Biomechanical Modelling of the Breast for Image-Guided Surgery

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Abstract

Patients who undergo breast-conserving surgery frequently require more than one operation due to the cancer not being completely excised at the first attempt. Image-guidance which exploits the 3D information available in preoperative dynamic contrast enhanced (DCE) magnetic resonance (MR) images may help to reduce the re-excision rate. However, significant deformation of the soft tissue of the breast occurs between imaging and surgery because these DCE MR images must be acquired with the patient positioned prone, but surgery is performed supine. This currently limits the suitability of MR imaging for guiding breast surgery.

This thesis proposes that a patient-specific biomechanical model, based on preoperative MR images acquired in the prone position, can assist the task of locating a surgical target within a supine patient. The ability of such models to simulate gravity-induced deformations of the breast is investigated. In addition to modelling the deformation between the prone and supine postures, it is shown that the breast submerged in water is an appropriate surrogate for the breast in the absence of gravity loading. This is used to investigate the material properties of the breast.

Non-rigid intensity-based image registration algorithms perform poorly when applied to the task of registering MR images of the prone and supine breast due to the large deformation. Therefore a hybrid registration technique which uses a biomechanical model to initialise an intensity-based non-rigid registration is proposed. This technique is assessed on three subjects.

An image-guided surgery system, based around this biomechanical model, is described and an initial clinical case reported. Validation against tracked ultrasound indicates that, for this one case, the visible margin of the lesion is localised to around 5mm. Finally, a study which investigates the feasibility of matching postoperative histology images with preoperative MR images is described.
I, Timothy John Carter, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Timothy John Carter, 6th May 2009
To Dr C.D. Coe
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# Table of Contents

Abstract........................................................................................................................................ 2

Acknowledgements..................................................................................................................... 5

Table of Contents ....................................................................................................................... 6

List of Figures.............................................................................................................................. 12

List of Tables ............................................................................................................................... 14

List of Acronyms ....................................................................................................................... 15

## Chapter 1 Introduction ........................................................................................................... 17
  1.1 The Clinical Problem ........................................................................................................... 17
  1.2 Technical Approach ............................................................................................................ 18
  1.3 Thesis Overview ................................................................................................................ 19
  1.4 Key Contributions ............................................................................................................. 21
  1.5 Software ........................................................................................................................... 22
  1.6 Ethics ................................................................................................................................. 23

## Chapter 2 Clinical Background ............................................................................................ 24
  2.1 Introduction ....................................................................................................................... 24
  2.2 Anatomy of the breast ....................................................................................................... 25
  2.3 Breast Cancer ................................................................................................................. 27
    2.3.1 Invasive Cancers ......................................................................................................... 27
    2.3.2 Carcinoma in Situ ....................................................................................................... 28
  2.4 Diagnosing Breast Cancer ............................................................................................... 28
  2.5 Imaging Breast Cancer ................................................................................................... 29
    2.5.1 X-Ray Mammography ............................................................................................. 29
    2.5.2 Ultrasound ............................................................................................................... 29
    2.5.3 Magnetic Resonance Imaging .................................................................................. 30
  2.6 Breast Surgery .................................................................................................................. 32
    2.6.1 Mastectomy .............................................................................................................. 32
    2.6.2 Breast conserving surgery ...................................................................................... 32
    2.6.3 Mastectomy vs. Breast conserving surgery ............................................................ 34
  2.7 Margins ............................................................................................................................. 35
  2.8 Pathology Correlation ..................................................................................................... 36
  2.9 Chapter Conclusion ......................................................................................................... 37

## Chapter 3 Biomechanical Modelling of the Breast ................................................................. 39
  3.1 Introduction ..................................................................................................................... 39
  3.2 Experimental Determination of Material Properties ....................................................... 40
    3.2.1 In-vivo Experiments to Determine Material Properties of breast tissue ............... 40
3.2.2 Ex-vivo Experiments to Determine Material Properties of breast tissue ........................................ 41
3.2.3 Limitations of Available Data about Material Properties of Breast Tissue .............................. 44
3.2.4 Material Properties of Skin ........................................................................................................ 45

3.3 Biomechanical Modelling and the Finite Element Method ................................................................. 45
3.3.1 Introduction ................................................................................................................................ 45
3.3.2 Deformation Modelling Using the Finite element method ............................................................ 47

3.4 Meshes ................................................................................................................................................ 47
3.4.1 Meshing Considerations ................................................................................................................. 47
3.4.2 Meshes of the Breast for Finite Element Modelling ........................................................................ 49

3.5 Boundary Conditions and Deformation Scenarios ............................................................................. 51
3.5.1 Displacement-based boundary conditions ...................................................................................... 52
3.5.2 Including the Effect of Gravity ....................................................................................................... 53

3.6 Incorporating Material Properties in the Biomechanical Model ......................................................... 56
3.6.1 Adipose and Fibroglandular tissue .............................................................................................. 56
3.6.2 Skin ............................................................................................................................................... 59
3.6.3 Tumour ............................................................................................................................................ 59

3.7 Chapter Conclusion ................................................................................................................................. 60

Chapter 4 Image Registration and Image-Guided Surgery ......................................................................... 61
4.1 Introduction ........................................................................................................................................ 61
4.2 Image Registration .............................................................................................................................. 62
4.3 Cost Functions ..................................................................................................................................... 62
4.3.1 Point-Based Cost Functions ........................................................................................................ 62
4.3.2 Surface-Based Cost Functions ..................................................................................................... 63
4.3.3 Voxel-Based Cost Functions ......................................................................................................... 64
4.4 Transformation Model .......................................................................................................................... 66
4.5 Image-Guided Surgery ........................................................................................................................ 73
4.6 Biomechanical Modelling for Image-Guided Surgery ........................................................................ 75
4.7 Intraoperative Measurements ........................................................................................................... 77
4.7.1 Measurement of surface displacements ...................................................................................... 78
4.7.2 Measurement of sub-surface displacements .............................................................................. 79
4.8 Application of Biomechanical Models for Image-Guided Surgery .................................................... 80
4.8.1 Neurosurgery ............................................................................................................................... 80
4.8.2 Liver ............................................................................................................................................... 83
4.9 Visualisation ......................................................................................................................................... 85
4.9.1 Monitor-based Display ................................................................................................................ 85
4.9.2 Augmented Reality ..................................................................................................................... 86
4.9.3 Robotics ......................................................................................................................................... 87
4.10 Image-Guided Breast Surgery .......................................................................................................... 88
4.11 Chapter Conclusion ............................................................................................................................. 90

Chapter 5 Building a Biomechanical Model of the Breast ......................................................................... 91
5.1 Introduction ........................................................................................................................................ 91
6.6.1 Introduction ...................................................................................................................... 121
6.6.2 Linear boundary condition scheme .................................................................................. 121
6.6.3 Quadratic boundary condition scheme ............................................................................. 121
6.6.4 Applying the boundary condition.................................................................................... 123
6.7 Modelling Using Revised Boundary Conditions and Material Properties ...................... 124
6.7.1 Introduction ...................................................................................................................... 124
6.7.2 Method ............................................................................................................................. 124
6.7.3 Results .............................................................................................................................. 125
6.7.4 Discussion ........................................................................................................................ 126
6.8 Chapter Conclusion............................................................................................................. 129

Chapter 7 Further Investigation of Material Properties.......................................................... 131
7.1 Introduction ......................................................................................................................... 131
7.2 Comparison of the Reference State and the Submerged State ........................................... 132
7.3 Introduction ......................................................................................................................... 132
7.4 Method .............................................................................................................................. 132
7.4.1 Results ............................................................................................................................ 132
7.4.2 Conclusion ....................................................................................................................... 133
7.5 Imaging the Submerged Breast ............................................................................................. 134
7.5.1 Introduction ...................................................................................................................... 134
7.5.2 Method ............................................................................................................................. 134
7.5.3 Results .............................................................................................................................. 134
7.5.4 Discussion and Conclusion ............................................................................................. 135
7.6 Recovering the Deformation Between Submerged and Prone ............................................ 136
7.6.1 Introduction ...................................................................................................................... 136
7.6.2 Method ............................................................................................................................. 136
7.6.3 Results .............................................................................................................................. 137
7.6.4 Discussion ....................................................................................................................... 137
7.7 Modelling the Deformation Between Submerged and Prone ............................................. 140
7.7.1 Introduction ...................................................................................................................... 140
7.7.2 Method ............................................................................................................................. 140
7.7.3 Results .............................................................................................................................. 142
7.7.4 Discussion and Conclusion ............................................................................................. 145
7.8 The influence of skin on the model ..................................................................................... 147
7.8.1 Introduction ...................................................................................................................... 147
7.8.2 Method ............................................................................................................................. 147
7.8.3 Results .............................................................................................................................. 147
7.8.4 Conclusion ....................................................................................................................... 148
7.9 Chapter Conclusion............................................................................................................. 148

Chapter 8 Registration of Prone and Supine MR Images of the Breast................................. 150
8.1 Introduction ......................................................................................................................... 150
8.2 Intensity-Based Registration ............................................................................................... 151
8.2.1 Introduction ...................................................................................................................... 151
8.2.2 Method .............................................................................................................................. 152
8.2.3 Results .............................................................................................................................. 154
8.2.4 Discussion ......................................................................................................................... 155
8.3 Finite Element Model-Based Registration .......................................................................... 157
  8.3.1 Introduction ...................................................................................................................... 157
  8.3.2 Method .............................................................................................................................. 157
  8.3.3 Results .............................................................................................................................. 161
  8.3.4 Discussion ......................................................................................................................... 164
8.4 Hybrid FEM-Fluid Registration ............................................................................................ 164
  8.4.1 Introduction ...................................................................................................................... 164
  8.4.2 Method .............................................................................................................................. 164
  8.4.3 Results .............................................................................................................................. 166
  8.4.4 Discussion ......................................................................................................................... 170
8.5 Chapter Conclusion ............................................................................................................. 171

Chapter 9  Image-Guided Breast Surgery .................................................................................. 173
  9.1 Introduction ......................................................................................................................... 173
  9.2 Intraoperative Imaging ....................................................................................................... 174
    9.2.1 Introduction ..................................................................................................................... 174
    9.2.2 Method and Assessment ............................................................................................... 175
    9.2.3 Results ............................................................................................................................ 178
    9.2.4 Conclusion ....................................................................................................................... 179
  9.3 Intraoperative Registration ................................................................................................. 179
    9.3.1 Introduction ..................................................................................................................... 179
    9.3.2 Method and Assessment ............................................................................................... 180
    9.3.3 Results ............................................................................................................................ 181
    9.3.4 Conclusion ....................................................................................................................... 181
  9.4 Intraoperative Visualisation ............................................................................................... 182
    9.4.1 Introduction ..................................................................................................................... 182
    9.4.2 Method ............................................................................................................................ 183
  9.5 Initial Clinical Experience ................................................................................................... 185
    9.5.1 Introduction ..................................................................................................................... 185
    9.5.2 Experience ....................................................................................................................... 185
    9.5.3 Validation and Surgeon’s Feedback ............................................................................... 189
    9.5.4 Conclusion ....................................................................................................................... 192
  9.6 Chapter Conclusion ............................................................................................................. 193

Chapter 10  Feasibility Study into Registration of Breast Pathology ........................................ 195
  10.1 Introduction ...................................................................................................................... 195
  10.2 Aligning Gross Histology Specimens with MR images .................................................... 196
    10.2.1 Introduction .................................................................................................................. 196
    10.2.2 Method ......................................................................................................................... 197
    10.2.3 Results and Discussion ............................................................................................... 200
## List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Anatomy of the breast</td>
<td>25</td>
</tr>
<tr>
<td>2.2</td>
<td>Muscles of the chest</td>
<td>26</td>
</tr>
<tr>
<td>2.3</td>
<td>DCE MR Uptake curves</td>
<td>31</td>
</tr>
<tr>
<td>3.1</td>
<td>Plot of ex-vivo measurements of adipose and fibroglandular tissue stiffness</td>
<td>43</td>
</tr>
<tr>
<td>4.1</td>
<td>Steps required to use biomechanical models for image-guided surgery</td>
<td>76</td>
</tr>
<tr>
<td>5.1</td>
<td>MR Visible Fiducial Markers</td>
<td>93</td>
</tr>
<tr>
<td>5.2</td>
<td>Breast Coil</td>
<td>94</td>
</tr>
<tr>
<td>5.3</td>
<td>Example slices through MR volumes of breast</td>
<td>95</td>
</tr>
<tr>
<td>5.4</td>
<td>Element shapes</td>
<td>97</td>
</tr>
<tr>
<td>5.5</td>
<td>Hemisphere Phantom</td>
<td>99</td>
</tr>
<tr>
<td>5.6</td>
<td>Subject-specific mesh</td>
<td>102</td>
</tr>
<tr>
<td>6.1</td>
<td>Flowchart showing how the reference state is computed</td>
<td>107</td>
</tr>
<tr>
<td>6.2</td>
<td>Recovering the reference state of a cube</td>
<td>108</td>
</tr>
<tr>
<td>6.3</td>
<td>Comparison of prone and supine breast shape</td>
<td>111</td>
</tr>
<tr>
<td>6.4</td>
<td>Orthogonal slices through MR image of the breast</td>
<td>112</td>
</tr>
<tr>
<td>6.5</td>
<td>Sections through MR image of Subject S2 showing shift of glandular tissue</td>
<td>113</td>
</tr>
<tr>
<td>6.6</td>
<td>Mastectomy Specimen</td>
<td>114</td>
</tr>
<tr>
<td>6.7</td>
<td>Measurements of simulated deformations of Subject S1</td>
<td>118</td>
</tr>
<tr>
<td>6.8</td>
<td>Images of deformations of subject S1</td>
<td>118</td>
</tr>
<tr>
<td>6.9</td>
<td>Measurements of simulated deformations of Subject S2</td>
<td>119</td>
</tr>
<tr>
<td>6.10</td>
<td>Images of deformations of subject S2</td>
<td>119</td>
</tr>
<tr>
<td>6.11</td>
<td>Measurements of simulated deformations of Subject S3</td>
<td>120</td>
</tr>
<tr>
<td>6.12</td>
<td>Images of deformations of subject S3</td>
<td>120</td>
</tr>
<tr>
<td>6.13</td>
<td>Column deforming under self-weight</td>
<td>122</td>
</tr>
<tr>
<td>6.14</td>
<td>Illustrative row of elements undergoing a 20% linear and quadratic compression</td>
<td>123</td>
</tr>
<tr>
<td>6.15</td>
<td>Reconstructed MR images showing effect of boundary conditions</td>
<td>127</td>
</tr>
<tr>
<td>6.16</td>
<td>Plots of mean skin fiducial and internal landmark errors: Subject S1</td>
<td>128</td>
</tr>
<tr>
<td>6.17</td>
<td>Plots of mean skin fiducial and internal landmark errors: Subject S2</td>
<td>128</td>
</tr>
<tr>
<td>6.18</td>
<td>Plots of mean skin fiducial and internal landmark errors: Subject S3</td>
<td>128</td>
</tr>
<tr>
<td>7.1</td>
<td>Simulation of the effect of submerging a cubic phantom in water</td>
<td>133</td>
</tr>
<tr>
<td>7.2</td>
<td>MR images of breast in supine, prone and submerged positions</td>
<td>135</td>
</tr>
<tr>
<td>7.3</td>
<td>Registration of images of the left breast</td>
<td>138</td>
</tr>
<tr>
<td>7.4</td>
<td>Registration of images of the right breast</td>
<td>139</td>
</tr>
<tr>
<td>7.5</td>
<td>Finite element mesh of submerged breast</td>
<td>141</td>
</tr>
<tr>
<td>7.6</td>
<td>Contour plots showing variation of error with respect to assumed material properties</td>
<td>143</td>
</tr>
<tr>
<td>7.7</td>
<td>Model of left breast with material properties which minimise the mean error</td>
<td>144</td>
</tr>
<tr>
<td>7.8</td>
<td>Model of right breast with material properties which minimise the mean error</td>
<td>144</td>
</tr>
</tbody>
</table>
Figure 7.9 Variation of mean error on nodes for models including skin .................................................. 148
Figure 8.1 Outline of Chapter 8 ........................................................................................................... 151
Figure 8.2 Example slices through supine images and prone images after intensity-based registration 156
Figure 8.3 Applying displacement loads on the surface ....................................................................... 159
Figure 8.4 Slices through supine images and prone images created under various alignment scenarios 163
Figure 8.5 Error on FEM-deformed landmarks before and after intensity-based registration .......... 168
Figure 8.6 Images obtained using hybrid registration ........................................................................... 169
Figure 8.7 Mean registrant errors for Subjects S1-3 measured in the prone space ............................... 172
Figure 9.1 Flowchart showing the preoperative and intraoperative steps ............................................ 174
Figure 9.2 Stereo Camera ..................................................................................................................... 176
Figure 9.3 Stereo camera images ......................................................................................................... 176
Figure 9.4 Stereo Camera in Operating Theatre .................................................................................. 177
Figure 9.5 Pointer with three retroreflective spheres ........................................................................... 184
Figure 9.6 Aligning the viewpoint ....................................................................................................... 185
Figure 9.7 MR images of Subject 4 ..................................................................................................... 187
Figure 9.8 Image guidance system being used in the operating theatre ............................................ 188
Figure 9.9 Comparison of lesion outlines marked by surgeon and computed by system.................... 189
Figure 9.10 Tracked ultrasound probe ................................................................................................ 191
Figure 9.11 Model-predicted lesion location overlaid on ultrasound image of lesion ....................... 191
Figure 10.1 Deformation between supine MR imaging and histology .................................................. 196
Figure 10.2 Breast in surgery and in the histology lab ....................................................................... 197
Figure 10.3 Sections through mastectomy specimen ........................................................................... 199
Figure 10.4 Aligned histology and MR image sections ................................................................. 201
Figure 10.5 Alignment of histology slides with gross mastectomy specimen (wide view) ............... 205
Figure 10.6 Alignment of histology slides with gross mastectomy specimen (magnified view) ....... 206
Figure C.1 Subject S1: Images showing effect of boundary conditions ........................................... 235
Figure C.2 Subject S2: Images showing effect of boundary conditions ............................................ 237
Figure C.3 Subject S3: Images showing effect of boundary conditions ............................................ 239
List of Tables

Table 3.1 Ex-vivo measurements of the Young's Modulus $E$ at a range of pre-strains ............................. 42
Table 3.2 Values assumed for Young’s Modulus $E$ and neo-Hookean parameter $\alpha$ in the literature ...... 57
Table 5.1 Subject Details. .......................................................................................................................... 92
Table 5.2 Volume of glandular tissue ........................................................................................................ 95
Table 5.3 Badly shaped elements ................................................................................................ ............... 99
Table 6.1 Recovery of reference state ...................................................................................................... 109
Table 6.2 Literature Mooney-Rivlin parameters for breast tissue ............................................................ 116
Table 7.1 Comparison of submerged model with reference state model................................................ 133
Table 8.1 Accuracy of rigid, fluid and FFD registration methods technique ..................................... 155
Table 8.2 Accuracy of FEM registration measured in the prone space ................................................. 162
Table 8.3 Accuracy of FEM registration measured in the supine space ................................................. 162
Table 8.4 Influence of fluid registration resolution levels on hybrid registration accuracy .......... 166
Table 8.5 Influence of different alignment approaches on hybrid registration accuracy ..................... 167
Table 8.6 Influence of different model alignment approaches on the hybrid registration technique .... 167
Table 9.1 Accuracy of Stereo Camera ............................................................................................ .......... 179
Table 9.2 Comparison of rigid, infinitesimal strain model and finite strain intraoperative models ...... 181
Table C.1 Subject S1: Results for boundary conditions which simulate a linear compression .......... 234
Table C.2 Subject S1: Results for boundary conditions which simulate a quadratic compression ... 234
Table C.3 Subject S2: Results for boundary conditions which simulate a linear compression .......... 236
Table C.4 Subject S2: Results for boundary conditions which simulate a quadratic compression ... 236
Table C.5 Subject S3: Results for boundary conditions which simulate a linear compression .......... 238
Table C.6 Subject S3: Results for boundary conditions which simulate a quadratic compression .... 238
# List of Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1D</td>
<td>1-Dimensional</td>
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<tr>
<td>2D</td>
<td>2-Dimensional</td>
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<tr>
<td>3D</td>
<td>3-Dimensional</td>
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<tr>
<td>AR</td>
<td>Augmented Reality</td>
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<tr>
<td>BEM</td>
<td>Boundary Element Method</td>
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<tr>
<td>CC</td>
<td>Normalised Cross-Correlation</td>
</tr>
<tr>
<td>CCD</td>
<td>Charge-Coupled Device</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DCE</td>
<td>Dynamic Contrast-Enhanced</td>
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<td>DCIS</td>
<td>Ductal Carcinoma In Situ</td>
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<tr>
<td>FEM</td>
<td>Finite Element Method or Finite Element Model</td>
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<td>FFD</td>
<td>Free-form Deformation</td>
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<td>FSA</td>
<td>Frozen Section Analysis</td>
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<td>GPU</td>
<td>Graphics Processor Unit</td>
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<tr>
<td>ICP</td>
<td>Iterative Closest Point</td>
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<tr>
<td>IDC</td>
<td>Invasive Ductal Carcinoma</td>
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<tr>
<td>ILC</td>
<td>Invasive Lobular Carcinoma</td>
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<tr>
<td>IRED</td>
<td>Infrared Emitting Diodes</td>
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<tr>
<td>LCIS</td>
<td>Lobular Carcinoma In Situ</td>
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<tr>
<td>MNE</td>
<td>Mean Normalised Error</td>
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<td>MR</td>
<td>Magnetic Resonance</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>NHS</td>
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<td>NHSBSP</td>
<td>National Health Service Breast Screening Programme</td>
</tr>
<tr>
<td>NMI</td>
<td>Normalised Mutual Information</td>
</tr>
<tr>
<td>NST</td>
<td>No Special Type</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>RMS</td>
<td>Root Mean Square</td>
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<tr>
<td>SAD</td>
<td>Sum of Absolute Differences</td>
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<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
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<tr>
<td>SSD</td>
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</tr>
<tr>
<td>TE</td>
<td>Echo Time</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition Time</td>
</tr>
<tr>
<td>TRE</td>
<td>Target Registration Error</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>XFEM</td>
<td>Extended Finite Element Method</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction

1.1 The Clinical Problem

One in nine women in the UK develops breast cancer at some point in her life. The treatment for breast cancer is surgery combined with, in some cases, adjuvant therapies. Twenty five years ago the standard surgical procedure was mastectomy but today a much less invasive option is available for most women: breast conserving surgery. In a breast conserving operation only the lesion and a small margin of healthy tissue surrounding it are removed.

To be confident that the breast conserving surgery is as effective as a mastectomy, it is essential to remove the entire lesion. This is checked by microscopically inspecting the margins of the excised tissue for cancer cells. Unfortunately, cancer cells are often found and that patient must undergo a further operation to excise more tissue. Failing to completely excise the cancer in a single attempt does not seem to increase the risk of recurrence. It does however increase risks associated with wound infection and general anaesthesia, have a negative impact on cosmetic appearance, increase the cost to the healthcare provider and increase the stress on a patient at an already difficult time.

The absence of distinct tissue boundaries within the breast makes achieving the complete excision of diffuse cancers and of small lesions a difficult task for the surgeon. Although the majority of cancers can be located by palpation, cancers such as ductal carcinoma in situ (DCIS) which are no stiffer than the surrounding tissue cannot be felt. Furthermore, the palpable extents of a lesion do not necessarily correlate well with histology findings. For impalpable lesions the
surgeon relies upon a guidewire inserted preoperatively under ultrasound guidance and upon X-ray mammograms to help him or her predict the extents of the cancer. Relating the single point identified by a guidewire or the 2D projection images of the compressed breast provided by X-ray mammograms to the 3D extents of a lesion during surgery is not straightforward.

Dynamic contrast-enhanced (DCE) magnetic resonance (MR) images can provide additional 3D information about the location of a cancer. In image-guided surgery, preoperatively acquired images are used by a surgeon to navigate to a target during the procedure. Image-guided surgery techniques in which organs are treated as rigid bodies are routinely used in neurosurgery and orthopaedic surgery. However, the accuracy of such techniques is compromised when soft tissue deformation occurs. A large deformation of the breast will occur between acquiring DCE MR images with the patient in a prone\(^1\) position (which is necessary to reduce breathing motion between images acquired at different timepoints) and performing the surgery with the patient positioned supine\(^2\). This currently limits the suitability of these images for guiding surgery. Furthermore it has not yet been demonstrated that the extents of the enhancement visible in DCE MR images spatially correspond to the extents seen in the histology (which can be considered to provide the ground truth).

This thesis develops techniques to account for the soft tissue deformation occurring. The primary clinical goal is to enable the routinely-acquired prone DCE MR images to be used to guide a surgeon who is performing breast-conserving surgery. It is hoped that that image-guided breast surgery could ultimately reduce the proportion of operations which must be repeated due to an incomplete initial excision.

### 1.2 Technical Approach

The core task is essentially to align a lesion delineated in a DCE MR image acquired whilst the patient is positioned prone with the patient lying supine on the operating table. The magnitude of the deformation which occurs makes this a challenging image registration task.

Although breathing motion means it is not currently practicable to acquire DCE MR images in the supine position, it is feasible to acquire images without contrast enhancement in this position. Since the supine position provides a much closer approximation to the surgical position than the prone position, the registration task can be split into two simpler tasks: preoperatively locating the cancer in the supine MR image and then intraoperatively locating the cancer within the patient on the operating table.

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\(^1\) Prone: Lying on front.

\(^2\) Supine: Lying on back.
For the preoperative task image intensity information is available in both the prone and supine
positions. However, the deformation of the breast between these positions is too large to be
captured by standard intensity-based image registration algorithms. I have therefore proposed a
hybrid registration approach. The gravity-induced deformation between supine and prone is first
simulated using a biomechanical model, and the correspondence are then refined using an
intensity-based algorithm.

In the operating theatre, the surface of the patient’s breast is acquired using a stereo camera
system. The biomechanical model which was used for the preoperative registration is now
deformed so that it aligns with the surface of the patient’s breast. This allows the location of the
lesion identified in the prone MR image to be located in the patient on the operating table.

If appropriate boundary conditions are applied on the biomechanical model, it should provide a
mechanism with which to match the prone DCE MR images with mastectomy specimens in the
histology laboratory. This would provide a means to establish whether the spatial extents of
enhancement seen in DCE MR images correspond to the extents determined by histological
analysis. An initial study into the feasibility of this approach is reported in this thesis.

1.3 Thesis Overview

Chapters 2-4: Background and Literature Review

Chapter 2 describes the clinical background to this thesis, including current practice in the
imaging and surgical treatment of breast cancer.

Chapter 3 reviews biomechanical modelling of the breast. Experiments reported in the literature
which have been performed to determine the material properties of the breast are reviewed.
Previous use of biomechanical models to simulate deformations of the breast is described and
discussed.

Chapter 4 provides a review of image registration techniques and image-guided surgery. The
first part of the chapter describes intensity-based registration suitable for aligning pairs of
volumetric images, such as MR images. Since such images can usually only be acquired
preoperatively, I discuss imaging suitable for intraoperative use. Many authors have attempted
to update the preoperative image information to match the surgical scene by building a
biomechanical model from the preoperative data and deforming it using boundary conditions
determined from the intraoperative data. As I have adopted a similar approach, albeit for a
larger deformation than these authors have generally considered, their experiences are reported.
Finally common approaches to the task of presenting this information to the surgeon are
described.
Chapters 5-10: Experimental Work

Chapters 5-10 describe my experimental work. The key goal of this thesis has been to design, build and test a system suitable for guiding supine surgery based on prone DCE MR imaging. The development and testing of this system can be followed through Chapters 5, 6, 8 and 9.

Chapter 5 deals with the construction of a biomechanical model suitable for modelling the deformation of the breast between the supine and prone postures. Soft biological tissue is generally assumed to be incompressible, and I investigate here whether this is an appropriate assumption for breast tissue. The behaviour of tetrahedral and hexahedral elements during large, gravity-induced deformations is investigated. Following this experiment a method to construct a subject-specific hexahedral mesh of the breast from a supine MR image is described.

In Chapter 6 the deformation of the breast between prone and supine postures is simulated using the model constructed in Chapter 5. It is first demonstrated that the reference state of an object (the state of an object without any loads acting on it) can be recovered effectively using commercially available finite element code. This is achieved by iteratively correcting an estimate of the reference state until simulating the influence of gravity acting on the reference state deforms it to match the gravity-loaded state actually observed. The influences of both boundary conditions and material properties on the model are then assessed.

Using the biomechanical model to simulate the deformation between supine and prone postures improves the correspondence between the images acquired in these postures, but the error is still too large to be clinically useful. Chapter 8 develops a hybrid registration technique in which the biomechanical model is used to obtain an initial estimate of the deformation occurring, and then an intensity-based registration algorithm is used to improve the alignment.

The registration technology developed in Chapter 8 enables the location of a cancer, originally delineated in the prone DCE MR images, to be identified in a biomechanical model constructed from supine MR images. In Chapter 9 the design of a system which enables the intraoperative location of the cancer to be determined is described. This system is based upon deforming the model so that the model surface aligns with the surface of the breast acquired using a stereo camera whilst the patient is on the operating table. The anticipated errors in the system are assessed. An initial clinical experience with the system is then described, including a validation of the computed lesion location against intraoperative tracked ultrasound images.

The biomechanical model of the breast is used for two further purposes which are closely related to the main theme of this thesis. In Chapter 7 I use the model to investigate the material properties of the breast in tension. This is done by demonstrating that the breast submerged in water is a good surrogate for the breast in the absence of gravity, and then comparing model
simulations between submerged and prone with the actual deformations occurring. The image-guided surgery system I have developed presupposes that DCE MR imaging is able to accurately determine the actual extents of cancer. In Chapter 10 I perform a feasibility study which investigates whether, if suitable boundary conditions applied to the biomechanical model, it may be possible to establish correspondence between DCE MR imaging and histology.

Chapter 11: Conclusion and Future Work

Chapter 11 summarises the experimental work reported in this thesis and the conclusions drawn. I then suggest interesting directions for future work.

1.4 Key Contributions

The key contributions of this thesis are:

- Demonstrating that the stress-free ‘reference’ state of a gravity-loaded object can be efficiently determined using a series of simulations run in commercially available finite element analysis software (Chapter 6).

- Assessing the ability of a biomechanical model to simulate the deformation of the breast between prone and supine. The assessment has been more thorough and performed for a greater number of subjects than has been reported by others (Chapter 6).

- Demonstrating that incorporating boundary conditions which reflect the motion of the breast around the chest wall greatly improves the accuracy of the model compared with the fixed boundary conditions which have previously been assumed (Chapter 6).

- Proposing and assessing a hybrid registration technique to register MR images of the breast acquired in the supine and prone postures (Chapter 8).

- Developing the first image-guided breast surgery system based on prone DCE MR images and an initial clinical demonstration of this system (Chapter 9).

- Proposing a framework for determining the material stiffness of breast tissue under tensions which are of the magnitude which gravity induces (Chapter 7).

- Proposing a framework for establishing the correspondence between DCE MR imaging and histology (Chapter 10).

A list of publications which I co-authored during my PhD is provided in Appendix A.
1.5 Software

The image segmentations described in this thesis were performed either using the Analyze\(^1\) software package or using scripts which I wrote in Matlab\(^2\). The ‘orthogonal viewers’ used to visualise 3D MR datasets were written by Daniel Rueckert and Julia Schnabel\(^3\), by Thomas Hartkens and by David Cash. 2D images were manipulated and segmented using GIMP\(^4\). Inhomogeneity correction of MR volumes was performed using the MIPAV\(^5\) software.

Two intensity-based image-registration algorithms were used in this thesis. The B-spline registration software was written by Daniel Rueckert and Julia Schnabel. The fluid registration software was written by Bill Crum.

All finite element modelling was done using Release 11 of the ANSYS\(^6\) finite element analysis suite. Geometric phantoms (i.e. cubes and hemispheres) were meshed using ANSYS’s built-in meshing functionality whilst all volunteer and patient-specific meshes were created, as described in the text, using the Matlab scripts which I wrote. Boundary conditions to be applied to the models were determined using Matlab scripts, also written by me, which outputted a series of commands in ANSYS’s built-in scripting language.

The intraoperative components of the image-guided breast surgery system were written by myself in C++, making extensive use of Visualisation Toolkit\(^7\) and compiled Matlab. The (entirely separate) image-guided surgery software which was used to collect tracked ultrasound images for validating the image-guidance system was written in C++ by Dean Barratt and myself.

Surface-fitting was performed using the ‘Gridfit’ Matlab scripts written by John D’Errico\(^8\). \(\text{k}\)-tree searches to identify closest points were performed using code by Guy Shechter\(^9\). Rigid, point-based registration was performed using an implementation of the algorithm of Arun et al. (1987) by Dean Barratt.

All the other algorithms used in this thesis were implemented by myself in Matlab.

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1 http://www.analyzedirect.com/Analyze/
2 http://www.mathworks.com/products/matlab/
3 http://www.doc.ic.ac.uk/~dr/software/
4 http://www.gimp.org
5 http://mipav.cit.nih.gov/
6 http://www.ansys.com/
7 http://www.vtk.org
8 http://www.mathworks.com/matlabcentral/fileexchange/8998
9 http://www.mathworks.com/matlabcentral/fileexchange/4586
1.6 Ethics

Ethical approval for all studies involving patients or volunteers was obtained from the Local Research Ethics Committee at Guy’s Hospital, London (approval reference numbers 00/11/09 and 03/05/08).
Chapter 2

Clinical Background

2.1 Introduction

This chapter provides the clinical background to support this thesis. It is not intended to provide a critical review of current knowledge and practice; rather it is intended to provide an introduction to the diagnosis and surgical treatment of breast cancer for the non-clinical reader. It starts with a description of normal breast anatomy, and of the types of primary breast cancer which can develop. The diagnostic process is briefly summarised with particular attention being paid to the imaging of breast cancer, since it is these images which will provide the basis for the work described in later chapters. Almost inevitably breast cancer will require a surgical intervention, and current surgical practice in the treatment of breast cancer is then outlined.

Breast conserving surgery operations, which aim to remove just the cancer and a surrounding margin of healthy tissues, often require a repeat operation because cancer cells are found, on histological examination, at the edge of the excised specimen. The significance of involved margins is briefly reviewed since it motivates the need for a surgical technique to achieve clear margins at the first attempt. The ultimate goal of the work described in this thesis is to develop such a technique. In pursuing this goal, this work relies upon the ability of MR imaging to accurately reflect the physical extents of a breast cancer. Therefore the final section of this chapter reviews the literature available on the spatial correspondence between breast cancer observed in MR images and histology. This motivates the work described in the final experimental chapter of this thesis.
2.2 Anatomy of the breast

The breast develops within layers of the superficial fascia of the anterior chest wall. Breast tissue extends from just below the level of the collar bone to around the level of the sixth or seventh rib and from the breast bone to the underarm (Figure 2.1). It is covered by skin which is usually thinner than that which covers adjacent regions.

Each breast contains a single mammary gland formed from a collection of 15 to 20 milk-producing glands which originally develop from sweat glands. The glands are lobes shaped like irregular pyramids, and in the adult female each lobe consists of several lobules. A lobule is composed of ductules and alveoli which share a common terminal duct: collectively this is known as a terminal duct-lobular unit. Each gland is drained by a lactiferous duct. As they approach the nipple these lactiferous ducts dilate to form ampulla which combine to form the six to eight ducts (Egan 1988) which emerge at the nipple. The ducts and lobules are enveloped in a stroma formed of both fibrous and adipose tissue: collectively this is known as fibroglandular tissue. This fibroglandular tissue is predominately in the upper outer quadrant of the breast (Fischer 2006). Surrounding the fibroglandular tissue, and forming the remainder of the breast tissue, is adipose tissue.

Throughout the body fibrous strands (known as retinaculum cutis or skin ligaments) connect the base of the dermis to the superficial fibres of the underlying deep fascia (Nash et al. 2004). Within the breast these strands are called Cooper’s suspensory ligaments. They are present throughout the adipose tissue of the breast, and provide support to the mammary gland.
Posterior to the breast, between the deep and superficial pectoral fascia, there is a region of areolar connective tissue known as the retromammary space. This permits a limited movement of the breast over the deep pectoral fascia. Beneath this fascia lie the muscles of the chest. The largest and most superficial of these is pectoralis major (Figure 2.2). It is a thick triangular-shaped muscle whose proximal attachment points are the medial half of the clavicle, the sternum, the costal cartilages of the upper ribs and the aponeurosis of the external oblique muscle and whose distal connection is to the humerus. It flexes, adducts and medially rotates the arm, as well as assisting inspiration. The posterior face of the breast lies upon the pectoralis major, serratus anterior, and external oblique muscles as well as the anterior rectus sheath. Whilst breast tissue can be attached through the areolar connective tissue to any exposed face of these muscles, the bond to the pectoralis major is most robust and most likely to be present. The axilla of the breast is anatomically associated with the pectoralis major, pectoralis minor subscapularis, teres major and latissimus dorsi muscles.

The structure of the breast will vary between patients (in particular with regard to the volume of adipose tissue), and it will also change significantly over time within the same patient. After the menopause breast can be expected to have an increased proportion of adipose tissue, and Cooper’s ligaments appear to stretch with age, providing less support. The material properties (discussed in Section 3.2) of a given breast are not fixed, but will vary due to hormonal influence through the menstrual cycle (Graham et al. 1995).

Interstitial fluid is drained from the breast through lymphatic vessels. This clear liquid is then filtered through lymph nodes, which are small, bean-shaped collections of immune system cells, which tend to swell in the presence of infection or cancer. 75% of the lymph from the breast
passes through the lymph nodes located in the axilla (Whiten 2006), so these axillary lymph nodes are often the first site of breast cancer metastasis.

Two-thirds of the blood supply to the breast comes from the internal mammary artery and its branches (DeCherney and Nathan 2003). These primarily supply the central and medial regions of the breast superior to the nipple, so the blood supply to the upper half of the breast is much greater than that to the lower half. The remainder of the blood supply is from the lateral branches of the intercostal arteries and the axillary artery. The veins which return blood to the heart follow similar paths to those of the arteries, although the axillary vein follows a less regular path than its arterial counterpart, which makes surgery in this region more complicated.

2.3 Breast Cancer

Breast cancer is the most common cancer in the UK: in 2005 there were over 45000 new cases diagnosed\(^1\). It predominantly affects women: less than 1% of these cases occurred in men. Over her lifetime a woman has a 1 in 9 chance of being diagnosed with breast cancer. A woman diagnosed with breast cancer today has an estimated 80% chance of surviving for 5 years and a 64% chance of surviving for 20 years (Office for National Statistics 2005). These survival rates have continually improved over the past 20 years. This is likely to be due not only to improved treatments but also to the earlier detection of cancer, helped by initiatives such as the NHS Breast Screening Programme (NHSBSP).

Breast cancers usually develop from the epithelial cells which line the terminal duct lobular unit. They are classified as non-invasive (or in situ) if they remain within the basement membrane of the ducts and lobules, or invasive if they breach this membrane and spread into the surrounding tissue (Dixon 2006). Although breast cancers which have not developed in this way do exist (for example, Phyllodes tumour which develops in the stroma and is usually benign) they are rare.

2.3.1 Invasive Cancers

Invasive cancers are categorised into either invasive ductal carcinoma (IDC), which represents 85% of invasive breast cancer, or invasive lobular carcinoma (ILC) based on their location. Lobular carcinoma is more frequently diffuse, multifocal or bilateral. Prognostic information about some cancers can be obtained by further classifying the cancers, based on growth patterns and cellular morphology, into special types: tubular, cribriform, medullary, mucoid, papillary or

classic lobular. Cancers which do not fall into one of these classifications are said to be of ‘no special type’ (NST). Prognostic information about these can be gained by scoring the differentiation of the tumour cells: less differentiated cells do not have the structure or function of normal cells and divide more frequently. These scores are grouped into three grades, with grade III cancers having the worst prognosis.

The presence of cancer cells in the vascular or lymphatic system increases the chance that they have travelled to regions beyond the breast. Consequently it is associated with an increased risk of both local and systemic recurrence.

### 2.3.2 Carcinoma in Situ

Although carcinoma in situ is not, of itself, malignant it has a 40% chance of becoming an invasive carcinoma over a 30 year period. It is therefore treated as an early form of cancer and excised. Ductal carcinoma in situ (DCIS) is the more commonly detected form, making up 4% of symptomatic cancers and 20% of the cancers detected during a screening program. It is usually, though not always, impalpable and may be associated with nipple discharge or Paget’s disease. The presence of DCIS may be indicated on X-ray mammography by microcalcifications. Widespread DCIS requires a mastectomy, but there is no consensus on the appropriate treatment for small foci of DCIS.

Lobular carcinoma in situ (LCIS) is usually an incidental finding on breast biopsy, since there are no characteristic clinical or mammographic features. It is associated with an increased risk of breast cancer, both within the same breast and in the contra-lateral breast. Possible treatment regimes include increased surveillance, chemoprevention and bilateral prophylactic mastectomy.

### 2.4 Diagnosing Breast Cancer

The standard of care in the diagnosis of breast cancer, both for cancers detected by a screening programme and symptomatic presentations, is triple assessment: the combination of clinical examination, biopsy and imaging. During clinical examination, the breasts are palpated to detect regions of abnormality such as a discrete mass or areas of asymmetric nodularity. The biopsy is most commonly performed as a core biopsy using a 14 gauge cutting needle, which can provide a definite histological diagnosis with a very low false positive rate.
2.5 Imaging Breast Cancer

2.5.1 X-Ray Mammography

X-ray mammography can be used to identify parenchymal distortions, radiographic masses and microcalcifications within the breast. Not all cancers are visible on X-ray: invasive lobular carcinomas often cause little or no mammographic abnormality (Hilleren et al. 1991; Krecke and Gisvold 1993). To acquire X-ray mammographic images the breast is compressed between two X-ray plates. Typically at least two compression directions are used: cranio-caudal and medio-lateral oblique. Further compressions or magnified views can be used to image abnormalities in more detail. Compressing the breast spreads out the tissue so that it can all be visualised and makes small abnormalities less likely to be obscured by overlying breast tissue. Since the tissue thickness is reduced by compression a smaller X-ray dose can be used and X-ray scatter is reduced, creating a sharper image. The act of compressing the breast reduces blurring due to motion.

Even if the diagnosis of breast cancer is clinically obvious in women of any age, mammography will be performed to examine for multifocal or contra-lateral disease. Since fibroglandular tissue is relatively dense X-ray mammograms are less helpful in younger women (<35 years) since their breasts have a greater proportion of fibroglandular tissue. However X-ray mammography is still performed prior to surgery to assess extent.

Since X-ray mammograms are two dimensional projection images of a compressed breast it is extremely challenging to precisely relate features identified in these images to the patient lying on the operating table.

2.5.2 Ultrasound

B-mode ultrasound is a cheap imaging modality which does not expose a patient to ionising radiation. It is particular effective at discriminating between cysts and cancers (Cardenosa 2003): in addition to appearing as anechoic, well-circumscribed masses, the ultrasound will pass through the hypoechoic cyst without losing much energy, so ‘posterior acoustic enhancement’ may be observed where the tissue behind will appear more echogenic than other tissues at a similar depth. Since the ultrasound probe is handheld the operator can observe how an abnormality responds to pressure: typically fluid-filled cysts will deform as a load is applied. Benign lesions tend to have smoother, clearly defined boundaries whilst malignant lesions tend to have indistinct or irregular margins. The blood flow to a lesion can be imaged using Doppler ultrasound. Although malignant lesions do tend to have a greater bloodflow than benign lesions
it is not possible to categorically distinguish them on imaging alone (Dixon 2006). Furthermore, it should be noted that not all lesions are visible on ultrasound.

Although ultrasound is often used to place a guidewire in an impalpable lesion, ultrasound images acquired prior to surgery are of limited use to the surgeon intraoperatively since it is difficult to extract spatial information from these 2D images unless not only the location and orientation of the probe but also the load applied is known. Intraoperative ultrasound is not commonly used due to a skilled operator being required to acquire and interpret the images effectively; having a radiologist available in theatres is not practicable.

### 2.5.3 Magnetic Resonance Imaging

Breast cancer can be imaged using contrast-enhanced MR imaging (Warren and Coulthard 2002). For a solid tumour to grow larger than a few millimetres in size, new blood vessels must form to support oxygenation of it. The new capillaries which form have a greater permeability than the existing ones (due to the effect of cytokinins that promote vessel growth and an abnormal basement membrane) and there is also an increased interstitial pressure and an increase in the amount of extracellular space. A paramagnetic contrast agent, injected into the bloodstream, can pass easily through the blood vessels and into the interstitium, which on MR imaging appears as enhancement. By acquiring MR images both before and at intervals after the administration of contrast agent the rate, shape and extent of enhancement can be monitored, and diagnostic information about the lesion inferred.

The rate of enhancement is usually analysed by plotting a signal intensity-time curve measured over the enhancing region (Figure 2.3). These enhancement curves can be grouped into three types (Kuhl et al. 1999). All types show an increase in signal intensity immediately after the injection of contrast agent (although malignant lesions usually tend to enhance faster than benign ones), but differ markedly in the intermediate and late post contrast periods. Type I curves continue to increase following the early post-contrast period and are predominantly exhibited by benign lesions (83% benign; 9% malignant). Types II curves show a marked plateau and type III curves decrease, showing a washout of contrast agent. These two curve types are predominantly exhibited by malignant lesions (Type II: 11.5% benign; 34% malignant. Type III: 5.5% benign; 57% malignant). It is not possible, however, to categorically distinguish between malignant and benign lesions on the basis of signal intensity-time curves alone.
Time

Signal Intensity

Ia

Ib

II

III

early postcontrast phase

intermediate and late postcontrast phase

Figure 2.3 DCE MR Uptake curves. Type 1 corresponds to a straight Ia or curved Ib line; enhancement continues over the entire dynamic study. Type II is a plateau curve with a sharp bend after the initial upstroke. Type III is a washout time course. Figure redrawn from Kuhl et al. (1999)

Further information about the likely nature of a lesion can be extracted from the pattern of enhancement and its morphological features. This is most clearly seen by creating a subtraction image between one of the post-contrast images and the pre-contrast image. Malignant lesions often show initial peripheral enhancement followed by a centripetal enhancement pattern, whilst benign lesions tend to show either peripheral enhancement with no following centripetal enhancement or a central enhancement. A speculated margin and irregular shape tends to indicate a malignant lesion, whilst lesions with smooth or lobulated borders are usually benign (Nunes et al. 1997a; Nunes et al. 1997b).

Patient motion during MR imaging causes artefacts (Warren and Coulthard 2002). This motion can occur both as a single image volume is acquired, when it manifests itself as image blurring, and between image volumes in a dynamic sequence, in which case it causes the volumes to be misaligned and so prevents contrast uptake curves from being accurately measured. Diagnostic MR imaging is performed with the patient positioned prone, with her breasts hanging pendulous into a special breast coil (shown in Figure 5.2), since breathing motion artefacts are much less in this posture than they would be were the patient positioned supine. Positioning the patient prone can also help to shift the breast away from the torso, which makes it easier to determine whether the pectoralis major muscle is involved.
Although MR imaging of the breast is usually carried out with the patient lying prone, surgery is carried out with the patient in the supine position. The large deformation of the breast between prone and supine means that prone MR images are of limited use for planning and guiding surgery. Therefore there has been some research into MR imaging techniques which allow the patient to be imaged in the supine position. Techniques have recently been developed which allow images of the breast to be acquired both at breath-hold (Tozaki and Fukuda 2006) and whilst the patient is freebreathing, but with her respiration monitored by a respiratory belt (Siegler et al. 2007). Although this second method has been extended so that only data acquired whilst motion is not occurring is used (Marshall et al. 2008), neither of these approaches seem likely to account well for the displacement of the breast which can be anticipated between timepoints in the dynamic sequence, which may be several minutes apart. Therefore it will not be possible to create subtraction images, or monitor signal intensity-time curves, but instead all information must be extracted from a single image. These disadvantages might be mitigated somewhat by only using the images for surgical guidance (rather than for diagnosis) and potentially registration could be used to align images acquired at different timepoints.

2.6 Breast Surgery

In almost all cases, the appropriate treatment for breast cancer is surgery to remove the tumour (Dixon 2006). The two broad options available are to perform a mastectomy or to perform breast conserving surgery, and these two options are described and compared below.

In addition to removing the tumour the surgeon will remove one (in the case of sentinel node biopsies) or more axillary lymph nodes for pathological assessment. Presence of cancer in one of these nodes indicates that cancer may have spread to other parts of the body, so is associated with a poor prognosis. The appropriate treatment if cancer is found in the axillary nodes is radical radiotherapy of the nodes or complete axillary clearance.

