using $\varepsilon'_r = 12.25$. Underestimating the reconstruction permittivity means that reflections appear to come from further away than they actually originate, compensating for the larger tumour size of $P_{11}$ compared to $P_{17}$. Hence, $P_{11}$ is visible in Fig. 4.3a but not Fig. 4.3c (lower estimate) whereas $P_{17}$ is visible in Fig. 4.3d but not Fig. 4.3b (higher estimate). This effect can also be seen when comparing the sensitivity using glandular-dependent and patient-specific estimation from Table 4.1 in the most dense phantom which improves from 27% to 45%.

4.3.3 Analysis of Errors in the Dielectric Estimate

In this section, the sensitivity with respect to errors in the reconstruction permittivity estimates is analysed. The sensitivities using the three idealised estimation methods are compared, which helps identify if one reconstruction permittivity estimate exists which is suitable to use for all individuals in the population.

The sensitivity for 22 tumour phantoms in four different breast phantoms is shown in Fig. 4.4 as the fixed-value reconstruction permittivity estimate varies between $\varepsilon'_r = 8$ and $\varepsilon'_r = 12.5$. Even within this range of fixed-value reconstruction permittivity estimates, the sensitivity suffers by assuming a fixed-value for all breast phantoms regardless of breast phantom density.

For example, where 36 out of 44 tumour phantoms (82%) can be detected in the least dense phantoms (0% and 10%) using glandular-dependent estimation ($\varepsilon'_{0\%}$), only 33 out of 44 (75%) can be detected using fixed-value estimation ($\varepsilon'_{15\%}$). Overestimating further and reconstructing images at $\varepsilon'_{20\%}$, only 24 out of 44 (55%) tumour phantoms can be detected in these less dense breast phantoms, 30% less than the optimal sensitivity. Conversely, for the more dense phantoms (20%), only 6 out of 22 (27%) tumour phantoms are detected when reconstructing images using $\varepsilon'_{0\%}$ compared to 17 out of 22 (77%) using the optimal estimate, $\varepsilon'_{20\%}$.

The mean sensitivity varies from 69% to 76% as the reconstruction permittivity estimate increases from $\varepsilon'_r = 9$ to $\varepsilon'_r = 11.25$. The sensitivity in breast phantoms of a given density varies much more within this range: when reconstructing using a fixed-value of $\varepsilon'_r = 9$, the sensitivity in the two less dense breast phantoms is 80%, higher than 59% when using $\varepsilon'_r = 11.25$. Conversely, in the two more dense breast phantoms, the sensitivity increases from 65% to 75% across the same range. As the reconstruction permittivity
Figure 4.4: The potential to use one fixed-value estimate of the reconstruction permittivity for image reconstruction in breast phantoms of varying density is investigated in this figure. Overall sensitivity for 88 cases is broken down into sensitivities in the four phantoms with VGF of 0%, 10%, 15% and 20%, i.e. maximum sensitivity would be to detect the tumour phantom in all 88 test cases. As the fixed-value estimate varies, lower reconstruction permittivity estimates increase the sensitivity in less dense phantoms and higher estimates increase the sensitivity in more dense phantoms. As expected, the overall optimal fixed-value reconstruction permittivity estimate is $\varepsilon_{r}^{15\%}$, lying in the middle of the range of reconstruction permittivity estimates. Using this value, there is optimal detection in the breast phantom with 15% glandular fraction, but also the sensitivity for the other breast phantoms is 10% below optimal. These results indicate that the optimal fixed-value estimate would depend on the particular patient population and that one ideal estimate does not exist. Furthermore, using glandular-dependent estimation instead of fixed-value estimation in these 88 cases could increase the true positive rate from 76% to 82%.

Finally, a challenging case for patient-specific estimation is shown in Fig. 4.5. Images of a tumour phantom ($P_{13}$) in a dense breast phantom (20%) are shown reconstructed at $\varepsilon_{r}^{\prime} \in \{9.5, 11.75\}$ in Figs. 4.5a and 4.5b respectively; both within the acceptable range of reconstruction permittivity
Figure 4.5: These images highlight a key challenge in the design of patient-specific beamformers: multiple images in the reconstruction permittivity range of interest can contain images which can be annotated as tumours. Images of a tumour phantom $P_{13}$ in a breast phantom with VGF of 20% are shown reconstructed at (a) $\varepsilon'_r = 9.5$ and (b) $\varepsilon'_r = 11.75$. Both images could be annotated as tumours, although the tumour would be reported in the wrong breast quadrant in the case of (a). It is important for reconstruction permittivity estimation methods to be able to distinguish these cases.

estimates for these breast phantoms. In Fig. 4.5b, the tumour response is clearly visible in the correct location, however, when the reconstruction permittivity is underestimated as in Fig. 4.5a, a spurious response in an incorrect location is visible with an SCR of 1.1 dB and similar amplitude to Fig. 4.5b. Although patient-specific estimation can increase sensitivity, particularly in dense breasts, it is important to ensure a patient-specific estimation algorithm can distinguish between cases such as those shown in Fig. 4.5.

4.4 Conclusions

This chapter establishes the growing need for patient-specific beamforming as microwave radar-based imaging is rolled out to larger patient studies with more diverse patient populations. Firstly, the challenges of estimating the propagation delay are discussed in Section 4.1 including the necessary assumptions required for practical implementations. The current under-
standing of the impact of these assumptions on image quality is discussed, and the need to estimate the effect of propagation delay estimation on sensitivity and specificity identified.

Existing methods for patient-specific beamforming are reviewed in Section 4.2 in light of the inherent assumptions identified in Section 4.1. Current methods can be broadly categorised into three groups—time-of-flight, complementary microwave imaging techniques and parameter search algorithms—and the advantages and disadvantages of each are highlighted. Although many methods have been proposed, these methods have not been tested on images without tumours, meaning only sensitivity could be estimated. The existing methods from the literature are used to develop three idealised approaches which can examine the benefits and disadvantages of existing methods. Three idealised approaches of increasing flexibility are examined in this chapter to evaluate the potential benefits of patient-specific beamforming. The results of applying these algorithms to the experimental test cases described in the previous chapter are shown in Section 4.3.

Firstly, the challenges to achieving high specificity in dense breasts are discussed in Section 4.3.1. Although the maximum image amplitude can reliably discriminate between images of tumours and images without tumours in less dense breast phantoms, images of dense breast phantoms and images of tumours can have similar characteristics. However, the data from Section 4.3.1 suggest that patient-specific beamforming does not negatively impact the expected specificity compared to fixed-value estimation, although the number of test cases (five) is too small to draw definitive conclusions.

Secondly, the expected sensitivities using the three estimation methods are shown in Section 4.3.2. These sensitivities suggest that patient-specific beamforming can improve the mean sensitivity substantially, from 65% to 80%. Similar to previous experimental work, sensitivity in very dense breast phantoms (30%) is very poor at less than < 50%. Unexpectedly, patient imaging studies have found that the sensitivity in dense breasts was 86% compared to 54% in less dense breast, but the sample size was too small (66 cases in total) to draw definitive conclusions [21]. However, the data presented in this chapter suggests that patient-specific estimation may be needed to achieve consistent sensitivity results in both dense and non-dense breasts.

Finally, the data presented in Section 4.3.3 suggests that it is difficult to find a population mean of the reconstruction permittivity without impacting the sensitivity. In particular, sensitivity in patient cohorts of a given breast VGF will vary depending on the reconstruction permittivity estimate employed. For the breast phantoms in this work, no one reconstruction permittivity estimate can achieve high sensitivities for all breast phantoms.
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The results in this chapter suggest that patient-specific beamforming is important for microwave radar-based breast imaging. The data suggest that patient-specific estimation that can select reconstruction permittivity estimates based on many factors including breast VGF can outperform fixed-value estimation, without impairing the specificity. The following chapter identifies suitable cost functions for parameter search algorithms which can be used to identify and reward images reconstructed with correctly estimated reconstruction permittivity.
Parameter Search Algorithms

Work from this chapter was published in Sensors in 2017 in an open access journal publication entitled “Parameter Search Algorithms for Microwave Radar-Based Breast Imaging: Focal Quality Metrics as Fitness Functions”.

This chapter identifies suitable cost functions which can be used to estimate the optimum reconstruction permittivity. Suitable cost functions reward images reconstructed using good estimates of the reconstruction permittivity and do not reward images reconstructed using poor estimates of the reconstruction permittivity.

Firstly, a simplified analytical model is used in Section 5.1 to estimate the point spread function (PSF) of the imaging system. This simplified analytical model is later used to estimate the effects of reconstruction permittivity misestimation in Section 5.4.1. The metrics used to compare and select the cost functions are described in Section 5.2. Next, focal quality metrics (FQMs) are proposed as cost functions which are described in Section 5.3. The results of applying the evaluation criteria in Section 5.2 to the FQM in Section 5.3 are shown in Section 5.4, and Section 5.5 concludes this chapter.

5.1 Simplified Analytical Model

The PSF of a simplified radar-based imaging system is calculated in this section which is used in Section 5.4.1 to identify characteristics of images reconstructed with correct and incorrect reconstruction permittivity estimates. The simplified analytical system allows the effects of under- and overestimating the reconstruction permittivity to be identified, and the trends observed from the simplified system are then compared to the experimental results later in this chapter.

The simplified, skinless, two-dimensional environment used to calculate the monostatic PSF is described in detail in [191]. In this section, without loss
of generality, the total electric field is calculated for monostatic acquisition. The Born approximation is used to linearise the scattering equation shown in Eq. (2.1) meaning that the total electric field recorded at \( \mathbf{a}' \) while an incident electric field at angular frequency \( \omega \) is transmitted from \( \mathbf{a} \) (represented by \( E_{\mathbf{a},\omega}(\mathbf{a}) \)), can be calculated as:

\[
E_{\mathbf{a},\omega}(\mathbf{a}) = \frac{j\omega \sqrt{\varepsilon'_r}}{2\pi c_0} P(\omega) \int \chi(\mathbf{r}) \exp \left[ \frac{-2j\omega \sqrt{\varepsilon'_r}}{c_0} \| \mathbf{r} - \mathbf{a} \| \right] d\mathbf{r} \tag{5.1}
\]

The known and lossless dielectric properties of the homogeneous are represented as \( \varepsilon'_r \). In this simplified situation, the scatterer is assumed to be a point scatterer located at \( \mathbf{r}^T \), which means that the contrast function \( \chi(\mathbf{r}) \) can be represented by:

\[
\chi(\mathbf{r}) = \chi^* \delta(\mathbf{r} - \mathbf{r}^T) \tag{5.2}
\]

where \( \chi^* \) is the known contrast of the point scatterer compared to the known dielectric properties of the lossless, homogeneous background medium, \( \varepsilon'_r \). Assuming (without loss of generality) that the pulse, \( P(\omega) \), has magnitude of unity at all frequencies, \( |P(\omega)| = 1 \quad \forall \omega \in \Omega \), the total electric field for the simplified imaging scenario at angular frequency \( \omega \) can be represented as:

\[
E_{\mathbf{a},\omega}(\mathbf{a}) = \frac{j\omega \sqrt{\varepsilon'_r}}{2\pi c_0} \chi^* \frac{\varepsilon'_r}{\| \mathbf{r}^T - \mathbf{a} \|} \exp \frac{-2j\omega \sqrt{\varepsilon'_r}}{c_0} \| \mathbf{r}^T - \mathbf{a} \| \tag{5.3}
\]

Substituting the above expression for the scattered energy Eq. (5.3) into the generic beamformer equation Eq. (2.2) and using the propagation time expression in Eq. (4.4) means the idealised PSF of the simplified monostatic imaging system for a given reconstruction permittivity, \( \varepsilon'_r \), can be calculated as follows:

\[
I(\mathbf{r}) \bigg|_{\varepsilon'_r} = \frac{j \chi^* \sqrt{\varepsilon'_r}}{2\pi c_0} \int_{\Omega} \int_{A} \exp \frac{2j\omega}{c_0} \left[ \sqrt{\varepsilon'_r} \| \mathbf{r} - \mathbf{a}_\theta \| - \sqrt{\varepsilon'_r} \| \mathbf{r}^T - \mathbf{a}_\theta \| \right] \frac{\| \mathbf{r}^T - \mathbf{a}_\theta \|}{\| \mathbf{r} - \mathbf{a}_\theta \|} d\mathbf{a}_\theta d\omega \tag{5.4}
\]

where the acquisition surface is defined as \( A = \mathbf{a}_\theta, \forall \theta, \ 0 \leq \theta < 2\pi \).

Assuming initially that \( \sqrt{\varepsilon'_r} = \sqrt{\varepsilon''_r} \), (that is, when the image is reconstructed with the correct estimate) Eq. (5.4) is maximised when the distance from the antenna to the point of interest is equal to the distance from the antenna to the point scatterer for all antennas (i.e., when the reconstruction permittivity equals the known permittivity of the homogeneous domain, the maximum image amplitude is at the point scatterer location). However, as the ratio between the reconstruction permittivity and the known permittivity, \( \sqrt{\varepsilon'_r/\varepsilon''_r} \), changes, the distance for a given antenna to maximise
the exponential changes proportionally. Due to radial spreading (and additionally due to losses in a realistic imaging domain), this means that the maximum intensity of the image moves towards the antenna closest to the scatterer. This effect can be observed in Section 5.4.1 by examining the one-dimensional PSFs generated by integrating Eq. (5.4) numerically.

The PSF of the system described in Chapter 3 is also measured experimentally. A dielectric point source can be approximated by an object that has a maximum radius less than a quarter of the wavelength in the object, \( r_{\text{max}} < \frac{1}{2} \lambda_{\text{min}} \) [186]. For a spherical scatterer with relative permittivity, \( 60 \leq \varepsilon_{r\text{target}} \leq 74 \) such as the tumour phantoms in this work, the maximum radius should be less than, \( r_{\text{max}} < 2.5 \text{ mm} \), if the maximum frequency in the reconstruction is, \( f_{\text{max}} = 3 \text{ GHz} \). The experimental PSFs are compared with the simplified theoretical analysis and the suitability of the metrics is assessed on the PSFs.

### 5.2 Cost Function Evaluation

A number of cost functions from other applications are proposed and compared in this chapter, both on the analytical PSF described in the previous section and using the experimental images from Chapter 3. Fundamentally, suitable cost functions reward images reconstructed with good reconstruction permittivity estimates and do not reward images reconstructed with poor reconstruction permittivity estimates. This fundamental property has been expressed as a number of qualitative characteristics in the literature, for example:

- accuracy: that the extremum lies at the correct value [192]–[194];
- reproducibility: that the extremum lies at the top of a narrow peak [192]–[195];
- broad range: that the extremum lies at the top of a peak with broad tails in either direction [192];
- generalisability: that the cost function is suitable for all cases [192], [195];
- and monotonicity: that the cost function is monotonic with respect to the parameter being optimised [195].

It is also important that these qualitative characteristics can be measured quantitatively, for example: range of peak [193], [194], [196], [197]; width
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of peak [193], [194], [196], [197]; number of false extrema [193], [194], [196], [197]; accuracy of peak [193], [194], [197]; and noise level [194]. However, not all of these quantitative criteria are directly applicable to the evaluation of cost functions for reconstruction permittivity estimation [59]. In particular, the effects of reconstruction permittivity misestimation are complex and unknown, particularly in light of the variance in breast composition observed in the population, and it may not be fair or true to assume that a cost function varies monotonically with respect to the reconstruction permittivity.

For this reason, four evaluation criteria are proposed in this section to evaluate cost functions:

1. the accuracy, \( \Delta \varepsilon'_r \): which measures the difference between the reconstruction permittivity selected by the parameter search algorithm and the true permittivity;

2. the localisation error, \( \Delta r \): measuring the difference between the location of the image maximum and the true location of the scatterer;

3. the SCR of the selected image, SCR;

4. and the signal-to-mean ratio (SMR) of the selected image, SMR.

These evaluation criteria help determine if the given cost function can identify:

1. images where the maximum image amplitude is in the target location without knowledge of the tumour location;

2. images of high quality which can be annotated as images of tumours.

This chapter proposes the use of FQMs as cost functions for reconstruction permittivity optimisation. The existing use cases for FQMs and their methods of action are described in the following section.

5.3 Focal Quality Metrics as Cost Functions

This chapter proposes the use of FQMs as cost functions for reconstruction permittivity estimation. FQMs are currently used in autofocus applications, where the goal is to find the optimal focal length for imaging, for example, in:

- microscopy [198]–[200];
- telescopic [201], [202];
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- digital still cameras [203]–[205];
- and digital video [206].

As well as autofocus applications, FQMs have been used for:

- shape from focus (also known as depth from focus or range from focus), where depth information about a scene is inferred from the focal quality of various regions of the image [207]–[209];
- and multi-focus, where multiple images of a scene taken at different focal lengths are fused to form one image with all objects in focus [195].

