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1        **The Simulation of Magnetic Resonance Elastography through**  
2                                    **Atherosclerosis**

3        L. E. J. Thomas-Seale<sup>1\*</sup>, L. Hollis<sup>1</sup>, D. Klatt<sup>2</sup>, I. Sack<sup>2</sup>, N. Roberts<sup>3</sup>, P. Pankaj<sup>4</sup> and P. R.  
4                                    Hoskins<sup>1</sup>

5        <sup>1</sup>*Centre for Cardiovascular Science, University of Edinburgh, Queen’s Medical Research*  
6                                    *Institute, 47 Little France Crescent, Edinburgh, UK.*

7        <sup>2</sup>*Department of Radiology, Charité - Universitätsmedizin Berlin, Berlin, Germany*

8        <sup>3</sup>*Clinical Research Imaging Centre, University of Edinburgh, 47 Little France Crescent,*  
9                                    *Edinburgh, UK.*

10       <sup>4</sup>*School of Engineering, University of Edinburgh, Alexander Graham Bell Building, The*  
11                                   *King’s Buildings, Edinburgh, UK.*

12    \* *Corresponding Author*

13  
14    *Address: Department of Mechanical Engineering, School of Engineering, University of*  
15    *Birmingham, Edgbaston, Birmingham, B15 2TT*

16    *Email: Email: [l.e.j.thomas-seale@bham.ac.uk](mailto:l.e.j.thomas-seale@bham.ac.uk) / [lauren.ej.thomas.seale@gmail.com](mailto:lauren.ej.thomas.seale@gmail.com)*

17    *Phone: (+44) 0121 4143622 / (+44) 07841 515310*

18  
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20

21 **Abstract**

22 The clinical diagnosis of atherosclerosis via the measurement of stenosis size is widely  
23 acknowledged as an imperfect criterion. The vulnerability of an atherosclerotic plaque to  
24 rupture is associated with its mechanical properties. The potential to image these mechanical  
25 properties using magnetic resonance elastography (MRE) was investigated through synthetic  
26 datasets.

27 An image of the steady state wave propagation, equivalent to the first harmonic, can be  
28 extracted directly from finite element analysis. Inversion of this displacement data yields a  
29 map of the shear modulus, known as an elastogram. The variation of plaque composition,  
30 stenosis size, Gaussian noise, filter thresholds and excitation frequency were explored.

31 A decreasing mean shear modulus with an increasing lipid composition was identified  
32 through all stenosis sizes. However the inversion algorithm showed sensitivity to parameter  
33 variation leading to artefacts which disrupted both the elastograms and quantitative trends. As  
34 noise was increased up to a realistic level, the contrast was maintained between the fully  
35 fibrous and lipid plaques but lost between the interim compositions. Although incorporating a  
36 Butterworth filter improved the performance of the algorithm, restrictive filter thresholds  
37 resulted in a reduction of the sensitivity of the algorithm to composition and noise variation.  
38 Increasing the excitation frequency improved the techniques ability to image the magnitude  
39 of the shear modulus and identify a contrast between compositions.

40 In conclusion, whilst the technique has the potential to image the shear modulus of  
41 atherosclerotic plaques, future research will require the integration of a heterogeneous  
42 inversion algorithm.

43

## 44 **1. Introduction**

45 Cardiovascular diseases (CVD) were responsible for 31% of global mortalities in 2011  
46 (Mendis et al., 2011). The root cause of the majority these deaths was atherosclerosis (Go et  
47 al., 2014). The pathogenesis of atherosclerosis is complex. The primary manifestation of  
48 atherosclerosis is an accumulation of lipid in the vascular wall caused by endothelial  
49 dysfunction (VanEpps and Vorp, 2007). However factors such as inflammation and  
50 biomechanics play a crucial role in the development of the disease (Libby et al., 2002). The  
51 rupture of a plaque may be associated with severe clinical events such as heart attack and  
52 stroke. The severity of an atherosclerotic plaque and the decision to refer the patient for  
53 surgery is based upon symptoms of ischemia and a measurement of the reduction in lumen  
54 diameter, known as a stenosis (Packard and Libby, 2008).

55 The outcome of surgical intervention via carotid endarterectomy, underwent analysis in the  
56 North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European  
57 Carotid Surgery Trial (ECST). Rothwell et al. (2003) pooled this data and found an 18.7%  
58 absolute risk reduction, 5 years post-surgery, for stenoses between 70% and 99%. This  
59 statistic demonstrates that approximately 5 endarterectomies are required to prevent the death  
60 or stroke of 1 patient. The economic burden of CVD is estimated to be \$315 billion in the  
61 USA and £19 billion in the UK (Townsend et al., 2012; Go et al., 2014).

62 A plaques vulnerability to rupture is associated with a number of factors including the size  
63 and consistency of the lipid pool, the thickness and mechanical properties of the fibrous cap,  
64 inflammation and fatigue in the fibrous cap (Falk et al., 1995). Research is focussed on more  
65 definitive diagnostic techniques including, imaging of the plaque composition (Corti and  
66 Fuster, 2011), molecular imaging (Mulder et al., 2014), imaging the tissue stiffness (De Korte  
67 et al., 2011) and imaging plaque stresses, known as patient specific modelling (Hoskins and  
68 Hardman, 2009).

69 Elastography is the overarching term given to elasticity imaging, using a combination of  
70 techniques to mechanically excite the tissue and modalities to image the response (Sarvazyan  
71 et al., 2011). An inversion algorithm is required to invert an image of displacement into an  
72 elastogram of the mechanical properties. Magnetic resonance elastography images the  
73 propagation of harmonic, low frequency, mechanical shear waves (Muthupillai et al., 1995).  
74 Arterial wall stiffness has been extracted using the Moens-Korteweg equation (Woodrum et  
75 al., 2006) and been applied to ex-vivo porcine aortas (Woodrum et al., 2009; Xu et al., 2012)  
76 and in-vivo abdominal aortas (Xu et al., 2013). The phase gradient inversion has identified  
77 changes in hypertensive aortic stiffness (Kolipaka et al., 2012). The local frequency  
78 estimation inversion has measured the relationship between aortic stiffness and age  
79 (Damughatla et al., 2015; Kenyhercz et al., 2015). The regional changes in shear modulus  
80 through ex-vivo porcine aortas have been measured by Zhang et al. (2016). Other studies  
81 have utilised interference elastography to visualise waves in the femoral artery (Zheng et al.,  
82 2007) and Fourier decomposed wave reflections to assess stenosis sizes in arterial phantoms  
83 (Woodrum et al., 2006).