2.6.1 Mastectomy

In a mastectomy the entire breast tissue is removed along with some overlying skin and, usually, the nipple and areola. In the most common procedure, a so-called modified radical mastectomy, the underlying chest wall muscles are left intact. Patients usually then receive breast reconstruction, which can be performed immediately or in a subsequent procedure.

2.6.2 Breast conserving surgery

The term ‘breast conserving surgery’ encompasses procedures ranging from a wide local excision (also known as a lumpectomy) to a partial mastectomy or quadrantectomy in which up
to a quarter of the breast is removed. The goal of this procedure is to remove the lesion and a margin of healthy tissue surrounding it, but to achieve an improved cosmetic result and to reduce surgical trauma for the patient by conserving the majority of the healthy tissue of the breast. Since wider excisions generally give poorer cosmetic results, a surgeon typically attempts to minimize both the amount of breast tissue removed and the amount of skin removed whilst ensuring the lesion is completely excised.

About 90% of detected lesions are palpable, although the palpable extents do not necessarily accurately reflect the extents determined by histology (Madjar et al. 1993). Smaller cancers are less likely to be identified by palpation: only around half of cancers smaller than 1cm were found by palpation ((Meden et al. 1995) reported in (Christiaens and de Wever 1996)). If a lesion is palpable, the surgeon will usually attempt to take out a cylinder of tissue which contains the tissue and a surrounding margin of healthy tissue through an incision made directly over the palpable mass. A macroscopic margin of 10mm of normal tissue should be allowed around the lesion (Dixon 2006). This 10mm margin provides a guide to the accuracy required of an image-guided surgery system such as the one developed in this thesis. The cylinder of tissue excised extends from the skin surface down to either the pectoral fascia or to a margin below the tumour, depending on factors such as the lesion’s location and the local standard practices.

If a lesion is not palpable, a hooked guidewire will usually be placed preoperatively by a radiologist under ultrasound guidance. X-ray mammograms are acquired to reveal the extents of the lesion relative to the clip. Based on these images, the surgeon will attempt to excise the entire lesion, along with a surgical margin of tissue. X-ray images of the specimen are usually acquired to help confirm that the lesion has been completely excised (Young et al. 2007). Targeting the excision of a lesion can be challenging after neo-adjuvant chemotherapy or hormone therapy has successfully caused the lesion to shrink. A clip can be placed at the site of the lesion prior to therapy to assist localisation (Dash et al. 1999). This clip can be located in a similar manner to an impalpable lesion.

To avoid spreading the cancer, and to aid pathological examination, the surgeon tries to avoid cutting into the cancer and to keep the specimen intact. It is marked (using either sutures or clips) so that the pathologist can roughly align the specimen to identify the faces of the specimen. All specimens are examined pathologically, and should this examination find that cancer cells are present at one or more margins a further operation is required to clear these involved margins. The significance of margins will be discussed in greater detail in Section 2.7.

Frozen section analysis (FSA) of the excised tissue may be performed, while the patient is still in theatre, to indicate whether the entire tumour has been removed or to reassess the severity of the disease. This allows margins to be shaved or a mastectomy carried out if necessary during
the same procedure. However FSA is expensive and has a lower diagnostic accuracy than permanent section analysis. Current UK guidelines are therefore that FSA should be performed only in unusual circumstances (Association of Breast Surgery at BASO 2009)

2.6.3 Mastectomy vs. Breast conserving surgery

Women diagnosed at early stages of invasive breast cancer have equivalent outcomes whether they are treated by breast conserving surgery (combined with post-operative radiation therapy) or by mastectomy (Arriagada et al. 1996; Fisher et al. 1989; Veronesi et al. 1993). 70% of the (predominantly early stage) non- and micro-invasive breast cancers detected by the UK NHS breast screening program in 2006/7 underwent breast conserving surgery (NHSBSP 2008). The majority (83%) of large invasive breast cancers (>50mm diameter) were treated with mastectomy, but only 18% of small cancers (<15mm) were treated in this way. The overall mastectomy rate for invasive cancers was 26%

Some studies have found that women whose breasts are preserved have fewer episodes of depression, anxiety, and insomnia (McArdle et al. 1990) and have an improved body image, higher satisfaction with treatment, and no more fear of recurrence than women treated with mastectomy (Curran et al. 1998), although not all studies have detected these psychological benefits (Poulsen et al. 1997). Patients who have received breast conserving surgery normally leave hospital the same day, or the following day. Patients who have had a mastectomy must usually stay in hospital for 3-5 days.

A several considerations can determine that a patient is unsuitable for breast-conserving surgery (Dixon 2006). These are predominately associated with the risk of local recurrence, although some patients who are clinically suitable for breast conserving surgery may choose to have mastectomy. Typically only smaller lesions (<4cm in a normal-sized breast) which are contained within a single quadrant of the breast are considered for breast conserving surgery, not least because unacceptable cosmetic results are generally achieved for larger excisions. In some cases neo-adjuvant chemotherapy or hormone therapy can shrink larger lesions prior to surgery or larger excisions can be filled using a latissimus dorsi mini-flap.

A patient is not suitable for breast conserving surgery if there are indications of the cancer being locally advanced (such as the tumour infiltrating the skin or chest wall, or the presence of matted involved axillary lymph nodes), extensive involvement of lymph nodes or the presence of metastases. A patient’s young age (<35 years), the presence of extensive in situ component, the presence of lymphatic or vascular invasion and higher histological grade tumours all increase the risk of local recurrence after a breast-conserving operation.
For breast-conserving surgery to be considered, it is important that a complete excision is anticipated. As will be described in more detail in Section 2.7, positive margins greatly increase the risk of local recurrence and so mastectomy is likely to be the more suitable treatment if complete excision is not otherwise anticipated. Similarly, if more than one focus of cancer is present then a mastectomy procedure is like to be considered the more appropriate option. If negative margins can be achieved (whilst preserving sufficient breast tissue) then breast-conserving surgery may be feasible. Even so, repeat operations due to positive margins are required in as many as 42% of patients treated with breast conserving surgery (Mullenix et al. 2004). The proportion may be even greater for specific scenarios: ILC measuring more than 2cm has been reported as having positive margins in 70% of cases (Mai et al. 2000). ILC has generally been found to require a greater number of re-excisions than IDC (Moore et al. 2000).

Following breast conserving surgery all patients should receive radiotherapy to the breast to reduce the risk of recurrence (Dixon 2006). If a patient is not suitable for post-operative radiotherapy - for example if she has severe cardiac or lung disease, or she is pregnant – then she is not suitable for breast-conserving surgery. Following mastectomy radiotherapy should be considered if the patient is at high risk of recurrence: for example if the pectoralis major muscle was involved, if there was lymphatic or vascular invasion, if there was axillary lymph node involvement, or if the tumour was large or grade III.

### 2.7 Margins

In a mastectomy all breast tissue is removed, therefore the surgeon can be relatively confident that all of a primary breast cancer has been removed. However there is a risk with breast conserving surgery that some cancer remains in the conserved tissue. An indication as to whether cancer does remain can be obtained by examining the margins of the excised specimen histologically – if pathology is found at the margin it is highly likely that cancer is still present in the surgical cavity, although the absence of pathology detected at the margin does not guarantee that all cancer has been completely excised.

(Singletary 2002) reviewed 34 studies examining the relationship between surgical margin and local recurrence in IDC, for patients with early stage breast cancer. In 30 of these studies the recurrence rate was greater in cases where tumour cells were directly at the cut edge of the surgical specimen (positive margins) than in cases where they were not. However increasing the distance required from the cut edge to the first tumour cells found for a margin considered ‘negative’ did not convincingly reduce the rate of local recurrence. In the situation that tumour cells were found close to (up to 1 or 2mm depending on the study), but not at, the specimen boundary the results of the studies were contradictory, with recurrence rates varying from being...
the same as positive margins to being the same as negative margins. The extent of disease at the margin has been found to be a predictor of local recurrence (DiBiase et al. 1998).

DCIS is considered to be a precursor to IDC, and so obtaining clear margins is similarly important. However, DCIS can be multifocal, with lesions ‘skipping’ along branches of a duct. This makes it hard to be certain that a margin found histologically not to have DCIS truly indicates the complete excision of DCIS. Therefore negative margins as large as 15mm (Silverstein et al. 1999) have been recommended. Whether such large margins convey a benefit is not clear, since a review of the papers studying the relationship between surgical margin and local recurrence in DCIS surprisingly found that although the margins in the majority of these studies were similar to those used with IDC, the local recurrence was not significantly increased (Singletary 2002).

Much less research has been conducted into the influence of LCIS and ILC being found at the surgical margins than has been performed for their ductal counterparts. Although the presence of LCIS is generally considered to be a risk factor for breast cancer rather than an actual precursor lesion (Bear et al. 2000), recent results have cast this in to doubt, with Jolly et al. (2006) finding that LCIS on the margin is associated with an increase in local recurrence. Bouvet et al. (1997) in a study of 74 patients with ILC who underwent breast-conserving surgery found, in a univariant analysis, that those with positive surgical margins were at increased risk of developing local recurrence. This is contradicted by the larger study (416 patients) by van den Broek et al. (2007) who found that margins positive for ILC had no influence on the risk of local recurrence despite a high proportion of the excisions being incomplete.

### 2.8 Pathology Correlation

Post-excision histology serves as the ground truth in the diagnosis of breast disease. The correlation of MR imaging and histology is therefore key to determining MR imaging’s sensitivity and specificity for detecting cancer, and its ability to target sites for excision.

Various researchers have looked for correlations between the morphology of lesions seen in the MR image and the histological grading of the tumour. For instance Orel et al. (1994) observed that fibroadenomas tend to have less irregular borders than carcinomas. Hochman et al. (1997) describe how fibroadenoma histology correlated with its MR appearance. However their observations do not appear to be based on aligned histological and MR images, but on histological samples taken from the general region suggested by the MR image. A similar level of spatial correlation was demonstrated by Weinstein et al. (1999) who, in a study to show the ability of MR contrast enhanced imaging to depict vascular permeability and extracellular
volume fraction of breast carcinoma, describe that these features shown by histology visually correlate well with these features in MR images. No details are given on how accurately these features were aligned, but it seems likely that gross regions were being selected.

Few attempts have been made to spatially match breast pathology with MR images. Harms et al. (1993) acquired contrast enhanced breast MR images prior to mastectomy, and the mastectomy specimens were frozen and sectioned. Reformatted images and the sections were then compared. Whilst they argue that “the extent of the enhancing lesion identified at MR imaging was directly correlated with the extent of histologic abnormality” it is unlikely that the images were accurately aligned, because no attempt has been made to compensate for the amount of deformation that can be expected during a mastectomy. Holland et al. (2000) imaged ex-vivo breast tissue samples at a higher spatial resolution than is clinically feasible. Details such as individual lobules, ducts, connective strands and blood vessels were recognisable in both the MR image and on the histology images.

Work has been carried out on spatially registering the histological and MR images of organs other than the breast. For example Chakravarty et al. (2006) and Bardinet et al. (2002) develop techniques for building models of the brain using histological slices, the latter registering the reconstructed histology volume to an MR volume. It should be noted, however, that there is significant macroscopic structure in the brain to aid the alignment of slices. Elsewhere in the body Taylor et al. (2004) have looked at registering ultrasound with histology for the prostate, using an affine registration method on fresh ex-vivo specimens.

2.9 Chapter Conclusion

The standard treatment for breast cancer is surgery, and the options have been described in this chapter. Women diagnosed with early stage invasive breast cancer have equivalent outcomes whether they are treated with breast conserving surgery or mastectomy, and so most receive conservational surgery. However in a significant proportion of these operations the cancer will not be completely excised at the first attempt, with cancer cells being found at the margins of the excised tissue.

Involved margins have been found to increase the risk of local recurrence, although the more limited evidence available is less conclusive for lobular carcinomas than for ductal carcinomas. Patients with positive margins therefore receive a repeat operation to attempt to achieve a complete excision.

The primary aim of this thesis is to develop an image-guidance system which might help a surgeon achieve a complete excision at the first attempt. DCE MR provides a three dimensional
representation of cancer by imaging the increased perfusion around the lesion. It may therefore prove to be a suitable imaging modality to base this guidance system on. However, it has not yet been conclusively shown that the extents of a lesion, as indicated by DCE MR, accurately align with those of the ground-truth provided by histology.
Chapter 3

Biomechanical Modelling of the Breast

3.1 Introduction

The very soft nature of the breast, and the large deformation which results between MR imaging and surgery, presents a challenge when attempting to register images of the breast in different postures. A plausible approach to assist the registration process and ensure that the resulting correspondences are reasonable is to introduce physical constraints via a biomechanical model. In this thesis a biomechanical model of the breast will be used for two purposes: modelling the deformation of the breast between the prone and supine positions to assist the registration of MR images acquired in these two positions and modelling the deformation of the breast between supine MR imaging and surgery.

The first part of this chapter summarises the experimentally determined material stiffness of the breast, as reported in the literature. Later in this chapter constitutive equations, which encapsulate these relationships into a form compatible with biomechanical modelling techniques, will be described.

The equations of continuum mechanics and of elasticity, which are used in biomechanical modelling to describe the deformation of solid bodies, are given in Appendix B. Since these partial differential equations are not, in general, directly solvable, their solution is typically approximated using techniques such as the finite element method. This is the approach I have chosen to use and so the essential equations of the finite element method are also summarised in Appendix B.
Chapter 3. Biomechanical Modelling of the Breast

The use of biomechanical models of the breast has predominantly been reported in the literature for modelling compressions similar to those performed during X-ray mammography, but recently some work has been done in modelling gravity-induced deformations of the breast. I summarise here the techniques which have been used to construct the models, the loads which have been applied and the boundary conditions which have been imposed. The performance of the models is reported.

3.2 Experimental Determination of Material Properties

The relationship between the stress (internal pressure) and the strain (a measure of deformation), referred to as the constitutive relationship, must be determined experimentally for each tissue type. For isotropic, linear elastic, materials this relationship depends upon just two parameters e.g. Young’s Modulus $E$ (a measure of the material stiffness, Equation B.19) and Poisson’s Ratio $\nu$ (a measure of the material compressibility, Equation B.20). However since the relationship is usually non-linear it should be determined over a range of pre-strain appropriate to the application. Experiments to determine elastic moduli have been performed using both in-vivo and ex-vivo samples.

3.2.1 In-vivo Experiments to Determine Material Properties of breast tissue

In-vivo measurements of breast material properties can be obtained using a technique known as elastography.

*Static Elastography*

In static (or quasistatic) elastography, the breast is imaged using either ultrasound, such as in (Ophir et al. 1996), or MR, such as in (Plewes et al. 2000), before and after applying a compression. A tissue strain map is then computed by estimating the displacement field between the images. If linear elasticity is assumed then this strain map (or ‘elastogram’) will correspond to the distribution of elastic moduli. Typically only small strains (less than 1%) are applied in order to simplify the process of determining the deformation field and because the constitutive relationship is non-linear at higher strains. Elastograms generated in this way indicate the relative, rather than absolute elastic moduli. Qualitative information may be sufficient for clinical diagnosis - for example (Thomas et al. 2006) found on 108 patients that using it in conjunction with B-mode ultrasound increased specificity to 91.5% compared with 78% for ultrasound alone - but in order to construct a model on which forces will be applied the absolute values of elastic moduli are required.
Dynamic Elastography

A quantitative estimate of the breast tissue’s elastic moduli can be made using dynamic elastography as in, for example, (Kruse et al. 2000; Lawrence et al. 1998; McKnight et al. 2002; Sinkus et al. 2000; Sinkus et al. 2005). Due to ultrasound’s poor signal-to-noise ratio the technique is more effective when using MR imaging than ultrasound imaging. In these dynamic MR elastography experiments, small amplitude shear waves are propagated through a tissue with a frequency of between 50 and 500Hz. These waves can be visualised using a synchronised MR sequence, and the shear modulus at a point in the material can be deduced from the wavelength. Once again, these techniques typically make the assumption that the strain is small. The mean Young’s modulus of adipose tissue measured using this approach has ranged from 0.7kPa (Sinkus et al. 2000) to 24.0kPa (McKnight et al. 2002) whilst the Young’s modulus of glandular tissue stiffness has ranged from 3.5kPa (Sinkus et al. 2000) to 37.5kPa (Kruse et al. 2000), but the sample size for these experiments has been very small (between one and nine subjects).

3.2.2 Ex-vivo Experiments to Determine Material Properties of breast tissue

Data about material properties of breast tissue at larger strains has been obtained ex-vivo using punch indentation tests, for example (Krouskop et al. 1998; Samani and Plewes 2004; Wellman 1999), and uniaxial compression experiments (Sarvazyan et al. 1994). This data is summarised in Table 3.1, with the data for adipose and fibroglandular tissue plotted in Figure 3.1. In a punch indentation test a piston is depressed into a thin sample of breast tissue, whilst in a uniaxial compression experiment a small sample of tissue is compressed between two plates. The force applied to the tissue is recorded with respect to its displacement and the material properties are deduced from these measurements. In punch indentation experiments the piston has a diameter of around 5mm which allows a tissue of a homogenous type to be tested, although the technique presented in (Samani and Plewes 2007) is suitable for samples which contain both normal and pathological tissue. All the experiments reported here were performed less than two hours after surgical excision.

No change in material properties was observed during this period (Krouskop et al. 1998; Samani et al. 2007). Although the experiments were performed at room temperature, Samani et al. (Samani et al. 2007) comments that, in an unreferenced previous study, maintaining the sample at body temperature did not have a measurable effect on a sample’s Young’s Modulus. All authors apart from Wellman (1999) and Samani and Plewes (2004) assume small strain, and all authors assume that biological tissue is approximately incompressible as observed by Fung (1993).
<table>
<thead>
<tr>
<th>Pre-strain</th>
<th>Reference</th>
<th>Adipose</th>
<th>Fibroglandular$^c$</th>
<th>DCIS</th>
<th>IDC$^d$</th>
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<td>Not Given</td>
<td>Sarvazyan et al. (1994)</td>
<td>$1.0 \pm 0.5^b$&lt;br&gt; n=20</td>
<td>$1.0 \pm 0.5^b$&lt;br&gt; n=20</td>
<td>$3.5 \pm 0.5$&lt;br&gt; n=18</td>
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<td>$16.38 \pm 1.55$&lt;br&gt; n=4</td>
<td>l: $10.4 \pm 2.6$&lt;br&gt; n=12&lt;br&gt; m: $20.0 \pm 4.2$&lt;br&gt; n=21&lt;br&gt; h: $42.5 \pm 12.5$&lt;br&gt; n=9</td>
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<td>$18 \pm 7$&lt;br&gt; n=8</td>
<td>f: $96 \pm 34$&lt;br&gt; n=18&lt;br&gt; g: $28 \pm 14$&lt;br&gt; n=31</td>
<td>$22 \pm 8$&lt;br&gt; n=23</td>
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<td>f: $244 \pm 85$&lt;br&gt; n=18&lt;br&gt; g: $48 \pm 15$&lt;br&gt; n=31</td>
<td>$218 \pm 87$&lt;br&gt; n=23</td>
<td>$558 \pm 180$&lt;br&gt; n=32</td>
</tr>
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Table 3.1 Ex-vivo measurements of the Young’s Modulus $E$ at a range of pre-strains for normal and pathological breast tissues /kPa. Values given are mean ± standard deviation. n is the number of patients in each study. $^a$Data for experiment at 0.1Hz. $^b$Data is given for a combined fatty and fibroglandular sample. $^c$Where separate data is provided for fibrous tissue and glandular tissue, these values are preceded by f: and g: respectively. $^d$Where separate data is provided for low, medium and high-grade IDC these values are preceded by l: m: and h: respectively.
Figure 3.1 Plot of ex-vivo measurements of adipose and fibroglandular tissue stiffness (a) adipose tissue (b) fibroglandular tissue. Data is from Table 3.1. Error bars give standard deviation.
Repeated loading and unloading can reduce hysteretic effects, and can also soften tissue. Pre-conditioning involves repeatedly loading and unloading the tissue so that a steady state is achieved for a given load cycle (Fung 1993). Pre-conditioning was performed by Krouskop et al. (1998), Samani et al. (2007), Samani and Plewes (2004) and Wellman (1999).

Both Wellman (1999) and Krouskop et al. (1998) found viscous effects to be negligible, although Wellman did note that some long time scale force relaxation was likely to occur. This is in contrast to brain tissue – the focus of the majority of soft tissue modelling for image guided surgery – which has been found to have a high strain-rate dependency (Miller and Chinzei 2002).

3.2.3 Limitations of Available Data about Material Properties of Breast Tissue

The ex-vivo data indicates that breast tissue material properties are non-linear (i.e. the Young’s Modulus determined depends on the level of pre-strain). However in-vivo data is only collected under small pre-strain conditions and the pre-strain used is not typically recorded. Therefore the in vivo data is of limited use for modelling large deformations of the breast.

Ex-vivo data is available for pre-strains of up to 20%. However all the data results from compression experiments and no data are available about the material properties of the breast in extension, which will be important when modelling gravity-induced deformations. There is no reason to believe these properties will be similar: experiments on brain tissue have found this non-load-bearing biological tissue to have very different material properties in extension to compression (Miller and Chinzei 2002).

The ex-vivo experiments are performed on small specimens. Therefore structures such as Cooper’s ligaments will be severed, altering the effective material property of the tissue sample. No attempt is made to account for anisotropy in the material properties. Further error in measured material properties may be introduced because the blood supply and interstitial fluids are not present, although efforts are made to keep the samples hydrated. Breast tissue is universally assumed to be incompressible, but this assumption is not experimentally validated. None of the experiments reported take account of pre-strain caused by gravity, hydration and tissue fibres, an issue which is recognised by Liu et al. (2004).

Significant variation between measurements is seen in the data. Whilst a proportion of this will be due to measurement error, much of it will be due to inter- (and even intra-) subject variability. The alteration with age in the way the breast is observed to deform, for instance, will not be purely due to a replacement of fibroglandular tissue with adipose tissue, but it will also be due to factors such as changes in the material properties of these components, a stretching of
Coopers ligaments and a weakening of the coupling between the breast and the surrounding tissues. On a much shorter time-scale, Lorenzen et al. (2003) found that fibroglandular tissue roughly doubled in stiffness through the course of the menstrual cycle.

### 3.2.4 Material Properties of Skin

Skin is organised into two layers. The more superficial of these is a thin layer of stratified epithelium cells and is called the epidermis. Below that lies the thicker dermis layer, which is predominantly composed of wavy coiled collagen and elastin fibres in a supporting matrix, or ‘ground substance’. The differing material properties and initial configurations of the two types of fibre result in the stress-strain relationship of skin being non-linear. At low strain the elastin component of skin dominates, leading to a linear stress-strain relationship. As the collagen fibres straighten out and come under load there is a gradual increasing of the material stiffness. Once all the collagen fibres are straight the stress-strain relationship becomes linear again, until finally these fibres fail. The meshed nature of collagen fibres results in anisotropic behaviour being observed, with stiffer behaviour being observed in the direction of so-called Langer’s lines (Langer 1861). The material properties of skin are strain-rate dependent, which can be attributed to the viscous resistance of the ground substance. The skin is normally under tension (Alexander and Cook 1977), which is illustrated by the appearance of wrinkles when the skin is subjected to compressive loads.

A range of experimental techniques have been used to quantify the material properties, and the measured value of Young’s modulus $E$ is highly dependent upon the choice of experiment technique. Typical experiments include indentation tests (Bader and Bowker 1983) ($E\approx1\text{kPa}$), tensile tests in which tabs are affixed to the skin and then pulled apart in a direction near-parallel to the skin surface (Manschot 1985) ($E\approx5\text{MPa}$ to $20\text{MPa}$ depending fibre direction), torsional tests in which a central disc is rotated whilst an encompassing ring remains fixed (Agache et al. 1980) ($E\approx1\text{MPa}$) and suction tests in which the deformation caused by a partial vacuum is measured (Barel et al. 1995) ($E\approx0.2\text{MPa}$).

### 3.3 Biomechanical Modelling and the Finite Element Method

#### 3.3.1 Introduction

The earliest approach to modelling soft tissue deformation, and one which has which has been applied to image-guided surgery, is the mass-spring model (Bucholz et al. 1997; Edwards et al. 1997). In these models, tissue is represented by a mesh of springs, with point masses placed at the connecting nodes. Due to their computational simplicity they can be rapidly updated to
Chapter 3. Biomechanical Modelling of the Breast

represent the dynamic behaviour of the system. Thus they are very well suited to surgical simulation (Liu et al. 2003), where deformations which appear realistic must be presented, and interacted with, in realtime, despite there being a potential decrease in accuracy. However, a significant challenge of mass-spring meshes is that their parameters have no physical analogue (Skrinjar and Duncan 1999), and so constitutive laws which describe the material properties cannot be incorporated into this framework in a straightforward fashion. An additional difficulty is that the discrete structure of a mass-spring mesh can lead to physically implausible anisotropic deformation. Furthermore, the requirements of image-guided surgery differ from those of surgical simulation. In image-guided surgery applications, unlike surgical simulations, it may be reasonable to consider the model to be quasi-static, and intraoperative measurements are available to act as boundary conditions on the model. It is, however, critical that the model accurately describes the tissue displacements.

A continuum representation of the material, in which mass and energy is distributed throughout the model, provides a more physically realistic representation than a mass-spring model, and is therefore more likely to be able to provide accurate predictions. The theory of elasticity provides a set of partial differential equations which describe the equilibrium conditions for a continuum body in terms of the external loads, the stresses and the strains within the body. For an arbitrarily shaped body this will not be analytically soluble, and so an approximation to the solution is instead found by reducing the dimensionality of the solution space.

The predominant technique used to solve such partial differential equations in continuum mechanics is the Finite Element Method (FEM). In the FEM a body is ‘meshed’ into a set of elements with simple topology which are connected at node points. Displacement are defined at the nodes but are interpolated within each element, which allows the behaviour of the body to be described using a finite number of variables.

An alternative approach used to solve partial differential equations in continuum mechanics is the boundary element method (BEM) (Ecabert et al. 2003). The BEM requires only a mesh of the surface rather than the whole volume. This offers significant potential advantages in terms of computational efficiency over the FEM, as well as requiring less complex mesh generation. However, the BEM is not very suitable for dealing with material heterogeneity, and the matrices of equation coefficients in the BEM are fully populated, unlike in the FEM. Moreover, non-linearity can be difficult to express in the BEM framework, as the required fundamental solution may not be easily available. Since the BEM reduces the dimensionality of the problem from a volume to a surface, it may prove an effective method for more rapidly computing deformations. Another approach to solve the partial differential equations is to use meshless methods (Doblare et al. 2005; Horton et al. 2007). When applying this technique the body is
discretised by a cloud of unconnected nodes rather than by elements which removes the often time-consuming overhead of having to create a mesh.

### 3.3.2 Deformation Modelling Using the Finite element method

In this thesis the finite element method will be used to model the deformations of the breast. This is due to its ability to handle heterogeneous materials types and to the widespread availability of well validated finite element analysis packages, such as the ANSYS software (ANSYS 2007) which was used in this work, which support a range of element types and material models. There is an extensive body of literature describing the finite element method, such as the textbooks by Bathe (1996), Bonet and Wood (1997), and Zienkiewicz and Taylor (2000). The method, and the key concepts behind it, are outlined in Appendix B. The following sections describe the key components of a finite element model of the breast: the underlying mesh; the application of boundary conditions and the incorporation of material properties.

### 3.4 Meshes

The first step in any finite element analysis is to discretise the irregular domain into a mesh of smaller, more regular elements. The first part of this section briefly describes the issues which must be considered when deciding how to construct this mesh. The second part describes the meshes which have been used for the finite element modelling of breast deformations.

#### 3.4.1 Meshing Considerations

*Elements*

The geometry of the underlying structures dictates the choice of element. Most biomechanical modelling of soft tissue has been performed using 3D (‘volumetric’ or ‘solid’) elements, although 2D (‘shell’, ‘plane’ or ‘membrane’) elements have been used for modelling membranes such as the skin and 1D elements may be suitable for modelling components such as ligaments. The most common volumetric element shapes are tetrahedral and hexahedral. Elements described by linear shape functions contain a node at each vertex and will have straight edges but curved edges can be created by using higher order shape functions. Examples of elements which use higher order shape functions include ten-noded tetrahedral elements with a quadratic shape function, which have an additional node on each edge (ANSYS 2007) and hexahedral elements with cubic-Hermite shape functions, which preserve continuity of the first derivative between elements, and so have more degrees of freedom at each node (Rajagopal 2007).
When linear tetrahedral elements are used it is possible to compute analytical integrands, whilst other element shapes generally require numerical integration using techniques such as Gaussian quadrature. However, linear tetrahedral elements are particularly susceptible to ‘locking’ when modelling almost incompressible materials such as biological tissue. Locking refers to an excessive stiffness of the mesh, resulting in smaller displacements being calculated than actually occur.

The accuracy and stability of the model solution is affected by the so-called “element quality”, which is a measure of the relative dimensions of each element. Many such metrics have been proposed, and a comprehensive review is available in (Field 2000). Details of the measures considered in this thesis are given in Section 5.6.1. Examples of badly-shaped elements include those which are significantly skewed and those which are needle-shaped. The badly shaped elements result not only in mesh-dependent interpolation errors, but also affect the solver by slowing it down, introducing large round-off errors (Shewchuk 2002) or even preventing it from converging. It is important that the element remains well-shaped throughout the deformation, since integrations are performed over the deformed element shape (Equation B.15).

**Meshes**

Patient-specific meshes are generally created from either MR or CT images of the patient. Either the mesh is constructed directly from the voxels of the image (or a downsampling of the voxels) or the boundaries of appropriate regions are extracted manually or semi-automatically and then the regions are meshed. The former of these approaches is termed ‘voxel-based’ whilst the latter is called ‘surface-based’. The elements in a mesh must share edge nodes with adjacent elements. In a structured mesh all interior nodes of the mesh have the same number of adjacent elements. In an unstructured mesh this requirement is relaxed, allowing any number of elements to join at a node. Typically unstructured meshes are composed of tetrahedral elements, whilst structured meshes have only hexahedral elements. Generating an unstructured tetrahedral mesh is more straightforward than a structured hexahedral mesh and automatic mesh generation software is widely available which can generate unstructured tetrahedral meshes of arbitrarily-shaped regions (Owen 1998). Similar software which can automatically generate structured meshes of an arbitrary complex structure is not available. The logical indexing of a structured mesh simplifies the process of imposing of boundary conditions on the model.

In order to simulate resection it is necessary to cut the finite element mesh. Using standard finite element techniques it is not possible to cut hexahedral meshes without introducing new element shapes, such as prismatic elements (Delingette and Ayache 2004). Simulating cutting using tetrahedral meshes is more straightforward since the divided tetrahedral element can simply be replaced with further tetrahedral elements, although the element quality may be reduced.
The processes of segmenting the noisy medical images, and meshing the resulting segmentation, are time-consuming and require human interaction. An approach to easing this burden is to adopt the concept of mesh-warping, in which non-rigid registration techniques are used to warp an atlas mesh to match a patient’s anatomy (Castellano-Smith et al. 2002; Couteau et al. 2000). For mesh-warping to be appropriate, it is necessary for a correspondence between an atlas image and a patient-specific image to be established. For the breast this correspondence may not exist, or may be very hard to be establish, since there is a large variation in breast structure and composition between patients. The meshing-warping approach is therefore not likely to be appropriate.

3.4.2 Mesos of the Breast for Finite Element Modelling

All reported finite element meshes of the breast are formed from segmentations of patient-specific images acquired in the prone position. Meshes are formed from MR images of the breast apart from the work by Yin et al. (2004) in which CT images are used. Contact between the breast and the surrounding breast coil assembly is not reported, but is likely to be present in some of these images. All structured meshes of the breast use 8-noded hexahedral elements for volumetric meshing, whilst the unstructured meshes use 10-noded tetrahedral elements for volumetric meshing. No author considers the heterogeneous nature of breast tissue during the meshing process. Instead, if different material properties are considered for adipose and fibroglandular tissues, this is done by assigning a material type to each element after meshing, based on the predominant material contained within that element.

Structured meshes

(Samani et al. 2001) considered both voxel-based and surface-based techniques. 2D meshes were created in the parallel sagittal slices, and then the slices were stacked to create a volumetric mesh. Using subsampled image voxels as elements resulted in a mesh of 16481 elements. The mesh surface had sharp steps. Mapping a cube by fitting polynomials to the boundaries in each slice resulted in a mesh of 2280 elements and a smooth surface. The surface-based approach was found to be more accurate. Skin was modelled as four-noded quadrilateral membrane elements.

(Azar et al. 2002) used a surface based technique. A 2D mesh was created from every other axial slice of an MR image. Adjacent meshes were then connected to form the mesh which had 2793 hexahedral elements. Skin was modelled using three-noded triangular elements. Azar et al. (2001) argue that by reslicing the volume with variable slice spacing it is possible to increase the density of the mesh close to regions of interest, whilst decreasing it away from these regions.
The authors do not consider how altering the mesh in this way would influence not just its
density, but also its quality.

Rajagopal (2007) created a patient-specific mesh of the breast by refining the anterior and
posterior faces of an initial deformed cuboid mesh to match a limited number of evenly spaced
axial slices selected from an MR dataset. Cubic-Hermite shape functions were used. Since these
shape functions have a higher degree of freedom, fewer elements were required to achieve the
same anatomical fidelity in the initial representation than would have been required if linear
shape functions were used. A mesh created in this way was used in (Rajagopal et al. 2007b) and
whilst it contained only 122 elements, it still had 5184 geometric degrees of freedom.

Pathmanathan (2006) created a finite element mesh by mapping a cube to the shape of the
breast. The anterior and posterior faces of the cube were fitted to the corresponding segmented
faces of the breast. The mesh had 4096 elements. For simulations which included skin, the skin
was either modelled as a layer of thin volumetric elements, or as a membrane which shared the
nodes of the underlying elements. For these simulations the number of elements was reduced to
either 288 or 512 to try to separate the issue of mesh quality from the experiment since the
denser mesh had a large number of badly shaped elements. Modelling skin as a thin membrane
rather than as a thin volumetric element was found to reduce the computation time and the
number of Newton iterations required to solve.

Ruiter et al. (2006) created a mesh containing 343 hexahedral elements by mapping a pre-
meshed cube to the shape of the breast in the MR image. In (Ruiter 2003) an alternative
approach was also considered in which the mesh was created from smoothed, down-sampled
voxels. This approach has a less smooth but more accurate surface. On phantom simulations
only small variations between the two approaches were found, and so the transfinite
interpolation method was used for all other simulations. Ruiter tested models both with and
without skin. Where included, skin was modelled using membrane elements. Three scenarios
were trialled: the skin is tightly coupled to the underlying tissue by sharing its nodes; skin as
enclosing membrane which does not share nodes posed as a contact problem with perfect sliding
(i.e. no friction); and skin as enclosing membrane which does not share nodes posed as a contact
problem with perfect adherence (i.e. with friction). Skin being modelled as tightly coupled
reduced the maximum error on a compression experiment and caused no change to the mean
error; all other scenarios resulted in increased errors.

Yin et al. (2004), unlike the other authors discussed here, created a mesh from a CT rather than
MR volume. Using a voxel-based approach they meshed the breast into cuboidal elements. The
resulting mesh had solid right angles which will not reflect the smooth breast surfaces.
Unstructured meshes

Tanner (2005) uses an unstructured mesh of 10-noded tetrahedral elements. Since these elements have non-linear shape functions locking of the elements should not occur. The 3D mesh is created by using the marching cubes algorithm (Lorensen and Cline 1987) followed by decimation to generate the triangulated surface from a blurred and downsampled segmentation of the breast volume, and then meshing the interior using the tools from the commercially available ANSYS finite element analysis software suite. The meshes generated contained between 34873 and 72765 elements, and so were significantly denser than other meshes reported. Whilst a denser mesh may be able to better reflect the discretisation between fatty and glandular tissue, over homogeneous regions a mesh need only be fine enough to converge to the correct numerical solution – and increasing the mesh density beyond this point will increase the computation time without increasing the solution accuracy. This may be reflected in the reported results where, on one compression volunteer dataset, utilising a denser mesh with fewer badly shaped elements improved the displacement errors by a mean of 0.01mm. Skin was included by adding 1mm thick triangular prism elements with additional mid-side nodes to the surface of the mesh.

Zhang et al. (2007) also used 10-noded tetrahedral elements, but extracted smoothed contours from MR slices before connecting them and merging them into a 3D volume. They report using an adaptive meshing technique in which regions of interest are meshed more finely but it is not clear that the adaptive meshing approach improves the results. The resulting mesh has 8744 elements.

3.5 Boundary Conditions and Deformation Scenarios

Biomechanical models of the breast have essentially been developed to simulate two different scenarios. The first is compression of the breast between two plates, such as that which occurs when acquiring X-ray mammograms or when obtaining biopsies under MR guidance. The second is the deformation of the breast which occurs when the patient changes posture between the prone position and the supine position, which occurs between DCE MR imaging and surgery. In both of these scenarios it is displacement between initial and deformed states which is of clinical interest rather than the stress which exists within the breast. However the type of loads imposed in order to model the two scenarios are significantly different.

When modelling compression, the boundary conditions have been imposed as nodal displacements rather than as surface tractions and the gravitational body force acting has been ignored in all the work published to date. When modelling prone-supine deformation both displacement boundary conditions (i.e. how the breast is tethered to the rest of the body) and
gravitational body forces must be considered. Since forces are prescribed in the prone-supine problem the absolute values of material properties must be considered, whilst in the compression scenario it is the ratio of the constituent material properties which will affect the deformation.

This section describes the way in which boundary conditions and other loading issues are incorporated in the model. The results are only reported in this section when an author has compared different loads imposed on the same model, otherwise the performance of the models are discussed along with the material properties in Section 3.6.

### 3.5.1 Displacement-based boundary conditions

Motivations for modelling compression of the breast includes guiding clinical biopsy, modelling compressions similar to X-ray mammography, registering X-ray and MR-mammography, validating non-rigid registration algorithms and elastography. All experiments reported here modelled the compression of the breast between plates unless otherwise stated. Two approaches to modelling the effect of the compression plates have been used. One approach imposes displacements on the surface nodes directly, whilst the other approach includes the compression plates in the simulation and models the interaction between the plates and the breast as a so-called contact problem. In a contact problem the requirement that the bodies cannot interpenetrate is introduced as a constraint, usually via penalty or Lagrange multiplier techniques (Bathe 1996).

Samani et al. (2001) modelled an 8mm compression of the breast which was modelled as a contact problem. Nodes of the model which lay on the chest wall were constrained to remain stationary. Yin et al. (2004) modelled a compression of 13.5mm (20%) and applied a similar boundary condition scheme, except that nodes attached on the chest wall were only constrained in the medio-lateral and anterior-posterior directions. Pathmanathan (2006) also modelled breast compression as a contact problem.

Azar et al. (2001, 2002) modelled the compression of a breast from being uncompressed to being compressed by 22%, and the compression of a breast from a compression of 12% to a compression of 26%. Displacement in the direction of plate motion was imposed on the surface nodes which were anticipated to be in contact for a given plate separation, but these nodes were free to slide along the plate. Nodes in the region of the chest wall were constrained to be stationary. Zhang et al. (2007) used a very similar boundary condition scheme, except that once a node is in contact with the compression plate it could not slide.
Ruiter (2003) simulates plate compression both as a contact problem and by directly imposing boundary conditions on surface nodes. In both cases nodes on the pectoral fascia are fixed. The accuracies of the two approaches were found to be comparable, but solving the model which had directly imposed boundary conditions was found to be twice as fast.

In an assessment of biomechanical models of the breast Tanner et al. (2006b) used a non-rigid registration algorithm (Rueckert et al. 1999) to determine the displacement of nodes lying on the surface of the breast during medio-lateral compressions. A range of boundary conditions were trialled which included applying these registration derived boundary conditions to the posterior, medial and lateral nodes, and setting the medial and posterior nodes to have zero displacements whilst imposing registration derived boundary conditions on the lateral nodes. Unsurprisingly, imposing less accurate or less constrained boundary conditions lead to higher errors. In experiments to simulate the deformation of the breast for the validation of a non-rigid registration algorithm (Tanner 2005) a range of deformations were modelled including displacement of a single surface node (intended to mimic a biopsy puncture), translation of a set of surface nodes, displacement of nodes on one side of the breast onto a plane, displacement of nodes on both sides of the breast onto a plane, and displacements of posterior nodes which were designed to simulate tension and relaxation of the pectoral muscles.

In the majority of these experiments it appears that sufficiently small compressions are applied that they do not cause the elements to become excessively distorted. For larger compressions, a technique known as rezoning can be used to avoid badly shaped elements being created as the mesh deforms. In this technique the simulation is stopped at an intermediate level of compression and a new mesh of the deformed model which contains only well shaped-elements is created. The intermediate solution for the stresses is then mapped onto the new mesh and the compression increased. This has been implemented for tetrahedral elements, and demonstrated for breast compressions, by Tanner et al. (2006a).

### 3.5.2 Including the Effect of Gravity

The deformation of the breast under the influence of gravity is of clinical interest, primarily because the deformation which occurs between prone MR imaging and supine surgery is caused by gravity. When modelling gravity deformations by applying forces on a finite element model the absolute values, rather than the ratios, of the elastic properties will determine the deformations which occur.

**The Reference State**

The biomechanical modelling described so far in this chapter assumes that the model in its initial shape is stress-free. This undeformed stress-free configuration is known as the reference
state. All the work discussed so far ignores any forces acting on the breast when the initial image from which the model is constructed was acquired. This is not strictly valid since gravity will be acting on the breast as it is imaged, and so this state cannot be considered ‘stress-free’.

It may be acceptable to ignore these effects when modelling deformations due only to displacement loads and to treat the image as though it were stress-free. However, when modelling deformations due to gravity the initial stresses should not be ignored. In the case of the deformation from prone to supine, undoing the deformation caused by gravity acting on the prone breast to recover the reference state can be expected to have as an important effect as applying gravity in the supine direction. If the constitutive equations are non-linear ignoring initial stresses will have an influence on the stress-strain relationship assumed.

It is therefore necessary to solve the inverse problem of determining the (unstressed) reference state of a deformable body from its deformed state and the known body forces. It is not clear that this reference state physically exists. Biological tissues with varying water contents which have grown under gravity-loaded conditions and which contain fibrous elements (such as Cooper’s ligaments) and membranes (such as the skin) are unlikely to have any configuration in which all stresses are zero. Cancer – the reason why most imaging will be performed – is the uncontrolled division of cells, and this is likely to introduce additional internal stresses. However within the limitations of current models, in which many assumptions such as the homogeneity of tissue are made, the reference state provides a useful approximation which makes modelling the prone-supine deformation possible.

**Computing the Reference State**

**Method 1 – reverse the direction of gravity** It is possible to solve a forward problem with the direction of gravity reversed. This would correctly predict the reference state within the linear elasticity domain, since the elasticity relationship is linear and the deformation gradient is assumed to be the same in the deformed and undeformed bodies. However this technique can only provide an approximation to the solution in the finite elasticity domain.

**Method 2 – solve an iterative sequence of forward deformations** The reference state is the state that, after loads are applied, will result in the known deformed state. Applying gravity to some initial assumption of the reference state will result in an estimate of the deformed state. By comparing the estimated deformed state with the known deformed state corrections can be made to the assumed reference state. This process can be repeated until applying gravity to the assumed reference state results in the known deformed state. This method may prove computationally expensive, but it can be implemented using commercially available finite-element packages.
Method 3 – directly solve the inverse problem. Method 3 is essentially a mathematical implementation of Method 2, with the goal being to determine a reference state such that the residual force at each node in the deformed state is zero. In a standard finite element analysis the forward problem is solved, in which the initial coordinates $X$ are known, but the deformed coordinates $x$ are unknown. The virtual work equation, which will be solved to find the unknown node positions, is a set of equations giving the residual forces $R$ (which will be zero in equilibrium), in terms of the internal and external nodal equivalent forces $T$ and $F$. These are expressed in terms of the unknown deformed coordinates $x$ (Equation B.38). To solve the inverse problem the virtual work equation can instead be reformulated to be a set of equations in terms of the undeformed coordinate $X$:

$$ R(X) = T(X) - F(X) = 0 $$

This is essentially the approach adopted by Pathmanathan (2006) and Rajagopal (2007a). Their approaches differ in implementation detail, since Pathmanathan uses an Eulerian formulation and analytically derives the tangent stiffness matrix, whilst Rajagopal et al. use a Lagrangian formulation and determines the tangent stiffness matrix by perturbing the parameters of the reference state.

Simulation Scenarios and Boundary Conditions

Pathmanathan (2006) imposes zero-displacement boundary conditions on all nodes on the surface of finite element mesh which lie below the skin surface, including those nodes on the faces of the model which connect the skin surface to the pectoral fascia. Prone to reference state and prone to supine deformations were modelled. On one example prone dataset (without a supine dataset for validation) he calculates a displacement of the nipple between prone and supine of 8.8mm (with a mean displacement over the breast of 1.1mm). This seems unrealistically small. When material stiffness of fat is reduced by an order of magnitude the nipple displacement increases to 21.0mm, but this still seems likely to be an underestimate.

Rajagopal (2007) applies zero-displacement boundary conditions on nodes lying on the posterior face of the model. The deformation from prone to reference state is modelled. The deformation between the prone position and a range of inclined positions is also modelled, but in this experiment no correction is made for initial stresses existing when the prone breast was imaged. A mesh of a breast imaged whilst partially submerged in water is constructed as an approximation to its shape in the reference state. The deformation caused by applying gravity to this model is then simulated.
Del Palomar et al. (del Palomar et al. 2008) modelled the deformation of the breast between prone and standing, but no details of the approach used to compensate for gravity are given.

### 3.6 Incorporating Material Properties in the Biomechanical Model

This section describes the how the material stiffness discussed in Section 3.2 has been incorporated into biomechanical models of the breast as constitutive equations. The accuracies achieved using these constitutive equations are reported, as are the effects on model accuracy of altering them.

In the following review it will be seen that several forms of constitutive equation have been used. These include modelling tissue as behaving in a linear elastic (piece-wise linear elastic) manner and fitting exponential functions to experimental data. For such material models the constitutive equation is expressed in terms of the stress and the strain. Hyperelastic materials, in which the work done by stresses in the deformation are only dependent on the initial and final configurations (i.e. not on the deformation path), have also been used. The constitutive equations of these materials are therefore typically expressed in terms of a stored strain energy function. It will be seen that the most common hyperelastic forms that have been used for modelling breast tissue are the neo-Hookean (Equation B.28) and the 5 parameter Mooney-Rivlin (Equation B.29) material models.

In following descriptions of the material properties which have been used for modelling breast tissue, a finite strain formulation of the finite element method was employed where a hyperelastic strain energy function was used; for the other material models an infinitesimal strain formulation was used.

#### 3.6.1 Adipose and Fibroglandular tissue

Since tissue is predominately composed of water - an incompressible fluid - soft biological tissue is generally considered to be incompressible (Fung 1993). This makes no allowance for any loss of total fluid volume - as might occur if blood volume is reduced under large compressions or when the patient is rotated from prone to supine. Tissue incompressibility was introduced into the model either setting Poisson’s ratio $\nu$ to be close to 0.5, or by using incompressible hyperelastic material properties in conjunction with a mixed displacement-pressure element formulation (described in Section B.5). The only models which considered breast tissue to be compressible were a subset of the described in (Tanner 2005) who considered Poisson’s ratios in the range $0.1 < \nu < 0.499$. A Poisson’s ratio of greater than 0.495 gives the best results on one compression data set, but on another dataset the boundary conditions introduced volume change and so Poisson’s ratios in the range $0.2 < \nu < 0.3$ were favoured.
Samani et al. (2001) fit a hyperelastic neo-Hookean model to the experimental data for adipose and glandular tissues collected by Wellman (1999) but provide no quantitative assessment. Azar (2001) and Azar et al. (Azar et al. 2000, 2002) fit exponential stress-strain curves to the data in Wellman (1999) and also stiffen the material models for fat at higher strains. This stiffening is proposed since the elements of their model ‘collapsed in on themselves’. They argue that this represents fat being ‘squeezed out of its location’ and that the stiffer material reflects Cooper’s ligaments. This argument does not seem compatible with an almost incompressible continuous material and instead it is possible that incompressibility constraints were being incorrectly implemented for this model.

Yin et al. (2004) used 2 parameter Mooney-Rivlin material models for adipose tissue and for fibroglandular tissue based the measurements of Krouskop et al. (1998). Zhang et al. (2007) assumed linear elasticity and did not distinguish between fibroglandular and adipose tissue.

Ruiter (2003) tested the models based on Wellman’s data described above, as well as several linear elastic models (Bakic 2000; Krouskop et al. 1998; Lorenzen et al. 2002). She also fitted linear elastic and neo-Hookean material models to these stress-strain relationships. These are shown in Table 3.2 for comparison with the values determined in this thesis.

