Quantification of Nonlinear Elastic Constants Using Polynomials in Quasi-Incompressible Soft Solids

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***Abstract*—Early detection of pathological processes is crucial for the prognosis and treatment of patients, which can be facilitated through studying tissue biomechanical properties. Shear wave elastography is a technique to estimate the shear modulus of tissue. Such measurements quantify elasticity linearized around an immediate state of local stress condition, under applied nature of excitation. Stress-strain is known to be nonlinearly related in tissues, and the quantification of such nonlinearity may be utilized to facilitate diagnostic and image analytic approaches. In this work, we compare different methods for quantifying such nonlinear relationships, in particular the estimation of elasticity parameters, including third (A) and fourth (D) order nonlinear elastic constants, from measurements. We study the fitness and robustness in approximating these parameters, and compare those in terms of tissue differentiation, applied to ex-vivo liver and muscle tissues.**

***Index Terms*—Ultrasound, elastography, biomechanics**

I. INTRODUCTION

Pathological processes in healthy tissues, such as cysts or malignant tumors, often result in a change in biomechanical tissue parameters. Noninvasive methods for characterizing tissue mechanical properties are of great interest as they can aid diagnostic procedures [1]. Shear-wave elastography (SWE) is a noninvasive technique in which the speed of shear-wave propagation is observed in ultrasound imaging in order to relate to the underlying tissue shear modulus [2]. This method has been investigated extensively for the diagnosis of diseases, such as breast cancer and liver cirrhosis [3], [4]. In the case of breast cancer, SWE has a good sensitivity, but a relatively poorer specificity, resulting in false positives [5]. Also, detection of small stiffness changes at early stages of pathologies are not possible reliably with SWE [6]. Additional biomechanical markers would facilitate diagnostic, screening, and staging procedures.

Characterizing non-linear biomechanical properties has been investigated in the literature [7]. It was shown in [8] that some forms of cancer with similar shear modulus values to those of healthy tissue at small strains may exhibit different non-linear stress-strain curves at larger strains. The phenomenon is known as acoustoelasticity (AE), describing changes in propagation speed under a static stress pre-loading, due to nonlinear effects between mechanical stress and finite strain in tissue. In deformed solids, AE affects the propagation speed of waves with relatively small amplitudes. Based on AE, recent studies [9], [10] have investigated the third order non-linear modulus (cf. [11]). It was theoretically shown that applying strains larger than a few percent is sufficient to perceive the influence of the fourth order elasticity constant [12]. In this paper we study the characterization of third and fourth order non-linear parameters in ex-vivo liver and muscle tissues by using ultrasound SWE in a quasi-static mechanical stress test setup.

II. MATERIALS AND METHODS

An AE measurement involves applying varying stresses (preloads) on the target tissue while measuring the wave propagation speed, in order to derive nonlinearity from (assumed/simplified) models. Differences between methods arise from the natures of applying preloading, measuring wave propagation, and the models utilized. We herein employ AE theory to determine mechanical parameters from shear-wave speed in elastic solid tissues under uniaxial compression. Using the equation of motion for elastic waves in a uniaxially-stressed solid, Gennisson et al. [13] derived the linear acoustoelastic dependence of the squared wave speed on uniaxial stress. Given shear-waves polarized along the axis of deformation (e.g. the transducer for generating shear-waves being on the same axis as the uniaxial compression), the following is obtained:

$$\rho v^2 = \mu_0 - \sigma \frac{A}{12\mu_0} \tag{1}$$

where μ_0 is the shear modulus in a stress free condition, A is the third order elastic constant, and σ is the applied stress.

