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Relative identifiability of anisotropic properties from magnetic resonance elastography

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Abstract

Although magnetic resonance elastography (MRE) has been used to estimate isotropic stiffness in the heart, myocardium is known to have anisotropic properties. This study investigated the determinability of global transversely isotropic material parameters using MRE and finite element modeling (FEM). A FEM-based material parameter identification method, using a displacement matching objective function, was evaluated in a gel phantom and simulations of a left ventricular (LV) geometry with a histology-derived fiber field. Material parameter estimation was performed in the presence of Gaussian noise. Parameter sweeps were analyzed and characteristics of the Hessian matrix at the optimal solution were used to evaluate the determinability of each constitutive parameter. Four out of five material stiffness parameters (Young's moduli E_1 and E_3 , shear modulus G_{13} and damping coefficient s), which describe a transversely isotropic linear elastic material, were well determined from the MRE displacement field using an iterative FEM inversion method. However the remaining parameter, Poisson's ratio, was least identifiable. In conclusion, Young's moduli, shear moduli and damping can theoretically be well determined from MRE data, but Poisson's ratio is not as well determined and could be set to a reasonable value for biological tissue (close to 0.5).

Graphical abstract

Parameters which describe a transversely isotropic material are not equally identifiable from MRE displacement fields. This is shown using a finite element model update method, based on minimizing the differences between simulated and measured displacements, with simulated and experimental phantom MRE displacements. Identifiability was compared using quantitative measures calculated from the Hessian of the objective function. At the incompressible limit, Poisson's ratio is not identifiable. Additionally, fibre Young's modulus is less identifiable than the transverse Young's modulus and shear modulus.

Keywords

magnetic resonance elastography; finite element modelling; phantom imaging; parameter identifiability

1. Introduction

Myocardial stiffness is an important determinant of cardiac function, and significant increases in global stiffness are thought to be associated with diastolic heart failure [1]. The complex mechanisms that lead to an increase in myocardial stiffness are not well understood [2]. Myocardial stiffness is anisotropic with greatest stiffness in the myocyte (fiber) direction, intermediate stiffness transverse to the myocytes in the plane of the layer, and least stiffness orthogonal to the layers [3]. Animal models of heart failure show an increase in fibrosis and loss of tissue anisotropy in the left ventricular (LV) myocardium [4]. Patients with heart failure with preserved ejection fraction (HFPEF) present with impaired filling, possibly due to increased stiffness. However, myocardial stiffness is not widely measured clinically or in research studies due to the invasiveness of measurements. Typically, a catheter is required to record ventricular pressure boundary conditions, in order to estimate material parameters from finite element analysis (FEA) of deformation information obtained from imaging [5]. A non-invasive estimate of myocardial stiffness may therefore be useful to characterize cardiovascular disease, including HFPEF.

Magnetic resonance elastography (MRE) is a non-invasive technique to estimate stiffness of soft tissues [6]. MRE is a three stage process in which 1) non-invasive, external actuators are

used to generate acoustic distortional waves in the tissue [7], 2) the wave displacements are quantified using a phase-contrast gradient or spin-echo MRI sequence [8], and 3) the displacement information is converted into stiffness maps using an inversion algorithm [9]. MRE has previously been used to investigate the effective stiffness of myocardium at various points in the cardiac cycle without the need for catheterization [7, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. Many studies, however, assumed that the myocardium is infinite and isotropic, even though myocardium is known to have anisotropic material properties [3]. By assuming an infinite material, reflection and absorption of waves can be ignored which will affect the accuracy of stiffness estimates [20]. Anisotropic properties of tissue have also been studied, primarily in skeletal muscle [21, 22, 23, 24, 25], brain [26, 27, 28, 29] and phantoms, which include a magnetically-aligned fibrin gel, a gel with embedded spandex fibers, a PVA gel made anisotropic through freeze/stretch cycling, and chicken breasts [30, 31, 32, 33, 34] using MRE. In these studies, either two, three, or five parameters were estimated to describe the anisotropic material properties. Fiber directions were either assigned using rule-based methods or using diffusion tensor MRI (DTMRI). With the development of DTMRI to examine cardiac fiber architecture, fiber information can be used in conjunction with MRE displacements in order to assess the patient-specific anisotropic properties of cardiac tissue [19]. This method can then be applied to investigate the progression of HFPEF by comparing the anisotropic stiffness parameters at various points in the development of the disease in order to gain a better understanding of the structural changes that occur. This paper presents preliminary work towards the quantification of homogeneous anisotropic parameters in myocardium by integrating FEA with DTMRI fiber data and MRE displacement data.

