How shaky is MRE? Bootstrap and Monte Carlo Analysis of Reliability

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Introduction Magnetic resonance elastography (MRE) [1] measures the mechanical properties of biological tissues *in vivo* through acquiring motion encoded phase signals of magnetic resonance imaging (MRI). Quantitative measurements of elasticity using MRE have been made for a variety of biological tissues [2,3,4]. MRE-measured elasticity varies greatly across studies for the same biological tissues due to different experimental setups and reconstruction algorithms. The acquisition and reconstruction of MRE data are known to be sensitive to noise. Understanding of error propagation through the mathematically complex MRE reconstruction algorithms is necessary to determine the accuracy and precision of calculated elasticity values and the impact of different acquisition and modelling methods on the uncertainties of MRE measures, but this has not been done previously. In order to estimate error propagation during MRE reconstruction, we investigated the uncertainties in elasticity estimates from simulated and real human brain data through statistical simulations and analysis using Monte Carlo simulation and bootstrap [5] algorithms. Bootstrapping is a resampling technique that can be used to estimate the uncertainties in the results of linear regression algorithms such as the ordinary least square (OLS) fitting used in MRE reconstruction. Bootstrapping has been used to estimate errors in diffusion tensor data in order to compare methodologies.

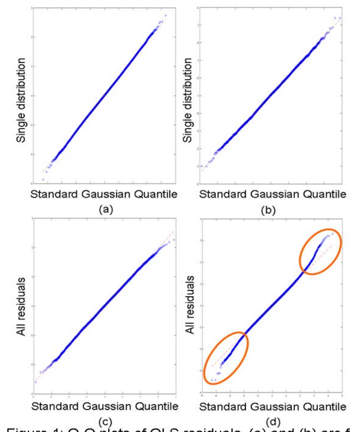

Figure 1: Q-Q plots of OLS residuals. (a) and (b) are for single dimension and single element of complex wave. (c) and (d) include all dimensions and elements. (a) and (c) are for homoscedastic noise. (b) and (d) are for heteroscedastic noise (SNR=25). Orange circles indicate heteroscedasticity.

Methods Propagation of a 60Hz complex mechanical wave of amplitude 20 µm through a homogeneous and isotropic elastic material with shear modulus (G') of 3 kPa was simulated with a finite element model. The MRE signal was calculated based on the mechanism of flow encoding gradients (FEG) used in a real experiment. Voxel size=2mm isotropic, matrix 96 x 96 x 7. Gaussian noise with SNR of 2 to 25, calculated from the signal averaged in space, was added to induce error in the data. For each SNR, two groups of simulated datasets were created with constant (homoscedastic noise) and non-constant (heteroscedastic noise) standard deviation (SD) across dimensions (x,y,z) and at different phases of the wave respectively. G' was calculated through fitting a complex wave to the data then OLS fitting (Eqn. 1) [3].

$$\mathbf{G} = (\mathbf{D}^T\mathbf{D})^{-1}\mathbf{D}^T\mathbf{u} \qquad (1)$$

where **G** consists of G', **D** consists of the Laplacian of the fitted complex wave, and **u** consists of the real and imaginary elements of the complex wave in 3D. Monte Carlo simulations (Fig. 2a,b) were conducted with 200 datasets with a SNR of 25 to provide 'gold standard' SE estimates for validation of the bootstrap method. A wild bootstrap [5] (Fig 2c,d) with 200 repetitions was applied for each of two datasets with homoscedastic and heteroscedastic noise. The SE of G' was then calculated and compared with the Monte Carlo results. Wild bootstrap was also applied to one real human brain dataset, with a SNR of 4 and a mechanical wave of 80 Hz for optimal transduction. Other parameters are similar to the simulation.

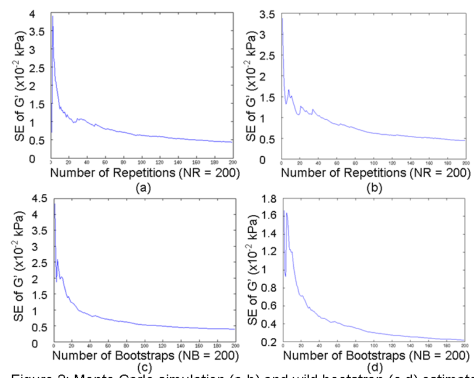

Figure 2: Monte Carlo simulation (a,b) and wild bootstrap (c,d) estimated SE of G'. (a) and (c) are for homoscedastic noise. (b) and (d) are for heteroscedastic noise (SNR=25).