In an optical system, a defocused image is blurred in comparison to a focused image [192], [204], [210]. Similarly, an incorrect reconstruction permittivity estimate means that the scattered signals are out of phase after synthetic focusing. Rather than coherent addition at the locations of dielectric scatterers, energy is spread around the site of the dielectric scatterer after synthetic focusing using poor reconstruction permittivity estimates. This similarity suggests that FQMs may be suitable for reconstruction permittivity estimation, and is evaluated in Section 5.3.

A well-focused image contains a large number of sharp edges and thus a lot of high-frequency spatial content. A defocused image, or blurred image, on the other hand contains less high-frequency spatial content. The majority of FQMs therefore estimate the frequency content of images and can be broadly classified based on their method of frequency content estimation. In this paper, five families of FQM were compared [211] which are described briefly in this section and in more detail in Appendix A.

Metrics based on the spatial derivative or gradient of the image have been widely used as FQMs, [193]–[195], [197], [198], [204], [211]. The first spatial derivative of the image can be used as a FQM since differentiation is analogous to high pass filtering, rewarding the higher frequency content of the image which correlates with clear and focused images. Gradient-based metrics, $\Phi^G$, are computationally simple and theoretically well understood.

While $\Phi^G$ uses first-order differentiation to estimate image quality, second-order differentiation has also been applied in Laplacian-based methods, $\Phi^L$. The energy of the Laplacian is a commonly used FQM [201], [210]–[212] and many kernels for estimating the discrete Laplacian in various axes exist.

The discrete wavelet transform (DWT) measures the frequency content of an image and hence the image quality. The high-frequency sub-bands of the DWT have been used as wavelet-based FQMs, $\Phi^W$, [211], [213]–[215]. Many filters and combinations of the wavelet have been studied.
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The discrete cosine transform (DCT) is a Fourier-based transform that directly measures the frequency content of an image to infer the image quality, which has been used in Fourier-based FQMs, $\Phi^F$, [196], [206], [211], [216]. Many different window sizes can be used, and different combinations of the components have been investigated.

Finally, statistics-based FQMs, $\Phi^S$, have also been constructed by analysing the grey-level luminance of the image. The variance of the grey-level luminance is a commonly used statistic and is analysed in this paper [193]–[195], [197], [204], [205], [211]. Statistics-based FQMs, $\Phi^S$, can often be computationally simple, and easy to implement.

5.4 Results

This results section identifies suitable cost functions from the FQMs described in the previous section, which can be used reward images with the characteristics of correctly reconstructed images. The data are presented in three sections:

1. the effect of incorrectly estimating the reconstruction permittivity is analysed in Section 5.4.1 using the simplified theoretical PSF developed in Eq. (5.4) and by estimating the PSF of the system described in Chapter 3 with the BRIGID phantom set;

2. promising cost functions are identified in Section 5.4.3 by evaluating all FQMs described using the homogeneous breast phantom from the BRIGID phantom set;

3. finally, the best performing metrics from Stage 2 are analysed in Section 5.4.3 in more complex and challenging test scenarios.

5.4.1 Characteristics of Incorrectly Reconstructed Images

The effects of incorrect average dielectric property estimation are first analysed using the theoretical PSFs in Fig. 5.1. Figure 5.1a shows the PSF of the ideal system obtained by numerically integrating Eq. (5.4). Additionally, the location of the strongest response in the image is shown in Fig. 5.1a. The true location of the dielectric point scatterer is at $T = 0.2R$.

A number of observations can be made from Fig. 5.1:
in general, the maximum amplitude of the PSF is when the reconstruction permittivity, \( \varepsilon'_r \), is equal to the true relative permittivity of the lossless medium, \( \varepsilon^*_r \), as is expected;

if the reconstruction permittivity is underestimated (i.e. \( \sqrt{\varepsilon'_r/\varepsilon^*_r} < 1 \)), the apparent location of the scatterer moves towards the closest antenna (closer to \( R \)). This localisation error is due to reflections appearing to come from closer than their true origin and the channels closest to the scatterer are dominant in the coherent summation;

conversely, if the reconstruction permittivity is overestimated, the apparent location of the scatterer moves towards the centre of the imaging domain (closer to 0). This localisation error is due to reflections appearing to come from further away than their true origin;

the number of sidelobes increases as the reconstruction permittivity estimate increases, in other words, there is higher spatial frequency content in PSFs generated using over-estimated reconstruction permittivity, \( \sqrt{\varepsilon'_r/\varepsilon^*_r} > 1 \);

it can be seen that as the reconstruction permittivity is overestimated, the width of the peak response decreases.
Figure 5.2: Effects of under- and overestimating the reconstruction permittivity on the estimated experimental PSF using the BRIGID phantom set. The localisation error, SCR and spatial frequency content of the image change as the reconstruction permittivity changes: (a) $\sqrt{\varepsilon'/\varepsilon^*} = 0.5$ shows the apparent location of the scatterer move towards the edge of the imaging domain; (b) $\sqrt{\varepsilon'/\varepsilon^*} = 1$ shows the maximum response of the image in the correct location; and (c) $\sqrt{\varepsilon'/\varepsilon^*} = 1.5$ shows the apparent location of the scatterer move towards the centre of the imaging domain.

- the localisation error is greater when underestimating the reconstruction permittivity compared to overestimating the reconstruction permittivity.

Similarly, the same analysis is repeated for the estimate of the experimental PSF. Coronal slices of the experimental PSF at the dielectric point scatterer location are shown in Fig. 5.2; Figs. 5.2a to 5.2c are reconstructed with effective average dielectric properties of $\varepsilon'_r \in \{1.5, 6, 13.5\}$ respectively, where fatty breast interior has dielectric properties of $\varepsilon^*_r = 6$. Hence, Figs. 5.2a to 5.2c are reconstructed with $\sqrt{\varepsilon'/\varepsilon^*} \in \{0.5, 1, 1.5\}$ respectively. Comparable trends can be observed in the PSF of the theoretical and experimental systems:

- the maximum amplitude of the images with incorrectly estimated effective average dielectric properties is much lower than the ideal image, 40% when underestimated and 9% when overestimated;

- the apparent location of the scatterer moves towards the closest antennas when the effective average dielectric properties are underestimated, i.e. $\sqrt{\varepsilon'/\varepsilon^*} < 1$;

- the apparent location of the scatterer moves towards the centre of the imaging domain when the effective average dielectric properties are overestimated, i.e. $\sqrt{\varepsilon'/\varepsilon^*} > 1$;
• Fig. 5.2c has more clutter with greater magnitude than Fig. 5.2a. This is similar to the theoretical case where the image reconstructed with overestimated effective average dielectric properties (i.e., \( \sqrt{\varepsilon' / \varepsilon_r} > 1 \)) has higher spatial frequency content;

• the area of the response decreases as the estimated effective average dielectric properties increases;

• the localisation error when overestimating the properties is less than when underestimating the properties.

Together, the idealised and experimental PSF analyses suggest that the reconstruction permittivity can have a substantial impact on the image quality. Specifically, the maximum image amplitude and the SCR can be much lower, the apparent location of the scatterer in the reconstructed image can change and the spatial frequency content of the image can be affected. The following section examines 23 FQMs to identify potentially suitable cost functions which reward images with the characteristics of correctly reconstructed images.

### 5.4.2 Cost Function Identification

To determine suitable cost functions for further evaluation, all FQMs were evaluated using tumour phantoms in a homogeneous breast phantom (0\%). The mean value of the evaluation criteria—\( \Delta \varepsilon'_r \), \( \Delta r \), SMR and SCR—are shown in Table 5.1 along with the rankings of each FQM. Within each type of FQM—Fourier-based (\( \Phi^F \)), Gaussian-based (\( \Phi^G \)), Laplacian-based (\( \Phi^L \)), statistics-based (\( \Phi^S \)) and wavelet-based (\( \Phi^W \))—each FQM is listed in order of rank and this rank is shown in the rightmost column. Additionally, the overall rank for all 23 FQMs is shown. The rank for each individual evaluation criterion is also indicated in parentheses.

Of all FQMs analysed, two FQMs appear to be appropriate cost functions for this application, the Central Moment, \( \Phi^S_{\text{ACM}} \) and the Gaussian Energy, \( \Phi^G_{\text{GSS}} \). The Central Moment, \( \Phi^S_{\text{ACM}} \), rewards images close to the known reconstruction permittivity, being on average within \( \Delta \varepsilon'_r = 0.7 \) of the known value of \( \varepsilon_r = 6 \). However, the Gaussian Energy, \( \Phi^G_{\text{GSS}} \), rewards images that are of a high quality, rewarding images that have the smallest localisation error, \( \Delta r \), and the best clutter suppression, SMR and SCR. Other FQMs based on the gradient, \( \Phi^G \), or statistics, \( \Phi^S \), of the image also reward images of high quality, ten of the top eleven FQMs use these methods of action.

All FQMs based on the Laplacian of the image, \( \Phi^L \), perform very similarly, selecting images with almost the same accuracy, \( \Delta \varepsilon'_r \), localisation error, \( \Delta r \),
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#### Table 5.1: Evaluation of performance of all metrics in homogeneous scenarios. Two overall ranks are shown, one within each method of action and another for all metrics analysed [local/global].

<table>
<thead>
<tr>
<th>Metric</th>
<th>$\Delta \varepsilon'$</th>
<th>$\Delta r$</th>
<th>SMR</th>
<th>SCR</th>
<th>Ranks</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Phi_R^F$</td>
<td>2.5 (1)</td>
<td>10.9 (1)</td>
<td>7.6 (1)</td>
<td>3.8 (1)</td>
<td>1/21</td>
</tr>
<tr>
<td>$\Phi_{RR}^F$</td>
<td>3.0 (2)</td>
<td>13.3 (2)</td>
<td>5.0 (2)</td>
<td>2.5 (2)</td>
<td>2/22</td>
</tr>
<tr>
<td>$\Phi_{GSS}^G$</td>
<td>1.4 (2)</td>
<td>4.6 (1)</td>
<td>18.3 (1)</td>
<td>8.5 (1)</td>
<td>1/2</td>
</tr>
<tr>
<td>$\Phi_{DMA}^G$</td>
<td>1.3 (1)</td>
<td>6.6 (2)</td>
<td>16.7 (2)</td>
<td>8.0 (2)</td>
<td>2/7</td>
</tr>
<tr>
<td>$\Phi_{TM}^G$</td>
<td>1.4 (3)</td>
<td>7.4 (3)</td>
<td>14.5 (3)</td>
<td>7.1 (3)</td>
<td>3/8</td>
</tr>
<tr>
<td>$\Phi_{DMS}^G$</td>
<td>1.5 (4)</td>
<td>7.4 (4)</td>
<td>14.5 (4)</td>
<td>7.1 (4)</td>
<td>4/10</td>
</tr>
<tr>
<td>$\Phi_{DSS}^G$</td>
<td>1.5 (4)</td>
<td>7.4 (4)</td>
<td>14.5 (4)</td>
<td>7.1 (4)</td>
<td>4/10</td>
</tr>
<tr>
<td>$\Phi_{TV}^G$</td>
<td>1.5 (6)</td>
<td>7.6 (6)</td>
<td>14.5 (6)</td>
<td>7.1 (6)</td>
<td>6/15</td>
</tr>
<tr>
<td>$\Phi_{LM}^L$</td>
<td>1.5 (1)</td>
<td>7.3 (1)</td>
<td>14.5 (1)</td>
<td>7.0 (4)</td>
<td>1/9</td>
</tr>
<tr>
<td>$\Phi_{D}^L$</td>
<td>1.5 (3)</td>
<td>7.3 (2)</td>
<td>14.5 (2)</td>
<td>7.0 (3)</td>
<td>2/12</td>
</tr>
<tr>
<td>$\Phi_{E}^L$</td>
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<td>7.6 (4)</td>
<td>14.4 (4)</td>
<td>7.0 (2)</td>
<td>4/16</td>
</tr>
<tr>
<td>$\Phi_{V}^L$</td>
<td>1.5 (3)</td>
<td>7.6 (4)</td>
<td>14.4 (4)</td>
<td>7.0 (2)</td>
<td>4/16</td>
</tr>
<tr>
<td>$\Phi_{ACM}^S$</td>
<td>0.7 (1)</td>
<td>5.2 (1)</td>
<td>17.1 (2)</td>
<td>8.3 (1)</td>
<td>1/1</td>
</tr>
<tr>
<td>$\Phi_{V}^S$</td>
<td>0.8 (2)</td>
<td>5.5 (3)</td>
<td>17.1 (3)</td>
<td>8.3 (2)</td>
<td>2/3</td>
</tr>
<tr>
<td>$\Phi_{VL}^S$</td>
<td>1.3 (5)</td>
<td>5.9 (4)</td>
<td>17.5 (1)</td>
<td>8.2 (3)</td>
<td>3/4</td>
</tr>
<tr>
<td>$\Phi_{VN}^S$</td>
<td>1.3 (4)</td>
<td>5.2 (2)</td>
<td>16.4 (5)</td>
<td>7.9 (5)</td>
<td>4/6</td>
</tr>
<tr>
<td>$\Phi_{C}^S$</td>
<td>1.3 (3)</td>
<td>6.6 (5)</td>
<td>16.7 (4)</td>
<td>8.1 (4)</td>
<td>4/5</td>
</tr>
<tr>
<td>$\Phi_{R}^S$</td>
<td>2.3 (6)</td>
<td>9.8 (6)</td>
<td>7.5 (7)</td>
<td>3.6 (7)</td>
<td>6/20</td>
</tr>
<tr>
<td>$\Phi_{HE}^S$</td>
<td>2.4 (7)</td>
<td>11.0 (7)</td>
<td>7.8 (6)</td>
<td>3.9 (6)</td>
<td>6/19</td>
</tr>
<tr>
<td>$\Phi_{V}^W$</td>
<td>1.5 (2)</td>
<td>7.3 (1)</td>
<td>14.5 (1)</td>
<td>7.0 (1)</td>
<td>1/12</td>
</tr>
<tr>
<td>$\Phi_{AS}^W$</td>
<td>1.5 (2)</td>
<td>7.3 (2)</td>
<td>14.5 (2)</td>
<td>7.0 (2)</td>
<td>2/14</td>
</tr>
<tr>
<td>$\Phi_{R}^W$</td>
<td>5.0 (3)</td>
<td>31.0 (3)</td>
<td>0.0 (3)</td>
<td>0.0 (3)</td>
<td>3/23</td>
</tr>
</tbody>
</table>
and clutter suppression, SMR and SCR. Five more FQMs perform very similarly to FQMs based on the Laplacian, $\Phi^L$: three based on the gradient of the image, $\Phi^G$, the Tenengrad mean, $\Phi^T_M$, the Squared Gradient, $\Phi^G_{DMS}$, and the Gradient Energy, $\Phi^G_{GSS}$; and two based on wavelet decomposition of the image, $\Phi^W$, the Detail Variance, $\Phi^W_{V}$, and the Absolute Detail Sum, $\Phi^W_{AS}$.

The two FQMs based on the Fourier transform, $\Phi^F$, do not perform well as cost functions in these simplified experimental scenarios, identifying images with poor clutter suppression, SMR and SCR. Additionally, the Fourier-based metrics, $\Phi^F$, select images with localisation errors that are, on average, greater than 10 mm, $\Delta r > 10$ mm. As shown in Fig. 5.2, images generated with underestimated effective average dielectric properties, $\sqrt{\varepsilon'_r/\varepsilon_r} \ll 1$, are characterised by large responses much closer to the nearest antenna than the true scatterer location. FQMs based on the Fourier transform, $\Phi^F$, reward these images resulting in poor performance [135]. These Fourier-based FQMs, $\Phi^F$, were first proposed for low-contrast images where they can be more effective [216], whereas the contrast evident when interpreting the radar-based energy reconstruction as an image is higher. Although the High-Low Reduced Ratio, $\Phi^F_{RR}$, performed better in noisy images than the High-Low Ratio, $\Phi^F_R$ in experimental photographs, that was not found for the radar-based images.

The Detail-Coarse Ratio, $\Phi^W_{R}$, fails to reward any correct image. Similarly to FQMs based on the Fourier transform, $\Phi^F$, the Detail-Coarse Ratio, $\Phi^W_{R}$ heavily rewards images generated with underestimated effective average dielectric properties, $\sqrt{\varepsilon'_r/\varepsilon_r} \ll 1$, such that it always rewards images reconstructed with permittivity equal to free space, $\varepsilon'_r = 1$.

Three candidate fitness functions were selected for further analysis in the subsequent section: the Gaussian Energy, $\Phi^G_{GSS}$; the Modified Laplacian, $\Phi^L_M$; the Central Moment, $\Phi^S_{ACM}$. The three FQMs use three different methods of action based on the image gradient, the image Laplacian and statistics of the image respectively.