An iterative FEA-MRE inversion method has been proposed previously [35, 36, 37, 38, 39, 40] to estimate isotropic material properties from elastography displacement data. Van Houten et al. [36, 38] developed a moving-subzone approach to measure heterogeneous material properties of breast tissue. FEA was also proposed as a method to estimate the global shear modulus of an isotropic phantom by modeling the contact and pressure between a pneumatic driver and phantom surface [41]. In another study, patient-specific finite element models of the lower leg were used to simulate elastography using a transient modal dynamic analysis [42]. Related to the heart, a method for simulating ultrasound elastography using FEM has been previously presented [43].

Our proposed methodology builds upon these FEA methods by using displacements from MRE as boundary conditions along with the true geometry and fiber architecture of the heart. We diverge from these previous studies by investigating the relative identifiability of each material parameter, in order to provide some confidence in the ability of iterative FEM inversion methods to accurately predict individual material parameters and to determine whether this is a well-posed inverse problem for which all material parameters can be uniquely determined. By incorporating data from three MR imaging modalities, cine SSFP, phase-contrast MRE, and DTMRI, this method aims to avoid assumptions of an infinite medium and material isotropy, in order to accurately model the geometry and mechanics of the heart during MRE and subsequently identify anisotropic material properties. The method was tested with a simulated anisotropic model of the LV, and with MRE phase-contrast images obtained from a gel phantom.

This work supersedes and substantially extends our limited preliminary studies which were reported in a conference proceeding [44]. Specifically, this paper reports the following developments: 1) MRE phantom validation experiment; 2) extended methods to estimate all transversely isotropic material parameters, 3) substantially developed simulations using realistic ground truth material parameters, and examining identifiability over a physiological range of Poisson's ratio; 4) extensively developed validation experiments for identifiability in the LV geometry with a wide range of parameter initializations; 5) quantitatively evaluated the relative identifiability of the material parameters; and 6) substantially extended conclusions.

2. Methods

2.1. Finite Element Equations of Motion

The direct steady-state dynamic analysis procedure in Abaqus 6.13 (Dassault Systèmes Simulia Corp., Providence, USA) was used to simulate MRE displacements. This is a perturbation procedure in which the response of a model to an applied harmonic load is calculated about the base state. The result is a set of complex harmonic nodal displacements, $\mathbf{u}^*$. The equation of motion is written as:

$$-\omega^2 \mathbf{M} \mathbf{u}^* + i\omega \mathbf{C} \mathbf{u}^* + \mathbf{K} \mathbf{u}^* = \mathbf{P}^* \quad (1)$$

where $\mathbf{P}^*$ is the complex forcing term, $\mathbf{u}^*$ is the complex displacement, $\mathbf{M}$ is the mass matrix, $\mathbf{C}$ is the damping matrix and $\mathbf{K}$ is the stiffness matrix. $\mathbf{K}$ can also be described as the internal stress in the system, dependent on the material properties.

Structural damping was applied in order to provide a means of extracting energy from the model as would be expected for biological tissue. Structural damping forces are proportional to forces caused by stressing the structure and oppose the velocity. One common representation of structural damping is through a complex stiffness matrix ($\mathbf{K}^*$) involving a real component ($\mathbf{K}_S$) and an imaginary component ($\mathbf{K}_L = \omega \mathbf{C}$); the latter acts as a loss modulus, which accounts for damping.

$$\mathbf{K}^* = i\mathbf{K}_L + \mathbf{K}_S = \mathbf{K}_S(is + 1) \quad (2)$$

where s is the structural damping coefficient, which is the ratio of imaginary to real component of stiffness. Although s , like other material parameters, may vary spatially within the myocardium, it is assumed to be constant in this formulation. Equation 1 then becomes:

$$-\omega^2 \mathbf{M} \mathbf{u}^* + (is + 1)\mathbf{K}_S \mathbf{u}^* = \mathbf{P}^* \quad (3)$$

If there are no forcing terms present ($\mathbf{P}^*$), Equation 3 becomes:

$$(is + 1)\mathbf{K}_s \mathbf{u}^* = \omega^2 \mathbf{M} \mathbf{u}^* \quad (4)$$

which is equivalent to the wave equation, commonly written as:

$$\mu \nabla^2 \mathbf{u}^* + (\lambda + \mu) \nabla (\nabla \cdot \mathbf{u}^*) = \rho \omega^2 \mathbf{u}^* \quad (5)$$

The spatial derivative operators as well as the material properties are contained within the stiffness matrix, $\mathbf{K}_s$.