<table>
<thead>
<tr>
<th></th>
<th>$\alpha_g$/kPa</th>
<th>$\alpha_f$/kPa</th>
<th>$E_g$/kPa</th>
<th>$E_f$/kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azar 2001</td>
<td>(15.1)</td>
<td>(2.3)</td>
<td>(71.6)</td>
<td>(10.7)</td>
</tr>
<tr>
<td>Azar 2001 (stiffened)</td>
<td>(15.1)</td>
<td>(15.1)</td>
<td>(71.6)</td>
<td>(71.6)</td>
</tr>
<tr>
<td>Samani et al. 2001</td>
<td>64.8</td>
<td>12.4</td>
<td>(895.8)</td>
<td>(77)</td>
</tr>
<tr>
<td>Krouskop et al. 1998</td>
<td>(15.6)</td>
<td>(3.5)</td>
<td>(73.9)</td>
<td>16.7</td>
</tr>
<tr>
<td>Bakic 2000</td>
<td>(12.6)</td>
<td>(10.1)</td>
<td>60</td>
<td>48.6</td>
</tr>
<tr>
<td>Lorenzen et al. 2002</td>
<td>(0.5)</td>
<td>(0.4)</td>
<td>2.5</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Table 3.2 Values assumed for Young’s Modulus $E$ and neo-Hookean parameter $\alpha$ in the literature

Values for $E$ or $\alpha$ which have been obtained by fitted to a different form of constitutive equation given in the original paper are given in parenthesis. Subscripts $f$ and $g$ indicate fat and glandular tissue. Azar 2001 (stiffened) gives values for Azar’s stiffened fat at higher strain, as described above. All values are from Ruiter (2003), Table 4.1

The effect of material property was tested on a compression scenario which introduced a mean (maximum) landmark displacement of 18.3 (25.7) mm. The choice of hyperelastic material parameters had a very small influence on nodal displacements, with mean (max) errors in the
range 3.1 to 3.3 mm (4.8 to 5.1mm). Slightly greater errors were seen for the linear elastic material models (mean errors of 3.1 to 3.5mm, max errors of 5.1 to 6.8mm), apparently because the implementation of linear elasticity used did not model incompressibility effectively.

On one example prone dataset (without a supine dataset for validation) Pathmanathan (2006) calculates a prone to supine displacement of the nipple 8.8mm using the 5-parameter Mooney-Rivlin parameters given by Samani and Plewes (2004). Changing the stiffness of adipose tissue was found to have a greater influence on displacements than changing the stiffness of fibroglandular tissue, as might be expected given the breast used in these experiments was predominately fat. Decreasing the stiffness of fat by a factor of 10 results in the nipple displacement increasing to 21.0mm, which still seems to be an unrealistically small deformation. Using a neo-Hookean material property for adipose tissue ($\alpha=0.5$ kPa) instead results in a nipple displacement of 12.6mm.

Tanner (2005) tested linear models in which fibroglandular tissue stiffness varied from the stiffness of adipose tissue to 20 times this and the non-linear models proposed by (Azar et al. 2000; Krouskop et al. 1998; Samani et al. 2001) approximated using piecewise-linear functions. She also fitted neo-Hookean and 5-parameter Mooney-Rivlin material models to these stress-strain functions to assess the effect of using a finite strain formulation: none of the finite strain formulations improved the accuracy of their infinitesimal counterpart.

Rajagopal (2007) modelled the breast as consisting of only one, neo-Hookean tissue type. The prone breast submerged in water was assumed without proof to provide a good approximation to the reference state and the model was constructed in this posture. The neo-Hookean parameter $\alpha$ was adjusted to achieve the best match between the surface of this model deformed by gravity and the breast surface in an approximately prone MR image constructed in this position. The value obtained was $c_1=0.08$ kPa with an RMS error over the surface of 5.1mm. Rajagopal et al. (2007b) reported a mean error of 3.7mm when calculating internal displacements for 4 landmarks in a single example MR slice using this set up. The supine surface was calculated with an RMS error of 7.4mm from submerged data, compared with calculating the reference state from the prone configuration using the inversion technique described in (Rajagopal et al. 2007a) which resulted in a RMS surface error of 9.1mm.

All biomechanical models of the breast reported have considered the breast’s constituent tissues to be both homogeneous and isotropic, apart from Pathmanathan (2006) who proposes transversely isotropic material model for adipose tissue which is intended to reflect the presence of Cooper’s ligaments and Tanner (2005) who found transverse isotropic materials improved landmark accuracy in a compression experiment on one volunteer, but showed no accuracy improvement on another volunteer dataset.
The experimental data underpinning the constitutive equations, as discussed in Section 3.2 only exists for breast tissue in compression. There is no evidence to suggest that these constitutive models are realistic for tissue in tension.

### 3.6.2 Skin

Samani et al. (2001) modelled skin as being linear elastic with a Young’s Modulus of 10.0kPa. Ruiter (2003) fitted a neo-Hookean model to this and found that, when skin was tightly coupled to the underlying tissue, the maximum error on the one simulation tested was slightly reduced but there was no change in the mean error.

Pathmanathan (2006) modelled skin using the hyperelastic material property proposed by Veronda and Westmann (1970). He found that small changes in skin stiffness had very little effect on the model when modelling prone-supine deformations, with the only significant effects occurring when skin stiffness was increased or decreased by a factor of 10. He suggests this may be because in the reference state human skin is under tension, and this is not being modelled.

Azar et al. (2001, 2002) used a piecewise-linear function to model the stress-strain relationship of skin. The model including skin computed the displacement of lesions with a mean (maximum) error of 3.7mm (7.3mm) compared with a mean (maximum) observed deformation of 12.3(19.9) mm during compression of the breasts of three patients. No results of the model without skin were presented.

Tanner (2005) modelled skin as being 10 times stiffer than adipose tissue for the linear and piecewise-linear models which she tested. Including skin improved maximum displacement errors for linear models by 0.25mm on average; for the other models including skin had very little effect for the two volunteer datasets used.

### 3.6.3 Tumour

The majority of authors have not included tumourous tissue in their model. Yin et al. (2004) included tumour in the model using a 2 parameter Mooney-Rivlin material model. Pathmanathan (2006) found that the model’s displacements were very insensitive to the introduction of a small simulated hard lesion and concludes that omitting the lesion would not be a major source of error. Ruiter (2003) found, when modelling a large compression, that failing to account for a simulated very stiff lesion of 15mm caused the displacement of its centre to be miscalculated by 3mm.
3.7 Chapter Conclusion

The finite element method is a well established technique for modelling mechanical deformations. It is widely considered to be appropriate for modelling the deformation of soft materials of known structure and composition under known loading conditions. However applying this technique to accurately predict deformations on a patient-specific basis remains challenging.

A number of factors will influence the accuracy of a biomechanical model when modelling deformations. One important aspect is whether the mesh on which it is constructed appropriately reflects physical reality, including features such as Cooper’s ligaments which are not visible in imaging. Whether the assumed reference configuration of this mesh is appropriate must also be considered. Two other key factors are how accurately the assumed material properties reflect the true material properties, and the completeness and accuracy of the boundary conditions.

The majority of biomechanical modelling of the breast has been to simulate compressions similar to those used during X-ray mammography or MR-guided biopsy. In this scenario only displacement boundary conditions are applied and therefore the absolute values of material properties are not important, since the deformation depends only on their ratio. For the compression scenario the influence of quite a wide range of modelling parameters on accuracy has been considered, albeit on a limited number of volunteers or patients. Of particular note is that the assumed material properties have been found to be less important than the application of suitable boundary conditions (Tanner et al. 2006b).

When gravity is applied the absolute values of material properties becomes important. Material properties for breast tissues have generally been inferred from ex-vivo compressions of small tissue samples or from elastography experiments performed at small strains. Since breast tissue has been shown to have non-linear material properties it seems unlikely that either of these sources is appropriate for modelling prone-supine deformations of the breast. The limited research into gravity-induced deformations of the breast has neglected influence of boundary conditions despite this being found to be of critical importance when modelling breast compressions. Furthermore each reported experiment has been limited to one patient or volunteer dataset and minimal validation has been performed.
Chapter 4

Image Registration and Image-Guided Surgery

4.1 Introduction

The quality of diagnostic imaging, such as magnetic resonance (MR) imaging and computed tomography (CT), has improved significantly over the past couple of decades. Detailed 3D images of anatomy, which can reveal the location, shape and size of pathology, are now available to surgeons prior to an operation.

For this information to be fully exploited, these 3D images (or information derived from them) must be aligned or ‘registered’ with the patient during the procedure in order to provide spatial navigation and guidance: a process known as image-guided surgery. This is conventionally achieved using a rigid body transformation. For a procedure involving soft tissue - such as breast surgery – tissue deformation between preoperative imaging and surgery can be expected. This means that the images used for guidance and the surgical reality will no longer match. If image-guided surgery is to be effective, it will be necessary to account for this non-rigid deformation in order to prevent the accuracy of the spatial guidance from being degraded.

If volumetric imaging such as CT, MR imaging or 3D ultrasound is available whilst the patient is in the surgical position, then it can be possible to use intensity-based registration algorithms to deform the preoperative images appropriately. These algorithms allow information throughout the volume to be used to drive the registration. Unfortunately, it is not usually feasible to acquire volumetric images in the operating theatre, but instead only relatively sparse data can be acquired using, for example, 2D ultrasound or surface imaging techniques. In this
situation achieving a good registration between preoperative imaging and surgery can be expected to be more dependent on the techniques used to regularise the transformation than the intensity-based methods were. A powerful approach is to use a biomechanically realistic model to simulate the deformations, and so warp the preoperative images to reflect the surgical scene. Once appropriate registration techniques have been used to compute the position of the cancer in the coordinate system of the operating theatre, it is necessary to present this information in a suitable manner to the surgeon.

This chapter commences with an overview of widely-used intensity-based registration approaches, predominantly following the review by Hill and Batchelor (Chapter 3, Hajnal et al. 2001). Methods of obtaining intraoperative data and using these data as boundary conditions on a biomechanical model in order to deform preoperative images to match the surgical scene are then reviewed. Finally the principal methods of displaying navigational information to the surgeon are briefly presented.

### 4.2 Image Registration

To make the most effective use of the information which is spatially encoded within a medical image it is often important to be able to establish spatial correspondence between it and either another medical image or the actual patient. Such information could be, for example, the extents of a lesion, the uptake of contrast agent at a specific location or the appearance of pathology in different modalities. The registration process aims to determine a transformation which maps, to a clinically acceptable accuracy, the ‘source’ image to another ‘target’ image, or to a coordinate system established relative to the patient. For the purposes of this thesis only the intra-subject registration of 3D datasets needs to be considered.

A registration algorithm has two key components: a cost function (or similarity metric) and a transformation model. The similarity metric assesses how well the target and deformed source images match, scored as a single real value. The transformation model describes the ways in which the source image is allowed to be deformed. An optimisation process is used to find the parameters of the transformation model which maximise the similarity metric.

### 4.3 Cost Functions

#### 4.3.1 Point-Based Cost Functions

Point-based registration relies upon identifying corresponding (homologous) pairs of points in the source and target images and then transforming the source image so that these points best align. Point-based cost functions are perhaps best suited to recovering rigid transformations,
although point correspondences have also been used to drive non-rigid registrations, as discussed under spline-based registration techniques in Section 4.4 below. Points are usually considered to be best aligned when the sum of the squared distances between target and transformed source points has its least value. This least squares approach is likely to be appropriate if the transformation occurring is truly rigid and the residual is merely due to normally distributed measurement errors. If the residual is primarily due to soft tissue deformation the errors are unlikely to be normally distributed but this approach may still provide a reasonable estimate of the rigid transformation, which can be later refined by a non-rigid registration.

These points used in such a scheme can be anatomical landmarks, geometric features or, as is frequently the case in image-guided surgery, ‘fiducial markers’ which have been implanted or adhered to the patient. Fiducial markers are much larger than the size of a voxel and are designed to be easily identifiable by having a high contrast in the relevant imaging modalities and a unique point which is easy to locate, either visually or by a ‘centre of mass’ calculation.

Point-based cost functions allow, in most cases, a closed-formed solution to the registration to be found (Arun et al. 1987). However the process of identifying these points will inevitably introduce a localisation error. It may not be practicable to identify sufficient homologous points to capture a non-rigid deformation.

4.3.2 Surface-Based Cost Functions

Identifying corresponding surfaces in medical images is usually a more straightforward task than identifying corresponding points. However, matching a pair of smooth surfaces can be subject to error in the direction tangential to the surface since the registration will be relatively poorly constrained in this direction. The majority of surface-based cost functions can be broken down into one of two classes: metrics which are based on features such as the surface curvature, and metrics calculated from the distance between points lying upon the two surfaces.

Feature-based metrics rely upon a pre-processing of the images to provide a compact description of the local surface shape in terms of scalar measurements. These scalar measurements provide the basis of a cost function which can be quantified using, for example, the techniques described in Section 4.3.3. An example of a feature-based method is that described by Maintz et al. (1996) which is based on locating ridges on a smoothed surface.

For surface-point-based methods the similarity criterion is the distance between pairs of points, and the chief challenge is to suitably identify corresponding pairs. When using such an approach, the process of extracting surface points will be subject to a segmentation error. The
most widely used point-based method is probably the Iterative Closest Point (ICP) algorithm (Besl and McKay 1992), which determines the closest point on one surface for each of a set of points lying on the second surface and then aligns these sets of corresponding points. This process is repeated until convergence is achieved. A non-rigid variant on this approach is used by Behrenbruch (2002) to match prone and supine MR images of the breast.

### 4.3.3 Voxel-Based Cost Functions

Voxel-based similarity metrics compute a measure of the image alignment directly from the voxel intensities. They are generally much more computationally expensive than point-based or surface-based similarity metrics. However, they typically do not require the labour-intensive pre-processing (such as feature identification and segmentation) which is needed by their point-based and surface-based counterparts.

The most widely used similarity measures are described in this section. The similarity measures can be helpfully divided into those that are suitable for registering two images of the same modality (‘intra-modal’) and those that are also capable of registering pairs of images of differing modalities (‘inter-modal’). The distinction between intra-modal and inter-modal registration is not pertinent to the point-based and surface based metrics described above, except that establishing correspondence between features in differing modalities, such as structural features observed in CT images and functional features in PET images, is not necessarily straightforward, and the influence of the threshold chosen when segmenting surfaces in the inter-modal case may have greater influence.

#### Intra-modality

Intra-modal similarity measures generally assume some relationship between the voxel intensities in the two images.

**Sum of Squared Differences (SSD)** The SSD similarity measure is given by:

\[
C_{SSD} = \frac{1}{N} \sum_{i} (I_A(p_i) - I_B(T(p_i)))^2
\]

Where \( T \) is the applied registration transformation that maps position \( p_i \) of voxel \( i \) from the coordinate system of an image \( A \) to that of image \( B \) and where \( I_A \) and \( I_B \) give the intensities at these locations. The measure is summed over the \( N \) voxels in image \( A \) that, after transformation, overlap with image \( B \).

This similarity measure is suitable for pairs of images of the same modality, since it assumes that corresponding tissues in each image have identical intensities. It is the optimal similarity metric if the only difference between the images is Gaussian noise. Although the difference
between Rician noise (the type of noise present in MR images, which is the modality used in this thesis) and Gaussian noise is small for most applications, the very misalignment which makes registration necessary will introduce differences. Due to the squared term, this image similarity metric is very sensitive to a small number of outlier voxels having a large intensity difference between images.

**Sum of Absolute Differences (SAD)** The SAD similarity measure is given by:

$$C_{SAD} = \frac{1}{N} \sum_{i} |I_A(p_i) - I_B(T(p_i))|$$

This similarity measure, which also assumes an identity relationship between voxel intensities and so is suitable only for registering images of the same modality, is less sensitive to outliers than the SSD.

**Normalised Cross-Correlation (CC)** The CC similarity measure is given by:

$$C_{CC} = \frac{\sum_{i} (I_A(p) - \mu_A) \cdot (I_B(T(p)) - \mu_B)}{\sqrt{\left(\sum_{i} (I_A(p) - \mu_A)^2\right) \cdot \left(\sum_{i} (I_B(T(p)) - \mu_B)^2\right)}}$$

where $\mu_A$ and $\mu_B$ are the mean voxel intensities in image $A$ and $B$ respectively. The CC similarity measure assumes a linear relationship between the intensity values in the images. Therefore, whilst it is still appropriate only for images of the same modality, it can accommodate images effectively being acquired with different intensity windowing.

**Inter-modality**

The relationship between voxel intensities assumed for intra-modality registration will not hold for inter-modality registrations. One set of approaches to the inter-modality registration problem pre-processes images of different modalities, either by mapping intensities (van den Elsen et al. 1994) or by extracting gradient features as described in Section 4.3.2, to make the images appear to be for the same modality.

A more broadly applicable approach to multi-modal registration is to use information-theoretic measures. These methods view registration as a process to maximise the amount of shared information between two images. Typically the amount of information in an image is calculated using the Shanner-Wiener entropy measure $H$. The image intensities are grouped into ‘bins’ of similar intensities. The Shanner-Wiener entropy measure is then described in terms of the marginal probability $p(a)$ of a voxel having an intensity $a$, summed over all the intensities in the image:

$$H(A) = -\sum_a p(a) \log p(a)$$
The need to select the number of bins used (typically between 32 and 256) introduces an additional, empirically chosen, parameter.

Several image similarity measures based on the Shanner-Wiener entropy have been proposed. For example, joint entropy measures the amount of information present in the combined image:

\[ H(A, B) = -\sum_a \sum_b p(a,b) \log p(a,b) \]

where \( p(a,b) \) is the joint probability of a voxel having intensity \( a \) in the first image and intensity \( b \) in the second image. Minimising the joint entropy achieves registration. However this measure is very sensitive to image overlap. In particular, if air is included in the image volume, a transformation which increases the amount of air overlapping in the two images will tend to reduce the joint entropy.

To avoid this, it is important to also consider the amount of information contributed to the overlapping volume by each image, which is provided by a measure known as mutual information (Maes et al. 1997; Viola 1995). Since changes in overlap of these low intensity regions can have a disproportionate contribution to this measure a more suitable similar measure is \textbf{normalised mutual information (NMI)} (Studholme et al. 1999):

\[ C_{NMI} = \frac{H(A) + H(B)}{H(A, B)} \]

\textit{Capture Range}

When voxel-based measures are used as the similarity metric, iterative techniques are typically required in order to determine correspondence. Global optimisation schemes are not practicable and instead local optimisation schemes must be used. These schemes are liable to getting trapped in local minima. Furthermore the resulting registrations process has a limited capture range: if there is insufficient initial overlap between corresponding regions in the source and target images then the optimisation scheme (for example conjugate gradient or downhill descent methods) will fail to head towards the global minima. A common way to address these issues is to use a multi-scale technique, whereby the registration is initially performed at a coarse resolution and then increasingly fine resolutions are used to achieve the final registration, for example (Crum et al. 2005; Rueckert et al. 1999).

\subsection*{4.4 Transformation Model}

The transformation model specifies the way in which the source image can be changed to match the target image. A number of transportation models have been proposed over the past couple of
decades. This section is not intended to be a comprehensive review of them, but instead is intended to describe the more common and relevant ones, and to highlight any modifications available to improve their ability to recover large deformations. A more comprehensive review can be found in (Holden 2008) and the references contained therein.

A diffeomorphic transformation is one which is smooth and invertible, so that every point in one image is represented by a corresponding point in the other image. It will not cause folding or tearing of the source image, and the Jacobian (defined in Equation B.10) of the deformation field is positive everywhere. This is often a desirable property when performing intra-subject registrations and, as will be noted in the following sub-sections, is not an inherent property of all transformation models.

**Rigid and Affine**

If a body does not significantly deform between two sets of imaging but is merely re-positioned - the ‘rigid body’ assumption - then the transformation can be described in terms of a translation followed by a rotation. If homogeneous coordinates are used then in 3D this can be described in terms of a 4 x 4 transformation matrix. In the rigid body case, the 12 variable components of this matrix depend on just 6 independent parameters. The number of independent parameters can be increased to 8 so that scaling and skewing are included in order to model a so-called affine transformation. Parallel lines remain parallel under an affine transform. For intra-subject registration an affine transformation is not particularly useful since it does not reflect the manner in which soft tissue deforms. Affine transformations however can be used to correct for scanner errors and to normalise between subjects.

Typically either a rigid or an affine transformation is used to align the source and target images prior to performing a non-rigid registration.

**Elastic**

Elasticity can be used as the basis of a non-rigid transformation model. The source image volume can be imagined to be formed of a block of linear elastic rubber. Forces to deform this source block and bring it into registration with the target image can either be derived directly from an image-similarity measure (Bajcsy and Kovacic 1989) or can be based on features or surfaces extracted from the image (Hagemann et al. 1999). For small deformations, the response at position \( x \) in this volume to a body force \( f \) derived from the image similarity measure will be given by the Navier-Cauchy equation, which follows from the equilibrium equation (Equation B.13):

\[
\mu \nabla^2 u + (\mu + \lambda) \nabla (\nabla \cdot u) + f(x) = 0
\]
where $\mathbf{u}$ is the current estimate of the displacement field, $\lambda$ and $\mu$ are Lamé’s first and second parameters, as defined in Equations B.21 and B.22.

Methods used to solve the Navier-Cauchy partial differential equation include finite differences (Broit 1981), finite element methods (Hagemann et al. 1999), and basis function expansion (Christensen et al. 1994).

In elastic registration’s most basic guise, realistic material properties are not assigned to tissues. Instead elasticity is used simply as a tool to regularise the deformation. It is possible to assign spatially varying material properties based on an image segmentation (Hagemann et al. 1999), but determining suitable parameters is challenging since, as discussed in the previous chapter, soft tissue can have non-linear material properties with respect to both strain and strain-rate. Indeed, it is not clear how strain-rate nonlinearity could be suitably incorporated into a registration framework.

Since the Navier-Cauchy equation is based upon the assumption of small deformations this approach is not strictly valid for larger deformations, and the deformation is not constrained to be diffeomorphic (Christensen et al. 1996). It is possible, though computationally expensive, to use formulations appropriate for large deformations: Xu and Nowinski (2001) apply small strain, large deformation theory to the problem of brain atlas registration.

Since the restoring force in an elastic registration increases with strain, large deformations are heavily penalised. This suggests that elastic registration is inappropriate for registering pairs of images if large deformations have occurred between them. Therefore, as will be apparent from the references in this section, it has primarily been used for neurological applications. However, Roose et al. (2008) have used linear elasticity to match MR images of prone breasts acquired at different time points. Their technique is driven by the weighted combination surface-matching (which assumes the breast is perfectly segmented in each image) and SSD image-intensity matching (applied only at the surface points). Their key motivation is to avoid unrealistic deformations (particularly volume change) and whilst they show their technique results in smaller volume change than an alternative registration scheme (free-form deformations, described below, driven by the SSD calculated for every voxel), they do not assess the accuracy of the resulting registration.

**Fluid**

In fluid registration, correspondence is obtained by modelling the deformation of the source image as the flow of a viscous liquid, where the deforming force at each time-step (or iteration) is derived from the image similarity measure. It should be noted that the use of the fluid
registration does not assume that the imaged material is a fluid and in fact meaningful registration results are unlikely for that scenario. Rather, this transportation model is used because the resulting deformation has some useful properties. Firstly, posing the registration in terms of an appropriate formulation of continuum mechanics means that the resulting deformation will be diffeomorphic. Secondly, large deformations are possible since for a viscous fluid the stress that constrains the deformation relaxes over time.

The response of this viscous fluid to a body force \( f \) derived from the image similarity measure is given by the Navier-Stokes equation:

\[
\mu \nabla^2 \mathbf{v} + (\mu + \lambda) \nabla (\nabla \cdot \mathbf{v}) + f(\mathbf{u}) = 0
\]

where \( \mathbf{v} \) is the instantaneous velocity field, \( \mu \) and \( \lambda \) are now coefficients of viscosity and \( \mathbf{u} \) is the current estimate of the displacement field which will depend on a point’s position \( \mathbf{x} \). The Navier-Stokes equation is identical to the Navier-Cauchy equation described above for elastic registration except that the partial differential operators act on the velocity rather that the displacement: it is this distinction which leads to the relaxation of stress over time.

The first term in the Navier-Stokes equation describes the constant volume viscous flow of the liquid, whilst the second term will be non-zero when regions expand or contract. Since the Navier-Stokes equation is not being used to describe a real fluid, the value of the viscosity parameters cannot be physically measured. Although they could be optimized on an application-specific basis, all authors except Lester et al. (1999) have chosen to set \( \mu = 1 \) and \( \lambda = 0 \), which balances the first two terms such that axial compression can occur without lateral expansion.

In contrast to solid mechanics, the partial differential equations of a fluid mechanics problem are typically solved in an Eulerian frame of reference on a discrete lattice, or grid. Although the transformation solved on the continuum would not become singular, the transformation solved at these discrete grid points can. To prevent this, a re-gridding strategy is typically used, which monitors the local Jacobian determinants. If any are less than a threshold (typically 0.5) the preceding transformation is applied to generate a new source image. These transformations are accumulated when the registration completes.

Historically, one of the disadvantages of fluid registration is that solution of the Navier-Stokes equations is computationally expensive and time-consuming. Typical algorithms used to solved this equation are successive over relation (Christensen et al. 1996) and full multigrid (Freeborough and Fox 1998). Recent work has shown the potential for graphics processing units to speed up the registration by parallelising the process (Noe et al. 2008).
The early applications of fluid registration were in the registration of neurological images (Christensen et al. 1997; Crum et al. 2001; Freeborough and Fox 1998), but it has also been applied to applications where larger deformation may be anticipated. For example, Crum et al. (2005) applied fluid registration to recover the deformation of the breast caused by compression between two plates as observed in MR images. On two volunteer datasets (using 12 landmarks per breast) they found that fluid registration could recover the deformations to a mean accuracy of 1.0-1.5mm compared with a mean landmark displacement of 6.4-6.8mm before registration.

In the technique presented by Melbourne et al. (2007) for registering dynamic contrast enhanced MR images of the liver based on principle component analysis, there is an underlying assumption that a non-rigid registration algorithm can recover the deformation of the liver through the breathing cycle in the absence of contrast enhancement. The exemplar registration algorithm used was fluid, and the resulting registered images were visually preferred to non-registered images.

The algorithm seems to perform less well for larger deformations however: Bond (2006) used the fluid algorithm described by Crum et al. (2005) to register pairs of 2D MR image slices of the colorectal region acquired pre- and post-treatment for cancer. She found that the positions of lymph nodes are recovered to 7mm, and that the registration algorithm fails (i.e. the resulting error is greater than an affine registration alone) on 2 out of the 10 cases.

Modifications to the fluid algorithm to make it more suitable for recovering large deformations have been proposed. Christensen et al. (2001) used a fluid algorithm to register CT images of the female pelvic region which were acquired during the 6-7 week course of radiotherapy treatment for cervical cancer. To cope with the large deformation between scans caused by the presence of different applicators and varying bowel and bladder contents, Christensen et al. use a ‘fluid-landmark’ registration to initialise the intensity-based fluid registration. In the fluid-landmark registration the cost function evaluated at each iteration consists of a similarity metric based on the distance between corresponding points in the two images and a term which penalises large gradients in the velocity field (with respect to both space and time) to ensure a smooth deformation. After the final iteration corresponding landmarks will be coincident.

Wang and Staib (2000) modified the fluid registration algorithm by introducing statistical shape information into the cost function. The technique is demonstrated on 2D warped brain and heart MR images, with the resulting registration error being halved for these cases compared with conventional fluid registration.

**Spline-based registration techniques**

Bookstein (1989) proposed the use of thin plate splines, for registering medical images. Thin-plate splines are a linear combination of radial basis functions. These splines minimise the
‘bending energy’, which is analogous to the strain energy stored when slightly bending a thin metal sheet. So-called control points are located at corresponding features in the source and target image. These control points can be arbitrarily located at distinctive features. The spline provides the displacement required to map the location of the control point in the target image to the corresponding point in the source image. Between control points the displacement field is smoothly interpolated by the spline. Rather than relying on manually identified corresponding features, the algorithm of Meyer et al. (1997) uses a voxel-based similarity measure to drive the registration. The suitability of thin-plate splines for registration is limited because the radial basis functions have infinite support, which results in each control point having a global influence on the transformation and the problem becoming very computationally expensive.

Free-form deformations (FFDs) are based on functions, such as B-splines, which provide only local support. This makes them more suitable for modelling local deformations and, compared with approaches based on thin-plate splines, they are computational efficient even if large numbers of control points are used. However, unlike with thin-plate splines, the control points must be arranged in a grid-like fashion with regular spacing \((\delta_x, \delta_y, \delta_z)\). The B-spline deformations can be expressed as a 3D tensor product of 1D B-splines:

\[
\mathbf{u}(x, y, z) = \sum_{l=0}^{3} \sum_{m=0}^{3} \sum_{n=0}^{3} B_l(u) B_m(v) B_n(w) \phi_{i+1,j+1,k+1}
\]

where

\[
i = \left\lfloor \frac{x}{\delta_x} \right\rfloor - 1; \quad j = \left\lfloor \frac{y}{\delta_y} \right\rfloor - 1; \quad k = \left\lfloor \frac{z}{\delta_z} \right\rfloor - 1;
\]

\[
u = \frac{x}{\delta_x}; \quad v = \frac{y}{\delta_y}; \quad w = \frac{z}{\delta_z}; \quad u = \frac{x}{\delta_x} \left(1 - \left\lfloor \frac{x}{\delta_x} \right\rfloor \right);
\]

and the B-spline basis functions \(B_i\) are given by:

\[
B_0(s) = (1-s)^3 / 6
\]
\[
B_1(s) = (3s^3 - 6s^2 + 4) / 6
\]
\[
B_2(s) = (-3s^3 + 3s^2 + 3s + 1) / 6
\]
\[
B_3(s) = s^3 / 6
\]

Ruecket et al. (1999) presented an FFD approach which incorporated a voxel similarity measure (normalised mutual information) in the cost function. This allowed the registration process to be automated by searching for the control point displacements that minimised the cost function. In addition to an image similarity measure, the cost function can include penalty terms which favour properties deemed to be desirable in the resulting transformation. Examples include the
3D counterpart of ‘bending energy’ to enforce smoothness (Rueckert et al. 1999), and volume preservation (Rohlfing et al. 2003).

The initial application of Rueckert’s algorithm was registering pre- and post-contrast MR images of the breast. Tanner et al. (2000) later showed that for such enhancing images the deformation field found by original algorithm included unrealistic changes in local volume. Therefore Tanner (2005) includes a volume preserving term in the cost function. In this work she showed, on data simulated using a biomechanical model, that FFDs with fine (20mm) control point spacing produced generally better results for large deformations, whilst larger (40mm) control point spacing produced better results for small deformations and the enhancing lesion. Applying the best performing registration configuration to the test data set reduced the mean registration error over the breast from 1.40mm to 0.45mm.

In addition to registering prone images of the breast, FFD-based registration has found widespread application in registering medical images: the following examples highlight some of the applications where large intra-subject deformations of soft tissue occur. In (McLeish et al. 2002) this algorithm was used in a study of heart motion through the breathing cycle. It has also been used to study motion through the cardiac cycle by registering tagged MR images with the end-diastolic frame for each subject and then registering the untagged end-diastolic of different subjects (Chandrashekara et al. 2004). Rohlfing et al. (2004) used FFD-based registration of gated MR images for modelling liver motion during the respiratory cycle. They found that the non-rigid deformation between distant timepoints in the cycle was sometimes too large (up to 34mm in one case) to be easily captured by the registration process, and therefore used the deformation field of the preceding timepoint as an initialisation for each registration.

Behrenbruch (2002) adapted the B-spline registration work of Hayton et al. (1999) to register prone and supine MR images of the breast using B-splines, driven by a surface matching algorithm. However no experimental validation was reported.

Bond (2006) found that an FFD-based registration algorithm was even less effective than a fluid registration algorithm when registering pairs of 2D MR image slices of the colorectal region acquired pre- and post-treatment for cancer: the positions of lymph nodes are recovered to only 30mm, and the algorithm failed on 4 out of the 10 cases.

Multi-resolution can be incorporated into an FFD framework by initially registering at a coarse image resolution using a coarse mesh of control points, and then increasing both the image and the mesh resolution (by introducing more control points) once convergence has been achieved at the coarse resolution (Rueckert et al. 1999).
Although the B-spline algorithm is not inherently diffeomorphic, one way to enforce this behaviour is to include a penalty term which prevents local volume change. Alternatively Rueckert et al. (2006) propose a method which uses a composition of FFDs, each of which is constrained to be diffeomorphic by limiting the maximum control point spacing (Choi and Lee 2000). For intra-subject registrations, Rueckert et al. found the latter approach to be more accurate than using a penalty term.

**Optical Flow and the Demons Algorithm**

Optical flow registration (Horn and Schunck 1981) is appropriate for tracking small scale motion in a time sequence of images. It is based on the assumption that the intensity of a given point remains constant between two timepoints, in which case the displacement can be approximated from

$$\Delta I + \nabla I \cdot u = 0$$

where $\Delta I$ is the temporal difference between a pair of images, $\nabla I$ is the spatial gradient and $u$ is the displacement between images.

Thirion (1998) proposed that non-rigid registration could be modelled as a diffusion process. Inspired by the ‘Maxwell’s demon’ thought experiment in thermodynamics, he created effectors, or demons, which applied a force to deform the source image. The force applied by these demons was derived from the optical flow equation, renormalized to prevent instability when the image gradient was small.

The demons algorithm is computationally attractive, because it is fast and is perhaps more straightforward to parallelise than other non-rigid registration algorithms (Muyan-Ozcelik et al. 2008). Since there are no constraints on the displacement, regularisation is typically performed by alternately applying the demons force and applying Gaussian blurring. A modification to the demons algorithm which limits the resulting deformation to be diffeomorphic has recently been proposed (Vercauteren et al. 2007). Although, like most non-rigid registration algorithms, the demons algorithm has mostly been used to register brain images, it has been demonstrated to have application in some organs which undergo larger deformations, such as the lung (Boldea et al. 2003).

### 4.5 Image-Guided Surgery

Using spatial information extracted from medical images to assist surgical navigation is a process known as image-guided surgery. The most common motivation for adopting image-guidance techniques is that they can make it possible to reduce the invasiveness of a procedure.
Although interventions such as placing a guidewire under ultrasound guidance could be considered ‘image-guided’ the term is normally applied only to those situations in which the coordinate system assigned to a patient is related to that of a medical image or atlas via a registration step. This concept almost pre-dates medical imaging since it can be traced back to the stereotactic frame invented a century ago at University College London Hospital by Sir Victor Horsley and Robert H Clarke (Horsley and Clarke 1908), only 13 years after the discovery of X-rays was published, which relied on atlas information.

In an attempt to provide 3D intraoperative guidance, both intraoperative CT (Lumsford 1982) and intraoperative MR (Black et al. 1997; Sutherland et al. 1999; Tronnier et al. 1997) scanners have been developed. However, these are expensive solutions both in terms of capital and running costs. Intraoperative CT is further limited because it involves ionising radiation, has relatively poor soft tissue discrimination and is limited to a fixed slice direction, whilst intraoperative MR is incompatible with conventional instruments, limits access to the patient and requires significant alterations to standard surgical practice.

Preoperative 3D imaging has several advantages over intraoperative imaging, and preoperative diagnostic images are routinely available. Diagnostic machines tend to have a better image quality because fewer compromises need be made in their design and in the scanning protocols that are used. In particular, the use of longer scan times can be used which significantly improves the signal to noise ratio in MR. Acquiring the images prior to surgery means that there is sufficient time for them to be carefully analysed and preoperative surgical plans to be prepared. With intraoperative MR or CT, professionals skilled in image interpretation (such as radiologists) need to be present during the prohibitively time-consuming process of the intervention, increasing costs still further.

Methods have been developed to align the preoperative image to the physical space in the operating theatre. Neurosurgery was one of the first application areas to adopt these methods. To allow alignment, it is necessary to establish a coordinate system within the operating theatre. The earliest techniques, whilst having a high mechanical accuracy, required stereotactic frames to be attached during both imaging and surgery (Maciunas et al. 1994). More recently, frameless tracking techniques have been developed. The most common of these techniques in current surgical practice is the optical localisation of a ‘tracked pointer’. In such an optical systems, the pointer typically has retro-reflective spheres or infrared emitting diodes (IREDs) mounted on its handle the locations of which are triangulated using a system of cameras. The pointer is calibrated so that its tip location is known relative to these spheres/IREDs. Examples of commercially optical localisers include the Polaris and Optotrak (Northern Digital Inc. Ontario, Canada), the easyTrack range (Atracsys IIC, Bottens, Switzerland) and the MicronTracker (Claron Technologies Inc., Toronto, Canada). Such devices require line-of-sight between the
cameras and the tracked points, which is not always straightforward to achieve. Early tracking systems tended to be mechanical, typically using passive articulated arms (Sandeman et al. 1994; Watanabe et al. 1991), but such mechanical systems are not often used these days since they are cumbersome in the surgical environment. Electromagnetic tracking devices (Raab et al. 1979; Reittner et al. 2002; Shahidi et al. 2002) have the significant advantage that they do not require line-of-sight but their accuracy can be affected by the presence of metal.

The coordinate transformation (or registration) between the preoperative medical image and the operating theatre is most commonly achieved by identifying markers which have been attached to the patient’s skin or bones and which are locatable in both the image and the operating theatre. This transformation is generally considered to be rigid. Closed form solutions exist for rigid transformations (Arun et al. 1987), and so registration can be rapidly achieved at the beginning of the surgical procedure.

Tissue deformation will cause inaccuracies when using a rigid-body transformation, which are often unacceptably large for many surgical applications. One possible solution to this problem is to use biomechanical models as a means of using additional information to constrain a non-rigid registration. This approach is described below.

4.6 Biomechanical Modelling for Image-Guided Surgery

In order to use a preoperative image to provide image-guidance for surgery on soft tissue, it is desirable to warp the image appropriately by using intraoperative measurements as constraints on the deformation. These measurements can be expected to be incomplete and of lower spatial resolution than the preoperative image. The registration method should bring corresponding points in the preoperative and intraoperative images into alignment and provide appropriate interpolation or extrapolation to predict the behaviour of the tissue in regions where intraoperative measurements are not available. When non-rigidly registering two 3D images, such as MR or CT, “mathematically based” transformation models, as described in Section 4.4, are typically used. However, given the sparse nature of the intraoperative measurements during image-guided surgery it is desirable to be able to also include information about the behaviour of the soft tissue. Biomechanical models, the principles of which were described in the previous chapter, should allow priors about the behaviour of tissue to be introduced as additional constraints. They therefore show promise as the basis of an intraoperative soft tissue registration technique. The steps necessary to use biomechanical models for image-guided surgery are illustrated in Figure 4.1.
Surgery imposes a number of practical restrictions on the modelling techniques. Perhaps the most significant of these is time. Whilst most surgery can be considered quasi-static, to be surgically useful model-updated images must be available to the surgeon within, at most, a few minutes. Although making a model increasingly comprehensive might make it able to describe tissue deformation more accurately, it is likely it will take longer to solve. The time constraints of image-guided surgery often require simplifications to be imposed in order to fulfil the computational requirements. These simplifications can occur at both the modelling stage (such as linearising the strain tensor or the constitutive law) and the numerical stage (for example, by using linear elements or explicit time integration). In the field of surgical simulation, Bro-Nielsen and Cotin (Bro-Nielsen and Cotin 1996) have applied a process called condensation to significantly reduce the size of the stiffness matrix to include only the surface nodes, whilst giving exactly the same results as would be given if all nodes were considered. Another approach, suitable for linear elasticity, is pre-computation. A unit force is applied to the surface nodes in each coordinate direction and the resulting deformation is stored. Then the deformation, due to any force or set of forces applied, can be computed by superposition (Cotin et al. 1999). Techniques have been developed which avoid the need to assemble the stiffness matrix, for instance the Tensor-Mass method (Cotin et al. 2000), which can allow elements to be easily removed from the mesh during surgery simulation. The original Mass-Tensor method proposed was valid only for small strains, but has since been extended to be appropriate for large strains (Picinbono et al. 2000). An alternative approach is to parallelise the finite element code: this is done by Taylor et al., who use an explicit formulation of the FEM (i.e. unlike the
quasi-static approach used in almost all papers discussed in this thesis, the time dependence
remains explicit) implemented on a graphics processor unit (GPU).

Building a comprehensive model is hampered by the fact that it is not generally possible to
know the stresses which are on, and present in, the organ in the preoperative image from which
the model will be built. Determining the material properties of soft tissue to use in the model
can be complicated, as illustrated in the discussions of the previous chapter. Also inter-subject
variability of these material properties can be expected, especially as pathology will be present
in patients.

Stresses acting on the organ during surgery are not generally available. Displacements of the
organ can be measured, but these will be subject to measurement error and, as the modalities of
preoperative and intraoperative images differ, establishing correspondence between anatomical
structures is difficult and will be a further source of error.

Recognising that having a complete knowledge of the initial conditions, boundary conditions
and loads on the model is not feasible, the selection of a suitable model requires the need to
comprehensively model the tissue behaviour against the requirement for deformations to be
computed rapidly. It is the effective incorporation of suitable intraoperative measurements as
boundary conditions that will allow simpler models to improve the accuracy of surgical
guidance.

4.7 Intraoperative Measurements

It is necessary to establish boundary conditions on the model during surgery, which will drive
the model so that it deforms to match the surgical situation. Although both stress and
displacement boundary conditions can be applied to a model, it is generally only feasible to
measure displacement data. This displacement data can be helpfully divided into two types –
surface displacements and sub-surface displacements.

Typically, an exact match between the measurements and the node points is imposed. This may
be inappropriate, both because of measurement uncertainty and as the discrete node points will
not coincide exactly with the measurement locations. As a result, unrealistic forces will be
computed and incorrect displacements might occur elsewhere in the model. One approach to
resolving this difficulty is to utilise data assimilation techniques which, given a non-perfect
model and noisy parameters, attempt to estimate the most likely state of the model whilst
simultaneously estimating the parameters of the model (Lunn 2003; Lunn et al. 2003a).
4.7.1 Measurement of surface displacements

**Contact**

It is possible to use a tracked pointer (described in Section 4.5) to acquire points on the surface (Cash et al. 2003; Hill et al. 1998; Ma and Ellis 2003). This technique has the advantages that the pointers are easily available, and the surgeon is likely to be familiar with their use. Whilst line-of-sight from the tracking unit to the pointer is required for optical tracking devices, line-of-sight to the pointer tip is not required, so points that would otherwise be occluded can be measured. The surgeon can establish correspondence between hand-picked points and anatomical landmarks visible in the images.

However, datasets collected with a pointer are usually very sparse and irregularly sampled. There is also a high likelihood of outliers due to excess contact force displacing the soft tissue, the pointer losing contact with the surface, or errors in establishing point correspondence. Furthermore, it can often take considerable time to collect a reasonable dataset. This technique, therefore, is not so suitable for measuring surface displacements that are to be applied as boundary conditions on a model.

**Laser Range Scanner**

A more densely and regularly sampled dataset can be acquired using a laser range scanner. A 3D surface may be rapidly acquired by translating a laser ‘stripe’ (Audette et al. 2003). The accuracy of such a system is typically of order 0.5mm (Audette et al. 2003; Miga et al. 2003). An extension to the laser range scanner technique has been used where a photographic texture map image is also acquired which can be overlaid on the surface acquired by the laser (Cash et al. 2003; Sinha et al. 2003).

Whilst laser range scanners circumvent some of the difficulties associated with using a hand-held pointer, they can suffer from specular reflections causing spurious or missing data points, and occlusions causing data to be missing. In addition, pooling fluid on the surface could result in the incorrect surface being measured. Establishing point-by-point correspondence is, in most cases, difficult when matching surfaces.

**Stereopsis**

Calibrated stereo cameras can also be used to recover surfaces. These stereo cameras may use the optical system of a standard surgical microscope (Sun et al. 2003) or an independent system (Skrinjar et al. 2001). For operations where surgical microscopes are appropriate, the cameras can be placed close to the surgical scene without obstructing the surgeon. However, the view that the surgeon acquires may not be the most appropriate for driving a model. These methods
Chapter 4. Image Registration and Image-Guided Surgery

rely on careful calibration of the stereo optics of the system including such effects as variable zoom.

When cameras are mounted independently, the surgeon may obstruct the view of the surface, but a larger field of view is generally available. Again, surgical lighting and specular reflections can cause problems for stereopsis systems, fluid can prevent the true surface from being detected and establishing a point-by-point correspondence is difficult. Stereo cameras can typically be used at a greater range then laser range scanners.

4.7.2 Measurement of sub-surface displacements

Ultrasound

Ultrasound is an important technology for obtaining information, non-invasively, about the position of sub-surface structures (Trantakis et al. 2002; Unsgaard et al. 2002). Existing methods generally involve tracking a 2D B-mode ultrasound probe using an external 3D localisation device to provide 3D image data on subcutaneous tissue, although ultrasound transducers capable of acquiring a 3D volume have recently become commercially available.

Although ultrasound is attractive since it is a portable, low-cost, safe, real-time and widely available imaging modality, ultrasound images are often difficult to interpret and are not amenable to automatic segmentation due to the presence of so-called speckle, geometric distortion and artefacts, such as acoustic shadowing, and low contrast. Therefore, time-consuming and labour-intensive manual or semi-automatic segmentation of anatomical features are currently necessary for most applications, and this presents an obstacle to the widespread adoption of ultrasound as a means of quantifying tissue displacement. It can be especially difficult to obtain high quality ultrasound images intraoperatively due to limited access or patient position and attenuation limits the depth to which tissue can be imaged. The quality of the images obtained is operator-dependent, and force may need to be applied on the imaged tissue with the ultrasound transducer, or an interface such as saline or gel to be introduced, to provide acoustic coupling. The presence of surgical instruments within the field-of-view may give rise to artefacts.

Although the high resolution of modern ultrasound scanners suggests that, in principle, accurate localisation of anatomical structures should be possible, in practice, this is rather more difficult. For example, Lunn et al. (2003b) demonstrate that freehand 3D ultrasound can detect the motion of spherical markers implanted in a porcine brain to within an accuracy of 1.1mm. However, the acoustic properties of these markers differ considerably from that of typical anatomical landmarks, and are consequently very much easier to localise.
Interventional Magnetic Resonance Imaging

An alternative method of measuring sub-surface tissue displacement is to use an interventional MR scanner (Ferrant et al. 2001; Nimsky et al. 2000). By using a few relatively low-resolution, intraoperative MR images to drive biomechanical models, information from preoperative CT and MR, acquired with longer acquisition times and carefully segmented, could be used in the operating theatre.

This technique has the advantages that a more complete dataset is available to provide boundary conditions, and the similar modalities of the pre- and intraoperative imaging may aid the task of establishing correspondence. Although this is a very expensive approach, and would involve a number of the disadvantages of intraoperative MR imaging already described above, it has the significant attraction that validation of a model’s suitability for the image-guided surgery task becomes a more tractable problem.

X-ray

X-ray fluoroscopy is perhaps the most widely used intraoperative imaging modality, but it remains a significant challenge to identify the 3D location of features from the 2D projection images such that these features could be used as boundary conditions. X-ray images exhibit relatively poor soft tissue contrast and so are most likely to provide useful information about soft tissue deformation either when contrast agent has been administered, such as in angiography, or near bony structures such as the spine (Penney et al. 2002). However, rotational C-arm X-ray systems which are capable of forming 3D images have relatively recently become available (Koppe et al. 1995; Moret et al. 1998). The increasing availability of these devices, and of interventional CT, means that in future systems X-ray imaging is likely to play a role in establishing boundary conditions on biomechanical models.

4.8 Application of Biomechanical Models for Image-Guided Surgery

Since biomechanical models have not previously been used to assist in image-guided surgery of the breast, I briefly review here experiences in the two soft-tissue applications where models have been used: neurosurgery and liver surgery.

4.8.1 Neurosurgery

The majority of the research on correcting for soft tissue deformation has focussed on neurosurgery. In part this has been driven by the existing use of image-guided surgery techniques in neurosurgery, which means that 3D images are available, and that surgeons are familiar with the guidance systems. Furthermore the skull constrains the brain, making this
problem better constrained than most other soft tissue deformations. The proximity of critical structures means that high accuracy is required when performing neurosurgery.

The deformation of brain tissue which occurs during neurosurgery is termed brain-shift. It is a complex process which occurs throughout an operation. Its causes include changes in pressure and fluid levels due to the release of cerebral spinal fluid after the dura mater has been opened, physiological responses to anaesthesia and retraction and resection performed by the surgeon. Several researchers have attempted to quantify the phenomenon of brain shift (Bucholz et al. 1997; Hartkens et al. 2003; Nimsky et al. 2000; Roberts et al. 1998). They report a mean shift of order 5-10mm and found that there are general trends for more radical surgery, such as tumour resection, to cause more brain shift than procedures such as biopsy. They also found that displacement is generally in the direction of gravity.

