**CAROTID PLAQUE CHARACTERIZATION WITH MEDICAL ULTRASOUND**by  
Matthew M. McCormick

A dissertation submitted in partial fulfillment of  
the requirements for the degree of

Doctor of Philosophy  
(Biomedical Engineering)  
at the  
UNIVERSITY OF WISCONSIN–MADISON  
2011

**Acknowledgements**

First, I would like to thank Dr. Tomy Varghese, my advisor. I would also like to thank other faculty members in the Ultrasound Group, Dr. James Zagzebski, Dr. Ernest Madsen, and Dr. Timothy Hall. I was a TA for the ultrasound course lab working with Jim Zagzebski, and I am always amazed by the time he takes to get into the lab even as the chair of Medical Physics, and I admire his humble, inquisitive attitude. I had the pleasure of working closely with Ernie Madsen, and I can only aspire to perform at his caliber as an experimentalist. Without his earnest involvement, we would not have solved the Mystery of the Planar Reflector Scum. The Siemens scanning system would not be in a sufficient functioning state to get the data that was obtained without Tim Hall’s efforts.

Thanks to Dr. Tim Hacker who allowed me to modify (and occasionally break) his VisualSonics system.

I greatly appreciated the assistance I have received and relationships I have built with the graduate students in the ultrasound research group. The names are too numerous to mention here, but special recognition should be given to Dr. Hairong Shi, who mentored me when I started, and Dr. Maritza Hobson, who guarded against unwanted visitors and cockroaches in our basement cave at the Medical Sciences Center.

Gratitude is owed to the Biomedical Engineering Department, which I am a member, but also the Medical Physics Department, which I am an adopted member. The Medical Physics students, faculty, and staff made the journey enjoyable.

The research I performed would not be possible without the valuable contributions of the team of which I was a part. Dr. Robert Dempsey not only performed the surgeries, but led the team with an attitude that promoted success: eagerness to try to understand the problems at hand, place resources where needed, and deliver patience when required. Dr. Mark Kliewer generously offered his skills as a radiologist, and his taste for good music. Dr. Carol Mitchell was undoubtedly the most valuable member of the team, and I doubt her passion for research, knowledge, and work ethic is matched in the field of ultrasonography. Thanks are also due to Pam Peterson and Cindy Colombo who put forth their best efforts in coordinating the research study.

Finally, I highly value my parents, Dr. Michael and Bernadette McCormick, and my siblings for their support. Also, the support of my uncle and aunt, Patrick and Sara McCormick and their family in Verona, WI was cherished.

**Abstract**

The most common cause of episodic stroke and cerebral ischemia is thought to be microemboli from carotid plaque. The bifurcation at the carotid bulb is a location prone to atherosclerosis. Some carotid plaques may be prone to rupture, which generates thrombi or plaque particulate that produce neural infarction. There is a significant clinical need for a method to determine which plaques are vulnerable to disruption so that surgical intervention or other prophylactic actions can be taken. In this dissertation, advances in diagnostic ultrasound imaging tools to address this need are proposed.

Focus is placed primarily on non-invasive, *in vivo* strain imaging techniques to quantify plaque vulnerability. It is hypothesized that strain, the mechanical distortion of tissue, is a direct measure of the tissue’s proximity to fatigue failure. A hierarchical block-matching motion tracking algorithm is developed. Displacements are estimated with improved robustness and precision by utilizing a Bayesian regularization algorithm and an unbiased subsample interpolation technique. A modified least-squares strain estimator is proposed to estimate strain images from a noisy displacement input while addressing the motion discontinuity at the wall-lumen boundary. Methods to track deformation over the cardiac cycle incorporate a dynamic frame skip criterion to process data frames with sufficient deformation to produce high signal-to-noise displacement and strain images. Algorithms to accumulate displacement and/or strain on particles in a region of interest over the cardiac cycle are described. New methods to visualize and characterize the deformation measured with the full 2D strain tensor are presented.