2.2. Material Model and Objective Function

Although myocardium is known to be an orthotropic material [3], secondary (sheet) and tertiary (sheet-normal) material orientations are difficult to determine using DTMRI [45] and there is currently controversy over whether material properties of myocardial laminae can be personalized [46]. Following many previous studies [5, 47, 48] we therefore used a transversely isotropic material model to describe the material behavior of myocardium. Five parameters are needed to define a transversely isotropic response: elastic parameters $E_1 (= E_2)$, E_3 , $G_{13} (= G_{23})$, and Poisson's ratios ν_{12} and $\nu_{13} (= \nu_{23})$, assuming a fiber direction aligned with the $[0\ 0\ 1]_T$ axis.

In nearly incompressible materials, the Poisson's ratio in the isotropic plane, ν_{12} , is related to the Poisson's ratio describing the fiber direction, ν_{13} , by $\nu_{12} = 1 - \nu_{13}$. Since biological tissue is nearly incompressible, this constraint was utilised, thereby reducing the number of parameters to four. The Poisson's ratios in the transverse-fiber directions (1–3, 2–3) are related to the Young's moduli and the Poisson's ratio in the fiber-transverse direction according to the following equation [49]:

$$\frac{\nu_{ij}}{E_i} = \frac{\nu_{ji}}{E_j} \quad (6)$$

In this study, the structural damping coefficient (s) was included in the parameters to be identified since it has been shown that omitting damping in elastography inversions can result in estimation errors up to 25% (at 67.5 Hz) [35]. Many studies set a value for Poisson's ratio under the assumption that any error in Poisson's ratio will not affect the shear modulus significantly since the longitudinal wavelength (affected by Poisson's ratio) is much longer than the shear wavelength [50, 34, 25]. However, other studies suggest that even small changes in Poisson's ratio near the incompressible limit can result in large deviations in stress within the material [51]. Therefore, five parameters were investigated in this study: s , E_1 , E_3 , G_{13} and ν_{31} .

The objective function to be minimized, $\%RMSE(u^*)$ was calculated as the root mean square of the Euclidean distances between nodal displacements generated from model predictions based on the use of the estimated parameters and ground truth displacements

generated from either the predictions based on the reference parameters, or from the MRE phantom data, and expressed as a percentage of the root mean squared ground truth displacement.

$$\% RMSE(u^*) = \frac{\sqrt{\frac{1}{3N} \sum \sum^{x,y,z} (u_{GT}^* - u_S^*)^2}}{\sqrt{\frac{1}{3N} \sum \sum^{x,y,z} (u_{GT}^*)^2}} \quad (7)$$

where subscripts S and GT denote the simulated and ground truth displacements, respectively; and N denotes the number of nodes. In all of the models, only the internal nodes, which were not subjected to displacement boundary constraints, were used to calculate the objective function.

2.3. Optimization Algorithm

An optimization algorithm, `fmin-cobyla`, provided in the Scipy optimization package of Python, was used to optimize the material parameters by minimising Equation 7. This is a nonlinearly constrained optimization that does not require knowledge of derivatives [52]. Each iteration forms a linear approximation to the objective and constraint functions by interpolation at the vertices of a simplex.

Due to the difference in the scale of parameters, particularly between the Young's moduli (~ 10) and Poisson's ratio (~ 0.5), parameters were linearly scaled prior to optimization so that a uniform initial step size could be used for each. The scaled initial parameter values were: $[100 \cdot s, E_1, E_3, G_{13} \text{ and } 1000 \cdot \nu_{31}]$ and an initial step size of 2 was used. The optimization finished when the trust region radius was smaller than $1e-2$ [53]. The same optimization algorithm and scaled parameters were used to determine the material properties of the phantom model from the displacement field obtained from the MRE experiment.