Brain-shift causes a degradation of the accuracy of the registration between the medical images and the brain. Since the late 1990s researchers have been considering how these shifts might be predicted and be taken into account during registration.

**Mechanical Properties of Brain Tissue**

The consensus is that brain tissue is a non-linear viscoelastic material. However measurements of its material properties have varied by an order of magnitude (Haug et al. 2004, Table B12). Gefen and Marguiles (2004) suggest that time between death and post-mortem examination is the dominant cause for this variability.

The tissue samples have been tested in-vivo, in-situ and in-vitro. These differing conditions might be expected to be one cause of the variation in the measurement of material properties. Gefen and Marguiles have found that only the long-term time constant of relaxation significantly decreases from in-vivo to in-situ, and that perfusion had no effect on any other property. These results differ from the significant decrease in stiffness which was predicted from simulations by Bilston (2002), and the experimental results of Metz et al. (1970) who found that the mechanical resistance of brain tissue to expansion of a balloon catheter decreased post-mortem, but the results agree with Miller et al. (2000)’s indentation experiment, performed on one swine. Gefen and Marguiles found that the difference between in vivo and in vitro results was greater, although transient properties were relatively unaffected. Miller and Chinzei (2002) performed in vitro uniaxial tension of swine brain tissue. In the study non-linear stress-strain relations were observed, and a strong dependence between stress and strain rate was recorded. Furthermore, they found that brain tissue is much more compliant in extension than in compression.
Biomechanical Modelling of Brain Tissue

Most researchers applying the FEM to image-guided surgery have focused on linear-elastic models of the brain, which benefit from computational simplicity and therefore are relatively quick to solve. Hexahedral (Skrinjar et al. 2001; Wittek et al. 2004) and linear tetrahedral (Clatz et al. 2003; Ferrant et al. 2001; Miga et al. 2000; Paulsen et al. 1999; Warfield et al. 2002) elements have both been used for modelling brain tissue. Skrinjar et al. (2001) used linear elasticity to model brain deformations, based on surface displacements, for two cases. A maximum landmark displacement of around 3.8mm was recovered, with a maximum model error of 1.4mm. Ferrant et al. (2001) used a linear elastic FEM to infer a volumetric deformation field from surface deformations, based on intraoperative MR. The mean distance and standard deviation between the predicted and measured location of 400 landmarks was $0.9 \pm 0.7$mm. Clatz et al. (2003) proposed, without quantitative evaluation, a linear elastic model to predict the gravity-induced deformation of the brain based on the cerebral spinal fluid levels during long procedures. Warfield et al. (2002) showed that results could be obtained in a surgically useful timeframe by using a parallel implementation and a linear elastic model. The use of elastic models has been extended by Hagemann et al. (1999) who coupled elastic and fluid models to describe the behaviour of solid tissue and cerebrospinal fluid. However the computation time reported (about 35 hours) was too significantly slow to be surgically useful despite only being implemented in 2D.

The sponge-like behaviour of the brain has prompted the application of a porous media model to represent the brain (Basser 1992; Nagashima et al. 1990a; Nagashima et al. 1990b; Tada and Nagashima 1994). This model, assuming infinitesimal deformation, has been extensively used by the group based at Dartmouth College in a series of porcine and human studies (Miga et al. 2000; Paulsen et al. 1999; Platenik et al. 2002). Validation experiments have included translation of a temporally located piston, balloon inflation and hemisphere retraction, and the predictions have been found to recover around 80% of the tissue motion. Applying the model to clinical cases found that the brain shifted, on average, 5.7mm in the direction of gravity and that model predictions were able to recover this motion to a mean error of 1.2mm.

The linear elastic FEMs discussed so far make the assumptions of small strain and small deformation, which allow linearity to be assumed. The appropriateness of using small deformation approximations to describe neurosurgery is debatable. There are certainly applications, such as the placement of electrodes for epilepsy treatment, which can be expected to cause limited disruption. Significant deformations can be expected during more invasive operations, where the benefits of modelling the deformation are arguably greater. In these cases large deformation theory may be more suitable. However, it should be borne in mind that the suitable integration of intraoperative measurements with the model will reduce any error
introduced by simplifications such as linearisations. The effect of such simplifications may be less significant than the effect of appropriately applying boundary conditions and constraints, especially as the initial conditions on the model cannot be accurately known.

Miller et al. (1999; 2000) introduced a non-linear viscoelastic model suitable for surgical procedures. Unlike the models discussed so far, the constitutive equations proposed attempt to account for the relationship between stress and strain-rate. Miller and Chinzei (2002) later modified the constitutive law, as they found it was unable to represent the behaviour of (ex vivo) brain tissue in tension. Wittek et al. (2004) used this non-linear material response function, and considered a fully non-linear FEM formulation appropriate for large deformations. They modelled the indentation of a brain by surgical tools driven approximately perpendicular to the surface of the brain. The calculated and measured reaction forces encouragingly agree to around 20%, but there is no assessment of the displacement accuracy, which is the criterion of most interest for image-guided surgery.

A porous media model valid for finite deformations is described by Taylor and Miller (2004) and Miller et al. (2005). They develop this model, in 2D, for the purpose of studying structural diseases of the brain. They argue that the timescale of the interstitial flow within the brain is large compared with the time scale relevant to surgical procedures, and that therefore the model is not appropriate for surgical simulation.

The majority of modelling studies have focussed on predicting deformation prior to any resection or retraction. The modelling of resection is not straightforward within an FEM framework, because cutting introduces discontinuities which cannot be treated within elements. Miga et al. (2001) address this issue by generating nodes along the retractor position before separating the mesh by the retractor thickness. Serby et al. (2001) use a technique in which new nodes are not introduced along the line of surgical incision, but existing ones are displaced to this line. Vigneron et al. (2004) examines the applicability to surgical resection of the extended finite element method (XFEM) (Moes et al. 1999) in which additional shape functions are introduced that remove the need for remeshing when modelling discontinuities.

4.8.2 Liver

The standard treatment for a malignant tumour in the liver is resection. Although preoperative imaging is available, there are few external landmarks to guide the surgeon intraoperatively (Herline et al. 1999). The crucial goal is to completely excise the tumour, but it would be preferable to preserve as much viable, healthy, tissue as possible. Furthermore the liver is highly vascular, and so accurately executing a preoperative plan which takes account of the blood vessels is important. Herline et al. found that interactive image-guided surgery appeared to be
feasible for open and laparoscopic hepatic procedures and that it might have the potential to improve intraoperative localisation.

**Mechanical Properties of Liver Tissue**

Ex-vivo testing has been performed on pig, dog and human livers, and liver tissue has been found to be viscoelastic and to have a non-linear constitutive relationship for strains greater than 0.2% (Liu and Bilston 2000; Sakuma et al. 2003; Wang et al. 1992). When the liver is perfused, blood makes up around half of its weight. Liu and Bilston (2002) have therefore commented that perfusion may have an important influence on the mechanical properties on such a soft tissue. This hypothesis is supported by the experimental results of Kerdok et al. (Kerdok et al. 2006). Therefore it is necessary to also consider in-vivo measurements. Melvin et al. (1973) performed in-vivo uniaxial compression studies on the livers of rhesus monkeys at several strain rates and at a true strain of up to -0.5. The data from the studies has been used by Miller (2000) and by Bergstrom and Boyce (2001) to fit a second-order non-linear strain-energy function and the parameters of an elastomeric model respectively, both of which were capable of adequately representing the experimental results. Compliance probe measurements of the human liver by Carter et al. (2001) found the elastic modulus of healthy liver to be 0.27 MPa and diseased liver to be 0.74 MPa, compared with ex-vivo porcine liver samples which have an elastic modulus of 4.0MPa. Kim et al. Kim et al. (2003) found that porcine liver during surgery exhibited nonlinear and time-dependent properties, with a mean elastic modulus of 31.8kPa. This is comparable with the results (20kPa and 60kPa for the mean long term and instantaneous elastic moduli respectively) obtained in aspiration experiments by Nava et al. (2008) on in-vivo human liver tissue. It is much stiffer than the value of 6.7kPa obtained by Huwart et al. (2006) using MR elastography on patients without substantial fibrosis, but this may reflect the greater strains involved.

**Biomechanical Modelling of Liver Tissue**

Many of the initial attempts to model the biomechanics of liver incorporate simplifications to reduce the computational time to acceptable levels during surgical simulation. Boux de Casson and Laugier (1999) developed a two compartment mass-spring damper model: an exterior 2D mesh of springs for the capsule of Glisson and an interior volumetric mesh for the liver parenchyma. As mentioned in Section 4.6, BroNielsen and Cotin (1996) applied a technique which meant only surface nodes need be considered and Cotin et al. (1999) used pre-computation to reduce the time required to calculate small deformations of a linear elastic model, a technique which was later extended to account for large deformations. Monserrat et al. (2001) employed the BEM for computing deformations upon the liver surface during surgical simulation. Finite element models have also been used to describe the deformation of the liver during the respiratory cycle (Brock et al. 2003).
The challenge of correcting for deformation of the liver to allow image-guided surgery was been pursued by Cash et al. (Cash et al. 2005; Cash et al. 2003) who acquired surfaces of the liver using a laser range scanner at breath hold. These surfaces are coupled to a linear-elastic finite element model of the liver built from preoperative CT to describe its intraoperative state.

### 4.9 Visualisation

The registration techniques described so far in this chapter aim to calculate the coordinates of targets, preoperatively identified in medical images, in the operating theatre. To complete the image-guided surgery task it is necessary to convey this information to the surgeon, or to guide him to this point, in an effective manner. Three main approaches to this task have been employed: overlaying the position of a tracked pointer on medical images displayed on a conventional monitor, augmented reality and robotics

#### 4.9.1 Monitor-based Display

By far the most common approach is to track a handheld tracked pointer and superimpose the position of this pointer on the pre-operative medical images (possibly updated to account for deformation), or information extracted from these images. By watching the monitor on which these images are displayed the surgeon can see the position of the pointer relative to an identified target.

The technology used to track the position of the pointer has already been briefly described in Section 4.5. One way that the position of the pointer can be presented to the surgeon is to overlay it on orthogonal slices through the image volume. Either the volume can remain fixed and the probe can appear as a cursor moving on it, in which case the probe must be suitably represented when it moved out of a slice plane, or the volume can be resliced so that it remains centred on the pointer tip. Depending on the surgical task, it can be more meaningful to present alternative sections, such as slices orthogonal to the axis of the pointer.

Rather than, or in addition to, presenting slices through the medical image, a rendering of the volume can be presented to the surgeon. Typically this is achieved using surface rendering techniques which require the volume to be segmented. Although this segmentation may be performed preoperatively it is likely to be a labour-intensive task whether manual or semi-automatic techniques are used. Data is routinely presented in this way when identifying skin fiducial markers and planning a craniotomy, since the skin/air boundary is easy to segment.

Tracked pointer-based visualisation techniques have the significant advantage that they are easy to implement. They also tend to be relatively straightforward to validate, since the distance
between observed and computed landmark positions can be measured. However, from a user’s point of view they leave much to be desired. Firstly, although it is possible to calibrate most surgical tools to act as a pointer by attaching markers to them, they typically require the surgeon to hold a pointer rather than the surgical tool of choice. Secondly, and most significantly, they require the surgeon to move a pointer whilst watching a computer screen rather than the pointer. Since the pointer could be located close to critical structures within the patient this is clearly not ideal. Finally, as guidance information is not being presented in the most intuitive way there is a learning curve associated with using such a device.

There is, of course, no need to limit the underlying image to one specific modality – a set of co-registered images can equally be presented. For example CT might be used to provide structural information for navigation, whilst SPECT (Single Proton Emission Computer Tomography) is used to provide functional information. Indeed, there is no requirement for the underlying image to be a medical image in the usual sense: the VISLAN system (Colchester et al. 1996) was able to present live intraoperative video overlaid with information derived from the preoperative imaging. This was found to provide the surgeon with helpful guidance when outlining a craniotomy. In the system however, unlike the augmented reality systems described next, the video image is not aligned with the surgeon’s view, and the information is still not being presented in such a way that it appears aligned with the actual patient in the real world.

4.9.2 Augmented Reality

A beguiling approach to avoid the shortcomings of monitor-based display is to use augmented reality (AR) techniques to overlay the surgeon’s view of the patient with the computer-generated image of structures extracted from the medical images. This avoids the need for the surgeon to look away from the patient whilst operating. Applications which already require the surgeon to view the scene through a lens - such as an endoscope (Kawamata et al. 2002) or a surgical microscope (Edwards et al. 2000) - are likely to prove the most suitable applications, but stand-alone (Blackwell et al. 2000) and head mounted displays (Birkfellner et al. 2002; Vogt et al. 2003) have also been developed. Although the AR images can be presented in mono, presenting them in stereo provides a better sense of depth, which allows points to be located more accurately (Birkfellner et al. 2003).

The AR devices which have been used for image-guided surgery can be divided into two categories: optical see-through, such as (Birkfellner et al. 2002), and video see-through, such as (Vogt et al. 2003). In optical see-through AR, the user looks at the surgical scene through a half-silvered mirror. Reflected in the mirror is a small visual display unit, and the optical and computer-generated views are merged by the mirror. Ideally the computer-generated views should be presented at the same range as the surgical scene since otherwise the eye cannot
accommodate both views at the same time, and one will appear blurred. In video see-through AR the half-silvered mirror is replaced by a visual display unit. Video cameras mounted on the unit acquire the scene, and the image created by combing this video image with the computer-generated virtual scene is displayed.

Unfortunately there are many intricacies which currently limit AR as effective image-guidance technology, not all of which are intuitively anticipated. Firstly, since structures to be displayed must be segmented from the medical images, there is an additional task compared with pointer-based technologies which can present the raw images. Whilst this is a minor issue in the research environment, it would have a major impact on surgical workflow if AR were to become a routine practice. Irrespective of this, there are a number of more fundamental limitations. Any lag in the display of the real or the virtual world is unlikely to be acceptable to a surgeon, and may even be dangerous: this limits the amount of ‘real-time’ processing of the images which can be performed. If AR is being used to view a scene which would normally be viewed with the naked eye, there is likely to be a reduction in the image quality or brightness due to the camera or half-silvered mirrors. If optical see-through AR is used the calibration must take account of the surgeon’s eye position: if this is not tracked then any relative displacement of the display with respect to the eye will introduce error. The mind uses a range of visual clues in addition to stereopsis in order to assess depth, including perspective, occlusion, and shadows. Correctly detecting and modelling effects such as the occlusion of a virtual object by a real object is challenging. Finally, the adoption of AR in the operating theatre is hindered by the poor user experience associated with recent devices: generally surgeons have not found that the benefits of AR outweigh the disadvantages of today’s relatively bulky and awkward devices.

4.9.3 Robotics

An alternative to presenting information to guide the surgeon to a target is to use a robot to position the surgeon at the target, or even to perform the surgery. Such ‘image-guided’ robots are distinctly different from telemanipulator robots such as the Da Vinci robot (Talamini et al. 2003) which mimic a surgeon’s actions, even if the surgeon is operating on the basis of an AR display. Commercial examples of such robots include Robodoc ( Curex o Technology Corporation, Sacramento, USA), Pathfinder ( ProSurgics Ltd., Bracknell, UK) and CASPAR (URS Ortho, Rastatt, Germany). Image-guided robots have not, however, been widely adopted. The reasons for this poor uptake include the fact that robots typically can assist in a narrower range of operations than a (cheaper) tracked-pointer system; they operate based purely on the basis of the medical images and cannot easily incorporate additional information such as tactile feedback and tissue colour in the way a surgeon would; they tend to be bulky and limit the surgeon’s access to the patient; there are safety issues related to having machinery moving close
to, or within, a patient and there are safety issues related to removing the robot rapidly from the operating site in an emergency (such as major bleed or a cardiac arrest). A final reason is that the surgeon likes to feel he is in control of the operation: this has resulted in the ‘active constraint’ approach of the Acrobot robot (The Acrobot Company, London, UK; Davies et al. 1997), which prevents the surgeon from milling outside a safe region rather than the robot itself performing the milling autonomously. As the technology to rapidly and accurately compensate for soft-tissue deformation becomes available robotics may become more commonly used, particularly for minimally invasive procedures.

4.10 Image-Guided Breast Surgery

The challenge of developing image-guidance systems for breast surgery has received little attention compared with neurosurgical applications. The reasons for this must include the limited availability, until comparatively recently, of 3D medical images of the breast and the highly deformable nature of breast tissue. However there have been three approaches of note, which are described below: using intraoperative MR imaging, projecting preoperative MR imaging onto the intraoperative breast and an augmented reality presentation of intraoperative ultrasound data.

Two groups have investigated the use of an open-configuration MR scanner (the 0.5T Sigma SP scanner from General Electric Medical Systems, Milwaukee, WI): Gould et al. (1998) removed benign tumours and Hirose et al. (2002) removed malignant tumours, using intervention contrast enhanced MR imaging first to locate the lesion and then to confirm the excision was complete. The latter reported that subtraction imaging was feasible, since the anaesthesiologist was able to suppress breathing during an imaging sequence. Several technical challenges needed to be overcome, such as identifying surgical equipment which could be used within the magnetic field, the presence of magnetic susceptibility artefacts at the air-tissue border which could be mistaken for residual tumour unless the cavity was filled with saline and fat saturation being ineffectual at the relatively low field strength of the open configuration magnet. Additionally, Hirose et al. found it was sometimes necessary to compare the interventional images with preoperative 1.5T diagnostic images to identify the tumour. Both groups concluded that interventional MR imaging was effective at the task, with Hirose et al. reporting that four patients (out of a total of twenty) would have needed to undergo a second procedure had the interventional MR images not prompted the surgeon to take additional shave margins.

Nakamura et al. (2007) develop a procedure for breast conserving surgery following neoadjuvant chemotherapy in which DCE MR images of the patient are acquired in a posture which approximates to the surgical position. During imaging fiducial markers are attached to the
breast at the nipple and in four orthogonal directions 5cm distant. A maximum intensity
projection image is constructed from the DCE MR images and is printed on a transparent sheet
at a reduced scale. This is projected onto the breast surface (such that it aligns with the markers)
prior to surgery to mark the resection boundary

The authors make no attempt to model errors, which can be anticipated both because the
projection is the vertical direction but the incision is normal to the skin surface and because of
the curvature of the breast (which means that the breast is not at a consistent distance from the
projector). However they report the mean distance between the actual and anticipated location
of a metallic clip is 2.6mm – a surprising low error. Encouragingly, they found their approach
both reduced the area of tissue resected, and the chance of a further resection being required.

Sato et al. (1998) developed an Augmented Reality system to guide breast surgery based on
ultrasound images, although it was only demonstrated retrospectively due to the time taken to
construct a representation of the lesion. The positions of an ultrasound probe and a video
camera were measured using an optical tracker, with both the ultrasound images and the video
images being appropriately calibrated. Immediately prior to surgery a sweep of the patient’s
breast was made using the ultrasound probe. A 3D model of the lesion was constructed from the
resulting ultrasound images and overlaid on the video images of the breast. The presented
overlays, when compared with extents of the palpable mass, visually appear accurate. However,
processing ultrasound images to extract a lesion within a suitable timeframe would be a
challenging task. Furthermore, as has been previously mentioned in this chapter, the quality of
ultrasound images is highly operator dependant. To acquire high quality images, particularly of
depth lesions, it will be necessary to apply a load which can be expected to deform the breast.

Since the MR images are acquired intraoperatively, deformation between imaging and surgery
is unlikely to be an issue in the first of the three approaches to image-guided breast surgery
discussed in this section. However, interventional MR for breast conserving surgery greatly
complicates what was previously a fairly straightforward procedure, and seems unlikely to
prove sufficiently cost-effective to become routine practice. Nakamura et al. assume that no
defformation occurs between preoperative MR imaging of the patient in a surgical position and
surgery (performed at a later date), whilst Sato et al. assume that there is negligible deformation
caused by contact between the ultrasound probe and the breast. It is perhaps noteworthy that
these groups are based in Japan: a smaller deformation can be anticipated in patients who have a
smaller breast size. It seems likely that a means to account for deformation must be developed if
image-guided breast surgery based on preoperative MR imaging or intraoperative ultrasound
imaging, is to become widely applicable.
4.11 Chapter Conclusion

Established non-rigid registration techniques exist for matching pairs of medical images. Most of these were originally developed for matching neurological images, and perform well when the deformation between images is small. However these registration algorithms perform poorly when a large deformation has occurred. One reason for this is that recovering a large deformation places great demands on the transformation model and regularisation constraints if the deformation is to remain physically plausible, but the transformation models either penalise large deformations or have no underlying physical basis. Another reason is that overlap between the source and target image will initially be poor, and so the global minimum of the similarity measure may lie outside the capture range of the optimisation process.

Intraoperative imaging usually provides a much sparser dataset than preoperative imaging, but soft tissue deformation can mean that the preoperative images cannot simply be rigidly aligned with the patient. Biomechanical models, built from preoperative images, are a powerful tool to update the preoperative images to match the patient during surgery using the intraoperative measurements as boundary conditions and this approach has been demonstrated for neurosurgery and open liver surgery. Typically displacement boundary conditions rather than forces are imposed on the model, and the effect of gravity is not explicitly modelled. The most effective way to establish these boundary conditions has not yet been established. The in-vivo mechanical properties of soft tissues are not well known, and this may affect the accuracy of this intraoperative registration technique.

Major challenges remain before biomechanical modelling can be widely incorporated into image-guided surgical applications. Perhaps most importantly, almost all the systems described in this chapter are retrospective: they show the ability of the models to predict behaviour, but they are not yet integrated into a system that could be used during surgery. It is important to demonstrate that boundary conditions can be determined, and the updated model configuration calculated, under the practical constraints which surgery imposes. Once the updated position of a surgical target has been calculated, it is necessary to communicate this to the surgeon in a meaningful way.
Chapter 5

Building a Biomechanical Model of the Breast

5.1 Introduction

A very large deformation of the breast occurs between the prone position in which DCE MR images are acquired and the supine position in which surgery is performed. One of the central tenets of this thesis is that a biomechanical model of the breast can be used to simulate this deformation, in order that this information can be used to help establish correspondence between the two postures. This is necessary because intensity based registration algorithms perform poorly when attempting to register MR images of the prone breast to the supine breast due to the size of the deformation.

This chapter describes the construction of the biomechanical models on which the deformation modelling performed in the following chapters will depend. Since each model is subject-specific and is built from a supine MR image of that subject, brief details are given of each subject as well as details of the imaging protocol. The protocol used for acquiring the prone MR images against which the modelling will be assessed is also given.

Two modelling choices are assessed in this chapter: incompressibility and element shape. MR images acquired in the prone and supine positions are used to confirm that breast tissue can reasonably be assumed to be incompressible. I then study whether tetrahedral or hexahedral elements become less badly distorted when large, gravity-induced deformations are modelled. This shows that hexahedral elements are less badly affected and so I describe a technique suitable for constructing a hexahedral element mesh of the breast.
5.2 Subject Recruitment

Symptomatic breast cancer patients (Subjects S1, S2 and S4) were recruited for this study by the surgeon (Nicolas Beechey-Newman) from patients referred to the breast unit at Guy’s Hospital, London where this study was undertaken. All patients in this study received DCE MR scans as part of their clinical assessment, and additional supine MR images without contrast were acquired for the purposes of this study. One volunteer (Subject S3) was recruited for inclusion in this study. Prone and supine MR images (without contrast) were acquired of this subject.

Details for the three subjects (Subjects S1-3) considered in this chapter and Chapters 5-7 are given in Table 5.1. Details for a further patient, Subject S4, are given in Chapter 9.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age /years</th>
<th>Breast</th>
<th>Cancer</th>
<th>Diameter /mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>39</td>
<td>Left</td>
<td>Invasive ductal carcinoma, Grade I</td>
<td>4</td>
</tr>
<tr>
<td>S2</td>
<td>70</td>
<td>Left</td>
<td>Invasive lobular carcinoma, Grade II</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extensive lobular carcinoma in-situ</td>
<td></td>
</tr>
<tr>
<td>S3</td>
<td>42</td>
<td>Both*</td>
<td>No cancer - asymptomatic volunteer</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5.1 Subject Details. Details and diameter of dominant mass for Subjects S1-S3 *Only the left breast of Subject S3 is considered in the analyses of this chapter, Chapter 7 and Chapter 8

5.3 Imaging the Breast

The MR imaging was performed at Guy’s Hospital on a Philips Gyroscan Intera 1.5T scanner. Self-adhesive fiducial markers were affixed to each subject’s breast prior to imaging to provide landmarks on the surface of the breast (Figure 5.1). Both prone and supine images of the breast were acquired during the same scanning session.

5.3.1 Supine imaging

The breast was imaged with the subject lying supine. The subject’s arm was positioned by her side. Placing the arm behind the head might be a better approximation to the surgical posture, but it was found to be less comfortable for the subject and so result in increased motion

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1 MM3002, IZI Medical Products Corp, Baltimore
artefacts. The images were acquired using the Q-body coil of the scanner, since the use of any coil resting on the breast applies additional forces which cause deformation of the breast from its natural supine shape. Imaging was performed in the axial plane. A 3D gradient echo sequence (TR= 14ms, TE= 4.1ms, flip=25° for subjects S1 and S2; TR= 9.4ms, TE= 4.6ms, flip=20° for subject S3) was used and a saturation band was placed over the heart to reduce motion artefacts. The images of Subjects S1 and S2 had an in-plane resolution of 0.7mm x 0.7mm, and a slice thickness of 2.5mm; images of Subject S3 had an in-plane resolution of 0.64mm x 0.64mm and a slice thickness of 1.25mm. Images were acquired without injection of contrast agent.

![Figure 5.1 MR Visible Fiducial Markers](a) Photograph of fiducial markers attached to surface of the breast (b) Appearance of section through marker in an MR image.

### 5.3.2 Prone Imaging

Prone images of symptomatic patients were acquired using a dedicated breast coil assembly. Most breast coil assemblies have separate apertures for each breast and incorporate clamps which fixate each breast. The breast coil assembly selected for these experiments however had just one aperture and no clamping mechanism (Figure 5.1a). This allowed most breasts to hang naturally under gravity, without contacting the sides of the coil. Using this device it is still not possible to image subjects with very large or very soft breasts without contact between the breasts and the surface of the coil causing the breasts to become greatly deformed (Figure 5.2b). No such subjects were included in this study.

The protocol for the prone image of the symptomatic patients (Subjects S1 and S2) was chosen to be identical to that of the dynamic contrast enhanced imaging sequence used clinically. The pre-contrast image from a dynamic sequence could therefore be used when imaging patients, and since the image was co-registered with the enhancing images the location of the cancer could be determined in the prone image. The imaging protocol used was therefore a 3D gradient
echo sequence (TR=20ms, TE=20ms, flip = 45°). These coronal images had an in-plane resolution of 0.7mm x 0.7mm and a slice thickness of 2.2mm. Whilst the prone images of the asymptomatic volunteer (Subject S3) were acquired with her breasts hanging in the breast coil aperture, the Q-body coil was used for imaging. The protocol used was identical to the supine protocol for this subject, except that no saturation band was used.

![Breast Coil](image1)

**Figure 5.2 Breast Coil** (a) Photograph of breast coil (b) MR image of very large, soft breast which has deformed due to contact with the coil

### 5.4 Assessment of the Compressibility of Breast Tissue

#### 5.4.1 Introduction

Since biological tissues consist predominantly of incompressible fluids such as water, they are commonly described as ‘incompressible’ (Fung 1993). It is conceivable however that, over the relatively long time period between prone and supine imaging, the gross volume of breast tissue could undergo a change in volume between the prone and supine position due to a change in fluid content – for example due to a change in blood pressure since the breast is elevated with respect to the heart.

Adipose breast tissue does not have clearly demarked borders in an MR image, but merges indistinguishably into the adjacent subcutaneous fat which is identical in nature and so has the same MR image intensity. It is therefore not possible to confidently determine whether there is a true change in volume of adipose breast tissue between prone and supine images, since it is not possible to be certain that the same tissue boundaries are identified in the prone and supine images. Fibroglandular tissue however does have distinct boundaries, so it is possible to examine whether there is a change in total fibroglandular volume.
5.4.2 Method

The Analyze software package\(^1\) was used to segment fibroglandular tissue semi-automatically using region-growing and manual editing of prone and supine MR images for the left breast of the three subjects. The volumes of tissue corresponding to fibroglandular tissue in the segmentations were calculated. Example prone and supine MR images, overlaid with the boundary of segmented glandular tissue, are shown in Figure 5.3.

![](image)

\(\text{Figure 5.3 Example slices through MR volumes of breast in (a) prone and (b) supine position, overlaid with the boundary of segmented fibroglandular tissue}\)

5.4.3 Results

The volume of segmented fibroglandular tissue in the prone and supine images and the percentage change in volume for each subject is given in Table 5.2. The percentage change in measured glandular volume from prone to supine ranges from -4% to +4%.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Volume glandular in prone /mm(^3)</th>
<th>Volume glandular in supine /mm(^3)</th>
<th>Volume change from prone to supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>53788</td>
<td>54905</td>
<td>-2%</td>
</tr>
<tr>
<td>S2</td>
<td>53101</td>
<td>50840</td>
<td>+4%</td>
</tr>
<tr>
<td>S3</td>
<td>103522</td>
<td>107366</td>
<td>-4%</td>
</tr>
</tbody>
</table>

\(\text{Table 5.2 Volume of glandular tissue measured in prone and supine images}\)

\(^1\) Biomedical Imaging Resource, Mayo Clinic, Rochester, USA
Chapter 5. Building a Biomechanical Model of the Breast

5.4.4 Conclusion

The measured change in volume of fibroglandular tissue is small, and does not show a consistent increase or decrease. The change in volume is of a scale which could easily be attributed to effects such as marginally different image content due to different sampling locations, image inhomogeneities and noise. Segmentation error will also contribute: because of the complex structure, blurring due to motion and finite slice thickness, segmentation of the tissues of the breast is a difficult task.

Whilst these results are for change in total volume of fibroglandular tissue (rather than local volume), modelling fibroglandular tissue as incompressible appears to be a reasonable assumption, and is consistent with assumptions made in models in the literature models discussed in Chapter 3. Adipose tissue in the breast will be under similar strains to the fibroglandular tissue. In the absence of conflicting evidence it seems reasonable to assume that adipose tissue is also incompressible. In the remainder of this thesis both adipose and fibroglandular tissues are assumed to be incompressible.

5.5 Biomechanical Modelling

In this thesis the finite element method is used to solve the partial differential equations describing the deformation of the body. Although alternative methods (such as the boundary element method) exist to model biomechanical tissues, the finite element method is the most commonly used, and allows boundary conditions and inhomogeneous material properties to be imposed in a straightforward and flexible way. The material properties of the breast are not strain rate dependent (see Section 3.2.2) and in this thesis only the positions of the breast in the prone and supine postures are of interest, as opposed to the motion over time that the breast is moving. The displacement of the breast can therefore be solved as a quasi-static equilibrium problem, without explicitly solving for the behaviour of the breast with respect to time.

Since breast tissue is very soft, large deformations can occur. It is anticipated that the assumption of small strains and small deflections will not be valid for modelling the deformations considered in this thesis, so infinitesimal strain theory would not be appropriate. Therefore finite strain theory is used for all modelling in this thesis, except where explicitly stated otherwise.

All finite element modelling was performed using Release 11 of the ANSYS finite element modelling suite. Since the previous section has indicated that breast tissue is incompressible a mixed displacement-pressure formulation of the finite element method is the most appropriate (described in Appendix Section B.5). The SOLID18x range of elements in ANSYS supports this
formulation, and these elements were used to model breast tissue. The SOLID 18x range of elements supports the modelling of tissue as a hyperelastic material. Two hyperelastic strain-energy functions are commonly found in the literature – Neo-Hookean (Equation B.28) and 5 parameter Mooney-Rivlin (Equation B.29). Both of these are considered in this thesis.

5.6 Experiment: Comparison of Volumetric Element Shapes

5.6.1 Introduction

When performing a finite strain analysis, integrals are performed over the deformed element shape (Equation B.34). Since during the modelling process the mesh upon which the solution is calculated is deformed, it is possible for a mesh which contains no badly shaped elements prior to an analysis to develop badly shaped elements during the analysis. These distorted elements can influence the results of an FEM analysis by creating mesh-dependent inaccuracies and can also cause the finite element solver to fail to converge.

The two basic element shapes which are commonly used as volumetric elements in finite element analysis are hexahedral elements and tetrahedral elements. As was described in Section 3.4, linear tetrahedral elements are known to ‘lock’ when modelling tissues which are incompressible or nearly incompressible. Since Section 5.4 concluded that breast tissues should be modelled as being incompressible, tetrahedral elements with linear shape functions (and therefore nodes at each corner but no mid-side nodes) are not appropriate for modelling deformations of the breast.

Figure 5.4 Element shapes (a) is a linear hexahedral element and (b) is a quadratic tetrahedral element. Node positions are indicated by a dot.
Since the deformation between prone and supine is large, will involve a significant rotation, there is the potential for elements to become badly distorted which, as described in Section 3.4, can cause modelling inaccuracies or prevent the finite element solver from converging. An analysis was therefore performed to determine whether linear hexahedral elements (which have a node at each vertex) or quadratic tetrahedral elements (which have a node on each edge as well as at each vertex) were less prone to becoming badly shaped when modelling deformations due to gravity and therefore more appropriate for modelling these breast deformations. These elements are illustrated in Figure 5.4.

Element distortion is assessed here by considering the shape of element faces and of cross-sections through each element, and the value of the Jacobian at points within the element. Mid-side nodes were ignored when assessing element shape. The shape-checking function within ANSYS software was used to assess the element shape quality against its standard, recommended criteria. Elements which exceeded the software’s ‘warning’ limit are considered ‘badly shaped’ and elements which exceeded the ‘error’ limit are considered ‘critically badly shaped’.

To compare the behaviour of hexahedral and tetrahedral elements under gravity-induced deformation a simple in-silico phantom was meshed using each type of element (into initially well-shaped elements). The deformation of the model due to gravity was simulated, and the quality of the elements in the final deformed meshes was then compared.

5.6.2 Method

The phantom consisted (in its reference state) of a solid hemisphere of density 900 kg/m³ and of radius 50mm. The material was modelled as having a neo-Hookean strain energy function where $\alpha = 0.1\text{kPa}$ in order that the model would undergo large deformation. All points on the flat face of the hemisphere were constrained to remain stationary and gravity of 9.81 m/s² was applied perpendicular to the flat face of the hemisphere, towards the apex of the hemisphere. The model therefore crudely represented gravity acting on a breast in the reference state deforming to its prone position.

The meshes were created using the meshing facilities within the ANSYS application. It would be most informative to compare equivalent meshes of each element shape, but it is not obvious what should be considered an ‘equivalent’ mesh. Two possibilities are encompassed in this analysis: meshes which have elements of approximately the same volume (i.e. contain the same number of elements) and meshes which have approximately the same number of degrees of freedom (i.e. nodes). A mesh of hexahedral elements (SOLID185 in ANSYS nomenclature) was therefore compared with two alternative meshes of tetrahedral elements (SOLID187).
5.6.3 Results

Deformed and undeformed meshes are shown in Figure 5.5. None of the three meshes contained badly shaped elements in the reference state. The number of badly shaped elements in the deformed state for each mesh is given in Table 5.3. The critically badly shaped element was due to a negative Jacobian ratio.\(^1\)

\[\text{Figure 5.5 Hemisphere Phantom} \text{ in reference state (upper) and deformed state (lower) for (a) hexahedral mesh with 5488 elements (b) Tetrahedral mesh with 3924 elements and (c) Tetrahedral mesh with 5816 elements}\]

<table>
<thead>
<tr>
<th>Element shape</th>
<th>Number of elements</th>
<th>Number of nodes</th>
<th>Badly shaped elements</th>
<th>Critically badly shaped elements</th>
<th>Time taken to solve (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexahedral</td>
<td>5488</td>
<td>6119</td>
<td>0</td>
<td>0</td>
<td>102</td>
</tr>
<tr>
<td>Tetrahedral</td>
<td>3924</td>
<td>6101</td>
<td>9</td>
<td>0</td>
<td>181</td>
</tr>
<tr>
<td>Tetrahedral</td>
<td>5816</td>
<td>8815</td>
<td>15</td>
<td>1</td>
<td>322</td>
</tr>
</tbody>
</table>

\[\text{Table 5.3 Badly shaped elements} \text{ Number of badly shaped elements created in hexahedral and tetrahedral meshes due to a gravity-induced deformation}\]

\(^1\) The determinate of the Jacobian matrix - which represents the magnitude of the mapping function between the model and the real world - was calculated at each corner node. The ratio of the largest to the smallest of these was defined as the Jacobian ratio. A negative Jacobian ratio is unphysical since it implies one node has been reflected whilst the other has not – i.e. the element has become inverted.
5.6.4 Conclusion

The hexahedral mesh took less time to solve, and had fewer badly shaped elements, than equivalent tetrahedral meshes. The faster convergence of the hexahedral mesh can be attributed to fewer bisections being required (since the elements do not get badly shaped) and to each hexahedral element having only one integration point, whilst each tetrahedral element has four.

Using hexahedral elements has a further advantage that it provides a structured mesh – since the elements are laid out in a grid-like fashion it is easy to identify, say, all the elements which lie along the skin boundary. However constructing a hexahedral mesh is more complicated, since essentially a cube must be mapped to the shape of the breast without generating badly-shaped elements.

The results indicate that hexahedral elements may be more appropriate for modelling large gravity-induced deformations of the breast, and therefore in this thesis volumes are meshed using hexahedral elements.

5.7 Creation of a subject-specific model

The biomechanical model is intended to perform two tasks – to model the preoperative deformation of the breast between the prone and supine positions during an MR imaging session, and to model the intraoperative deformation of a supine breast between MR imaging and surgery. It seems likely that a deformation from supine to prone will be more reproducible than the reverse, since in the prone state the breast is freely hanging which will provide a more stable equilibrium position than exists in the supine state where the breast is in contact with the curved surface of the chest wall. Therefore the model is constructed in the supine position, and this has the additional advantage that the same model can be used for both preoperative and intraoperative purposes.

The constructed model includes elements assigned to the material types of fibroglandular tissue and fatty tissue. Cooper’s ligaments are not included in the model since they are not visible in the MR images. Skin is also excluded from the initial model since for compression experiments it has been found to have little influence (Ruiter 2003; Tanner et al. 2006b) and there is some evidence that the same is true for gravity-induced deformations (Pathmanathan 2006). The effect of including skin in the model will be explored in Section 7.8.

5.7.1 Cropping and Segmentation

In an MR image the fatty breast tissue appears to merge seamless into the surrounding subcutaneous fat and so does not have clearly defined, unambiguous boundaries in all
directions. It is therefore necessary to define slightly arbitrary boundaries to the breast for the purpose of building the model.

Prior to segmentation the supine MR image was cropped to include only the region of interest. The medial boundary of the cropped image was the midline of the body (i.e. the sternum), and the lateral boundary was such that the entire torso was enclosed. In the anterior direction all tissue was included, whilst the posterior limit of the cropped image was approximately the centre of the torso. The armpit was chosen as the superior boundary because when performing a clinical prone MR scan of the breast the little breast tissue which is in the region superior to the armpit is outside the breast coil, and therefore is of poor image quality and not generally inspected by a radiologist. Excluding the region superior to the armpit avoids two additional modelling difficulties. Firstly the lateral edge of this region is tethered around the shoulder, which is a markedly different attachment to the region inferior to the armpit, which is tethered around the torso. It therefore requires different boundary conditions to the rest of the breast. Secondly, excluding this region allows a smooth mesh to be created, without creating the distorted elements which would be required to model tissue around the armpit. The inferior boundary was chosen such that it was just inferior to the infra-mammary crease.

Segmentation of the breast was performed using the Analyze software package. The exterior boundary was extracted using a spline curve manually fitted to the contour of skin surface of the breast in each slice. The interior boundary, which divides the breast from the pectoral muscle and the other structures of the chest wall along the retro-mammary space, was demarcated in the same way.

Fiducial markers attached to the skin are external to the breast, and so they are not included in the segmentation. However the coordinates of the centre of each marker at the skin surface were recorded.

5.7.2 Construction of the mesh

The results of the experiment described in Section 5.6 indicate that hexahedral elements are best suited for modelling large gravity-induced deformations. Therefore the finite element mesh of the breast was created from hexahedral elements. The structured hexahedral mesh was formed, in effect, by mapping a meshed cube to the shape of the supine breast.

The segmented MR volume of the breast created in the previous section was re-sliced into transverse slices with a 2.5 mm slice separation. A 2D mesh was created from each of these slices (Figure 5.6a). This was done by determining the points at which rays projected radially from a point in the medial posterior corner of the image intersected the breast. The vector
between corresponding interior (i.e. pectoral fascia) and exterior (i.e. skin) intersections was evenly divided to create 1D elements, with a node at each end, in the radial direction. These nodes were shared if there was an adjacent element. The 1D elements in adjacent rays were then connected to create 2D quadrilateral elements. Finally quadrilateral elements in adjacent slices were connected to form the hexahedral elements of the 3D model (Figure 5.6b).

![Image](image.png)

(a) Quadrilateral mesh overlaid on the MR image from which it is created (b) hexahedral mesh formed by connecting adjacent quadrilateral meshes.

Figure 5.6 Subject-specific mesh

It is important that the extracted boundaries are smooth surfaces. Not only is the physical anatomy of these regions generally smooth, which should be reflected in the model, but sharp edges would result in high local stress intensities which are not in reality present and could result in inaccurate displacement predictions. Having smooth surfaces is also important for the modelling which is performed in later chapters – for example when simulating sliding boundary conditions along the pectoral fascia (Chapter 6) and when deforming the model such that its surface aligns with the breast surface in a prone MR volume (Chapter 8). Therefore smooth approximating surfaces were fitted to the nodes lying on the interior (pectoral fascia) and exterior (skin) of the model. The positions of nodes lying on the surface of the model were adjusted so that they lay on this smoothed surface. The positions of nodes lying within the model were also adjusted so that every 1D element lying on a given ray had the same length.

The meshes used in this thesis consisted of 30 x 5 elements in the transverse plane, and an element size of 2.5 mm in the superior-inferior direction.

5.7.3 Allocation of material type

The material segmentation performed in Section 5.7.1 was used to assign material properties to each element. If the centroid of a voxel lay within an element then the voxel was considered to be within the element since the voxels were much smaller than the volumetric elements. For each element the number of voxels of each material type lying within it was counted, and the element was assigned the material type with the higher count.
Whilst this approach ignores the effect of the minor material type, combining two material types within the same element would not be straightforward. Since the material properties are not well known assigning them on a finer scale may be of limited benefit, especially as the influence of other components of the breast such as Cooper’s ligaments and skin are ignored. Although the presence of sharp element corners on the boundary between material types is not desirable, the errors caused by assigning material properties in this way are likely to be small compared with the effects of the boundary condition and material property assumptions.

5.8 Using model deformations to deform MR image

The following chapters describe a range of model deformations. The method used in this thesis to warp the MR image in accordance with the model deformation is described here. In the following description the MR image from which the model was constructed is referred to as the source image. The image to be reconstructed from this source image using the model deformation is referred to as the target image.

The target image was populated by considering each voxel in this image in turn. The element in the deformed model in which the centre of the target voxel lay was identified. This location was then determined in terms of the shape functions of the element. Since in terms of the shape functions the coordinates of a material point is identical in both the deformed and the undeformed element (albeit with different real-world node positions), the location of this point in the source image can be determined. The intensity of this point in the source image, found by trilinearly interpolating the local voxel intensities, was assigned to the voxel in the target image.

5.9 Chapter Conclusion

This chapter has described the aspects considered when constructing a finite element model of the breast for modelling supine to prone deformation. Comparison of prone and supine MR images supports, for the scenario of prone-supine deformation, the widely-reported assumption that breast tissue is incompressible. To model incompressibility using a mixed displacement-pressure formulation of the finite element method in the commercially-available ANSYS finite element suite it is necessary to adopt elements which support hyperelastic material properties. A comparison of these elements undergoing large gravity-induced deformations indicates that the hexahedral elements are less susceptible to becoming badly distorted than tetrahedral elements.

In the last section of the chapter I describe a technique to construct a subject-specific hexahedral mesh from the supine MR image, and to assign material types to each of the elements. It is anticipated that this mesh will be suitable for two key tasks: for modelling prone-supine
deformation in Chapter 6 and for modelling the deformation occurring between imaging and surgery in Chapter 9.
Chapter 6

Modelling Deformation of the Breast between Prone and Supine Positions

6.1 Introduction

It should be possible to establish correspondence between prone and supine positions of the breast using a biomechanical model. Several groups have modelled this deformation but, as described in Chapter 3, limited assessment has been performed of their models. When modelling the deformation between supine and prone it is necessary to account for the stresses which exist in a model due to gravity acting whilst the patient is being imaged (Section 3.5.2). I therefore develop a technique to recover the reference state from a gravity-loaded state. This technique is initially assessed against simulated data, and then used on patient and volunteer data in the later sections of this chapter.

The deformation of the breast between the supine and the prone positions, as revealed in MR images, is investigated. I then assess the ability of a biomechanical model to simulate the deformation of the breast between these positions on three subjects. The first simulations to be assessed assume published material properties and, in accordance with the modelling literature, assume that the posterior face of the model remains fixed. The predictions of such models are found to not be in accordance with the observed deformations. I introduce boundary conditions which are intended to better reflect the motion of the breast along the chest wall. I then assess the behaviour of models which incorporate these boundary conditions, and whose material stiffness is adjusted to reflect the deformations observed in vivo.
6.2 Technique to Recover a Model’s Reference State

6.2.1 Introduction

Section 3.5.2 discussed why, because unknown strains due to gravity exist in the breast when it is imaged, it is necessary to determine the reference state of the breast. In this ‘zero-gravity’ state no strains exist within the model. The reference state can be deformed to the prone or supine state by applying gravity in the appropriate direction.

It was identified that three categories of approach are possible: crude approximation of reference state by applying gravity in the reverse direction on the deformed breast; iteratively solving the forward problem, refining the estimate of the reference state at each iteration; and reformulating the finite element equations to solve the inverse problem. The technique proposed in this section falls into the iterative solution of the forward problem category.

6.2.2 Method

A schematic of the reference state recovery scheme is shown in Figure 6.1. The model is constructed in the supine position, with nodes in position $S_{true}$. A body force of the same magnitude as that due to gravity but acting in the opposite direction is applied. This provides an initial estimate of the node positions $R_{est}$ in the reference state. Any stresses formed by deforming the model to this position from the supine position are neglected.

The body force due to gravity is applied to the estimate of the reference state $R_{est}$. The resulting node positions $S_{est}$ in the supine state will be close to the known true supine node positions $S_{true}$. The node positions in the current estimate of the reference state are updated according to the equation:

$$R'_{est} = R_{est} + (S_{true} - S_{est})$$

Where $R_{est}$ is the current estimate of the reference state and $R'_{est}$ is the updated estimate of this reference state. The deformation to supine and update of the node positions can be repeated until

$$\max|S_{true} - S_{est}| < tol.$$ 

In all experiments reported in this thesis the tolerance $tol=0.05\text{mm}$. This is consistent with recovering the supine state to a sub-voxel accuracy in the MR images from which the breast models are constructed.
6.3 Assessment of Reference State Recovery on Phantom Data

6.3.1 Introduction

To validate the reference state recovery technique described in the previous section, the technique was used to recover the known reference state of an in-silico phantom from the phantom’s deformed state.

6.3.2 Method

The phantom, before deformation, consisted of a cube with an edge length of 50mm rigidly fixed at all points on its lower face. The material was modelled as being incompressible, isotropic and homogenous. It was assigned a density of 1000 kg m$^{-3}$ and had a neo-Hookean strain energy function where $\alpha=0.25$ kPa. Gravity was taken to be 9.81 ms$^{-2}$.
The cube was meshed into hexahedral elements. Meshes of several resolutions were compared; the details of these are given in Table 6.1. Nodes which lay upon the lower face of the cube were constrained to have zero displacement. Deformation due to gravity was then simulated, and the position of the nodes in the deformed state determined.

The reference state recovery technique described in Section 6.2 was used to recover the position of the nodes in the reference state from the deformed mesh. The computed reference state node locations were compared with the known reference node locations in the original reference state model.

6.3.3 Results

Images of the cubic phantom in its true reference state, gravity-deformed state and recovered reference state are shown in Figure 6.2. The mean displacement of the mesh between reference and deformed state was 6.8 mm and the maximum displacement was 11 mm. The accuracy of reference state recovery, and the time taken to recover the reference state, is given in Table 6.1.