Other diagnostic ultrasound techniques, high-frequency 3D ultrasound and transcranial Doppler ultrasound, which have the potential to support the strain findings, are also studied. Experimental methods to characterize the high-frequency acoustic properties of a tissue-mimicking reference phantom are shown to be effective. The reference phantom is used to create 3D integrated backscatter coefficient images of excised carotid plaques. Transcranial Doppler is studied as method to detect intracranial microemboli and blood flow-dynamics.

Initial results from patients imaged prior to endarterectomy suggest that strain imaging detects conditions that are traditionally considered high risk including soft plaque composition, unstable morphology, abnormal hemodynamics, and shear of plaque against tethering tissue that can be exacerbated by neoangiogenesis. Non-invasive carotid strain imaging is a potentially useful tool for detecting unstable carotid plaque.

**Contents**

**Abstract**

**Acknowledgements**

**Contents**

**List of Figures**

**List of Tables**

**Chapter 1 : Objectives 1**

* 1. Research Statement 1
  2. Organization of the Dissertation 1

**Chapter 2 : Human Health Significance 3**

2.1 Etiology of stroke and the role of atherosclerotic plaque 3

2.2 Clinical carotid ultrasound and plaque characterization 7

2.2.1 Vulnerable plaque 7

2.2.2 Plaque characterization with other methods and imaging modalities 10

2.2.3 Plaque characterization with diagnostic ultrasound 16

2.3 References 32

**Chapter 3 : Recursive Bayesian Regularization Applied to Ultrasound Strain Imaging 49**

3.1 Improvement of strain image quality with regularization 50

3.2 Prior efforts in regularization 52

3.3 Recursive Bayesian regularization 56

3.3.1 Algorithm 57

3.3.1 Implementation 60

3.4 Experimental methods and results 62

3.4.1 Uniform strain simulations and phantoms 62

3.4.2 Circular inclusion simulations and phantoms 65

3.4.3 Optimal SRS 70

3.4.4 Addressing a carotid reverberation 73

3.4.5 Improvement of a liver ablation 79

3.5 Discussion 82

3.6 Summary 85

3.7 References 87

**Chapter 4 : Unbiased Subsample Displacement Interpolation 90**

4.1 Previously explored methods for subsample tracking 90

4.1.1 Methods that use properties of cross-correlation 91

4.1.2 Parametric and non-parametric methods 92

4.2 2D sinc interpolation with numerical optimization 94

4.3 Numerical properties of 2D sinc interpolation 95

4.3.1 Motion tracking algorithm used in testing 96

4.3.2 Tissue-mimicking phantom 97

4.3.3 Ultrasound mechanics simulation 98

4.3.4 Behavior of optimization methods 98

4.4 Applications of this method 106

4.5 References 108

**Chapter 5 : Calculating Strain From Displacement 111**

5.1 The strain tensor 111

5.1.1 Mechanical model 111

5.1.2 Application in ultrasound 126

5.2 Methods for estimating strain from displacement 130

5.2.1 Finite difference based methods 134

5.2.2 Derivative of Gaussian 139

5.2.3 A modified least-squares strain estimator 140

5.2.4 B-spline fitting 145

5.3 Useful quantities derived from the strain tensor 147

5.3.1 Principal strains 147

5.3.2 Representation of the 2D strain tensor as an ellipse 148

5.3.3 Combination of normal strains and shear strain into a single strain index151

5.4 Generating accumulated strain from a time series 153

5.4.1 Dynamic frame skip 153

5.4.2 Eulerian approach to accumulated strain 156

5.5 References 159

**Chapter 6 : High Frequency Phantom Characterization 163**

6.1 Tissue-mimicking phantoms 164

6.2 Attenuation characterization 165

6.3 Phase velocity characterization 175

6.4 Absolute backscatter estimation 179

6.4.1 Generation of spectra 180

6.4.2 Faran scattering model 185

6.4.3 Backscatter coefficient results 186

6.5 References 190