84 The use of finite element analysis (FEA) is common across the modalities of elastography. It  
85 is primarily used as a method of inversion and a selection of studies have used FEA to invert  
86 strain images through atherosclerosis (Franquet et al., 2013; Bertoglio et al., 2014). FEA has  
87 also been used to create synthetic data sets to assess inversion algorithms (Van Houten et al.,  
88 2001; Miller et al., 2015) and explore the sensitivity of technique parameters (Chen et al.,  
89 2005). Baldewsing et al. (2004) and Doherty et al. (2013) assessed the application of  
90 ultrasound elastography to atherosclerosis by varying the geometric and mechanical  
91 properties within finite element models.

92 Measuring arterial stiffness is well established (Parker, 2009), however the term ‘stiffness’ is  
93 used as an overarching term for arterial characteristics that change with response to age or

94 disease (Hamilton et al., 2007). Imaging the specific mechanical properties of arteries is far  
95 less wide-spread, the literature contains conflicting results (Barrett et al., 2009) and  
96 vasculature-specific experimental data is required (Holzapfel et al., 2014). The parameters of  
97 constitutive models for arterial tissue can be extracted using mechanical testing (Holzapfel et  
98 al., 2000; Holzapfel et al., 2005). The documentation of the viscoelastic properties of healthy  
99 and diseased human arterial tissue is extremely limited. The well cited studies by Loree et al.  
100 (1994) and Lee et al. (1991) document the dynamic analysis and viscoelastic properties from  
101 ex-vivo samples of the lipid pool and fibrous cap. Viscoelastic properties have been extracted  
102 from in-vivo pressure displacement data by Valdez-Jasso et al. (2011). In recent years  
103 ultrasound elastography has shown promising results in quantifying the mechanical properties  
104 of atherosclerotic plaques (De Korte et al., 2011).

105 A preliminary computational investigation into the variation of the MRE steady state shear  
106 wave response through atherosclerotic plaques was undertaken by Thomas-Seale et al.  
107 (2011). The aim of this paper is to investigate the potential for MRE to image the shear  
108 modulus of atherosclerotic plaques through synthetic datasets.

## 109 **2. Method**

### 110 **2.1 Finite Element Analysis**

111 A direct solution, steady state FEA (Abaqus/CAE, Dassault Systèmes Simulia Corp.,  
112 Providence, Rhode Island, USA) was applied to allow extraction of a complex wave image,  
113 analogous to the first harmonic of Fourier transformed experimental phase images.

114 The 3D geometry (Rhinoceros, McNeel, Seattle, Washington, USA) is displayed in Fig. 1 and  
115 Table 1. A plaque and vessel wall was embedded in a block of homogeneous tissue to  
116 replicate the transmission of shear waves in-vivo. The global axes and nomenclature are

117 depicted in Fig. 1a and 1b. The region of interest (ROI) is defined as the atherosclerotic  
118 plaque.

119 The dimensions of the plaque were based upon a cosine function (Eq. 1), the severity of the  
120 stenosis (Eq. 2) and 100% eccentricity (Eq. 3) (Ahmed and Giddens, 1983; Tang et al., 2004).

121 The nomenclature is displayed in Fig. 1 and defined as follows; radius  $R_0$ , healthy lumen  
122 diameter  $\phi_0$ , stenosis  $S$  and the diameter of the narrowest section  $\phi_s$ . At a distance  $z$  along  
123 the vessel, where  $z_1$  and  $z_2$  are both ends of the stenosis and  $R(z)$  is the radius of the vessel.

124 The eccentricity is defined as  $E_c$  and  $e$  is the distance between the centre point of the vessel  
125 and lumen.

$$R(z) = R_0 - SR_0 \{1 - \cos[2\pi(z - z_1)/(z_2 - z_1)]\}/2 \quad (1)$$

$$S = (\phi_0 - \phi_s)/\phi_0 \times 100\% \quad (2)$$

$$E_c = e/[(\phi_0 - \phi_s)/2] \times 100\% \quad (3)$$

126 The disease development was modelled by varying the stenosis size and incremental changes  
127 in the spherical lipid pool volume. The lipid pool sphere was absent for the fully fibrous and  
128 fully lipid plaque geometries. The fibrous cap was modelled as 0.25mm (Loree et al., 1992).

129 The geometry was meshed using hybrid and acoustic, linear, tetrahedron and hexahedron  
130 elements. The ROI was meshed using an element edge length of 0.5mm. Propagating away  
131 from the ROI the element edge length was gradually increased up to 2mm.

132 The blood was modelled as static and assigned acoustic properties (Hoskins, 2007). The soft  
133 tissues were modelled as isotropic, Hookean, viscoelastic materials with a density of  
134  $1047\text{kgm}^{-3}$  (Hoskins, 2010) and a Poisson's ratio of 0.5 (Fung, 1993). The viscoelasticity was  
135 represented by the dynamic shear modulus  $G$ ; composed of the storage  $G'$  and loss modulus  
136  $G''$  (Eq. 4). The dynamic modulus can be defined by the shear modulus  $\mu$ , shear viscosity  $\eta$   
137 and frequency  $\omega$  using a rheological model.

$$G(\omega) = G'(\omega) + iG''(\omega) \quad (4)$$

138 The viscoelastic properties of human arteries were taken from the most applicable research  
 139 available; these are summarised in Table 2. The material properties for the healthy and  
 140 diseased arterial wall, excluding the fibrous cap and lipid pool, were taken from the Neo-  
 141 Hookean hyperelastic model outlined by Holzapfel et al. (2002). This constitutive model  
 142 behaves like an elastic solid under small deformations (Bower, 2010). For these tissues the  
 143 viscoelasticity was modelled using the Voigt model (Eq. 5 - 7). The shear viscosity was fixed  
 144 at 80Pas (Valdez-Jasso et al., 2011).