![Figure 6.2 Recovering the reference state of a cube](image)

(a) Cube in true reference state; (b) Cube deformed to 'supine' state; (c) Reference state recovered by reversing gravity; (d) Reference state recovered using iterative correction approach
### Table 6.1 Recovery of reference state

<table>
<thead>
<tr>
<th>Number of elements</th>
<th>Number of iterations</th>
<th>Time to solve forward problem /s</th>
<th>Time to solve backward problem /s</th>
<th>Mean (std. dev.) node error /mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>$5^3$</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td>0.049 (0.026)</td>
</tr>
<tr>
<td>$10^3$</td>
<td>3</td>
<td>7</td>
<td>39</td>
<td>0.025 (0.015)</td>
</tr>
<tr>
<td>$15^3$</td>
<td>4</td>
<td>39</td>
<td>216</td>
<td>0.015 (0.012)</td>
</tr>
</tbody>
</table>

**Accuracy of reference state recovery, and the time taken, for a range of element sizes**

### 6.3.4 Discussion

Iteratively solving the forward problem and updating the estimate of the reference state has been found to be an effective way to solve the inverse problem. For all mesh resolutions tested the reference state was recovered with a mean accuracy of better than 0.05mm.

Alternative approaches to this inverse problem, which directly invert the problem, have been implemented by Pathmanathan (2006) and (Rajagopal et al. 2007a), but these require modifications to the finite element code itself, whilst the technique described here can be incorporated with standard finite element software without requiring alternations to the source code. In principle the direct inversion approach should be faster – Pathmanathan takes only 18% more time to solve the inverse problem than the forward problem. However there are advantages to using commercial finite element code. The use of a commercial package allows rapid prototyping since it is relatively straightforward to alter factors such as material models, element types or solution techniques. Furthermore not only have commercial packages been more extensively tested and validated than most code for which source is available but it is also likely to have been optimised - in spite of the inverse problem taking six times as long as the forward problem in this phantom experiment, only 39 seconds was taken to recover the reference state for a mesh with $10^3$ elements. This is much faster than has been reported for the direct inversion approach (451 seconds) (Pathmanathan 2006), although direct comparisons are not possible since insufficient data is provided to exactly replicate the reported direct inversion experiment.

In this chapter the reference state will be computed by iteratively solving the forward problem and updating the reference state.
6.4 Observation of Deformation of the Breast

6.4.1 Introduction

This section provides an initial examination of the gross behaviour of breast tissue. Information about the deformation occurring between supine and prone postures is gleaned from MR images. In addition remarks are made based on the inspection of mastectomy specimens, and the observation of breast surgery.

6.4.2 Method

The prone and supine MR images for Subjects S1, S2 and S3 were coarsely aligned by rotating each prone volume by 180° about the cranio-caudle axis and translating such that the sternums in each pair of prone and supine volumes aligned. The MR images were then visually compared. Additionally, in order to highlight the gross deformation occurring, for each subject a representative transverse slice through the supine MR image and the corresponding slice through the aligned prone MR image were chosen. The outlines of breast tissue and of glandular tissue were manually drawn on these slices using GIMP1. The positions of a branch from the main mammary artery which runs in a superior-inferior direction, the posterior-lateral corner edge of the pectoralis major muscle and any fiducial markers which were visible in the image slice were also marked.

In addition to examining the MR images, numerous breast surgery procedures (both wide local excisions and mastectomies) were observed. The sectioning of these unfixed specimens in the histology laboratory was also observed.

6.4.3 Results and Discussion

Figure 6.3 shows transverse sections through MR images of the breasts of three subjects, and the corresponding outlines. These images show, in addition to the anticipated posterior-anterior deformation, a significant motion in the latero-medial direction. This suggests that the ‘fixed’ boundary condition, which has so far been assumed in the literature, is a very poor approximation to reality. Indeed the blood vessel appears to ‘slide’ around the chest wall. The distance from the sternum to the blood vessel is reduced by 26%, 25% and 17% in the prone image compared with the supine image (measured around the torso) for subjects S1, S2 and S3 respectively. Similarly the distance to the lateral edge of the pectoralis major muscle is reduced by 26%, 19% and 26%.

1 http://www.gimp.org/
Chapter 6. Modelling Deformation of the Breast between Prone and Supine Positions

Figure 6.3 Comparison of prone and supine breast shape Transverse slices through MR images of Subjects S1, S2 and S3 in the prone position, in the supine position and an overlay of the outlines of these images. In the outline images supine features are in green, and prone features are in red. Skin fiducial markers are marked with a round dot, the lateral edge of the pectoralis major with a square dot and a blood vessel branching from the main mammary artery with a diamond-shaped dot.

Inspection of the prone and supine MR volumes for these three subjects found that there is a large displacement in the transverse plane. There is more limited motion out of this plane. This motion occurs further away from the chest wall for subjects S1 and S2, and both close to and far
away from the chest wall in subject S3. Slices through the breast in the sagittal and coronal planes (as shown for subject S2 in Figure 6.4) provide little insight into the deformation occurring, due to the very large out of plane motion occurring in these directions. The maximum length of glandular tissue in the superior-inferior direction (measured by selecting the most superior and most inferior transverse planes which contain glandular tissue) in the prone image is 83%, 66% and 52% of its length in the supine image for Subjects S1, S2 and S3 respectively.

Figure 6.4 Orthogonal slices through MR image of the breast of subject S2 in (a) supine position (b) prone position. In each image views are (clockwise from top left) sagittal, transverse and coronal. The curser indicates the cutting planes and is centred on the same coordinates in prone and supine images after rigid alignment of their chest walls.

Figure 6.5 shows a transverse slice through subject S2 in the prone and supine position. In the supine position glandular tissue can be seen to be very close (less than 2mm) to the pectoral muscle. However, in the prone MR volume there appears to be much more fatty tissue separating the glandular tissue from the pectoral muscle, with the glandular tissue and pectoral muscle separated by at least 10mm for all slices in this region. It does not seem plausible that the fatty tissue has stretched to 5 times its initial length, as would be required if the breast is indeed a continuous solid medium attached along its posterior fascia to the underlying muscle. One possible alternative explanation for this observed deformation is that, since fat is liquid at body temperature (Krouskop et al. 1998) it can be displaced from behind the glandular tissue and ‘ooze’ to a new position within the breast, and this type of behaviour during plate compression is suggested by Azar et al. (2000) for this reason. However the fat, even if liquid, will still be compartmentalised by plasma membranes (Thibodeau and Patton 2004). Therefore, an explanation that seems to me to be more physically reasonable is that the adipose tissue
should not be considered as one continuous material, but instead consists of discrete but contiguous ‘blobs’ (or compartments) of fatty tissue which are able to slide over each other, and therefore can be displaced from behind the glandular tissue.

![Figure 6.5 Sections through MR image of Subject S2 showing shift of glandular tissue](image)

**Figure 6.5 Sections through MR image of Subject S2 showing shift of glandular tissue** Transverse sections through (a) supine and (b) prone MR image of subject S2 superior to the nipple showing glandular tissue shifting away from pectoral muscle.

This ‘blobby’ structure can be observed in images of the gross mastectomy specimen (Figure 6.6). The proposed interaction of these blobs sliding over each other is not apparent in ex-vivo specimens, though this could possibly be attributed to fat solidifying at room temperature. Blobs sliding over each other would be constituent with softer gross material properties being observed in larger tissue specimens than are measured for the smaller specimens used in rheology experiments.

Between the breast and the underlying muscles is the retromammary space. It contains loose areolar tissue and allows the breast to slide on the muscles of the chest wall (Kopans 2006). Some of the retromammary fascia forms connective tissue extensions which pass through the retromammary space and join the pectoralis fascia (Hamdi et al. 2005). The retromammary space is a ‘potential’ space: since it does not completely isolate the breast cancer can spread through the vessels and lymphatics which penetrate the chest wall (Kopans 2006). The two fascias can however be easily separated (Tank 2008). This plane of blunt dissection can be seen in the photograph in Figure 6.6c. The deformation observed when a subject is repositioned from supine to prone therefore seems to be due to a combination of the motion of breast tissue on the underlying muscles and the displacement of the underlying muscles, especially the pectoralis major muscle. Since this muscle arises from the sternum and clavicle and attaches to the
humerus it moves in a way that is consistent with the observed deformation being predominantly in the transverse plane.

Figure 6.6 Mastectomy Specimen of subject S1: (a) Gross specimen (b) Coronal section though posterior portion of specimen (c) Specimen being removed during surgery. The dissection plane along the retromammary space between pectoral muscle and breast tissue is clearly visible.

6.4.4 Conclusion

In addition to the posterior-anterior motion, a large displacement around the torso towards the sternum of around 20% occurs between prone and supine. Little motion in the superior-inferior direction is observed close to the pectoral fascia for two subjects (S1 and S2), although more motion is observed in this region for the third subject (S3). Displacements are observed which are not well explained if breast tissue is considered to be a continuous solid medium without the possibility of components sliding over each other. Such a model may however prove sufficiently accurate for the purposes described in the later chapters of this thesis.
6.5 Modelling Using Boundary Conditions and Material Properties from the Literature

6.5.1 Introduction

The ability of the model to simulate the deformation which a breast undergoes between supine and prone was assessed by constructing subject-specific models in the supine position, and then deforming them to the prone position. The simulated prone breast was compared with an MR of the breast acquired in the prone position. The performance of five sets of constitutive equations proposed in the literature (and variations on these) was assessed. In this section zero-displacement boundary conditions were assumed along the pectoral fascia, in keeping with all prone-supine experiments previously reported by others (see Section 3.5).

6.5.2 Method

Model Construction

Finite element models for three subjects S1, S2 and S3 were constructed in the supine position using the approach described in the previous chapter. Details for the three subjects are given in Table 5.1.

Boundary conditions

Zero-displacement boundary conditions were imposed upon all nodes along the posterior face of the model (see Figure 5.6b for an image of the model). Zero displacement boundary conditions were also imposed upon the medial and lateral faces of the model in keeping with the assumptions made in the literature (reported in Section 3.5). No boundary conditions were imposed upon nodes lying upon the superior and inferior faces of the model because this would result in some elements having boundary conditions imposed on all but one node. Since breast tissue is modelled as being incompressible these elements would be over-constrained.

Material properties

As described in the previous chapter, in order that incompressibility constraints could be imposed, the tissue was modelled as hyperelastic. Two hyperelastic strain-energy functions are considered here: the one parameter Neo-Hookean strain-energy function and the five parameter Mooney-Rivlin strain-energy function.

Four paired sets of literature values for the Mooney-Rivlin parameters (as defined in Equation B.29) which describe the fibroglandular and adipose tissue properties were trialled. They are listed in Table 6.2. Additionally four sets of “ten times softer” Mooney-Rivlin materials were modelled, by multiplying each of these parameters by a factor of 0.1. Material properties in
which tissues were modelled as being neo-Hookean were also trialled. In this case, fibroglandular tissue was assumed to have identical stiffness to adipose tissue, so that all breast tissue is described by a single neo-Hookean parameter $\alpha$, where $\alpha$ is defined in Eqn. B.28). Neo-Hookean parameters of value $\alpha \in \{0.1, 0.5, 1.0, 5.0\}$ kPa were tested.

Elements identified as fat were assigned a density of 938kg/m$^3$ whilst elements identified as fibroglandular were assigned a density of 1035kg/m$^3$ (Johns and Yaffe 1987).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tissue</th>
<th>$\alpha_{10}$ /kPa</th>
<th>$\alpha_{01}$ /kPa</th>
<th>$\alpha_{20}$ /kPa</th>
<th>$\alpha_{11}$ /kPa</th>
<th>$\alpha_{02}$ /kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azar et al. (2000) *</td>
<td>adipose</td>
<td>50.03</td>
<td>-37.13</td>
<td>48.42</td>
<td>-0.69</td>
<td>1.43</td>
</tr>
<tr>
<td></td>
<td>fibroglandular</td>
<td>42.83</td>
<td>-36.54</td>
<td>51.83</td>
<td>7.33</td>
<td>0.52</td>
</tr>
<tr>
<td>Krouskop et al. (1998) *</td>
<td>adipose</td>
<td>5.83</td>
<td>-3.14</td>
<td>0.90</td>
<td>0.64</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>fibroglandular</td>
<td>26.07</td>
<td>-15.56</td>
<td>8.10</td>
<td>1.71</td>
<td>0.31</td>
</tr>
<tr>
<td>Samani et al. (2001) *</td>
<td>adipose</td>
<td>10.00</td>
<td>-7.14</td>
<td>3.12</td>
<td>1.82</td>
<td>2.07</td>
</tr>
<tr>
<td></td>
<td>fibroglandular</td>
<td>263.15</td>
<td>-231.32</td>
<td>387.50</td>
<td>55.81</td>
<td>-0.02</td>
</tr>
<tr>
<td>Samani and</td>
<td>adipose</td>
<td>0.31</td>
<td>0.30</td>
<td>3.80</td>
<td>2.25</td>
<td>4.72</td>
</tr>
</tbody>
</table>

Table 6.2 Literature Mooney-Rivlin parameters for breast tissue *References labelled with an asterisk are for fits of a five parameter Mooney-Rivlin model to the referenced data as given by Tanner (2005)

Model deformation

The reference state was recovered using the approach described in Section 6.2. For the softer neo-Hookean material properties trialled, when gravity in the posterior direction was applied upon the initial estimate of the reference state, the resulting estimated supine state was not a good approximation to the actual supine state. In this situation badly shaped elements can be created in the updated reference state and, ultimately, the technique fails to converge. Therefore the approach was slightly modified: an initial material property which was stiff enough for the technique to converge was chosen and the reference state for this material property was found. This reference state was then used as the initial estimate of the reference state for a softer material property, and the reference state for the softer material property found. The process was repeated until the reference state for a model of the desired stiffness was calculated.

Gravity was then applied to the reference state model to deform it to the prone position.
Assessment

The simulated deformation was qualitatively assessed by deforming the supine MR image according to the model displacements and then visually comparing the actual prone image with the image generated from the model displacements. The method used to create this deformed image was described in Section 5.8. Quantitative assessment was provided by comparing the distance from the nipple to the closest point on anterior face of the pectoral muscle measured in the prone image with this distance measured in the deformed model. The distance between the nipple location in the prone image and in the deformed model was not used as a metric since it penalised the incorrect rotation of breast tissue in addition to incorrect extension.

6.5.3 Results

Figure 6.7, Figure 6.9 and Figure 6.11 compare the distance from the posterior face of the model to the nipple after deforming the models of subjects S1, S2 and S3 respectively for the range of material stiffnesses trialled with the distance measured in the actual prone and supine MR images. The 5-parameter Mooney-Rivlin models underestimate the increase in distance between the nipple and the posterior face of the model when the subject is repositioned from the supine to the prone posture by at least 75%, even for parameters 10 times softer than the literature values. Only models with the softest neo-Hookean material property trialled ($\alpha = 0.1\,\text{kPa}$) exceed this increase. The figures also show the mean magnitude of displacement for each of these material stiffnesses, which is less than 7mm for all but the softest neo-Hookean material property trialled. Simulated prone images generated using the model displacements with Mooney-Rivlin values based on Samani and Plewes (2004) and using neo-Hookean parameters are shown in Figure 6.8, Figure 6.10 and Figure 6.12 since the two constitutive equations resulted in the greatest deformation.

6.5.4 Discussion

The computed deformation between prone and supine is much smaller than that actually observed, except for the softest neo-Hookean material. This material property is much softer than the tissue properties reported in the literature. The deformed models which use this material property have a much narrower width of breast (in the medio-lateral direction) than the real prone breast. However, fibroglandular tissue close to the pectoral fascia in the deformed model is in a more lateral position than is observed in the prone MR image. In all cases the MR image warped into a prone position by the model deformation is visually a poor approximation to the prone MR image when using material stiffnesses from the literature and, in accordance with the literature models, assuming fixed boundary conditions on the posterior model face.
Figure 6.7 Measurements of simulated deformations of Subject S1 Columns show the distance from the nipple to the posterior face of the breast and diamonds show the mean displacement of model’s nodes for a range of material stiffnesses using boundary conditions from the literature.

Figure 6.8 Images of deformations of subject S1 Transverse slices through original MR volumes and MR volumes deformed to the prone configuration according to the model displacements for a range of material models.
Figure 6.9 Measurements of simulated deformations of Subject S2 Columns show the distance from the nipple to the posterior face of the breast and diamonds show the mean displacement of model’s nodes for a range of material stiffnesses using boundary conditions from the literature.

Figure 6.10 Images of deformations of subject S2 Transverse slices through original MR volumes and MR volumes deformed to the prone configuration according to the model displacements for a range of material models.
Figure 6.11 Measurements of simulated deformations of Subject S3 Columns show the distance from the nipple to the posterior face of the breast and diamonds show the mean displacement of model’s nodes for a range of material stiffnesses using boundary conditions from the literature.

Figure 6.12 Images of deformations of subject S3 Transverse slices through original MR volumes and MR volumes deformed to the prone configuration according to the model displacements for a range of material models.
6.6 Boundary Conditions which Simulate Sliding of Posterior Face

6.6.1 Introduction
The models of the previous section fail to realistically simulate the deformation of the breast. These models assumed that the posterior face of the model remained rigid. They therefore do not take into account the ‘sliding’ motion of breast tissue towards the sternum which was identified in Section 6.4. There is insufficient information in the images to extract a point-to-point correspondence between prone and supine in order to derive the boundary conditions. Therefore two simplified models for the boundary condition displacements are proposed and tested here. These models simulate the sliding as a compression of the posterior face of the model around the torso in a roughly latero-medial direction. Points on the posterior face are constrained to remain in the same axial plane. Since breast tissue is being modelled as incompressible, this can be expected to result in expansion of breast tissue in the anterior direction.

6.6.2 Linear boundary condition scheme
A simple approximation to the motion occurring along the pectoral fascia is to assume that the nodes along the posterior face of the model are linearly compressed. In implementing this assumption the nodes are translated a distance along this face towards the medial edge by a distance proportional to the nodes original distance from the medial edge. All distances are measured by linearly interpolating between the nodes of this face.

6.6.3 Quadratic boundary condition scheme
Symmetry dictates that there must be zero-displacement boundary conditions along the midline of the body. The lateral margin of the breast appears to be quite unconstrained by the skin and subcutaneous fat which extends around from the breast to behind the subject. Therefore, when the patient is in the prone position, the greatest compression of the breast might be expected medially, with the compression reducing towards zero with increasing distance from the midline of the body. When the patient is in the supine position the loads are reversed, with the greatest extension of breast tissue occurring medially, and the extension reducing towards zero with increasing distance from the midline.

This behaviour along the chest wall is somewhat similar to the behaviour of a column of material deforming under its own weight, and therefore suggests that the boundary conditions based upon the self-deformation of a column might be appropriate.
As a simple analogy, consider a linear elastic rod which has a length $L$ and which has a cross-sectional area $A$, which is assumed not to be altered by the longitudinal deformation occurring. The rod has a mass density $\rho$ and a Young’s modulus $E$. It is in a vertical orientation and is supported at its lower end, as shown in Figure 6.13. Gravity $g$ acts vertically downwards.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{column_deforming.png}
\caption{Column deforming under self-weight}
\end{figure}

The displacement at a point with a distance $y$ from the top of the undeformed rod is $u(y)$. The stress $\sigma(y)$ due to the weight of rod $F(y)$ above point $y$ is given by

$$\sigma(y) = \frac{F(y)}{A} = \rho gy$$

and the strain $\varepsilon(y)$ at this point is given by

$$\varepsilon(y) = -\frac{du(y)}{dy}.$$ 

Since

$$E = \frac{\sigma(y)}{\varepsilon(y)}$$

it is found that

$$u = \frac{\rho g}{2E} \left( L^2 - y^2 \right) \gamma \left( L^2 - y^2 \right)$$

Based on this deformation, ‘quadratic’ boundary conditions are proposed, in which nodes on the posterior face of the model are displaced along the posterior face (whilst remaining in the same transverse plane), with $u$ and $y$ measured along the pectoral fascia. The distance $u$ that each node is displaced is determined by the above equation, with $\gamma$ being chosen to achieve the desired
global scale of deformation (described in more detail in the following section). \( y = 0 \) corresponds to the lateral edge of the undeformed model and \( y = L \) corresponds to the medial edge.

### 6.6.4 Applying the boundary condition

When calculating the displacements of the nodes on the posterior face of the model under both linear and quadratic boundary conditions a zero-displacement boundary condition is imposed in the superior-inferior direction on all nodes lying on this face. The nodes are displaced along the pectoral fascia towards the sternum a distance (measured by linearly interpolating between adjacent nodes in the supine configuration) calculated according to the boundary condition scheme. Since breast tissue is being modelled as being incompressible, a 1D compression along the posterior face in the latero-medial direction, combined with a zero-displacement boundary condition in the superior-inferior direction, will lead to an expansion of breast tissue in the posterior-anterior direction.

Nodes along the medial face of the model have a zero-displacement boundary condition imposed on them. Each node on the lateral face has the same displacement imposed upon it as was calculated for the corresponding lateral-face node lying on the pectoral fascia.

The amount of ‘sliding’ of the breast around the chest wall which occurs in the reference configuration is unknown. Therefore here it is assumed that half of the deformation occurs in the transition from the supine state to the reference state, and half of it occurs in the transition from the reference state to the prone state. To allow comparison, the scale of the deformation is given by the change in size of the most medial element in each transverse plane. For example for a compression quoted as being 20% (illustrated in Figure 6.14), if the element in the supine model has an edge length (in the approximately medio-lateral direction) of \( L_{\text{elem}} \) then, this element will have an edge length of \( 0.8L_{\text{elem}} \) in the prone position and \( 0.9L_{\text{elem}} \) in the reference position.

![Figure 6.14 Illustrative row of elements undergoing a 20% linear and quadratic compression](image-url)
6.7 Modelling Using Revised Boundary Conditions and Material Properties

6.7.1 Introduction

The previous section proposed two alternative pectoral fascia boundary conditions which might improve the accuracy of the model’s deformation predictions. This section assesses the accuracy of models using these boundary conditions. Recognising that literature material properties used in Section 6.5 did not correspond to the observed deformations in the images, in this section the material stiffnesses are fitted to the observed deformation.

6.7.2 Method

Model construction

Models were constructed as described in the 6.5.2 for the same three subjects.

Boundary conditions

Displacement boundary conditions were applied as described in the previous section. A range of boundary conditions were trialled for compressions along the chest wall of between 0% and 30% in steps of 10%.

Material properties

As in previous model constructions, each element was assigned a material type of either adipose or fibroglandular according to the material predominant within it in the image segmentation. Adipose elements were assigned a density of 938kg/m³ and fibroglandular elements were assigned a density of 1035kg/m³ (Johns and Yaffe 1987).

Mooney-Rivlin models having the literature material parameters given in Table 6.2 were trialled. Neo-Hookean material models were also trialled. Since consistent material values are not available, and for simplicity, in the neo-Hookean case identical material stiffnesses were assigned to fibroglandular tissue and to fatty tissue. For both Mooney-Rivlin and neo-Hookean materials the material stiffness parameters were multiplied by a factor so that they could be adjusted to match the observed deformation, as described below.

The node corresponding to the nipple position was identified in the supine model. This made it possible to automatically calculate the distance $d_{nm}$ between this node and the closest point on the pectoral fascia (i.e. the posterior face of the model) in the deformed model. The distance $d_p$ from the nipple to the closest point on the anterior face of the pectoral muscle in the prone image was manually measured. For each set of boundary conditions and material parameters trialled the...
factor by which the material stiffness was multiplied was altered in steps of 0.01 until $d_m > d_p$.
The factor which minimised $|d_m - d_p|$ was then selected to identify the appropriate material stiffness.

Assessment

The MR image of the prone breast was rigidly transformed manually so that the chest wall appeared visually aligned with the chest in the supine MR image, and therefore with the biomechanical model of the breast.

Qualitative visual assessment was performed by warping the supine MR image according to the model deformations and comparing the model-deformed MR image with the prone MR image.

Quantitative assessment was performed based on the location of landmarks and skin-attached fiducial markers. The coordinates of the eight fiducial markers attached to the surface of the breast and a further eight landmark features within the volume of the breast were identified in the prone and supine MR images for each subject. The Euclidean distance between the landmark/marker location observed in the prone image and the location predicted by the model was computed.

6.7.3 Results

The models based on Mooney-Rivlin material parameters were found to substantially underestimate the deformation occurring such that $d_m < d_p$ for all cases where the multiplicative factor was greater than 0.1. Softer Mooney-Rivlin material parameters were not tested since, given this very large disagreement between the literature values and the trialled values, it seems inappropriate to base the material models on such specific models. Therefore only models using the neo-Hookean material parameters were analyzed.

Figure 6.15 shows example slices through supine MR images after they have been warped according to the model deformations for a selection of the boundary conditions considered. The outline of the corresponding prone MR is overlaid on each image. Example slices through the entire range of material properties trialled are presented the figures of Appendix C.

Plots of the mean errors on internal landmarks and skin fiducial markers are shown in Figures Figure 6.16, Figure 6.17 and Figure 6.18. Maximum errors and the neo-Hookean parameters calculated for each level of compression are available in the tables of Appendix C. The mean landmark error was minimised for a linear compression of 20% for all subjects and a quadratic compression of either 20% (Subjects S1 and S2) or 30% (Subject S3). In all cases the minimum mean landmark error is less in the linear than in the quadratic case. The mean landmark errors in
the linear 20% compressions are 9.7, 9.6 and 15.6mm for Subjects S1, S2 and S3 respectively, and the corresponding maximum errors are 17.9, 21.0 and 23.1mm. Skin fiducial marker errors are larger, which reflects their more peripheral location. The values of the neo-Hookean material parameter $\alpha$ for the 20% linear compression case were 0.22, 0.15 and 0.085kPa for the three subjects, which is much softer than the literature reports (see Table 3.2).

Visually the best match between observed and modelled deformation occurs in the 20% linear compression case. The introduction of sliding motion has resulted in a more realistic displacement of the glandular tissue, although the displacement away from the chest wall of the glandular of tissue in the medial region appears to be underestimated. In all cases - but especially in the case of Subject S3 - the width of the breast in the medio-lateral direction is underestimated by the model.

### 6.7.4 Discussion

Introducing a boundary condition scheme in which the posterior nodes were displaced along the pectoral fascia improved the accuracy of the model predictions, and resulted in a visually more realistic deformation. The linear compression scheme proposed performed better than the quadratic compression scheme proposed.
Figure 6.15 Reconstructed MR images showing effect of boundary conditions. Transverse slices through MR images of Subjects S1-3, warped using a selection of boundary conditions. Images for a greater range of boundary conditions, and details of the material stiffnesses used, are available in Appendix C.
Figure 6.16 Plots of mean skin fiducial and internal landmark errors: Subject S1 for a range of (a) linear (b) quadratic boundary conditions

Figure 6.17 Plots of mean skin fiducial and internal landmark errors: Subject S2 for a range of (a) linear (b) quadratic boundary conditions

Figure 6.18 Plots of mean skin fiducial and internal landmark errors: Subject S3 for a range of (a) linear (b) quadratic boundary conditions
Chapter 6. Modelling Deformation of the Breast between Prone and Supine Positions

6.8 Chapter Conclusion

When modelling the deformation of the breast between the prone and supine positions, it is necessary to account for effects of gravity acting during imaging. I have shown here that - assuming suitable boundary conditions are known - iteratively updating an estimated reference state and deforming it to the supine position until the estimated and actual supine models match is an effective and sufficiently efficient technique to recover the reference state of a model constructed from gravity-loaded images. Once the reference state is known it is straightforward to deform this model to the prone position.

Using this technique the deformation for three subjects was modelled and assessed against the observed deformation. The material properties stated in the literature were found to be too stiff to reproduce the deformation occurring since they drastically underestimate the real deformation. Therefore fibroglandular and adipose tissues were considered to have identical neo-Hookean properties, and the neo-Hookean material parameter was fitted to the observed deformation. Inspection of the MR images of the breasts in the prone and supine position revealed that there is significant ‘sliding’ motion of breast tissue around the torso. Approximating this behaviour within the model was found to improve the accuracy of the model prediction on internal landmarks by about a third in all cases.

Certain deformations which can be observed in the MR images - such as the glandular tissue being almost in contact with the pectoral muscle in the supine position but well separated in the prone position - are not well explained by a finite element model which treats the breast as continuous material. In order to simulate the scale of deformation observed, softer material properties are required than have been reported in the compression rheology experiments described in Section 3.2. This is compatible with the ‘blob’ explanation for the observed behaviour suggested in Section 6.4 - when individual blobs are compressed they each have relatively stiff properties, but when the gross anatomy is considered the blobs would be able to move over each other and therefore result in the effective properties being softer. Further investigation of breast tissue material properties is reported in Chapter 7.

Coopers ligaments, whose location and behaviour (especially under the deformation between supine and prone when they can be expected to go from being unloaded to being loaded) are not well understood, will influence the deformation occurring. In keeping with all other breast modelling work, these ligaments are not explicitly included in this simplified model of the breast. Their influence may, to some extent, be encapsulated by an apparent increase in the stiffness of other breast tissues, although this will not capture their anisotropic nature.
Skin can be expected to affect the deformation of the breast. Its influence on a model will be highly dependent upon how it is tethered at the margins of the model. These boundary conditions are not well understood. Furthermore the correct way to model the skin/breast tissue interface is not apparent - modelling a tight coupling between the two tissues in the reference state would result in the skin ruckling when the breast tissue becomes compressed since the skin is much stiffer than breast tissue. A potential solution would be to model the skin as being under tension, which more closely represents what is actually happening. In this situation the ‘zero-strain’ reference state assumed in this thesis would no longer be valid. Pathanathan (2006) started to address the theoretical issues associated with including skin under tension in a biomechanical breast model deforming under gravity, but there is significant work required before such a model could be implemented. For these reasons skin was not included in the model, but the influence of including skin on a biomechanical model of the breast will be examined in Chapter 7.

When assessing the model it is necessary to bear in mind that the ultimate purpose of modelling the supine-prone deformation of the breast is to enable points identified in a prone MR image to be identified during surgery to an appropriate accuracy. This accuracy was identified in Section 2.6.2 as being about 10mm. On the three subjects I have considered in this chapter, the model is able to recover landmark locations to a mean error of 9.7, 9.6 and 15.6mm. This compares very favourably with the rigid errors of 46.9, 51.5 and 70.5mm, but is not quite within the tolerance required for surgery - particularly since the supine-prone modelling accuracy is just one contribution to the total system error. I propose a method to further improve this supine-prone registration accuracy in Chapter 8.
Chapter 7

Further Investigation of Material Properties

7.1 Introduction

One of the major obstacles when constructing a biomechanical model of the breast for modelling deformation between the supine and prone postures is the lack of appropriate values for the material properties available in the literature. As was described in the literature review of Chapter 3, rheological experiments to date have sought to establish material models only for much smaller deformations than occur between prone and supine and only for material in compression. If gravitation loads are imposed on a model it is necessary to know the true values for material parameters, whereas in the scenario of modelling mammographic compressions by applying just displacement boundary conditions only relative values would be needed. The challenge of determining appropriate material models for this deformation is compounded by the lack of a known reference state.

In this chapter I demonstrate that the reference state of an object can be reasonably approximated by submerging it in water. An intensity-based non-rigid registration algorithm is then used to establish point-by-point correspondence between the submerged and prone breast images.

I construct a model of the breast in its reference state from the submerged images and simulate the deformation to free-pendulous prone for a range of material stiffnesses. The effect of varying the material properties on the accuracy of the model is assessed by comparing the simulated deformation with that recovered by the registration algorithm.
7.2 Comparison of the Reference State and the Submerged State

7.3 Introduction

This section addresses the question “is the shape of an object when it is submerged in water a reasonable approximation to the shape of that object in its reference state?”. A simple in silico phantom is constructed here and the effect of submerging this phantom in water is simulated.

7.4 Method

The phantom, in its reference state, consisted of a cube with an edge length of 50mm. It was modelled as being made from a homogenous incompressible material which obeyed a neo-Hookean constitutive law. The experiment was repeated for materials of differing stiffness and density, as is shown in Table 7.1.

The cube was meshed into $10^3$ hexahedral elements. All nodes on the upper face were constrained to have zero displacement. Gravity (9.81ms$^{-2}$) was modelled as acting vertically downwards, normal to this face. The effect of immersing the phantom in water (which has a density of 1000kg/m$^3$) until the upper face was level with the water surface was simulated by applying a pressure on the outer surfaces of the phantom. The pressure was given by:

$$ P = \rho gh $$

where $P$ is the hydrostatic pressure, $g$ is the acceleration due to gravity and $h$ is the depth below the water surface.

7.4.1 Results

The mean and maximum difference between node locations in the reference state and submerged states for the material properties trialled are given in Table 7.1. Images of the model in reference, prone and submerged states are shown in Figure 7.1 for the combination of material parameters where this difference was greatest.
Table 7.1 Comparison of submerged model with reference state model

<table>
<thead>
<tr>
<th>Density /(\text{kg/m}^3)</th>
<th>(\alpha) /(\text{kPa})</th>
<th>900</th>
<th>1000</th>
<th>1100</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>1.06 (1.79)</td>
<td>0.02 (0.19)</td>
<td>1.18 (1.97)</td>
<td></td>
</tr>
<tr>
<td>.50</td>
<td>0.47 (0.80)</td>
<td>0.01 (0.10)</td>
<td>0.50 (0.84)</td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>0.23 (0.38)</td>
<td>0.00 (0.05)</td>
<td>0.23 (0.39)</td>
<td></td>
</tr>
</tbody>
</table>

Mean (maximum) difference in mm between submerged and reference state node positions

Figure 7.1 Simulation of the effect of submerging a cubic phantom in water
(a) Phantom in reference state; (b) Phantom deformed by gravity; (c) submerged phantom deformed by gravity. Images are for a phantom of density 1100\(\text{kg/m}^3\) and with \(\alpha=0.25\text{kPa}\)

### 7.4.2 Conclusion

The shape of a submerged incompressible cube of a similar density to water appears to be a good approximation to the shape of that cube in its reference state, with a mean difference between submerged and reference state of less than 1.2mm for the worst performing combination of the material properties trialled. The behaviour of an enclosing membrane such as skin would not be expected to significantly influence this if it is under zero strain at the reference state. This is assumed here, although in reality skin will be under slight tension (Alexander and Cook 1977).

Since the densities of fat and fibroglandular tissues, 938\(\text{kg/m}^3\) and 1035\(\text{kg/m}^3\) respectively (Johns and Yaffe 1987), are more similar to the density of water than the densities trialled, it seems likely that the reference state of the breast can be reasonably approximated by the submerged breast. This conclusion is subject to the caveat that in practice there may be no such
thing as a ‘reference state’, since it is possible that strains will exist within the breast for every possible configuration.

### 7.5 Imaging the Submerged Breast

#### 7.5.1 Introduction

Since the submerged breast appears to provide a reasonable approximation to the breast’s reference state MR images were acquired of a volunteer’s breasts when submerged in water. Corresponding MR images in the prone and supine positions were acquired for comparison with the submerged breast, and to enable an analysis of the soft tissue deformation which occurs between these positions to be performed.

#### 7.5.2 Method

The MR protocol used to acquire images of Subject S3 on the Philips Gyroscan Intera 1.5T MR scanner at Guy’s Hospital, London is detailed in Section 5.3. The Q-body coil was used for all imaging. The first ‘supine’ image volume was acquired with the subject in the supine position. She was then rotated into a prone position with her breasts hanging into the depression of the breast coil assembly shown in Figure 5.2 and an image volume was acquired with the subject in this ‘prone’ position. Without moving the volunteer or scanner bed, water was pumped through a plastic pipe into the coil assembly depression from outside the scanner. The water level was monitored using real-time sagittal images. Once the coil assembly depression had been filled with water a ‘submerged’ image volume was acquired using the same imaging protocol as for the prone images.

#### 7.5.3 Results

Example transverse slices through the supine, prone and submerged image volumes are shown in Figure 7.2. The images appear to be of sufficient quality to follow the gross deformations which are occurring. Since the volunteer did not move between the prone and submerged images being acquired the motion of the chest wall, including the pectoralis major muscle, between the prone and submerged images appears to be negligible. The MR scanner bore is a narrow enclosed space, and there are risks associated with having large volumes of water in an open container in the MR scanner. It was therefore not possible to immerse the torso of the volunteer such that her breasts were completely submerged, as can be seen in Figure 7.2c.
Figure 7.2 MR images of breast in supine, prone and submerged positions. Example transverse slices through the (a) supine (b) prone and (c) submerged breasts

7.5.4 Discussion and Conclusion

There appears to be relatively little motion in the region close to the chest wall between the submerged and prone images, but there is very considerable motion along this wall between the submerged and supine images. One cause of this is that the chest wall is not completely submerged and therefore the ‘submerged’ position is, in effect, more similar to the prone than it is to the supine position. This distortion is exaggerated by the breast being in the prone position immediately prior to being in the ‘submerged’ position and because the surrounding tissues are approximately in their prone position.

Although imaging the breast whilst it is submerged in water is feasible, breast tissue close to the chest wall, particularly in the higher lateral regions, cannot be submerged. Therefore the reference state of the breast can be estimated only for regions of the prone breast away from the chest using this technique.
In conclusion, the images of the submerged breast are of sufficient resolution and quality that a model of the breast can be constructed from them and they provide an estimate of the reference state for the portion of the breast which becomes submerged.

7.6 Recovering the Deformation Between Submerged and Prone

7.6.1 Introduction

To assess the ability of a model to simulate the deformation from the reference state to the prone state, it is desirable to know the point-by-point correspondence between the prone image and the submerged image which acts as a surrogate reference image. Whilst it will be shown in the next chapter that the deformation from prone to supine is too large to capture using ‘off-the-shelf’ registration algorithms, the deformation between submerged and prone is much smaller. This section will demonstrate that it is possible, for suitably acquired images, to recover this deformation to a reasonable accuracy using a viscous fluid non-rigid registration algorithm.

7.6.2 Method

The prone and submerged image volumes acquired as described in the previous section were cropped to regions of interest which enclosed each breast individually. The background (water or air) was segmented along the skin surface in both the prone and the submerged volume using region-growing and semi-automatic methods in Analyse. This removed a fat-shift artefact which lay along the skin surface, and served to prevent unreliable registration results around the nipple caused by the nipple having a similar intensity to the surrounding water. Although fiducial markers were attached to the skin surface, their locations were not used in the experiments of this chapter and they were removed during this background segmentation.

The prone breast (source image) was registered to the submerged breast (target image) using the fluid registration algorithm described in Section 4.4. Image forces were not applied to regions of the target image identified in the segmentation as being background. A multi-resolution approach was adopted using four levels (⅛-image resolution ¼-image resolution, ½-image resolution and actual image resolution). A normalised cross-correlation similarity measure was used since the same MR sequence was used to acquire both image volumes.

The registration accuracy was assessed by visually comparing the registration-deformed prone image with the target submerged image. A target registration error was calculated using 8 corresponding sub-surface landmarks identified in the free-pendulous prone and submerged breasts. This target registration error was computed in the free-pendulous space.
7.6.3 Results

Example slices through the initial and deformed image volumes are shown in Figure 7.3(a-c) and Figure 7.4(a-c). The deformed prone image visually appears to correspond well with the submerged target image.

Figure 7.3d and Figure 7.4d show the difference between the submerged and warped images. The images are shown to match well with the greatest mismatch appearing in the very inferior portion of the breast. The subsampled deformation field for the submerged breast is shown in Figure 7.3c and Figure 7.4c. The head of each arrow identifies a particular voxel in the deformed image, whilst the tail of the arrow corresponds to the source of that voxel’s intensity in the prone image. The deformation fields appear plausible. The mean (maximum) target registration error was calculated as 1.0(1.53) mm for the left breast and 1.6 (2.2) mm for the right breast.

7.6.4 Discussion

Both the left breast and right breast have a significant glandular volume containing few discernable features. In this region there is little information to drive, or to validate, a registration. Therefore the error in these regions could be higher than a visual inspection might suggest. Apart from at the nipples, the glandular tissue is surrounded by adipose tissue and the features along this interface may help to keep the registration within the glandular volume accurate.

The deformation fields appear plausible and the registration results in regions containing identifiable features appear visually good, with a TRE of around 1mm. Therefore in the remainder of this chapter it will be assumed that fluid registration can recover the deformation between submerged and prone to a sufficiently greater accuracy than a biomechanical model which does not exploit image intensity information. This means that the fluid registration can be considered a gold standard against which the biomechanical model can be assessed.
Figure 7.3 Registration of images of the left breast Sagittal, coronal and transverse slices through the left breast: (a) submerged breast after segmentation of background (b) prone breast after segmentation of background (c) prone breast after being warped according to the overlaid deformation field from the image registration. Only the in-plane components of the 3D warp are shown (d) image showing the difference between the submerged and the warped prone image
Figure 7.4 Registration of images of the right breast Sagittal, coronal and transverse slices through the right breast: (a) submerged breast after segmentation of background (b) prone breast after segmentation of background (c) prone breast after being warped according to the overlaid deformation field from the image registration. Only the in-plane components of the 3D warp are shown (d) image showing the difference between the submerged and the warped prone image
7.7 Modelling the Deformation Between Submerged and Prone

7.7.1 Introduction

Since the submerged breast provides a good approximation to the reference state configuration of the breast, and it appears that intensity-based registration can recover the deformation of the breast between the submerged and the prone positions sufficiently accurately, it is possible to assess the behaviour of a biomechanical breast model against a known, gravity-induced deformation from the reference state. Since boundary conditions for the model can be extracted from the non-rigid deformation field they are much better known than in the full prone-supine situation discussed in the previous chapter. This increases the relative influence of changes in material stiffness. It therefore becomes practicable to assess the effect of varying fibroglandular and adipose material properties independently. Material stiffnesses for the components of breast tissue can be found by determining those values which optimise the agreement between the prediction of a biomechanical model and the deformation recovered by image registration.

7.7.2 Method

A finite element model was constructed from the segmented MR image volume of each submerged breast created in Section 7.6. The finite element mesh was constructed so that the model’s posterior face was parallel to the water surface. This face was located below the water level and anterior to the pectoral muscle so that muscle tissue was not included in the model.

First the volume was resliced to have a slice thickness of 2.5mm. Each of these slices was meshed into quadrilateral elements as shown in Figure 7.5a. The elements had a width of 4mm in the medio-lateral direction. The height of each element edge in the anterior-posterior direction was determined by dividing the vertical distance from a manually selected constant depth below the water surface to the breast edge (smoothed, as in Section 5.7, over the entire breast in 3D) into six equal sections. Corresponding quadrilateral elements (where present) in adjacent slices were then connected to form hexahedral elements (ANSYS element type solid185). The resulting mesh for the right breast is shown in Figure 7.5b.

As with the models of the previous chapters, the MR image was semi-automatically segmented using Analyze, and each element in the model was assigned a material type of either adipose or fibroglandular tissue according to the predominant material contained within the element in this segmentation. Adipose elements were assigned a density of 938kg/m³, and fibroglandular elements a density of 1035kg/m³ (Johns and Yaffe 1987).
Both adipose and fibroglandular tissue was modelled as obeying a neo-Hookean constitutive relationship. Values of $\alpha_g$ and $\alpha_a$ which describe this relationship (see Equation B.28) for fibroglandular and adipose tissue respectively were varied in steps of 0.1kPa between 0.1kPa and 1.5kPa.

Figure 7.5 Finite element mesh of submerged breast (a) Example transverse slice through quadrilateral mesh overlaid on an MR image of the submerged right breast (b) final mesh of right breast, viewed from a superior lateral position.

A body force corresponding to the acceleration due to gravity (9.81 m/s$^2$) was applied to the model towards the anterior, perpendicular to the water surface. The reference state of the breast was taken to be identical to the submerged state and so internal stresses were assumed to be zero.

Displacement boundary conditions were applied on all nodes of those faces of the model which truncate tissue which is, in reality, continuous - i.e. the large posterior face and the much smaller superior, inferior, medial and lateral faces of the model. These boundary conditions were applied according to the deformation field calculated by the intensity-based non-rigid registration in Section 7.6. In this way the deformation due to the motion of surrounding tissue can be accounted for in the model as well as the gravity-induced deformation.

The model was assessed by comparing positions of nodes in the gravity-deformed finite element model with the position of the nodes displaced according to the non-rigid intensity-based registration deformation field obtained in Section 7.6. The intensity-based registration was considered to provide the ‘gold standard’ and therefore disagreements between the intensity-based registration and the finite element model prediction are reported as model errors.
7.7.3 Results

Contour plots showing how the mean displacement error varies as the material stiffness is changed are shown in Figure 7.6. Nodes of the model which have prescribed displacement boundary conditions were not included when calculating the mean displacement error.

The deformation of the left breast from the prone position to the submerged position involved a mean (maximum) nodal displacement of 10.1 (19.0) mm according to the intensity-based registration results. When modelling this, the mean error on each node was minimised when $a_g = 0.3\text{kPa}$ and $a_a = 0.3\text{kPa}$. The mean (maximum) error was 1.1 (7.1) mm for these material parameters. The deformation of right breast from the prone position to the submerged position involved a mean (maximum) nodal displacement of 7.3 (12.4) mm according to the intensity-based registration results. When modelling this, the mean error on each node was minimised when $a_g = 0.4\text{kPa}$ and $a_a = 0.8\text{kPa}$. The mean (maximum) error was 0.7 (3.4) mm for these material parameters.

If the mean of the left and right breast neo-Hookean parameters are assumed ($a_g = 0.35\text{kPa}$; $a_a = 0.55\text{kPa}$), then a mean (maximum) error of 1.2 (6.6) mm for the left breast and 0.7 (3.0) mm for the right breast is found.

Figure 7.7 and Figure 7.8 show the submerged model and compare its shape after gravity-induced deformation with its shape after deformation according to the intensity-based registration. The magnitudes of the errors over the skin surface are shown colour-coded on the submerged breast for the combination of material properties which minimised the mean error.
Figure 7.6 Contour plots showing variation of error with respect to assumed material properties

Contour plots showing how mean nodal error (in mm) varies with fibroglandular and adipose material stiffness for the (a) left breast (b) right breast. The minimum error in each plot is marked with a red star. $\alpha_g$ and $\alpha_a$ denote the neo-Hookean parameters for adipose and fibroglandular tissue respectively.
Figure 7.7 Model of left breast with material properties which minimise the mean error (a) in submerged position (b) deformed to prone position by gravity (c) deformed to prone position according to registration (d-e) gravity (blue) and registration-deformed (purple) models overlaid, so surface appears blue if registered surface lies below gravity-deformed surface (f) Submerged model colour-coded by the error on the surface in mm. Viewing directions:(a-d) latero-medial (e) medio-lateral (f) anterior-posterior

Figure 7.8 Model of right breast with material properties which minimise the mean error (a) in submerged position (b) deformed to prone position by gravity (c) deformed to prone position according to registration (d-e) gravity (blue) and registration-deformed (purple) models overlaid, so surface appears blue if registered surface lies below gravity-deformed surface (f) Submerged model colour-coded by the error on the surface in mm. Viewing directions:(a-d) latero-medial (e) medio-lateral (f) anterior-posterior
7.7.4 Discussion and Conclusion

The mean nodal displacement occurring is of order 10mm. This is recovered to better than 2mm for all but the very softest material properties trialled. This indicates that imposing the correct boundary conditions has a much greater effect than the choice of material properties. Whilst this result is well known when applying only displacement boundary conditions, here it is shown to also be true when applying body forces on a soft tissue model. The contour plots show that the models are slightly less sensitive to changes in fatty tissue material properties than fibroglandular tissue. This result is likely to be influenced by changes in the proportion of fibroglandular vs. adipose tissue between patients. The residual error is large compared with the rate of change of the mean error as material properties are altered, except for the very softest material properties trialled. This suggests that minimising the mean error to determine the material properties of the breast may not be accurate.

The mean error is lower for the right breast than for the left. The fluid registration, against which the model is being assessed, has a higher TRE for the right breast so this could possibly be attributable to the fluid registration failing to capture the fine detail and so providing a smoother deformation field which the model is better able to recreate. This explanation seems consistent with the observation that the error measured over the right breast is less sensitive to the choice of material parameters than the error over the left breast.

The mean error was found to be minimised when fibroglandular tissue had the same stiffness as adipose tissue for the left breast, and when it was less stiff than adipose tissue for the right. As was seen reported in Section 3.2, glandular tissue is generally considered to be stiffer than adipose tissue. One possible reason for the results reported here disagreeing is that literature reports have all been for materials in compression. An alternative explanation is that the fatty tissue is along the periphery of the breast and so adjacent to the skin. Therefore the result being quoted for adipose tissue may in fact reflect the combined material properties of skin and fatty tissue. This will be investigated in the next section.

The overlap between the model deformed by gravity and deformed by the registration appears generally good with the greatest error occurring in the region of the nipple for both breasts. This could reflect a poor fluid registration in this region (since there is no fibroglandular/adipose boundary to constrain it). It could also be attributable to the nipple’s location, far away from the nodes at which displacement boundary conditions were imposed. Another possibility is that this is an artefact of the optimisation chosen: improving the fit between model and registration displacement fields within the volume of the breast might achieve in the lowest mean error over all the nodes, even if this is at the expense of a large error at the edge of the breast.
The error in the ‘gold standard’ intensity-based deformation, against which the biomechanical model is tested, is of a similar scale to the difference between the model and registration results. This fluid registration algorithm is heavily dependent on the image information since it does not have a realistic physical basis underlying it, and there are no constraints such as volume-preservation inherent in it, so unrealistic deformations can occur. This may contribute to the measured error. Conversely the registration algorithm may be interpolating across regions containing little intensity information (such as large regions of glandular tissue) in a similar manner to the biomechanical model, which can be expected to result in erroneously small measured errors.