**Chapter 7 : High-frequency Plaque Characterization 192**

7.1 Creation of parametric images of excised plaque 192

7.2. B-Mode image creation 195

7.3 3D high frequency plaque volumes 191

7.4 References 206

**Chapter 8 : Transcranial Doppler Monitoring of the Middle Cerebral Artery 207**

8.1 Physiological insights from transcranial Doppler 207

8.2. Methods to increase robustness of unstable data 209

8.2.1 Examination room protocol 209

8.2.1 Retrospective inspection 211

8.3 Microemboli and peak velocity results 214

8.4 References 220

**Chapter 9 : *In vivo* Quantification of Carotid Plaque Strain 222**

9.1 Hierarchical framework 222

9.1.1 Multi-level motion tracking 222

9.1.2 Search region refinement 225

9.1.3 Inter-level matching-block scaling 226

9.2 Displacement estimation 227

9.3 Strain estimation 230

9.4 Calculation of derived quantities 231

9.5 *In vivo* case studies 238

9.5.1 Hypoechoic plaque with high strain 238

9.5.2 Importance of morphology 240

9.5.3 Strain with turbulent flow 242

9.5.4 Strain at the plaque-adventitia interface 244

9.5.5 Calcified plaque with shadowing 246

9.5.6 Artifact from out-of-plane motion 248

9.6 References 251

**Chapter 10 : Conclusion 254**

10.1 Summary 254

10.2 Future Work 256

**Appendix A : High-frequency 3D Data Analysis 258**

A.1 Collection and analysis of 3D RF data 258

A.1.1 VisualSonics Vevo 770 system 258

A.1.2 File storage and metadata extraction 261

A.1.3 Scan conversion and volume concatenation 266

A.1.4 Data streaming. 269

A.2 References 272

**Appendix B : In vivo Plaque Strain Estimates 273**

**List of Figures**

Fig. 3.1 *SNRe* for different regularization methods. 64

Fig. 3.2 Phantom axial strain images for different regularization methods. 67

Fig. 3.3 Simulation axial strain images for different regularization methods. 68

Fig. 3.4 Inclusion MARD for different regularization methods. 69

Fig. 3.5 Error measure versus SRS. 71

Fig. 3.6 SRS variation with algorithm parameters. 72

Fig. 3.7 Matching-block and search region in a carotid B-Mode. 74

Fig. 3.8 Probability image for the matching kernel’s displacement. 75

Fig. 3.9 Carotid ROI at iteration 0. 76

Fig. 3.10 Carotid ROI at iteration 1. 76

Fig. 3.11 Carotid ROI at iteration 2. 77

Fig. 3.12 Carotid ROI at iteration 3. 77

Fig. 3.13 Carotid axial strain for different regularization methods. 79

Fig. 3.14 Liver ablation axial strain for different regularization methods. 81

Fig. 4.1 *SNRe* performance of subsample interpolation methods. 100

Fig. 4.2 Subsample interpolation methods on axial inclusion strain image. 102

Fig. 4.3 Sinc window type and lateral *SNRe*. 103

Fig. 4.4 Sinc window radius and lateral *SNRe.* 104

Fig. 4.5 Convergence verse initial simplex offset. 105

Fig. 5.1 Solid body displacement. 112

Fig. 5.2 Solid body segment displacement. 113

Fig. 5.3 Solid body two differential segments. 115

Fig. 5.4 Solid body change in inner product. 118

Fig. 5.5 Solid body segments orthogonal in the reference configuration. 119

Fig. 5.6 Solid body identical segments in the deformed configuration. 124

Fig. 5.7 Diagnostic linear ultrasound array. 128

Fig. 5.8 Mechanical model of cylindrical inclusion. 131

Fig. 5.9 Inclusion ideal input displacements. 132

Fig. 5.10 Inclusion ideal input strain. 132

Fig. 5.11 Inclusion Pre- and post-deformation RF images. 133

Fig. 5.12 Inclusion tracked displacements. 134

Fig. 5.13 Inclusion central difference strains. 135

Fig. 5.14 Inclusion higher-order accurate strain. 138

Fig. 5.15 Inclusion derivative of Gaussian strain. 140

Fig. 5.16 Inclusion strain linear least-squares strain. 142

Fig. 5.17 Discontinuity in carotid displacement. 143

Fig. 5.18 Modified linear least-squares and carotid displacement discontinuity. 144