2.4. Phantom Experiment

A gradient-recalled echo MRE sequence [54] was used to collect wave images of a PVC cylindrical gel phantom using a 3T MR scanner (Tim Trio, Siemens Healthcare, Erlangen, Germany) with gradients of 27 mT/m (2.7 G/cm) and a slew rate of 164 μs (TR = 25 ms, TE = 21.27 ms). A pneumatic driver system (Resoundant Inc., Rochester, MN) was used to apply a harmonic load to the phantom at 60 Hz. Phase-contrast images (native resolution = 128×64 voxels, reconstructed resolution = 256×256 voxels) were collected at 16 longitudinal locations in the mid-region of the phantom. At each location, three images were collected that encode phase in three orthogonal directions. The timing of the pneumatic driver was triggered by the timing of the motion encoding gradient to collect four different phase offsets. Each phase image collected is known as a wave image and is equivalent to imaging the dynamic displacement at one instant in time. A discrete Fourier transform was used to fit a sinusoid to the four phase offsets (Figure 1), at each pixel.

This was converted to a complex displacement d (μm) by the following equation:

$$d = \left(\frac{A}{2048} \right) \pi \cdot MENC \quad (8)$$

where MENC is the motion-encoding coefficient in units of $\mu\text{m}/\text{rad}$ and A is the first harmonic resulting from the discrete Fourier transform. The MENC value for the experiments was $13.3 \mu\text{m}/\text{rad}$. The resulting complex displacement image contained masked real and imaginary displacement values for each slice in each orthogonal direction (x, y and z).

The finite element model represented the geometry of the imaged portion of a cylindrical phantom with a radius of 76.2 mm and a height of 80 mm (16 slices, with 5 mm slice thickness). The model of the phantom consisted of 30,954 nodes and 28,280 hexahedral elements. Image data, which has a higher in plane resolution than the FE model, were interpolated at finite element nodes using a cubic-spline interpolation. The interpolated displacements at the bottom and side surfaces were used as boundary conditions in the finite element model. Both isotropic and transversely isotropic linear elastic constitutive relations were used. In the isotropic model, only three parameters were estimated: ν , E and ρ . In the inversion utilising the transversely isotropic model, the resulting fiber and cross-fiber stiffnesses were expected to be the same.

2.5. Finite Element Modelling and Simulations

Vibration simulations were performed in an anatomically accurate canine LV geometry. The model contained 5490 nodes and 4320 first-order hexahedral hybrid elements. Hybrid elements solve for the pressure field independently of the displacements and aim to avoid volumetric locking in nearly incompressible materials. Physiologically realistic helical fibers [55] measured from histology were embedded using FE interpolation of nodal parameters. Fiber angles measured with respect to the short axis plane varied from approximately -60 degrees to $+60$ degrees transmurally from epicardium to endocardium, respectively. The epicardial basal nodes were fixed and a sinusoidal displacement with an amplitude of 0.2 mm at 80 Hz was prescribed at 41 epicardial nodes at the apex (Figure 2b).

A local orientation was defined within each element where the local $[0 \ 0 \ 1]_T$ axis was designated to be aligned with the fiber direction. Stiffness values were defined based on cardiac anisotropic shear moduli measured from ultrasound elastography [56] which were derived from mechanical shear waves between 100 – 400 Hz. Despite the difference in loading frequency from this study, values were comparable to anisotropic MRE measurements of skeletal muscle measured in [25] between 30 – 60 Hz. The fiber direction was assigned a Young's modulus (E_3) of 10.5 kPa, moduli in the transverse directions (E_1 , E_2) were set to 6.5 kPa and the fiber shear moduli (G_{13} , G_{23}) were set to 2.5 kPa. The structural damping coefficient was set to 0.1; the Poisson's ratio was set to 0.49999999; and a density of $1.06 \text{ g}/\text{cm}^3$ was assumed.