### 5.4.3 Detailed Analysis

Table 5.2 analyses the three FQMs identified from the previous section—
the Gaussian Energy, $\Phi^G_{GSS}$, the Modified Laplacian, $\Phi^L_M$; the Central Moment, $\Phi^S_{ACM}$— in breast phantoms of increasing VGF, from 10% to 30%. Five spherical tumours from the BRIGID phantom set ($P_1$–$P_5$) of increasing diameter from $d = 5.3$ mm to $d = 20.2$ mm are used to estimate the suitability of the candidate FQMs. The many factors which affect the optimal reconstruction permittivity estimate are discussed in Chapter 4.
which makes it difficult to determine the “true” reconstruction permittivity for these three breast phantoms; hence, the accuracy, $\Delta \varepsilon'$, is not shown because the accuracy, $\Delta \varepsilon'$, is of limited value when the true reconstruction permittivity is not known exactly.

Table 5.2: $\Delta r$, SMR and SCR evaluated for spherical targets of increasing diameter in phantoms of increasing heterogeneity.

<table>
<thead>
<tr>
<th>$\Delta r$ (mm)</th>
<th>SMR (dB)</th>
<th>SCR (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Phi_G^{GSS}$</td>
<td>$\Phi_M^L$</td>
</tr>
<tr>
<td>$10% \text{ VGF}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$d = 5.3 \text{ mm}$</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>$d = 7.8 \text{ mm}$</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>$d = 10.9 \text{ mm}$</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$d = 13.1 \text{ mm}$</td>
<td>2</td>
<td>63</td>
</tr>
<tr>
<td>$d = 20.2 \text{ mm}$</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>$20% \text{ VGF}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$d = 5.3 \text{ mm}$</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>$d = 7.8 \text{ mm}$</td>
<td>21</td>
<td>76</td>
</tr>
<tr>
<td>$d = 10.9 \text{ mm}$</td>
<td>45</td>
<td>52</td>
</tr>
<tr>
<td>$d = 13.1 \text{ mm}$</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>$d = 20.2 \text{ mm}$</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>$30% \text{ VGF}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$d = 5.3 \text{ mm}$</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td>$d = 7.8 \text{ mm}$</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>$d = 10.9 \text{ mm}$</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>$d = 13.1 \text{ mm}$</td>
<td>39</td>
<td>28</td>
</tr>
<tr>
<td>$d = 20.2 \text{ mm}$</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

In the least dense breast phantom (rows 1–5 of Table 5.2; 10% VGF), the Gaussian Energy, $\Phi_G^{GSS}$, and the Central Moment, $\Phi_{ACM}^S$, perform very similarly, rewarding images with reconstruction permittivity estimates within $\Delta \varepsilon' = 0.25$ of each other for all five tumour phantoms. The SCR for the chosen images for all three FQMs in this case is within 0.3 dB of the maximum. The Modified Laplacian, $\Phi_M^L$, rewards almost the same images except for the fourth tumour model where the maximum response in the most rewarded
image is not in the correct location. In this particular case \((d = 13.1\, \text{mm})\),
the Modified Laplacian, \(\Phi_{LM}^M\), rewards an image with a higher SMR and
similar SCR than the Gaussian Energy, \(\Phi_{GSS}^G\), and the Central Moment,
\(\Phi_{ACM}^S\), but the maximum response is in the wrong location.

Figures 5.3a and 5.3b show the images rewarded by the Gaussian Energy,
\(\Phi_{GSS}^G\), and the Modified Laplacian, \(\Phi_{LM}^M\), respectively in this case. Although
the Gaussian Energy, \(\Phi_{GSS}^G\), rewards an image where the tumour target
is clearly identifiable in the correct location, the Modified Laplacian, \(\Phi_{LM}^M\)
rewards an alternative image more highly. The image shown in Fig. 5.3b is
reconstructed with underestimated reconstruction permittivity and exhibits
the characteristics of underestimated images identified earlier: the primary
response in the image is much closer to the nearest antenna.

As the VGF increases to 20% and 30%, the quality of the optimal image
decreases due to increased reflections from other structures within the breast.
In particular, the maximum response within the image is much further from
the true tumour phantom location and the tumour phantom location is not
correctly determined. The Gaussian Energy, \(\Phi_{GSS}^G\), and the Central Moment,
\(\Phi_{ACM}^S\), again reward similar images for all tumour models.

Coronal, sagittal and axial slices of the reconstructed images of \(P_4\) in a
phantom with 30% VGF are shown in Figs. 5.3c and 5.3d, corresponding
to the image most rewarded using the Gaussian Energy, \(\Phi_{GSS}^G\), and the
Modified Laplacian, \(\Phi_{LM}^M\), respectively. In this challenging case, no image
is reconstructed that accurately identifies the tumour phantom location,
the Modified Laplacian, \(\Phi_{LM}^M\), rewards an image reconstructed with lower
average dielectric properties with a large apparent response close to the
skin. Both the Gaussian Energy, \(\Phi_{GSS}^G\), and the Modified Laplacian, \(\Phi_{LM}^M\),
reward an image with a bright response in this case, although the location of
this response is approximately 40 mm away from the true tumour phantom
location.

Many FQMs are found to have very similar performance in this work, in
both simplified and realistic scenarios. For example, gradient-based metrics,
\(\Phi^G\):

- can be calculated easily from the image using simple and well-known
  kernels in two and three dimensions;
- have a well-understood method of action as differentiation is analagous
to high-pass filtering;
- and identify the optimal image in heterogeneous phantoms with different
  tumour sizes.
Figure 5.3: Shown are coronal, sagittal and axial slices of images of the tumour model $P_3$. (a) and (b) are in a phantom with 10% VGF and (c) and (d) are in a phantom with 30% VGF. (a) and (c) are the images selected by the Gaussian Energy, $\Phi^G$, and (b) and (d) are the images selected by the Modified Laplacian, $\Phi^L$. The actual target location is marked by the dotted, red ellipse in each slice.
Additionally, the Gaussian Energy, $\Phi^G_{\text{GSS}}$, is shown in this work to be a suitable cost function in three-dimensional images with realistic artefact removal.

5.5 Conclusions

In this chapter, promising cost functions for estimating the reconstruction permittivity are proposed and evaluated in complex and challenging experimental test scenarios. The FQMs evaluated have been used in autofocus applications for more than forty years and a variety of FQMs identified from the literature are evaluated in this chapter.

A simplified analytical scenario is first used to identify characteristics of images reconstructed with incorrectly estimated reconstruction permittivity. This analysis highlights how the maximum amplitude and the spatial frequency content of the image can be impacted by under- or overestimating the reconstruction permittivity. Similar trends are observed from the experimental PSF including how the location of the maximum response in the image moves compared to the true scatterer location as the reconstruction permittivity varies. These characteristics of images reconstructed with under- and overestimated reconstruction permittivity suggest that FQMs may be suitable cost functions for reconstruction permittivity estimation.

Five types of FQM are compared based on different operators, including the image gradient, Laplacian, wavelet-decomposition, Fourier Transform and statistics of the image. Gradient-based and statistics-based were found to perform well overall while also being well-understood, computationally simple and are robust in challenging experimental imaging scenarios. Many cost functions based on the image gradient or statistics perform similarly, which is an indication that FQMs are appropriate cost functions for reconstruction permittivity estimation.

In the following chapter, the identified cost function is applied to five clinical case studies. Although with a small sample size, the following chapter helps to evaluate if the identified cost function is robust in realistic and complex situations, for patients with and without disease.
Clinical Case Studies

The preceding chapters of this thesis, Chapters 3 to 5, focused on evaluating the benefits of patient-specific beamformers and proposed cost functions which could be used to design and implement a practical patient-specific beamformer. The advantages and disadvantages of patient-specific beamforming and the proposed cost functions were evaluated using experimental data from the BRIGID phantom set (presented in Chapter 3 and [160]).

In this chapter, the performance of the proposed cost functions is analysed in five clinical case studies from the TSAR system developed by the University of Calgary and described in Section 2.3. These clinical case studies were first published in [26] using fixed-value reconstruction permittivity estimation with the DAS beamformer, in a preliminary study of a parameter search reconstruction permittivity estimation algorithm in [27], and used in a beamformer comparative study in [53]. In this thesis, these five clinical case studies are used to investigate the potential of patient-specific beamforming to improve the sensitivity without impairing the specificity of radar-based breast imaging algorithms. Although only five clinical case studies are available, this analysis helps to identify if additional challenges presented by patient data such as patient movement and breathing, affect the patient-specific cost function identified in the previous chapter. Results from the three case studies without carcinoma help evaluate if patient-specific beamforming increases the risks of false positives, although a more comprehensive clinical dataset would be required to estimate the change in sensitivity and specificity due to patient-specific beamforming compared to fixed-value estimation.

As well as the challenges identified in Section 2.3.6 such as coupling of microwave energy into the breast and patient movement during the microwave scan, a number of additional complexities exist when assessing reconstruction permittivity estimation algorithms using clinical data:

1. radar-based images are typically compared to images from other modalities such as mammography, ultrasound or magnetic resonance imaging
which are acquired from different orientations;

2. images from other modalities exploit different properties of human tissues (such as x-ray attenuation using mammography) which makes it difficult to compare the breast structures between images from different modalities. For example, microcalcifications are very prominent in mammograms but may not be visible at all in radar-based images;

3. the breast often contains multiple regions of interest, for example, metaplastic carcinoma and benign lesions in the right breast of Patient 1 in Section 6.2.1, and it is not clear what the optimal radar-based image should look like in these cases;

4. the true dielectric properties of the breast are not known quantitatively, only qualitative assessments of breast density from mammography are known, which measures the proportions and distribution of glandular tissues but not the dielectric properties.

In light of these complexities, five clinical case studies is not enough to permit definitive conclusions to be drawn, however, these clinical case studies are useful to help identify weaknesses of patient-specific beamforming not apparent from the experimental evaluation in previous chapters.

6.1 Patient Population and Clinical Procedure

In this section, the patient population and clinical procedure is outlined. All patient images were reconstructed using scattered data acquired from the TSAR system developed at the University of Calgary and were originally published in [26]. The operational system itself is described fully in [217] and the next generation system is described in detail in [218]. Other patient imaging studies using these data, such as [26], [27], [53], are reviewed in detail in Section 2.3.5.

All patients were recruited from the Breast Health Clinic, Foothills Medical Centre, Calgary, AB, Canada and provided written informed consent to participate in the study (E-22121 approved by the Conjoint Health Research Ethics Board, University of Calgary, AB, Canada). Patients with a breast size corresponding to a B or C cup with suspicious areas in the breast not located in the axilla were considered for inclusion in the study. Only patients who were eligible for magnetic resonance imaging (for example, no metallic implants) were included.
Prior to the radar-based imaging scan of the breast with TSAR, the ipsilateral breast was scanned using magnetic resonance imaging no more than four days before the TSAR scan, except for one patient which was twelve days earlier. The magnetic resonance image was acquired using a 1.5T scanner with breast coils, and both pre-contrast and subtracted images were used as part of the clinical history of the patient. Additional clinical information such as recent mammograms, ultrasound studies, image reports, biopsy results and pathology report were also assessed to provide a complete clinical history of the patient.

Five clinical case studies are analysed in detail in this chapter, and the relevant clinical information for each case is summarised in Table 6.1. The case studies cover three BI-RADS density categories: scattered heterogeneous (category b) in the case of Patient 3, heterogeneous (category c) in cases 1, 4 and 5, and extremely dense for case 2. Cases 1–3 are called Group A and are characterised by having clearly identified disease. Cases 4 and 5 are called Group B in the original study in [26], and multiple suspicious lesions were identified from the complete clinical history. The findings of the original study in [26] are discussed in detail in Section 2.3.5.

For each patient scan, the patient lay prone on the examination table with the breast pendant through an opening in the table. The breast was immersed in a tank of canola oil which has relative permittivity of 2.5 and conductivity of 0.04 S m\(^{-1}\) up to 12 GHz. A single balanced antipodal Vivaldi antenna with director (BAVA-D), described in [219], was used to acquire the scattered signals from up to 200 antenna locations around the breast. The antenna can move in the sagittal direction (vertically) and the tank and antenna rotate to illuminate from all angles in the coronal plane (horizontal).

Scattered data were acquired between 50 MHz and 15 GHz and three measurements were averaged to improve the noise floor. A second scan using the same antenna locations but without the patient breast was also...
performed. This scan without the patient breast was used for calibration. After calibration, the scattered data were shaped with a differentiated Gaussian pulse with centre frequency of 4 GHz and a FWHM of 6.3 GHz. A phase shift was also introduced to compensate for the antenna aperture location.

The Neighbourhood-based Skin Subtraction artefact removal algorithm was employed to isolate reflections from the breast interior [220]. TSAR includes a laser ranging system mounted on the same positioning arm as the antenna, which measures the distance to the skin for each antenna location. After artefact removal, the signals are synthetically focused and the image is reconstructed using the DAS beamformer. The imaging domain is divided into two regions:

1. the coupling medium with a known relative permittivity of $\varepsilon_{\text{cm}} = 2.5$;
2. and the breast interior with an assumed reconstruction permittivity, $\varepsilon'_r$, as in previous chapters.

The imaging domain is confined to the area within the breast as calculated from the laser data and the cost function from the previous chapter, $\Phi^G_{\text{GSS}}$, is used to calculate the fitness of each image in the following section.

### 6.2 Results

This section analyses the five patient results in detail based on the application of the cost functions identified in previous chapters and the regions of interest identified from the clinical history of the patient.

The cost function values for each of the five patients are shown in Fig. 6.1. Considered together, some trends are visible. Firstly, with the exception of Patient 3, the majority of local maxima of fitness occur for approximately $\varepsilon'_r \leq 10$. Similarly, the fitness of images reconstructed with lower reconstruction permittivity tends to be higher than those reconstructed with higher reconstruction permittivity: in cases such as Patient 2, a downward trend in fitness is visible as the reconstruction permittivity increases.

Secondly, the fitness for many patients show multiple local maxima. In some cases, such as Patient 1, the local maximum at $\varepsilon'_r = 10.4$ is 25% lower than the global maximum at $\varepsilon'_r = 5.4$. In other cases, such as Patient 4, the local maximum at $\varepsilon'_r = 5.4$ is only 5% lower than the global maximum at $\varepsilon'_r = 6.6$.

Finally, the images analysed in the original study were reconstructed at $\varepsilon'_r = 9$ in all cases. In these five patient cases, the original images are
not rewarded highly by the cost function, the original images reconstructed at $\varepsilon'_r = 9$ are not local or global maxima. The results of each individual patient are discussed in detail in the following subsections.

6.2.1 Metaplastic Carcinoma (Case 1)

The right breast of the 53 year old Patient 1 was scanned. Three regions of interest in the breast were identified from mammography, the magnetic resonance image and the microwave image from the original study, [26], which are described here:

- $R^1_1$ corresponding to a 10 mm mass detected at the 4 o’clock radian using mammography. The same mass was detected at the 5 o’clock radian using magnetic resonance imaging. Postsurgical pathology indicated that the mass in $R^1_1$ was a grade II/III metaplastic carcinoma;

- $R^1_2$ is a possibly benign lesion detected at the 7 o’clock radian through magnetic resonance imaging but not mentioned in the pathology report;

- $R^1_3$ refers to a cluster of glandular tissues located at the 11 o’clock radian.
Figure 6.2: Images of high fitness and the image from the original study of Patient 1 are compared in coronal, sagittal and axial slices, as well as in three dimensions. The clinical regions of interest (corresponding to the metaplastic carcinoma, a possibly benign lesion and fibroglandular tissues) are also shown.

The approximate locations of the three regions—$R^1_1$, $R^1_2$ and $R^3_3$—are shown in Fig. 6.2 by the solid, dashed and dotted lines respectively.

Two images are highly rewarded by the cost function in Fig. 6.1 for this patient: a global maximum at $\varepsilon'_r = 5.4$ and a local maximum at $\varepsilon'_r = 10.2$. To compare the images, the regions of high intensity from both images
Table 6.2: Images of high fitness and the image from the original study corresponding to Patient 1 are quantitatively compared. The maximum amplitude and location of large responses in the images are compared to the clinical regions of interest. In this case, the cost function rewards an image with one clear response corresponding to the location of a metaplastic carcinoma identified from the clinical history of the patient.

<table>
<thead>
<tr>
<th>$\varepsilon'_r = 5.4$</th>
<th>$\varepsilon'_r = 10.4$</th>
<th>$\varepsilon'_r = 9.0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_1$</td>
<td>$M_1$</td>
<td>$M_1$</td>
</tr>
<tr>
<td>$M_2$</td>
<td>$M_2$</td>
<td>$M_2$</td>
</tr>
<tr>
<td>$M_3$</td>
<td>$M_3$</td>
<td>$M_3$</td>
</tr>
</tbody>
</table>

Max. (dB)  

<table>
<thead>
<tr>
<th>Region</th>
<th>$R^1_1$</th>
<th>$R^1_2$</th>
<th>$R^1_3$</th>
<th>$R^1_1$</th>
<th>$R^1_2$</th>
<th>$R^1_3$</th>
</tr>
</thead>
</table>

are shown in Fig. 6.2. Regions from the image at the global maximum at $\varepsilon'_r = 5.4$ are shown in purple whereas those from the image at the local maximum at $\varepsilon'_r = 10.4$ are shown in blue. The image reconstructed at $\varepsilon'_r = 9.0$ is also shown in red in Fig. 6.2. Sagittal, orthographic, coronal and axial projections of the high intensity regions from both images are shown in Figs. 6.2a to 6.2d in addition to the skin surface.