Both glandular tissue and adipose tissue are modelled here as obeying a neo-Hookean constitutive relationship due to its simplicity, but it is very unlikely that either tissue can be modelled as accurately following this 1-parameter relationship over a large stress range. However, the general approach proposed here is in principle suitable to be extended to higher order constitutive relationships, although it seems likely that the accuracy of the image registration would have to be improved in order to determine the increased number of parameters accurately.

The model assumes that the breast can be modelled as a continuous incompressible medium but if tissues within the breast are able to slide over each other, this will not be valid. Fluid registration cannot directly model sliding either, so it is uncertain how sliding behaviour will affect the results. Coopers ligaments are not modelled since they cannot be seen on MR images, but they are likely to influence the deformation between the submerged state and the prone state. Their influence will be greatest if they are relaxed when the breast is submerged but become under tension as the breast is loaded. A ‘partial volume effect’ due to each element being assigned to a specific material type but actually containing a mix of material types will limit the accuracy with which material properties can be determined. Skin is also excluded from this model; the effects of including skin will be investigated in the next section.
7.8 The influence of skin on the model

7.8.1 Introduction

None of the models tested in the preceding sections and chapters have included skin. It has been found by other researchers to have limited influence on the deformations of the breast (see Section 3.6.2). However this result is somewhat counter-intuitive and certainly has not been comprehensively proven for the prone-supine deformation scenario. In this section the effects of adding skin to the model is investigated.

7.8.2 Method

Skin was modelled a membrane over the surface of the model constructed in Section 7.7 by adding a 1mm thick layer of quadrilateral shell elements (ANSYS element type shell181) to the anterior face of the model. The skin elements shared the nodes of the underlying breast tissue and so were tightly coupled to the breast tissue elements. Skin was assigned a density of 1000kg/m³. It was modelled as being completely incompressible and as obeying a neo-Hookean constitutive relationship described by neo-Hookean parameter $\alpha_s$.

The deformation between submerged and free-pendulous prone was simulated as in Section 7.7. The fibroglandular and adipose tissue material properties which minimised the mean error on the nodal displacements for a range of skin stiffness were determined using an exhaustive search (to the nearest 0.05kPa for fibroglandular and adipose tissue and to the nearest 2 kPa for skin). Again, nodes upon which displacement boundary conditions were imposed were not included in this assessment.

7.8.3 Results

Figure 7.9 shows the effect of varying the skin stiffness on the mean nodal error for the left and right breasts.

The mean (maximum) nodal error for the left breast was 1.0 (5.7) mm, which occurred when $\alpha_s=5$kPa, $\alpha_g=0.2$kPa and $\alpha_a=0.1$kPa. The mean (maximum) nodal error for the right breast was 0.6 (3.8) mm, which occurred when $\alpha_s=11$kPa, $\alpha_g=0.2$kPa and $\alpha_a=0.15$kPa. Taking the mean of these parameter values ($\alpha_s=8$kPa, $\alpha_g=0.2$kPa and $\alpha_a=0.125$ kPa) results in a mean (maximum for these parameter values) error of 1.1 (5.7) mm for the left breast and 0.7 (3.3) mm for the right breast.
The mean nodal error cannot be greatly reduced by increasing the stiffness of skin. This perhaps reflects the over-riding influence that the boundary conditions, rather than the material properties, have on the model.

![Graph](image)

**Figure 7.9 Variation of mean error on nodes for models including skin.** Results for models without skin are marked by diamonds.

### 7.8.4 Conclusion

The mean nodal error cannot be greatly reduced by increasing the stiffness of skin, and varying material properties seems to have only a minor effect. This perhaps reflects the over-riding influence that effective boundary conditions have on the model. Varying the skin properties for the left breast shows a much more marked minimum than varying the skin properties for the right breast, although the mean errors are smaller for the right breast. As discussed in Section 7.7.4, this perhaps reflects that the fluid registration is achieving a more accurate ‘gold-standard’ registration for the left breast. Possibly a distinct minimum would be achieved for the correct material properties if a perfect gold standard were available.

### 7.9 Chapter Conclusion

The material stiffness of the breast under the strains experienced during deformation between prone and supine (particularly values for breast tissue in tension) are not well known. In this chapter I have proposed that comparing a model against a ‘gold standard’ intensity-based
registration may provide a mechanism to determine these material properties. The deformation
between submerged and free-pendulous prone is used since the submerged state is a good
approximation to the reference state.

The optimised biomechanical models were able to recover around 90% of the mean
displacement occurring. I found that $0.1 < \alpha_a < 0.8$ kPa and that $0.2 < \alpha_g < 0.4$ kPa depending on
which breast was being modelled and whether skin was included. The TRE of the ‘gold-
standard’ intensity-based registration is of a similar order to the difference between the
deformation determined by this intensity-based registration and the optimised model. This limits
the precision with which the material properties can be determined.

Ruiter (2003) fitted neo-Hookean constitutive relationships to the range of constitutive
relationships for breast tissue available in the literature, which are all based on data for tissue in
compression. The values obtained were given in Table 3.2. She found that $0.4 < \alpha_a < 15.1$ kPa and
that $0.5 < \alpha_g < 64.8$ kPa. The neo-Hookean parameters found here for breast tissues in tension are
at the smaller extreme of, or are smaller than, these values. However there is no reason to expect
material properties to be identical in tension and compression. Indeed brain tissue, which is
another biological tissue whose primary function is not structural, has similarly been found to be
stiffer in compression than in tension (Miller and Chinzei 2002).

Despite the mean nodal displacement occurring being of order 10mm, this displacement is
recovered to a mean of better than 2mm for all but the very softest material properties
considered in the model. This highlights that imposing the correct boundary conditions has a
much greater effect than the choice of material properties. Although this result is well known
when applying only displacement boundary conditions, here it is shown to also be true when
applying body forces on a soft tissue model.
Chapter 8

Registration of Prone and Supine MR Images of the Breast

8.1 Introduction

The motivation for the biomechanical modelling of the breast developed in this thesis is to assist in establishing correspondence between a DCE MR image of the breast acquired with the patient positioned prone and the patient in the supine surgical position. The preceding chapters have examined how accurately it is possible to model the deformation occurring between prone and supine positions. In the clinical setting, it is possible to acquire, in addition to the standard diagnostic DCE MR images in the prone position, an MR image without contrast enhancement in the supine position. Such an image will be a much better approximation to the surgical situation than the prone images, and so if correspondence can be established between the prone and supine images, the task of finding the correspondence between diagnostic images and the surgical position is greatly simplified.

In this chapter I approach the task of recovering the deformation of the breast between prone and supine from an image-registration perspective. The outline of this chapter is shown in Figure 8.1. The first experiments of this chapter attempt to recover the deformation using standard non-rigid intensity-based registration algorithms. As expected, these algorithms are found to be inadequate, so I investigate whether the biomechanical model of the breast used in the preceding chapters can be used for registration. The modelling is adapted to allow information from the MR images about the shape of the prone breast to be incorporated. I then propose and assess a hybrid registration technique which uses the model-based registration results as an initialisation step for an intensity-based registration process.
Accuracies in this chapter will be quoted in both supine space and prone space. The accuracy quoted in the supine space (after accounting for the errors due to other components of an image-guided surgery system) is the accuracy with which the surgeon’s question “Where do I go?” can be answered. The accuracy quoted in the prone space is the accuracy with which the question “Where am I?” can be answered. Both questions will ultimately need to be answered during an operation - since the breast lacks clear dissection planes identifying a particular tissue boundary is challenging for the surgeon.

### 8.2 Intensity-Based Registration

#### 8.2.1 Introduction

Two widely-used state-of-the-art intensity-based non-rigid image registration algorithms, which have been shown in the literature to be effective at matching pairs of MR images of the prone
breast, were assessed for the task of matching pairs of prone and supine MR images of the breast. The registration algorithms assessed were a free-form deformation algorithm (Rueckert et al. 1999) and a viscous fluid registration algorithm (Crum et al. 2005), which were described in Section 4.4.

### 8.2.2 Method

#### Image Preparation

The registration techniques were assessed for MR images of three subjects (S1-3). Although surgery is performed supine with the arm extended distally the bore of an MR scanner prevents the arm being stretched out sideways in this way. In initial experiments the subjects found the ‘hand behind head’ position, which is perhaps the closest approximation to the surgical position possible within the scanner, uncomfortable and this resulted in large motion artefacts being visible in the images. Therefore all imaging in this chapter is of patients with their arms lying by their sides. The protocol used to acquire the images was described in Section 5.3.

The existing segmentation, which was used in Chapter 5 to create the models, was used here to assign a value to all voxels in the supine image which lay outside the breast. Identifying these voxels as being outside the region of interest means it is possible to exclude them from the intensity-based registration so that organs, such as the heart, which are independent from the breast and undergo large displacements or deformations between prone and supine do not influence the registration. It also makes a fair comparison possible between the registrations reported in this section and those reported in later sections, in which voxels outside the model of the breast will not be included. No region of interest was demarcated in the prone MR image.

Low frequency variations in the signal intensity exist in the MR images, primarily due to the non-uniformity of the radio frequency coils and the effects of patient anatomy. This inhomogeneity was reduced in both the prone and supine images using the nonparametric non-uniform intensity normalization method (Sled et al. 1998) in the implementation by McAuliffe et al. (2001).

#### Rigid Registration

The locations of corresponding pairs of skin fiducial markers were manually identified in the prone and supine MR volumes. A transformation between the prone and supine images was computed by rigidly transforming the marker locations in the prone image to minimise the distance (in the least squares sense) between homologous markers using the technique described by Arun et al. (1987).
Chapter 8. Registration of Prone and Supine MR Images of the Breast

The supine MR volume was sub-sampled to have isotropic voxels with an edge length equal to the longest edge length in the original supine image volume. The rigid transformation was applied to the prone volume to create an aligned prone MR volume which has the same voxel dimension as the isotropic supine volume. The prone volume was transformed rather than the supine volume to avoid reducing the quality of the supine image with an interpolation step, since the prone volume is of a higher initial quality due to less breathing motion and (in the case of Subjects S1 and S2) because the breast coil was used.

**Fluid Registration**

The ability of a fluid registration algorithm to recover the deformation between the aligned supine and prone MR volumes was tested using the fluid registration technique reported by Crum et al. (2005).

In the implementation of the fluid registration algorithm which was used in this thesis, the region of interest must be defined in the target space. Therefore the isotropic supine image created above was used as the target image, and the rigidly co-registered isotropically sampled prone image created above was used as the source image. The image force $f$, as defined in the fluid sub-section of Section 4.4, was set to zero for all voxels labelled as being outside the region of interest in the target image. For all other voxels the image force was derived from the gradient of the similarity measure. Cross-correlation was used as the similarity measure, since the prone and supine MR volumes were acquired with similar MR sequences. The viscosity constants $\mu$ and $\lambda$ which describe the fluid’s behaviour were set to 1 and 0, as has generally been assumed in the literature (see Section 4.4). A stopping condition based on the change in similarity measure at each iteration was used to terminate the registration.

Initial trial registrations indicated that because the deformation is so large, the source and target images need to be substantially sub-sampled and blurred. A range of subsampling and blurring factors were trialled, but none achieved good results. One example registration scheme is reported here for illustration. In this scheme the images to be registered were greatly sub-sampled (by a factor of $2^4$ in each direction) in an attempt to avoid local minima and so recover the gross shape of the breast. The images were blurred using a Gaussian filter with the variance recommended by Crum et al. (2005).

**Free-Form Deformation Registration**

The ability of an FFD registration algorithm to recover the deformation between the aligned supine and prone MR volumes was also tested using the FFD algorithm proposed by Rueckert et al. (1999).
The isotropically sampled supine image was selected as the target image and the rigidly co-registered isotropically sampled prone image was selected as the source image. Cross-correlation was again chosen as the image similarity measure. Intensity pairs where the target voxel was identified as being outside the region of interest did not contribute to the image similarity so that they did not influence the registration.

Initial trial registrations indicated that because the deformation was so large, it was necessary to sub-sample and blur the source and target images and to use coarse control point spacing in order to prevent the registration from immediately getting caught in local minima. Therefore for the experiment reported in this section the target and source images were blurred using a isotropic 2.5mm Gaussian kernel, were sub-sampled to have a voxel dimension of 5mm and a control point spacing of 40mm was used for the registration. Given the number of parameters which can be empirically tuned, is almost certain that these are not the optimum values. However the results are indicative of the ability of the FFD algorithm to register prone and supine MR images based on intensity information alone.

Assessment

The registration accuracy was assessed on the same eight internal landmarks for each subject which were used to assess the models in Chapter 6. Since the target image was in the supine space, the accuracy was measured in the prone (source) space. This is because the deformation field points to the to a source location for each voxel in the target space.

The error on each landmark was computed as the Euclidean distance between the position of the landmark identified in the prone image and the location of the corresponding landmark in the supine image after applying the non-rigid deformation field and the appropriate rigid transformation.

8.2.3 Results

The mean and maximum errors on the eight landmarks using the three registration techniques (rigid, fluid + rigid and FFD + rigid) for each subject are shown in Table 8.1. Example slices through the registered volumes are shown in Figure 8.2.
Table 8.1 Accuracy of rigid, fluid and FFD registration methods technique. Accuracy is measured in the prone space on three subjects (S1-3)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Rigid Registration mean (max) /mm</th>
<th>Fluid + Rigid Registration mean (max) /mm</th>
<th>FFD + Rigid Registration mean (max) /mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>15.6 (25.8)</td>
<td>13.7 (23.1)</td>
<td>33.1 (46.4)</td>
</tr>
<tr>
<td>S2</td>
<td>16.4 (23.7)</td>
<td>10.5 (28.6)</td>
<td>31.5 (52.7)</td>
</tr>
<tr>
<td>S3</td>
<td>28.9 (47.8)</td>
<td>31.0 (50.4)</td>
<td>35.5 (64.9)</td>
</tr>
</tbody>
</table>

8.2.4 Discussion

Fluid registration slightly improved the mean registration accuracy compared with the rigid registration results for two out of the three subjects, and performed slightly worse than rigid registration for the third subject. Free-form deformation based registration failed to register any of the prone-supine pairs of images. It created unrealistic deformations which resulted in a much worse registration accuracy than was provided by the rigid registration.

Whilst the two non-rigid registration techniques trialled were intensity-based rather than feature-based, they rely upon some of the corresponding structures in prone and supine overlapping sufficiently that their alignment can be improved on the basis of intensity information in the images. Although it is not necessary for all structures to initially be overlapping, since improving the alignment of those structures which do initially overlap should improve the alignment of other structures, poor initial alignment increases the likelihood of incorrect local minima. In the case of prone and supine images of the breast it would appear that there is so little initial overlap that the correct global minima lies outside the capture range of the intensity-based registrations trialled and the large distortions of the breast created by the registration algorithms do not improve the registration accuracy.

It has not been proved that every intensity-based registration algorithm, with every possible choice of tuning parameter, will fail to capture the large deformation of the breast which occurs between the prone and supine posture. However, the experience of the registration experiments reported here indicates that an algorithm which is driven purely by the image data, and so contains no prior knowledge about the anticipated deformation, is unlikely to be well-suited to capturing this deformation.
Figure 8.2 Example slices through supine images and prone images after intensity-based registration: rigid alignment, fluid + rigid registration and FFD + rigid registration.
8.3 Finite Element Model-Based Registration

8.3.1 Introduction

An alternative to performing an intensity-based registration to derive the observed deformation is to use a biomechanical model to predict the deformation occurring due to gravity, and to warp the MR image according to this deformation. In this respect, the biomechanical modelling of the prone-supine deformation developed in the previous chapters can be considered a registration procedure.

In Chapter 6 the information in the prone image is only used (other than for assessment purposes) to measure the distance from the pectoral fascia to the nipple in the prone position in order to provide an indication of the material stiffness and to rigidly align the chest walls. Much more information than this is available in the prone image, for example the locations of the fiducial markers which are attached to the skin; the position of the skin surface and, ultimately, the full intensity information. In this section I will examine the effect of including knowledge of fiducial marker locations and the position of the skin surface on the model’s ability to accurately predict the displacement of internal landmarks.

8.3.2 Method

Four registration scenarios are compared in this section:

(a) Undeformed supine volume rigidly aligned with the chest wall

(b) Gravity-deformed model rigidly aligned with the chest wall

(c) Gravity-deformed model rigidly aligned with fiducial markers

(d) Gravity-deformed model non-rigidly aligned with skin surface

Chapters 5 and 6 have described how a finite element model of the breast in the supine position can be constructed and then deformed to approximately the prone position by simulating gravity. Imposing a displacement boundary condition corresponding to a linear medio-lateral compression of 20% on the posterior face of the model was found to most accurately simulate the deformation. Therefore in this chapter the gravity-deformed models which were created with this boundary condition in Chapter 6 are used.
Scenario (a): Undeformed supine volume rigidly aligned with the chest wall
Scenario (b): Gravity-deformed model rigidly aligned with the chest wall

In Scenario (a) the prone MR image was rigidly transformed manually such that the chest wall visually appears aligned with the supine MR image. The same transformation was used to align the prone image with the gravity deformed model in Scenario (b).

Scenario (c): Gravity-Deformed Model Rigidly Aligned with Fiducial Markers

To calculate the rigid transformation which aligns the prone image with the gravity-deformed model in Scenario (c), the locations of the corresponding pairs of skin fiducial markers were manually identified in the prone and supine MR images. The marker location was considered to be the point at which the rotational axis of symmetry of the marker (see Figure 5.1 for an image of a fiducial marker) intersected the skin surface, and so the marker lay on the surface of an element of the model. Since the locations of this element’s nodes are known in the supine and gravity-deformed positions, it was possible to use the element’s linear shape functions to transform the fiducial marker location into its gravity-deformed position. The rigid transformation between the gravity-deformed model and the prone images was then calculated by aligning the fiducial markers using the least squares technique described in by Arun et al. (1987).

Scenario (d): Gravity-Deformed Model Non-Rigidly Aligned with Skin Surface

In Scenario (d) the gravity deformed model from scenario (c) was further deformed so that the skin surface of the model aligned with the skin surface in the prone MR image. To obtain the prone skin surface, points lying on the skin surface in the prone MR image were extracted by traversing all voxels of the MR in five orthogonal voxel directions (i.e. all apart from the posterior-to-anterior direction) and recording the point at which a manually determined intensity threshold was crossed. A smooth approximating surface was fitted to these points (in the least squares sense, subject to a regularisation term which penalised curvature). Then a dense set of points covering the skin surface was extracted from this smoothed surface. This effectively removed outliers from the surface data. The prone skin surface point cloud was initially rigidly aligned with the model using the transformation calculated in Scenario (c).

An iterative approach was used to non-rigidly align the model surface with the skin surface extracted from the prone MR image. At each iteration a smoothed unit ‘vertex normal’ \( n \) was calculated for each node on the skin surface of the model as follows. First, the unsmoothed vertex normal for node \( i \) was computed by creating a local surface triangulation from the node and the skin surface nodes adjacent in the finite element mesh. This is necessary because the faces of hexahedral elements do not have a clearly defined normal as the quadrilateral elements can have twist. The unit normal for each of these triangles was calculated in the direction away
from the body, and the unsmoothed vertex normal was found by calculating the mean of these normals. The vertex normals were then normalised, smoothed and then normalized again to obtain \( n_i \).

The closest point in the dense prone skin surface point cloud to each of the nodes was identified using a kd-tree approach to reduce the search time required (Bentley 1975). If the vector from the node to this point is called \( c_i \), then the length \( l_i \) of this vector projected onto the vertex normal is given as \( l_i = |c_i \cdot n_i| \). A displacement boundary condition was imposed upon the node which displaced it a distance \( \gamma l_i \) in the direction \( n_i \), but imposed no constraints in the directions perpendicular to this direction. \( \gamma \) had a value of 0.5 for the first iteration (when the two surfaces are not expected to be in close alignment) but 1 for all further iterations. In this way the model was brought into alignment with the prone skin surface whilst leaving it free to slide tangential to the skin surface, constrained only by the biomechanics of the model, as illustrated in Figure 8.3. This technique is essentially the approach proposed by Cash et al. (2005).

![Figure 8.3 Applying displacement loads on the surface.](image)

*Figure 8.3 Applying displacement loads on the surface.* At each iteration, a model surface node (marked with a dot), is constrained to move a set distance in the vertex normal direction (marked with a solid line and solid arrow) but can slide parallel to the surface tangent (marked with a dotted line).

After every update of the model prior to the final deformation, the rigid registration between the locations of the fiducial markers in the prone MR image and in current deformed model was calculated and the prone skin points transformed accordingly. The process of applying boundary conditions on the model was then repeated. A total of four iterations were used in the work reported here, since this resulted in every surface node in the final model being aligned with the target surface to better than 0.1mm in all cases.
It was assumed that the relatively small deformations from the estimated prone equilibrium state could be modelled as though this state was a true reference state. Therefore stresses in the model which were formed during the deformation from supine to prone were not included in the model. Furthermore, since the purpose of this surface-alignment process is to improve correspondence rather than to simulate an actual physical behaviour, stresses formed during this deformation process were not preserved between iterations. Instead, since small deformations of a body in equilibrium were being modelled, each intermediate solution was effectively assumed to be a reference states. This approach meant that no gravitational body force was applied to the model after the initial supine-to-prone deformation, so it was possible to avoid imposing boundary conditions along the posterior face of the model. This was desirable because the boundary conditions assumed during supine-prone deformation will not have perfectly captured the deformation. Therefore the effect of aligning the skin surface should dominate the deformation, with the tissue close to the chest wall will adopting a position consistent with this skin alignment.

Applying displacement boundary conditions which forced the fiducial marker locations in the model and prone MR image to align was considered. However this was found to cause very large distortions in the surrounding elements, similar to the distortions that might be expected if a pin were stuck into the skin and then pulled sideways. Since the fiducial marker points are not expected to behave differently to any other point on the breast surface, this behaviour is unphysical, and - if the element distortions are large enough - can prevent the model from converging. This approach was therefore not adopted.

During the surface alignment stage of this registration the density assigned to materials no longer affected the deformation because (after the initial step of simulating the gravity-induced deformation) a gravitational body force was not being applied to the model. Furthermore it was now the relative, rather than absolute, stiffness of material which was of importance. Just as was assumed when modelling gravity-deformation, adipose and fibroglandular tissue were treated here as incompressible materials which both obeyed the same neo-Hookean constitutive law.

Assessment

The registration error was measured in both the prone and the supine space. The error measured in the prone space indicates the accuracy with which a point selected in the supine MR image can be located using the registration algorithm in the prone MR image, whilst the error measured in the supine space indicates the accuracy with which a point selected in the prone image can be located in the supine image.

The accuracy of the proposed finite element model-based registration techniques were assessed for Subjects S1-3, using the same eight internal landmarks that were identified and used for
model assessment in Chapter 6. The error on each landmark in the prone space was computed by identifying the element in the undeformed model in which the landmark lay and then deforming this point according to the displacement of the nodes of this element using the element’s shape function. This point was then rigidly transformed into the prone coordinate system using the appropriate rigid transformation. The distance between the coordinate of the displaced supine landmark and the prone landmark was then measured.

Accuracy in the supine space was calculated in a similar way, by rigidly transforming the prone landmark coordinates into the supine coordinate system, identifying which deformed element the point lay within, displacing this point according to the element’s node displacements from deformed to undeformed and then measuring the distance between the displaced prone landmark and the supine landmark. Since the model is built from the supine MR, every point within the supine breast will lie within the model. However, since the model does not perfectly simulate the prone breast, not every point within the prone breast will coincide, after rigid transformation, with a point in the deformed model. The numbers of points which fall inside the model are recorded in the results section. Points which fall outside the model are excluded from the accuracy calculations.

### 8.3.3 Results

Table 8.2 and Table 8.3 give the mean and maximum error landmarks in the prone and supine space respectively. Figure 8.4 shows example slices through the deformed volumes.

In general the errors appear to be higher in the supine space than in the prone space for a given patient/alignment scenario. More accurate registration results are always achieved by either aligning the gravity-deformed model with the skin fiducial markers or with the skin surface. Visually the alignment of the model-deformed supine image with the prone image appears better for scenario d. This is reflected in the FEM registration accuracy measured on landmarks in the prone space although, surprisingly, not in the supine space. This is partly (but certainly not entirely) due to different landmarks falling outside the prone-deformed model for different scenarios.

The simulated prone-supine deformation for Subject S3 does not capture the deformation as well as simulations for Subjects S1 and S2. In particular the width of breast tissue in the medial-lateral direction is underestimated. For Subject S3 this is associated with in a thin strip of tissue medially. When the model of Subject S3 is aligned with the prone skin surface the posterior face of the model is drawn out of alignment with the pectoral fascia and this thin strip of tissue is significantly displaced, so much so that the unconstrained medial edge of the breast tissue appears to curl in the Scenario (d) image for Subject S3 in Figure 8.4.
### Table 8.2 Accuracy of FEM registration measured in the prone space

<table>
<thead>
<tr>
<th>Subject</th>
<th>Scenario (a) rigid aligned on chest wall mean (max) /mm</th>
<th>Scenario (b) gravity aligned on chest wall mean (max) /mm</th>
<th>Scenario (c) gravity aligned on markers mean (max) /mm</th>
<th>Scenario (d) gravity + surface aligned on markers mean (max) /mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>46.9 (69.7)</td>
<td>9.6 (17.9)</td>
<td>13.7 (20.4)</td>
<td>9.6 (13.9)</td>
</tr>
<tr>
<td>S2</td>
<td>51.5 (65.1)</td>
<td>9.6 (21.0)</td>
<td>7.2 (11.9)</td>
<td>7.4 (9.9)</td>
</tr>
<tr>
<td>S3</td>
<td>70.0 (104.6)</td>
<td>15.5 (23.0)</td>
<td>15.2 (26.5)</td>
<td>13.3 (27.4)</td>
</tr>
</tbody>
</table>

Table 8.2 Accuracy of FEM registration measured in the prone space for four scenarios on three subjects. Lowest mean errors for each subject are highlighted.

### Table 8.3 Accuracy of FEM registration measured in the supine space

<table>
<thead>
<tr>
<th>Subject</th>
<th>Scenario (a) rigid aligned on chest wall mean (max)/mm</th>
<th>Scenario (b) gravity aligned on chest wall mean (max)/mm [num]*</th>
<th>Scenario (c) gravity aligned on markers mean (max)/mm [num]*</th>
<th>Scenario (d) gravity + surface aligned on markers mean (max)/mm [num]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>46.9 (69.7)</td>
<td>11.5 (26.0) [8]</td>
<td>12.0 (12.7) [7]</td>
<td>10.1 (16.2) [8]</td>
</tr>
<tr>
<td>S2</td>
<td>51.5 (65.1)</td>
<td>13.4 (27.8) [8]</td>
<td>10.4 (17.4) [8]</td>
<td>11.8 (20.9) [7]</td>
</tr>
<tr>
<td>S3</td>
<td>70.0 (104.6)</td>
<td>17.6 (39.7) [6]</td>
<td>14.2 (20.9) [4]</td>
<td>15.8 (25.9) [5]</td>
</tr>
</tbody>
</table>

Table 8.3 Accuracy of FEM registration measured in the supine space for four scenarios on three subjects. * num is the number of prone landmarks (out of 8 in total) which fall within the deformed supine model after rigid transformation. Lowest mean errors for each subject are highlighted,
### Figure 8.4 Slices through supine images and prone images created under various alignment scenarios

<table>
<thead>
<tr>
<th>Subject</th>
<th>Prone Scenario (a)</th>
<th>Supine Scenario (b)</th>
<th>Deformed Supine Scenario (c)</th>
<th>Deformed supine Scenario (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rigid aligned on chest</td>
<td>gravity aligned on chest</td>
<td>gravity aligned on markers</td>
<td>gravity + surface aligned on markers</td>
</tr>
</tbody>
</table>

- **Subject S1**
- **Subject S2**
- **Subject S3**
8.3.4 Discussion

This section proposed that a gravity-deformed model can be used to establish correspondence between prone and supine images. The preceding chapters aimed to simulate as realistically as was practicable the processes causing the deformation. In this section the goal is to achieve the best correspondence possible between the prone and supine images. Consequently the breast is aligned, or loads are applied, in a way designed to improve the alignment between the prone and model-deformed supine images, rather than to be physically realistic. Both these scenarios (termed scenario (c) and scenario (d) above) were able to recover around 80% of the deformation which remained after rigidly aligning the breast on the chest wall.

8.4 Hybrid FEM-Fluid Registration

8.4.1 Introduction

The first experiments of this chapter found that the intensity distributions corresponding to homologous features in the original prone and supine images were so poorly aligned that intensity-based registration algorithms did not achieve good results. The FEM-based registration method described in the previous section performed better, but clearly much more information is available in the images than was exploited by the algorithm. This section explores whether the improved alignment provided by a FEM-based registration method brings features into sufficient alignment that a standard intensity-based registration algorithm can improve upon the accuracy offered by using a FEM-based alone.

The combination of an intensity-based non-rigid registration with the biomechanical model’s estimation of the deformation is described in this thesis as the ‘hybrid’ registration technique. The influence of employing each of the four scenarios for aligning the finite element model described in the previous section as the FEM-based registration step on the resulting hybrid registration accuracy is examined here. The effect of using different resolution levels for the intensity-based registration step is also investigated.

8.4.2 Method

The prone image was treated as the source image, and the model-deformed supine image was treated as the target image. By treating the model-deformed image as the target image, it was straightforward during the intensity-based registration step to assign zero image force to any voxel in the target image which lay outside the volume described by the deformed model.
Warping the images according to the FEM deformation

The prone and supine MR images for the three subjects (S1-3) were corrected for image inhomogeneity using the method described by Sled et al. (1998). The model deformations for each scenario have already been determined in Chapter 6 and the previous section. Images were created from the nodal displacements as described in Section 5.8. Only scenarios (b)-(d) were considered since the rigid alignment (scenario (a)) was found in Section 8.2 to provide insufficient initialisation for intensity-based registration.

Intensity-based registration of the warped and prone images

For each scenario considered, the appropriate rigid transformation (as calculated in Section 8.3) was applied to the prone MR image to align it with the model-warped image. The fluid non-registration algorithm described by Crum et al. (2005) was used to register the prone and warped image volumes. Viscous fluid was chosen as the transformation model since, as discussed in Section 4.4 of the literature review, it is appropriate for large deformations. Also, because the implementation used does not enforce volume conservation and the transformation model is quite different to the elastic deformation assumed during the finite element modelling steps, the fluid registration may be able to recover some of the errors introduced by incorrect modelling assumptions. The viscosity constants $\mu$ and $\lambda$ which describe the behaviour of this fluid were set to 1 and 0 respectively, since these value are the ones usually used for fluid registration, and have been reported in the literature as being successful when matching pairs of MR images of the breast in the prone position (see Section 4.4).

Since the prone images and the supine images from which the warped images are created are MR volumes which were acquired with similar acquisition protocols, normalised cross-correlation was selected as the image-similarity measure from which all other image forces were computed. A stopping condition based on the change in similarity measure at each iteration was used to terminate the registration at each multi-scale resolution when there was no further improvement in image similarity.

The fluid registration algorithm used can be run at single or multiple resolution levels. To investigate the influence of intensity-based registration scale on the hybrid registration accuracy, a range of resolution levels were trialled using the surface-aligned finite element model created in scenario (d) of Section 8.3. The resolution levels considered were three single resolution levels labelled M33, M22, M11 (representing $\frac{1}{8}$, $\frac{1}{4}$, $\frac{1}{2}$ image resolutions respectively) and three multi-resolution levels labelled M23, M12 and M13 (representing $\frac{1}{4}$ than $\frac{1}{4}$, $\frac{1}{4}$ then $\frac{1}{2}$ and $\frac{1}{4}$ then $\frac{1}{2}$ image resolutions respectively). On the basis of the results of this experiment, when assessing the effect of varying the FEM alignment scenario, the fluid registration was run at a single resolution level of $\frac{1}{4}$ image resolution.
Assessing the registration

The registration was assessed on the same eight landmarks for each subject used in the previous section. The effect of varying the intensity-based registration resolution level was assessed in the prone space. The fluid registrations were inverted using an iterative process which, in conjunction with the known nodal displacements between prone and supine, allowed the accuracy of the hybrid registrations for the various finite element model alignment scenarios to be assessed in the supine space as well as in the prone space.

8.4.3 Results

Table 8.4 shows the effect of varying the resolution level of the fluid registration on the hybrid registration accuracy. Table 8.5 and Table 8.6 show the effect of different model alignment approaches on the hybrid registration accuracy in the prone and supine space. Figure 8.5 illustrates the error on each landmark before and after fluid registration, and Figure 8.6 shows example slices through the final hybrid-registered volume. The significance of these results will be discussed in the following sub-section.

The error for Subject 3 is much larger than for the other subjects, therefore to allow comparison of the effect of resolution level the ‘mean normalised error’ (MNE) was calculated: the errors for each subject were normalised relative to the best-performing registration for that subject and the mean of these normalised errors (over all subjects) was considered.

<table>
<thead>
<tr>
<th>Subject</th>
<th>None Mean (max)/mm</th>
<th>M11 Mean (max)/mm</th>
<th>M12 Mean (max)/mm</th>
<th>M13 Mean (max)/mm</th>
<th>M22 Mean (max)/mm</th>
<th>M23 Mean (max)/mm</th>
<th>M33 Mean (max)/mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>9.6 (13.9)</td>
<td>7.0 (12.4)</td>
<td>6.8 (12.8)</td>
<td>7.3 (13.0)</td>
<td>6.9 (12.9)</td>
<td>7.3 (12.9)</td>
<td>7.1 (12.9)</td>
</tr>
<tr>
<td>S2</td>
<td>7.4 (9.9)</td>
<td>6.3 (13.2)</td>
<td>6.3 (12.9)</td>
<td>6.9 (12.8)</td>
<td>6.1 (11.5)</td>
<td>6.6 (12.0)</td>
<td>6.7 (12.0)</td>
</tr>
<tr>
<td>S3</td>
<td>13.3 (27.4)</td>
<td>12.0 (27.1)</td>
<td>11.7 (24.5)</td>
<td>11.3 (20.1)</td>
<td>11.9 (24.5)</td>
<td>11.8 (22.3)</td>
<td>12.5 (24.1)</td>
</tr>
<tr>
<td>MNE*</td>
<td>1.09</td>
<td>1.04</td>
<td>1.02</td>
<td>1.07</td>
<td>1.02</td>
<td>1.07</td>
<td>1.08</td>
</tr>
</tbody>
</table>

Table 8.4 Influence of fluid registration resolution levels on hybrid registration accuracy

Accuracy is measured in the prone space for three subjects. Column labelled ‘None’ is the registration error using the surface-aligned gravity-deformed FEM but no fluid registration (scenario (d) in Section 8.3). Lowest mean errors for each subject are highlighted. *MNE is the mean normalised error, calculated as described in the results section.
### Table 8.5 Influence of different alignment approaches on hybrid registration accuracy.
Accuracy is measured in the prone space for three subjects. Lowest mean errors for each subject are highlighted.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Scenario (b) gravity aligned on chest wall mean (max) /mm</th>
<th>Scenario (c) gravity aligned on markers mean (max) /mm</th>
<th>Scenario (d) gravity + surface aligned on markers mean (max) /mm</th>
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</thead>
<tbody>
<tr>
<td>S1</td>
<td>7.9 (15.6)</td>
<td>8.1 (15.3)</td>
<td>6.9 (12.9)</td>
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<tr>
<td>S2</td>
<td>11.7 (19.8)</td>
<td>10.1 (19.3)</td>
<td>6.1 (11.2)</td>
</tr>
<tr>
<td>S3</td>
<td>14.5 (21.3)</td>
<td>13.7 (22.6)</td>
<td>11.9 (24.4)</td>
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</tbody>
</table>

### Table 8.6 Influence of different model alignment approaches on the hybrid registration technique.
Accuracy is measured in the supine space. * num is the number of prone landmarks (out of 8 in total) which fall within the deformed supine finite element model after fluid transformation.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Scenario (b) gravity aligned on chest wall mean (max) /mm [num]</th>
<th>Scenario (c) gravity aligned on markers mean (max) /mm [num]</th>
<th>Scenario (d) gravity + surface aligned on markers mean (max) /mm [num]</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>7.61 (20.0) [8]</td>
<td>8.8 (16.5) [7]</td>
<td>6.9 (16.6) [8]</td>
</tr>
<tr>
<td>S2</td>
<td>14.1 (26.6) [8]</td>
<td>17.8 (48.9) [8]</td>
<td>6.8 (11.1) [8]</td>
</tr>
<tr>
<td>S3</td>
<td>19.3 (39.6) [6]</td>
<td>15.5 (26.6) [5]</td>
<td>10.3 (20.3) [7]</td>
</tr>
</tbody>
</table>
Subject | Error Measured in Prone Posture | Error Measured in Supine Posture

S1

S2

S3

Figure 8.5 Error on FEM-deformed landmarks before and after intensity-based registration. Errors are given in both prone and supine space. Values are for the surface-based FEM (scenario (d)).
<table>
<thead>
<tr>
<th>Subject</th>
<th>Prone</th>
<th>Deformed Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td><img src="image1.png" alt="Prone Image" /></td>
<td><img src="image2.png" alt="Deformed Supine Image" /></td>
</tr>
<tr>
<td>S2</td>
<td><img src="image3.png" alt="Prone Image" /></td>
<td><img src="image4.png" alt="Deformed Supine Image" /></td>
</tr>
<tr>
<td>S3</td>
<td><img src="image5.png" alt="Prone Image" /></td>
<td><img src="image6.png" alt="Deformed Supine Image" /></td>
</tr>
</tbody>
</table>

**Figure 8.6 Images obtained using hybrid registration**  Orthogonal slices through the prone image volume and the supine image volume after deforming it according to the hybrid registration. The boundary of fatty tissue in the deformed supine image is shown overlaid in red on the prone image.
8.4.4 Discussion

For all the cases considered here, applying a fluid registration step after the finite element registration improved the mean registration accuracy. The improvement in accuracy does not appear to be very sensitive to the choice of multi-resolution level (Table 8.4). Whilst increasing the number of levels used can be expected to increase the image similarity, this does not necessarily result in increased registration accuracy since the improved image similarity may be achieved by incorrect and unphysical deformations such as local volume changes. In terms of the MNE, the best performing single- or multi-resolution scheme was $\frac{1}{4}$-image-resolution (level M22 in Table 8.4). Using this resolution level, the improvements in registration error over the surface-aligned, gravity deformed model were 28%, 18% and 11% for subjects S1, S2 and S3 respectively.

For all subjects, using the surface-aligned model in the registration process provided substantially better registration accuracy (in both the prone and supine space) than the alternative strategies for aligning the model. An additional advantage of the fluid registration step is that it causes more points in the prone image to lie within the model. For Subject S2 one landmark did not coincide with a point in the model prior to fluid registration and all landmarks fell inside the model after fluid registration. For Subject S3 three landmarks were initially outside the model, which was reduced to just one landmark after fluid registration. All landmarks for Subject S1 fell inside the model, both before and after fluid registration. The registration accuracies on each landmark using the finite element-based registration scheme and the hybrid registration scheme are shown in Figure 8.5.

Figure 8.6 shows slices through the registered images in the prone space. Although the deformed supine image shows much less fine detail than the prone image, visually the alignment of internal and external tissue boundaries appears generally good. Since both the finite element model and the fluid registration treat the image as a continuous object, one feature of the deformation which is not captured by the hybrid registration process is the way glandular tissue appears in contact with the pectoral muscle in the supine image but is significantly separated from it in the prone image (visible in sagittal and transverse sections of Subject S1).

The mean landmark errors using the hybrid registration technique were 6.9, 6.1 and 11.9mm in the prone space and 6.9, 6.8 and 10.3mm in the supine space for Subjects S1, S2 and S3 respectively. This is a major improvement over the rigid registration accuracies of 15.6, 16.4 and 28.9mm determined in Section 8.2.
8.5 Chapter Conclusion

The aim of this chapter was to determine a technique suitable for registering prone and supine MR images of the breast. Rigidly transformed images did not align well, and it was found that standard non-rigid intensity-based registration algorithms also performed poorly. Therefore I investigated the use of a gravity-deformed biomechanical model, as developed in the preceding chapters. This model was found to provide better registration accuracy than both the rigid registration and the non-rigid intensity-based algorithms trialled. The registration accuracy was further improved by aligning the surface of the model with the surface of the breast in the prone MR image.

Corresponding intensity features in the model-aligned images were found to have sufficient overlap that an intensity-based registration algorithm was able to further improve the registration accuracy. I chose to use a fluid registration algorithm for this purpose, since this algorithm’s proponents have argued that such algorithms are suitable for recovering large deformations. Furthermore, the fluid transportation model is significantly different to the hyperelastic model used to obtain the initial estimate of the deformation and the fluid registration performed better than the B-spline based registration algorithm in recovering the full prone-supine deformation. However it can be anticipated that other intensity based registration algorithms could be used within this framework.

One limitation of the proposed hybrid registration scheme is that it is possible for a point in the prone MR image not to be coincident (after the fluid registration step) with the deformed model, and so the corresponding point in the supine MR cannot be established. However this situation occurred for only one of the internal landmarks considered here. Improving the biomechanical modelling beyond the level achieved in the previous chapters would make this situation less likely to occur, and can also be expected to achieve better registration results.
Chapter 8. Registration of Prone and Supine MR Images of the Breast

Figure 8.7 Mean registrant errors for Subjects S1-3 measured in the prone space using the techniques reported in this chapter. ‘FEM (Gravity)’ results are for the model aligned on fiducial markers. Fluid registration in ‘Hybrid’ registration technique is performed at ¼-image-resolution.

Figure 8.7 summarises the accuracies achieved by the registration techniques which were trialled in this chapter. The hybrid registration approach can be seen, on the three cases considered, to be a major improvement over the other approaches, especially the rigid and viscous fluid registration options which might otherwise be considered ‘off-the-shelf’ solutions to this registration problem. Validation on further cases is required.

I found that the mean registration errors using the hybrid registration technique were 6.9, 6.8 and 10.3mm for Subjects S1, S2 and S3 respectively when measured in the supine space. Whether this accuracy is sufficient to be clinically useful for the image-guidance task motivating this thesis will be discussed in the next chapter, which describes the development of a prototype image-guidance system for breast surgery.
Chapter 9

Image-Guided Breast Surgery

9.1 Introduction

In this chapter I address the clinical application, describing the prototype image guided surgery system which I built in order to investigate the clinical utility of image-guided breast surgery based on pre-operative DCE MR imaging.

The necessary steps for providing image-guidance in the approach used in this thesis are summarised in the flowchart of Figure 9.1. Since an MR image acquired of a patient in the supine position is a much closer approximation to the surgical position than the prone DCE images, a supine MR image (without contrast enhancement) was acquired. The registration technique described in the previous chapter is used to transform the lesion into the supine image space. As part of this registration procedure a biomechanical model of the supine breast is constructed. I used a stereo camera system to acquire the 3D surface of the breast when the patient was on the operating table. The biomechanical model was then deformed to align with this intraoperative surface in order to compute the intraoperative location of the lesion. The location of the lesion was displayed to the surgeon beneath a rendering of the skin surface.

The preoperative prone-supine registration process has been described in Chapter 8, so this chapter describes the intraoperative imaging, registration and visualisation techniques used to complete the system. It concludes with a description of what I believe to be the first ever breast surgery case in which preoperative MR data was deformed to match the surgical situation.
The system indicates a lesion’s location immediately prior to the first incision. It does not, however, attempt to model deformations caused by manipulation of the breast during surgery or surgical incisions. It is anticipated that presenting this information when the patient is positioned ready for surgery will provide useful guidance, helping the surgeon to visualise the 3D distribution of cancer. As well as helping the surgeon to achieve a complete excision, this information should also help the surgeon to plan the incision which, particularly for breast surgery, is cosmetically important.

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**Figure 9.1 Flowchart showing the preoperative and intraoperative steps**

---

### 9.2 Intraoperative Imaging

#### 9.2.1 Introduction

The modalities which can be used to image the breast were reviewed in Section 2.5 and the modalities which have been used to establish intraoperative boundary conditions on
biomechanical models were discussed in Section 4.7. Tracked ultrasound and surface imaging seem the most appropriate modalities to assist in the task of updating MR-based information during breast surgery, since they do not involve exposing the patient to ionising radiation, are cheap, and can be acquired in a standard operating theatre. Of these, ultrasound imaging has the advantage that sub-surface information is available to help drive the registration. However real-time segmentation of features is challenging, and whilst compressing the breast with the probe is necessary to acquire optimal images, the deformation this causes must be accounted for. Also, when using a 2D probe, acquiring datasets that span the region of interest at suitable spatial sampling is time-consuming. Whilst surface imaging lacks information about any features that are at depth, extracting dense clouds of datapoints is swift and does not deform the breast. There is not need to perform segmentation provided only the breast (and not, for example, the surgeon’s hands) is in the field of view.

Whilst the depth information available may make ultrasound more suitable for coping with more complex deformations, such as the effects of excision, these deformations are beyond the scope of this initial system. Incorporating biomechanical knowledge into the registration process might mitigate the lack of depth information available by constraining the deformation which is extrapolated below the surface to be physically reasonable.

As it appeared the more straightforward approach, and since it integrated well with this thesis’s underlying theme of using biomechanical models to aid registration, it was decided to use surface data to drive the registration process in the operating theatre. Two automatic surface imaging approaches are available: stereopsis and laser scanning. The images reconstructed by the two systems are likely to be similar. A stereopsis system was chosen, since it allows the imaging device to be located further from the patient, making it easier to mount in the operating theatre. These systems have the further advantage that acquiring texture images that are co-registered to the surface is straightforward.

This section details the specifications of the chosen system, and describes an experiment performed to assess its accuracy for our application.

### 9.2.2 Method and Assessment

**Description of Stereo Camera System**

Intraoperative images of the breast were acquired using a stereo camera system produced by VisionRT Ltd (London, UK) which is shown in Figure 9.2. The camera system has three CCD cameras. Two of these (the structure cameras) are used to acquire images for reconstructing the surface structure, whilst the third (the texture camera) is used to acquire a texture image. The three cameras are calibrated using an implementation of Tsai (1987)’s 2D algorithm supplied by
the camera manufacturer. Since the calibration uses simultaneously acquired images of the same calibration object, the three cameras share the same coordinate system.

![Stereo Camera Image](image)

**Figure 9.2 Stereo Camera** Stereo camera, structure cameras, texture camera and projector are labelled S, T and P respectively.

The structure images are acquired at the same time as a light flash is projected through a speckled pattern template. Corresponding features in the projected speckled pattern (Figure 9.3a) are automatically identified in the two images, and the positions of these points calculated by triangulation to form a surface (Figure 9.3b). This processing is performed on a desktop computer which is connected to the camera system. Immediately after the speckled images have been acquired, a texture image is acquired using the third camera and a light flash without speckle (Figure 9.3c). This texture image can be projected onto the reconstructed surface, which allows ink marks drawn on the surface to be used as fiducial markers.

![Stereo Camera Images](image)

**Figure 9.3 Stereo camera images** Images of rigid plastic torso (a) image acquired with structure camera and texture flash (b) reconstructed 3D surface (c) acquired with texture camera without texture flash
The lenses on the system were chosen, and the cameras on the system were aligned, such that the region of reconstruction was approximately 300mm x 400 mm at a range of 1.5m. Under this set-up, the reconstructed surface consisted of around 3500 points, with approximately 3.5mm inter-point spacing. The process of acquiring and reconstructing a surface takes around 8 seconds. Surfaces could be acquired only every 10 seconds, since the projector flash requires time to charge.

*Using the Stereo Camera System in the Operating theatre*

During surgery the patient was positioned supine, with her arm on the involved side horizontally abducted, perpendicular to her body. The surgeon typically stands inferior to the arm, with his assistant standing superior, and the scrub nurse stands on the opposite side of the patient’s body. There is therefore space to place the stereo camera at the distal end of the arm, at a distance of approximately 1.5m from the breast, as shown in Figure 9.4. From this position the camera has line of sight to the breast, and the camera does not obstruct the surgeon. The surface of the breast was acquired using the stereo camera prior to incision in five operations to confirm that images could be acquired under operating theatre conditions.

*Figure 9.4 Stereo Camera in Operating Theatre* Stereo camera is indicated by arrow. It is positioned at the end of the patient’s arm, which is just visible to the left of the surgeon who is in the foreground.