For relatively large tissue deformations, the quadratic form of (1) should be considered, yielding another (fourth-order) nonlinearity parameter. This parameter was studied in [14] by performing an acoustoelastic measurement followed by an additional measurement involving finite amplitude shear-waves. Assuming large acoustoelastic effects and starting from (1), Destrade et al. [12] related the squared wave-speed of an infinitesimal wave traveling in an incompressible solid to the corresponding small-magnitude uniaxial predeformation. Accordingly, for a shear-wave polarized along the axis of deformation:

$$\rho v^2 = \mu_0 + (\frac{A}{4})e + (2\mu_0 + A + 3D)e^2 \tag{2}$$

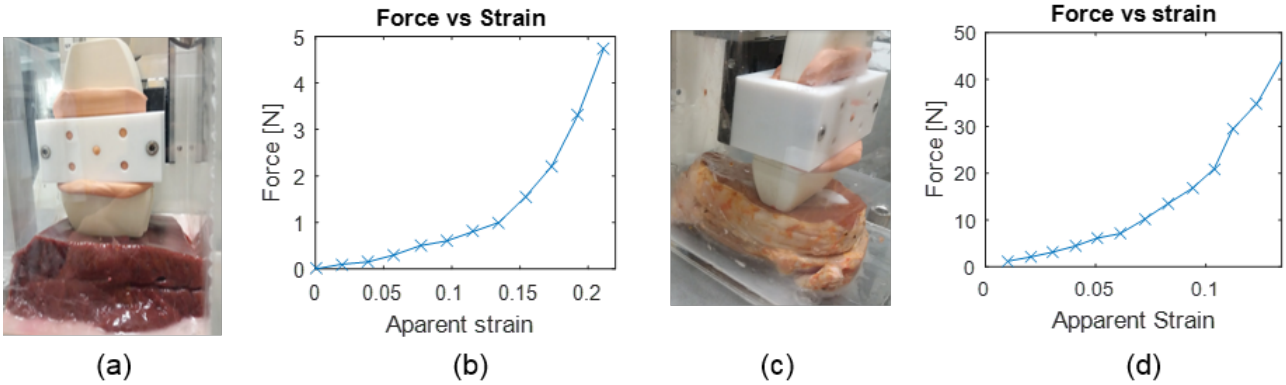

Fig. 1. Experimental setup for liver (a) and muscle (c) with the corresponding force measurement values (b,d).

where ρ is the tissue density, v is the shear wave speed, e is the applied elongation (e>0) or compression (e<0), and D is the fourth order elastic constant. For quasi-incompressible materials (i.e., Poissons ratio ≈ 0.5), shear-wave velocity can be related to Youngs modulus with $E = 3\rho v^2$. With $E = \frac{\partial \sigma}{\partial e}$, stress can be related to strain by integrating Eq.(2), as follows:

$$\sigma = 3\mu_0 e + \frac{3}{8}Ae^2 + (2\mu_0 + A + D)e^3 + C \tag{3}$$

with the constant of integration, C, being null, since the stress is zero at zero strain.

Apparent tangent shear modulus of tissue at each loading step i can be computed using $\mu = \rho v^2$. Considering $\mu = \frac{1}{3}\frac{\partial \sigma}{\partial e}$, the apparent tangent shear modulus is then

$$3\mu_i = \frac{(\sigma_{i+1} - \sigma_i)}{(e_{i+1} - e_i)} \tag{4}$$

Assuming uniaxiality, apparent stress can be computed by

$$\sigma_{i+1} = \sigma_i + 3\mu_i(e_{i+1} - e_i) \tag{5}$$

with σ_0 being the stress at initial step, which was considered to be close to 0 Pa as the probe is barely in contact with tissue, exerting minimal stress.

III. Experiments

Comprehensive experiments (CompExp) were carried out using a motorized compression-tensile test system (Andilog Stentor II) providing precise compressions and corresponding force readings. An ultrasound probe (ATL L7-4) attached to the compression system was used to subject ex-vivo bovine liver and porcine muscle tissues to compression in 0.5 mm steps, up to 5 mm (corresponding to a nominal strain of around 20%, for the liver with initial thickness of 26 mm), while measuring required forces. Experimental setup and the force-strain profiles are shown in Fig. 1.

At each compression step, shear-wave measurements were carried out using a Verasonics (Seattle, WA, USA) ultrasound system. Following focused shear-wave excitations, ultrafast plane-wave images were collected and shear-wave speed was estimated from tracked displacements based on in-house developed algorithms; see example images in Fig. 2. Mean shear-wave velocity within homogeneous tissue regions at each compression step were related to shear-modulus using $\mu = \rho v^2$.