Considering the image at the global maximum at $\varepsilon'_r = 5.4$ alone (blue in Fig. 6.2), a large response is visible near $R^1_1$ corresponding to the malignant tumour. The response is elongated along the sagittal axis (FWHM of 41 mm as can be seen in Figs. 6.2a and 6.2d), but is smaller along the vertical and axial axes with an average FWHM of 9 mm in the coronal plane (shown in Fig. 6.2c). The other response in the image at the global maximum is 6 dB lower in amplitude, considerably smaller (less than 10 mm maximum FWHM) and located at the edge of the imaging domain.

The image at the local maximum at $\varepsilon'_r = 10.4$ (shown in red in Fig. 6.2) contains three main groups of responses in the three regions of interest, $R^1_1$, $R^1_2$ and $R^1_3$. The response with the highest energy is located close to $R^1_2$ and corresponds to a possible benign lesion. This maximum response has an average FWHM of 8 mm in the coronal plane. The other responses in the image are at least 6 dB lower in amplitude than the maximum response. The next two responses are located in $R^1_3$ and $R^1_2$ respectively, corresponding to a fibroglandular cluster and the malignant lesion. Similar to the image at the global maximum, the responses are elongated along the sagittal axis, with FWHM of 23 mm, 38 mm and 25 mm in this direction for the first three responses.

Comparing the three images, the maximum amplitude of the image reconstructed at $\varepsilon'_r = 10.4$ is 1.6 dB lower than the image reconstructed at
$\varepsilon_r^' = 5.4$, the global maximum for this patient. Both images show some energy in $R_1^1$ corresponding to the malignant tumour, and the response in $R_1^1$ at the global maximum is the response of maximum amplitude in all images.

The two images rewarded by the cost function at $\varepsilon_r^' = 5.4$ and $\varepsilon_r^' = 10.4$ are quantitatively compared to the image used in the original study, [26], in Table 6.2. The amplitudes are normalised such that the maximum amplitude is 0 dB. The image from the original study, [26], showed energy in all three regions of interest, with the maximum energy corresponding to the malignant lesion in $R_1^1$. The maximum energy in the other two regions of interest—$R_2^1$ and $R_3^1$—was 1.4 dB and 0.6 dB below the maximum energy. The maximum energy in $R_1^1$ is 5.48 dB below the global maximum image reconstructed at $\varepsilon_r^' = 5.4$.

6.2.2 Fibroadenolipoma (Case 2)

Case 2 involved a 64-year-old woman with a fibroadenolipoma in the lower inner quadrant of her left breast. The mammography report notes the breast tissue is extremely dense (BI-RADS Category D). As discussed in Section 2.1.1, fibroadenolipomas (also known as hamartomas) are typically benign masses containing an admixture of ducts, lobules, fibrous stroma and adipose tissues in varying proportions. The contrast between the fibroadenolipoma and the surrounding tissue is uncertain, particularly in a breast noted as heterogeneously dense.

The global maximum of the cost function in Fig. 6.1 is located at $\varepsilon_r^' = 4$ with a local maximum at $\varepsilon_r^' = 6.8$. Both images are shown in Fig. 6.3 in blue and red respectively. The image reconstructed at the local maximum at $\varepsilon_r^' = 6.8$ shows many responses in the lower inner quadrant, which is consistent with the clinical history of the patient reporting a fibroadenolipoma in that quadrant. However, the image is very difficult to interpret with multiple responses of similar magnitude. The image reconstructed at the global maximum at $\varepsilon_r^' = 4$ also shows a lot of energy in the lower inner quadrant, but also some smaller responses elsewhere in the breast, including in the upper outer quadrant, although this response is 6 dB lower in amplitude than the main response in the image at $\varepsilon_r^' = 4$. The image reconstructed at $\varepsilon_r^' = 9.0$ is similar to the image at $\varepsilon_r^' = 6.8$ but with lower overall amplitude (3 dB lower). Although the image reconstructed at $\varepsilon_r^' = 9.0$ also contains a response in the lower inner quadrant which may correspond to the fibroadenolipoma, there is also many other responses with similar magnitude in the image.
Figure 6.3: Images of high fitness of the left breast of Patient 2 are compared. Responses in the images may be consistent with a fibroadenolipoma in the lower inner quadrant, although interpretation of the images is challenging due to the dense nature of the breast tissue and the large number of responses in the images.
Extremely dense breasts such as that of Patient 2 would be expected to have higher dielectric properties as they contain a lot of fibrous and glandular tissues. However, the cost function rewards images reconstructed at lower dielectric properties very highly. Although it is difficult to draw any definite conclusions as the dielectric properties of the breast are not certain, it is likely the images rewarded by the cost function are reconstructed below the average dielectric properties of this particular breast and the images contain mostly spurious noise and clutter.

However, across the entire reconstruction permittivity range, no one image is characterised by one single response. As may be expected from a breast noted as extremely dense, all images contain many responses of similar magnitude. The poor image quality of this clinical case study may also be explained by a number of other factors, such as:

- uncertain contrast between the fibroadenoma and the glandular and fibrous tissues in the rest of the breast;
- difficulty in isolating reflections from the benign lesion from the reflections from the other glandular and fibrous structures in the breast;
- or acquisition challenges due to high attenuation in the dense breast tissues;

Due to these confounding factors, it is difficult to predict what a “correct” radar-based image should look like for this clinical case study.

### 6.2.3 Invasive Ductal Carcinoma (Case 3)

The left breast of the 35-year-old Patient 3 was scanned. The mammogram indicated extensive microcalcifications around the 3 o’clock position in the lateral aspect and the magnetic resonance report showed enhancements from the 2 o’clock to 6 o’clock radian. Additionally, the magnetic resonance report showed a focal mass near the nipple. A region of invasive ductal carcinoma in the upper outer quadrant of the breast was reported after post-mastectomy pathology. The invasive ductal carcinoma was measured as $4\,\text{cm} \times 2\,\text{cm} \times 2\,\text{cm}$, although due to the location of the diseased tissue near the chest wall, it is uncertain how much of the disease was present within the imaging domain.

A prominent global maximum is present in the cost function at $\varepsilon''_r = 15.2$. This corresponds to an image with a single response located in the centre of the breast about 3 cm from the nipple. This response has an SMR of 44.98 dB and is nearly 11 dB larger in magnitude than the next highest
Figure 6.4: Images of high fitness of the left breast of Patient 3 are compared. The patient had extensive invasive ductal carcinoma in the upper outer quadrant that was not detected in the images, possibly as the disease was close to the chest wall and did not extend into the imaging domain. A very prominent response was observed using higher estimates of reconstruction permittivity, which may be an artefact.
response. This prominent response may correspond to the focal mass that was identified in the magnetic resonance image or, similar to Patient 2, this may be an artefact. The minor peak at $\varepsilon'_r = 12.8$ also shows a response in the same location as the global maximum, but with an SMR of 40 dB.

The image in the original study, reconstructed at $\varepsilon'_r = 9$, is shown with the image at the local maximum at $\varepsilon'_r = 4$ in Fig. 6.4. In the original image, the maximum response is located just above the nipple which could potentially correspond to the focal mass detected in the magnetic resonance image. In the image at the local maximum at $\varepsilon'_r = 4$, the maximum responses in the image are located towards the chest wall.

Although the breast contained extensive disease in this case study, no image clearly shows a response which could definitively be said to correspond to the invasive ductal carcinoma. The breast was noted as scattered heterogeneous according to the mammogram, meaning the average dielectric properties of the breast would be expected to be low. However, the image reconstructed at $\varepsilon'_r = 15.2$ is highly rewarded. Although this may correspond to a focal mass noted in the clinical history of the patient, it may also be an artefact due to reconstruction with overestimated dielectric properties.

### 6.2.4 Necrosis and Cysts (Case 4)

Patient 4 was 44 years old when her left breast was scanned with TSAR. Ultrasound and magnetic resonance imaging of the left breast showed an 11 mm $\times$ 7 mm lesion at the 10 o’clock radian which was determined as a fat necrosis from pathology. Two cysts were also reported near the fat necrosis. Similarly to the fibroadenolipoma for Patient 2, neither the exact contrast between the necrotic tissue and the surrounding breast is known, nor the exact locations where responses would be expected in the radar-based image.

The global maximum of the cost function is located at $\varepsilon'_r = 6.6$ with a local maximum at $\varepsilon'_r = 5.2$. These two images, along with the original image at $\varepsilon'_r = 9$ are shown in Fig. 6.5. As can be seen, all three images contain many responses scattered throughout the breast.

Firstly, considering the global maximum at $\varepsilon'_r = 6.6$, the highest magnitude response is located in the upper outer quadrant. This response is nearly 5 dB higher than the next highest response and has an SMR of 25.61 dB. Two other responses located in the upper inner and the lower outer quadrants were within 5 dB of the highest amplitude in the image, and had SMRs of 20.69 dB and 20.26 dB respectively.

Secondly, looking at the image at the local maximum at $\varepsilon'_r = 5.2$, the highest magnitude response is located in the lower inner quadrant. Similar to the global maximum at $\varepsilon'_r = 6.6$, a number of responses are visible in all four
Figure 6.5: Images of high fitness and the image from the original study of Patient 4 are compared. The patient breast contained multiple benign lesions including a fat necrosis and multiple cysts. All three images contained multiple responses, but due to difficulties reconciling the clinical history and the microwave images, it is not certain if these responses correspond to the benign lesions.
breast quadrants. For example, responses within 5 dB of the main response can be seen in the lower outer quadrant and the upper outer quadrant with SMRs of 18.74 dB and 18.36 dB compared to 21.62 dB for the main response.

Finally, comparing the images rewarded by the cost function to the image reconstructed at $\epsilon'_r = 9$, all three images show responses in many quadrants of the breast. Due to the difficulties in reconciling the complex clinical history of the breast with the image, it is not clear if these responses correspond directly to any of the benign lesions in the breast.

6.2.5 No Breast Disease (Case 5)

Patient 5 was 32 years old when her left breast was scanned. The patient had no history of breast disease and the mammography report indicated the left breast was heterogeneous (BI-RADS) with some glandular tissue both on the inner and outer sides of the breast. An initial magnetic resonance image suggested an unidentified lesion at 4 o’clock which was not apparent from mammography, a follow-up ultrasound or on a second magnetic resonance image.

The image at $\epsilon'_r = 4$ is the most highly rewarded by the cost function, with a local maximum at $\epsilon'_r = 6.4$. These images, as well as the image from the original study at $\epsilon'_r = 9$ are shown in Fig. 6.6. In all three images, responses on the inner side of the breast are visible close to the skin. These possibly correspond to fibroglandular tissue in these locations. In all the three images at increasing reconstruction permittivity, the SMRs were 21.77 dB, 26.28 dB and 28.2 dB and the main response was 6 dB, 4.89 dB and 5 dB higher than the next strongest response. In the images rewarded by the cost function and image in the original study, this case would likely be a false positive.

6.2.6 Discussion

It is difficult to draw definitive conclusions from these clinical cases studies due to the small number of cases examined in detailed and the challenges associated with comparing images from different imaging modalities. In addition to differences in the orientation of the patient, breast compression between modalities, it is not often clear what the optimal radar-based image should look like when multiple lesions of uncertain dielectric properties are known to be in the breast. Despite these challenges, these clinical case studies are useful for identifying potential limitations of patient-specific beamforming in representative screening cases.
Figure 6.6: Images of high fitness as well as the image from the original study of Patient 5 are compared. Although the initial magnetic resonance images suggested an unidentified lesion, no disease was identified from subsequent investigations. Although no known disease was present, all images contain a response similar in magnitude to those identified as corresponding to lesions.
Considering the case with known disease in a known location (Case 1), the cost function correctly rewards the image where the metaplastic carcinoma is detected. Compared to the image in the original study, the image rewarded by the cost function has higher amplitude (by 5.5 dB) and no other prominent response exists in the image. In contrast, the image in the original study shows multiple responses of similar magnitude which correspond to another suspected benign lesion and possibly to some fibroglandular tissue. Although only one isolated case, this improvement in the image is a suggestion that patient-specific beamforming may be useful to improve tumour detection.

However, Case 1 also highlights a potential challenge for microwave imaging. The patient breast contains multiple lesions (both benign and malignant) and also some clusters of fibroglandular tissues. Although the cost function correctly identifies an image where the malignant tumour is most prominent, reconstructing with overestimated properties results in an image where the benign lesion is most prominent. For breasts with multiple lesions, it may not be possible to see all lesions in an image reconstructed at a single reconstruction permittivity. Although broad conclusions cannot be drawn from an individual clinical case study, this is similar to the effect observed in Fig. 4.3 where changing the tumour phantom shape and size changed the optimal reconstruction permittivity required to see the tumour phantom in the image.

Cases 2 to 4 are challenging to interpret due to uncertainties as to the dielectric composition of the respective patient breasts. Although some responses in the image may correspond to lesions identified in other imaging modalities, it is unclear where exactly these lesions are and what the expected contrast between the dielectric properties of these lesions and the other healthy tissues would be. A further complication is observed in Case 3 where the extensive disease in the breast may or may not be in the imaging domain of TSAR. However, these cases demonstrate the potential for spurious responses if the reconstruction permittivity is selected from a very broad range. For example, in Case 2 which is noted as a very dense breast, images reconstructed with very low estimates were highly rewarded. A similar trend was previously observed in early numerical work and may suggest that it is necessary to restrict the reconstruction permittivity to a range of likely values [135].

Comparing Case 1 and Case 5 considers the patient with known disease in a known location to healthy breast with no known disease identified from magnetic resonance imaging, ultrasound or mammogram. As suggested in the previous chapter, images of healthy breasts can often have similar characteristics to images of tumours, such as the prominent response visible in the three images shown in Fig. 6.6. The previous chapter also examined
the image amplitude as a means of distinguishing true and false positives, and suggests that the image amplitude may be useful in less dense breasts. In the original study, the image in Case 5 is 1.6 dB lower than the image in Case 1. However, the images rewarded by the cost function are higher in amplitude for Case 1 and lower in amplitude in Case 5, meaning the difference grows to 10.4 dB. Although this improvement in the differences between the amplitudes of diseased and healthy breast images is encouraging, it is difficult to draw any conclusions from a single comparison.

6.3 Conclusions

In this chapter, the parameter search algorithm proposed in this thesis is tested in five clinical case studies. The clinical case studies were obtained from the first generation TSAR operational system developed at the University of Calgary and the microwave images were analysed using knowledge of the clinical history of the patient including recent mammograms, magnetic resonance images and pathology reports where available. No definitive conclusions or trends can be drawn from only five clinical case studies, and in three of the five cases, a lot of uncertainty exists as to the dielectric composition of the breast and the location and extent of lesions in the patient breast. Despite these limitations, some interesting results were observed from the clinical case studies.

Firstly, in one case study (Case 1: the only case with known disease in a known location), reconstruction permittivity estimation rewards an image where a response corresponding to this tumour is identified. When compared to the fixed-value estimate used in the original study, the tumour response has a higher SMR, SCR and amplitude. While this is consistent with the conclusions of the previous chapter, it is merely a suggestion that patient-specific beamforming may improve the sensitivity.

Secondly, it may be possible to reconstruct two images with the characteristics of correctly reconstructed images (tumour) within the relative permittivity range as seen in Patients 1. In the case of Patient 1, this may correspond to another benign lesion within the breast. It may be necessary to reconstruct multiple images with various reconstruction permittivity estimates to obtain a complete picture of the entire breast. At the very least, this clinical case study suggests that further testing in breasts with multiple regions of interest need to be investigated further.

Thirdly, these images are consistent with the hypothesis that obtaining high specificity with radar-based imaging may be difficult, but that patient-specific beamforming does not increase the false positives. For example,
images reconstructed using fixed-value estimation and patient-specific estimation in the case of Patients 1 and 5 show a main response with similar SMR and SCR. However, it is interesting to note that the difference in amplitude between the healthy and diseased breast increases from 1.6 dB for fixed-value estimation to 10.4 dB for patient-specific beamforming.

Finally, these cases studies are useful for identifying potential limitations of patient-specific beamforming. In many of the clinical cases, images reconstructed with very low reconstruction permittivity estimates are highly rewarded, including for a breast which was classed as extremely dense from mammography (contrary to expectations). It is difficult to understand why exactly this may be as the dielectric properties of those breasts are not well known, but this surprising result does suggest that if a very broad reconstruction permittivity search space is used, images with spurious responses may be reconstructed.
Conclusions

This chapter summarises the research objectives, experimental methods and results of this thesis. The motivation and main findings of this thesis are summarised in Section 7.1 including the main conclusions of this thesis. Appropriate future work to further develop and extend the findings of this thesis are presented in Section 7.2 which concludes this thesis.