$$G_{Voigt}(\omega) = \mu + i\omega\eta \quad (5)$$

$$G_{Voigt}'(\omega) = \mu \quad (6)$$

$$G_{Voigt}''(\omega) = \omega\eta \quad (7)$$

145 The surrounding tissue was given the viscoelastic properties of muscle (Klatt et al., 2010).  
 146 The values of the shear modulus and shear viscosity for the lipid pool and fibrous cap were  
 147 approximated by extrapolating the low frequency investigations of Loree et al. (1994), for a  
 148 0% cholesterol lipid, and Lee et al. (1991), for a cellular fibrous cap, into the frequency range  
 149 used in this study. The shear moduli of these extrapolated values are comparable to those  
 150 utilised by Holzapfel et al. (2002). The Maxwell model (Eq. 8 - 10) was used to represent the  
 151 viscoelastic behaviour of the surrounding tissue, fibrous cap and lipid pool, due to the  
 152 frequency dependence of the storage modulus demonstrated in the cited studies (Lee et al.,  
 153 1991; Loree et al., 1994; Klatt et al., 2010).

$$G_{Maxwell}(\omega) = \frac{i\omega\eta\mu}{\mu + i\omega\eta} \quad (8)$$

$$G_{Maxwell}'(\omega) = \frac{\omega^2\eta^2\mu}{\mu^2 + \omega^2\eta^2} \quad (9)$$



$$G_{Maxwell}''(\omega) = \frac{\omega\eta\mu^2}{\mu^2 + \omega^2\eta^2} \quad (10)$$

154 Equations (11) and (12) define the Voigt and Maxwell model in terms of the loss angle,  $\delta$ .  
 155 Under small oscillatory loads, the loss angle describes the response of a viscoelastic material.  
 156 The loss angle is defined as the arctangent of the loss to storage modulus (Fulcher et al.,  
 157 2009). When the stress and strain are in phase, the material response is purely elastic and the  
 158 loss angle is  $0^\circ$  (Barnes et al., 1989). When the stress and strain are out of phase, the material  
 159 response is purely viscous and the loss angle is  $90^\circ$  (Barnes et al., 1989).

$$\delta_{Voigt} = a \tan \frac{\omega\eta}{\mu} \quad (11)$$

$$\delta_{Maxwell} = a \tan \frac{\mu}{\omega\eta} \quad (12)$$

160 The Voigt model has shown a good correlation to in-vivo arterial pressure-area dynamics  
 161 (Valdez-Jasso et al., 2011). The storage modulus shows no dependence on excitation  
 162 frequency and the loss modulus increases with frequency. Hence the Voigt model  
 163 demonstrates an increasing loss angle with frequency, and the material response becomes  
 164 more viscous. The loss angle of the Maxwell model, as applied to the surrounding tissue,  
 165 lipid pool and fibrous cap, peaks at  $\omega = \mu/\eta$ . Above this frequency the decreasing loss  
 166 modulus dominates the loss angle and makes the tissue behave more elastically with  
 167 frequency.

168 The load nodes were isolated on the top surface of the model, shown in Fig. 1c. Harmonic,  
 169 shear wave excitation was simulated using a sinusoidal load of  $6 \times 10^{-4} \text{N}$ , applied parallel to  
 170 the Z axis. The excitation frequency was varied between 50Hz and 200Hz. Symmetric  
 171 boundary conditions were applied to the outer faces of the surrounding tissue, except the  
 172 loading surface.

## 173 2.2 Inversion Algorithm

174 The displacement was extracted using a pixel size of  $1\text{mm}^2$  through an imaging plane parallel  
175 to the X and Y axes. The displacement was averaged over a 2mm slice thickness, centred on  
176 the plaque, synonymous to an MRI voxel. Noise was added to the simulated data using the  
177 method outlined by Miller et al. (2015). The standard deviation of the signal  $\sigma_{signal}$ , was  
178 calculated using the real and imaginary wave amplitudes through the ROI. The distribution  
179 was modelled as Gaussian with a zero mean and standard deviation,  $\sigma_{noise}$ , derived by (Eq.  
180 13), where  $1\% \leq N \leq 20\%$ .

$$\sigma_{noise} = N\% \cdot \sigma_{signal} \quad (13)$$

181 The displacement data was inverted into an elastogram using the Helmholtz algorithm (Eq.  
182 14) (MATLAB R2011a, MathWorks, Natick, Massachusetts, USA). The derivation of this  
183 algorithm is described by Klatt et al. (2006). The dynamic shear modulus  $G(\omega)$ , was yielded  
184 by the Fourier transformed complex displacement  $U$ , wave excitation frequency  $\omega$  and  
185 tissue density  $\rho$ . The Laplacian,  $\nabla^2 U$ , was calculated from second order spatial derivatives  
186 (Eq. 15). The dynamic shear modulus may be expressed in terms of the shear modulus  $\mu$  and  
187 shear viscosity  $\eta$  using a rheological model. In this study the Voigt model was utilised (Eq.  
188 5).

$$G(\omega) = \frac{-\rho\omega^2 U}{\nabla^2 U} \quad (14)$$

$$\nabla^2 U = \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \quad (15)$$

189 A 2D Butterworth filter was used to suppress noise and compression wave components (Klatt  
190 et al., 2007; Clayton et al., 2011). The shear modulus formed the focus of this study; it is  
191 displayed in elastograms and as a spatially averaged value through the ROI using the mean of

192 20 noisy cycles. Unless explicitly stated the technique parameters were fixed at  $N = 2\%$  ,  
193 100Hz with filter thresholds of  $5\text{m}^{-1}$  and  $1000000\text{m}^{-1}$ .

### 194 **3. Results**

195 The wave images of Fig. 2 show that as the composition of the plaque become more lipid, the  
196 wave displacement through the low shear modulus material becomes visible. Although the  
197 geometry of the lipid pools can-not be identified in the elastograms, the decrease in the shear  
198 modulus can be seen through the stenosis as the lipid composition increases. The wave  
199 images of Fig. 3 display decreasing wavelengths and increasing attenuation with increasing  
200 frequency. The shear moduli through the elastograms increase with frequency. This  
201 observation is complemented by Fig. 4c.