Results and Discussion The Q-Q plots (Fig. 1) of residuals of OLS fitting in 8,000 simulated voxels showed Gaussian distribution within a single dimension (Fig. 1a, b) either with homoscedastic or heteroscedastic noise. The Q-Q plot of all residuals (Fig. 1c, d) in 3D however, showed heteroscedasticity (Orange circles, Fig. 1d) of variance for the datasets with heteroscedastic noise. Monte Carlo (MC, Table 1) estimated bias of mean G' was 0.7% and 4 times the SE with heteroscedastic noise, while the bias was minimal in the homoscedastic case. Also, there was a significant underestimate of 60% (0.0020 versus 0.0050) for the SE of G' using wild bootstrap (WB) compared to the Monte Carlo simulation with heteroscedastic noise, while there was only 1.6% (0.0049 versus 0.0050) underestimate with homoscedastic noise. At low SNR bootstrap estimated root mean square error (RMSE) increased significantly more with heteroscedastic than homoscedastic noise. This is due to the substantial increase in bias which accounts for a large proportion of the RMSE. The coefficient of variance (CV), which is the ratio between SE and mean G', also increased more with heteroscedastic noise when the SNR decreased. The OLS fitting was shown to work accurately (RMSE<3.1%) with homoscedastic noise even with a low SNR of 4, while the RMSE and bias were substantial when there was heteroscedastic noise and the SNR was low (≤5). This is possibly because OLS fitting does not account for heteroscedasticity as well as a bias induced by the preprocessing of complex wave fitting. Bootstrap estimated CV was higher for the human data than the simulated data with the same SNR, possibly due to the difficulty of accurately estimating SNR in phase data, in which the noise distribution and the bias of mean G' were not known. Results also verified the maintenance of Gaussian distribution through the error propagation from MRE data to the residuals during reconstruction (Fig 1). Also, we showed that there was heteroscedasticity of residuals induced by heteroscedastic noise in the MRE data. Further simulations with heteroscedastic noise distributions similar to real experiment will examine whether OLS fitting is adequate, or if weighted least square (WLS) [5] or other fitting methods are needed for MRE reconstruction.

	Homoscedastic noise				Heteroscedastic noise				Human Data		
	Mean (% bias)	SE	CV	RMSE	Mean (% bias)	SE	CV	RMSE	Mean	SE	CV
MC SNR=25	3.04 (1.3%)	0.0050	0.16%	1.3%	3.02 (0.7%)	0.0050	0.16%	0.69%	-	-	-
WB											
SNR=25	3.00 (0)	0.0049	0.16%	0.16%	3.02 (0.7%)	0.0020	0.06%	0.67%	-	-	-
SNR=20	3.08 (2.7%)	0.0061	0.20%	2.6%	3.07 (2.3%)	0.0067	0.22%	2.3%	-	-	-
SNR=15	3.09 (3.0%)	0.0084	0.27%	2.9%	3.07 (2.3%)	0.0091	0.30%	2.3%	-	-	-
SNR=10	3.09 (3.0%)	0.0129	0.42%	2.9%	3.06 (2.0%)	0.0140	0.46%	2.0%	-	-	-
SNR=5	3.03 (1.0%)	0.0264	0.87%	3.1%	2.89 (3.7%)	0.0292	1.0%	11%	-	-	-
SNR=4	2.96 (1.3%)	0.0324	1.1%	1.7%	2.76 (8.0%)	0.0365	1.3%	8.1%	1.47	0.0358	2.4%
SNR=2	2.32 (23%)	0.0466	2.0%	23%	1.86 (38%)	0.0574	3.1%	38%	-	-	-

Table 1: Monte Carlo (MC) and wild bootstrap (WB) estimated mean, SE, CV and RMSE of G' (kPa).

Conclusions We have quantified the uncertainty of MRE in simulated and real human brain data. The RMSE are low with the homoscedastic and heteroscedastic noise when the SNR is moderately high, which indicates a high accuracy and precision of MRE reconstruction. The bootstrap results, compared to the Monte Carlo simulation as a gold standard, suggest that WLS fitting within MRE reconstruction might be needed to account for heteroscedasticity of noise. Moreover, this study has calculated the error propagation from raw MRE data to the residuals of OLS fitting during MRE reconstruction, which cannot be quantified analytically and has not been investigated previously to our knowledge. We have developed a platform to quantitatively estimate the uncertainty in MRE data. Further investigations with more comprehensive simulations of noise and real MRE data will allow evaluation of the validity of MRE measurements with different experimental setups and reconstruction algorithms. Bootstrapping techniques are a promising method for evaluating reliability of MRE estimates of soft tissue elasticity.

References

[1] Muthupillai R. et al., 1995. Science 269 (5232), 1854 – 1857.
[2] Sack, I. et al., 2002. Magnetic Resonance Imaging, 20 (1), 95–104.
[3] Sinkus, R. et al., 2000. Physics in Medicine and Biology, 45, 1649–1664.
[4] Huwart, L. et al., 2008. Gastroenterology 135 (1), 32–40.
[5] Efron, B., Tibshirani, R., 1993. Chapman and Hall, New York.