7.1 Summary and Conclusions

Breast cancer is a leading cause of morbidity and mortality for women of all ages and ethnicities. Breast anatomy varies between individuals in terms of size, shape and tissue composition, and many breast abnormalities from benign breast diseases to invasive breast cancers can occur. Many modifiable and non-modifiable risk factors for breast cancer have been identified, but in the absence of reliable methods to prevent breast cancer entirely, the WHO recommend programmes for the early detection and early diagnosis.

Early detection of breast cancer is primarily achieved through asymptomatic breast screening. Mammography is the current gold-standard screening methodology, although no consensus exists as to the optimal screening frequency or benefits of asymptomatic mammographic screening in terms of individual morbidity and mortality. However, the sensitivity and specificity of mammography are known to suffer in individuals with more fibrous or glandular tissues, known as dense breasts. Higher breast density is more common among younger women, meaning that mammography is unsuitable for asymptomatic screening of this cohort.

Chapter 1 introduces the motivation for this thesis in detail, in particular, how microwave imaging can address the limitations of mammography in younger women or those with denser breasts. The primary contributions of this thesis include a comprehensive analysis of the effects of breast composition variance on sensitivity and specificity of microwave radar-based
imaging and the design and evaluation of methods to address this variance in a realistic screening scenario.

Chapter 2 discusses the background of breast anatomy, breast cancer, microwave imaging and the challenges facing microwave imaging in detail. The diversity of breast abnormalities that are observed in the population are identified, including those associated with increased cancer risk, those that can mimic cancer or precursors to cancer, and the complex nature of breast cancer in terms of presentation and prognosis is summarised. Leading existing imaging modalities are discussed and the limitations of these modalities are identified. Next, the theory of microwave imaging and reconstruction techniques is discussed and the leading operational microwave breast imaging systems (those that have been used with patients) are reviewed in detail. Finally, the remaining challenges for microwave imaging are discussed, including both challenges associated with: patient movement, interpatient variation and intrapatient variation.

Chapter 3 describes the experimental hardware and breast phantoms used to help answer the primary research question of this thesis. The breast phantoms are designed to model the normal variation in breast composition seen in the population, including breast phantoms which are composed of up to 30% glandular tissues by volume. A variety of tumour phantoms were also manufactured which mimic the different shapes and sizes of breast tumours that are observed in clinical practice. Each of the five breast phantoms can be combined with each of the twenty-two tumour phantoms for a complete test platform of 110 test cases. In addition, microwave imaging scans of each of the five phantoms without a tumour phantom present were acquired. The acquisition hardware was designed in light of the review of operational microwave imaging systems conducted in Chapter 2 and each aspect of the imaging system is described. The challenges associated with image analysis are also discussed, as well as the metrics used in this thesis to distinguish images of cases with cancer and images of cases without cancer.

Chapter 4 establishes the importance of breast composition as a parameter for radar-based imaging. Using the diverse breast and tumour phantoms test cases described in Chapter 3, the benefits of using a patient-specific beamformer that adapts to each individual patient, and how the assumptions of radar-based breast imaging algorithms may affect the reconstruction permittivity estimate. The results suggest that a patient-specific beamformer can improve the sensitivity of radar-based imaging without impairing the specificity, although the number of cases is too small to draw truly definite conclusions. The data indicate that the reconstruction permittivity varies due to the VGF of the breast, but also due to other factors, potentially the tumour size, shape and location.
Chapter 5 proposes suitable cost functions which can be used in optimisation algorithms to design the patient-specific beamformer. Firstly, the characteristics of images reconstructed with poor estimates of the breast composition are identified, first from simplified analytical models and secondly using the experimental system described in Chapter 3. FQMs are proposed as suitable cost functions which reward images reconstructed with good estimates while penalising images reconstructed with poor estimates of the reconstruction permittivity. These experimental results suggest that FQMs based on the image gradient can be used in the design of patient-specific beamformers.

Chapter 6 analyses the proposed FQM in a series of five clinical case studies from TSAR designed by the University of Calgary (study number E-22121 from the Conjoint Health Research Ethics Board [26]). Despite uncertainties as to the dielectric composition of a number of the case studies, the results in Chapter 6 are consistent with the previous chapters of this thesis. Importantly, these clinical case studies also highlight some additional challenges for reconstruction permittivity estimation in clinical practice, and potential limitations of the algorithm. In the one case of known disease in a known location, the parameter search algorithm selects an improved image compared to fixed-value estimation. As in the experimental study in Chapter 4, the images of the patient cases without disease can have characteristics similar to those of images of patient cases with disease. However, interestingly, in the only case of a breast without any abnormalities, the parameter search algorithm selects an image with lower amplitude than selected using fixed-value estimation in the original study.

7.2 Future Work

The patient-specific beamformer proposed in this thesis could be extended in a number of ways to improve the performance and robustness of the method. The assumption of a frequency- and spatially-invariant reconstruction permittivity (as in this thesis) could be further examined. Preliminary indications from TSAR suggest that assuming a frequency-invariant reconstruction permittivity has a minimal impact on image quality [27], but future work could consider the incident frequency range, and both mono- and multistatic acquisition hardware. For example, preliminary studies using MARIA® have suggested that the magnitude of the frequency response of lesions above 5 GHz may be useful for distinguishing benign and cancerous lesions [221]. Further small studies using MARIA® have suggested that comparing images reconstructed using different frequency bandwidths may
also be useful for distinguishing benign and cancerous lesions [24]. In combination with differences due to the shape of benign and cancerous lesions [222], these techniques provide additional information to help distinguish images of patients with and without cancer.

Secondly, early studies have suggested that assuming straight-line propagation paths does not impact image quality [186], but future studies could estimate the benefits of improved propagation models of the imaging domain. In many operational systems, it is possible to determine shape and curvature of the skin through co-mounted lasers as in TSAR or using the microwave energy sampled using the antenna array. This information could be used to determine the angle of incidence of the transmitted energy on the breast surface which may improve the accuracy of the propagation path length calculations. However, more theoretical work is needed to determine if this approach could have a tangible impact on image quality.

Thirdly, a numerical study suggests that increased knowledge of the dielectric composition of the imaging domain increases image quality [187]. While use of a regional distribution of dielectric properties would increase the accuracy of the forward propagation model used for synthetic focusing, no realistic methods have been proposed to obtain a priori knowledge of the imaging domain, nor has an optimal method to exploit such a priori knowledge been proposed. Similarly, no analysis on the limitations of assuming a spatially-invariant reconstruction permittivity have been published. More theoretical work in this area could identify if the spatially-invariant reconstruction permittivity assumption is appropriate for the variety of breast compositions observed in the population.

The optimal antenna locations and spacing should also be considered. Some preliminary numerical studies have suggested that irregular antenna locations may improve the image quality by reducing the amount of redundant information in the collected scan. Many operational systems collect backscattered signals using a ring of antennas in the coronal plane, which may limit the quality of the backscattered signals in cases where the skin of the breast is not parallel to the sagittal axis (approaching the nipple for example). Other systems use a regular pattern which may reduce the amount of independent information in the backscattered signals. Hence, more work is needed to determine the factors influencing the optimal antenna locations and the effects of the antenna locations and numbers of channels on the image quality.

The patient-specific beamformer proposed in this thesis uses the original DAS. Many extensions have been proposed to the DAS technique [49], and many beamformer comparative studies have been published [53]. However, these comparative studies have typically used fixed-value reconstruction
CHAPTER 7. CONCLUSIONS

estimation only [54]. The patient imaging results in Chapter 6 (in particular Patient 1 with known disease) suggest that patient-specific reconstruction estimation may have a tangible impact on the image quality. Future comparative studies should consider both reconstruction permittivity estimation as well as variants and extensions of the basic DAS technique. Moreover, beamformer comparative studies have compared performance in terms of SCR, SMR and localisation error [54] and not in terms of sensitivity or specificity of the algorithm on large populations. More work is needed to evaluate the reconstruction algorithm that can best enable the clinician to distinguish healthy, benign and malignant patient images.

Future work should also consider optimal image visualisation methods. Image interpretation varies between systems: some operational systems have not used the image amplitude as a factor in the clinical decision (such as MARIA®), whereas other smaller studies using TSAR have suggested that the amplitude of the image may be useful. Characteristics or features of images need to be identified which can reliably distinguish between images of patients with cancer and images of patients without cancer. Additionally, the method of image display which optimises the clinical value of the image needs to be determined. The colour palette, discretisation levels, two- and three-dimensional visualisation techniques and hardware used for display may all impact the clinical value of the image.

Quality assurance of microwave imaging also needs to be considered before imaging devices are used in large, and possibly multicentre clinical investigations. Initial work has been presented on developing a standard phantom that can be used to evaluate and compare microwave imaging systems experimentally [160], [172]. Comparative results using these phantoms have not yet been published. Further work in this area is necessary, not only to compare different microwave imaging systems to each other, but also to verify the correct operation of a given system during a long-running trial or while in use. For example, in magnetic resonance imaging, standard phantoms have been developed in conjunction with standard evaluation criteria, which allow the fidelity of images and signals to be verified [223].

The role of microwave breast imaging in the current patient pathway also needs to be considered. Health Technology Assessments (HTAs) are increasingly used to improve decision making by regulatory and reimbursement bodies, and will be required for radar-based imaging before clinical adoption. Can microwave breast imaging play a role in asymptomatic screening as in [21]; as a low-cost monitoring tool to identify high risk patients as in [34]; as an adjunct to existing technologies including multimodality imaging [224]; or as monitoring for neoadjuvant chemotherapy [18]? This is particularly important as countries are now beginning to question the value of mammog-
raphy screening in light of recent evidence indicating that mammography screening has little or no impact on breast cancer mortality rates [7], [8].

Finally, future clinical studies must be designed with larger populations, adhering to Good Clinical Practice (GCP) and with sufficient statistical power to assess the sensitivity and specificity of the method. It will be important to control for bias in the selection of the populations, and also to consider international variance in breast composition, such as the higher breast density observed among Asian women compared to European women. Careful consideration will be required to select study populations which will help answer some outstanding questions, such as the ability of a microwave imaging system to help clinicians distinguish healthy patients (with and without benign breast diseases) from those with invasive cancers.

In addition to the technical improvements suggested in this section, future system development will need to be guided by regulations and safety standards. For example, any coupling medium used needs to have desirable dielectric and mechanical properties, but also needs to be biocompatible and approved for use with humans. Additionally, manufacture, transportation, storage and disposal of the coupling medium needs to be considered, as the distribution and preparation of the coupling medium affects the complexity and cost of the scan. Operational systems requiring minimal amounts of or no coupling medium both have lower operational costs in financial and staffing terms, but each scan also has a lower environmental impact in terms of waste disposal.

Future clinical studies with optimised operational systems, in combination with improved beamformers such as those described in this thesis, will help accelerate the translation of microwave imaging from the research bench to the patient bedside, where radar-based imaging will hopefully have a real and tangible impact on patient care and outcomes.
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In this appendix, the 23 FQMs used in this thesis are described in detail. All FQMs were originally identified from a review conducted by Pertuz et al. [211] and have been used in shape-from-focus and autofocus applications previously.

In general, FQMs estimate the high frequency content of the image, as clear and focused images tend to feature more high-frequency content [192], [210]. In the context of microwave radar breast imaging, this means energy is concentrated at scatterer locations and not distributed around the image in clutter. FQMs can be broadly classified based on their method of action, that is, how they estimate the high frequency content of the image. Appendices A.1 to A.5, summarise the method of action of each type of FQM and describe all 23 FQMs in detail.

A.1 Fourier-based

The DCT is a Fourier transform that uses cosines as the basis functions. The DCT directly measures the frequency content of the image, as an estimation the image quality. The energy of the high frequency components of the DCT (which is an estimate of the the variance of the luminance of an image) has been used as a focal quality measure [206]. However, it was found that the energy of the high frequency components is sensitive to image contrast and that the ratio of the high frequency energy to the low frequency components is more homologous [216]. Different window sizes have also been used, either eight pixels square [196], [206], [211] or four pixels square [216].

Two metrics were considered in this category:

- the High-Low Ratio, $\Phi_{FR}$, [216];
- and the High-Low Reduced Ratio, $\Phi_{FRR}$, [196].

Both metrics are summarized in Table A.1. The High-Low Reduced Ratio, $\Phi_{FRR}$, considers just the lower frequency components which are dominant [196],
### APPENDIX A. FOCAL QUALITY METRICS

**Table A.1:** Summary of the names, abbreviations and methods of action of the FQMs used in this thesis. \( \text{var}[X] \) represents the variance of \( X \) across the imaging area, and \( \langle X \rangle \) represents the mean of \( X \) across the imaging area.

<table>
<thead>
<tr>
<th>Name</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Low Ratio</td>
<td>( \Phi_{FR}^F = \left\langle \frac{\sum_{(n,m) \neq (0,0)} F_{x,y}(n,m)^2}{F_{x,y}(0,0)^2} \right\rangle )</td>
</tr>
<tr>
<td>High-Low Reduced Ratio</td>
<td>( \Phi_{RR}^F = \left\langle \frac{\sum_{(n,m) \neq (0,0)} F_{x,y}(n,m)^2}{F_{x,y}(0,0)^2} \right\rangle )</td>
</tr>
<tr>
<td>Absolute Gradient</td>
<td>( \Phi_{DMA}^G = \left\langle \text{max}_{D \in {X,Y}}</td>
</tr>
<tr>
<td>Squared Gradient</td>
<td>( \Phi_{DMS}^G = \left\langle \text{max}_{D \in {X,Y}}</td>
</tr>
<tr>
<td>Brenner Gradient</td>
<td>( \Phi_{BMS}^G = \left\langle \text{max}_{D \in {X,Y}}</td>
</tr>
<tr>
<td>Gradient Energy</td>
<td>( \Phi_{DSS}^G = \left\langle</td>
</tr>
<tr>
<td>Gaussian Energy</td>
<td>( \Phi_{GSS}^G = \left\langle</td>
</tr>
<tr>
<td>Tenengrad Mean</td>
<td>( \Phi_{TM}^G = \left\langle \text{max}_{D \in {X,Y}} I_D^P(x,y)^2 \right\rangle )</td>
</tr>
<tr>
<td>Tenengrad Variance</td>
<td>( \Phi_{TV}^G = \text{var}\left[ \text{max}_{D \in {X,Y}} I_D^P \right])</td>
</tr>
<tr>
<td>Laplacian Energy</td>
<td>( \Phi_{L}^L = \left\langle</td>
</tr>
<tr>
<td>Modified Laplacian</td>
<td>( \Phi_{LM}^L = \left\langle</td>
</tr>
<tr>
<td>Diagonal Laplacian</td>
<td>( \Phi_{D}^L = \left\langle \Phi_{LM}^L(x,y) + \sum_{n \in {1,2}}</td>
</tr>
<tr>
<td>Laplacian Variance</td>
<td>( \Phi_{L}^V = \text{var}\left[ L * I \right])</td>
</tr>
<tr>
<td>Variance</td>
<td>( \Phi_{V}^S = \text{var}\left[ I(x,y) \right])</td>
</tr>
<tr>
<td>Normalised Variance</td>
<td>( \Phi_{VN}^S = \frac{1}{\langle I(x,y) \rangle} \text{var}\left[ I(x,y) \right])</td>
</tr>
<tr>
<td>Localised Variance</td>
<td>( \Phi_{VL}^S = \text{var}\left[ L_{dx}(x,y) \right])</td>
</tr>
<tr>
<td>Contrast</td>
<td>( \Phi_{C}^S = \left\langle \sum_{i \in W} \sum_{j \in W} I(x,y) - I(x+i,y+j) \right\rangle )</td>
</tr>
<tr>
<td>Mean Ratio</td>
<td>( \Phi_{R}^S = \left\langle \text{max} \left{ \frac{\mu(x,y)}{\mu(x,y)}, \frac{I(x,y)}{\mu(x,y)} \right} \right\rangle )</td>
</tr>
<tr>
<td>Entropy</td>
<td>( \Phi_{HE}^S = H(I_H) )</td>
</tr>
<tr>
<td>Central Moment</td>
<td>( \Phi_{ACM}^S = \sum_{k}</td>
</tr>
<tr>
<td>Absolute Detail Sum</td>
<td>( \Phi_{AS}^W = \left\langle \sum_{n \in {LH,H,H,H}}</td>
</tr>
<tr>
<td>Detail Variance</td>
<td>( \Phi_{V}^W = \left\langle \sum_{n \in {LH,H,H,H}} \text{var}\left[ W_n^1 \right]\right\rangle )</td>
</tr>
<tr>
<td>Detail-Coarse Ratio</td>
<td>( \Phi_{R}^W = \left\langle \frac{W_n^H(x,y)^2+W_n^H(x,y)^2+W_n^H(x,y)^2}{W_n^L(x,y)^2+W_n^L(x,y)^2+W_n^L(x,y)^2} \right\rangle )</td>
</tr>
</tbody>
</table>
in particular:

\[ P_r = \{(1, 0), (2, 0), (1, 1), (0, 1), (0, 2)\} \tag{A.1} \]

Both FQMs used the more common window-size of eight pixels square.