Stress-strain relation was extracted using two different approaches: First one using the force-sensor measurements at each compression step, which then correspond to *quasi-static* excitation response, hence called QS experiment and results. A second set of results was obtained from the shear wave speed measurements, called SW experiment and results. Note that both set of results utilize the nominal strains observed on the compression device.

QS apparent stress was obtained by diving the measured force to the transducer area, i.e. $\sigma = \frac{F}{A}$. Non-linear behavior of both tissues can already be seen from the exerted compressive force, cf. Fig. 1 (b,d). In order to compute the QS apparent tangent shear modulus corresponding to the measured forces, Eq.(4) was used. For the SW data, the apparent tangent shear modulus was calculated from the shear wave speed from $\mu = \rho v^2$. Equation (5) was used to compute SW apparent stress from computed tangent modulus. AE effect can be seen in Fig. 2, where the shear wave speed increases with applied nominal strain from 1.4 m/s at "uncompressed" initial state to 3.2 m/s at 20% strain.

IV. Results and Discussion

We used polynomial fitting to estimate the elastic parameters by least square approximation. This was done by fitting both QS and SW datasets with the equations defined in (1, 2, 3) by using the MATLAB fitting toolbox.

Using (1) the third order elastic constant was determined from the slope of the apparent tangent shear modulus as a function of applied stress, cf. Fig. 3(a).

This was calculated for both QS and SW cases. Both third and fourth order elastic constants could be determined using Eq.(2) from the quadratic equations relating apparent tangent shear modulus to nominal strain. However, in our experiments, this approach was found not to be stable; see Fig. 3(b). Alternatively, we estimated the aforementioned constants using the third order polynomial stress strain relationship in Eq.(3),

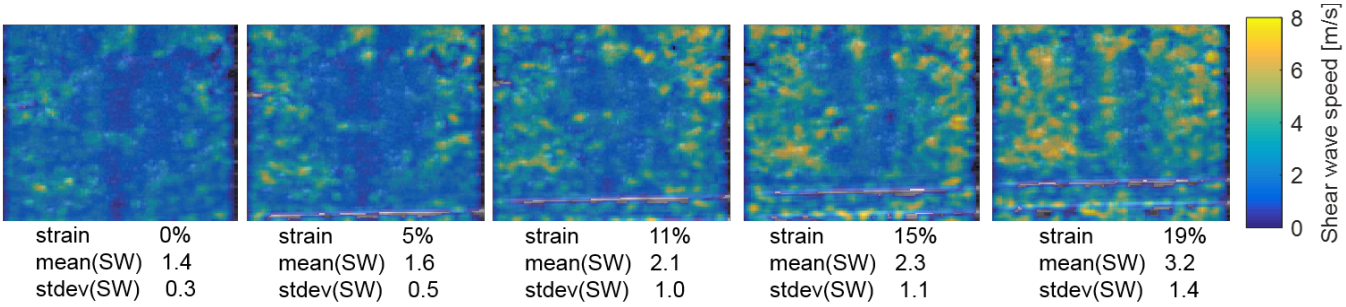

Fig. 2. Shear wave speed measurements at compression levels corresponding to nominal strain levels of 0, 5, 10, 15, 20%

which we observed to yield a more robust parameter fitting, see Fig. 3(c).

For the CompExp fine compression liver experiment, where eleven data points were available, the A parameter was recovered using the linear and third order relationships. Both of them resulted in a similar range for shear-modulus measurements ([-77.35,-70.52] kPa) comparable to literature values ([-130, -80 kPa]) [7], [9]. The second order strain-shear modulus relationship (2) resulted in a large parameter range for A in all our experiments, with a mean around 0, hence no parameters could be estimated robustly from this estimator. Using (3) D parameters were estimated at 347.7 kPA. The μ parameter was found to be similar using all proposed methods above (range of [1.6, 2.63] kPa for the SW case and [1.2, 1.52] kPa for the QS case). The QS A and D parameters were found to be in a similar order of magnitude wrt. the SW data, with A ([-44.73, -52.06] kPa) and the D (430.3 kPa) A difference between parameters measured using QS and SW methods is expected, as tissue response to external excitation may vary with excitation frequency.