202 All data sets in Fig. 4 show a contrast between the fully fibrous and lipid compositions. The  
203 magnitude of the mean shear modulus, the amount of contrast and the smoothness of the  
204 trend is degraded by the increase in noise. Figure 4a shows that at  $N = 2\%$  , and a frequency  
205 of 100Hz, there is a contrast between the incremental lipid volumes through all stenosis sizes.  
206 At  $N = 10\%$  and  $N = 20\%$  the fully fibrous compositions maintain a higher mean shear  
207 modulus than the fully lipid compositions, however the incremental decrease in contrast is  
208 lost. Table 3 omits the effects of filters and displays the raw shear modulus variation with  $N$   
209 and plaque composition. Both Table 3 and Fig. 4a show degradation in contrast between  
210 compositions with increasing noise. The predicted shear moduli are one or two orders of  
211 magnitude lower than the simulated shear moduli.

212 Figure 4b shows that the  $5\text{m}^{-1}$  to  $1000000\text{m}^{-1}$  and  $10\text{m}^{-1}$  to  $1000\text{m}^{-1}$  filter ranges improve the  
213 performance of the algorithm in terms of magnitudes and contrast between compositions. As  
214 the filter thresholds are narrowed to between  $15\text{m}^{-1}$  and  $500\text{m}^{-1}$ , the distinctive wave  
215 behaviour between compositions is over smoothed and the magnitudes and contrasts are

216 reduced. At the narrowest filter thresholds, similar to those found in experimental work (Klatt  
217 et al., 2007), the algorithm becomes insensitive to any variation in noise.

#### 218 **4. Discussion**

219 Harmonic wave propagation through an isotropic, homogeneous, incompressible, linear  
220 elastic medium in the absence of body forces can be described by the Helmholtz equation  
221 (Manduca et al., 2001). The limitations of the inversion algorithm are discussed in depth in  
222 (Barbone and Gokhale, 2004; Papazoglou et al., 2008). In this study, the discrete and noisy  
223 data through the heterogeneous application created artefacts, which can be seen in Fig. 2.

224 Through a homogeneous medium, harmonic wave propagation will lead to a displacement  
225 and Laplacian term of opposite polarity. With reference to Eq. (14), this generates a positive  
226 and thus real dynamic shear modulus. In discrete data the Laplacian is calculated from the  
227 second order spatial gradients, Eq. (15), using two pixels adjacent to the pixel of interest.  
228 Inhomogeneities through the medium, or step changes in the wave behaviour, change the  
229 magnitude of this second order derivative. This can lead to errors in the shear moduli. This  
230 exaggeration of gradients can be seen by comparing the visibly low level of noise in the wave  
231 images of Fig 2. to the pronounced noise through the corresponding elastograms. Most  
232 crucially, if the displacement and Laplacian are of the same polarity an impossible, negative  
233 dynamic shear modulus is yielded. This numerical limitation was demonstrated by Thomas-  
234 Seale (2015). In these cases the impossible values are equated to zero.

235 Along boundaries, similar artefacts can be identified as a line of over or underestimated  
236 pixels. Beyond the X axis edge of the elastogram, there is no information. This reduces the  
237 size of the Laplacian and creates an artefact of overestimated shear moduli. Since there is  
238 minimal wave propagation parallel to the Y axis, there are no gradients and therefore no  
239 artefacts adjacent to this edge. Along the edge of the lumen, there is an interface between the

240 blood and artery wall. Within 1mm there is also an interface between the artery wall and  
241 surrounding tissue. On the upper interface there is an underestimated artefact of two pixels  
242 deep. This is generated by the inflated spatial derivatives adjacent to the zero displacement of  
243 the blood. On the lower interface there are lines of both underestimated pixels and  
244 overestimated pixels. Observing the wave images of Fig. 2, the most pertinent difference  
245 between the wave intersecting the upper and lower interface is the phase. Figure 3 shows that  
246 the location of the zero pixel artefacts and the magnitude of the artefacts above and below the  
247 lumen, change with frequency. It can be concluded that these artefacts show a dependency on  
248 the phase of the wave. This reflection suggests that a multi-frequency inversion could  
249 alleviate the effect of these artefacts.

250 Figure 3 and 4c show an increase in shear modulus with frequency. MRE excitation  
251 frequency is strongly linked to resolution (Sinkus et al., 2000; Parker et al., 2005). The  
252 increase in technique resolution with excitation frequency can be identified by the emerging  
253 visibility of the lipid pool through the wave image at higher frequencies. As the wavelength  
254 decreases, the contrast and detectability of inclusions are increased. Only a fraction of the  
255 wave motion is captured within the plaque, therefore the algorithm can-not interpret the true  
256 shear modulus. At 200Hz the wave propagation below the lumen is highly attenuated and the  
257 amplitude oscillates around  $\pm 5\mu m$ . This low amplitude combined with a 2mm element edge  
258 and voxel of resolution  $1mm^2 \times 2mm$  generated a discretisation error which followed through  
259 to errors in the shear moduli.

260 The degradation of the results of Table 3 and Fig. 4a with increasing noise stems from the  
261 disruption in the clarity of the wave gradients and hence the ability of the algorithm to  
262 calculate the shear modulus. Noise, increases step changes in the wave displacement and  
263 hence exasperates the artefacts. This conclusion is supported by the increase in standard  
264 deviation with noise, relative to the mean, for the majority of compositions in Table 3.

265 The Butterworth filter smooths out noise and compression wave components. Under pure  
266 shear excitation, MRE through an incompressible medium allows compressional effects to be  
267 neglected (Mariappan et al., 2010). In this simulated study the only interference with the  
268 shear wave propagation are refracted and reflected waves, therefore noise was the dominant  
269 component to be filtered.

270 The juxtaposition between the fact that filters smooth the data and therefore improve the  
271 function of the inversion algorithm, and the fact the essence of this study lies in identifying  
272 the difference in wave behaviour between the heterogeneous compositions, results in an  
273 oxymoron. Thomas-Seale (2015) varied the thresholds through their full range and concluded  
274 that over filtering of the wave images, through this heterogeneous application, can manipulate  
275 the results. The filter thresholds could be optimised to this application and each frequency,  
276 however even under these idealised conditions, the inversion algorithm is ill-suited to this  
277 highly heterogeneous application. Attempting to improve its function by filtering also  
278 smooths the essential contrast between compositions; this is shown in Fig. 4b.