### A.2 Gradient-based

Gradient-based FQMs, \( \Phi^G \), use approximations of the gradient or the first-derivative of the image to estimate the high-frequency content and hence the image quality. Differentiation is considered analogous to high-pass filtering, so these methods reward high-frequency content in the image. Different approximations of the gradient have been used: first-order differences, \( I_X^G \), [194], [195], [197], [204]; Brenner gradient, \( I_X^B \), [193], [194], [197], [198]; Gaussian derivative, \( I_X^G \); and Tenengrad, \( I_X^T \), [194], [195], [197], [209], [210], [225], [226].

Different combinations of the components of the gradient have also been looked at: one-dimensional approximations [193], [194], [198], [227]; maximum component approximations [197], [211]; and component sum [194]–[196], [204], [209], [210], [225], [226], [228].

Additionally, prior to summation, either the absolute value of the components of the gradient [194], [197] or the squared value of the components of the gradient, [193]–[198], [204], [209], [210], [225]–[228] can be used.

Based on these variants, seven metrics were analysed in this category:

- the Absolute Gradient, \( \Phi^G_{DMA} \), [197];
- the Squared Gradient, \( \Phi^G_{DMS} \), [197];
- the Brenner Gradient, \( \Phi^G_{BMS} \), [193], [194], [197], [198];
- the Gradient Energy, \( \Phi^G_{DSS} \), [195], [204], [229];
- the Gaussian Energy, \( \Phi^G_{GSS} \), [227], [228];
- the Tenengrad mean, \( \Phi^G_{TM} \), [194], [195], [209], [210], [226];
- and the Tenengrad variance, \( \Phi^G_{TV} \), [226].

One-dimensional approximations were not used as they underperform compared to the multi-dimensional metrics [197].
A.3 Laplacian-based

Laplacian-based FQMs use second-order differentiation to reward higher frequency content in the image and hence reward images of higher quality. The second-order derivative is approximated by convolving a Laplacian kernel (two-dimensional) with the image, where the kernel, $L$, is given by:

$$L = \frac{1}{6} \begin{pmatrix} 1 & 4 & 1 \\ 4 & -20 & 4 \\ 1 & 4 & 1 \end{pmatrix}$$ (A.2)

The Laplacian kernel can also be applied in each direction independently, where the kernels in the $x$ and $y$ directions are given by:

$$L_x = L_y^T = \begin{pmatrix} -1 & 2 & -1 \end{pmatrix}$$ (A.3)

Finally, the Laplacian kernel can also be estimated along the diagonals where the kernels along the two diagonals, $L_d1$ and $L_d2$, are given by:

$$L_d = \frac{1}{\sqrt{2}} \begin{pmatrix} 0 & 0 & 1 \\ 0 & -2 & 0 \\ 1 & 0 & 0 \end{pmatrix}, \quad L_d' = \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 & 0 \\ 0 & -2 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$ (A.4)

Four metrics were considered in this category:

- the Laplacian Energy, $\Phi^L_E$, [192], [201], [210], [212];
- the Modified Laplacian Energy, $\Phi^L_M$, [208];
- the Diagonal Laplacian Energy, $\Phi^L_D$, [230];
- and the Laplacian Variance ($\Phi^L_V$) [226].

Higher-order derivatives are not considered in this paper as it was found that these are affected by noise in images compared to the first and second derivatives [212].

A.4 Statistics-based

Statistics-based metrics analyse the distribution of values of the image or the histogram of the image. Five metrics were considered:

- the Variance, $\Phi^S_V$, [193]–[195], [197], [203]–[207], [209];
- the Normalized Variance, $\Phi^S_{VN}$, [194], [196], [197];
APPENDIX A. FOCAL QUALITY METRICS

- the Localized Variance, $\Phi_{S_{VL}}$, [226];
- the Contrast, $\Phi_{S_{C}}$, [231];
- and the Mean Ratio ($\Phi_{S_{R}}$) [209].

Two more metrics were also considered, which use statistics of the histogram of the gray-level luminance as a measure of focus:

- the Entropy, $\Phi_{S_{HE}}$, [193], [194], [197], [205], [207], [215];
- and the Central Moment, $\Phi_{S_{ACM}}$, [211], [232].

All metrics are summarized in Table A.1 where $\mu(x, y)$ represents the average of the neighbourhood (with the neighbourhood defined as the 15 pixel square window around the pixel of interest, $(x, y)$) and where $W = \{-1, 0, 1\}$. $H(x)$ represents the entropy of $x$; $I_H$ represents the histogram of the grey-level luminance of the image, with $k$ representing each value in the histogram and $P_k$ representing the frequency of occurrence of that level.

A.5 Wavelet-based

Wavelet-based transforms use the DWT to describe the frequency content of the image and reward images of higher quality. The DWT decomposes the image into three detail sub-bands—$W_{HL}^1$, $W_{HH}^1$, and $W_{HH}^1$—and the coarse approximation sub-band, $W_{LL}^1$. To create higher-level transforms, the coarse approximation sub-band is successively decomposed.

Three metrics were considered in this category:

- the Absolute Detail Sum, $\Phi_{S_{AS}}$, [211], [213], [215];
- the Detail Variance, $\Phi_{S_{V}}$, [213], [215];
- and the Detail-Coarse Ratio, $\Phi_{S_{R}}$, [211], [215].

In this paper, a commonly used configuration with a first-order DWT with db6 filter (Daubechies filter with six vanishing moments) was used [211], [213], [215].
Journal Publications Arising from this Thesis

The first page of the six published journal publications are included in the following sections.
B.1 Focal quality metrics for the objective evaluation of confocal microwave images

This journal paper was published in the International Journal of Microwave and Wireless Technologies by the Cambridge University Press in 2017. This journal paper has received 9 citations and the journal has an impact factor of 0.745 at the time of publication of this thesis.
Focal quality metrics for the objective evaluation of confocal microwave images

DECLAN O’LOUGHLIN, FINN KREWER, MARTIN GLAVIN, EDWARD JONES AND MARTIN O’HALLORAN

Confocal microwave imaging for breast cancer detection relies on accurate knowledge of the average dielectric properties of the patient-specific breast. When accurately estimated, coherent addition will occur at the tumor site, producing a clear and sharp image thereof. Conversely, if the average dielectric properties are poorly estimated, a blurred, unfocused image will be reconstructed, potentially obscuring cancerous lesions. Several methods have been proposed to estimate the patient-specific average dielectric properties, for example, time-of-flight estimation. However, such methods are specific to the individual imaging hardware, can be susceptible to multipath propagation and assume the chosen paths are representative of the whole volume. In this paper, a novel method to estimate the patient-specific average dielectric properties is presented, based on focal quality metrics (FQMs); used historically to measure the clarity and focus of microscopic or digital photographic images. These FQMs are applied to confocal microwave breast images to assess their focus, and hence estimate the patient-specific average dielectric properties. In this way, FQMs can be used to generate the optimum microwave image of the breast. The performance and robustness of these FQMs for microwave breast imaging applications is examined in this paper and preliminary results are presented and discussed.

Keywords: Radar applications, Quality of life/medical diagnosis and imaging systems

Received 18 October 2016; Revised 1 May 2017; Accepted 7 May 2017; first published online 27 June 2017

1. INTRODUCTION

Over the last 15 years, confocal microwave imaging (CMI) has emerged as a promising diagnostic method for breast cancer detection. CMI has the potential to provide a safe, non-ionizing, and comfortable method for breast cancer screening [1–3]. An early-stage study looked at the variability in measurements with repeated scans of healthy volunteers over a 2–8 month period, confirming that the scan was comfortable and identifying some areas of variability between scans [2]. Another study considered nine patients, with breasts both with and without disease, with many of the reconstructed images being consistent with the clinical history of the patient [1]. A larger, more recent study with 86 patients has shown a sensitivity of 74% comparing well with radiological results on the same sample. Considering only the dense breasts, sensitivity was 86%, which is better than the radiological results for the same subset of patients [3]. These studies have also highlighted the requirement for good estimates of the patient-specific dielectric properties in order to create a sharp and focused image of the breast. Consequently, a number of these groups have begun to examine new methods to estimate the patient-specific average dielectric properties, as part of the breast imaging process [4–9]. In this paper, a new method to estimate the average dielectric properties is presented and evaluated.

The physical basis for CMI is the dielectric contrast between healthy and cancerous breast tissue [6] and the ability to identify the source of reflected microwave energy from within the breast. The source of the reflected energy is a significant dielectric scatterer, and its precise location can be established using an estimate of the average dielectric properties of the breast. The average dielectric properties of the breast are used by the CMI beamformer to calculate the speed of propagation within the breast, and ultimately reconstruct an image of the breast [10]. An incorrect estimate of the average dielectric properties reduces coherent addition at dielectric scatterer locations, which in turn reduces the magnitude of the image at these locations and increases the clutter in the image. This can make tumor detection more difficult or in some cases impossible.

In light of the importance of the average dielectric properties as an imaging parameter, several methods to estimate the patient-specific average dielectric properties have been developed. These include methods to estimate the average dielectric properties from time-of-flight signals in the original patient scan [8, 9] as well as average dielectric properties estimation from a separate scan with additional hardware [4, 5, 11, 12]. A simplified inverse scattering problem was used in [9] to estimate the average dielectric properties from the original backscattered signals. Time-of-flight measurements were used to estimate interior properties in numerical studies [8], while promising multipath propagation measurements were used in some experimental studies [4, 5, 11, 12].
B.2 Parameter Search Algorithms for Microwave Radar-based Breast Imaging: Focal Quality Metrics as Fitness Functions

This journal paper was published in Sensors by MDPI in 2017. This open-access journal article was published in a special issue entitled “Sensors for Microwave Imaging and Detection” in the section Remote Sensors which was edited by Prof. Natalia K. Nikolova, McMaster University, Ontario, Canada. This journal article has received 8 citations and the journal has an impact factor of 2.475 at the time of publication of this thesis.
Parameter Search Algorithms for Microwave Radar-Based Breast Imaging: Focal Quality Metrics as Fitness Functions

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Abstract: Inaccurate estimation of average dielectric properties can have a tangible impact on microwave radar-based breast images. Despite this, recent patient imaging studies have used a fixed estimate although this is known to vary from patient to patient. Parameter search algorithms are a promising technique for estimating the average dielectric properties from the reconstructed microwave images themselves without additional hardware. In this work, qualities of accurately reconstructed images are identified from point spread functions. As the qualities of accurately reconstructed microwave images are similar to the qualities of focused microscopic and photographic images, this work proposes the use of focal quality metrics for average dielectric property estimation. The robustness of the parameter search is evaluated using experimental dielectrically heterogeneous phantoms on the three-dimensional volumetric image. Based on a very broad initial estimate of the average dielectric properties, this paper shows how these metrics can be used as suitable fitness functions in parameter search algorithms to reconstruct clear and focused microwave radar images.

Keywords: biomedical electromagnetic imaging; microwave imaging; ultrawideband radar

1. Introduction

In recent years, microwave imaging has shown promising results in early breast imaging clinical trials. In particular, an ongoing study with over 200 patients shows sensitivities equivalent to mammography, and slightly higher than mammography in dense breasts [1,2]. Other studies have analysed the variability of measurements of healthy volunteers over time-frames of two to eight months and analysed the comfort levels of patients [3]. Previous studies have also shown for eight patients with and without disease that the reconstructed images are consistent with the clinical history of the patient [4].

In general, microwave radar imaging for breast cancer can be considered analogous to synthetic aperture radar, where a synthetic aperture array of non-directional antennas sequentially illuminates the imaging domain and backscattered signals are collected either at the transmitting antenna (monostatic) or at the transmitting antenna and other receivers (multistatic). These backscattered signals are then synthetically focused to points within the imaging domain and the energy of the summed signal used as the intensity of the point. At points where dielectric scatterers are located, coherent addition occurs resulting in a larger energy than the surrounding area.

This technique relies on a number of assumptions:

1. that sufficient contrast exists between cancerous and healthy tissues [5];
B.3 Microwave Breast Imaging: experimental tumour phantoms for the evaluation of new breast cancer diagnosis systems

This journal paper was published in Biomedical Physics & Engineering Express by the IOP in 2018. This journal paper has 4 citations at the time of publication of this thesis.
Microwave Breast Imaging: experimental tumour phantoms for the evaluation of new breast cancer diagnosis systems

Bárbara L Oliveira, Declan O’Loughlin, Martin O’Halloran, Emily Porter, Martin Glavin and Edward Jones

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Keywords: microwave imaging, dielectric materials, dielectric measurements, tumour phantoms, tumour diagnosis

Abstract
In this paper, a new set of tumour phantoms for the experimental evaluation of Microwave Breast Imaging (MBI) as a method to diagnose breast cancer is presented. The phantoms were based on previously developed numerical models that had been clinically validated, supporting the appropriateness of the phantoms for the development of experimental systems. The proposed tumour phantom set was developed using polyurethane rubber with graphite and carbon-black powders and is the first to incorporate a large number of different shapes and levels of spiculation to emulate different levels of tumour malignancy. A series of spherical, non-spiculated targets was fabricated to model benign tumours, and a series of targets with irregular shapes and increasing spiculation was fabricated to model malignant tumours. The tumour phantoms can be combined with a variety of breast phantoms fabricated with the same method, which are unique in their diversity of glandular tissue content. The modular design of the phantom set allows for tumour and breast phantoms to be dynamically combined, creating an experimental test platform for MBI with a total of 154 cases. Moreover, the dielectric properties of the phantoms display good agreement with the literature, and the phantoms are constructed using materials that have demonstrated stable properties over time. Results also demonstrate how the shape and level of spiculation of a tumour can influence microwave reflections, and therefore impact the performance of imaging and diagnostic systems.

1. Introduction

Microwave Breast Imaging (MBI) for the detection of breast cancer has seen significant research and commercial development in recent years. At the time of writing, at least 4 experimental systems have already been tested with patients [1–7], with preliminary results indicating that MBI has the potential to match state-of-the-art breast screening methods. However, most experimental and clinical MBI studies have focused primarily on the detection of tumours in the breast, and the diagnosis of tumours according to their level of malignancy is usually seen as a secondary concern. In fact, while the automated diagnosis of breast cancer using MBI has already shown promise, the vast majority of studies that have proposed classification strategies for this purpose have been tested only on numerical data [8–12].

The experimental evaluation of a prototype system is a necessary precursor to its clinical use, as it helps to examine system performance in representative, but controlled, real-word conditions. Laboratory phantoms allow for an accurate assessment of key elements in system hardware and software, such as: performance of the system in terms of repeatability, stability, resolution and Point Spread Function (PSF), and the effect of experimental errors and noise in algorithmic performance. In addition, laboratory phantoms can also play a role in quality assurance of clinical MBI systems, as is common practice with other clinical imaging methods [13].

Different examples of experimental phantoms for the evaluation of MBI systems can already be found in the literature, e.g. [14–22]. The available phantoms mostly differ in the type of Tissue-Mimicking Material (TMM) used to recreate the properties of breast
APPENDIX B. JOURNAL PUBLICATIONS ARISING FROM THIS THESIS

B.4 Microwave Breast Imaging: Clinical Advances and Remaining Challenges

This journal paper was published in Transactions on Biomedical Engineering by the IEEE in 2018. This journal article has received 10 citations and the journal has an impact factor of 4.288 at the time of publication of this thesis.
Microwave Breast Imaging: Clinical Advances and Remaining Challenges

Declan O’Loughlin, Martin O’Halloran, Brian M. Moloney, Martin Glavin, Edward Jones, and M. Adnan Elahi

Abstract—Objective: Microwave breast imaging has seen significant academic and commercial development in recent years, with four new operational microwave imaging systems used with patients since 2016. In this paper, a comprehensive review of these recent clinical advances is presented, comparing patient populations and study outcomes. For the first time, the designs of operational microwave imaging systems are compared in detail.

Methods: First, the current understanding of dielectric properties of human breast tissues is reviewed, considering evidence from operational microwave imaging systems and from dielectric properties measurement studies. Second, design features of operational microwave imaging systems are discussed in terms of advantages and disadvantages during clinical operation. Results: Reported results from patient imaging trials are compared, contrasting the principal results from each trial. Additionally, clinical experience from each trial is highlighted, identifying desirable system design features for clinical use. Conclusions: Increasingly, evidence from patient imaging studies indicate that a contrast in dielectric properties between healthy and cancerous breast tissues exists. However, despite the significant and encouraging results from patient trials, variation still exists in the microwave imaging system design. Significance: This study seeks to define the current state of the art in microwave breast imaging, and identify suitable design characteristics for ease of clinical use.

Index Terms—Microwave imaging, dielectric properties, breast imaging.

I. INTRODUCTION

MICROWAVE imaging for biomedical applications has been researched for over forty years, and numerous reviews, books and editorials have been published on the potential benefits [1]–[14]. However, reviews from both 1982 and 2016 suggest microwave imaging as a “promising imaging modality” [2], [11], despite considerable research effort in the intervening 40 years. A book chapter by Bolomey [14], published in 2018, provides a detailed history and timeline of microwave imaging for biomedical applications, including comparisons to existing imaging modalities like radiography, computed tomography (CT) and ultrasound. The chapter identifies microwave imaging as being in a clinical acceptance phase prior to a transition to clinical practice. The chapter also suggests that the results of the operational microwave imaging systems currently engaged in trials should be used as guidelines to improve and modify microwave imaging systems with the same clinical objectives.