Table I presents estimated parameters with the upper and lower 95% confidence intervals. Based on these reported results and confidence intervals, the second order fitting was found to be unstable. It can be seen that all of the methods have a good fit, however the confidence interval for the linear fitting is narrower, indicating a relatively better estimator. This is also likely due to a lower-order model being more stable with less parameters to estimate compared to second and third order formulations.

In a practical scenario, such as in a clinical setup, the force measurements would not be readily available and any external measurements cannot be related to the internal tissue stresses due to unknown anatomical boundary conditions. Moreover, a large number of compression points may be infeasible to obtaine in vivo. For this reasons we conducted a clinical feasibility experiment (FeasExp) on ex-vivo liver, utilizing only few (herein, 4) compression steps while acquiring ultrasound SW measurements. Results are reported in TableI. It is seen that the A parameter could be recovered using the linear stress-shear modulus relationship (1), yielding values of -72.6 kPa – comparable to CompExp case. Both second and third order relationships resulted in unstable results for the A parameter, likely due to only four data points being available.

Similar results were obtained for the ex-vivo porcine muscle, where seven compression steps were used (Fig. 4). Table II presents estimated parameters and corresponding confidence intervals. For the muscle, only the linear fitting resulted in a reliable A parameter. Both second and third order estimations resulted in large confidence intervals, hence being unstable estimators.

TABLE I
NONLINEAR PARAMETER ESTIMATION USING SWE AND QS MEASUREMENTS FOR LIVER

Liver	Linear fitting		Second order fitting			Third order fitting		
	μ [kPa]	A [kPa]	μ [kPa]	A [kPa]	D [kPa]	μ [kPa]	A [kPa]	D [kPa]
Liver CompExp SW	1.6	-77.35	1.92	0	61.54	2.63	-70.52	347.7
lower conf. int.	1.03	-86.92	1.04	-80.14	-47.87	2.32	107.3	264.4
upper conf. Int	2.07	-67.78	2.81	80.14	170.9	2.94	-34.01	431
Liver CompExp QS	1.41	-44.73	1.52	0	90.53	1.24	-52.06	430.3
lower conf. int.	1.07	-47.8	1.1	-28.2	-14.4	0.598	-86.6	355.6
upper conf. int	1.746	-41.64	1.94	28.2	195.5	1.89	-17.21	504.9
Liver FeasExp SW	2.2	-72.6	2.4	0	64.81	0	-194.1	210.1
lower conf. int.	-0.6	-111.1	-11.37	-1143	-715.1	-29.69	-3313	-348.8
upper conf. int	5.1	-34.24	15.77	1143	844.8	29.69	2924	770.3

TABLE II
NONLINEAR PARAMETER ESTIMATION USING SWE AND QS MEASUREMENTS FOR MUSCLE

Muscle	Linear fitting		Second order fitting			Third order fitting		
	μ [kPa]	A [kPa]	μ [kPa]	A [kPa]	D [kPa]	μ [kPa]	A [kPa]	D [kPa]
SW	8.918	-408.0	10.48	0	573.3	11.89	-54.05	185
lower conf. int.	7.271	-439.6	6.569	-488	-162.5	8.874	-523.9	57.4
upper conf. int	10.56	-376.4	14.39	488.1	1309	14.902	415.8	312.6
QS	11.53	-239.1	12.22	-95.5	0	11.8	-152.3	233.3
lower conf. int.	10.81	-265.0	11.5	-187	-137.8	11.3	-292.4	20.16
upper conf. int	12.26	-213.2	12.95	-4.31	137.8	12.31	-12.2	446.5

V. CONCLUSIONS

In this paper we measured third and fourth order nonlinear elasticity parameters of ex-vivo liver and muscle samples using a motorized compression setup and shear-wave speed measurements, corresponding to quasi-static deformation and a dynamic excitation. We have shown that for both measurements, a second order fitting of the strain shear modulus leads to an unstable parameter estimation. We have demonstrated that a third order fitting of the strain-stress curves is preferred for determining both the third and fourth order constants, while a linear fitting of the stress-shear modulus curves is more robust in determining only the third order constant. The recovered parameters were similar to those reported in the literature.