Gaussian noise was added to the real and imaginary components of the boundary displacements prior to estimation of the material parameters. Noise in MR images can be

adequately modelled as Gaussian, given that the signal-to-noise ratio is above 3 [57]. In the LV model, epicardial displacements from the ground truth case with added noise were prescribed on the outer surface. The Gaussian distribution of noise, added to the x, y and z components of displacement independently, had a mean of zero and a standard deviation computed as:

$$\sigma_{noise}^k = 15\% \cdot \sigma_{disp} \quad (9)$$

where σ_{disp} was the standard deviation of the ground truth displacement field. The scaling factor of 15% was chosen following other MRE simulation studies [58] which corresponds to an SNR of approximately five. A Monte-Carlo simulation was run (30 repeated simulations) with random Gaussian noise on the boundary conditions re-generated at each run. Initial estimates for the optimizations were randomly assigned from a normal distribution with the reference (or true) value as the mean and 20% of the reference parameter as the standard deviation, which was arbitrarily chosen. A second Monte-Carlo simulation was run in which the initial estimates were similarly varied except the Poisson's ratio was fixed ($\nu_{31} = 0.49999999$).

2.6. Determinability of Material Parameters

Three criteria were evaluated in order to assess the determinability of the material parameters from the Hessian matrix, $\mathbf{H}$, computed at the minimum of the objective function [59, 60].

D-Optimality Criterion—This is related to the volume of the indifference region, defined by the p-dimensional hyperellipsoid with size determined by the eigenvalues of the Hessian matrix. The area is called the indifference region since varying the material parameters within this region doesn't affect the error function significantly. Since this volume is inversely proportional to the determinant of the Hessian, a D-optimal design would maximize $\det(\mathbf{H})$.

Eccentricity Criterion—The eccentricity, or ratio of the longest to shortest axis of the ellipsoid describing the region of indifference, is a measure of the discrepancy between the least- and best-determined linear combination of parameters. The ratio of the largest eigenvalue to the smallest eigenvalue reflects the ellipsoidal eccentricity. An eccentric-optimal design would minimize $\text{cond}(\mathbf{H})$. Since the four parameters evaluated in this study are of different scales (by three orders of magnitude), the eccentricity criterion was evaluated from a Hessian computed using parameter vectors that were normalized to have equal magnitude, $\mathbf{H}_{norm}$.

M-Optimality Criterion—The third criterion relates to the interaction between material parameters. An ellipsoid axis, which lies at some angle with respect to parameter axes, indicates a correlation between parameters. Interaction between parameters is minimal when the determinant of the scaled Hessian matrix, $M = \det(\tilde{\mathbf{H}})$, is equal to one. The (i, j) entry of $\tilde{\mathbf{H}}$ can be written as:

$$\tilde{h}_{ij} = \frac{h_{ij}}{\sqrt{h_{ii}h_{jj}}} \quad (10)$$

where i and j range over the number of parameters in the optimization.

3. Results

3.1. Isotropic Phantom

The resulting material properties from the isotropic parameter estimation in the gel phantom were: $s = 0.10$, $E = 16.65$ kPa and $\nu = 0.4998$ (RMSE = 16.46%). Figure 3 shows the objective function plots from the parameter sweep for phantom model. The objective function shows a clear minimum in the Young's Modulus (E) but large valleys along the Poisson's ratio and structural damping directions.

The D-optimality value ($\det(\mathbf{H})$) for identifiability was 1.028×10^{12} ; the eccentricity value ($\text{cond}(\mathbf{H}_{\text{norm}})$) was 26.19; and the M-optimality ($\det(\tilde{\mathbf{H}})$) value was 0.901. Since the parameters are largely independent ($\det(\tilde{\mathbf{H}})$ close to 1), the identifiability of each individual parameter can be associated with the eigenvalue corresponding to that parameter's eigenvector. There was a large difference between the identifiability of the Young's modulus compared to the structural damping coefficient and Poisson's ratio (Eccentricity > 1). The structural damping coefficient was least identifiable (eigenvalue = 1.027), followed by the Poisson's ratio (eigenvalue = 3.720), leaving Young's modulus as the most identifiable parameter (eigenvalue = 26.89).

3.2. Anisotropic Left Ventricular Simulation

Figure 4 shows the LV ground truth displacement maps and Figure 5 shows the objective function plots for the LV parameter sweep. Based on the Hessian at the minimum of the objective function for the LV parameter sweep, the D-optimality criterion ($\det(\mathbf{H})$) for identifiability was 6.730×10^{21} ; the eccentricity value ($\text{cond}(\mathbf{H}_{\text{norm}})$) was 256.34; and the M-optimality ($\det(\tilde{\mathbf{H}})$) value was 0.943. The parameters in order from least identifiable to most identifiable for the LV model were: ν_{12} , E_3 , s , G_{13} and E_1 . The eccentricity was very high indicating that there was a large discrepancy between the identifiability of the most identifiable parameter (E_1) and the least identifiable parameter (ν_{31}). The M-optimality value (0.943) close to one indicates weak dependence between parameters in the LV model.