Fig. 5.19 Inclusion B-spline strains. 146

Fig. 5.20 Inclusion strain tensor ellipses. 151

Fig. 5.21 Dynamic frame skip. 155

Fig. 5.22 Mesh warping. 158

Fig. 6.1 Phantom glass bead size distributions. 165

Fig. 6.2 High-frequency narrowband substitution apparatus. 166

Fig. 6.3 Substitution method transducers’ impulse responses. 168

Fig. 6.4 Narrowband waveform averaging. 169

Fig. 6.5 Narrowband waveform amplitudes changes with frequency. 170

Fig. 6.6 Narrowband spectrogram. 171

Fig. 6.7 Saran transmission coefficient changes with frequency. 173

Fig. 6.8 High-frequency attenuation coefficients. 175

Fig. 6.9 Velocity delay locations. 178

Fig. 6.10 5000E phase velocity vs. frequency. 179

Fig. 6.11 Phantom and reflector power spectra. 181

Fig. 6.12 Reflector spectrum harmonics. 182

Fig. 6.13 Phantom and reflector waveforms. 184

Fig. 6.14 Vevo 770 Digital-RF mode screenshots. 184

Fig. 6.15 Absolute backscatter coefficients. 187

Fig. 7.1 High-frequency plaque scanning apparatus. 193

Fig. 7.2 RF signal and its envelope. 195

Fig. 7.3 Subject 142 gross pathology and 3D ultrasound. 198

Fig. 7.4 Subject 144 gross pathology and 3D ultrasound. 199

Fig. 7.5 Subject 154 gross pathology and 3D ultrasound. 202

Fig. 7.6 Subject 158 gross pathology and 3D ultrasound. 203

Fig. 8.1 TCD velocity waveforms. 212

Fig. 8.2 Example content of Multidop-L2 *TX?* file. 213

Fig. 9.1 Scale-space images for multi-resolution motion tracking. 224

Fig. 9.2 Improvements in *SNRe* from inter-level matching-block scaling. 227

Fig. 9.3 Displacement estimation parameter configuration file. 228

Fig. 9.4 Strain estimation parameter configuration file. 231

Fig. 9.5 Subject 157 ROIs. 232

Fig. 9.6 Axial strain curves from Subject 157. 233

Fig. 9.7 Shear strain curves from Subject 157. 234

Fig. 9.8 Lateral strain curves from Subject 157. 234

Fig. 9.9 Strain metric curves from Subject 157. 237

Fig. 9.10 Hypoechoic plaque with high strain. 239

Fig. 9.11 Importance of morphology. 241

Fig. 9.12 Strain with turbulent flow 243

Fig. 9.13 Strain at the plaque-adventitia interface 245

Fig. 9.14 Calcified plaque with shadowing 247

Fig. 9.15 Artifact from out-of-plane motion 249

Fig. A.1 VisualSonics Vevo 770 251

Fig. A.2 Vevo 770 transducer and stepper motor. 260

Fig. A.3 Vevo 770 Digital-RF user interface. 262

Fig. A.4 Example data from a Vevo 770 .rdi file. 263

Fig. A.5 Transformation of header file into XML format. 265

Fig. A.6 Rendered html version of header file. 266

Fig. A.7 Vevo 770 transducer geometry. 268

Fig. A.8 Streaming of MRI images subject to an affine transform. 270

Fig. A.9 Peak memory usage when changing the number of frames per stream. 271

**List of Tables**

Table 4.1 Sinc window functions 94

Table 4.2 Interpolation times. 105

Table 5.1 Higher order accurate derivative coefficients. 138

Table 6.1 Phantom power law attenuation fits. 175

Table 6.1 Phantom phase velocities . 179

Table 8.1 TCD detected microemboli HITS per subject. 215

Table 8.2 MCA peak velocities. 216

Table 9.1 Downsampling schedule for multi-resolution image registration. 224

Table B.1 Maximum absolute principal strain estimates. 273

Table B.2 Maximum shear strain estimates. 277

Table B.3 Distortional energy estimates. 281

Table B.4 Total strain energy estimates. 284

Table B.5 Lateral strain estimates. 288

Table B.6 Shear strain estimates. 292

Table B.6 Axial strain estimates. 296