279 The Helmholtz inversion algorithm has shown extreme sensitivity throughout this  
280 application. The location, presentation and severity of artefacts have demonstrated a  
281 dependence on noise, inhomogenities and excitation frequency. This has created a level of  
282 unpredictability in the analysis seen by the artefacts in the elastograms and sporadic high and  
283 low values throughout the quantitative trends. In Fig. 4c, this is noticeable through the  
284 200Hz, maximum noise analysis due to the combination of high noise and large gradients. In  
285 conclusion, although this technique shows promise, identifying accurate mechanical  
286 properties and contrast between plaque compositions hinges on developing a more applicable,  
287 heterogeneous inversion algorithm.

288 This research, has allowed assessment of the technique and identification of the areas that  
289 require development. However the idealised nature of the study is limiting. It has focussed on

290 a system with simplified parameters and has neglected the wave interaction with surrounding  
291 organs and the cardiac cycle. The Voigt and Maxwell models are arguably not sophisticated  
292 enough to fully describe the mechanical behaviour of arterial tissue and they are also not  
293 ideal under wide frequency ranges (Yasar et al., 2013). The voxel resolution in this study was  
294 idealised. Experimentally, an increase in resolution results in a decrease of signal to noise  
295 ratio (McRobbie, 2007), therefore increasing the resolution will compound the limitations  
296 seen in this research. This study has neglected the stiffness created by the shape of the ROI.  
297 There is potential here to develop an inversion algorithm that is more applicable to the  
298 cylindrical form of arterial structures. This concept has been broached in the work of  
299 Kolipaka et al. (2009) through bounded media. Realistic methods of extracting and modelling  
300 noise vary throughout MRE literature (Papazoglou et al., 2008; McGee et al., 2011). The  
301 limitation of the method applied in this research (Miller et al., 2015), is that the standard  
302 deviation, and hence noise level, changes with composition and frequency.

## 303 **5. Conclusion**

304 Simulated MRE through atherosclerotic plaques has allowed preliminary analysis of the  
305 technique. A contrast between plaque composition and size was identified through the mean  
306 shear modulus. However the inversion algorithm was sensitive to parameter variation and  
307 constrained by the limitations of the discrete, noisy and heterogeneous data in this study.  
308 Whilst filtering improved its accuracy, narrow filter thresholds also reduced the essential  
309 contrast between the compositions. An increase in frequency, improved the resolution of the  
310 technique in terms of magnitude and contrast. An inversion algorithm applicable to  
311 heterogeneous tissue is required to continue this research.

312

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315

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317



318 **Conflict of Interest Statement**

319 There are no personal or financial conflicts of interest associated with this study.

320

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519 **List of Tables**

520 **Table 1.** The geometric parameters of the surrounding tissue, arterial wall and atherosclerotic  
521 plaque components. The values are taken from the following references \*(Schulze-Bauer et  
522 al., 2003) and \*\*(Loree et al., 1992). (*1 Column*)

523 **Table 2.** The material properties of the surrounding tissue, arterial wall, atherosclerotic  
524 plaque components and blood. The values are taken from the following references \*(Hoskins,  
525 2010), \*\*(Klatt et al., 2010), +(Holzapfel et al., 2002), ++(Valdez-Jasso et al., 2011), #(Lee et  
526 al., 1991), ##(Loree et al., 1994), ^(Hoskins, 2007). (*1 Column*)

527 **Table 3.** The mean predicted shear modulus through an 80% stenosis with variations in  
528 composition and Gaussian noise. (*1.5 Columns*)

529

530



531 **List of Figures**

532 **Figure 1.** The simulation geometry of the 70% stenosis plaque with a 30mm<sup>3</sup> lipid pool and  
533 0.25mm fibrous cap: (a) the longitudinal cross sectional view through the plaque, (b) the axial  
534 cross sectional view through the plaque and (c) the full model geometry, global axes, mesh  
535 and load nodes. *(1.5 Columns)*

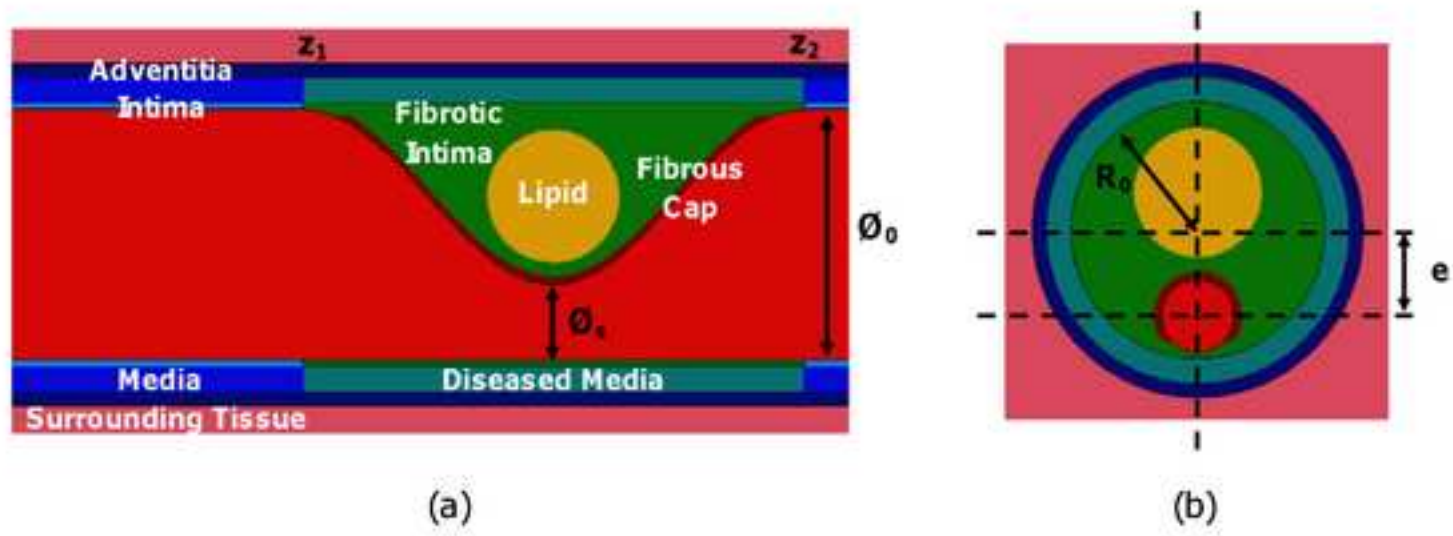
536 **Figure 2.** The real components of the complex wave images and shear modulus elastograms  
537 through an 80% stenosis with plaque compositions as follows; fully fibrous, a 20mm<sup>3</sup> lipid  
538 pool (LP), a 40mm<sup>3</sup> lipid pool and fully lipid. *(1.5 Column)*