*Assessment of camera accuracy*

The accuracy of the surface acquired by the stereo camera system was assessed by comparing the surface with points acquired using an Optotrak Certus Sensor (Northern Digital Inc., Ontario, Canada). The Optotrak Certus device is claimed by the manufacturer to have a 3D accuracy of 0.15mm. Therefore the Optotrak Certus coordinates were assumed to provide the ground truth. The rigid torso of a male mannequin was used as the test object. Eight crosses
were marked on the surface of the breast of this mannequin to act as fiducial marker locations (visible in Figure 9.3c).

The torso was spatially tracked by the Optotrak system using a reference object rigidly attached to it. The coordinates of points on the breast recorded using a tracked pointer were therefore not affected by rigid displacement of the breast. The position of each fiducial marker was determined by touching it with a tracked pointer three times and calculating the mean location. The surface was acquired by measuring the coordinates of a further 1000 points distributed over the surface of the breast using the tracked pointer.

Three sets of images of this mannequin were acquired from different positions using the stereo camera and the corresponding surfaces were reconstructed. The 3D coordinates of the fiducial markers on the surface were computed using the co-registered texture map. The surface points recorded using the Optotrak were rigidly registered with each surface using the fiducial marker locations. The closest point in each stereo camera surface to each registered Optotrak point was calculated. The vector between these two points was projected onto the unit normal of the stereo camera surface at this point. The magnitude of this vector gave the distance from the Optotrak surface point to the stereo camera surface. This distance was interpreted as the error in the stereo camera surface at this point.

It should be noted that this error measure is a point to surface distance (rather than a target registration error), and that lower mean registration errors would be achieved using an ICP algorithm rather than performing a rigid registration based on fiducial markers locations. However this approach to assessing the accuracy is appropriate since it is consistent with the technique which will later be used to perform deformable intraoperative registration.

9.2.3 Results

For all cases in which the stereo camera system was trialled in theatres it was found that, provided the adjustable overhead lamps were not pointing directly at the breast which prevented the speckled pattern from being visible, images suitable for reconstruction could be acquired by adjusting the lens apertures to suit the lighting conditions. The surgeon did not feel that dimming the lamps or pointing them away from the breast whilst acquiring the images interfered unduly with the procedure, especially as the goal of the initial system is to provide guidance before the first incision.

The results of assessing the stereo camera surface accuracy on a mannequin are given in Table 9.1. The mean residual error on the fiducial marker locations was 0.6mm. The resulting mean error for the surface alignment was 0.4mm. The reconstructed surface is smooth and the error
tends to increase towards the edge of the breast. This may indicate that the error is predominantly due to inaccuracy in locating the points used for the point-based registration.

<table>
<thead>
<tr>
<th></th>
<th>Fiducial Marker Error</th>
<th>Surface Error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (max) /mm</td>
<td>Mean (max) /mm</td>
</tr>
<tr>
<td>Stereo Camera Surface 1</td>
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<td>0.31 (1.93)</td>
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<td>Stereo Camera Surface 2</td>
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<td>0.45 (1.75)</td>
</tr>
<tr>
<td>Stereo Camera Surface 3</td>
<td>0.59 (0.92)</td>
<td>0.48 (1.44)</td>
</tr>
</tbody>
</table>

Table 9.1 Accuracy of Stereo Camera
Residual error on fiducial marker alignment after rigid registration and error on surface alignment for three acquisitions of the rigid mannequin surface

9.2.4 Conclusion

The stereo camera system can reconstruct the surface of the breast under operating theatre conditions, although the maximum acquisition rate is one surface every ten seconds. The error in the reconstructed surfaces is small compared with the anticipated overall registration error. Therefore the stereo camera system appears to be appropriate for acquiring intraoperative images to drive the registration process.

9.3 Intraoperative Registration

9.3.1 Introduction

A hybrid registration technique which is designed for the task of locating a lesion (which has previously been identified in prone DCE MR images) in a supine MR image was described in Chapter 8. This supine image will present a much closer approximation to the surgical position than the prone MR image. The match will not be exact because during imaging the patient’s arm is by her side, but during surgery her arm is extended perpendicularly to her body. Furthermore, the breast is such a soft deformable tissue that small alterations in the position of the breast with respect to the direction of gravity will have a notable influence. The surface acquired by the stereo camera described above is used to drive the intraoperative registration. The registration is based on a biomechanical model, which helps to constrain the deformation to be physically plausible.

The hybrid registration algorithm used to match the prone and supine images requires a finite element mesh to be constructed from the supine MR image. The same mesh was used here as the basis for modelling the intraoperative deformation. The ability of a biomechanical model to recover the deformation between imaging and surgery, based upon only surface information,
was assessed by simulating the intraoperative skin surface from an additional supine MR image, and measuring the accuracy with which sub-surface landmark displacements could be predicted by the model.

9.3.2 Method and Assessment

Fiducial Markers

Fiducial markers were attached to the skin surface during MR imaging. These markers were removed after imaging, but their locations were marked with ink on the skin surface so that these positions could be identified in the operating theatre. The fiducial marker locations (identified in the supine MR image from which the finite element model was constructed) were initially used to rigidly align the finite element model with the stereo camera surface, and then to impose boundary conditions whilst deforming the model. The intraoperative locations of the fiducial markers were identified by using a mouse to select the marker locations visible in the texture image overlaid on a stereo camera surface.

Model

In addition to the rigid registration, two deformable models were considered for intraoperative registration. Both models considered breast tissue to be a homogenous material. One model assumed infinitesimal strain. It treated tissue as a linear elastic material, and near incompressibility was simulated by assuming a Poisson’s ratio of 0.495. The other model used a finite strain formulation, and modelled breast tissue as obeying a neo-Hookean constitutive relationship. In this case incompressibility was modelled using a mixed displacement-pressure element formulation.

Boundary Conditions

Since the model does not undergo large changes in orientation with respect to gravity, it is assumed that internal loads due to the gravity acting during imaging can be ignored, and only displacement boundary conditions need be considered.

Displacement loads were applied on the node closest to each fiducial marker such that the node became coincident with the homologous fiducial marker location in the stereo camera image. Displacement loads were applied on all other nodes lying on the skin surface of the model in the direction normal to the skin surface, and with a magnitude equal to the distance from the node to the closest point on the skin surface projected onto the normal direction. These nodes were not constrained in the direction tangential to the skin surface. In order that the results were available within the surgical timeframe, and because this deformation was small, this one-step approach
was adopted, rather than the iterative approach adopted for matching surfaces described in the previous chapter.

Assessment

The intraoperative registration technique was assessed for two subjects by simulating the intraoperative surface from an additional supine MR image. The details for one of these subjects, Subject S2, were given in Section 5.2. Details for the other, Subject S4, are given in Section 9.5. The breast was segmented using the Analyze software package, and then a triangulated surface was extracted using the marching cubes algorithm (Lorensen and Cline 1987). Prone imaging was performed in-between acquiring the supine images, and so the pairs of supine images were notably displaced. The ability of the model to recover the deformation occurring was assessed on eight pairs of landmarks identified in the images.

9.3.3 Results

The model-based registration accuracies are compared in Table 9.2 with the registration accuracies achieved by rigidly registering the fiducial marker locations. The time taken to compute the model deformations for the two model types are compared. It can be seen that the finite strain and infinitesimal strain models have similar accuracies, but that the finite strain model takes at least 15 times longer to compute the deformation. The ‘automatic time-step’ functionality and the default direct sparse solver (ANSYS 2007) were used to compute the finite strain deformation.

<table>
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<td></td>
<td>error /mm</td>
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</tr>
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<td>2.6 (5.1)</td>
<td>2.5 (5.0)</td>
</tr>
</tbody>
</table>

Table 9.2 Comparison of rigid, infinitesimal strain model and finite strain intraoperative models

Mean and maximum errors were calculated on 8 pairs of internal landmarks. Time taken to compute the deformation is given for the infinitesimal strain and finite strain models.

9.3.4 Conclusion

This section has indicated that displacement boundary conditions applied on only the skin surface of a biomechanical model can approximately halve the landmark error compared with assuming a rigid registration, to a mean error of around 2mm. The model deformation took
much less time to compute when infinitesimal rather than finite strain was assumed, and there was not a large difference between the accuracies of the two models.

It is likely that the time taken to compute the deformation could be reduced by optimising the solver options within ANSYS. A recent technique consistent with the finite strain formulation which might allow much greater speed-up is to use parallelised explicit dynamic code running on graphics processor units (GPUs) (Taylor et al. 2008). However, using the finite strain formulation does not appear to result in a large increase in accuracy, because the boundary conditions and material properties are not completely known. Since the infinitesimal strain model can compute deformations within timeframes appropriate for this application, the explicit dynamics approach has not been investigated, and the infinitesimal strain model is used to compute intraoperative deformations. Furthermore this linearised model can be guaranteed to converge, and in the surgical environment reliability is arguably more important than a small improvement in accuracy.

A limitation of the assessment described above is that the deformation which is caused by moving the arm into the surgical position is not included. It was not possible to measure the effect of different arm positions, because the ‘arm outstretched’ surgical position is not possible within the bore of the MR scanner, and significant motion artefact was present when the subject’s arm was in a position other than by her side. The assessment is further limited because the two skin surfaces are extracted from images acquired using the same modality: inaccuracy caused by the segmentation of the tissue/air boundary may be greater when two different imaging modalities are used. Section 9.5 will describe an attempt to measure the accuracy of the entire system, which will take these factors into account.

9.4 Intraoperative Visualisation

9.4.1 Introduction

Conventional image guidance relies on relating the tip of a tracked pointer which is placed on, or in, a patient to a point in an MR image, a CT image or a surgical plan which includes a surface rendering derived from one of these images. As the soft tissue of the breast is so deformable the modelling described above has sought to calculate the position of the lesion before deformation caused by surgical manipulation and incision has occurred. The guidance system must therefore indicate the position of the lesion, which can lie deep within the breast, without needing the skin to be cut. Since it is not possible to place the pointer at the lesion, the conventional pointer-based approach is not suitable for this application. This is reinforced by the risk that attempting to identify points within certain types of cancer with a pointer could cause
the cancer to spread. Furthermore, the goal of this device is to identify not just one point, but to convey the shape and extents of the cancer.

Given these restrictions, stereo augmented reality systems seem likely to be the most effective technology for conveying navigational information before and during breast surgery. However these systems are not widely available and developing such a system is beyond the scope of this thesis which addresses the issue of soft tissue deformation. Therefore simple and inexpensive visualisation approaches are developed and used here. These approaches exploit the information available from the stereo camera which is primarily used to acquire images to drive the intraoperative registration. The purpose of providing the visualisation is to enable assessment of whether intraoperative image-guidance is likely to prove beneficial in breast surgery. If image-guidance does seem useful, it is anticipated that more sophisticated visualisation techniques will need to be incorporated.

9.4.2 Method

*Surface rendering overlaid with live video texture image*

The primary technique adopted for visualisation in the operating theatre was the presentation of a semi-transparent surface rendering of the stereo camera skin surface, with the lesion displayed underneath. This was implemented using the visualisation toolkit (www.vtk.org). Images of the breast were acquired and the surface was reconstructed whenever the stereo camera or the patient was displaced. The latest surface was then automatically displayed on the screen of the visualisation computer, and the position of the lesion recomputed.

The limited refresh rate of the stereo camera, and difficulties caused by occlusions of the breast surface which occurred when hands were in the image, meant that the stereo-camera surface could not be updated in real-time. However, live video from the texture camera of the stereo camera was overlaid on the rendered skin surface in order to provide real-time visual feedback. It was therefore possible to transfer information about the extents of a lesion, as seen from a given viewpoint, onto the patient by gently drawing on the skin whilst watching the visualisation. Provided the skin surface was not deformed, when the tip of a pen was in contact with the skin it appeared in the correct 3D position in the rendered image.

Prior to surgery, the region of enhancement corresponding to the lesion was segmented in a subtraction image formed from the prone pre-contrast MR image and the post-contrast image showing the greatest enhancement. The triangulated surface of the segmented lesion was extracted using the marching cubes algorithm. The surface was smoothed and decimated to reduce the number of vertices – and therefore the intraoperative computational task. The displacement field between prone and supine, as computed using the hybrid registration method
described in the previous chapter, was used to displace each vertex of the lesion to the appropriate location in the supine model. During surgery, the positions of the lesion vertices in the supine model were displaced according to the computed model deformation. The deformed lesion was then displayed beneath the stereo-camera skin surface. So that the lesion was visible, the opacity of the skin texture image was adjustable.

Pointer-based guidance

A pointer tracking system was implemented using live images from the three cameras of the stereo camera system. The pointer was fitted with retroreflective spheres (Figure 9.5), and a light was mounted next to the camera system. The spheres therefore show up as regions of very high intensity which can be rapidly located in each image using a simple centre of mass approach after thresholding the image. Since each camera has been calibrated, the 3D position of each sphere can be calculated, and the location of the pointer tip determined by pivoting the pointer about its tip and calculating the invariant point.

Figure 9.5 Pointer with three retroreflective spheres

A key purpose of the pointer was to allow the virtual camera to be aligned with a particular viewpoint of the actual scene. The pointer was held so that its tip was seen to align with (although actually being some distance from) each of three fiducial markers on the imaged surface in turn (Figure 9.6a). These pointer tip locations were recorded. These points were then displayed as spheres in the 3D scene displayed on a computer monitor which showed the reconstructed surface. Note that the fiducial marker locations and the pointer tip locations are measured and presented in the same coordinate system (that of the stereo camera). Before aligning the view, the spheres will not align with the fiducial markers (Figure 9.6b). Adjusting the virtual camera so that each sphere aligns with its corresponding fiducial marker allows the viewpoint to be rapidly replicated (Figure 9.6c). The aim of this process is not to provide a perfect registration, but to allow the viewer to very rapidly orientate the scene to his view and so better understand the visualisation.
Figure 9.6 Aligning the viewpoint (a) pointer tip is aligned with three fiducial markers in turn and the positions are recorded. (b) pointer tip locations are presented as spheres in front of the stereo camera surface (c) when the view is correctly aligned the spheres are seen to coincide with the corresponding fiducial markers.

9.5 Initial Clinical Experience

9.5.1 Introduction

The system has been demonstrated in the operating theatre on one clinical case to date. The primary aim was to compare the position and extents of the lesion as determined by the image guidance system with those determined by clinical palpation and by ultrasound guidance. Another aim of this initial case was to show that the location of the lesion could be calculated within a surgically useful timeframe and under the conditions, such as theatre lights and limited access, applicable in the operating theatre. Since this is the first time in which deforming preoperative image information to match the intraoperative scene for the purpose of image guidance has been applied to breast surgery, a final aim was to generate feedback from the surgeon about the most effective way to present navigational guidance during breast surgery.

9.5.2 Experience

Clinical Details

The patient (Subject S4) was a 47 year old female with a palpable lesion in the upper outer quadrant of her left breast. The lesion was found clinically to be very superficial and have a
diameter of 18mm. Ultrasound findings were consistent with the clinical findings, with the lesion having a diameter of 20mm. The lesion was not visible in X-ray mammograms. When DCE MR imaging was performed seven days before the operation, the lesion appeared as a speculated mass in the left axilla. It had a diameter of 35mm, which is much larger than it appeared in other modalities, and it extended right down to the pectoral muscle.

A fairly large surgical excision was planned which extended right down to the pectoral muscle. The decision to perform the large excision was motivated by the MR findings, and because performing a deep excision in this region of the breast is straightforward and provides a better cosmetic result.

**MR Imaging and Preoperative Registration Details**

The imaging for this patient was performed using the 1.5T Siemens Avanto MR scanner at St. Thomas’ Hospital, London. The supine images were acquired using the body coil to avoid mechanical loads on the breast surface. A 3D gradient echo sequence (TR=4.9ms, TE=1.6ms, flip =12° with fat suppression) was used to acquire images with voxel size 0.7mm x 0.7mm x 2.5mm.

The DCE MR imaging protocol adopted was the standard clinical breast imaging protocol used at St. Thomas’ Hospital. In addition a prone image without fat suppression was acquired prior to this sequence and the injection of contrast. This image was used for registration because it clearly showed the structure of the breast and because the protocol was similar to both that used for supine imaging and that used for developing the registration algorithm in Chapter 8. A 3D gradient echo sequence (TR=11ms, TE=4.8ms, flip =25°) was used and the image had a voxel size 1.3mm x 1.3mm x 4.0mm. The DCE MR images were acquired using a 3D gradient echo sequence with fat suppression (TR=4.9ms, TE=1.8ms, flip =12°) and these images had a voxel size 0.6mm x 0.6mm x 1.0mm. Negligible patient movement was visible between the images in the MR sequence or between these images and the image acquired without fat suppression. This natural alignment means that subtraction images to reveal contrast uptake can be obtained without additional registration of the DCE images and that the locations of features identified in these subtraction images are identical in the unenhanced image acquired without fat suppression.

Unlike the breast coil assembly used at Guy’s Hospital to image Subjects S1-S3, the breast coil assembly on this scanner enclosed each breast separately. There was therefore more contact between the breast and the coil assembly, which caused a greater deformation of the breast, particularly in the medio-lateral direction.
Figure 9.7 MR images of Subject 4  Transverse slices through (a) prone pre-contrast MR image (b) prone subtraction image (formed from maximum contrast-enhanced MR image minus pre-contrast MR image) and (c) supine pre-contrast MR image. Image (d) shows the prone MR image deformed according to hybrid registration to match supine MR. The outline of the lesion, which was originally segmented in the prone subtraction image, is overlaid in green on the slices (after deforming according to the registration deformation field for the supine images).

Transverse slices through the prone and supine MR volumes are shown in Figure 9.7a and Figure 9.7b respectively. It was observed that, due to much greater contact with the breast coil on this scanner, there was much more ‘sliding’ motion of the breast around the torso between prone and supine than had been observed in the previous experiments. This ‘compression’ was measured using landmarks to be around 40% - much greater than the compression of around 20% that was measured in Chapter 6 for subjects imaged on a Philips scanner. Therefore during the biomechanical initialisation step of the preoperative prone-supine registration a linear sliding of 40% was modelled. Figure 9.7c shows the prone MR image deformed using the prone-supine registration’s deformation field into the supine configuration. The lesion, as
revealed by DCE MR imaging, was segmented in the prone images by myself based upon the radiologist’s report. The registration was then used to determine the position of the lesion in the supine model. The position of this cancer is overlaid on the MR images of Figure 9.7.

_Intraoperative Update and Display_

The image-guidance system which incorporated the intraoperative registration technique described in Section 9.3 was used to calculate and display the position of the lesion. This was performed once the patient had been stabilised on the operating table (Figure 9.8a), immediately prior to sterilization. Computing the updated lesion location took 45 seconds. The maximum dimension of the lesion was 42mm. The position of the lesion was indicated as a surface rendering (Figure 9.8b) using the approach described in Section 9.4.

_Breathing motion_

The patient was ventilated throughout the study. Breathing motion appeared to be predominately due to diaphragm motion rather than being due to thoracic motion. This was quantitatively assessed by acquiring 5 surfaces of the breast at random positions in the breathing cycle. The mean (maximum) distance between any two surfaces was 0.36 (4.66) mm, with the greatest motion occurring to the medial and lateral extremes of the inferior face of the breast -- well away from the area of surgical interest in this case. If breathing motion should prove an issue in future cases, it is feasible to temporarily suspend ventilation for a few minutes after hyperventilating the patient with pure oxygen.

*Figure 9.8  Image guidance system being used in the operating theatre. (a)The displays are visible in the background and the stereo camera is indicated with an arrow in the upper left corner. The patient is just visible in the foreground. (b) Surface rendering of breast as presented during surgery. The lesion is shown in green. The virtual camera is positioned inferior, anterior and lateral to the breast.*
9.5.3 Validation and Surgeon’s Feedback

Validation against Palpation

The predicted location of the lesion was compared with the surgeon’s opinion of the lesion’s location based on palpating the lesion. This was achieved by asking the surgeon (Nicolas Beechey-Newman) to draw the parallel projection of the lesion extents (as determined by palpation) on the skin surface. This marking was performed for two orthogonal directions: first the anterior posterior direction and then the medio-lateral direction. For each, images were acquired of the skin surface with the stereo camera. Additionally, for each projection direction a further set of images was acquired whilst the surgeon held a rod, aligned with the projection direction, next to the breast. The coordinates of the rod ends were calculated by determining the closest point (in a least squares sense) to vectors which passed through the principle points of each camera (the two structure and one texture cameras) and the ends of the rod manually identified in the corresponding three images. A virtual camera viewed (in parallel projection) a surface rendering of the computed lesion location, a semi-transparent rendering of the stereo-camera surface with texture overlay, and the markers indicating the rod ends. By adjusting the camera position so that the rod ends aligned, it was possible to align the view to be anterior-posterior or latero-medial as appropriate. After alignment, the overlap was assessed by comparing the extents of the computed lesion location with the extents drawn on the skin surface (and so visible on the stereo-camera surface).

Figure 9.9 Comparison of lesion outlines marked by surgeon and computed by system (a) medio-lateral projection and (b) anterior-posterior projection of lesion outline according to surgeon (in red) and according to image-guidance system (in green). The scale in each image is measured at the place where surgeon marked the projection on the skin surface. Note that the surgeon’s marking in anterior-posterior view is very superficial - the tissue which appears superior and lateral to this marking is actually tissue of the armpit lying posterior to the breast.
The projections of the position of the lesion determined by the model and by the surgeon are shown for the two views in Figure 9.9. In the medio-lateral view the two projections overlap (maximum overlap is 5mm). However in the anterior-posterior view there is no overlap (closest approach is 14mm). Compared with the size of the lesion projections the overlap is poor. A major reason for the lack of overlap is experimental error, since the surgeon found it challenging to mark the location of the lesion in this way. In particular he felt that when marking the lesion in the anterior-posterior viewing direction he was only able to feel the most peripheral part of the lesion. Certainly the position of the lesion marked in this view does not seem reasonable, since it is so superficial that it will be predominantly skin rather than breast tissue and it has almost zero cross-sectional area from this direction.

Validation against Tracked Ultrasound

As an alternative method to assess the system accuracy, the lesion was also imaged using an ultrasound scanner (Philips-ATL HDI 5000, Philips Medical Systems). The imaging itself was performed by an operator experienced in ultrasound imaging. The 15-7 MHz broadband linear array transducer (CL15-7) was spatially tracked using an Optotrak Certus sensor, shown in Figure 9.10. The ultrasound image had been calibrated such that the position of any pixel within an ultrasound image was also known in the 3D coordinate system of the Optotrak sensor. A simple point-target phantom, consisting of a pin attached to the bottom of a waterbath, was used to perform this calibration (Barratt et al. 2001). The residual error on this point after calibration was 0.43mm.

The positions of the fiducial markers on the surface of the breast were recorded using a pointer tracked using the Optotrak sensor. This allowed ultrasound images to be rigidly aligned with the breast surface. Care was taken to deform the breast minimally whilst imaging so that this rigid transformation remained reasonable. As the breast was not being compressed, the ultrasound images were not as good quality as can be achieved under standard diagnostic conditions and it was not possible to image the deep margin of the lesion. However this approach made it possible to identify the shallow margin of the lesion in ultrasound images, and rigidly align it with the model predictions.

Example ultrasound slices overlaid with the outline of model-deformed lesion identified in the MR image are shown in Figure 9.11. A good match between the ultrasound images and the lesion boundaries predicted from MR is observed, with the margin identified in the two modalities agreeing to within about 5mm where visible.
Figure 9.10 Tracked ultrasound probe. (a) 20 infra-red emitting diode affixed to the cross to allow the probes position to be tracked by (b) Optotrak Certus Sensor.

Figure 9.11 Model-predicted lesion location overlaid on ultrasound image of lesion. Model prediction is in green, margin of lesion visible in ultrasound is outlined in red. The scale on the right hand side of each image is in cm.
Comparison with Histology

Histology, rather than preoperative imaging, should be considered to be the ground truth about the presence of cancer. The excised tissue measured 140mm (roughly in the direction from the shoulder to the base of the sternum) by 50mm (from the skin surface to the pectoral muscle) by 60mm. The lesion was found on histological analysis to be a grade III invasive ductal carcinoma, and to have been completely excised. It had, on microscopic analysis, a maximum dimension of 45mm, with a 1mm satellite lesion located superior and medially. The lesion extended to within 2mm from the pectoral muscle. The macroscopic appearance of the lesion in the histology lab was slightly smaller, with a maximum dimension of 35mm.

There is a large discrepancy between the size of lesion found on histological analysis (45mm) and the size of the lesion estimated by clinical palpation (18mm) or ultrasound imaging (20mm). The histological size of the lesion is much more consistent with the size computed by the image-guided surgery system by deforming the MR image (42mm). Similarly, both clinical palpation and ultrasound imaging indicated that the lesion was much more peripheral than histology found it to be, whilst MR imaging correctly indicated that it extended down to the pectoral muscle.

Feedback from Surgeon

Feedback from the surgeon was sought on the presentation of navigational information. He found the surface rendering to be a helpful way to present the guidance, allowing him to form a better picture in his mind of the cancer location. He felt that this approach would be particularly suitable for DCIS, which is irregularly shaped, whilst locating small lesions might be better achieved by using pointer-based technology.

Since the system has not been thoroughly validated, the surgeon was asked to ignore the system’s guidance when planning excision.

9.5.4 Conclusion

The image guided surgery system has been successfully demonstrated on one patient case. There was a good match between the boundary of the lesion visible on ultrasound imaging and the boundary indicated by the guidance system, with the lesion boundaries agreeing to within 5mm. This result, which is more accurate than might have been expected given the hybrid prone-supine registration errors measured in the previous chapter, may be due in part to the boundary of the lesion coinciding with a strong fibroglandular-adipose tissue boundary in the MR images. The overlap with the palpable mass location was less good but this may be, in part, due to experimental error. The size of the lesion measured using the guidance system (42mm)
was much larger than the lesion size measured using ultrasound (20mm) and clinical palpation (18mm), and was in agreement with the size measured histologically (45mm).

Histology is considered to be the ground truth for the presence of cancer. Since there is such a large disagreement between cancer sizes detected by the various modalities, it is important to be able to show the correspondence between points in images and the histological specimen. This is particularly important in the case of MR imaging, since dynamic contrast enhancement can only be observed in vivo. This is the topic of the next chapter.

9.6 Chapter Conclusion

This chapter has described the components of the image-guidance system for breast surgery which I constructed. The accuracy of surfaces reconstructed using a stereo camera system and the stereo camera’s suitability for intraoperative imaging of the breast have been assessed. I have proposed and assessed an intraoperative registration technique which deforms a biomechanical model of the breast, built from supine preoperative MR images, to match the intraoperative surface. Finally I have reported the first clinical experience with an image-guided breast surgery system.

The main contributors to the overall error, excluding the accuracy with which a radiologist can identify the lesion and the accuracy with which a surgeon can excise the region identified by the system, are the errors in the preoperative prone-supine registration described in the previous chapter and the intraoperative registration described in Section 9.3.

The mean hybrid prone-supine registration accuracy was identified in the previous chapter as being 6.9mm, 6.1mm and 11.9mm on three subjects. The mean intraoperative registration accuracy was estimated at 1.8mm and 2.6mm on two subjects. The stereo camera was able to acquire the surface of the breast to an accuracy of around 0.4mm Assuming the errors to be independent - which may not be valid, since both registrations depend upon the same model – allows the errors to be added in quadrature which suggests an overall mean accuracy of around 6mm to 12mm. Surgeons typically aim to leave a macroscopic margin of healthy tissue of 10mm around a lesion to account for the imprecision inherent in current clinical practice. This indicates that the prototype system has an accuracy similar to that of current practice. Since the system does not rely upon lesions being palpable, its accuracy may already be sufficient to be of some clinical use for these difficult cases. It is clear however that prone-supine registration is the step which introduces by far the greatest error, and the large maximum errors are of particular concern. An alternative approach to this registration problem will be discussed, along with other future work, in Chapter 11.
The overall accuracy of the system was also assessed by measuring the location of the lesion using tracked ultrasound for one patient. The deep margins of the lesion were not visible on the ultrasound image, but the error on the margins which were visible was less than 5mm. Although limited conclusions can be drawn from just one case, especially given the larger errors determined above, this is within the 10mm accuracy identified as clinically required and so is an encouraging result.
Chapter 10

Feasibility Study into Registration of Breast Pathology

10.1 Introduction

The initial clinical experience of image-guided breast surgery, described in the previous chapter, highlighted that there can be a significant discrepancy between the size of a palpable mass measured clinically and the region of enhancement visible in DCE MR images. Histology provides the ground truth about the presence of cancer. It is therefore important to be able to relate both the MR and the surgical findings to the histology.

It was seen in Section 2.8 that previous research has not sought to establish one-to-one spatial correspondence between MR imaging and histology for the breast. Instead more general features, such as size and morphology, have been compared. One of the barriers to establishing a one-to-one correspondence is the scale of soft tissue deformation occurring between imaging and histology. In this chapter I perform a preliminary investigation into the feasibility of using the biomechanical model developed in this thesis to simulate this deformation and assist this registration task.
10.2 Aligning Gross Histology Specimens with MR images

10.2.1 Introduction

During imaging the posterior face of the breast is curved around the patient’s torso. In the dissection room the specimen is placed with this face lying on a flat dissection board, and so this face becomes planar. In order to match images of histology with MR images it is necessary to recover this large deformation. The scale of the deformation is illustrated in Figure 10.1, in which the outline of a transverse section at the level of the nipple through a histology section (imaged using a stereo camera) is overlaid on a transverse slice of that patient’s supine MR image.

I propose that the biomechanical model which I have developed for the registration of prone and supine MR images and for modelling intraoperative deformation may also be used to model the deformation between supine MR imaging and surgery. This supine model is appropriate because the breast in the supine posture is more similar in shape to the mastectomy specimen than the prone posture is. Using such a biomechanical model allows gravity combined with a simple boundary condition along the posterior wall to be used to drive the deformation, with the material properties ensuring that the breast tissue deforms in a plausible way. Once the correspondence between supine MR imaging and histology is known, it would be possible to determine the correspondence between prone DCE MR imaging and histology using the methodology of Chapter 8 to match the prone and supine MR images. The proposed technique is used here to match photographs of gross histology with MR imaging. For this exploratory work, images of one subject (Subject S1) who was undergoing a prophylactic mastectomy of the left breast are considered.

![Figure 10.1 Deformation between supine MR imaging and histology.](image)
10.2.2 Method

Imaging

The MR protocol used to acquire images of this patient was described in Section 5.3. The images were acquired on the day before surgery. No DCE MR images are considered in this example dataset since the left breast was asymptomatic. If a dynamic sequence of images were available it would be possible to associate not just the voxel image intensity in the structural image but also the contrast uptake curve for this voxel with a physical point in the mastectomy specimen.

Surgery

The subject underwent a skin-conserving modified radical mastectomy of the left breast followed by immediate reconstruction. In this procedure the nipple and a very small region of skin surrounding it were excised along with the breast tissue, but the majority of the skin was preserved. The breast tissue was excised down to the pectoral fascia. Prior to the first incision vital blue dye was injected subcutaneously at the site of each fiducial marker. The planned incision and the locations of the fiducial markers on the skin can be seen in Figure 10.2a. The resulting mastectomy specimen, and the blue stain which marks the fiducial marker locations, can be seen in Figure 10.2b.

![Figure 10.2 Breast in surgery and in the histology lab. (a) Breast immediately prior to mastectomy (b) corresponding mastectomy specimen roughly aligned in the histology lab](image-url)


**Histology sectioning**

The specimen was sectioned without fixation within 15 minutes of excision. The specimen was sectioned fresh, rather than after fixation, to avoid the shrinkage which occurs during fixation and because sectioning allows formalin to penetrate better during the fixation step. The specimen was placed on a flat dissection board and photographed using a digital camera mounted on a copy stand. In addition, images were acquired using the stereo camera. The fresh mastectomy sample is shown in Figure 10.3a. The faces of the specimen were painted in different colours (Figure 10.3b) to aid the alignment of slices after sectioning. Coronal slices of approximately 5mm thickness were then sectioned freehand, starting with the posterior slice. The anterior and posterior faces of each slice were photographed and the slices were imaged using the stereo camera. The anterior faces of the slices are shown in Figure 10.3c-f. Blocks were then removed for processing into microscope slides and the anterior face re-photographed. Realigning the slides with the gross specimen will be considered in the next section.

Coronal sectioning of fresh specimens in this way was a standard practice in the research pathology laboratory in which the protocol was developed (Cancer Research UK Breast Pathology Laboratory, Guy’s Hospital, London). However it was necessary for this patient’s surgery to be performed at a different hospital (St Thomas’ Hospital, London) in order for the patient to receive immediate reconstruction. The histology sectioning was therefore performed by the pathologist at the St. Thomas’ Hospital NHS pathology laboratory. In this laboratory fresh specimens were not routinely handled, and specimens were typically sectioned in a sagittal direction. It can be seen in Figure 10.3 that, due to being unpractised at coronal sectioning, the pathologist had difficulty in obtaining even coronal slices. Slices obtained at the laboratory which routinely handled fresh specimens are much more even, as will be observed in Figure 10.5.
Figure 10.3 Sections through mastectomy specimen

(a) mastectomy specimen
(b) mastectomy specimen painted to indicate faces.
(c-f) coronal sections through mastectomy with (c) being the most posterior section and (f) being the most anterior section.

Simulating the deformation between supine imaging and gross histology

During supine images the posterior face of the breast curves around the torso. During histological sectioning this face is planar. This deformation was modelled by applying displacement boundary conditions to a biomechanical model of the breast constructed from a supine MR image. The biomechanical model was constructed in the manner described in Chapter 5. Since only displacement boundary conditions were applied to the model it is the ratio of the material parameters rather than their absolute values which was of importance, and the material density did not affect the deformation. In the work report in this chapter adipose and fibroglandular tissue were assumed to obey the same neo-Hookean constitutive relationship.
Displacement boundary conditions were applied on all the posterior nodes of the model in the anterior-posterior direction (but with no constraints applied in the directions perpendicular to this) which forced these nodes into the same coronal plane. To stop the model from sliding freely on this plane, additional boundary conditions were placed on two additional sets of nodes lying on the posterior face. The first of these sets consisted of those nodes which lay along the midline of the model in the medio-lateral direction. They were constrained to have zero displacement in the medio-lateral direction. The second set consisted of those nodes which lay approximately along the midline of the model in the superior-inferior direction which were constrained to have zero displacement in the superior-inferior direction.

The model was deformed using the finite strain formulation of the finite element method. The nodal displacements were used to deform the supine MR into the histology configuration. The coordinates of the skin fiducial markers, as identified in the supine MR image, were similarly transformed.

**Aligning the deformed supine image with gross histology**

The photographs of histology were scaled using the rulers which had been included in all the images. The scaled image of each section was rigidly aligned by hand with the image of the unsectioned specimen.

The fiducial marker locations were identified in the scaled image of the unsectioned specimen. The fiducial marker locations in the deformed MR image were projected into the coronal plane. The 2D rigid transformation was calculated which minimised (in the least squares sense) the distance between the fiducial marker locations in the mastectomy photograph and the projected fiducial marker locations in the deformed MR. This transformation was applied to the MR image to align it with the histology images.

The stereo camera images were used to calculate the mean thickness of each slice. Corresponding coronal slices through the deformed MR image were generated.

### 10.2.3 Results and Discussion

The anterior faces of the two sections which were originally closest to the chest wall are shown in Figure 10.4. Regions of predominately glandular tissue have been manually outlined on the histology photographs. These outlines are overlaid on the slice through the co-registered deformed MR volume.
Figure 10.4 Aligned histology and MR image sections (a) and (c) show photographs of coronal sections through mastectomy specimen with boundary of fibroglandular tissue overlaid in green. (b) and (c) show corresponding sections through model-deformed MR volume, with fibroglandular outline from photographs of sections overlaid. Each black square on the measures visible in the image has a length of 10mm.

The boundary between adipose and fibroglandular tissue in the MR image and the histology specimen appears to be broadly similar after the MR image has been warped according to the biomechanical model’s deformation and aligned on fiducial marker locations. Corresponding features can conceivably be identified, and suggest a registration accuracy of 10-20mm. Since the breast is a three-dimensional object it is however unlikely that exact correspondences are being observed as some features will have moved out of the plane of the slice. Furthermore MR images shows an ‘average’ intensity within the slice whilst pathology shows the tissue composition at the cut.
Whilst it might be possible to improve the image similarity by introducing a 2D intensity-based registration step which matches the MR image and histological photograph in a non-rigid way, there is no ground truth available to validate that the registration does improve the true correspondence. Future work should look at implanting distinctive, MR visible, fiducial markers within the breast to allow the registration error to be quantified.

10.2.4 Conclusion

The deformation of the breast between surgery and histology is very large. Although the correspondence is not exact, using a biomechanical model greatly increases the similarity between supine MR images and photographs of gross histological specimens. Since the previous chapter showed that the correspondence between prone and supine MR images could be established, this is an important step towards establishing correspondence between histological findings and DCE MR images. The next section investigates whether microscopic histological findings can be aligned with the gross specimens.

10.3 Aligning Microscopic Histology with Gross Histology Specimens

10.3.1 Introduction

The previous section showed that it seems possible to match photographs of gross histology mastectomy sections to a supine MR image of the breast. Using the registration methodology of Chapter 8 to match supine MR images with prone MR images, it should therefore be possible to relate gross histology to prone DCE MR images. The presence of breast cancer in a particular tissue sample is determined in the pathology lab by creating microscope slides from the gross specimen, and examining these slides under a microscope. This section shows that these microscope slides can in principle be aligned with the gross specimen - and therefore the microscopic histology can be matched to the DCE MR images, to a tolerance defined by the registration and modelling accuracy described above.

10.3.2 Method

The spatial alignment of the microscopic histology findings with photographs of the gross specimen was performed on one dataset (Subject S5). The 40 year patient had grade II invasive ductal carcinoma and DCIS, and a modified radical mastectomy was performed. The mastectomy sectioning and microscopic analysis were performed by the pathologist (Corrado D’Arrigo) at the Cancer Research UK Breast Pathology Laboratory, Guy’s Hospital. Suitable MR images of this subject were not available.
During surgery a stitch had been placed superior to the nipple, which was used to orient the specimen on the dissection bench. The fresh specimen was placed on a sheet of stiff paper and a photograph of the specimen was acquired using a digital camera mounted on a copy stand. A long blade was then used to cut coronally approximately 8mm from the posterior. This slice was left on the sheet of paper and the remaining tissue transferred to a new sheet. A photograph was then acquired of the anterior face of the slice. This process was then repeated until the entire breast had been sectioned. The slices are identified by a number $n$, where $n=1$ is the posterior slice and $n=n_{\text{max}}$ is the anterior slice containing the nipple. The slices of tissue, still on their sheets of paper, were stacked and placed in formalin to fix overnight. The paper served to reduce deformation of the slices due to handling, and no attempt was made to image the posterior faces prior to fixation to avoid deforming the tissue.

Once the sections had fixed, they were removed from the formalin and both the anterior and posterior faces were photographed. Blocks were then cut from the fixed sections. The posterior faces of the blocks and the sections were imaged. The blocks were then wax processed overnight. In this procedure the tissue is dehydrated using ethanol, and then impregnated using paraffin wax to replace the ethanol. Microscope slides were prepared from these blocks by taking very thin slices from the posterior face using a microtome. The slides were stained to highlight differences in cell morphology. These slides were then digitised using a flatbed scanner. The slides were examined microscopically by a pathologist and the cancerous regions were annotated onto the digitised images.

The images of the sections, blocks and slides were loaded as separate layers into the GNU Image Manipulation Program (www.gimp.org). Each layer was appropriately scaled, and images showing posterior faces were reflected. The layers were manually transformed so that the faces visually appeared optimally aligned. Rigid transformations were used to align the sections and blocks of tissue as affine transformations provided no obvious improvement in alignment. However shearing appears to occur when the very thin slices are taken and prepared as microscope slides, and so affine transformation was allowed when aligning images of the microscope slides.
The alignment process followed was:

- anterior face of fresh section n was aligned with anterior face of fixed section n using a rigid transformation.

- posterior face of fixed slice n+1 was aligned with the anterior face of fixed slice n using a rigid transformation.

- posterior faces of blocks from slice n+1 and remainder of slice n+1 after blocking was aligned with posterior face of fixed slice n+1 before blocking using rigid transformations.

- microscope slides were aligned with corresponding blocks from slice n+1 using an affine transformation.

The regions of carcinoma identified by the pathologist in the microscope slides were then overlaid on the image of the fresh section.

10.3.3 Results and Discussion

Example images of the alignment steps are shown in Figure 10.5. Figure 10.5f shows a section of the fresh mastectomy specimen overlaid with the location of carcinoma which was identified in the pathology slides and then registered. As can be seen in the magnified views of Figure 10.6, the accuracy of each step seems good. Visual assessment suggests the overall registration accuracy is typically better than 5 mm, although there is clearly non-rigid deformation occurring which cannot be captured by this piece-wise rigid approach. Because the same features are being used to visually align the images and to assess the registration accuracy, there isn’t a ground truth available in this dataset to objectively assess the registration accuracy.

Figure 10.5c and d shows posterior and anterior faces which lie upon the same slicing plane, and so they might be expected to be identical apart from a reflection. However they appear quite dissimilar. This suggests that tissue may cut more easily at the boundary between different tissue types, and during the slicing process the tissue or the blade is deforming (or they both are) to allow the blade to take a ‘path of least resistance’ between tissue types.

This initial investigation into matching microscopic histology to gross histology sections indicates that although the registration task is challenging, it appears feasible to track the deformations which occur at each step.
Figure 10.5 Alignment of histology slides with gross mastectomy specimen (wide view) (a)
mastectomy specimen (b) anterior face of fresh slice 3. Boundary of adipose tissue is outlined in blue, and
this outline is also overlaid on images a, c and d to aid comparison (c) anterior face of fixed slice 3 (d)
reflected posterior face of fixed slice 4 (e) reflected posterior face of fixed slice 4 after blocking,
corresponding aligned reflected blocks and corresponding aligned reflected slides. Blocks labelled A and
B are shown at a greater magnification in Figure 10.6 (f) cancer delineated in slides overlaid on fresh slice
3. The solid red regions are areas of dense carcinoma and the lines encircle regions of diffuse carcinoma.
Figure 10.6 Alignment of histology slides with gross mastectomy specimen (magnified view) Rigidly aligned slides, blocks and sections corresponding to slides A and B labelled in Figure 10.5e shown at greater magnification. Gridlines with 10mm spacing are overlaid.
10.4 Chapter Conclusion

This chapter has described my initial investigation into registering microscopic histology with DCE MR images. Its core contribution is to show that a biomechanical model might help to register gross histology sections with MR images. In addition it shows that the other part of the registration task - matching microscopic images to the gross histology - appears tractable.

Combining the two techniques presented in this chapter, along with the prone-supine registration technique presented in Chapter 8, offers a method to compare slides of histology with the contrast enhancement occurring at the corresponding location in an MR image. In conjunction with the image-guided surgery described in the previous chapter, this starts to connect the processes of preoperative diagnosis, surgery and postoperative confirmation which, at least in terms of spatial information, are currently distinct.

Whilst I describe only an initial exploratory experiment, attempts to spatially register breast pathology images with prone DCE MR images have not previously been reported. If greater reliance is to be placed on DCE MR images for diagnostic purposes, and particularly if these images are to be used to guide surgery, then it is important that the spatial correspondence between contrast enhancement and pathology be understood. In this chapter I have proposed registration techniques which may help to achieve this.
Chapter 11

Conclusion and Future Work

11.1 Introduction

The principal aim of this thesis has been to develop an image guidance system for breast surgery. In this chapter I will summarise my experimental work towards this goal. The four key areas that this work has addressed are:

- Construction of a biomechanical model of the breast and an investigation into the influence of boundary conditions and of material properties on this model.

- Registration of prone and supine MR images of the breast using a hybrid registration technique. This hybrid technique uses the biomechanical model to initialise an intensity-based non-rigid registration.

- Construction of an image-guided breast surgery system, including a report of the first clinical case. This system uses the biomechanical model of the breast to account for intraoperative deformation.

- A feasibility study into whether spatial correspondence can be established between histology (which serves as the ground truth) and the MR imaging used to direct the image-guided surgery.

The limitations of this work are then discussed, and key areas for future work identified.

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11.2 Summary of Thesis

11.2.1 Modelling Gravity-Induced Deformations

A key contribution of this thesis has been to investigate whether a finite element model can be used to accurately simulate the large, gravity-induced deformations which the breast undergoes between the prone and supine positions. Other researchers have previously applied gravitational loads to finite element models of the breast. However, in this thesis I have constructed models for a greater number of subjects and have assessed the simulated deformations more thoroughly. Furthermore, I have also considered more realistic boundary conditions along the pectoral fascia.

A method to construct a finite element model of the breast suitable for the simulations performed in this thesis is proposed in Chapter 5. This model is constructed from an MR image of the patient acquired in the supine position. Since gravity was acting on the breast when this image was acquired, unknown stresses exist within the supine model which must be accounted for when modelling gravitationally-induced deformations. This is done by determining the shape of the model in its stress-free ‘reference state’. In Chapter 6 I have shown that an effective way to find this reference state is to update an initial estimate until applying gravity to the estimated reference state results in a model which aligns with the original supine model. This approach is sufficiently fast and, unlike the approaches to finding the reference state that others have used, is straightforward to implement using commercially available finite element analysis software.

Inspection of pairs of MR images of the breast in prone and supine positions showed that there was significant sliding motion of tissue along the chest wall. Therefore, in Chapter 6 I compared the effect of two possible boundary conditions which describe the motion of nodes on this face with the previously assumed fixed boundary conditions: a linear compression of the tissue along this face in a roughly latero-medial direction and a quadratic compression in the same direction. On the tested cases I found that modelling the sliding motion as a linear compression was most effective, with a 20% compression improving the accuracy of the model by about a third.

In Chapter 6 I also considered the effect of varying the material stiffness of breast tissue on the simulated deformation. The values for this stiffness reported in the literature stem either from small compression in-vivo elastography experiments, or from compressions of small ex-vivo specimens. These experiments do not consider the behaviour of breast tissue in extension, or the behaviour of in-vivo tissue under larger strains. I found that using these values substantially underestimated the deformation which actually occurs between the supine and prone positions. Therefore, when modelling the deformation from the supine to the prone position, I have
assumed that all breast tissue components obey the same incompressible neo-Hookean constitutive relationship. This allows the single parameter which describing this relationship to be fitted to the observed deformation. On the three subjects for which the model was assessed the neo-Hookean parameter $\alpha$ was found to have values of between 0.09 and 0.22kPa. The model was found to be able to recover landmark locations to a mean error of 9.7, 9.6 and 15.6mm, compared with errors of 46.9, 51.5 and 70.5mm if the non-rigid deformation was not accounted for.

In Chapter 7 I have shown that submerging the breast in water provides a good approximation to the reference state of the breast. I also found that intensity-based registration algorithms are able to match MR images of the submerged breast with MR images of the breast in a prone free-pendulous position. The resulting deformation field can be used to apply relatively accurate boundary conditions on a finite element model constructed in the reference state, as well as to assess the accuracy with which the model can predict the deformation. Modelling this deformation allowed the influence of varying fibroglandular, adipose and skin material properties independently to be assessed. The material properties of glandular tissue determined varied between 0.1 and 0.4 kPa and the material properties of adipose tissue determined varied between 0.2 and 0.8kPa, depending on which breast was being modelled and whether skin was included. The accuracy of the ‘gold-standard’ intensity-based registration limited the accuracy with which these material properties can be determined. However, I found that the simulated deformation was insensitive to the choice of material properties, indicating that the choice of boundary conditions is much more important than the choice of material properties.

11.2.2 Registration of Prone and Supine MR Images

Diagnostic MR imaging of the breast is performed with the patient in the prone position to reduce motion artefacts in the dynamic contrast-enhanced sequence. Images acquired with the patient in the supine position provide a much closer approximation to the surgical position, and so are more suitable for registering to the patient intraoperatively. It is therefore desirable to register prone and supine MR images in order to locate the cancer within the supine image. I was unable to recover this deformation using the two widely-used non-rigid registration methods (viscous fluid registration and B-spline registration) which I tested. I believe that this is due to insufficient initial overlap between corresponding regions in the prone and supine images caused by the large displacements.

I have proposed in Chapter 8 that the deformation modelling developed in the preceding chapters could be used as the basis for a registration method. Using the biomechanical model to simulate the deformation between supine and prone improves the alignment between the prone and the model-deformed supine MR images. There is then sufficient overlap between the prone
MR image and the model-deformed supine image that an intensity-based non-rigid registration can be effective. The mean registration errors using this technique, measured in the prone space, were 6.9, 6.8 and 10.3mm for Subjects S1, S2 and S3 respectively.

11.2.3 Image-Guided Breast Surgery

The ultimate goal of this research has been to develop a system which can indicate to the surgeon the location of breast cancer during surgery, based on preoperative DCE MR images. I have described this system, and an initial clinical experience using it, in Chapter 9.