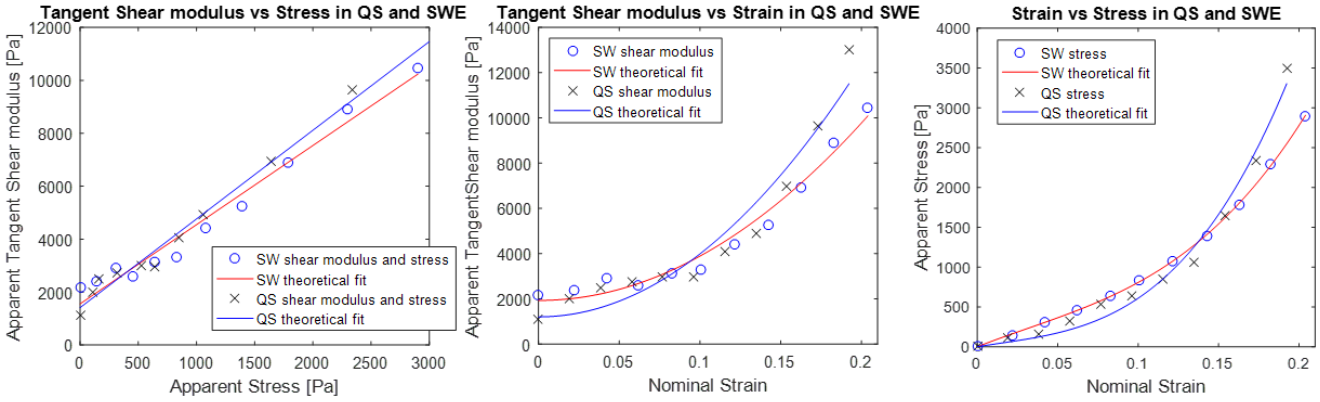

Fig. 3. Nonlinear parameter estimation in ex-vivo liver using CompExp fine compressions of 0.5 mm steps with a motorized system for linear (a), quadratic (b) and third order fit (c) parameters estimated using QS and SW approaches.

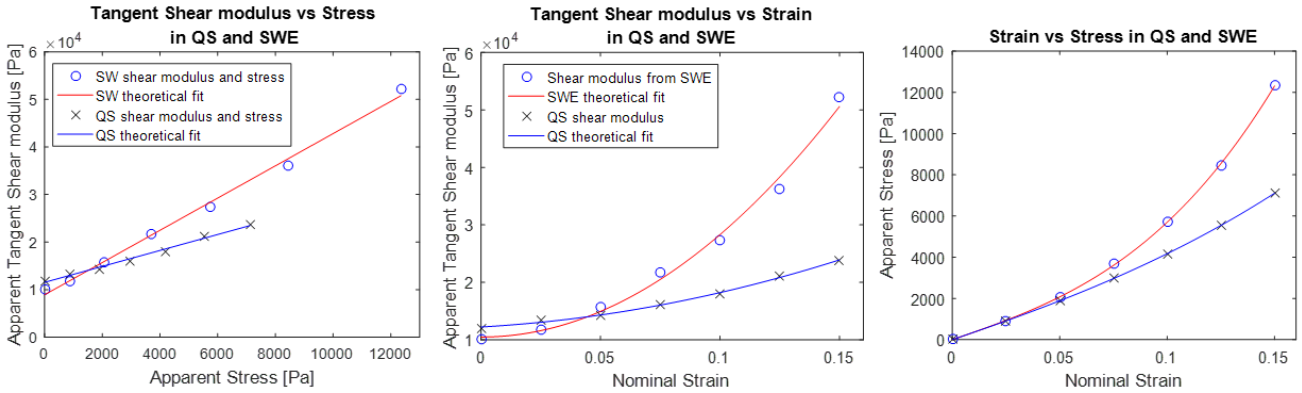

Fig. 4. Nonlinear parameter estimation for a porcine muscle tissue using SWE and QS measurements in 1 mm compression steps (7 steps) using a motorized sensor system with a linear (a), quadratic (b) and third order fit (c).

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