539 **Figure 3.** The real components of the complex wave images and shear modulus elastograms  
540 through an 80% stenosis with a 30mm<sup>3</sup> lipid pool composition, at excitation frequencies  
541 50Hz, 100Hz, 150Hz, and 200Hz. *(1.5 Column)*

542 **Figure 4.** The mean predicted shear modulus through an 80% stenosis with variations in  
543 composition, Gaussian noise and (a) stenosis, (b) filter thresholds and (c) excitation  
544 frequency. *(2 Columns)*

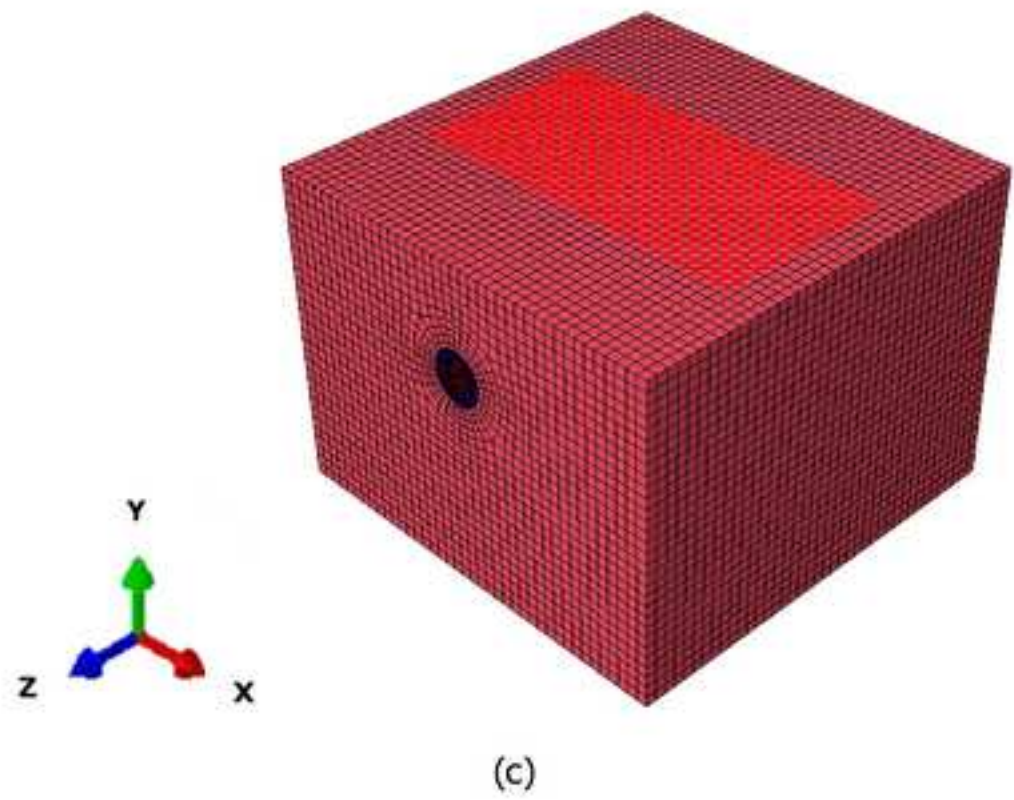
545

546



(a)

(b)



(c)

Figure 2 Rev. 2

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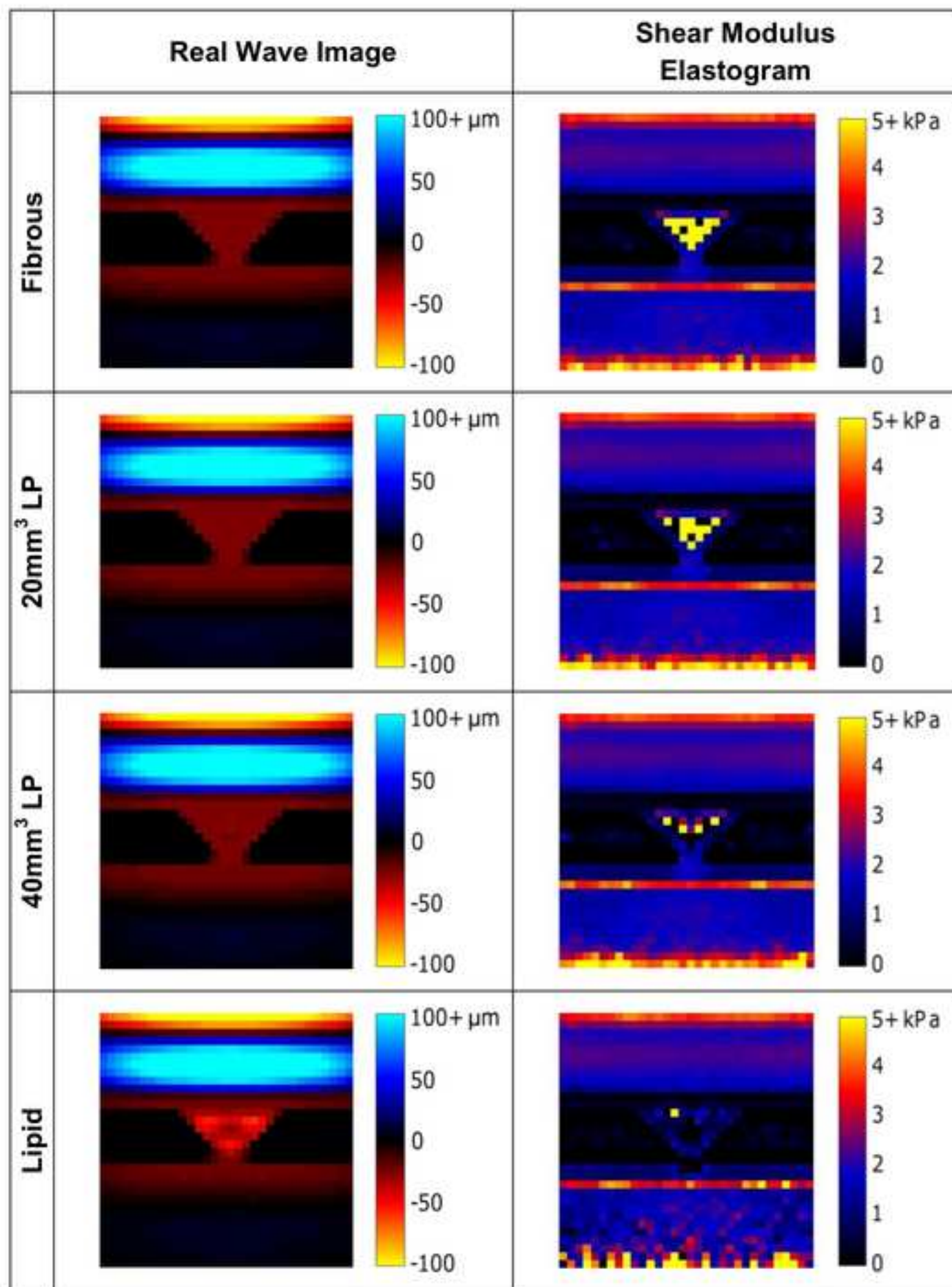