As part of the clinical acceptance phase of imaging modality development identified in [14], a number of clinical evaluations of microwave breast imaging systems have been demonstrated in the literature [15]–[38]. Two of these systems are being used in on-going clinical trials [26], [34], one of which is being developed commercially by Micrima Ltd (Bristol, the UK). Another system is being developed commercially by Microwave Vision Group (Villebon-sur-Yvette, France) with clinical evaluation planned for the very near future [39]. However, considerable variance in design exists between the operational microwave systems in terms of technical design parameters, patient interface and reconstructions algorithms.

In terms of technical design, although most operational systems collect multistatic data (recording using antennas other than the transmitting antenna), monostatic acquisition (recording and transmitting using the same antenna) has been investigated in [27]. Backscattered data has been collected as low as 0.5 GHz in [15] and as high as 9 GHz in [38].

Although most operational systems require the patient to lie prone on an examination table, some require the breast to be in direct contact with a solid coupling shell [22], [38], while some require the breast to be immersed in a coupling medium [19], [27], [34]. A wearable system requiring no coupling medium has been demonstrated [35] and a handheld system used to scan the patient’s breast in the supine position, has very recently been developed [33].

Clinical investigations with microwave imaging systems have ranged in size from two patients with disease [38] to as large as over 200 patients [24]. Patients undergoing neoadjuvant chemotherapy have also been studied [19].
B.5 Evaluation of Image Reconstruction Algorithms for Confocal Microwave Imaging: Application to Patient Data

This journal paper was published in Sensors by MDPI in 2018. This open-access journal article was published in a special issue entitled “Sensors for Microwave Imaging and Detection” in the section Remote Sensors which was edited by Prof. Natalia K. Nikolova, McMaster University, Ontario, Canada. This journal article has received 3 citations and the journal has an impact factor of 2.475 at the time of publication of this thesis.
Evaluation of Image Reconstruction Algorithms for Confocal Microwave Imaging: Application to Patient Data

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Abstract: Confocal Microwave Imaging (CMI) for the early detection of breast cancer has been under development for over two decades and is currently going through early-phase clinical evaluation. The image reconstruction algorithm is a key signal processing component of any CMI-based breast imaging system and impacts the efficacy of CMI in detecting breast cancer. Several image reconstruction algorithms for CMI have been developed since its inception. These image reconstruction algorithms have been previously evaluated and compared, using both numerical and physical breast models, and healthy volunteer data. However, no study has been performed to evaluate the performance of image reconstruction algorithms using clinical patient data. In this study, a variety of imaging algorithms, including both data-independent and data-adaptive algorithms, were evaluated using data obtained from a small-scale patient study conducted at the University of Calgary. Six imaging algorithms were applied to reconstruct 3D images of five clinical patients. Reconstructed images for each algorithm and each patient were compared to the available clinical reports, in terms of abnormality detection and localisation. The imaging quality of each algorithm was evaluated using appropriate quality metrics. The results of the conventional Delay-and-Sum algorithm and the Delay-Multiply-and-Sum (DMAS) algorithm were found to be consistent with the clinical information, with DMAS producing better quality images compared to all other algorithms.

Keywords: microwave imaging; ultra wideband radar; breast cancer; artifact removal; patient study

1. Introduction

Confocal Microwave Imaging (CMI) is an emerging imaging modality for the detection of breast cancer. One important signal processing challenge in reconstructing high quality breast images using CMI is the image reconstruction algorithm itself. An effective image reconstruction algorithm provides an accurate localisation of tumours, while suppressing clutter due to healthy breast tissues and any residual artifacts from preprocessing.

Several image reconstruction algorithms for CMI have been developed over the last two decades [1–13]. These algorithms have been categorised as Data Independent (DI) beamforming and Data Adaptive (DA) beamforming algorithms in the literature [14]. Both DI and DA beamforming algorithms are based on the principle of coherent addition of backscattered radar signals, which are collected after illuminating the breast with Ultra-Wideband Radar (UWB) pulses. In Data-Independent (DI) beamforming algorithms, coherent addition is performed based on an assumed propagation
APPENDIX B. JOURNAL PUBLICATIONS ARISING FROM THIS THESIS

B.6 Sensitivity and Specificity Estimation Using Patient-Specific Microwave Imaging in Diverse Experimental Breast Phantoms

This journal paper was published in the Transactions on Medical Imaging by IEEE in 2018. This journal has an impact factor of 6.13 at the time of publication of this thesis.
Sensitivity and Specificity Estimation Using Patient-Specific Microwave Imaging in Diverse Experimental Breast Phantoms

Declan O'Loughlin, Bárbara L. Oliveira, Adam Santorelli, Emily Porter, Martin Glavin, Edward Jones, Milica Popović, and Martin O’Halloran

Abstract—Many new clinical investigations of microwave breast imaging have been published in recent years. Trials with over one hundred participants have indicated the potential of microwave imaging to detect breast cancer, with particularly encouraging sensitivity results reported from women with dense breasts. The next phase of clinical trials will involve larger and more diverse populations, including women with no breast abnormalities or benign breast diseases. These trials will need to address clinical efficacy in terms of sensitivity and specificity. A number of challenges exist when using microwave imaging with broad populations: 1) addressing the substantial variance in breast composition observed in the population and 2) achieving high specificity given differences between individuals. This paper analyses these challenges using a diverse phantom set which models the variance in breast composition and tumor shape and size seen in the population. The data show that the sensitivity of microwave breast imaging in breasts of differing density can suffer if patient-specific beamforming is not used. Moreover, the results suggest that achieving high specificity in dense breasts may be difficult, but that patient-specific beamforming does not adversely affect the expected specificity. In summary, this paper finds that patient-specific beamforming has a tangible impact on expected sensitivity in experimental cases and that achieving high specificity in dense breasts may be challenging.

Index Terms—Microwave, breast, evaluation and performance, image reconstruction, analytical methods, image quality assessment.

I. INTRODUCTION

In recent years, a number of clinical investigations of microwave radar-based imaging have been published [1]–[4]. Clinical evidence includes trials with over 200 patients using MARIA® [1] which is being commercialised by Micrima Ltd. (Bristol, the UK). A competing system is being developed commercially by Microwave Vision Group (Villebon-sur-Yvette, France) with clinical trials commencing at the National University of Ireland Galway, Ireland [5]. The next phase of clinical trials will draw on the experience of the earlier stage trials, and investigate the sensitivity and specificity of microwave breast imaging in detail [6], [7], including identifying the reconstruction algorithms which achieve the highest sensitivity and specificity [8]. Although many books, reviews and open-source implementations of microwave imaging algorithms have been published [7], [9], [10], many practical challenges exist in translating microwave imaging algorithms to the clinic, broadly categorised as follows:

1) imaging living tissue with real blood flow and temperature changes [11];
2) patient positioning and movement [4], [12];
3) intrapatient variation due to the menstrual cycle, hormonal changes and or weight differences [4];
4) interpatient variation in breast composition [13].

Challenges 1–3 have been previously analysed using results from patient imaging studies with a variety of systems:

1) fast acquisition times (under a minute), reducing the effect of variations [1], [12];
2) automated verification of position [1], [14];
3) signal and image variability using a wearable system with healthy control subjects over a period of up to eight months [4].

However, the importance of accounting for breast variability in the imaging algorithms (Challenge 4) remains unknown and how this challenge can impact the expected sensitivity and specificity of microwave radar-based imaging is examined in this paper.

Fundamentally, microwave radar-based imaging algorithms (beamformers) require an estimate of the propagation speed within the breast to synthetically focus the signals to individual points [15]. The propagation speed can be determined from the dielectric properties of breast tissues, where, broadly speaking, the breast consists of adipose tissues with lower dielectric properties and glandular tissues with higher dielectric properties. The proportions of glandular and adipose tissues can vary substantially between patients, between 0% and 50% by volume [16].
Conference Publications Arising from this Thesis

The first page of the seven accepted conference publications are included in the following sections.
APPENDIX C. CONFERENCE PUBLICATIONS ARISING FROM THIS THESIS

C.1 Optimisation of Confocal Microwave Breast Images using Focal Quality Metrics

This conference abstract was presented at the 22nd BioEngineering in Ireland (BINI22) in Galway, Ireland in 2016. This presentation was awarded the Best BioElectronics Speaker Prize.
OPTIMISATION OF CONFOCAL MICROWAVE BREAST IMAGES USING IMAGE FOCAL METRICS

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INTRODUCTION

Microwave Breast Imaging (MBI) is a promising emerging method for breast cancer screening. MBI relies on a contrast between the dielectric properties of cancerous and healthy tissues at microwave frequencies (Hagness et al., 1998). The current standard for breast cancer detection is X-ray mammography, which is limited both in terms of sensitivity, specificity and the dangers associated with ionising radiation. In comparison, MBI uses low-power non-ionising microwave radiation to identify the presence and location of breast cancer. Additionally, MBI does not require the uncomfortable compression of the breast associated with X-ray mammography, and is potentially very low cost.

A key factor in generating a clear and focused MBI image of the interior of the breast is estimating the average permittivity of the breast. The average permittivity of the breast varies between patients, and can have a significant effect on the quality of the reconstructed image. Early MBI algorithms used published estimates of the dielectric properties (Fear and Stuchly, 2001) to create images. However, as MBI systems move towards early-stage clinical trials, this is insufficient. One potential method to estimate the patient-specific average permittivity involves the use of image focal methods.

This paper discusses the use of focal quality metrics to independently evaluate the quality of the microwave image, and whether this approach can be used to estimate the dielectric properties of a patient’s breast.

MATERIALS AND METHODS

Focal quality metrics (FQMs) have been used in autofocus (Russell and Douglas, 2007) and shape-from-focus (Pertuz et al., 2013) applications to objectively measure image quality. In general, FQMs operate by estimating the high frequency content of the image in question (Groen et al., 1985).

FQMs can be broadly subdivided into categories based on their method of action as identified in a recent review (Pertuz et al., 2013): gradient-based, laplacian-based, wavelet-based, fourier-based and statistic-based. In this paper, one FQM from each category was evaluated as a potential method to automatically estimate the patient specific dielectric properties of the breast.

RESULTS AND DISCUSSION

Preliminary results indicate that FQMs can be used to objectively measure the image quality and in turn estimate the patient-specific dielectric properties. Sample images showing the importance of this permittivity value are shown in Figure 1. These results suggest that FQMs are valuable for estimating this value, but further work needs to be completed to evaluate the optimum FQM in more complex scenarios in three-dimensional breast imaging.

![Sample images showing the importance of this permittivity value](image)

Figure 1 Sample images of the breast generating using confocal microwave imaging. 1(b) shows the image generated using an accurate estimation of the dielectric properties, where the tumour is clearly identifiable in the red circle. 1(a) shows an image of the same breast with an inaccurate estimation of the dielectric properties; the tumour is in the incorrect location and obscured by noise in the image.

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REFERENCES

C.2 Estimating Average Dielectric Properties for Microwave Breast Imaging Using Focal Quality Metrics

This conference paper was presented at the 10th European Conference on Antennas and Propagation (EuCAP) in Davos, Switzerland in 2016.
Abstract—Confocal Microwave Imaging algorithms synthetically focus backscattered radar signals to create an image of the breast. Spatial focusing is achieved by delaying the received signals by the round-trip propagation delay to the voxels of interest. A key component in calculating propagation time is a good estimate of the average dielectric properties of the breast, because the accuracy of the reconstructed image varies significantly with the value of average dielectric properties used.

This paper investigates the use of focal quality metrics to estimate the optimal average dielectric properties to use to reconstruct an image of the breast. Focal quality metrics have long been used to find optimally focused images in microscopy and camera systems without prior knowledge of the imaged object’s location or texture. In this paper, five common focusing algorithms from autofocus and shape-from-focus applications are compared to investigate whether these focal quality metrics can be used to estimate the patient-specific average dielectric properties.

Index Terms—focal quality metrics, microwave imaging, breast cancer detection, autofocus techniques, biomedical imaging

I. INTRODUCTION
Microwave imaging exploits dielectric contrasts between cancerous and healthy tissues at microwave frequencies to detect breast tumours. Confocal Microwave Imaging (CMI) is one widely used method to convert the microwave reflections into useful images of the breast [1]–[8]. CMI beamformers synthetically focus backscattered signals from each voxel in the imaging area successively to construct an energy profile of the breast. Regions of high energy in the resultant images suggest the presence of a significant dielectric scatterer (i.e. a tumour). This image reconstruction technique is based on a number of assumptions [9], primarily:

• that sufficient contrast in dielectric properties exists between healthy tissues and tumours;
• that the dielectric properties of the breast are such that coherent addition can occur at scatterers;
• and that representative average dielectric properties can be found which can be used to estimate propagation delays and synthetically focus signals.

Many different methods have been used to estimate the average dielectric properties to ensure a clear and focused image of the breast can be formed. Originally, published dielectric properties of adipose tissues were used [1], [2], [5], [6], [8], [10]. Others considered the skin and immersion medium, but still used published values of dielectric properties of adipose tissues for the breast interior [3], [7]. However, there is often a considerable difference between these published values and the patient-specific average dielectric properties. This difference in estimated average dielectric properties results in an incorrect estimation of the average microwave propagation speed, and therefore a poorly reconstructed CMI breast image. Improved performance was demonstrated in [11] where the average dielectric properties of the interior of the breast were calculated from the backscattered signals using inverse scattering. Time-of-flight measurements were used to estimate interior properties in numerical studies [12], while promising multi-path propagation measurements were used in some experimental studies [13], [14].

Rather than adding an additional step to the microwave breast imaging procedure to estimate the microwave propagation speed, the authors propose the use of focal quality metrics (FQMs) to optimise the assumed average dielectric properties. The FQMs presented in this paper are analysed to see if image quality is correlated with a well-focused image. If good correlation is established, then there is potential to use the FQM as a method to fine-tune the average dielectric estimate, and consequently to optimise the microwave breast image.

The remainder of the paper is structured as follows: Section II describes the FQMs used and the rational for their selection; Section III describes how the chosen FQMs are evaluated in terms of fitness and the images on which they are analysed; Section IV describes the results and Section V concludes the paper.

II. FOCAL QUALITY METRICS
In this paper, five FQMs were described and compared. FQMs can broadly be divided based on their method of action, and one metric from each of the families identified in a recent review of FQMs were chosen in this paper [15]. In general, FQMs operate by estimating the high-frequency spatial content of the image [16].

A. Gradient-based focal quality metric ($\Phi_G$)
Approximations to the first derivative or gradient of the image have been widely used as FQMs, [15], [17]–[22]. The first-order difference of the image is commonly used as a computationally efficient estimation of the first spatial derivative, and is used in this work. The absolute value of the gradient is analysed here, which is commonly used as a
C.3 Adaptive Microwave Breast Imaging: Experimental Performance Evaluation

This conference paper was presented at the 24th BioEngineering in Ireland (BINI) in Meath, Ireland in 2018.
INTRODUCTION

Microwave Breast Imaging has seen increased use in early stage clinical trials in recent years, for example, a commercial system has now imaged over 200 patients in an on-going clinical trial (Bannister, 2016). The trial has indicated microwave imaging may be a low-cost, safe and comfortable methodology for asymptomatic breast cancer screening.

Microwave breast imaging researchers are now focusing on translational challenges and the intended use of microwave imaging in the clinic. For example, the breast is known to vary from patient to patient, both in terms of size and shape, but also tissue composition and associated dielectric properties (Lazebnik, 2007). An estimate of the breast dielectric properties is a key parameter affecting the image quality of microwave radar-based breast images (O’Loughlin, 2007). However, all clinical trials to date have used a single average dielectric properties estimate for all patients, despite the variance of this parameter and the known adverse effect on image quality.

This work looks at the potential impact of an adaptive microwave breast imaging algorithm on overall system performance, estimating the average dielectric properties on case-by-case basis.

MATERIALS AND METHODS

The breast was modelled using rubber-based breast phantoms (Garrett 2015). Four were manufactured, modelling different breast radiographic densities and average dielectric properties as would be expected in the population. Fig. 1(b) shows a sample phantom with 10% glandular tissue by volume. Five tumours of between 5 mm and 20 mm in diameter were also modelled, shown in Fig 1(c).

Microwave backscattered data were collected using an experimental prototype at NUIG, shown in Fig 1(a). A parameter search algorithm was used to estimate the average dielectric properties for the adaptive imaging algorithm. The image quality and tumour localisation accuracy using the adaptive imaging algorithm were compared to the image quality using a best-case single estimate.