Parameter values resulting from the 30 material parameter estimations with simulated noise were: $s = 0.118 \pm 0.011$, $E_1 = 6.555 \pm 0.214$ kPa, $E_3 = 10.459 \pm 1.014$ kPa, $G_{13} = 2.513 \pm 0.077$ kPa and $\nu_{31} = 0.464 \pm 0.053$. The optimization was then repeated while fixing Poisson's ratio and only s , E_1 , E_3 and G_{13} were estimated. The resulting parameters when Poisson's ratio was fixed were: $s = 0.120 \pm 0.015$, $E_1 = 6.538 \pm 0.054$ kPa, $E_3 = 11.027 \pm 0.628$ kPa and $G_{13} = 2.526 \pm 0.054$. Box plots in Figure 6 show the spread of identified parameters when Poisson's ratio was estimated and when it was fixed. The damping coefficient was consistently overestimated (true parameter = 0.1).

3.3. Anisotropic Estimation of the Isotropic Phantom

The anisotropic estimation process applied to the isotropic phantom displacements resulted in the following material parameter estimations: $s = 0.10$, $E_1 = 16.75$ kPa, $E_3 = 16.75$ kPa, $G_{13} = 5.65$ and $\nu_{31} = 0.50$ (RMSE = 16.20%). Figure 7 shows the objective function plots from the anisotropic parameter sweep for the model of the phantom. The plots of the surfaces of the objective function show clear minima in some but not all parameters. It is noticeable, simply from the existence of valleys in the objective function, that not all parameters are equally identifiable.

The D-optimality value ($\det(\mathbf{H})$) for identifiability was $3.521\text{e}12$; the eccentricity value ($\text{cond}(\mathbf{H}_{\text{norm}})$) was 77.82; and the M-optimality ($\det(\tilde{\mathbf{H}})$) value was 0.811. Since the phantom material was isotropic, there was interaction between the parameters E_1 and E_3 , which then resulted in the lower M-optimality value (<1). However, the eigenvectors showed little to no interaction between the Young's moduli, shear modulus and Poisson's ratio. The eigenvectors also showed slight interaction between the Young's moduli and the structural damping coefficient. The parameters in order from least to most identifiable (magnitude of eigenvalue) were: s , ν_{31} , E_3 , E_1 and G_{13} . The shear parameter was much more identifiable than all other parameters, since the eigenvalue was more than 25x greater than that of the next biggest eigenvalue (E_1).

4. Discussion and Conclusions

Myocardium is known to have anisotropic material properties, which has been shown to be important in the efficient mechanical performance of the heart [61]. Results from the LV simulations demonstrated the identifiability of fiber and cross-fiber material parameters based solely on the displacement field of a distortional wave as obtained in MRE.

High eccentricity values for the LV model and phantom indicate that some parameters were more identifiable than others. More specifically, from the eigenvectors and eigenvalues, the Poisson's ratio was the least identifiable parameter in the LV anisotropic inversion whereas the Young's modulus in the transverse direction (E_1) and the fiber shear modulus (G_{13}) were the most identifiable parameters. From the anisotropic parameter sweep of the phantom, the structural damping coefficient, s was the least identifiable parameter while G_{13} was the most identifiable. The lack of identifiability of the Poisson's ratio can be understood visually based on the large valley seen along the direction of the Poisson's ratio in the plots of the objective function from the parameter sweeps in Figure 3 and Figure 5. The valleys indicate that changing the Poisson's ratio close to 0.5 had little to no effect on the wave propagation in the simulated harmonic data. Additional experimental simulations were run (data not shown) where reference values of 0.4999 and 0.495 were chosen for Poisson's ratios. Around 0.4999, the Poisson's ratio was still not identifiable, indicated by a valley in the objective function and small associated eigenvalue. However, at $\nu = 0.495$, changes in Poisson's ratio had a greater effect on the wave propagation and, consequently, the objective function. However, since values of Poisson's ratio closer to 0.5 are more physiologically realistic, this paper investigated the identifiability of a value closer to 0.5.