Figure 3 Rev. 2

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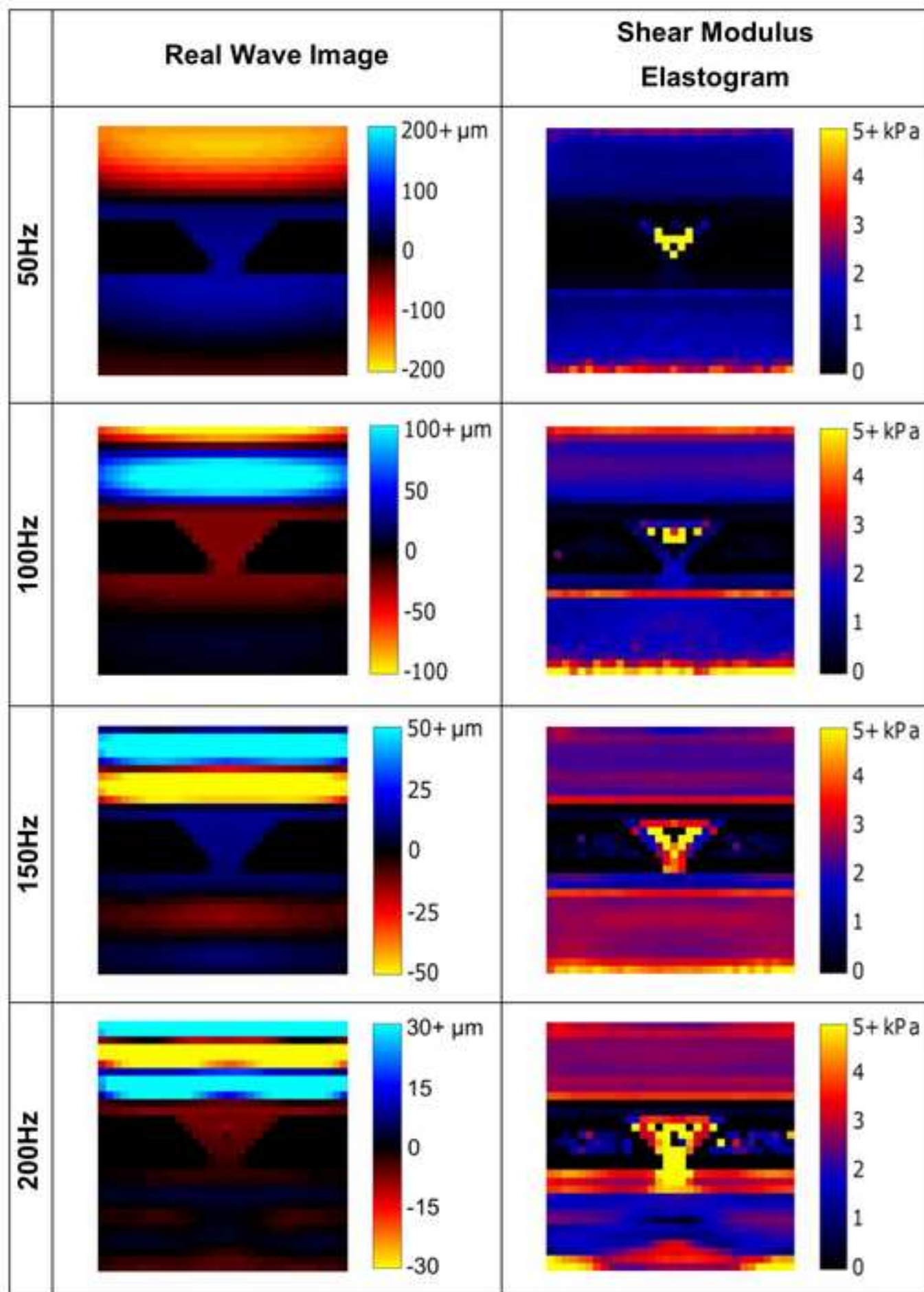
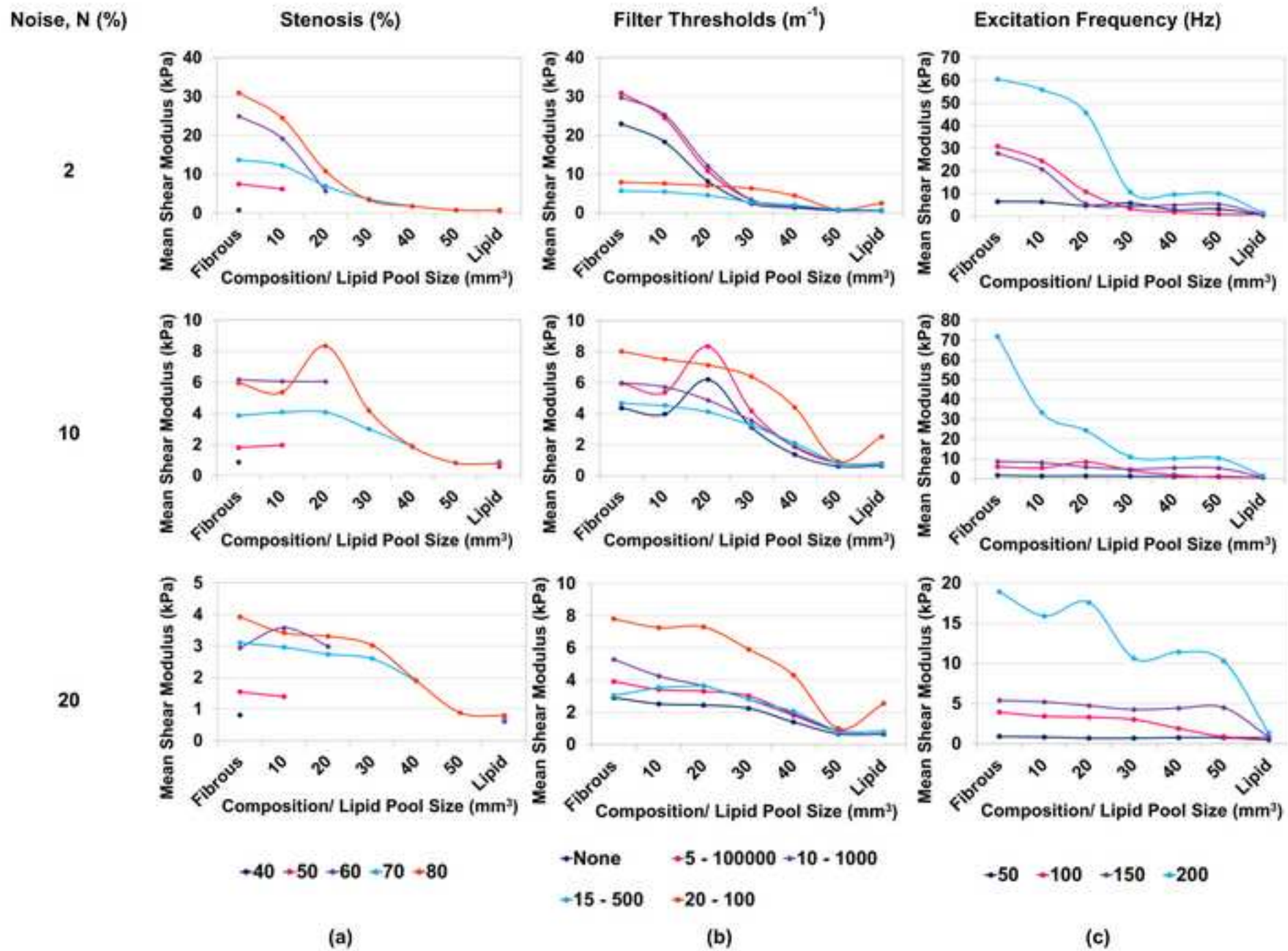