The position of a lesion can be revealed by DCE MR imaging with the patient in the prone position. The corresponding location within a biomechanical model of the breast (built from an MR image acquired in the supine position) was determined prior to an operation using the non-rigid registration method which was previously described in Chapter 8. Once in the operating theatre, a stereo camera system was used to reconstruct the skin surface of the breast. The surface of the biomechanical model was deformed so that it matched this skin surface, which caused the deeper tissue, such as the target lesion, to be appropriately displaced. The mean registration accuracy of this intraoperative step was estimated at 1.8mm and 2.6mm on two subjects. The error in measuring the surface location was around 0.4mm. This suggests an overall registration accuracy, from preoperative imaging to surgery, of between 6mm and 12mm.

The complete image-guided surgery system has been used to provide guidance in the operating theatre on one patient case. There was a good match (<5mm) between the boundary of the target lesion computed by the guidance system and the superficial lesion boundary which was visible on tracked ultrasound images. The size of the lesion measured using the guidance system (42mm) was much larger than the lesion size measured using ultrasound (20mm) and clinical palpation (18mm), and was in agreement with the size measured histologically (45mm). This is an encouraging result, although limited conclusions can be drawn from a single case.

Surgeons typically aim to leave a macroscopic margin of 10mm of healthy tissue around a lesion. The prototype system therefore has an accuracy which might be clinically useful, particularly for locating impalpable lesions. However the relatively large maximum errors observed mean that the system is not yet suitable for clinical use.

11.2.4 Matching Pathology, Surgery and Imaging

The use of DCE MR imaging as the basis for an image-guided surgery system presumes that it can be used to delineate the extents of a cancer on a fine scale. It is therefore important to
understand precisely how the enhancing region in the images relates to the physical pathology. This was perhaps highlighted in the initial image-guided breast surgery case described in Chapter 9, where the size of the lesion measured using the conventional indicators of clinical palpation and ultrasound markedly disagreed with the DCE MR-based guidance system findings (although in this case there was a good match between DCE MR derived results and pathology using the crude metric of maximum lesion dimension). The large deformation of the breast which occurs between in-vivo MR imaging and ex-vivo histopathology makes understanding this relationship a challenging task.

Chapter 10 describes two experiments that I performed which together form a procedure for spatially registering microscopic histology images with prone DCE MR images of the breast. This feasibility study illustrates the challenging nature of this task due to relatively unconstrained deformations occurring, and it also shows that using a finite element model to incorporate biomechanical knowledge may help to account for the deformation between MR imaging and pathology imaging. This may help to understand how the region enhancing in an MR image is related to the cancer on a cellular level. Whilst these are only exploratory experiments, they are the first work to describe a framework for spatially registering DCE MR images of the breast with the postoperative histological imaging.

11.3 Future work

11.3.1 Modelling Deformation of the Breast between Supine and Prone

There is clearly scope to improve the accuracy with which the deformation between supine and prone is modelled. Chapter 7 highlighted (for the smaller deformation between the submerged and free-pendulous prone states) that if the boundary conditions on a model are accurate then the realistic modelling of the deformation is quite insensitive to the assumed material properties. The actual boundary conditions for the prone-supine case will be more complex than the two relatively simple boundary condition schemes trialled in this thesis. Improved imaging of the region around the pectoral muscle might allow more accurate boundary conditions to be established on the posterior face of the breast, which may significantly increase the ability of the model to predict deformation over the entire breast. Determining these boundary conditions will be complicated by the fact that the coupling between the pectoral muscle and the breast tissue reduces with the age of the subject and will vary greatly between subjects.

The current model used for prone-supine modelling is over-simplified: for example it does not include skin or Cooper’s ligaments, and it assigns the same stiffness to both fibroglandular and adipose tissue. However all of these tissues, except Cooper’s ligaments, were considered
independently when modelling the deformation between prone images of the breast partially submerged and free-pendulous. Including them was not found to markedly improve the model’s accuracy. Furthermore, the accuracy was found to be quite insensitive to variations in their values. Trialling more complex constitutive equations and including the influence of Cooper’s ligaments (perhaps by modelling tissue as anisotropic) may improve the accuracy of the model. There is scope, perhaps, to use the material properties determined in Chapter 7 for breast tissue in extension and so just fit material properties to the model in compression. I believe, however, that improving the material models will prove much less important than improving the boundary conditions.

For the model to be able to reflect the composition of the breast faithfully, it would need to be constructed on a finer scale. This is because currently each element, which is modelled as being of purely one material type, in reality consists of a mix of the two material types. Creating a fine hexahedral mesh with well-shaped elements will be challenging, particularly if boundaries of elements should follow the boundaries of material types. Almost inevitably, some of these elements will become badly shaped when modelling the large, gravity-induced deformation and a strategy would need to be developed to address this. If such a model were constructed on a finer scale, it could perhaps include individual Cooper’s ligaments, and reflect the appearance of fat the ‘blob-like’ structures as observed in Chapter 6. However, for this to be effective I believe it will be necessary to consider how the small structures within the breast interact, unlike the current approach which models the breast as one continuous elastic medium. In a complete, fine-scale, model it will perhaps be necessary to model these blobs of fat as being able to slide over each other to some extent, and possibly Coopers ligaments will need to be modelled as being securely attached at their ends but not contiguous with the tissue which surrounds them over their length. At such a scale it might be necessary to consider material properties which reflect the unconstrained fluid content of tissue. To construct such a model, better images are likely to be required than are currently available clinically. However, this could prove an informative ex-vivo experiment, using micro-CT or small-bore high-field MR to obtain fine resolution images.

Given the challenges associated with creating a model at a finer resolution, it may instead prove fruitful to determine the material properties of gross regions of the in-vivo breast at large strains and in extension as well as compression. Whilst individualising such data to a specific patient will be challenging, some dependencies, such as the age of the patient, the proportion of each material type or some measure of tissue stiffness which can be practically assessed on patients, may become evident. This information could potentially be included in the model on a phenomenological basis rather than attempting to assign material properties to specific materials.
When considering potential improvements to the prone-supine modelling it is important to bear in mind the ultimate purpose of the modelling, and to take a pragmatic view as to the accuracy required. Here the purpose of the modelling is to provide a ‘good enough’ estimate of the deformation to initialise an intensity-based registration algorithm, which in turn must provide a ‘good enough’ estimate of the lesion location to make image-guided surgery feasible. Therefore any steps to improve the model which will greatly increase the time it takes to build (such as making it significantly finer) or solve (such as considering the interaction of internal structures as a contact problem) for each patient seem inappropriate. They may, however, be appropriate if the model is to be used to gain a deeper understanding of the spatial correlation between histology and DCE MR imaging.

11.3.2 Registration of Prone and Supine MR Images

The greatest contribution to the overall error of the image-guided surgery system stems from the supine-to-prone registration step. Using the techniques discussed above to improve the accuracy of the deformation modelling can be expected to improve the accuracy of this registration step.

The deformation is modelled from the supine position to the prone position. A disadvantage of simulating the deformation in this direction is that the fluid registration step can potentially fail to transform a point on the periphery of the prone breast to lie within the prone-deformed model. The biomechanical deformation field is defined only for points within the model, so the location of such a point within the supine breast cannot be determined. This was not, however, found to be an issue on the subjects considered. Modelling the deformation from the prone to the supine position would avoid this hazard, but it seems likely that the breast in the supine position is in a less stable equilibrium position and therefore inaccuracies in the boundary conditions on the model would have a greater effect. It would also require an additional model to be constructed for the intraoperative registration step. It would therefore be helpful to extend the biomechanical registration step such that points just outside the model are also deformed. This could be achieved by, for example, fitting spline curves to the biomechanical deformation field to allow it to be extrapolated.

One of the reasons that registering prone and supine MR images of the breast is so challenging is that there is a poor initial overlap between corresponding features. An alternative to initialising the registration using a biomechanical model would be to identify corresponding features and to use these to drive the registration. Such features could, for example, be used to initialise a registration in the manner proposed by Christiansen et al. (2001). However, I have found identifying corresponding features in a supine and prone pair of images a difficult task to perform by eye, so it is unlikely to be well suited to being automated.
To avoid having to perform the supine-to-prone registration, and so avoid the associated errors, it would be necessary to perform DCE MR imaging in the supine position. This is not currently practicable because breathing motion prevents contrast uptake from being monitored in a series of supine-acquired images. However, it may prove practicable to register this series of images to remove the effects of motion. For this to be effective it is likely that each image in the sequence would have to be acquired rapidly (possibly using parallel imaging techniques) at breath-hold. As described in Section 2.5.3, there has so far been only limited investigation of supine MR imaging of the breast.

The influence of breathing motion is not accounted for in this thesis. This motion will have the greatest effect on the breast’s position when the patient is in the supine position. During supine MR imaging the motion will result in the image being blurred. Although these images will be centred on some mid-breath position, the accuracy with which surfaces can be extracted to construct the biomechanical model will inevitably be reduced, and the information content available to drive an intensity-based registration will also be reduced. As mentioned above, faster MR imaging techniques, such as using multiple coils to perform parallel imaging, would allow images of the breast to be acquired at breath-hold. Positioning such coils on the breast would mean that there are unknown loads acting on the breast, and care would have to be taken to ensure that tissue on the lateral side of the patient was adequately imaged, but this approach could potentially allow the effect of motion to be removed from supine imaging.

11.3.3 Image-Guided Breast Surgery

Using a biomechanical model as the basis for the intraoperative registration step appears to be an efficient and sufficiently accurate approach, with the measured intraoperative registration error being low compared with the preoperative registration error. There is potential for a finite strain formulation of the finite element method to be used (in spite of the time limitations associated with image-guided surgery) by using an implementation which exploits the parallel capabilities of the graphics processor units, such that reported by Taylor et al. (2008). Currently no attempt is made to model external loads imposed on the breast during surgery (such as the surgeon manipulating the breast), or to model cutting. Accounting for these actions within the model would allow registration to be performed throughout a procedure, rather than just immediately prior to it. However, obtaining and imposing suitable boundary conditions will be a challenging task.

During the intraoperative registration step, boundary conditions are imposed only on the skin surface. In principle, deeper boundary conditions could be obtained using ultrasound imaging. However to acquire good quality ultrasound images of deep features, such as the boundary between breast tissue and the pectoral muscle, it is likely that pressure will need to be applied
with the ultrasound probe to ensure good acoustic coupling and to compress the breast. The resulting deformation of the breast will confound the registration problem. Furthermore, acquiring these images with a standard ultrasound transducer which can only acquire 2D slices will take considerable time (compared with the length of time breathing can be safely suspended for). However, the increasing availability of ultrasound transducers capable of acquiring 3D volumes suggests that further investigation of this issue may be worthwhile.

Breathing motion occurs during the period between the surface of the breast being acquired by the stereo camera in the operating theatre, and guidance being provided to the surgeon. Since an anaesthetised patient is mechanically ventilated, suspending respiration at a given point in the breathing cycle (probably the inhale position, since this would allow breathing to be suspended for the longest time) would remove this motion. The repeatability of a given point in the respiratory cycle (so that guidance can be provided during surgery as well as before surgery) needs to be experimentally verified.

When the intraoperative registration accuracy was assessed using an additional MR scan, it was not possible for the subject’s arm to be in the surgical position due to the narrow scanner bore. Therefore the registration error may be underestimated, particularly in the upper-outer quadrant. It would be possible to repeat this experiment using an open-bore MR scanner which allows the subject’s arm to be extended, but it is ultimately the overall system accuracy which is of importance. Further assessment of overall accuracy of the guidance system, as performed in the initial clinical case, is therefore crucial. A suitable cohort of patients for this work may be patients who have had an MR-visible coil placed at the site of a cancer before receiving neo-adjvant chemotherapy. This coil would provide a point landmark visible in MR and ultrasound images and so allow precise assessment of the system accuracy. A limitation of this cohort of patients is that the chemotherapy may influence the biomechanical properties of breast tissue.

It is not sufficient merely to calculate the location of a cancer within a patient on the operating table: it is also necessary to present this information to the surgeon in an effective manner. Modelling cutting within the finite element framework is still very much an open research question, and so the system is currently limited to providing guidance before the first incision. In this thesis the position of the cancer with the breast was presented intraoperatively as a virtual scene displayed on a computer monitor. Although tools were developed to align the visualisation with the surgeon’s viewpoint, and to allow the surgeon to draw corresponding points on the surface of the actual patient, it seems likely that a more immersive experience, such as augmented reality, will eventually prove more effective in helping the surgeon to understand the location of the cancer. There is significant overlap between the requirements for image-guided breast surgery and breast radiotherapy, but the latter involves no cutting or manipulation of the breast, and a coordinate system within which therapy is delivered, is already
explicitly established. Radiotherapy therefore circumvents some of the significant challenges that the implementation of image-guided breast surgery involves, and therefore may prove a very suitable application for the technology developed in this thesis.

11.3.4 Matching Pathology, Surgery and Imaging

The ultimate test of the system will be to histologically assess the margins of tissue excised under image-guidance. A significant source of error in this may be the accuracy with which a radiologist can draw around a lesion in an MR image based upon the contrast enhancement. In the initial clinical trial of the image-guided surgery system the cancer was segmented by a non-clinician (myself) based upon the radiologist’s report. No attempt was made to examine the inter- or intra-observer accuracy when performing this registration because the much more important question of how accurately the region of enhancement reflects location of cancer cells is, as yet, unanswered. There may not be a perfect match because DCE MR images reflect phenomena associated with cancer, such as regions of increased vasculature, increased vascular permeability and increased interstitial space, rather than directly imaging the cancer cells which must be excised. Chapter 10 laid out a possible framework for addressing this question, but clearly much more work is required before it can be properly answered.

Chapters 8 and 9 attempted to find correspondence between the supine MR images and the prone DCE MR images and between the supine MR images and surgery. The framework proposed in Chapter 10 aims to establish correspondence between the supine MR images and gross histology, and between the gross histology and microscopic histology. Unfortunately, a complete dataset containing suitable images of a single subject was not available. Clearly an interesting next step would be to perform this experiment on a complete dataset. In particular, this would make it possible to examine how well the pathology visible under a microscope aligns with the contrast enhancement observed in the MR image.

Chapter 10 provides an initial study into the feasibility of establishing correspondence between MR imaging and histology. There are several areas where the approach taken can be improved. For example, no attempt is currently made to account for the non-rigid deformation that occurs between the gross sections and the microscope slides. Although the error introduced by this deformation appears to be relatively small, there appears to be sufficient intensity information that, given a transportation mode which imposes suitable constraints, it should be possible to align these images better. Non-rigid deformation also occurs when the gross specimen is being sectioned into slices. The pathologist’s blade appears to take a ‘path of least resistance’ between structures during this sectioning, which makes registration to recover the non-rigid deformation challenging, since few corresponding features are present in the two cut faces. Initial trials in which wool soaked in hot wax was threaded through the gross specimen before sectioning, so
that the wax sets to form solid point landmarks visible in each face after sectioning, appear successful, and introducing this approach into the workflow of Chapter 10 may help the gross alignment process.

There is also scope to improve accuracy of the registration of the supine MR image with the mastectomy sections through the mastectomy. Increasing the amount of information available in the supine MR, for example by acquiring the MR images at breath-hold to reduce blurring, may allow an intensity-based registration step to be performed after the biomechanical model step. Reducing the thickness of the mastectomy specimens might allow the 3D nature of the mastectomy dataset to be exploited more effectively in this intensity-based registration, but the thinner slices would also increase the amount of non-rigid deformation occurring. A particular challenge in all the work involving the histology images is that there is no obvious ground-truth available for validation. Establishing an effective ground-truth, for example by inserting markers which are visible in both MR and histology imaging, but which do not interfere with the preparation of histology slides, is a crucial next step to allow improved registration algorithms to be developed.

11.4 Conclusion

This thesis has described the development of an image-guidance system for breast surgery. This is a challenging image-registration task because of the large deformations which occur between pre-operative imaging and breast surgery, as well as between surgery and histology. To account for these large deformations, I have proposed registration techniques which are based on a biomechanical model of the breast. There is still significant work required to improve the accuracy of these registrations; however this thesis has provided a framework for this work, and the results of the initial clinical case performed are encouraging.
Appendix A

Publications

A.1 Papers in Peer-Reviewed Journals


A.2 Papers in Peer-Reviewed Conference Proceedings


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1 2nd prize, MIAR Student Paper Competition 2006
2 Runner-up, MICCAI Young Scientist Award 2008
Appendix A. Publications

A.3 Conference Abstracts

A.4 Book Chapters

A.5 Other Publications


¹ Runner-up in the Built Environment, Engineering Sciences, MAPS category 2005
² Runner-up in the Built Environment, Engineering Sciences, MAPS category 2006
Appendix B

The Finite Element Method for Continuum Mechanics

B.1 Introduction

This appendix provides an outline of the continuum mechanics and the finite element method concepts necessary to support this thesis. The derivation used predominantly follows that of Bonet and Wood (1997), and this textbook is recommended to the reader should greater detail be desired.

B.2 Continuum Mechanics

A deformable body can be considered to consist of an infinity of individual particles. The assemblage of particles are identified by their initial positions $X$ at time $t=0$ with respect to the Cartesian basis. The current position, at time $t$, of each particle is given by the coordinates $x$ with respect to an alternative Cartesian basis. The motion occurring can be described by a mapping (Bonet and Wood 1997, Equation 3.1):

$$x = \phi(X,t)$$ \hspace{1cm} B.1

Since the deformed coordinate system differs from the initial coordinate system it is necessary to distinguish between them. In a material (or Lagrangian) description quantities are defined in terms of the undeformed body. In a spatial (or Eulerian) description quantities are defined in terms of the deformed body.
The displacement vector field relates positions in the deformed configuration to the initial configuration:

\[ \mathbf{u} = \mathbf{x} - \mathbf{X} \]  \hspace{1cm} \text{B.2}

**Deformation Gradient Tensor and Strain Tensors**

The deformation gradient tensor describes the relative positions of two adjacent particles after deformation in terms of their relative positions before deformation. The deformation gradient tensor \( \mathbf{F} \) is defined as (ibid. and Slaughter 2002, Equation 3.2.46):

\[ \mathbf{F} = \frac{\partial \mathbf{\phi}}{\partial \mathbf{X}} = \nabla \mathbf{\phi} = \mathbf{I} + \nabla \mathbf{u} \]  \hspace{1cm} \text{B.3}

Strain tensors characterise the change of material elements between the initial and deformed configurations. Consider the positions of two material particles \( Q_1 \) and \( Q_2 \) which are given relative to the nearby point \( P \) by the elemental vectors \( d\mathbf{X}_1 \) and \( d\mathbf{X}_2 \). In general, a deformation of the body will involve both a stretching and a change in the enclosed angle between these two vectors as they deform to \( d\mathbf{x}_1 \) and \( d\mathbf{x}_2 \). In terms of the material vectors \( d\mathbf{X}_1 \) and \( d\mathbf{X}_2 \), the spatial scalar product \( d\mathbf{x}_1 \cdot d\mathbf{x}_2 \) is given by (Bonet & Wood, Equation 3.14):

\[ d\mathbf{x}_1 \cdot d\mathbf{x}_2 = d\mathbf{X}_1 \cdot \mathbf{C} d\mathbf{X}_2 \]  \hspace{1cm} \text{B.4}

where \( \mathbf{C} \) is the right Cauchy-Green deformation tensor defined as (ibid., Equation 3.15):

\[ \mathbf{C} = \mathbf{F}^T \mathbf{F} \]  \hspace{1cm} \text{B.5}

It follows that the change in scalar product is given by (ibid., Equation 3.18a):

\[ \frac{1}{2} (d\mathbf{x}_1 \cdot d\mathbf{x}_2 - d\mathbf{X}_1 \cdot d\mathbf{X}_2) = d\mathbf{X}_1 \cdot E d\mathbf{X}_2 \]  \hspace{1cm} \text{B.6}

Where \( \mathbf{E} \) is the Green-Lagrange strain tensor which is defined as (ibid., Equation 3.18b)

\[ \mathbf{E} = \frac{1}{2} (\mathbf{C} - \mathbf{I}) \]  \hspace{1cm} \text{B.7}

In terms of the displacement field, this can be expressed as (Slaughter, Equation 3.2.48)

\[ \mathbf{E} = \frac{1}{2} \left( \nabla \mathbf{u} + (\nabla \mathbf{u})^T + (\nabla \mathbf{u})^T \cdot (\nabla \mathbf{u}) \right) \]  \hspace{1cm} \text{B.8}

In an ‘infinitesimal strain’ analysis \( \mathbf{u} \) is assumed to be small compared with the dimensions of the body and geometrical changes are ignored. Therefore Lagrangian and Eulerian quantities are not distinguished in an infinitesimal strain analysis. In the case of infinitesimal strain the second order terms can be neglected and the Green-Lagrangian strain tensor reduces to the infinitesimal strain tensor (ibid., Equation 3.4.14):

\[ \mathbf{e} = \frac{1}{2} \left( \nabla \mathbf{u} + (\nabla \mathbf{u})^T \right) \]  \hspace{1cm} \text{B.9}
The volume change caused by a deformation from an initial volume $V$ to a current volume $v$ is given by the Jacobian $J$, where (Bonet & Wood 1997, Equation 3.57)

$$J = |F| = \frac{dv}{dV} \quad \text{(B.10)}$$

**Stress and Equilibrium**

The Cauchy stress tensor represents the force measured per unit deformed area acting on the deformed body. The Cauchy stress tensor $\sigma$ relates the normal vector $n$, in the current configuration, to the traction vector $t$ (ibid., Equation 4.7a):

$$t(n) = \sigma n \quad \text{(B.11)}$$

The differential static equilibrium equations arise from considering the translational equilibrium of a general deformable body defined by a volume $v$ with boundary area $\partial v$. Ignoring inertial forces, the body is under the action of body forces $f$ per unit volume and traction forces $t$ per unit area $a$ acting on the boundary. Translational equilibrium implies that the sum of all forces acting on the body vanishes (ibid., Equation 4.12):

$$\int_{\partial v} t(da) + \int_v f dv = 0 \quad \text{(B.12)}$$

Using the Gauss theorem the left hand side can be re-written as an integral over the volume which remains equal to zero. Since the equation is valid over any enclosed region the integral can be removed. Finally, a residual force per unit volume $r$ can be anticipated in situations where equilibrium has not yet been satisfied, which leads to the equation (ibid., Equation 4.16):

$$\nabla \cdot \sigma + f = r \quad \text{(B.13)}$$

**Principle of virtual work**

The principle of virtual work is based upon an imaginary small deformation of the current configuration of a body by an arbitrary velocity. The term ‘virtual’ and the symbol ‘$\delta$’ are used to indicate that the deformation is imaginary, and this arbitrary velocity is called the virtual velocity $\delta v$. The virtual work $\delta w$ (per unit volume and time) done by the residual force $r$ during this virtual motion will be $r \cdot \delta v$. If the body is in equilibrium $r = 0$ so (ibid., Equation 4.22):

$$\delta v = r \cdot \delta v = 0 \quad \text{(B.14)}$$

Integrating over the whole body and applying appropriate substitutions leads to an expression for the virtual work $\delta W$ in the spatial configuration\(^1\) (ibid., Equation 4.27):

$$\delta W(\phi, \delta v) = \int_\sigma : \delta \phi dv - \int_\sigma f \cdot \delta \phi dv - \int_{\partial v} t \cdot \delta \phi da = 0 \quad \text{(B.15)}$$

---

\(^1\) Notation: $A:B$ denotes the double product of two tensors. It is a scalar of magnitude of $\text{tr}(A^T B)$. 

where \( d \) is the rate of deformation tensor (ibid., from Equations 3.91 and 3.101):

\[
d = \frac{1}{2} (\nabla v + \nabla v^T)
\]

B.16

In the above equation \( \sigma \) and \( d \) are termed ‘work conjugate’ with respect to the current deformed volume, because their product gives the internal work done by the stresses per current unit volume. The first Piola-Kirchoff stress tensor \( P \) and \( \delta F \) are work conjugate with respect to with the initially undeformed configuration, as are the second Piola-Kirchoff stress tensor \( S \) and \( \dot{E} \). \( P \) represents the force per unit area measured in the current configuration acting on the initial configuration and is given by (ibid., Equation 4.34a)

\[
P = J\sigma F^{-T}
\]

B.17

Although a physical interpretation of the Piola-Kirchoff stress tensor \( S \) in terms of surface traction is not possible (Holzapfel 2000) this contrived, but importantly totally material, stress tensor is commonly used to formulate the constitutive equations which describe a material behaviour, as will be seen in Section A.3. \( S \) is given by (Bonet & Wood 1997, Equation 4.41b)

\[
S = JF^{-1}\sigma F^{-T}
\]

B.18

In the above equation \( \sigma \) can be described as Piola push forward of \( S \). This operation combines a ‘push forward’ operation (which relates quantities in the material and spatial configurations) combined with the volume scaling \( J \).

### B.3 Material properties

A material is considered elastic if stress is a function of strain only. The purpose of the constitutive equation for an elastic material is to relate the stress tensor with the strain tensor. Two special cases of elasticity are considered in this thesis: linear elasticity and hyperelasticity.

**Linear Elasticity:**

Linear elasticity assumes both infinitesimal strain (so-called geometric linearity) and that a linear relationship exists between stress and strain (so-called physical linearity). Stress and strain are related by an elasticity tensor which for an isotropic linear elastic material depends on just two parameters - the Young’s modulus \( E \) (Tilley 2004, Equation S4.1)

\[
E = \frac{\sigma_{\text{axial}}}{\varepsilon_{\text{axial}}}
\]

B.19

and the Poisson’s ratio (ibid., Equation S4.5)

\[
v = -\frac{\varepsilon_{\text{transverse}}}{\varepsilon_{\text{axial}}}
\]

B.20
These two parameters are related to Lamé’s first parameter $\lambda$ and the shear modulus $\mu$ (also known as Lamé’s second parameter) by the following relationships (Bathe 1996, p298):

$$
\begin{align*}
\lambda &= \frac{E\nu}{(1+\nu)(1-2\nu)} \quad \text{B.21} \\
\mu &= \frac{E}{2(1+\nu)} \quad \text{B.22}
\end{align*}
$$

**Hyperelasticity**

In a hyperelastic material the work done by the stresses in the deformation are only dependent on the initial and final configurations. For such materials a stored strain energy function (or elastic potential) $\Psi$ per unit undeformed volume can be established as the work done by the stresses in deforming a body. The stress can be determined as a derivative of this function. For example, the second Piola-Kirchoff stress tensor $S$ can be found as (Bonet & Wood 1997, Equation 5.7):

$$
S = \frac{\partial \Psi}{\partial E} \quad \text{B.23}
$$

The Lagrangian elasticity tensor $C$ provides the linearised relationship between second Piola-Kirchoff stress tensor $S$ and the Green-Lagrange strain tensor $E$ (ibid., Equation 5.9):

$$
DS[u] = C \cdot DE[u] \quad \text{B.24}
$$

where the notation $D\ldots[u]$ indicates the directional derivative$^1$ with respect to displacement $u$. $C$ is given by the partial derivatives (ibid., Equation 5.11):

$$
C = \frac{\partial S}{\partial E} = 2 \frac{\partial S}{\partial C} = 4 \frac{\partial^3 \Psi}{\partial C \partial C \partial C} \quad \text{B.25}
$$

The spatial elasticity tensor $c$ is defined as the Piola push forward of $C$.

If the material being described is isotropic then the relationship between the elastic potential $\Psi$ and the right Cauchy-Green deformation tensor $C$ is independent of the material axes chosen, and is therefore a function of the invariants$^2$ of $C$ only.

---

$^1$ The directional derivative of a function results from a first order Taylor series expansion of that function and it provides the change of the function due to a small change in something upon which the function depends - in this case the displacement $u$.

$^2$ The invariants of a tensor are intrinsic magnitudes which remain constant under rotation.
The strain-energy function of the hyperelastic materials considered in this thesis are given in terms of the so-called modified invariants $\bar{T}_1, \bar{T}_2, \bar{T}_3$ (Holzapfel 2000, Equations 6.109-6.111):

\[
\bar{T}_1 = \text{tr}(\mathbf{C}) \\
\bar{T}_2 = \frac{1}{2} \left[ \text{tr}(\mathbf{C})^2 - \text{tr}(\mathbf{C}^2) \right] \\
\bar{T}_3 = |\mathbf{C}| = 1
\]  

Where $\mathbf{C}$ is the modified right Cauchy-Green tensor, which is the volume preserving (distortional) term after a multiplicative decomposition of $\mathbf{F}$, and hence $\mathbf{C}$, into volume changing (dilational) and volume-preserving terms (ibid, 6.79):

\[
\mathbf{C} = J^{-\frac{2}{3}} \mathbf{C}
\]

Two hyperelastic functions are considered. One of these is the neo-Hookean model, which is essentially a one parameter Mooney-Rivlin model (ANSYS 2007, Equation 192):

\[
\Psi(\mathbf{C}) = \alpha(\bar{T}_1 - 3) + \frac{1}{d}(J - 1)^2
\]

where $\alpha$ can be identified as being equal to half the shear modulus $\mu$ and $d$ is the so-called material incompressibility parameter. The other is the five parameter Mooney-Rivlin model (ibid., Equation 4-162):

\[
\Psi(\mathbf{C}) = \alpha_{10}(\bar{T}_1 - 3) + \alpha_{10}(\bar{T}_2 - 3) + \alpha_{20}(\bar{T}_1 - 3)^2 + \alpha_{11}(\bar{T}_1 - 3)(\bar{T}_2 - 3) \\
+ \alpha_{02}(\bar{T}_2 - 3)^2 + \frac{1}{d}(J - 1)^2
\]

where the material parameters $\alpha_{10}$, $\alpha_{10}$, $\alpha_{11}$ and $\alpha_{02}$ must be experimentally determined.

**B.4 The Finite Element Method**

For a given scenario the solution to the virtual work equation is given by the deformed configuration $\phi$ in which no residual forces act. However, the equation is non-linear with respect to be geometry (unless infinitesimal strain is assumed) and (generally) material properties, and so it cannot be solved directly. In the finite element method an approximation to the solution is obtained by linearising and discretising the virtual work equation with respect to the nodal solutions. The resulting equations can then be solved using a Newton-Raphson type iterative solution. In this way the nonlinear problem is replaced by a sequence of linear problems which are straightforward to solve at each iteration.
Appendix B. The Finite Element Method for Continuum Mechanics

For a trial solution \( \phi_k \) the virtual work equation (Equation B.15) can be linearised in the direction of an increment \( u \) in \( \phi_k \) as (Bonet and Wood 1997, Equation 6.2)

\[
\delta W(\phi_k, \delta \phi) + D\delta W(\phi_k, \delta \phi)[u] = 0 \tag{B.30}
\]

The directional derivative term will provide the tangent stiffness matrix, which is the operator used later in the Newton-Raphson process that adjusts the current nodal positions so that the deformation-dependent equivalent nodal forces tend toward being in equilibrium with the external equivalent nodal forces.

Discretisation

The body, in its initial configuration, is divided (‘meshed’) into simple elements connected at key points known as nodes. The practicalities of creating this mesh are described in Section 3.4.

The initial geometry can be interpolated in terms of the particles \( X_a \) defining the element nodes and the shape functions \( N_a(\xi_1, \xi_2, \xi_3) \) as (ibid., Equation 7.1):

\[
X = \sum_{a=1}^{n} N_a(\xi_1, \xi_2, \xi_3)X_a \tag{B.31}
\]

where \( n \) denotes the number of nodes. If a field variable, such as displacement, is approximated using the same interpolation functions as the shape functions, then the element is described as being isoparametric. For such elements the motion of the body can be described in terms of the current position \( x_a(t) \) of the nodes as (ibid., Equation 7.2):

\[
x = \sum_{a=1}^{n} N_a x_a(t) \tag{B.32}
\]

The discretised virtual velocity interpolation is obtained by differentiating this with respect to time (ibid., Equation 7.3)

\[
\delta v = \sum_{a=1}^{n} N_a \dot{x}_a(t) \tag{B.33}
\]

and equivalent terms for the discretised virtual rate of deformation and the discretised linear strain tensor can be similarly found.

This leads to the discretised virtual work (Equation B.15) being written for node \( a \) of element \( e \) as (ibid., Equation 7.14):

\[
\delta W^{(e)}(\phi, N_a \delta \phi_a) = \delta \phi_a \cdot \left( \int_{\partial e} \sigma \nabla N_a \cdot d\gamma - \int_{\partial e} N_a f \cdot d\gamma - \int_{\partial e} N_a t \cdot d\alpha \right) \tag{B.34}
\]
The virtual work per element \((e)\) could equivalently be expressed in terms of the internal and external equivalent nodal forces \(T_a^{(e)}\) and \(F_a^{(e)}\) as (ibid., Equation 7.15)

\[
\delta W^{(e)}(\phi, N_a \delta \phi_a) = \delta \phi_a \cdot \left[ T_a^{(e)} - F_a^{(e)} \right]
\]

where

\[
T_a^{(e)} = \int_{e} \sigma \nabla N_a \, dv \quad \text{and} \quad F_a^{(e)} = \int_{e} N_a f \, dv + \int_{\partial e} N_a t_a \, da
\]

Assembling all the internal and external nodal equivalent forces into vectors \(T\) and \(F\), the residual forces into vector \(R\) and the virtual velocities into vector \(\delta \tilde{v}\) allows the discretised virtual work equation to be written as (ibid., Equation 7.20):

\[
\delta W(\phi, \delta \tilde{v}) = \delta \tilde{v}^T (T - F) = \delta \tilde{v}^T R
\]

Since the internal equivalent forces are nonlinear functions of the current nodal positions, the nonlinear equilibrium equations can be assembled in terms of the vector \(x\) of unknown current nodal positions as (ibid., Equation 7.22)

\[
R(x) = T(x) - F(x) = 0
\]

**Linearised internal virtual work and the Tangent Stiffness Matrix**

The virtual work equation can be split into internal and external work components (ibid., Equation 7.29):

\[
\delta W(\phi, \delta \tilde{v}) = \delta W_{int}(\phi, \delta \tilde{v}) - \delta W_{ext}(\phi, \delta \tilde{v})
\]

This can be linearised in the direction \(u\) to give

\[
D\delta W(\phi, \delta \tilde{v})[u] = D\delta W_{int}(\phi, \delta \tilde{v})[u] - D\delta W_{ext}(\phi, \delta \tilde{v})[u]
\]

The internal virtual work after being linearised can be further divided into the constitutive component and geometric stress components respectively as (ibid., Equation 7.31):

\[
D\delta W_{int}(\phi, \delta \tilde{v})[u] = D\delta W_{c}(\phi, \delta \tilde{v})[u] + D\delta W_{g}(\phi, \delta \tilde{v})[u]
\]

\[
= \int_{e} \delta \tilde{d} : c : \tilde{e} \, dv + \int_{e} \sigma : (\nabla u)^T \nabla \delta \tilde{v} \, dv
\]
Replacing $\delta d$ and $\epsilon$ with appropriate discretisations allows the constitutive contribution of Equation B.37 for element $(e)$ linking nodes $a$ and $b$ to be written as (ibid., Equations 7.34 and 7.35)

$$D \delta W^{(e)}_c(\phi, N_a \delta \phi_a)[N_b u_b] = \delta \phi_a \cdot K^{(e)}_{c,ab} u_b;$$

$$[K^{(e)}_{c,ab}]_{ij} = \int_{\Omega} \sum_{k=1}^{3} \frac{\partial N_{a,k}}{\partial x_i} \partial_{ijkl} \epsilon_{ijkl} \delta \phi_k dV; \quad i, j = 1, 2, 3 \quad B.42$$

where $K_c$ is, in indicial notation, the constitutive component of the tangent matrix relating node $a$ to $b$ in element $(e)$.

The initial stress component of Equation B.41 can be derived as (ibid., Equation 7.45)

$$D \delta W^{(e)}_a(\phi, N_a \delta \phi_a)[N_b u_b] = \delta \phi_a \cdot K^{(e)}_{a,ab} u_b;$$

$$[K^{(e)}_{a,ab}]_{ij} = \int_{\Omega} \sum_{k=1}^{3} \frac{\partial N_{a,k}}{\partial x_i} \epsilon_{ijkl} \delta \phi_k dV; \quad i, j = 1, 2, 3 \quad B.43$$

Where $K^{(e)}_{a,ab}$ are the components of the so-called initial stress matrix.

The external virtual work due to a gravitational body force is not deformation dependent, and so its contribution to the virtual work after linearization with respect to a deformation is zero. However if traction forces are applied they will contribute to the linearised virtual work. For example, in the specific case of uniform normal pressure the external work component of Equation B.40 can be derived as (ibid., Equation 7.50)

$$D \delta W^{(e)}_{ext}(\phi, N_a \delta \phi_a)[N_b u_b] = \delta \phi_a \cdot K^{(e)}_{ext,ab} u_b;$$

$$K^{(e)}_{ext,ab} = \mathcal{E} \Phi^{(e)}_{ab}; \quad [K^{(e)}_{ext,ab}]_{ij} = \sum_{k=1}^{3} \epsilon_{ijkl} K^{(e)}_{p,ab,k}; \quad i, j = 1, 2, 3 \quad B.44$$

Where $\mathcal{E}$ is the third order alternating tensor ($E_{ijk}=\pm 1$ or zero depending on the parity of the $ijk$ permutation).

Equations B.42, B.43 and B.44 can be summed over all the contributions from all elements to give the total linearised virtual work in terms of a tangent stiffness matrix $K$, the complete virtual velocity vector $\delta \nu^T$ and the corresponding nodal displacement vector $u$ (ibid., Equation 7.53a):

$$D \delta W(\phi, \delta \nu)[u] = \delta \nu^T Ku \quad B.45$$
An alternative approach to obtaining this tangent stiffness matrix is to acquire it numerically from the relationship (ibid., Equation 7.65)

\[ K = \frac{\partial R}{\partial x} \quad \text{B.46} \]

by perturbing each of the solution degrees of freedom by a small amount and approximating the partial derivative using a finite difference approach.

**Solving**

Substituting Equations B.45 and B.37 into B.30, and recognizing that the virtual velocities are arbitrary, allows the discretised Newton-Raphson scheme to be formulated as (Bathe 1996, Equations 8.80-8.83):

\[
\begin{align*}
R_k &= F - T_k \\
K_k u_{k+1} &= -R(x_k); \\
x_{k+1} &= x_k + u_{k+1}
\end{align*} \quad \text{B.47}
\]

Where the subscript indicates the iteration at which the variable is evaluated, and where \( k=1,2,3,\ldots \)

Although for certain loading situations it is theoretically possible to achieve a direct solution, typically the load is incremented in a series of increments since the more increments used the easier it is to find a converged solution for a given load step. Furthermore, the assumption is made above that the external applied loads is deformation-independent, which is not generally valid. However, it is often sufficient, if the loading is applied in sufficiently small steps, to compute using the intensity of loading corresponding to the current load step, but over the volume and area calculated in the previous iteration (Bathe 1996). The internal forces \( T \) and the nodal positions \( x \) for each load step are initialised as those of the final iteration of the preceding load step.

**B.5 Modifications Necessary to Model Incompressibility**

The compressibility of linear elastic materials can be defined in terms of the Poisson’s ratio \( \nu \) (Equation B.20), where \( \nu=0.5 \) for a completely incompressible material. The compressibility of hyperelastic material is given by the material incompressibility parameter \( d \) in Equations B.28 and B.29. In these hyperelastic strain-energy equations, the Jacobian \( J \) is constrained to equal to one for a completely incompressible material.
The principle of virtual work as expressed in Equation B.15 is not suitable as the basis for modelling almost incompressible tissues, since for these materials any error during the iterative solution process in the predicted volumetric strain will result in a very large hydrostatic pressure (or, in the case of completely incompressible tissues, infinite). The over-stiffening that this causes is known as volumetric locking. Typically $\nu$ is set to around 0.495 rather than 0.5 when modelling biological tissues as behaving linear elastically in an attempt to prevent volumetric locking. When modelling hyperelastic materials volumetric locking is instead avoided by using a modified scheme, known as the mixed displacement-pressure formulation, in which the hydrostatic pressure is solved for on a global level rather than being calculated from volumetric strain.

The first step in this modification is to identify a total potential energy functional whose directional derivative with respect to displacement yields the principle of virtual work. The right Cauchy-Green tensor $C$ is then, as in Equation B.27, decomposed into a purely volumetric component and a purely distortional component $\overline{C}$, and the volume constraint is introduced into the functional via an additional variable - the Lagrange multiplier $p$ - which can be identified as the hydrostatic pressure. The modified functional is (Bonet & Wood 1997, Equations 6.28 and 6.29):

$$\Pi_L(\phi, p) = \int_V \Psi(\overline{C})dV - \int_V f_0 \cdot \phi dV - \int_{\partial V} \sigma \cdot \phi dA + \int_V p(1-J)dV$$

in which the incompressibility constraint has been expressed in terms of the Jacobian $J$.

By considering the directional derivative of this functional with respect to $\phi$ and $p$ independently and then linearising the resulting equations, the discretised Newton-Raphson scheme can be formulated in a similar way to the pure displacement formulation described previously. It differs however in that there are now two unknowns, namely the pressure and the nodal displacement (Bathe 1996, Equation 4.147):

$$\begin{bmatrix} K_{uu} & K_{up} \\ K_{pu} & K_{pp} \end{bmatrix} \begin{bmatrix} u \\ p \end{bmatrix} = \begin{bmatrix} -R \\ 0 \end{bmatrix}$$

To prevent this mixed displacement-pressure scheme from behaving like a pure displacement scheme it is important that the pressure interpolation is independent from the displacement interpolation. Typically this is achieved by computing the pressure discontinuously as a constant for each element, whilst displacement continues to be interpolated over each element.
Appendix C

Results of Supine-Prone Modelling Experiments

The tables and figures of this appendix give more detailed results for the supine-prone deformation modelling experiment reported in Section 6.7.
Appendix C: Results of Supine-Prone Modelling Experiments

<table>
<thead>
<tr>
<th>Compression /%</th>
<th>α /kPa</th>
<th>Mean (max.) error on fiducials /mm</th>
<th>Mean (max) error on landmarks /mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>-</td>
<td>43.6 (59.3)</td>
<td>46.9 (69.7)</td>
</tr>
<tr>
<td>0</td>
<td>0.16</td>
<td>13.4 (20.8)</td>
<td>14.5 (22.2)</td>
</tr>
<tr>
<td>10</td>
<td>0.19</td>
<td>10.8 (18.9)</td>
<td>11.0 (15.9)</td>
</tr>
<tr>
<td>20</td>
<td>0.22</td>
<td>13.9 (24.6)</td>
<td>9.7 (17.9)</td>
</tr>
<tr>
<td>30</td>
<td>0.27</td>
<td>19.8 (30.2)</td>
<td>12.8 (23.1)</td>
</tr>
<tr>
<td>40</td>
<td>0.37</td>
<td>26.5 (36.0)</td>
<td>18.4 (29.0)</td>
</tr>
</tbody>
</table>

Table C.1 Subject S1: Results for boundary conditions which simulate a linear compression.

Fiducial and landmark errors are given for a range of boundary conditions which simulate a compression along the pectoral fascia. The value of neo-Hookean parameter $\alpha$ (determined by fitting) which was used for the simulation is also given.

<table>
<thead>
<tr>
<th>Compression /%</th>
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<td>40</td>
<td>0.23</td>
<td>19.5 (30.4)</td>
<td>14.3 (25.0)</td>
</tr>
</tbody>
</table>

Table C.2 Subject S1: Results for boundary conditions which simulate a quadratic compression.

Fiducial and landmark errors are given for a range of boundary conditions which simulate a compression along the pectoral fascia. The value of neo-Hookean parameter $\alpha$ (determined by fitting) which was used for the simulation is also given.
Figure C.1 Subject S1: Images showing effect of boundary conditions. Slice through prone MR volume, supine MR volume and the supine MR volume after deformation according to model displacements for a fixed boundary condition and a range of linear and quadratic boundary conditions. The neo-Hookean material models used are given in Table C.1 and Table C.2. The prone skin surface and glandular outline is overlaid on each image in red.
<table>
<thead>
<tr>
<th>Compression /%</th>
<th>$\alpha$ /kPa</th>
<th>Mean (max.) error on fiducials /mm</th>
<th>Mean (max) error on landmarks /mm</th>
</tr>
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<tbody>
<tr>
<td>Supine</td>
<td>-</td>
<td>42.3 (64.7)</td>
<td>51.5 (65.1)</td>
</tr>
<tr>
<td>0</td>
<td>0.12</td>
<td>19.2 (50.6)</td>
<td>14.4 (25.3)</td>
</tr>
<tr>
<td>10</td>
<td>0.13</td>
<td>18.2 (35.1)</td>
<td>10.4 (17.6)</td>
</tr>
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</tr>
<tr>
<td>40</td>
<td>0.21</td>
<td>27.4 (43.0)</td>
<td>21.5 (29.5)</td>
</tr>
</tbody>
</table>

Table C.3 Subject S2: Results for boundary conditions which simulate a linear compression.

Fiducial and landmark errors are given for a range of boundary conditions which simulate a compression along the pectoral fascia. The value of neo-Hookean parameter $\alpha$ (determined by fitting) which was used for the simulation is also given.

<table>
<thead>
<tr>
<th>Compression /%</th>
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<th>Mean (max) error on landmarks /mm</th>
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<tr>
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<td>0.12</td>
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<td>10</td>
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<td>18.5 (42.4)</td>
<td>11.8 (18.1)</td>
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<tr>
<td>20</td>
<td>0.14</td>
<td>18.0 (34.1)</td>
<td>10.2 (18.4)</td>
</tr>
<tr>
<td>30</td>
<td>0.14</td>
<td>20.2 (33.1)</td>
<td>11.8 (24.8)</td>
</tr>
<tr>
<td>40</td>
<td>0.16</td>
<td>21.0 (34.5)</td>
<td>19.4 (26.3)</td>
</tr>
</tbody>
</table>

Table C.4 Subject S2: Results for boundary conditions which simulate a quadratic compression.

Fiducial and landmark errors are given for a range of boundary conditions which simulate a compression along the pectoral fascia. The value of neo-Hookean parameter $\alpha$ (determined by fitting) which was used for the simulation is also given.
Figure C.2 Subject S2: Images showing effect of boundary conditions Slice through prone MR volume, supine MR volume and the supine MR volume after deformation according to model displacements for a fixed boundary condition and a range of linear and quadratic boundary conditions. The neo-Hookean material models used are given in Table C.3 and C.4. The prone skin surface and glandular outline is overlaid on each image in red.
Table C.5 Subject S3: Results for boundary conditions which simulate a linear compression.

Fiducial and landmark errors are given for a range of boundary conditions which simulate a compression along the pectoral fascia. The value of neo-Hookean parameter $\alpha$ (determined by fitting) which was used for the simulation is also given.

<table>
<thead>
<tr>
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<th>$\alpha$ /kPa</th>
<th>Mean (max.) error on fiducials /mm</th>
<th>Mean (max) error on landmarks /mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
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<td>70.0 (104.6)</td>
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<td>15.6 (23.1)</td>
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<td>23.2 (40.2)</td>
<td>17.2 (26.3)</td>
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<td>40</td>
<td>0.110</td>
<td>28.9 (51.3)</td>
<td>21.6 (32.9)</td>
</tr>
</tbody>
</table>

Table C.6 Subject S3: Results for boundary conditions which simulate a quadratic compression.

Fiducial and landmark errors are given for a range of boundary conditions which simulate a compression along the pectoral fascia. The value of neo-Hookean parameter $\alpha$ (determined by fitting) which was used for the simulation is also given.

<table>
<thead>
<tr>
<th>Compression /%</th>
<th>$\alpha$ /kPa</th>
<th>Mean (max.) error on fiducials /mm</th>
<th>Mean (max) error on landmarks /mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>-</td>
<td>54.0 (74.3)</td>
<td>70.0 (104.6)</td>
</tr>
<tr>
<td>0</td>
<td>0.065</td>
<td>17.5 (27.3)</td>
<td>22.8 (40.1)</td>
</tr>
<tr>
<td>10</td>
<td>0.075</td>
<td>15.8 (23.6)</td>
<td>20.5 (35.9)</td>
</tr>
<tr>
<td>20</td>
<td>0.080</td>
<td>15.8 (21.4)</td>
<td>17.9 (30.3)</td>
</tr>
<tr>
<td>30</td>
<td>0.085</td>
<td>17.8 (24.4)</td>
<td>17.3 (25.3)</td>
</tr>
<tr>
<td>40</td>
<td>0.090</td>
<td>21.1 (31.4)</td>
<td>18.5 (26.0)</td>
</tr>
</tbody>
</table>
Figure C.3 Subject S3: Images showing effect of boundary conditions Slice through prone MR volume, supine MR volume and the supine MR volume after deformation according to model displacements for a fixed boundary condition and a range of linear and quadratic boundary conditions. The neo-Hookean material models used are given in Table C.5 and C.6. The prone skin surface and glandular outline is overlaid on each image in red.
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