RESULTS

Using an adaptive imaging algorithm, 14 tumours are located (70%) with a mean signal-to-clutter ratio (SCR) of 3.2 dB (meaning the magnitude of the tumour response in the image is 3.2 dB higher than any other response in the image). In comparison, when using a single average dielectric properties estimate for all cases, 12 tumours are found (60%), with a mean SCR of 1.9 dB; 1.3 dB lower than for the adaptive algorithm. Additionally, overestimating the average dielectric properties by 10% means that only 7 tumours are located, only 35%; compared to 70% for the adaptive algorithm.

DISCUSSION

This study indicates that an adaptive beamformer that estimates the average dielectric properties on a case-by-case basis can improve system performance. An incorrect average dielectric properties estimate can results in lower image quality and higher false negatives. Increasingly, microwave breast imaging is being tested clinically in patient imaging trials, and these results suggest that an adaptive algorithm can have a tangible impact on image quality and tumour detection.

REFERENCES

APPENDIX C. CONFERENCE PUBLICATIONS ARISING FROM THIS THESIS

C.4 Open-source Software for Microwave Radar-based Image Reconstruction

This conference paper was presented at the 12th European Conference on Antennas and Propagation (EuCAP) in London, the UK in 2018.
Abstract—The Microwave Radar-based Imaging Toolbox (MERIT) project aims to produce a robust, consistent framework for microwave imaging signal processing and reconstruction. Open-source scientific software has successfully been used in others domains, such as EIDORS for Electrical Impedance Tomography, MEEP for finite-difference time domain modelling, and gprMax for ground-penetrating radar. Open-source software in these domains has facilitated researchers to draw on collective expertise without having to re-implement commonly used algorithms. Similarly, MERIT contains reference implementations of leading microwave imaging algorithms and processing stages; enabling rapid development and testing of new microwave imaging software.

Index Terms—antenna, propagation, measurement.

I. INTRODUCTION

This work introduces the Microwave Radar-based Imaging Toolbox (MERIT) project: a MATLAB framework for developing and optimising microwave imaging algorithms. MERIT is freely available on GitHub (https://github.com/EMFMed/MERIT); and can also be used with the open-source Octave. Microwave imaging is a promising technique for imaging for a wide-range of medical applications. Suitable areas identified in the literature, include, among others, breast cancer imaging which has seen significant academic and commercial development [1]–[6].

Open-source software has been used in other domains to provide a common reference framework for algorithm development. Open-source software also facilitates new prototype development, allowing researchers to focus on clinical translational activities without having to implement imaging algorithms from scratch. The Electrical Impedance and Diffuse Optical Reconstruction Software (EIDORS) package is commonly used in electrical impedance tomography (EIT) [7]. Designed with software engineering principles in mind, the EIDORS package facilitates the use of advanced EIT algorithms in experimental, industrial and clinical applications and as a platform for new algorithm development.

Many algorithms have been demonstrated for microwave imaging for all stages of the imaging process, from signal processing for artefact removal to three dimensional beamforming [1]–[6], [8]–[17]. MERIT provides optimised implementations of the leading microwave imaging algorithms, enabling the development of future microwave imaging prototype research. MERIT is designed in accordance with software engineering best practice: providing a modular and flexible framework for microwave imaging algorithm use and development. All algorithms are designed to run on both central processing units (CPUs) and graphical processing units (GPUs), substantially reducing the computational time.

A comprehensive test and benchmark suite is also provided, allowing for rapid prototyping and verification of algorithm implementations. Developed algorithms can be easily optimised to run on a GPU without changing the reference implementation. The rest of this paper is structured as follows: Section II describes the theory of radar-based imaging including a review of leading algorithms. Section III describes how the essential imaging steps are implemented in MERIT, visualising and analysing images and usage examples. Finally, Section IV concludes the paper, identifying the advantages of open-source imaging software and future steps.

II. RADAR-BASED IMAGING: BACKGROUND

In general, radar-based imaging is analogous to synthetic aperture radar in the near-field. An antenna is used to illuminate the imaging domain and backscattered signals are collected using either:

- the transmitting antenna (monostatic);
- or additional antennas surrounding the imaging domain (multistatic).

This can be repeated using multiple antennas or antenna locations so that a sufficient number of channels are available for imaging. Backscattered signals can be acquired in both time and frequency domains.

Before imaging, collected backscattered signals are often preprocessed to remove reflections or artefacts from components in the system, the edges of the imaging domain or patient-device interface. For example, algorithms to remove reflections from the skin or skull are important for breast and head imaging. After processing to remove reflections and artefacts, signals are ready for beamforming.

Many algorithms have been proposed for artefact removal. Initially, Average Subtraction subtracted the mean response for all channels from a given channel [10], [18]. This method assumes that the artefacts (e.g. incident pulses, skin reflections) are similar in each channel but that the imaged object response varies. Later algorithms extended this idea, using adaptive filtering to remove the common artefact for each channel [19]. Adaptive filtering compensates for channel-to-channel variation in the artefact.

Rotational subtraction has also been proposed [13]. Two scans are required, one taken at a fixed rotational offset from the other. Provided the imaged object does not lie
APPENDIX C. CONFERENCE PUBLICATIONS ARISING FROM THIS THESIS

C.5 Evaluation of Experimental Microwave Radar-based Images: Evaluation Criteria

This conference paper was presented at the IEEE Antennas and Propagation Symposium (APS) in Boston, MA, USA in 2018.
Evaluation of Experimental Microwave Radar-Based Images: Evaluation Criteria

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Abstract—Microwave imaging has seen an increasing amount of clinical trials in the last two years, including ongoing and planned commercial development. The rapidly increasing number of studies with patient imaging is encouraging researchers to focus on the challenges of translating microwave imaging algorithms to clinical use. A large number of imaging algorithms have been proposed for radar-based imaging, however few detailed comparisons of these algorithms using realistic experimental or patient data have been published. This paper looks at two leading radar-based algorithms in experimental phantoms with and without tumours present. It shows that although some algorithms improve image quality when the tumour is present, the algorithms can also increase false positives in breast phantoms containing glandular structures.

I. Introduction

Many algorithms have been proposed for microwave imaging and these have been comprehensively reviewed in recent books and reviews [1], [2]. Although a number of studies have compared algorithms in idealised situations, few have considered performance using realistic artefact removal [3], [4]. No study to date has compared performance when using average dielectric properties estimation, which has been shown to have a positive impact on image quality [5], [6]. Additionally, few comparisons have included test scenarios both with and without tumours.

The goal of this paper is to highlight the importance of evaluating imaging algorithms on true positives and false positives in experimental breast phantoms. The ideal algorithm weights areas corresponding to tumours highly and does not reward cases where no tumours are present. Additionally, algorithms need to be robust to additional sources of noise due to clinical use, such as patient movement, patient breathing or inconsistent coupling between antennas and the breast [7]. In this work, two leading, imaging algorithms identified from a recent comparison [4] are analysed in a realistic experimental scenario.

II. Methods

Delay-and-Sum (DAS) [8] and Delay-Multiply-and-Sum (DMAS) [9] are used for image reconstruction. Recent evaluations have identified DMAS as effectively suppressing background clutter in images containing tumours [4]. DMAS extends DAS by pair-wise multiplying each signal prior to summation which greatly increases the processing time [9]. For both algorithms, backscattered data was first processed using rotational subtraction [3], [6] to dampen the skin response and other artefacts. Signals were then synthetically focused to points within the imaging domain, where the average dielectric properties were estimated using a parameter search algorithm [6].

The experimental breast and tumour phantoms used in this paper are described in [6]. The imaging algorithms are assessed on images from a breast phantom with 15% glandular tissue by volume. Images reconstructed with 8 mm, 10 mm and 13 mm diameter tumours are analysed, as well as with no tumour present. The maximum amplitudes, signal-to-clutter (SCR) and signal-to-mean ratios (SMR) for the tumour and no tumour images are compared, defined as in [4].

III. Results

Images using DAS and DMAS are shown in fig. 1. Comparing the DMAS images to those reconstructed using DAS (figs. 1c and 1d to figs. 1a and 1b), it can be seen that although DMAS improves the quality of the image when the tumour is present, DMAS also improves the the quality of the images with no tumour present.

Quantatively, images from the three tumours and none are summarised in table I. For both DAS and DMAS, the tumour images have higher amplitudes compared to images with no tumour present. The SCR and SMR of images where tumours are present are also higher than without tumours present. In general, the SCR and SMR of DMAS images is higher than that of DAS images, as is the difference between the SCR and SMR of images with tumours compared to images without tumours present. However, for both SCR and SMR, DMAS improves the image without a tumour by a similar amount to images using from the 10 mm and 13 mm tumours respectively.

IV. Conclusions

Many algorithms have been proposed for microwave imaging, however few realistic comparisons using experimental or patient data are available. Additionally, experimental comparisons typically use cases where tumours are
APPENDIX C. CONFERENCE PUBLICATIONS ARISING FROM THIS THESIS

C.6 Effects of Interpatient Variance on Microwave Breast Images: Experimental Evaluation

This conference paper was presented at the 40th Annual Conference of the Engineering in Medicine and Biology Society (EMBC) in Honolulu, HI, USA in 2018. in Boston, MA, USA in 2018.
Effects of Interpatient Variance on Microwave Breast Images: Experimental Evaluation

Declan O’Loughlin, Bárbara L. Oliveira, Martin Glavin, Edward Jones and Martin O’Halloran

Abstract—Microwave breast imaging has seen significant developments in recent years, including new clinical trials and formation of a number of spin-out companies. Although many algorithms for microwave breast imaging have been developed, there are significant challenges in translating these algorithms to the clinic. For example, movement due to patient breathing can affect the scan, and both the breast and breast abnormalities vary significantly from patient to patient. As breast density is a known independent risk factor for cancer and cancerous tumours have different shapes and margins to benign tumours, the effect of interpatient variance on the microwave image is important. This work analyses the effect on image quality of tumour shape, size and breast density. Using the diverse and representative BRIGID experimental dataset, images of a variety of tumours are compared to images without tumours present. This work suggests that it is difficult to distinguish images with and without tumours present using existing metrics.

I. Introduction

In recent years, a number of clinical evaluations of microwave breast imaging have been published [1]–[6]. An on-going trial with the MARIA® system is being commercialised by Micrima Ltd. (Bristol, the UK) has shown equivalent sensitivities to mammography with over 200 cases [1], [7]. Particularly encouraging results have been demonstrated in dense breasts, a known independent risk factor for breast cancer [1], [8]. Another commercial imaging system is being developed by Microwave Vision Group (Villebon-sur-Yvette, France) with clinical trials commencing in the very near future [9] and comprehensive reviews of these clinical trials have been published [10], [11].

The increasing amount of commercial activity and clinical evidence available motivates researchers to consider the substantial challenges in translating microwave radar-based imaging to the clinic. For example, the breast varies substantially from patient to patient in size, shape and composition [12]. Additionally, tumours vary significantly in clinical practice, and shape and boundary in particular is an important factor influencing the clinical decision [13].

This work evaluates the effect of breast composition and tumour shape and size on microwave radar-based images. The diverse, experimental BRIGID breast phantom set is used, containing breast phantoms modelling a variety of densities that can be combined with different tumour phantoms modelling both benign and malignant cases. This allows the effect of breast composition for a given tumour phantom to be estimated as well as the effect of tumour size and shape to be analysed. Additionally, this modular breast phantom set allows the images of the phantom with and without the tumour present to be compared, which is important when designing software to display the image to the clinician.

II. Methods

The BRIGID phantom set used in this work has been described in [14]. Breast composition can vary substantially from patient to patient, for example, one study with 240 women aged between 35 and 82 found that the volume fraction of glandular tissues varies between 0% and 50% [12]. The most dense phantom in this work contains 30% glandular tissue, greater than 90% of patients in [12].

Tumour shape, in particular the tumour margin, is an important factor for assessing malignancy. Benign tumours are characterized by smooth, regular borders whereas malignant tumours are characterized by irregular or spiculated borders as they are growing [13]. The tumour phantoms in this work are modelled based on these principles and are shown in [14].

Backscattered data were acquired in the frequency domain using a ZNB40 2 port vector network analyser (VNA) and ZN-Z84 24 port switching matrix. As described in [15], 24 antennas were distributed around a 7 cm radius hemisphere, collecting 276 independent channels. The antennas operating characteristics are described fully in [14] and have been previously been demonstrated in a sixteen-antenna array with patients in [5].

Rotational subtraction was used to isolate the tumour response as has been used in recent clinical trials [1]. Multistatic Delay-and-Sum from the MERIT toolbox [17], with parameter search algorithms described in [18]–[20] were used for reconstruction. Imaging was completed in the frequency domain using 51 frequency points linearly spaced between 2 GHz and 4 GHz.

Considering operational microwave imaging systems that have been used with patients with disease [1], [2], [4], a number of different display methods have been used. The image is thresholded and normalised with respect to the image amplitude in [1], [4]. DICOM-compatible images are displayed to the clinician in [1]. Other studies have displayed the entire image and have suggested that it may be possible to use the image amplitude to determine if an abnormality is present or not [2].
APPENDIX C. CONFERENCE PUBLICATIONS ARISING FROM THIS THESIS

C.7 Advantages and Disadvantages of Parameter Search Algorithms for Permittivity Estimation for Microwave Breast Imaging

This conference paper was presented at the 13th European Conference on Antennas and Propagation (EuCAP) in Kraków, Poland in 2019.
Advantages and Disadvantages of Parameter Search Algorithms for Permittivity Estimation for Microwave Breast Imaging

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Abstract—Multiple clinical investigations of radar-based breast imaging devices have been demonstrated in recent years, including two competing commercial systems which are currently being tested in clinics. Ongoing trials include participants with both dense and non-dense breasts and the average dielectric properties of the breast can vary substantially with density. Numerous studies have shown that this normal variance in the dielectric properties of the breast between individuals can impact both the image quality and the expected sensitivity of radar-based breast imaging. This paper examines the potential to use parameter search algorithms to improve the sensitivity of radar-based breast imaging. Although these parameter search algorithms have been shown to improve image quality in a limited number of test cases, this is the first analysis of the potential impact of realistic dielectric properties estimation on the sensitivity of radar-based imaging.

I. INTRODUCTION

Radar-based breast imaging is an emerging imaging modality for the early detection of breast cancer [1], [2]. A number of clinical investigations of radar-based breast imaging systems have recently been published [3]–[8]. Two competing systems are being developed commercially: the MARIA® system by Micrima Ltd. (Bristol, the UK) which is undergoing trials with 994 participants [3]; and the Wavelia system by Microwave Vision SA (Villebon-sur-Yvette, France) which is being used in a pilot clinical investigation at the National University of Ireland Galway with 30 participants [9]. Particularly encouraging results have been demonstrated in dense breasts using MARIA®, a known independent risk factor for breast cancer [3], [10]. Comprehensive reviews of these clinical studies and the other imaging systems used with human participants have been published [1], [11].

As research in radar-based imaging moves towards larger and larger clinical investigations, it is important to use imaging algorithms that are suitable for all women, regardless of breast composition. The breast varies substantially from individual to individual in terms of tissue composition, from very little fibrous and glandular tissues to as much as 50% by volume [12]. The breast tissue composition in terms of proportions of glandular tissue by volume is known to impact both the image quality and the sensitivity achievable with radar-based breast imaging [13], [14]. A number of methods to account for the variance in breast tissue composition have been proposed, however, most have only been tested in a limited number of simplified test-cases [15]–[19].

In this work, the sensitivity achieved using dielectric properties estimation algorithm is compared to the current state-of-the-art method, known as fixed-value estimation. Fixed-value estimation selects one estimate of the average dielectric properties of the breast for all test-cases, however, previous work has shown that the sensitivity can be impaired by errors in this estimate [14]. Parameter search algorithms are a promising approach for dielectric properties estimation for radar-based imaging, and have been tested using both experimental and clinical data [18], [19]. However, these studies have used a limited number of test cases and have primarily focused on the potential of parameter search algorithms to improve the image quality and have not considered the sensitivity. For the first time, this work examines the potential impact of parameter search algorithms on the sensitivity of radar-based imaging, whereas previous work using the same algorithm has looked only at image quality in a limited number of case studies [18].

The following section describes the methods including the experimental data set and the dielectric properties estimation algorithm. Section 3 describes the results, including the potential sensitivity that can be achieved, and the disadvantages of the dielectric properties estimation approach and Section 4 concludes this work.

II. METHODS

Fundamentally, radar-based imaging uses knowledge of propagation within the breast to “synthetically focus” backscattered signals to points in the imaging domain. As described in [18], a number of assumptions are required for practical implementation of a radar-based imaging algorithm. These assumptions can be divided into two main types:

- simplifying the imaging domain to a homogeneous layer with assumed dielectric properties;
- and using the same dielectric properties estimate for each individual breast (fixed-value estimate).

This work addresses the second assumption. Where previous work in [14] used idealised dielectric properties estimation algorithms to identify if the fixed-value estimate assumption affects the sensitivity, this work uses parameter search algorithms to identify suitable estimates without prior knowledge of the tumour location or dielectric properties of the breast.

The chosen parameter search algorithm was first proposed in [18] and was shown to be potentially suitable for