Figure 4 Rev. 2  
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<b>Tissue</b>	<b>Geometric Parameter</b>	<b>Value</b>
<b>Surrounding Tissue</b>	Length	80.00 mm
	Width	80.00 mm
	Depth	60.00 mm
<b>Stenosis</b>	Length	14.52 mm
<b>Intima</b>	Inner Radius	3.63 mm*
	Thickness	0.17 mm*
<b>Media</b>	Inner Radius	3.80 mm*
	Thickness	0.73 mm*
<b>Adventitia</b>	Inner Radius	4.53 mm*
	Thickness	0.43 mm*
<b>Fibrous Cap</b>	Thickness	0.25/0.5/0.75mm**
<b>Lipid Pool</b>	Volume	0/10/20/30/40/50/ Total mm <sup>3</sup>

<b>Tissue</b>	<b>Density (kgm<sup>-3</sup>)</b>	<b>Shear Modulus (kPa)</b>	<b>Bulk Modulus (kPa)</b>	<b>Shear Viscosity (Pas)</b>
<b>Surrounding Tissue</b>	1047*	2.3**	-	17.0**
<b>Intima</b>	1047*	150.0 <sup>+</sup>	-	80.0 <sup>++</sup>
<b>Fibrotic Intima</b>	1047*	221.0 <sup>+</sup>	-	80.0 <sup>++</sup>
<b>Media</b>	1047*	34.0 <sup>+</sup>	-	80.0 <sup>++</sup>
<b>Diseased Media</b>	1047*	757.0 <sup>+</sup>	-	80.0 <sup>++</sup>
<b>Adventitia</b>	1047*	50.0 <sup>+</sup>	-	80.0 <sup>++</sup>
<b>Fibrous Cap</b>	1047*	208.4 <sup>#</sup>	-	19820.0 <sup>#</sup>
<b>Lipid</b>	1047*	0.1 <sup>##</sup>	-	6.4 <sup>##</sup>
<b>Blood</b>	1060 <sup>^</sup>	-	2.67x10 <sup>6^</sup>	-

Table 3 Rev. 2

Noise, N (%)	Mean/Standard Deviation Predicted Shear Modulus (kPa)						
	Fibrous Plaque	Lipid Pool Volume					Lipid Plaque
		10mm <sup>3</sup>	20mm <sup>3</sup>	30mm <sup>3</sup>	40mm <sup>3</sup>	50mm <sup>3</sup>	
<b>Omitted</b>	30.9	29.9	5.2	2.4	1.3	0.6	0.6
<b>1</b>	30.1/5.0	22.5/2.4	9.0/4.5	2.4/0.1	1.3/0.0	0.6/0.0	0.6/0.0
<b>2</b>	23.0/4.3	18.3/3.7	8.2/3.4	2.4/0.2	1.3/0.0	0.6/0.0	0.6/0.0
<b>5</b>	7.3/2.3	9.6/5.7	5.8/2.6	3.0/1.2	1.3/0.0	0.6/0.0	0.6/0.0
<b>10</b>	4.4/0.8	4.0/0.8	6.2/5.3	3.1/1.6	1.4/0.1	0.6/0.0	0.6/0.1
<b>15</b>	3.2/1.1	3.7/1.1	3.1/1.6	2.1/0.4	1.4/0.3	0.6/0.1	0.7/0.2
<b>20</b>	2.9/1.0	2.5/0.7	2.4/0.7	2.2/0.6	1.4/0.2	0.7/0.1	0.6/0.1
<b>Mean Simulated Shear Modulus</b>	<b>219.6</b>	<b>190.2</b>	<b>172.9</b>	<b>158.5</b>	<b>145.5</b>	<b>133.6</b>	<b>23.1</b>



## **Conflict of Interest Statement**

There are no personal or financial conflicts of interest associated with this study.