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# The simulation of magnetic resonance elastography through atherosclerosis

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ABSTRACT

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

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

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

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



## 1. Introduction

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

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

A plaques vulnerability to rupture is associated with a number of factors including the size and consistency of the lipid pool, the thickness and mechanical properties of the fibrous cap, inflammation and fatigue in the fibrous cap (Falk et al., 1995). Research is focussed on more definitive diagnostic techniques including, imaging of the plaque composition (Corti and Fuster, 2011),

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molecular imaging (Mulder et al., 2014), imaging the tissue stiffness (De Korte et al., 2011) and imaging plaque stresses, known as patient specific modelling (Hoskins and Hardman, 2009).

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

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

Measuring arterial stiffness is well established (Parker, 2009), however the term ‘stiffness’ is used as an overarching term for arterial characteristics that change with response to age or disease (Hamilton et al., 2007). Imaging the specific mechanical properties of arteries is far less wide-spread, the literature contains conflicting results (Barrett et al., 2009) and vasculature-specific experimental data is required (Holzapfel et al., 2014). The parameters of constitutive models for arterial tissue can be extracted using mechanical testing (Holzapfel et al., 2000; Holzapfel et al., 2005). The documentation of the viscoelastic properties of healthy and diseased human arterial tissue is extremely limited. The well cited studies by Loree et al. (1994) and Lee et al. (1991) document the dynamic analysis and viscoelastic properties from ex-vivo samples of the lipid pool and fibrous cap. Viscoelastic properties have been extracted from in-vivo pressure displacement data by Valdez-Jasso et al. (2011). In recent years ultrasound elastography has shown promising results in quantifying the mechanical properties of atherosclerotic plaques (De Korte et al., 2011).

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

## 2. Method

### 2.1. Finite element analysis

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

The 3D geometry (Rhinoceros, McNeel, Seattle, Washington, USA) is displayed in Fig. 1 and Table 1. A plaque and vessel wall was embedded in a block of homogeneous tissue to replicate the transmission of shear waves in-vivo. The global axes and nomenclature are depicted in Fig. 1a and b. The region of interest (ROI) is defined as the atherosclerotic plaque.

The dimensions of the plaque were based upon a cosine function (Eq. (1)), the severity of the stenosis (Eq. (2)) and 100% eccentricity (Eq. (3)) (Ahmed and Giddens, 1983; Tang et al., 2004). The nomenclature is displayed in Fig. 1 and defined as follows; radius $R_0$, healthy lumen diameter $\phi_0$, stenosis $S$ and the diameter of the narrowest section $\phi_s$. At a distance $z$ along the vessel, where $z_1$ and $z_2$ are both ends of the stenosis, $R(z)$ is the radius of the vessel. The eccentricity is defined as $E_c$ and $e$ is the distance between the centre point of the vessel and lumen.

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

$$S = (\phi_0 - \phi_s)/\phi_0 \times 100\% \tag{2}$$

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

The disease development was modelled by varying the stenosis size and incremental changes in the spherical lipid pool volume. The lipid pool sphere was absent for the fully fibrous and fully lipid plaque geometries. The fibrous cap was modelled as 0.25 mm (Loree et al., 1992). The geometry was meshed using hybrid and acoustic, linear, tetrahedron and hexahedron elements. The ROI was meshed using an element edge length of 0.5 mm. Propagating away from the ROI the element edge length was gradually increased up to 2 mm.

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

$$G(\omega) = G'(\omega) + iG''(\omega) \tag{4}$$

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

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

$$G'_{Voigt}(\omega) = \mu \tag{6}$$

$$G''_{Voigt}(\omega) = \omega\eta \tag{7}$$

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

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

$$G'_{Maxwell}(\omega) = \frac{\omega^2\eta^2\mu}{\mu^2 + \omega^2\eta^2} \tag{9}$$

$$G''_{Maxwell}(\omega) = \frac{\omega\eta\mu^2}{\mu^2 + \omega^2\eta^2} \tag{10}$$

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

$$\delta_{Voigt} = a\tan\frac{\omega\eta}{\mu} \tag{11}$$