For the LV model, the transversely isotropic material parameter estimations resulted in mean values close to the true parameters. Only the structural damping coefficient was systematically overestimated. This experiment validated the relative identifiability of the parameters shown by the parameter sweeps. The E_1 and G_{13} parameters were best identified, whereas E_3 showed larger variance (Figure 6). Using this optimization algorithm, ν_{31} was not well identified in the LV model.

For the phantom, the optimization of isotropic linear elastic parameters resulted in a damping coefficient of 0.10, Young's modulus of 16.65 kPa and Poisson's ratio of 0.4998. The shear modulus of the phantom had previously been measured to be 5.45 kPa using multi-model direct inversion (MMDI), an inversion algorithm used to calculate the isotropic shear modulus from MRE displacement maps [62]. Since the PVC gel phantom can be assumed to be isotropic, shear stiffness is related to Young's modulus by:

$$G_{12} = \frac{E_1}{2(1 + \nu)} \quad (11)$$

resulting in a MMDI Young's modulus of 16.35 ± 0.66 kPa. The Young's modulus determined through our FEA-MRE method differs from that determined from the MMDI method by 1.83%. The MMDI method uses direct inversion of the Helmholtz wave equation, which requires the calculation of high-order derivatives. The method also does not take into account the material damping, which could be one reason for the small discrepancy between the resulting Young's moduli.

Overall, this work indicates that using displacement data from MRE to identify the shear modulus and Young's moduli is a well-posed problem. However, the parameters are not equally identifiable. As well as providing information on the relative identifiability of anisotropic parameters from MRE displacement data, this method also provides a way of measuring global anisotropic properties in patient-specific models that does not assume an infinite medium or lack of wave reflections and attenuation. However, due to the lack of identifiability of a Poisson's ratio close 0.5, future studies should set a reasonable value and not optimize for this parameter.

Limitations of this study include the assumptions made in the constitutive equation. Although myocardium is known to be non-linearly hyperelastic under large deformations, linear elasticity is considered to be adequate in the current application, given the small strains induced by MRE (about 30 microns). In practice, MRE data can be acquired at different time points in the cardiac cycle in order to estimate the nonlinear variation in stiffness throughout the cycle. There is evidence that myocardium is fully orthotropic with different stiffnesses in fiber, cross-fiber, and laminar directions [3]. However, there is controversy about whether more than one family of laminae are present [63] and many groups have therefore employed transversely isotropic constitutive equations [5]. Since DTMRI measurement of secondary and tertiary material structure orientations is difficult [45], we restricted our analysis to transversely isotropic materials.

Another limitation of this model is the fact that the damping coefficient is considered isotropic. In one study [25] identifying three complex moduli (E_3^* , G_{12}^* and G_{13}^*) to describe a transversely isotropic material, the structural damping coefficient (also called the loss factor) was greater for the fiber shear (G_{13}) than for the shear in the isotropic plane (G_{12}), indicating that damping in skeletal muscle may be anisotropic. Future studies could include anisotropic damping. However, whether or not the damping coefficient provides clinically relevant information is controversial and may depend on the type of tissue being imaged. Some studies have reported correlations between inflammation and changes in viscoelastic parameters (e.g. [64]), such as the loss modulus, while others have observed no relationship (e.g. [65]). Stiffness (particularly in the fiber and cross-fiber directions) has tangible meaning as it gives insight into changes in muscle fibers (fiber direction) as well as collagen in-growth (cross-fiber direction). In future studies, an anisotropic phantom (e.g. [32, 30]) will be used to further validate these results and other inversion methods utilising MRE, DTI and SSFP data.

Isotropic myocardial shear stiffness has successfully been measured from MRE experiments [15, 66, 67, 11, 16, 68] and so it is assumed that sufficient wave propagation can be achieved experimentally. However, the loading applied to the LV model in this experiment is idealised and does not necessarily represent the true harmonic motion that would occur in the left ventricle during cardiac MRE. In the future, various loading conditions should be tested to evaluate their effect on parameter identifiability in an LV model.

This study demonstrates that, in a nearly incompressible medium, four (s , E_1 , E_3 , G_{13}) out of five material properties used to describe a transversely isotropic linear elastic material are uniquely identifiable from simulated MRE displacement fields using a FEA model of harmonic steady-state wave propagation. As a material diverges from incompressibility (the Poisson's ratio decreases), the Poisson's ratio becomes more identifiable. When Gaussian noise was added to the LV optimizations, the solution was more dependent on the initial estimate. However, fixing Poisson's ratio improved estimation of the damping s , E_1 and G_{13} . In a transversely-isotropic model, there is a reasonable degree of confidence when predicting the transverse Young's modulus (E_1) as well as the fiber shear (G_{13}) using this method; however, less confidence in the prediction of the fiber Young's modulus (E_3) and the damping coefficient (s). These results are consistent with a previous Monte-Carlo simulation study ($n = 30$) [50] which identified three parameters to describe a transversely isotropic linear elastic material: μ , the shear modulus in the isotropic plane, ϕ , related to the shear anisotropy and ζ , related to the tensile anisotropy. From the estimations with added Gaussian noise (SNR = 10), mean global estimates of μ and ϕ were within 25% of the true values. However, the mean global estimate of ζ was always underestimated and varied by 40%. Estimating E_3 necessitates the existence of fast shear waves [50, 33, 34, 69], which induce fiber stretching, in the MRE displacement field. In the LV simulations in this study, a lack of adequate fast shear waves may account for the fact that E_3 was consistently less identifiable than E_1 and G_{13} . As has been presented in these recent studies investigating transversely isotropic properties estimated from MRE, other loading configurations should also be tested, which may improve the identifiability of the fiber Young's modulus.

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Figure 1. MRE phase contrast images from four phase offsets. Each image is a 2D axial slice through the phantom and represents displacement in the vertical direction in the images.

Figure 2.

a) LV model showing embedded fibers as blue line segments b) boundary conditions at apical nodes in red, which were displaced 0.2 mm/80 Hz in the x-direction and 3) epicardial basal nodes in red that were fixed (right).

Figure 3. Percent RMSE for a) E_1 and s and b) ν_{12} and E_1 . Plots are shown with additional interpolated data points; black spheres indicate points at which error values were calculated.

Figure 4.

a) Displacement maps at five points (a–e) during one harmonic cycle in the ground truth FE LV model. Panels a–e show a section through the long axis of the LV and the color maps represent magnitude of the displacement ($\sqrt{x^2 + y^2 + z^2}$); red: +0.2 mm, blue: 0 mm.

Figure 5.

A representative example of plots of the objective function. Percent RMSE is plotted for parameters: a) G_{13} vs. E_1 , b) E_1 vs. s , c) v_{31} vs. E_3 and d) G_{13} vs. E_3 ; black spheres indicate points at which error values were calculated. Note the difference in scales between the plots.

Figure 6.

Box plots of material parameter estimation results for the a) damping coefficient, b) transverse Young's modulus, c) fiber Young's modulus, d) fiber shear modulus and e) Poisson's ratio. Boxplots show results from optimizations when varying Poisson's ratio ("Variable v ") and when fixing Poisson's ratio in the fiber-transverse direction (" $v = 0.49999999$ "). Both Monte-Carlo simulations ($n=30$) used varying initial estimates.

Figure 7.

A representative example of plots of the objective function. Percent RMSE is plotted for parameters: a) G_{13} vs. E_1 , b) E_1 vs. s , c) v_{12} vs. E_3 and d) G_{13} vs. E_3 ; black spheres indicate points at which error values were calculated.

Table 1

Summary of optimality criteria determined from the Hessian of the objective functions at the minimum.

	D-Opt	Eccentricity	M-Opt
LV	6.730e21	256.34	0.943
Phantom-Iso	1.028e12	26.19	0.901
Phantom-Aniso	3.521e12	77.82	0.811

Table 2

Results from material parameter estimations

	Damping (ς)	Transverse Young's Modulus (E_1)	Fiber Young's Modulus (E_3)	Fiber Shear Modulus (G_{13})	Poisson's Ratio (ν_{31})
Phantom Anisotropic	0.10	16.75 kPa	16.75 kPa	5.65 kPa	0.499
LV	0.118 $\pm$ 0.011	6.555 $\pm$ 0.214 kPa	10.459 $\pm$ 1.014 kPa	2.513 $\pm$ 0.077 kPa	0.464 $\pm$ 0.053
LV (fixed ν)	0.120 $\pm$ 0.015	6.538 $\pm$ 0.054 kPa	11.027 $\pm$ 0.628 kPa	2.526 $\pm$ 0.054 kPa	$\equiv$ 0.499999999